

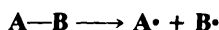
14

FREE-RADICAL SUBSTITUTION

MECHANISMS

Free-Radical Mechanisms in General¹

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, i.e., a cleavage in which each fragment retains one electron:



This is called an *initiation* step. It may happen spontaneously or may be induced by heat or light (see the discussion on p. 193), depending on the type of bond. Peroxides, including hydrogen peroxide, dialkyl, diacyl, and alkyl acyl peroxides, and peracids 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 in another way, by a one-electron transfer (loss or gain), e.g., $\text{A}^+ + \text{e}^- \rightarrow \text{A}\cdot$. One-electron transfers usually involve inorganic ions or electrochemical processes.

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:²



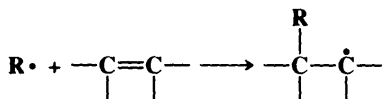
This type of step is called *termination*, and it ends the reaction as far as these particular radicals are concerned.³ However, it is not often that termination follows *directly* upon initiation. The reason is that most radicals are very reactive and will react with the first available species with 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

¹For books on free-radical mechanisms, see Nonhebel; Tedder; Walton *Radicals*; Cambridge University Press: Cambridge, 1979; Nonhebel; Walton *Free-Radical Chemistry*; Cambridge University Press: London, 1974; Huyser *Free-Radical Chain Reactions*; Wiley: New York, 1970; Pryor *Free Radicals*; McGraw-Hill: New York, 1966; For reviews, see Huyser, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 1-59; Lloyd, *CHEMTECH* **1971**, 176-180, 371-381, 687-696, **1972**, 182-188. For monographs on the use of free-radical reactions in synthesis, see Giese *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, 1986; Davies; Parrott *Free Radicals in Organic Synthesis*; Springer: New York, 1978. For reviews, see Curran *Synthesis* **1988**, 417-439, 489-513; Ramaiah *Tetrahedron* **1987**, *43*, 3541-3676.

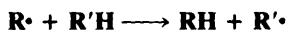
²For a review of the stereochemistry of this type of combination reaction, see Porter; Krebs *Top. Stereochem.* **1988**, *18*, 97-127.

³Another type of termination is disproportionation (see p. 194).

(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, e.g.,



in which case it may be another free radical; or it may consist of two particles, e.g.,



in which case one must be a molecule and one a free radical, but in any case 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*,⁴ 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 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, e.g., alkyl radicals, chains are long, since reactions occur with many molecules; but with radicals of low reactivity, e.g., 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.⁵

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

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.⁶
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.
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. 247). Quantum yields can be quite high, e.g., 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, e.g., nitric oxide, molecular oxygen, or benzoquinone. These substances are called *inhibitors*.⁷

In this chapter are discussed free-radical substitution reactions. Free-radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. 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.

⁴For a discussion of radical chain reactions from a synthetic point of view, see Walling *Tetrahedron* **1985**, *41*, 3887.

⁵For a discussion of the kinetic aspects of radical chain reactions, see Huyser *Free-Radical Chain Reactions*, Ref. 1, pp. 39-65.

⁶For a discussion, see Mayo *J. Am. Chem. Soc.* **1967**, *89*, 2654.

⁷For a review of the action of inhibitors, see Denisov; Khudyakov *Chem. Rev.* **1967**, *87*, 1313-1357.

Free-Radical Substitution Mechanisms⁸

In a free-radical substitution reaction



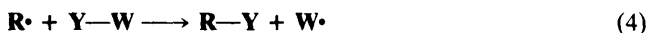
there must first be a cleavage of the substrate RX so that R• radicals are produced. This can happen by a spontaneous cleavage



or it can be caused by light or heat, or, more often, there is no actual cleavage, but R• is produced by an *abstraction*



W• is produced by adding a compound, such as a peroxide, that spontaneously forms free radicals. Such a compound is called an *initiator*. Once R• is formed, it can go to product in two ways, by abstraction

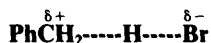


or by coupling with another radical



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 SH1 (H for homolytic), and abstraction steps like (3) and (4) have been called SH2; reactions can be classified as SH1 or SH2 on the basis of whether RX is converted to R by (2) or (3).⁹ 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 than slightly endothermic, see pp. 683, 693). 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:



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.¹⁰ However, as we might expect, substituents have a smaller effect here ($\rho \approx -1.4$) than they do in reactions where a completely ionic intermediate is involved, e.g., the S_N1 mechanism (see p. 344). Other evidence for polar transition states in radical abstraction reactions is mentioned on p. 685. For abstraction by radicals such as methyl or phenyl, polar effects are

⁸For a review, see Poutsma, in *Kochi Free Radicals*, vol. 2; Wiley: New York, 1973, pp. 113-158.

⁹Elieil, in *Newman Steric Effects in Organic Chemistry*; Wiley: New York, 1956, pp. 142-143.

¹⁰For example, see Pearson; Martin *J. Am. Chem. Soc.* **1963**, *85*, 354, 3142; Kim; Choi; Kang *J. Am. Chem. Soc.* **1985**, *107*, 4234.

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.¹¹ Those radicals (e.g., Br•) that have a tendency to abstract electron-rich hydrogen atoms are called *electrophilic radicals*.

When the reaction step $R-X \rightarrow R\cdot$ 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 inversion¹² and retention¹³ of configuration have been reported, and in the reactions mentioned on p. 682.

Mechanisms at an Aromatic Substrate¹⁴

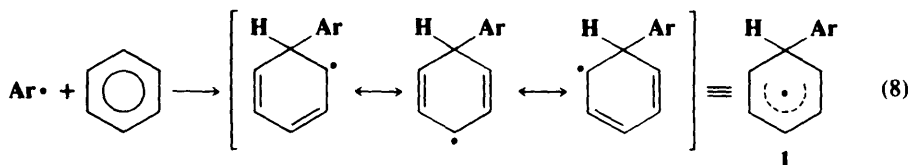
When R in reaction (1) is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes such as the following (see 4-18, 4-21, and 4-22):



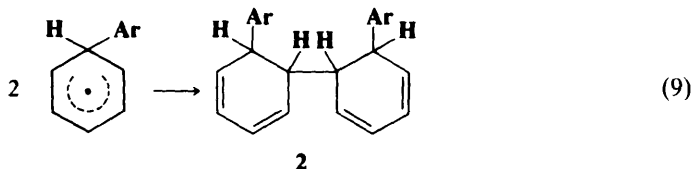
which occur in solution, the coupling of two rings cannot be explained on the basis of a simple abstraction



since, as discussed on p. 683, 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:



The intermediate is relatively stable because of the resonance. The reaction can terminate in three ways: by simple coupling, or by disproportionation

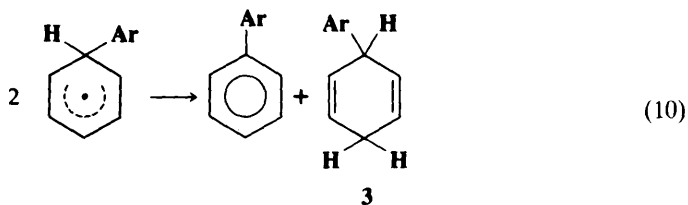


¹¹For example, see Kalatzis; Williams *J. Chem. Soc. B* **1966**, 1112; Pryor; Tonellato; Fuller; Jumonville *J. Org. Chem.* **1969**, *34*, 2018.

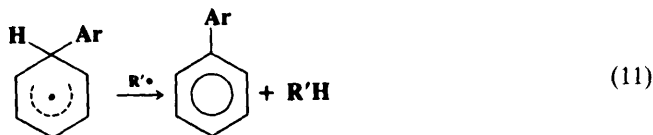
¹²Altman; Nelson *J. Am. Chem. Soc.* **1969**, *91*, 5163.

¹³Jacobus; Pensak *Chem. Commun.* **1969**, 400.

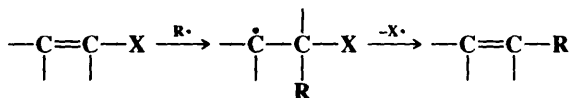
¹⁴For reviews, see Kobrina *Russ. Chem. Rev.* **1977**, *46*, 348-360; Perkins, in Kochi, Ref. 8, vol. 2, 231-271; Bolton; Williams, *Adv. Free-Radical Chem.* **1975**, *5*, 1-25; Nonhebel; Walton, Ref. 1, pp. 417-469; Minisci; Porta *Adv. Heterocycl. Chem.* **1974**, *16*, 123-180; Bass; Nababsing *Adv. Free-Radical Chem.* **1972**, *4*, 1-47; Hey *Bull. Soc. Chim. Fr.* **1968**, 1591.



or, if a species (R'^{\bullet}) is present which abstracts hydrogen, by abstraction¹⁵



2 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 2 and 3,¹⁶ though normally under the reaction conditions dihydrobiphenyls like 3 are oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate 1 by CIDNP¹⁷ 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 OH^{\bullet} radical takes place by the same mechanism. A similar mechanism has been shown for substitution at some vinylic and acetylenic substrates, e.g.:¹⁸



This is reminiscent of the nucleophilic tetrahedral mechanism at a vinylic carbon (p. 336)

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 (4-1) 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 to 94% substitution at the carbon adjacent to the bromine already in the molecule.¹⁹ This result is especially surprising because, as we shall see (p. 685), positions close to a polar group such as bromine should actually be *deactivated* by the electron-withdrawing field effect

¹⁵1 can also be oxidized to the arene ArPh by atmospheric O_2 . For a discussion of the mechanism of this oxidation, see Narita; Tezuka *J. Am. Chem. Soc.* **1982**, *104*, 7316.

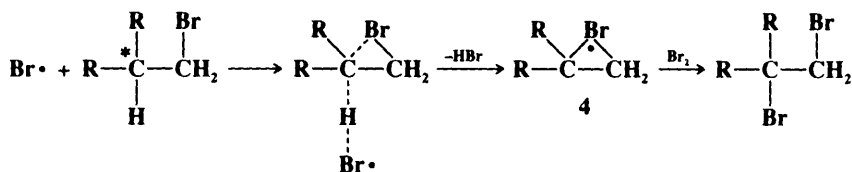
¹⁶De Tar; Long *J. Am. Chem. Soc.* **1958**, *80*, 4742. See also Ref. 334.

¹⁷Fahrenholtz; Trozzolo *J. Am. Chem. Soc.* **1972**, *94*, 282.

¹⁸Russell; Ngovivatchai *Tetrahedron Lett.* **1986**, *27*, 3479, and references cited therein.

¹⁹Thaler *J. Am. Chem. Soc.* **1963**, *85*, 2607. See also Traynham; Hines *J. Am. Chem. Soc.* **1968**, *90*, 5208; Ucciani; Pierri; Naudet *Bull. Soc. Chim. Fr.* **1970**, 791; Hargis *J. Org. Chem.* **1973**, *38*, 346.

of the bromine. The unusual regioselectivity is explained by a mechanism in which abstraction (3) is assisted by a neighboring bromine atom:²⁰



In the normal mechanism, $\text{Br}\cdot$ abstracts a hydrogen from RH , leaving $\text{R}\cdot$. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a bridged free radical, 4).²¹ In the final step (very similar to $\text{R}\cdot + \text{Br}_2 \rightarrow \text{RBr} + \text{Br}\cdot$) 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.²⁰ 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.²² This is just what would be predicted if some of the 4 present abstracted D from DBr . There is evidence that Cl can form bridged radicals,²³ though esr spectra show that the bridging is not necessarily symmetrical.²⁴ Still more evidence for bridging by Br has been found in isotope effect and other studies.²⁵ 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 $[\text{PhCOO}\cdot + \text{CH}_2\text{CH}_2\text{Br}]$ within a solvent cage.²⁶ This evidence indicates that under these conditions $\text{BrCH}_2\text{CH}_2\cdot$ 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 reaction²⁷ (4-39), and in abstraction of iodine atoms by the phenyl radical.²⁸ Participation by other neighboring groups, e.g. SR , SiR_3 , SnR_3 , has also been reported.²⁹

²⁰Skell; Tuleen; Readio *J. Am. Chem. Soc.* **1963**, *85*, 2849. For other stereochemical evidence, see Huyser; Feng *J. Org. Chem.* **1971**, *36*, 731. For another explanation, see Lloyd; Wood *J. Am. Chem. Soc.* **1975**, *97*, 5986.

²¹For a monograph, see Kaplan *Bridged Free Radicals*; Marcel Dekker: New York, 1972. For reviews, see Skell; Traynham *Acc. Chem. Res.* **1984**, *17*, 160-166; Skell; Shea, in Kochi, Ref. 8, vol. 2, pp. 809-852.

²²Shea; Skell *J. Am. Chem. Soc.* **1973**, *95*, 283.

²³Everly; Schweinsberg; Traynham *J. Am. Chem. Soc.* **1978**, *100*, 1200; Wells; Franke *Tetrahedron Lett.* **1979**, 4681.

²⁴Bowles; Hudson; Jackson *Chem. Phys. Lett.* **1970**, *5*, 552; Cooper; Hudson; Jackson *Tetrahedron Lett.* **1973**, 831; Chen; Elson; Kochi *J. Am. Chem. Soc.* **1973**, *95*, 5341.

²⁵Skell; Readio *J. Am. Chem. Soc.* **1964**, *86*, 3334; Skell; Pavlis; Lewis; Shea *J. Am. Chem. Soc.* **1973**, *95*, 6735; Juneja; Hodnett *J. Am. Chem. Soc.* **1967**, *89*, 5685; Lewis; Kozuka *J. Am. Chem. Soc.* **1973**, *95*, 282; Cain; Solly *J. Chem. Soc., Chem. Commun.* **1974**, 148; Chenier; Tremblay; Howard *J. Am. Chem. Soc.* **1975**, *97*, 1618; Howard; Chenier; Holden *Can. J. Chem.* **1977**, *55*, 1463. See however Tanner; Blackburn; Kosugi; Ruo *J. Am. Chem. Soc.* **1977**, *99*, 2714.

²⁶Hargis; Shevlin *J. Chem. Soc., Chem. Commun.* **1973**, 179.

²⁷Applequist; Werner *J. Org. Chem.* **1963**, *28*, 48.

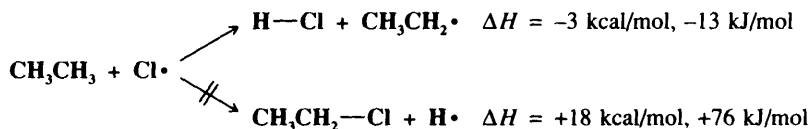
²⁸Danen; Winter *J. Am. Chem. Soc.* **1971**, *93*, 716.

²⁹Tuleen; Bentrude; Martin *J. Am. Chem. Soc.* **1963**, *85*, 1938; Fisher; Martin *J. Am. Chem. Soc.* **1966**, *88*, 3382; Jackson; Ingold; Griller; Nazran *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 Rectz *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 173-180 [*Angew. Chem.* *91*, 185-192].

REACTIVITY

Reactivity for Aliphatic Substrates³⁰

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-³¹ or trivalent atom³² (except in strained systems, see p. 757)³³ and seldom a divalent one.³⁴ 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 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 $\text{C}_2\text{H}_5-\text{H}$ bond is broken ($D = 100 \text{ kcal/mol, } 419 \text{ kJ/mol}$, from Table 5.3) whichever pathway is taken, but in the former case an $\text{H}-\text{Cl}$ bond is formed ($D = 103 \text{ kcal/mol, } 432 \text{ kJ/mol}$) while in the latter case it is a $\text{C}_2\text{H}_5-\text{Cl}$ bond ($D = 82 \text{ kcal/mol, } 343 \text{ kJ/mol}$). Thus the first reaction is favored because it is exothermic by 3 kcal/mol ($100 - 103$) [13 kJ/mol ($419 - 432$)], while the latter is endothermic by 18 kcal/mol ($100 - 82$) [76 kJ/mol ($419 - 343$)].³⁵ 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.

Most studies of aliphatic reactivity have been made with hydrogen as the leaving atom and chlorine atoms as the abstracting species.³⁶ 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. We discuss the position of attack under several headings:³⁷

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 $\text{C}-\text{H}$ bonds (Table 5.3). The extent of the preference

³⁰For a review of the factors involved in reactivity and regioselectivity in free-radical substitutions and additions, see Tedder *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401-410 [*Angew. Chem.* **94**, 433-442].

³¹Abstraction of a tetravalent carbon has been seen in the abstraction by $\text{F}\cdot$ of R from RCl : Firouzbakht; Ferrieri; Wolf; Rack *J. Am. Chem. Soc.* **1987**, *109*, 2213.

³²See, for example, Back *Can. J. Chem.* **1983**, *61*, 916.

³³For an example of an abstraction occurring to a small extent at an unstrained carbon atom, see Jackson; Townson *J. Chem. Soc., Perkin Trans. 2* **1980**, 1452. See also Johnson *Acc. Chem. Res.* **1983**, *16*, 343-349.

³⁴For a monograph on abstractions of divalent and higher-valent atoms, see Ingold; Roberts *Free-Radical Substitution Reactions*; Wiley: New York, 1971.

³⁵ 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.

³⁶For a review that lists many rate constants for abstraction of hydrogen at various positions of many molecules, see Hendry; Mill; Piszkiwicz; Howard; Eigenmann *J. Phys. Chem. Ref. Data* **1974**, *3*, 937-978.

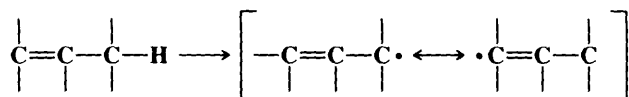
³⁷For reviews, see Tedder *Tetrahedron* **1982**, *38*, 313-329; Kerr, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 18; Elsevier: New York, 1976, pp. 39-109; Russell, in Kochi, Ref. 8, vol. 2, pp. 275-331; Rüchardt *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 830-843 [*Angew. Chem.* **82**, 845-858]; Poutsma *Methods Free-Radical Chem.* **1969**, *1*, 79-193; Davidson *Q. Rev., Chem. Soc.* **1967**, *21*, 249-258; Pryor; Fuller; Stanley *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 phase³⁸

Temp., °C	Primary	Secondary	Tertiary
100	1	4.3	7.0
600	1	2.1	2.6

depends on the selectivity of the abstracting radical and on the temperature. Table 14.1 shows³⁸ that at high temperatures selectivity decreases, as might be expected.³⁹ 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 H₂SO₄ with N-chloro-di-*t*-butylamine and N-chloro-*t*-butyl-*t*-pentylamine, the primary hydrogens are abstracted 1.7 times *faster* than the tertiary hydrogen.⁴⁰ In this case the attacking radicals (the radical ions R₂NH^{•+}, see p. 692) are bulky enough for steric hindrance to become a major factor.

2. Olefins. 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. This is generally attributed⁴¹ to resonance stabilization of the allylic radical:



As might be expected, allylic rearrangements (see p. 327) are common in these cases.⁴²

3. Alkyl side chains of aromatic rings. The preferential position of attack on a side chain is usually the one α 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:⁴³

	Me-H	MeCH ₂ -H	Me ₂ CH-H	Me ₃ C-H	PhCH ₂ -H	Ph ₂ CH-H	Ph ₃ C-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

³⁸Hass; McBee; Weber *Ind. Eng. Chem.* **1936**, 28, 333.

³⁹For a similar result with phenyl radicals, see Kopinke; Zimmermann; Anders *J. Org. Chem.* **1989**, 54, 3571.

⁴⁰Deno; Fishbein; Wyckoff *J. Am. Chem. Soc.* **1971**, 93, 2065. Similar steric effects, though not a reversal of primary-tertiary reactivity, were found by Dneprovskii; Mil'tsov *J. Org. Chem. USSR* **1988**, 24, 1836.

⁴¹See however Kwart; Brechbiel; Miles; Kwart *J. Org. Chem.* **1982**, 47, 4524.

⁴²For reviews, see Wilt, in Kochi, Ref. 8, vol. 1, pp. 458-466.

⁴³Russell, Ref. 37, p. 289.

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 σ° scales (similar to the σ , σ^+ and σ^- scales discussed in Chapter 9) have been developed for benzylic radicals.⁴⁴

4. *Compounds containing electron-withdrawing substituents.* In halogenations electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type Z—CH₂—CH₃ are attacked predominantly or exclusively at the β position when Z is COOH, COCl, COOR, SO₂Cl, or CX₃. Such compounds as acetic acid and acetyl chloride are not attacked at all. This is in sharp contrast to electrophilic halogenations (2-4 to 2-6), where *only* the α position is substituted. This deactivation of α 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. 679. 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:⁴⁵

CH ₃ —CH ₂ —COOH		
Me•	1	7.8
Cl•	1	0.03

Some radicals, e.g., *t*-butyl,⁴⁶ benzyl,⁴⁷ and cyclopropyl,⁴⁸ are *nucleophilic* (they tend to abstract electron-poor hydrogen atoms). The phenyl radical appears to have a very small degree of nucleophilic character.⁴⁹ 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. 679) that abstraction of an α hydrogen atom from ring-substituted toluenes can be correlated by the Hammett equation.

5. *Stereoelectronic effects.* On p. 334 we saw 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 ($\sim 30^\circ$) with the unshared orbitals of the O or N much more easily than from those with a large angle ($\sim 90^\circ$). For example, the starred hydrogen of **5** was abstracted about 8 times faster than the starred hydrogen of **6**.⁵⁰

⁴⁴Sec. for example, Dinçtürk; Jackson *J. Chem. Soc., Perkin Trans. 2* **1981**, 1127; Dust; Arnold *J. Am. Chem. Soc.* **1983**, *105*, 1221, 6531; Creary; Mehrsheikh-Mohammadi; McDonald *J. Org. Chem.* **1987**, *52*, 3254, **1989**, *54*, 2904; Fisher; Dershem; Prewitt *J. Org. Chem.* **1990**, *55*, 1040.

⁴⁵Russell, Ref. 37, p. 311.

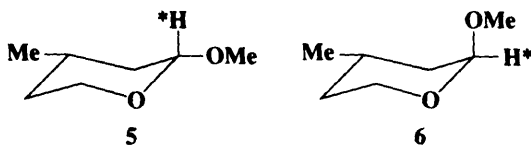
⁴⁶Pryor; Davis; Stanley *J. Am. Chem. Soc.* **1973**, *95*, 4754; Pryor; Tang; Tang; Church *J. Am. Chem. Soc.* **1982**, *104*, 2885; Dütsch; Fischer *Int. J. Chem. Kinet.* **1982**, *14*, 195.

⁴⁷Clerici; Minisci; Porta *Tetrahedron* **1973**, *29*, 2775.

⁴⁸Stefani; Chuang; Todd *J. Am. Chem. Soc.* **1970**, *92*, 4168.

⁴⁹Suehiro; Suzuki; Tsuchida; Yamazaki *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3324.

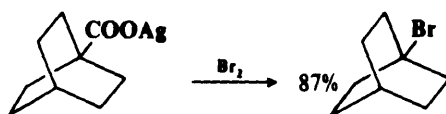
⁵⁰Hayday; McKelvey *J. Org. Chem.* **1976**, *41*, 2222. For additional examples, see Malatesta; Ingold *J. Am. Chem. Soc.* **1981**, *103*, 609; Beckwith; Easton *J. Am. Chem. Soc.* **1981**, *103*, 615; Beckwith; Westwood *Aust. J. Chem.* **1983**, *36*, 2123; Griller; Howard; Marriott; Scaiano *J. Am. Chem. Soc.* **1981**, *103*, 619. For a stereoselective abstraction step, see Dneprovskii; Pertsikov; Temnikova *J. Org. Chem. USSR* **1982**, *18*, 1951. See also Bunce; Cheung; Langshaw *J. Org. Chem.* **1986**, *51*, 5421.



Abstraction of a halogen has been studied much less,⁵¹ but the order of reactivity is $\text{RI} > \text{RBr} > \text{RCl} \gg \text{RF}$.

