CHAPTER 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, although 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] Note 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 will find ourselves painted into a corner. Nevertheless, the basic idea has served organic chemistry well. Note that

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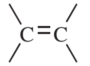
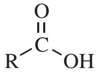
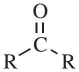
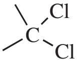
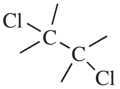
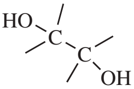
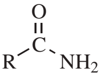
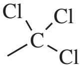
[1] For more extensive tables, with subclassifications, see Soloveichik, S.; Krakauer, H. *J. Chem. Educ.* ***1966***, *43*, 532.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March

TABLE 19.1. Categories of Simple Functional Groups Arranged According to Oxidation State[a]

RH		—C≡C—	 $R-C(=O)-OH$	CO_2
	ROH RCl RNH_2 and so on	 $R-C(=O)-R$    and so on	 $R-C(=O)-NH_2$  and so on	CCl_4
		Approximate Oxidation Number		
−4	−2	0	+2	+4

[a] 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.

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.

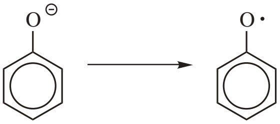
Of course, there is no oxidation without a concurrent reduction. However, we classify reactions as oxidations or reductions depending on whether the *organic compound* is oxidized or reduced. In some cases, both the oxidant and reductant are organic; those reactions are treated separately at the end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

MECHANISMS

Noted that our definition of oxidation has nothing to do with mechanism. Thus the conversion of bromomethane to methanol with KOH (**10-1**) and to methane with $LiAlH_4$ (**19-53**) have the same S_N2 mechanisms, but one is a reduction (according to our definition) 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 10–18.[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, most reactions involved the bond change C=C → W–C–C–Y yet a relatively few mechanisms covered those 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.

Although we 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 (**15-13**), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones (**19-76**), where again it is 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, **14-29**). An important example of (b) is oxidation of amines and phenolate ions:



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

[3] Wiberg, K.B. *Surv. Prog. Chem.* ***1963***, *1*, 211.

[4] For a monograph on direct electron-transfer mechanisms, see Eberson, L. *Electron Transfer Reactions in Organic Chemistry*, Springer, NY, ***1987***. For a review, see Eberson, L. *Adv. Phys. Org. Chem.* ***1982***, *18*, 79. For a review of multistage electron-transfer mechanisms, see Deuchert, K.; Hünig, S. *Angew. Chem. Int. Ed.* ***1978***, *17*, 875.

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

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. 264) 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 (**19-35**). Another is the Cannizzaro reaction (**19-81**). Reactions in which a carbocation abstracts a hydride ion belong in this category:[8]

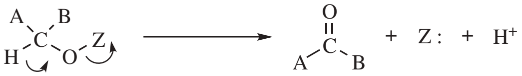
$$R^+ + R'H \longrightarrow RH + R'^+$$

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 **14-1** 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:



Z is usually CrO_3H, MnO_3, or a similar inorganic acid moiety. One example of this mechanism will be seen in **19-23**, where A was an alkyl or aryl group, B was OH, and Z was CrO_3H. Another is the oxidation of a secondary alcohol to a ketone (**19-3**), where A and B are alkyl or aryl groups and Z is also CrO_3H. In the lead tetraacetate oxidation of glycols (**19-7**) the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. Note 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 alkene (**15-39**).

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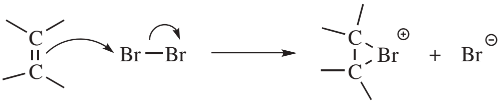
[6] For a review of the oxidation of phenols, see Mihailović, M.Lj.; Čeković, Z., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 505–592.

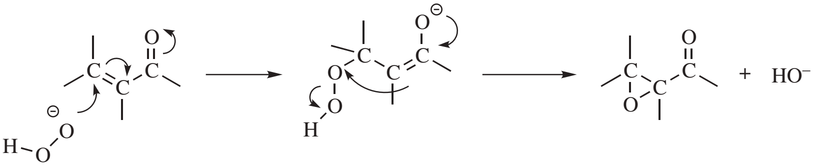
[7] For a review, see Watt, C.I.F. *Adv. Phys. Org. Chem.* ***1988***, *24*, 57.

[8] For a review of these reactions, see Nenitzescu, C.D., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 463–520.



An example from this chapter is found in **19-29**:

6. *Addition–Elimination Mechanisms*. In the reaction between α,β-unsaturated ketones and alkaline peroxide (**15-50**), 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 hydroxide ion 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 (**19-17**). 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, for example, acid dichromate or $LiAlH_4$ (except for a discussion of selectivity of reducing agents, p. 1787). Some oxidizing or reducing agents are fairly specific in their action, attacking only one or a few types of substrate.

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

Others, like acid dichromate, permanganate, $LiAlH_4$, and catalytic hydrogenation, are much more versatile.[10,9,11]

OXIDATIONS[11,2]

In some cases, oxidations have been placed in another chapter. The oxidation of an alkene to a diol (**15-48**), and aromatic compound to a diol (**15-49**), or oxidation to an epoxide (**15-50**) are placed in Chapter 15, for consistency with the concept of addition to a π-bond. Diamination of an alkene (**15-53**) and formation of aziridines (**15-54**) are in Chapter 15 for the same reason. Most other oxidations have been placed here. The reactions in this section are classified into groups depending on

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[10] For books on certain oxidizing agents, see Mijs, W.J.; de Jonge, C.R.J.I. *Organic Synthesis by Oxidation with Metal Compounds*, Plenum, NY, ***1986***; Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***; Arndt, D. *Manganese Compounds as Oxidizing Agents in Organic Chemistry*, Open Court Publishing Company, La Salle, IL, ***1981***; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, Open Court Publishing Company, La Salle, IL, ***1980***. For some reviews, see Curci, R. *Adv. Oxygenated Processes* ***1990***, *2*, 1 (dioxiranes); Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205 (dioxiranes); Murray, R.W. *Chem. Rev.* ***1989***, *89*, 1187; *Mol. Struc. Energ.* ***1988***, *5*, 311 (dioxiranes); Kafafi, S.A.; Martinez, R.I.; Herron J.T. *Mol. Struc. Energ.* ***1988***, *5*, 283 (dioxiranes); Krief, A.; Hevesi, L. *Organoselenium Chemistry I*; Springer, NY, ***1988***, pp. 76–103 (seleninic anhydrides and acids); Ley, S.V., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 163–206 (seleninic anhydrides and acids); Barton, D.H.R.; Finet, J. *Pure Appl. Chem.* ***1987***, *59*, 937 [bismuth(V)]; Fatiadi, A.J. *Synthesis* ***1987***, 85 (KMnO4); Rubottom, G.M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, ***1982***, pp. 1–145 (lead tetraacetate); Fatiadi, A.J., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 147–335; *Synthesis* ***1974***, 229 (HIO_4); Fatiadi, A.J. *Synthesis* ***1976***, 65, 133 (MnO_2); Ogata, Y., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 295–342 (nitric acid and nitrogen oxides); McKillop, A. *Pure Appl. Chem.* ***1975***, *43*, 463 (thallium nitrate); Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 143–174 (MnO_2); George, M.V.; Balachandran, K.S. *Chem. Rev.* ***1975***, *75*, 491 (nickel peroxide); Courtney, J.L.; Swansborough, K.F. *Rev. Pure Appl. Chem.* ***1972***, *22*, 47 (ruthenium tetroxide); Ho, T.L. *Synthesis* ***1973***, 347 (ceric ion); Aylward, J.B. *Q. Rev. Chem. Soc.* ***1971***, *25*, 407 (lead tetraacetate); Meth-Cohn, O.; Suschitzky, H. *Chem. Ind. (London)* ***1969***, 443 (MnO_2); Sklarz, B. *Q. Rev. Chem. Soc.* ***1967***, *21*, 3 (HIO_4); Korshunov, S.P.; Vereshchagin, L.I. *Russ. Chem. Rev.* ***1966***, *35*, 942 (MnO_2); Weinberg, N.L.; Weinberg, H.R. *Chem. Rev.* ***1968***, *68*, 449 (electrochemical oxidation). For reviews of the behavior of certain reducing agents, see Keefer, L.K.; Lunn, G. *Chem. Rev.* ***1989***, *89*, 459 (Ni—Al alloy); Málek, J. *Org. React.* ***1988***, *36*, 249; ***1985***, *34*, 1–317 (metal alkoxyaluminum hydrides); Alpatova, N.M.; Zabusova, S.E.; Tomilov, A.P. *Russ. Chem. Rev.* ***1986***, *55*, 99 (solvated electrons generated electrochemically); Caubère, P. *Angew. Chem. Int. Ed.* ***1983***, *22*, 599 (modified sodium hydride); Nagai, Y. *Org. Prep. Proced. Int.* ***1980***, *12*, 13 (hydrosilanes); Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–294 ($LiAlH_4$); Winterfeldt, E. *Synthesis* ***1975***, 617 (diisobutylaluminum hydride and triisobutylaluminum), Hückel, W. *Fortschr. Chem. Forsch.* ***1966***, *6*, 197 (metals in ammonia or amines). For books on reductions with metal hydrides, see Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Štrouf, O.; Čásenský, B.; Kubánek, V. *Sodium Dihydrido-bis(2-methoxyethoxo)aluminate (SDMA)*, Elsevier, NY, ***1985***; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***. Also see, House, H.O. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, NY, ***1972***.

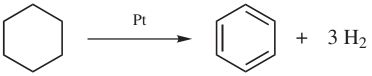
[11] For books on oxidation reactions, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, 2 vols., Academic Press, NY, ***1985, 1988*** [The first volume pertains to hydrocarbon substrates; the second mostly to oxygen- and nitrogen-containing substrates]; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***; Augustine, R.L.; Trecker, D.J. *Oxidation*, 2 vols., Marcel Dekker, NY, ***1969, 1971***.

the type of bond change involved. These groups are (A) eliminations of hydrogen, (B) oxidations 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

19-1 Aromatization of Six-Membered Rings

Hexahydro-terelimination



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, although 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,[14] and nickel. In this case, the reaction is the reverse of double-bond hydrogenation (**15-11** and **15-15**), and presumably the mechanism is also the reverse, although not much is known.[15] Cyclohexene has been detected as an intermediate in the conversion of cyclohexane to benzene, using Pt.[16] The substrate is heated with the catalyst at ~ 300–350°C. The reactions can often be carried out under milder

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[12] For reviews, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, **1985**, pp. 16–22, 217–222; Fu, P.P.; Harvey, R.G. *Chem. Rev.* ***1978***, *78*, 317; Valenta, Z., in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 1–76; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 34–44.

[13] For a review, see Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 1–59.

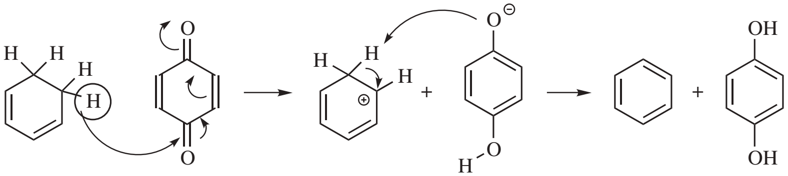
[14] Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* ***2001***, *66*, 186; Cossy, J.; Belotti, D. *Org. Lett.* ***2002***, *4*, 2557.

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

[16] Land, D.P.; Pettiette-Hall, C.L.; McIver, Jr., R.T.; Hemminger, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 5970.

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. Other transition metals can be used, including $TiCl_4$-NEt_3.[17] 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.[18] For polycylic systems, heating with oxygen on activated carbon generates the aromatic compound, as in the conversion of dihydroanthracene to anthracene.[19]

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.[20]
3. Quinones,[21] 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).[22] 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:[23,21]



Among other reagents[24] that have been used for aromatization of six-membered rings are atmospheric oxygen, MnO_2,[25] $KMnO_4$-Al_2O_3,[26] SeO_2, various strong bases,[27]

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[17] Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* ***2002***, *43*, 2785.

[18] Marshall, J.L.; Miiller, D.E.; Ihrig, A.M. *Tetrahedron Lett.* ***1973***, 3491.

[19] Nakamichi, N.; Kawabata, H.; Hiyashi, M. *J. Org. Chem.* ***2003***, *68*, 8272.

[20] House, H.O.; Orchin, M. *J. Am. Chem. Soc.* ***1960***, *82*, 639; Silverwood, H.A.; Orchin, M. *J. Org. Chem.* ***1962***, *27*, 3401.

[21] For reviews, see Becker, H.; Turner, A.B., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 1351–1384; Becker, H., in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 335–423.

[22] For reviews of DDQ, see Turner, A.B., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 193–225; Walker, D.; Hiebert, J.D. *Chem. Rev.* ***1967***, *67*, 153.

[23] Braude, E.A.; Jackman, L.M.; Linstead, R.P.; Lowe, G. *J. Chem. Soc.* ***1960***, 3123, 3133; Trost, B.M. *J. Am. Chem. Soc.* ***1967***, *89*, 1847. See also, Stoos, F.; Roč ek, J. *J. Am. Chem. Soc.* ***1972***, *94*, 2719; Hashish, Z.M.; Hoodless, I.M. *Can. J. Chem.* ***1976***, *54*, 2261; Müller, P.; Joly, D.; Mermoud, F. *Helv. Chim. Acta* ***1984***, *67*, 105; Radtke, R.; Hintze, H.; Rösler, K.; Heesing, A. *Chem. Ber.* ***1990***, *123*, 627. Also see, Höfler, C.; Rüchardt, C. *Liebigs Ann. Chem.* ***1996***, 183.

[24] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 187–191.

[25] See, for example, Leffingwell, J.C.; Bluhm, H.J. *Chem. Commun.* ***1969***, 1151.

[26] McBride, C.M.; Chrisman, W.; Harris, C.E.; Singaram, B. *Tetrahedron Lett.* ***1999***, *40*, 45.

[27] For a review, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 483–503. See also, Reetz, M.T.; Eibach, F. *Liebigs Ann. Chem.* ***1978***, 1598; Trost, B.M.; Rigby, J.H. *Tetrahedron Lett.* ***1978***, 1667.

chromic acid,[28] H_2SO_4 and a ruthenium catalyst,[29] and SeO_2 on $P_2O_5/Me_3SiOSiMe_3$.[30] 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. Quinones react with allylic silanes and a $Bi(OTf)_3$ catalyst to give 2-allyl hydroquinone.[31] Similar reaction with acetic anhydride rather than an allylic silane leads to a 2-acetoxy hydroquinone.[32]

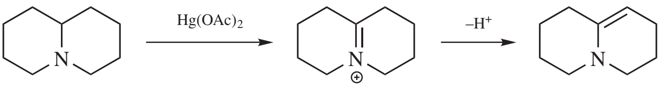
Heteroatom rings, as found in quinoline derivatives, for example, can be generated from amino-ketones with [hydroxy(tosyloxy)iodo]benzene and perchloric acid[33] or with $NaHSO_4$—$Na_2Cr_2O_7$ on wet silica.[34] Dihydropyridines are converted to pyridines with $NaNO_2$–oxalic acid and wet silica[35] $BaMnO_4$,[36] $FeCl_3$–acetic acid,[37] $Mg(HSO_4)_2$—$NaNO_2$,[38] NO^+-18-crown-6-$H(NO_3)_2^-$,[39] or with nicotinium dichromate.[40] Cyclic imines are converted to pyridine derivatives with NCS, and then excess sodium methoxide.[41]

Note that hydrogenolysis of cyclohexane leads to *n*-hexane with hydrogen and an iridium catalyst.[42]

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

19-2 Dehydrogenations Yielding Carbon–Carbon Double Bonds

Dihydro-elimination



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[28] Müller, P.; Pautex, N.; Hagemann, H. *Chimia* ***1988***, *42*, 414.

[29] Tanaka, H.; Ikeno, T.; Yamada, T. *Synlett* ***2003***, 576.

[30] Lee, J.G.; Kim, K.C. *Tetrahedron Lett.* ***1992***, *33*, 6363.

[31] Yadav, J.S.; Reddy, B.V.S.; Swamy, T. *Tetrahedron Lett.* ***2003***, *44*, 4861.

[32] Yadav, J.S.; Reddy, B.V.S.; Swamy, T.; Rao, K.R. *Tetrahedron Lett.* ***2004***, *45*, 6037.

[33] Varma, R.S.; Kumar, D. *Tetrahedron Lett.* ***1998***, *39*, 9113.

[34] Damavandi, J.A.; Zolfigol, M.A.; Karami, B. *Synth. Commun.* ***2001***, *31*, 3183.

[35] Zolfigol, M.A.; Kiany-Borazjani, M.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. *Synth. Comm.* ***2000***, *30*, 551.

[36] Memarian, H.R.; Sadeghi, M.M.; Momeni, A.R. *Synth. Commun.* ***2001***, *31*, 2241.

[37] Lu, J.; Bai, Y.; Wang, Z.; Yang, B.Q.; Li, W. *Synth. Commun.* ***2001***, *31*, 2625.

[38] Zolfigol, M.A.; Kiany-Borazjani, M.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. *Synth. Commun.* ***200***, *30*, 3919.

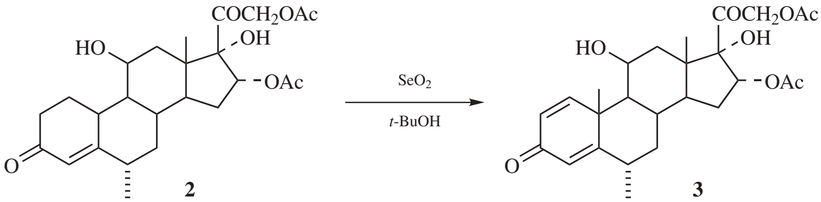
[39] Zolfigol, M.A.; Zebarjadian, M.H.; Sadeghi, M.M.; Mohammadpoor-Baltork, I. Memarian, H.R.; Shamsipur, M. *Synth. Commun.* ***2001***, *31*, 929.

[40] Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R.; Sobhani, S. *Synth. Commun.* ***2000***, *30*, 1661.

[41] DeKimpe, N.; Keppens, M.; Fonck, G. *Chem. Commun.* ***1996***, 635.

[42] Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 1658.

Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, although industrially mixtures of alkenes are obtained in this way from mixtures of alkanes (generally by heating with chromia–alumina catalysts). There are, however, some notable exceptions. Heating cyclooctane with an iridium catalyst leads to cyclooctene.[43] Treating alkenes that have an allylic hydrogen with $CrCl_2$ converts them to allenes.[44] It is not surprising, however, that most of the exceptions 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.[45] One example is the synthesis developed by Leonard and co-workers,[46] in which tertiary amines give enamines (**10-69**) when treated with mercuric acetate[47] (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[48] (though this reagent more often gives **19-17**). This reaction has been most often applied in the steroid series, an example being formation of **2** from **3**.[49] In a similar manner, Hünig's base, diisopropylethylamine, was converted to the enamine *N,N*-diisopropyl-*N*-vinylamine by heating with an iridium catalyst.[50]



2 **3**

Similarly, SeO_2 has been used to dehydrogenate 1,4-diketones[51] ($RCOCH_2CH_2COR \rightarrow RCOCH{=}CHCOR$) and 1,2-diarylalkanes ($ArCH_2CH_2Ar \rightarrow ArCH{=}CHAr$). These conversions can also be carried out by certain quinones, most notably DDQ (see **19-1**).[22] Ketones have been converted to conjugated ketones with

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[43] Göttker-Schnetmann, I.; White, P.; Brookhart, M. *J. Am. Chem. Soc.* ***2004***, *126*, 1804.

[44] Takai, K.; Kokumai, R.; Toshikawa, S. *Synlett* ***2002***, 1164.

[45] For a review, see Haines, A.J. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 6–16, 206–216. For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 251–256.

[46] For example, see Leonard, N.J.; Musker, W.K. *J. Am. Chem. Soc.* ***1959***, *81*, 5631; ***1960***, *82*, 5148.

[47] For reviews, see Haynes, L.W.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed. Marcel Dekker, NY, ***1988***, pp. 103–163; Lee, D.G., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 102–107.

[48] For reviews, see Back, T.G., in Patai, S. *The Chemistry of Organic Selenium and Tellurium Compounds*, pt. 2, Wiley, NY, ***1987***, pp. 91–213, 110–114; Jerussi, R.A. *Sel. Org. Transform.* ***1970***, *1*, 301, see pp. 315–321.

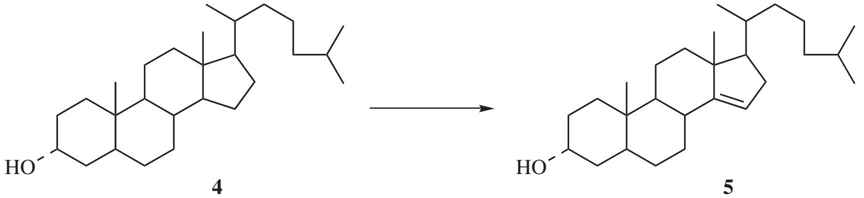
[49] Bernstein, S.; Littell, R. *J. Am. Chem. Soc.* ***1960***, *82*, 1235.

[50] Zhang, X.; Fried, A.; Knapp,S.; Goldman, A.S. *Chem. Commun.* ***2003***, 2060.

[51] For example, see Barnes, C.S.; Barton, D.H.R. *J. Chem. Soc.* ***1953***, 1419.

Ph(S=O)OMe and KH,[52] and also with (pyridyl)S(=O)OMe/KH, and then $CuSO_4$.[53] Silyl enol ethers also give the conjugated ketone upon treatment with ceric ammonium nitrate in DMF[54] or with $Pd(OAc)_2/NaOAc/O_2$.[55] Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone → cyclopentenone) by $PdCl_2$,[56] by $FeCl_3$,[57] and by benzeneseleninic anhydride[58] (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[59] or with triphenylmethyl cation[60] (for another indirect method, see **17-12**). Simple linear alkanes have been converted to alkenes by treatment with certain transition-metal compounds.[61]



4 **5**

An entirely different approach to specific dehydrogenation has been reported by R. Breslow[62] and by J.E. Baldwin.[63] By means of this approach it was possible, for example, to convert 3α-cholestanol (**4**) to 5α-cholest-14-en-3α-ol (**5**), thus introducing a double bond at a specific site remote from any functional group.[64] This was

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[52] Resek, J.E.; Meyers, A.I. *Tetrahedron Lett.* ***1995***, *36*, 7051.

[53] Trost, B.M.; Parquette, J.R. *J. Org. Chem.* ***1993***, *58*, 1579.

[54] Evans, P.A.; Longmire, J.M.; Modi, D.P. *Tetrahedron Lett.* ***1995***, *36*, 3985.

[55] Larock, R.C.; Hightower, T.R.; Kraus, G.A.; Hahn, P.; Zheng, O. *Tetrahedron Lett.* ***1995***, *36*, 2423.

[56] Bierling, B.; Kirschke, K.; Oberender, H.; Schultz, M. *J. Prakt. Chem.* ***1972***, *314*, 170; Kirschke, K.; Müller, H.; Timm, D. *J. Prakt. Chem.* ***1975***, *317*, 807; Mincione, E.; Ortaggi, G.; Sirna, A. *Synthesis* ***1977***, 773; Mukaiyama, T.; Ohshima, M.; Nakatsuka, T. *Chem. Lett.* ***1983***, 1207. See also, Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 103–110.

[57] Cardinale, G.; Laan, J.A.M.; Russell, S.W.; Ward, J.P. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 199.

[58] Barton, D.H.R.; Hui, R.A.H.F.; Ley, S.V.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1919; Barton, D.H.R.; Godfrey, C.R.A.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1947.

[59] Jung, M.E.; Pan, Y.; Rathke, M.W.; Sullivan, D.F.; Woodbury, R.P. *J. Org. Chem.* ***1977***, *42*, 3961.

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

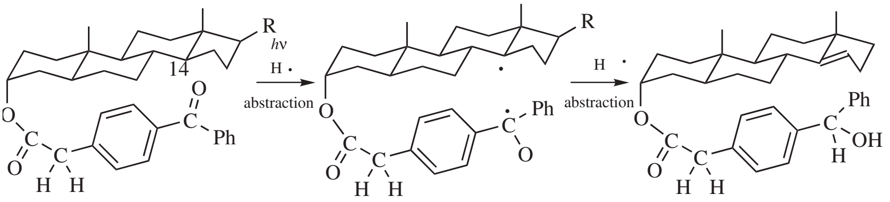
[61] See Burchard, T.; Felkin, H. *Nouv. J. Chim.* ***1986***, *10*, 673; Burk, M.J.; Crabtree, R.H. *J. Am. Chem. Soc.* ***1987***, *109*, 8025; Renneke, R.F.; Hill, C.L. *New J. Chem.* ***1987***, *11*, 763; *Angew. Chem. Int. Ed.* ***1988***, *27*, 1526; *J. Am. Chem. Soc.* ***1988***, *110*, 5461; Maguire, J.A.; Boese, W.T.; Goldman, A.S. *J. Am. Chem. Soc.* ***1989***, *111*, 7088; Sakakura, T.; Ishida, K.; Tanaka, M. *Chem. Lett.* ***1990***, 585; and references cited therein.

[62] Breslow, R.; Baldwin, S.W. *J. Am. Chem. Soc.* ***1970***, *92*, 732. For reviews, see Breslow, R. *Chemtracts: Org. Chem.* ***1988***, *1*, 333; *Acc. Chem. Res.* ***1980***, *13*, 170; *Isr. J. Chem.* ***1979***, *18*, 187; *Chem. Soc. Rev.* ***1972***, *1*, 553.

[63] Baldwin, J.E.; Bhatnagar, A.K.; Harper, R.W. *Chem. Commun.* ***1970***, 659.

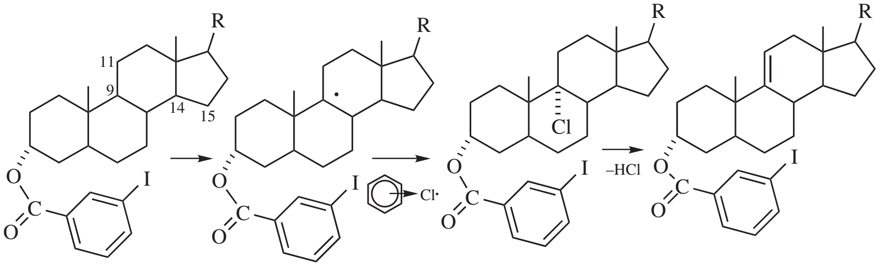
[64] For other methods of introducting a remote double bond, see Čeković, Z.; Cvetković, M. *Tetrahedron Lett.* ***1982***, *23*, 3791; Czekay, G.; Drewello, T.; Schwarz, H. *J. Am. Chem. Soc.* ***1989***, *111*, 4561. See also, Bégué, J. *J. Org. Chem.* ***1982***, *47*, 4268; Nagata, R.; Saito, I. *Synlett* ***1990***, 291.

accomplished by conversion of **4** to the ester **6**, followed by irradiation of **6**, which gave 55% **8**, which was then



6 **7** **8**

hydrolyzed to **5**. The radiation excites the benzophenone portion of **6** (p. $$$), which then abstracts hydrogen from the 14 position to give the diradical **7**, which undergoes another internal abstraction to give **8**. In other cases, diradicals like **7** can close to a macrocyclic lactone (**19-17**). In an alternate approach,[65] a 9(11) double bond was introduced into a steroid nucleus by reaction of the *m*-iodo ester **9** with $PhICl_2$ and uv light, which results in hydrogen being abstracted regioselectively from the 9 position, resulting in chlorination at that position. Dehydrohalogenation of **10** gives the 9(11)-unsaturated steroid **11**. 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, **19-17**).



9 **10** **11**

Certain 1,2-diarylalkenes ArCH=CHAr' have been converted to the corresponding alkynes ArC≡CAr' by treatment with *t*-BuOK in DMF.[66] Dihydroindoles are converted to indoles with *N,N′,N″*-trichloro-1,3,5-triazin-2,4,6-trione and DBU.[67]

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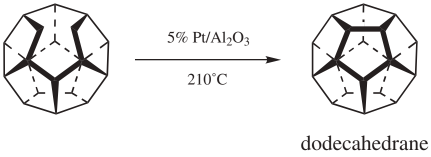
[65] Breslow, R.; Corcoran, R.J.; Snider, B.B.; Doll, R.J.; Khanna, P.L.; Kaleya, R. *J. Am. Chem. Soc.* ***1977***, *99*, 905. For related approaches, see Wolner, D. *Tetrahedron Lett.* ***1979***, 4613; Breslow, R.; Brandl, M.; Hunger, J.; Adams, A.D. *J. Am. Chem. Soc.* ***1987***, *109*, 3799; Batr, R.; Breslow, R. *Tetrahedron Lett.* ***1989***, *30*, 535; Orito, K.; Ohto, M.; Suginome, H. *J. Chem. Soc. Chem. Commun.* ***1990***, 1076.

[66] Akiyama, S.; Nakatsuji, S.; Nomura, K.; Matsuda, K.; Nakashima, K. *J. Chem. Soc. Chem. Commun.* ***1991***, 948.

[67] Tilstam, U.; Harre, M.; Heckrodt, T.; Weinmann, H. *Tetrahedron Lett.* ***2001***, *42*, 5385.

