19

OXIDATIONS AND REDUCTIONS

First we must examine what we mean when we speak of oxidation and reduction. Inorganic chemists define oxidation in two ways: loss of electrons and increase in oxidation number. In organic chemistry, these definitions, while still technically correct, are not easy to apply. While electrons are directly transferred in some organic oxidations and reductions, the mechanisms of most of these reactions do not involve a direct electron transfer. As for oxidation number, while this is easy to apply in some cases, e.g., the oxidation number of carbon in CH_4 is -4, in most cases attempts to apply the concept lead to fractional values or to apparent absurdities. Thus carbon in propane has an oxidation number of -2.67 and in butane of -2.5, though organic chemists seldom think of these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (e.g., the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure. The practice in organic chemistry has been to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one.* Reduction is the opposite. For the simple functional groups this series is shown in Table 19.1.[1] It should be noted that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as chloromethane, but 1,2-dichloropropane is in a higher one. Obviously, such distinctions are somewhat arbitrary, and if we attempt to carry them too far, we shall find ourselves painted into a corner. Nevertheless, the basic idea has served organic chemistry well. It should be noted that conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen (Lavoisier's original definition of oxidation). The reverse is true for reductions.

Of course, there is no oxidation without a concurrent reduction. However, we classify reactions as oxidations or reductions depending on whether the *organic compound* is oxidized or reduced. In some cases both the oxidant and reductant are organic; those reactions are treated separately at the end of the chapter.

MECHANISMS

It must be noted that our definition of oxidation has nothing to do with mechanism. Thus the conversion of bromomethane to methanol with KOH (**0-1**) and to methane with $LiAlH_4$ (**0-76**) have the same SN2 mechanisms, but one is a reduction (according to our definition)

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[1] For more extensive tables, with subclassifications, see Soloveichik; Krakauer *J. Chem. Educ.* **1966**, *43*, 532-535.

TABLE 19.1 Categories of simple functional groups arranged according to oxidation state

Oxidation is the conversion of a functional group in a molecule to a higher category; reduction is conversion to a lower one. Conversions within a category are neither oxidations nor reductions. The numbers given at the bottom are only approximations

RH	$-\overset{|}{C}{=}\overset{|}{C}-$ ROH RCl RNH_2 etc.	$-C{\equiv}C-$ $R-\underset{\overset{\|}{O}}{C}-R$ $-\underset{\underset{Cl}{|}}{\overset{|}{C}}-Cl$ $-\underset{\underset{Cl}{|}}{\overset{|}{C}}-\underset{\underset{Cl}{|}}{\overset{|}{C}}-$ $-\underset{\underset{OH}{|}}{\overset{|}{C}}-\underset{\underset{OH}{|}}{\overset{|}{C}}-$ etc.	$R-\underset{\overset{\|}{O}}{C}-OH$ $R-\underset{\overset{\|}{O}}{C}-NH_2$ $-\underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{C}}-Cl$ etc.	CO_2 CCl_4
Approximate oxidation number				
-4	-2	0	$+2$	$+4$

and the other is not. It is impractical to consider the mechanisms of oxidation and reduction reactions in broad categories in this chapter as we have done for the reactions considered in Chapters 10 to 18.[2] The main reason is that the mechanisms are too diverse, and this in turn is because the bond changes are too different. For example, in Chapter 15, all the reactions involved the bond change C=C → W—C—C—Y and a relatively few mechanisms covered all the reactions. But for oxidations and reductions the bond changes are far more diverse. Another reason is that the mechanism of a given oxidation or reduction reaction can vary greatly with the oxidizing or reducing agent employed. Very often the mechanism has been studied intensively for only one or a few of many possible agents.

Though we therefore do not cover oxidation and reduction mechanisms in the same way as we have covered other mechanisms, it is still possible to list a few broad mechanistic categories. In doing this, we follow the scheme of Wiberg.[3]

1. *Direct electron transfer.*[4] We have already met some reactions in which the reduction is a direct gain of electrons or the oxidation a direct loss of them. An example is the Birch reduction (**5-10**), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones (**9-62**), where again it is

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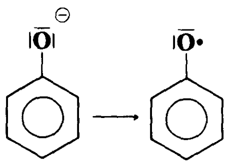
[2] For monographs on oxidation mechanisms, see Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 16; Elsevier: New York, 1980; *Oxidation in Organic Chemistry*; Academic Press: New York, pt. A [Wiberg], 1965, pts. B, C, and D [Trahanovsky], 1973, 1978, 1982; Waters *Mechanisms of Oxidation of Organic Compounds*; Wiley: New York, 1964; Stewart *Oxidation Mechanisms*; W. A. Benjamin: New York, 1964. For a review, see Stewart *Isot. Org. Chem.* **1976**, *2*, 271-310.

[3] Wiberg *Surv. Prog. Chem.* **1963**, *1*, 211-248.

[4] For a monograph on direct electron-transfer mechanisms, see Eberson *Electron Transfer Reactions in Organic Chemistry*; Springer: New York, 1987. For a review, see Eberson *Adv. Phys. Org. Chem.* **1982**, *18*, 79-185. For a review of multistage electron-transfer mechanisms, see Deuchert; Hünig *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 875-886 [*Angew. Chem. 90*, 927-938].

a metal that supplies the electrons. This kind of mechanism is found largely in three types of reaction:[5] (a) the oxidation or reduction of a free radical (oxidation to a positive or reduction to a negative ion), (b) the oxidation of a negative ion or the reduction of a positive ion to a comparatively stable free radical, and (c) electrolytic oxidations or reductions (an example is the Kolbe reaction, **4-38**). An important example of (b) is oxidation of amines and phenolate ions:



These reactions occur easily because of the relative stability of the radicals involved.[6] The single electron transfer mechanism (SET), which we have met several times (e.g., p. 307) is an important case.

2. *Hydride transfer.*[7] In some reactions a hydride ion is transferred to or from the substrate. The reduction of epoxides with $LiAlH_4$ is an example (**0-80**). Another is the Cannizzaro reaction (**9-69**). Reactions in which a carbocation abstracts a hydride ion belong in this category:[8]

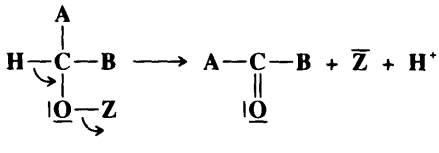
$$R^+ + R'H \longrightarrow RH + R'^+$$

3. *Hydrogen-atom transfer.* Many oxidation and reduction reactions are free-radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of **4-1** involves abstraction of hydrogen:

$$RH + Cl\bullet \longrightarrow R\bullet + HCl$$

This is the case for many of the reactions of Chapter 14.

4. *Formation of ester intermediates.* A number of oxidations involve the formation of an ester intermediate (usually of an inorganic acid), and then the cleavage of this intermediate:



$$\mathrm{H{-}\overset{A}{\underset{O-Z}{C}}{-}B} \longrightarrow \mathrm{A{-}\underset{\|}{\underset{O}{C}}{-}B} + \bar{Z} + H^+$$

Z is usually CrO_3H, MnO_3, or a similar inorganic acid moiety. One example of this mechanism was seen in **4-6**, where A was an alkyl or aryl group, B was OH, and Z was CrO_3H.

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[5] Littler; Sayce *J. Chem. Soc.* **1964**, 2545.

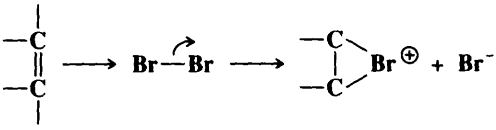
[6] For a review of the oxidation of phenols, see Mihailović; Čeković, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 505-592.

[7] For a review, see Watt *Adv. Phys. Org. Chem.* **1988**, *24*, 57-112.

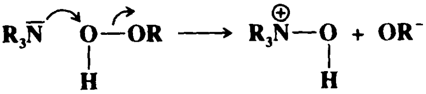
[8] For a review of these reactions, see Nenitzescu, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 463-520.

Another is the oxidation of a secondary alcohol to a ketone (**9-3**), where A and B are alkyl or aryl groups and Z is also CrO_3H. In the lead tetraacetate oxidation of glycols (**9-7**) the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. It should be noted that the cleavage shown is an example of an E2 elimination.

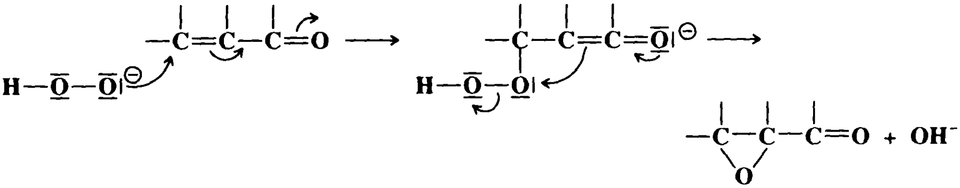
5. *Displacement mechanisms.* In these reactions the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an olefin (**5-26**).



An example from this chapter is found in **9-28**:



6. *Addition–elimination mechanisms.* In the reaction between α,β-unsaturated ketones and alkaline peroxide (**5-36**), the oxidizing agent adds to the substrate and then part of it is lost:



In this case the oxygen of the oxidizing agent is in oxidation state -1 and the OH^- departs with its oxygen in the -2 state, so it is reduced and the substrate oxidized. There are several reactions that follow this pattern of addition of an oxidizing agent and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with SeO_2 (**9-16**). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these six categories are not mutually exclusive.

REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with our practice in the other chapters.[9] This means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent, e.g., acid dichromate or $LiAlH_4$ (except for a discussion of selectivity of reducing agents, p. 1206). Some oxidizing or reducing agents are fairly specific in their action, attacking only

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[9] For a table of oxidation and reduction reactions, and the oxidizing and reducing agents for each, see Hudlicky *J. Chem. Educ.* **1977**, *54*, 100-106.

one or a few types of substrate. Others, like acid dichromate, permanganate, $LiAlH_4$, and catalytic hydrogenation, are much more versatile.[10]

When an oxidation or a reduction could be considered in a previous chapter, this was done. For example, the catalytic hydrogenation of olefins is a reduction, but it is also an addition to the C=C bond and was treated in Chapter 15. In this chapter are discussed only those reactions that do not fit into the nine categories of Chapters 10 to 18. An exception to this rule was made for reactions that involve elimination of hydrogen (**9-1** to **9-6**) which were not treated in Chapter 17 because the mechanisms generally differ from those in that chapter.

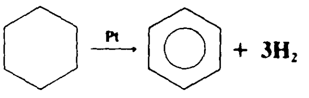
Oxidations[11]

The reactions in this section are classified into groups depending on the type of bond change involved. These groups are: (A) eliminations of hydrogen, (B) reactions involving cleavage of carbon–carbon bonds, (C) reactions involving replacement of hydrogen by oxygen, (D) reactions in which oxygen is added to the substrate, and (E) oxidative coupling.

A. Eliminations of Hydrogen

9-1 Aromatization of Six-Membered Rings

Hexahydro-terelimination



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[10] For books on certain oxidizing agents, see Mijs; de Jonge *Organic Synthesis by Oxidation with Metal Compounds*; Plenum: New York, 1986; Cainelli; Cardillo *Chromium Oxidations in Organic Chemistry*; Springer: New York, 1984; Arndt *Manganese Compounds as Oxidizing Agents in Organic Chemistry*; Open Court Publishing Company: La Salle, IL, 1981; Lee *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*; Open Court Publishing Company: La Salle, IL, 1980. For some reviews, see Curci *Adv. Oxygenated Processes* **1990,** *2*, 1-59 (dioxiranes); Adam; Curci; Edwards *Acc. Chem. Res.* **1989,** *22*, 205-211 (dioxiranes); Murray *Chem. Rev.* **1989,** *89*, 1187-1201, *Mol. Struc. Energ.* **1988,** *5*, 311-351 (dioxiranes); Kafafi; Martinez; Herron *Mol. Struc. Energ.* **1988,** *5*, 283-310 (dioxiranes); Krief; Hevesi *Organoselenium Chemistry I*; Springer: New York, 1988, pp. 76-103 (seleninic anhydrides and acids); Ley, in Liotta *Organoselenium Chemistry*; Wiley: New York, 1987, pp. 163-206 (seleninic anhydrides and acids); Barton; Finet *Pure Appl. Chem.* **1987,** *59*, 937-946 [bismuth(V)]; Fatiadi *Synthesis* **1987,** 85-127 ($KMnO_4$); Rubottom, in Trahanovsky, Ref. 2, pt. D, 1982, pp. 1-145 (lead tetraacetate); Fatiadi, in Pizey *Synthetic Reagents*, vol. 4; Wiley: New York, 1981, pp. 147-335, *Synthesis* **1974,** 229-272 (HIO_4); Fatiadi *Synthesis* **1976,** 65-104, 133-167 (MnO_2); Ogata; in Trahanovsky, Ref. 2, pt. C, pp. 295-342, 1978 (nitric acid and nitrogen oxides); McKillop, *Pure Appl. Chem.* **1975,** *43*, 463-479 (thallium nitrate); Pizey *Synthetic Reagents*, vol. 2, Wiley: New York, 1974, pp. 143-174 (MnO_2); George; Balachandran *Chem. Rev.* **1975,** *75*, 491-519 (nickel peroxide); Courtney; Swansborough *Rev. Pure Appl. Chem.* **1972,** *22*, 47-54 (ruthenium tetroxide); Ho *Synthesis* **1973,** 347-354 (ceric ion); Aylward *Q. Rev., Chem. Soc.* **1971,** *25*, 407-429 (lead tetraacetate); Meth-Cohn; Suschitzky *Chem. Ind.* (*London*) **1969,** 443-450 (MnO_2); Sklarz *Q. Rev. Chem. Soc.* **1967,** *21*, 3-28 (HIO_4); Korshunov; Vereshchagin *Russ. Chem. Rev.* **1966,** *35*, 942-957(MnO_2); Weinberg; Weinberg *Chem. Rev.* **1968,** *68*, 449-523 (electrochemical oxidation). For reviews of the behavior of certain reducing agents, see Keefer; Lunn *Chem. Rev.* **1989,** *89*, 459-502 (Ni–Al alloy); Málek *Org. React.* **1988,** *36*, 249-590, **1985,** *34*, 1-317 (metal alkoxyaluminum hydrides); Alpatova; Zabusova; Tomilov *Russ. Chem. Rev.* **1986,** *55*, 99-112 (solvated electrons generated electrochemically); Caubère *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 599-613 [*Angew. Chem.* *95*, 597-611] (modified sodium hydride); Nagai *Org. Prep. Proced. Int.* **1980,** *12*, 13-48 (hydrosilanes); Pizey *Synthetic Reagents*, vol. 1; Wiley: New York, 1974, pp. 101-294 ($LiAlH_4$); Winterfeldt *Synthesis* **1975,** 617-630 (diisobutylaluminum hydride and triisobutylaluminum); Hückel *Fortschr. Chem. Forsch.* **1966,** *6*, 197-250 (metals in ammonia or amines). For books on reductions with metal hydrides, see Seyden-Penne *Reductions by the Alumino- and Borohydrides*; VCH: New York, 1991; Štrouf; Časenský; Kubánek *Sodium Dihydrido-bis(2-methoxyethoxo)aluminate (SDMA)*; Elsevier: New York, 1985; Hajós *Complex Hydrides*; Elsevier: New York, 1979. Also see House *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972; Refs. 9 and 11.

[11] For books on oxidation reactions, see Hudlický *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990; Haines *Methods for the Oxidation of Organic Compounds*, 2 vols.; Academic Press: New York, 1985, 1988 [The first volume (we refer to this as Haines-1985) pertains to hydrocarbon substrates; the second (Haines-1988) mostly to oxygen- and nitrogen-containing substrates]; Chinn *Selection of Oxidants in Synthesis*; Marcel Dekker: New York, 1971; Augustine; Trecker *Oxidation*, 2 vols.; Marcel Dekker: New York, 1969, 1971; Ref. 2.

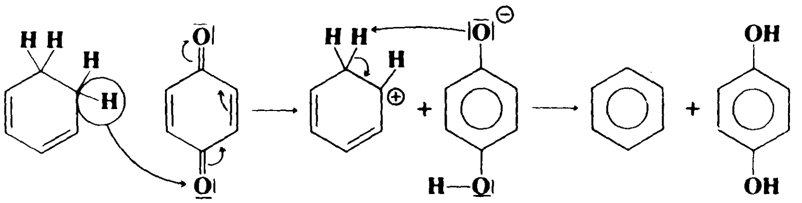
Six-membered alicyclic rings can be aromatized in a number of ways.[12] Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction can also be applied to heterocyclic five- and six-membered rings. Many groups may be present on the ring without interference, and even *gem*-dialkyl substitution does not always prevent the reaction: In such cases one alkyl group often migrates or is eliminated. However, more drastic conditions are usually required for this. In some cases OH and COOH groups are lost from the ring. Cyclic ketones are converted to phenols. Seven-membered and larger rings are often isomerized to six-membered aromatic rings, though this is not the case for partially hydrogenated azulene systems (which are frequently found in nature); these are converted to azulenes.

There are three types of reagents most frequently used to effect aromatization.

1. Hydrogenation catalysts,[13] such as platinum, palladium, nickel, etc. In this case the reaction is the reverse of double-bond hydrogenation (**5-9** and **5-11**), and presumably the mechanism is also the reverse, though not much is known.[14] Cyclohexene has been detected as an intermediate in the conversion of cyclohexane to benzene, using Pt.[15] The substrate is heated with the catalyst at about 300 to 350°C. The reactions can often be carried out under milder conditions if a hydrogen acceptor, such as maleic acid, cyclohexene, or benzene, is present to remove hydrogen as it is formed. The acceptor is reduced to the saturated compound. It has been reported that dehydrogenation of 1-methylcyclohexene-1-^{13}C over an alumina catalyst gave toluene with the label partially scrambled throughout the aromatic ring.[16]

2. The elements sulfur and selenium, which combine with the hydrogen evolved to give, respectively, H_2S and H_2Se. Little is known about this mechanism either.[17]

3. Quinones,[18] which become reduced to the corresponding hydroquinones. Two important quinones often used for aromatizations are chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[19] The latter is more reactive and can be used in cases where the substrate is difficult to dehydrogenate. It is likely that the mechanism involves a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion:[20]



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[12] For reviews, see Haines-1985, Ref. 11, pp. 16-22, 217-222; Fu; Harvey *Chem. Rev.* **1978,** *78,* 317-361; Valenta, in Bentley; Kirby *Elucidation of Chemical Structures by Physical and Chemical Methods* (vol. 4 of Weissberger *Techniques of Chemistry*), 2nd ed., pt. 2; Wiley: New York, 1973, pp. 1-76; House, Ref. 10, pp. 34-44.

[13] For a review, see Rylander *Organic Synthesis with Noble Metal Catalysts*; Academic Press: New York, 1973, pp. 1-59.

[14] For a discussion, see Tsai; Friend; Muetterties *J. Am. Chem. Soc.* **1982,** *104,* 2539. See also Augustine; Thompson *J. Org. Chem.* **1987,** *52,* 1911.

[15] Land; Pettiette-Hall; McIver; Hemminger *J. Am. Chem. Soc.* **1989,** *111,* 5970.

[16] Marshall; Miiller; Ihrig *Tetrahedron Lett.* **1973,** 3491.

[17] House; Orchin *J. Am. Chem. Soc.* **1960,** *82,* 639; Silverwood; Orchin *J. Org. Chem.* **1962,** *27,* 3401.

[18] For reviews, see Becker; Turner, in Patai; Rappoport *The Chemistry of the Quinonoid Compounds*, vol. 2, pt. 2; Wiley: New York, 1988, pp. 1351-1384; Becker, in Patai *The Chemistry of the Quinonoid Compounds*, vol. 1, pt. 1, Wiley: New York, 1974, pp. 335-423.

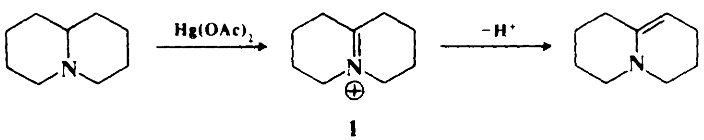
[19] For reviews of DDQ, see Turner, in Pizey, Ref. 10, vol. 3, 1977, pp. 193-225; Walker; Hiebert *Chem. Rev.* **1967,** *67,* 153-195.

[20] Braude; Jackman; Linstead; Lowe *J. Chem. Soc.* **1960,** 3123, 3133; Trost *J. Am. Chem. Soc.* **1967,** *89,* 1847; Ref. 18. See also Stoos; Roček *J. Am. Chem. Soc.* **1972,** *94,* 2719; Hashish; Hoodless *Can. J. Chem.* **1976,** *54,* 2261; Müller; Joly; Mermoud *Helv. Chim. Acta* **1984,** *67,* 105; Radtke; Hintze; Rösler; Heesing *Chem. Ber.* **1990,** *123,* 627.

Among other reagents[21] that have been used are atmospheric oxygen, MnO_2,[22] SeO_2, various strong bases,[23] chromic acid,[24] and activated charcoal.[25] The last-mentioned reagent also dehydrogenates cyclopentanes to cyclopentadienes. In some instances the hydrogen is not released as H_2 or transferred to an external oxidizing agent but instead serves to reduce another molecule of substrate. This is a disproportionation reaction and can be illustrated by the conversion of cyclohexene to cyclohexane and benzene.

OS **II,** 214, 423; **III,** 310, 358, 729, 807; **IV,** 536; **VI,** 731. Also see OS **III,** 329.

9-2 Dehydrogenations Yielding Carbon–Carbon Double Bonds
Dihydro-elimination



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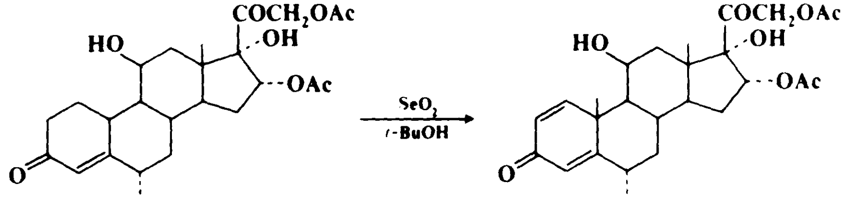
Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, though industrially mixtures of olefins are obtained in this way from mixtures of alkanes (generally by heating with chromia–alumina catalysts). There are, however, some notable exceptions, and it is not surprising that these generally involve cases where the new double bond can be in conjugation with a double bond or with an unshared pair of electrons already present.[26] One example is the synthesis developed by Leonard and co-workers,[27] in which tertiary amines give enamines when treated with mercuric acetate[28] (see the example above). In this case the initial product is the iminium ion **1** which loses a proton to give the enamine. In another example, the oxidizing agent SeO_2 can in certain cases convert a carbonyl compound to an α,β-unsaturated carbonyl compound by removing H_2[30] (though this reagent more often gives **9-16**). This reaction has been most often applied in the steroid series, an example being[31]



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[21] For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 93-97.

[22] See, for example, Leffingwell; Bluhm *Chem. Commun.* **1969,** 1151.

[23] For a review, see Pines; Stalick *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*; Academic Press: New York, 1977, pp. 483-503. See also Reetz; Eibach *Liebigs Ann. Chem.* **1978,** 1598; Trost; Rigby *Tetrahedron Lett.* **1978,** 1667.

[24] Müller; Pautex; Hagemann *Chimia* **1988,** *42*, 414.

[25] Shuikin; Naryschkina *J. Prakt. Chem.* **1961,** [4] *13*, 183.

[26] For a review, see Haines-1985, Ref. 11, pp. 6-16, 206-216. For lists of examples, with references, see Ref. 21, pp. 129-131.

[27] For example, see Leonard; Hay; Fulmer; Gash *J. Am. Chem. Soc.* **1955,** *77*, 439; Leonard; Musker *J. Am. Chem. Soc.* **1959,** *81*, 5631, **1960,** *82*, 5148.

[28] For reviews, see Haynes; Cook, in Cook *Enamines*, 2nd ed. Marcel Dekker: New York, 1988, pp. 103-163; Lee, in Augustine, Ref. 11, vol. 1, pp. 102-107.

[29] This reaction can also be accomplished with I_2: Wadsworth; Detty; Murray; Weidner; Haley *J. Org. Chem.* **1984,** *49*, 2676.

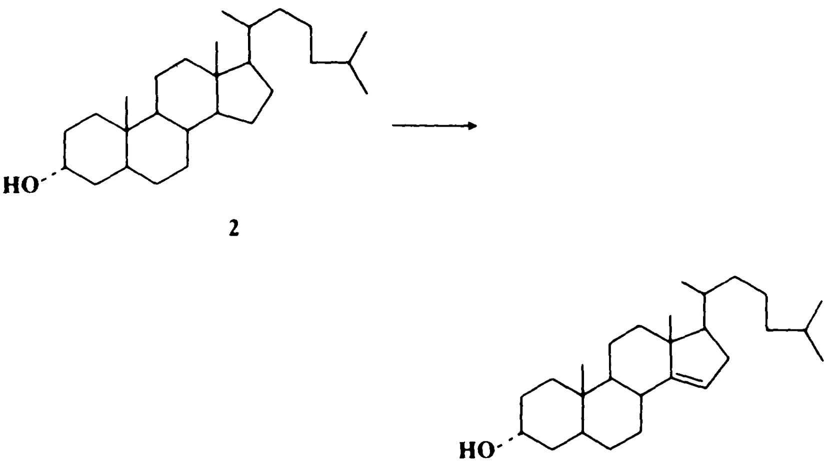
[30] For reviews, see Back, in Patai *The Chemistry of Organic Selenium and Tellurium Compounds*, pt. 2; Wiley: New York, 1987, pp. 91-213, pp. 110-114; Jerussi *Sel. Org. Transform.* **1970,** *1*, 301-326, pp. 315-321; Trachtenberg, in Augustine, Ref. 11, pp. 166-174.

[31] Bernstein; Littell *J. Am. Chem. Soc.* **1960,** *82*, 1235.

Similarly, SeO_2 has been used to dehydrogenate 1,4-diketones[32] ($RCOCH_2CH_2COR \rightarrow RCOCH{=}CHCOR$) and 1,2-diarylalkanes ($ArCH_2CH_2Ar \rightarrow ArCH{=}CHAr$). These conversions can also be carried out by certain quinones, most notably DDQ (see **9-1**).[19] Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone → cyclopentenone) by $PdCl_2$,[33] by $FeCl_3$,[34] and by benzeneseleninic anhydride[35] (this reagent also dehydrogenates lactones in a similar manner), among other reagents.

In an indirect method of achieving this conversion, the silyl enol ether of a simple ketone is treated with DDQ[36] or with triphenylmethyl cation[37] (for another indirect method, see **7-12**). Simple linear alkanes have been converted to alkenes by treatment with certain transition metal compounds.[38]

An entirely different approach to specific dehydrogenation has been reported by R. Breslow[39] and by J. E. Baldwin.[40] By means of this approach it was possible, for example, to convert 3α-cholestanol (**2**) to 5α-cholest-14-en-3α-ol (**3**), thus introducing a double bond at a specific site remote from any functional group.[41] This was accomplished by conversion of **2** to the ester **4**, followed by irradiation of **4**, which gave 55% **6**, which was then hydrolyzed



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[32] For example, see Barnes; Barton *J. Chem. Soc.* **1953,** 1419.

[33] Bierling; Kirschke; Oberender; Schultz *J. Prakt. Chem.* **1972,** *314,* 170; Kirschke; Müller; Timm *J. Prakt. Chem.* **1975,** *317,* 807; Mincione; Ortaggi; Sirna *Synthesis* **1977,** 773; Mukaiyama; Ohshima; Nakatsuka *Chem. Lett.* **1983,** 1207. See also Heck *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, pp. 103-110.

[34] Cardinale; Laan; Russell; Ward *Recl. Trav. Chim. Pays-Bas* **1982,** *101,* 199.

[35] Barton; Hui; Ley; Williams *J. Chem. Soc., Perkin Trans. 1* **1982,** 1919; Barton; Godfrey; Morzycki; Motherwell; Ley *J. Chem. Soc., Perkin Trans. 1* **1982,** 1947.

[36] Jung; Pan; Rathke; Sullivan; Woodbury *J. Org. Chem.* **1977,** *42,* 3961.

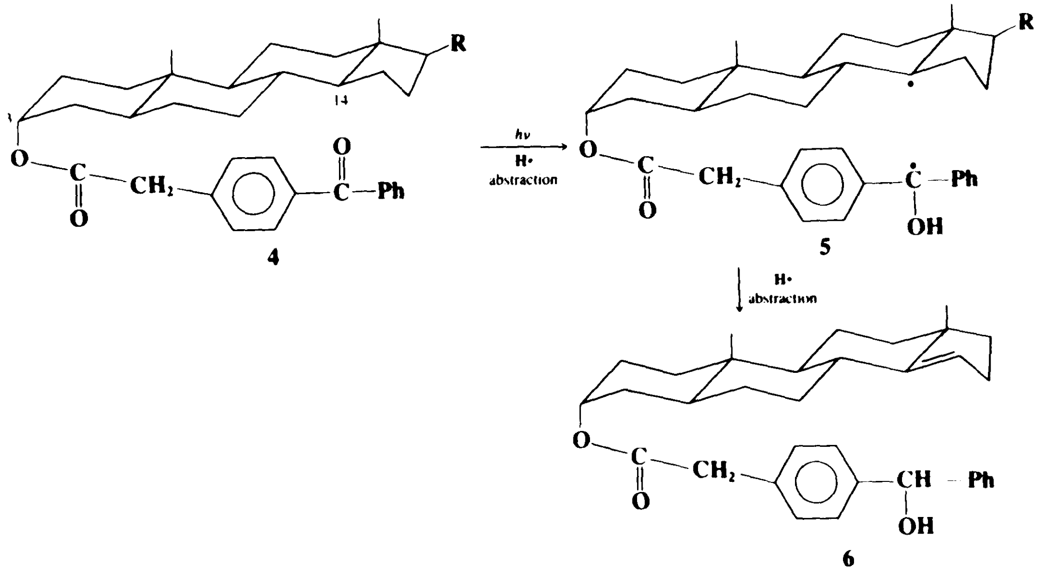
[37] Ryu; Murai; Hatayama; Sonoda *Tetrahedron Lett.* **1978,** 3455. For another method, which can also be applied to enol acetates, see Tsuji; Minami; Shimizu *Tetrahedron Lett.* **1983,** *24,* 5635, 5639.

[38] See Burchard; Felkin *Nouv. J. Chim.* **1986,** *10,* 673; Burk; Crabtree *J. Am. Chem. Soc.* **1987,** *109,* 8025; Renneke; Hill *New J. Chem.* **1987,** *11,* 763, *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 1526 [*Angew. Chem. 100,* 1583], *J. Am. Chem. Soc.* **1988,** *110,* 5461; Maguire; Boese; Goldman *J. Am. Chem. Soc.* **1989,** *111,* 7088; Sakakura; Ishida; Tanaka *Chem. Lett.* **1990,** 585; and references cited in these papers.

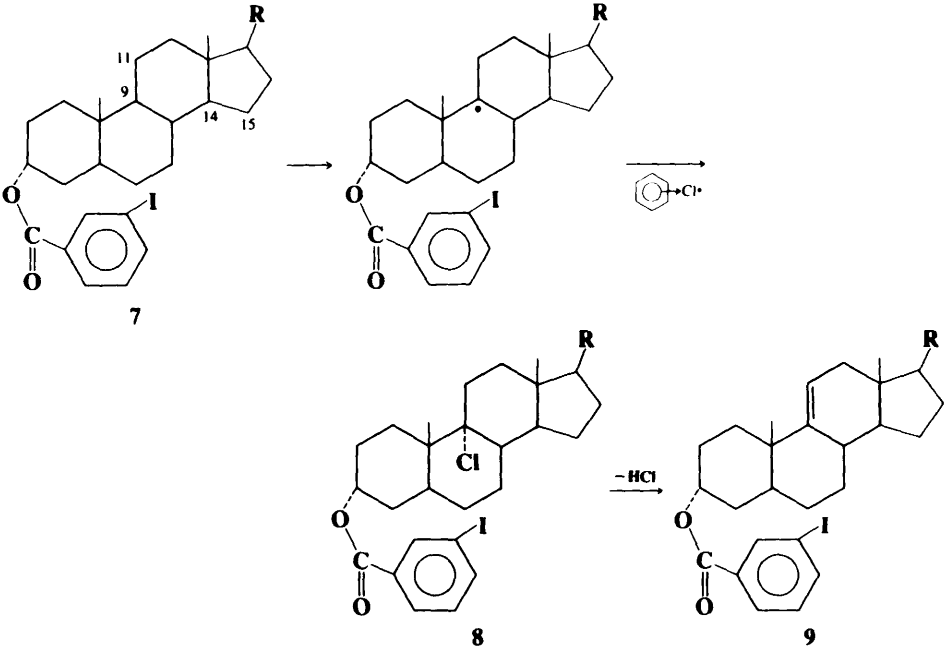
[39] Breslow; Baldwin *J. Am. Chem. Soc.* **1970,** *92,* 732. For reviews, see Breslow *Chemtracts: Org. Chem.* **1988,** *1,* 333-348, *Acc. Chem. Res.* **1980,** *13,* 170-177, *Isr. J. Chem.* **1979,** *18,* 187-191, *Chem. Soc. Rev.* **1972,** *1,* 553-580.

[40] Baldwin; Bhatnagar; Harper *Chem. Commun.* **1970,** 659.

[41] For other methods of introducing a remote double bond, see Čeković; Cvetković *Tetrahedron Lett.* **1982,** *23,* 3791; Czekay; Drewello; Schwarz *J. Am. Chem. Soc.* **1989,** *111,* 4561. See also Bégué *J. Org. Chem.* **1982,** *47,* 4268; Nagata; Saito *Synlett* **1990,** 291-300.



to **3**. The radiation excites the benzophenone portion of **4** (p. 246), which then abstracts hydrogen from the 14 position to give the diradical **5** which undergoes another internal abstraction to give **6**. In other cases, diradicals like **5** can close to a macrocyclic lactone (**9-16**). In an alternate approach,[42] a 9(11) double bond was introduced into a steroid nucleus by reaction of the *m*-iodo ester **7** with $PhICl_2$ and uv light, which results in hydrogen being



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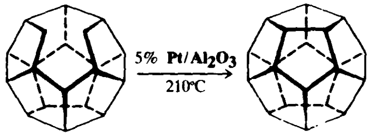
[42] Breslow; Corcoran; Snider; Doll; Khanna; Kaleya *J. Am. Chem. Soc.* **1977**, *99*, 905. For related approaches, see Wolner *Tetrahedron Lett.* **1979**, 4613; Breslow; Heyer *J. Am. Chem. Soc.* **1982**, *104*, 2045; Breslow; Guo *Tetrahedron Lett.* **1987**, *28*, 3187; Breslow; Brandl; Hunger; Adams *J. Am. Chem. Soc.* **1987**, *109*, 3799; Batra; Breslow *Tetrahedron Lett.* **1989**, *30*, 535; Orito; Ohto; Suginome *J. Chem. Soc., Chem. Commun.* **1990**, 1076.

abstracted regioselectively from the 9 position, resulting in chlorination at that position. Dehydrohalogenation of **8** gives the 9(11)-unsaturated steroid **9.** In contrast, use of the para isomer of **7** results in chlorination at the 14 position and loss of HCl gives the 14-unsaturated steroid. These reactions are among the very few ways to introduce functionality at a specific site remote from any functional group (see also **9-16**).

Certain 1,2-diarylalkenes ArCH═CHAr′ have been converted to the corresponding alkynes ArC≡CAr′ by treatment with *t*-BuOK in DMF.[42a]

A different kind of dehydrogenation was used in the final step of Paquette's synthesis of dodecahedrane:[43]



dodecahedrane

OS **V,** 428, **VII,** 4, 473.

9-3 Oxidation or Dehydrogenation of Alcohols to Aldehydes and Ketones
***C,O*-Dihydro-elimination**

$$\mathbf{RCH_2OH \xrightarrow[\text{chromite}]{\text{copper}} RCHO}$$

$$\mathbf{RCHOHR' \xrightarrow[H_2SO_4]{K_2Cr_2O_7} RCOR'}$$

Primary alcohols can be converted to aldehydes and secondary alcohols to ketones in four main ways:[44]

1. *With strong oxidizing agents.*[45] Secondary alcohols are easily oxidized to ketones by acid dichromate[46] at room temperature or slightly above. Though this is the most common reagent, many other strong oxidizing agents (e.g., KMnO$_4$, Br$_2$, MnO$_2$, ruthenium tetroxide,[47] etc.) have also been employed. A solution of chromic acid and sulfuric acid in water is known as the *Jones reagent.*[48] When secondary alcohols are dissolved in acetone, titration with the Jones reagent oxidizes them to ketones rapidly and in high yield without disturbing any double or triple bonds that may be present (see **9-10**) and without epimerizing an adjacent

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[42a] Akiyama; Nakatsuji; Nomura; Matsuda; Nakashima *J. Chem. Soc., Chem. Commun.* **1991,** 948.

[43] Paquette; Ternansky; Balogh; Kentgen *J. Am. Chem. Soc.* **1983,** *105*, 5446; Paquette; Weber; Kobayashi; Miyahara *J. Am. Chem. Soc.* **1988,** *110*, 8591. For a monograph on dodecahedrane and related compounds, see Paquette; Doherty *Polyquinane Chemistry;* Springer: New York, 1987. For reviews, see, in Olah *Cage Hydrocarbons*; Wiley: New York, 1990, the reviews by Paquette, pp. 313-352, and by Fessner; Prinzbach, pp. 353-405; Paquette *Chem. Rev.* **1989,** *89*, 1051-1065, *Top. Curr. Chem.* **1984,** *119*, 1-158, in Lindberg *Strategies and Tactics in Organic Synthesis*; Academic Press: New York, 1984, pp. 175-200.

[44] For reviews, see Hudlický, Ref. 11, pp. 114-126, 132-149; Haines-1988, Ref. 11, pp. 5-148, 326-390; Müller, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 469-538; Cullis; Fish, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 129-157. For a lengthy list of reagents, with references, see Ref. 21, pp. 604-615.

[45] For thorough discussions, see Lee, Ref. 28, pp. 56-81; and (with respect to chromium and managanese reagents) House, Ref. 10, pp. 257-273.

[46] Various forms of H$_2$CrO$_4$ and of CrO$_3$ are used for this reaction. For a review, see Cainelli; Cardillo, Ref. 10, pp. 118-216. For discussions, see Fieser; Fieser *Reagents for Organic Synthesis*, vol. 1; Wiley: New York, 1967, pp. 142-147, 1059-1064, and subsequent volumes in this series.

[47] For a review, see Lee; van den Engh, in Trahanovsky, Ref. 2, pt. B, pp. 197-222.

[48] Bowden; Heilbron; Jones; Weedon *J. Chem. Soc.* **1946,** 39; Bowers; Halsall; Jones; Lemin *J. Chem. Soc.* **1953,** 2548.

chiral center.[49] The Jones reagent also oxidizes primary allylic alcohols to the corresponding aldehydes.[50] Three other Cr(VI) reagents commonly used[51] are dipyridine Cr(VI) oxide (Collins's reagent),[52] pyridinium chlorochromate (Corey's reagent),[53] and pyridinium dichromate.[54] MnO_2 is also a fairly specific reagent for OH groups and is often used to oxidize allylic alcohols to α,β-unsaturated aldehydes or ketones. For acid-sensitive compounds CrO_3 in HMPA,[55] a CrO_3–pyridine complex,[56] or trimethylsilyl chromates[57] can be used. Sodium hypochlorite in acetic acid is useful for oxidizing larger amounts of secondary alcohols.[58] The oxidizing agent can be supported on a polymer.[59] Both chromic acid[60] and permanganate[61] have been used in this way (see p. 421). Phase transfer catalysis has also been used with permanganate,[62] chromic acid,[63] and ruthenium tetroxide.[64] Phase transfer catalysis is particularly useful because the oxidizing agents are insoluble in most organic solvents, while the substrates are generally insoluble in water (see p. 362). Ultrasound has been used for $KMnO_4$ oxidations.[65]

Most of these oxidizing agents have also been used to convert primary alcohols to aldehydes, but precautions must be taken that the aldehyde is not further oxidized to the carboxylic acid (**9-22**).[66] One way to halt oxidation is by distillation of the aldehyde as it is formed. The following are among the oxidizing agents that have been used to convert at least some primary alcohols to aldehydes:[67] dimethyl sulfoxide (see **9-20**), Collins's reagent, Corey's reagent, pyridinium dichromate, tetrapropylammonium perruthenate Pr_4N^+ RuO_4^-,[68] ceric ammonium nitrate (CAN),[69] $Na_2Cr_2O_7$ in water,[70] Ag_2CO_3-on-celite,[71] hot

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[49] For example, see Djerassi; Hart; Warawa *J. Am. Chem. Soc.* **1964,** *86*, 78.

[50] Harding; May; Dick *J. Org. Chem.* **1975,** *40*, 1664.

[51] For a comparative study of Jones's, Collins's, and Corey's reagents, see Warrener; Lee; Russell; Paddon-Row *Aust. J. Chem.* **1978,** *31*, 1113.

[52] Collins; Hess; Frank *Tetrahedron Lett.* **1968,** 3363; Ratcliffe; Rodehorst *J. Org. Chem.* **1970,** *35*, 4000; Stensiö *Acta Chem. Scand.* **1971,** *25*, 1125; Collins; Hess *Org. Synth. VI*, 644; Sharpless; Akashi *J. Am. Chem. Soc.* **1975,** *97*, 5927.

[53] Corey; Suggs *Tetrahedron Lett.* **1975,** 2647. For reviews of this and related reagents, see Luzzio; Guziec *Org. Prep. Proced. Int.* **1988,** *20*, 533-584; Piancatelli; Scettri; D'Auria *Synthesis* **1982,** 245-258. For an improved method of preparing this reagent, see Agarwal; Tiwari; Sharma *Tetrahedron* **1990,** *46*, 4417.

[54] Coates; Corrigan *Chem. Ind.* (*London*) **1969,** 1594; Corey; Schmidt *Tetrahedron Lett.* **1979,** 399; Czernecki; Georgoulis; Stevens; Vijayakumaran *Tetrahedron Lett.* **1985,** *26*, 1699.

[55] Cardillo; Orena; Sandri *Synthesis* **1976,** 394.

[56] Poos; Arth; Beyler; Sarett *J. Am. Chem. Soc.* **1953,** *75*, 422.

[57] Moiseenkov; Cheskis; Veselovskii; Veselovskii; Romanovich; Chizhov *J. Org. Chem. USSR* **1987,** *23*, 1646.

[58] Stevens; Chapman; Weller *J. Org. Chem.* **1980,** *45*, 2030. See also Schneider; Weber; Faller *J. Org. Chem.* **1982,** *47*, 364; Mohrig; Nienhuis; Linck; van Zoeren; Fox; Mahaffy *J. Chem. Educ.* **1985,** *62*, 519.

[59] For a review of oxidations and other reactions with supported reagents, see McKillop; Young *Synthesis* **1979,** 401-422.

[60] Cainelli; Cardillo; Orena; Sandri *J. Am. Chem. Soc.* **1976,** *98*, 6737; Santaniello; Ponti; Manzocchi *Synthesis* **1978,** 534. See also San Filippo; Chern *J. Org. Chem.* **1977,** *42*, 2182.

[61] Regen; Koteel *J. Am. Chem. Soc.* **1977,** *99*, 3837; Noureldin; Lee *Tetrahedron Lett.* **1981,** *22*, 4889. See also Menger; Lee *J. Org. Chem.* **1979,** *44*, 3446.