Reactivity at a Bridgehead⁵²

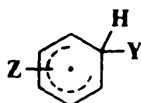
Many free-radical reactions have been observed at bridgehead carbons, e.g. (see 4-39),⁵³



demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl peroxide gave mostly 2-chloronorbornane, though the bridgehead position is tertiary.⁵⁴ So, while bridgehead free-radical substitution is possible, it is not preferred, presumably because of the strain involved.⁵⁵

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; i.e., we need to know which position on the ring will be attacked to give the intermediate



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

⁵¹For a review, see Danen *Methods Free-Radical Chem.* **1974**, *5*, 1-99.

⁵²For reviews, see Bingham; Schleyer *Fortschr. Chem. Forsch.* **1971**, *18*, 1-102, pp. 79-81; Fort; Schleyer *Adv. Alicyclic Chem.* **1966**, *1*, 283-370, pp. 337-352.

⁵³Grob; Ohta; Renk; Weiss *Helv. Chim. Acta* **1958**, *41*, 1191.

⁵⁴Roberts; Urbanek; Armstrong *J. Am. Chem. Soc.* **1949**, *71*, 3049. See also Kooymann; Vegter *Tetrahedron* **1958**, *4*, 382; Walling; Mayahi *J. Am. Chem. Soc.* **1959**, *81*, 1485.

⁵⁵See, for example, Koch; Gleicher *J. Am. Chem. Soc.* **1971**, *93*, 1657.

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:⁵⁶

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.

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 $\text{XC}_6\text{H}_4\text{Y}$ showed that substitution ortho to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).⁵⁷ 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. 516) are not great.⁵⁸ Partial rate factors for a few groups are given in Table 14.2.⁵⁹

6. Although hydrogen is the leaving group in most free-radical aromatic substitutions, ipso attack (p. 512) and ipso substitution (e.g., with Br, NO_2 , or CH_3CO as the leaving group) have been found in certain cases.⁶⁰

Reactivity in the Attacking Radical⁶¹

We have already seen that some radicals are much more selective than others (p. 684). The bromine atom is so selective that when only primary hydrogens are available, as in neo-

TABLE 14.2 Partial rate factors for attack of substituted benzenes by phenyl radicals generated from Bz_2O_2 (reaction 4-21)⁵⁹

Z	Partial rate factor		
	<i>o</i>	<i>m</i>	<i>p</i>
H	1	1	1
NO₂	5.50	0.86	4.90
CH₃	4.70	1.24	3.55
CMe₃	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

⁵⁶De Tar *J. Am. Chem. Soc.* **1961**, *83*, 1014 (book review); Dickerman; Vermont *J. Am. Chem. Soc.* **1962**, *84*, 4150; Morrison; Cazes; Samkoff; Howe *J. Am. Chem. Soc.* **1962**, *84*, 4152; Ohta; Tokumaru *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3218; Vidal; Court; Bonnier *J. Chem. Soc. Perkin Trans. 2* **1973**, 2071; Tezuka; Ichikawa; Marusawa; Narita *Chem. Lett.* **1983**, 1013.

⁵⁷Davies; Hey; Summers *J. Chem. Soc. C* **1970**, 2653.

⁵⁸For a quantitative treatment, see Charton; Charton *Bull. Soc. Chim. Fr.* **1988**, 199.

⁵⁹Davies; Hey; Summers *J. Chem. Soc. C* **1971**, 2681.

⁶⁰For reviews, see Traynham *J. Chem. Educ.* **1983**, *60*, 937-941; *Chem. Rev.* **1979**, *79*, 323-330; Tiecco *Acc. Chem. Res.* **1980**, *13*, 51-57; *Pure Appl. Chem.* **1981**, *53*, 239-258.

⁶¹For reviews with respect to $\text{CH}_3\cdot$ and $\text{CF}_3\cdot$, see Trotman-Dickenson *Adv. Free-Radical Chem.* **1965**, *1*, 1-38; Spirin *Russ. Chem. Rev.* **1969**, *38*, 529-539; Gray; Herod; Jones *Chem. Rev.* **1971**, *71*, 247-294.

pentane or *t*-butylbenzene, the reaction is slow or nonexistent; and isobutane can be selectively brominated to give *t*-butyl bromide in high yields. However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes, e.g., ethylbenzene and cumene, takes place exclusively at the α position,⁶² emphasizing the selectivity of Br \cdot . 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.

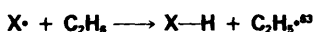
Some radicals, e.g., triphenylmethyl, are so unreactive that they abstract hydrogens very poorly if at all. Table 14.3 lists some common free radicals in approximate order of reactivity.⁶³

It has been mentioned that some free radicals, e.g., chloro, are electrophilic and some, e.g., *t*-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 Reactivity⁶⁵

As has been 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% (CH₃)₂CHCH(CH₃)CH₂Cl and 40% (CH₃)₂CHCCl(CH₃)₂, while in aromatic solvents the ratio became about 10:90.⁶⁶ This result is attributed to complex

TABLE 14.3 Some common free radicals in decreasing order of activity
The E values represent activation energies for the reaction



iso-Pr \cdot is less active than Me \cdot and *t*-Bu \cdot still less so⁶⁴

Radical	E		Radical	E	
	kcal/mol	kJ/mol		kcal/mol	kJ/mol
F \cdot	0.3	1.3	H \cdot	9.0	38
Cl \cdot	1.0	4.2	Me \cdot	11.8	49.4
MeO \cdot	7.1	30	Br \cdot	13.2	55.2
CF ₃ \cdot	7.5	31			

⁶²Huyser *Free-Radical Chain Reactions*. Ref. 1, p. 97.

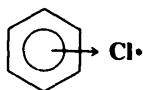
⁶³Trotman-Dickenson, Ref. 61.

⁶⁴Kharasch; Hambling; Rudy *J. Org. Chem.* **1959**, *24*, 303.

⁶⁵For reviews, see Reichardt *Solvent Effects in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, 1979, pp. 110-123; Martin, in Kochi, Ref. 8, vol. 2, pp. 493-524; Huyser *Adv. Free-Radical Chem.* **1965**, *1*, 77-135.

⁶⁶Russell *J. Am. Chem. Soc.* **1958**, *80*, 4987, 4997, 5002. *J. Org. Chem.* **1959**, *24*, 300.

formation between the aromatic solvent and the chlorine atom which makes the chlorine more selective.⁶⁷ This type of effect is not found in cases where the differences in abstract-



7

ability are caused by field effects of electron-withdrawing groups (p. 685). In such cases aromatic solvents make little difference.⁶⁸ The complex 7 has been detected⁶⁹ as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl_4 .⁷⁰ Differences caused by solvents have also been reported in reactions of other radicals.⁷¹ Some of the anomalous results obtained in the chlorination of aromatic side chains (p. 685) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.⁷² 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 .⁷³ However, these differences are not caused by formation of a complex between $\text{Cl}\cdot$ and the solvent.

REACTIONS

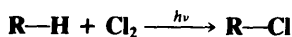
The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (from the diazonium ion); these are considered first.

Hydrogen as Leaving Group

A. Substitution by Halogen

4-1 Halogenation at an Alkyl Carbon⁷⁴

Halogenation or Halo-de-hydrogenation



⁶⁷See also Soumilion; Bruylants *Bull. Soc. Chim. Belg.* **1969**, 78, 425; Potter; Tedder *J. Chem. Soc., Perkin Trans. 2* **1982**, 1689; Aver'yanov; Ruban; Shvets *J. Org. Chem. USSR* **1987**, 23, 782; Aver'yanov; Ruban *J. Org. Chem. USSR* **1987**, 23, 1119; Raner; Luszyk; Ingold *J. Am. Chem. Soc.* **1989**, 111, 3652; Ingold; Luszyk; Raner *Acc. Chem. Res.* **1990**, 23, 219-225.

⁶⁸Russell *Tetrahedron* **1960**, 8, 101; Nagai; Horikawa; Ryang; Tokura *Bull. Chem. Soc. Jpn.* **1971**, 44, 2771.

⁶⁹It has been contended that another species, a chlorocyclohexadienyl radical (the structure of which is the same as **1**, except that Cl replaces Ar), can also be attacking when the solvent is benzene: Skell; Baxter; Taylor *J. Am. Chem. Soc.* **1983**, 105, 120; Skell; Baxter; Tanko; Chebolu *J. Am. Chem. Soc.* **1986**, 108, 6300. For arguments against this proposal, see Bunce; Ingold; Landers; Luszyk; Scaiano *J. Am. Chem. Soc.* **1985**, 107, 5464; Walling *J. Org. Chem.* **1988**, 53, 305; Aver'yanov; Shvets; Semenov *J. Org. Chem. USSR* **1990**, 26, 1261.

⁷⁰Bühler *Helv. Chim. Acta* **1968**, 51, 1558. For other spectral observations, see Raner; Luszyk; Ingold *J. Phys. Chem.* **1989**, 93, 564.

⁷¹Walling; Azar *J. Org. Chem.* **1968**, 33, 3885; Walling; Wagner *J. Am. Chem. Soc.* **1963**, 85, 2333; Ito; Matsuda *J. Am. Chem. Soc.* **1982**, 104, 568; Minisci; Vismara; Fontana; Morini; Serravalle; Giordano *J. Org. Chem.* **1987**, 52, 730.

⁷²Russell; Ito; Hendry *J. Am. Chem. Soc.* **1963**, 85, 2976; Corbiau; Bruylants *Bull. Soc. Chim. Belg.* **1970**, 79, 203, 211; Newkirk; Gleicher *J. Am. Chem. Soc.* **1974**, 96, 3543.

⁷³See Raner; Luszyk; Ingold *J. Org. Chem.* **1988**, 53, 5220.

⁷⁴For lists of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 311-313.

Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or uv light.⁷⁵ 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. 684; 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 (2-4 to 2-6), 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 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.⁷⁶ Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (1-11). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include H_2 , olefins, higher alkanes, lower alkanes, and halogen derivatives of these compounds.

The bromine atom is much more selective than the chlorine atom. As indicated on p. 688, it is often possible to brominate tertiary and benzylic positions selectively. High regioselectivity can also be obtained where the neighboring-group mechanism (p. 681) can operate.

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,⁷⁷ but seldom, because it is too reactive and hard to control.⁷⁸ It often breaks carbon chains down into smaller units, a side reaction that sometimes becomes troublesome in chlorinations too. Fluorination^{78a} has been achieved by the use of chlorine trifluoride ClF_3 at -75°C .⁷⁹ 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.⁸⁰ For example, adamantane gave 75% 1-fluoroadamantane. F_2 at -70°C , diluted with N_2 ,⁸¹ and bromine trifluoride at $25\text{--}35^\circ\text{C}$ ⁸² are also highly regioselective for tertiary

⁷⁵For reviews, see Poutsma, in Kochi, Ref. 8, vol. 2, pp. 159-229; Huyser, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 1; Wiley: New York, 1973, pp. 549-607; Poutsma, Ref. 37 (chlorination); Thaler *Methods Free-Radical Chem.* **1969**, 2, 121-227 (bromination).

⁷⁶Dermer; Edmison *Chem. Rev.* **1957**, 57, 77-122, pp. 110-112. An example of free-radical ring halogenation can be found in Engelsma; Kooyman *Revl. Trav. Chim. Pays-Bas* **1961**, 80, 526, 537. For a review of aromatic halogenation in the gas phase, see Kooyman *Adv. Free-Radical Chem.* **1965**, 1, 137-153.

⁷⁷Rozen *Acc. Chem. Res.* **1988**, 21, 307-312; Purrington; Kagen; Patrick *Chem. Rev.* **1986**, 86, 997-1018, pp. 1003-1005; Gerstenberger; Haas *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 647-667 [*Angew. Chem.* 93, 659-680]; Hudlický *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 *Chimia* **1985**, 39, 305-311.

⁷⁸However, 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, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 805-825; Lagow; Margrave *Prog. Inorg. Chem.* **1979**, 26, 161-210. See also Adcock; Horita; Renk *J. Am. Chem. Soc.* **1981**, 103, 6937; Adcock; Evans *J. Org. Chem.* **1984**, 49, 2719; Huang; Lagow *Bull. Soc. Chim. Fr.* **1986**, 993.

^{78a}For a monograph on fluorinating agents, see German; Zemskov *New Fluorinating Agents in Organic Synthesis*; Springer: New York, 1989.

⁷⁹Brower *J. Org. Chem.* **1987**, 52, 798.

⁸⁰Alker; Barton; Hesse; Lister-James; Markwell; Pechet; Rozen; Takeshita; Toh *Nouv. J. Chem.* **1980**, 4, 239.

⁸¹Rozen; Gal; Faust *J. Am. Chem. Soc.* **1980**, 102, 6860; Gal; Rozen *Tetrahedron Lett.* **1984**, 25, 449; Rozen; Ben-Shushan *J. Org. Chem.* **1986**, 51, 3522; Rozen; Gal *J. Org. Chem.* **1987**, 52, 4928, **1988**, 53, 2803; Ref. 80.

⁸²Boguslavskaya; Kartashov; Chuvatkin *J. Org. Chem. USSR* **1989**, 25, 1835.

positions. These reactions probably have electrophilic,⁸³ not free-radical mechanisms. In fact, the success of the F₂ 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,⁸⁴ but iodinations are seldom attempted, largely because the HI formed reduces the alkyl iodide.

Many other halogenation agents have been employed, the most common of which is suluryl chloride SO₂Cl₂.⁸⁵ A mixture of Br₂ and HgO is a more active brominating agent than bromine alone.⁸⁶ The actual brominating agent in this case is believed to be bromine monoxide Br₂O. Among other agents used have been N-bromosuccinimide (see 4-2), CCl₄,⁸⁷ dichlorine monoxide Cl₂O,⁸⁸ BrCCl₃,⁸⁹ PCl₅,⁹⁰ phosgene, *t*-butyl hypobromite⁹¹ and hypochlorite,⁹² and N-haloamines and sulfuric acid.⁹³ In all these cases a chain-initiating catalyst is required, usually peroxides or uv light.

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.⁹³ In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the ω - 1 position).⁹⁴ Some typical selectivity values are⁹⁵

CH₃—CH₂—CH₂—CH₂—CH₂—CH₂—CH₃	Ref. 96
1 56 29 14	
CH₃—CH₂—CH₂—CH₂—CH₂—CH₂—CH₂—CH₂—OH	Ref. 97
1 92 3 1 1 2 0 0	
CH₃—CH₂—CH₂—CH₂—CH₂—CH₂—COOMe	Ref. 98
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,⁹⁹ and adamantane and bicyclo[2.2.2]octane at the bridgeheads¹⁰⁰ by this procedure. The reasons for the high ω - 1 specificity are not clearly understood.¹⁰¹ Alkyl bromides can be regioselectively chlorinated

⁸³See, for example, Rozen; *Gal J. Org. Chem.* **1987**, 52, 2769.

⁸⁴Gover; Willard *J. Am. Chem. Soc.* **1960**, 82, 3816.

⁸⁵For a review of this reagent, see Tabushi; Kitaguchi, in *Pizey Synthetic Reagents*, vol. 4; Wiley: New York, 1981, pp. 336-396.

⁸⁶Bunce *Can. J. Chem.* **1972**, 50, 3109.

⁸⁷For a discussion of the mechanism with this reagent, see Hawari; Davis; Engel; Gilbert; Griller *J. Am. Chem. Soc.* **1985**, 107, 4721.

⁸⁸Marsh; Farnham; Sam; Smart *J. Am. Chem. Soc.* **1982**, 104, 4680.

⁸⁹Huysen *J. Am. Chem. Soc.* **1960**, 82, 391; Baldwin; O'Neill *Synth. Commun.* **1976**, 6, 109.

⁹⁰Wyman; Wang; Freeman *J. Org. Chem.* **1963**, 28, 3173.

⁹¹Walling; Padwa *J. Org. Chem.* **1962**, 27, 2976.

⁹²Walling; Mintz *J. Am. Chem. Soc.* **1967**, 89, 1515.

⁹³For reviews, see Minisci *Synthesis* **1973**, 1-24; Deno *Methods Free-Radical Chem.* **1972**, 3, 135-154; Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972**, 4, 203-284.

⁹⁴The ω - 1 regioselectivity diminishes when the chains are longer than 10 carbons; see Deno; Jedziniak *Tetrahedron Lett.* **1976**, 1259; Konen; Maxwell; Silbert *J. Org. Chem.* **1979**, 44, 3594.

⁹⁵The 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 H₂SO₄; see Deno; Pohl *J. Org. Chem.* **1975**, 40, 380.

⁹⁶Bernardi; Galli; Minisci *J. Chem. Soc. B* **1968**, 324. See also Deno; Gladfelter; Pohl *J. Org. Chem.* **1979**, 44, 3728; Fuller; Lindsay Smith; Norman; Higgins *J. Chem. Soc., Perkin Trans. 2* **1981**, 545.

⁹⁷Deno; Billups; Fishbein; Pierson; Whalen; Wyckoff *J. Am. Chem. Soc.* **1971**, 93, 438.

⁹⁸Minisci; Galli; Galli; Bernardi *Tetrahedron Lett.* **1967**, 2207; Minisci; Gardini; Bertini *Can. J. Chem.* **1970**, 48, 544.

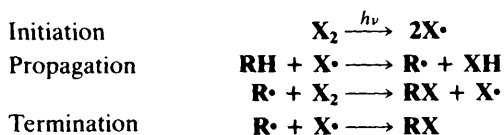
⁹⁹Kämper; Schäfer; Luftmann *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 306 [*Angew. Chem.* 88, 334].

¹⁰⁰Smith; Billups *J. Am. Chem. Soc.* **1974**, 96, 4307.

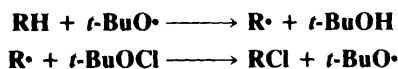
¹⁰¹It has been reported that the selectivity in one case is in accord with a pure electrostatic (field effect) explanation: Dneprovskii; Mil'tsov; Arbuзов *J. Org. Chem. USSR* **1988**, 24, 1826. See also Tanner; Arhart; McIntzer *Tetrahedron* **1985**, 41, 4261; Ref. 95.

one carbon away from the bromine (to give *vic*-bromochlorides) by treatment with PCl_5 .¹⁰² Alkyl chlorides can be converted to *vic*-dichlorides by treatment with MoCl_5 .¹⁰³ Enhanced selectivity at a terminal position of *n*-alkanes has been achieved by absorbing the substrate onto a pentasil zeolite.¹⁰⁴ In another regioselective chlorination, alkanesulfonamides $\text{RCH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{NHR}'$ are converted primarily to $\text{RCHClCH}_2\text{CH}_2\text{SO}_2\text{NHR}'$ by sodium peroxydisulfate $\text{Na}_2\text{S}_2\text{O}_8$ and CuCl_2 .¹⁰⁵ For regioselective chlorination at certain positions of the steroid nucleus, see 9-2.

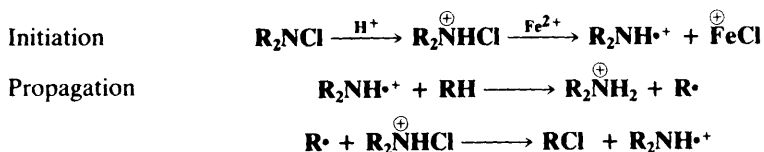
In almost all cases, the mechanism involves a free-radical chain:



When the reagent is halogen, initiation occurs as shown above.¹⁰⁶ 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 *t*-BuOCl have been formulated as¹⁰⁷



and the abstracting radicals in the case of N-haloamines are the aminium radical cations $\text{R}_2\text{NH}\cdot^+$ (p. 527), with the following mechanism (in the case of initiation by Fe^{2+}):⁹³



This mechanism is similar to that of the Hofmann-Löffler reaction (8-42).

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. Thus, products like H_2 , higher alkanes, and higher alkyl halides can be

¹⁰²Luche; Bertin; Kagan *Tetrahedron Lett.* **1974**, 759.

¹⁰³San Filippo; Sowinski; Romano *J. Org. Chem.* **1975**, *40*, 3463.

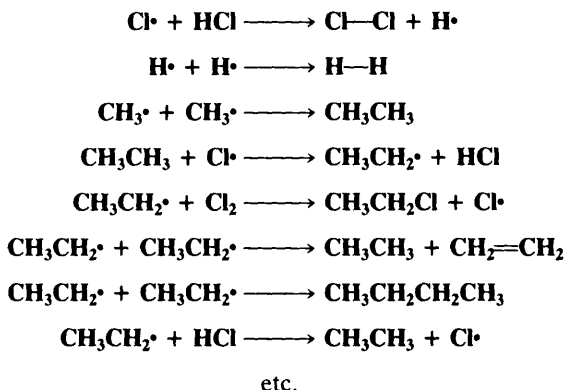
¹⁰⁴Turro; Fehlner; Hessler; Welsh; Ruderman; Firnberg; Braun *J. Org. Chem.* **1988**, *53*, 3731.

¹⁰⁵Nikishin; Troyansky; Lazareva *Tetrahedron Lett.* **1985**, *26*, 3743.

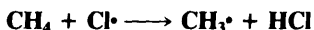
¹⁰⁶There is evidence (unusually high amounts of multiply chlorinated products) that under certain conditions in the reaction of RH with Cl_2 , the products of the second propagation step ($\text{RX} + \text{X}\cdot$) are enclosed within a solvent cage. See Skell; Baxter *J. Am. Chem. Soc.* **1985**, *107*, 2823; Raner; Luszyk; Ingold *J. Am. Chem. Soc.* **1988**, *110*, 3519; Tanko; Anderson *J. Am. Chem. Soc.* **1988**, *110*, 3525.

¹⁰⁷Carlsson; Ingold *J. Am. Chem. Soc.* **1967**, *89*, 4885, 4891; Walling; Kurkov *J. Am. Chem. Soc.* **1967**, *89*, 4895; Walling; McGuinness *J. Am. Chem. Soc.* **1969**, *91*, 2053. See also Zhulin; Rubinshtein *Bull. Acad. Sci. USSR. Div. Chem. Sci.* **1977**, *26*, 2082.

accounted for by steps like these (these are for chlorination of methane, but analogous steps can be written for other substrates):



At least when methane is the substrate, the rate-determining step is



since an isotope effect of 12.1 was observed at 0°C.¹⁰⁸ For chlorinations, chains are very long, typically 10⁴ to 10⁶ 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				kJ/mol			
	F ₂	Cl ₂	Br ₂	I ₂	F ₂	Cl ₂	Br ₂	I ₂
CH₄ + X· → CH₃· + HX	-31	+2	+17	+34	-132	+6	+72	+140
CH₃· + X₂ → CH₃X + X·	-70	-26	-24	-21	-293	-113	-100	-87

In each case D for CH₃—H is 105 kcal/mol (438 kJ/mol), while D values for the other bonds involved are given in Table 14.4.¹⁰⁹ F₂ is so reactive¹¹⁰ that neither uv light nor any other initiation is needed (total $\Delta H = -101$ kcal/mol; -425 kJ/mol);¹¹¹ while Br₂ and I₂ 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 Br₂ and I₂. It is apparent that the most important single factor causing the order of halogen reactivity

¹⁰⁸Wiberg; Motell *Tetrahedron* **1963**, *19*, 2009.

¹⁰⁹Kerr, in *Weast Handbook of Chemistry and Physics*, 69th ed.; CRC Press: Boca Raton, FL, 1988. pp. F174-F189.

¹¹⁰It has been reported that the reaction of F atoms with CH₄ at 25 K takes place with practically zero activation energy: Johnson; Andrews *J. Am. Chem. Soc.* **1980**, *102*, 5736.