A different kind of dehydrogenation was used in the final step of Paquette's synthesis of dodecahedrane:[68]



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

19-3 Oxidation or Dehydrogenation of Alcohols to Aldehydes and Ketones

***C,O*-Dihydro-elimination**

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

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

Primary alcohols can be converted to aldehydes and secondary alcohols to ketones in seven main ways:[69]

1. *With Strong Oxidizing Agents.*[70] Secondary alcohols are easily oxidized to ketones by acid dichromate[71] at room temperature or slightly above. Many

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[68] Paquette, L.A.; Weber, J.C.; Kobayashi, T.; Miyahara, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 8591. For a monograph on dodecahedrane and related compounds, see Paquette, L.A.; Doherty, A.M. *Polyquinane Chemistry*; Springer, NY, ***1987***. For reviews, see, in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, the reviews by Paquette, L.A. pp. 313–352, and by Fessner, W.; Prinzbach, H. pp. 353–405; Paquette, L.A. *Chem. Rev.* ***1989***, *89*, 1051; *Top. Curr. Chem.* ***1984***, *119*, 1, in Lindberg, T. *Strategies and Tactics in Organic Synthesis*, Academic Press, NY, ***1984***, pp. 175–200.

[69] For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 114–126, 132–149; Haines, A.M. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 5–148, 326–390; Müller, P., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 469–538; Cullis, C.F.; Fish, A., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 129–157. For a lengthy list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1234–1250.

[70] For thorough discussions, see Lee, D.G., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 56–81; and (with respect to chromium and managanese reagents) House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 257–273.

[71] Various forms of H2CrO4 and of CrO3 are used for this reaction. For a review, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Publishers Co., La Salle, IL, ***1981***, pp. 118–216. For discussions, see Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 142–147, 1059–1064, and subsequent volumes in this series.

other strong oxidizing agents ($KMnO_4$,[72] ruthenium tetroxide,[73] etc.) have also been employed. A solution of chromic acid and sulfuric acid in water is known as the *Jones reagent*.[74] 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 **19-10**) and without epimerizing an adjacent stereogenic center.[75] The Jones reagent can also oxidize primary allylic alcohols to the corresponding aldehydes,[76] although overoxidation to the carboxylic acid is a problem. Oxidative cleavage of primary alcohols has been observed in the presence of molecular sieve 3 Å.[77] Indeed, for the oxidation of allylic alcohols three other Cr(VI) reagents are commonly used,[78] dipyridine Cr(VI) oxide (*Collins' reagent*),[79] pyridinium chlorochromate (PCC),[80] and pyridinium dichromate (PDC).[81] The PCC is somewhat acidic, and acid-catalyzed rearrangements have been observed.[82] A variety of amines and diamines have been converted to tetraalkylammonium halochromates or dichromates. Examples include *N*-benzyl 1,4-diazabicyclo[2.2.2]octane ammonium dichromate with microwave irradiation,[83] γ-picolinium chlorochromate,[84] and quinolinium

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[72] For oxidation with $KMnO_4$ on alumina with no solvent, see Hajipour, A.R.; Mallakpour, S.E.; Imanzadeh, G. *Chem. Lett.* ***1999***, 99. For oxidation with silica-supported KMnO4, see Takemoto, T.; Yasuda, K.; Ley, S.V. *Synlett* ***2001***, 1555. For oxidation in the ionic liquid bmim BF4, 1-butyl-3-methylimidazolium tetrafluoroborate: Kumar, A.; Jain, N.; Chauhan, S.M.S. *Synth. Commun.* ***2004***, *34*, 2835.

[73] For a review, see Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B Academic Press, NY, ***1973***, pp. 197–222.

[74] Bowden, K.; Heilbron I.M.; Jones, E.R.H.; Weedon, B.C.L. *J. Chem. Soc.* ***1946***, 39; Bowers, A.; Halsall, T.G.; Jones, E.R.H.; Lemin, A.J. *J. Chem. Soc.* ***1953***, 2548. Also see, Scott, S.L.; Bakac, A.; Espenson, J.H. *J. Am. Chem. Soc.* ***1992***, *114*, 4605. For an oxidation with Jones reagent on silica in dichloromethane, see Ali, M.H.; Wiggin, C.J. *Synth. Commun.* ***2001***, *31*, 1389; Ali, M.H.; Wiggin, C.J. *Synth. Commun.* ***2001***, *31*, 3383.

[75] For example, see Djerassi, C.; Hart, P.A.; Warawa, E.J. *J. Am. Chem. Soc.* ***1964***, *86*, 78.

[76] Harding, K.E.; May, L.M.; Dick, K.F. *J. Org. Chem.* ***1975***, *40*, 1664.

[77] Fernandes, R.A.; Kumar, P. *Tetrahedron Lett.* ***2003***, *44*, 1275.

[78] For a comparative study of Jones's, Collins's, and Corey's reagents, see Warrener, R.N.; Lee, T.S.; Russell, R.A.; Paddon-Row, M.N. *Aust. J. Chem.* ***1978***, *31*, 1113.

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

[80] Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* ***1975***, 2647. For reviews of this and related reagents, see Luzzio, F.A.; Guziec, Jr., F.S. *Org. Prep. Proced. Int.* ***1988***, *20*, 533; Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* ***1982***, 245. For an improved method of preparing this reagent, see Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990***, *46*, 4417. For a PCC oxidation with no solvent, see Salehi, P.; Firouzabadi, H.; Farrokhi, A.; Gholizadeh, M. *Synthesis* ***2001***, 2273.

[81] Coates, W.M.; Corrigan, J.R. *Chem. Ind. (London)* ***1969***, 1594; Corey, E.J.; Schmidt, G. *Tetrahedron Lett.* ***1979***, 399; Czernecki, S.; Georgoulis, C.; Stevens, C.L.; Vijayakumaran, K. *Tetrahedron Lett.* ***1985***, *26*, 1699.

[82] See Ren, S.-K.; Wang, F.; Dou, H.-N.; Fan, C.-A.; He, L.; Song, Z.-L.; Xia, W.-J.; Li, D-R.; Jia, Y.-X.; Li, X.; Tu, Y.-Q. *Synthesis* ***2001***, 2384.

[83] Hajipour, A.R.; Mallakpour, S.E.; Khoee, S. *Synlett* ***2000***, 740.

[84] Khodaei, M.M.; Salehi, P.; Goodarzi, M. *Synth. Commun.* ***2001***, *31*, 1253.

fluorochromate.[85] benzyltriphenylphosphonium chlorochromate has been used in a similar manner.[86] Ammonium dichromate with HIO_3 on wet silica gel[87] or ammonium chlorochromate on Montmorillonite K10[88] have also been used. The MnO_2[89] reagent is also a fairly specific reagent for oxidation of allylic and benzylic OH groups in preference to aliphatic substrates. For acid-sensitive compounds, CrO_3 in HMPA[90] or trimethylsilyl chromates[91] can be used. Benzylic alcohols are oxidized to aldehydes with $BaCr_2O_7$ in acetonitrile.[92] Both CrO_3[93] and MnO_2[94] have been used to oxidized primary and benzylic alcohols, respectively, under solvent-free conditions. A catalytic mixture of *N*-hydroxyphthalimide, $Co(OAc)_2$ and mcpba oxidizes secondary alcohols to ketones.[95] Chromium trioxide with aqueous *tert*-butylhydroperoxide oxidizes benzylic alcohols with microwave irradiation.[96] Oxidizing agents have been supported on a polymer,[97] including chromic acid[98] and permanganate,[99] as well as poly[vinyl(pyridinium fluorochromate)].[100] Microwave induced oxidation of benzylic alcohols was reported using zeolite-supported ferric nitrate.[101] Microwave irradiation of CrO_3 with various co-reagents oxidizes alcohols.[102] Phase-transfer catalysis has also been used with permanganate,[103] chromic acid,[104] and

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[85] Rajkumar, G.A.; Arabindoo, B.; Murugesan, V. *Synth. Commun.* ***1999***, *29*, 2105.

[86] Hajipour, A.R.; Mallakpour, S.E.; Backnejad, H. *Synth. Commun.* ***2000***, *30*, 3855.

[87] Shirini, F.; Zolfigol, M.A.; Azadbar, M.R. *Russ. J. Org. Chem.* ***2001***, *37*, 1600.

[88] Heravi, M.M.; Kiakojoori, R.; Tabar-Hydar, K. *Monat. Chem.* ***1999***, *130*, 581.

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ruthenium tetroxide.[105] 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. 508). Ultrasound has been used for $KMnO_4$ oxidations.[106] A catalytic amount of $Cr(acac)_3$ in conjunction with H_5IO_5 oxidizes benzylic alcohols to aldehydes.[107]

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 (**19-22**).[108] When powerful oxidants, such as chromic acid, are used, 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:[109] Collins' reagent, pyridinium chlorochromate and pyridinium dichromate, pyridinium dichromate, $Na_2Cr_2O_7$ in water,[110] $K_2Cr_2O_7$ in DMF at 100°C,[111] CrO_3 on silica gel,[112] wet CrO_3 on alumina with microwave irradiation,[113] $MeReO_3$,[114] HNO_3 with a $Yb(OTf)_3$ catalyst,[115] $FeBr_3$-H_2O_2,[116] a catalytic amount of $AuSiO_2$,[117] cerium (IV) immobilized on silica with $NaBrO_3$,[118] a bismuth catalyst,[119] O_2 with transition metal

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catalysts,[120] RuO_2 with a zeolite catalyst,[121] and CuCl–phenanthroline.[122]

Tetrapropylammonium perruthenate (Pr_4N^+ RuO_4^-; also called TPAP; the *Ley reagent*)[123] has become an important oxidizing agent. This reagent has been bound to a polymer.[124] In the presence of molecular oxygen, it is catalytic in TPAP.[125] A polymer-bound morpholine *N*-oxide has been used in conjunction with a catalytic amount of TPAP.[126] Propargylic alcohols are oxidized to propargylic aldehydes with $TiCl_4/NEt_3$.[127] Methods have been developed for recovery of the catalyst and reuse of TPAP.[128]

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[129] are H_2O_2–ammonium molybdate,[130] $NaBrO_3$–CAN,[131] and NaOCl in HOAc,[132] while $RuCl_2(PPh_3)_3$–benzene,[133]

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osmium tetroxide,[134] and $Br_2Ni(OBz)_2$[135] oxidize primary OH groups in the presence of a secondary OH group.[136] Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in the presence of saturated alcohols by the use of potassium manganate $KMnO_4$ under phase-transfer conditions.[137] On the other hand, Fremy's salt (see **19-4**) selectively oxidizes benzylic alcohols and not allylic or saturated ones.[138] Certain zirconocene complexes can selectively oxidize only one OH group of a diol, even if both are primary.[139] α-Hydroxy ketones are oxidized to 1,2-diketones with $Bi(NO_3)_3$ and a $Cu(OAc)_2$ catalyst,[140] ferric chloride (solid state),[141] or O_2 and a vanadium catalyst.[142] Tetrabutylammonium periodate oxidizes primary alcohols to aldehydes,[143] as does benzyltriphenylphosphonium periodate.[144] α-Hydroxyl phosphonate esters are oxidized to the α-keto phosphonate ester with zinc dichromate, without solvent[145] or with CrO_3 on alumina with microwave irradiation.[146]

O-Trimethylsilyl ethers of benzylic alcohols are oxidized to the corresponding aldehyde with CrO_3 on wet alumina.[147] Treatment with MnO_2/$AlCl_3$ leads to similar oxidation,[148] as does $NaBrO_3$ in aq. MeCN[149] or K_2FeO_4 on clay.[150] Oxidation of trimethylsilyl ethers with O_2, a catalytic amount of *N*-hydroxyphthalimide and a cobalt catalyst give an aldehyde.[151] Microwave irradiation with $BiCl_3$ oxidizes benzylic TMS ethers to the aldehyde.[152] Microwave irradiation on zeolite supported ferric nitrate has been used.[153] *O*-Tetrahydropyranyl ethers (*O*-THP) have been oxidized to the aldehyde with ferric nitrate on zeolites.[154]

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2. *The Oppenauer Oxidation*. When a ketone in the presence of an aluminum alkoxide is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation*.[155] This is the reverse of the Meerwein–Ponndorf–Verley reaction (**19-36**) and the mechanism is also the reverse. The ketones most commonly used are acetone, butanone, and cyclohexanone. The most common base is aluminum *tert*-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. An iridium catalyst[156] has been developed for the Oppenauer oxidation, and also a water-soluble iridium catalyst[157] An uncatalyzed reaction under supercritical conditions was reported.[158]
3. *With DMSO-Based Reagents*. An alcohol is treated with DMSO, DCC,[159] and anhydrous phosphoric acid[160] in what is called *Moffatt oxidation*. In this way, a primary alcohol can be converted to the aldehyde with no carboxylic acid being produced. The strong acid conditions are sometimes a problem, and complete removal of the dicyclohexylurea by-product can be difficult. The use of oxalyl chloride and DMSO at low temperature, the Swern oxidation,[161] is generally more practical and widely used. Maintaining the low reaction temperature is essential in this reaction however, since the reagent generated *in situ* decomposes at temperatures significantly below ambient.

   Similar oxidation of alcohols has been carried out with DMSO and other reagents[162] in place of DCC: acetic anhydride,[163] SO_3–pyridine–triethylamine,[164] trifluoroacetic anhydride,[165] tosyl chloride,[166] $Ph_3P^+Br^-$,[167]

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P_2O_5-Et_3N,[168] trichloromethyl chloroformate,[169] trimethylamine *N*-oxide,[170] 2,4,6-trichlorotriazine,[171] a molybdenum catalyst and O_2,[172] KI and $NaHCO_3$,[173] and methanesulfonic anhydride.[517] Dimethyl sulfoxide in 48% HBr oxidizes benzylic alcohols the aryl aldehydes.[174] Note that Swern oxidation of molecules having alcohol moieties, as well as a disulfide, leads to the ketone without oxidation of the sulfur.[175] Sulfoxides other than DMSO can be used in conjunction with oxalyl chloride for the oxidation of alcohols,[176] including fluorinated sulfoxides[177] and a polymer-bound sulfoxide.[178]

4. *TEMPO and Related Reagents*. The nitroxyl radical TEMPO has been used in conjunction with coreagents, including mcpba[179] Br_2—$NaNO_2$,[180] O_2 with transition-metal catalysts,[181] CuBr•SMe_2—$C_8F_{17}Br$,[182] $CuBr_2$(bpy)-air (bpy=2, 2′-bipyridyl),[183] Oxone®,[184] CuBr•SMe_2 in perfluorous solvents,[185] 2,4,6-trichlorotriazine,[186] enzymes,[187] H_5IO_6,[188] and NCS.[189] Silica-supported TEMPO,[190] polymer-bound TEMPO,[191] and PEG–TEMPO[192] (where PEG is polyethylene glycol) have been used. The TEMPO compound has also been used with a polymer-bound hypervalent iodine reagent[193] (see below). A catalytic reaction using 5% TEMPO and 5% CuCl with O_2 in an

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[181] **Mo**: Ben-Daniel, R.; Alssteers, P.; Neumann, R. *J. Org. Chem.* ***2001***, *66*, 8650. **Ru**: Dijksman, A.; Marino-González, A.; Payeras, A.M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 6826; Dijksman, A.; Arends, I.W.C.E.; Sheldon, R.A. *Chem. Commun.* ***1999***, 1591. **Mn/Co:** Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* ***2001***, *42*, 6651.

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[183] Gamez, P.; Arends, I.W.C.E.; Reedijk, J.; Sheldon, R.A. *Chem. Commun.* ***2003***, 2414.

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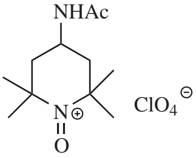
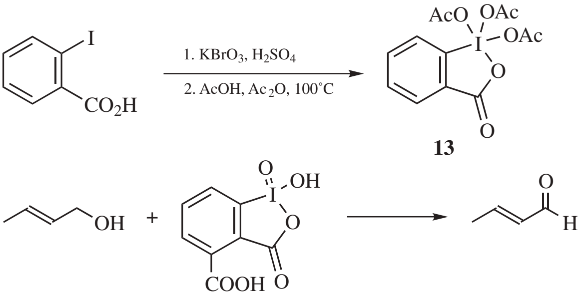
ionic liquid oxidizes benzylic alcohols to the corresponding aldehyde.[194] Other nitroxyl radical oxidizing agents are known.[195] A related oxidizing agent is oxoammonium salt **12** (*Bobbitt's reagent)*, a stable and nonhygroscopic salt that oxidizes primary and secondary alcohols in dichloromethane.[196]



12

5. *With Hypervalent Iodine Reagents.*[197] Treatment of 2-iodobenzoic acid with $KBrO_3$ in sulfuric acid and heating the resulting product to 100°C with acetic anhydride and acetic acid gives hypervalent iodine reagent **13**, the so-called *Dess–Martin Periodinane.*[198] This reagent reacts with alcohols at ambient temperature to give the corresponding aldehyde or ketone.[199] The reaction is accelerated by water[200] and a water-soluble periodinane (*o*-iodoxybenzoic acid, **14**) has been prepared that oxidized allylic alcohols to conjugated aldehydes.[201]



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[194] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Ansar, I.A.; Gree, R. *Org. Lett.* ***2002***, *4*, 1507.

[195] de Nooy, A.E.J.; Besemer, A.C.; van Bekkum, H. *Synthesis* ***1996***, 1153; Leanna, M.R.; Sowin, T.J.; Morton, H.E. *Tetrahedron Lett.* ***1992***, *33*, 5029.

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[199] For example, see Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* ***1994***, *35*, 8019.

[200] Meyer, S.D.; Schreiber, S.L. *J. Org. Chem.* ***1994***, *59*, 7549. In aqueous β-cyclodextrin-acetone solution, see Surendra, K.; Krishnaveni, N.S.; Reddy, M.A.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003***, *68*, 2058.

[201] Thottumkara, A.P.; Vinod, T.K. *Tetrahedron Lett* ***2001***, *43*, 569.

The reagent has an indefinite shelf-life in a sealed container, but hydrolysis occurs upon long-term exposure to atmospheric moisture. A note of CAUTION! The Dess–Martin reagent can be shock sensitive under some conditions and explode >200°C.[202] Other hypervalent iodine oxidizing reagents are known,[203] including $PhI(OAc)_2$/TEMPO,[204] $PhI(OAc)_2$–chromium salen,[205] stabilized iodoxybenzoic acid,[206] and $PhI(OAc)_2$ supported on alumina with microwave irradiation.[207] Microwave irradiation of benzylic alcohols with PhI(OH)OTs gave the corresponding aldehyde.[208] Hypervalent iodine compounds have been used in ionic liquids.[209] Heating benzylic alcohols with *o*-iodoxybenzoic acid under solvent-free conditions gave the aldehyde.[210] Cyclopropylcarbinyl alcohols are oxidized to the corresponding cyclopropyl ketone or aldehyde with PhIO and a chromium–salen catalyst.[211] The Dess–Martin reagent oxidized aryl aldoximes to aryl aldehydes.[212]

6. *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 were prepared in this manner. Catalytic dehydrogenation is more often used industrially than as a laboratory method. However, procedures using copper oxide,[213] copper(II) complexes,[214] rhodium complexes,[215] ruthenium complexes,[216] Raney nickel,[217] and palladium complexes[218] (under phase-transfer conditions)[219]

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[218] For a discussion of the enantioselective palladium(II) oxidation, see Mandal, S.K.; Jensen, D.R.; Pugsley, J.S.; Sigman, M.S. *J. Org. Chem.* ***2003***, *68*, 4600. See also Mandal, S.K.; Sigman, M.S. *J. Org. Chem.* ***2003***, *68*, 7535; Guram, A.S.; Bei, X.; Turner, H.W. *Org. Lett.* ***2003***, *5*, 2485; Ganchegui, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* ***2002***, *43*, 6641. For a review, see Muzart, J. *Tetrahedron* ***2003***, *59*, 5789.

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have been reported. Allylic alcohols[220] are oxidized to the corresponding saturated aldehyde or ketone by heating with a rhodium catalyst, and benzylic alcohols are converted to the aldehyde with a rhodium catalyst.[221] Photolysis with an iron catalyst gives similar results.[222] Propargylic alcohols are oxidized by heating with a vanadium catalyst.[223] Secondary alcohols are oxidized with $Bi(NO_3)_3$ on Montmorillonite.[224]

7. *Miscellaneous Reagents*.[225] Nitric acid in dichloromethane oxidizes benzylic alcohols to the corresponding ketone. [226] Bromine is an effective oxidant, and iodine under photochemical conditions has been used.[227] Heating a 1,2-diol with NBS in CCl_4 gave the 1,2-diketone.[228] *N*-Bromosuccinimide with β-cyclodextrin oxidizes tetrahydropyranyl ethers in water.[229] Iodine has been used in conjunction with DMSO and hydrazine.[230] Sodium bromate (NaOBr) in conjunction with HCl oxidizes α-hydroxy esters to α-keto esters.[231] Enzymatic oxidations have been reported.[232] Dimethyl dioxirane[233] oxidizes benzylic alcohols to the corresponding aldehyde,[234] and dioxirane reagents are sufficiently mild that an α,β-epoxy alcohol was oxidized to the corresponding ketone, without disturbing the epoxide, using methyl trifluoromethyl dioxirane.[235] Hydrogen peroxide with urea oxidizes aryl aldehydes in formic acid.[236] Potassium monoperoxysulfate in the presence of a

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[230] Gogoi, P.; Sarmah, G.K.; Konwar, D. *J. Org. Chem.* ***2004***, *69*, 5153.

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[233] For a discussion of whether dioxirane oxidation is electrophilic or nucleophilic, see Deubel, D.V. *J. Org. Chem.* ***2001***, *66*, 3790.

[234] Baumstark, A.L.; Kovac, F.; Vasquez, P.C. *Can. J. Chem.* ***1999***, *77*, 308. For a discussion of the mechanism, see Angelis, Y.S.; Hatzakis, N.S.; Smonou, I.; Orfanoupoulos, M. *Tetrahedron Lett.* ***2001***, *42*, 3753.

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chiral ketone oxidizes 1,2-diols to α-hydroxy ketones enantioselectively.[237] Potassium monoperoxysulfate also oxidizes secondary alcohols in the presence of O_2.[238] air in the presence of a zeolite oxidizes benzylic alcohols. [239] The reagent $Br^+(collidine)_2PF_6$ oxidizes benzylic alcohols to the corresponding aldehyde.[240] Sodium hypochlorite in acetic acid is useful for oxidizing larger amounts of secondary alcohols.[241] Calcium hypochlorite on moist alumina with microwave irradiation has been used to oxidize benzylic alcohols.[242] Chlorosulfimines, Ar(Cl)S=N—*t*-Bu, oxidize primary alcohols to aldehydes.[243] This latter reagent is generated from ArS—NH*t*-Bu and NCS.[244] Benzylic alcohols are converted to aldehydes with DBU (p. $$$) and Ar_3BCl_2.[245] Microwave irradiation of benzylic alcohols with $Co(CO_3)_2$ on silica gel generates the aryl aldehyde.[246]

Primary and secondary alcohols can also be oxidized, indirectly, through their esters (see **19-21**). 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.[247] The currently accepted mechanism is essentially that proposed by Westheimer.[248] The first two steps constitute an example of category 4 (p. 1706).

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[241] Stevens, R.V.; Chapman, K.T.; Weller, H.N. *J. Org. Chem.* ***1980***, *45*, 2030. See also, Schneider, M.; Weber, J.; Faller, P. *J. Org. Chem.* ***1982***, *47*, 364; Mohrig, J.R.; Nienhuis, D.M.; Linck, C.F.; van Zoeren, C.; Fox, B.G.; Mahaffy, P.G. *J. Chem. Educ.* ***1985***, *62*, 519. For a reaction with aqueous NaOCl and a guanidinium salt, see Xie, H.; Zhang, S.; Duan, H. *Tetrahedron Lett.* ***2004***, *45*, 2013.

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[247] See Müller, P. *Chimia* ***1977***, *31*, 209; Wiberg, K.B., in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 142–170; Venkatasubramanian, N. *J. Sci. Ind. Res.* ***1963***, *22*, 397; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 49–71; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 37–48; Durand, R.; Geneste, P.; Lamaty, G.; Moreau, C.; Pomarès, O.; Roque, J.P. *Recl. Trav. Chim. Pays-Bas* ***1978***, *97*, 42; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* ***1985***, *41*, 205.

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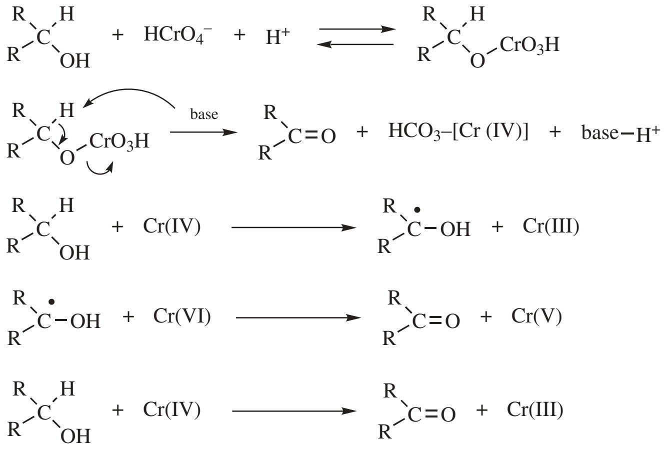
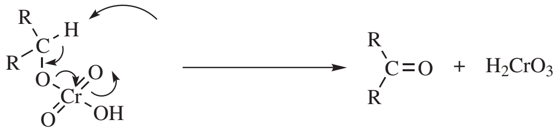


The base in the second step may be water, although it is also possible[249] that in some cases no external base is involved and that the proton is transferred directly to one of the CrO_3H oxygens in which case the Cr(IV) species



produced would be H_2CrO_3. Part of the evidence for this mechanism was the isotope effect of $\sim$ 6 found on use of MeCDOHMe, showing that the a hydrogen is removed in the rate-determining step.[250] Note that, as in **19-23** the substrate is oxidized by three different oxidation states of chromium.[251]

With other oxidizing agents, mechanisms are less clear.[252] It seems certain that some oxidizing agents operate by a hydride-shift mechanism,[253] for example,

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[249] Stewart, R.; Lee, D.G. *Can. J. Chem.* ***1964***, *42*, 439; Awasthy, A.; Roek, J.; Moriarty, R.M. *J. Am. Chem. Soc.* ***1967***, *89*, 5400; Kwart, H.; Nickle, J.H. *J. Am. Chem. Soc.* ***1979***, *98*, 2881 and cited rererences; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* ***1986***, *42*, 681. See also Müller, P.; Perlberger, J. *Helv. Chim. Acta* ***1974***, *57*, 1943; Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990***, *46*, 1963.

[250] Westheimer, F.H.; Nicolaides, N. *J. Am. Chem. Soc.* ***1949***, *71*, 25. For other evidence, see Brownell, R.; Leo, A.; Chang, Y.W.; Westheimer, F.H. *J. Am. Chem. Soc.* ***1960***, *82*, 406; Roč ek, J.; Westheimer, F.H.; Eschenmoser, A.; Moldoványi, L.; Schreiber, J. *Helv. Chim. Acta* ***1962***, *45*, 2554; Lee, D.G.; Stewart, R. *J. Org. Chem.* ***1967***, *32*, 2868; Wiberg, K.B.; Schäfer, H. *J. Am. Chem. Soc.* ***1967***, *89*, 455; ***1969***, *91*, 927, 933; Müller, P. *Helv. Chim. Acta* ***1970***, *53*, 1869; ***1971***, *54*, 2000, Lee, D.G.; Raptis, M. *Tetrahedron* ***1973***, *29*, 1481.

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[252] For a review, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 264–277.

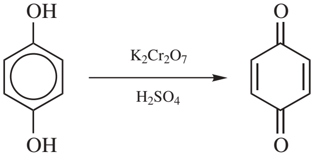
[253] See Barter, R.M.; Littler, J.S. *J. Chem. Soc. B* ***1967***, 205. For evidence that oxidation by HNO_2 involves a hydride shift, see Moodie, R.B.; Richards, S.N. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1833; Ross, D.S.; Gu, C.; Hum, G.P.; Malhotra, R. *Int. J. Chem. Kinet.* ***1986***, *18*,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

dehydrogenation with triphenylmethyl cation[254] and the Oppenauer oxidation, and some by a free-radical mechanism, (e.g., oxidation with $S_2O_8^{2-}$[255] and with VO_2^+.[256]). A summary of many proposed mechanisms is given by Littler.[257]

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; **VIII**, 43, 367, 386; **IX**, 132, 432. Also see, OS **IV**, 283; **VIII**, 363, 501.

19-4 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.[258] Either or both OH groups can be replaced by NH_2 groups to give the same products, although 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, although with the last yields are poor. Many oxidizing agents have been used: acid dichromate,[259] silver oxide, silver carbonate, lead tetraacetate, HIO_4, NBS—H_2O—H_2SO_4,[260] MnO_2 on Bentonite with microwave irradiation,[261] dimethyl dioxirane,[262] and atmospheric oxygen,[263] to name a few. Substituted phenols, such as 4-($CH_2CH_2CH_2COOH$) phenol, are oxidized with a polymer-bound hypervalent iodine reagent to give a quinone with a spirocyclic lactone unit at C-4.[264] Oxidation

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[254] Bonthrone, W.; Reid, D.H. *J. Chem. Soc.* ***1959***, 2773.