[62] For a review of phase transfer assisted permanganate oxidations, see Lee, in Trahanovsky, Ref. 2, pt. D, pp. 147-206.

[63] See for example, Hutchins; Natale; Cook *Tetrahedron Lett.* **1977,** 4167; Landini; Montanari; Rolla *Synthesis* **1979,** 134; Pletcher; Tait *J. Chem. Soc., Perkin Trans. 2* **1979,** 788.

[64] Morris; Kiely *J. Org. Chem.* **1987,** *52*, 1149.

[65] Yamawaki; Sumi; Ando; Hanfusa *Chem. Lett.* **1983,** 379.

[66] Though ketones are much less susceptible to further oxidation than aldehydes, such oxidation is possible (**9-8**), and care must be taken to avoid it, usually by controlling the temperature and/or the oxidizing agent.

[67] For some other reagents, not mentioned here, see Kaneda; Kawanishi; Teranishi *Chem. Lett.* **1984,** 1481; Semmelhack; Schmid; Cortés; Chou *J. Am. Chem. Soc.* **1984,** *106*, 3374; Cameron; Bocarsly *J. Am. Chem. Soc.* **1985,** *107*, 6116; Anelli; Biffi; Montanari; Quici *J. Org. Chem.* **1987,** *52*, 2559; Bilgrien; Davis; Drago *J. Am. Chem. Soc.* **1987,** *109*, 3786; Nishiguchi; Asano *J. Org. Chem.* **1989,** *54*, 1531; Dess; Martin *J. Am. Chem. Soc.* **1991,** *113*, 7277. See also Ref. 21, pp. 604-615.

[68] Griffith; Ley; Whitcombe; White *J. Chem. Soc., Chem. Commun.* **1987,** 1625; Griffith; Ley *Aldrichimica Acta* **1990,** *23*, 13-19.

[69] Trahanovsky; Young *J. Chem. Soc.* **1965,** 5777; Trahanovsky; Young; Brown *J. Org. Chem.* **1967,** *32*, 3865.

[70] Lee; Spitzer *J. Org. Chem.* **1970,** *35*, 3589. See also Rao; Filler *J. Org. Chem.* **1974,** *39*, 3304; Lou *Synth. Commun.* **1989,** *19*, 1841, *Chem. Ind. (London)* **1989,** 312.

[71] Fetizon; Golfier *C. R. Acad. Sci., Ser. C* **1968,** *267*, 900; Kakis; Fetizon; Douchkine; Golfier; Mourgues; Prange *J. Org. Chem.* **1974,** *39*, 523.

HNO_3 in aqueous glyme,[72] O_2–pyridine–CuCl,[73] $Pb(OAc)_4$–pyridine,[74] and benzoyl peroxide–$NiBr_2$.[75] Most of these reagents also oxidize secondary alcohols to ketones. Reagents that can be used specifically to oxidize a secondary OH group in the presence of a primary OH group[76] are Cl_2–pyridine,[77] H_2O_2–ammonium molybdate,[78] $NaBrO_3$–CAN,[79] and NaOCl in HOAc,[80] while $RuCl_2(PPh_3)_3$–benzene,[81] osmium tetroxide,[82] 2,2′-bipyridylchromium peroxide,[83] and Br_2–$Ni(OBz)_2$[84] oxidize primary OH groups in the presence of a secondary OH group.[85] Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in the presence of saturated alcohols by the use of potassium manganate K_2MnO_4 under phase transfer conditions.[86] On the other hand, Fremy's salt (see **9-4**) selectively oxidizes benzylic alcohols and not allylic or saturated ones.[87] Benzylic alcohols can also be oxidized to aldehydes by NH_4NO_3 or $NaNO_2$ in aqueous F_3CCOOH,[88] by H_2O_2–HBr,[89] and by *m*-chloroperbenzoic acid–HCl–DMF,[90] among other reagents. Certain zirconocene complexes can selectively oxidize only one OH group of a diol, even if both are primary.[91]

2. *By catalytic dehydrogenation.* For the conversion of primary alcohols to aldehydes, dehydrogenation catalysts have the advantage over strong oxidizing agents that further oxidation to the carboxylic acid is prevented. Copper chromite is the agent most often used, but other catalysts, e.g., silver and copper, have also been employed. Many ketones have also been prepared in this manner. Catalytic dehydrogenation is more often used industrially than as a laboratory method. However, convenient laboratory procedures using copper oxide,[92] Raney nickel,[93] and palladium acetate (under phase transfer conditions)[94] have been reported.

3. *The Oppenauer oxidation.* When a ketone in the presence of base is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation.*[95] This is the reverse of the Meerwein–Pondorf–Verley reaction (**6-25**), and the mechanism is also the reverse. The ketones most commonly used are acetone, butanone, and cyclohexanone. The most common base is aluminum *t*-butoxide. The chief advantage of the method is its high selectivity. Although the method is most often used for the preparation of ketones, it has also been used for aldehydes.

4. *With N-bromosuccinimide or related compounds.* These compounds are chemose-

[72] McKillop; Ford *Synth. Commun.* **1972,** *2,* 307.

[73] Jallabert; Riviere *Tetrahedron Lett.* **1977,** 1215.

[74] Partch *Tetrahedron Lett.* **1964,** 3071; Partch; Monthony *Tetrahedron Lett.* **1967,** 4427. See also Brocksom; Ferreira *J. Chem. Res. (S)* **1980,** 412; Mihailović; Konstantinović; Vukićević *Tetrahedron Lett.* **1986,** *27,* 2287.

[75] Doyle; Patrie; Williams *J. Org. Chem.* **1979,** *44,* 2955.

[76] For other methods, see Jung; Speltz *J. Am. Chem. Soc.* **1976,** *98,* 7882; Jung; Brown *Tetrahedron Lett.* **1978,** 2771; Kaneda; Kawanishi; Jitsukawa; Teranishi *Tetrahedron Lett.* **1983,** *24,* 5009; Siedlecka; Skarżewski; Młochowski *Tetrahedron Lett.* **1990,** *31,* 2177.

[77] Wicha; Zarecki *Tetrahedron Lett.* **1974,** 3059.

[78] Trost; Masuyama *Isr. J. Chem.* **1984,** *24,* 134. For a method involving H_2O_2 and another catalyst, see Sakata; Ishii *J. Org. Chem.* **1991,** *56,* 6233.

[79] Tomioka; Oshima; Nozaki *Tetrahedron Lett.* **1982,** *23,* 539.

[80] Stevens; Chapman; Stubbs; Tam; Albizati *Tetrahedron Lett.* **1982,** *23,* 4647.

[81] Tomioka; Takai; Oshima; Nozaki *Tetrahedron Lett.* **1981,** *22,* 1605.

[82] Maione; Romeo *Synthesis* **1984,** 955.

[83] Firouzabadi; Iranpoor; Kiaeezadeh; Toofan *Tetrahedron* **1986,** *42,* 719

[84] Doyle; Bagheri *J. Org. Chem.* **1981,** *46,* 4806; Doyle; Dow; Bagheri; Patrie *J. Org. Chem.* **1983,** *48,* 476.

[85] For a list of references to the selective oxidation of various types of alcohol, see Kulkarni; Mathew T *Tetrahedron* **1990,** *31,* 4497.

[86] Kim; Chung; Cho; Hahn *Tetrahedron Lett.* **1989,** *30,* 2559. See also Kim; Song; Lee; Hahn *Tetrahedron Lett.* **1986,** *27,* 2875.

[87] Morey; Dzielenziak; Saa *Chem. Lett.* **1985,** 263.

[88] Rodkin; Shtern; Cheprakov; Makhon'kov; Mardaleishvili; Beletskaya *J. Org. Chem. USSR* **1988,** *24,* 434.

[89] Dakka; Sasson *Bull. Soc. Chim. Fr.* **1988,** 756.

[90] Kim; Jung; Kim; Ryu *Synth. Commun.* **1990,** *20,* 637.

[91] Nakano; Terada; Ishii; Ogawa *Synthesis* **1986,** 774.

[92] Sheikh; Eadon *Tetrahedron Lett.* **1972,** 257.

[93] Krafft; Zorc *J. Org. Chem.* **1986,** *51,* 5482.

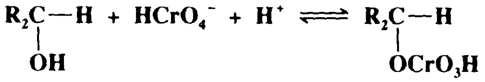
[94] Choudary; Reddy; Kantam; Jamil *Tetrahedron Lett.* **1985,** *26,* 6257.

[95] For a review, see Djerassi *Org. React.* **1951,** *6,* 207-272.

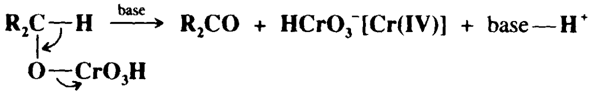
lective oxidizing agents and often oxidize OH groups without disturbing other oxidizable groups.[96] N-Bromosuccinimide does not oxidize aliphatic primary alcohols, but N-chlorosuccinimide does. With these reagents it is often possible to oxidize only one of several OH groups that may be present in a molecule. The combination of N-iodosuccinimide and Bu_4N^+ I^- oxidizes primary (to aldehydes) and secondary alcohols in high yields.[97]

Primary and secondary alcohols can also be oxidized, indirectly, through their esters (see **9-20**). In some cases, isolation of the ester is not required and the alcohol can then be oxidized to the aldehyde or ketone in one step.

The mechanism of oxidation with acid dichromate has been intensely studied.[98] The currently accepted mechanism is essentially that proposed by Westheimer.[99] The first two steps constitute an example of category 4 (p. 1160).



$$\underset{OH}{R_2C{-}H} + HCrO_4^- + H^+ \rightleftharpoons \underset{OCrO_3H}{R_2C{-}H}$$



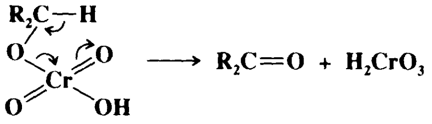
$$\underset{O{-}CrO_3H}{R_2C{-}H} \xrightarrow{\text{base}} R_2CO + HCrO_3^-[Cr(IV)] + \text{base}{-}H^+$$

$$R_2CHOH + Cr(IV) \longrightarrow R_2\dot{C}OH + Cr(III)$$

$$R_2\dot{C}OH + Cr(VI) \longrightarrow R_2CO + Cr(V)$$

$$R_2CHOH + Cr(V) \longrightarrow R_2CO + Cr(III)$$

The base in the second step may be water, though it is also possible[100] that in some cases no external base is involved and that the proton is transferred directly to one of the CrO_3H oxygens in which case the Cr(IV) species produced would be H_2CrO_3. Part of the evidence for this mechanism was the isotope effect of about 6 found on use of MeCDOHMe, showing that the α hydrogen is removed in the rate-determining step.[101] Note that, as in **4-6,** the substrate is oxidized by three different oxidation states of chromium.[102]



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[96] For a review, see Filler *Chem. Rev.* **1963,** *63*, 21-43, pp. 22-28.

[97] Hanessian; Wong; Therien *Synthesis* **1981,** 394.

[98] See Müller *Chimia* **1977,** *31*, 209-218; Wiberg, in Wiberg, Ref. 2, pp. 142-170; Venkatasubramanian *J. Sci. Ind. Res.* **1963,** *22*, 397-400; Waters, Ref. 2, pp. 49-71; Stewart, Ref. 2, pp. 37-48; Durand; Geneste; Lamaty; Moreau; Pomarès; Roque *Recl. Trav. Chim. Pays-Bas* **1978,** *97*, 42; Sengupta; Samanta; Basu *Tetrahedron* **1985,** *41*, 205.

[99] Westheimer *Chem. Rev.* **1949,** *45*, 419-451, p. 434; Holloway; Cohen; Westheimer *J. Am. Chem. Soc.* **1951,** *73*, 65.

[100] Kwart; Francis *J. Am. Chem. Soc.* **1959,** *81*, 2116; Stewart; Lee *Can. J. Chem.* **1964,** *42*, 439; Awasthy; Roček; Moriarty *J. Am. Chem. Soc.* **1967,** *89*, 5400; Kwart; Nickle *J. Am. Chem. Soc.* **1973,** *95*, 3394, **1974,** *96*, 7572, **1979,** *98*, 2881; Sengupta; Samanta; Basu *Tetrahedron* **1986,** *42*, 681. See also Müller; Perlberger *Helv. Chim. Acta* **1974,** *57*, 1943; Agarwal; Tiwari; Sharma *Tetrahedron* **1990,** *46*, 1963.

[101] Westheimer; Nicolaides *J. Am. Chem. Soc.* **1949,** *71*, 25. For other evidence, see Brownell; Leo; Chang; Westheimer *J. Am. Chem. Soc.* **1960,** *82*, 406; Roček; Westheimer; Eschenmoser; Moldoványi; Schreiber *Helv. Chim. Acta* **1962,** *45*, 2554; Lee; Stewart *J. Org. Chem.* **1967,** *32*, 2868; Wiberg; Schäfer *J. Am. Chem. Soc.* **1967,** *89*, 455; **1969,** *91*, 927, 933; Müller *Helv. Chim. Acta* **1970,** *53*, 1869, **1971,** *54*, 2000, Lee; Raptis *Tetrahedron* **1973,** *29*, 1481.

[102] Rahman; Roček *J. Am. Chem. Soc.* **1971,** *93*, 5455, 5462; Doyle; Swedo; Roček *J. Am. Chem. Soc.* **1973,** *95*, 8352; Wiberg; Mukherjee *J. Am. Chem. Soc.* **1974,** *96*, 1884, 6647.

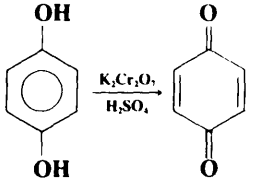
With other oxidizing agents, mechanisms are less clear.[103] It seems certain that some oxidizing agents operate by a hydride-shift mechanism,[104] e.g., dehydrogenation with triphenylmethyl cation[105] and the Oppenauer oxidation, and some by a free-radical mechanism, e.g., oxidation with $S_2O_8^{2-}$ [106] and with VO_2^+.[107] A summary of many proposed mechanisms is given by Littler.[108]

Secondary alkyl ethers can be oxidized to ketones by bromine (e.g., $Me_2CHOCHMe_2 + Br_2 \rightarrow Me_2CO$).[109] Primary alkyl ethers give carboxylic acids (**9-22**) with bromine, but can be cleaved to aldehydes with 1-chlorobenzotriazole.[110]

OS **I,** 87, 211, 241, 340; **II,** 139, 541; **III,** 37, 207; **IV,** 189, 192, 195, 467, 813, 838; **V,** 242, 310, 324, 692, 852, 866; **VI,** 218, 220, 373, 644, 1033; **VII,** 102, 112, 114, 177, 258, 297; **65,** 81; **68,** 175; **69,** 212. Also see OS **IV,** 283; **65,** 243; **66,** 14.

9-4 Oxidation of Phenols and Aromatic Amines to Quinones

1/*O*,6/*O*-Dihydro-elimination



Ortho and para diols are easily oxidized to *ortho*- and *para*-quinones, respectively.[111] Either or both OH groups can be replaced by NH_2 groups to give the same products, though for the preparation of *ortho*-quinones only OH groups are normally satisfactory. The reaction has been successfully carried out with other groups para to OH or NH_2; halogen, OR, Me, *t*-Bu, and even H, though with the last yields are poor. Many oxidizing agents have been used: acid dichromate,[112] silver oxide, silver carbonate, lead tetraacetate, HIO_4, and atmospheric oxygen, to name a few. A particularly effective reagent for rings with only one OH or NH_2 group is $(KSO_3)_2N—O\bullet$ (dipotassium nitrosodisulfonate; Fremy's salt), which is a stable free radical.[113] Phenols, even some whose para positions are unoccupied, can be oxidized to *ortho*-quinones with diphenylseleninic anhydride.[114]

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[103] For a review, see Cockerill; Harrison, in Patai *The Chemistry of Functional Groups, Supplement A*, pt. 1; Wiley: New York, 1977, pp. 264-277.

[104] See Barter; Littler *J. Chem. Soc. B.* **1967,** 205. For evidence that oxidation by HNO_2 involves a hydride shift, see Moodie; Richards *J. Chem. Soc., Perkin Trans. 2* **1986,** 1833; Ross; Gu; Hum; Malhotra *Int. J. Chem. Kinet.* **1986,** *18*, 1277.

[105] Bonthrone; Reid *J. Chem. Soc.* **1959,** 2773.

[106] Ball; Crutchfield; Edwards *J. Org. Chem.* **1960,** *25*, 1599; Bida; Curci; Edwards *Int. J. Chem. Kinet.* **1973,** *5*, 859; Snook; Hamilton *J. Am. Chem. Soc.* **1974,** *96*, 860; Walling; Camaioni *J. Org. Chem.* **1978,** *43*, 3266; Clerici; Minisci; Ogawa; Surzur *Tetrahedron Lett.* **1978,** 1149; Beylerian; Khachatrian *J. Chem. Soc., Perkin Trans. 2* **1984,** 1937.

[107] Littler; Waters *J. Chem. Soc.* **1959,** 4046.

[108] Littler *J. Chem. Soc.* **1962,** 2190.

[109] Deno; Potter *J. Am. Chem. Soc.* **1967,** *89*, 3550, 3555. See also Miller, Wolf; Mayeda *J. Am. Chem. Soc.* **1971,** *93*, 3306; Saigo; Morikawa; Mukaiyama *Chem. Lett.* **1975,** 145; Olah; Gupta; Fung *Synthesis* **1980,** 897.

[110] Pojer *Aust. J. Chem.* **1980,** *32*, 2787.

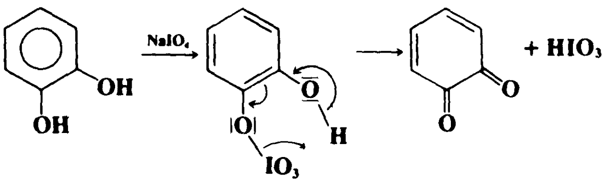
[111] For reviews, see Haines-1988, Ref. 11, pp. 305-323, 438-447; Naruta; Maruyama in Patai, Rappoport, Ref. 18, pt. 1, pp. 247-276; Thomson, in Patai, Ref. 18, pt. 1, pp. 112-132.

[112] For a review of this oxidation with chromium reagents, see Cainelli; Cardillo, Ref. 10, pp. 92-117.

[113] For a review of oxidation with this salt, see Zimmer; Lankin; Horgan *Chem. Rev.* **1971,** *71*, 229-246.

[114] Barton; Brewster; Ley; Rosenfeld *J. Chem. Soc., Chem. Commun.* **1976,** 985; Barton; Ley, in *Further Perspectives in Organic Chemistry*; North Holland Publishing Co.: Amsterdam, 1979, pp. 53-66. For another way of accomplishing this, see Krohn; Rieger; Khanbabaee *Chem. Ber.* **1989,** *122*, 2323.

Less is known about the mechanism than is the case for **9-3**, but, as in that case, it seems to vary with the oxidizing agent. For oxidation of catechol with $NaIO_4$, it was found that the reaction conducted in $H_2{}^{18}O$ gave unlabeled quinone,[115] so the following mechanism[116] was proposed:



When catechol was oxidized with MnO_4^- under aprotic conditions, a semiquinone radical ion intermediate was involved.[117] For autoxidations (i.e., with atmospheric oxygen) a free-radical mechanism is known to operate.[118]

OS **I,** 383, 482, 511; **II,** 175, 254, 430, 553; **III,** 663, 753; **IV,** 148; **VI,** 412, 480, 1010.

9-5 Dehydrogenation of Amines

1/1/*N*,2/2/*C*-Tetrahydro-bielimination

$$RCH_2NH_2 \xrightarrow[2.\,H_2O]{1.\,IF_5} RCN$$

Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out with a variety of reagents, among others, IF_5,[119] lead tetraacetate,[120] nickel peroxide,[121] NaOCl in micelles,[122] $K_2S_2O_8$–$NiSO_4$,[123] and CuCl–O_2–pyridine.[124] Several methods have been reported for the dehydrogenation of secondary amines to imines.[125] Among them[126] are treatment with(1) iodosylbenzene PhIO alone or in the presence of a ruthenium complex,[127] (2) Me_2SO and oxalyl chloride,[128] and (3) *t*-BuOOH and a rhenium catalyst.[129]

A reaction that involves dehydrogenation to an imine which then reacts further is the reaction of primary or secondary amines with palladium black.[130] The imine initially formed by the dehydrogenation reacts with another molecule of the same or a different amine to give an aminal, which loses NH_3 or RNH_2 to give a secondary or tertiary amine. An example

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[115] Adler; Falkehag; Smith *Acta Chem. Scand.* **1962,** *16,* 529.

[116] This mechanism is an example of category 4 (p. 1160).

[117] Bock; Jaculi *Angew. Chem. Int. Ed. Engl.* **1984,** *23,* 305 [*Angew. Chem. 96,* 298].

[118] Sheldon; Kochi *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981, pp. 368-381; Walling *Free Radicals in Solution*; Wiley: New York, 1957, pp. 457-461.

[119] Stevens *J. Org. Chem.* **1961,** *26,* 2531.

[120] Stojiljković; Andrejević; Mihailović *Tetrahedron* **1967,** *23,* 721.

[121] Nakagawa; Tsuji *Chem. Pharm. Bull.* **1963,** *11,* 296. See also Xu; Yamaguchi; Tanabe *Chem. Lett.* **1988,** 281.

[122] Juršić *J. Chem. Res. (S)* **1988,** 168.

[123] Yamazaki; Yamazaki *Bull. Chem. Soc. Jpn.* **1990,** *63,* 301.

[124] Kametani; Takahashi; Ohsawa; Ihara *Synthesis* **1977,** 245; Capdevielle; Lavigne; Maumy *Synthesis* **1989,** 453, *Tetrahedron* **1990,** 2835; Capdevielle; Lavigne; Sparfel; Baranne-Lafont; Cuong; Maumy *Tetrahedron Lett.* **1990,** *31,* 3305.

[125] For a review, see Dayagi; Degani, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond*; Wiley: New York, 1970, pp. 117-124.

[126] For other methods, see Cornejo; Larson; Mendenhall *J. Org. Chem.* **1985,** *50,* 5382; Nishinaga; Yamazaki; Matsuura *Tetrahedron Lett.* **1988,** *29,* 4115.

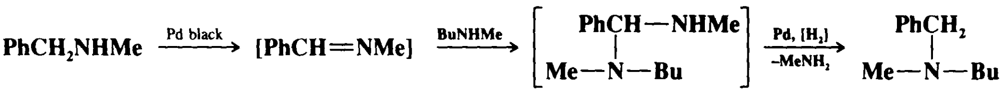
[127] Müller; Gilabert *Tetrahedron* **1988,** *44,* 7171.

[128] Keirs; Overton *J. Chem. Soc., Chem. Commun.* **1987,** 1660.

[129] Murahashi; Naota; Taki *J. Chem. Soc., Chem. Commun.* **1985,** 613.

[130] Murahashi; Yoshimura; Tsumiyama; Kojima *J. Am. Chem. Soc.* **1983,** *105,* 5002. See also Wilson; Laine *J. Am. Chem. Soc.* **1985,** *107,* 361.

is the reaction between N-methylbenzylamine and butylmethylamine, which produces 95% N-methyl-N-butylbenzylamine.



$$\mathrm{PhCH_2NHMe} \xrightarrow{\text{Pd black}} [\mathrm{PhCH{=}NMe}] \xrightarrow{\text{BuNHMe}} \left[\begin{array}{c} \mathrm{PhCH{-}NHMe} \\ | \\ \mathrm{Me{-}N{-}Bu} \end{array}\right] \xrightarrow[\text{-MeNH}_2]{\text{Pd, [H}_2\text{]}} \begin{array}{c} \mathrm{PhCH_2} \\ | \\ \mathrm{Me{-}N{-}Bu} \end{array}$$

Another method for the conversion of primary to secondary amines ($2RNH_2 \rightarrow R_2NH$) involves treatment with a catalytic amount of sodium hydride.[131] This reaction also involves an imine intermediate.

9-6 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines
1/*N*,2/*N*-Dihydro-elimination

$$\mathrm{Ar{-}NH{-}NH{-}Ar} \xrightarrow{\text{NaOBr}} \mathrm{Ar{-}N{=}N{-}Ar}$$

N,N'-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, HgO,[132] $K_3Fe(CN)_6$ under phase transfer conditions,[133] benzeneseleninic anhydride,[134] MnO_2 (this reagent yields cis azobenzenes),[135] $CuCl_2$, and air and NaOH.[136] The reaction is also applicable to N,N'-dialkyl- and N,N'-diacylhydrazines. Hydrazines (both alkyl and aryl) substituted on only one side also give azo compounds,[137] but these are unstable and decompose to nitrogen and the hydrocarbon:

$$\mathrm{Ar{-}NH{-}NH_2} \longrightarrow [\mathrm{Ar{-}N{=}NH}] \longrightarrow \mathrm{ArH} + \mathrm{N_2}$$

When hydrazones are oxidized with HgO, Ag_2O, MnO_2, lead tetraacetate, or certain other oxidizing agents, diazo compounds are obtained[138] (see also **7-28**):

$$\mathrm{R_2C{=}N{-}NH_2} \xrightarrow{\text{HgO}} \mathrm{R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}}$$

Hydrazones of the form $ArCH{=}NNH_2$ react with HgO in solvents such as diglyme or ethanol to give nitriles ArCN.[139] Aromatic hydroxylamines are easily oxidized to nitroso compounds, most commonly by acid dichromate.[140]

$$\mathrm{Ar{-}NH{-}OH} \xrightarrow{\text{CrO}_3} \mathrm{Ar{-}N{=}O}$$

OS **II,** 496; **III,** 351, 356, 375, 668; **IV,** 66, 411; **V,** 96, 160, 897; **VI,** 78, 161, 334, 392, 803, 936; **VII,** 56. Also see OS **V,** 258.

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[131] Richey; Erickson *Tetrahedron Lett.* **1972,** 2807; Erickson; Richey *Tetrahedron Lett.* **1972,** 2811.

[132] For a review of HgO, see Pizey, Ref. 10, vol. 1, 1974, pp. 295-319.

[133] Dimroth; Tüncher *Synthesis* **1977,** 339.

[134] Barton; Lester; Ley *J. Chem. Soc., Chem. Commun.* **1978,** 276; Back *J. Chem. Soc., Chem. Commun.* **1978,** 278.

[135] Hyatt *Tetrahedron Lett.* **1977,** 141.

[136] For a review, see Newbold, in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1; Wiley: New York, 1975, pp. 543-557, 564-573.

[137] See Mannen; Itano *Tetrahedron* **1973,** *29*, 3497.

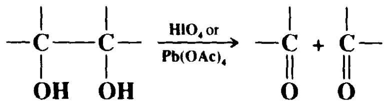
[138] For a review, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 233-256.

[139] Mobbs; Suschitzky *Tetrahedron Lett.* **1971,** 361.

[140] For a review, see Hudlický, Ref. 11, pp. 231-232.

B. Oxidations Involving Cleavage of Carbon–Carbon Bonds[141]

9-7 Oxidative Cleavage of Glycols and Related Compounds
2/O-De-hydrogen-uncoupling



$$\underset{\text{OH}}{\overset{|}{\underset{|}{-\text{C}}}}-\underset{\text{OH}}{\overset{|}{\underset{|}{\text{C}-}}} \xrightarrow[\text{Pb(OAc)}_4]{\text{HIO}_4\text{ or}} \underset{\text{O}}{\overset{|}{\underset{\|}{-\text{C}}}} + \underset{\text{O}}{\overset{|}{\underset{\|}{\text{C}-}}}$$

1,2-Glycols are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.[142] The products are 2 moles of aldehyde, or 2 moles of ketone, or 1 mole of each, depending on the groups attached to the two carbons. The yields are so good that olefins are often converted to glycols (**5-35**) and then cleaved with HIO_4 or $Pb(OAc)_4$ rather than being cleaved directly with ozone (**9-9**) or dichromate or permanganate (**9-10**). A number of other oxidizing agents also give the same products, among them[143] activated MnO_2,[144] thallium(III) salts,[145] pyridinium chlorochromate,[146] and O_2 catalyzed by Co(III) salts.[147] Permanganate, dichromate, and several other oxidizing agents[148] also cleave glycols, giving carboxylic acids rather than aldehydes, but these reagents are seldom used synthetically. Electrochemical oxidation is an efficient method, and is useful not only for diols, but also for their mono- and dimethoxy derivatives.[149]

The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water and lead tetraacetate in organic solvents. When three or more OH groups are located on adjacent carbons, the middle one (or ones) is converted to formic acid.

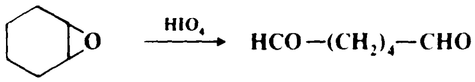
Similar cleavage is undergone by other compounds that contain oxygens or nitrogens on adjacent carbons:

β-Amino alcohols

α-Hydroxy aldehydes and ketones

α-Diketones α-Keto aldehydes Glyoxal

α-Diketones and α-hydroxy ketones are also cleaved by alkaline H_2O_2.[150] HIO_4 has been used to cleave epoxides to aldehydes,[151] e.g.,



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[141] For a review, see Bentley, in Bentley; Kirby, Ref. 12, pp. 137-254.

[142] For reviews covering both reagents, see Haines-1988, Ref. 11, pp. 277-301, 432-437; House, Ref. 10, pp. 3353-363; Perlin, in Augustine *Oxidation*, vol. 1; Marcel Dekker: New York, 1969, pp. 189-212; Bunton, in Wiberg, Ref. 2, pp. 367-407. For reviews of lead tetraacetate, see Rubottom, Ref. 10; Aylward, Ref. 10. For reviews of HIO_4, see Fatiadi, Ref. 10; Sklarz, Ref. 10.

[143] For a list of reagents, with references, see Ref. 21, pp. 615-616.

[144] Adler; Becker *Acta Chem. Scand.* **1961,** *15*, 849; Ohloff; Giersch *Angew. Chem. Int. Ed. Engl.* **1973,** *12*, 401 [*Angew. Chem. 85*, 401].

[145] McKillop; Raphael; Taylor *J. Org. Chem.* **1972,** *37*, 4204.

[146] Cisneros; Fernández; Hernández *Synth. Comm.* **1982,** *12*, 833.

[147] de Vries; Schors *Tetrahedron Lett.* **1968,** 5689.

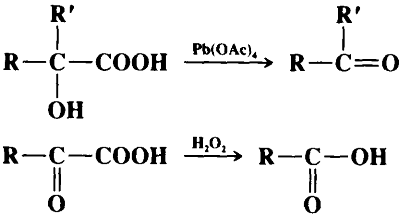
[148] For a list of reagents, with references, see Ref. 21, pp. 836-837.

[149] For a review, see Shono *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer: New York, 1984, pp. 31-37. See also Ruholl; Schäfer *Synthesis* **1988,** 54.

[150] See, for example, Ogata; Sawaki; Shiroyama *J. Org. Chem.* **1977,** *42*, 4061.

[151] Nagarkatti; Ashley *Tetrahedron Lett.* **1973,** 4599.

α-Hydroxy acids and α-keto acids are not cleaved by HIO_4 but are cleaved by $Pb(OAc)_4$, alkaline H_2O_2, and other reagents. These are oxidative decarboxylations. α-Hydroxy acids give aldehydes or ketones, and α-keto acids give carboxylic acids:

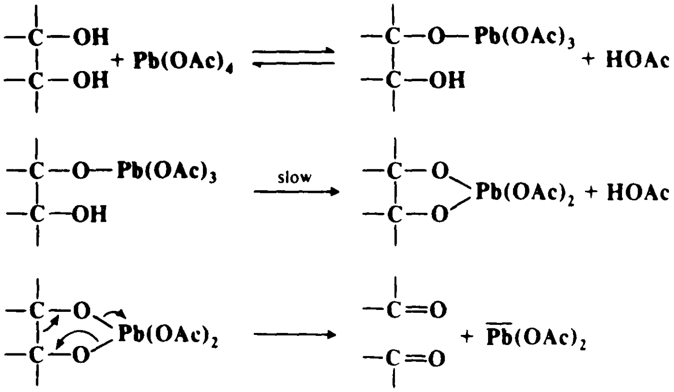


$$R-\overset{\displaystyle R'}{\underset{\displaystyle OH}{C}}-COOH \xrightarrow{Pb(OAc)_4} R-\overset{\displaystyle R'}{C}=O$$

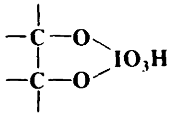
$$R-\underset{\underset{\displaystyle O}{\|}}{C}-COOH \xrightarrow{H_2O_2} R-\underset{\underset{\displaystyle O}{\|}}{C}-OH$$

Also see **9-13** and **9-14**.

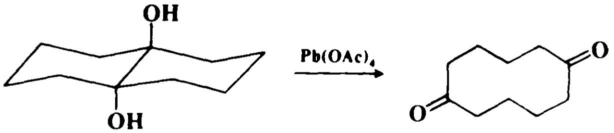
The mechanism of glycol oxidation with $Pb(OAc)_4$ was proposed by Criegee:[152]



This mechanism is supported by these facts: (1) the kinetics are second order (first order in each reactant); (2) added acetic acid retards the reaction (drives the equilibrium to the left); and (3) cis glycols react much more rapidly than trans glycols.[153] For periodic acid the mechanism is similar, with the intermediate[154]



However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols that cannot form such an ester (e.g., **10**) are nevertheless cleaved by lead



10

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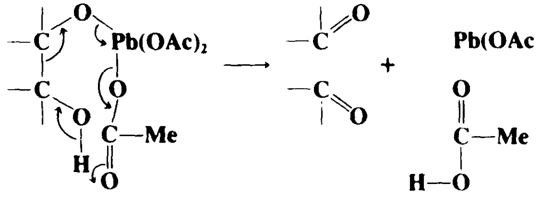
[152] Criegee; Kraft; Rank *Liebigs Ann. Chem.* **1933**, *507*, 159. For reviews, see Waters, Ref. 2, pp. 72-81; Stewart, Ref. 2, pp. 97-106.

[153] For example, see Criegee; Höger; Huber; Kruck; Marktscheffel; Schellenberger *Liebigs Ann. Chem.* **1956**, *599*, 81.

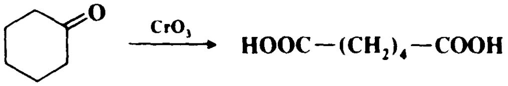
[154] Buist; Bunton; Miles *J. Chem. Soc.* **1959**, 743; Buist; Bunton; Hipperson *J. Chem. Soc. B* **1971**, 2128.

tetraacetate (though other glycols that cannot form cyclic esters are *not* cleaved, by either reagent[155]). To account for cases like **10**, a cyclic transition state has been proposed:[153]



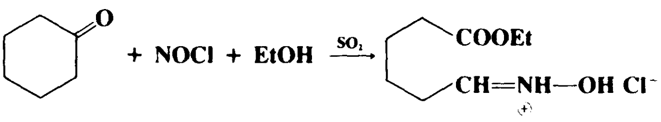
OS **IV**, 124; **VII**, 185; **68**, 162.

9-8 Oxidative Cleavage of Ketones, Aldehydes, and Alcohols
Cycloalkanone oxidative ring opening

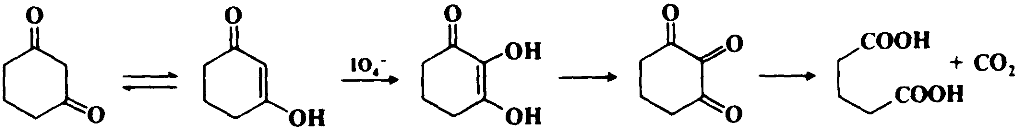


Oxidative cleavage of open-chain ketones or alcohols[156] is seldom a useful preparative procedure, not because these compounds do not undergo oxidation (they do, except for diaryl ketones) but because the result is generally a hopeless mixture. However, the reaction is quite useful for cyclic ketones and the corresponding secondary alcohols, the dicarboxylic acid being prepared in good yield. The formation of adipic acid from cyclohexanone (shown above) is an important industrial procedure. Acid dichromate and permanganate are the most common oxidizing agents, though autoxidation (oxidation with atmospheric oxygen) in alkaline solution[157] and potassium superoxide under phase transfer conditions[158] have also been used. The last-mentioned reagent has also been used to cleave open-chain ketones to give carboxylic acid products in good yield.[158]

Cyclic ketones can also be cleaved by treatment with NOCl and an alcohol in liquid SO_2 to give an ω-oximinocarboxylic ester, e.g.,[159]



Cyclic 1,3-diketones, which exist mainly in the monoenolic form, can be cleaved with sodium periodate with loss of one carbon, e.g.,[160]



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[155] Angyal; Young *J. Am. Chem. Soc.* **1959,** *81,* 5251.

[156] For a review of metal ion-catalyzed oxidative cleavage of alcohols, see Trahanovsky *Methods Free-Radical Chem.* **1973,** *4,* 133-169. For a review of the oxidation of aldehydes and ketones, see Verter, in Zabicky *The Chemistry of the Carbonyl Group,* pt. 2; Wiley: New York, 1970, pp. 71-156.

[157] Wallace; Pobiner; Schriesheim *J. Org. Chem.* **1965,** *30,* 3768. See also Osowska-Pacewicka; Alper *J. Org. Chem.* **1988,** *53,* 808.

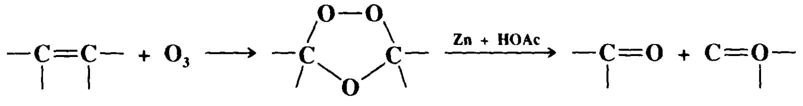
[158] Lissel; Dehmlow *Tetrahedron Lett.* **1978,** 3689; Sotiriou; Lee; Giese *J. Org. Chem.* **1990,** 55, 2159.

[159] Rogić; Vitrone; Swerdloff *J. Am. Chem. Soc.* **1977,** 99, 1156; Moorhoff; Paquette *J. Org. Chem.* **1991,** 56, 703.

[160] Wolfrom; Bobbitt *J. Am. Chem. Soc.* **1956,** *78,* 2489.

The species actually undergoing the cleavage is the triketone, so this is an example of **9-7.**
OS **I,** 18; **IV,** 19; **VI,** 690. See also OS **VI,** 1024.

9-9 Ozonolysis
Oxo-uncoupling



11

When compounds containing double bonds are treated with ozone, usually at low temperatures, they are converted to compounds called *ozonides* (**11**) that can be isolated but, because some of them are explosive, are more often decomposed with zinc and acetic acid or catalytic hydrogenation to give 2 moles of aldehyde, or 2 moles of ketone, or 1 mole of each, depending on the groups attached to the olefin.[161] The decomposition of **11** has also been carried out with many other reducing agents, among them trimethyl phosphite,[162] thiourea,[163] and dimethyl sulfide.[164] However, ozonides can also be *oxidized* with oxygen, peracids, or H_2O_2 to give ketones and/or carboxylic acids or *reduced* with $LiAlH_4$, $NaBH_4$, BH_3, or catalytic hydrogenation with excess H_2 to give 2 moles of alcohol.[165] Ozonides can also be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines,[166] or with an alcohol and anhydrous HCl to give the corresponding carboxylic esters.[167] Ozonolysis is therefore an important synthetic reaction.

A wide variety of olefins undergo ozonolysis, including cyclic ones, where cleavage gives rise to one bifunctional product. Olefins in which the double bond is connected to electron-donating groups react many times faster than those in which it is connected to electron-withdrawing groups.[168] The reaction has often been carried out on compounds containing more than one double bond; generally all the bonds are cleaved. In some cases, especially when bulky groups are present, conversion of the substrate to an epoxide (**5-36**) becomes an important side reaction and can be the main reaction.[169] Ozonolysis of triple bonds[170] is less common and the reaction proceeds less easily, since ozone is an electrophilic agent[171]

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[161] For monographs, see Razumovskii; Zaikov *Ozone and its Reactions with Organic Compounds*; Elsevier: New York, 1984; Bailey *Ozonation in Organic Chemistry*, 2 vols.; Academic Press: New York, 1978, 1982. For reviews, see Odinokov; Tolstikov *Russ. Chem. Rev.* **1981,** *50*, 636-657; Belew, in Augustine; Trecker, Ref. 11, vol. 1, pp. 259-335; Menyailo; Pospelov *Russ. Chem. Rev.* **1967,** *36*, 284-294. For a review with respect to vinylic ethers, see Kuczkowski *Adv. Oxygenated Processes* **1991,** *3*, 1-42. For a review with respect to haloalkenes, see Gillies; Kuczkowski *Isr. J. Chem.* **1983,** *23*, 446-450.

[162] Knowles; Thompson *J. Org. Chem.* **1960,** *25*, 1031.

[163] Gupta; Soman; Dev *Tetrahedron* **1982,** *38*, 3013.

[164] Pappas; Keaveney; Gancher; Berger *Tetrahedron Lett.* **1966,** 4273.

[165] Sousa; Bluhm *J. Org. Chem.* **1960,** *25*, 108; Diaper; Mitchell *Can. J. Chem.* **1960,** *38*, 1976; Diaper; Strachan *Can. J. Chem.* **1967,** *45*, 33; White; King; O'Brien *Tetrahedron Lett.* **1971,** 3587; Flippin; Gallagher; Jalali-Araghi *J. Org. Chem.* **1989,** *54*, 1430.

[166] Diaper; Mitchell *Can. J. Chem.* **1962,** *40*, 1189; Benton; Kiess *J. Org. Chem.* **1960,** *25*, 470; Pollart; Miller *J. Org. Chem.* **1962,** *27*, 2392; White; King; O'Brien *Tetrahedron Lett.* **1971,** 3591.

[167] Neumeister; Keul; Saxena; Griesbaum *Angew. Chem. Int. Ed. Engl.* **1978,** *17*, 939 [*Angew. Chem. 90*, 999]. See also Schreiber; Claus; Reagan *Tetrahedron Lett.* **1982,** *23*, 3867; Cardinale; Grimmelikhuysen; Laan; Ward *Tetrahedron* **1984,** *40*, 1881.

[168] Pryor; Giamalva; Church *J. Am. Chem. Soc.* **1983,** *105*, 6858, **1985,** *107*, 2793.

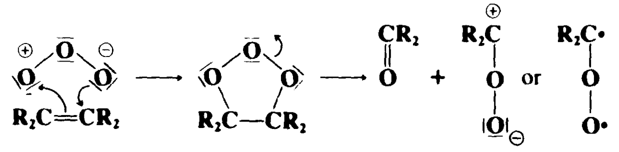
[169] See, for example, Bailey; Lane *J. Am. Chem. Soc.* **1967,** *89*, 4473; Gillies *J. Am. Chem. Soc.* **1975,** *97*, 1276; Bailey; Hwang; Chiang *J. Org. Chem.* **1985,** *50*, 231.

[170] For a discussion of the mechanism of ozonolysis of triple bonds, see Pryor; Govindan; Church *J. Am. Chem. Soc.* **1982,** *104*, 7563.

[171] See, for example, Wibaut; Sixma *Recl. Trav. Chim. Pays-Bas* **1952,** *71*, 761; Williamson; Cvetanović *J. Am. Chem. Soc.* **1968,** *90*, 4248; Razumovskii; Zaikov *J. Org. Chem. USSR* **1972,** *8*, 468, 473; Klutsch; Fliszár *Can. J. Chem.* **1972,** *50*, 2841.