¹¹¹For F₂ the following initiation step is possible: F₂ + RH → R· + F· + HF [first demonstrated by Miller; Koch; McLafferty *J. Am. Chem. Soc.* **1956**, *78*, 4992]. ΔH for this reaction is equal to the small positive value of 5 kcal/mol (21 kJ/mol). 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 (159 kJ/mol) 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 F₂ molecules. Indeed, it is the magnitude of this energy that is responsible for the cleavage of carbon chains by F₂.

TABLE 14.4 Some D values¹⁰⁹

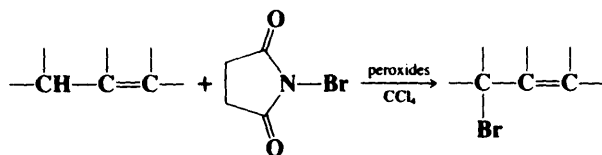
Bond	D	
	kcal/mol	kJ/mol
H-F	136	570
H-Cl	103	432
H-Br	88	366
H-I	71	298
F-F	38	159
Cl-Cl	59	243
Br-Br	46	193
I-I	36	151
CH ₃ -F	108	452
CH ₃ -Cl	85	356
CH ₃ -Br	70	293
CH ₃ -I	57	238

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 $AgSbF_6$.¹¹² Direct chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneseleninyl chloride $PhSe(O)Cl$ and $AlCl_3$ or $AlBr_3$.¹¹³ However, while some substituted alkenes give high yields of chloro substitution products, others (such as styrene) undergo addition of Cl_2 to the double bond (5-26).¹¹³ Electrophilic fluorination has already been mentioned (p. 690).

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; 65, 68.

4-2 Allylic Halogenation Halogenation or Halo-de-hydrogenation



This reaction is a special case of 4-1, but is important enough to be treated separately.¹¹⁴ Olefins can be halogenated in the allylic position by a number of reagents, of which N-bromosuccinimide (NBS)¹¹⁵ is by far the most common. When this reagent is used, the

¹¹²Olah; Renner; Schilling; *Mo J. Am. Chem. Soc.* **1973**, 95, 7686. See also Olah; Wu; *Farooq J. Org. Chem.* **1989**, 54, 1463.

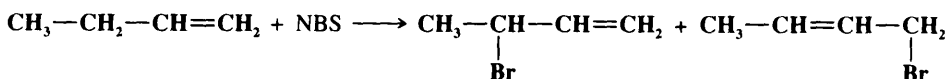
¹¹³Kamigata; Satoh; Yoshida *Bull. Chem. Soc. Jpn.* **1988**, 44, 449.

¹¹⁴For a review, see Nechvatal *Adv. Free-Radical Chem.* **1972**, 4, 175-201.

¹¹⁵For a review of this reagent, see Pizey, *Ref. 85*, vol. 2, pp. 1-63, 1974.

reaction is known as *Wohl-Ziegler bromination*. A nonpolar solvent is used, most often CCl_4 . Other N-bromo amides have also been used. To a much lesser extent, allylic chlorination has been carried out, with N-chlorosuccinimide, N-chloro-N-cyclohexylbenzenesulfonamide,¹¹⁶ or *t*-butyl hypochlorite.¹¹⁷ With any reagent an initiator is needed; this is usually a peroxide or, less often, uv light.

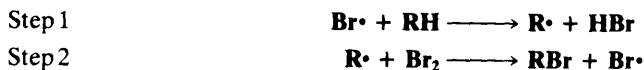
The reaction is usually quite specific at the allylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained, e.g.,



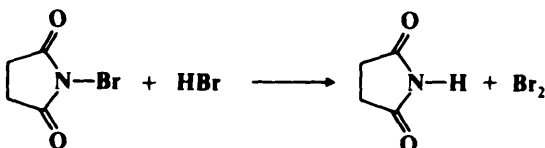
When a double bond has two different allylic positions, e.g., $\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_3$, a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.¹¹⁸ It is possible to brominate both sides of the double bond.¹¹⁹ 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.

NBS is also a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, to a $\text{C}\equiv\text{C}$ 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.¹²⁰

That the mechanism of allylic bromination is of the free-radical type was demonstrated by Dauben and McCoy,¹²¹ who showed that the reaction is very sensitive to free-radical 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 $\text{Br}\cdot$. Once it is formed, the main propagation steps are



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 1.¹²² The main evidence for this

¹¹⁶Theilacker; Wessel *Liebigs Ann. Chem.* **1967**, 703, 34.

¹¹⁷Walling; Thaler *J. Am. Chem. Soc.* **1961**, 83, 3877.

¹¹⁸Dauben; McCoy *J. Org. Chem.* **1959**, 24, 1577.

¹¹⁹Ucciani; Naudet *Bull. Soc. Chim. Fr.* **1962**, 871.

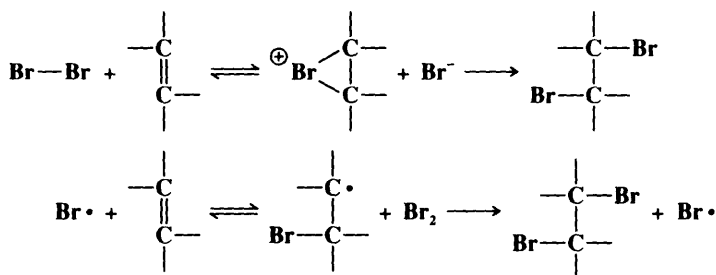
¹²⁰Peiffer *Bull. Soc. Chim. Fr.* **1963**, 537.

¹²¹Dauben; McCoy *J. Am. Chem. Soc.* **1959**, 81, 4863.

¹²²This mechanism was originally suggested by Adam; Gosselain; Goldfinger *Nature* **1953**, 171, 704, *Bull. Soc. Chim. Belg.* **1956**, 65, 533.

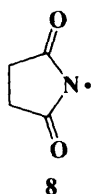
mechanism is that NBS and Br_2 show similar selectivity¹²³ and that the various N-bromo amides also show similar selectivity,¹²⁴ which is consistent with the hypothesis that the same species is abstracting in each case.¹²⁵

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 5-26). 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:



The other bromine atom comes from another bromine-containing molecule or ion. 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 olefin 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.¹²⁶

When NBS is used to brominate non-olefinic substrates such as alkanes, another mechanism, involving abstraction of the hydrogen of the substrate by the succinimidyl radical¹²⁷ **8** can operate.¹²⁸ This mechanism is facilitated by solvents (such as CH_2Cl_2 , CHCl_3 , or



¹²³Walling; Rieger; Tanner *J. Am. Chem. Soc.* **1963**, *85*, 3129; Russell; Desmond *J. Am. Chem. Soc.* **1963**, *85*, 3139; Russell; DeBoer; Desmond *J. Am. Chem. Soc.* **1963**, *85*, 365; Pearson; Martin *J. Am. Chem. Soc.* **1963**, *85*, 3142; Skell; Tuleen; Readio *J. Am. Chem. Soc.* **1963**, *85*, 2850.

¹²⁴Walling; Rieger *J. Am. Chem. Soc.* **1963**, *85*, 3134; Pearson; Martin, Ref. 123; Incremona; Martin *J. Am. Chem. Soc.* **1970**, *92*, 627.

¹²⁵For other evidence, see Day; Lindstrom; Skell *J. Am. Chem. Soc.* **1974**, *96*, 5616.

¹²⁶McGrath; Tedder *Proc. Chem. Soc.* **1961**, 80.

¹²⁷For a review of this radical, see Chow; Naguib *Rev. Chem. Intermed.* **1984**, *5*, 325-345.

¹²⁸Skell; Day *Acc. Chem. Res.* **1978**, *11*, 381; Walling; El-Taliawi; Zhao *J. Am. Chem. Soc.* **1983**, *105*, 5119; Tanner; Reed; Tan; Meintzer; Walling; Sopchik *J. Am. Chem. Soc.* **1985**, *107*, 6576; Lüning; Skell *Tetrahedron* **1985**, *41*, 4289; Skell; Lüning; McBain; Tanko *J. Am. Chem. Soc.* **1986**, *108*, 121; Lüning; Seshadri; Skell *J. Org. Chem.* **1986**, *51*, 2071; Chow; Zhao *J. Org. Chem.* **1987**, *52*, 1931, **1989**, *54*, 530; Zhang; Dong; Jiang; Chow *Can. J. Chem.* **1990**, *68*, 1668.

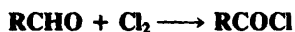
MeCN) in which NBS is more soluble, and by the presence of small amounts of an alkene that lacks an allylic hydrogen (e.g., ethene). The alkene serves to scavenge any $\text{Br}\cdot$ that forms from the reagent. Among the evidence for the mechanism involving **8** are abstraction selectivities similar to those of $\text{Cl}\cdot$ atoms and the isolation of β -bromopropionyl isocyanate $\text{BrCH}_2\text{CH}_2\text{CONCO}$, which is formed by ring-opening of **8**.

Allylic chlorination has also been carried out¹²⁹ with N-chlorosuccinimide 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.¹³⁰ A free-radical mechanism is unlikely in these reactions.

OS IV, 108; V, 825; VI, 462.

4-3 Halogenation of Aldehydes

Halogenation or Halo-de-hydrogenation



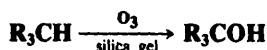
Aldehydes can be directly converted to acyl chlorides by treatment with chlorine; however, the reaction operates only when the aldehyde does not contain an α hydrogen and even then it is not very useful. When there is an α hydrogen, α halogenation (**2-4**) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2 ¹³¹ and $t\text{-BOCl}$.¹³² The mechanisms are probably of the free-radical type. NBS, with AIBN (p. 664) as a catalyst, has been used to convert aldehydes to acyl bromides.¹³³

OS I, 155.

B. Substitution by Oxygen

4-4 Hydroxylation at an Aliphatic Carbon

Hydroxylation or Hydroxy-de-hydrogenation



Compounds containing susceptible C—H bonds can be oxidized to alcohols.¹³⁴ Nearly always, the C—H bond involved is tertiary, so the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free-radical attack than primary and secondary bonds and partly because the reagents involved would oxidize primary and secondary alcohols further. In the best method the reagent is ozone and the substrate is absorbed on silica gel.¹³⁵ Yields as high as 99% have been obtained by this method. Other reagents, which often give much lower yields, are chromic acid,¹³⁶ alkaline permanganate,¹³⁷ potassium

¹²⁹Hori; Sharpless *J. Org. Chem.* **1979**, *44*, 4204.

¹³⁰Torii; Tanaka; Tada; Nagao; Sasaoka *Chem. Lett.* **1984**, 877.

¹³¹Arai *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1280, **1965**, *38*, 252.

¹³²Walling; Mintz, Ref. 92.

¹³³Markó; Mekhalifa *Tetrahedron Lett.* **1990**, *31*, 7237. For a related procedure, see Cheung *Tetrahedron Lett.* **1979**, 3809.

¹³⁴For reviews, see Chinn *Selection of Oxidants in Synthesis*; Marcel Dekker: New York, 1971, pp. 7-11; Lee, in *Augustine Oxidation*, vol. 1; Marcel Dekker: New York, 1969, pp. 2-6. For a monograph on all types of alkane activation, see Hill *Activation and Functionalization of Alkanes*; Wiley: New York, 1989.

¹³⁵Cohen; Keinan; Mazur; Varkony *J. Org. Chem.* **1975**, *40*, 2141, *Org. Synth.* *VI*, 43; Keinan; Mazur *Synthesis* **1976**, 523; McKillop; Young *Synthesis* **1979**, 401-422, pp. 418-419.

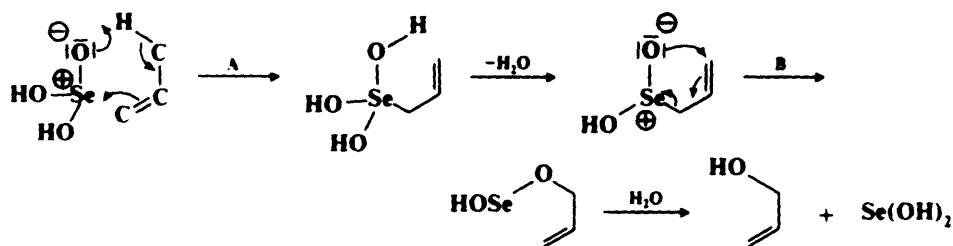
¹³⁶For a review, see Cainelli; Cardillo *Chromium Oxidations in Organic Chemistry*; Springer: New York, 1984, pp. 8-23.

¹³⁷Eastman; Quinn *J. Am. Chem. Soc.* **1969**, *82*, 4249.

hydrogen persulfate KHSO_5 ,¹³⁸ methyl(trifluoromethyl)dioxirane,¹³⁹ ruthenium tetroxide RuO_4 ,¹⁴⁰ F_2 in $\text{MeCN-H}_2\text{O}$,¹⁴¹ sodium chlorite NaClO_2 with a metalloporphyrin catalyst,¹⁴² and certain perbenzoic acids.¹⁴³ Alkanes and cycloalkanes have been oxidized at secondary positions, to a mixture of alcohols and trifluoroacetates, by 30% aqueous H_2O_2 in trifluoroacetic acid.¹⁴⁴ This reagent does not oxidize the alcohols further and ketones are not found. As in the case of chlorination with N-haloamines and sulfuric acid (see 4-1), the $\omega - 1$ position is the most favored. Another reagent¹⁴⁵ that oxidizes secondary positions is iodosylbenzene, catalyzed by Fe(III)-porphyrin catalysts.¹⁴⁶ Use of an optically active Fe(III)-porphyrin gave enantioselective hydroxylation, with moderate enantiomeric excesses.¹⁴⁷

When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $\text{R}_3\text{C}^\bullet$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give $\text{R}_3\text{COCr}^{4+}$, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.¹⁴⁸ The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.¹⁴⁹

Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position (see also 9-16).¹⁵⁰ Allylic rearrangements are common. There is evidence that the mechanism does not involve free radicals but includes two pericyclic steps (A and B):¹⁵¹



The step marked A is similar to the ene synthesis (5-16). The step marked B is a [2,3] sigmatropic rearrangement (see 8-37). The reaction can also be accomplished with

¹³⁸De Poorter; Ricci; Meunier *Tetrahedron Lett.* **1985**, 26, 4459.

¹³⁹Mello; Fiorentino; Fusco; Curci *J. Am. Chem. Soc.* **1989**, 111, 6749. For a review of dioxiranes as oxidizing agents, see Adam; Curci; Edwards *Acc. Chem. Res.* **1989**, 22, 205-211. See also Murray; Jeyaraman; Mohan *J. Am. Chem. Soc.* **1986**, 108, 2470.

¹⁴⁰Bakke; Lundquist *Acta Chem. Scand., Ser. B* **1966**, 40, 430; Tenaglia; Terranova; Waegell *Tetrahedron Lett.* **1989**, 30, 5271; Bakke; Braenden *Acta Chem. Scand.* **1991**, 45, 418.

¹⁴¹Rozen; Brand; Kol *J. Am. Chem. Soc.* **1989**, 111, 8325.

¹⁴²Collman; Tanaka; Hembre; Brauman *J. Am. Chem. Soc.* **1990**, 112, 3689.

¹⁴³Schneider; Müller *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 146 [*Angew. Chem.* 94, 153]; *J. Org. Chem.* **1985**, 50, 4609; Takaishi; Fujikura; Inamoto *Synthesis* **1983**, 293; Tori; Sono; Asakawa *Bull. Chem. Soc. Jpn.* **1985**, 58, 2669. See also Querci; Ricci *Tetrahedron Lett.* **1990**, 31, 1779.

¹⁴⁴Deno; Jedziniak; Messer; Meyer; Stroud; Tomesko *Tetrahedron* **1977**, 33, 2503.

¹⁴⁵For other procedures, see Sharma; Sonawane; Dev *Tetrahedron* **1985**, 41, 2483; Nam; Valentine *New J. Chem.* **1989**, 13, 677.

¹⁴⁶See Groves; Nemo *J. Am. Chem. Soc.* **1983**, 105, 6243.

¹⁴⁷Groves; Viski *J. Org. Chem.* **1990**, 55, 3628.

¹⁴⁸Wiberg; Foster *J. Am. Chem. Soc.* **1961**, 83, 423, *Chem. Ind. (London)* **1961**, 108; Wiberg; Eisenthal *Tetrahedron* **1964**, 20, 1151.

¹⁴⁹Wiberg; Fox *J. Am. Chem. Soc.* **1963**, 85, 3487; Brauman; Pandell *J. Am. Chem. Soc.* **1970**, 92, 329; Stewart; Spitzer *Can. J. Chem.* **1978**, 56, 1273.

¹⁵⁰For reviews, see Rabjohn, *Org. React.* **1976**, 24, 261-415; Jerussi *Sel. Org. Transform.* **1970**, 1, 301-326; Trachtenberg, in Augustine, Ref. 134, pp. 123-153.

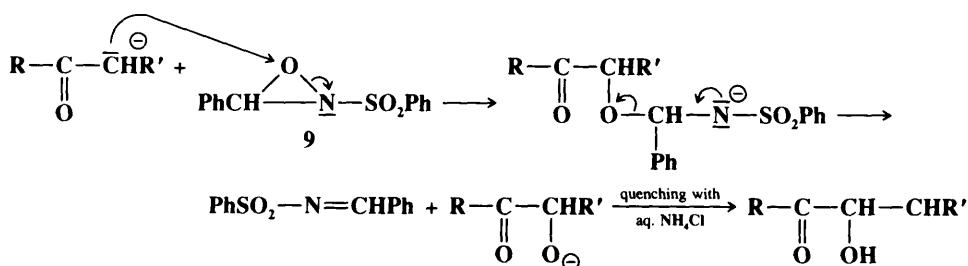
¹⁵¹Sharpless; Lauer *J. Am. Chem. Soc.* **1972**, 94, 7154; Arigoni; Vasella; Sharpless; Jensen *J. Am. Chem. Soc.* **1973**, 95, 7917; Woggon; Ruther; Egli *J. Chem. Soc., Chem. Commun.* **1980**, 706. For other mechanistic proposals, see Schaefer; Horvath; Klein *J. Org. Chem.* **1968**, 33, 2647; Trachtenberg; Nelson; Carver *J. Org. Chem.* **1970**, 35, 1653; Bhalerao; Rapoport *J. Am. Chem. Soc.* **1971**, 93, 4835; Stephenson; Speth *J. Org. Chem.* **1979**, 44, 4683.

t-butyl hydroperoxide, if SeO_2 is present in catalytic amounts (the *Sharpless method*).¹⁵² The SeO_2 is the actual reagent; the peroxide reoxidizes the $\text{Se}(\text{OH})_2$.¹⁵³ This method makes work-up easier, but gives significant amounts of side products when the double bond is in a ring.¹⁵⁴ Alkynes generally give α, α' dihydroxylation.¹⁵⁵

Ketones and carboxylic esters can be α hydroxylated by treatment of their enolate forms (prepared by adding the ketone or ester to lithium diisopropylamide) with a molybdenum peroxide reagent (MoO_5 -pyridine-HMPA) in THF-hexane at -70°C .¹⁵⁶ The enolate forms of amides and esters¹⁵⁷ and the enamine derivatives of ketones¹⁵⁸ can similarly be converted to their α hydroxy derivatives by reaction with molecular oxygen. The MoO_5 method can also be applied to certain nitriles.¹⁵⁶ Ketones have also been α hydroxylated by treating the corresponding silyl enol ethers with *m*-chloroperbenzoic acid,¹⁵⁹ or with certain other oxidizing agents.¹⁶⁰ When the silyl enol ethers are treated with iodosobenzene in the presence of trimethylsilyl trifluoromethyl sulfonate, the product is the α -keto triflate.¹⁶¹

Ketones can be α hydroxylated in good yields, without conversion to the enolates, by treatment with the hypervalent iodine reagents¹⁶² *o*-iodosobenzoic acid¹⁶³ or phenyliodosoacetate $\text{PhI}(\text{OAc})_2$ in methanolic NaOH .¹⁶⁴ The latter reagent has also been used on carboxylic esters.¹⁶⁵ O_2 and a chiral phase transfer catalyst gave enantioselective α hydroxylation of ketones, if the α position was tertiary.¹⁶⁶

A different method for the conversion of ketones to α -hydroxy ketones consists of treating the enolate with a 2-sulfonyloxaziridine (such as **9**).¹⁶⁷ This is not a free-radical process; the following mechanism is likely:



¹⁵²Umbreit; Sharpless *J. Am. Chem. Soc.* **1977**, *99*, 5526. See also Uemura; Fukuzawa; Toshimitsu; Okano *Tetrahedron Lett.* **1982**, *23*, 87; Singh; Sabharwal; Sayal; Chhabra *Chem. Ind. (London)* **1989**, 533.

¹⁵³For the use of the peroxide with O_2 instead of SeO_2 , see Sabol; Wiglesworth; Watt *Synth. Commun.* **1988**, *18*, 1.

¹⁵⁴Warpchowski; Chabaud; Sharpless *J. Org. Chem.* **1982**, *47*, 2897.

¹⁵⁵Chabaud; Sharpless *J. Org. Chem.* **1979**, *44*, 4202.

¹⁵⁶Vedejs *J. Am. Chem. Soc.* **1974**, *96*, 5944; Vedejs; Telschow *J. Org. Chem.* **1976**, *41*, 740; Vedejs; Larsen *Org. Synth. VII*, 277; Gamboni; Tamm *Tetrahedron Lett.* **1986**, *27*, 3999; *Helv. Chim. Acta* **1986**, *69*, 615. See also Anderson; Smith *Synlett* **1990**, 107.

¹⁵⁷Wasserman; Lipshutz *Tetrahedron Lett.* **1975**, 1731. For another method, see Pohmakotr; Winotai *Synth. Commun.* **1988**, *18*, 2141.

¹⁵⁸Cuvigny; Valette; Larcheveque; Normant *J. Organomet. Chem.* **1978**, *155*, 147.

¹⁵⁹Rubottom; Vazquez; Pelegrina *Tetrahedron Lett.* **1974**, 4319; Rubottom; Gruber *J. Org. Chem.* **1978**, *43*, 1599; Hassner; Reuss; Pinnick *J. Org. Chem.* **1975**, *40*, 3427; Andriamialisoa; Langlois; Langlois *Tetrahedron Lett.* **1985**, *26*, 3563; Rubottom; Gruber; Juve; Charleson *Org. Synth. VII*, 282. See also Horiguchi; Nakamura; Kuwajima *Tetrahedron Lett.* **1989**, *30*, 3323.

¹⁶⁰McCormick; Tomasik; Johnson *Tetrahedron Lett.* **1981**, *22*, 607; Moriarty; Prakash; Duncan *Synthesis* **1985**, 943; Iwata; Takemoto; Nakamura; Imanishi *Tetrahedron Lett.* **1985**, *26*, 3227; Davis; Sheppard *J. Org. Chem.* **1987**, *52*, 954; Takai; Yamada; Rhode; Mukaiyama *Chem. Lett.* **1991**, 281.

¹⁶¹Moriarty; Epa; Penmasta; Awasthi *Tetrahedron Lett.* **1989**, *30*, 667.

¹⁶²For a review, see Moriarty; Prakash *Acc. Chem. Res.* **1986**, *19*, 244-250.

¹⁶³Moriarty; Hou *Tetrahedron Lett.* **1984**, *25*, 691; Moriarty; Hou; Prakash; Arora *Org. Synth. VII*, 263.

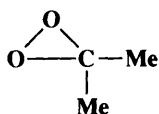
¹⁶⁴Moriarty; Hu; Gupta *Tetrahedron Lett.* **1981**, *22*, 1283.

¹⁶⁵Moriarty; Hu *Tetrahedron Lett.* **1981**, *22*, 2747.

¹⁶⁶Masui; Ando; Shioiri *Tetrahedron Lett.* **1988**, *29*, 2835.

¹⁶⁷Davis; Vishwakarma; Billmers; Finn *J. Org. Chem.* **1984**, *49*, 3241.