[255] Ball, D.L.; Crutchfield, M.M.; Edwards, J.O. *J. Org. Chem.* ***1960***, *25*, 1599; Bida, G.; Curci, R.; Edwards, J.O. *Int. J. Chem. Kinet.* ***1973***, *5*, 859; Snook, M.E.; Hamilton, G.A. *J. Am. Chem. Soc.* ***1974***, *96*, 860; Walling, C.; Camaioni, D.M. *J. Org. Chem.* ***1978***, *43*, 3266; Clerici, A.; Minisci, F.; Ogawa, K.; Surzur, J. *Tetrahedron Lett.* ***1978***, 1149; Beylerian, N.M.; Khachatrian, A.G. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1937.

[256] Littler, J.S.; Waters, W.A. *J. Chem. Soc.* ***1959***, 4046.

[257] Littler, J.S. *J. Chem. Soc.* ***1962***, 2190.

[258] For reviews, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 305–323, 438–447; Naruta, Y.; Maruyama, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 247–276; Thomson, R.H., in Patai, S. *The Chemistry of the Quinoiid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 112–132.

[259] For a review of this oxidation with chromium reagents, see Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 92–117.

[260] Kim, D.W.; Choi, H.Y.; Lee, K.Y.; Chi, D.Y. *Org. Lett.* ***2001***, *3*, 445.

[261] Gómez-Lara, J.; Gutiérrez-Perez, R.; Penieres-Carrillo, G.; López-Cortés, J.G.; Escudero-Salas, A.; Alvarez-Toledano, C. *Synth. Commun.* ***2000***, *30*, 2713.

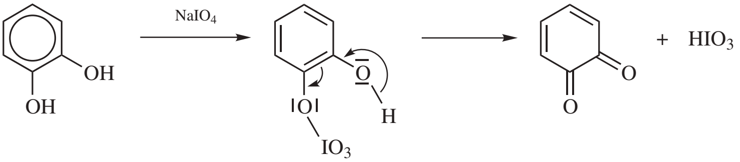
[262] Adam, W.; Schönberger, A. *Tetrahedron Lett.* ***1992***, *33*, 53.

[263] For an example on activated silica gel, see Hashemi, M.M.; Beni, Y.A. *J. Chem. Res. (S)* ***1998***, 138.

[264] Ley, S.V.; Thomas, A.W.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 669.

has been done photochemically with O_2 and tetraphenylporphine.[265] A particularly effective reagent for rings with only one OH or NH_2 group is $(KSO_3)_2N—O•$ (dipotassium nitrosodisulfonate; *Fremy's salt*), which is a stable free radical.[266] Phenols, even some whose para positions are unoccupied, can be oxidized to ortho-quinones with diphenylseleninic anhydride.[267] Quinoid coupling products are obtained from substituted phenol treated with O_2, a dicopper complex, and mushroom tyrosinase.[268]

Less is known about the mechanism than is the case for **19-3**, 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,[269] so the following mechanism[270] was proposed:



When catechol was oxidized with MnO_4^- under aprotic conditions, a semiquinone radical ion intermediate was involved.[271] For autoxidations[272] (i.e., with atmospheric oxygen) a free-radical mechanism is known to operate.[273]

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

19-5 Dehydrogenation of Amines

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

$$RCH_2NH_2 \longrightarrow RCN$$

Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out with a variety of reagents, among others, lead tetraacetate,[274] NaOCl,[275]

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[265] Cossy, J.; Belotti, S. *Tetrahedron Lett.* ***2001***, *42*, 4329.

[266] For a review of oxidation with this salt, see Zimmer, H.; Lankin, D.C.; Horgan, S.W. *Chem. Rev.* ***1971***, *71*, 229.

[267] Barton, D.H.R.; Brewster, A.G.; Ley, S.V.; Rosenfeld, M.N. *J. Chem. Soc. Chem. Commun.* ***1976***, 985; Barton, D.H.R.; Ley, S.V., in *Further Perspectives in Organic Chemistry*, North-Holland Publishing Co., Amsterdam, The Netherlands, ***1979***, pp. 53–66. For another way of accomplishing this, see Krohn, K.; Rieger, H.; Khanbabaee, K. *Chem. Ber.* ***1989***, *122*, 2323.

[268] Gupta, R.; Mukherjee, R. *Tetrahedron Lett.* ***2000***, *41*, 7763.

[269] Adler, E.; Falkehag, I.; Smith, B. *Acta Chem. Scand.* ***1962***, *16*, 529.

[270] This mechanism is an example of category 4 (p. $$$).

[271] Bock, H.; Jaculi, D. *Angew. Chem. Int. Ed.* ***1984***, *23*, 305.

[272] For an example, see Rathore, R.; Bosch, E.; Kochi, J.K. *Tetrahedron Lett.* ***1994***, *35*, 1335.

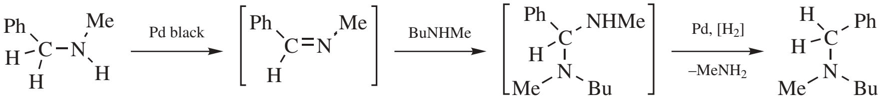
[273] Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 368–381; Walling, C. *Free Radicals in Solution*, Wiley, NY, ***1957***, pp. 457–461.

[274] Stojiljković, A.; Andrejević, V.; Mihailović, M.Lj. *Tetrahedron* ***1967***, *23*, 721.

[275] Yamazaki, S. *Synth. Commun.* ***1997***, *27*, 3559; Juršic, B. *J. Chem. Res. (S)* ***1988***, 168.

$K_2S_2O_8/NiSO_4$,[276] $Me_3N/O/OsO_4$,[277] $Ru/Al_2O_3/O_2$,[278] and $CuCl/O_2$/pyridine.[279] Several methods have been reported for the dehydrogenation of secondary amines to imines.[280] Among them[281] are treatment with (*1*) iodosylbenzene (PhIO) alone or in the presence of a ruthenium complex,[282] (*2*) DMSO and oxalyl chloride,[283] and (*3*) *t*-BuOOH and a rhenium catalyst.[284] *N*-Tosyl aziridines are converted to *N*-tosyl imines when heated with a palladium catalyst.[285] An interesting variation treats pyrrolidine with iodobenzene and a rhodium catalyst to give 2-phenylpyrroline.[286]

A reaction that involves dehydrogenation to an imine that then reacts further is the reaction of primary or secondary amines[287] with palladium black.[288] 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 is the reaction between *N*-methylbenzylamine and butylmethylamine, which produces 95% *N*-methyl-*N*-butylbenzylamine.



19-6 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines

1/*N*,2/*N*-Dihydro-elimination

$$\text{Ar—NH—NH—Ar} \xrightarrow{\text{NaOBr}} \text{Ar—N=N—Ar}$$

N,N′-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, HgO,[289] $K_3Fe(CN)_6$ under phase-transfer

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[276] Yamazaki, S.; Yamazaki, Y. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 301.

[277] Gao, S.; Herzig, D.; Wang, B. *Synthesis* ***2001***, 544.

[278] Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1480.

[279] Kametani, T.; Takahashi, K.; Ohsawa, T.; Ihara, M. *Synthesis* ***1977***, 245; Capdevielle, P.; Lavigne, A.; Maumy, M. *Synthesis* ***1989***, 453; *Tetrahedron* ***1990***, 2835; Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Cuong, N.K.; Maumy, M. *Tetrahedron Lett.* ***1990***, *31*, 3305.

[280] For a review, see Dayagi, S.; Degani, Y., in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 117–124.

[281] For other methods, see Cornejo, J.J.; Larson, K.D.; Mendenhall, G.D. *J. Org. Chem.* ***1985***, *50*, 5382; Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* ***1988***, *29*, 4115.

[282] Müller, P.; Gilabert, D.M. *Tetrahedron* ***1988***, *44*, 7171.

[283] Keirs, D.; Overton, K. *J. Chem. Soc. Chem. Commun.* ***1987***, 1660.

[284] Murahashi, S.; Naot, T.; Taki, H. *J. Chem. Soc. Chem. Commun.* ***1985***, 613.

[285] Wolfe, J.P.; Ney, J.E. *Org. Lett.* ***2003***, *5*, 4607.

[286] Sezen, B.; Sames, D. *J. Am. Chem. Soc.* ***2004***, *126*, 13244.

[287] See Larsen, J.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 2*, ***1992***, 1213. Also see, Yamaguchi, J.; Takeda, T. *Chem. Lett.* ***1992***, 1933; Yamazaki, S. *Chem. Lett.* ***1992***, 823.

[288] Murahashi, S.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* ***1983***, *105*, 5002. See also, Wilson, Jr., R.B.; Laine, R.M. *J. Am. Chem. Soc.* ***1985***, *107*, 361.

[289] For a review of HgO, see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 295–319.

conditions[290] or with galvinoxyl,[291] $FeCl_3$,[292] MnO_2 (this reagent yields cis-azobenzenes),[293] $CuCl_2$, and air and NaOH.[294] 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,[295] but these are unstable and decompose to nitrogen and the hydrocarbon:

$$\text{Ar—NH—NH}_2 \longrightarrow [\,\text{Ar—N=NH}\,] \longrightarrow \text{ArH} + \text{N}_2$$

Aniline derivatives are converted to azo compounds by heating with cetyltrimethylammonium dichromate in chloroform.[296] When hydrazones are oxidized with HgO, Ag_2O, MnO_2, lead tetraacetate, or certain other oxidizing agents, diazo compounds are obtained:[297]

$$\text{R}_2\text{C=N—NH}_2 \xrightarrow{\text{HgO}} \text{R}_2\text{C=}\overset{\oplus}{\text{N}}\text{=}\overset{\ominus}{\text{N}}$$

Hydrazones of the form ArCH=NNH_2 react with HgO in solvents, such as diglyme or ethanol, to give nitriles ArCN.[298] It is possible to oxidize dimethylhydrazones (R—C=N—NMe_2) to the corresponding nitrile (R—C≡N) with $MeReO_3$/H_2O_2[299] magnesium monoperoxyphthalate (MMPP),[300] or with dimethyl dioxirane.[301] Oxone® on wet alumina also converts hydrazones to nitriles with microwave irradiation.[302]

In a related reaction, 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,[303] and sodium perborate in acetic acid. *tert*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.[304] Aromatic hydroxylamines (Ar—NH—OH) are easily oxidized to nitroso compounds (Ar—N=O), most commonly by acid dichromate.[305] Oximes of

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[290] Dimroth, K.; Tüncher, W. *Synthesis* ***1977***, 339.

[291] Wang, X.-Y.; Wang, Y.-L.; Li, J.-P.; Duan, Z.F.; Zhang, Z.-Y. *Synth. Commun.* ***1999***, *29*, 2271.

[292] Wang, C.-L.; Wang, X.-X.; Wang, X.-Y.; Xiao, J.-P.; Wang, Y.-L. *Synth. Commun.* ***1999***, *29*, 3435.

[293] Hyatt, J.A. *Tetrahedron Lett.* ***1977***, 141.

[294] For a review, see Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 543–557, 564–573.

[295] See Mannen, S.; Itano, H.A. *Tetrahedron* ***1973***, *29*, 3497.

[296] Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004***, *45*, 1371.

[297] For a review, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 233–256.

[298] Mobbs, D.B.; Suschitzky, H. *Tetrahedron Lett.* ***1971***, 361.

[299] Stanković, S.; Espenson, J.H. *Chem. Commun.* ***1998***, 1579.

[300] Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M.; Vázquez, J. *Tetrahedron Lett.* ***1993***, *34*, 141.

[301] Altamura, A.; D'Accolti, L.; Detomaso, A.; Dinoi, A.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* ***1998***, *39*, 2009.

[302] Ramalingam, T.; Reddy, B.V.S.; Srinivas, R.; Yadav, J.S. *Synth. Commun.* ***2000***, *30*, 4507.

[303] Firouzabadi, H.; Mostafavipoor, Z. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 914.

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

[305] For a review, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 231–232.

aromatic aldehydes are converted to aryl nitriles with $InCl_3$[306] (ketoximes give a Beckmann rearrangement, **18-17**).

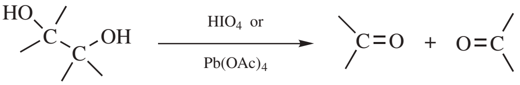
Nitrones, $C{=}N^+(R){=}O^-$, are generated by the oxidation of *N*-hydroxyl secondary amines with 5% aq. NaOCl.[307] Secondary amines, such as dibenzylamine, can be converted to the corresponding nitrone by heating with cumyl hydroperoxide in the presence of a titanium catalyst.[308] Imines are oxidized to amides with mcpba and $BF_3{\bullet}OEt_2$.[309]

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. For oxidation of primary amines, see OS **V**, 341.

B. Oxidations Involving Cleavage of Carbon–Carbon Bonds[310]

19-7 Oxidative Cleavage of Glycols and Related Compounds

2/*O*-De-hydrogen-uncoupling



1,2-Glycols are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.[311] The products are 2 equivalents of aldehyde, or 2 equivalents of ketone, or 1 equivalent of each, depending on the groups attached to the two carbons. The yields are so good that alkenes are often converted to glycols (**15-48**), and then cleaved with HIO_4 or $Pb(OAc)_4$ rather than being cleaved directly with ozone (**19-9**) or dichromate or permanganate (**19-10**). The diol can be generated and cleaved *in situ* from an alkene to give the carbonyl compounds.[312]

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[306] Barman, D.C.; Thakur, A.J.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2000***, 1196.

[307] Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* ***1999***, *64*, 7243.

[308] Forcato, M.; Nugent, W.A.; Licini, G. *Tetrahedron Lett.* ***2003***, *44*, 49.

[309] An, G.-i.; Rhee, H. *Synlett* ***2003***, 876.

[310] For a review, see Bentley, K.W., in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 137–254.

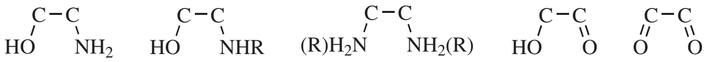
[311] For reviews covering both reagents, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 277–301, 432–437; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 3353–363; Perlin, A.S., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 189–212; Bunton, C.A., in Wiberg, K.B., in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 367–407. For reviews of lead tetraacetate, see Rubottom, G.M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, ***1982***, p. 1; Aylward, J.B. *Q. Rev. Chem. Soc.* ***1971***, *25*, 407. For reviews of HIO_4, see Fatiadi, A.J. *Synthesis* ***1976***, 65,133; Sklarz, B. *Q. Rev. Chem. Soc.* ***1967***, *21*, 3.

[312] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* ***2004***, *6*, 3217.

A number of other oxidizing agents also give the same products, among them[313] activated MnO_2,[314] O_2 and a ruthenium catalyst,[315] PPh_3–DEAD,[316] and pyridinium chlorochromate.[317] Permanganate, dichromate, and several other oxidizing agents[318] 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.[319]

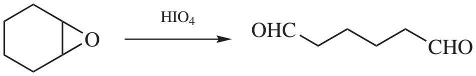
The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water and lead tetraacetate in organic solvents. Chiral lead carboxylates have been prepared for the oxidative cleavage of 1,2-diols.[320] When three or more OH groups are located on adjacent carbons, the middle one (or ones) is converted to formic acid.

Other compounds that contain oxygens or nitrogens on adjacent carbons undergo similar cleavage:



β-Amino alcohols 1,2-Diamines α-Hydroxy aldehydes and ketones α-Diketones a-keto aldehydes Glyoxal

Cyclic 1,2-diamines are cleaved to diketones with dimethyl dioxirane.[321] α-Diketones and α-hydroxy ketones are also cleaved by alkaline H_2O_2.[322] The HIO_4 has been used to cleave epoxides to aldehydes,[323] for example,



α-Hydroxy acids and α-keto acids are not cleaved by HIO_4, but are cleaved by $NaIO_4$ in methanol in the presence of a crown ether,[324] $Pb(OAc)_4$, alkaline H_2O_2,

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[313] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1250–1255.

[314] Adler, E.; Becker, H. *Acta Chem. Scand.* ***1961***, *15*, 849; Ohloff, G.; Giersch, W. *Angew. Chem. Int. Ed.* ***1973***, *12*, 401.

[315] Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* ***1999***, *1*, 713.

[316] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R. *Tetrahedron Lett.* ***2000***, *41*, 1959.

[317] Cisneros, A.; Fernández, S.; Hernández, J.E. *Synth. Commun.* ***1982***, *12*, 833.

[318] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1650–1652.

[319] For a review, see Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 31–37. See also, Ruholl, H.; Schäfer, H.J. *Synthesis* ***1988***, 54.

[320] Lena, J.I.C.; Sesenoglu, Ö.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* ***2001***, *42*, 21.

[321] Gagnon, J.L.; Zajac, Jr., W.W. *Tetrahedron Lett.* ***1995***, *36*, 1803.

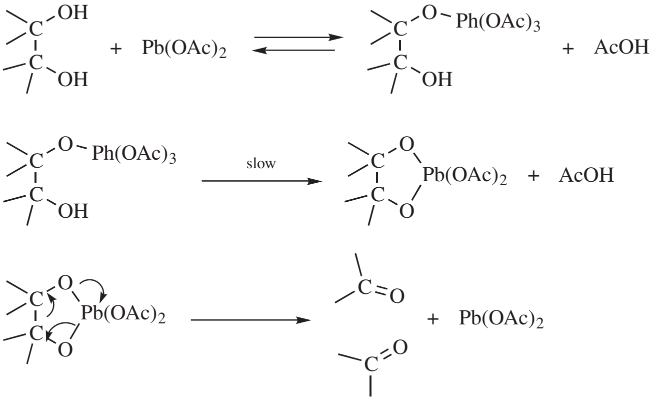
[322] See, for example, Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* ***1977***, *42*, 4061.

[323] Nagarkatti, J.P.; Ashley, K.R. *Tetrahedron Lett.* ***1973***, 4599.

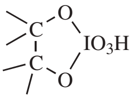
[324] Kore, A.R.; Sagar, A.D.; Salunkhe, M.M. *Org. Prep. Proceed. Int.* ***1995***, *27*, 373.

and other reagents. These are oxidative decarboxylations. α-Hydroxy acids give aldehydes or ketones, and α-keto acids give carboxylic acids. Also see, **19-12** and **19-13**.

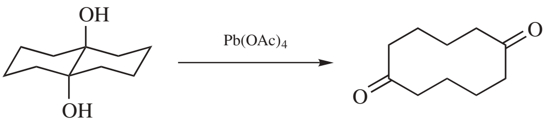
The mechanism of glycol oxidation with $Pb(OAc)_4$ was proposed by Criegee:[325]



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.[326] For periodic acid, the mechanism is similar, with the intermediate[327]



However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols that cannot form such an ester (e.g., **15**) are nevertheless cleaved by lead tetraacetate



15

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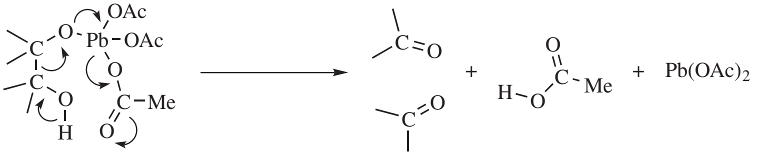
[325] Criegee, R.; Kraft, L.; Rank, B. *Liebigs Ann. Chem.* ***1933***, *507*, 159. For reviews, see Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 72–81; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 97–106.

[326] For example, see Criegee, R.; Höger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenberger, H. *Liebigs Ann. Chem.* ***1956***, *599*, 81.

[327] Buist, G.J.; Bunton, C.A.; Hipperson, W.C.P. *J. Chem. Soc. B* ***1971***, 2128.

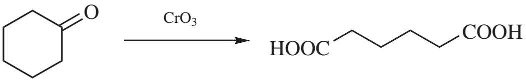
(though other glycols that cannot form cyclic esters are *not* cleaved, by either reagent[328]). To account for cases like **15**, a cyclic transition state has been proposed:[326]



OS **IV**, 124; **VII**, 185; **VIII**, 396.

19-8 Oxidative Cleavage of Ketones, Aldehydes, and Alcohols

Cycloalkanone oxidative ring opening



Oxidative cleavage of open-chain ketones or alcohols[329] 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. Aryl methyl ketones, such as acetophenone, however, are readily oxidized to aryl carboxylic acids with Re_2O_7 and 70% aqueous *tert*-butyl hydroperoxide.[330] Oxygen with a mixture of manganese and cobalt catalysts give similar oxidative cleavage,[331] and do hypervalent iodine compounds.[332] 1,3-Diketones, such as 1,3-diphenyl-1,3-propanedione, are oxidatively cleaved with aqueous Oxone® to give benzoic acid.[333] Noted that in the presence of benzaldehyde, aliphatic ketones are cleaved to give aliphatic carboxylic acids by treatment with BF_3(g) in refluxing hexane.[334] Aldehydes, such as $PhCH_2CHO$, are cleaved to benzaldehyde with phosphonium dichromate in refluxing acetonitrile.[335]

Despite problems with acyclic ketones, 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, although autoxidation (oxidation with

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[328] Angyal, S.J.; Young, R.J. *J. Am. Chem. Soc.* ***1959***, *81*, 5251.

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

[330] Gurunath, S.; Sudalai, A. *Synlett* ***1999***, 559.

[331] Minisci, F.; Recupero, F.; Fontana, F.; Bjørsvik, H.-R.; Liguori, L. *Synlett* ***2002***, 610.

[332] Lee, J.C.; Choi, J.-H.; Lee, Y.C. *Synlett* ***2001***, 1563.

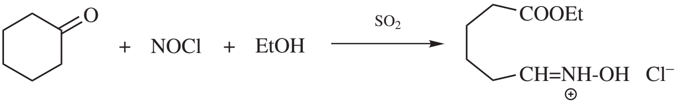
[333] Ashford, S.W.; Grega, K.C. *J. Org. Chem.* ***2001***, *66*, 1523.

[334] Kabalka, G.W.; Li, N.-S.; Tejedor, D.; Malladi, R.R.; Gao, X.; Trotman, S. *Synth. Commun.* ***1999***, *29*, 2783.

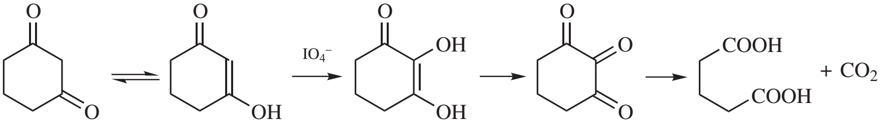
[335] Hajipour, A.R.; Mohammadpoor-Baltork, I.; Niknam, K. *Org. Prep. Proceed. Int.* ***1999***, *31*, 335.

atmospheric oxygen) in alkaline solution[336] and potassium superoxide under phase-transfer conditions[337] have also been used. Other reagents include LiOCl/Chlorox[338] and $MeOCO_2Me$ at 195°C.[339] Silyl-ketones have been cleaved to esters using electrolysis in alcohol solvents.[340] Cyclic 1,3-diketones are converted to α,ω-diesters with an excess of $KHSO_5$ in methanol.[341] Cyclic α-chloro ketones are cleaved to give an α,ω-functionalized compound (acetal-ester) when treated with cerium (IV) sulfate tetrahydrate and O_2.[342]

Cyclic ketones can also be cleaved by treatment with NOCl and an alcohol in liquid SO_2 to give an ω-oximinocarboxylic ester, for example,[343]



Cyclic 1,3-diketones, which exist mainly in the mono-enolic form, can be cleaved with sodium periodate with loss of one carbon, for example,[344]

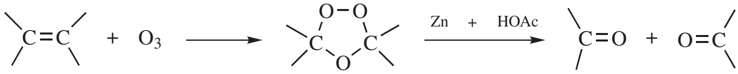


The species actually undergoing the cleavage is the triketone, so this is an example of **19-7**.

OS **I**, 18; **IV**, 19; **VI**, 690. See also, OS **VI**, 1024.

19-9 Ozonolysis

Oxo-uncoupling



16

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[336] Wallace, T.J.; Pobiner, H.; Schriesheim, A. *J. Org. Chem.* ***1965***, *30*, 3768; Bjørsvik, H.-R.; Liguori, L.; González, R.R.; Merinero, J.A.V. *Tetrahedron Lett.* ***2002***, *43*, 4985. See also, Osowska-Pacewicka, K.; Alper, H. *J. Org. Chem.* ***1988***, *53*, 808.

[337] Lissel, M.; Dehmlow, E.V. *Tetrahedron Lett.* ***1978***, 3689; Sotiriou, C.; Lee, W.; Giese, R.W. *J. Org. Chem.* ***1990***, *55*, 2159.

[338] Madler, M.M.; Klucik, J.; Soell, P.S.; Brown, C.W.; Liu, S.; Berlin, K.D.; Benbrook, D.M.; Birckbichler, P.J.; Nelson, E.C. *Org. Prep. Proceed. Int.* ***1998***, *30*, 230.

[339] Selva, M.; Marques, C.A.; Tundo, P. *Gazz. Chim. Ital.* ***1993***, *123*, 515.

[340] Yoshida, J.; Itoh, M.; Matsunaga, S.; Isoe, S. *J. Org. Chem.* ***1992***, *57*, 4877.

[341] Yan, J.; Travis, B.R.; Borhan, B. *J. Org. Chem.* ***2004***, *69*, 9299.

[342] He, L.; Horiuchi, C.A. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 2515.

[343] Rogić, M.M.; Vitrone, J.; Swerdloff, M.D. *J. Am. Chem. Soc.* ***1977***, *99*, 1156; Moorhoff, C.M.; Paquette, L.A. *J. Org. Chem.* ***1991***, *56*, 703.

[344] Wolfrom, M.L.; Bobbitt, J.M. *J. Am. Chem. Soc.* ***1956***, *78*, 2489.

When compounds containing double bonds are treated with ozone, usually at low temperatures, they are converted to compounds called *ozonides* (**16**) 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 equivalents of aldehyde, or 2 equivalents of ketone, or 1 equivalent of each, depending on the groups attached to the alkene.[345] The decomposition of **16** has also been carried out with triethylamine[346] and with reducing agents, among them trimethyl phosphite,[347] thiourea,[348] and dimethyl sulfide.[349] However, ozonides can also be *oxidized* with oxygen, peroxyacids, 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 equivalents alcohol.[350] Ozonides can also be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines,[351] or with an alcohol and anhydrous HCl to give the corresponding carboxylic esters.[352] Ozonolysis is therefore an important synthetic reaction.

A wide variety of alkenes undergo ozonolysis, including cyclic ones, where cleavage gives rise to one bifunctional product. Alkenes 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.[353] 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 (**15-50**) becomes an important side reaction and can be the main reaction.[354] Rearrangement is possible in some cases.[355] Ozonolysis of triple bonds[356] is less common and the reaction proceeds less easily,

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[345] For monographs, see Razumovskii, S.D.; Zaikov, G.E. *Ozone and its Reactions with Organic Compounds*; Elsevier, NY, ***1984***; Bailey, P.S. *Ozonation in Organic Chemistry*, 2 vols., Academic Press, NY, ***1978, 1982***. For reviews, see Odinokov, V.N.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1981***, *50*, 636; Belew, J.S., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 259–335; Menyailo, A.T.; Pospelov, M.V. *Russ. Chem. Rev.* ***1967***, *36*, 284. For a review with respect to vinylic ethers, see Kuczkowski, R.L. *Adv. Oxygenated Processes* ***1991***, *3*, 1. For a review with respect to haloalkenes, see Gillies, C.W.; Kuczkowski, R.L. *Isr. J. Chem.* ***1983***, *23*, 446.

[346] Hon, Y.-S.; Lin, S.-W.; Chen, Y.-J. *Synth. Commun.* ***1993***, *23*, 1543.

[347] Knowles, W.S.; Thompson, Q.E. *J. Org. Chem.* ***1960***, *25*, 1031.

[348] Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* ***1982***, *38*, 3013.

[349] Pappas, J.J.; Keaveney, W.P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* ***1966***, 4273.

[350] Sousa, J.A.; Bluhm, A.L. *J. Org. Chem.* ***1960***, *25*, 108; Diaper, D.G.M.; Strachan, W.M.J. *Can. J. Chem.* ***1967***, *45*, 33; White, R.W.; King, S.W.; O'Brien, J.L. *Tetrahedron Lett.* ***1971***, 3587; Flippin, L.A.; Gallagher, D.W.; Jalali-Araghi, K. *J. Org. Chem.* ***1989***, *54*, 1430.

[351] Diaper, D.G.M.; Mitchell, D.L. *Can. J. Chem.* ***1962***, *40*, 1189; Benton, F.L.; Kiess, A.A. *J. Org. Chem.* ***1960***, *25*, 470; Pollart, K.A.; Miller, R.E. *J. Org. Chem.* ***1962***, *27*, 2392; White, R.W.; King, S.W.; O'Brien, J.L. *Tetrahedron Lett.* ***1971***, 3591.