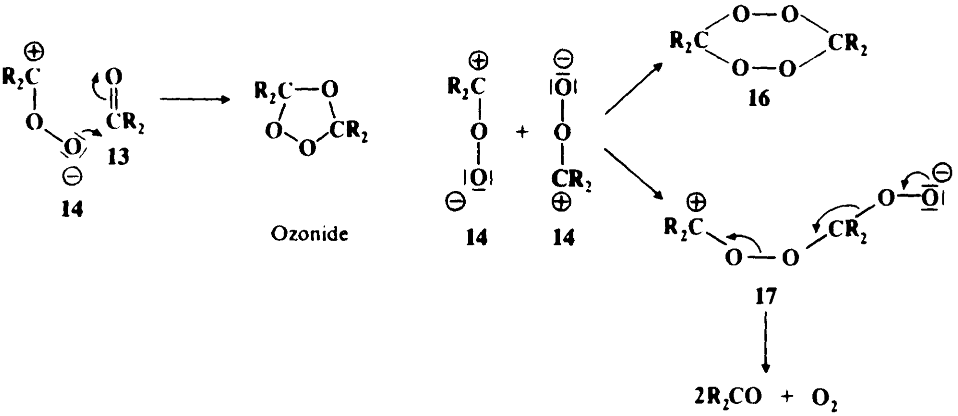
and prefers double to triple bonds (p. 748). Compounds that contain triple bonds generally give carboxylic acids, though sometimes ozone oxidizes them to α-diketones (**9-27**). Aromatic compounds are also attacked less readily than olefins, but have often been cleaved. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives 3 moles of glyoxal (HCOCHO), and *o*-xylene gives a glyoxal/MeCOCHO/MeCOCOMe ratio of 3:2:1, which shows that in this case cleavage is statistical. With polycyclic aromatic compounds the site of attack depends on the structure of the molecule and on the solvent.[172]

Although a large amount of work has been done on the mechanism of ozonization (formation of **11**), not all the details are known. The basic mechanism was formulated by Criegee.[173] The first step of the Criegee mechanism is a 1,3 dipolar addition (**5-46**) of ozone to the substrate to give the "initial" or "primary" ozonide, the structure of which has been shown to be the 1,2,3-trioxolane **12** by microwave and other spectral methods.[174] However,



12 **13** **14** **15**

12 is highly unstable and cleaves to an aldehyde or ketone (**13**) and an intermediate which Criegee showed as a zwitterion (**14**) but which may be a diradical (**15**). This compound is usually referred to as a carbonyl oxide.[175] The carbonyl oxide (which we will represent as **14**) can then undergo various reactions, three of which lead to normal products. One is a recombination with **13**, the second a dimerization to the bisperoxide **16**, and the third a



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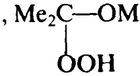
[172] Dobinson; Bailey *Tetrahedron Lett.* **1960** (No. 13) 14; O'Murchu *Synthesis* **1989**, 880.

[173] For reviews, see Kuczkowski *Acc. Chem. Res.* **1983**, *16*, 42-47; Razumovskii; Zaikov *Russ. Chem. Rev.* **1980**, *49*, 1163-1180; Criegee *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 745-752 [*Angew. Chem.* *87*, 765-771]; Murray *Acc. Chem. Res.* **1968**, *1*, 313-320.

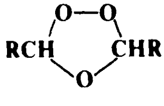
[174] Gillies; Gillies; Suenram; Lovas *J. Am. Chem. Soc.* **1988**, *110*, 7991. See also Criegee; Schröder *Chem. Ber.* **1960**, *93*, 689; Durham; Greenwood *J. Org. Chem.* **1968**, *33*, 1629; Bailey; Carter; Fischer; Thompson *Can. J. Chem.* **1973**, *51*, 1278; Hisatsune; Shinoda; Heicklen *J. Am. Chem. Soc.* **1979**, *101*, 2524; Mile; Morris; Alcock *J. Chem. Soc., Perkin Trans. 2* **1979**, 1644; Kohlmiller; Andrews *J. Am. Chem. Soc.* **1981**, *103*, 2578; McGarrity; Prodolliet *J. Org. Chem.* **1984**, *49*, 4465.

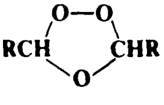
[175] For reviews of carbonyl oxides, see Sander *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 344-354 [*Angew. Chem.* *102*, 362-372]; Brunelle *Chem. Rev.* **1991**, *91*, 335-362.

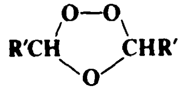
kind of dimerization to **17.**[176] If the first path is taken (this is normally possible only if **13** is an aldehyde; most ketones do not do this[177]), hydrolysis of the ozonide gives the normal products. If **16** is formed, hydrolysis of it gives one of the products, and of course **13,** which then does not undergo further reaction, is the other. **17,** if formed, can decompose directly, as shown, to give the normal products and oxygen. In protic solvents, **14** is converted to a hydroperoxide, and these have been isolated, for example,



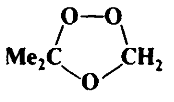
$Me_2\underset{\displaystyle OOH}{\overset{}{C}}—OMe$ from $Me_2C{=}CMe_2$ in methanol. Further evidence for the mechanism is that **16** can be isolated in some cases, e.g., from $Me_2C{=}CMe_2$. But perhaps the most impressive evidence comes from the detection of cross products. In the Criegee mechanism, the two parts of the original olefin break apart and then recombine to form the ozonide. In the case of an unsymmetrical olefin RCH=CHR′ there should be three ozonides:







since there are two different aldehydes **13** and two different species **14,** and these can recombine in the three ways shown. Actually *six* ozonides, corresponding to the cis and trans forms of these three, were isolated and characterized for methyl oleate.[178] Similar results have been reported for smaller olefins, e.g., 2-pentene, 4-nonene, and even 2-methyl-2-pentene.[179] The last-mentioned case is especially interesting, since it is quite plausible that this compound would cleave in only one way, so that only one ozonide (in cis and trans versions) would be found; but this is not so, and three were found for this case too. However, terminal olefins give little or no cross ozonide formation.[180] In general, the less alkylated end of the olefin tends to go to **13** and the other to **14.** Still other evidence[181] for the Criegee mechanism is: (1) When $Me_2C{=}CMe_2$ was ozonized in the presence of HCHO, the ozonide **18** could be isolated;[182] (2) **14** prepared in an entirely different manner (photooxidation of diazo compounds), reacted with aldehydes to give ozonides;[183] and (3) cis and trans olefins generally give the same ozonide, which would be expected if they cleave first.[184] However,



18

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[176] Fliszár; Gravel; Cavalieri *Can. J. Chem.* **1966,** *44,* 67, 1013; Fliszár; Chylińska *Can. J. Chem.* **1967,** *45,* 29, **1968,** *46,* 783.

[177] It follows that tetrasubstituted alkenes do not normally give ozonides. However, they do give the normal cleavage products (ketones) by the other pathways. For the preparation of ozonides from tetrasubstituted alkenes by ozonolysis on polyethylene, see Griesbaum; Volpp; Greinert; Greunig; Schmid; Henke *J. Org. Chem.* **1989,** *54,* 383.

[178] Riezebos; Grimmelikhuysen; van Dorp *Recl. Trav. Chim. Pays-Bas* **1963,** *82,* 1234; Privett; Nickell *J. Am. Oil Chem. Soc.* **1964,** *41,* 72.

[179] Loan; Murray; Story *J. Am. Chem. Soc.* **1965,** *87,* 737; Lorenz; Parks *J. Org. Chem.* **1965,** *30,* 1976.

[180] Murray; Williams *J. Org. Chem.* **1969,** *34,* 1891.

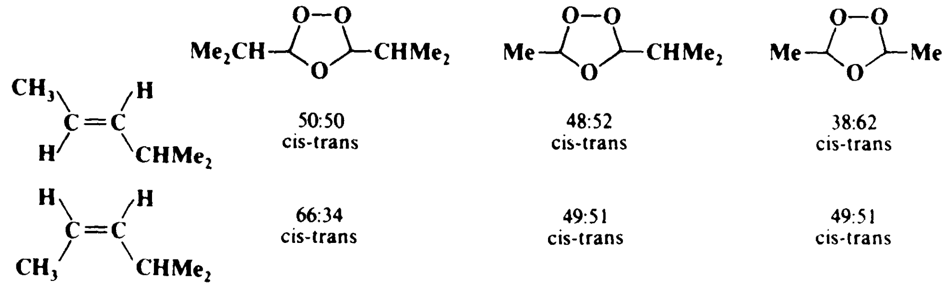
[181] For further evidence, see Keul; Choi; Kuczkowski *J. Org. Chem.* **1985,** *50,* 3365; Mori; Nojima; Kusabayashi *J. Am. Chem. Soc.* **1987,** *109,* 4407; Pierrot; El Idrissi; Santelli *Tetrahedron Lett.* **1989,** *30,* 461; Wojciechowski; Chiang; Kuczkowski *J. Org. Chem.* **1990,** *55,* 1120; Paryzek; Martynow; Swoboda *J. Chem. Soc., Perkin Trans. 1* **1990,** 1220; Murray; Morgan *J. Org. Chem.* **1991,** *56,* 684, 6123.

[182] Even ketones can react with **14** to form ozonides, provided they are present in large excess: Criegee; Korber *Chem. Ber.* **1971,** *104,* 1812.

[183] Murray; Suzui *J. Am. Chem. Soc.* **1973,** *95,* 3343; Higley; Murray *J. Am. Chem. Soc.* **1974,** *96,* 3330.

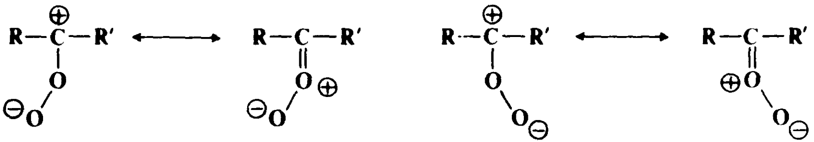
[184] See, for example, Murray; Williams *J. Org. Chem.* **1969,** *34,* 1896.

this was not true for $Me_3CCH{=}CHCMe_3$, where the cis olefin gave the cis ozonide (chiefly), and the trans gave the trans.[185] The latter result is not compatible with the Criegee mechanism. Also incompatible with the Criegee mechanism was the finding that the cis/trans ratios of symmetrical (cross) ozonides obtained from *cis*- and *trans*-4-methyl-2-pentene were not the same.[186]



If the Criegee mechanism operated as shown above, the cis/trans ratio for each of the two cross ozonides would have to be identical for the cis and trans olefins, since in this mechanism they are completely cleaved.

The above stereochemical results have been explained[187] on the basis of the Criegee mechanism with the following refinements: (1) The formation of **12** is stereospecific, as expected from a 1,3 dipolar cycloaddition. (2) Once they are formed, **14** and **13** remain attracted to each other, much like an ion pair. (3) **14** exists in syn and anti forms, which are produced in different amounts and can hold their shapes, at least for a time. This is plausible if we remember that a C=O canonical form contributes to the structure of **14.** (4) The combination of **14** and **13** is also a 1,3 dipolar cycloaddition, so configuration is retained in this step too.[188]



syn-**14** *anti*-**14**

Evidence that the basic Criegee mechanism operates even in these cases comes from ^{18}O labeling experiments, making use of the fact, mentioned above, that mixed ozonides (e.g., **18**) can be isolated when an external aldehyde is added. Both the normal and modified Criegee mechanisms predict that if ^{18}O-labeled aldehyde is added to the ozonolysis mixture, the label will appear in the ether oxygen (see the reaction between **14** and **13**), and this is what is found.[189] There is evidence that the anti-**14** couples much more readily than the syn-**14**.[190]

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[185] Schröder *Chem. Ber.* **1962,** *95,* 733; Kolsaker *Acta Chem. Scand., Ser. B* **1978,** *32,* 557.

[186] Murray; Youssefyeh; Story *J. Am. Chem. Soc.* **1966,** *88,* 3143, 3655; Story; Murray; Youssefyeh *J. Am. Chem. Soc.* **1966,** *88,* 3144. Also see Greenwood *J. Am. Chem. Soc.* **1966,** *88,* 3146; Choe; Srinivasan; Kuczkowski *J. Am. Chem. Soc.* **1983,** *105,* 4703.

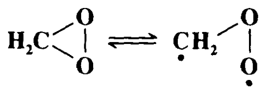
[187] Bauld; Thompson; Hudson; Bailey *J. Am. Chem. Soc.* **1968,** *90,* 1822; Bailey; Ferrell *J. Am. Chem. Soc.* **1978,** *100,* 899; Keul; Kuczkowski *J. Am. Chem. Soc.* **1985,** *50,* 3371.

[188] For isotope-effect evidence that this step is concerted in some cases, see Choe; Painter; Kuczkowski *J. Am. Chem. Soc.* **1984,** *106,* 2891. However, there is evidence that it may not always be concerted: See, for example, Murray; Su *J. Org. Chem.* **1983,** *48,* 817.

[189] Bishop; Denson; Story *Tetrahedron Lett.* **1968,** 5739; Fliszár; Carles; Renard *J. Am. Chem. Soc.* **1968,** *90,* 1364; Fliszár; Carles *J. Am. Chem. Soc.* **1969,** *91,* 2637; Gillies; Kuczkowski *J. Am. Chem. Soc.* **1972,** *94,* 7609; Higley; Murray *J. Am. Chem. Soc.* **1976,** *98,* 4526; Mazur; Kuczkowski *J. Org. Chem.* **1979,** *44,* 3185.

[190] Mile; Morris *J. Chem. Soc., Chem. Commun.* **1978,** 263.

The ozonolysis of ethylene in the liquid phase (without a solvent) was shown to take place by the Criegee mechanism.[191] This reaction has been used to study the structure of the intermediate **14** or **15**. The compound dioxirane (**19**) was identified in the reaction mixture[192] at low temperatures and is probably in equilibrium with the biradical **15** (R = H).



19 **15(R = H)**

Ozonolysis in the gas phase is not generally carried out in the laboratory. However, the reaction is important because it takes place in the atmosphere and contributes to air pollution.[193] There is much evidence that the Criegee mechanism operates in the gas phase too, though the products are more complex because of other reactions that also take place.[194]

OS **V**, 489, 493; **VI**, 976; **VII**, 168. Also see OS **IV**, 554. For the preparation of ozone, see OS **III**, 673.

9-10 Oxidative Cleavage of Double Bonds and Aromatic Rings
Oxo-de-alkylidene-bisubstitution, etc.

$$R_2C{=}CHR \xrightarrow{CrO_3} R_2C{=}O + RCOOH$$

Double bonds can be cleaved by many oxidizing agents,[195] the most common of which are neutral or acid permanganate and acid dichromate. The products are generally 2 moles of ketone, 2 moles of carboxylic acid, or 1 mole of each, depending on what groups are attached to the olefin. With ordinary solutions of permanganate or dichromate yields are generally low, and the reaction is seldom a useful synthetic method; but high yields can be obtained by oxidizing with $KMnO_4$ dissolved in benzene containing the crown ether dicyclohexano-18-crown-6 (see p. 82).[196] The crown ether coordinates with K^+, permitting the $KMnO_4$ to dissolve in benzene. Another reagent frequently used for synthetic purposes is the *Lemieux–von Rudloff reagent*: HIO_4 containing a trace of MnO_4^-.[197] The MnO_4^- is the actual oxidizing agent, being reduced to the manganate stage, and the purpose of the HIO_4 is to reoxidize the manganate back to MnO_4^-. Another reagent that behaves similarly is $NaIO_4$–ruthenium tetroxide.[198]

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[191] Fong; Kuczkowski *J. Am. Chem. Soc.* **1980,** *102*, 4763.

[192] Suenram; Lovas *J. Am. Chem. Soc.* **1978,** *100*, 5117. See, however, Ishiguro; Hirano; Sawaki *J. Org. Chem.* **1988,** *53*, 5397.

[193] For a review of the mechanisms of reactions of organic compounds with ozone in the gas phase, see Atkinson; Carter *Chem. Rev.* **1984,** *84*, 437-470.

[194] See Ref. 193, pp. 452-454; Kühne; Forster; Hulliger; Ruprecht; Bauder; Günthard *Helv. Chim. Acta* **1980,** *63*, 1971; Martinez; Herron *J. Phys. Chem.* **1988,** *92*, 4644.

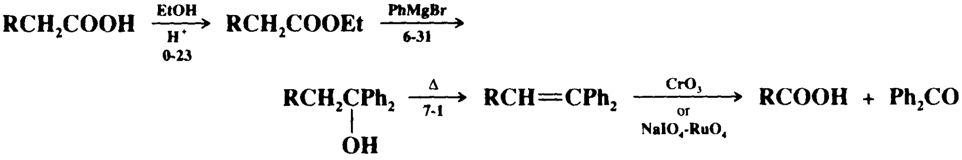
[195] For a review of the oxidation of C=C and C=N bonds, see Henry; Lange, in Patai, Ref. 103, pp. 965-1098. For a review of oxidative cleavages of C=C double bonds and aromatic rings, see Hudlický, Ref. 11, pp. 77-84, 96-98. For reviews with respect to chromium reagents, see Badanyan; Minasyan; Vardapetyan *Russ. Chem. Rev.* **1987,** *56*, 740-755; Cainelli; Cardillo, Ref. 10, pp. 59-92. For a list of reagents, with references, see Ref. 21, p. 828.

[196] Sam; Simmons *J. Am. Chem. Soc.* **1972,** *94*, 4024. See also Lee; Chang *J. Org. Chem.* **1978,** *43*, 1532.

[197] Lemieux; Rudloff *Can. J. Chem.* **1955,** *33*, 1701, 1710; Rudloff *Can. J. Chem.* **1955,** *33*, 1714, **1956,** *34*, 1413, **1965,** *43*, 1784.

[198] For a review, see Lee; van den Engh, in Trahanovsky, Ref. 2, pt. B, pp. 186-192. For the use of $NaIO_4$-OsO_4, see Cainelli; Contento; Manescalchi; Plessi *Synthesis* **1989,** 47.

The *Barbier–Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage by acid dichromate ($NaIO_4$–ruthenium tetroxide has also been used), but this is cleavage of a 1,1-diphenyl olefin, which generally gives good yields:



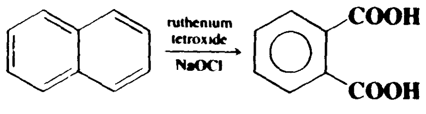
$$RCH_2COOH \xrightarrow[H^+]{EtOH} RCH_2COOEt \xrightarrow[6\text{-}31]{PhMgBr} \underset{\displaystyle OH}{RCH_2\overset{|}{C}Ph_2} \xrightarrow[7\text{-}1]{\Delta} RCH{=}CPh_2 \xrightarrow[\text{or } NaIO_4\text{-}RuO_4]{CrO_3} RCOOH + Ph_2CO$$

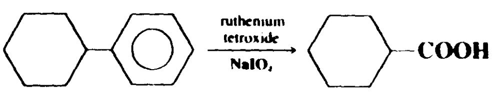
0-23

With certain reagents, the oxidation of double bonds can be stopped at the aldehyde stage, and in these cases the products are the same as in the ozonolysis procedure. Among these reagents are chromyl trichloroacetate,[199] *t*-butyl iodoxybenzene,[200] $KMnO_4$ in THF–H_2O,[201] and $NaIO_4$–OsO_4.[202] Enol ethers $RC(OR')\!=\!CH_2$ have been cleaved to carboxylic esters $RC(OR')\!=\!O$ by atmospheric oxygen.[203]

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (**5-35**) or cyclic ester,[204] and then further oxidation as in **9-7**.[205] In line with the electrophilic attack on the olefin, triple bonds are more resistant to oxidation than double bonds. Terminal triple-bond compounds can be cleaved to carboxylic acids ($RC{\equiv}CH \rightarrow RCOOH$) with thallium(III) nitrate[206] or with [bis(trifluoroacetoxy)iodo]pentafluorobenzene $C_6F_5I(OCOCF_3)_2$,[207] among other reagents.

Aromatic rings can be cleaved with strong enough oxidizing agents. An important laboratory reagent for this purpose is ruthenium tetroxide along with a cooxidant such as $NaIO_4$ or NaOCl (household bleach can be used).[208] Examples[209] are the oxidation of naphthalene to phthalic acid[210] and, even more remarkably, of cyclohexylbenzene to cyclohexanecarboxylic acid[211] (note the contrast with **9-11**). The latter conversion was also accomplished with ozone.[212] Another reagent that oxidizes aromatic rings is air catalyzed by V_2O_5. The





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[199] Schildknecht; Föttinger *Liebigs Ann. Chem.* **1962,** *659,* 20.

[200] Ranganathan; Ranganathan; Singh *Tetrahedron Lett.* **1985,** *26,* 4955.

[201] Viski; Szeverényi; Simándi *J. Org. Chem.* **1986,** *51,* 3213.

[202] Pappo; Allen; Lemieux; Johnson *J. Org. Chem.* **1956,** *21,* 478.

[203] Taylor *J. Chem. Res. (S)* **1987,** 178. For a similar oxidation with RuO_4, see Torii; Inokuchi; Kondo *J. Org. Chem.* **1985,** *50,* 4980.

[204] See, for example, Lee; Spitzer *J. Org. Chem.* **1976,** *41,* 3644; Lee; Chang; Helliwell *J. Org. Chem.* **1976,** *41,* 3644, 3646.

[205] There is evidence that oxidation with Cr(VI) in aqueous acetic acid involves an epoxide intermediate: Awasthy; Roček *J. Am. Chem. Soc.* **1969,** *91,* 991; Roček; Drozd *J. Am. Chem. Soc.* **1970,** *92,* 6668.

[206] McKillop; Oldenziel; Swann; Taylor; Robey *J. Am. Chem. Soc.* **1973,** *95,* 1296.

[207] Moriarty; Penmasta; Awasthi; Prakash *J. Org. Chem.* **1988,** *53,* 6124.

[208] Ruthenium tetroxide is an expensive reagent, but the cost can be greatly reduced by the use of an inexpensive cooxidant such as NaOCl, the function of which is to oxidize RuO_2 back to ruthenium tetroxide.

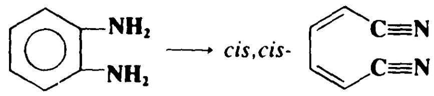
[209] For other examples, see Piatak; Herbst; Wicha Caspi *J. Org. Chem.* **1969,** *34,* 116; Wolfe; Hasan; Campbell *Chem. Commun.* **1970,** 1420; Ayres; Hossain *Chem. Commun.* **1972,** 428; Nuñez; Martín *J. Org. Chem.* **1990,** *55,* 1928.

[210] Spitzer; Lee *J. Org. Chem.* **1974,** *39,* 2468.

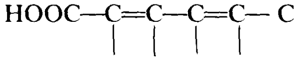
[211] Caputo; Fuchs *Tetrahedron Lett.* **1967,** 4729.

[212] Klein; Steinmetz *Tetrahedron Lett.* **1975,** 4249. For other reagents that convert an aromatic ring to COOH and leave alkyl groups untouched, see Deno; Greigger; Messer; Meyer; Stroud *Tetrahedron Lett.* **1977,** 1703; Liotta; Hoff *J. Org. Chem.* **1980,** *45,* 2887; Chakraborti; Ghatak *J. Chem. Soc., Perkin Trans. 1* **1985,** 2605.

oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride (p. 794) by this reagent are important industrial procedures.[213] *o*-Diamines have been oxidized with nickel peroxide, with lead tetraacetate,[214] and with O_2 catalyzed by CuCl:[215]



The last-named reagent also cleaves *o*-dihydroxybenzenes (catechols) to give, in the presence of MeOH, the monomethylated dicarboxylic acids $HOOC—\underset{|}{C}=\underset{|}{C}—\underset{|}{C}=\underset{|}{C}—COOMe$.[216]

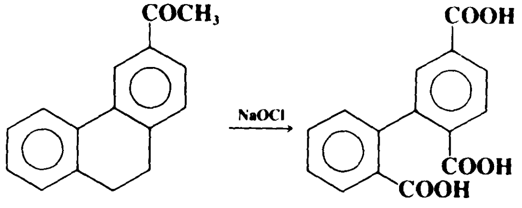


OS **II,** 53, 523; **III,** 39, 234, 449; **IV,** 136, 484, 824; **V,** 393; **VI,** 662, 690; **VII,** 397; **66,** 180; **68,** 41. Also see OS **II,** 551.

9-11 Oxidation of Aromatic Side Chains
Oxo,hydroxy-de-dihydro,methyl-tersubstitution

$$\mathbf{ArR \xrightarrow{KMnO_4} ArCOOH}$$

Alkyl chains on aromatic rings can be oxidized to COOH groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate.[218] The method is most often applied to the methyl group, though longer side chains can also be cleaved. However, tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.[219] It is usually difficult to oxidize an R group on a fused aromatic system without cleaving the ring or oxidizing it to a quinone (**9-19**). However, this has been done (e.g., 2-methylnaphthalene was converted to 2-naphthoic acid) with aqueous $Na_2Cr_2O_7$.[220] Functional groups can be present anywhere on the side chain and, if in the α position, greatly increase the ease of oxidation. An exception is an α phenyl group. In such cases the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each ring gets one carbon atom, e.g.,



It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity[221] toward most reagents is $CH_2Ar > CHR_2 > CH_2R > CH_3$.[222] Groups

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[213] For a review, see Pyatnitskii *Russ. Chem. Rev.* **1976,** *45,* 762-776.

[214] Nakagawa; Onoue *Tetrahedron Lett.* **1965,** 1433, *Chem. Commun.* **1966,** 396.

[215] Kajimoto; Takahashi; Tsuji *J. Org. Chem.* **1976,** *41,* 1389.

[216] Tsuji; Takayanagi *Tetrahedron* **1978,** *34* 641; Bankston *Org. Synth. 66,* 180.

[217] This is the name if R = ethyl. The IUPAC names will obviously differ, depending on the R group.

[218] For many examples, see Hudlický, Ref. 11, pp. 105-109; Lee, Ref. 10, pp. 43-64. For a review with chromium oxidizing agents, see Cainelli; Cardillo, Ref. 10, pp. 23-33.

[219] Brandenberger; Maas; Dvoretzky *J. Am. Chem. Soc.* **1961,** *83,* 2146.

[220] Friedman; Fishel; Shechter *J. Org. Chem.* **1965,** *30,* 1453.

[221] Oxidation with Co(III) is an exception. The methyl group is oxidized in preference to the other alkyl groups: Onopchenko; Schulz; Seekircher *J. Org. Chem.* **1972,** *37,* 1414

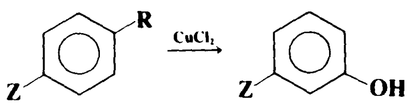
[222] For example, see Foster; Hickinbottom *J. Chem. Soc.* **1960,** 680; Ferguson; Wims *J. Org. Chem.* **1960,** *25,* 668.

on the ring susceptible to oxidation (OH, NHR, NH_2, etc.) must be protected. The oxidation can be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in **4-9,** with a hydroperoxide intermediate. With this procedure it is possible to isolate ketones from $ArCH_2R$, and this is often done.[223]

The mechanism has been studied for the closely related reaction: $Ar_2CH_2 + CrO_3 \rightarrow Ar_2C{=}O$.[224] A deuterium isotope effect of 6.4 was found, indicating that the rate-determining step is either $Ar_2CH_2 \rightarrow Ar_2CH\bullet$ or $Ar_2CH_2 \rightarrow Ar_2CH^+$. Either way this explains why tertiary groups are not converted to COOH and why the reactivity order is $CHR_2 > CH_2R > CH_3$, as mentioned above. Both free radicals and carbocations exhibit this order of stability (Chapter 5). The two possibilities are examples of categories 2 and 3 (p. 1160). Just how the radical or the cation goes on to the product is not known.

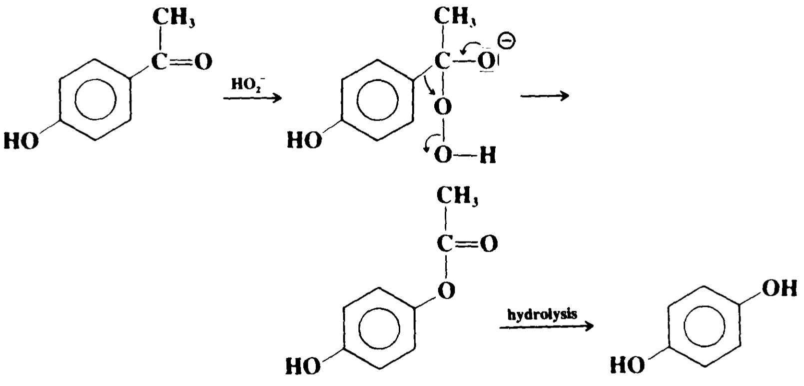
OS **I,** 159, 385, 392, 543; **II,** 135, 428; **III,** 334, 420, 740, 791, 820, 822; **V,** 617, 810.

9-12 Oxidative Cleavage of Alkyl Groups from Rings
Hydroxy-de-alkyl-*cine*-substitution



It is possible to replace an alkyl group on a ring by an OH group. When the alkyl group is one oxidizable to COOH (**9-11**), cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.[225] This reaction is used industrially to convert toluene to phenol.

In another kind of reaction, an aromatic aldehyde ArCHO or ketone ArCOR′ is converted to a phenol ArOH on treatment with alkaline H_2O_2,[226] but there must be an OH or NH_2 group in the ortho or para position. This is called the *Dakin reaction*.[227] The mechanism may be similar to that of the Baeyer–Villiger reaction (**8-20**):[228]



20

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[223] For a review, see Pines; Stalick, Ref. 23, pp. 508-543.

[224] Wiberg; Evans *Tetrahedron* **1960,** *8*, 313.

[225] Kaeding *J. Org. Chem.* **1961,** *26*, 3144. For a discussion, see Lee; van den Engh, in Trahanovsky, Ref. 2, pt B, pp. 91-94.

[226] For a convenient procedure, see Hocking *Can. J. Chem.* **1973,** *51*, 2384.

[227] See Schubert; Kintner, in Patai *The Chemistry of the Carbonyl Group*, Ref. 44, pp. 749-752.

[228] For a discussion, see Hocking; Bhandari; Shell; Smyth *J. Org. Chem.* **1982,** *47*, 4208.

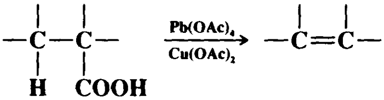
The intermediate **20** has been isolated.[229] The reaction has been performed on aromatic aldehydes with an alkoxy group in the ring, and no OH or NH_2. In this case acidic H_2O_2 was used.[230]

OS **I,** 149; **III,** 759.

9-13 Oxidative Decarboxylation

$$\mathrm{RCOOH} \xrightarrow{\mathrm{Pb(OAc)_4}} \mathrm{ROAc}$$

Acetoxy-de-carboxy-substitution



$$\underset{\mathrm{H}}{\overset{|}{\underset{|}{-\mathrm{C}}}}-\underset{\mathrm{COOH}}{\overset{|}{\underset{|}{\mathrm{C}-}}} \xrightarrow[\mathrm{Cu(OAc)_2}]{\mathrm{Pb(OAc)_4}} -\overset{|}{\mathrm{C}}=\overset{|}{\mathrm{C}}-$$

Hydro-carboxy-elimination

Carboxylic acids can be decarboxylated[231] with lead tetraacetate to give a variety of products, among them the ester ROAc (formed by replacement of COOH by an acetoxy group), the alkane RH (see **2-40**), and, if a β hydrogen is present, the alkene formed by elimination of H and COOH, as well as numerous other products arising from rearrangements, internal cyclizations,[232] and reactions with solvent molecules. When R is tertiary, the chief product is usually the alkene, which is often obtained in good yield. High yields of alkenes can also be obtained when R is primary or secondary, in this case by the use of $Cu(OAc)_2$ along with the $Pb(OAc)_4$.[233] In the absence of $Cu(OAc)_2$, primary acids give mostly alkanes (though yields are generally low) and secondary acids may give carboxylic esters or alkenes. Carboxylic esters have been obtained in good yields from some secondary acids, from β,γ-unsaturated acids, and from acids in which R is a benzylic group. Other oxidizing agents,[234] including Co(III), Ag(II), Mn(III), and Ce(IV), have also been used to effect oxidative decarboxylation.[235]

The mechanism with lead tetraacetate is generally accepted to be of the free-radical type.[236] First there is an interchange of ester groups:

$$\mathrm{Pb(OAc)_4} + \mathrm{RCOOH} \longrightarrow \underset{\mathbf{21}}{\mathrm{Pb(OAc)_3OCOR}} \quad \text{or} \quad \underset{\mathbf{22}}{\mathrm{Pb(OAc)_2(OCOR)_2}}$$

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[229] Hocking; Ko; Smyth *Can. J. Chem.* **1978,** *56*, 2646.

[230] Matsumoto; Kobayashi; Hotta *J. Org. Chem.* **1984,** *49*, 4740.

[231] For reviews, see Serguchev; Beletskaya *Russ. Chem. Rev.* **1980,** *49*, 1119-1134; Sheldon; Kochi *Org. React.* **1972,** *19*, 279-421.

[232] For examples, see Moriarty, Walsh; Gopal *Tetrahedron Lett.* **1966,** 4363; Davies; Waring *J. Chem. Soc. C.* **1968,** 1865, 2337.

[233] Bacha; Kochi *Tetrahedron* **1968,** *24*, 2215; Ogibin; Katzin; Nikishin *Synthesis* **1974,** 889.

[234] For references, see Trahanovsky; Cramer; Brixius *J. Am. Chem. Soc.* **1974,** *96*, 1077; Kochi *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978, pp. 99-106. See also Dessau; Heiba *J. Org. Chem.* **1975,** *40*, 3647; Fristad; Fry; Klang *J. Org. Chem.* **1983,** *48*, 3575; Barton; Crich; Motherwell *J. Chem. Soc., Chem. Commun.* **1984,** 242; Toussaint; Capdevielle; Maumy *Tetrahedron Lett.* **1984,** *25*, 3819.

[235] For another method, see Barton; Bridon; Zard *Tetrahedron* **1989,** *45*, 2615.

[236] Kochi *J. Am. Chem. Soc.* **1965,** *87*, 1811, 3609; Starnes *J. Am. Chem. Soc.* **1964,** *86*, 5603; Davies; Waring *Chem. Commun.* **1965,** 263; Kochi; Bacha; Bethea *J. Am. Chem. Soc.* **1967,** *89*, 6538; Cantello; Mellor; Scholes *J. Chem. Soc., Perkin Trans. 2* **1974,** 348; Beckwith; Cross; Gream *Aust. J. Chem.* **1974,** *27*, 1673, 1693.

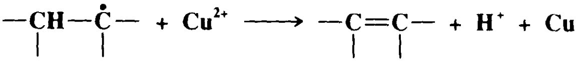
There follows a free-radical chain mechanism (shown for **21** though **22** and other lead esters can behave similarly)

$$\text{Initiation}\qquad \underset{\mathbf{21}}{\mathrm{Pb(OAc)_3OCOR}} \longrightarrow \dot{\mathrm{P}}\mathrm{b(OAc)_3} + \mathrm{R\cdot} + \mathrm{CO_2}$$

$$\text{Propagation}\qquad \mathrm{R\cdot} + \mathrm{Pb(OAc)_3OCOR} \longrightarrow \mathrm{R^+} + \dot{\mathrm{P}}\mathrm{b(OAc)_2OCOR} + \mathrm{OAc^-}$$

$$\dot{\mathrm{P}}\mathrm{b(OAc)_2OCOR} \longrightarrow \mathrm{Pb(OAc)_2} + \mathrm{R\cdot} + \mathrm{CO_2}$$

Products can then be formed either from R• or R$^+$. Primary R• abstract H from solvent molecules to give RH. R$^+$ can lose H$^+$ to give an alkene, react with HOAc to give the carboxylic ester, react with solvent molecules or with another functional group in the same molecule, or rearrange, thus accounting for the large number of possible products. R• can also dimerize to give RR. The effect of Cu^{2+} ions[237] is to oxidize the radicals to alkenes,



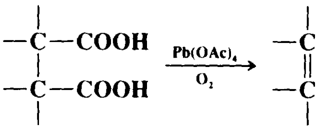
$$-\mathrm{CH}-\dot{\mathrm{C}}- + \mathrm{Cu^{2+}} \longrightarrow -\mathrm{C}{=}\mathrm{C}- + \mathrm{H^+} + \mathrm{Cu^+}$$

thus producing good yields of alkenes from primary and secondary substrates. Cu^{2+} has no effect on tertiary radicals, because these are efficiently oxidized to alkenes by lead tetraacetate.

In another type of oxidative decarboxylation, arylacetic acids can be oxidized to aldehydes with one less carbon ($\mathrm{ArCH_2COOH} \rightarrow \mathrm{ArCHO}$) by tetrabutylammonium periodate.[238] Simple aliphatic carboxylic acids were converted to nitriles with one less carbon ($\mathrm{RCH_2COOH} \rightarrow \mathrm{RC{\equiv}N}$) by treatment with trifluoroacetic anhydride and $\mathrm{NaNO_2}$ in $\mathrm{F_3CCOOH}$.[239]

See also **4-39.**

9-14 Bisdecarboxylation
Dicarboxy-elimination



$$\begin{array}{c}|\\-\mathrm{C}-\mathrm{COOH}\\|\\-\mathrm{C}-\mathrm{COOH}\\|\end{array} \xrightarrow[\mathrm{O_2}]{\mathrm{Pb(OAc)_4}} \begin{array}{c}|\\-\mathrm{C}\\\|\\-\mathrm{C}\\|\end{array}$$

Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bisdecarboxylated with lead tetraacetate in the presence of $\mathrm{O_2}$.[231] The reaction is of wide scope. The elimination is stereoselective, but not stereospecific (both *meso*- and *dl*-2,3-diphenylsuccinic acid gave *trans*-stilbene);[240] a concerted mechanism is thus unlikely. The

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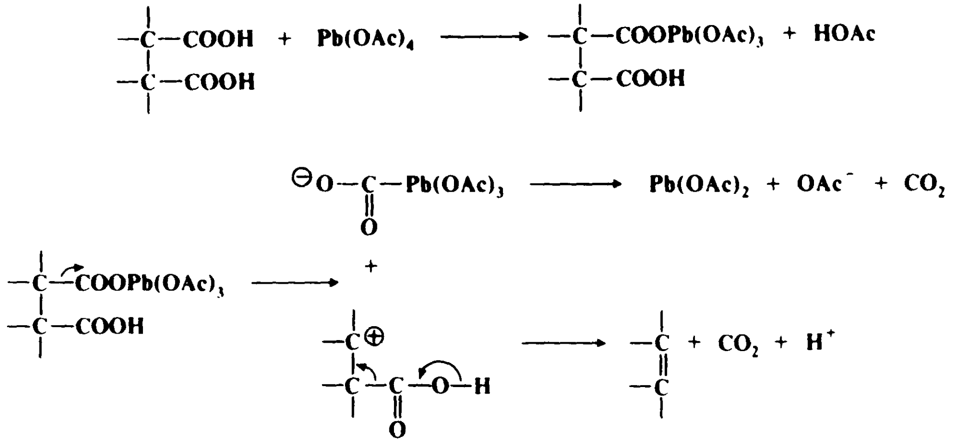
[237] Bacha; Kochi *J. Org. Chem.* **1968,** *33,* 83; Kochi; Bacha *J. Org. Chem.* **1968,** *33,* 2746; Torssell *Ark. Kemi* **1970,** *31,* 401.

[238] Santaniello; Ponti; Manzocchi *Tetrahedron Lett.* **1980,** *21,* 2655. For other methods of accomplishing this and similar conversions, see Cohen; Song; Fager; Deets *J. Am. Chem. Soc.* **1967,** *89,* 4968; Wasserman; Lipshutz *Tetrahedron Lett.* **1975,** 4611; Kaberia; Vickery *J. Chem. Soc., Chem. Commun.* **1978,** 459; Doleschall; Tóth *Tetrahedron* **1980,** *36,* 1649.

[239] Smushkevich; Usorov; Suvorov *J. Org. Chem. USSR* **1975,** *11,* 653.

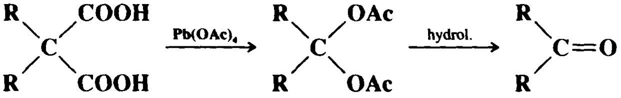
[240] Corey; Casanova *J. Am. Chem. Soc.* **1963,** *85,* 165.

following mechanism is not inconsistent with the data:



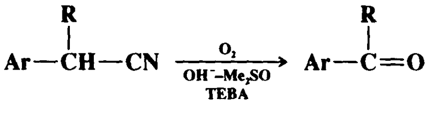
though a free-radical mechanism seems to hold in some cases. Bisdecarboxylation of succinic acid derivatives to give alkenes[241] has also been carried out by other methods, including treatment of the corresponding anhydrides with nickel, iron, or rhodium complexes,[242] by decomposition of the corresponding bis peresters,[243] and electrolytically.[244]

Compounds containing geminal carboxyl groups (disubstituted malonic acid derivatives) can also be bisdecarboxylated with lead tetraacetate,[245] *gem*-diacetates (acylals) being produced, which are easily hydrolyzable to ketones:[246]



9-15 Oxidative Decyanation

Oxo-de-hydro,cyano-bisubstitution



$$\text{Ar—}\overset{\text{R}}{\overset{|}{\text{CH}}}\text{—CN} \xrightarrow[\text{OH}^-\text{-Me}_2\text{SO}\ \text{TEBA}]{\text{O}_2} \text{Ar—}\overset{\text{R}}{\overset{|}{\text{C}}}\text{=O}$$

α-Substituted aryl nitriles having a sufficiently acidic α hydrogen can be converted to ketones by oxidation with air under phase transfer conditions.[247] The nitrile is added to NaOH in benzene or Me_2SO containing a catalytic amount of triethylbenzylammonium chloride

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[241] For a review, see De Lucchi; Modena *Tetrahedron* **1984**, *40*, 2585-2632, pp. 2591-2608.

[242] Trost; Chen *Tetrahedron Lett.* **1971**, 2603.

[243] Cain; Vukov; Masamune *Chem. Commun.* **1969**, 98.

[244] Plieninger; Lehnert *Chem. Ber.* **1967**, *100*, 2427; Radlick; Klem; Spurlock; Sims; van Tamelen; Whitesides *Tetrahedron Lett.* **1968**, 5117; Westberg; Dauben *Tetrahedron Lett.* **1968**, 5123. For additional references, see Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 253-254.

[245] For a similar reaction with ceric ammonium nitrate, see Salomon; Roy; Salomon *Tetrahedron Lett.* **1988**, *29*, 769.

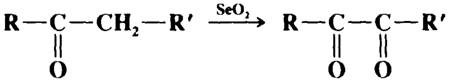
[246] Tufariello; Kissel *Tetrahedron Lett.* **1966**, 6145.

[247] For other methods of achieving this conversion, with references, see Ref. 21, p. 618.