The method is also successful for carboxylic esters¹⁶⁷ and N,N-disubstituted amides,¹⁶⁸ and can be made enantioselective by the use of a chiral oxaziridine.¹⁶⁹ Dimethyldioxirane also oxidizes ketones (through their enolate forms) to α -hydroxy ketones.^{169a}



Dimethyldioxirane

Tetrahydrofuran was converted to the hemiacetal 2-hydroxytetrahydrofuran (which was relatively stable under the conditions used) by electrolysis in water¹⁷⁰ (see also 4-7).

OS IV, 23; VI, 43, 946; VII, 263, 277, 282.

4-5 Hydroxylation at an Aromatic Carbon¹⁷¹

Hydroxylation or Hydroxy-de-hydrogenation



A mixture of hydrogen peroxide and ferrous sulfate,¹⁷² called *Fenton's reagent*,¹⁷³ can be used to hydroxylate aromatic rings, though yields are usually not high.¹⁷⁴ Biaryls are usually side products.¹⁷⁵ Among other reagents used have been H_2O_2 and titanous ion; O_2 and Cu(I) ¹⁷⁶ or Fe(III) ,¹⁷⁷ a mixture of ferrous ion, oxygen, ascorbic acid, and ethylenetetra-aminetetraacetic acid (*Udenfriend's reagent*);¹⁷⁸ α -azo hydroperoxides $\text{ArN}=\text{NCHPhOOH}$;¹⁷⁹ O_2 and KOH in liquid NH_3 ;¹⁸⁰ and peracids such as pernitrous and trifluoroperacetic 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 such as $\text{HO}\cdot + \text{ArH} \rightarrow \text{Ar}\cdot + \text{H}_2\text{O}$) are not intermediates. The mechanism is essentially that outlined on p. 680, with $\text{HO}\cdot$ as the attacking species,¹⁸¹ formed by



¹⁶⁸Davis; Vishwakarma *Tetrahedron Lett.* **1985**, 26, 3539.

¹⁶⁹Evans; Morrissey; Dorow *J. Am. Chem. Soc.* **1985**, 107, 4346; Davis; Ulatowski; Haque *J. Org. Chem.* **1987**, 52, 5288; Enders; Bhushan *Tetrahedron Lett.* **1988**, 29, 2437; Davis; Sheppard; Chen; Haque *J. Am. Chem. Soc.* **1990**, 112, 6679; Davis; Weismiller *J. Org. Chem.* **1990**, 55, 3715.

^{169a}Guertin; Chan *Tetrahedron Lett.* **1991**, 32, 715.

¹⁷⁰Wermeckes; Beck; Schulz *Tetrahedron* **1987**, 43, 577.

¹⁷¹For reviews, see Vysotskaya *Russ. Chem. Rev.* **1973**, 42, 851-856; Sangster, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 133-191; Metelitsa *Russ. Chem. Rev.* **1971**, 40, 563-580; Enisov; Metelitsa *Russ. Chem. Rev.* **1968**, 37, 656-665; Loudon *Prog. Org. Chem.* **1961**, 5, 47-72.

¹⁷²For a review of reactions of H_2O_2 and metal ions with all kinds of organic compounds, including aromatic rings, see Sosnovsky; Rawlinson, in Swern *Organic Peroxides*, vol. 2; Wiley: New York, 1970, pp. 269-336. See also Sheldon; Kochi *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

¹⁷³For a discussion of Fenton's reagent, see Walling *Acc. Chem. Res.* **1975**, 8, 125-131.

¹⁷⁴Yields can be improved with phase transfer catalysis: Karakhanov; Narin; Filippova; Dedov *Doklad. Chem.* **1987**, 292, 81.

¹⁷⁵See the discussion of the aromatic free-radical substitution mechanism on pp. 680-681.

¹⁷⁶See Karlin; Hayes; Gultneh; Cruse; McKown; Hutchinson; Zubieta *J. Am. Chem. Soc.* **1984**, 106, 2121; Cruse; Kaderli; Meyer; Zuberbühler; Karlin *J. Am. Chem. Soc.* **1988**, 110, 5020; Ito; Kunai; Okada; Sasaki *J. Org. Chem.* **1988**, 53, 296.

¹⁷⁷Funabiki; Tsujimoto; Ozawa; Yoshida *Chem. Lett.* **1989**, 1267.

¹⁷⁸Udenfriend; Clark; Axelrod; Brodie *J. Biol. Chem.* **1954**, 208, 731; Brodie; Shore; Udenfriend *J. Biol. Chem.* **1954**, 208, 741. See also Tamagaki; Suzuki; Tagaki *Bull. Chem. Soc. Jpn.* **1989**, 62, 148, 153, 159.

¹⁷⁹Tezuka; Narita; Ando; Oae *J. Am. Chem. Soc.* **1981**, 103, 3045.

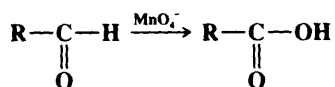
¹⁸⁰Malykhin; Kolesnichenko; Shteingarts *J. Org. Chem. USSR* **1986**, 22, 720.

¹⁸¹Jefcoate; Lindsay Smith; Norman; *J. Chem. Soc. B* **1969**, 1013; Brook; Castle; Lindsay Smith; Higgins; Morris *J. Chem. Soc., Perkin Trans. 2* **1982**, 687; Lai; Piette *Tetrahedron Lett.* **1979**, 775; Kunai; Hata; Ito; Sasaki *J. Am. Chem. Soc.* **1986**, 108, 6012.

The rate-determining step is formation of HO• and not its reaction with the aromatic substrate.

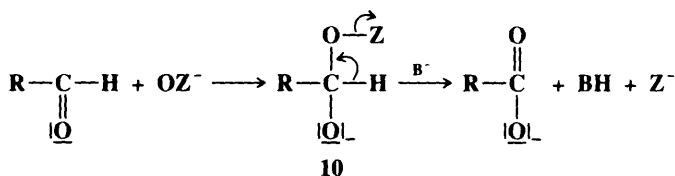
See also 1-29.

4-6 Oxidation of Aldehydes to Carboxylic Acids Hydroxylation or Hydroxy-de-hydrogenation



Oxidation of aldehydes to carboxylic acids is one of the most common oxidation reactions in organic chemistry¹⁸² and has been carried out with many oxidizing agents, the most popular of which is permanganate in acid, basic, or neutral solution.¹⁸³ Chromic acid¹⁸⁴ and bromine are other reagents frequently employed. Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. Benedict's and Fehling's solutions oxidize aldehydes,¹⁸⁵ and a test for aldehydes depends on this reaction, but the method is seldom used for preparative purposes and in any case gives very poor results with aromatic aldehydes. α,β -Unsaturated aldehydes can be oxidized by sodium chlorite without disturbing the double bond.¹⁸⁶ Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxy acid RCO_3H ,¹⁸⁷ which with another molecule of aldehyde disproportionates to give two molecules of acid (see 4-9).¹⁸⁸

Mechanisms of aldehyde oxidation¹⁸⁹ are not firmly established, but there seem to be at least two main types—a free-radical mechanism and an ionic one. In the free-radical process, the aldehydic hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species OZ^- to the carbonyl bond to give **10** in alkaline solution and **11** in acid or neutral solution. The aldehydic hydrogen of **10** or **11** is then lost as a proton to a base, while Z leaves with its electron pair.



¹⁸²For reviews, see Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1988, pp. 241-263, 423-428; Chinn, Ref. 134, pp. 63-70; Lee, Ref. 134, pp. 81-86.

¹⁸³For lists of some of the oxidizing agents used, with references, see Hudlicky *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990, pp. 174-180; Ref. 74, pp. 838-840; Srivastava; Venkataramani *Synth. Commun.* **1988**, *18*, 2193. See also Haines, Ref. 182.

¹⁸⁴For a review, see Cainelli; Cardillo, Ref. 136, pp. 217-225.

¹⁸⁵For a review, see Nigh, in Trahanovsky *Oxidation in Organic Chemistry*, pt. B; Academic Press: New York, 1973, pp. 31-34.

¹⁸⁶Bal; Childers; Pinnick *Tetrahedron* **1981**, *37*, 2091; Dalcanale; Montanari *J. Org. Chem.* **1986**, *51*, 567. See also Bayle; Perez; Courtieu *Bull. Soc. Chim. Fr.* **1990**, 565.

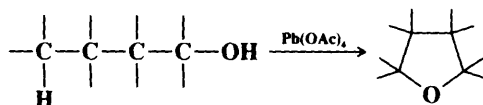
¹⁸⁷For a review of the preparation of peroxy acids by this and other methods, see Swern, in Swern, Ref. 172, vol. 1, pp. 313-516.

¹⁸⁸For reviews of the autoxidation of aldehydes, see Vardanyan; Nalbandyan *Russ. Chem. Rev.* **1985**, *54*, 532-543 (gas phase); Sajus; Séréce de Roch, in Bamford; Tipper, Ref. 37, vol. 16, 1980, pp. 89-124 (liquid phase); Maslov; Blyumberg *Russ. Chem. Rev.* **1976**, *45*, 155-167 (liquid phase). For a review of photochemical oxidation of aldehydes by O_2 , see Niclausse; Lemaire; Letort *Adv. Photochem.* **1966**, *4*, 25-48. For a discussion of the mechanism of catalyzed atmospheric oxidation of aldehydes, see Larkin *J. Org. Chem.* **1990**, *55*, 1563.

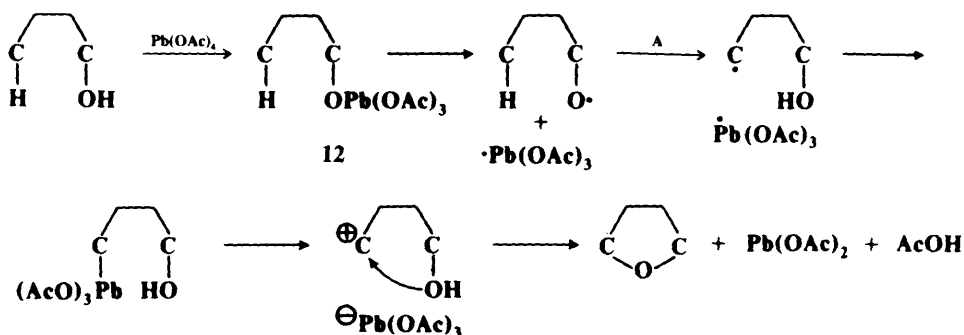
¹⁸⁹For a review, see Roček, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 461-505.

4-8 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.¹⁹⁶ The reaction is usually carried out at about 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),¹⁹⁷ with iodosobenzene diacetate and I_2 ,¹⁹⁸ and with ceric ammonium nitrate (CAN).¹⁹⁹ The following mechanism is likely for the lead tetraacetate reaction:²⁰⁰



though **12** has never been isolated. The step marked **A** is a 1,5 internal hydrogen abstraction. Such abstractions are well-known (see p. 1153) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6 abstractions).²⁰¹

Reactions that sometimes compete are oxidation to the aldehyde or acid (**9-3** and **9-22**) and fragmentation of the substrate. When the OH group is on a ring of at least seven

¹⁹⁶For reviews, see Mihailović; Partch *Sel. Org. Transform.* **1972**, 2, 97-182; Milhailović; Čeković *Synthesis* **1970**, 209-224. For a review of the chemistry of lead tetraacetate, see Butler, in Pizey, Ref. 85, vol. 3, 1977, pp. 277-419.

¹⁹⁷Akhtar; Barton *J. Am. Chem. Soc.* **1964**, 86, 1528; Sneen; Matheny *J. Am. Chem. Soc.* **1964**, 86, 3905, 5503; Roscher; Shaffer *Tetrahedron* **1984**, 40, 2643. For a review, see Kalvoda; Heusler *Synthesis* **1971**, 501-526. For a list of references, see Ref. 74, p. 445.

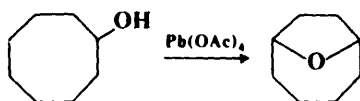
¹⁹⁸Concepción; Francisco; Hernández; Salazar; Suárez *Tetrahedron Lett.* **1984**, 25, 1953; Furuta; Nagata; Yamamoto *Tetrahedron Lett.* **1988**, 29, 2215.

¹⁹⁹See, for example, Trahanovsky; Young; Nave *Tetrahedron Lett.* **1969**, 2501; Doyle; Zuidema; Bade *J. Org. Chem.* **1975**, 40, 1454.

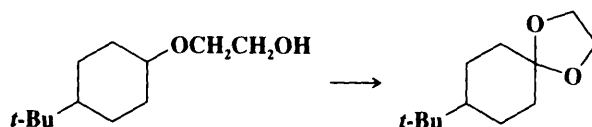
²⁰⁰Milhailović; Čeković; Maksimović; Jeremić; Lorenc; Mamuzić *Tetrahedron* **1965**, 21, 2799.

²⁰¹Milhailović; Čeković; Jeremić *Tetrahedron* **1965**, 21, 2813.

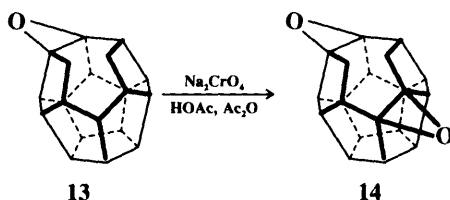
members, a transannular product can be formed, e.g.,²⁰²



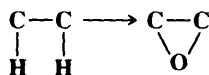
β -Hydroxy ethers can give cyclic acetals, e.g.,²⁰³



A different kind of formation of a cyclic ether was reported by Paquette and Kobayashi,²⁰⁴ who found that when the epoxide **13** of secododecahedrane was treated with sodium chro-



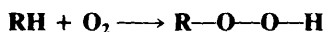
mate and $\text{HOAc}-\text{Ac}_2\text{O}$, the diepoxide **14** was obtained. Thus, the unusual transformation



was achieved in this case. It is likely that the large degree of strain in this system was at least partially responsible for the formation of this product.

There are no references in *Organic Syntheses*, but see OS V, 692; VI, 958, for related reactions.

4-9 Formation of Hydroperoxides Hydroperoxy-de-hydrogenation



The slow atmospheric oxidation (*slow* meaning without combustion) of $\text{C}-\text{H}$ to $\text{C}-\text{O}-\text{O}-\text{H}$ is called *autoxidation*.²⁰⁵ 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. The hydroperoxides produced often react further

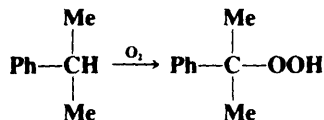
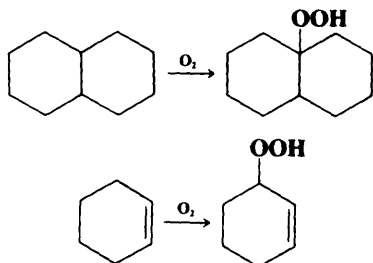
²⁰²Cope; Gordon; Moon; Park *J. Am. Chem. Soc.* **1965**, 87, 3119; Moriarty; Walsh *Tetrahedron Lett.* **1965**, 465; Milhailović; Čeković; Andrejević; Matić; Jeremić *Tetrahedron* **1968**, 24, 4947.

²⁰³Furuta et al., Ref. 198.

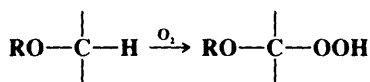
²⁰⁴Paquette; Kobayashi *Tetrahedron Lett.* **1987**, 28, 3531.

²⁰⁵The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. For reviews, see Sheldon; Kochi *Adv. Catal.* **1976**, 25, 272-413; Howard, in Kochi, Ref. 8, vol. 2, pp. 3-62; Lloyd *Methods Free-Radical Chem.* **1973**, 4, 1-131; Betts *Q. Rev., Chem. Soc.* **1971**, 25, 265-288; Huyser *Free-Radical Chain Reactions*, Ref. 1, pp. 306-312; Chinn, Ref. 134, pp. 29-39; Ingold *Acc. Chem. Res.* **1969**, 2, 1-9; Mayo *Acc. Chem. Res.* **1968**, 1, 193-201. For monographs on these and similar reactions, see Bamford; Tipper, Ref. 37, Vol. 16, 1980; Sheldon; Kochi, Ref. 172.

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.²⁰⁶ It is because of autoxidation that foods, rubber, paint, lubricating oils, etc. 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,²⁰⁷ and these are the ones we have seen before (pp. 683-685), 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,²⁰⁸ and allylic (though allylic rearrangements are common) R.²⁰⁹ The following are actual examples:

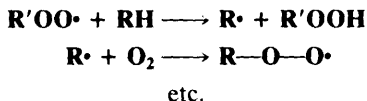


Another susceptible position is aldehydic C—H, but the peracids so produced are not easily isolated¹⁸⁷ since they are converted to the corresponding carboxylic acids (4-6). The α positions of ethers are also easily attacked by oxygen:



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.²¹⁰

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^{\bullet}) is produced by some initiating process, it reacts with oxygen²¹¹ to give $R'-O-O^{\bullet}$; since this type of radical *does* abstract hydrogen, the chain is



²⁰⁶For a review of the synthesis of alkyl peroxides and hydroperoxides, see Sheldon, in Patai *The Chemistry of Peroxides*; Wiley: New York, 1983, pp. 161-200.

²⁰⁷For a discussion, see Korcek; Chenier; Howard; Ingold *Can. J. Chem.* **1972**, *50*, 2285, and other papers in this series.

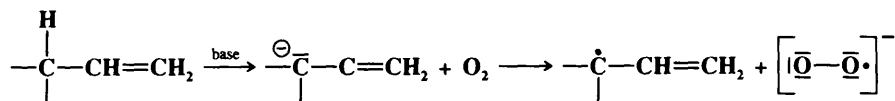
²⁰⁸For a method that gives good yields at benzylic positions, see Santamaria; Jroundi; Rigaudy *Tetrahedron Lett.* **1989**, *30*, 4677.

²⁰⁹For a review of autoxidation at allylic and benzylic positions, see Voronenkov; Vinogradov; Belyaev *Russ. Chem. Rev.* **1970**, *39*, 944-952.

²¹⁰For methods of detection and removal of peroxides from ether solvents, see Gordon; Ford *The Chemist's Companion*; Wiley: New York, 1972, p. 437; Burfield, *J. Org. Chem.* **1982**, *47*, 3821.

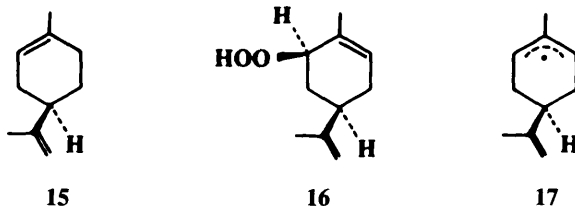
²¹¹See, for example Schwetlick *J. Chem. Soc., Perkin Trans. 2* **1988**, 2007.

In at least some cases (in alkaline media)²¹² the radical R• can be produced by formation of a carbanion and its oxidation (by O₂) to a radical, e.g.,²¹³



Autoxidations in alkaline media can also proceed by a different mechanism: R—H + base → R⁻ + O₂ → ROO⁻.²¹⁴

When alkenes are treated with oxygen that has been photosensitized (p. 241), they are substituted by OOH in the allylic position in a synthetically useful reaction.²¹⁵ Although superficially similar to autoxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not the ground-state oxygen (a triplet) but an excited singlet state²¹⁶ (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,²¹⁷ e.g., by the reaction between H₂O₂ and NaOCl²¹⁸ or sodium molybdate,²¹⁹ or between ozone and triphenyl phosphite.²²⁰ The oxygen generated by either photochemical or nonphotochemical methods reacts with olefins in the same way;²²¹ 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 (15) with singlet oxygen. Among other products is the optically active hydroperoxide 16, though if 17 were an inter-



²¹²For a review of base-catalyzed autoxidations in general, see Sosnovsky; Zaret, in Swern, Ref. 172, vol. 1, pp. 517-560.

²¹³Barton; Jones *J. Chem. Soc.* **1965**, 3563; Russell; Bemis *J. Am. Chem. Soc.* **1966**, 88, 5491.

²¹⁴Gersmann; Bickel *J. Chem. Soc. B* **1971**, 2230.

²¹⁵For reviews, see Frimer; Stephenson, in Frimer, Ref. 216, vol. 2, pp. 67-91; Wasserman; Ives *Tetrahedron* **1981**, 37, 1825-1852; Gollnick; Kuhn, in Wasserman; Murray, Ref. 216, pp. 287-427; Denny; Nickon *Org. React.* **1973**, 20, 133-336; Adams, in Augustine, Ref. 134, vol. 2, pp. 65-112.

²¹⁶For books on singlet oxygen, see Frimer *Singlet O₂*, 4 vols.; CRC Press: Boca Raton, FL, 1985; Wasserman; Murray *Singlet Oxygen*; Academic Press: New York, 1979. For reviews, see Frimer, in Patai, Ref. 206, pp. 201-234; Gorman; Rodgers, *Chem. Soc. Rev.* **1981**, 10, 205-231; Shinkarenko; Aleskovskii *Russ. Chem. Rev.* **1981**, 50, 220-231; Shlyapintokh; Ivanov *Russ. Chem. Rev.* **1976**, 45, 99-110; Ohloff *Pure Appl. Chem.* **1975**, 43, 481-502; Kearns *Chem. Rev.* **1971**, 71, 395-427; Wayne *Adv. Photochem.* **1969**, 7, 311-371.

²¹⁷For reviews, see Turro; Ramamurthy, in *de Mayo Rearrangements in Ground and Excited States*, vol. 3; Academic Press: New York, 1980, pp. 1-23; Murray, in Wasserman; Murray, Ref. 216, pp. 59-114. For a general monograph, see Adam; Cilento, *Chemical and Biological Generation of Excited States*; Academic Press: New York, 1982.

²¹⁸Footo; Wexler *J. Am. Chem. Soc.* **1964**, 86, 3879.

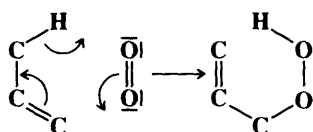
²¹⁹Aubry; Cazin; Duprat *J. Org. Chem.* **1989**, 54, 726.

²²⁰Murray; Kaplan *J. Am. Chem. Soc.* **1969**, 91, 5358; Bartlett; Mendenhall; Durham *J. Org. Chem.* **1980**, 45, 4269.

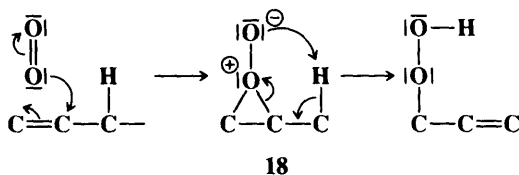
²²¹Footo; Wexler; Ando; Higgins *J. Am. Chem. Soc.* **1968**, 90, 975. See also McKcown; Waters *J. Chem. Soc. B* **1966**, 1040.

mediate, it could not give an optically active product since it possesses a plane of symmetry.²²² In contrast, autoxidation of **15** gave optically inactive **16** (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 tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the olefin.²²³ In simple trisubstituted olefins, there is a general preference for the hydrogen to be removed from the more highly congested side of the double bond.²²⁴ With *cis*-alkenes of the form RCH=CHR', the hydrogen is removed from the larger R group.²²⁵ Many functional groups in an allylic position cause the hydrogen to be removed from that side rather than the other (geminal selectivity).²²⁶ Also, in alkyl-substituted alkenes, the hydrogen that is preferentially removed is the one geminal to the larger substituent on the double bond.²²⁷

Several mechanisms have been proposed for the reaction with singlet oxygen.²²⁸ One of these is a pericyclic mechanism, similar to that of the ene synthesis (**5-16**) and to the first



step of the reaction between alkenes and SeO₂(**4-4**). However, there is strong evidence against this mechanism,²²⁹ and a more likely mechanism involves addition of singlet oxygen to the double bond to give a perepoxide (**18**),²³⁰ followed by internal proton transfer.²³¹



18

Still other proposed mechanisms involve diradicals or dipolar intermediates.²³² OS IV, 895.