[352] Neumeister, J.; Keul, H.; Saxena, M.P.; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1978***, *17*, 939. See also, Schreiber, S.L.; Claus, R.E.; Reagan, J. *Tetrahedron Lett.* ***1982***, *23*, 3867; Cardinale, G.; Grimmelikhuysen, J.C.; Laan, J.A.M.; Ward, J.P. *Tetrahedron* ***1984***, *40*, 1881.

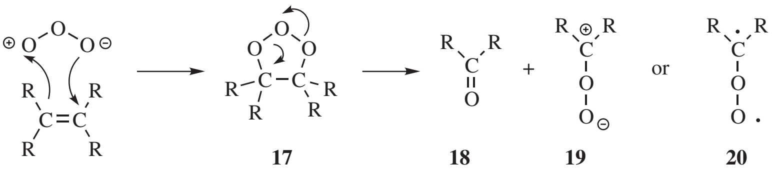
[353] Pryor, W.A.; Giamalva, D.; Church, D.F. *J. Am. Chem. Soc.* ***1985***, *107*, 2793.

[354] See, for example, Bailey, P.S.; Lane, A.G. *J. Am. Chem. Soc.* ***1967***, *89*, 4473; Gillies, C.W. *J. Am. Chem. Soc.* ***1975***, *97*, 1276; Bailey, P.S.; Hwang, H.H.; Chiang, C. *J. Org. Chem.* ***1985***, *50*, 231.

[355] For an example, see Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Cuerva, J.M.; Segovia, A. *Synlett.* ***2000***, *1*269.

[356] For a discussion of the mechanism of ozonolysis of triple bonds, see Pryor, W.A.; Govindan, C.K.; Church, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 7563.

since ozone is an electrophilic agent[357] and prefers double to triple bonds (p. 1017). Compounds that contain triple bonds generally give carboxylic acids, although sometimes ozone oxidizes them to α-diketones (**19-26**). Aromatic compounds are also attacked less readily than alkenes, but have often been cleaved. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives three equivalents 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.[358]



Although a large amount of work has been done on the mechanism of ozonization (formation of **16**), not all the details are known. The basic mechanism was formulated by Criegee.[359] The first step of the Criegee mechanism[360] is a 1,3-dipolar addition (**15-58**) 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, **17**, by microwave and other spectral methods.[361] A primary ozonide has been trapped.[362] However, **17** is highly unstable and cleaves to an aldehyde or ketone (**18**) and an intermediate,[363] which Criegee showed as a zwitterion (**19**), but which may be a diradical (**20**). This compound is usually referred to as a carbonyl oxide.[364] The carbonyl oxide (which we will represent as **19**) can then undergo various reactions, three of which lead to normal products. One is a recombination with **18**, the second

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[357] See, for example, Wibaut, J.P.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1952***, *71*, 761; Williamson, D.G.; Cvetanovi, R.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4248; Razumovskii, S.D.; Zaikov, G.E. *J. Org. Chem. USSR* ***1972***, *8*, 468, 473; Klutsch, G.; Fliszár, S. *Can. J. Chem.* ***1972***, *50*, 2841.

[358] Dobinson, F.; Bailey, P.S. *Tetrahedron Lett.* ***1960*** (No. 13) 14; O'Murchu, C. *Synthesis* ***1989***, 880.

[359] For reviews, see Kuczkowski, R.L. *Acc. Chem. Res.* ***1983***, *16*, 42; Razumovskii, S.D.; Zaikov, G.E. *Russ. Chem. Rev.* ***1980***, *49*, 1163; Criegee, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 745; Murray, R.W. *Acc. Chem. Res.* ***1968***, *1*, 313.

[360] For a modified-Criegee mechanism, see Ponec, R.; Yuzhakov, G.; Haas, Y.; Samuni, U. *J. Org. Chem.* ***1997***, *62*, 2757.

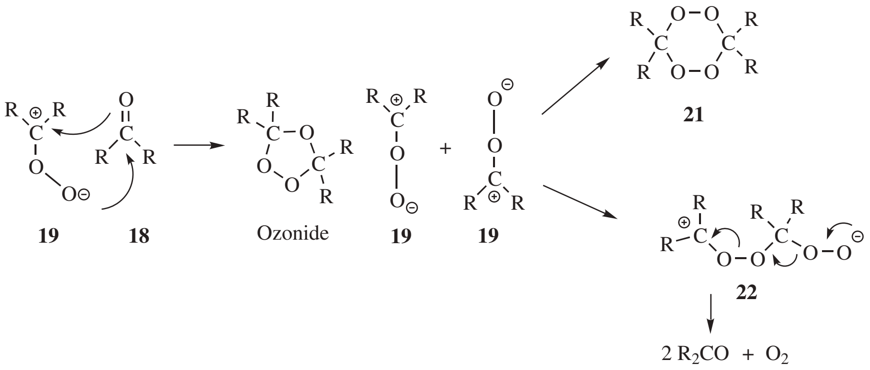
[361] Gillies, J.Z.; Gillies, C.W.; Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7991. See also, Criegee, R.; Schröder, G. *Chem. Ber.* ***1960***, *93*, 689; Durham, L.J.; Greenwood, F.L. *J. Org. Chem.* ***1968***, *33*, 1629; Bailey, P.S.; Carter, Jr., T.P.; Fischer, C.M.; Thompson, J.A. *Can. J. Chem.* ***1973***, *51*, 1278; Hisatsune, I.C.; Shinoda, K.; Heicklen, J. *J. Am. Chem. Soc.* ***1979***, *101*, 2524; Mile, B.; Morris, G.W.; Alcock, W.G. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 1644; Kohlmiller, C.K.; Andrews, L. *J. Am. Chem. Soc.* ***1981***, *103*, 2578; McGarrity, J.F.; Prodolliet, J. *J. Org. Chem.* ***1984***, *49*, 4465.

[362] Jung, M.E.; Davidov, P. *Org. Lett.* ***2001***, *3*, 627.

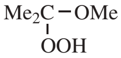
[363] A Criegee intermediate has been detected for the ozonolysis of 2-butene; see Fajgar, R.; Vítek, J.; Haas, Y.; Pola, J. *Tetrahedron Lett.* ***1996***, *37*, 3391.

[364] For reviews of carbonyl oxides, see Sander, W. *Angew. Chem. Int. Ed.* ***1990***, *29*, 344; Brunelle, W.H. *Chem. Rev.* ***1991***, *91*, 335.

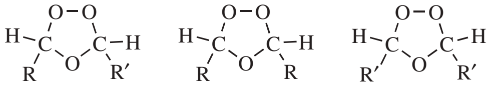
a dimerization to the bis(peroxide) **21**, and the third a kind of dimerization to **22**.[365] If the first path is taken (this is normally



possible only if **15** is an aldehyde; most ketones do not do this[366]) the product is an ozonide (a 1,2,4-trioxolane),[367] and hydrolysis of the ozonide gives the normal products. If **21** is formed, hydrolysis of it gives one of the products, and, of course, **18**, which then does not undergo further reaction, is the other. Intermediate **22**, if formed, can decompose directly, as shown, to give the normal products and oxygen. In protic solvents, **19** is converted to a hydroperoxide, and these have been isolated, for example,


$Me_2C(OOH)-OMe$

from $Me_2C{=}CMe_2$ in methanol. Further evidence for the mechanism is that **21** can be isolated in some cases, for example, 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 alkene break apart and then recombine to form the ozonide. In the case of an unsymmetrical alkene, RCH=CHR′, there should be three ozonides:



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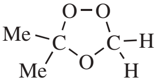
[365] Fliszár, S.; Chylińska, J.B. *Can. J. Chem.* ***1967***, *45*, 29; ***1968***, *46*, 783.

[366] 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, K.; Volpp, W.; Greinert, R.; Greunig, H.; Schmid, J.; Henke, H. *J. Org. Chem.* ***1989***, *54*, 383.

[367] Kamata, M.; Komatsu, K.i.; Akaba, R. *Tetrahedron Lett.* ***2001***, *42*, 9203. For a report of an isolable ozonide, see dos Santos, C.; de Rosso, C.R.S.; Imamura, P.M. *Synth. Commun.* ***1999***, *29*, 1903.

since there are two different aldehydes **18** and two different species **19**, 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.[368] Similar results have been reported for smaller alkenes, for example, 2-pentene, 4-nonene, and even 2-methyl-2-pentene.[369] 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 alkenes give little or no cross-ozonide formation.[370] In general, the less alkylated end of the alkene tends to go to **18** and the other to **19**. Still other evidence[371] for the Criegee mechanism is (*1*) When $Me_2C{=}CMe_2$ was ozonized in the presence of HCHO, the ozonide **23** could be isolated;[372] (*2*) **19** prepared in an entirely different manner (photooxidation of diazo compounds), reacted with aldehydes to give ozonides;[373] and (*3*) cis- and trans-alkenes generally give the same ozonide, which would be expected if they cleave first.[374] However, this was not true for $Me_3CCH{=}CHCMe_3$, where the cis-alkene gave the cis-ozonide (chiefly), and the trans gave the trans.[375] 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.[376]



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[368] Riezebos, G.; Grimmelikhuysen, J.C.; van Dorp, D.A. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 1234; Privett, O.S.; Nickell, E.C. *J. Am. Oil Chem. Soc.* ***1964***, *41*, 72.

[369] Loan, L.D.; Murray, R.W.; Story, P.R. *J. Am. Chem. Soc.* ***1965***, *87*, 737; Lorenz, O.; Parks, C.R. *J. Org. Chem.* ***1965***, *30*, 1976.

[370] Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969***, *34*, 1891.

[371] For further evidence, see Mori, M.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* ***1987***, *109*, 4407; Pierrot, M.; El Idrissi, M.; Santelli, M. *Tetrahedron Lett.* ***1989***, *30*, 461; Wojciechowski, B.J.; Chiang, C.; Kuczkowski, R.L. *J. Org. Chem.* ***1990***, *55*, 1120; Paryzek, Z.; Martynow, J.; Swoboda, W. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 1220; Murray, R.W.; Morgan, M.M. *J. Org. Chem.* ***1991***, *56*, 684, 6123.

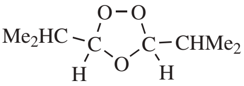
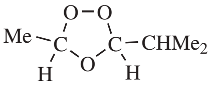
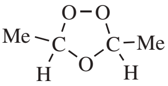
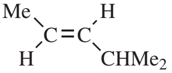
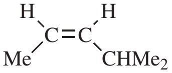
[372] Even ketones can react with **19** to form ozonides, provided they are present in large excess: Criegee, R.; Korber, H. *Chem. Ber.* ***1971***, *104*, 1812.

[373] Murray, R.W.; Suzui, A. *J. Am. Chem. Soc.* ***1973***, *95*, 3343; Higley, D.P.; Murray, R.W. *J. Am. Chem. Soc.* ***1974***, *96*, 3330.

[374] See, for example, Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969***, *34*, 1896.

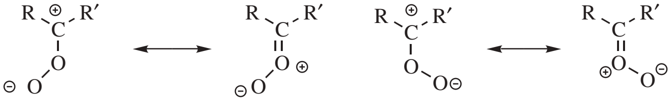
[375] Schröder, G. *Chem. Ber.* ***1962***, *95*, 733; Kolsaker, P. *Acta Chem. Scand. Ser. B* ***1978***, *32*, 557.

[376] Murray, R.W.; Youssefyeh, R.D.; Story, P.R. *J. Am. Chem. Soc.* ***1966***, *88*, 3143, 3655; Story, P.R.; Murray, R.W.; Youssefyeh, R.D. *J. Am. Chem. Soc.* ***1966***, *88*, 3144. Also see, Greenwood, F.L. *J. Am. Chem. Soc.* ***1966***, *88*, 3146; Choe, J.; Srinivasan, M.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1983***, *105*, 4703.

			
	50-50 cis–trans	48-52 cis–trans	38-62 cis–trans
	66-34 cis–trans	49-51 cis–trans	49-51 cis–trans

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-alkenes, since in this mechanism they are completely cleaved.

The above stereochemical results have been explained[377] on the basis of the Criegee mechanism with the following refinements: (*1*) The formation of **17** is stereospecific, as expected from a 1,3-dipolar cycloaddition. (*2*) Once they are formed, **19** and **18** remain attracted to each other, much like an ion pair. (*3*) Intermediate **19** exists in syn and anti forms, which are produced in different amounts and can hold their shapes, at least for a time. This is



syn-**16** *anti*-**16**

plausible if we remember that a C=O canonical form contributes to the structure of **19**. (*4*) The combination of **19** and **18** is also a 1,3-dipolar cycloaddition, so configuration is retained in this step too.[378]

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., **23**) 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 **19** and **18**), and this is what is found.[379] There is evidence that the *anti*-**19** couples much more readily than the *syn*-**19**. [380]

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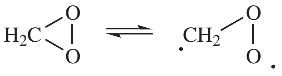
[377] Bauld, N.L.; Thompson, J.A.; Hudson, C.E.; Bailey, P.S. *J. Am. Chem. Soc.* ***1968***, *90*, 1822; Bailey, P.S.; Ferrell, T.M. *J. Am. Chem. Soc.* ***1978***, *100*, 899; Keul, H.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1985***, *50*, 3371.

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

[379] Bishop, C.E.; Denson, D.D.; Story, P.R. *Tetrahedron Lett.* ***1968***, 5739; Fliszár, S.; Carles, J. *J. Am. Chem. Soc.* ***1969***, *91*, 2637; Gillies, C.W.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1972***, *94*, 7609; Higley, D.P.; Murray, R.W. *J. Am. Chem. Soc.* ***1976***, *98*, 4526; Mazur, U.; Kuczkowski, R.L. *J. Org. Chem.* ***1979***, *44*, 3185.

[380] Mile, B.; Morris, G.M. *J. Chem. Soc. Chem. Commun.* ***1978***, 263.

The ozonolysis of ethylene[381] in the liquid phase (without a solvent) was shown to take place by the Criegee mechanism.[382] This reaction has been used to study the structure of the intermediate **19** or **20**. The compound dioxirane (**24**) was identified in the reaction mixture[383] at low temperatures and is probably in equilibrium with the biradical **20** (R = H). Dioxirane has been produced in solution, but it oxidatively cleaves dialkyl ethers (e.g., Et—O—Et) via a chain radical process, [384] so the choice of solvent is important.



24 **20** (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.[385] There is much evidence that the Criegee mechanism operates in the gas phase too, although the products are more complex because of other reactions that also take place.[386]

OS **V**, 489, 493; **VI**, 976; **VII**, 168; **IX**, 314. Also see OS **IV**, 554. For the preparation of ozone, see OS **III**, 673.

19-10 Oxidative Cleavage of Double Bonds and Aromatic Rings

Oxo-de-alkylidene-bisubstitution, and so on.

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

Carbon–carbon double bonds can be cleaved by many oxidizing agents,[387] the most common of which are neutral or acid permanganate and acid dichromate. The

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[381] For a discussion of intermediates in the formation of the ozonide in this reaction, see Samuni, U.; Fraenkel, R.; Haas, Y.; Fajgar, R.; Pola, J. *J. Am. Chem. Soc.* ***1996***, *118*, 3687.

[382] Fong, G.D.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1980***, *102*, 4763.

[383] Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5117. See, however, Ishiguro, K.; Hirano, Y.; Sawaki, Y. *J. Org. Chem.* ***1988***, *53*, 5397.

[384] Ferrer, M.; Sánchez-Baeza, F.; Casas, J.; Messeguer, A. *Tetrahedron Lett.* ***1994***, *35*, 2981.

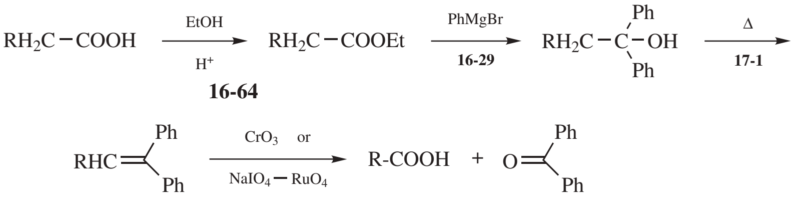
[385] For a review of the mechanisms of reactions of organic compounds with ozone in the gas phase, see Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984***, *84*, 437.

[386] See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984***, *84*, 437, 452–454; Kühne, H.; Forster, M.; Hulliger, J.; Ruprecht, H.; Bauder, A.; Günthard, H. *Helv. Chim. Acta* ***1980***, *63*, 1971; Martinez, R.I.; Herron J.T. *J. Phys. Chem.* ***1988***, *92*, 4644.

[387] For a review of the oxidation of C=C and C=N bonds, see Henry, P.M.; Lange, G.L., in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 965–1098. For a review of oxidative cleavages of C=C double bonds and aromatic rings, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 77–84, 96–98. For reviews with respect to chromium reagents, see Badanyan, Sh.O.; Minasyan, T.T.; Vardapetyan, S.K. *Russ. Chem. Rev.* ***1987***, *56*, 740; Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 59–92. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1634.

products are generally 2 equivalents of ketone, 2 equivalents of carboxylic acid, or 1 equivalent of each, depending on what groups are attached to the alkene. 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. 120).[388] The crown ether coordinates with K^+, permitting the $KMnO_4$ to dissolve in benzene. A mixture of aq. $KMnO_4$ and $NaIO_4$ on sand is also effective.[389] Another reagent frequently used for synthetic purposes is the *Lemieux–von Rudloff reagent*: HIO_4 containing a trace of MnO_4^-.[390] 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.[391] Cyclic alkenes are cleaved to α,ω-diketones, keto-acids or dicarboxylic acids. Cyclic alkenes are cleaved to dialdehydes with $KMnO_4$•$CuSO_4$ in dichloromethane.[392] Hydrogen peroxide on supported heteropolyacid cleaves cyclic alkenes.[393] A combination of $RuCl_3/HIO_5$ oxidatively cleaves cyclic alkenes to dicarboxylic acids.[394]

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 alkene, which generally gives good yields:



Addition of a catalytic amount of OsO_4 to Jones reagent (**19-3**) leads to good yields of the carboxylic acid from simple alkenes.[395] A combination of Oxone® and OsO_4 in DMF cleaves alkenes to carboxylic acids.[396] 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

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[388] Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1972***, *94*, 4024. See also, Lee, D.G.; Chang, V.S. *J. Org. Chem.* ***1978***, *43*, 1532.

[389] Huang, B.; Gupton, J.T.; Hansen, K.C.; Idoux, J.P. *Synth. Commun.* ***1996***, *26*, 165.

[390] Lemieux, R.U.; Rudloff, E. von *Can. J. Chem.* ***1955***, *33*, 1701, 1710; Rudloff, E. von *Can. J. Chem.* ***1955***, *33*, 1714; ***1956***, *34*, 1413; ***1965***, *43*, 1784.

[391] For a review, see Lee, D.G.; van den Engh, M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 186–192. For the use of $NaIO_4$–OsO_4, see Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* ***1989***, 47.

[392] Göksu, S.; Altudda, R.; Sütbeyaz, Y. *Synth. Commun.* ***2000***, *30*, 1615.

[393] Brooks, C.D.; Huang, L.-c.; McCarron, M.; Johnstone, R.A.W. *Chem. Commun.* ***1999***, 37.

[394] Griffith, W.P.; Shoair, A.G.; Suriaatmaja, M. *Synth. Commun.* ***2000***, *30*, 3091.

[395] Henry, J.R.; Weinreb, S.M. *J. Org. Chem.* ***1993***, *58*, 4745.

[396] Travis, B.R.; Narayan, R.S.; Borhan, B. *J. Am. Chem. Soc.* ***2002***, *124*, 3824.

tert-butyl iodoxybenzene,[397] $KMnO_4$ in THF–H_2O,[398] and $NaIO_4$–OsO_4.[399] Electrolysis with $LiClO_4$ in aqueous acetonitrile also cleaves alkenes to give the aldehyde.[400] Enol ethers, $RC(OR'){=}CH_2$, have been cleaved to carboxylic esters, $RC(OR'){=}O$, by atmospheric oxygen.[401]

Cleavage of alkynes is generally rather difficult, but treatment of internal alkynes with an excess of Oxone® with a ruthenium catalyst leads to aliphatic carboxylic acids.[402]

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (**15-29**) or cyclic ester,[403] and then further oxidation as in **19-7**.[404] In line with the electrophilic attack on the alkene, triple bonds are more resistant to oxidation than double bonds. Terminal triple-bond compounds can be cleaved to carboxylic acids ($RC{\equiv}CH \longrightarrow RCOOH$) with thallium(III) nitrate[405] or with [bis(trifluoroacetoxy)iodo]pentafluorobenzene [i.e., $C_6F_5I(OCOCF_3)_2$],[406] 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 co-oxidant, such as $NaIO_4$ or NaOCl (household bleach can be used).[407] Examples[408] are the oxidation of naphthalene to phthalic acid[409] and, even more remarkably, of cyclohexylbenzene to cyclohexanecarboxylic acid[410] (note the contrast with **19-11**). The latter conversion was also accomplished with ozone.[411] Another reagent that oxidizes aromatic rings is air catalyzed by V_2O_5. The oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride by this reagent are

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[397] Ranganathan, S.; Ranganathan, D.; Singh, S.K. *Tetrahedron Lett.* ***1985***, *26*, 4955.

[398] Viski, P.; Szeverényi, Z.; Simándi, L.I. *J. Org. Chem.* ***1986***, *51*, 3213.

[399] Pappo, R.; Allen Jr., D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.* ***1956***, *21*, 478.

[400] Maki, S.; Niwa, H.; Hirano, T. *Synlett* ***1997***, 1385.

[401] Taylor, R. *J. Chem. Res. (S)* ***1987***, 178. For a similar oxidation with RuO4, see Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* ***1985***, *50*, 4980.

[402] Yang, D.; Chen, F.; Dong, Z.-M.; Zhang, D.-W. *J. Org. Chem.* ***2004***, *69*, 2221.

[403] See, for example, Lee, D.G.; Spitzer, U.A. *J. Org. Chem.* ***1976***, *41*, 3644; Lee, D.G.; Chang, V.S.; Helliwell, S. *J. Org. Chem.* ***1976***, *41*, 3644, 3646.

[404] There is evidence that oxidation with Cr(VI) in aqueous acetic acid involves an epoxide intermediate: Roč ek, J.; Drozd, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 6668.

[405] McKillop, A.; Oldenziel, O.H.; Swann, B.P.; Taylor, E.C.; Robey, R.L. *J. Am. Chem. Soc.* ***1973***, *95*, 1296.

[406] Moriarty, R.M.; Penmasta, R.; Awasthi, A.K.; Prakash, I. *J. Org. Chem.* ***1988***, *53*, 6124.

[407] 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 RuO2 back to ruthenium tetroxide.

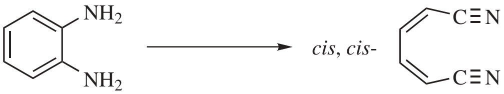
[408] For other examples, see Piatak, D.M.; Herbst, G.; Wicha, J.; Caspi, E. *J. Org. Chem.* ***1969***, *34*, 116; Wolfe, S.; Hasan, S.K.; Campbell, J.R. *Chem. Commun.* ***1970***, 1420; Ayres, D.C.; Hossain, A.M.M. *Chem. Commun.* ***1972***, 428; Nuñez, M.T.; Martín, V.S. *J. Org. Chem.* ***1990***, *55*, 1928.

[409] Spitzer, U.A.; Lee, D.G. *J. Org. Chem.* ***1974***, *39*, 2468.

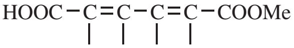
[410] Caputo, J.A.; Fuchs, R. *Tetrahedron Lett.* ***1967***, 4729.

[411] Klein, H.; Steinmetz, A. *Tetrahedron Lett.* ***1975***, 4249. For other reagents that convert an aromatic ring to COOH and leave alkyl groups untouched, see Deno, N.C.; Greigger, B.A.; Messer, L.A.; Meyer, M.D.; Stroud, S.G. *Tetrahedron Lett.* ***1977***, 1703; Liotta, R.; Hoff, W.S. *J. Org. Chem.* ***1980***, *45*, 2887; Chakraborti, A.K.; Ghatak, U.R. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 2605.

important industrial procedures.[412] *o*-Diamines have been oxidized with nickel peroxide, with lead tetraacetate,[413] and with O_2 catalyzed by CuCl:[414]



The last-named reagent also cleaves *o*-dihydroxybenzenes (catechols) to give, in the presence of MeOH, the mono-methylated dicarboxylic acids .[415]



$$\text{HOOC}-\underset{|}{\text{C}}=\underset{|}{\text{C}}-\underset{|}{\text{C}}=\underset{|}{\text{C}}-\text{COOMe}$$

Enamines ($R'_2C{=}NR_2$) are oxidatively cleaved with potassium dichromate in sulfuric acid to the ketone ($R'_2C{=}O$).[416]

OS **II**, 53, 523; **III**, 39, 234, 449; **IV**, 136, 484, 824; **V**, 393; **VI**, 662, 690; **VII**, 397; **VIII**, 377, 490; **IX**, 530. Also see, OS **II**, 551.

19-11 Oxidation of Aromatic Side Chains

Oxo,hydroxy-de-dihydro,methyl-tersubstitution

$$\text{ArR} \xrightarrow{\text{KMnO}_4} \text{ArCOOH}$$

Alkyl chains on aromatic rings can be oxidized to COOH groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate.[417] The method is most often applied to the methyl group, although 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.[418] It is usually difficult to oxidize an R group on a fused aromatic system without cleaving the ring or oxidizing it to a quinone (**19-19**). However, this has been done (e.g., 2-methylnaphthalene was converted to 2-naphthoic acid) with aqueous $Na_2Cr_2O_7$.[419] Aryl methyl groups are oxidized to aryl COOH with NaOCl in acetonitrile,[420] or with NBS in aq. NaOH under photochemical conditions.[421] 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 a phenyl group. In such cases, the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each

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[412] For a review, see Pyatnitskii, Yu.I. *Russ. Chem. Rev.* ***1976***, *45*, 762.

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

[414] Kajimoto, T.; Takahashi, H.; Tsuji, J. *J. Org. Chem.* ***1976***, *41*, 1389.

[415] Tsuji, J.; Takayanag, H.i *Tetrahedron* ***1978***, *34*, 641; Bankston, D. *Org. Synth.* *66*, 180.

[416] Harris, C.E.; Lee, L.Y.; Dorr, H.; Singaram, B. *Tetrahedron Lett.* ***1995***, *36*, 2921.

[417] For many examples, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 105-109; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, Open-Court Pub. Co., La Salle, IL, ***1980***, pp. 43–64. For a review with chromium oxidizing agents, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Publishing Co., La Salle, IL, ***1981***, pp. 23–33.

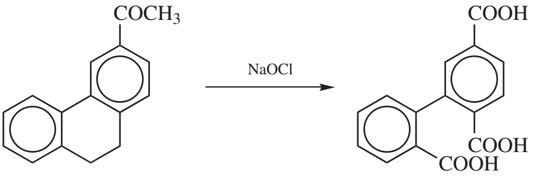
[418] Brandenberger, S.G.; Maas, L.W.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 2146.

[419] Friedman, L.; Fishel, D.L.; Shechter, H. *J. Org. Chem.* ***1965***, *30*, 1453.

[420] Yamazaki, S. *Synth. Commun.* ***1999***, *29*, 2211.

[421] Itoh, A.; Kodama, T.; Hashimoto, S.; Masaki, Y. *Synthesis* ***2003***, 2289.

ring gets one carbon atom, as in the clevvage of the 9,10-bond of dihydrophenanthrenes **25** to **26**.



25 **26**

It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity[422] toward most reagents is $CH_2Ar > CHR_2 > CH_2R > CH_3$.[423] Groups 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 **14-7**, with a hydroperoxide intermediate. With this procedure it is possible to isolate ketones from $ArCH_2R$, and this is often done.[424]

The mechanism has been studied for the closely related reaction: $Ar_2CH_2 + CrO_3 \rightarrow Ar_2C{=}O$.[425] 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. 1706). Just how the radical or the cation goes on to the product is not known.

When the alkyl group is one oxidizable to COOH (**19-11**), cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.[426] 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,[427] but there must be an OH or NH_2 group in the ortho or para position. This is called the *Dakin reaction*.[428] The mechanism may be similar to that of the Baeyer–Villiger reaction (**18-19**):[429]

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

[423] For example, see Foster, G.; Hickinbottom, W.J. *J. Chem. Soc.* ***1960***, 680; Ferguson, L.N.; Wims, A.I. *J. Org. Chem.* ***1960***, *25*, 668.

[424] For a review, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 508–543.

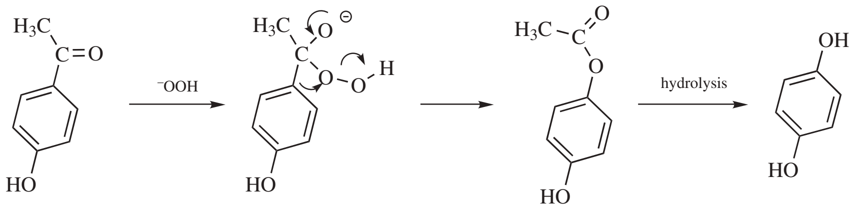
[425] Wiberg, K.B.; Evans, R.J. *Tetrahedron* ***1960***, *8*, 313.