(TEBA).[248] This reaction could not be applied to aliphatic nitriles, but an indirect method for achieving this conversion is given in **9-57**. α-Dialkylamino nitriles can be converted to ketones [$R_2C(NMe_2)CN \rightarrow R_2C{=}O$] by hydrolysis with $CuSO_4$ in aqueous methanol[249] or by autoxidation in the presence of *t*-BuOK.[250]

C. Reactions Involving Replacement of Hydrogen by Oxygen

9-16 Oxidation of Methylene to Carbonyl
Oxo-de-dihydro-bisubstitution



$$R{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}R' \xrightarrow{SeO_2} R{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}R'$$

Methyl or methylene groups α to a carbonyl can be oxidized with selenium dioxide to give, respectively, α-keto aldehydes and α-diketones.[251] The reaction can also be carried out α to an aromatic ring or to a double bond, though in the latter case, hydroxylation (see **4-4**) is the more common result. Although SeO_2 is the reagent most often used, the reaction has also been carried out with N_2O_3 and other oxidizing agents.[252] Substrates most easily oxidized contain two aryl groups on CH_2, and these substrates can be oxidized with many oxidizing agents (see **9-11**). Monoaryl alkanes have been oxidized to alkyl aryl ketones with several oxidizing agents, including CrO_3–acetic acid,[253] the Jones reagent,[254] pyridinium chlorochromate,[255] ceric ammonium nitrate,[256] benzeneseleninic anhydride PhSe(O)OSe(O)Ph,[257] a silver ion–persulfate couple,[258] and DDQ,[259] as well as with SeO_2. Alkenes of the form $C{=}C{-}CH_2$ have been oxidized to α,β-unsaturated ketones[260] by sodium dichromate in HOAc–Ac_2O, by aqueous Na_2O_2 (α,β-unsaturated alkenes),[261] by *t*-BuOOH and chromium compounds,[262] by 2-pyridineseleninic anhydride,[263] by CrO_3–pyridine complex,[264] and by mercuric salts,[265] among other reagents, as well as electrolytically.[266] CrO_3–pyridine[267] and *t*-BuOOH–chromium compounds[268] have also been used to convert alkynes of the form $C{\equiv}C{-}CH_2$ to α-keto acetylenes. Methyl ketones RCOMe react with ammonium peroxy-

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[248] Masuyama; Ueno; Okawara *Chem. Lett.* **1977,** 1439; Donetti; Boniardi; Ezhaya *Synthesis* **1980,** 1009; Kulp; McGee *J. Org. Chem.* **1983,** *48*, 4097.

[249] Büchi; Liang; Wüest *Tetrahedron Lett.* **1978,** 2763.

[250] Chuang; Yang; Chang; Fang *Synlett* **1990,** 733.

[251] For reviews of oxidation by SeO_2, see Krief; Hevesi, Ref. 10, pp. 115-180; Krongauz *Russ. Chem. Rev.* **1977,** *46*, 59-75; Rabjohn *Org. React.* **1976,** *24*, 261-415; Trachtenberg, in Augustine; Trecker, Ref. 11, pp. 119-187.

[252] For other methods, see Wasserman; Ives *J. Org. Chem.* **1978,** *43*, 3238, **1985,** *50*, 3573; Rao; Stuber; Ulrich *J. Org. Chem.* **1979,** *44*, 456.

[253] For example, see Harms; Eisenbraun *Org. Prep. Proced. Int.* **1972,** *4*, 67.

[254] Rangarajan; Eisenbraun *J. Org. Chem.* **1985,** *50*, 2435.

[255] Rathore; Saxena; Chandrasekaran *Synth. Commun.* **1986,** *16*, 1493.

[256] Syper *Tetrahedron Lett.* **1966,** 4493.

[257] Barton; Hui; Ley *J. Chem. Soc., Perkin Trans. 1* **1982,** 2179.

[258] Daniher *Org. Prep. Proced.* **1970,** *2*, 207; Bhatt; Perumal *Tetrahedron Lett.* **1981,** *22*, 2605.

[259] Lee; Harvey *J. Org. Chem.* **1988,** *53*, 4587.

[260] For a review, see Muzart *Bull. Soc. Chim. Fr.* **1986,** 65-77. For a list of reagents, with references, see Ref. 21, pp. 592-593.

[261] Holland; Daum; Riemland *Tetrahedron Lett.* **1981,** *22*, 5127.

[262] Pearson; Chen; Han; Hsu; Ray *J. Chem. Soc., Perkin Trans. 1* **1985,** 267; Muzart *Tetrahedron Lett.* **1987,** *28*, 2131; Chidambaram; Chandrasekaran *J. Org. Chem.* **1987,** *52*, 5048.

[263] Barton; Crich *Tetrahedron* **1985,** *41*, 4359.

[264] Dauben; Lorber; Fullerton *J. Org. Chem.* **1969,** *34*, 3587; Fullerton; Chen *Synth. Commun.* **1976,** *6*, 217.

[265] Arzoumanian; Metzger *Synthesis* **1971,** 527-536; Charavel; Metzger *Bull. Soc. Chim. Fr.* **1968,** 4102.

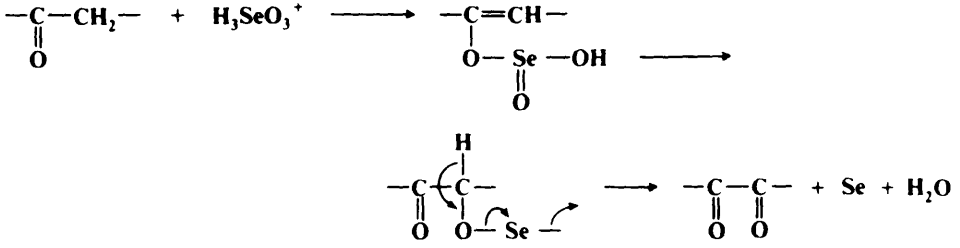
[266] Madurro; Chiericato; De Giovani; Romero *Tetrahedron Lett.* **1988,** *29*, 765.

[267] Shaw; Sherry *Tetrahedron Lett.* **1971,** 4379; Sheats; Olli; Stout; Lundeen; Justus; Nigh *J. Org. Chem.* **1979,** *44*, 4075.

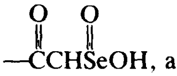
[268] Muzart; Piva *Tetrahedron Lett.* **1988,** *29*, 2321.

disulfate $(NH_4)_2S_2O_8$ and a catalytic amount of diphenyl diselenide in MeOH to give α-keto acetals $RCOCH(OMe_2)$.[269]

Two mechanisms have been suggested for the reaction with SeO_2. One of these involves a selenate ester of the enol:[270]

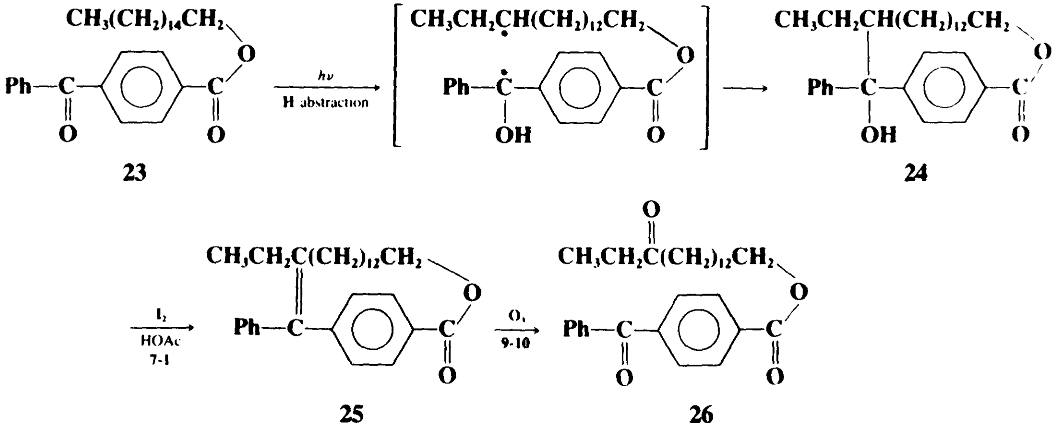


In the other proposed mechanism,[271] the principal intermediate is a β-ketoseleninic acid



$-\overset{O}{\overset{\|}{C}}CH\overset{O}{\overset{\|}{Se}}OH$, and a selenate ester is not involved.

It has proved possible to convert CH_2 to C═O groups, even if they are not near any functional groups, indirectly, by the remote oxidation method of Breslow[39] (see **9-2**). In a typical example, the keto ester **23** was irradiated to give the hydroxy lactone **24**, which was



23 **24** **25** **26**

dehydrated to **25**. Ozonolysis of **25** gave the diketo ester **26**, in which the C-14 CH_2 group of **23** has been oxidized to a C═O group.[272] The reaction was not completely regioselective: **26** comprised about 60% of the product, with the remainder consisting of other compounds in which the keto group was located at C-12, C-15, and other positions along the carbon chain. Greater regioselectivity was achieved when the aromatic portion was connected to the chain at two positions.[273] In the method so far described, the reaction takes place because one portion of a molecule (the benzophenone moiety) abstracts hydrogen from another

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[269] Tiecco; Testaferri; Tingoli; Bartoli *J. Org. Chem.* **1990,** *55*, 4523.

[270] Corey; Schaefer *J. Am. Chem. Soc.* **1960,** *82*, 918.

[271] Sharpless; Gordon *J. Am. Chem. Soc.* **1976,** *98*, 300.

[272] Breslow; Winnik *J. Am. Chem. Soc.* **1969,** *91*, 3083; Breslow; Rothbard; Herman; Rodriguez *J. Am. Chem. Soc.* **1978,** *100*, 1213.

[273] Breslow; Rajagopalan; Schwarz *J. Am. Chem. Soc.* **1981,** *103*, 2905.

portion of the same molecule, i.e., the two portions are connected by a series of covalent bonds. However, the reaction can also be carried out where the two reacting centers are actually in different molecules, providing the two molecules are held together by hydrogen bonding. For example, one of the CH_2 groups of *n*-hexadecanol monosuccinate $CH_3(CH_2)_{14}CH_2OCOCH_2CH_2COOH$ was oxidized to a C=O group by applying the above procedure to a mixture of it and benzophenone-4-carboxylic acid *p*-$PhCOC_6H_4COOH$ in CCl_4.[274]

Other remote oxidations[275] have also been reported. Among these are conversion of aryl ketones $ArCO(CH_2)_3R$ to 1,4-diketones $ArCO(CH_2)_2COR$ by photoirradiation in the presence of such oxidizing agents as $K_2Cr_2O_7$ or $KMnO_4$,[276] and conversion of alkyl ketones $RCO(CH_2)_3R'$ to 1,3- and 1,4-diketones with $Na_2S_2O_8$ and $FeSO_4$.[277]

It is possible to perform the conversion $CH_2 \rightarrow C{=}O$ on an alkane, with no functional groups at all, though the most success has been achieved with substrates in which all CH_2 groups are equivalent, such as unsubstituted cycloalkanes. One method uses H_2O_2 and bis(picolinato)iron(II). With this method, cyclohexane was converted with 72% efficiency to give 95% cyclohexanone and 5% cyclohexanol.[278] The same type of conversion, with lower yields (20-30%), has been achieved with the *Gif system*.[279] There are several variations. One consists of pyridine–acetic acid, with H_2O_2 as oxidizing agent and tris(picolinato)iron(III) as catalyst.[280] Other Gif systems use O_2 as oxidizing agent and zinc as a reductant.[281] The selectivity of the Gif systems towards alkyl carbons is $CH_2 > CH \geq CH_3$, which is unusual, and shows that a simple free-radical mechanism (see p. 683) is not involved.[282] Another reagent that can oxidize the CH_2 of an alkane is methyl(trifluoromethyl)dioxirane, but this produces CH—OH more often than C=O (see **4-4**).[283]

OS **I,** 266; **II,** 509; **III,** 1, 420, 438; **IV,** 189, 229, 579; **VI,** 48. Also see OS **IV,** 23.

9-17 Oxidation of Arylmethanes

Oxo-de-dihydro-bisubstitution

$$ArCH_3 \xrightarrow{CrO_2Cl_2} ArCHO$$

Methyl groups on an aromatic ring can be oxidized to the aldehyde stage by several oxidizing agents. The reaction is a special case of **9-16.** When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction*[284] and the yields are high.[285] Another oxidizing agent is a mixture of CrO_3 and Ac_2O. In this case the reaction stops at the aldehyde stage because

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[274] Breslow; Scholl *J. Am. Chem. Soc.* **1971,** *93*, 2331. See also Breslow; Heyer *Tetrahedron Lett.* **1983,** *24*, 5039.

[275] See also Beckwith; Duong *J. Chem. Soc., Chem. Commun.* **1978,** 413.

[276] Mitani; Tamada; Uehara; Koyama *Tetrahedron Lett.* **1984,** *25*, 2805.

[277] Nikishin; Troyansky; Lazareva *Tetrahedron Lett.* **1984,** *25*, 4987.

[278] Sheu; Richert; Cofré; Ross; Sobkowiak; Sawyer; Kanofsky *J. Am. Chem. Soc.* **1990,** *112*, 1936. See also Sheu; Sobkowiak; Jeon; Sawyer *J. Am. Chem. Soc.* **1990,** *112*, 879; Tung; Sawyer *J. Am. Chem. Soc.* **1990,** *112*, 8214.

[279] Named for Gif-sur-Yvette, France, where it was discovered.

[280] About-Jaudet; Barton; Csuhai; Ozbalik *Tetrahedron Lett.* **1990,** *31*, 1657.

[281] See Barton; Boivin; Gastiger; Morzycki; Hay-Motherwell; Motherwell; Ozbalik; Schwartzentruber *J. Chem. Soc., Perkin Trans. 1* **1986,** 947; Barton; Csuhai; Ozbalik *Tetrahedron* **1990,** *46*, 3743.

[282] Barton; Csuhai; Doller; Ozbalik; Senglet *Tetrahedron Lett.* **1990,** *31*, 3097. For mechanistic studies, see Barton; Csuhai; Ozbalik *Tetrahedron Lett.* **1990,** *31*, 2817; Barton; Csuhai; Doller; Balavoine *J. Chem. Soc., Chem. Commun.* **1990,** 1787; Barton; Doller; Geletii *Tetrahedron Lett.* **1991,** *32*, 3811; Knight; Perkins *J. Chem. Soc., Chem. Commun.* **1991,** 925.

[283] Mello; Fiorentino; Fusco; Curci *J. Am. Chem. Soc.* **1989,** *111*, 6749.

[284] The name Étard reaction is often applied to any oxidation with chromyl chloride, e.g., oxidation of glycols (**9-7**), olefins (**9-10**), etc.

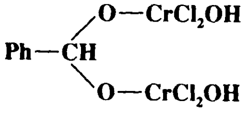
[285] For a review, see Hartford; Darrin *Chem. Rev.* **1958,** *58*, 1-61, pp. 25-53.

the initial product is $ArCH(OAc)_2$ (an acylal), which is resistant to further oxidation. Hydrolysis of the acylal gives the aldehyde.

Among other oxidizing agents[286] that have been used to accomplish the conversion of $ArCH_3$ to ArCHO are ceric ammonium nitrate,[287] ceric trifluoroacetate,[288] benzeneseleninic anhydride,[257] $KMnO_4$–Et_3N,[289] and silver(II) oxide.[290] Oxidation of $ArCH_3$ to carboxylic acids is considered at **9-11.**

Conversion of $ArCH_3$ to ArCHO can also be achieved indirectly by bromination to give $ArCHBr_2$ (**4-1**), followed by hydrolysis (**0-2**).

The mechanism of the Étard reaction is not completely known.[291] An insoluble complex is formed on addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but what the structure is is not fully settled, though many proposals have been made as to its structure and as to how it is hydrolyzed. It is known that $ArCH_2Cl$ is not an intermediate (see **9-20**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements[292] indicate that the complex from toluene is **27,** a structure first proposed by Étard. According to this proposal the reaction stops after only two hydrogens have been replaced because of the insolubility of **27.** There is a disagreement on how **27** is formed, assuming that the complex has this structure. Both an ionic[293] and a free-radical[294] process have been proposed. An entirely different structure for the complex was proposed by Nenitzescu and co-workers.[295] On the basis of esr studies they proposed that the complex is $PhCH_2OCrCl_2OCrOCl_2OH$, which is isomeric with **27.** However, this view has been challenged by Wiberg and Eisenthal,[294] who interpret the esr result as being in accord with **27.** Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.[296]

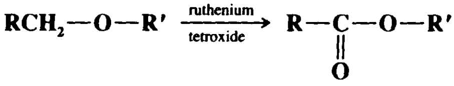


27

OS **II,** 441; **III,** 641; **IV,** 31, 713.

9-18 Oxidation of Ethers to Carboxylic Esters and Related Reactions

Oxo-de-dihydro-bisubstitution



$$RCH_2—O—R' \xrightarrow[\text{tetroxide}]{\text{ruthenium}} R—\underset{\underset{O}{\|}}{C}—O—R'$$

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[286] For a review of the use of oxidizing agents that are regenerated electrochemically, see Steckhan *Top. Curr. Chem.* **1987,** *142,* 1-69; pp. 12-17.

[287] Trahanovsky; Young *J. Org. Chem.* **1966,** *31,* 2033; Radhakrishna Murti; Pati *Chem. Ind.* (*London*) **1967,** 702; Ref. 256.

[288] Marrocco; Brilmyer *J. Org. Chem.* **1983,** *48,* 1487. See also Kreh; Spotnitz; Lundquist *J. Org. Chem.* **1989,** *54,* 1526.

[289] Li; Liu *Synthesis* **1989,** 293.

[290] Syper *Tetrahedron Lett.* **1967,** 4193.

[291] For a review, see Nenitzescu *Bull. Soc. Chim. Fr.* **1968,** 1349-1357.

[292] Wheeler *Can. J. Chem.* **1960,** *38,* 2137. See also Makhija; Stairs *Can. J. Chem.* **1968,** *46,* 1255.

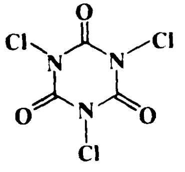
[293] Stairs *Can. J. Chem.* **1964,** *42,* 550.

[294] Wiberg; Eisenthal *Tetrahedron* **1964,** *20,* 1151. See also Gragerov; Ponomarchuk *J. Org. Chem. USSR* **1969,** *6,* 1125.

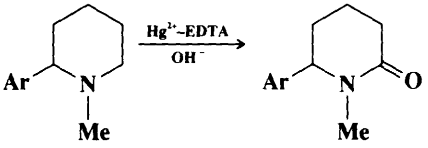
[295] Necşoiu; Balaban; Pascaru; Sliam; Elian; Nenitzescu *Tetrahedron* **1963,** *19,* 1133; Necşoiu; Przemetchi; Ghenciulescu; Rentea; Nenitzescu *Tetrahedron* **1966,** *22,* 3037.

[296] Duffin; Tucker *Chem. Ind.* (*London*) **1966,** 1262, *Tetrahedron* **1968,** *24,* 6999.

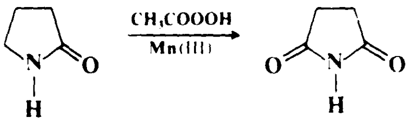
Ethers in which at least one group is primary alkyl can be oxidized to the corresponding carboxylic esters in high yields with ruthenium tetroxide.[297] Cyclic ethers give lactones. The reaction, a special case of **9-16,** has also been accomplished with CrO_3 in sulfuric acid,[298] with benzyltriethylammonium permanganate,[299] and with trichloroisocyanuric acid in the presence of an excess of water.[300] In a similar reaction, cyclic tertiary amines (e.g., **28**) can be converted to lactams by oxidation with Hg(II)–EDTA complex in basic solution.[301] Lactams, which need not be N-substituted (e.g., **29**), can be converted to cyclic imides by oxidation with a hydroperoxide or peracid and an Mn(II) or Mn(III) salt.[302] Certain tertiary amines containing a methyl group can be oxidized[303] to formamides ($R_2NCH_3 \rightarrow R_2NCHO$) by MnO_2,[304] CrO_3–pyridine,[305] O_2 and platinum,[306] or other oxidizing agents, but the reaction is not general.



Trichloroisocyanuric acid



28



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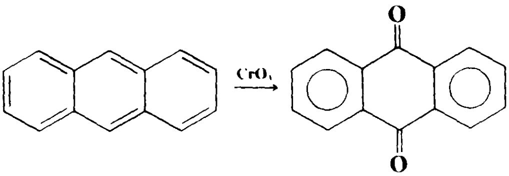
9-19 Oxidation of Aromatic Hydrocarbons to Quinones
Arene–quinone transformation



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[297] Berkowitz; Rylander *J. Am. Chem. Soc.* **1958,** *80,* 6682; Lee; van den Engh, in Trahanovsky, Ref. 2, pt. B, pp. 222-225; Smith; Scarborough *Synth. Commun.* **1980,** *10,* 205; Carlsen; Katsuki; Martin; Sharpless *J. Org. Chem.* **1981,** *46,* 3936.

[298] Henbest; Nicholls *J. Chem. Soc.* **1959,** 221, 227; Harrison; Harrison *Chem. Commun* **1966,** 752.

[299] Schmidt; Schäfer *Angew. Chem. Int. Ed. Engl.* **1979,** *18,* 69 [*Angew. Chem. 91,* 78].

[300] Juenge; Beal *Tetrahedron Lett.* **1968,** 5819; Juenge; Corey; Beal *Tetrahedron* **1971,** *27,* 2671.

[301] Wenkert; Angell *Synth. Commun.* **1988,** *18,* 1331.

[302] Doumaux; McKeon; Trecker *J. Am. Chem. Soc.* **1969,** *91,* 3992; Doumaux; Trecker *J. Org. Chem.* **1970,** *35,* 2121.

[303] See also Bettoni; Carbonara; Franchini; Tortorella *Tetrahedron* **1981,** *37,* 4159; Schmidt; Schäfer *Angew. Chem. Int. Ed. Engl.* **1981,** *20,* 109 [*Angew. Chem. 93,* 124].

[304] See, for example, Henbest; Thomas *J. Chem. Soc.* **1957,** 3032; Henbest; Stratford *J. Chem. Soc. C* **1966,** 995.

[305] Cavé; Kan-Fan; Potier; Le Men; Janot *Tetrahedron* **1967,** *23,* 4691.

[306] Davis; Rosenblatt *Tetrahedron Lett.* **1968,** 4085.

Condensed aromatic systems (including naphthalenes) can be directly oxidized to quinones by various oxidizing agents.[307] Yields are generally not high, though good yields have been reported with ceric ammonium sulfate.[308] Benzene cannot be so oxidized by strong oxidizing agents but can be electrolytically oxidized to benzoquinone.[309]

OS **IV,** 698, 757. Also see OS **II,** 554.

9-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes[310]

Oxo-de-hydro,halo-bisubstitution

$$\mathbf{RCH_2Cl \xrightarrow{(CH_3)_2SO} RCHO}$$

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with dimethyl sulfoxide.[311] Tosyl esters of primary alcohols can be similarly converted to aldehydes,[312] and epoxides[313] give α-hydroxy ketones or aldehydes.[314] The reaction with tosyl esters is an indirect way of oxidizing primary alcohols to aldehydes (**9-3**). This type of oxidation can also be carried out without isolation of an intermediate ester: The alcohol is treated with dimethyl sulfoxide, dicyclohexylcarbodiimide (DCC),[315] and anhydrous phosphoric acid.[316] In this way a primary alcohol can be converted to the aldehyde with no carboxylic acid being produced.

Similar oxidation of alcohols has been carried out with dimethyl sulfoxide and other reagents[317] in place of DCC: acetic anhydride,[318] SO_3–pyridine–triethylamine,[319] trifluoroacetic anhydride,[320] oxalyl chloride,[321] tosyl chloride,[322] chlorine,[323] bromine,[324] $AgBF_4$–Et_3N,[325] P_2O_5–Et_3N,[326] phenyl dichlorophosphate,[327] trichloromethyl chloroformate,[328] tri-

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[307] For reviews, see Naruta; Maruyama, in Patai; Rappoport, Ref. 18, vol. 2, pt. 1, 1988, pp. 242-247; Hudlický, Ref. 11, pp. 94-96; Haines-1985, Ref. 11, pp. 182-185, 358-360; Thomson, in Patai, Ref. 18, 1974, pp. 132-134. See also Šket; Zupan *Synth. Commun.* **1990,** *20,* 933; Ref. 112.

[308] Periasamy; Bhatt *Synthesis* **1977,** 330; Balanikas; Hussain; Amin; Hecht *J. Org. Chem.* **1988,** *53,* 1007.

[309] See, for example, Ito; Katayama; Kunai; Sasaki *Tetrahedron Lett.* **1989,** *30,* 205.

[310] For reviews of the reactions in this section, see Tidwell *Org. React.* **1990,** *39,* 297-572, *Synthesis* **1990,** 857-870; Haines-1988, Ref. 11, pp. 171-181, 402-406; Durst *Adv. Org. Chem.* **1969,** *6,* 285-388, pp. 343-356; Epstein; Sweat *Chem. Rev.* **1967,** *67,* 247-260; Moffatt, in Augustine; Trecker, Ref. 11, vol. 2, pp. 1-64. For a list of reagents, with references, see Ref. 21, pp. 599-600.

[311] Nace; Monagle *J. Org. Chem.* **1959,** *24,* 1792; Kornblum; Jones; Anderson *J. Am. Chem. Soc.* **1959,** *81,* 4113.

[312] Kornblum; Jones; Anderson, Ref. 311.

[313] Epoxides can be converted to α-halo ketones by treatment with bromodimethylsulfonium bromide: Olah; Vankar; Arvanaghi *Tetrahedron Lett.* **1979,** 3653.

[314] Cohen; Tsuji *J. Org. Chem.* **1961,** *26,* 1681; Tsuji *Tetrahedron Lett.* **1966,** 2413; Santosusso; Swern *Tetrahedron Lett.* **1968,** 4261, *J. Org. Chem.* **1975,** *40,* 2764.

[315] The DCC is converted to dicyclohexylurea, which in some cases is difficult to separate from the product. One way to avoid this problem is to use a carbodiimide linked to an insoluble polymer: Weinshenker; Shen *Tetrahedron Lett.* **1972,** 3285.

[316] Pfitzner; Moffatt *J. Am. Chem. Soc.* **1965,** *87,* 5661, 5670; Fenselau; Moffatt *J. Am. Chem. Soc.* **1966,** *88,* 1762; Albright; Goldman *J. Org. Chem.* **1965,** *30,* 1107.

[317] For a review of activated Me_2SO reagents and their use in this reaction, see Mancuso; Swern *Synthesis* **1981,** 165-185.

[318] Albright; Goldman *J. Am. Chem. Soc.* **1967,** *89,* 2416.

[319] Parikh; Doering *J. Am. Chem. Soc.* **1967,** *89,* 5507.

[320] Huang; Omura; Swern *Synthesis* **1978,** 297.

[321] Omura; Swern *Tetrahedron* **1978,** *34,* 1651. See also Marx; Tidwell *J. Org. Chem.* **1984,** *49,* 788.

[322] Albright *J. Org. Chem.* **1974,** *39,* 1977.

[323] Corey; Kim *Tetrahedron Lett.* **1973,** 919.

[324] Munavu *J. Org. Chem.* **1980,** *45* 3341.

[325] Ganem; Boeckman *Tetrahedron Lett.* **1974,** 917.

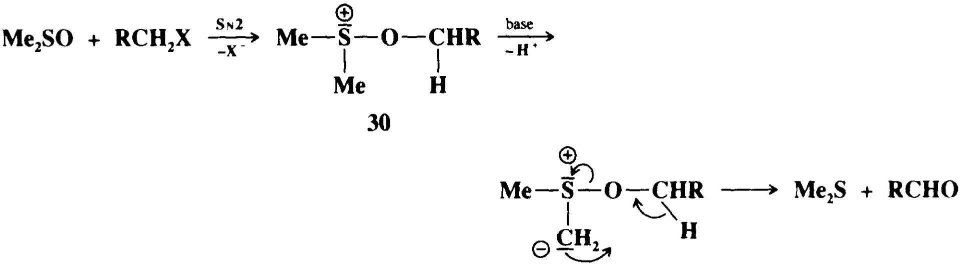
[326] Taber; Amedio; Jung *J. Org. Chem.* **1987,** *52,* 5621.

[327] Liu; Nyangulu *Tetrahedron Lett.* **1988,** *29,* 3167.

[328] Takano; Inomata; Tomita; Yanase; Samizu; Ogasawara *Tetrahedron Lett.* **1988,** *29,* 6619.

methylamine oxide,[329] KI and $NaHCO_3$,[330] and methanesulfonic anhydride,[322] among others. When oxalyl chloride is used, the method is called *Swern oxidation*.

The mechanism of these dimethyl sulfoxide oxidations is probably as follows:[331]



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31

though in some cases the base abstracts a proton directly from the carbon being oxidized, in which case the ylide **31** is not an intermediate. Alkoxysulfonium salts **30** have been isolated.[332] This mechanism predicts that secondary compounds should be oxidizable to ketones, and this is the case. In a related procedure for the oxidation of alcohols, the intermediate **30**[333] is formed without the use of dimethyl sulfoxide by treating the substrate with a complex generated from chlorine or N-chlorosuccinimide and dimethyl sulfide.[334]

Another way to oxidize primary alkyl halides to aldehydes is by the use of hexamethylenetetramine followed by water. However, this reaction, called the *Sommelet reaction*,[335] is limited to benzylic halides. The reaction is seldom useful when the R in RCH_2Cl is alkyl. The first part of the reaction is conversion to the amine $ArCH_2NH_2$ (**0-44**), which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step that is the actual Sommelet reaction, though the entire process can be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine ($ArCH_2N{=}CH_2$) with formaldehyde liberated from the reagent. The key step then follows: transfer of hydrogen from another mole of the arylamine to the imine:

$$ArCH_2N{=}CH_2 + ArCH_2NH_2 \longrightarrow ArCH_2NHCH_3 + ArCH{=}NH$$

This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine.

Other reagents that convert benzylic halides to aldehydes are 2-nitropropane–NaOEt in EtOH,[336] mercury(I) nitrate followed by ethanolic alkali,[337] and pyridine followed by *p*-nitrosodimethylaniline and then water. The last procedure is called the *Kröhnke reaction*. Primary halides in general have been oxidized to aldehydes by trimethylamine oxide,[338] by

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[329] Godfrey; Ganem *Tetrahedron Lett.* **1990,** *31*, 4825.

[330] Bauer; Macomber *J. Org. Chem.* **1975,** *40*, 1990.

[331] Pfitzner; Moffatt *J. Am. Chem. Soc.* **1965,** *87*, 5661; Johnson; Phillips *J. Org. Chem.* **1967,** *32*, 1926; Torssell *Acta Chem. Scand.* **1967,** *21*, 1.

[332] Torssell *Tetrahedron Lett.* **1966,** 4445; Johnson; Phillips, Ref. 331; Khuddus; Swern *J. Am. Chem. Soc.* **1973,** 95, 8393.

[333] It has been suggested that in the DCC reaction, **30** is not involved, but the ylide **31** is formed directly from a precursor containing DCC and dimethyl sulfoxide: Torssell, Ref. 332; Moffatt *J. Org. Chem.* **1971,** *36*, 1909.

[334] Vilsmaier; Sprügel *Liebigs Ann. Chem.* **1971,** *747*, 151; Corey; Kim *J. Am. Chem. Soc.* **1972,** *94*, 7586, *J. Org. Chem.* **1973,** *38*, 1233; McCormick *Tetrahedron Lett.* **1974,** 1701; Katayama; Fukuda; Watanabe; Yamauchi *Synthesis* **1988,** 178.

[335] For a review, see Angyal *Org. React.* **1954,** *8*, 197-217.

[336] Hass; Bender *J. Am. Chem. Soc.* **1949,** *71*, 1767.

[337] McKillop; Ford *Synth. Commun.* **1974,** *4*, 45.

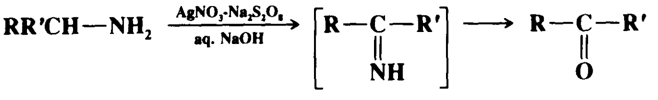
[338] Franzen; Otto *Chem. Ber.* **1961,** *94*, 1360.

4-dimethylaminopyridine-N-oxide,[339] by other amine oxides (for allylic chlorides)[340] and by K_2CrO_4 in HMPA in the presence of a crown ether.[341] The first of these procedures has also been applied to primary tosylates.[338]

OS **II,** 336: **III,** 811; **IV,** 690, 918, 932; **V,** 242, 668, 825, 852, 872. Also see OS **V,** 689; **VI,** 218.

9-21 Oxidation of Amines or Nitro Compounds to Aldehydes, Ketones, or Dihalides

Oxo-de-hydro,amino-bisubstitution (overall transformation)



$$\mathrm{RR'CH{-}NH_2} \xrightarrow[\text{aq. NaOH}]{\mathrm{AgNO_3\text{-}Na_2S_2O_8}} \left[\begin{array}{c} \mathrm{R{-}C{-}R'} \\ \| \\ \mathrm{NH} \end{array}\right] \longrightarrow \begin{array}{c} \mathrm{R{-}C{-}R'} \\ \| \\ \mathrm{O} \end{array}$$

Primary aliphatic amines can be oxidized to aldehydes or ketones[342] by reaction with Ag(II) prepared in situ by treatment of silver nitrate with sodium persulfate.[343] The reaction consists of dehydrogenation to the imine (**9-5**) followed by hydrolysis. Other reagents used[344] have been nitrosobenzene[345] or N-bromoacetamide[346] (for benzylic amines), 3,5-di-*t*-butyl-1,2-benzoquinone,[347] *m*-trifluoromethylbenzenesulfonyl peroxide,[348] diphenylseleninic anhydride,[349] $PdCl_2$ or $AuCl_3$,[350] and aqueous NaOCl with phase-transfer catalysts.[351] Benzylic amine salts $PhCHRNR'_2H^+\ Cl^-$ (R,R' = H or alkyl) give benzaldehydes or aryl ketones when heated in Me_2SO.[352] Several indirect methods for achieving the conversion $RR'CHNH_2 \rightarrow RR'C{=}O$ (R' = alkyl, aryl, or H) have been reported.[353]

Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aqueous bromine[354] and with neutral permanganate.[355] The other product of this reaction is the amine with one less alkyl group.

In a different type of procedure, primary alkyl primary amines can be converted to *gem*-dihalides [$RCH_2NH_2 \rightarrow RCHX_2$ (X = Br or Cl)] by treatment with an alkyl nitrite and the anhydrous copper(I) halide.[356]

Primary and secondary aliphatic nitro compounds have been oxidized to aldehydes and ketones, respectively ($RR'CHNO_2 \rightarrow RR'C{=}O$) with sodium chlorite under phase transfer conditions,[357] as well as with other reagents.[358]

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[339] Mukaiyama; Inanaga; Yamaguchi *Bull. Chem. Soc. Jpn.* **1981,** *54,* 2221.

[340] Suzuki; Onishi; Fujita; Misawa; Otera *Bull. Chem. Soc. Jpn.* **1986,** *59,* 3287.

[341] Cardillo; Orena; Sandri *J. Chem. Soc. Chem. Commun.* **1976,** 190, *Tetrahedron Lett.* **1976,** 3985. For related procedures, see Landini; Rolla *Chem. Ind.* (*London*) **1979,** 213; Thuy; Maitte *Bull. Soc. Chim. Belg.* **1989,** *98,* 221.

[342] For a review, see Haines-1988, Ref. 11, pp. 200-220, 411-415.

[343] Bacon; Stewart *J. Chem. Soc. C* **1966,** 1384. See also Lee; Clarke *Tetrahedron Lett.* **1967,** 415.

[344] For lists of reagents, with references, see Ref. 21, pp. 601-602; Hudlický, Ref. 11, p. 240.

[345] Suzuki; Weisburger *Tetrahedron Lett.* **1966,** 5409, *J. Chem. Soc. C* **1968,** 199.

[346] Banerji *Bull. Chem. Soc. Jpn.* **1988,** *61,* 3717.

[347] Corey; Achiwa *J. Am. Chem. Soc.* **1969,** *91,* 1429. For a study of the mechanism, see Klein; Bargas; Horak *J. Org. Chem.* **1988,** *53,* 5994.

[348] Hoffman; Kumar *J. Org. Chem.* **1984,** *49,* 4011.

[349] Czarny *J. Chem. Soc., Chem. Commun.* **1976,** 81. See also Czarny *Synth. Commun.* **1976,** *6,* 285.

[350] Kuehne; Hall *J. Org. Chem.* **1976,** *41,* 2742.

[351] Lee; Freedman *Tetrahedron Lett.* **1976,** 1641.

[352] Traynelis; Ode *J. Org. Chem.* **1970,** *35,* 2207. For other methods, see Takabe; Yamada *Chem. Ind.* (*London*) **1982,** 959; Azran; Buchman; Pri-Bar *Bull. Soc. Chim. Belg.* **1990,** *99,* 345.

[353] See, for example, Dinizio; Watt *J. Am. Chem. Soc.* **1975,** *97,* 6900; Black; Blackman *Aust. J. Chem.* **1975,** *28,* 2547; Scully; Davis *J. Org. Chem.* **1978,** *43,* 1467; Doleschall *Tetrahedron Lett.* **1978,** 2131; Babler; Invergo *J. Org. Chem.* **1981,** *46,* 1937.

[354] Deno; Fruit *J. Am. Chem. Soc.* **1968,** *90,* 3502.

[355] Rawalay; Shechter *J. Org. Chem.* **1967,** *32,* 3129. For another procedure, see Monković; Wong; Bachand *Synthesis* **1985,** 770.

[356] Doyle; Siegfried *J. Chem. Soc., Chem. Commun.* **1976,** 433.

[357] Ballini; Petrini *Tetrahedron Lett.* **1989,** *30,* 5329.

[358] For a list of reagents, with references, see Ref. 21, p. 603.

9-22 Oxidation of Primary Alcohols to Carboxylic Acids or Carboxylic Esters

Oxo-de-dihydro-bisubstitution

$$RCH_2OH \xrightarrow{CrO_3} RCOOH$$

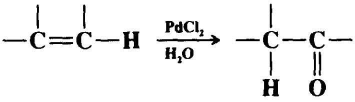
Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents including chromic acid, permanganate, and nitric acid.[359] The reaction can be looked on as a combination of **9-3** and **4-6.** When acidic conditions are used, a considerable amount of carboxylic ester $RCOOCH_2R$ is often isolated, though this is probably not formed by a combination of the acid with unreacted alcohol, but by a combination of intermediate aldehyde with unreacted alcohol to give an acetal or hemiacetal, which is oxidized to the ester.[360] $RCOOCH_2R$ can be made the main product by treating the alcohol with (1) $Ru_3(CO)_{12}$ and diphenylacetylene, or with a complex formed from these two reagents;[361] (2) Pd salts and CCl_4 in the presence of K_2CO_3;[362] or (3) $RuH_2(PPh_3)_4$.[363] Primary alcohols RCH_2OH can be directly oxidized to acyl fluorides RCOF with cesium fluoroxysulfate.[364] Lactones can be prepared by oxidizing diols in which at least one OH is primary.[365]

Primary alkyl ethers can be selectively cleaved to carboxylic acids by aqueous Br_2 ($RCH_2OR' \rightarrow RCOOH$).[109] Aldehydes RCHO can be directly converted to carboxylic esters RCOOR' by treatment with Br_2 in the presence of an alcohol.[366]

OS **I,** 138, 168; **IV,** 499, 677; **V,** 580; **VII,** 406. Also see OS **III,** 745.

9-23 Oxidation of Olefins to Aldehydes and Ketones

1/Oxo-(1/→2/hydro)-*migro*-attachment



$$-\overset{|}{C}=\overset{|}{C}-H \xrightarrow[H_2O]{PdCl_2} -\underset{H}{\overset{|}{\underset{|}{C}}}-\underset{O}{\underset{\|}{C}}-$$

Monosubstituted and 1,2-disubstituted olefins can be oxidized to aldehydes and ketones by palladium chloride and similar salts of noble metals.[367] 1,1-Disubstituted olefins generally give poor results. The reaction is used industrially to prepare acetaldehyde from ethylene

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[359] For reviews, see Hudlický, Ref. 11, pp. 127-132; Haines-1988, Ref. 11, 148-165, 391-401. For a list of reagents, with references, see Ref. 21, pp. 834-835.

[360] Craig; Horning *J. Org. Chem.* **1960,** *25,* 2098. See also Berthon; Forestiere; Leleu; Sillion *Tetrahedron Lett.* **1981,** *22,* 4073; Nwaukwa; Keehn *Tetrahedron Lett,* **1982,** *23,* 35.

[361] Blum; Shvo *J. Organomet. Chem.* **1984,** *263,* 93, *Isr. J. Chem.* **1984,** *24,* 144.

[362] Nagashima; Sato; Tsuji *Tetrahedron* **1985,** *41,* 5645.

[363] Murahashi; Naota; Ito; Maeda; Taki *J. Org. Chem.* **1987,** *52,* 4319. For another method, see Markó; Mekhalfia; Ollis *Synlett* **1990,** 347.

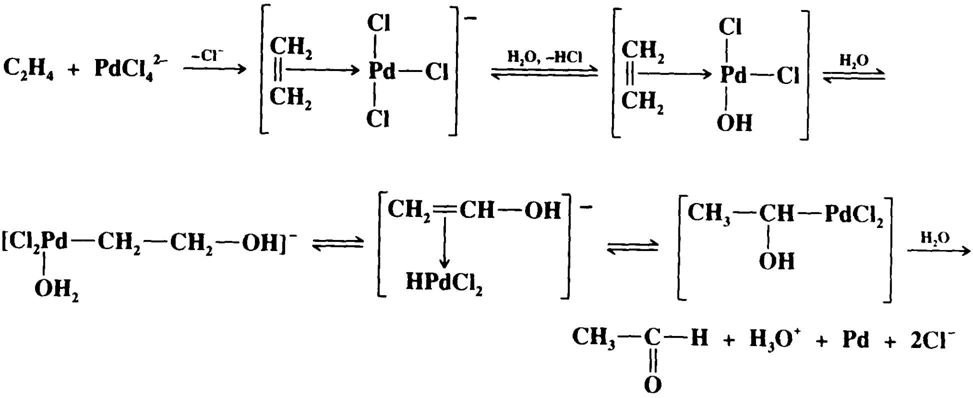
[364] Stavber; Planinšek; Zupan *Tetrahedron Lett.* **1989,** *30,* 6095.

[365] For examples of the preparation of lactones by oxidation of diols, see Doyle; Bagheri *J. Org. Chem.* **1981,** *46,* 4806; Ishii; Suzuki; Ikariya; Saburi; Yoshikawa *J. Org. Chem.* **1986,** *51,* 2822; Jefford; Wang *J. Chem. Soc., Chem. Commun.* **1988,** 634; Jones; Jakovac *Org. Synth. VII,* 406. For a list of reagents used to effect this conversion, with references, see Ref. 21, pp. 837-838.

[366] Williams; Klingler; Allen; Lichtenthaler *Tetrahedron Lett.* **1988,** *29,* 5087; Al Neirabeyeh; Pujol *Tetrahedron Lett.* **1990,** *31,* 2273. For other methods, see Sundararaman; Walker; Djerassi *Tetrahedron Lett.* **1978,** 1627; Grigg; Mitchell; Sutthivaiyakit *Tetrahedron* **1981,** *37,* 4313; Massoui; Beaupère; Nadjo; Uzan *J. Organomet. Chem.* **1983,** *259,* 345; O'Connor; Just *Tetrahedron Lett.* **1987,** *28,* 3235; McDonald; Holcomb; Kennedy; Kirkpatrick; Leathers; Vanemon *J. Org. Chem.* **1989,** *54,* 1212. For a list of reagents, with references, see Ref. 21, pp. 840-841.

[367] For a monograph, see Henry *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel Publishing Co.: Dordrecht, 1980. For reviews, see Tsuji *Organic Synthesis with Palladium Compounds*; Springer: New York, 1980, pp. 6-12, *Synthesis* **1990,** 739-749, **1984,** 369-384, *Adv. Org. Chem.* **1969,** *6,* 109-255, pp. 119-131; Heck *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985, pp. 59-80; Sheldon; Kochi, Ref. 118, pp. 189-193, 299-303; Henry *Adv. Organomet. Chem.* **1975,** *13,* 363-452, pp. 378-388; Jira; Freiesleben *Organomet. React.* **1972,** *3,* 1-190, pp. 1-44; Khan; Martell *Homogeneous Catalysis by Metal Complexes,* vol. 2; Academic Press: New York, 1974, pp. 77-91; Hüttel *Synthesis* 225-255, **1970,** pp. 225-236; Aguiló *Adv. Organomet. Chem.* **1967,** *5,* 321-352; Bird *Transition Metal Intermediates in Organic Synthesis*; Academic Press: New York, 1967, pp. 88-111.