²²²Schenck; Gollnick; Buchwald; Schroeter; Ohloff *Liebigs Ann. Chem.* **1964**, 674, 93; Schenck; Neumüller; Ohloff; Schroeter *Liebigs Ann. Chem.* **1965**, 687, 26.

²²³For example, see Foote; Denny *J. Am. Chem. Soc.* **1971**, 93, 5162.

²²⁴Schulte-Elte; Müller; Rautenstrauch *Helv. Chim. Acta* **1978**, 61, 2777; Orfanopoulos; Grdina; Stephenson *J. Am. Chem. Soc.* **1979**, 101, 275; Rautenstrauch; Thommen; Schulte-Elte *Helv. Chim. Acta* **1986**, 69, 1638.

²²⁵Orfanopoulos; Stratakis; Elemes *Tetrahedron Lett.* **1989**, 30, 4875.

²²⁶Clennan; Chen; Koola *J. Am. Chem. Soc.* **1990**, 112, 5193, and references cited therein.

²²⁷Orfanopoulos; Stratakis; Elemes *J. Am. Chem. Soc.* **1990**, 112, 6417.

²²⁸For reviews of the mechanism, see Frimer; Stephenson, Ref. 215, pp. 80-87; Stephenson; Grdina; Orfanopoulos *Acc. Chem. Res.* **1980**, 13, 419-425; Gollnick; Kuhn, Ref. 215, pp. 288-341; Frimer *Chem. Rev.* **1979**, 79, 359-387; Foote *Acc. Chem. Res.* **1968**, 1, 104-110, *Pure Appl. Chem.* **1971**, 27, 635-645; Gollnick *Adv. Photochem.* **1968**, 6, 1-122; Kearns, Ref. 216.

²²⁹Asveld; Kellogg *J. Org. Chem.* **1982**, 47, 1250.

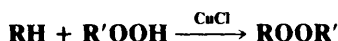
²³⁰For a review of perepoxides as intermediates in organic reactions, see Mitchell *Chem. Soc. Rev.* **1985**, 14, 399-419, pp. 401-406.

²³¹For evidence in favor of this mechanism, at least with some kinds of substrates, see Jefford; Rimbault *J. Am. Chem. Soc.* **1978**, 100, 6437; Okada; Mukai *J. Am. Chem. Soc.* **1979**, 100, 6509; Paquette; Hertel; Gleiter; Böhm *J. Am. Chem. Soc.* **1978**, 100, 6510; Hurst; Wilson; Schuster *Tetrahedron* **1985**, 41, 2191; Wilson; Schuster *J. Org. Chem.* **1986**, 51, 2056; Davies; Schiesser *Tetrahedron Lett.* **1989**, 30, 7099; Orfanopoulos; Smonou; Foote *J. Am. Chem. Soc.* **1990**, 112, 3607.

²³²See, for example, Jefford *Helv. Chim. Acta* **1981**, 64, 2534.

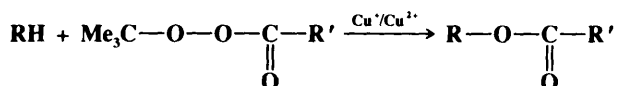
4-10 Formation of Peroxides

Alkyldioxy-de-hydrogenation

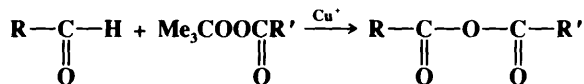


Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts, e.g., cobalt and manganese salts.²³³ Very high yields can be obtained. The type of hydrogen replaced is similar to that with N-bromosuccinimide (4-2), i.e., 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 R₂NCH₃, since the product R₂NHCH₂OOR' can easily be hydrolyzed by acid (0-6) to give R₂NH.²³⁴

4-11 Acyloxylation or Acyloxy-de-hydrogenation



Susceptible positions of organic compounds can be directly acyloxyated²³⁵ by *t*-butyl peresters, the most frequently used being acetic and benzoic (R' = Me or Ph).²³⁶ 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 4-9: benzylic, allylic, and the α position of ethers and sulfides. Terminal olefins are substituted almost entirely in the 3 position, i.e., with only a small amount of allylic rearrangement, but internal olefins generally give mixtures containing a large amount of allylic-shift product. If the reaction with olefins is carried out in an excess of 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,²³⁷ mercuric acetate,²³⁸ and palladium(II) acetate.²³⁹ 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 α to two carbonyl groups (ZCH₂Z'). It is likely that in the latter cases

²³³For a review, see Sosnovsky; Rawlinson, Ref. 172, pp. 153-268. See also Murahashi; Naota; Kuwabara; Saito; Kumobayashi; Akutagawa *J. Am. Chem. Soc.* **1990**, *112*, 7820; Ref. 206.

²³⁴See Murahashi; Naota; Yonemura *J. Am. Chem. Soc.* **1988**, *110*, 8256.

²³⁵For a list of reagents, with references, see Ref. 74, pp. 823-827ff, 841-842.

²³⁶For reviews, see Rawlinson; Sosnovsky *Synthesis* **1972**, 1-28; Sosnovsky; Rawlinson, in Swern, Ref. 172, vol. 1, pp. 585-608; Doumaux, in Augustine, Ref. 134, vol. 2, 1971, pp. 141-185.

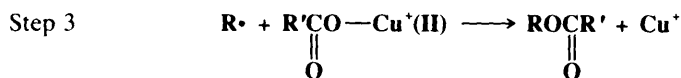
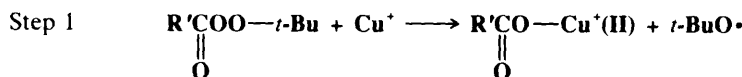
²³⁷For a review of lead tetraacetate, see Butler, Ref. 196.

²³⁸For reviews, see Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 190-208; Rawlinson; Sosnovsky *Synthesis* **1973**, 567-602.

²³⁹Hansson; Heumann; Rein; Åkermark *J. Org. Chem.* **1990**, *55*, 975; Byström; Larsson; Åkermark *J. Org. Chem.* **1990**, *55*, 5674.

it is the enol forms that react. Ketones can be α -acyloxyated indirectly by treatment of various enol derivatives with metallic acetates, for example, silyl enol ethers with silver carboxylates-iodine,²⁴⁰ enol thioethers with lead tetraacetate,²⁴¹ and enamines²⁴² with lead tetraacetate²⁴³ or thallium triacetate.²⁴⁴ α,β -Unsaturated ketones can be acyloxyated in good yields in the α' position with manganese triacetate.²⁴⁵ Palladium acetate converts alkenes to vinylic and/or allylic acetates.²⁴⁶ Lead tetraacetate even acyloxyates alkanes, in a slow reaction (10 days to 2 weeks), with tertiary and secondary positions greatly favored over primary ones.²⁴⁷ Yields are as high as 50%. Acyloxylation of certain alkanes has also been reported with palladium(II) acetate.²⁴⁸

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following:²⁴⁹



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This mechanism, involving a free radical $\text{R}\cdot$, is compatible with the allylic rearrangements found.²⁵⁰ The finding that *t*-butyl peresters labeled with ¹⁸O in the carbonyl oxygen gave ester with 50% of the label in each oxygen²⁵¹ is in accord with a combination of $\text{R}\cdot$ with the intermediate **19**, in which the copper is ionically bound, so that the oxygens are essentially equivalent. Other evidence is that *t*-butoxy radicals have been trapped with dienes.²⁵² Much less is known about the mechanisms of the reactions with metal acetates.²⁵³

Free-radical acyloxylation of aromatic substrates²⁵⁴ has been accomplished with a number of reagents including copper(II) acetate,²⁵⁵ benzoyl peroxide-iodine,²⁵⁶ silver(II) complexes,²⁵⁷ and cobalt(III) trifluoroacetate.²⁵⁸

OS III, 3; V, 70, 151; 68, 109.

²⁴⁰Rubottom; Mott; *J. Org. Chem.* **1981**, *46*, 2717.

²⁴¹Trost; Tanigawa *J. Am. Chem. Soc.* **1979**, *101*, 4413.

²⁴²For a review, see Cook, in *Cook Enamines*, 2nd ed.; Marcel Dekker: New York, 1988, pp. 251-258.

²⁴³See Butler, *Chem. Ind. (London)* **1976**, 499-500.

²⁴⁴Kuchnc; Giacobbe *J. Org. Chem.* **1968**, *33*, 3359.

²⁴⁵Dunlap; Sabol; *Watt Tetrahedron Lett.* **1984**, *25*, 5839; Demir; Sayrac; *Watt Synthesis* **1990**, 1119.

²⁴⁶For reviews, see Rylander *Organic Synthesis with Noble Metal Catalysts*; Academic Press: New York, 1973, pp. 80-87; Jira; Freiesleben *Organomet. React.* **1972**, *3*, 1-190, pp. 44-84; Heck *Fortschr. Chem. Forsch.* **1971**, *16*, 221-242, pp. 231-237; Tsuji *Adv. Org. Chem.* **1969**, *6*, 109-255, pp. 132-143.

²⁴⁷Bestre; Cole; *Crank Tetrahedron Lett.* **1983**, *24*, 3891; Mosher; Cox *Tetrahedron Lett.* **1985**, *26*, 3753.

²⁴⁸This was done in trifluoroacetic acid, and the products were trifluoroacetates; Sen; Gretz; Oliver; *Jiang New J. Chem.* **1989**, *13*, 755.

²⁴⁹Kharasch; Sosnovsky; Yang *J. Am. Chem. Soc.* **1959**, *81*, 5819; Kochi; Mains *J. Org. Chem.* **1965**, *30*, 1862. See also Beckwith; Zavitsas *J. Am. Chem. Soc.* **1986**, *108*, 8230.

²⁵⁰Goering; Mayer *J. Am. Chem. Soc.* **1964**, *86*, 3753; Denney; Appelbaum; Denney *J. Am. Chem. Soc.* **1962**, *84*, 4969.

²⁵¹Denney; Denney; Feig *Tetrahedron Lett.* **1959**, no. 15, p. 19.

²⁵²Kochi *J. Am. Chem. Soc.* **1962**, *84*, 2785, 3271; Story *Tetrahedron Lett.* **1962**, 401.

²⁵³See, for example, Jones; Mellor *J. Chem. Soc., Perkin Trans. 2* **1977**, 511.

²⁵⁴For a review, see Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1985, pp. 177-180, 351-355.

²⁵⁵Takizawa; Tateishi; Sugiyama; Yoshida; Yoshihara *J. Chem. Soc., Chem. Commun.* **1991**, 104. See also Kaeding; Kerlinger; Collins *J. Org. Chem.* **1965**, *30*, 3754.

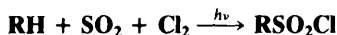
²⁵⁶For example, see Kovacic; Reid; *Brittain J. Org. Chem.* **1970**, *35*, 2152.

²⁵⁷Nyberg; Wistrand *J. Org. Chem.* **1978**, *43*, 2613.

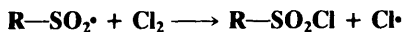
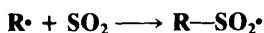
²⁵⁸Kochi; Tank; Bernath *J. Am. Chem. Soc.* **1973**, *95*, 7114; DiCosimo; Szabo *J. Org. Chem.* **1986**, *51*, 1365.

C. Substitution by Sulfur

4-12 Chlorosulfonation or Chlorosulfo-de-hydrogenation



The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.²⁵⁹ In scope and range of products obtained, the reaction is similar to 4-1. The mechanism is also similar, except that there are two additional main propagation steps:

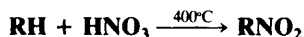


*Chlorosulfenation*²⁶⁰ can be accomplished by treatment with SOCl_2 and uv light: $\text{RH} + \text{SOCl}_2 \xrightarrow{h\nu} \text{RSCl}$.

D. Substitution by Nitrogen

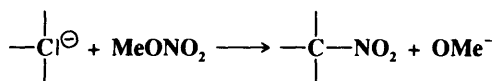
4-13 Nitration of Alkanes

Nitration or Nitro-de-hydrogenation



Nitration of alkanes²⁶¹ can be carried out in the gas phase at about 400°C or in the liquid phase. The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs.²⁶² A free-radical mechanism is involved.²⁶³

Activated positions (e.g., $\text{ZCH}_2\text{Z}'$ compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,²⁶⁴ or by alkyl nitrates under alkaline conditions.²⁶⁵ In the latter case it is the carbanionic form of the substrate that is actually nitrated. What is isolated under these alkaline conditions is the conjugate base of the nitro



compound. Yields are not high. Of course, the mechanism in this case is not of the free-radical type, but is electrophilic substitution with respect to the carbon (similar to the mechanisms of 2-7 and 2-8). Positions activated by only one electron-withdrawing group, e.g., α positions of simple ketones, nitriles, sulfones, or N,N-dialkyl amides, can be nitrated with alkyl nitrates if a very strong base, e.g., *t*-BuOK or NaNH_2 , is present to convert the substrate to the carbanionic form.²⁶⁶ Electrophilic nitration of alkanes has been performed

²⁵⁹For a review, see Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 126-131.

²⁶⁰Müller; Schmidt *Chem. Ber.* **1963**, *96*, 3050, **1964**, *97*, 2614. For a review of the formation and reactions of sulfonyl halides, see Kühle *Synthesis* **1970**, 561-580, **1971**, 563-586, 617-638.

²⁶¹For reviews, see Olah; Malhotra; Narang *Nitration*; VCH: New York, 1989, pp. 219-295; Ogata, in Trahanovsky, Ref. 185, part C, 1978, pp. 295-342; Ballod; Shtern *Russ. Chem. Rev.* **1976**, *45*, 721-737.

²⁶²For a discussion of the mechanism of this cleavage, see Matasa; Hass *Can. J. Chem.* **1971**, *49*, 1284.

²⁶³Titov *Tetrahedron* **1963**, *19*, 557-580.

²⁶⁴Sifniades *J. Org. Chem.* **1975**, *40*, 3562.

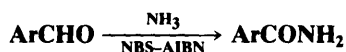
²⁶⁵For a review, see Larson, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, vol. 1; Wiley: New York, 1969, pp. 310-316.

²⁶⁶For examples, see Feuer; Shepherd; Savides *J. Am. Chem. Soc.* **1956**, *78*, 4364; Feuer; Lawrence *J. Org. Chem.* **1972**, *37*, 2662; Truce; Christensen *Tetrahedron* **1969**, *25*, 181; Pfeffer; Silbert *Tetrahedron Lett.* **1970**, 699; Feuer; Spinicelli *J. Org. Chem.* **1976**, *41*, 2981; Feuer; Van Buren; Grutzner *J. Org. Chem.* **1978**, *43*, 4676.

with nitronium salts, e.g., $\text{NO}_2^+ \text{PF}_6^-$ and with $\text{HNO}_3\text{-H}_2\text{SO}_4$ mixtures, but mixtures of nitration and cleavage products are obtained and yields are generally low.²⁶⁷

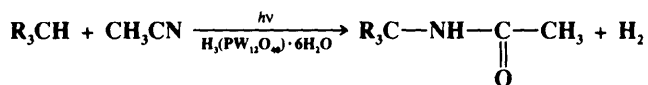
Aliphatic nitro compounds can be α nitrated [$\text{R}_2\text{CHNO}_2 \rightarrow \text{R}_2\text{C}(\text{NO}_2)_2$] by treatment of their conjugate bases RCNO_2^- with NO_2^- and $\text{K}_3\text{Fe}(\text{CN})_6$.²⁶⁸
OS I, 390; II, 440, 512.

4-14 The Direct Conversion of Aldehydes to Amides Amination or Amino-de-hydrogenation



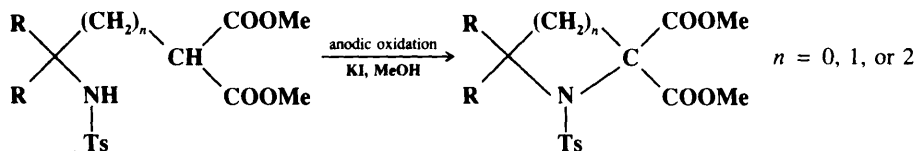
Aliphatic and aromatic aldehydes have been converted to the corresponding amides with ammonia or a primary or secondary amine, N-bromosuccinimide, and a catalytic amount of AIBN (p. 664).²⁶⁹ In a reaction of more limited scope, amides are obtained from aromatic and α,β -unsaturated aldehydes by treatment with dry ammonia gas and nickel peroxide.²⁷⁰ Best yields (80 to 90%) are obtained at -25 to -20°C . The reaction has also been performed with MnO_2 and NaCN along with ammonia or an amine at 0°C in isopropyl alcohol,²⁷¹ and with a secondary amine and a palladium acetate catalyst.²⁷² In the nickel peroxide reaction the corresponding alcohols (ArCH_2OH) have also been used as substrates. For an indirect way of converting aldehydes to amides, see 2-31. Thioamides RCSNR'_2 have been prepared in good yield from thioaldehydes (produced in situ from phosphoranes and sulfur) and secondary amines.²⁷³

4-15 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.²⁷⁴ 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 (9-2).

An electrochemical method for amination has been reported by Shono and co-workers.²⁷⁵ 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.

²⁶⁷Olah; Lin *J. Am. Chem. Soc.* **1973**, *93*, 1259. See also Bach; Holubka; Badger; Rajan *J. Am. Chem. Soc.* **1979**, *101*, 4416.

²⁶⁸Matacz; Piotrowska; Urbanski *Pol. J. Chem.* **1979**, *53*, 187; Kornblum; Singh; Kelly *J. Org. Chem.* **1983**, *48*, 332; Garver; Grakauskas; Baum *J. Org. Chem.* **1985**, *50*, 1699.

²⁶⁹Markó; Mekhalifa. Ref. 133.

²⁷⁰Nakagawa; Onoue; Minami *Chem. Commun.* **1966**, 17.

²⁷¹Gilman *Chem. Commun.* **1971**, 733.

²⁷²Tamaru; Yamada; Yoshida *Synthesis* **1983**, 474.

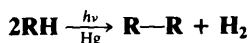
²⁷³Okuma; Komiya; Ohta *Chem. Lett.* **1988**, 1145.

²⁷⁴Renneke; Hill *J. Am. Chem. Soc.* **1986**, *108*, 3528.

²⁷⁵Shono; Matsumura; Katoh; Ohshita *Chem. Lett.* **1988**, 1065.

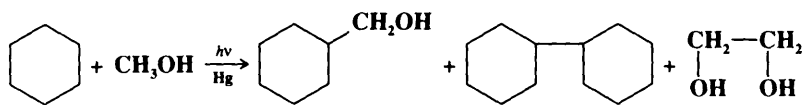
E. Substitution by Carbon In these reactions a new carbon-carbon bond is formed, and they may be given the collective title *coupling reactions*. In each case an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or olefin to give the coupling product.²⁷⁶

4-16 Simple Coupling at a Susceptible Position De-hydrogen-coupling

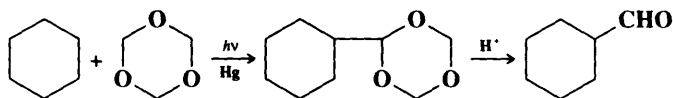


Alkanes can be dimerized by vapor-phase mercury photosensitization²⁷⁷ in a synthetically useful process. Best results are obtained for coupling at tertiary positions, but compounds lacking tertiary hydrogens (e.g., cyclohexane) also give good yields. Dimerization of *n*-alkanes gives secondary-secondary coupling in a nearly statistical distribution, with primary positions essentially unaffected. Alcohols and ethers dimerize at the position α to the oxygen [e.g., $2\text{EtOH} \rightarrow \text{MeCH(OH)CH(OH)Me}$].

When a mixture of compounds is treated, cross-dimerization and homodimerization take place statistically, e.g.:



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 (0-6) gives an



aldehyde, thus achieving the conversion $\text{RH} \rightarrow \text{RCHO}$. 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 α to the $\text{C}=\text{O}$ group), and amides (which couple α to the nitrogen) by running it in the presence of H_2 .²⁷⁸ Under these conditions it is likely that the excited Hg abstracts $\text{H}\cdot$ from H_2 , and that the remaining $\text{H}\cdot$ abstracts H from the substrate.

In an older reaction, substrates RH are treated with peroxides, which decompose to give a radical that abstracts a hydrogen from RH to give $\text{R}\cdot$, which dimerizes. Dialkyl and diacyl peroxides have been used, as well as Fenton's reagent (p. 700). This reaction is far from general, though in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,²⁷⁹ as well as those α to a phenyl group (especially if there is also an α -alkyl or α -chloro group),²⁸⁰ an ether group,²⁸¹ a carbonyl group,²⁸² a

²⁷⁶For a monograph on the formation of C—C bonds by radical reactions, see Giese, Ref. 1. For a review of arylation at carbon, see Abramovitch; Barton; Finet *Tetrahedron* **1988**, *44*, 3039-3071. For a review of aryl-aryl coupling, see Sainsbury *Tetrahedron* **1980**, *36*, 3327-3359.

²⁷⁷Brown; Crabtree *J. Am. Chem. Soc.* **1989**, *111*, 2935, 2946, *J. Chem. Educ.* **1988**, *65*, 290.

²⁷⁸Boojamra; Crabtree; Ferguson; Muedas *Tetrahedron Lett.* **1989**, *30*, 5583.

²⁷⁹Meshcheryakov; Érzyutova *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1966**, 94.

²⁸⁰McBay; Tucker; Groves *J. Org. Chem.* **1959**, *24*, 536; Johnston; Williams *J. Chem. Soc.* **1960**, 1168.

²⁸¹Pfordte; Leuschner *Liebigs. Ann. Chem.* **1961**, 643, 1.

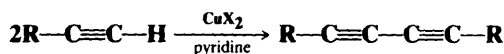
²⁸²Kharasch; McBay; Urry *J. Am. Chem. Soc.* **1948**, *70*, 1269; Leffingwell *Chem. Commun.* **1970**, 357; Hawkins; Large *J. Chem. Soc., Perkin Trans. 1* **1974**, 280.

cyano group,²⁸³ a dialkylamino group,²⁸⁴ or a carboxylic ester group, either the acid or alcohol side.²⁸⁵

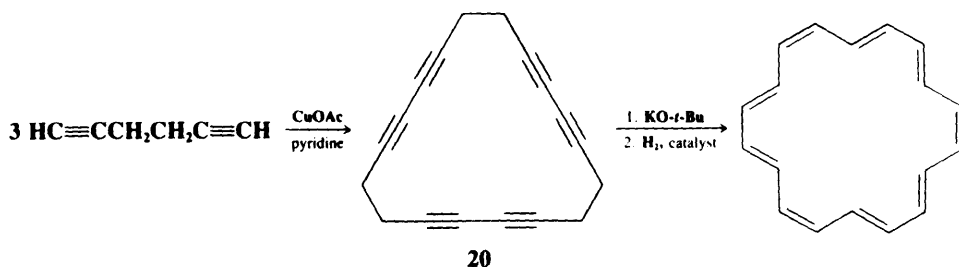
OS IV, 367; V, 1026; VII, 482.

4-17 Coupling of Alkynes

De-hydrogen-coupling

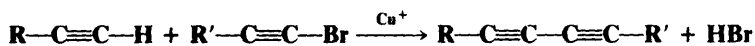


Terminal alkynes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes in high yields, is called the *Eglinton reaction*.²⁸⁶ The large-ring annulenes of Sondheimer et al. (see p. 62) were prepared by rearrangement and hydrogenation of cyclic polyynes,²⁸⁷ prepared by Eglinton coupling of terminal diynes, e.g.,²⁸⁸



20 is a cyclic trimer of 1,5-hexadiyne. 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. 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. Unsymmetrical diynes can be prepared by *Cadiot-Chodkiewicz* coupling:²⁸⁹



This may be regarded as a variation of **0-100** 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. Propargyl halides also give the reaction.²⁹⁰ A variation of the *Cadiot-Chodkiewicz* method

²⁸³Kharasch; Sosnovsky *Tetrahedron* **1958**, *3*, 97.