[426] Kaeding, W.W. *J. Org. Chem.* ***1961***, *26*, 3144. For a discussion, see Lee, D.G.; van den Engh, M., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 91–94.

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

[428] See Schubert, W.M.; Kintner, R.R., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 749–752.

[429] For a discussion, see Hocking, M.B.; Bhandari, K.; Shell, B.; Smyth, T.A. *J. Org. Chem.* ***1982***, *47*, 4208.



27

The intermediate **27** has been isolated.[430] 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.[431] The Dakin reaction has been done in ionic liquids.[432]

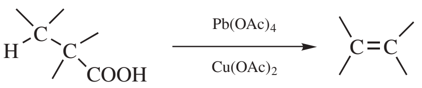
OS **I**, 159, 385, 392, 543; **II**, 135, 428; **III**, 334, 420, 740, 791, 820, 822; **V**, 617, 810. Also see, OS **I**, 149; **III**, 759.

19-12 Oxidative Decarboxylation

Acetoxy-de-carboxy-substitution

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

Hydro-carboxyl-elimination



Carboxylic acids can be decarboxylated[433] 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 **12-40**), and, if α,β hydrogen is present, the alkene formed by elimination of H and COOH, as well as numerous other products arising from rearrangements, internal cyclizations,[434] 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 $Pb(OAc)_4$.[435] In the absence of $Cu(OAc)_2$, primary acids give mostly alkanes (though yields are

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[430] Hocking, M.B.; Ko, M.; Smyth, T.A. *Can. J. Chem.* ***1978***, *56*, 2646.

[431] Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* ***1984***, *49*, 4740.

[432] In bmim PF6, 1-butyl-3-methylimidazolium hexafluorophosphate: Zambrano, J.L.; Dorta, R. *Synlett* ***2003***, 1545.

[433] For reviews, see Serguchev, Yu.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1980***, *49*, 1119; Sheldon, R.A.; Kochi, J.K. *Org. React.* ***1972***, *19*, 279.

[434] For examples, see Moriarty, R.M.; Walsh, H.G.; Gopal, H. *Tetrahedron Lett.* ***1966***, 4363; Davies, D.I.; Waring, C. *J. Chem. Soc. C* ***1968***, 1865, 2337.

[435] Bacha, J.D.; Kochi, J.K. *Tetrahedron* ***1968***, *24*, 2215; Ogibin, Yu.N.; Katzin, M.I.; Nikishin, G.I. *Synthesis* ***1974***, 889.

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,[436] including Co(III), Ag(II), Mn(III), and Ce(IV), have also been used to effect oxidative decarboxylation.[437]

The mechanism with lead tetraacetate is generally accepted to be of the free-radical type.[438] First, there is an interchange of ester groups:

$$\mathrm{Pb(OAc)_4} + \mathrm{RCOOH} \longrightarrow \underset{\mathbf{28}}{\mathrm{Rb(OAc)_3OCOR}} \quad \text{or} \quad \underset{\mathbf{29}}{\mathrm{Pb(OAc)_2(OCOR)_2}}$$

There follows a free-radical chain mechanism (shown for **28** although **29** and other lead esters can behave similarly)

$$\underset{\mathbf{23}}{\mathrm{Pb(OAc)_3OCOR}} \longrightarrow \bullet\,\mathrm{Pb(OAc)_3} + \mathrm{R}\bullet + \mathrm{CO_2}$$

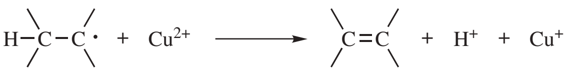
Initiation

$$\mathrm{R}\bullet + \mathrm{Pb(OAc)_3OCOR} \longrightarrow \mathrm{R^+} + \bullet\,\mathrm{Pb(OAc)_2OCOR} + \mathrm{OAc^-}$$

$$\bullet\,\mathrm{Pb(OAc)_2OCOR} \longrightarrow \mathrm{Pb(OAc)_2} + \mathrm{R}\bullet + \mathrm{CO_2}$$

Propagation

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. The R• group can also dimerize to give RR. The effect of Cu^{2+} ions[439] is to oxidize the radicals to alkenes, thus producing good yields of alkenes from primary and secondary substrates. The Cu^{2+} ion has no effect on tertiary radicals, because these are efficiently oxidized to alkenes by lead tetraacetate.



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

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[436] For references, see Trahanovsky, W.S.; Cramer, J.; Brixius, D.W. *J. Am. Chem. Soc.* ***1974***, *96*, 1077; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 99–106. See also, Dessau, R.M.; Heiba, E.I. *J. Org. Chem.* ***1975***, *40*, 3647; Fristad, W.E.; Fry, M.A.; Klang, J.A. *J. Org. Chem.* ***1983***, *48*, 3575; Barton, D.H.R.; Crich, D.; Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* ***1984***, 242; Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* ***1984***, *25*, 3819.

[437] For another method, see Barton, D.H.R.; Bridon, D.; Zard, S.Z. *Tetrahedron* ***1989***, *45*, 2615.

[438] Starnes, Jr., W.H. *J. Am. Chem. Soc.* ***1964***, *86*, 5603; Davies, D.I.; Waring, C. *Chem. Commun.* ***1965***, 263; Kochi, J.K.; Bacha, J.D.; Bethea III, T.W. *J. Am. Chem. Soc.* ***1967***, *89*, 6538; Cantello, B.C.C.; Mellor, J.M.; Scholes, G. *J. Chem. Soc. Perkin Trans. 2*, ***1974***, 348; Beckwith, A.L.J.; Cross, R.T.; Gream, G.E. *Aust. J. Chem.* ***1974***, *27*, 1673, 1693.

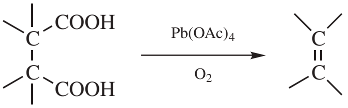
[439] Bacha, J.D.; Kochi, J.K. *J. Org. Chem.* ***1968***, *33*, 83; Kochi, J.K.; Bacha, J.D. *J. Org. Chem.* ***1968***, *33*, 2746; Torssell, K. *Ark. Kemi*, ***1970***, *31*, 401.

In another type of oxidative decarboxylation, arylacetic acids can be oxidized to aldehydes with one less carbon ($ArCH_2COOH \rightarrow ArCHO$) by tetrabutylammonium periodate.[440] Simple aliphatic carboxylic acids were converted to nitriles with one less carbon ($RCH_2COOH \rightarrow RC{\equiv}N$) by treatment with trifluoroacetic anhydride and $NaNO_2$ in F_3CCOOH.[441]

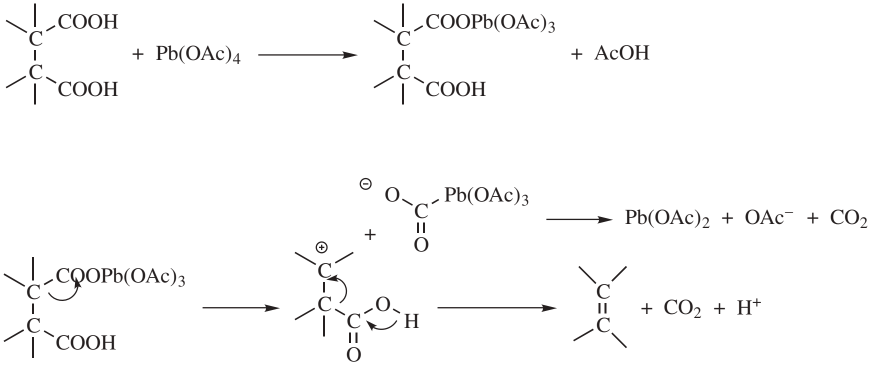
See also, **14-37**.

19-13 Bisdecarboxylation

Dicarboxy-elimination



Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bisdecarboxylated with lead tetraacetate in the presence of O_2.[433] The reaction is of wide scope. The elimination is stereoselective, but not stereospecific (both *meso*- and *dl*-2,3-diphenylsuccinic acid gave *trans*-stilbene);[442] a concerted mechanism is thus unlikely. The following mechanism is not inconsistent with the data:



though a free-radical mechanism seems to hold in some cases. Bis(decarboxylation) of succinic acid derivatives to give alkenes[443] has also been carried out by other methods, including treatment of the corresponding anhydrides with nickel, iron,

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

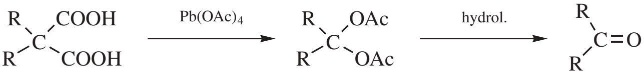
[441] Smushkevich, Yu.I.; Usorov, M.I.; Suvorov, N.N. *J. Org. Chem. USSR* ***1975***, *11*, 653.

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

[443] For a review, see De Lucchi, O.; Modena, G. *Tetrahedron* ***1984***, *40*, 2585, 2591–2608.

or rhodium complexes,[444] by decomposition of the corresponding bis(peroxyesters),[445] and electrolytically.[446]

Compounds containing geminal carboxyl groups (disubstituted malonic acid derivatives) can also be bisdecarboxylated with lead tetraacetate,[447] *gem*-diacetates (acylals) being produced, which are easily hydrolyzable to ketones:[448]



A related reaction involves α-substituted aryl nitriles having a sufficiently acidic α hydrogen, which can be converted to ketones by oxidation with air under phase transfer conditions.[449] The nitrile is added to NaOH in benzene or DMSO containing a catalytic amount of triethylbenzylammonium chloride (TEBA).[450] This reaction could not be applied to aliphatic nitriles, but an indirect method for achieving this conversion is given in **19-60**. 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[451] or by autoxidation in the presence of *t*-BuOK.[452]

C. Reactions Involving Replacement of Hydrogen by Heteroatoms

19-14 Hydroxylation at an Aliphatic Carbon

Hydroxylation or **Hydroxy-de-hydrogenation**

$$R_3CH \xrightarrow[\text{silica gel}]{O_3} R_3COH$$

Compounds containing susceptible C—H bonds can be oxidized to alcohols.[453] Nearly always, the C—H bond involved is tertiary, so the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free-radical attack than primary and secondary bonds and partly because the reagents involved

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[444] Trost, B.M.; Chen, E.N. *Tetrahedron Lett.* ***1971***, 2603.

[445] Cain, E.N.; Vukov, R.; Masamune, S. *Chem. Commun.* ***1969***, 98.

[446] Plieninger, H.; Lehnert, W. *Chem. Ber.* ***1967***, *100*, 2427; Radlick, P.; Klem, R.; Spurlock, S.; Sims, J.J.; van Tamelen, E.E.; Whitesides, T. *Tetrahedron Lett.* ***1968***, 5117; Westberg, H.H.; Dauben Jr., H.J. *Tetrahedron Lett.* ***1968***, 5123. For additional references, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 253–254.

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

[448] Tufariello, J.J.; Kissel, W.J. *Tetrahedron Lett.* ***1966***, 6145.

[449] For other methods of achieving this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1260.

[450] Masuyama, Y.; Ueno, Y.; Okawara, M. *Chem. Lett.* ***1977***, 1439; Donetti, A.; Boniardi, O.; Ezhaya, A. *Synthesis* ***1980***, 1009; Kulp, S.S.; McGee, M.J. *J. Org. Chem.* ***1983***, *48*, 4097.

[451] Büchi, G.; Liang, P.H.; Wüest, H. *Tetrahedron Lett.* ***1978***, 2763.

[452] Chuang, T.; Yang, C.; Chang, C.; Fang, J. *Synlett* ***1990***, 733.

[453] For reviews, see Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***, pp. 7–11; Lee, D.G., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 2–6. For a monograph on all types of alkane activation, see Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***.

would oxidize primary and secondary alcohols further. In the best method, the reagent is ozone and the substrate is absorbed on silica gel.[454] Yields as high as 99% have been obtained by this method. Other reagents are chromic acid,[455] potassium hydrogen persulfate ($KHSO_5$),[456] ruthenium tetroxide (RuO_4),[457] 2,6-dichloropyridine *N*-oxide with a ruthenium catalyst,[458] thallium acetate,[459] sodium chlorite ($NaClO_2$) with a metalloporphyrin catalyst,[460] and certain peroxybenzoic acids.[461] Alkanes and cycloalkanes have been oxidized at secondary positions, to a mixture of alcohols and trifluoroacetates, by 30% aq. H_2O_2 in trifluoroacetic acid.[462] This reagent does not oxidize the alcohols further and ketones are not found. As in the case of chlorination with *N*-haloamines and sulfuric acid (see **14-1**), the ω - 1 position is the most favored. Another reagent[463] that oxidizes secondary positions is iodosylbenzene, catalyzed by Fe^{III}–porphyrin catalysts.[464] Use of an optically active Fe^{III}–porphyrin gave enantioselective hydroxylation, with moderate ee.[465]

When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $R_3C\bullet$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give R_3COCr^{4+}, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.[466] The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.[467]

Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position (see also, **19-17**).[468] This reaction also produces conjugated aldehydes in some cases.[469] Allylic rearrangements are common. There is

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[454] Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T.H. *J. Org. Chem.* ***1975***, *40*, 2141; *Org. Synth.* ***VI***, 43; Keinan, E.; Mazur, Y. *Synthesis* ***1976***, 523; McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401, see pp. 418–419.

[455] For a review, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 8–23.

[456] De Poorter, B.; Ricci, M.; Meunier, B. *Tetrahedron Lett.* ***1985***, *26*, 4459.

[457] Tenaglia, A.; Terranova, E.; Waegell, B. *Tetrahedron Lett.* ***1989***, *30*, 5271; Bakke, J.M.; Braenden, J.E. *Acta Chem. Scand.* ***1991***, *45*, 418.

[458] Ohtake, H.; Higuchi, T.; Hirobe, M. *J. Am. Chem. Soc.* ***1992***, *114*, 10660.

[459] Lee, J.C.; Park, C.; Choi, Y. *Synth. Commun.* ***1997***, *27*, 4079.

[460] Collman, J.P.; Tanaka, H.; Hembre, R.T.; Brauman, J.I. *J. Am. Chem. Soc.* ***1990***, *112*, 3689.

[461] Schneider, H.; Müller, W. *Angew. Chem. Int. Ed.* ***1982***, *21*, 146; *J. Org. Chem.* ***1985***, *50*, 4609; Takaishi, N.; Fujikura, Y.; Inamoto, Y. *Synthesis* ***1983***, 293; Tori, M.; Sono, M.; Asakawa, Y. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2669. See also, Querci, C.; Ricci, M. *Tetrahedron Lett.* ***1990***, *31*, 1779.

[462] Deno, N.C.; Jedziniak, E.J.; Messer, L.A.; Meyer, M.D.; Stroud, S.G.; Tomezsko, E.S. *Tetrahedron* ***1977***, *33*, 2503.

[463] For other procedures, see Sharma, S.N.; Sonawane, H.R.; Dev, S. *Tetrahedron* ***1985***, *41*, 2483; Nam, W.; Valentine, J.S. *New J. Chem.* ***1989***, *13*, 677.

[464] See Groves, J.T.; Nemo, T.E. *J. Am. Chem. Soc.* ***1983***, *105*, 6243.

[465] Groves, J.T.; Viski, P. *J. Org. Chem.* ***1990***, *55*, 3628.

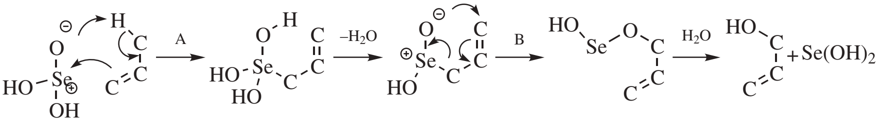
[466] Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964***, *20*, 1151.

[467] Wiberg, K.B.; Fox, A.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3487; Brauman, J.I.; Pandell, A.J. *J. Am. Chem. Soc.* ***1970***, *92*, 329; Stewart, R.; Spitzer, U.A. *Can. J. Chem.* ***1978***, *56*, 1273.

[468] For reviews, see Rabjohn, N. *Org. React.* ***1976***, *24*, 261; Jerussi, R.A. *Sel. Org. Transform.* ***1970***, *1*, 301; Trachtenberg, E.N., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 123–153.

[469] Singh, J.; Sharma, M.; Kad, G.L.; Chhabra, B.R. *J. Chem. Res. (S)* ***1997***, 264.

evidence that the mechanism does not involve free radicals, but includes two pericyclic steps (A and B):[470]



The step marked A is similar to the ene synthesis (**15-23**). The step marked B is a [2,3]-sigmatropic rearrangement (see **18-35**). The reaction can also be accomplished with *tert*-butyl hydroperoxide, if SeO_2 is present in catalytic amounts (the *Sharpless method*).[471] The SeO_2 is the actual reagent; the peroxide reoxidizes the $Se(OH)_2$.[472] This method makes work-up easier, but gives significant amounts of side products when the double bond is in a ring.[473] Alkynes generally give α,α'-dihydroxylation.[474]

Ketones and carboxylic esters can be α hydroxylated by treatment of their enolate forms (prepared by adding the ketone or ester to LDA) with a molybdenum peroxide reagent (MoO_5–pyridine–HMPA) in THF–hexane at −70°C.[475] The reaction of ketones with Ti(O*i*Pr)$_4$, diethyl tartrate and *tert*-butylhydroperoxide gave the α-hydroxy ketone with good enantioselectively, albeit in low yield.[476] The enolate forms of amides and esters[477] and the enamine derivatives of ketones[478] can similarly be converted to their α hydroxy derivatives by reaction with molecular oxygen. The MoO_5 method can also be applied to certain nitriles.[479] Ketones have also been α hydroxylated by treating the corresponding silyl enol ethers

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[470] Arigoni, D.; Vasella, A.; Sharpless, K.B.; Jensen, H.P. *J. Am. Chem. Soc.* ***1973***, *95*, 7917; Woggon, W.; Ruther, F.; Egli, H. *J. Chem. Soc. Chem. Commun.* ***1980***, 706. For other mechanistic proposals, see Schaefer, J.P.; Horvath, B.; Klein, H.P. *J. Org. Chem.* ***1968***, *33*, 2647; Trachtenberg, E.N.; Nelson, C.H.; Carver, J.R. *J. Org. Chem.* ***1970***, *35*, 1653; Bhalerao, U.T.; Rapoport, H. *J. Am. Chem. Soc.* ***1971***, *93*, 4835; Stephenson, L.M.; Speth, D.R. *J. Org. Chem.* ***1979***, *44*, 4683.

[471] Umbreit, M.A.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977***, *99*, 5526. See also, Uemura, S.; Fukuzawa, S.; Toshimitsu, A.; Okano, M. *Tetrahedron Lett.* ***1982***, *23*, 87; Singh, J.; Sabharwal, A.; Sayal, P.K.; Chhabra, B.R. *Chem. Ind. (London)* ***1989***, 533.

[472] For the use of the peroxide with O2 instead of SeO2, see Sabol, M.R.; Wiglesworth, C.; Watt, D.S. *Synth. Commun.* ***1988***, *18*, 1.

[473] Warpehoski, M.A.; Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1982***, *47*, 2897.

[474] Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 4202.

[475] Vedejs, E.; Telschow, J.E. *J. Org. Chem.* ***1976***, *41*, 740; Vedejs, E.; Larsen, S. *Org. Synth.* ***VII***, 277; Gamboni, R.; Tamm, C. *Tetrahedron Lett.* ***1986***, *27*, 3999; *Helv. Chim. Acta* ***1986***, *69*, 615. See also, Anderson, J.C.; Smith, S.C. *Synlett* ***1990***, 107; Hara, O.; Takizawa, J.-i.; Yamatake, T.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* ***1999***, *40*, 7787.

[476] Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron* ***2002***, *58*, 7321.

[477] Wasserman, H.H.; Lipshutz, B.H. *Tetrahedron Lett.* ***1975***, 1731. For another method, see Pohmakotr, M.; Winotai, C. *Synth. Commun.* ***1988***, *18*, 2141.

[478] Cuvigny, T.; Valette, G.; Larcheveque, M.; Normant, H. *J. Organomet. Chem.* ***1978***, *155*, 147.

[479] Rubottom, G.M.; Gruber, J.M. *J. Org. Chem.* ***1978***, *43*, 1599; Hassner, A.; Reuss, R.H.; Pinnick, H.W. *J. Org. Chem.* ***1975***, *40*, 3427; Andriamialisoa, R.Z.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* ***1985***, *26*, 3563; Rubottom, G.M.; Gruber, J.M.; Juve, Jr., H.D.; Charleson, D.A. *Org. Synth.* ***VII***, 282. See also, Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 3323.

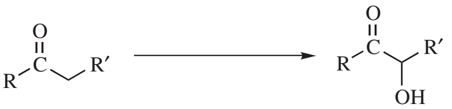
with *m*-chloroperoxybenzoic acid,[179] or with certain other oxidizing agents.[480] When the silyl enol ethers are treated with iodosobenzene in the presence of trimethylsilyl trifluoromethyl sulfonate, the product is the α-keto triflate.[481]

Tetrahydrofuran was converted to the hemiacetal 2-hydroxytetrahydrofuran (which was relatively stable under the conditions used) by electrolysis in water.[482]

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

19-15 Oxidation of Methylene to OH, O_2CR, or OR

Hydroxy (or alkoxy) -de-dihydro-bisubstitution



Methyl or methylene groups α to a carbonyl can be oxidized to give α-hydroxy ketones, aldehydes, or carboxylic acid derivatives. Ketones can be α hydroxylated in good yields, without conversion to the enolates, by treatment with the hypervalent iodine reagents[483] *o*-iodosobenzoic acid[484] or phenyliodoso acetate, $PhI(OAc)_2$, in methanolic NaOH.[485] The latter reagent has also been used on carboxylic esters.[486] Dioxygen (O_2) and a chiral phase-transfer catalyst gave enantioselective α-hydroxylation of ketones, if the α position was tertiary.[487] Dimethyl dioxirane is quite effective for hydroxylation of 1,3-dicarbonyl compounds,[488] and O_2 with a manganese catalyst also gives hydroxylation of such compounds.[489] Oxygen with a cerium catalyst α-hydroxylates β-keto esters.[490] Ceric ammonium nitrate has been used to hydroxylate C-2 of dibenzyl malonate.[491] Methyl ketones (RCOMe) react with ammonium peroxydisulfate, $(NH_4)_2S_2O_8$, and a catalytic amount of diphenyl diselenide in MeOH to give α-keto acetals, $RCOCH(OMe_2)$.[492]

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[480] McCormick, J.P.; Tomasik, W.; Johnson, M.W. *Tetrahedron Lett.* ***1981***, *22*, 607; Moriarty, R.M.; Prakash, O.; Duncan, M.P. *Synthesis* ***1985***, 943; Iwata, C.; Takemoto, Y.; Nakamura, A.; Imanishi, T. *Tetrahedron Lett.* ***1985***, *26*, 3227; Davis, F.A.; Sheppard, A.C. *J. Org. Chem.* ***1987***, *52*, 954; Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* ***1991***, 281.

[481] Moriarty, R.M.; Epa, W.R.; Penmasta, R.; Awasthi, A.K. *Tetrahedron Lett.* ***1989***, *30*, 667.

[482] Wermeckes, B.; Beck, F.; Schulz, H. *Tetrahedron* ***1987***, *43*, 577.

[483] For a review, see Moriarty, R.M.; Prakash, O. *Acc. Chem. Res.* ***1986***, *19*, 244. Also see, Reddy, D.R.; Thornton, E.R. *J. Chem. Soc. Chem. Commun.* ***1992***, 172.

[484] Moriarty, R.M.; Hou, K. *Tetrahedron Lett.* ***1984***, *25*, 691; Moriarty, R.M.; Hou, K.; Prakash, O.; Arora, S.K. *Org. Synth.* ***VII***, 263.

[485] Moriarty, R.M.; Hu, H.; Gupta, S.C. *Tetrahedron Lett.* ***1981***, *22*, 1283. See Moriarty, R.M.; Berglund, B.A.; Penmasta, R. *Tetrahedron Lett.* ***1992***, *33*, 6065 for reactions with $PhI(O_2CCF_3)_2$.

[486] Moriarty, R.M.; Hu, H. *Tetrahedron Lett.* ***1981***, *22*, 2747.

[487] Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* ***1988***, *29*, 2835.

[488] Adam, W.; Smerz, A.K. *Tetrahedron* ***1996***, *52*, 5799. See Hull, L.A.; Budhai, L. *Tetrahedron Lett.* ***1993***, *34*, 5039 for a discussion of the thermal decomposition of dimethyl dioxirane. See Murray, R.W.; Singh, M.; Jeyaraman, R. *J. Am. Chem. Soc.* ***1992***, *114*, 1346 for the preparation of new dioxiranes.

[489] Christoffers, J. *J. Org. Chem.* ***1999***, *64*, 7668.

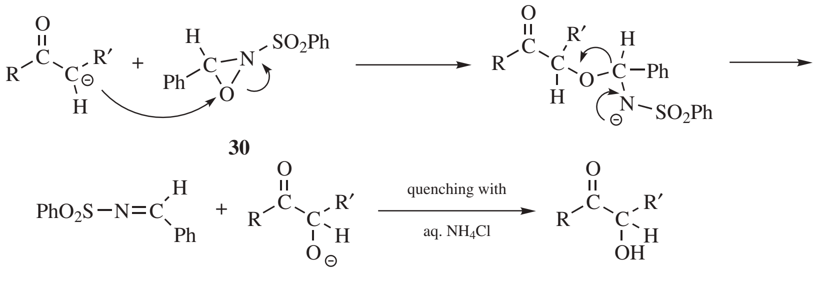
[490] Christoffers, J.; Werner, T. *Synlett* ***2002***, 119.

[491] Nair, V.; Nair, L.G.; Mathew, J. *Tetrahedron Lett.* ***1998***, *39*, 2801.

[492] Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *J. Org. Chem.* ***1990***, *55*, 4523.

α-Acetoxylation of ketones with concurrent α-arylation occurs when ketones react with $Mn(OAc)_3$ in benzene.[493] α-Acetoxylation of ketones can occur under similar conditions without arylation.[494] α-Methyl ketones are converted to the α-acetoxy derivative under the same conditions.[495] Thallium (III) triflate converts acetophenone to α-formyloxy acetophenone.[496] α-Tosyloxy ketones are generated from acetophenone derivatives using PhI(OH)OTs.[497]

A different method for the conversion of ketones to α-hydroxy ketones consists of treating the enolate anion with a 2-sulfonyloxaziridine (e.g., **30**).[498] This is not a free-radical process; the following mechanism is likely:



The method is also successful for carboxylic esters[351],[499] and *N,N*-disubstituted amides,[500] and can be made enantioselective by the use of a chiral oxaziridine.[501] Dimethyldioxirane also oxidizes ketones (through their enolate forms) to α-hydroxy ketones.[502] Titanium enolates can be oxidized with *tert*-butyl hydroperoxide [503] or with dimethyl dioxirane[504] and hydrolyzed with aqueous ammonium fluoride to give the α-hydroxy ketone. Ketones are converted to the α-oxamino derivative (O=C–CH$_2$- → O=C–CHONHPh) with excellent enantioselectivity using

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[493] Tanyeli, C.; Özdemïrhan, D.; Sezen, B. *Tetrahedron* ***2002***, *58*, 9983.

[494] Tanyeli, C.; Tosun, A.; Turkut, E.; Sezen, B. *Tetrahedron* ***2003***, *59*, 1055; Demir, A.S.; Reis, Ö.; Igdir, A.C. *Tetrahedron* ***2004***, *60*, 3427.

[495] Tanyeli, C.; Iyigün,. *Tetrahedron* ***2003***, *59*, 7135.

[496] Lee, J.C.; Jin, Y.S.; Choi, J.-H. *Chem. Commun.* ***2001***, 956.

[497] Nabana, T.; Togo, H. *J. Org. Chem.* ***2002***, *67*, 4362.

[498] Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.* ***1984***, *49*, 3241.

[499] For formation of α-benzyloxy lactones, see Brodsky, B.H.; DuBois, J. *Org. Lett.* ***2004***, *6*, 2619.

[500] Davis, F.A.; Vishwakarma, L.C. *Tetrahedron Lett.* ***1985***, *26*, 3539.

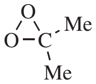
[501] Evans, D.A.; Morrissey, M.M.; Dorow, R.L. *J. Am. Chem. Soc.* ***1985***, *107*, 4346; Enders, D.; Bhushan, V. *Tetrahedron Lett.* ***1988***, *29*, 2437; Davis, F.A.; Sheppard, A.C.; Chen, B.; Haque, M.S. *J. Am. Chem. Soc.* ***1990***, *112*, 6679; Davis, F.A.; Weismiller, M.C. *J. Org. Chem.* ***1990***, *55*, 3715.

[502] Guertin, K.R.; Chan, T.H. *Tetrahedron Lett.* ***1991***, *32*, 715.

[503] Schulz, M.; Kluge, R.; Schüßler, M.; Hoffmann, F. *Tetrahedron* ***1995***, *51*, 3175.

[504] Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* ***1994***, *59*, 2358.