(the *Wacker process*), but it is also suitable for laboratory preparations. The palladium chloride is reduced to palladium. Because the reagent is expensive, the reaction is usually carried out with a cooxidant, most often $CuCl_2$, whose function is to reoxidize the Pd to Pd(II). The $CuCl_2$ is reduced to Cu(I), which itself is reoxidized to Cu(II) by air, so that atmospheric oxygen is the only oxidizing agent actually used up. Many other cooxidants have been tried, among them O_3, Fe^{3+}, and PbO_2. The principal product is an aldehyde only from ethylene: With other olefins Markovnikov's rule is followed, and ketones are formed predominantly. The generally accepted mechanism involves π complexes of palladium.[368]



This mechanism accounts for the fact, established by deuterium labeling, that the four hydrogens of the acetaldehyde all come from the original ethylene and none from the solvent.

Similar reactions have been carried out with other oxidizing agents. An example involving migration of an alkyl group instead of hydrogen is oxidation of $Me_2C{=}CMe_2$ with peroxytrifluoroacetic acid–boron trifluoride to give Me_3COMe (pinacolone).[369] This reaction consists of epoxidation (**5-36**) followed by pinacol rearrangement of the epoxide (**8-2**). A migration is also involved in the conversion of $ArCH{=}CHCH_3$ to $ArCH(CH_3)CHO$ by treatment with I_2–Ag_2O in aqueous dioxane.[370]

Other reagents used have been chromyl chloride[371] (e.g., $Me_3CCH_2CMe{=}CH_2 \rightarrow Me_3CCH_2CHMeCHO$), $Pb(OAc)_4$–F_3CCOOH[372] (e.g., $PhCH{=}CH_2 \rightarrow PhCH_2CHO$), thallium(III) nitrate–methanol[373] (e.g, cyclohexene → cyclopentanecarboxaldehyde), Cl_2 or Br_2 and $AgNO_3$,[374] disiamylborane followed by pyridinium chlorochromate,[375] H_2O_2 and a Pd catalyst,[376] H_2O–$PdCl_2$–polyethylene glycol,[377] O_2 and a catalyst,[378] CrO_3–H_2SO_4–Hg(II)

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[368] Henry *J. Am. Chem. Soc.* **1966,** *88,* 1595, **1972,** *94,* 4437; Jira; Sedlmeier; Smidt *Liebigs Ann. Chem.* **1966,** *693,* 99; Hosokawa; Maitlis *J. Am. Chem. Soc.* **1973,** *95,* 4924; Moiseev; Levanda; Vargaftik *J. Am. Chem. Soc.* **1974,** *96,* 1003; Bäckvall; Åkermark; Ljunggren *J. Chem. Soc., Chem. Commun.* **1977,** 264, *J. Am. Chem. Soc.* **1979,** *101,* 2411; Zaw; Henry *J. Org. Chem.* **1990,** *55,* 1842.

[369] Hart; Lerner *J. Org. Chem.* **1967,** *32,* 2669.

[370] Kikuchi; Kogure; Toyoda *Chem. Lett.* **1984,** 341.

[371] Freeman; Cameron; DuBois *J. Org. Chem.* **1968,** *33,* 3970; Freeman; Arledge *J. Org. Chem.* **1972,** *37,* 2656. See also Sharpless, Teranishi; Bäckvall *J. Am. Chem. Soc.* **1977,** *99,* 3120.

[372] Lethbridge; Norman; Thomas *J. Chem. Soc., Perkin Trans. 1* **1973,** 35.

[373] McKillop; Hunt; Kienzle; Bigham; Taylor *J. Am. Chem. Soc.* **1973,** *95,* 3635. See also Grant; Liau; Low *Aust. J. Chem.* **1975,** *28,* 903.

[374] Kakis; Brase; Oshima *J. Org. Chem.* **1971,** *36,* 4117.

[375] Brown; Kulkarni; Rao *Synthesis* **1980,** 151.

[376] Roussel; Mimoun *J. Org. Chem.* **1980,** *45,* 5387.

[377] Alper; Januszkiewicz; Smith *Tetrahedron Lett.* **1985,** *26,* 2263.

[378] See, for example, Zombeck; Hamilton; Drago *J. Am. Chem. Soc.* **1982,** *104,* 6782; Januszkiewicz; Alper *Tetrahedron Lett.* **1983,** *24,* 5159, 5163; Bäckvall; Hopkins *Tetrahedron Lett.* **1988,** *29,* 2885; Chipperfield; Shana'a; Webster *J. Organomet. Chem.* **1988,** *341,* 511; Sage; Gore; Guilmet *Tetrahedron Lett.* **1989,** *30,* 6319.

salts,[379] $HgSO_4$–H_2O,[380] and $Hg(OAc)_2$ followed by $PdCl_2$.[381] The reaction has also been accomplished electrochemically.[382]

Alkenes have also been converted to more-highly-oxidized products. Examples are: (1) Treatment with $KMnO_4$ in aqueous acetone containing acetic acid gives α-hydroxy ketones.[383] (2) 1,2-Disubstituted and trisubstituted alkenes give α-chloro ketones when oxidized with chromyl chloride in acetone: $RCH{=}CR'R'' \rightarrow RCOCClR'R''$.[384] (3) α-Iodo ketones can be prepared by treating alkenes with bis(*sym*-collidine)iodine(I) tetrafluoroborate.[385] (4) $KMnO_4$ in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.[386]

Enol ethers are oxidized to carboxylic esters ($RCH{=}CHOR' \rightarrow RCH_2COOR'$) with pyridinium chlorochromate[387] and enamines to α-amino ketones ($R^1CH{=}CR^2NR^3_2 \rightarrow R^1COCR^2NR^3_2$) with N-sulfonyloxaziridines.[388] Enamines $R^1R^4C{=}CR^2NR^3_2$ ($R^4 \neq H$) do not give these products, but lose the amino group to give α-hydroxy ketones $R^1R^4C(OH)COR^2$.[388] Carboxylic acids can be prepared from terminal alkynes ($RC{\equiv}CH \rightarrow RCH_2COOH$) by conversion of the alkyne to its thiophenyl ether ($RC{\equiv}CSPh$) and treatment of this with $HgSO_4$ in $HOAc$–H_2SO_4.[389]

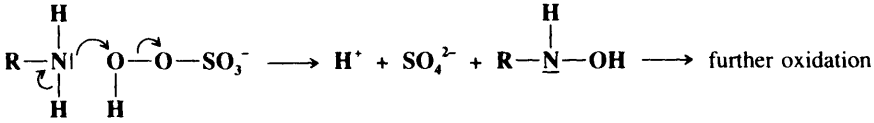
OS **VI,** 1028; **VII,** 137; **67,** 121.

9-24 Oxidation of Amines to Nitroso Compounds and Hydroxylamines

***N*-Oxo-de-dihydro-bisubstitution**

$$\mathbf{ArNH_2 \xrightarrow{H_2SO_5} Ar{-}N{=}O}$$

Primary aromatic amines can be oxidized[390] to nitroso compounds. Most often the conversion is accomplished by Caro's acid (H_2SO_5) or with H_2O_2 in HOAc.[391] Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions are generally oxidized to the nitroso compounds. Primary aliphatic amines can be oxidized in this manner, but the nitroso compound is stable only if there is no α hydrogen. If there is an α hydrogen, the compound tautomerizes to the oxime.[392] Among the reagents used for this oxidation are sodium perborate[393] and Na_2WO_4–H_2O_2.[394] The mechanism with H_2SO_5 has been postulated to be an example of category 5 (p. 1161).[395]



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[379] Rogers; McDermott; Whitesides *J. Org. Chem.* **1975,** *40*, 3577.

[380] Arzoumanian; Aune; Guitard; Metzger *J. Org. Chem.* **1974,** *39*, 3445.

[381] Rodeheaver; Hunt *Chem. Commun.* **1971,** 818. See also Hunt; Rodeheaver *Tetrahedron Lett.* **1972,** 3595.

[382] See Tsuji; Minato *Tetrahedron Lett.* **1987,** *28*, 3683.

[383] Srinivasan; Lee *Synthesis* **1979,** 520. See also Baskaran; Das; Chandrasekaran *J. Org. Chem.* **1989,** *54*, 5182.

[384] Sharpless; Teranishi *J. Org. Chem.* **1973,** *38*, 185. See also Cardillo; Shimizu *J. Org. Chem.* **1978,** *42*, 4268; D'Ascoli; D'Auria; Nucciarelli; Piancatelli; Scettri *Tetrahedron Lett.* **1980,** *21*, 4521; Kageyama; Tobito; Katoh; Ueno; Okawara *Chem. Lett.* **1983,** 1481; Lee; Ha *Tetrahedron Lett.* **1989,** *30*, 193.

[385] Evans; Schauble *Synthesis* **1986,** 727.

[386] Sharpless; Lauer; Repič; Teranishi; Williams, *J. Am. Chem. Soc.* **1971,** *93*, 3303; Jensen; Sharpless *J. Org. Chem.* **1974,** *39*, 2314.

[387] Piancatelli; Scettri; D'Auria *Tetrahedron Lett.* **1977,** 3483. When $R^1CR^2C{=}CR^3OR^4$ are used, cleavage of the double bond takes place instead: Baskaran; Islam; Raghavan; Chandrasekaran *Chem. Lett.* **1987,** 1175.

[388] Davis; Sheppard *Tetrahedron Lett.* **1988,** *29*, 4365.

[389] Abrams *Can. J. Chem.* **1983,** *61*, 2423.

[390] For reviews on the oxidation of amines, see Rosenblatt; Burrows, in Patai The *Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 1085-1149; Challis; Butler, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 320-338. For reviews confined to primary aromatic amines, see Hedayatullah *Bull. Soc. Chim. Fr.* **1972,** 2957; Surville; Jozefowicz; Buvet *Ann. Chem.* (*Paris*) **1967,** [14] 2, 149-157.

[391] Holmes; Bayer *J. Am. Chem. Soc.* **1960,** *82*, 3454.

[392] For example, see Kahr; Berther *Chem. Ber.* **1960,** *93*, 132.

[393] Zajac; Darcy; Subong; Buzby *Tetrahedron Lett.* **1989,** *30*, 6495.

[394] Corey; Gross *Org. Synth.* *65*, 166.

[395] Gragerov; Levit *J. Gen Chem. USSR* **1960,** *30*, 3690.

Secondary amines R_2NH are oxidized to hydroxylamines R_2NHOH (which are resistant to further oxidation) by dimethyldioxirane[396] and by benzoyl peroxide and Na_2HPO_4.[397]

OS **III,** 334; **65,** 166.

9-25 Oxidation of Primary Amines, Oximes, Azides, Isocyanates, or Nitroso Compounds to Nitro Compounds

$$\mathbf{R_3CNH_2 \xrightarrow{KMnO_4} R_3CNO_2}$$

$$\mathbf{R_2C{=}NOH \xrightarrow{F_3CCOOOH} R_2CHNO_2}$$

Tertiary alkyl primary amines can be oxidized to nitro compounds in excellent yields with $KMnO_4$.[398] This type of nitro compound is not easily prepared in other ways. All classes of primary amine (including primary, secondary, and tertiary alkyl as well as aryl) are oxidized to nitro compounds in high yields with dimethyldioxirane.[399] Other reagents that oxidize various types of primary amines to nitro compounds are dry ozone,[400] various peracids,[401] including peracetic and peroxytrifluoroacetic acids, *t*-butyl hydroperoxide in the presence of certain molybdenum and vanadium compounds,[402] F_2–H_2O–MeCN,[402a] and sodium perborate.[403]

Dimethyldioxirane in wet acetone oxidizes isocyanates to nitro compounds ($RNCO \rightarrow RNO_2$).[404] Oximes can be oxidized to nitro compounds with peroxytrifluoroacetic acid, among other ways.[398] Primary and secondary alkyl azides have been converted to nitro compounds by treatment with Ph_3P followed by ozone.[405] Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.[406]

OS **III,** 334; **V,** 367, 845; **VI,** 803.

9-26 Oxidation of Thiols and Other Sulfur Compounds to Sulfonic Acids

Thiol-sulfonic acid oxidation

$$\mathbf{RSH \xrightarrow{HNO_3} RSO_3H}$$

Thiols, sulfoxides, sulfones, disulfides,[407] and other sulfur compounds can be oxidized to sulfonic acids with many oxidizing agents, though for synthetic purposes the reaction is most important for thiols.[408] Among oxidizing agents used are boiling nitric acid and barium

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[396] Murray; Singh *Synth. Commun.* **1989,** *19,* 3509. This reagent also oxidizes primary amines to hydroxylamines: Wittman; Halcomb; Danishefsky *J. Org. Chem.* **1990,** *55,* 1981.

[397] Biloski; Ganem *Synthesis* **1983,** 537.

[398] Larson, in Feuer *The Chemistry of the Nitro and Nitroso Groups,* vol. 1; Wiley: New York, 1969, pp. 306-310. See also Barnes; Patterson *J. Org. Chem.* **1976,** *41,* 733. For reviews of oxidations of nitrogen compounds, see Butler *Chem. Rev.* **1984,** *84,* 249-276; Boyer *Chem. Rev.* **1980,** *80,* 495-561.

[399] Murray; Rajadhyaksha; Mohan *J. Org. Chem.* **1989,** *54,* 5783. See also Zabrowski; Moorman; Beck *Tetrahedron Lett.* **1988,** *29,* 4501.

[400] Keinan; Mazur *J. Org. Chem.* **1977,** *42* 844; Bachman; Strawn *J. Org. Chem.* **1968,** *33,* 313.

[401] Emmons *J. Am. Chem. Soc.* **1957,** *79,* 5528; Gilbert; Borden *J. Org. Chem.* **1979,** *44,* 659.

[402] Howe; Hiatt *J. Org. Chem.* **1970,** *35,* 4007. See also Nielsen; Atkins; Norris; Coon; Sitzmann *J. Org. Chem.* **1980,** *45,* 2341.

[402a] Kol; Rozen *J. Chem. Soc., Chem. Commun.* **1991,** 567.

[403] McKillop; Tarbin *Tetrahedron* **1987,** *43,* 1753.

[404] Eaton; Wicks *J. Org. Chem.* **1988,** *53,* 5353.

[405] Corey; Samuelsson; Luzzio *J. Am. Chem. Soc.* **1984,** *106,* 3682.

[406] See Boyer, in Feuer, Ref. 398, pp. 264-265.

[407] For a review of the oxidation of disulfides, see Savige; Maclaren, in Kharasch; Meyers *Organic Sulfur Compounds,* vol. 2; pp. 367-402, Pergamon, New York, 1966.

[408] For a general review of the oxidation of thiols, see Capozzi; Modena, in Patai *The Chemistry of the Thiol Group,* pt. 2; Wiley: New York, 1974, pp. 785-839. For a review specifically on the oxidation to sulfonic acids, see Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 217-239.

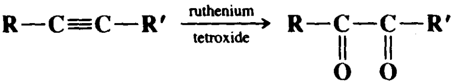
permanganate. Autoxidation (oxidation by atmospheric oxygen) can be accomplished in basic solution.[409] Oxidation of thiols with chlorine and water gives sulfonyl chlorides directly.[410] Thiols can also be oxidized to disulfides (**9-35**).

OS **II,** 471; **III,** 226. Also see OS **V,** 1070.

D. Reactions in Which Oxygen is Added to the Substrate

9-27 The Oxidation of Alkynes to α-Diketones

Dioxo-biaddition



$$R-C\equiv C-R' \xrightarrow[\text{tetroxide}]{\text{ruthenium}} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R'$$

Internal alkynes have been oxidized[411] to α-diketones by several oxidizing agents,[412] including ruthenium tetroxide,[413] neutral $KMnO_4$,[414] SeO_2 with a small amount of H_2SO_4,[415] bis(trifluoroacetoxy)iodobenzene,[416] $NaIO_4$–RuO_2,[417] I_2–Me_2SO,[418] and thallium(III) nitrate,[206] as well as by electrooxidation.[419] Ozone generally oxidizes triple-bond compounds to carboxylic acids (**9-9**), but α-diketones are sometimes obtained instead. SeO_2 with a small amount of H_2SO_4 oxidizes arylacetylenes to α-keto acids ($ArC\equiv CH \rightarrow ArCOCOOH$),[415] while H_2O_2–$Hg(OAc)_2$ together with a molybdenate salt oxidizes them to α-keto aldehydes, though yields are not high.[420]

9-28 Oxidation of Tertiary Amines to Amine Oxides

***N*-Oxygen-attachment**

$$R_3N \xrightarrow{H_2O_2} R_3\overset{\oplus}{N}-\overset{\ominus}{O}$$

Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peracids are also important reagents for this purpose. Pyridine and its derivatives are oxidized only by peracids.[421] In the attack by hydrogen peroxide there is first formed a trialkylammonium peroxide, a hydrogen-bonded complex represented as $R_3N{\cdot}H_2O_2$, which can be isolated.[422] The decomposition of this complex probably involves an attack by the

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[409] Wallace; Schriesheim *Tetrahedron* **1965,** *21,* 2271.

[410] For a review, see Gilbert, Ref. 408, pp. 202-214.

[411] For a review of this reaction, see Haines-1985, Ref. 11, pp. 153-162, 332-338. For a review of oxidations of triple bonds in general, see Simándi, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C,* pt. 1; Wiley: New York, 1983, pp. 513-570.

[412] For a list of reagents, with references, see Hudlický, Ref. 11, p. 92.

[413] Gopal; Gordon *Tetrahedron Lett.* **1971,** 2941.

[414] Khan; Newman *J. Org. Chem.* **1952,** *17,* 1063; Srinivasan; Lee *J. Org. Chem.* **1979,** *44,* 1574; Lee; Lee; Chandler *J. Org. Chem.* **1985,** *50,* 4306.

[415] Sonoda; Yamamoto; Murai; Tsutsumi *Chem. Lett.* **1972,** 229.

[416] Vasil'eva; Khalfina; Karpitskaya; Merkushev *J. Org. Chem. USSR* **1987,** *23,* 1967.

[417] Zibuck; Seebach *Helv. Chim. Acta* **1988,** *71,* 237.

[418] Yusybov; Filimonov *Synthesis* **1991,** 131.

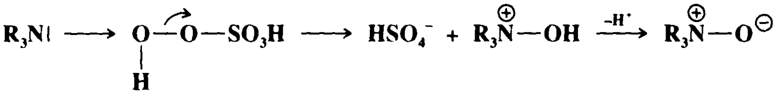
[419] Torii; Inokuchi; Hirata *Synthesis* **1987,** 377.

[420] Ballistreri; Failla; Tomaselli *J. Org. Chem.* **1988,** *53,* 830.

[421] For reviews, see Albini; Pietra *Heterocyclic N-Oxides;* CRC Press: Boca Raton, FL, 1991, pp. 31-41; Katritzky; Lagowski *Chemistry of the Heterocyclic N-Oxides;* Academic Press: New York, 1971, pp. 21-72, 539-542.

[422] Oswald; Guertin *J. Org. Chem.* **1963,** *28,* 651.

OH^+ moiety of the H_2O_2. Oxidation with Caro's acid has been shown to proceed in this manner:[423]



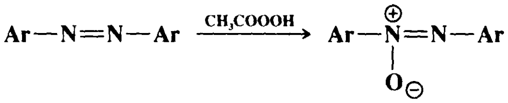
$$R_3N\!:\ \longrightarrow\ \underset{\displaystyle H}{O}{-}O{-}SO_3H\ \longrightarrow\ HSO_4^- + R_3\overset{\oplus}{N}{-}OH\ \xrightarrow{-H^+}\ R_3\overset{\oplus}{N}{-}O^{\ominus}$$

This mechanism is the same as that of **9-24**; the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peracids is probably the same. Racemic β-hydroxy tertary amines have been resolved by oxidizing them with *t*-BuOOH and a chiral catalyst—one enantiomer reacts faster than the other.[424] This kinetic resolution gives products with enantiomeric excesses of >90%.

OS **IV**, 612, 704, 828; **VI**, 342, 501; **69**, 226.

9-29 Oxidation of Azobenzenes to Azoxybenzenes

N-Oxygen-attachment

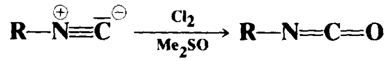


$$Ar{-}N{=}N{-}Ar\ \xrightarrow{CH_3COOOH}\ Ar{-}\underset{\displaystyle O^{\ominus}}{\overset{\oplus}{N}}{=}N{-}Ar$$

Azo compounds can be oxidized to azoxy compounds by peracids[425] or by hydroperoxides and molybdenum complexes.[426] The mechanism is probably the same as that of **9-28.**[427]

9-30 Oxidation of Isocyanides to Isocyanates

Oxygen-attachment



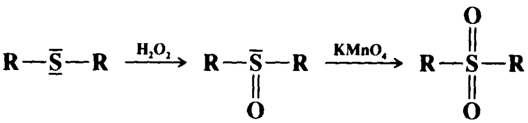
$$R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}\ \xrightarrow[Me_2SO]{Cl_2}\ R{-}N{=}C{=}O$$

Isocyanides have been oxidized to isocyanates with HgO and with O_3, as well as with a halogen and dimethyl sulfoxide (or pyridine N-oxide).[428] In the latter case the oxidizing agent is the halogen, which converts the isocyanide to $R{-}N{=}CCl_2$ which is hydrolyzed to the isocyanate.[429] Cyanide ion has been oxidized to cyanate ion with many oxidizing agents.

Isocyanides can be converted to isothiocyanates (RNC → RNCS) by treatment with a disulfide such as PhCOSSCOPh and thallium(I) acetate or lead(II) acetate.[430]

9-31 Oxidation of Thioethers to Sulfoxides and Sulfones

S-Oxygen-attachment



$$R{-}\underline{\overline{S}}{-}R\ \xrightarrow{H_2O_2}\ R{-}\underset{\underset{\displaystyle O}{\|}}{\overline{S}}{-}R\ \xrightarrow{KMnO_4}\ R{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}{-}R$$

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[423] Ogata; Tabushi *Bull. Chem. Soc. Jpn.* **1958,** *31*, 969.

[424] Miyano; Lu; Viti; Sharpless *J. Org. Chem.* **1985,** *50*, 4350.

[425] For reviews, see Yandovskii; Gidaspov; Tselinskii *Russ. Chem. Rev.* **1981,** *50*, 164-179; Newbold, Ref. 136, pp. 557-563, 573-593.

[426] Johnson; Gould *J. Org. Chem.* **1974,** *39*, 407.

[427] Mitsuhashi; Simamura; Tezuka *Chem. Commun.* **1970,** 1300.

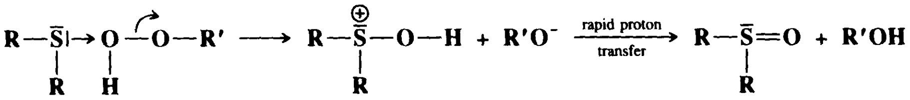
[428] For a review, see Simándi, Ref. 411, pp. 559-562.

[429] Johnson; Daughhetee *J. Org. Chem.* **1964,** *29*, 246; Johnson; Krutzsch *J. Org. Chem.* **1967,** *32*, 1939.

[430] Tanaka; Uemura; Okano *Bull. Chem. Soc. Jpn.* **1977,** *50*, 2785.

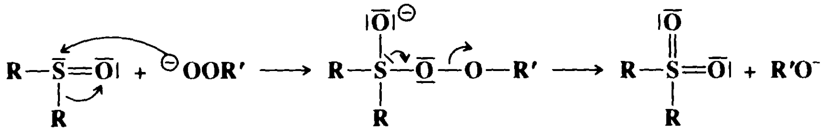
Thioethers can be oxidized to sulfoxides by 1 mole of 30% H_2O_2 or by many other oxidizing agents,[431] including $NaIO_4$,[432] t-BuOCl,[433] calcium hypochlorite $Ca(OCl)_2$,[434] sodium chlorite $NaClO_2$,[434] sodium hypochlorite NaOCl,[435] dioxiranes,[436] HNO_3 and an $AuCl_4^-$ catalyst,[437] O_2 and a ceric ammonium nitrate catalyst,[438] acyl nitrites,[439] sodium perborate,[403] and peracids.[440] Sulfoxides can be further oxidized to sulfones by another mole of H_2O_2, $KMnO_4$, sodium perborate, potassium hydrogen persulfate $KHSO_5$,[441] or a number of other agents. If enough oxidizing agent is present, thioethers can be directly converted to sulfones without isolation of the sulfoxides.[442] These reactions give high yields, and many functional groups do not interfere.[443] As with tertiary amines (**9-28**), racemic thioethers can be kinetically resolved by oxidation to sulfoxides with an optically active reagent, and this has often been done.[444] Selenides R_2Se can be oxidized to selenoxides and selenones.[445]

When the oxidizing agent is a peroxide, the mechanism[446] of oxidation to the sulfoxide is similar to that of **9-28**.[447]



$$\underset{R}{\underset{|}{R-\overline{S}|}}\rightarrow \underset{H}{\underset{|}{O}}-O-R' \longrightarrow R-\underset{R}{\underset{|}{\overset{\oplus}{\overline{S}}}}-O-H + R'O^- \xrightarrow[\text{transfer}]{\text{rapid proton}} R-\underset{R}{\underset{|}{\overline{S}}}=O + R'OH$$

The second oxidation, which is normally slower than the first[448] (which is why sulfoxides are so easily isolable), has the same mechanism in neutral or acid solution, but in basic solution it has been shown that the conjugate base of the peroxy compound ($R'OO^-$) also attacks the SO group as a nucleophile:[449]



$$\underset{R}{\underset{|}{R-\overline{S}}}=\overline{O}| + {}^{\ominus}OOR' \longrightarrow R-\underset{R}{\underset{|}{\overset{|\overline{O}|^{\ominus}}{\overset{|}{S}}}}-\overline{O}-O-R' \longrightarrow R-\underset{R}{\underset{|}{\overset{|\overline{O}}{\overset{\|}{S}}}}=\overline{O}| + R'O^-$$

---

[431] For reviews, see Hudlický, Ref. 11, pp. 252-263; Drabowicz; Kiełbasinski; Mikołajczyk, in Patai; Rappoport; Stirling *The Chemistry of Sulphones and Sulphoxides;* Wiley: New York, 1988, pp. 233-378, pp. 235-255; Madesclaire *Tetrahedron* **1986,** *42,* 5459-5495; Block, in Patai *Supplement E,* Ref. 44, pt. 1, pp. 539-608. For reviews on methods of synthesis of sulfoxides, see Drabowicz; Mikołajczyk *Org. Prep. Proced. Int.* **1982,** *14,* 45-89; Oae, in Oae *The Organic Chemistry of Sulfur;* Plenum: New York, 1977, pp. 385-390. For a review with respect to enzymic oxidation, see Holland *Chem. Rev.* **1988,** *88,* 473-485.

[432] Leonard; Johnson *J. Org. Chem.* **1962,** *27,* 282; Hiskey; Harpold *J. Org. Chem.* **1967,** *32,* 3191.

[433] Walling; Mintz *J. Org. Chem.* **1967,** *32,* 1286; Skattebøl; Boulette; Solomon *J. Org. Chem.* **1967,** *32,* 3111.

[434] Weber; Scheider; Salami; Paquer *Recl. Trav. Chim. Pays-Bas* **1986,** *105,* 99.

[435] Ramsden; Drago; Riley *J. Am. Chem. Soc.* **1989,** *111,* 3958.

[436] Colonna; Gaggero *Tetrahedron Lett.* **1989,** *30,* 6233.

[437] Gasparrini; Giovannoli; Misiti; Natile; Palmieri *J. Org. Chem.* **1990,** *55,* 1323.

[438] Riley; Smith; Correa *J. Am. Chem. Soc.* **1988,** *110,* 177.

[439] Louw; Vermeeren; van Asten; Ultée *J. Chem. Soc., Chem. Commun.* **1976,** 496.

[440] For lists of some of the many oxidizing agents used in this reaction, see Ref. 431 and Block *Reactions of Organosulfur Compounds;* Academic Press: New York, 1978, p. 16.

[441] Trost; Curran *Tetrahedron Lett.* **1981,** *22,* 1287.

[442] For a review, see Schank, in Patai; Rappoport; Stirling, Ref. 431, pp. 165-231, pp. 205-213.

[443] For a review of the oxidation of α-halo sulfides, see Venier; Barager *Org. Prep. Proced. Int.* **1974,** *6,* 77-102, pp. 85-86.

[444] For reviews, see Kagan; Rebiere *Synlett* **1990,** 643-650; Drabowicz; Kiełbasinski; Mikołajczyk, Ref. 431, pp. 288-297; Madesclaire, Ref. 431, pp. 5481-5488. See also Zhao; Samuel; Kagan *Tetrahedron* **1987,** *43,* 5135; Glahsl; Herrmann *J. Chem. Soc., Perkin Trans. 1* **1988,** 1753; Davis; ThimmaReddy; Weismiller *J. Am. Chem. Soc.* **1989,** *111,* 5964; Di Furia; Licini; Modena; Valle *Bull. Soc. Chim. Fr.* **1990,** 734; Ref. 436.

[445] See Reich; in Trahanovsky, Ref. 2, pt. C, pp. 7-13; Davis; Stringer; Billmers *Tetrahedron Lett.* **1983,** *24,* 1213; Kobayashi; Ohkubo; Shimizu *Bull. Chem. Soc. Jpn.* **1986,** *59,* 503.

[446] For discussions of the mechanism with various other agents, see Rajasekaran; Baskaran; Gnanasekaran *J. Chem. Soc., Perkin Trans. 2* **1984,** 1183; Srinivasan; Chellamani; Rajagopal *J. Org. Chem.* **1985,** *50,* 1201; Agarwal; Bhatt; Banerji *J. Phys. Org. Chem.* **1990,** *3,* 174; Lee ; Chen *J. Org. Chem.* **1991,** *56,* 5346.

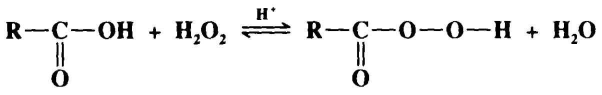
[447] Modena; Todesco *J. Chem. Soc.* 4920, **1962,** and references cited therein.

[448] There are some reagents that oxidize sulfoxides in preference to sulfides, e.g., $NaMnO_4$: see Henbest; Khan *Chem. Commun.* **1968,** 1036.

[449] Curci; Modena *Tetrahedron Lett.* **1963,** 1749, *Tetrahedron Lett.* **1966,** *22,* 1227; Curci; Di Furia; Modena *J. Chem. Soc., Perkin Trans. 2* **1978,** 603. See also Oae; Takata *Tetrahedron Lett.* **1980,** *21,* 3213; Akasaka; Ando *J. Chem. Soc., Chem. Commun.* **1983,** 1203.

OS **V,** 791; **VI,** 403, 404, 482; **VII,** 453, 491; **67,** 157; **68,** 49. Also see OS **V,** 723; **VI,** 23.

9-32 Oxidation of Carboxylic Acids to Peroxy Acids
Peroxy-de-hydroxy-substitution

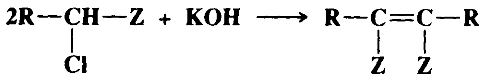


$$R{-}\underset{\underset{O}{\|}}{C}{-}OH + H_2O_2 \overset{H^+}{\rightleftharpoons} R{-}\underset{\underset{O}{\|}}{C}{-}O{-}O{-}H + H_2O$$

The oxidation of carboxylic acids with H_2O_2 and an acid catalyst is the best general method for the preparation of peroxy acids.[450] The most common catalyst for aliphatic R is concentrated sulfuric acid. The reaction is an equilibrium and is driven to the right by removal of water or by the use of excess reagents. For aromatic R the best catalyst is methanesulfonic acid, which is also used as the solvent.

E. Oxidative Coupling

9-33 Coupling Involving Carbanions
De-hydro,chloro-coupling



$$2R{-}\underset{\underset{Cl}{|}}{CH}{-}Z + KOH \longrightarrow R{-}\underset{\underset{Z}{|}}{C}{=}\underset{\underset{Z}{|}}{C}{-}R$$

Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon can be dimerized to olefins by treatment with bases. Z may be nitro, aryl, etc. It is likely that in most cases the mechanism[451] involves nucleophilic substitution followed by elimination[452] (illustrated for benzyl chloride):

$$PhCH_2Cl \xrightarrow{\text{base}} Ph\overset{\ominus}{C}HCl \xrightarrow[S_N]{PhCH_2Cl} PhCHClCH_2Ph \xrightarrow{-HCl} PhCH{=}CHPh$$

α,α-Dibromotoluenes $ArCHBr_2$ give tolanes $ArC{\equiv}CAr$, by debromination of the intermediates $ArCBr{=}CBrAr$.[453] In a related reaction, diarylmethane dihalides Ar_2CX_2 have been dimerized to tetraaryl alkenes $Ar_2C{=}CAr_2$ with sodium selenide,[454] with copper,[455] with iron(II) oxalate dihydrate,[456] and with iron pentacarbonyl.[457]

A somewhat different type of coupling is observed when salts of β-keto esters, arylacetonitriles $ArCH_2CN$, and other compounds of the form ZCH_2Z' are treated with an

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[450] For a review of the preparation of peroxy acids, see Swern, in Swern *Organic Peroxides*, vol. 1; Wiley: New York, 1970, pp. 313-516.

[451] For discussion, see Saunders; Cockerill *Mechanisms of Elimination Reactions*; Wiley: New York, 1973, pp. 548-554.

[452] For example, see Hauser; Brasen; Skell; Kantor; Brodhag *J. Am. Chem. Soc.* **1956,** *78*, 1653; Hoeg; Lusk *J. Organomet. Chem.* **1966,** *5*, 1; Reisdorf; Normant *Organomet. Chem. Synth.* **1972,** *1*, 375; Hanna; Wideman *Chem. Ind. (London)* **1968,** 486. In some cases a radical anion chain mechanism can take place: Bethell; Bird *J. Chem. Soc., Perkin Trans. 2* **1977,** 1856.

[453] Vernigor; Shalaev; Luk'yanets *J. Org. Chem. USSR* **1981,** *17*, 317.

[454] Okamoto; Yano *J. Org. Chem.* **1969,** *34*, 1492.

[455] Buckles; Matlack *Org. Synth. IV*, 914.

[456] Khurana; Maikap; Mehta *Synthesis* **1990,** 731.

[457] Coffey *J. Am. Chem. Soc.* **1961,** *83*, 1623.

oxidizing agent such as iodine,[458] PbO_2,[459] Ag_2O,[460] Cu(II) salts,[461] or a Cu-amine-O_2 system,[462] e.g.,

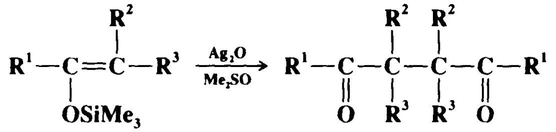
$$Ar_2CH_2 \xrightarrow[\text{liq. NH}_3]{\text{NaNH}_2} Ar\overset{\ominus}{CH} + I_2 \longrightarrow Ar_2CH{-}CHAr_2$$

In this case the product is a substituted alkane rather than an alkene. This reaction has been used to close rings.[463] Arylmethanesulfonyl chlorides $ArCH_2SO_2Cl$ couple to give ArCH=CHAr when treated with Et_3N.[464]

OS **II,** 273; **IV,** 372, 869, 914; **68,** 198. Also see OS **I,** 46; **IV,** 877.

9-34 Dimerization of Silyl Enol Ethers or of Lithium Enolates

3/*O*-De-trimethylsilyl-1/*C*-coupling



$$R^1{-}\underset{\underset{OSiMe_3}{|}}{C}{=}\overset{\overset{R^2}{|}}{C}{-}R^3 \xrightarrow[\text{Me}_2\text{SO}]{\text{Ag}_2\text{O}} R^1{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R^2}{|}}{\underset{\underset{R^3}{|}}{C}}{-}\overset{\overset{R^2}{|}}{\underset{\underset{R^3}{|}}{C}}{-}\underset{\underset{O}{\|}}{C}{-}R^1$$

32

Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with Ag_2O in dimethyl sulfoxide or certain other polar aprotic solvents.[465] The reaction has been performed with R^2, R^3 = hydrogen or alkyl, though best yields are obtained when $R^2 = R^3 = H$. In certain cases, unsymmetrical 1,4-diketones have been prepared by using a mixture of two silyl enol ethers. Other reagents that have been used to achieve either symmetrical or cross-coupled products are iodosobenzene-BF_3-Et_2O,[466] ceric ammonium nitrate,[467] and lead tetraacetate.[468] If R^1 = OR (in which case the substrate is a ketene silyl acetal), dimerization with $TiCl_4$ leads to a dialkyl succinate (**32**, R^1 = OR).[469]

In a similar reaction, lithium enolates $RC(Li){=}CH_2$ were dimerized to 1,4-diketones $RCOCH_2CH_2COR$ with $CuCl_2$, $FeCl_3$, or copper(II) triflate, in a nonprotic solvent.[470]

OS **69,** 173.

9-35 Oxidation of Thiols to Disulfides

***S*-De-hydrogen-coupling**

$$2RSH \xrightarrow{H_2O_2} RSSR$$

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[458] See, for example, Kaiser *J. Am. Chem. Soc.* **1967,** *89*, 3659; Belletire; Spletzer; Pinhas *Tetrahedron Lett.* **1984,** *25*, 5969; Mignani; Lahousse; Merényi; Janousek; Viehe *Tetrahedron Lett.* **1985,** *26*, 4607; Aurell; Gil; Tortajada; Mestres *Synthesis* **1990,** 317.

[459] Brettle; Seddon *J. Chem. Soc., C.* **1970,** 1320.

[460] Ito; Fujii; Konoike; Saegusa *Synth. Commun.* **1976,** 6, 429.

[461] Rathke; Lindert *J. Am. Chem. Soc.* **1971,** *93*, 4605; Baudin; Julia; Rolando; Verpeaux *Bull. Soc. Chim. Fr.* **1987,** 493.

[462] de Jongh; de Jonge; Mijs *J. Org. Chem.* **1971,** *36*, 3160.

[463] Chung; Dunn *J. Org. Chem.* **1983,** *48*, 1125.

[464] King; Durst *Tetrahedron Lett.* **1963,** 585; King; Harding *Can. J. Chem.* **1976,** *54*, 2652; Nakayama; Tanuma; Honda; Hoshino *Tetrahedron Lett.* **1984,** *25*, 4553.

[465] Ito; Konoike; Saegusa *J. Am. Chem. Soc.* **1975,** *97*, 649.

[466] Moriarty; Prakash; Duncan *J. Chem. Soc., Perkin Trans. 1* **1987,** 559.

[467] Baciocchi; Casu; Ruzziconi *Tetrahedron Lett.* **1989,** *30*, 3707.

[468] Moriarty; Penmasta; Prakash *Tetrahedron Lett.* **1987,** *28*, 873.

[469] Inaba; Ojima *Tetrahedron Lett.* **1977,** 2009. See also Totten; Wenke; Rhodes *Synth. Commun.* **1985,** *15*, 291, 301.

[470] Ito; Konoike; Harada; Saegusa *J. Am. Chem. Soc.* **1977,** *99*, 1487; Kobayashi; Taguchi; Tokuno *Tetrahedron Lett.* **1977,** 3741; Frazier; Harlow *J. Org. Chem.* **1980,** *45*, 5408.

Thiols are easily oxidized to disulfides.[471] Hydrogen peroxide is the most common reagent,[472] but many oxidizing agents give the reaction, among them thallium(III) acetate,[473] Me_2SO–I_2,[474] Br_2 under phase transfer conditions,[475] methoxytributyltin–$FeCl_3$,[476] sodium perborate,[477] NO,[478] and NO_2.[478] It can also be done electrochemically.[479] However, strong oxidizing agents may give **9-26.** Even the oxygen in the air oxidizes thiols on standing, if a small amount of base is present. The reaction is reversible (see **9-61**), and the interconversion between cysteine and cystine is an important one in biochemistry.

The mechanism has been studied for several oxidizing agents and varies with the agent.[480] For oxygen it is [481]

$$\mathbf{RSH + B^- \rightleftharpoons RS^- + BH}$$

$$\mathbf{RS^- + O_2 \longrightarrow RS\cdot + \dot{O}_2{}^-}$$

$$\mathbf{RS^- + \dot{O}_2{}^- \longrightarrow RS\cdot + O_2{}^{2-}}$$

$$\mathbf{2RS\cdot \longrightarrow RSSR}$$

$$\mathbf{O_2{}^{2-} + BH \longrightarrow OH^- + B^- + O_2}$$

With respect to the sulfur, this mechanism is similar to that of **4-17,** involving as it does loss of a proton, oxidation to a free radical, and radical coupling.

Unsymmetrical disulfides can be prepared[482] by treatment of a thiol RSH with diethyl azodicarboxylate EtOOCN=NCOOEt to give an adduct, to which another thiol R'SH is then added, producing the disulfide RSSR'.[483]

OS **III,** 86, 116.

9-36 Oxidation of Amines to Azo or Azoxy Compounds

***N*-De-bishydrogen-coupling**

$$\mathbf{ArNH_2 \xrightarrow{MnO_2} Ar{-}N{=}N{-}Ar}$$

Primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them MnO_2, lead tetraacetate, O_2 and a base, barium permanganate,[484] and sodium perborate in acetic acid. *t*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.[485]

OS **V,** 341.

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[471] For a review, see Capozzi; Modena, Ref. 408, pp. 785-839. For a list of reagents, with references, see Block, Ref. 440.

[472] It has been pointed out that, nevertheless, H_2O_2 is not a very good reagent for this reaction, since it gives sulfonic acids (**9-26**) as well as disulfides: Evans; Doi; Musker *J. Org. Chem.* **1990,** *55,* 2337.

[473] Uemura; Tanaka; Okano *Bull. Chem. Soc. Jpn.* **1977,** *50,* 220.

[474] Aida; Akasaka; Furukawa; Oae *Bull. Chem. Soc. Jpn.* **1976,** *49,* 1441. See also Fristad; Peterson *Synth. Commun.* **1985,** *15,* 1.

[475] Drabowicz; Mikołajczyk *Synthesis* **1980,** 32.

[476] Sato; Otera; Nozaki *Tetrahedron Lett.* **1990,** *31,* 3591.

[477] McKillop; Koyunçu *Tetrahedron Lett.* **1990,** *31,* 5007.

[478] Pryor; Church; Govindan; Crank *J. Org. Chem.* **1982,** *47,* 156.

[479] See, for example, Leite; Pardini; Viertler *Synth. Commun.* **1990,** *20,* 393. For a review, see Shono, Ref. 149, pp. 38-43.

[480] See Tarbell, in Kharasch, *Organic Sulfur Compounds*; Pergamon: Elmsford, NY, 1961, pp. 97-102.

[481] Wallace; Schriesheim; Bartok *J. Org. Chem.* **1963,** *28,* 1311.

[482] Mukaiyama; Takahashi *Tetrahedron Lett.* **1968,** 5907.

[483] For other methods, see Boustany; Sullivan *Tetrahedron Lett.* **1970,** 3547; Harpp; Ash; Back; Gleason; Orwig; VanHorn; Snyder *Tetrahedron Lett.* **1970,** 3551; Oae; Fukushima; Kim *J. Chem. Soc., Chem. Commun.* **1977,** 407.