²⁸⁴Schwetlick; Jentsch; Karl; Wolter *J. Prakt. Chem.* **1964**, [4] 25, 95.

²⁸⁵Boguslavskaya; Razuvaev *J. Gen. Chem. USSR* **1963**, *33*, 1967.

²⁸⁶For reviews, see Simándi, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 529-534; Nigh, Ref. 185, pp. 11-31; Cadiot; Chodkiewicz, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 597-647.

²⁸⁷For a review of cyclic alkynes, see Nakagawa, in Patai *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2; Wiley: New York, 1978, pp. 635-712.

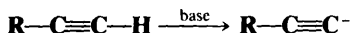
²⁸⁸Sondheimer; Wolovsky *J. Am. Chem. Soc.* **1962**, *84*, 260; Sondheimer; Wolovsky; Amiel *J. Am. Chem. Soc.* **1962**, *84*, 274.

²⁸⁹Chodkiewicz *Ann. Chim. (Paris)* **1957**, [13] 2, 819.

²⁹⁰Sevin; Chodkiewicz; Cadiot *Bull. Soc. Chim. Fr.* **1974**, 913.

consists of treating a haloalkyne ($R'C\equiv CX$) with a copper acetylide ($RC\equiv CCu$).²⁹¹ 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.²⁹² This protecting group can also be used in the Eglinton or Glaser methods.²⁹³

The mechanism of the Eglinton and Glaser reactions probably begins with loss of a proton



since there is a base present and acetylenic protons are acidic. The last step is probably the coupling of two radicals:

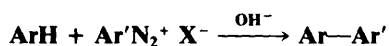


but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,²⁹⁴ and depend on the oxidizing agent. It is known, of course, that cuprous ion can form complexes with triple bonds.

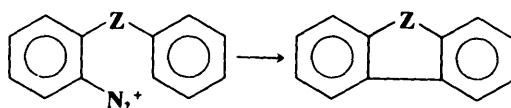
OS V, 517; VI, 68, 925; 65, 52.

4-18 Arylation of Aromatic Compounds by Diazonium Salts

Arylation or Aryl-de-hydrogenation



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*,²⁹⁵ it has been performed on several types of aromatic rings and on quinones. Yields are not high (usually under 40%) because of the many side reactions undergone by diazonium salts, though higher yields have been obtained under phase transfer conditions.²⁹⁶ The conditions of the Meerwein reaction (4-19), 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 Me_2SO).²⁹⁷ When the Gomberg–Bachmann reaction is performed intramolecularly, either by the alkaline solution or by the copper–ion procedure,



it is called the *Pschorr ring closure*²⁹⁸ and yields are usually somewhat higher. Still higher yields have been obtained by carrying out the Pschorr reaction electrochemically.²⁹⁹ 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

²⁹¹Curtis; Taylor *J. Chem. Soc. C* **1971**, 186.

²⁹²Eastmond; Walton *Tetrahedron* **1972**, 28, 4591; Ghose; Walton *Synthesis* **1974**, 890.

²⁹³Johnson; Walton *Tetrahedron* **1972**, 28, 5221.

²⁹⁴See the discussions in Nigh, Ref. 185, pp. 27-31; Fedenok; Berdnikov; Shvartsberg *J. Org. Chem. USSR* **1973**, 9, 1806; Clifford; Waters *J. Chem. Soc.* **1963**, 3056.

²⁹⁵For reviews, see Bolton; Williams *Chem. Soc. Rev.* **1966**, 15, 261-289; Hey *Adv. Free-Radical Chem.* **1966**, 2, 47-86. For a review applied to heterocyclic substrates, see Vernin; Dou; Metzger *Bull. Soc. Chim. Fr.* **1972**, 1173-1203.

²⁹⁶Beadle; Korzeniowski; Rosenberg; Garcia-Slaga; Gokel *J. Org. Chem.* **1964**, 49, 1594.

²⁹⁷Kamigata; Kurihara; Minato; Kobayashi *Bull. Chem. Soc. Jpn.* **1971**, 44, 3152.

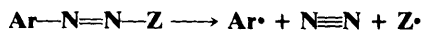
²⁹⁸For a review, see Abramovitch *Adv. Free-Radical Chem.* **1966**, 2, 87-138.

²⁹⁹Elofson; Gadallah *J. Org. Chem.* **1971**, 36, 1769.

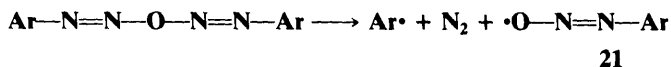
diazotize the amine substrate with isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.³⁰⁰

Other compounds with nitrogen–nitrogen bonds have been used instead of diazonium salts. Among these are N-nitroso amides [ArN(NO)COR], triazenes,³⁰¹ and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.³⁰²

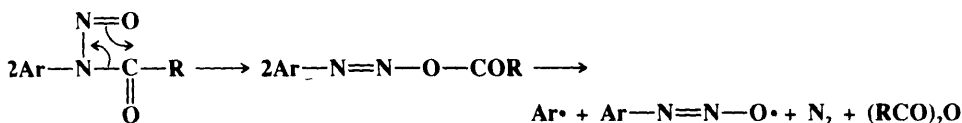
In each case the mechanism involves generation of an aryl radical from a covalent azo compound. In acid solution diazonium salts are ionic and their reactions are polar. When they cleave, the product is an aryl cation (see p. 644). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals:



Under Gomberg–Bachmann conditions, the species that cleaves is the anhydride:³⁰³



The aryl radical thus formed attacks the substrate to give the intermediate **1** (p. 680), from which the radical **21** abstracts hydrogen to give the product. N-Nitroso amides probably rearrange to N-acyloxy compounds, which cleave to give aryl radicals:³⁰⁴

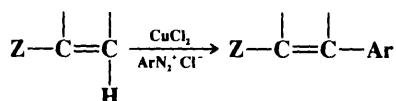


There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.³⁰⁵

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. 644).³⁰⁶ Under certain conditions the ordinary Gomberg–Bachmann reaction can also involve attack by aryl cations.³⁰⁷

OS I, 113; IV, 718.

4-19 Arylation of Activated Olefins by Diazonium Salts. Meerwein Arylation Arylation or Aryl-de-hydrogenation



³⁰⁰Chauncy; Gellert *Aust. J. Chem.* **1969**, *22*, 993. See also Duclos; Tung; Rapoport *J. Org. Chem.* **1984**, *49*, 5243.

³⁰¹See, for example, Patrick; Willaredt; DeGonia *J. Org. Chem.* **1985**, *50*, 2232; Butler; O'Shea; Shelly *J. Chem. Soc., Perkin Trans. 1* **1987**, 1039.

³⁰²Cadogan *J. Chem. Soc.* **1962**, 4257; Fillipi; Vernin; Dou; Metzger; Perkins *Bull. Soc. Chim. Fr.* **1974**, 1075.

³⁰³Rüchardt; Merz *Tetrahedron Lett.* **1964**, 2431; Eliel; Saha; Meyerson *J. Org. Chem.* **1965**, *30*, 2451.

³⁰⁴Cadogan; Murray; Sharp *J. Chem. Soc., Perkin Trans. 2* **1976**, 583, and references cited therein.

³⁰⁵Gragerov; Levit *J. Org. Chem. USSR* **1968**, *4*, 7.

³⁰⁶For an alternative to the second mechanism, see Gadallah; Cantu; Elofson *J. Org. Chem.* **1973**, *38*, 2386.

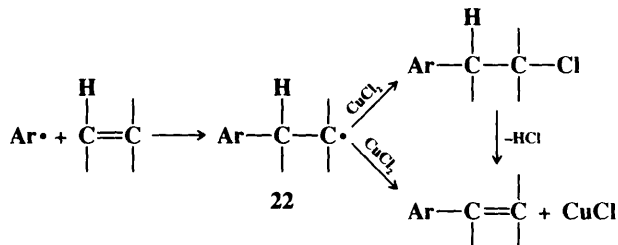
³⁰⁷For examples; see Kobori; Kobayashi; Minato *Bull. Chem. Soc., Jpn.* **1970**, *43*, 223; Cooper; Perkins *Tetrahedron Lett.* **1969**, 2477; Burri; Zollinger *Helv. Chim. Acta* **1973**, *56*, 2204; Eustathopoulos; Rinaudo; Bonnier *Bull. Soc. Chim. Fr.* **1974**, 2911. For a discussion, see Zollinger *Acc. Chem. Res.* **1973**, *6*, 335-341, pp. 338-339.

Olefins 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 chloride³⁰⁸ catalyst. This is called the *Meerwein arylation reaction*.³⁰⁹ Addition of ArCl to the double bond (to

give $Z-\overset{\text{Cl}}{\underset{\text{H}}{\text{C}}}-\overset{\text{Ar}}{\text{C}}$) is a side reaction (5-33). 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 olefin.³¹⁰

The mechanism is probably of the free-radical type, with $\text{Ar}\cdot$ forming as in 4-25 and then³¹¹



The radical **22** 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.

OS IV, 15.

4-20 Arylation and Alkylation of Olefins by Organopalladium Compounds.

The Heck Reaction

Alkylation or **Alkyl-de-hydrogenation**, etc.



Arylation of olefins can also be achieved³¹² by treatment with an "arylpalladium" reagent that can be generated in situ by several³¹³ methods: (1) by treatment of an aryl bromide with a palladium-triarylphosphine complex ($\text{ArBr} \rightarrow \text{"ArPdBr"}$);³¹⁴ (2) by treatment of an aryl iodide³¹⁵ with palladium acetate³¹⁶ in the presence of a base such as tributylamine or

³⁰⁸ FeCl_2 is also effective: Ganushchak; Obushak; Luka *J. Org. Chem. USSR* **1981**, 17, 765.

³⁰⁹For reviews, see Dombrovskii *Russ. Chem. Rev.* **1984**, 53, 943-955; Rondstedt *Org. React.* **1976**, 24, 225-259.

³¹⁰Doyle; Siegfried; Elliott; Dellaria *J. Org. Chem.* **1977**, 42, 2431.

³¹¹Dickerman; Vermont *J. Am. Chem. Soc.* **1962**, 84, 4150; Morrison; Cazes; Samkoff; Howe *J. Am. Chem. Soc.* **1962**, 84, 4152.

³¹²For reviews of this and related reactions, see Heck *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985, pp. 179-321; Ryabov *Synthesis* **1985**, 233-252; Heck *Org. React.* **1982**, 27, 345-390; *Adv. Catal.* **1977**, 26, 323-349; Volkova; Levitin; Vol'pin *Russ. Chem. Rev.* **1975**, 44, 552-560; Moritani; Fujiwara *Synthesis* **1973**, 524-533; Jira; Freiesleben *Organomet. React.* **1972**, 3, 1-190, pp. 84-105.

³¹³For other methods, see Murahashi; Yamamura; Mita *J. Org. Chem.* **1977**, 42, 2870; Luong-Thi; Riviere *J. Chem. Soc., Chem. Commun.* **1978**, 918; Akiyama; Miyazaki; Kaneda; Teranishi; Fujiwara; Abe; Taniguchi *J. Org. Chem.* **1980**, 45, 2359; Tsuji; Nagashima *Tetrahedron* **1984**, 40, 2699; Kikukawa; Naritomi; He; Wada; Matsuda *J. Org. Chem.* **1985**, 50, 299; Chen; Yang *Tetrahedron Lett.* **1986**, 27, 1171; Kasahara; Izumi; Miyamoto; Sakai *Chem. Ind. (London)* **1989**, 192; Miura; Hashimoto; Itoh; Nomura *Tetrahedron Lett.* **1989**, 30, 975.

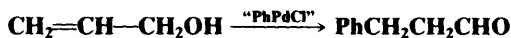
³¹⁴For reviews, see Heck *Acc. Chem. Res.* **1979**, 12, 146-151; *Pure Appl. Chem.* **1978**, 50, 691-701. See also Bender; Stakem; Heck *J. Org. Chem.* **1982**, 47, 1278; Spencer *J. Organomet. Chem.* **1983**, 258, 101.

³¹⁵For a method that uses an aryl chloride, but converts it to an aryl iodide in situ, see Bozell; Vogt *J. Am. Chem. Soc.* **1988**, 110, 2655.

³¹⁶For a more efficient palladium reagent, see Andersson; Karabelas; Hallberg; Andersson *J. Org. Chem.* **1985**, 50, 3891. See also Merlic; Semmelhack *J. Organomet. Chem.* **1990**, 391, C23.

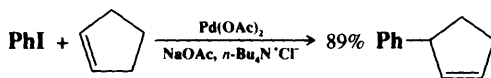
potassium acetate ($\text{ArI} \rightarrow \text{ArPdI}$);³¹⁷ (3) by treatment of an arylmercury compound (either Ar_2Hg or ArHgX) with LiPdCl_3 ($\text{ArHgX} \rightarrow \text{ArPdX}$)³¹⁸ (in some cases other noble metal salts have been used); or (4) by the reaction of an aromatic compound with palladium acetate or palladium metal and silver acetate in acetic acid [in this case an aryl *hydrogen* is replaced ($\text{ArH} \rightarrow \text{ArPdOAc}$)].³¹⁹ Whichever of these methods is used, the reaction is known as the *Heck reaction*.

Unlike 4-19, the Heck reaction is not limited to activated substrates. The substrate can be a simple olefin, or it can contain a variety of functional groups, such as ester, ether,^{319a} carboxyl, phenolic, or cyano groups.³²⁰ Primary and secondary allylic alcohols (and even nonallylic unsaturated alcohols³²¹) give aldehydes or ketones that are products of double-bond migration,³²² e.g.,



Ethylene is the most reactive olefin. Increasing substitution lowers the reactivity. Substitution therefore takes place at the less highly substituted side of the double bond.³²³ Alkylation can also be accomplished, but only if the alkyl group lacks a β hydrogen, e.g., the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.³²⁴ However, vinylic groups, even those possessing β hydrogens, have been successfully introduced (to give 1,3-dienes) by the reaction of the olefin with a vinylic halide in the presence of a trialkylamine and a catalyst composed of palladium acetate and a triarylphosphine at 100 to 150°C.³²⁵ The reaction has also been done with terminal alkynes as substrates.³²⁶

The evidence is in accord with an addition-elimination mechanism (addition of ArPdX followed by elimination of HPdX) in most cases.³²⁷ The reactions are stereospecific, yielding products expected from syn addition followed by syn elimination.³²⁸ Because the product is formed by an elimination step, with suitable substrates the double bond can go the other way, resulting in allylic rearrangement, e.g.,³²⁹



The Heck reaction has also been performed intramolecularly.³³⁰
OS VI, 815; VII, 361.

³¹⁷Mizoroki; Mori; Ozaki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; Mori; Mizoroki; Ozaki *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505; Heck; Nolley *J. Org. Chem.* **1972**, *37*, 2320; Ziegler; Heck *J. Org. Chem.* **1978**, *43*, 2941; Hirao; Enda; Ohshiro; Agawa *Chem. Lett.* **1981**, 403; Jeffery *J. Chem. Soc., Chem. Commun.* **1984**, 1287; Bumagin; More; Beltskaya *J. Organomet. Chem.* **1989**, *371*, 397; Larock; Johnson *J. Chem. Soc., Chem. Commun.* **1989**, 1368.

³¹⁸Heck *J. Am. Chem. Soc.* **1968**, *90*, 5518, 5526, 5535. For a review, see Larock, Ref. 238, pp. 273-292.

³¹⁹See, for example, Fujiwara; Moritani; Matsuda *Tetrahedron* **1968**, *24*, 4819; Fujiwara; Maruyama; Yoshidomi; Taniguchi *J. Org. Chem.* **1981**, *46*, 851. For a review, see Kozhevnikov *Russ. Chem. Rev.* **1983**, *52*, 138-151.

^{319a}For a review pertaining to enol ethers, see Daves *Adv. Met.-Org. Chem.* **1991**, *2*, 59-99.

³²⁰For a review of cases where the olefin contains an α hetero atom, see Daves; Hallberg *Chem. Rev.* **1989**, *89*, 1433-1445.

³²¹Larock; Leung; Stolz-Dunn *Tetrahedron Lett.* **1989**, *30*, 6629.

³²²See, for example, Melpolder; Heck *J. Org. Chem.* **1976**, *41*, 265; Chalk; Magennis *J. Org. Chem.* **1976**, *41*, 273, 1206.

³²³Heck *J. Am. Chem. Soc.* **1969**, *91*, 6707, **1971**, *93*, 6896.

³²⁴Heck *J. Organomet. Chem.* **1972**, *37*, 389; Heck; Nolley, Ref. 317.

³²⁵Dieck; Heck *J. Org. Chem.* **1975**, *40*, 1083; Kim; Patel; Heck *J. Org. Chem.* **1981**, *46*, 1067; Heck *Pure Appl. Chem.* **1981**, *53*, 2323-2332. See also Luong-Thi; Riviere *Tetrahedron Lett.* **1979**, 4657; Jeffery *Tetrahedron Lett.* **1985**, *26*, 2667. *J. Chem. Soc., Chem. Commun.* **1991**, 324; Scott; Peña; Swärd; Stoessel; Stille *J. Org. Chem.* **1985**, *50*, 2302; Larock; Gong *J. Org. Chem.* **1989**, *54*, 2047.

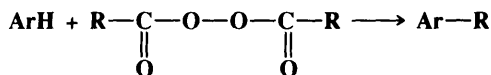
³²⁶Cassar *J. Organomet. Chem.* **1975**, *93*, 253; Dieck; Heck *J. Organomet. Chem.* **1975**, *93*, 259; Sonogashira; Tohda; Hagihara *Tetrahedron Lett.* **1975**, 4467; Singh; Just *J. Org. Chem.* **1989**, *54*, 4453. See also Heck *Palladium Reagents in Organic Syntheses*, Ref. 312, pp. 299-306.

³²⁷Heck *J. Am. Chem. Soc.* **1969**, *91*, 6707; Shue *J. Am. Chem. Soc.* **1971**, *93*, 7116; Heck; Nolley, Ref. 317.

³²⁸Heck, Ref. 327; Moritani; Danno; Fujiwara; Teranishi *Bull. Chem. Soc. Jpn.* **1971**, *44*, 578.

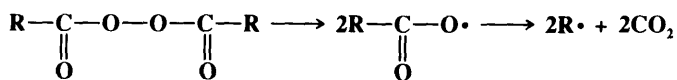
³²⁹Larock; Baker *Tetrahedron Lett.* **1988**, *29*, 905. Also see Larock; Gong; Baker *Tetrahedron Lett.* **1989**, *30*, 2603.

³³⁰See, for example, Abelman; Oh; Overman *J. Org. Chem.* **1987**, *52*, 4130; Negishi; Zhang; O'Connor *Tetrahedron Lett.* **1988**, *29*, 2915; Larock; Song; Baker; Gong *Tetrahedron Lett.* **1988**, *29*, 2919.

4-21 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 **4-18**, though the reagent is different.³³¹ It is used less often than **4-18**, but the scope is similar. When R = alkyl, the scope is more limited.³³² 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. 680 (CIDNP has been observed³³³); the radicals are produced by



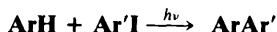
Since no relatively stable free radical is present (such as **21** in **4-18**), most of the product arises from dimerization and disproportionation.³³⁴ The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts the hydrogen from **1** and reduces the extent of side reactions.³³⁵

Aromatic compounds can also be arylated by aryllead tricarboxylates.³³⁶ Best yields (~70 to 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 α phenylated) by triphenylbismuth dichloride or by certain other Bi(V) reagents.³³⁷ O-Phenylation is a possible side reaction. As with the aryllead tricarboxylate reactions, a free-radical mechanism is unlikely.³³⁸

OS V, 51. See also OS V, 952; VI, 890.

4-22 Photochemical Arylation of Aromatic Compounds**Arylation or Aryl-de-hydrogenation**

Another free-radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.³³⁹ Yields are generally higher than in **4-18** or **4-21**. The aryl iodide may contain OH

³³¹For reviews, see Ref. 295.

³³²For reviews of the free-radical alkylation of aromatic compounds, see Tiecco; Testaferri *React. Intermed. (Plenum)* **1983**, 3, 61-11; Dou; Vernin; Metzger *Bull. Soc. Chim. Fr.* **1971**, 4593.

³³³Kaptein; Freeman; Hill; Bargon *J. Chem. Soc., Chem. Commun.* **1973**, 953.

³³⁴We have given the main steps that lead to biphenyls. The mechanism is actually more complicated than this and includes more than 100 elementary steps resulting in many side products, including those mentioned on p. 681: DeTar; Long; Rendleman; Bradley; Duncan *J. Am. Chem. Soc.* **1967**, 89, 4051; DeTar *J. Am. Chem. Soc.* **1967**, 89, 4058. See also Jandu; Nicolopolou; Perkins *J. Chem. Res. (S)* **1985**, 88.

³³⁵Chalfont; Hey; Liang; Perkins *J. Chem. Soc. B* **1971**, 233.

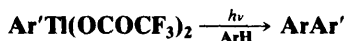
³³⁶Bell; Kalman; May; Pinhey; Sternhell *Aust. J. Chem.* **1979**, 32, 1531.

³³⁷For a review, see Abramovitch; Barton; Finet, Ref. 276, pp. 3040-3047.

³³⁸Barton; Finet; Giannotti; Halley *J. Chem. Soc., Perkin Trans. 1* **1987**, 241.

³³⁹Wolf; Kharasch *J. Org. Chem.* **1965**, 30, 2493. For a review, see Sharma; Kharasch *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 36-44 [*Angew. Chem.* 80, 69-77].

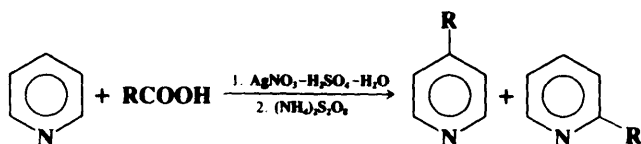
or COOH groups. The mechanism is similar to that of **4-18**. The aryl radicals are generated by the photolytic cleavage $\text{ArI} \rightarrow \text{Ar}\cdot + \text{I}\cdot$. The reaction has been applied to intramolecular arylation (analogous to the Pschorr reaction).³⁴⁰ A similar reaction is photolysis of an arylthallium bis(trifluoroacetate) (**2-22**) in an aromatic solvent. Here too, an unsymmetrical biaryl is produced in good yields.³⁴¹



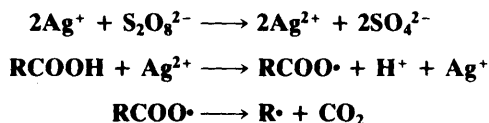
In this case it is the C—Tl bond that is cleaved to give aryl radicals.

4-23 Alkylation, Acylation, and Carbalkoxylation of Nitrogen Heterocycles³⁴²

Alkylation or Alkyl-de-hydrogenation, etc.



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.³⁴³ R can be primary, secondary, or tertiary. The attacking species is $\text{R}\cdot$, formed by³⁴⁴



A hydroxymethyl group can be introduced ($\text{ArH} \rightarrow \text{ArCH}_2\text{OH}$) by several variations of this method.³⁴⁵ Alkylation of these substrates can also be accomplished by generating the alkyl radicals in other ways: from hydroperoxides and FeSO_4 ,³⁴⁶ from alkyl iodides and $\text{H}_2\text{O}_2\text{-Fe(II)}$,³⁴⁷ from carboxylic acids and lead tetraacetate, or from the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate.³⁴⁸ The reaction has also been applied to acetophenone and ferrocene.³⁴⁹

³⁴⁰See, for example, Kupchan; Wormser *J. Org. Chem.* **1965**, *30*, 3792; Jeffs; Hansen *J. Am. Chem. Soc.* **1967**, *89*, 2798; Thyagarajan; Kharasch; Lewis; Wolf *Chem. Commun.* **1967**, 614.