PhN=O and L-proline[505] or (S)-proline.[506] Aldehydes undergo a similar oxidation.[507] α-Lithio sulfones have been hydroxylated with $Me_3SiOO\textit{t}$-Bu.[508]



Dimethyldioxirane

α-Hydroxyketones can be generated from silyl enol ethers with a catalytic amount of $MeReO_3$ and H_2O_2.[509] Silyl ketene ethers are converted to α-hydroxy esters with H_2O_2 and methyl trioxorhenium.[510] The α′-position of α,β-unsaturated ketones can be selectively oxidized.[511] *N*-Acyl amines are converted to the α-hydroxy derivative with PhIO and a manganese–salen catalyst.[512] Note that homoallylic-type oxidation occurs when an α,α-dimethyl oxime ether is treated with $PhI(OAc)_2$ and a palladium catalyst in acetic acid–acetic anhydride, converting one of the methyl groups to an acetoxymethyl.[513]

Simple alkanes can be converted to esters with dialkyloxiranes. Cyclic alkanes are oxidized to alcohols with dimethyl dioxirane.[514] Cyclohexane was converted to cyclohexyl trifluoroacetate with di(trifluoromethyl) dioxirane and trifluoroacetic anhydride[515] and also with $RuCl_3/MeCO_3H/CF_3CO_2H$.[516] Dimethyl dioxirane converts alkanes to alcohols in some cases.[517] Adamantane is converted to adamantyl alcohol with DDQ (p. 1710) and triflic acid.[518] The mechanism of oxygen insertion into alkanes has been examined.[519]

Benzylic methylene groups are more readily oxidized to benzylic alcohols when compared to simple alkanes. Typical reagents include manganese–salen and PhIO[520] or peroxides.[521] α-Hydroxy ethers are also generated by reaction of this regents with ethers.[522] *N*-Benzyl phthalimide reacts with NBS, NaOAc, and acetic

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acid to give *N*-(α-acetoxybenzyl)phthalimide.[523] Methanesulfonic acid and CuO converts ketones to α-mesyloxy (—OMs) ketones[524] and PhI(OH)OTs converts ketones to α-tosyloxy (—OTs) ketones.[525] Aryl methyl carbinols ArCH(OH)Me react with polymer-bound hypervalent iodine complexes, (polymer)–I(OH)OTs, to give a homobenzylic tosylate, $ArCH(OH)CH_2OTs$.[526] Similar oxidation to an acetoxy benzyl derivative was accomplished with $PhI(OAc)_2$ in acetic acid with a palladium catalyst,[527] and with PhI(OH)OTs in aq. DMSO.[528] With minimal water, cerium (IV) triflate converts benzylic arenes to benzylic alcohols, although the major product is the ketone when >15% of water is present.[529]

Allylic hydroxylation[530] with selenium dioxide often gives aldehydes (**19-17**), but in the presence of acetic anhydride and oxygen, SeO_2 converts alkenes to homoallylic acetates as the major product, C=C—C—C → C=C—C—C—OAc.[531] Allylic benzyloxylation occurs when an alkene is treated with *t*-BuOOCOPh and a Cu—Na zeolite,[532] a copper catalyst,[533] or with a chiral copper catalyst to give modest enantioselectivity.[534] Allylic methylene groups can be converted to ester (—CH—OCOR) derivatives in a similar manner using copper triflate.[535] Cupric acetate has also been used,[536] as well as Cu_2O.[537] Acyl peroxides have been used as well.[538] α-Acetoxylation of allylic alkenes can proceed with allylic rearrangement.[539]

Hydroxylation can be accomplished using enzymatic systems. In the presence of *Bacillus megaterium* and oxygen, cyclohexane is converted to cyclohexanol.[540] Allylic oxidation to an allylic alcohol was accomplished with cultured cells of *Gossypium hirsutum*.[541] Benzylic arenes are converted to the corresponding α-hydroxy compound by treatment with the enzymes of *Bacillus megaterium*, with

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modest enantioselectivity.[542] Cyclic amines react with *Pseudomonas oleovorans* GPol to give hydroxy amines; *N*-benzylpyrrolidine is converted to 3-hydroxy *N*-benzylpyrrolidine.[543] *Sphingomonas* sp. HXN-200 gives similar results.[544] In a similar manner, lactams are converted to the corresponding 3-hydroxy lactam with *sphingomonas* sp. HXN-200.[545] *N*-Benzyl piperidine is converted to the 4-hydroxy derivative under the same conditions. [546] The reaction of tetradecanoic acid with the α-oxidase from *Pisum sativum*, in the presence of molecular oxygen, gives 2(*R*)-hydroxytetradecanoic acid with high asymmetric induction.[547]

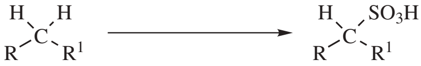
19-16 Oxidation of Methylene to Heteroatom Functional Groups Other Than Oxygen or Carbonyl

Amino (or amido) -de-dihydro-bisubstitution

α-Amination or amidation of a CH unit is possible in some cases. Cyclic alkanes are converted to the *N*-alkyl *N*-tosylamine with PhI=NTs and a copper complex.[548] Benzylic CH, such as in ethylbenzene, is oxidized with $PhI(OAc)_2$ in the presence of $TsNH_2$ and a fluorinated manganese porphyrin to give the corresponding *N*-tosylamine, PhCHMe(NHTs).[549] Alkenes with an allylic CH react with PhI=NTs and a ruthenium catalysts to give an allylic *N*-tosylamine.[550] When an α-keto ester reacts with DEAD (diethyl azodicarboxylate) and a chiral copper complex, an α- carbamate is formed, $RCH(NHCO_2Et)C(=O)CO_2Et$, with modest enantioselectivity.[551]

Similar reactions are possible, in some cases, to produce sulfur containing compounds.

Sulfo-de-dihydro-bisubstitution



Cyclic alkanes are converted to the corresponding alkylsulfonic acid with SO_2/O_2 and a vanadium catalyst.[552]

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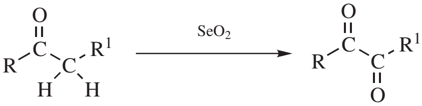
19-17 Oxidation of Methylene to Carbonyl

Oxo-de-dihydro-bisubstitution



Methyl or methylene groups α to a carbonyl can be oxidized with selenium dioxide to give, respectively, α-keto aldehydes (see **19-18**) and α-diketones.[553] The reaction can also be carried out a to an aromatic ring or to a double bond, although in the latter case, hydroxylation (see **19-14**) is the more common result. Selenium dioxide, SeO_2, is the reagent most often used, but the reaction has also been carried out with N_2O_3 and other oxidizing agents,[554] including hypervalent iodine compounds.[555] Sodium nitrite/HCl oxidizes cyclic ketones to the diketone.[556] Substrates most easily oxidized contain two aryl groups on CH_2, and these substrates can be oxidized with many oxidizing agents (see **19-11**). The benzylic position of arenes have been oxidized to alkyl aryl ketones with several oxidizing agents, including CrO_3–acetic acid,[557] the Jones reagent,[558] CrO_3 on silica,[559] pyridinium chlorochromate,[560] DDQ,[561] CrO_2Cl_2 with ultrasound,[562] $KMnO_4$ supported on MnO_2,[563] $KMnO_4$ on alumina with microwave irradiation[564] or on Montmorillonite K10 with either ultrasound or microwave irradiation,[565] $KMnO_4/CuSO_4$ neat[566] or with ultrasound,[567] $NaBrO_3/CeO_2$,[568] manganese–salen/PhIO,[569] *tert*-butylhydroperoxide and a ruthenium catalyst,[570] $Ru(OH)_x$–Al_2O_3 and O_2,[571] hydrogen peroxide with a copper catalyst,[572] as well as with SeO_2. The combination of O_2 and

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mcpba oxidizes benzylic arenes to aryl ketones.[573] Note that benzyl methyl ether is oxidized to methyl benzoate with $KMnO_4$ in the presence of benzyltriethylammonium chloride.[574]

Alkenes of the form C=C—CH_2 (an allylic position) have been oxidized to α,β-unsaturated ketones[575] by sodium dichromate in HOAc—Ac_2O, by *t*-BuOOH and chromium compounds,[576] *t*-BuOOH and a palladium catalyst,[577] or a rhodium catalyst,[578] as well as electrolytically.[579] Oxygen, $MeSO_3H$ a palladium catalysts and a molybdobanadophosphate catalyst convert cyclic alkenes to saturated cyclic ketones.[580] Thallium(III) nitrate in aqueous acetic acid converts allylic alkenes to the corresponding saturated ketone, even in the presence of a primary alcohol elsewhere in the molecule.[581] The propargylic position of internal alkynes are oxidized to give propargylic ketones with an iron catalyst,[582] or with O_2/*t*-BuOOH in the presence of $CuCl_2 \bullet H_2O$.[583]

Cyclic amines are oxidized to lactams using a mixture of $RuCl_3$ and $NaIO_4$.[584] Lactams are also formed using $KMnO_4$ with benzyltriethylammonium chloride.[585] Tertiary amines are converted to amides[586] and cyclic tertiary amines can be converted to lactams by oxidation with Hg^{II}–EDTA complex in basic solution.[587] Lactams, which need not be *N*-substituted, can be converted to cyclic imides by oxidation with a hydroperoxide or peroxyacid and an Mn(II) or Mn(III) salt.[588] Lactams are oxidized to cyclic imides with oxygen and $Co(OAc)_2$ in the presence *N*-hydroxysuccinimide.[589]

Ethers in which at least one group is primary alkyl can be oxidized to the corresponding carboxylic esters in high yields with ruthenium tetroxide.[590] Molecular

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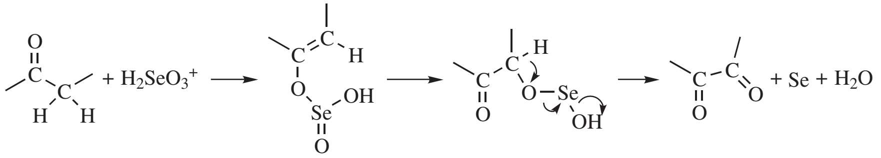
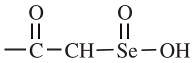
oxygen with a binuclear copperII complex[591] or $PdCl_2/CuCl_2/CO$[592] also converts ethers to esters. In a variation, benzyl *tert*-butyl ethers are oxidized to benzaldehyde derivatives with NO and *N*-hydroxysuccinimide.[593] Cyclic ethers are oxidized to lactones.[594] Cyclic ethers are oxidized to lactones with CrO_3/Me_3SiONO_2.[595] Lactones are also formed from cyclic ethers with $NaBrO_3$–$KHSO_4$ in water.[596]The reaction has also been accomplished with CrO_3 in sulfuric acid,[597] and with benzyltriethylammonium permanganate.[598]

Two mechanisms have been suggested for the reaction with SeO_2. One of these involves a selenate ester of the enol:[599]



In the other proposed mechanism,[600] the principal intermediate is α β-ketoseleninic acid



$$-\overset{\overset{O}{\|}}{C}-CH-\overset{\overset{O}{\|}}{Se}-OH$$

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[62] (see **19-2**). In a typical example, the keto ester **31** was irradiated to give the hydroxy lactone **32**, which was dehydrated to **33**. Ozonolysis of **33** gave the diketo ester

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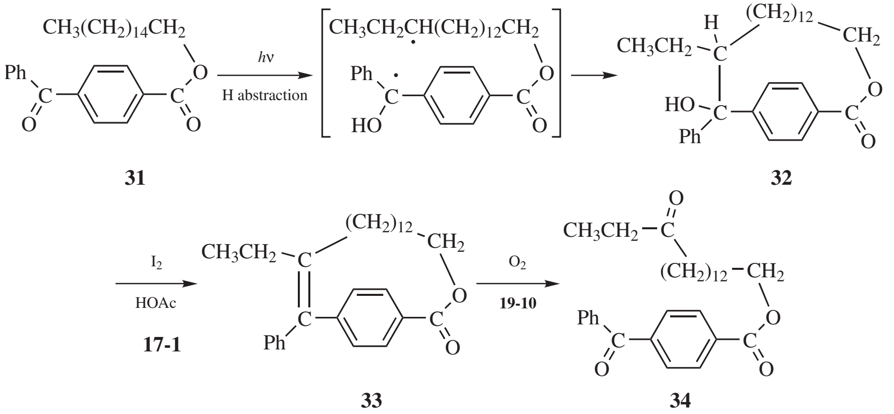
[599] Corey, E.J.; Schaefer, J.P. *J. Am. Chem. Soc.* ***1960***, *82*, 918.

[600] Sharpless, K.B.; Gordon, K.M. *J. Am. Chem. Soc.* ***1976***, *98*, 300.



31 32 33 34

34, in which the C-14 CH_2 group of **31** has been oxidized to a C=O group.[601] The reaction was not completely regioselective: **34** comprised ~ 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.[602] In the method so far described, the reaction takes place because one portion of a molecule (the benzophenone moiety) abstracts hydrogen from another portion of the same molecule, that is, 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.[603]

Other remote oxidations[604] 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 $KMnO_4$,[605] and conversion of alkyl ketones, $RCO(CH_2)_3R'$, to 1,3- and 1,4-diketones with $Na_2S_2O_8$ and $FeSO_4$.[606] 2-Octanol was oxidized to give 2-propyl-5-methyl γ-butyrolactone with lead tetraacetate in a CO atmosphere.[607]

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[601] Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M.L. *J. Am. Chem. Soc.* ***1978***, *100*, 1213.

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

[603] Breslow, R.; Scholl, P.C. *J. Am. Chem. Soc.* ***1971***, *93*, 2331. See also, Breslow, R.; Heyer, D. *Tetrahedron Lett.* ***1983***, *24*, 5039.

[604] See also Beckwith, A.L.J.; Duong, T. *J. Chem. Soc. Chem. Commun.* ***1978***, 413.

[605] Mitani, M.; Tamada, M.; Uehara, S.; Koyama, K. *Tetrahedron Lett.* ***1984***, *25*, 2805. For an alternative photochemical procedure, see Negele, S.; Wieser, K.; Severin, T. *J. Org. Chem.* ***1998***, *63*, 1138.

[606] Nikishin, G.I.; Troyansky, E.I.; Lazareva, M.I. *Tetrahedron Lett.* ***1984***, *25*, 4987.

[607] Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* ***1998***, *120*, 8692. Also see, Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* ***1994***, *116*, 5473.

It is possible to perform the conversion $CH_2 \rightarrow C{=}O$ on an alkane, with no functional groups at all, although 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). Hydrogen peroxide and trifluoroacetic acid has also been used for oxidation of alkanes.[608] With this method, cyclohexane was converted with 72% efficiency to give 95% cyclohexanone and 5% cyclohexanol.[609] This was also accomplished with $BaRu(O)_2(OH)_3$.[610] The same type of conversion, with lower yields (20–30%), has been achieved with the *Gif system*.[611] There are several variations. One consists of pyridine–acetic acid, with H_2O_2 as oxidizing agent and tris(picolinato)iron(III) as catalyst.[612] Other Gif systems use O_2 as oxidizing agent and zinc as a reductant.[613] The selectivity of the Gif systems toward alkyl carbons is $CH_2 > CH \geq CH_3$, which is unusual, and shows that a simple free-radical mechanism (see p. 942) is not involved.[614] 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 **19-14**; **19-15**).[615] Simple unfunctionalized alkanes are oxidized to esters when treated with $CBr_4/2\ AlBr_3$ and CO, but in very low yield.[616] Cyclic alkanes are oxidized to a mixture of the alcohol and the ketone with $PhI(OAc)_2$ and a manganese complex in an ionic liquid.[617] Oxidation of cyclic alkanes to cyclic ketones was accomplished using a ruthenium catalyst.[618]

OS **I**, 266; **II**, 509; **III**, 1, 420, 438; **IV**, 189, 229, 579; **VI**, 48; **IX**, 396. Also see, OS **IV**, 23.

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[608] Camaioni, D.M.; Bays, J.T.; Shaw, W.J.; Linehan, J.C.; Birnbaum, J.C. *J. Org. Chem.* ***2001***, *66*, 789.

[609] Sheu, C.; Richert, S.A.; Cofré, P.; Ross Jr., B.; Sobkowiak, A.; Sawyer, D.T.; Kanofsky, J.R. *J. Am. Chem. Soc.* ***1990***, *112*, 1936. See also, Sheu, C.; Sobkowiak, A.; Jeon, S.; Sawyer, D.T. *J. Am. Chem. Soc.* ***1990***, *112*, 879; Tung, H.; Sawyer, D.T. *J. Am. Chem. Soc.* ***1990***, *112*, 8214.

[610] Lau, T.-C.; Mak, C.-K. *J. Chem. Soc. Chem. Commun.* ***1993***, 766.

[611] Named for Gif-sur-Yvette, France, where it was discovered. See Schuchardt, U.; Jannini, M.J.D.M.; Richens, D.T.; Guerreiro, M.C.; Spinacé, E.V. *Tetrahedron* ***2001***, *57*, 2685.

[612] About-Jaudet, E.; Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.* ***1990***, *31*, 1657. Also see, Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F. *Tetrahedron Lett.* ***1994***, *35*, 3759; Barton, D.H.R.; Bévière, S.D.; Chavasiri, W.; Doller, D.; Hu, B. *Tetrahedron Lett.* ***1992***, *33*, 5473. For a review of the mechanism, see Barton, D.H.R. *Chem. Soc. Rev.* ***1996***, *25*, 237.

[613] See Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron* ***1990***, *46*, 3743, and references cited therein.

[614] Barton, D.H.R.; Csuhai, E.; Doller, D.; Ozbalik, N.; Senglet, N. *Tetrahedron Lett.* ***1990***, *31*, 3097. For mechanistic studies, see Barton, D.H.R.; Doller, D.; Geletii, Y.V. *Tetrahedron Lett.* ***1991***, *32*, 3911, and references cited therein; Knight, C.; Perkins, M.J. *J. Chem. Soc. Chem. Commun.* ***1991***, 925. Also see, Minisci, F.; Fontana, F. *Tetrahedron Lett.* ***1994***, *35*, 1427; Barton, D.H.R.; Hill, D.R. *Tetrahedron Lett.* ***1994***, *35*, 1431.

[615] Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6749; D'Accolti, L.; Dinoi, A.; Fusco, C.; Russo, A.; Curci, R. *J. Org. Chem.* ***2003***, *68*, 7806.

[616] Akhrem, I.; Orlinkov, A.; Afanas'eva, L.; Petrovskii, P.; Vitt, S. *Tetrahedron Lett.* ***1999***, *40*, 5897.

[617] In bmim PF6, 1-butyl-3-methylimidazolium hexafluorophosphate: Li, Z.; Xiu, C.-G.; Xu, C.-Z. *Tetrahedron Lett.* ***2003***, *44*, 9229.

[618] Che, C.-M.; Cheng, K.-W.; Chan, M.C.W.; Lau, T.-C.; Mak, C.-K. *J. Org. Chem.* ***2000***, *65*, 7996.

19-18 Oxidation of Arylmethanes to Aldehydes

Oxo-de-dihydro-bisubstitution

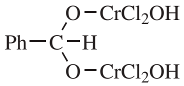
$$\mathrm{ArCH_3} \xrightarrow{\mathrm{CrO_2Cl_2}} \mathrm{ArCHO}$$

Methyl groups on an aromatic ring can be oxidized to the aldehyde stage by several oxidizing agents. The reaction is a special case of **19-17**. When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction*[619] and the yields are high.[620] Another oxidizing agent is a mixture of CrO_3 and Ac_2O. In this case, the reaction stops at the aldehyde stage because 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[621] that have been used to accomplish the conversion of $ArCH_3$ to ArCHO are ceric ammonium nitrate,[622] ceric trifluoroacetate,[623] hypervalent iodoso compounds (see **19-3**),[624] urea–H_2O_2 with micrwoave irradiation,[625] and silver(II) oxide.[626] Oxidation of $ArCH_3$ to carboxylic acids is considered at **19-11**.

Conversion of $ArCH_3$ to ArCHO can also be achieved indirectly by bromination to give $ArCHBr_2$ (**14-1**), followed by hydrolysis (**10-2**).

The mechanism of the Étard reaction is not completely known.[627] 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 the identity of the structure is not fully settled, although many proposals have been made as to its structure and as to how it is hydrolyzed.



$$\mathrm{Ph{-}\overset{O-CrCl_2OH}{\underset{O-CrCl_2OH}{C}}{-}H}$$

35

It is known that $ArCH_2Cl$ is not an intermediate (see **19-20**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements[628]

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[619] The name Étard reaction is often applied to any oxidation with chromyl chloride, for example, oxidation of glycols (**19-7**), alkenes (**19-10**), and so on.

[620] For a review, see Hartford, W.H.; Darrin, M. *Chem. Rev.* ***1958***, *58*, 1, see pp. 25–53.

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

[622] Trahanovsky, W.S.; Young, L.B. *J. Org. Chem.* ***1966***, *31*, 2033; Radhakrishna Murti, P.S.; Pati, S.C. *Chem. Ind. (London)* ***1967***, 702; Syper, L. *Tetrahedron Lett.* ***1967***, 4193. For oxidation with ceric ammonium nitrate and KBrO3, see Ganin, E.; Amer, I. *Synth. Commun.* ***1995***, *25*, 3149.

[623] Marrocco, M.; Brilmyer, G. *J. Org. Chem.* ***1983***, *48*, 1487. See also, Kreh, R.P.; Spotnitz, R.M.; Lundquist, J.T. *J. Org. Chem.* ***1989***, *54*, 1526.

[624] Nicolaou, K.C.; Baran, P.S.; Zhong, Y.-L. *J. Am. Chem. Soc.* ***2001***, *123*, 3183.

[625] Paul, S.; Nanda, P.; Gupta, R. *Synlett* ***2004***, 531.

[626] Syper, L. *Tetrahedron Lett.* ***1967***, 4193.

[627] For a review, see Nenitzescu, C.D. *Bull. Soc. Chim. Fr.* ***1968***, 1349.

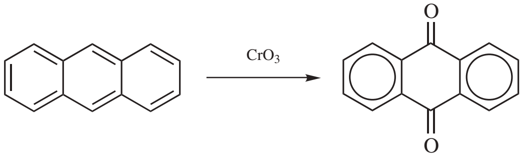
[628] Wheeler, O.H. *Can. J. Chem.* ***1960***, *38*, 2137. See also, Makhija, R.C.; Stairs, R.A. *Can. J. Chem.* ***1968***, *46*, 1255.

indicate that the complex from toluene is **35**, 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 **35**. There is a disagreement on how **35** is formed, assuming that the complex has this structure. Both an ionic[629] and a free-radical[630] process have been proposed. An entirely different structure for the complex was proposed by Nenitzescu and co-workers.[631] On the basis of esr studies, they proposed that the complex is $PhCH_2OCrCl_2OCrOCl_2OH$, which is isomeric with **35**. However, this view has been challenged by Wiberg and Eisenthal,[336] who interpret the esr result as being in accord with **35**. Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.[632]

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

19-19 Oxidation of Aromatic Hydrocarbons to Quinones

Arene-quinone transformation



Condensed aromatic systems (including naphthalenes) can be directly oxidized to quinones by various oxidizing agents.[258,633] Yields are generally not high, although good yields have been reported with ceric ammonium sulfate.[634] Benzene cannot be so oxidized by strong oxidizing agents, but can be electrolytically oxidized to benzoquinone.[635] Naphthalene derivatives, however, are oxidized to naphthoquinones with H_5IO_6 and CrO_3.[636] 1,4-Dimethoxy aromatic compounds are oxidized to para-quinones with an excess of CoF_3 in water–dioxane.[637]

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

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[629] Stairs, R.A. *Can. J. Chem.* ***1964***, *42*, 550.

[630] Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964***, *20*, 1151. See also, Gragerov, I.P.; Ponomarchuk, M.P. *J. Org. Chem. USSR* ***1969***, *6*, 1125.

[631] Necşoiu, I.; Przemetchi, V.; Ghenciulescu, A.; Rentea, C.N.; Nenitzescu, C.D. *Tetrahedron* ***1966***, *22*, 3037.

[632] Duffin, H.C.; Tucker, R.B. *Chem. Ind. (London)* ***1966***, 1262; *Tetrahedron* ***1968***, *24*, 6999.

[633] For reviews, see Naruta, Y.; Maruyama, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 242–247; Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 94–96; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 182–185, 358–360; Thomson, R.H., in Patai, S. *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 132–134. See also, Sket, B.; Zupan, M. *Synth. Commun.* ***1990***, *20*, 933.

[634] Periasamy, M.; Bhatt, M.V. *Synthesis* ***1977***, 330; Balanikas, G.; Hussain, N.; Amin, S.; Hecht, S.S. *J. Org. Chem.* ***1988***, *53*, 1007.

[635] See, for example, Ito, S.; Katayama, R.; Kunai, A.; Sasaki, K. *Tetrahedron Lett.* ***1989***, *30*, 205.

[636] Yamazaki, S. *Tetrahedron Lett.* ***2001***, *42*, 3355.

[637] Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* ***1999***, 1474.

19-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes[638]

Oxo-de-hydro, halo-bisubstitution

$$RCH_2Cl \xrightarrow{Me_2SO} RCHO$$

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with dimethyl sulfoxide,[639] in what has been called the *Kornblum reaction*. In Kornblum's original work, the reaction of α-halo ketones with DMSO at elevated temperatures gave good yields of the corresponding glyoxal (an α-keto-aldehyde).[640] If the glyoxal could be removed from the reaction medium by distillation as it was formed, the reaction was very efficient. In many cases, it was difficult to isolate high boiling glyoxals from DMSO. Primary and secondary[641] alkyl iodides or tosylates[642] can be converted to aldehydes or ketones, although they are much less reactive than α-halo ketones. Epoxides[643] have been used to give α-hydroxy ketones or aldehydes.[644] The reaction with tosyl esters is an indirect way of oxidizing primary alcohols to aldehydes (**19-3**). Primary chlorides with DMSO, NaBr, and ZnO give the corresponding aldehyde when heated to 140°C.[645] Primary allylic bromides with a cyano group on the C=C unit are converted to conjugated α-cyano aldehydes with DMSO and $NaHCO_3$ at room temperature.[646]

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[638] For reviews of the reactions in this section, see Tidwell, T.T. *Org. React.* ***1990***, *39*, 297; *Synthesis* ***1990***, 857; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 171–181, 402–406; Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285, see pp. 343–356; Epstein, W.W.; Sweat, F.W. *Chem. Rev.* ***1967***, *67*, 247; Moffatt, J.G., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 1–64. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1222–1225.

[639] Nace, H.R.; Monagle, J.J. *J. Org. Chem.* ***1959***, *24*, 1792; Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4113. This reaction is promoted by microwave irradiation; see Villemin, D.; Hammadi, M. *Synth. Commun.* ***1995***, *25*, 3141.

[640] Kornblum, N.; Powers, J.W.; Anderson, G.J.; Jones, W.J.; Larson, H.O.; Levand, O.; Weaver, W.M. *J. Am. Chem. Soc.* ***1957***, *79*, 6562.

[641] Baizer, M.M. *J. Org. Chem.*, ***1960***, *25*, 670.

[642] Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4113.

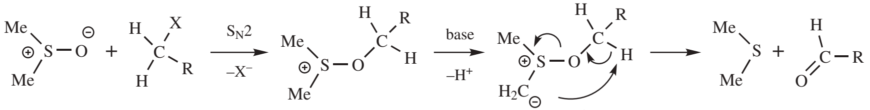
[643] Epoxides can be converted to α-halo ketones by treatment with bromodimethylsulfonium bromide: Olah, G.A.; Vankar, Y.D.; Arvanaghi, M. *Tetrahedron Lett.* ***1979***, 3653.

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

[645] Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001***, *31*, 667; Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001***, *31*, 3395.

[646] Ravichandran, S. *Synth. Commun.* ***2001***, *31*, 2185.

The mechanism of these DMSO oxidations is probably as follows:[647]



36 **37**

although in some cases the base abstracts a proton directly from the carbon being oxidized, in which case the ylid **37** is not an intermediate. Alkoxysulfonium salts (**36**) have been isolated.[648] 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 **36**[649] is formed without the use of DMSO by treating the substrate with a complex generated from chlorine or NCS and dimethyl sulfide.[650]

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*,[651] 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 $ArCH_2NH_2$, 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, although 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. This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine. Another method that converts secondary bromides to ketones heads the bromide with $NaIO_4$ in DMF.[652]

Another reagent that convert benzylic halides to aldehydes is pyridine followed by *p*-nitrosodimethylaniline and then water, called the *Kröhnke reaction*. Primary halides and tosylates have been oxidized to aldehydes by trimethylamine *N*-oxide,[653] and by pyridine *N*-oxide with microwave irradiation.[654]

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[647] Pfitzner, K.E.; Moffatt, J.G. *J. Am. Chem. Soc.* ***1965***, *87*, 5661; Johnson, C.R.; Phillips, W.G. *J. Org. Chem.* ***1967***, *32*, 1926; Torssell, K. *Acta Chem. Scand.* ***1967***, *21*, 1.

[648] Torssell, K. *Tetrahedron Lett.* ***1966***, 4445; Johnson, C.R.; Phillips, W.G. *J. Org. Chem.* ***1967***, *32*, 1926; Khuddus, M.A.; Swern, D. *J. Am. Chem. Soc.* ***1973***, *95*, 8393.