[484] Firouzabadi; Mostafavipoor *Bull. Chem. Soc. Jpn.* **1983,** *56,* 914.

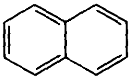
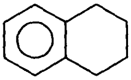
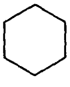
[485] Kosswig *Liebigs Ann. Chem.* **1971,** *749,* 206.

Reductions: Selectivity[486]

It is often necessary to reduce one group in a molecule without affecting another reducible group. It is usually possible to find a reducing agent that will do this. The most common broad-spectrum reducing agents are the metal hydrides[487] and hydrogen (with a catalyst).[488] Many different metal-hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced chemoselectively. Tables 19.2, 19.3, and 19.4 list the reactivity of various functional groups toward catalytic hydrogenation, $LiAlH_4$, and BH_3, respectively.[489] Table 19.5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.[490] Of course, the tables cannot be exact, because the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce

TABLE 19.2 The ease of reduction of various functional groups toward catalytic hydrogenation[489]

The groups are listed in approximate order of ease of reduction

Reaction	Substrate	Product	
0-83	$RCOCl$	$RCHO$	Easiest
9-47	RNO_2	RNH_2	
5-9	$RC\equiv CR$	$RCH{=}CHR$	
6-25	$RCHO$	RCH_2OH	
5-9	$RCH{=}CHR$	RCH_2CH_2R	
6-25	$RCOR$	$RCHOHR$	
0-79	$ArCH_2OR$	$ArCH_3 + ROH$	
6-27	$RC\equiv N$	RCH_2NH_2	
5-10			
9-42	$RCOOR'$	$RCH_2OH + R'OH$	
9-39	$RCONHR'$	RCH_2NHR	
5-10			Most difficult
9-38	$RCOO^-$		Inert

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[486] For monographs on reductions in general, see Hudlický *Reductions in Organic Chemisty*; Wiley: New York, 1984; Augustine *Reduction*; Marcel Dekker: New York, 1968. For a review, see Candlin; Rennie, in Bentley; Kirby, Ref. 12, pp. 77-135.

[487] For discussions of selectivity with metal hydride reducing agents, see Brown; Krishnamurthy *Tetrahedron*, **1979,** *35*, 567-607; Walker *Chem. Soc. Rev.* **1976,** *5*, 23-50; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 209-251, Rerick, in Augustine, Ref. 486. For books, see, in Ref. 10, the works by Seyden-Penne, Štrouf et al., and Hajós.

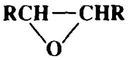
[488] For a discussion of catalyst selectivity for hydrogenations, see Rylander *Aldrichimica Acta* **1979,** *12*, 53-57. See also Rylander *Hydrogenation Methods*; Academic Press: New York, 1985.

[489] Table 19.2 is from House, Ref. 10, p. 9. Tables 19.3 and 19.4 are from Brown, Ref. 487, pp. 213 and 232, respectively.

[490] The first ten columns are from Brown; Krishnamurthy, Ref. 487, p. 604. The column on $(i\text{-}Bu)_2AlH$ is from Yoon; Gyoung *J. Org. Chem.* **1985,** *50*, 2443; the one on $NaAlEt_2H_2$ from Stinson, *Chem. Eng. News* Nov. 3, **1980,** *58*, No. 44, 19; and the one on $LiBEt_3H$ from Brown; Kim; Krishnamurthy *J. Org. Chem.* **1980,** *45*, 1. For similar tables that show additional reducting agents, see Pelter; Smith; Brown, Ref. 494, p. 129; Hajós, Ref. 10, pp. 16-17. For tables showing which agents reduce a wide variety of functional groups, see Hudlický, Ref. 486, pp. 177-200.

TABLE 19.3 The ease of reduction of various functional groups with $LiAlH_4$ in ether[489]

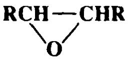
However, $LiAlH_4$ is a very powerful reagent, and much less chemoselectivity is possible here than with most of the other metal hydrides

Reaction	Substrate	Product	
6-25	RCHO	RCH_2OH	Easiest
6-25	RCOR	RCHOHR	
9-45	RCOCl	RCH_2OH	
9-42	Lactone	Diol	
0-80		RCH_2CHOHR	
9-42	RCOOR′	$RCH_2OH + R'OH$	
9-38	RCOOH	RCH_2OH	
9-38	$RCOO^-$	RCH_2OH	
9-39	$RCONR'_2$	$RCH_2NR'_2$	
6-27	$RC{\equiv}N$	RCH_2NH_2	
9-47	RNO_2	RNH_2	
9-67	$ArNO_2$	$ArN{=}NAr$	Most difficult
5-9	$RCH{=}CHR$		Inert

which groups.[491] $LiAlH_4$ is very powerful and unselective reagent.[492] Consequently, other metal hydrides are generally used when chemoselectivity is required. As mentioned on p. 917, a number of less reactive (and more selective) reagents have been prepared by replacing some of the hydrogens of $LiAlH_4$ with alkoxy groups (by treatment of $LiAlH_4$ with ROH).[493] Most of the metal hydrides are nucleophilic reagents and attack the carbon atom of a carbon-hetero single or multiple bond. However, BH_3[494] and AlH_3[495] are electrophiles (Lewis acids)

TABLE 19.4 The ease of reduction of various functional groups with borane[489]

It is evident that this reagent and $LiAlH_4$ (Table 19.3) complement each other

Reaction	Substrate	Product	
9-38	RCOOH	RCH_2OH	Easiest
5-12	$RCH{=}CHR$	$(RCH_2CHR)_3B$	
6-25	RCOR	RCHOHR	
6-27	RCN	RCH_2NH_2	
0-80		RCH_2CHOHR	
9-42	RCOOR′	$RCH_2OH + R'OH$	Most difficult
0-83, 9-45	RCOCl		Inert

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[491] See also the table in Ref. 9.

[492] For a review of $LiAlH_4$, see Pizey, Ref. 10, vol. 1 pp. 101-194.

[493] For reviews of reductions by these reagents, see Málek Ref. 10; Málek; Černy *Synthesis* **1972,** 217-234.

[494] See Brown; Heim; Yoon *J. Am. Chem. Soc.* **1970,** *92,* 1637; Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 319-371. For reviews of reductions with BH_3, see Wade *J. Mol. Catal.* **1983,** *18,* 273-297 (BH_3 and a catalyst); Lane *Chem. Rev.* **1976,** *76,* 773-799, *Aldrichimica Acta* **1977,** *10,* 41-51; Brown; Krishnamurthy *Aldrichimica Acta* **1979,** *12,* 3-11. For reviews of reduction with borane derivatives, see Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 125-164; Pelter *Chem. Ind.* (*London*) **1976,** 888-896.

[495] See Brown; Yoon *J. Am. Chem. Soc.* **1966,** *88,* 1464; Yoon; Brown *J. Am. Chem. Soc.* **1968,** *90,* 2927.

TABLE 19.5 Reactivity of various functional groups with some metal hydrides and toward catalytic hydrogenation.[490] ± indicates a borderline case.

	Reaction	$NaBH_4$ in EtOH	$NaBH_4$ + LiCl in diglyme	$NaBH_4$ + $AlCl_3$ in diglyme	BH_3–THF[487]	Bis-3-methyl-2-butyl-borane (disiamylborane) in THF[498]	9-BBN[499]	LiAlH(O-*t*-Bu)$_3$ in THF	LiAlH(OMe)$_3$ in THF	$LiAlH_4$ in ether	AlH_3 in THF[495]	$LiBEt_3H$[501]	(i-Bu)$_2$AlH(DIBALH)	$NaAlEt_2H_2$	Catalytic hydrogenation
6-25	$RCHO \rightarrow RCH_2OH$	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6-25	$RCOR \rightarrow RCHOHR$	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0-83 9-45	$RCOCl \nearrow RCHO$ $RCOCl \searrow RCH_2OH$	+[496]	+	+	−	−	+	+	+	+	+	+	+	+	+
9-42	Lactone → diol	−	+	+	+	+	+	±	+	+	+	+	+	+	+
0-80	Epoxide → alcohol	−	+	+	+	±	±	±	+	+	+	+	+	+	+
9-42	$RCOOR' \rightarrow RCH_2OH + R'OH$	−	+	+	±	−	±	±	+	+	+	+	+	+	+
9-38	$RCOOH \rightarrow RCH_2OH$	−	−	+	+	−	±	−	+	+	+	−	+	+	−
9-38	$RCOO^- \rightarrow RCH_2OH$	−	−	+	−	−	−	−	+	+	+	−	−		−
9-39 0-85	$RCONR_2' \nearrow RCH_2NR'_2$ $RCONR_2' \searrow RCHO$	−	−	−	+	+	+	−	+	+	+	+	+	+	+
6-27	$RC{\equiv}N \rightarrow RCH_2NH_2$	−	−	−	+	−	±	−	+	+	+	±	+[497]	+	+
9-47 9-67	$RNO_2 \nearrow RNH_2$ $RNO_2 \searrow RN{=}NR$	−	−	−	−	−	−	−	+	+	−	−	+[500]	+	+
5-9	$RCH{=}CHR \rightarrow RCH_2CH_2R$	−	−	−	+	+	+	−	−	−	−	+	−	−	+

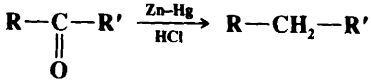
and attack the hetero atom. This accounts for the different patterns of selectivity shown in the tables.

The reactions in this section are grouped into classifications based on bond changes, similar to those used for the oxidation reactions. These sections are: (A) reactions involving replacement of oxygen by hydrogen, (B) reactions in which oxygen is removed from the substrate, (C) reduction with cleavage, and (D) reductive coupling.

A. Reactions Involving Replacement of Oxygen by Hydrogen. In reactions **9-37** to **9-41**, a C=O is reduced to a CH_2 group.

9-37 Reduction of Carbonyl to Methylene in Aldehydes and Ketones

Dihydro-de-oxo-bisubstitution



$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[HCl]{Zn-Hg} R-CH_2-R'$$

There are various ways of reducing the C=O group of aldehydes and ketones to CH_2.[502] The two oldest, but still very popular, methods are the *Clemmensen reduction* and the *Wolff–Kishner reduction*. The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam and aqueous HCl.[503] Ketones are reduced more often than aldehydes. In the Wolff–Kishner reduction,[504] the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The *Huang–Minlon modification*[505] of the Wolff–Kishner reaction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. The reaction can also be carried out under more moderate conditions (room temperature) in dimethyl sulfoxide with potassium *t*-butoxide as base.[506] The Wolff–Kishner reaction can also be applied to the semicarbazones of aldehydes or ketones. The Clemmensen reduction is usually easier to perform, but it fails for acid-sensitive and high-molecular-weight substrates. For these cases the Wolff–Kishner reduction is quite useful. For high-molecular-weight substrates, a modified Clemmensen reduction, using activated zinc and gaseous HCl in an organic solvent such as ether or acetic anhydride, has proved successful.[507] The Clemmensen and Wolff–Kishner reactions are complementary, since the former uses acidic and the latter basic conditions.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many other functional groups present. However, certain types of aldehydes and ketones do not give normal reduction products. Under Clemmensen conditions,[508] α-hydroxy ketones give either ketones (hydrogenolysis of the OH, **0-78**) or olefins, and 1,3-diones usually

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[496] Reacts with solvent, reduced in aprotic solvents.

[497] Reduced to aldehyde (**6-28**).

[498] Brown; Bigley; Arora; Yoon *J. Am. Chem. Soc.* **1970,** *92,* 7161. For reductions with thexylborane, see Brown; Heim; Yoon *J. Org. Chem.* **1972,** *37,* 2942.

[499] Brown; Krishnamurthy; Yoon *J. Org. Chem.* **1976,** *41,* 1778.

[500] Reduced to hydroxylamine (**9-49**).

[501] Brown; Kim; Krishnamurthy, Ref. 490. For a review of the synthesis of alkyl-substituted borohydrides, see Brown; Singaram; Singaram *J. Organomet. Chem.* **1982,** *239,* 43-64.

[502] For a review, see Reusch, in Augustine, Ref. 486, pp. 171-211.

[503] For a review, see Vedejs *Org. React.* **1975,** *22,* 401-422. For a discussion of experimental conditions, see Fieser; Fieser, Ref. 46, vol. 1, pp. 1287-1289.

[504] For a review, see Todd *Org. React.* **1948,** *4,* 378-422.

[505] Huang-Minlon *J. Am. Chem. Soc.* **1946,** *68,* 2487, **1949,** *71,* 3301.

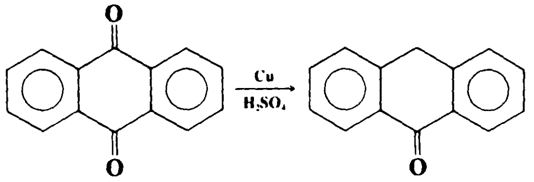
[506] Cram; Sahyun; Knox *J. Am. Chem. Soc.* **1962,** *84,* 1734.

[507] Yamamura; Ueda; Hirata *Chem. Commun.* **1967,** 1049; Toda; Hayashi; Hirata; Yamamura *Bull. Chem. Soc. Jpn.* **1972,** *45,* 264.

[508] For a review of Clemmensen reduction of diketones and unsaturated ketones, see Buchanan; Woodgate *Q. Rev. Chem. Soc.* **1969,** *23,* 522-536.

undergo rearrangement, e.g., $MeCOCH_2COMe \rightarrow MeCOCHMe_2$.[509] Neither method is suitable for α,β-unsaturated ketones. These give pyrazolines[510] under Wolff-Kishner conditions, while under Clemmensen conditions both groups of these molecules may be reduced or if only one group is reduced, it is the C=C bond.[511] Sterically hindered ketones are resistant to both the Clemmensen and Huang–Minlon procedures but can be reduced by vigorous treatment with anhydrous hydrazine.[512] In the Clemmensen reduction, pinacols (**9-62**) are often side products.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2.[513] Among these are H_2 and a catalyst at 180 to 250°C,[514] triisopropyl phosphite P(O-i-Pr)$_3$,[515] and, for aryl ketones (ArCOR and ArCOAr), $LiAlH_4$–$AlCl_3$,[516] $LiAlH_4$–P_2I_4,[517] Li–NH_3,[518] $NaBH_4$–F_3CCOOH,[519] $NaBH_4$–$AlCl_3$,[520] BH_3–*t*-$BuNH_2$–$AlCl_3$,[521] CO–Se–H_2O,[522] $HCOONH_4$–Pd–C,[523] or trialkylsilanes in F_3CCOOH.[524] Most of these reagents also reduce aryl aldehydes ArCHO to methylbenzenes $ArCH_3$.[525] Aliphatic aldehydes RCHO can be reduced to RCH_3 with titanocene dichloride($C_5H_5)_2TiCl_2$.[526] One carbonyl group of 1,2-diketones can be selectively reduced by H_2S with an amine catalyst[527] or by HI in refluxing acetic acid.[528] One carbonyl group of quinones can be reduced with copper and sulfuric acid or with tin and HCl:[529]



One carbonyl group of 1,3-diketones was selectively reduced by catalytic hydrogenolysis.[530]

An indirect method of accomplishing the reaction is reduction of tosylhydrazones (R_2C=N—NHTs) to R_2CH_2 with $NaBH_4$, BH_3, catecholborane, bis(benzyloxy)borane,

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[509] Cusack; Davis *J. Org. Chem.* **1965,** *30,* 2062; Wenkert; Kariv *Chem. Commun.* **1965,** 570; Galton; Kalafer; Beringer *J. Org. Chem.* **1970,** *35,* 1.

[510] Pyrazolines can be converted to cyclopropanes; see **7-46.**

[511] See, however, Banerjee; Alvárez; Santana; Carrasco *Tetrahedron* **1986,** *42,* 6615.

[512] Barton; Ives; Thomas *J. Chem. Soc.* **1955,** 2056.

[513] For a list, with references, see Ref. 21, pp. 35-38.

[514] See for example, Maier; Bergmann; Bleicher; Schleyer *Tetrahedron Lett.* **1981,** *22,* 4227. For a review of the mechanism, see Pavlenko *Russ. Chem. Rev.* **1989,** *58,* 453-469.

[515] Olah; Wu *Synlett* **1990,** 54.

[516] Nystrom; Berger *J. Am. Chem. Soc.* **1958,** *80,* 2896. See also Volod'kin; Ershov; Portnykh *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1967,** 384.

[517] Suzuki; Masuda; Kubota; Osuka *Chem. Lett.* **1983,** 909.

[518] Hall; Lipsky; McEnroe; Bartels *J. Org. Chem.* **1971,** *36,* 2588.

[519] Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985,** *17,* 317-384.

[520] Ono; Suzuki; Kamimura *Synthesis* **1987,** 736.

[521] Lau; Tardif; Dufresne; Scheigetz *J. Org. Chem.* **1989,** *54,* 491.

[522] Nishiyama; Hamanaka; Ogawa; Kambe; Sonoda *J. Org. Chem.* **1988,** *53,* 1326.

[523] Ram; Spicer *Tetrahedron Lett.* **1988,** *29,* 3741.

[524] Kursanov; Parnes; Loim *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1966,** 1245; West; Donnelly; Kooistra; Doyle *J. Org. Chem.* **1973,** *38,* 2675. See also Fry; Orfanopoulos; Adlington; Dittman; Silverman *J. Org. Chem.* **1978,** *43,* 374; Olah; Arvanaghi; Ohannesian *Synthesis* **1986,** 770.

[525] See, for example, Hall; Bartels; Engman *J. Org. Chem.* **1972,** *37,* 760; Kursanov; Parnes; Loim; Bakalova *Doklad. Chem.* **1968,** *179,* 328; Zahalka; Alper *Organometallics* **1986,** *5,* 1909.

[526] van Tamelen; Gladys *J. Am. Chem. Soc.* **1974,** *96,* 5290.

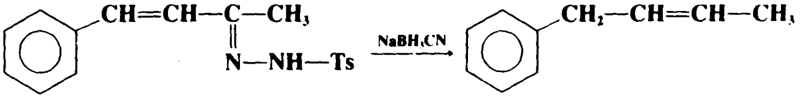
[527] Mayer; Hiller; Nitzschke; Jentzsch *Angew. Chem. Int. Ed. Engl.* **1963,** *2,* 370-373 [*Angew. Chem.* *75,* 1011-1014].

[528] Reusch; LeMahieu *J. Am. Chem. Soc.* **1964,** *86,* 3068.

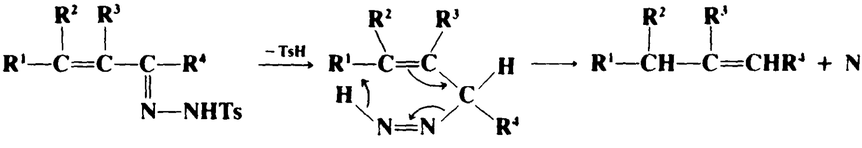
[529] Meyer *Org. Synth. I,* 60; Macleod; Allen *Org. Synth. II,* 62.

[530] Cormier; McCauley *Synth. Commun.* **1988,** *18,* 675.

NaBH$_3$CN, or bis(triphenylphosphine)copper(I) tetrahydroborate.[531] The reduction of α,β-unsaturated tosylhydrazones with NaBH$_3$CN, with NaBH$_4$–HOAc, or with catecholborane proceeds with migration of the double bond to the position formerly occupied by the carbonyl carbon, even if this removes the double bond from conjugation with an aromatic ring,[532] e.g.,



A cyclic mechanism is apparently involved:



Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization of this (**4-36**).

The first step in the mechanism[533] of the Wolff–Kishner reaction consists of formation of the hydrazone (**6-20**).

$$R_2C{=}O \longrightarrow R_2C{=}N{-}NH_2$$

It is this species that undergoes reduction in the presence of base, most likely in the following manner:

$$R_2C{=}N{-}NH_2 \xrightleftharpoons{OH^-} R_2CH{-}N{=}NH + OH^- \longrightarrow R_2CH{-}N{=}N^{\ominus} + H_2O$$

$$R_2CH{-}N{=}N^{\ominus} \xrightarrow{-N_2} R_2\bar{C}H^{\ominus} \xrightarrow{H_2O} R_2CH_2 + OH^-$$

Not much is known about the mechanism of the Clemmensen reduction. Several mechanisms have been proposed,[534] including one going through a zinc–carbene intermediate.[535] One thing reasonably certain is that the corresponding alcohol is not an intermediate, since alcohols prepared in other ways fail to give the reaction. Note that the alcohol is not an intermediate in the Wolff-Kishner reduction either.

OS **I,** 60; **II,** 62, 499; **III,** 410, 444, 513, 786; **IV,** 203, 510; **V,** 533, 747; **VI,** 62, 293, 919; **VII,** 393. Also see OS **IV,** 218; **VII,** 18.

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[531] Caglioti; Magi *Tetrahedron* **1963,** *19,* 1127; Fischer; Pelah; Williams; Djerassi *Chem. Ber.* **1965,** *98,* 3236; Elphimoff-Felkin; Verrier *Tetrahedron Lett.* **1968,** 1515; Hutchins; Milewski; Maryanoff *J. Am. Chem. Soc.* **1973,** *95,* 3662; Cacchi; Caglioti; Paolucci *Bull. Chem. Soc. Jpn.* **1974,** *47,* 2323; Lane *Synthesis* **1975,** 135-146, pp. 145-146; Kabalka; Yang; Chandler; Baker *Synthesis* **1977,** 124; Kabalka; Summers *J. Org. Chem.* **1981,** *46,* 1217; Fleet; Harding; Whitcombe *Tetrahedron Lett.* **1980,** *21,* 4031; Miller; Yang; Weigel; Han; Liu *J. Org. Chem.* **1989,** *54,* 4175.

[532] Hutchins; Kacher; Rua *J. Org. Chem.* **1975,** *40,* 923; Kabalka; Yang; Baker *J. Org. Chem.* **1976,** *41,* 574; Taylor; Djerassi *J. Am. Chem. Soc.* **1976,** *98,* 2275; Hutchins; Natale *J. Org. Chem.* **1978,** *43,* 2299; Greene *Tetrahedron Lett.* **1979,** 63.

[533] For a review of the mechanism, see Szmant *Angew. Chem. Int. Ed. Engl.* **1968,** *7,* 120-128 [*Angew. Chem. 80,* 141-149].

[534] See, for example, Horner; Schmitt *Liebigs Ann. Chem.* **1978,** 1617; Poutsma; Wolthius *J. Org. Chem.* **1959,** *24,* 875; Nakabayashi *J. Am. Chem. Soc.* **1960,** *82,* 3900, 3906; Di Vona; Rosnati *J. Org. Chem.* **1991,** *56,* 4269.

[535] Burdon; Price *J. Chem. Soc., Chem. Commun.* **1986,** 893.

9-38 Reduction of Carboxylic Acids to Alcohols
Dihydro-de-oxo-bisubstitution

$$\mathbf{RCOOH \xrightarrow{LiAlH_4} RCH_2OH}$$

Carboxylic acids are easily reduced to primary alcohols by $LiAlH_4$.[536] The reaction does not stop at the aldehyde stage (but see **0-84**). The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used,[537] but not $NaBH_4$ (see Table 19.5).[538] Catalytic hydrogenation is also generally ineffective.[539] Borane is particularly good for carboxyl groups (Table 19.4) and permits selective reduction of them in the presence of many other groups (though the reaction with double bonds takes place at about the same rate).[540] Borane also reduces carboxylic acid salts.[541] Aluminum hydride reduces COOH groups without affecting carbon–halogen bonds in the same molecule. The reduction has also been carried out with SmI_2 in basic media.[541a]

OS **III,** 60; **VII,** 221; 530; **65,** 173; **66,** 160; **68,** 77.

9-39 Reduction of Amides to Amines
Dihydro-deoxo-bisubstitution

$$\mathbf{RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2}$$

Amides can be reduced[542] to amines with $LiAlH_4$ or by catalytic hydrogenation, though high temperatures and pressures are usually required for the latter. Even with $LiAlH_4$ the reaction is more difficult than the reduction of most other functional groups, and other groups often can be reduced without disturbing an amide function. $NaBH_4$ by itself does not reduce amides, though it does so in the presence of certain other reagents.[543] Substituted amides can be similarly reduced:

$$\mathbf{RCONHR' \longrightarrow RCH_2NHR'}$$

$$\mathbf{RCONR'_2 \longrightarrow RCH_2NR'_2}$$

Borane[544] and sodium in 1-propanol[545] are good reducing agents for all three types of amides. Another reagent that reduces disubstituted amides to amines is trichlorosilane.[546] Sodium

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[536] For a review, see Gaylord *Reduction with Complex Metal Hydrides*; Wiley: New York, 1956, pp. 322-373.

[537] For a list of reagents, with references, see Ref. 21, pp. 548-549.

[538] $NaBH_4$ in the presence of $Me_2N{=}CHCl^+ \ Cl^-$ reduces carboxylic acids to primary alcohols chemoselectively in the presence of halide, ester, and nitrile groups: Fujisawa; Mori; Sato *Chem. Lett.* **1983,** 835.

[539] See Rylander *Hydrogenation Methods*, Ref. 488, pp. 78-79.

[540] Brown; Korytnyk *J. Am. Chem. Soc.* **1960,** *82*, 3866; Batrakov; Bergel'son *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965,** 348; Pelter; Hutchings; Levitt; Smith *Chem. Commun.* **1970,** 347; Brown; Stocky *J. Am. Chem. Soc.* **1977,** *99*, 8218.

[541] Yoon; Cho *Tetrahedron Lett.* **1982,** *23*, 2475.

[541a] Kamochi; Kudo *Chem. Lett.* **1991,** 893.

[542] For a review, see Challis; Challis, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 795-801. For a review of the reduction of amides, lactams, and imides with metallic hydrides, see Gaylord, Ref. 536, pp. 544-636. For a list of reagents, with references, see Ref. 21, pp. 432-433.

[543] See, for example, Satoh; Suzuki; Suzuki; Miyaji; Imai *Tetrahedron Lett.* **1969,** 4555; Rahman; Basha; Waheed; Ahmed *Tetrahedron Lett.* **1976,** 219; Kuehne; Shannon *J. Org. Chem.* **1977,** *42*, 2082; Wann; Thorsen; Kreevoy *J. Org. Chem.* **1981,** *46*, 2579; Mandal; Giri; Pakrashi *Synthesis* **1987,** 1128; Akaboro; Takanohashi *Chem. Lett.* **1990,** 251.

[544] Brown; Heim *J. Org. Chem.* **1973,** *38*, 912; Brown; Narasimhan; Choi *Synthesis* **1981,** 441, 996; Krishnamurthy *Tetrahedron Lett.* **1982,** *23*, 3315; Bonnat; Hercouet; Le Corre *Synth. Commun.* **1991,** *21*, 1579.

[545] Bhandari; Sharma; Chatterjee *Chem. Ind. (London)* **1990,** 547.

[546] Nagata; Dohmaru; Tsurugi *Chem. Lett.* **1972,** 989. See also Benkeser; Li; Mozdzen *J. Organomet. Chem.* **1979,** *178*, 21.

(dimethylamino)borohydride reduces unsubstituted and disubstituted, but not monosubstituted amides.[547]

With some $RCONR'_2$, $LiAlH_4$ causes cleavage, and the aldehyde (**0-85**) or alcohol is obtained. Lithium triethylborohydride produces the alcohol with most N,N-disubstituted amides, though not with unsubstituted or N-substituted amides.[548] Lactams are reduced to cyclic amines in high yields with $LiAlH_4$, though cleavage sometimes occurs here too. Imides are generally reduced on both sides, though it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, though with acyclic imides cleavage is often obtained, e.g.,[549]

$$\mathbf{PhN(COMe)_2 \longrightarrow PhNHEt}$$

Acyl sulfonamides have been reduced ($RCONHSO_2Ph \rightarrow RCH_2NHSO_2Ph$) with BH_3–SMe_2.[550]

OS **IV,** 339, 354, 564; **VI,** 382; **VII,** 41.

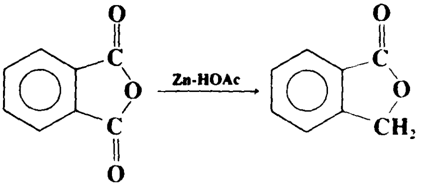
9-40 Reduction of Carboxylic Esters to Ethers
Dihydro-de-oxo-bisubstitution

$$\mathbf{RCOOR' \xrightarrow[LiAlH_4]{BF_3\text{-etherate}} RCH_2OR'}$$

Carboxylic esters and lactones have been reduced to ethers, though the more usual course is the obtention of 2 moles of alcohol (**9-42**). Reduction to ethers has been accomplished with a reagent prepared from BF_3–etherate and either $LiAlH_4$, $LiBH_4$, or $NaBH_4$,[551] with trichlorosilane and uv light,[552] and with catalytic hydrogenation. The reaction with the BF_3 reagent apparently succeeds with secondary R', but not with primary R', which give **9-42.** Lactones give cyclic ethers.[553] Thiono esters RCSOR' can be reduced to ethers RCH_2OR' with Raney nickel (**4-36**).[554] Since the thiono esters can be prepared from carboxylic esters (**6-11**), this provides an indirect method for the conversion of carboxylic esters to ethers. Thiol esters RCOSR' have been reduced to thioethers RCH_2SR'.[555]

See also **9-43, 0-81.**

9-41 Reduction of Cyclic Anhydrides to Lactones
Dihydro-de-oxo-bisubstitution



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[547] Hutchins; Learn; El-Telbany; Stercho *J. Org. Chem.* **1984,** *49,* 2438.

[548] Brown; Kim *Synthesis* **1977,** 635.

[549] Witkop; Patrick *J. Am. Chem. Soc.* **1952,** *74,* 3861.

[550] Belletire; Fry *Synth. Commun.* **1988,** *18,* 29.

[551] Pettit; Ghatak; Green; Kasturi; Piatak *J. Org. Chem.* **1961,** *26,* 1685; Pettit; Green; Kasturi; Ghatak *Tetrahedron* **1962,** *18,* 953; Ager; Sutherland *J. Chem. Soc., Chem. Commun* **1982,** 248. See also Dias; Pettit *J. Org. Chem.* **1971,** *36,* 3485.

[552] Tsurugi; Nakao; Fukumoto *J. Am. Chem. Soc.* **1969,** *91,* 4587; Nagata; Dohmaru; Tsurugi *J. Org. Chem.* **1973,** *38,* 795; Baldwin; Doll; Haut *J. Org. Chem.* **1974,** *39,* 2470; Baldwin; Haut *J. Org. Chem.* **1975,** *40,* 3885. See also Kraus; Frazier; Roth; Taschner; Neuenschwander *J. Org. Chem.* **1981,** *46,* 2417.

[553] See, for example, Pettit; Kasturi; Green; Knight *J. Org. Chem.* **1961,** *26,* 4773; Edward; Ferland *Chem. Ind. (London)* **1964,** 975.

[554] Baxter; Bradshaw *J. Org. Chem.* **1981,** *46,* 831.

[555] Eliel; Daignault *J. Org. Chem.* **1964,** *29,* 1630; Bublitz *J. Org. Chem.* **1967,** *32,* 1630.

Cyclic anhydrides can give lactones if reduced with Zn–HOAc, with hydrogen and platinum or $RuCl_2(Ph_3P)_3$,[556] with $NaBH_4$,[557] or even with $LiAlH_4$, though with the last-mentioned reagent diols are the more usual product (**9-44**). With some reagents the reaction can be accomplished regioselectively, i.e., only a specific one of the two C=O groups of an unsymmetrical anhydride is reduced.[558] Open-chain anhydrides either are not reduced at all (e.g., with $NaBH_4$) or give 2 moles of alcohol.

There are no *Organic Syntheses* references, but see OS **II,** 526, for a related reaction.

9-42 Reduction of Carboxylic Esters to Alcohols

Dihydro,hydroxy-de-oxo,alkoxy-tersubstitution

$$\mathbf{RCOOR' \xrightarrow{LiAlH_4} RCH_2OH + R'OH}$$

$LiAlH_4$ reduces carboxylic esters to give 2 moles of alcohol.[559] The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining R'OH, this is a method of "hydrolyzing" esters. Lactones yield diols. Among the reagents that give the same products[560] are DIBALH, lithium triethylborohydride, and BH_3–SMe_2 in refluxing THF.[561] $NaBH_4$ reduces phenolic esters, especially those containing electron-withdrawing groups,[562] but its reaction with other esters is usually so slow that such reactions are seldom feasible (though exceptions are known[563]), and it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. However, $NaBH_4$ reduces esters in the presence of certain compounds (see Table 19.5).[564] Carboxylic esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,[565] though high pressures and temperatures are required. Ester functions generally survive low-pressure catalytic hydrogenations. Before the discovery of $LiAlH_4$, the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault–Blanc procedure*. This procedure is still sometimes used where selectivity is necessary. See also **9-40, 9-43,** and **0-81.**

OS **II,** 154, 325, 372, 468; **III,** 671; **IV,** 834; **VI,** 781; **VII,** 356; **68,** 92.

9-43 Reduction of Carboxylic Acids and Esters to Alkanes

Trihydro-de-alkoxy,oxo-tersubstitution, etc.

$$\mathbf{RCOOR' \xrightarrow{(C_5H_5)_2TiCl_2} RCH_3 + R'OH}$$

The reagent titanocene dichloride reduces carboxylic esters in a different manner from that of **0-81, 9-40,** or **9-42.** The products are the alkane RCH_3 and the alcohol R'OH.[526] The mechanism probably involves an alkene intermediate. Aromatic acids can be reduced to methylbenzenes by a procedure involving refluxing first with trichlorosilane in MeCN, then

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[556] Lyons *J. Chem. Soc., Chem. Commun.* **1975,** 412; Morand; Kayser *J. Chem. Soc., Chem. Commun.* **1976,** 314. See also Hara; Wada *Chem. Lett.* **1991,** 553.

[557] Bailey; Johnson *J. Org. Chem.* **1970,** *35,* 3574.

[558] See, for example, Kayser; Salvador; Morand *Can. J. Chem.* **1983,** *61,* 439; Ikariya; Osakada; Ishii; Osawa; Saburi; Yoshikawa *Bull. Chem. Soc. Jpn.* **1984,** *57,* 897; Soucy; Favreau; Kayser *J. Org. Chem.* **1987,** *52,* 129.

[559] For a review, see Gaylord, Ref. 536, pp. 391-531.

[560] For a list of reagents, with references, see Ref. 21, pp. 549-551.

[561] Brown; Choi *Synthesis* **1981,** 439; Brown; Choi; Narasimhan *J. Org. Chem.* **1982,** *47,* 3153.

[562] Takahashi; Cohen *J. Org. Chem.* **1970,** *35,* 1505.

[563] For example, see Brown; Rapoport *J. Org. Chem.* **1963,** *28,* 3261; Bianco; Passacantilli; Righi *Synth. Commun.* **1988,** *18,* 1765.

[564] See also Kikugawa *Chem. Lett.* **1975,** 1029; Santaniello; Ferraboschi; Sozzani *J. Org. Chem.* **1981,** *46,* 4584; Brown; Narasimhan; Choi *J. Org. Chem.* **1982,** *47,* 4702; Soai; Oyamada; Takase; Ookawa *Bull. Chem. Soc. Jpn.* **1984,** *57,* 1948; Guida; Entreken; Guida *J. Org. Chem.* **1984,** *49,* 3024.

[565] For a review, see Adkins, *Org. React.* **1954,** *8,* 1-27.

with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).[566] The following sequence has been suggested:[566]

$$\mathrm{ArCOOH} \xrightarrow{\mathrm{SiHCl_3}} \mathrm{(ArCO)_2O} \xrightarrow[\mathrm{R_3N}]{\mathrm{SiHCl_3}} \mathrm{ArCH_2SiCl_3} \xrightarrow[\mathrm{MeOH}]{\mathrm{KOH}} \mathrm{ArCH_3}$$

Esters of aromatic acids are not reduced by this procedure, so an aromatic COOH group can be reduced in the presence of a COOR′ group.[567] However, it is also possible to reduce aromatic ester groups, by a variation of the trichlorosilane procedure.[568] *o*- and *p*-hydroxybenzoic acids and their esters have been reduced to cresols $HOC_6H_4CH_3$ with sodium bis(2-methoxyethoxy)aluminum hydride $NaAlH_2(OC_2H_4OMe)_2$ (*Red-Al*).[569]

Carboxylic acids can also be converted to alkanes, indirectly,[570] by reduction of the corresponding tosylhydrazides $RCONHNH_2$ with $LiAlH_4$ or borane.[571]

OS **VI,** 747.

9-44 Reduction of Anhydrides to Alcohols

$$\mathrm{RCOOCOR} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{2RCH_2OH}$$

$LiAlH_4$ usually reduces open-chain anhydrides to give 2 moles of alcohol. With cyclic anhydrides the reaction with $LiAlH_4$ can be controlled to give either diols or lactones[572] (see **9-41**). $NaBH_4$ in THF, with dropwise addition of methanol, reduces open-chain anhydrides to one mole of primary alcohol and one mole of carboxylic acid.[573]

OS **VI,** 482.

9-45 Reduction of Acyl Halides to Alcohols

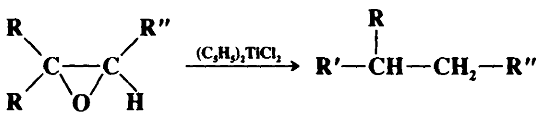
Dihydro,hydroxy-de-halo,oxo-tersubstitution

$$\mathrm{RCOCl} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH}$$

Acyl halides are reduced[574] to alcohols by $LiAlH_4$ or $NaBH_4$, as well as by other metal hydrides (Table 19.5), but not by borane. The reaction may be regarded as a combination of **9-37** and **0-76.**

OS **IV,** 271.

9-46 Complete Reduction of Epoxides



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[566] Benkeser; Foley; Gaul; Li *J. Am. Chem. Soc.* **1970,** *92,* 3232.

[567] Benkeser; Ehler *J. Org. Chem.* **1973,** *38,* 3660.

[568] Benkeser; Mozdzen; Muth *J. Org. Chem.* **1979,** *44,* 2185.

[569] Černý; Málek *Tetrahedron Lett.* **1969,** 1739, *Collect. Czech. Chem. Commun.* **1970,** *35,* 2030.

[570] For another indirect method, which can also be applied to acid derivatives, see Degani; Fochi *J. Chem. Soc., Perkin Trans. 1* **1978,** 1133. For a direct method, see Le Deit; Cron; Le Corre *Tetrahedron Lett.* **1991,** *32,* 2759.

[571] Attanasi; Caglioti; Gasparrini; Misiti *Tetrahedron* **1975,** *31,* 341, and references cited therein.

[572] Bloomfield; Lee *J. Org. Chem.* **1967,** *32,* 3919.

[573] Soai; Yokoyama; Mochida *Synthesis* **1987,** 647.

[574] For a review of the reduction of acyl halides, see Wheeler, in Patai *The Chemistry of Acyl Halides*; Wiley: New York, 1972, pp. 231-251. For a list of reagents, with references, see Ref. 21, p. 549.

Though the usual product of epoxide reductions is the alcohol (**0-80**), epoxides are reduced all the way to the alkane by titanocene dichloride[526] and by $Et_3SiH–BH_3$.[575]

9-47 Reduction of Nitro Compounds to Amines

$$\mathbf{RNO_2 \xrightarrow[HCl]{Zn} RNH_2}$$

Both aliphatic[576] and aromatic nitro compounds can be reduced to amines, though the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn, or Fe (or sometimes other metals) and acid, and catalytic hydrogenation.[577] Among other reagents used[578] have been $AlH_3–AlCl_3$, hydrazine and a catalyst,[579] $TiCl_3$,[580] $Al–NiCl_2–THF$,[581] formic acid and Pd–C,[582] and sulfides such as NaHS, $(NH_4)_2S$, or polysulfides. The reaction with sulfides or polysulfides is called the *Zinin reduction*.[583] The reagent sodium dihydro(trithio)borate $NaBH_2S_3$ reduces aromatic nitro compounds to amines,[584] but aliphatic nitro compounds give other products (see **9-58**). In contrast, $LiAlH_4$ reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (**9-67**). Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, though both aliphatic and aromatic nitro compounds have been reduced to amines with $NaBH_4$ and various catalysts, such as $NiCl_2$ or $CoCl_2$.[585] Treatment of aromatic nitro compounds with $NaBH_4$ alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact[586] or in cleavage of the nitro group from the ring.[587] With $(NH_4)_2S$ or other sulfides or polysulfides it is often possible to reduce just one of two or three nitro groups on an aromatic ring or on two different rings in one molecule.[588] The nitro groups of N-nitro compounds can also be reduced to amino groups, e.g., nitrourea $NH_2CONHNO_2$ gives semicarbazide $NH_2CONHNH_2$.

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (**9-49**), hydrazobenzenes (**9-68**),

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[575] Fry; Mraz *Tetrahedron Lett.* **1979,** 849.

[576] For a review of selective reduction of aliphatic nitro compounds without disturbance of other functional groups, see Ioffe; Tartakovskii; Novikov *Russ. Chem. Rev.* **1966,** *35*, 19-32.

[577] For reviews, see Rylander *Hydrogenation Methods*, Ref. 488, pp. 104-116, *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967, pp. 168-202.

[578] For a list of reagents, with references, see Ref. 21, pp. 411-415.

[579] An explosion has been reported with *o*-chloronitro compounds: Rondestvedt; Johnson *Synthesis* **1977,** 851. For a review of the use of hydrazine, see Furst; Berlo; Hooton *Chem. Rev.* **1965,** *65*, 51-68, pp. 52-60. See also Yuste; Saldaña; Walls *Tetrahedron Lett.* **1982,** *23*, 147; Adger; Young *Tetrahedron Lett.* **1984,** *25*, 5219.

[580] Ho; Wong *Synthesis* **1974,** 45. See also George; Chandrasekaran *Synth. Commun.* **1983,** *13*, 495.

[581] Sarmah; Barua *Tetrahedron Lett.* **1990,** *31*, 4065.

[582] Entwistle; Jackson; Johnstone; Telford *J. Chem. Soc., Perkin Trans. 1* **1977,** 443. See also Terpko; Heck *J. Org. Chem.* **1980,** *45*, 4992; Babler; Sarussi *Synth. Commun.* **1981,** *11*, 925.

[583] For a review of the Zinin reduction, see Porter *Org. React.* **1973,** *20*, 455-481.

[584] Lalancette; Brindle *Can. J. Chem.* **1971,** *49*, 2990. See also Maki; Sugiyama; Kikuchi; Seto *Chem. Lett.* **1975,** 1093.

[585] See, for example, Jardine; McQuillin *Chem. Commun.* **1970,** 626; Hanaya; Muramatsu; Kudo; Chow *J. Chem. Soc., Perkin Trans. 1* **1979,** 2409; Ono; Sasaki; Yaginuma *Chem. Ind.* (*London*) **1983,** 480; Osby; Ganem *Tetrahedron Lett.* **1985,** *26*, 6413; Petrini; Ballini; Rosini *Synthesis* **1987,** 713; He; Zhao; Pan; Wang *Synth. Commun.* **1989,** *19*, 3047.