³⁴¹Taylor; Kienzie; McKillop *J. Am. Chem. Soc.* **1970**, *92*, 6088.

³⁴²For reviews; see Heinisch *Heterocycles* **1987**, *26*, 481-496; Minisci; Vismara; Fontana *Heterocycles* **1989**, *28*, 489-519; Minisci *Top. Curr. Chem.* **1976**, *62*, 1-48, pp. 17-46, *Synthesis* **1973**, 1-24, pp. 12-19. For a review of substitution of carbon groups on nitrogen heterocycles, see Vorbrüggen; Maas *Heterocycles* **1988**, *27*, 2659-2776.

³⁴³Minisci; Mondelli; Gardini; Porta *Tetrahedron* **1972**, *28*, 2403; Citterio; Minisci; Franchi *J. Org. Chem.* **1980**, *45*, 4752; Fontana; Minisci; Barbosa; Vismara *Tetrahedron* **1990**, *46*, 2525.

³⁴⁴Anderson; Kochi *J. Am. Chem. Soc.* **1970**, *92*, 1651.

³⁴⁵See Citterio; Gentile; Minisci; Serravalle; Ventura *Tetrahedron* **1985**, *41*, 617; Katz; Mistry; Mitchell *Synth. Commun.* **1989**, *19*, 317.

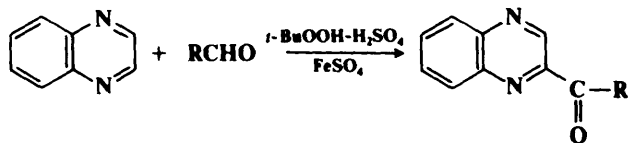
³⁴⁶Minisci; Selva; Porta; Barilli; Gardini *Tetrahedron* **1972**, *28*, 2415.

³⁴⁷Fontana; Minisci; Barbosa; Vismara *Acta Chem. Scand.* **1989**, *43*, 995.

³⁴⁸Minisci; Vismara; Fontana; Barbosa *Tetrahedron Lett.* **1989**, *30*, 4569.

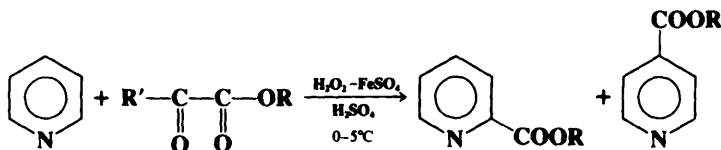
³⁴⁹Din; Meth-Cohn; Walshe *Tetrahedron Lett.* **1979**, 4783.

Protonated nitrogen heterocycles can be acylated by treatment with an aldehyde, *t*-butyl hydroperoxide, sulfuric acid, and ferrous sulfate, e.g.,³⁵⁰

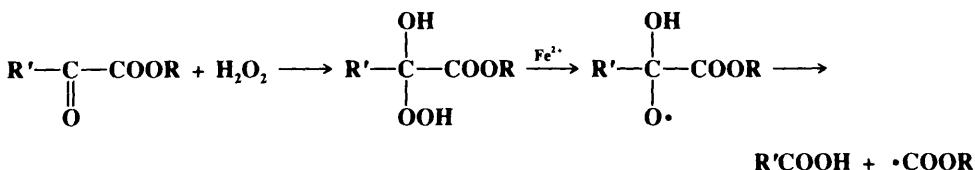


These alkylation and acylation reactions are important because Friedel-Crafts alkylation and acylation (1-12, 1-14) cannot be applied to most nitrogen heterocycles. See also 3-17.

Protonated nitrogen heterocycles can be carbalkoxylated³⁵¹ by treatment with esters of α -keto acids and Fenton's reagent:



The attack is by $\cdot\text{COOR}$ radicals generated from the esters:



Similarly, a carbamoyl group can be introduced³⁵² by the use of the radicals $\text{H}_2\text{NC}\cdot$ or $\text{Me}_2\text{NC}\cdot$ generated from formamide or dimethylformamide and H_2SO_4 , H_2O_2 , and FeSO_4 or other oxidants.

N_2 as Leaving Group³⁵³

In these reactions diazonium salts are cleaved to aryl radicals,³⁵⁴ in most cases with the assistance of copper salts. Reactions 4-18 and 4-19 may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts, see 3-20 to 3-24.

4-24 Replacement of the Diazonium Group by Hydrogen

Dediazoniation or Hydro-de-diazoniation



³⁵⁰Caronna; Gardini; Minisci *Chem. Commun.* **1969**, 201; Arnoldi; Bellatti; Caronna; Citterio; Minisci; Porta; Sesana *Gazz. Chim. Ital.* **1977**, 107, 491.

³⁵¹Bernardi; Caronna; Galli; Minisci; Perchinunno *Tetrahedron Lett.* **1973**, 645; Heinisch; Lötsch *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 692 [*Angew. Chem.* 97, 694].

³⁵²Minisci; Gardini; Galli; Bertini *Tetrahedron Lett.* **1970**, 15; Minisci; Citterio; Vismara; Giordano *Tetrahedron* **1985**, 41, 4157.

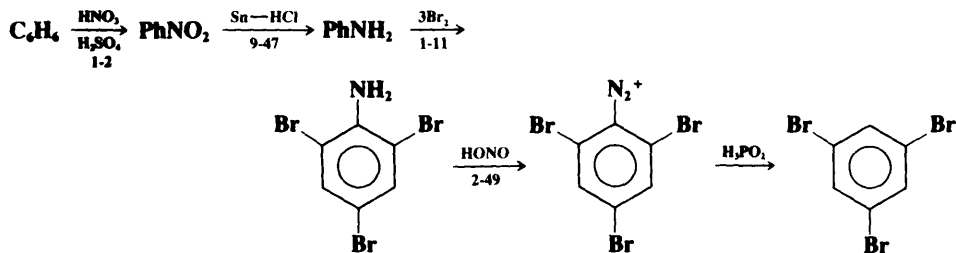
³⁵³For a review, see Wulfman, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 1; Wiley: New York, 1978, pp. 286-297.

³⁵⁴For reviews, see Galli *Chem. Rev.* **1988**, 88, 765-792; Zollinger *Acc. Chem. Res.* **1973**, 6, 355-341, pp. 339-341.

Reduction of the diazonium group (*dediazonation*) provides an indirect method for the removal of an amino group from an aromatic ring.³⁵⁵ The best and most common way of accomplishing this is by use of hypophosphorous acid H_3PO_2 , though many other reducing agents³⁵⁶ have been used, among them ethanol, HMPA,³⁵⁶ thiophenol,³⁵⁷ and sodium stannite. Ethanol was the earliest reagent used, and it frequently gives good yields, but often ethers (ArOEt) are side products. When H_3PO_2 is used, 5 to 15 moles of this reagent are required per mole of substrate. Diazonium salts can be reduced in nonaqueous media by several methods,³⁵⁸ including treatment with Bu_3SnH or Et_3SiH in ethers or MeCN ³⁵⁹ and by isolation as the BF_4^- salt and reduction of this with NaBH_4 in DMF.³⁶⁰ Aromatic amines can be deaminated ($\text{ArNH}_2 \rightarrow \text{ArH}$) in one laboratory step by treatment with an alkyl nitrite in DMF³⁶¹ or boiling THF.³⁶² The corresponding diazonium salt is an intermediate.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic ($\text{S}_{\text{N}}1$) mechanism while the reduction to ArH proceeds by a free-radical process.³⁶³ The reduction with H_3PO_2 is also believed to have a free-radical mechanism.³⁶⁴ In the reduction with NaBH_4 , an aryldiazene intermediate ($\text{ArN}=\text{NH}$) has been demonstrated,³⁶⁵ arising from nucleophilic attack by BH_4^- on the β nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution.³⁶⁶ It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical Ar^\cdot or the corresponding anion Ar^- may be involved.³⁶⁷

An important use of the dediazonation reaction is to remove an amino group after it has been used to direct one or more other groups to ortho and para positions. For example, the compound 1,3,5-tribromobenzene cannot be prepared by direct bromination of benzene because the bromo group is ortho-para-directing; however, this compound is easily prepared by the following sequence:



³⁵⁵For a review, see Zollinger in Patai; Rappoport, Ref. 286, pp. 603-669.

³⁵⁶For lists of some of these, with references, see Ref. 74, p. 25; Tröndlin; Rüchardt *Chem. Ber.* **1977**, *110*, 2494.

³⁵⁷Shono; Matsumura; Tsubata *Chem. Lett.* **1979**, 1051.

³⁵⁸For a list of some of these, with references, see Korzeniowski; Blum; Gokel *J. Org. Chem.* **1977**, *42*, 1469.

³⁵⁹Nakayama; Yoshida; Simamura *Tetrahedron* **1970**, *26*, 4609.

³⁶⁰Hendrickson *J. Am. Chem. Soc.* **1961**, *83*, 1251. See also Threadgill; Gledhill *J. Chem. Soc., Perkin Trans. 1* **1986**, 873.

³⁶¹Doyle; Dellaria; Siegfried; Bishop *J. Org. Chem.* **1977**, *42*, 3494.

³⁶²Cadogan; Molina *J. Chem. Soc., Perkin Trans. 1* **1973**, 541.

³⁶³For examples, see DeTar; Turetzky *J. Am. Chem. Soc.* **1955**, *77*, 1745, **1956**, *78*, 3925, 3928; DeTar; Kosuge *J. Am. Chem. Soc.* **1958**, *80*, 6072; Lewis; Chambers *J. Am. Chem. Soc.* **1971**, *93*, 3267; Broxton; Bunnnett; Paik *J. Org. Chem.* **1977**, *42*, 643.

³⁶⁴See, for example, Kornblum; Cooper; Taylor *J. Am. Chem. Soc.* **1950**, *72*, 3013; Beckwith *Aust. J. Chem.* **1972**, *25*, 1887; Levit; Kiprianova; Gragerov *J. Org. Chem. USSR* **1975**, *11*, 2395.

³⁶⁵Bloch; Musso; Záhorszky *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 370 [*Angew. Chem.* *81*, 392]; König; Musso; Záhorszky *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 45 [*Angew. Chem.* *84*, 33]; McKenna; Traylor *J. Am. Chem. Soc.* **1971**, *93*, 2313.

³⁶⁶Huang; Kosower *J. Am. Chem. Soc.* **1968**, *90*, 2354, 2362, 2367; Smith; Hillhouse *J. Am. Chem. Soc.* **1988**, *110*, 4066.

³⁶⁷Rieker; Niederer; Leibfritz *Tetrahedron Lett.* **1969**, 4287; Kosower; Huang; Tsuji *J. Am. Chem. Soc.* **1969**, *91*, 2325; König; Musso; Záhorszky, Ref. 365; Broxton; McLeish *Aust. J. Chem.* **1983**, *36*, 1031.

Many other compounds that would otherwise be difficult to prepare are easily synthesized with the aid of the dediazonation reaction.

Unwanted dediazonation can be suppressed by using hexasulfonated calix[6]arenes (see p. 84).³⁶⁸

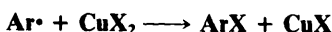
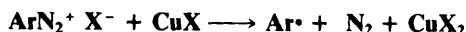
OS I, 133, 415; II, 353, 592; III, 295; IV, 947; VI, 334.

4-25 Replacement of the Diazonium Group by Chlorine or Bromine Chloro-de-diazonation, etc.



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*. 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 1-16). 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:³⁶⁹



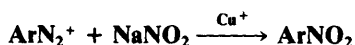
The first step involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.

Aryl bromides and chlorides can be prepared from primary aromatic amines in one step by several procedures,³⁷⁰ including treatment of the amine (1) with *t*-butyl nitrite and anhydrous CuCl₂ or CuBr₂ at 65°C,³⁷¹ and (2) with *t*-butyl thionitrite or *t*-butyl thionitrate and CuCl₂ or CuBr₂ at room temperature.³⁷² These procedures are, in effect, a combination of 2-49 and the Sandmeyer reaction. A further advantage is that cooling to 0°C is not needed.

For the preparation of fluorides and iodides from diazonium salts, see 3-24 and 3-23.

OS I, 135, 136, 162, 170; II, 130; III, 185; IV, 160. Also see OS III, 136; IV, 182.

4-26 Nitro-de-diazonation



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 4-25 and 4-28, it was discovered by Sandmeyer. BF₄⁻ is often used as the negative ion to avoid competition from the chloride ion. The mechanism is probably like that of 4-25.³⁷³ If electron-withdrawing

³⁶⁸Shinkai; Mori; Araki; Manabe *Bull. Chem. Soc. Jpn.* **1987**, 60, 3679.

³⁶⁹Dickerman; Weiss; Ingberman *J. Org. Chem.* **1956**, 21, 380, *J. Am. Chem. Soc.* **1958**, 80, 1904; Kochi *J. Am. Chem. Soc.* **1957**, 79, 2942; Dickerman; DeSouza; Jacobson *J. Org. Chem.* **1969**, 34, 710; Galli *J. Chem. Soc., Perkin Trans. 2* **1981**, 1459, **1982**, 1139, **1984**, 897. See also Hanson; Jones; Gilbert; Timms *J. Chem. Soc., Perkin Trans. 2* **1991**, 1009.

³⁷⁰For other procedures, see Brackman; Smit *Recl. Trav. Chim. Pays-Bas* **1966**, 85, 857; Cadogan; Roy; Smith *J. Chem. Soc. C* **1966**, 1249.

³⁷¹Doyle; Siegfried; Dellaria *J. Org. Chem.* **1977**, 42, 2426.

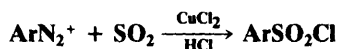
³⁷²Oae; Shinham; Kim *Chem. Lett.* **1979**, 939, *Bull. Chem. Soc. Jpn.* **1980**, 53, 1065.

³⁷³For discussions, see Oppenorth; Rüchardt *Liebigs Ann. Chem.* **1974**, 1333; Singh; Kumar; Khanna *Tetrahedron Lett.* **1982**, 23, 5191.

groups are present, the catalyst is not needed; NaNO_2 alone gives nitro compounds in high yields.³⁷⁴

OS II, 225; III, 341.

4-27 Replacement of the Diazonium Group by Sulfur-containing Groups Chlorosulfo-de-diazonation



Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of cupric chloride.³⁷⁵ The use of FeSO_4 and copper metal instead of CuCl_2 gives sulfinic acids ArSO_2H .³⁷⁶ See also 3-21.

OS V, 60; VII, 508.

4-28 Cyano-de-diazonation

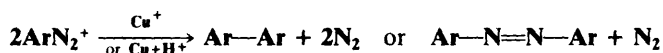


This reaction, also called the *Sandmeyer reaction*, is similar to 4-25 in scope and mechanism. It is usually conducted in neutral solution to avoid liberation of HCN .

OS I, 514.

4-29 Aryl Dimerization with Diazonium Salts

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

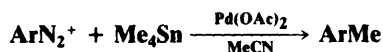


When diazonium salts are treated with cuprous ion (or with copper and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from 4-18 (and from 1-4) in that *both* aryl groups in the product originate from ArN_2^+ , i.e., hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.³⁷⁷

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

4-30 Methylation and Vinylation of Diazonium Salts

Methyl-de-diazonation, etc.



A methyl group can be introduced into an aromatic ring by treatment of diazonium salts with tetramethyltin and a palladium acetate catalyst.³⁷⁸ The reaction has been performed with Me, Cl, Br, and NO_2 groups on the ring. A vinylic group can be introduced with $\text{CH}_2=\text{CHSnBu}_3$.

³⁷⁴Bagal; Pevzner; Frolov *J. Org. Chem. USSR* **1969**, 5, 1767.

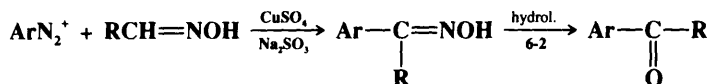
³⁷⁵Gilbert *Synthesis* **1969**, 1-10, p. 6.

³⁷⁶Wittig; Hoffmann *Org. Synth. V*, 60.

³⁷⁷See Cohen; Lewarchik; Tarino *J. Am. Chem. Soc.* **1974**, 96, 7753.

³⁷⁸Kikukawa; Kono; Wada; Matsuda *J. Org. Chem.* **1983**, 48, 1333.

4-31 Conversion of Diazonium Salts to Aldehydes, Ketones, or Carboxylic Acids **Acyl-de-diazonation**, etc.



Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes (R = H) or ketones.³⁷⁹ A copper sulfate–sodium sulfite catalyst is essential. In most cases higher yields (40 to 60%) are obtained when the reaction is used for aldehydes than for ketones. In another method³⁸⁰ for achieving the conversion $\text{ArN}_2^+ \rightarrow \text{ArCOR}$, diazonium salts are treated with R_4Sn and CO with palladium acetate as catalyst.³⁸¹ In a different kind of reaction, silyl enol ethers of aryl ketones $\text{Ar}'\text{C}(\text{OSiMe}_3)=\text{CHR}$ react with solid diazonium fluoroborates $\text{ArN}_2^+ \text{BF}_4^-$ to give ketones $\text{ArCHRCOAr}'$.³⁸² This is, in effect, an α arylation of the aryl ketone.

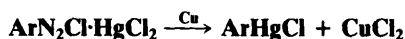
Carboxylic acids can be prepared in moderate-to-high yields by treatment of diazonium fluoroborates with carbon monoxide and palladium acetate³⁸³ or copper(II) chloride.³⁸⁴ The mixed anhydride ArCOOCOME is an intermediate that can be isolated. Other mixed anhydrides can be prepared by the use of other salts instead of sodium acetate.³⁸⁵ An aryl-palladium compound is probably an intermediate.³⁸⁵

OS V, 139.

4-32 Replacement of the Diazonium Group by a Metal **Metallo-de-diazonation**



Aromatic organometallic compounds can be prepared by the treatment of diazonium salts (most often fluoroborates) with metals.³⁸⁶ Among the metals used have been Hg, Tl, Sn, Pb, Sb, and Bi. Another method consists of treating the double salt of the diazonium salt and a metal chloride with a metallic powder, e.g.,

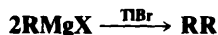


Organometallic compounds of Hg,³⁸⁷ Ge, Sn, and As have been among those prepared by this method. The mechanisms are not clear and may be either homolytic or heterolytic.

OS II, 381, 432, 494; III, 665.

Metals as Leaving Groups

4-33 Coupling of Grignard Reagents **De-metallo-coupling**



³⁷⁹Beech *J. Chem. Soc.* **1954**, 1297.

³⁸⁰For still another method, see Citterio; Serravalle; Vismara *Tetrahedron Lett.* **1982**, 23, 1831.

³⁸¹Kikukawa; Idemoto; Katayama; Kono; Wada; Matsuda *J. Chem. Soc., Perkin Trans. 1* **1987**, 1511.

³⁸²Sakakura; Hara; Tanaka *J. Chem. Soc., Chem. Commun.* **1985**, 1545.

³⁸³Nagira; Kikukawa; Wada; Matsuda *J. Org. Chem.* **1980**, 45, 2365.

³⁸⁴Olah; Wu; Bagno; Prakash *Synlett* **1990**, 596.

³⁸⁵Kikukawa; Kono; Nagira; Wada; Matsuda *Tetrahedron Lett.* **1980**, 21, 2877; *J. Org. Chem.* **1981**, 46, 4413.

³⁸⁶For a review, see Reutov; Ptitsyna *Organomet. React.* **1972**, 4, 73-162.

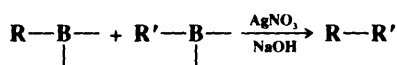
³⁸⁷For reviews with respect to Hg, see Wardell, in Zuckerman *Inorganic Reactions and Methods*, vol. 11; VCH: New York, 1988, pp. 320-323; Larock, Ref. 238, pp. 97-101.

Grignard reagents can be coupled to give symmetrical dimers³⁸⁸ by treatment with either thallium(I) bromide³⁸⁹ or with a transition-metal halide such as CrCl₂, CrCl₃, CoCl₂, CoBr₂, or CuCl₂.³⁹⁰ 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.³⁹¹ Vinylic and alkynyl Grignard reagents can be coupled (to give 1,3-dienes and 1,3-diynes, respectively) by treatment with thionyl chloride.³⁹² Primary alkyl, vinylic, aryl, and benzylic Grignard reagents give symmetrical dimers in high yield (~90%) when treated with a silver(I) salt, e.g., AgNO₃, AgBr, AgClO₄, in the presence of a nitrogen-containing oxidizing agent such as lithium nitrate, methyl nitrate, or NO₂.³⁹³ This method has been used to close rings of 4, 5, and 6 members.³⁹⁴

The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (2-35), followed by its decomposition to free radicals.³⁹⁵

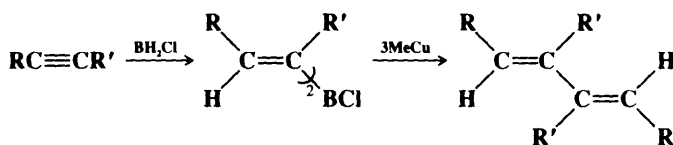
OS VI, 488.

4-34 Coupling of Boranes Alkyl-de-dialkylboration



Alkylboranes can be coupled by treatment with silver nitrate and base.³⁹⁶ Since alkylboranes are easily prepared from olefins (5-12), this is essentially a way of coupling and reducing olefins; in fact, olefins can be hydroborated and coupled in the same flask. For symmetrical coupling (R = R') yields range from 60 to 80% for terminal olefins and from 35 to 50% for internal ones. Unsymmetrical coupling has also been carried out,³⁹⁷ but with lower yields. Arylboranes react similarly, yielding biaryls.³⁹⁸ The mechanism is probably of the free-radical type.

Vinylic dimerization can be achieved by treatment of divinylchloroboranes (prepared by addition of BH₂Cl to alkynes; see 5-12) with methylcopper. (*E,E*)-1,3-Dienes are prepared in high yields.³⁹⁹



³⁸⁸For a list of reagents, with references, see Ref. 74, pp. 48-49.

³⁸⁹McKillop; Elsom; Taylor *J. Am. Chem. Soc.* **1968**, *90*, 2423, *Tetrahedron* **1970**, *26*, 4041.

³⁹⁰For reviews, see Kauffmann *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 291-305 [*Angew. Chem.* *86*, 321-335]; Elsom; Hunt; McKillop *Organomet. Chem. Rev., Sect. A* **1972**, *8*, 135-152; Nigh, Ref. 185, pp. 85-91.

³⁹¹Taylor; Bennett; Heinz; Lashley *J. Org. Chem.* **1961**, *46*, 2194; Cheng; Luo *Tetrahedron Lett.* **1968**, *29*, 1293.

³⁹²Uchida; Nakazawa; Kondo; Iwata; Matsuda *J. Org. Chem.* **1972**, *37*, 3749.

³⁹³Tamura; Kochi *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1120.

³⁹⁴Whitesides; Gutowski *J. Org. Chem.* **1976**, *41*, 2882.

³⁹⁵For a review of the mechanism, see Kashin; Beletskaya *Russ. Chem. Rev.* **1982**, *51*, 503-526.

³⁹⁶Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 306-308.

³⁹⁷Brown; Verbrugge; Snyder *J. Am. Chem. Soc.* **1961**, *83*, 1001.

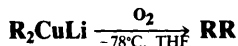
³⁹⁸Breuer; Broster *Tetrahedron Lett.* **1972**, 2193.

³⁹⁹Yamamoto; Yatagai; Maruyama; Sonoda; Murahashi *J. Am. Chem. Soc.* **1977**, *99*, 5652, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3427. For other methods of dimerizing vinylic boron compounds, see Rao; Kumar; Devaprabhakara *J. Organomet. Chem.* **1979**, *179*, C7; Campbell; Brown *J. Org. Chem.* **1980**, *45*, 549.