[649] It has been suggested that in the DCC reaction, **36** is not involved, but the ylid **37** is formed directly from a precursor containing DCC and DMSO: Torssell, K. *Tetrahedron Lett.* ***1966***, 4445; Moffatt, J.G. *J. Org. Chem.* ***1971***, *36*, 1909.

[650] Vilsmaier, E.; Sprügel, W. *Liebigs Ann. Chem.* ***1971***, *747*, 151; Corey, E.J.; Kim, C.U. *J. Am. Chem. Soc.* ***1972***, *94*, 7586; *J. Org. Chem.* ***1973***, *38*, 1233; McCormick, J.P. *Tetrahedron Lett.* ***1974***, 1701; Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *Synthesis* ***1988***, 178.

[651] For a review, see Angyal, S.J. *Org. React.* ***1954***, *8*, 197.

[652] Das, S.; Panigrahi, A.K.; Maikap, G.C. *Tetrahedron Lett.* ***2003***, *44*, 1375.

[653] Franzen, V.; Otto, S. *Chem. Ber.* ***1961***, *94*, 1360. For the use of other amine oxides, see Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3287.

[654] Barbry, D.; Champagne, P. *Tetrahedron Lett.* ***1996***, *37*, 7725.

In a clearly related reaction, benzylic bromides are oxidized to aryl carboxylic acids by photolysis in acetone in the presence of mesoporous silica.[655]

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

19-21 Oxidation of Amines or Nitro Compounds to Aldehydes, Ketones, or Dihalides

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

Primary aliphatic amines can be oxidized to aldehydes or ketones.[656] Other reagents used[657] have been *N*-bromoacetamide[658] (for benzylic amines), 3,5-di-*tert*-butyl-1,2-benzoquinone,[659] and aqueous NaOCl with phase-transfer catalysts.[660] Benzylic amine salts $PhCHRNR'_2\ H^+\ Cl^-$ (R,R′ = H or alkyl) give benzaldehydes or aryl ketones when heated in DMSO.[661] Several indirect methods for achieving the conversion $RR'CHNH_2 \rightarrow RR'C{=}O$ (R′ = alkyl, aryl, or H) have been reported.[662]

Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aqueous bromine[663] and with neutral permanganate.[664] 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.[665]

Primary and secondary aliphatic nitro compounds have been oxidized to aldehydes and ketones, respectively ($RR'CHNO_2 \rightarrow RR'C{=}O$) with sodium chlorite

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[655] Itoh, A.; Kodama, T.; Inagaki, S.; Masaki, Y. *Org. Lett.* ***2000***, *2*, 2455.

[656] For a review, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 200–220, 411–415.

[657] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1225–1227; Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, p. 240.

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

[659] Corey, E.J.; Achiwa, K. *J. Am. Chem. Soc.* ***1969***, *91*, 1429. For a study of the mechanism, see Klein, R.F.X.; Bargas, L.M.; Horak, V. *J. Org. Chem.* ***1988***, *53*, 5994.

[660] Lee, G.A.; Freedman, H.H. *Tetrahedron Lett.* ***1976***, 1641.

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

[662] See, for example, Dinizo, S.E.; Watt, D.S. *J. Am. Chem. Soc.* ***1975***, *97*, 6900; Black, D.S.; Blackman, N.A. *Aust. J. Chem.* ***1975***, *28*, 2547; Scully, Jr., F.E.; Davis, R.C. *J. Org. Chem.* ***1978***, *43*, 1467; Doleschall, G. *Tetrahedron Lett.* ***1978***, 2131; Babler, J.H.; Invergo, B.J. *J. Org. Chem.* ***1981***, *46*, 1937.

[663] Deno, N.C.; Fruit, Jr., R.E. *J. Am. Chem. Soc.* ***1968***, *90*, 3502.

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

[665] Doyle, M.P.; Siegfried, B. *J. Chem. Soc. Chem. Commun.* ***1976***, 433.

under phase transfer conditions,[666] tetrapropylammonium perruthenate (TPAP),[667] Oxone®,[668] as well as with other reagents.[669] Vinyl nitro compounds were converted to α-alkylated ketones, with good enantioselectivity, using R_2Zn, a chiral copper catalyst followed by hydrolysis with 20% aqueous sulfuric acid.[670]

19-22 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,[671] and nitric acid.[672] Other reagents include H_5IO_6/CrO_3.[673] The reaction can be looked on as a combination of **19-3** and **19-23**. When acidic conditions are used, a considerable amount of carboxylic ester $RCOOCH_2R$ is often isolated, although 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.[674] Aliphatic primary alcohols are converted to the carboxylic acid with 30% aq. H_2O_2, tetrabutylammonium hydrogen sulfate and a tungsten catalyst with microwave irradiation.[675] Oxone® in DMF also converts aliphatic aldehydes to the corresponding carboxylic acid.[676] Benzylic alcohols are oxidized to benzoic acid derivatives by treatment first with TEMPO[677] (p. 274), and then $NaClO_2$.[678] A combination of $NaClO_2$ and NaH_2PO_4 in aq. DMSO oxidizes aldehydes to acids even in the presence of a disulfide

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[666] Ballini, R.; Petrini, M. *Tetrahedron Lett.* ***1989***, *30*, 5329.

[667] Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 207.

[668] Ceccherelli, P.; Curini, M., Marcotullio, M.C.; Epifano, F.; Rosati, O. *Synth. Commun.* ***1998***, *28*, 3057.

[669] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1227–1228.

[670] Luchaco-Cullis, C.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2002***, *124*, 8192.

[671] For a discussion of the mechanism of this oxidation, see Rankin, K.N.; Liu, Q.; Hendry, J.; Yee, H.; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* ***1998***, *39*, 1095.

[672] For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 127–132; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, 148–165, 391–401. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1646–1650.

[673] Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Lett.* ***1998***, *39*, 5323

[674] Craig, J.C.; Horning, E.C. *J. Org. Chem.* ***1960***, *25*, 2098. See also, Berthon, B.; Forestiere, A.; Leleu, G.; Sillion, B. *Tetrahedron Lett.* ***1981***, *22*, 4073; Nwaukwa, S.O.; Keehn, P.M. *Tetrahedron Lett.* ***1982***, *23*, 35.

[675] Bogdał, D.; Łukasiewicz, M. *Synlett* ***2000***, 143.

[676] Travis, B.R.; Sivakumar, M.; Hollist, G.O.; Borhan, B. *Org. Lett.* ***2003***, *5*, 1031.

[677] For other oxidations of this type utilizing TEMPO, see DeLuca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* ***2003***, *68*, 4999. For a reaction using polymer-bound TEMPO, see Yasuda, K.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1024.

[678] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *J. Org. Chem.* ***1999***, *64*, 2564.

elsewhere in the molecule.[679] Similar oxidation to the acid occurred with $NaIO_4/RuCl_3$ in aqueous acetonitrile,[680] 30% aq. H_2O_2, and a cobalt–salen catalyst,[681] or oxygen on alumina with microwave irradiation.[682] Aliphatic alcohols are converted to a symmetrical ester ($RCH_2OH \rightarrow RCOOCH_2R$) by oxidation with PCC on aluminum without solvent.[683] Oxone in aqueous methanol also converts aryl aldehydes to the corresponding ester.[684] Allylic alcohols are converted to conjugated esters with MnO_2, NaCN in methanol–acetic acid.[685] Primary alcohols are oxidized to the methyl ester with trichloroisocyanuric acid in methanol.[686] This reagent also converts diols to lactones.

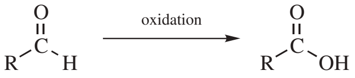
Primary alcohols RCH_2OH can be directly oxidized to acyl fluorides RCOF with cesium fluoroxysulfate.[687] Lactones can be prepared by oxidizing diols in which at least one OH is primary,[688] and addition of a chiral additive, such as sparteine, leads to lactones with high asymmetric induction.[689] 2-(3-Hydroxypropyl)aniline was oxidized to an acyl derivative that cyclized to give a lactam when heated with a rhodium catalyst.[690]

Primary alkyl ethers can be selectively cleaved to carboxylic acids by aq. Br_2 ($RCH_2OR' \rightarrow RCOOH$).[691] Secondary allylic alcohols are converted to ketones with 70% *tert*-butylhydroperoxide with a CrO_3 catalyst.[692]

OS **I**, 138, 168; **IV**, 499, 677; **V**, 580; **VII**, 406; **IX**, 462; **81**, 195. Also see, OS **III**, 745.

19-23 Oxidation of Aldehydes to Carboxylic Acids

Hydroxylation or **Hydroxy-de-hydrogenation**



$$R{-}\overset{O}{\overset{\|}{C}}{-}H \xrightarrow{\text{oxidation}} R{-}\overset{O}{\overset{\|}{C}}{-}OH$$

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[679] Fang, X.; Bandarage, U.P.; Wang, T.; Schroeder, J.D.; Garvey, D.S. *Synlett* ***2003***, 489.

[680] Prashad, M.; Lu, Y.; Kim, H.-Y.; Hu, B.; Repic, O.; Blacklock, T.J. *Synth. Commun.* ***1999***, *29*, 2937.

[681] Das, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2003***, *44*, 6033.

[682] Reddy, D.S.; Reddy, P.P.; Reddy, P.S.N. *Synth. Commun.* ***1999***, *29*, 2949.

[683] Bhar, S.; Chaudjuri, S.K. *Tetrahedron* ***2003***, *59*, 3493.

[684] Koo, B.-S.; Kim, E.-H.; Lee, K.-J. *Synth. Commun.* ***2002***, *32*, 2275.

[685] Foot, J.S.; Kanno, H.; Giblin, G.M.P.; Taylor, R.J.K. *Synlett* ***2002***, 1293.

[686] Hiegel, G.A.; Gilley, C.B. *Synth. Commun.* ***2003***, *33*, 2003.

[687] Stavber, S.; Planinsek, Z.; Zupan, M. *Tetrahedron Lett.* ***1989***, *30*, 6095.

[688] For examples of the preparation of lactones by oxidation of diols, see Jefford, C.W.; Wang, Y. *J. Chem. Soc. Chem. Commun.* ***1988***, 634; Jones, J.B.; Hirano, M.; Yakabe, S.; Morimoto, T. *Synth. Commun.* ***1998***, *28*, 123; Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* ***2002***, *4*, 2361; Hansen, T.M.; Florence, G.J.; Lugo-Mas, P.; Chen, J.; Abrams, J.N.; Forsynth, C.J. *Tetrahedron Lett.* ***2003***, *44*, 57; Suzuki, T.; Morita, K.; Matsuo, Y.; Hiroi, K. *Tetrahedron Lett.* ***2003***, *44,* 2003. For a list of reagents used to effect this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1650–1652.

[689] Yanagisawa, Y.; Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J.M. *Chem. Lett.* ***1996***, 1043.

[690] Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* ***2004***, *6*, 2785.

[691] Although these references refer to oxidation of alkyl ethers to ketones, oxidation to carboxylic acids is also possible. See Deno, N.C.; Potter, N.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3550, 3555. See also, Miller, L.L.; Wolf, J.F.; Mayeda, E.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3306; Saigo, K.; Morikawa, A.; Mukaiyama, T. *Chem. Lett.* ***1975***, 145; Olah, G.A.; Gupta, B.G.B.; Fung, A.P. *Synthesis* ***1980***, 897.

[692] Chandrasekhar, S.; Mohanty, P.K.; Ramachander, T. *Synlett* ***1999***, 1063.

Oxidation of aldehydes-to-carboxylic acids is quite common[693] and has been carried out with many oxidizing agents, the most popular of which is permanganate in acid, basic, or neutral solution.[694] Chromic acid,[695] bromine, and Oxone®,[696] are other reagents frequently employed. Bromate exchange resin in refluxing acetone oxidizes aryl aldehydes-to aryl-carboxylic acids.[697] Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. Benedict's and Fehling's solutions oxidize aldehydes,[698] and there is a test for aldehydes that depends on this reaction, but the method is seldom used for preparative purposes. In any case, it gives very poor results with aromatic aldehydes. α,β-Unsaturated aldehydes can be oxidized by sodium chlorite without disturbing the double bond.[699] Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxy acid RCO_3H,[700] which with another molecule of aldehyde, disproportionates to give two molecules of acid (see **14-7**).[701] Aryl aldehydes are converted to the corresponding aryl carboxylic ester with hydrogen peroxide and a V_2O_5 catalyst[702] or a titanosilicate[703] in an alcohol solvent. Heating an α-bromoaldhyde with an alcohol and a triazolium carbene leads to the corresponding ester.[704] *N*-Bromophthalimide and mercuric

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[693] For reviews, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 241–263, 423–428; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***, pp. 63–70; Lee, D.G., in Augustine, R.L. *Oxidataion*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 81–86.

[694] For lists of some of the oxidizing agents used, with references, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 174–180; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1653–1661; Srivastava, R.G.; Venkataramani, P.S. *Synth. Commun.* ***1988***, *18*, 2193. See also, Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***.

[695] For a review, see Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 217–225.

[696] Webb, K.S.; Ruszkay, S.J. *Tetrahedron* ***1998***, *54*, 401.

[697] Chetri, A.B.; Kalita, B.; Das, P.J. *Synth. Commun.* ***2000***, *30*, 3317.

[698] For a review, see Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 31–34.

[699] Bal, B.S.; Childers Jr., W.E.; Pinnick, H.W. *Tetrahedron* ***1981***, *37*, 2091; Dalcanale, E.; Montanari, F. *J. Org. Chem.* ***1986***, *51*, 567. See also Bayle, J.P.; Perez, F.; Courtieu, J. *Bull. Soc. Chim. Fr.* ***1990***, 565.

[700] For a review of the preparation of peroxy acids by this and other methods, see Swern, D., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516.

[701] For reviews of the autoxidation of aldehydes, see Vardanyan, I.A.; Nalbandyan, A.B. *Russ. Chem. Rev.* ***1985***, *54*, 532 (gas phase); Sajus, L.; Sérée de Roch, I., in Bamford, C.H., Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***, pp. 89–124 (liquid phase); Maslov, S.A.; Blyumberg, E.A. *Russ. Chem. Rev.* ***1976***, *45*, 155 (liquid phase). For a review of photochemical oxidation of aldehydes by O2, see Niclause, M.; Lemaire, J.; Letort, M. *Adv. Photochem.* ***1966***, *4*, 25. For a discussion of the mechanism of catalyzed atmospheric oxidation of aldehydes, see Larkin, D.R. *J. Org. Chem.* ***1990***, *55*, 1563.

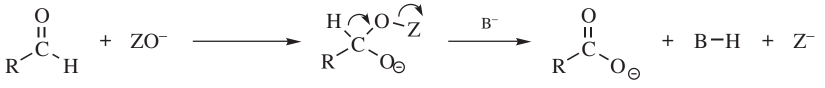
[702] Gopinath, R.; Patel, B.K. *Org. Lett.* ***2000***, *2*, 577.

[703] Chavan, S.P.; Dantale, S.W.; Govande, C.A.; Venkatraman, M.S.; Praveen, C. *Synlett* ***2002***, 267.

[704] Reynolds, N.T.; de Alaniz, J.R.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 9518.

acetate oxidizes aryl aldehydes to aryl carboxylic acids in chloroform at room temperature.[705] An aldehyde can be converted to the carboxylic acid by treatment with 30% hydrogen peroxide and methyl(trioctyl)ammonium hydrogen sulfate at 90°C.[706] Aryl aldehydes are similarly oxidized by a mixture of hydrogen peroxide and selenium dioxide (SeO_2).[707] Aldehydes (RCHO) can be directly converted to carboxylic esters (RCOOR′) by treatment with Br_2 in the presence of an alcohol.[708] Polymer-bound hypervalent iodine + TEMPO oxidizes aldehydes to acids.[709]

Mechanisms of aldehyde oxidation[710] are not firmly established, but there seem to be at least two main types: a free-radical mechanism and an ionic one. In the free-radical process, the aldehydic hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species ^{-}OZ to the carbonyl bond to give **38** in alkaline solution and **39** in acid or neutral solution. The aldehydic hydrogen of **38** or **39** is then lost as a proton to a base, while Z leaves with its electron pair.



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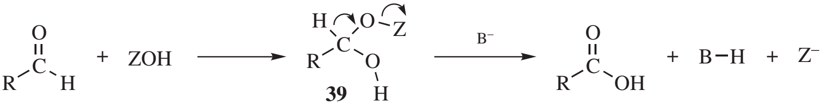

39

For oxidation with acid dichromate the picture seems to be quite complex, with several processes of both types going on:[711]

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[705] Anjum, A.; Srinivas, P. *Chem. Lett.* ***2001***, 900.

[706] Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M.; Noyori, R. *Tetrahedron Lett.* ***2000***, *41*, 1439.

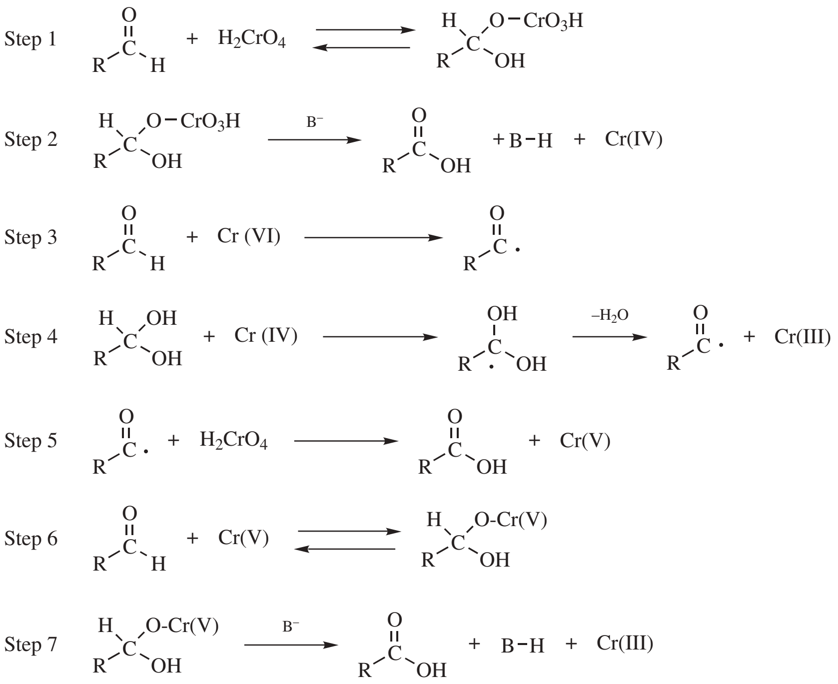
[707] Wójtowicz, H.; Brząszcz, M.; Kloc, K.; Młochowski, J. *Tetrahedron* ***2001***, *57*, 9743.

[708] Williams, D.R.; Klingler, F.D.; Allen, E.E.; Lichtenthaler, F.W. *Tetrahedron Lett.* ***1988***, *29*, 5087; Al Neirabeyeh, M.; Pujol, M.D. *Tetrahedron Lett.* ***1990***, *31*, 2273. For other methods, see Sundararaman, P.; Walker, E.C.; Djerassi, C. *Tetrahedron Lett.* ***1978***, 1627; Grigg, R.; Mitchell, T.R.B.; Sutthivaiyakit, S. *Tetrahedron* ***1981***, *37*, 4313; Massoui, M.; Beaupère, D.; Nadjo, L.; Uzan, R. *J. Organomet. Chem.* ***1983***, *259*, 345; O'Connor, B.; Just, G. *Tetrahedron Lett.* ***1987***, *28*, 3235; McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* ***1989***, *54*, 1212. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1661–1669.

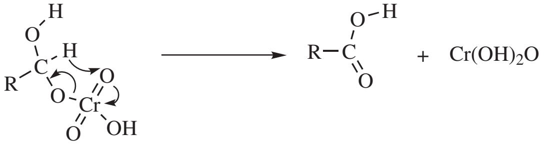
[709] Tashino, Y.; Togo, H. *Synlett* ***2004***, 2010.

[710] For a review, see Roček, J., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 461–505.

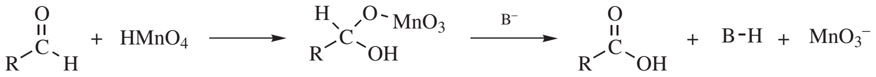
[711] Wiberg, K.B.; Szeimies, G. *J. Am. Chem. Soc.* ***1974***, *96*, 1889. See also, Roček, J.; Ng, C. *J. Am. Chem. Soc.* ***1974***, *96*, 1522, 2840; Sen Gupta, S.; Dey, S.; Sen Gupta, K.K. *Tetrahedron* ***1990***, *46*, 2431.



Steps 1 and 2 constitute an oxidation by the ionic pathway by Cr(VI), and steps 6 and 7 a similar oxidation by Cr(V), which is produced by an electron-transfer process. Either Cr(VI) (step 3) or Cr(IV) (step 4) [Cr(IV) is produced in step 2] may abstract a hydrogen and the resulting acyl radical is converted to carboxylic acid in step 5. Thus, chromium in three oxidation states is instrumental in oxidizing aldehydes. Still another possible process has been proposed in which the chromic acid ester decomposes as follows:[712]



The mechanism with permanganate is less well known, but an ionic mechanism has been proposed[713] for neutral and acid permanganate, similar to steps 1 and 2 for dichromate:



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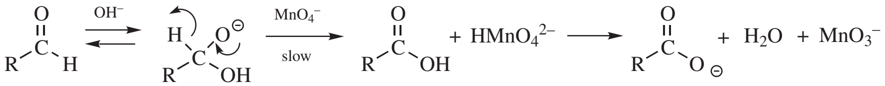
[712] See Roček, J.; Ng, C. *J. Org. Chem.* ***1973***, *38*, 3348.

[713] See, for example, Freeman, F.; Lin, D.K.; Moore, G.R. *J. Org. Chem.* ***1982***, *47*, 56; Jain, A.L.; Banerji, K.K. *J. Chem. Res. (S)* ***1983***, 60.

For alkaline permanganate, the following mechanism has been proposed:[714]



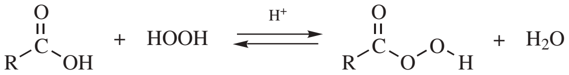
$$Mn(V) + Mn(VII) \longrightarrow 2Mn(VI)$$

OS **I**, 166; **II**, 302, 315, 538; **III**, 745; **IV**, 302, 493, 499, 919, 972, 974.

The conversion of thioketones to sulfines ($R_2C{=}S{=}O$) is difficult to categorize into the sections available, and it placed after oxidation of ketones and aldehydes. The reaction of a thioketone with hydrogen peroxide and a catalytic amount of MTO (methyl trioxorhenium) gives the sulfine.[715]

19-24 Oxidation of Carboxylic Acids to Peroxy Acids

Peroxy-de-hydroxy-substitution

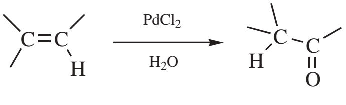


The oxidation of carboxylic acids with H_2O_2 and an acid catalyst is the best general method for the preparation of peroxy acids.[716] A mixture of $Me_2C(OMe)OOH$ and DCC has also been used.[717] The most common catalyst for aliphatic R is concentrated sulfuric acid. The reaction is an equilibrium 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.

D. Reactions in Which Oxygen is Added to the Substrate

19-25 Oxidation of Alkenes to Aldehydes and Ketones

1/Oxo-(1/→2/hydro)-*migro*-attachment



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[714] Freeman, F.; Brant, J.B.; Hester, N.B.; Kamego, A.A.; Kasner, M.L.; McLaughlin, T.G.; Paul, E.W. *J. Org. Chem.* ***1970***, *35*, 982.

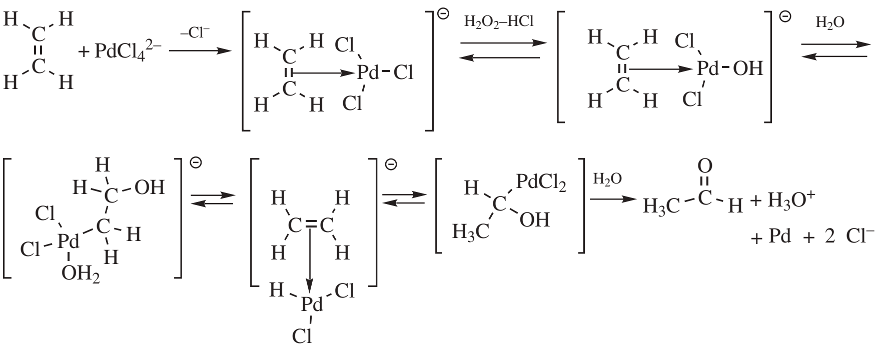
[715] Huang, R.; Espenson, J.H. *J. Org. Chem.* ***1999***, *64*, 6935.

[716] For a review of the preparation of peroxy acids, see Swern, D., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516.

[717] Dussault, P.; Sahli, A. *J. Org. Chem.* ***1992***, *57*, 1009.

Monosubstituted and 1,2-disubstituted alkenes can be oxidized to aldehydes and ketones by palladium chloride and similar salts of noble metals.[718] 1,1-Disubstituted alkenes generally give poor results. The reaction is used industrially to prepare acetaldehyde from ethylene (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 co-oxidant, 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 co-oxidants have been tried, among them O_3, Fe^{3+}, and PbO_2. Terminal alkenes are oxidized to methyl ketones with O_2 and a palladium catalyst with 20% pyridine in Z-propanol.[719] *tert*-Butylhydroperoxide in bromoperfluorooctane–benzene oxidizes styrene to acetophenone in a Wacker-type process.[720] The principal product is an aldehyde only from ethylene: With other alkenes Markovnikov's rule is followed, and ketones are formed predominantly.

The generally accepted mechanism involves π complexes of palladium.[721]



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.

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[718] For a monograph, see Henry, P.M. *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Reidel Publishing Co., Dordrecht, ***1980***. For reviews, see Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer, NY, ***1980***, pp. 6–12; *Synthesis* ***1990***, 739; ***1984***, 369; *Adv. Org. Chem.* ***1969***, *6*, 109, see pp. 119–131; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 59–80; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 189–193, 299–303; Henry, P.M. *Adv. Organomet. Chem.* ***1975***, *13*, 363, see pp. 378–388; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, pp. 1–44; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 77–91; Hüttel, R. *Synthesis* ***1970***, 225, see pp. 225–236; Aguiló, A. *Adv. Organomet. Chem.* ***1967***, *5*, 321; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 88–111.

[719] Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1915.

[720] Betzemeier, B.; Lhermitte, F.; Knochel, P. *Tetrahedron Lett.* ***1998***, *39*, 6667.

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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).[722] This reaction consists of epoxidation (**15-50**) followed by pinacol rearrangement of the epoxide (**18-2**). 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.[723]

Other reagents used have been $Pb(OAc)_4$–F_3CCOOH[724] (e.g., $PhCH{=}CH_2 \rightarrow PhCH_2CHO$), H_2O_2 and a Pd catalyst,[725] H_2O–$PdCl_2$–polyethylene glycol,[726] CrO_3–H_2SO_4–Hg(II) salts,[727] and $Hg(OAc)_2$ followed by $PdCl_2$.[728] The reaction has also been accomplished electrochemically.[729] Terminal alkenes react with ceric ammonium nitrate in methanol to give α-methoxy ketones.[730]

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.[731] (*2*) 1,2-Disubstituted and trisubstituted alkenes give α-chloro ketones when oxidized with chromyl chloride in acetone: $RCH{=}CR'R^2 \rightarrow RCOCClR'R^2$.[732] (*3*) α-Iodo ketones can be prepared by treating alkenes with bis-(*sym*-collidine)iodine(I) tetrafluoroborate.[733] (*4*) potassium permanganate in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.[734]

Enol ethers are oxidized to carboxylic esters ($RCH{=}CHOR' \rightarrow RCH_2COOR'$) with PCC[735] and enamines to α-amino ketones ($R^1CH{=}CR_2NR \rightarrow R^1COCR_2NR$) with *N*-sulfonyloxaziridines.[736] 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.[736] Carboxylic acids can be prepared from terminal alkynes ($RC{\equiv}CH \rightarrow$

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[729] See Tsuji, J.; Minato, M. *Tetrahedron Lett.* ***1987***, *28*, 3683.

[730] Nair, V.; Nair, L.G.; Panicker, S.B.; Sheeba, V.; Augustine, A. *Chem. Lett.* ***2000***, 584.

[731] Srinivasan, N.S.; Lee, D.G. *Synthesis* ***1979***, 520. See also, Baskaran, S.; Das, J.; Chandrasekaran, S. *J. Org. Chem.* ***1989***, *54*, 5182.

[732] Sharpless, K.B.; Teranishi, A.Y. *J. Org. Chem.* ***1973***, *38*, 185. See also, Cardillo, G.; Shimizu, M. *J. Org. Chem.* ***1978***, *42*, 4268; D'Ascoli, R.; D'Auria, M.; Nucciarelli, L.; Piancatelli, G.; Scettri, A. *Tetrahedron Lett.* ***1980***, *21*, 4521; Kageyama, T.; Tobito, Y.; Katoh, A.; Ueno, Y.; Okawara, M. *Chem. Lett.* ***1983***, 1481; Lee, J.G.; Ha, D.S. *Tetrahedron Lett.* ***1989***, *30*, 193.