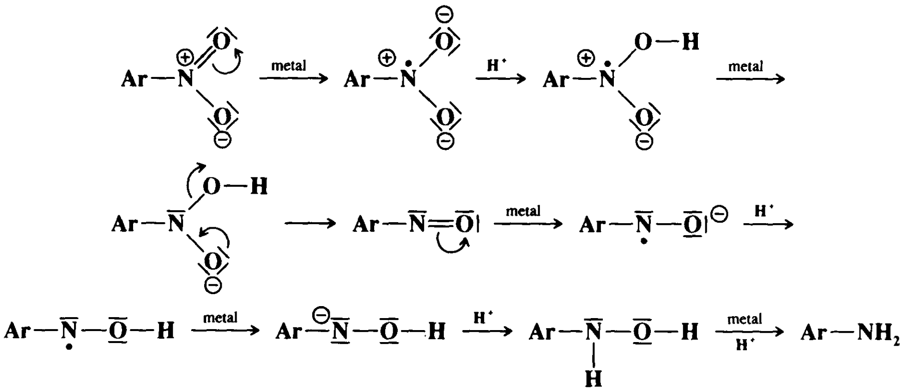
[586] Severin; Schmitz *Chem. Ber.* **1962,** *95*, 1417; Severin; Adam *Chem. Ber.* **1963,** *96*, 448.

[587] Kaplan *J. Am. Chem. Soc.* **1964,** *86*, 740. See also Swanwick; Waters *Chem. Commun.* **1970,** 63.

[588] This result has also been achieved by hydrogenation with certain catalysts [Lyle; LaMattina, *Synthesis* **1974,** 726; Knifton *J. Org. Chem.* **1976,** *41*, 1200; Ono; Terasaki; Tsuruoka *Chem. Ind.* (*London*) **1983,** 477], and with hydrazine hydrate and Raney nickel: Ayyangar; Kalkote; Lugade; Nikrad; Sharma *Bull. Chem. Soc. Jpn.* **1983,** *56*, 3159.

azobenzenes (**9-67**), and azoxybenzenes (**9-66**) can be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates (see however, **9-48**). Reduction by metals in mineral acids cannot be stopped, but always produces the amine. Amines are also the products when nitro compounds, both alkyl and aryl, are reduced with $HCOONH_4$–Pd–C.[589] Many other functional groups (e.g., COOH, COOR, CN, amide) are not affected by this reagent (though ketones are reduced—see **9-37**). With optically active alkyl substrates this method gives retention of configuration.[590]

The mechanisms of these reductions have been very little studied, though it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (**9-50**), and hydroxylamines can be isolated (**9-49**). With metals and acid the following path has been suggested:[591]



OS **I,** 52, 240, 455, 485; **II,** 130, 160, 175, 254, 447, 471, 501, 617; **III,** 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV,** 31, 357; **V,** 30, 346, 552, 567, 829, 1067, 1130.

9-48 Reduction of Nitro Compounds to Nitroso Compounds
N-Oxygen-detachment

$$ArNO_2 \xrightarrow[H_2O]{h\nu,\ CN^-} ArNO$$

Certain aromatic nitroso compounds can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 *M* aqueous KCN with uv light.[592] The reaction has also been performed electrochemically.[593] When nitro compounds are treated with most reducing agents, nitroso compounds are either not formed or react further under the reaction conditions and cannot be isolated. N-Nitroamines have been reduced to N-nitrosoamines with Bu_3SnH–azobisisobutyrylnitrile.[594]

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[589] Ram; Ehrenkaufer *Tetrahedron Lett.* **1984,** *25,* 3415.

[590] Barrett; Spilling *Tetrahedron Lett.* **1988,** *29,* 5733.

[591] House, Ref. 10, p. 211.

[592] Petersen; Letsinger *Tetrahedron Lett.* **1971,** 2197; Vink; Cornelisse; Havinga *Recl. Trav. Chim. Pays-Bas* **1971,** *90,* 1333.

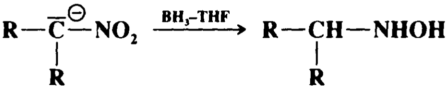
[593] Lamoureux; Moinet *Bull. Soc. Chim. Fr.* **1988,** 59.

[594] de Armas; Francisco; Hernández; Suárez *Tetrahedron Lett.* **1986,** *27,* 3195.

9-49 Reduction of Nitro Compounds to Hydroxylamines

$$\mathrm{ArNO_2} \xrightarrow[\mathrm{H_2O}]{\mathrm{Zn}} \mathrm{ArNHOH}$$

When aromatic nitro compounds are reduced with zinc and water under neutral conditions,[595] hydroxylamines are formed. Among other reagents used for this purpose have been SmI_2,[596] N_2H_4–Rh–C,[597] and $NaBH_4$–Se.[598] Borane in THF reduces aliphatic nitro compounds (in the form of their salts) to hydroxylamines:[599]



$$\mathrm{R{-}\overset{\ominus}{\underset{\substack{|\\ R}}{C}}{-}NO_2} \xrightarrow{\mathrm{BH_3\text{-}THF}} \mathrm{R{-}\underset{\substack{|\\ R}}{C}H{-}NHOH}$$

Nitro compounds have been reduced electrochemically, to hydroxylamines as well as to other products.[600]

OS **I,** 445; **III,** 668; **IV,** 148; **VI,** 803; **67,** 187.

9-50 Reduction of Nitroso Compounds and Hydroxylamines to Amines

$$\mathrm{RNO} \xrightarrow[\mathrm{HCl}]{\mathrm{Zn}} \mathrm{RNH_2}$$

***N*-Dihydro-de-oxo-bisubstitution**

$$\mathrm{RNHOH} \xrightarrow[\mathrm{HCl}]{\mathrm{Zn}} \mathrm{RNH_2}$$

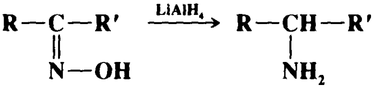
***N*-Hydro-de-hydroxylation** or ***N*-Dehydroxylation**

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents that reduce nitro compounds (**9-47**). N-Nitroso compounds are similarly reduced to hydrazines:[601]

$$\mathrm{R_2N{-}NO} \longrightarrow \mathrm{R_2N{-}NH_2}$$

OS **I,** 511; **II,** 33, 202, 211, 418; **III,** 91; **IV,** 247. See also OS **65,** 166.

9-51 Reduction of Oximes to Primary Amines or Aziridines



$$\mathrm{R{-}\underset{\substack{\|\\ N{-}OH}}{C}{-}R'} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{R{-}\underset{\substack{|\\ NH_2}}{C}H{-}R'}$$

Both aldoximes and ketoximes can be reduced to primary amines with $LiAlH_4$. The reaction is slower than with ketones, so that, for example, PhCOCH=NOH gave 34% Ph-

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[595] For some other methods of accomplishing this conversion, see Rondestvedt; Johnson *Synthesis* **1977,** 850; Entwistle; Gilkerson; Johnstone; Telford *Tetrahedron* **1978,** *34,* 213.

[596] Kende; Mendoza *Tetrahedron Lett.* **1991,** *32,* 1699.

[597] Oxley; Adger; Sasse; Forth *Org. Synth. 67,* 187.

[598] Yanada; Yamaguchi; Meguri; Uchida *J. Chem. Soc., Chem. Commun.* **1986,** 1655.

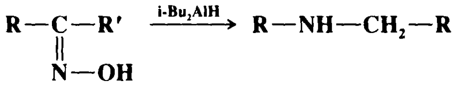
[599] Feuer; Bartlett; Vincent; Anderson *J. Org. Chem.* **1965,** *31,* 2880.

[600] For reviews of the electroreduction of nitro compounds, see Fry, Ref. 244, pp. 188-198; Lund, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 285-313.

[601] For examples of this reduction, accomplished with titanium reagents, see Entwistle; Johnstone; Wilby *Tetrahedron* **1982,** *38,* 419; Lunn; Sansone; Keefer *J. Org. Chem.* **1984,** *49,* 3470.

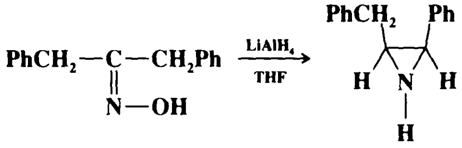
CHOHCH=NOH.[602] Among other reducing agents that give this reduction[603] are zinc and acetic acid, sodium ethoxide, BH_3,[604] $NaBH_3CN$-$TiCl_3$,[605] and sodium and an alcohol.[606] Catalytic hydrogenation is also effective.[607] The reduction has been performed enantioselectively with baker's yeast[608] and with Ph_2SiH_2 and an optically active rhodium complex catalyst.[609]

When the reducing agent is DIBALH, the product is a secondary amine, arising from a rearrangement:[610]



$$\underset{\displaystyle N-OH}{R-\overset{}{C}-R'} \xrightarrow{i\text{-}Bu_2AlH} R-NH-CH_2-R'$$

With certain oximes (e.g., those of the type $ArCH_2CR$=NOH), treatment with $LiAlH_4$ gives aziridines,[611] e.g.,



Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including Zn-HCl and H_2 and Raney nickel.

Oximes have been reduced in a different way, to give imines (RR'C=NOH → RR'C=NH), which are generally unstable but which can be trapped to give useful products. Among reagents used for this purpose have been Bu_3P-SPh_2[612] and $Ru_3(CO)_{12}$.[613]

Oximes can also be reduced to hydroxylamines (**6-26**).

OS **II,** 318; **III,** 513; **V,** 32, 83, 373, 376.

9-52 Reduction of Azides to Primary Amines
***N*-Dihydro-de-diazo-bisubstitution**

$$RN_3 \xrightarrow{LiAlH_4} RNH_2$$

Azides are easily reduced to primary amines by $LiAlH_4$, as well as by a number of other reducing agents,[614] including $NaBH_4$, PPh_3 (with this reagent, the process is called the

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[602] Felkin *C. R. Acad. Sci.* **1950,** *230,* 304.

[603] For a list of reagents, with references, see Ref. 21, p. 424.

[604] Feuer; Braunstein *J. Org. Chem.* **1969,** *34,* 1817.

[605] Leeds; Kirst *Synth. Commun.* **1988,** *18,* 777.

[606] For example, see Sugden; Patel *Chem. Ind. (London)* **1972,** 683.

[607] For a review, see Rylander *Catalytic Hydrogenation over Platinum Metals,* Ref. 577, pp. 139-159.

[608] Gibbs; Barnes *Tetrahedron Lett.* **1990,** *31,* 5555.

[609] Brunner; Becker; Gauder *Organometallics* **1986,** *5,* 739.

[610] Sasatani; Miyazaki; Maruoka; Yamamoto *Tetrahedron Lett.* **1983,** *24,* 4711. See also Rerick; Trottier; Daignault; DeFoe *Tetrahedron Lett.* **1963,** 629; Petrarca; Emery *Tetrahedron Lett.* **1963,** 635; Graham; Williams *Tetrahedron* **1965,** *21,* 3263.

[611] For a review, see Kotera; Kitahonoki *Org. Prep. Proced.* **1969,** *1,* 305-324. For examples, see Shandala; Solomon; Waight *J. Chem. Soc.* **1965,** 892; Kitahonoki; Takano; Matsuura; Kotera *Tetrahedron* **1969,** *25,* 335; Landor; Sonola; Tatchell *J. Chem. Soc., Perkin Trans. 1* **1974,** 1294; Ferrero; Rouillard; Decouzon; Azzaro *Tetrahedron Lett.* **1974,** 131; Diab; Laurent; Mison *Tetrahedron Lett.* **1974,** 1605.

[612] Barton; Motherwell; Simon; Zard *J. Chem. Soc., Chem. Commun.* **1984,** 337.

[613] Akazome; Tsuji; Watanabe *Chem. Lett.* **1990,** 635.

[614] For a review, see Scriven; Turnbull *Chem. Rev.* **1988,** *88,* 297-368, pp. 321-327. For lists of reagents, with references, see Ref. 21, pp. 409-410; Rolla *J. Org. Chem.* **1982,** *47,* 4327.

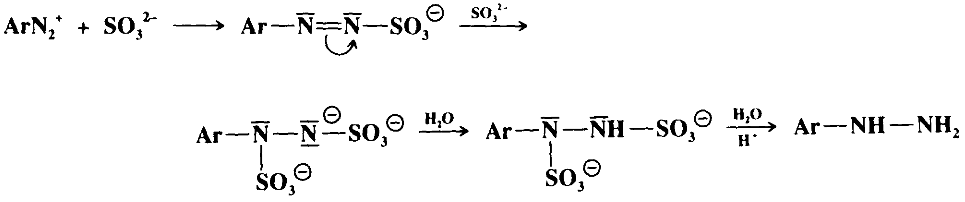
Staudinger reaction),[615] H_2 and a catalyst, Mg or Ca in MeOH,[616] N_2H_4–Pd,[617] and tin complexes prepared from $SnCl_2$ or $Sn(SR)_2$.[618] This reaction, combined with $RX \rightarrow RN_3$ (**0-61**), is an important way of converting alkyl halides RX to primary amines RNH_2; in some cases the two procedures have been combined into one laboratory step.[619] Sulfonyl azides RSO_2N_3 have been reduced to sulfonamides RSO_2NH_2 by irradiation in isopropyl alcohol[620] and with NaH.[621]

OS **V,** 586; **VII,** 433.

9-53 Reduction of Miscellaneous Nitrogen Compounds

$R{-}N{=}C{=}O \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$	**Isocyanate-methylamine transformation**
$R{-}N{=}C{=}S \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$	**Isothiocyanate-methylamine transformation**
$Ar{-}N{=}N{-}Ar \xrightarrow[\text{catalyst}]{H_2} Ar{-}NH{-}NH{-}Ar$	***N,N*-Dihydro-addition**
$ArN_2^+\ Cl^- \xrightarrow{Na_2SO_3} ArNHNH_2$	**Diazonium-arylhydrazone reduction**
$R_2N{-}NO \xrightarrow[Ni]{H_2} R_2NH$	***N*-Hydro-de-nitroso-substitution**

Isocyanates and isothiocyanates are reduced to methylamines on treatment with $LiAlH_4$. $LiAlH_4$ does not usually reduce azo compounds[622] (indeed these are the products from $LiAlH_4$ reduction of nitro compounds, **9-67**), but these can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide[623] (see **5-9**). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism.[624]



The initial product is a salt of hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment. Diazonium salts can also be reduced to arenes (**4-24**). N-Nitrosoamines

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[615] First reported by Staudinger; Meyer *Helv. Chim. Acta* **1919,** *2,* 635.

[616] Maiti; Spevak; Narender Reddy *Synth. Commun.* **1988,** *18,* 1201.

[617] Malik; Preston; Archibald; Cohen; Baum *Synthesis* **1989,** 450.

[618] Bartra; Romea; Urpí; Vilarrasa *Tetrahedron* **1990,** *46,* 587.

[619] See, for example, Koziara; Osowska-Pacewicka; Zawadzki; Zwierzak *Synthesis* **1985,** 202, **1987,** 487. The reactions **0-67, 0-61,** and **9-52** have also been accomplished in one laboratory step: Koziara *J. Chem. Res. (S)* **1989,** 296.

[620] Reagen; Nickon *J. Am. Chem. Soc.* **1968,** *90,* 4096.

[621] Lee; Closson *Tetrahedron Lett.* **1974,** 381.

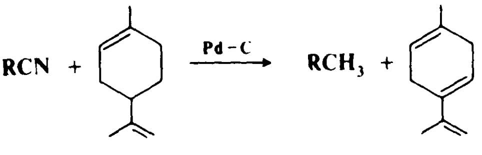
[622] For a review see Newbold, in Patai, Ref. 136, pt. 2, pp. 601, 604-614.

[623] For example, see Ioffe; Sergeeva; Dumpis *J. Org. Chem. USSR* **1969,** *5,* 1683.

[624] Huisgen; Lux *Chem. Ber.* **1960,** *93,* 540.

can be denitrosated to secondary amines by a number of reducing agents, including H_2 and a catalyst,[625] BF_3-THF-$NaHCO_3$,[626] and $NaBH_4$-$TiCl_4$,[627] as well as by hydrolysis.[628]

A cyano group can be reduced to a methyl group by treatment with a terpene such as limonene (which acts as reducing agent) in the presence of palladium–charcoal.[629] H_2 is also



Limonene

effective,[630] though higher temperatures are required. R may be alkyl or aryl. Cyano groups CN have also been reduced to CH_2OH, in the vapor phase, with 2-propanol and zirconium oxide.[631]

OS **I,** 442; **III,** 475. Also see OS **V,** 43.

9-54 Reduction of Sulfonyl Halides and Sulfonic Acids to Thiols

$$RSO_2Cl \xrightarrow{LiAlH_4} RSH$$

Thiols can be prepared by the reduction of sulfonyl halides[632] with $LiAlH_4$. Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Sulfonic acids have been reduced to thiols with a mixture of triphenylphosphine and either I_2 or a diaryl disulfide.[633] Disulfides RSSR can also be produced.[634] For the reduction of sulfonyl chlorides to sulfinic acids, see **0-118.**

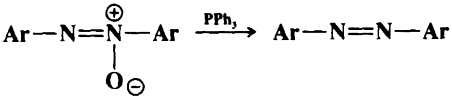
OS **I,** 504; **IV,** 695; **V,** 843.

B. Reactions in Which an Oxygen Is Removed from the Substrate

9-55 Reduction of Amine Oxides and Azoxy Compounds

N-Oxygen-detachment

$$R_3\overset{\oplus}{N}-\overset{\ominus}{O} \xrightarrow{PPh_3} R_3N$$



$$Ar-N=\overset{\oplus}{\underset{\underset{O^{\ominus}}{|}}{N}}-Ar \xrightarrow{PPh_3} Ar-N=N-Ar$$

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[625] Enders; Hassel; Pieter; Renger; Seebach *Synthesis* **1976,** 548.

[626] Jeyaraman; Ravindran *Tetrahedron Lett.* **1990,** *31,* 2787.

[627] Kano; Tanaka; Sugino; Shibuya; Hibino *Synthesis* **1980,** 741.

[628] Fridman; Mukhametshin; Novikov *Russ. Chem. Rev.* **1971,** *40,* 34-50, pp. 41-42.

[629] Kindler; Lührs *Chem. Ber.* **1966,** *99,* 227, *Liebigs Ann. Chem.* **1967,** *707,* 26.

[630] See also Andrade; Maier; Zapf; Schleyer *Synthesis* **1980,** 802; Brown; Foubister *Synthesis* **1982,** 1036.

[631] Takahashi; Shibagaki; Matsushita *Chem. Lett.* **1990,** 311.

[632] For a review, see Wardell, in Patai, Ref. 408, pp. 216-220.

[633] Oae; Togo *Bull. Chem. Soc. Jpn.* **1983,** *56,* 3802, **1984,** *57,* 232.

[634] For example, see Alper *Angew. Chem. Int. Ed. Engl.* **1969,** *8,* 677 [*Angew. Chem. 81,* 706]; Chan; Montillier; Van Horn; Harpp *J. Am. Chem. Soc.* **1970,** *92,* 7224. See also Olah; Narang; Field; Karpeles *J. Org. Chem.* **1981,** *46,* 2408; Oae; Togo *Synthesis* **1982,** 152, *Bull. Chem. Soc. Jpn.* **1983,** *56,* 3813; Suzuki; Tani; Osuka *Chem. Lett.* **1984,** 139; Babu; Bhatt *Tetrahedron Lett.* **1986,** *27,* 1073; Narayana; Padmanabhan; Kabalka *Synlett* **1991,** 125.

Amine oxides[635] and azoxy compounds (both alkyl and aryl)[636] can be reduced practically quantitatively with triphenylphosphine.[637] Other reducing agents, e.g., $LiAlH_4$, H_2–Ni, PCl_3, CS_2,[638] NaHTe,[639] $TiCl_3$,[640] $TiCl_4$ with $LiAlH_4$, $SbCl_2$, or NaI,[641] and sulfur have also been used. Nitrile oxides[642] $R{-}C{\equiv}\overset{\oplus}{N}{-}\overset{\ominus}{O}$ can be reduced to nitriles with trialkylphosphines,[643] and isocyanates RNCO to isocyanides RNC with Cl_3SiH–Et_3N.[644]

OS **IV**, 166. See also OS **67**, 20.

9-56 Reduction of Sulfoxides and Sulfones

S-Oxygen-detachment

$$R{-}\underset{\displaystyle O}{\underset{\|}{S}}{-}R \xrightarrow{LiAlH_4} R{-}S{-}R$$

Sulfoxides can be reduced to sulfides by many reagents,[645] among them $LiAlH_4$, HI, Bu_3SnH,[646] $TiCl_2$,[647] $MeSiCl_3$–NaI,[648] H_2–Pd–C,[649] $NaBH_4$–$FeCl_3$,[650] NaBr,[651] $TiCl_4$–NaI,[652] Ph_3P,[653] and *t*-BuBr.[654] Sulfones, however, are usually stable to reducing agents, though they have been reduced to sulfides with DIBALH $(i\text{-}Bu)_2AlH$.[655] A less general reagent is $LiAlH_4$, which reduces some sulfones to sulfides, but not others.[656] Both sulfoxides and sulfones can be reduced by heating with sulfur (which is oxidized to SO_2), though the reaction with sulfoxides proceeds at a lower temperature. It has been shown by using substrate labeled with ^{35}S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since about 75% of the original radioactivity of the sulfone is lost.[657] This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*. There is no direct general method for the reduction of sulfones to sulfoxides,

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[635] For reviews of the reduction of heterocyclic amine oxides, see Albini; Pietra, Ref. 421, pp. 120-134; Katritzky; Lagowski, Ref. 421, pp. 166-231.

[636] For a review, see Newbold, in Patai, Ref. 136, pt. 2, pp. 602-603, 614-624.

[637] For a review, see Rowley, in Cadogan *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979, pp. 295-350.

[638] Yoshimura; Asada; Oae *Bull. Chem. Soc. Jpn.* **1982,** *55*, 3000.

[639] Barton; Fekih; Lusinchi *Tetrahedron Lett.* **1985,** *26*, 4603.

[640] Kuz'min; Mizhiritskii; Kogan *J. Org. Chem. USSR* **1989,** *25*, 596.

[641] Malinowski; Kaczmarek *Synthesis* **1987,** 1013; Kaczmarek; Malinowski; Balicki *Bull. Soc. Chim. Belg.* **1988,** *97*, 787.

[642] For reviews of the chemistry of nitrile oxides, see Torssell *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988, pp. 55-74; Grundmann *Fortschr. Chem. Forsch.* **1966,** *7*, 62-127.

[643] Grundmann; Frommeld *J. Org. Chem.* **1965,** *30*, 2077.

[644] Baldwin; Derome; Riordan *Tetrahedron* **1983,** *39*, 2989.

[645] For reviews, see Kukushkin *Russ. Chem. Rev.* **1990,** *59*, 844-852; Madesclaire *Tetrahedron* **1988,** *44*, 6537-6580; Drabowicz; Togo; Mikołajczyk; Oae *Org. Prep. Proced. Int.* **1984,** *16*, 171-198; Drabowicz; Numata; Oae *Org. Prep. Proced. Int.* **1977,** *9*, 63-83. For a list of reagents, with references, see Block, Ref. 440.

[646] Kozuka; Furumai; Akasaka; Oae *Chem. Ind. (London)* **1974,** 496.

[647] Drabowicz; Mikołajczyk *Synthesis* **1978,** 138. For the use of $TiCl_3$, see Ho; Wong *Synth. Commun.* **1973,** *3*, 37.

[648] Olah; Husain; Singh; Mehrotra *J. Org. Chem.* **1983,** *48*, 3667. See also Schmidt; Russ *Chem. Ber.* **1981,** *114*, 822.

[649] Ogura; Yamashita; Tsuchihashi *Synthesis* **1975,** 385.

[650] Lin; Zhang *Synth. Commun.* **1987,** *17*, 1403.

[651] Bernard; Caredda; Piras; Serra *Synthesis* **1990,** 329.

[652] Balicki *Synthesis* **1991,** 155.

[653] For a review, see Ref. 637, pp. 301-304.

[654] Tenca; Dossena; Marchelli; Casnati *Synthesis* **1981,** 141.

[655] Gardner; Kaiser; Krubiner; Lucas *Can. J. Chem.* **1973,** *51*, 1419.

[656] Bordwell; McKellin *J. Am. Chem. Soc.* **1951,** *73*, 2251; Whitney; Cram *J. Org. Chem.* **1970,** *35*, 3964; Weber; Stromquist; Ito *Tetrahedron Lett.* **1974,** 2595.

[657] Oae; Kawamura *Bull. Chem. Soc. Jpn.* **1963,** *36*, 163; Kiso; Oae *Bull. Chem. Soc. Jpn.* **1967,** *40*, 1722. See also Oae; Nakai; Tsuchida; Furukawa *Bull. Chem. Soc. Jpn.* **1971,** *44*, 445.

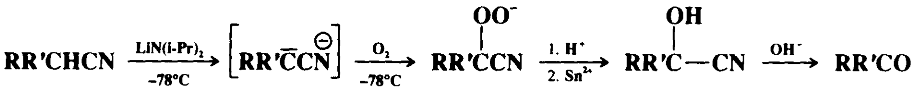
but an indirect method has been reported.[658] Selenoxides can be reduced to selenides with a number of reagents.[659]

9-57 Reduction of Hydroperoxides

$$\mathrm{R{-}O{-}O{-}H} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{ROH}$$

Hydroperoxides can be reduced to alcohols with $LiAlH_4$ or Ph_3P[660] or by catalytic hydrogenation. This functional group is very susceptible to catalytic hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.[661]

The reaction is an important step in a method for the oxidative decyanation of nitriles containing an α hydrogen.[662] The nitrile is first converted to the α-hydroperoxy nitrile by treatment with base at $-78°C$ followed by O_2. The hydroperoxy nitrile is then reduced to



$$\mathrm{RR'CHCN} \xrightarrow[-78^\circ\mathrm{C}]{\mathrm{LiN(i\text{-}Pr)_2}} \left[\mathrm{RR'}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{CN}\right] \xrightarrow[-78^\circ\mathrm{C}]{\mathrm{O_2}} \mathrm{RR'}\overset{\mathrm{OO^-}}{\overset{|}{\mathrm{C}}}\mathrm{CN} \xrightarrow[2.\ \mathrm{Sn^{2+}}]{1.\ \mathrm{H^+}} \mathrm{RR'}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}{-}\mathrm{CN} \xrightarrow{\mathrm{OH^-}} \mathrm{RR'CO}$$

the cyanohydrin, which is cleaved (the reverse of **6-49**) to the corresponding ketone. The method is not successful for the preparation of aldehydes (R' = H).

9-58 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles

$$\mathrm{RCH_2NO_2} \xrightarrow[\mathrm{HOAc}]{\mathrm{Zn}} \mathrm{RCH{=}NOH}$$

Nitro compounds that contain an α hydrogen can be reduced to oximes with zinc dust in HOAc[663] or with other reagents, among them Co–Cu(II) salts in alkanediamines,[664] CS_2–Et_3N,[665] $CrCl_2$,[666] and (for α-nitro sulfones) $NaNO_2$.[667] α-Nitro alkenes have been converted to oximes ($-\overset{|}{C}{=}\overset{|}{C}{-}NO_2 \rightarrow -\overset{|}{C}H{-}\overset{|}{C}{=}NOH$) with sodium hypophosphite and with Pb–HOAc–DMF, as well as with certain other reagents.[668]

Primary aliphatic nitro compounds can be reduced to nitriles with sodium dihydro(trithio)borate.[584] Secondary compounds give mostly ketones (e.g., nitrocyclohexane

$$\mathrm{RCH_2NO_2} \xrightarrow{\mathrm{NaBH_2S_3}} \mathrm{RC{\equiv}N}$$

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[658] Still; Ablenas *J. Org. Chem.* **1983,** *48,* 1617.

[659] See for example, Sakaki; Oae *Chem. Lett.* **1977,** 1003; Still; Hasan; Turnbull *Can. J. Chem.* **1978,** *56,* 1423; Denis; Krief *J. Chem. Soc., Chem. Commun.* **1980,** 544.

[660] For a review, see Ref. 637, pp. 318-320.

[661] Rebeller; Clément *Bull. Soc. Chim. Fr.* **1964,** 1302.

[662] Freerksen; Selikson; Wroble; Kyler; Watt *J. Org. Chem.* **1983,** *48,* 4087. This paper also reports several other methods for achieving this conversion.

[663] Johnson; Degering *J. Am. Chem. Soc.* **1939,** *61,* 3194.

[664] Knifton *J. Org. Chem.* **1973,** *38,* 3296.

[665] Barton; Fernandez; Richard; Zard *Tetrahedron* **1987,** *43,* 551; Albanese; Landini; Penso *Synthesis* **1990,** 333.

[666] Hanson; Organ *J. Chem. Soc. C* **1970,** 1182; Hanson *Synthesis* **1974,** 1-8, pp. 7-8.

[667] Zeilstra; Engberts *Synthesis* **1974,** 49.

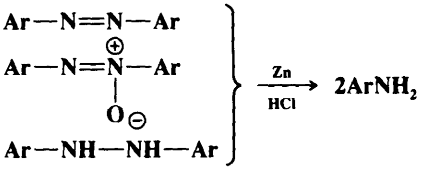
[668] See Varma; Varma; Kabalka *Synth. Commun.* **1986,** *16,* 91; Kabalka; Pace; Wadgaonkar *Synth. Commun.* **1990,** *20,* 2453; Sera; Yamauchi; Yamada; Itoh *Synlett* **1990,** 477.

gave 45% cyclohexanone, 30% cyclohexanone oxime, and 19% N-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent. See also **9-47.**

OS **IV,** 932.

C. Reduction with Cleavage

9-59 Reduction of Azo, Azoxy, and Hydrazo Compounds to Amines



Azo, azoxy, and hydrazo compounds can all be reduced to amines.[669] Metals (notably zinc) and acids, and $Na_2S_2O_4$, are frequently used as reducing agents. Borane reduces azo compounds to amines, though it does not reduce nitro compounds.[670] $LiAlH_4$ does not reduce hydrazo compounds or azo compounds, though with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds, $LiAlH_4$ gives only azo compounds (**9-55**).

OS **I,** 49; **II,** 35, 39; **III,** 360. Also see OS **II,** 290.

9-60 Reduction of Peroxides

O-Hydrogen-uncoupling

$$\mathbf{R{-}O{-}O{-}R \xrightarrow{LiAlH_4} 2ROH}$$

Peroxides are cleaved to 2 moles of alcohols by $LiAlH_4$ or by catalytic hydrogenation. Peroxides can be reduced to ethers with $P(OEt)_3$.[671]

$$\mathbf{ROOR + P(OEt)_3 \longrightarrow ROR + OP(OEt)_3}$$

In a similar reaction, disulfides RSSR′ can be converted to sulfides RSR′ by treatment with tris(diethylamino)phosphine $(Et_2N)_3P$.[672]

OS **VI,** 130.

9-61 Reduction of Disulfides to Thiols

S-Hydrogen-uncoupling

$$\mathbf{RSSR \xrightarrow[H^+]{Zn} 2RSH}$$

Disulfides can be reduced to thiols by mild reducing agents,[673] such as zinc and dilute acid or Ph_3P and H_2O.[674] The reaction can also be accomplished simply by heating with alkali.[675]

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[669] For a review, see Newbold, in Patai, Ref. 136, pt. 2, pp. 629-637.

[670] Brown; Subba Rao *J. Am. Chem. Soc.* **1960,** *82*, 681.

[671] Horner; Jurgeleit *Liebigs Ann. Chem.* **1955,** *591*, 138. See also Ref. 637, pp. 320-322.

[672] Harpp; Gleason; Snyder *J. Am. Chem. Soc.* **1968,** *90*, 4181; Harpp; Gleason *J. Am. Chem. Soc.* **1971,** *93*, 2437. For another method, see Comasseto; Lang; Ferreira; Simonelli; Correia *J. Organomet. Chem.* **1987,** *334*, 329.

[673] For a review, see Wardell, in Patai, Ref. 408, pp. 220-229.

[674] Overman; Smoot; Overman *Synthesis* **1974,** 59.

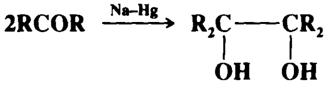
[675] For discussions, see Danehy; Hunter *J. Org. Chem.* **1967,** *32*, 2047; Danehy, in Ref. 407, pp. 337-349.

Among other reagents used have been LiAlH$_4$, KBH(O-i-Pr)$_3$,[676] and hydrazine or substituted hydrazines.[678]

OS **II**, 580. Also see OS **IV**, 295.

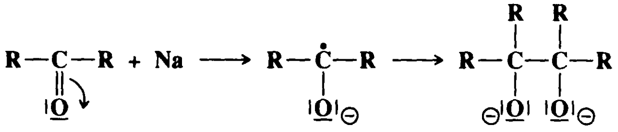
D. Reductive Coupling

9-62 Bimolecular Reduction of Aldehydes and Ketones to 1,2-Diols
2/*O*-Hydrogen-coupling



$$2\mathrm{RCOR} \xrightarrow{\mathrm{Na\text{-}Hg}} \underset{\mathrm{OH}}{\mathrm{R_2C}}\text{——}\underset{\mathrm{OH}}{\mathrm{CR_2}}$$

1,2-Diols (pinacols) can be synthesized by reduction of aldehydes and ketones with active metals such as sodium, magnesium, or aluminum.[679] Aromatic ketones give better yields than aliphatic ones. The use of a Mg–MgI$_2$ mixture has been called the *Gomberg–Bachmann pinacol synthesis*. As with a number of other reactions involving sodium, there is a direct electron transfer here, converting the ketone or aldehyde to a ketyl, which dimerizes.



Other reagents have been used,[680] including SmI$_2$,[681] Ce–I$_2$,[682] Yb,[683] and a reagent prepared from TiCl$_4$ and Mg amalgam[684] (a low-valent titanium reagent; see **9-64**). Dialdehydes have been cyclized by this reaction (with TiCl$_3$) to give cyclic 1,2-diols in good yield.[685] Unsymmetrical coupling between two different aldehydes has been achieved by the use of a vanadium complex,[686] while TiCl$_3$ in aqueous solution has been used to couple two different ketones.[687]

The dimerization of ketones to 1,2-diols can also be accomplished photochemically; indeed, this is one of the most common photochemical reactions.[688] The substrate, which

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[676] Brown; Nazer; Cha *Synthesis* **1984,** 498.

[677] Krishnamurthy; Aimino *J. Org. Chem.* **1989,** *54*, 4458.

[678] Maiti; Spevak; Singh; Micetich; Narender Reddy *Synth. Commun.* **1988,** *18*, 575.

[679] For efficient methods, see Schreibmann *Tetrahedron Lett.* **1970,** 4271; Fürstner; Csuk; Rohrer; Weidmann *J. Chem. Soc., Perkin Trans. 1* **1988,** 1729.

[680] For a list of reagents, with references, see Ref. 21, pp. 547-548.

[681] Namy; Souppe; Kagan *Tetrahedron Lett.* **1983,** *24*, 765.

[682] Imamoto; Kusumoto; Hatanaka; Yokoyama *Tetrahedron Lett.* **1982,** *23*, 1353.

[683] Hou; Takamine; Fujiwara; Taniguchi *Chem. Lett.* **1987,** 2061.

[684] Corey; Danheiser; Chandrasekaran *J. Org. Chem.* **1976,** *41*, 260; Pons; Zahra; Santelli *Tetrahedron Lett.* **1981,** *22*, 3965. For some other titanium-containing reagents, see Clerici; Porta *J. Org. Chem.* **1985,** *50*, 76; Handa; Inanaga *Tetrahedron Lett.* **1987,** *28*, 5717. For a review of such coupling with Ti and V halides, see Lai *Org. Prep. Proced. Int.* **1980,** *12*, 363-391.

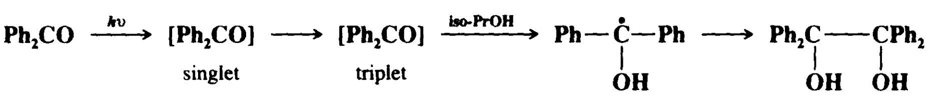
[685] McMurry; Rico *Tetrahedron Lett.* **1989,** *30*, 1169. For other cyclization reactions of dialdehydes and ketoaldehydes, see Molander; Kenny *J. Am. Chem. Soc.* **1989,** *111*, 8236; Raw; Pedersen *J. Org. Chem.* **1991,** *56*, 830; Chiara; Cabri; Hanessian *Tetrahedron Lett.* **1991,** *32*, 1125.

[686] Freudenberger; Konradi; Pedersen *J. Am. Chem. Soc.* **1989,** *111*, 8014.

[687] Clerici; Porta *J. Org. Chem.* **1982,** *47*, 2852, *Tetrahedron* **1983,** *39*, 1239. For some other unsymmetrical couplings, see Hou; Takamine; Aoki; Shiraishi; Fujiwara; Taniguchi *J. Chem. Soc., Chem. Commun.* **1988,** 668; Delair; Luche *J. Chem. Soc., Chem. Commun.* **1989,** 398; Takahara; Freudenberger; Konradi; Pedersen *Tetrahedron Lett.* **1989,** *30*, 7177.

[688] For reviews, see Schönberg *Preparative Organic Photochemistry*; Springer: New York, 1968, pp. 203-217; Neckers *Mechanistic Organic Photochemistry*; Reinhold: New York, 1967, pp. 163-177; Calvert; Pitts *Photochemistry*; Wiley: New York, 1966, pp. 532-536; Turro *Modern Molecular Photochemistry*; W.A. Benjamin: New York, 1978, pp. 363-385; Kan *Organic Photochemisty*; McGraw-Hill: New York, 1966, pp. 222-229.

is usually a diaryl or aryl alkyl ketone (though a few aromatic aldehydes and dialkyl ketones have been dimerized), is irradiated with uv light in the presence of a hydrogen donor such as isopropyl alcohol, toluene, or an amine.[689] In the case of benzophenone, irradiated in the presence of 2-propanol, the ketone molecule initially undergoes $n \rightarrow \pi^*$ excitation, and the singlet species thus formed crosses to the T_1 state with a very high efficiency. The T_1



$$\mathrm{Ph_2CO} \xrightarrow{h\nu} \underset{\text{singlet}}{[\mathrm{Ph_2CO}]} \longrightarrow \underset{\text{triplet}}{[\mathrm{Ph_2CO}]} \xrightarrow{\text{iso-PrOH}} \mathrm{Ph{-}}\underset{\mathrm{OH}}{\dot{\mathrm{C}}}\mathrm{{-}Ph} \longrightarrow \mathrm{Ph_2}\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{{-}{-}}\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{Ph_2}$$

33

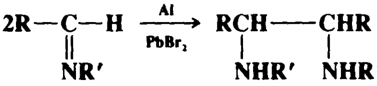
species abstracts hydrogen from the alcohol (p. 246) and then dimerizes. The iso-PrO• radical, which is formed by this process, donates H• to another molecule of ground-state benzophenone, producing acetone and another molecule of **33**. This mechanism[690] predicts that the quantum yield for the disappearance of benzophenone should be 2, since each quantum

$$\text{iso-}\mathrm{PrO\bullet} + \mathrm{Ph_2CO} \longrightarrow \mathrm{Me_2CO} + \mathrm{Ph_2\dot{C}OH}$$

33

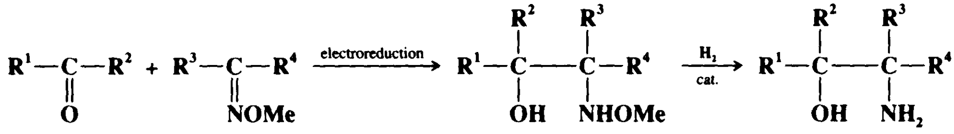
of light results in the conversion of 2 moles of benzophenone to **33**. Under favorable experimental conditions the observed quantum yield does approach 2. Benzophenone abstracts hydrogen with very high efficiency. Other aromatic ketones are dimerized with lower quantum yields, and some (e.g., *p*-aminobenzophenone, *o*-methylacetophenone) cannot be dimerized at all in 2-propanol (though *p*-aminobenzophenone, for example, can be dimerized in cyclohexane[691]). The reaction has also been carried out electrochemically.[692]

In a similar type of process, imines have been dimerized to give 1,2-diamines, by a number of procedures, including treatment with Al–$\mathrm{PbBr_2}$,[693] with $\mathrm{TiCl_4}$–Mg,[694] with $\mathrm{SmI_2}$,[695]



$$2\mathrm{R{-}}\underset{\mathrm{NR'}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}H} \xrightarrow[\mathrm{PbBr_2}]{\mathrm{Al}} \underset{\mathrm{NHR'}}{\mathrm{RCH}}\mathrm{{-}{-}}\underset{\mathrm{NHR'}}{\mathrm{CHR}}$$

and (for silylated imines) $\mathrm{NbCl_4(THF)_2}$.[696] When electroreduction was used, it was even possible to obtain cross products, by coupling a ketone to an O-methyl oxime:[697]



$$\mathrm{R^1{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}R^2} + \mathrm{R^3{-}}\underset{\mathrm{NOMe}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}R^4} \xrightarrow{\text{electroreduction}} \mathrm{R^1{-}}\overset{\mathrm{R^2}}{\underset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}{-}}\overset{\mathrm{R^3}}{\underset{\mathrm{NHOMe}}{\mathrm{C}}}\mathrm{{-}R^4} \xrightarrow[\text{cat.}]{\mathrm{H_2}} \mathrm{R^1{-}}\overset{\mathrm{R^2}}{\underset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}{-}}\overset{\mathrm{R^3}}{\underset{\mathrm{NH_2}}{\mathrm{C}}}\mathrm{{-}R^4}$$

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[689] For a review of amines as hydrogen donors in this reaction, see Cohen; Parola; Parsons *Chem. Rev.* **1973**, *73*, 141-161.

[690] For some of the evidence for this mechanism, see Pitts; Letsinger; Taylor; Patterson; Recktenwald; Martin *J. Am. Chem. Soc.* **1959**, *81*, 1068; Hammond; Moore *J. Am. Chem. Soc.* **1959**, *81*, 6334; Moore; Hammond; Foss *J. Am. Chem. Soc.* **1961**, *83*, 2789; Huyser; Neckers *J. Am. Chem. Soc.* **1963**, *85*, 3641.

[691] Porter; Suppan *Proc. Chem. Soc.* **1964**, 191.

[692] For reviews, see Fry, Ref. 244, pp. 174-180; Shono, Ref. 149, pp. 137-140; Baizer; Petrovich *Prog. Phys. Org. Chem.* **1970**, 7, 189-227. For a review of electrolytic reductive coupling, see Baizer, in Baizer, Lund, Ref. 600, pp. 639-689.

[693] Tanaka; Dhimane; Fujita; Ikemoto; Torii *Tetrahedron Lett.* **1988**, *29*, 3811.

[694] Betschart; Seebach *Helv. Chim. Acta* **1987**, *70*, 2215; Betschart; Schmidt; Seebach *Helv. Chim. Acta* **1988**, *71*, 1999; Mangeney; Tejero; Alexakis; Grosjean; Normant *Synthesis* **1988**, 255.

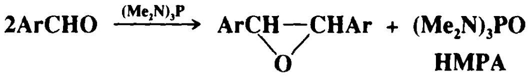
[695] Enholm; Forbes; Holub *Synth. Commun.* **1990**, *20*, 981; Imamoto; Nishimura *Chem. Lett.* **1990**, 1141.

[696] Roskamp; Pedersen *J. Am. Chem. Soc.* **1987**, *109*, 3152.

[697] Shono; Kise; Fujimoto *Tetrahedron Lett.* **1991**, *32*, 525.

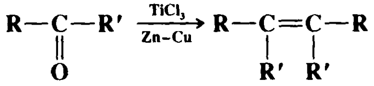
The N-methoxyamino alcohol could then be reduced to the amino alcohol.[697]
OS **I**, 459; **II**, 71.