In a similar reaction, symmetrical conjugated diynes $\text{RC}\equiv\text{C}-\text{C}\equiv\text{CR}$ can be prepared by reaction of lithium dialkylalkynylborates $\text{Li}^+ [\text{R}'_2\text{B}(\text{C}\equiv\text{CR})_2]^-$ with iodine.⁴⁰⁰

4-35 Coupling of Other Organometallic Reagents³⁸⁸

De-metallo-coupling



Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O_2 at -78°C in THF.⁴⁰¹ The reaction is successful for R = primary and secondary alkyl, vinylic, or aryl. Other oxidizing agents, e.g., 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.⁴⁰² The finding of retention of configuration for this reaction demonstrates that free-radical intermediates are not involved. Lithium organoaluminates LiAlR_4 are dimerized to RR by treatment with $\text{Cu}(\text{OAc})_2$.⁴⁰³ Terminal vinylic alanes (prepared by 5-13) can be dimerized to 1,3-dienes with CuCl in THF.⁴⁰⁴ Symmetrical 1,3-dienes can also be prepared in high yields by treatment of vinylic mercury chlorides⁴⁰⁵ with LiCl and a rhodium catalyst⁴⁰⁶ and by treatment of vinylic tin compounds with a palladium catalyst.⁴⁰⁷ Arylmercuric salts are converted to biaryls by treatment with copper and a catalytic amount of PdCl_2 .⁴⁰⁸ Vinylic, alkynyl, and aryl tin compounds were dimerized with $\text{Cu}(\text{NO}_3)_2$.⁴⁰⁹ Alkyl- and aryllithium compounds can be dimerized by transition-metal halides in a reaction similar to 4-33.⁴¹⁰ Triarylbismuth compounds Ar_3Bi react with palladium(0) complexes to give biaryls ArAr .⁴¹¹ Unsymmetrical coupling of vinylic, alkynyl, and arylmercury compounds was achieved in moderate-to-good yields by treatment with alkyl and vinylic dialkylcopper reagents, e.g., $\text{PhCH}=\text{CHHgCl} + \text{Me}_2\text{CuLi} \rightarrow \text{PhCH}=\text{CHMe}$.⁴¹² Unsymmetrical biaryls were prepared by treating a cyanocuprate $\text{ArCu}(\text{CN})\text{Li}$ (prepared from ArLi and CuCN) with an aryllithium $\text{Ar}'\text{Li}$.^{412a}

Halogen as Leaving Group

The conversion of RX to RH can occur by a free-radical mechanism but is treated at 0-76.

⁴⁰⁰Pelter; Smith; Tabata *J. Chem. Soc., Chem. Commun.* **1975**, 857. For extensions to unsymmetrical conjugated diynes, see Pelter; Hughes; Smith; Tabata *Tetrahedron Lett.* **1976**, 4385; Sinclair; Brown *J. Org. Chem.* **1976**, 41, 1078.

⁴⁰¹Whitesides; SanFilippo; Casey; Panek *J. Am. Chem. Soc.* **1967**, 89, 5302. See also Kauffmann; Kuhlmann; Sahn; Schrecken *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 541 [*Angew. Chem.* 80, 566]; Bertz; Gibson *J. Am. Chem. Soc.* **1986**, 108, 8286.

⁴⁰²Whitesides; Casey; Krieger *J. Am. Chem. Soc.* **1971**, 93, 1379; Walborsky; Banks; Banks; Duraisamy *Organometallics* **1982**, 1, 667; Rao; Periasamy *J. Chem. Soc., Chem. Commun.* **1987**, 495. See also Lambert; Duffley; Dalzell; Razdan *J. Org. Chem.* **1982**, 47, 3350.

⁴⁰³Sato; Mori; Sato *Chem. Lett.* **1978**, 1337.

⁴⁰⁴Zweifel; Miller *J. Am. Chem. Soc.* **1970**, 92, 6678.

⁴⁰⁵For reviews of coupling with organomercury compounds, see Russell *Acc. Chem. Res.* **1989**, 22, 1-8; Larock, Ref. 238, pp. 240-248.

⁴⁰⁶Larock; Bernhardt *J. Org. Chem.* **1977**, 42, 1680. For extension to unsymmetrical 1,3-dienes, see Larock; Riefling *J. Org. Chem.* **1978**, 43, 1468.

⁴⁰⁷Tolstikov; Miftakhov; Danilova; Vel'der; Spirikhin *Synthesis* **1989**, 633.

⁴⁰⁸Kretschmer; Glowinski *J. Org. Chem.* **1976**, 41, 2661. See also Bumagin; Kalinovskii; Beletskaya *J. Org. Chem. USSR* **1982**, 18, 1151; Larock; Bernhardt, Ref. 406.

⁴⁰⁹Ghosal; Luke; Kyler *J. Org. Chem.* **1987**, 52, 4296.

⁴¹⁰Morizur *Bull. Soc. Chim. Fr.* **1964**, 1331.

⁴¹¹Barton; Ozbalik; Ramesh *Tetrahedron* **1988**, 44, 5661.

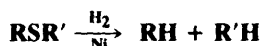
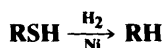
⁴¹²Larock; Leach *Tetrahedron Lett.* **1981**, 22, 3435; *Organometallics* **1982**, 1, 74. For another method, see Larock; Hershberger *Tetrahedron Lett.* **1981**, 22, 2443.

^{412a}Lipshutz; Siegmund; Garcia *J. Am. Chem. Soc.* **1991**, 113, 8161.

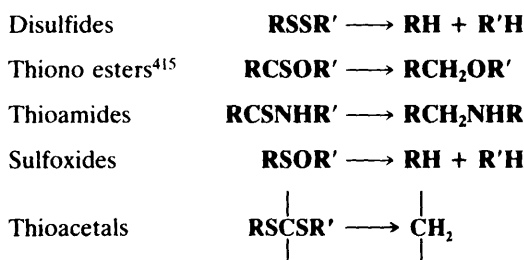
Sulfur as Leaving Group

4-36 Desulfurization with Raney Nickel

Hydro-de-mercapto-substitution, etc.

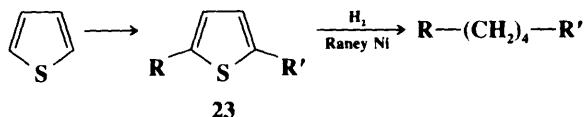


Thiols and thioethers,⁴¹³ both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.⁴¹⁴ The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, among them:



The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see 9-37), can also give the olefin if an α hydrogen is present.⁴¹⁶ In most of the examples given, R can also be aryl. Other reagents⁴¹⁷ have also been used.⁴¹⁸

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, followed by reduction:



Thiophenes can also be desulfurized to alkenes ($\text{RCH}_2\text{CH}=\text{CHCH}_2\text{R}'$ from 23) with a nickel boride catalyst prepared from nickel(II) chloride and NaBH_4 in methanol.⁴¹⁹ It is possible to reduce just one SR group of a dithioacetal by treatment with borane-pyridine

⁴¹³For a review of the reduction of thioethers, see Block, in Patai *The Chemistry of Functional Groups, Supplement E*, pt. 1; Wiley: New York, 1980, pp. 585-600.

⁴¹⁴For reviews, see Belen'kii, in Belen'kii *Chemistry of Organosulfur Compounds*; Ellis Horwood: Chichester, 1990, pp. 193-228; Pettit; van Tamelen *Org. React.* **1962**, *12*, 356-529; Hauptmann; Walter *Chem. Rev.* **1962**, *62*, 347-404.

⁴¹⁵See Baxter; Bradshaw *J. Org. Chem.* **1981**, *46*, 831.

⁴¹⁶Fishman; Torigoe; Guzik *J. Org. Chem.* **1963**, *28*, 1443.

⁴¹⁷For lists of reagents, with references, see Ref. 74, pp. 31-35. For a review with respect to transition-metal reagents, see Luh; Ni *Synthesis* **1990**, 89-103. For some very efficient nickel-containing reagents, see Becker; Fort; Vanderesse; Caubère *J. Org. Chem.* **1989**, *54*, 4848.

⁴¹⁸For example, diphosphorus tetraiodide by Suzuki; Tani; Takeuchi *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2421; Shigemasa; Ogawa; Sashiwa; Saimoto *Tetrahedron Lett.* **1989**, *30*, 1277; $\text{NiBr}_2\text{-Ph}_3\text{P-LiAlH}_4$ by Ho; Lam; Luh *J. Org. Chem.* **1989**, *54*, 4474.

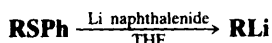
⁴¹⁹Schut; Engberts; Wynberg *Synth. Commun.* **1972**, *2*, 415.

in trifluoroacetic acid or in CH_2Cl_2 in the presence of AlCl_3 .⁴²⁰ Phenyl selenides RSePh can be reduced to RH with Ph_3SnH ⁴²¹ and with nickel boride.⁴²²

The exact mechanisms of the Raney nickel reactions are still in doubt, though they are probably of the free-radical type.⁴²³ It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds, i.e., the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the olefins and the failure to isolate any potential sulfur-containing intermediates.⁴²⁴

OS IV, 638; V, 419; VI, 109, 581, 601. See also OS VII, 124, 476.

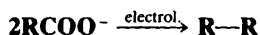
4-37 Conversion of Sulfides to Organolithium Compounds Lithio-de-phenylthio-substitution



Sulfides can be cleaved, with a phenylthio group replaced by a lithium,⁴²⁵ by treatment with lithium or lithium naphthalenide in THF.⁴²⁶ Good yields have been obtained with $\text{R} =$ primary, secondary, or tertiary alkyl, or allylic,⁴²⁷ 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.⁴²⁸ The reaction has also been used to prepare α -lithio ethers and α -lithio organosilanes.⁴²⁵ For some of these compounds lithium 1-(dimethylamino)naphthalenide is a better reagent than either Li or lithium naphthalenide.⁴²⁹ The mechanism is presumably of the free-radical type.

Carbon as Leaving Group

4-38 Decarboxylative Dimerization. The Kolbe Reaction De-carboxylide-coupling



Electrolysis of carboxylate ions, which results in decarboxylation and combination of the resulting radicals, is called the *Kolbe reaction*.⁴³⁰ It is used to prepare symmetrical RR , where R is straight- or branched-chained, except that little or no yield is obtained when there is α branching. The reaction is not successful for $\text{R} =$ aryl. Many functional groups

⁴²⁰Kikugawa *J. Chem. Soc., Perkin Trans. 1* **1984**, 609.

⁴²¹Clive; Chittattu; Wong *J. Chem. Soc., Chem. Commun.* **1978**, 41.

⁴²²Back *J. Chem. Soc., Chem. Commun.* **1984**, 1417.

⁴²³For a review, see Bonner; Grimm, in Kharasch; Meyers *The Chemistry of Organic Sulfur Compounds*, vol. 2; Pergamon: New York, 1966, pp. 35-71, 410-413. For a review of the mechanism of desulfurization on molybdenum surfaces, see Friend; Roberts *Acc. Chem. Res.* **1988**, *21*, 394-400.

⁴²⁴Owens; Ahmberg *Can. J. Chem.* **1962**, *40*, 941.

⁴²⁵For a review, see Cohen; Bhupathy *Acc. Chem. Res.* **1989**, *22*, 152-161.

⁴²⁶Screttas; Micha-Screttas *J. Org. Chem.* **1978**, *43*, 1064, **1979**, *44*, 713.

⁴²⁷See Cohen; Guo *Tetrahedron* **1986**, *42*, 2803.

⁴²⁸See, for example, Cohen; Sherbine; Matz; Hutchins; McHenry; Willey *J. Am. Chem. Soc.* **1984**, *106*, 3245; Ager *J. Chem. Soc., Perkin Trans. 1* **1986**, 183; Ref. 426.

⁴²⁹See Cohen; Matz *Synth. Commun.* **1980**, *10*, 311.

⁴³⁰For reviews, see Schäfer *Top. Curr. Chem.* **1990**, *152*, 91-151, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911-934 [*Angew. Chem.* *93*, 978-1000]; Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 238-253; Ebersson; Utley, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 435-462; Gilde *Methods Free-Radical Chem.* **1972**, *3*, 1-82; Ebersson, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 53-101; Vijn; Conway *Chem. Rev.* **1967**, *67*, 623-664.

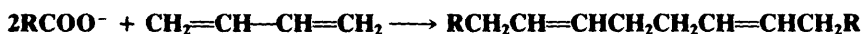
may be present, though many others inhibit the reaction.⁴³⁰ Unsymmetrical RR' have been made by coupling mixtures of acid salts.

A free-radical mechanism is involved:



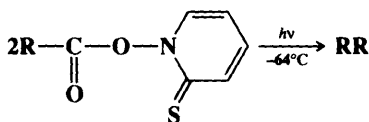
There is much evidence⁴³¹ for this mechanism, including side products (RH, alkenes) characteristic of free-radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, see p. 744). Other side products (ROH, RCOOR) are sometimes found; these stem from further oxidation of the radical R• to the carbocation R⁺.⁴³²

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur:⁴³³



The radical R• adds to the conjugated system to give RCH₂CH=CHCH₂•, which dimerizes. Another possible product is RCH₂CH=CHCH₂R, from coupling of the two kinds of radicals.⁴³⁴

In a non-electrolytic reaction, which is limited to R = primary alkyl, the thiohydroxamic esters **24** give dimers when irradiated at -64°C in an argon atmosphere.⁴³⁵



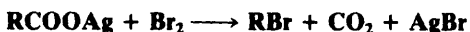
24

In another non-electrolytic process, arylacetic acids are converted to *vic*-diaryl compounds $2\text{ArCR}_2\text{COOH} \rightarrow \text{ArCR}_2\text{CR}_2\text{Ar}$ by treatment with sodium persulfate $\text{Na}_2\text{S}_2\text{O}_8$ and a catalytic amount of AgNO_3 .⁴³⁶ Both of these reactions involve dimerization of free radicals. In still another process, electron-deficient aromatic acyl chlorides are dimerized to biaryls ($2\text{ArCOCl} \rightarrow \text{ArAr}$) by treatment with a disilane R_3SiSiR_3 and a palladium catalyst.⁴³⁷

OS III, 401; V, 445, 463; VII, 181.

4-39 The Hunsdiecker Reaction

Bromo-de-carboxylation



Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction*⁴³⁸ and is a way of decreasing the length of a carbon chain by one unit.⁴³⁹ The reaction is of

⁴³¹For other evidence, see Kraeutler; Jaeger; Bard *J. Am. Chem. Soc.* **1978**, *100*, 4903.

⁴³²See Corey; Bauld; La Londe; Casanova; Kaiser *J. Am. Chem. Soc.* **1960**, *82*, 2645.

⁴³³Lindsey; Peterson *J. Am. Chem. Soc.* **1959**, *81*, 2073; Khrizolitova; Mirkind; Fioshin *J. Org. Chem. USSR* **1968**, *4*, 1640; Bruno; Dubois *Bull. Soc. Chim. Fr.* **1973**, 2270.

⁴³⁴Smith; Gilde *J. Am. Chem. Soc.* **1959**, *81*, 5325, **1961**, *83*, 1355; Schäfer; Pistorius *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 841 [*Angew. Chem.* **84**, 893].

⁴³⁵Barton; Bridon; Fernandez-Picot; Zard *Tetrahedron* **1967**, *43*, 2733.

⁴³⁶Fristad; Klang *Tetrahedron Lett.* **1983**, *24*, 2219.

⁴³⁷Krafft; Rich; McDermott *J. Org. Chem.* **1990**, *55*, 5430.

⁴³⁸This reaction was first reported by the Russian composer-chemist Alexander Borodin: *Liebigs Ann. Chem.* **1861**, *119*, 121.

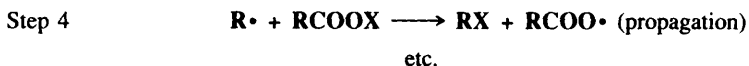
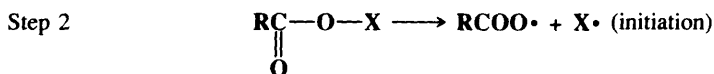
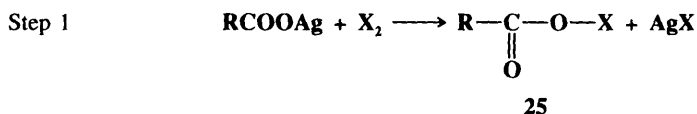
⁴³⁹For reviews, see Wilson *Org. React.* **1957**, *9*, 332-388; Johnson; Ingham *Chem. Rev.* **1956**, *56*, 219-269.

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 α substituted. 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.

When iodine is the reagent, the ratio between the reactants is very important and determines the products. A 1:1 ratio of salt to iodine gives the alkyl halide, as above. 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.⁴⁴⁰ 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.⁴⁴¹

Other methods for accomplishing the conversion $\text{RCOOH} \rightarrow \text{RX}$ are:⁴⁴² (1) treatment of thallium(I) carboxylates⁴⁴³ with bromine;⁴⁴⁴ (2) treatment of carboxylic acids with lead tetraacetate and halide ions (Cl^- , Br^- , or I^-);⁴⁴⁵ (3) reaction of the acids with lead tetraacetate and N-chlorosuccinimide, which gives tertiary and secondary chlorides in good yields but is not good for R = primary alkyl or phenyl;⁴⁴⁶ (4) the reaction between a diacyl peroxide and CuCl_2 , CuBr_2 , or CuI_2 ⁴⁴⁷ [this reaction also takes place with $\text{Cu}(\text{SCN})_2$, and $\text{Cu}(\text{CN})_2$]; (5) treatment of thiohydroxamic esters (**24**) with CCl_4 , BrCCl_3 (which gives bromination), CHI_3 , or CH_2I_2 in the presence of a radical initiator;⁴⁴⁸ (6) photolysis of benzophenone oxime esters of carboxylic acids in CCl_4 ($\text{RCON}=\text{CPh}_2 \rightarrow \text{RCl}$).⁴⁴⁹ Alkyl fluorides can be prepared in moderate to good yields by treating carboxylic acids RCOOH with XeF_2 .⁴⁵⁰ 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:



⁴⁴⁰Bachman; Kite; Tuccarbasu; Tullman *J. Org. Chem.* **1970**, *35*, 3167.

⁴⁴¹Cristol; Firth *J. Org. Chem.* **1961**, *26*, 280. See also Meyers; Fleming *J. Org. Chem.* **1979**, *44*, 3405, and references cited therein.

⁴⁴²For a list of reagents, with references, see Ref. 74, pp. 381-382.

⁴⁴³These salts are easy to prepare and purify; see Ref. 444.

⁴⁴⁴McKillop; Bromley; Taylor *J. Org. Chem.* **1969**, *34*, 1172; Cambie; Hayward; Jurlina; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1981**, 2608.

⁴⁴⁵Kochi *J. Am. Chem. Soc.* **1965**, *87*, 2500, *J. Org. Chem.* **1965**, *30*, 3265. For a review, see Sheldon; Kochi *Org. React.* **1972**, *19*, 279-421, pp. 326-334, 390-399.

⁴⁴⁶Becker; Geisel; Grob; Kuhnen *Synthesis* **1973**, 493.

⁴⁴⁷Jenkins; Kochi *J. Org. Chem.* **1971**, *36*, 3095, 3103.

⁴⁴⁸Barton; Crich; Motherwell *Tetrahedron Lett.* **1983**, *24*, 4979; Barton; Lacher; Zard *Tetrahedron* **1987**, *43*, 4321; Stofer; Lion *Bull. Soc. Chim. Belg.* **1987**, *96*, 623; Della; Tsanaktisidus *Aust. J. Chem.* **1989**, *42*, 61.

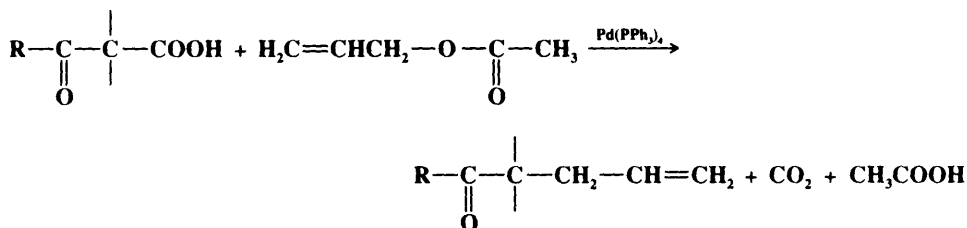
⁴⁴⁹Hasebe; Tsuchiya *Tetrahedron Lett.* **1988**, *29*, 6287.

⁴⁵⁰Patrick; Johri; White; Bertrand; Mokhtar; Kilbourn; Welch **1986**, *Can. J. Chem.* *64*, 138. For another method, see Grakauskas *J. Org. Chem.* **1969**, *34*, 2446.

The first step is not a free-radical process, and its actual mechanism is not known.⁴⁵¹ **25** is an acyl hypophalite 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. 682); 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 (**0-24**) to give the ester.⁴⁵² See also **9-13**.

OS **III**, 578; **V**, 126; **VI**, 179. See also OS **VI**, 403.

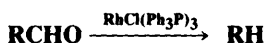
4-40 Decarboxylative Allylation Allyl-de-carboxylation



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.⁴⁵³ The reaction is successful for various substituted allylic groups. The less-highly-substituted end of the allylic group forms the new bond. Thus, both $\text{CH}_2=\text{CHCHMeOAc}$ and $\text{MeCH}=\text{CHCH}_2\text{OAc}$

gave $\text{RCO}-\text{C}-\text{CH}_2\text{CH}=\text{CHMe}$ as the product.

4-41 Decarbonylation of Aldehydes and Acyl Halides Carbonyl-extrusion



Aldehydes, both aliphatic and aromatic, can be decarbonylated⁴⁵⁴ by heating with chlorotris(triphenylphosphine)rhodium⁴⁵⁵ or other catalysts such as palladium.⁴⁵⁶ $\text{RhCl}(\text{Ph}_3\text{P})_3$ is often called *Wilkinson's catalyst*.⁴⁵⁷ In an older reaction aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*t*-peroxide or other peroxides,⁴⁵⁸ usually in a solution

⁴⁵¹When 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; Isaacs; Tumi *Chem. Lett.* **1964**, 1471.

⁴⁵²Oae; Kashiwagi; Kozuka *Bull. Chem. Soc. Jpn.* **1966**, 39, 2441; Bunce; Murray *Tetrahedron* **1971**, 27, 5323.

⁴⁵³Tsuda; Okada; Nishi; Saegusa *J. Org. Chem.* **1986**, 51, 421.

⁴⁵⁴For reviews, see Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987, pp. 768-775; Baird, in Patai *The Chemistry of Functional Groups, Supplement B*, pt. 2; Wiley: New York, 1979, pp. 825-857; Tsuji, in Wender; Pino *Organic Syntheses Via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 595-654; Tsuji; Ohno *Synthesis* **1969**, 157-169; Bird *Transition Metal Intermediates in Organic Synthesis*; Academic Press: New York, 1967, pp. 239-247.

⁴⁵⁵Tsuji; Ohno *Tetrahedron Lett.* **1965**, 3969; Ohno; Tsuji *J. Am. Chem. Soc.* **1968**, 90, 99; Baird; Nyman; Wilkinson *J. Chem. Soc. A* **1968**, 348.

⁴⁵⁶For a review, see Rylander, Ref. 246, pp. 260-267.

⁴⁵⁷For a review of this catalyst, see Jardine *Prog. Inorg. Chem.* **1981**, 28, 63-202.

⁴⁵⁸For reviews of free-radical aldehyde decarbonylations, see Vinogradov; Nikishin *Russ. Chem. Rev.* **1971**, 40, 916-932; Schubert; Kintner, in Patai, Ref. 189, pp. 711-735.