9-63 Bimolecular Reduction of Aldehydes and Ketones to Epoxides
Aldehyde-oxirane transformation



Aromatic aldehydes can be dimerized to epoxides by treatment with hexamethylphosphorus triamide.[698] The reagent[699] is converted to hexamethylphosphoric triamide (HMPA). The reaction can be used for the preparation of mixed epoxides by the use of a mixture of two aldehydes in which the less reactive aldehyde predominates. Epoxides have also been prepared by treatment of aromatic aldehydes or ketones with the anions $(Me_2N)_2\overset{\ominus}{P}{=}O$ and $(EtO)_2\overset{\ominus}{P}{=}O$ (derived, respectively, by treatment with an alkali metal of HMPA or triethyl phosphite).[700]
OS **V**, 358.

9-64 Bimolecular Reduction of Aldehydes or Ketones to Alkenes
De-oxygen-coupling



$$R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R' \xrightarrow[\text{Zn-Cu}]{TiCl_3} R{-}\underset{\underset{\displaystyle R'}{|}}{C}{=}\underset{\underset{\displaystyle R'}{|}}{C}{-}R$$

Aldehydes and ketones, both aromatic and aliphatic (including cyclic ketones), can be converted in high yields to dimeric alkenes by treatment with $TiCl_3$ and a zinc–copper couple.[701] This is called the *McMurry reaction*.[702] The reagent produced in this way is called a *low-valent titanium reagent*, and the reaction has also been accomplished[703] with low-valent titanium reagents prepared in other ways, e.g., from Mg and a $TiCl_3$–THF complex,[704] from $TiCl_4$ and Zn or Mg,[705] from $TiCl_3$ and $LiAlH_4$,[706] from $TiCl_3$ and lamellar potassium graphite,[707] from $TiCl_3$ and K or Li,[708] as well as with Zn–Me_3SiCl[709] and with certain compounds prepared from WCl_6 and either lithium, lithium iodide, $LiAlH_4$, or an

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[698] Mark *J. Am. Chem. Soc.* **1963,** 85, 1884; Newman; Blum *J. Am. Chem. Soc.* **1964,** *86*, 5598.

[699] For the preparation of the reagent, see Mark *Org. Synth. V*, 602.

[700] Normant *Bull. Soc. Chim. Fr.* **1966,** 3601.

[701] McMurry; Fleming; Kees; Krepski *J. Org. Chem.* **1978,** *43*, 3255. For an optimized procedure, see McMurry; Lectka; Rico *J. Org. Chem.* **1989,** *54*, 3748.

[702] For reviews, see McMurry *Chem. Rev.* **1989,** *89*, 1513-1524, *Acc. Chem. Res.* **1983,** *16*, 405-511; Lenoir *Synthesis* **1989,** 883-897; Betschart; Seebach *Chimia* **1989,** *43*, 39-49; Lai, Ref. 684. For related reviews, see Kahn; Rieke *Chem. Rev.* **1988,** *88*, 733-745; Pons; Santelli *Tetrahedron* **1988,** *44*, 4295-4312.

[703] For a list of reagents, with references, see Ref. 21, pp. 160-161.

[704] Tyrlik; Wolochowicz *Bull. Soc. Chim. Fr.* **1973,** 2147.

[705] Mukaiyama; Sato; Hanna *Chem. Lett.* **1973,** 1041; Lenoir *Synthesis* **1977,** 553; Lenoir; Burghard *J. Chem. Res. (S)* **1980,** 396; Carroll; Taylor *Aust. J. Chem.* **1990,** *43*, 1439.

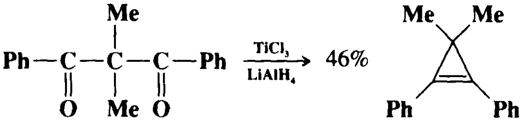
[706] McMurry; Fleming *J. Am. Chem. Soc.* **1974,** *96*, 4708; Dams; Malinowski; Geise *Bull. Soc. Chim. Belg.* **1982,** *91*, 149, 311; Bottino; Finocchiaro; Libertini; Reale; Recca *J. Chem. Soc., Perkin Trans. 2* **1982,** 77. This reagent has been reported to give capricious results; see McMurry; Fleming, Ref. 708.

[707] Fürstner; Weidmann *Synthesis* **1987,** 1071.

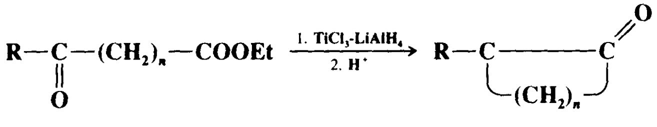
[708] McMurry; Fleming *J. Org. Chem.* **1976,** *41*, 896; Richardson *Synth. Commun.* **1981,** *11*, 895.

[709] Banerjee; Sulbaran de Carrasco; Frydrych-Houge; Motherwell *J. Chem. Soc., Chem. Commun.* **1986,** 1803.

alkyllithium[710] (see **7-21**). The reaction has been used to convert dialdehydes and diketones to cycloalkenes.[711] Rings of 3 to 16 and 22 members have been closed in this way, e.g.,[712]



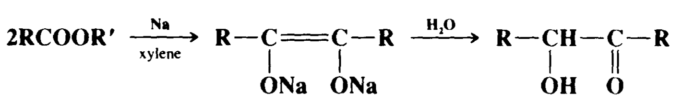
The same reaction on a keto ester gives a cycloalkanone.[713]



Unsymmetrical alkenes can be prepared from a mixture of two ketones, if one is in excess.[714] The mechanism consists of initial coupling of two radical species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated.[715]

OS **VII**, 1.

9-65 Acyloin Ester Condensation



$$2\text{RCOOR}' \xrightarrow[\text{xylene}]{\text{Na}} \underset{\text{ONa}}{\text{R—C}}{=}\underset{\text{ONa}}{\text{C—R}} \xrightarrow{\text{H}_2\text{O}} \text{R—}\underset{\text{OH}}{\text{CH}}\text{—}\underset{\text{O}}{\overset{}{\text{C}}}\text{—R}$$

34

When carboxylic esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place, and the product is an α-hydroxy ketone (called an acyloin).[716] The reaction, called the *acyloin ester condensation*, is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way, for example, R = $C_{17}H_{35}$, but for high-molecular-weight esters, toluene or xylene is used as the solvent. The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.[717] The yields are 50 to 60% for the preparation of 6- and 7-membered rings, 30 to 40% for 8- and 9-membered, and 60 to 95% for rings of 10 to 20 members. Even larger rings have been closed in this manner. This is one of the best ways of closing rings of 10 members or more. The reaction has been used to close 4-membered rings,[718] though this is generally not

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[710] Sharpless; Umbreit; Nieh; Flood *J. Am. Chem. Soc.* **1972,** *94*, 6538; Fujiwara; Ishikawa; Akiyama; Teranishi *J. Org. Chem.* **1978,** *43*, 2477; Dams; Malinowski; Geise, Ref. 706. See also Petit; Mortreux; Petit *J. Chem. Soc., Chem. Commun.* **1984,** 341; Chisholm; Klang *J. Am. Chem. Soc.* **1989,** *111*, 2324.

[711] Baumstark; Bechara; Semigran *Tetrahedron Lett.* **1976,** 3265; McMurry; Fleming; Kees; Krepski, Ref. 701.

[712] Baumstark; McCloskey; Witt *J. Org. Chem.* **1978,** *43*, 3609.

[713] McMurry; Miller *J. Am. Chem. Soc.* **1983,** *105*, 1660.

[714] McMurry; Fleming; Kees; Krepski, Ref. 701; Nishida; Kataoka *J. Org. Chem.* **1978,** *43*, 1612; Coe; Scriven *J. Chem. Soc., Perkin Trans. 1* **1986,** 475; Chisholm; Klang, Ref. 710.

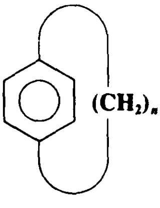
[715] McMurry; Fleming; Kees; Krepski, Ref. 701; Dams; Malinowski; Westdorp; Geise *J. Org. Chem.* **1982,** *47*, 248.

[716] For a review, see Bloomfield; Owsley; Nelke *Org. React.* **1976,** *23*, 259-403. For a list of reactions, with references, see Ref. 21, pp. 645-646.

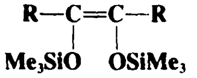
[717] For a review of cyclizations by means of the acyloin condensation, see Finley, *Chem. Rev.* **1964,** *64*, 573-589.

[718] Cope; Herrick *J. Am. Chem. Soc.* **1950,** *72*, 983; Bloomfield; Irelan *J. Org. Chem.* **1966,** *31*, 2017.

successful. The presence of double or triple bonds does not interfere.[719] Even a benzene ring can be present, and many paracyclophane derivatives (**35**) with $n = 9$ or more have



35



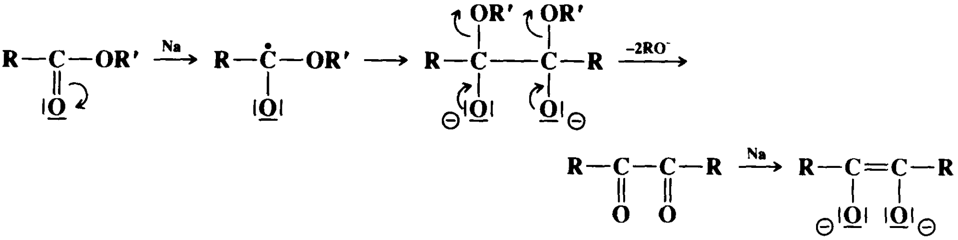
$\mathrm{R{-}\underset{Me_3SiO}{C}{=}\underset{OSiMe_3}{C}{-}R}$

36

been synthesized in this manner.[720]

Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane Me_3SiCl, in which case the dianion **34** is converted to the bis silyl enol ether **36**, which can be isolated and subsequently hydrolyzed to the acyloin with aqueous acid.[721] This is now the standard way to conduct the acyloin condensation. Among other things, this method inhibits the Dieckmann condensation[722] (**0-108**), which otherwise competes with the acyloin condensation when a 5-, 6-, or 7-membered ring can be closed (note that the ring formed by a Dieckmann condensation is always one carbon atom smaller than that formed by an acyloin condensation of the same substrate). The Me_3SiCl method is especially good for the closing of four-membered rings.[723] Yields of 4-, 5-, and 6-membered rings are improved by the use of ultrasound.[724]

The mechanism is not known with certainty, but it is usually presumed that the diketone RCOCOR is an intermediate,[725] since small amounts of it are usually isolated as side products, and when it is resistant to reduction (e.g., *t*-Bu—COCO—*t*-Bu), it is the major product. A possible sequence (analogous to that of **9-62**) is



In order to account for the ready formation of large rings, which means that the two ends of the chain must approach each other even though this is conformationally unfavorable for

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[719] Cram; Gaston *J. Am. Chem. Soc.* **1960,** *82*, 6386.

[720] For a review, see Cram *Rec. Chem. Prog.* **1959,** *20*, 71.

[721] Schräpler; Rühlmann *Chem. Ber.* **1964,** *97*, 1383. For a review of the Me_3SiCl method, see Rühlmann *Synthesis* **1971,** 236-253.

[722] Bloomfield *Tetrahedron Lett.* **1968,** 591.

[723] Bloomfield *Tetrahedron Lett.* **1968,** 587; Gream; Worthley *Tetrahedron Lett.* **1968,** 3319; Wynberg; Reiffers; Strating *Recl. Trav. Chim. Pays-Bas* **1970,** *89*, 982; Bloomfield; Martin; Nelke *J. Chem. Soc., Chem. Commun.* **1972,** 96.

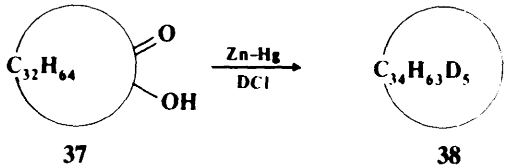
[724] Fadel; Canet; Salaün *Synlett* **1990,** 89.

[725] Another mechanism, involving addition of the ketyl to another molecule of ester (rather than a dimerization of two ketyl radicals), in which a diketone is not an intermediate, has been proposed: Bloomfield; Owsley; Ainsworth; Robertson *J. Org. Chem.* **1975,** *40*, 393.

long chains, it may be postulated that the two ends become attached to nearby sites on the surface of the sodium.

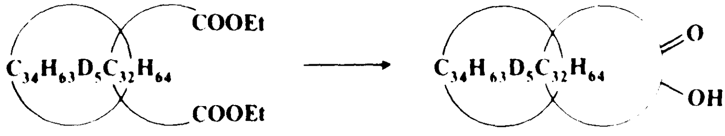
In a related reaction, aromatic carboxylic acids were condensed to α-diketones (2ArCOOH → ArCOCOAr) on treatment with excess Li in dry THF in the presence of ultrasound.[726]

The acyloin condensation was used in an ingenious manner to prepare the first reported catenane (see p. 91).[727] The catenane (**39**) was prepared by a statistical synthesis (p. 91) in the following manner: An acyloin condensation was performed on the diethyl ester of the C_{34} dicarboxylic acid (tetratriacontandioic acid) to give the cyclic acyloin **37**. This was reduced by a Clemmensen reduction with DCl in D_2O instead of HCl in H_2O, thus producing a C_{34} cycloalkane containing deuterium (**38**):[728]



37 **38**

38 contained about five atoms of deuterium per molecule. The reaction was then repeated, this time *in a 1:1 mixture of xylene and* **38** *as solvent.* It was hoped that some of the molecules of ester would be threaded through **38** before they closed:



39

The first thing that was done with the product was to remove by chromatography the **38** that had been used as the solvent. The remaining material still contained deuterium, as determined by ir spectra, even with all the **38** gone. This was strong evidence that the material consisted not only of **37**, but also of **39**. As further evidence, the mixture was oxidized to open up the acyloin rings (**9-7**). From the oxidation product was isolated the C_{34} diacid (as expected) *containing no deuterium*, and **38**, containing deuterium. The total yield of **39** and **37** was 5 to 20%, but the percentage of **39** in this mixture was only about 1 to 2%.[728] This synthesis of a catenane produced only a small yield and relied on chance, on the probability that a diester molecule would be threaded through **38** before it closed.

Several *directed* syntheses of catenanes have also been reported. One of these relies upon coordination of ligands to a metallic ion to achieve the proper geometry. An example is shown in Figure 19.1.[729] 2,9-Bis(*p*-hydroxyphenyl)-1,10-phenanthroline **40** is converted to the macrocycle **42** by treatment with the polyether **41**, in a Williamson reaction, under

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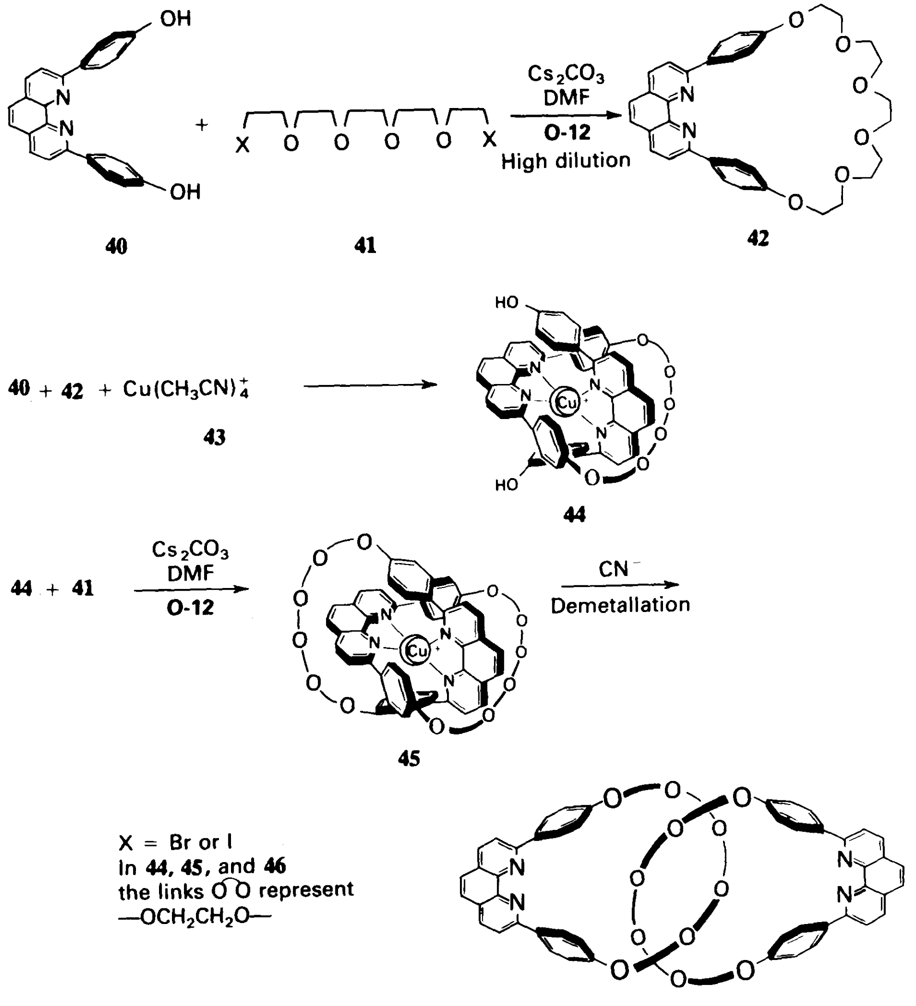
[726] Karaman; Fry *Tetrahedron Lett.* **1989,** *30*, 6267.

[727] For reviews of the synthesis of catenanes, see Sauvage *Acc. Chem. Res.* **1990,** *23*, 319-327, *Nouv. J. Chim.* **1985,** 9, 299-310; Dietrich-Buchecker; Sauvage *Chem. Rev.* **1987,** *87*, 795-810.

[728] This work was done by Wasserman *J. Am. Chem. Soc.* **1960,** *82*, 4433. For other statistical syntheses, see Wolovsky *J. Am. Chem. Soc.* **1970,** *92*, 2132; Ben-Efraim; Batich; Wasserman *J. Am. Chem. Soc.* **1970,** *92*, 2133; Agam; Zilkha *J. Am. Chem. Soc.* **1976,** *98*, 5214; Schill; Schweickert; Fritz; Vetter *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 889 [*Angew. Chem.* *95*, 909].

[729] Dietrich-Buchecker; Sauvage; Kintzinger *Tetrahedron Lett.* **1983,** *24*, 5095; Dietrich-Buchecker; Sauvage; Kern *J. Am. Chem. Soc.* **1984,** *106*, 3043; Dietrich-Buchecker; Sauvage *Tetrahedron* **1990,** *46*, 503.



X = Br or I
In 44, 45, and 46
the links O⌒O represent
—OCH_2CH_2O—

FIGURE 19.1 Synthesis of the catenane 46.[729]

high dilution conditions. **42**, combined with another molecule of **40**, forms a coordination compound **44** when a mixture of **40** and **42** is treated with a copper complex **43**. The two phenolic OH groups of **44** are in proper positions so that when combined with additional **41**, the interlocking copper complex **45** (called a *catenate*) is formed. In the final step, the copper is removed by treatment with CN^- (which preferentially coordinates with Cu^+) to give the catenane **46**. **45** was obtained in 42% yield from **42**. **45** was also obtained more directly, by treatment of **40** with the complex **43**, which forms another complex in which the two molecules of **40** coordinate with the copper. This, treated with two moles of **41**, generates **45**. A similar strategy was used to prepare [3]catenanes.[730]

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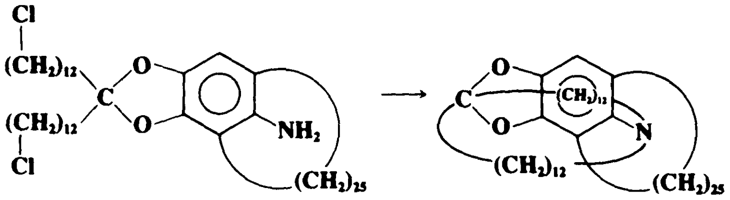
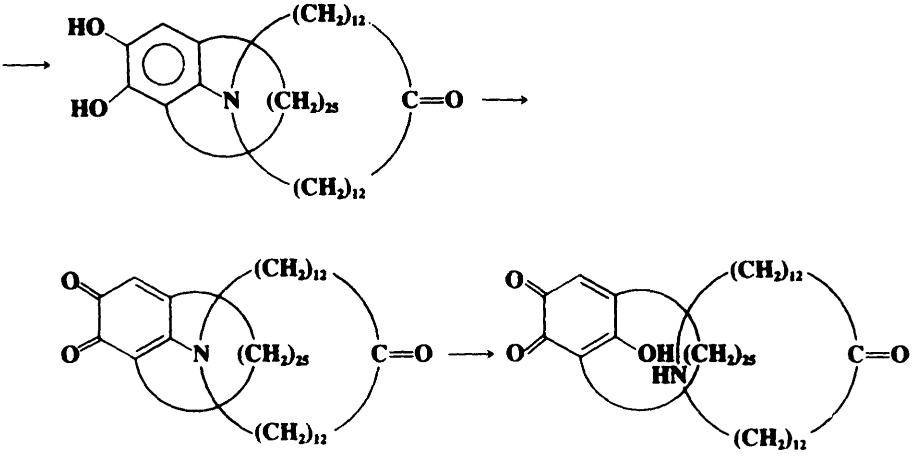
[729] Sauvage; Weiss *J. Am. Chem. Soc.* **1985,** *107*, 6108. For other preparations of [3]catenanes, see Dietrich-Buchecker; Hemmert; Khémiss; Sauvage *J. Am. Chem. Soc.* **1990,** *112*, 8002; Ashton et al. *Angew. Chem. Int. Ed. Engl.* **1991,** *30*, 1039 [*Angew. Chem. 103*, 1055]. See also Guilhem; Pascard; Sauvage; Weiss *J. Am. Chem. Soc.* **1988,** *110*, 8711.

Another directed synthesis of catenanes[731] does not use a metallic ion. The key step in this approach[732] was formation of a tertiary amine by **0-43**. Sterically, one of the halide groups of **47** is above the plane, and the other below it, so that ring closure must occur *through* the 28-membered ring. After **48** was formed, the acetal was cleaved (**0-6**). It was then necessary to cleave the remaining bond holding the two rings together, i.e., the C—N bond. This was done by oxidation to the *ortho*-quinone (**9-4**), which converted the amine function to an enamine, which was hydrolyzable (**6-2**) with acid to give the catenane (**49**):



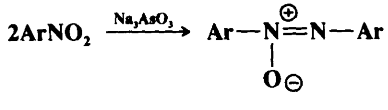
47 **48**



49

OS **II**, 114; **IV**, 840; **VI**, 167.

9-66 Reduction of Nitro to Azoxy Compounds
Nitro-azoxy reductive transformation



$$2\mathrm{ArNO_2} \xrightarrow{\mathrm{Na_3AsO_3}} \mathrm{Ar{-}\overset{\oplus}{\underset{\substack{|\\ \mathrm{O}\ominus}}{N}}{=}N{-}Ar}$$

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[731] For still others, see Schill; Schweickert; Fritz; Vetter *Chem. Ber.* **1988**, *121*, 961; Ashton; Goodnow; Kaifer; Reddington; Slawin; Spencer; Stoddart; Vicent; Williams *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1396 [*Angew. Chem.* *101*, 1404]; Brown; Philp; Stoddart *Synlett* **1991**, 459.

[732] Schill; Lüttringhaus *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 546 [*Angew. Chem.* *76*, 567]; Schill *Chem. Ber.* **1965**, *98*, 2906, **1966**, *99*, 2689, **1967**, *100*, 2021; Logemann; Rissler; Schill; Fritz *Chem. Ber.* **1981**, *114*, 2245. For the preparation of [3]catenanes by a similar approach, see Schill; Zürcher *Chem. Ber.* **1977**, *110*, 2046; Rissler; Schill; Fritz; Vetter *Chem. Ber.* **1986**, *119*, 1374.

Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, NaTeH,[733] lead,[734] $NaBH_4$–PhTeTePh,[735] and glucose. The most probable mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (**9-49**), and these combine (**2-53**). The combination step is rapid compared to the reduction process.[736] Nitroso compounds can be reduced to azoxy compounds with triethyl phosphite or triphenylphosphine[737] or with an alkaline aqueous solution of an alcohol.[738]

OS **II,** 57.

9-67 Reduction of Nitro to Azo Compounds

***N*-De-bisoxygen-coupling**

$$2ArNO_2 \xrightarrow{LiAlH_4} Ar{-}N{=}N{-}Ar$$

Nitro compounds can be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and zinc and alkali are the most common. With many of these reagents, slight differences in conditions can lead either to the azo or azoxy (**9-66**) compound. Analogously to **9-66,** this reaction may be looked on as a combination of ArN=O and $ArNH_2$ (**2-52**). However, when the reducing agent was $HOCH_2CH_2ONa$[739] or $NaBH_4$,[740] it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with $LiAlH_4$.

OS **III,** 103.

9-68 Reduction of Nitro to Hydrazo Compounds

***N*-Hydrogen-de-bisoxygen-coupling**

$$2ArNO_2 \xrightarrow[NaOH]{Zn} Ar{-}NH{-}NH{-}Ar$$

Nitro compounds can be reduced to hydrazo compounds with zinc and sodium hydroxide, with hydrazine hydrate and Raney nickel,[741] or with $LiAlH_4$ mixed with a metal chloride such as $TiCl_4$ or VCl_3.[742] The reduction has also been accomplished electrochemically.

Reactions in Which an Organic Substrate is Both Oxidized and Reduced

Some reactions that belong in this category have been considered in earlier chapters. Among these are the Tollens' condensation (**6-46**), the benzil–benzilic acid rearrangement (**8-6**), and the Wallach rearrangement (**8-45**).

9-69 The Cannizzaro Reaction

Cannizzaro Aldehyde Disproportionation

$$2ArCHO \xrightarrow{NaOH} ArCH_2OH + ArCOO^-$$

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[733] Osuka; Shimizu; Suzuki *Chem. Lett.* **1983,** 1373.

[734] Azoo; Grimshaw *J. Chem. Soc. C* **1968,** 2403.

[735] Ohe; Uemura; Sugita; Masuda; Taga *J. Org. Chem.* **1989,** *54,* 4169.

[736] Ogata; Mibae *J. Org. Chem.* **1962,** *27,* 2048.

[737] Bunyan; Cadogan *J. Chem. Soc.* **1963,** 42.

[738] See, for example, Hutton; Waters *J. Chem. Soc. B* **1968,** 191. See also Porta; Pizzotti; Cenini *J. Organomet. Chem.* **1981,** *222,* 279.

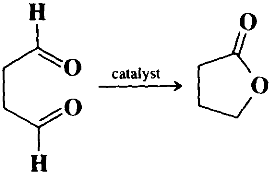
[739] Tadros; Ishak; Bassili *J. Chem. Soc.* **1959,** 627.

[740] Hutchins; Lamson; Rufa; Milewski; Maryanoff *J. Org. Chem.* **1971,** *36,* 803.

[741] Furst; Moore *J. Am. Chem. Soc.* **1957,** *79,* 5492.

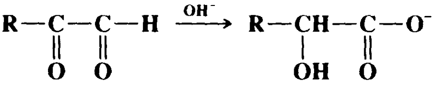
[742] Olah *J. Am. Chem. Soc.* **1959,** *81,* 3165.

Aromatic aldehydes, and aliphatic ones with no α hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.[743] In this reaction one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α hydrogen do not give the reaction, because when these compounds are treated with base the aldol reaction (**6-39**) is much faster.[744] Normally, the best yield of acid or alcohol is 50% each, but this can be altered in certain cases. When the aldehyde contains a hydroxide group in the ring, excess base oxidizes the alcohol formed and the acid can be prepared in high yield (the OH^- is reduced to H_2). On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde. In this case the formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed Cannizzaro reaction*. The Tollens' condensation (**6-46**) includes a crossed Cannizzaro reaction as its last step. A Cannizzaro reaction run on 1,4-dialdehydes (note that α hydrogens are present here) with a rhodium phosphine complex catalyst gives ring closure, e.g.,[745]



The product is the lactone derived from the hydroxy acid that would result from a normal Cannizzaro reaction.

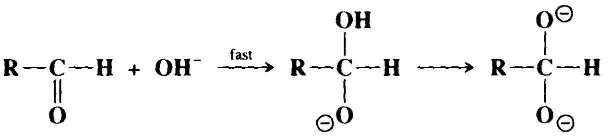
α-Keto aldehydes give internal Cannizzaro reactions:



$$R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-H \xrightarrow{OH^-} R-\underset{\underset{OH}{|}}{CH}-\underset{\underset{O}{\|}}{C}-O^-$$

This product is also obtained on alkaline hydrolysis of compounds of the formula $RCOCHX_2$. Similar reactions have been performed on α-keto acetals[746] and γ-keto aldehydes.

The mechanism[747] of the Cannizzaro reaction[748] involves a hydride shift (an example of mechanism type 2, p. 1160). First OH^- adds to the C=O to give **50**, which may lose a proton in the basic solution to give the diion **51**.



$$R-\underset{\underset{O}{\|}}{C}-H + OH^- \xrightarrow{fast} R-\overset{\overset{OH}{|}}{\underset{\underset{\ominus O}{|}}{C}}-H \longrightarrow R-\overset{\overset{O^\ominus}{|}}{\underset{\underset{O_\ominus}{|}}{C}}-H$$

50 **51**

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[743] For a review, see Geissman *Org. React.* **1944,** *2,* 94-113.

[744] An exception is cyclopropanecarboxaldehyde: van der Maeden; Steinberg; de Boer *Recl. Trav. Chim. Pays-Bas* **1972,** *91,* 221.

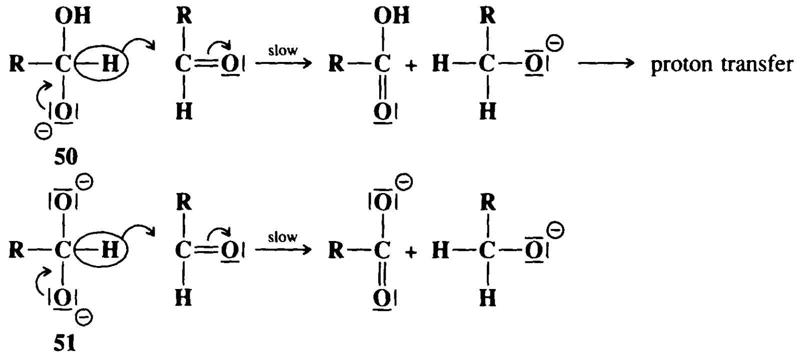
[745] Bergens; Fairlie; Bosnich *Organometallics* **1990,** *9,* 566.

[746] Thompson *J. Org. Chem.* **1967,** *32,* 3947.

[747] For evidence that an SET pathway may intervene, see Ashby; Coleman; Gamasa *J. Org. Chem.* **1987,** *52,* 4079; Fuentes; Marinas; Sinisterra *Tetrahedron Lett.* **1987,** *28,* 2947.

[748] See for example, Swain; Powell; Sheppard; Morgan *J. Am. Chem. Soc.* **1979,** *101,* 3576; Watt *Adv. Phys. Org. Chem.* **1988,** *24,* 57-112, pp. 81-86.

The strong electron-donating character of O^- greatly facilitates the ability of the aldehydic hydrogen to leave with its electron pair. Of course, this effect is even stronger in **51.** When the hydride does leave, it attacks another molecule of aldehyde. The hydride can come from **50** or **51:**



If the hydride ion comes from **50,** the final step is a rapid proton transfer. In the other case, the acid salt is formed directly, and the alkoxide ion acquires a proton from the solvent. Evidence for this mechanism is: (1) The reaction can be first order in base and second order in substrate (thus going through **50**) or, at higher base concentrations, second order in each (going through **51**); and (2) when the reaction was run in D_2O, the recovered alcohol contained no α deuterium,[749] indicating that the hydrogen comes from another mole of aldehyde and not from the medium.[750]

OS **I,** 276; **II,** 590; **III,** 538; **IV,** 110.

9-70 The Tishchenko Reaction

Tishchenko aldehyde-ester disproportionation

$$\mathbf{2RCHO \xrightarrow{Al(OEt)_3} RCOOCH_2R}$$

When aldehydes, with or without α hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another reduced, as in **9-69,** but here they are found as the ester. The process is called the *Tishchenko reaction*. Crossed Tishchenko reactions are also possible. With more strongly basic alkoxides, such as magnesium or sodium alkoxides, aldehydes with an α hydrogen give the aldol reaction. Like **9-69,** this reaction has a mechanism that involves hydride transfer.[751] The Tishchenko reaction can also be catalyzed[752] by ruthenium complexes,[753] by boric acid,[754] and, for aromatic aldehydes, by disodium tetracarbonylferrate $Na_2Fe(CO)_4$.[755]

OS **I,** 104.

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[749] Fredenhagen; Bonhoeffer *Z. Phys. Chem., Abt. A* **1938,** *181*, 379; Hauser; Hamrick; Stewart *J. Org. Chem.* **1956,** *21*, 260.

[750] When the reaction was run at 100°C in $MeOH-H_2O$, isotopic exchange was observed (the product from PhCDO had lost some of its deuterium): Swain; Powell; Lynch; Alpha; Dunlap *J. Am. Chem. Soc.* **1979,** *101*, 3584. Side reactions were postulated to account for the loss of deuterium. See, however, Chung *J. Chem. Soc., Chem. Commun.* **1982,** 480.

[751] See, for example, Zakharkin; Sorokina *J. Gen. Chem. USSR* **1967,** *37*, 525; Saegusa; Ueshima; Kitagawa *Bull. Chem. Soc. Jpn.* **1969,** *42*, 248; Ogata; Kishi *Tetrahedron* **1969,** *25*, 929.

[752] For a list of reagents, with references, see Ref. 21, p. 840.

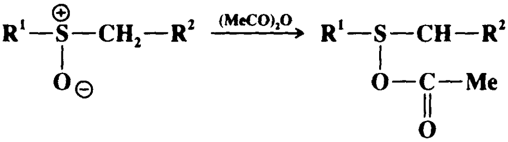
[753] Ito; Horino; Koshiro; Yamamoto *Bull. Chem. Soc. Jpn.* **1982,** *55*, 504.

[754] Stapp *J. Org. Chem.* **1973,** *38*, 1433.

[755] Yamashita; Watanabe; Mitsudo; Takegami *Bull. Chem. Soc. Jpn.* **1976,** *49*, 3597.

9-71 The Pummerer Rearrangement

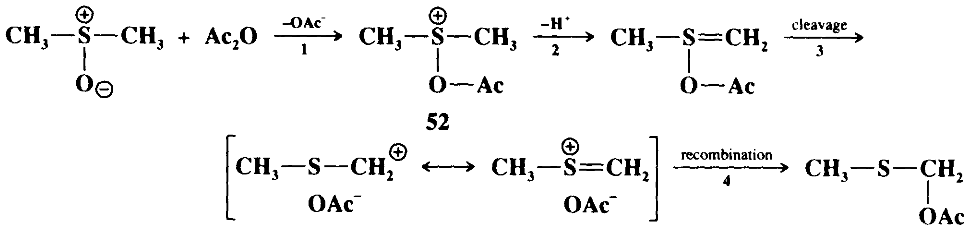
Pummerer methyl sulfoxide rearrangement



$$R^1-\underset{O^{\ominus}}{\underset{|}{\overset{\oplus}{S}}}-CH_2-R^2 \xrightarrow{(MeCO)_2O} R^1-\underset{O-\underset{\underset{O}{\|}}{C}-Me}{\underset{|}{S}}-CH-R^2$$

When sulfoxides bearing an α hydrogen are treated with acetic anhydride, the product is an α-acetoxy sulfide. This is one example of *the Pummerer rearrangement*, in which the sulfur is reduced while an adjacent carbon is oxidized.[756] The product is readily hydrolyzed (**0-6**) to the aldehyde R^2CHO.[757] Besides acetic anhydride, other anhydrides and acyl halides give similar products. Inorganic acids such as HCl also give the reaction, and $RSOCH_2R'$ can be converted to $RSCHClR'$ in this way. Sulfoxides can also be converted to α-halo sulfides[758] by other reagents, including sulfuryl chloride, N-bromosuccinimide, and N-chlorosuccinimide.

The following 4-step mechanism has been proposed for the reaction between acetic anhydride and dimethyl sulfoxide:[759]



52

For dimethyl sulfoxide and acetic anhydride, step 4 is intermolecular, as shown by ^{18}O isotopic labeling studies.[760] With other substrates, however, step 4 can be inter- or intramolecular, depending on the structure of the sulfoxide.[761] Depending on the substrate and reagent, any of the first three steps can be rate-determining. In the case of Me_2SO treated with $(F_3CCO)_2O$ the intermediate corresponding to **52**[762] could be isolated at low temperature, and on warming gave the expected product.[763] There is much other evidence for this mechanism.[764]

9-72 The Willgerodt Reaction

Willgerodt carbonyl transformation

$$ArCOCH_3 \xrightarrow{(NH_4)_2S_x} ArCH_2CONH_2 + ArCH_2COO^- \ NH_4^+$$

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[756] For reviews, see De Lucchi; Miotti; Modena *Org. React.* **1991,** *40*, 157-405; Warren *Chem. Ind. (London)* **1980,** 824-828; Oae; Numata *Isot. Org. Chem.* **1980,** 5, 45-102; Block, Ref. 440, pp. 154-162.

[757] See, for example, Sugihara; Tanikaga; Kaji *Synthesis* **1978,** 881.

[758] For a review of α-chloro sulfides, see Dilworth; McKervey *Tetrahedron* **1986,** *42*, 3731-3752.

[759] See, for example, Numata; Itoh; Yoshimura; Oae *Bull. Chem. Soc. Jpn.* **1983,** *56*, 257.

[760] Oae; Kitao; Kawamura; Kitaoka *Tetrahedron* **1963,** *19*, 817.

[761] See, for example, Itoh; Numata; Yoshimura; Oae *Bull. Chem. Soc. Jpn.* **1983,** *56*, 266; Oae; Itoh; Numata; Yoshimura *Bull. Chem. Soc. Jpn.* **1983,** *56*, 270.

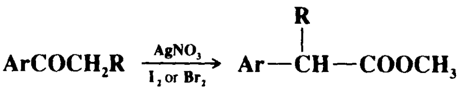
[762] For a review of sulfur-containing cations, see Marino *Top. Sulfur Chem.* **1976,** *1*, 1-110.

[763] Sharma; Swern *Tetrahedron Lett.* **1974,** 1503.

[764] See Block, Ref. 440, pp. 154-156; Oae; Numata, Ref. 756, pp. 48-71; Wolfe; Kazmaier *Can. J. Chem.* **1979,** *57*, 2388, 2397; Russell; Mikol *Mech. Mol. Migr.* **1968,** *1*, 157-207.

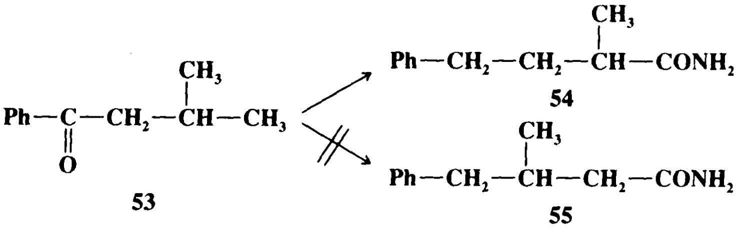
In the *Willgerodt reaction* a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid by heating with ammonium polysulfide.[765] The carbonyl group of the product is always at the end of the chain. Thus $ArCOCH_2CH_3$ gives the amide and the salt of $ArCH_2CH_2COOH$, and $ArCOCH_2CH_2CH_3$ gives derivatives of $ArCH_2CH_2CH_2COOH$. However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinylic and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. The use of sulfur and a dry primary or secondary amine (or ammonia) as the reagent is called the *Kindler modification* of the Willgerodt reaction.[766] The product in this case is $Ar(CH_2)_nCSNR_2$,[767] which can be hydrolyzed to the acid. Particularly good results are obtained with morpholine as the amine. For volatile amines the HCl salts can be used instead, with NaOAc in DMF at 100°C.[768] Dimethylamine has also been used in the form of dimethylammonium dimethylcarbamate $Me_2NCOO^- \ Me_2NH_2^+$.[769] The Kindler modification has also been applied to aliphatic ketones.[770]

Alkyl aryl ketones can be converted to arylacetic acid derivatives in an entirely different manner. The reaction consists of treatment of the substrate with silver nitrate and I_2 or Br_2,[771] or with thallium nitrate, MeOH, and trimethyl orthoformate adsorbed on K-10, an acidic clay.[772]



$$ArCOCH_2R \xrightarrow[I_2 \text{ or } Br_2]{AgNO_3} Ar{-}\overset{\displaystyle R}{\overset{|}{C}}H{-}COOCH_3 \qquad R = H, Me, Et$$

The mechanism of the Willgerodt reaction is not completely known, but some conceivable mechanisms can be excluded. Thus, one might suppose that the alkyl group becomes completely detached from the ring and then attacks it with its other end. However, this possibility is ruled out by experiments such as the following: When isobutyl phenyl ketone (**53**) is subjected to the Willgerodt reaction, the product is **54**, not **55**, which would arise if the end carbon of the ketone became bonded to the ring in the product:[773]



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[765] For a review, see Brown *Synthesis* **1975,** 358-375.

[766] For a review, see Mayer, in Oae, Ref. 431, pp. 58-63. For a study of the optimum conditions for this reaction, see Lundstedt; Carlson; Shabana *Acta Chem. Scand., Ser. B* **1987,** *41,* 157, and other papers in this series. See also Carlson; Lundstedt *Acta Chem. Scand., Ser. B* **1987,** *41,* 164.

[767] The reaction between ketones, sulfur, and ammonia can also lead to heterocyclic compounds. For a review, see Asinger; Offermanns *Angew. Chem. Int. Ed. Engl.* **1967,** *6,* 907-919 [*Angew. Chem.* *79,* 953-965].

[768] Amupitan *Synthesis* **1983,** 730.

[769] Schroth; Andersch *Synthesis* **1989,** 202.

[770] See Dutron-Woitrin; Merényi; Viehe *Synthesis* **1985,** 77.

[771] Higgins; Thomas *J. Chem. Soc., Perkin Trans. 1* **1982,** 235. See also Higgins; Thomas *J. Chem. Soc., Perkin Trans. 1* **1983,** 1483.

[772] Taylor; Chiang; McKillop; White *J. Am. Chem. Soc.* **1976,** *98,* 6750; Taylor; Conley; Katz; McKillop *J. Org. Chem.* **1984,** *49,* 3840.

[773] King; McMillan *J. Am. Chem. Soc.* **1946,** *68,* 632.

This also excludes a cyclic-intermediate mechanism similar to that of the Claisen rearrangement (**8-35**). Another important fact is that the reaction is successful for singly branched side chains, such as **53,** but not for doubly branched side chains, as in $PhCOCMe_3$.[773] Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus $PhCOCH_2CH_3$, $PhCH_2COMe$, and $PhCH_2CH_2CHO$ all give $PhCH_2CH_2CONH_2$.[774] All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain, though just what form these take is not certain. Initial reduction to the hydrocarbon can be ruled out, since alkylbenzenes do not give the reaction. In certain cases imines[775] or enamines[776] have been isolated from primary and secondary amines, respectively, and these have been shown to give the normal products, leading to the suggestion that they may be reaction intermediates.

[774] For an example of this type of behavior, see Asinger, Saus; Mayer *Monatsh. Chem.* **1967,** *98,* 825.

[775] Asinger; Halcour *Monatsh. Chem.* **1964,** *95,* 24. See also Nakova; Tolkachev; Evstigneeva *J. Org. Chem. USSR* **1975,** *11,* 2660.

[776] Mayer, in Janssen *Organosulfur Chemistry*; Wiley: New York, 1967, pp. 229-232.