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

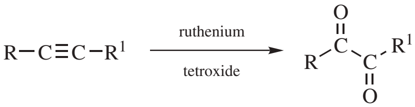
[736] Davis, F.A.; Sheppard, A.C. *Tetrahedron Lett.* ***1988***, *29*, 4365.

RCH_2COOH) by conversion of the alkyne to its phenylthio ether ($RC\equiv CSPh$) and treatment of this with $HgSO_4$ in $HOAc–H_2SO_4$.[737]

OS **VI**, 1028; **VII**, 137; **VIII**, 208.

19-26 The Oxidation of Alkynes to α-Diketones

Dioxo-biaddition



Internal alkynes have been oxidized[738] to α-diketones by several oxidizing agents,[739] including neutral $KMnO_4$,[740] bis(trifluoroacetoxy)iodobenzene,[741] $NaIO_4–RuO_2$,[742] I_2–DMSO,[743] $MeReO_3/H_2O_2$,[744] as well as by electrooxidation.[745] A ruthenium complex with a small amount of trifluoroacetic acid converts internal alkynes to the α-diketone.[746] Ozone generally oxidizes triple-bond compounds to carboxylic acids (**19-9**), but α-diketones are sometimes obtained instead. Selenium dioxide (SeO_2) with a small amount of H_2SO_4 oxidizes alkynes to α-diketones as well as arylacetylenes to α-keto acids ($ArC\equiv CH \rightarrow ArCOCOOH$).[747]

19-27 Oxidation of Amines to Nitroso Compounds and Hydroxylamines and Related

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

$$ArNH_2 \xrightarrow{H_2SO_5} Ar–N{=}O$$

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[737] Abrams. S. R. *Can. J. Chem.* ***1983***, *61*, 2423.

[738] For a review of this reaction, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 153–162, 332-338. For a review of oxidations of triple bonds in general, see Simándi, L.I., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 513–570.

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[740] Khan, N.A.; Newman, M.S. *J. Org. Chem.* ***1952***, *17*, 1063; Lee, D.G.; Lee, E.J.; Chandler, W.D. *J. Org. Chem.* ***1985***, *50*, 4306; Tatlock, J.H. *J. Org. Chem.* ***1995***, *60*, 6221.

[741] Vasil'eva, V.P.; Khalfina, I.L.; Karpitskaya, L.G.; Merkushev, E.B. *J. Org. Chem. USSR* ***1987***, *23*, 1967.

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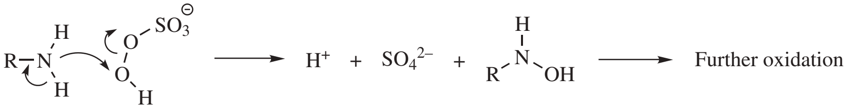
Primary aromatic amines can be oxidized[748] to nitroso compounds. Most often the conversion is accomplished by Caro's acid (H_2SO_5) or with H_2O_2 in HOAc.[749] Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions are generally 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.[750] Among the reagents used for this oxidation are sodium perborate[751] H_2O_2 with a titanium complex,[752] HOF generated *in situ*,[753] and Na_2WO_4/H_2O_2.[754] The mechanism with H_2SO_5 has been postulated to be an example of category 5 (p. 1706).[755]



Secondary amines, R_2NH, are oxidized to hydroxylamines (R_2NHOH) which are resistant to further oxidation, by dimethyldioxirane[756] and by benzoyl peroxide and Na_2HPO_4.[757] Oxone® on silica also oxidizes secondary alcohols to the hydroxylamine.[758] Hydroxylamines are formed when secondary amines react with the enzyme cyclohexanone monooxygenase.[759] Carbamates, such as *N*-Boc amines, are converted tot he *N*-hydroxy compound with bis(trifluoromethyl)-dioxirane.[760] Note that secondary alcohols can be converted to nitrones with aq. H_2O_2 and a phosphotungstate polymer complex, presumably via an hydroxylamine (see **19-28**) formed *in situ*.[761] Dialkylamiens are oxidized to the *N*-nitroso compound with N_2O_2 on polyvinylpyrrolidinone.[762]

OS **III**, 334; **VIII**, 93; **80**, 207.

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[748] For reviews on the oxidation of amines, see Rosenblatt, D.H.; Burrows, E.P., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 1085–1149; Challis, B.C.; Butler, A.R., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 320–338. For reviews confined to primary aromatic amines, see Hedayatullah, M. *Bull. Soc. Chim. Fr.* ***1972***, 2957; Surville, R. De; Jozefowicz, M.; Buvet, R. *Ann. Chim. (Paris)* ***1967***, *[14]* 2, 149.

[749] Holmes, R.R.; Bayer, R.P. *J. Am. Chem. Soc.* ***1960***, *82*, 3454.

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

[751] Zajac Jr., W.W.; Darcy, M.G.; Subong, A.P.; Buzby, J.H. *Tetrahedron Lett.* ***1989***, *30*, 6495.

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[756] Murray, R.W.; Singh, M. *Synth. Commun.* ***1989***, *19*, 3509. This reagent also oxidizes primary amines to hydroxylamines: Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J. *J. Org. Chem.* ***1990***, *55*, 1981.

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[758] Fields, J.D.; Kropp, P.J. *J. Org. Chem.* ***2000***, *65*, 5937.

[759] Colonna, S.; Pironti, V.; Carrea, G.; Pasta, P.; Zambianchi, F. *Tetahedron* ***2004***, *60*, 569.

[760] Detomaso, A.; Curci, R. *Tetrahedron Lett.* ***2001***, *42*, 755.

[761] Yamada, Y.M.A.; Tabata, H.; Takahashi, H.; Ikegami, S. *Synlett* ***2002***, 2031.

[762] Iranpoor, N.; Firouzabadi, H.; Pourali, A.R. *Synthesis* ***2003***, 1591.

19-28 Oxidation of Primary Amines, Oximes, Azides, Isocyanates, or Nitroso Compounds to Nitro Compounds

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

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

Tertiary alkyl primary amines can be oxidized to nitro compounds in excellent yields with $KMnO_4$.[763] 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.[764] Other reagents that oxidize various types of primary amines to nitro compounds are dry ozone,[765] various peroxyacids,[766] $MeReO_3/H_2O_2$,[767] Oxone®,[768] *tert*-butyl hydroperoxide in the presence of certain molybdenum and vanadium compounds,[769] and sodium perborate.[770]

Dimethyldioxirane in wet acetone oxidizes isocyanates to nitro compounds ($RNCO \rightarrow RNO_2$).[771] Oximes can be oxidized to nitro compounds with peroxytrifluoroacetic acid, or Oxone®,[772] sodium perborate,[773] among other ways.[763] Secondary hydroxylamines are also oxidized to nitrones with MnO_2 in dichloromethane.[774] Primary and secondary alkyl azides have been converted to nitro compounds by treatment with Ph_3P followed by ozone.[775] Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.[776]

OS **III**, 334; **V**, 367, 845; **VI**, 803; **81**, 204.

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[763] Larson, H.O., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 306–310. See also, Barnes, M.W.; Patterson, J.M. *J. Org. Chem.* ***1976***, *41*, 733. For reviews of oxidations of nitrogen compounds, see Butler, R.N. *Chem. Rev.* ***1984***, *84*, 249; Boyer, J.H. *Chem. Rev.* ***1980***, *80*, 495.

[764] Murray, R.W.; Rajadhyaksha, S.N.; Mohan, L. *J. Org. Chem.* ***1989***, *54*, 5783. See also, Zabrowski, D.L.; Moorman, A.E.; Beck Jr., K.R. *Tetrahedron Lett.* ***1988***, *29*, 4501.

[765] Keinan, E.; Mazur, Y. *J. Org. Chem.* ***1977***, *42* 844; Bachman, G.B.; Strawn, K.G. *J. Org. Chem.* ***1968***, *33*, 313.

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[767] Murray, R.W.; Iyanar, K.; Chen, J.; Wearing, J.T. *Tetrahedron Lett.* ***1996***, *37*, 805; Cardona, F.; Soldaini, G.; Goti, A. *Synlett* ***2004***, 1553.

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[770] McKillop, A.; Tarbin, J.A. *Tetrahedron* ***1987***, *43*, 1753.

[771] Eaton, P.E.; Wicks, G.E. *J. Org. Chem.* ***1988***, *53*, 5353.

[772] Bose, D.S.; Vanajatha, G. *Synth. Commun.* ***1998***, *28*, 4531.

[773] Olah, G.A.; Ramaiah, P.; Lee, G.K.; Prakash, G.K.S. *Synlett* ***1992***, 337.

[774] Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* ***2001***, *42*, 6503.

[775] Corey, E.J.; Samuelsson, B.; Luzzio, F.A. *J. Am. Chem. Soc.* ***1984***, *106*, 3682.

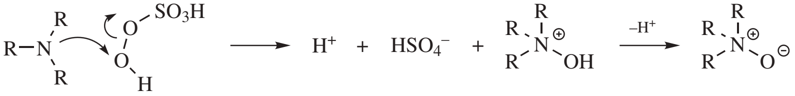
[776] See Boyer, J.H., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 264–265.

19-29 Oxidation of Tertiary Amines to Amine Oxides

N-Oxygen-attachment

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

Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peroxyacids are also important reagents for this purpose. Pyridine and its derivatives are oxidized by peroxyacids[777] rather than hydrogen peroxide. Note, however, that urea–H_2O_2 in formic acid does indeed oxidize pyridine.[778] In the attack by hydrogen peroxide there is first formed a trialkylammonium peroxide, a hydrogen-bonded complex represented as $R_3N{\bullet}H_2O_2$, which can be isolated.[779] The decomposition of this complex probably involves an attack by the OH moiety of the H_2O_2. Oxidation with Caro's acid has been shown to proceed in this manner:[780]



This mechanism is the same as that of **19-27**; the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peroxyacids is probably the same. A green procedure for oxidation of tertiary amines has been developed, using a Mg–Al complex with aq. hydrogen peroxide.[781]

An alternative oxidation using O_2 and a $RuCl_3$ catalyst converted pyridine to pyridine *N*-oxide.[782] Bromamine-T and $RuCl_3$ in aq. acetonitrile also oxidizes pyridine to the *N*-oxide.[783] Tertiary amines are oxidized to the *N*-oxide with O_2 and Fe_2O_3 in the presence of an aliphatic aldehyde.[784] Oxygen and a cobalt–Schiff base complex also oxidzes tertiary amines, including pyridine.[785]

It is noted that azo compounds can be oxidized to azoxy compounds by peroxyacids[786] or by hydroperoxides and molybdenum complexes.[787]

Analogous to the oxidation of tertiary amines, tertiary phosphines are oxidized to phosphine oxides, ($R_3P{=}O$). Triphenylphosphine is converted to triphenylphosphine

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[777] For reviews, see Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, ***1991***, pp. 31–41; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 21–72, 539–542.

[778] Balicki, R.; Goliski, J. *Synth. Commun.* ***2000***, *30*, 1529.

[779] Oswald, A.A.; Guertin, D.L. *J. Org. Chem.* ***1963***, *28*, 651.

[780] Ogata, Y.; Tabushi, I. *Bull. Chem. Soc. Jpn.* ***1958***, *31*, 969.

[781] Choudary, B.M.; Bharathi, B.; Reddy, Ch.V.; Kantam, M.L.; Raghavan, K.V. *Chem. Commun.* ***2001***, 1736.

[782] Jain, S.L.; Sain, B. *Chem. Commun.* ***2002***, 1040.

[783] Sharma, V.B.; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2004***, *45*, 4281.

[784] Wang, F.; Zhang, H.; Song, G.; Lu, X. *Synth. Commun.* ***1999***, *29*, 11.

[785] Jain, S.L.; Sain, B. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1265.

[786] For reviews, see Yandovskii, V.N.; Gidaspov, B.V.; Tselinskii, I.V. *Russ. Chem. Rev.* ***1981***, *50*, 164; Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 557–563, 573–593.

[787] Johnson, N.A.; Gould, E.S. *J. Org. Chem.* ***1974***, *39*, 407. For a mechanistic discussion, see Mitsuhashi, T.; Simamura, O.; Tezuka, Y. *Chem. Commun.* ***1970***, 1300.

oxide with N_2O at 100°C, for example. Triphenylphosphine is also oxidized with PhIO on Montmorillonite K10.[788] *tert*-Butylhydroperoxide oxides $Ph_3 \rightarrow BH_3$ to $Ph_3P{=}O$.[789]

OS **IV**, 612, 704, 828; **VI**, 342, 501; **VIII**, 87.

19-30 Oxidation of Thiols and Other Sulfur Compounds to Sulfonic Acids

Thiol-sulfonic acid oxidation

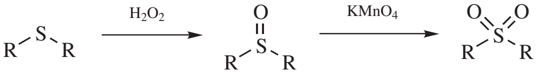
$$RSH \xrightarrow{HNO_3} RSO_3H$$

Thiols, sulfoxides, sulfones, disulfides,[790] and other sulfur compounds can be oxidized to sulfonic acids with many oxidizing agents, but for synthetic purposes the reaction is most important for thiols.[791] Among oxidizing agents used are boiling nitric acid, barium permanganate, and dimethyl dioxirane.[792] Autoxidation (oxidation by atmospheric oxygen) can be accomplished in basic solution.[793] Oxidation of thiols with chlorine and water gives sulfonyl chlorides directly.[794] Thiols can also be oxidized to disulfides (**19-34**).

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

19-31 Oxidation of Thioethers to Sulfoxides and Sulfones

***S*-Oxygen-attachment**



Thioethers can be oxidized to sulfoxides by 1 equivalent of 30% H_2O_2 or by many other oxidizing agents,[795] including H_2O_2–flavin catalyst,[796] H_2O_2 and a

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[788] Mielniczak, G.; Łopusiński, A. *Synlett* ***2001***, 505.

[789] Uziel, J.; Darcel, C.; Moulin, D.; Bauduin, C.; Juge, S. *Tetrahedron Asymmetry* ***2001***, *12*, 1441.

[790] For a review of the oxidation of disulfides, see Savige, W.E.; Maclaren, J.A., in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2; pp. 367–402, Pergamon, NY, ***1966***.

[791] For a general review of the oxidation of thiols, see Capozzi, G.; Modena, G., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 785–839. For a review specifically on the oxidation to sulfonic acids, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 217–239.

[792] Gu, D.; Harpp, D.N. *Tetrahedron Lett.* ***1993***, *34*, 67.

[793] Wallace, T.J.; Schriesheim, A. *Tetrahedron* ***1965***, *21*, 2271.

[794] For a review, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 202–214.

[795] For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC ***1990***, pp. 252–263; Drabowicz, J.; Kiełbasinski, P.; Mikołajczyk, M., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 233–378, pp. 235–255; Madesclaire, M. *Tetrahedron* ***1986***, *42*, 5459; Block, E., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 539–608. For reviews on methods of synthesis of sulfoxides, see Drabowicz, J.; Mikołajczyk, M. *Org. Prep. Proced. Int.* ***1982***, *14*, 45; Oae, S., in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 385–390. For a review with respect to enzymic oxidation, see Holland, H.L. *Chem. Rev.* ***1988***, *88*, 473.

[796] Lindén, A.A.; Krüger, L.; Bäckvall, J.-E. *J. Org. Chem.* ***2003***, *68*, 5890.

$Sc(OTf)_3$ catalyst,[797] $NaIO_4$,[798] dioxiranes,[799] $MeReO_3/H_2O_2$,[800] O_2 and a ceric ammonium nitrate catalyst,[801] trichloroisocyanuric acid,[802] $BnPh_3P\ HSO_5$,[803] KO_2/Me_3SiCl,[804] $Fe(NO_3)_3/FeBr_3$/air,[805] singlet oxygen on MB–Bentonite composite,[806] MnO_2 with a H_2SO_4/SiO_2 catalyst,[807] hexamethylene triamine-Br_2 with $CHCl_3$—H_2O,[808] sodium perborate,[770] $H_5IO_6/FeCl_3$,[809] hypervalent iodine compounds,[810] and peroxyacids.[811] Sulfoxides can be further oxidized to sulfones by another equivalent of H_2O_2, $KMnO_4$, sodium perborate, or a number of other agents. If enough oxidizing agent is present, thioethers can be directly converted to sulfones without isolation of the sulfoxides.[812] Thioethers can be oxidized directly to the sulfone by treatment with excess NaOCl[813] tetramethylperruthenate (TPAP,)[814] H_2O_2 and an iron catalyst,[815] H_2O_2 and 10% Na_2WO_4,[816] H_2O_2/AcOH/$MgSO_4$,[817] urea–H_2O_2,[818] peroxy monosulfate and a manganese catalyst,[819] or with $NaIO_4$/catalytic $RuCl_3$.[820]

These reactions give high yields, and many functional groups do not interfere.[821] As with tertiary amines (**19-29**), racemic thioethers can be kinetically resolved by

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[800] Yamazaki, S. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 2955. A combination of H2O2 and Na2WO2 gives oxidation to the sulfone, see Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* ***2001***, *66*, 8192.

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[805] Martín, S.E.; Rossi, L.I. *Tetrahedron Lett.* ***2001***, *42*, 7147.

[806] Madhavan, D.; Pitchumani, K. *Tetrahedron* ***2001***, *57*, 8391.

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[810] Shukla, V.G.; Salgaonkar, P.D.; Akamanchi, K.G. *J. Org. Chem.* ***2003***, *68*, 5422.

[811] For lists of some of the many oxidizing agents used in this reaction, see Ref. 672 and Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, p. 16.

[812] For a review, see Schank, K., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231, 205–213.

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[814] Guertin, K.R.; Kende, A.S. *Tetrahedron Lett.* ***1993***, *34*, 5369.

[815] Margues, A.; Marin, M.; Ruasse, M.-F. *J. Org. Chem.* ***2001***, *66*, 7588.

[816] Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. *Tetrahedron* ***2001***, *57*, 2469.

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[818] Balicki, R. *Synth. Commun.* ***1999***, *29*, 2235.

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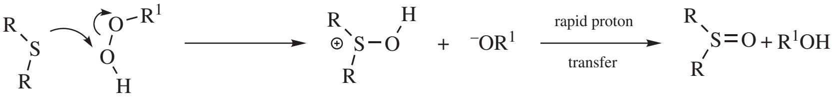
[821] For a review of the oxidation of α-halo sulfides, see Venier, C.G.; Barager III, H.J. *Org. Prep. Proced. Int.* ***1974***, *6*, 77, pp. 85-86.

oxidation to sulfoxides with an optically active reagent, and this has often been done.[822] In addition, the use of chiral additives in conjunction with various oxidizing agents leads to chiral nonracemic sulfoxide with good-to-excellent enantioselectivity.[823] Asymmetric oxidation using bacterial monooxygenases is known,[824]and horseradish peroxidase gives modest enantioselectivity.[825] Chiral sulfur reagents are also known.[826] Selenides (R_2Se) can be oxidized to selenoxides and selenones.[827] It is possible to oxidize a thioether to a sulfoxide in the presence of an alcohol moiety using MnO_2/HCl.[828] Alkyl disulfides give oxidation of one sulfur to give a (RS—S(=O)R compound with good enantioselectivity when using aqueous hydrogen peroxide, a catalytic amount of a vanadium catalyst and a chiral Schiff base ligand.[829] *N*-Sulfonyloxaziridines can be used to oxidize sulfides to sulfoxides.[830]

When the oxidizing agent is a peroxide, the mechanism[831] of oxidation to the sulfoxide is similar to that of **19-29**.[832]



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[822] For reviews, see Kagan, H.B.; Rebiere, F. *Synlett* ***1990***, 643; Drabowicz, J.; Kiebasinski, P.; Mikołajczyk, M. *Org. Prep. Proceed. Int.* ***1982***, *14*, 45, see p. 288.

[823] For example, see Donnoli, M.I.; Superchi, S.; Rosini, C. *J. Org. Chem.* ***1998***, *63*, 9392; Brunel, J.-M.; Kagan, H.B. *Synlett* ***1996***, 404; Brunel, J.-M.; Diter, P.; Deutsch, M.; Kagan, H.B. *J. Org. Chem.* ***1995***, *60*, 8086; Davis, F.A.; Reddy, R.T.; Han, W.; Carroll, P.J. *J. Am. Chem. Soc*, ***1992***, *114*, 1428; Palucki, M.; Hanson, P.; Jacobsen, E.N. *Tetrahedron Lett.* ***1992***, *33*, 7111; Sandrinelli, F.; Perrio, S.; Beslin, P. *Org. Lett.* ***1999***, *1*, 1177; Tokunaga, M.; Ota, M.; Haga, M.-a.; Wakatsuki, Y. *Tetrahedron Lett.* ***2001***, *42*, 3865; Massa, A.; Lattanzi, A.; Siniscalchi, F.R.; Scettri, A. *Tetrahedron Asymmetry* ***2001***, *12*, 2775; Sun, J.; Zhu, C.; Dai, Z.; Yang, M.; Pan, Y.; Hu, H. *J. Org. Chem.* ***2004***, *69*, 8500; Krief, A.; Lonez, F. *Tetrahedron Lett.* ***2002***, *43*, 6255; Massa, A.; Sinissalchi, F.R.; Bugatti, V.; Lattanzi, A.; Scettri, A. *Tetrahederon Asymmetry* ***2002***, *13*, 1277; Barbarini, A.; Maggi, R.; Muratori, M.; Sartori, G.; Sartorio, R. *Tetrahedron Asymmetry* ***2004***, *15*, 2467; Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* ***2002***, 161.

[824] Colonna, S.; Gaggero, N.; Pasta, P.; Ottolina, G. *Chem. Commun.* ***1996***, 2303; Pasta, P.; Carrea, G.; Holland, H.L.; Dallavalle, S. *Tetrahedron Asymmetry*, ***1995***, *6*, 933.

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[826] Mikołajczyk, M.; Drabowicz, J.; Kiełbasiński, P. *Chiral Sulfur Reagents*, CRC Press, Boca Raton, FL, ***1997***.

[827] See Reich, H.J., in Trahanovsky, W.S. *Oxidations in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 7–13; Davis, F.A.; Stringer, O.D.; Billmers, J.M. *Tetrahedron Lett.* ***1983***, *24*, 1213; Kobayashi, M.; Ohkubo, H.; Shimizu, T. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 503.

[828] Gabbi, C.; Ghelfi, F.; Grandi, R. *Synth. Commun.* ***1997***, *27*, 2857.

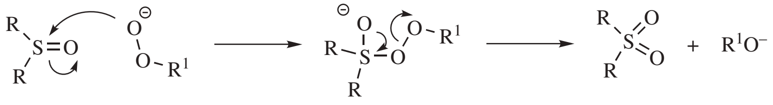
[829] Blum, S.A.; Bergman, R.G.; Ellman, J.A. *J. Org. Chem.* ***2003***, *68*, 150.

[830] For a review of *N*-sulfonyloxaziridines, see: Davis, F.A.; Sheppard, A.C. *Tetrahedron* ***1989***, *45*, 5703. For the use of trifluoromethyl substituted *N*-phosphinoyloxaziridines, see Jennings, W.B.; O'Shea, J.H.; Schweppe, A. *Tetrahedron Lett.* ***2001***, *42*, 101.

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

[832] Modena, G.; Todesco, P.E. *J. Chem. Soc.* ***1962***, 4920, and references cited therein.

The second oxidation, which is normally slower than the first[833] (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:[834]

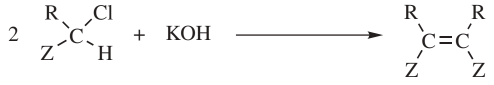


OS **V**, 791; **VI**, 403, 404, 482; **VII**, 453, 491; **VIII**, 464, 543; **IX**, 63; **80**, 190. Also see, OS **V**, 723; **VI**, 23.

E. Oxidative Coupling

19-32 Coupling Involving Carbanions

De-hydro,chloro-coupling



Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon can be dimerized to alkenes by treatment with bases. The Z group may be nitro, aryl, and so on. It is likely that in most cases the mechanism[835] involves nucleophilic substitution followed by elimination[836] (illustrated for benzyl chloride):

$$\text{PhCH}_2\text{Cl} \xrightarrow{\text{base}} \overset{\ominus}{\text{PhCHCl}} \xrightarrow[\text{S}_\text{N}]{\text{PhCH}_2\text{Cl}} \text{PhCHClCH}_2\text{Ph} \xrightarrow{-\text{HCl}} \text{PhCH=CHPh}$$

α,α-Dibromotoluenes ($ArCHBr_2$) give tolanes $ArC{\equiv}CAr$), by debromination of the intermediates $ArCBr{=}CBrAr$.[837] In a related reaction, diarylmethane dihalides

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[833] There are some reagents that oxidize sulfoxides in preference to sulfides, for example, NaMnO4: see Henbest, H.B.; Khan, S.A. *Chem. Commun.* ***1968***, 1036.

[834] Curci, R.; Di Furia, F.; Modena, G. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 603, and references cited therein. See also, Oae, S.; Takata, T. *Tetrahedron Lett.* ***1980***, *21*, 3213; Akasaka, T.; Ando, W. *J. Chem. Soc. Chem. Commun.* ***1983***, 1203.

[835] For discussion, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 548–554.

[836] For example, see Hauser, C.R.; Brasen, W.R.; Skell, P.S.; Kantor, S.W.; Brodhag, A.E. *J. Am. Chem. Soc.* ***1956***, *78*, 1653; Hoeg, D.F.; Lusk, D.I. *J. Organomet. Chem.* ***1966***, *5*, 1; Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* ***1972***, *1*, 375; Hanna, S.B.; Wideman, L.G. *Chem. Ind. (London)* ***1968***, 486. In some cases, a radical anion chain mechanism can take place: Bethell, D.; Bird, R. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1856.

[837] Vernigor, E.M.; Shalaev, V.K.; Luk'yanets, E.A. *J. Org. Chem. USSR* ***1981***, *17*, 317.

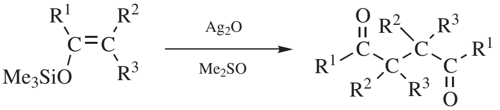
(Ar_2CX_2) have been dimerized to tetraaryl alkenes ($Ar_2C{=}CAr_2$) with copper,[838] and with iron(II) oxalate dihydrate.[839]

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 oxidizing agent, such as iodine,[840] or Cu(II) salts.[841] Arylmethanesulfonyl chlorides ($ArCH_2SO_2Cl$) couple to give ArCH=CHAr when treated with Et_3N.[842]

OS **II**, 273; **IV**, 372, 869, 914; **VIII**, 298. Also see, OS **I**, 46; **IV**, 877.

19-33 Dimerization of Silyl Enol Ethers or of Lithium Enolates

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



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Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with Ag_2O in DMSO or certain other polar aprotic solvents.[843] The reaction has been performed with R^2, R^3 = hydrogen or alkyl, although 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,[844] ceric ammonium nitrate,[845] and lead tetraacetate.[846] If R^1 = OR (in which case the substrate is a ketene silyl acetal), dimerization with $TiCl_4$ leads to a dialkyl succinate (**40**, R^1 = OR).[847]

In a similar reaction, lithium enolates, RC(OLi)=CH_2, were dimerized to 1,4-diketones ($RCOCH_2CH_2COR$) with $CuCl_2$, $FeCl_3$, or copper(II) triflate, in a nonprotic solvent.[848]

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[838] Buckles, R.E.; Matlack, G.M. *Org. Synth. **IV***, 914.

[839] Khurana, J.M.; Maikap, G.C.; Mehta, S. *Synthesis* ***1990***, 731.

[840] See, for example, Kaiser, E.M. *J. Am. Chem. Soc.* ***1967***, *89*, 3659; Belletire, J.L.; Spletzer, E.G.; Pinhas, A.R. *Tetrahedron Lett.* ***1984***, *25*, 5969; Mignani, S.; Lahousse, F.; Merényi, R.; Janousek, Z.; Viehe, H.G. *Tetrahedron Lett.* ***1985***, *26*, 4607; Aurell, M.J.; Gil, S.; Tortajada, A.; Mestres, R. *Synthesis* ***1990***, 317.

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

[842] King, J.F.; Durst, T. *Tetrahedron Lett.* ***1963***, 585; King, J.F.; Harding, D.R.K. *Can. J. Chem.* ***1976***, *54*, 2652; Nakayama, J.; Tanuma, M.; Honda, Y.; Hoshino, M. *Tetrahedron Lett.* ***1984***, *25*, 4553.

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

[844] Moriarty, R.; Prakash, O.; Duncan, M.P. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 559.

[845] Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* ***1989***, *30*, 3707.

[846] Moriarty, R.M.; Penmasta, R.; Prakash, I. *Tetrahedron Lett.* ***1987***, *28*, 873.

[847] Inaba, S.; Ojima, I. *Tetrahedron Lett.* ***1977***, 2009. See also, Totten, G.E.; Wenke, G.; Rhodes, Y.E. *Synth. Commun.* ***1985***, *15*, 291, 301.

[848] Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* ***1977***, *99*, 1487; Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* ***1977***, 3741; Frazier Jr., R.H.; Harlow, R.L. *J. Org. Chem.* ***1980***, *45*, 5408.

OS **VIII**, 467.

19-34 Oxidation of Thiols to Disulfides

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

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

Thiols are easily oxidized to disulfides.[849] Hydrogen peroxide is the most common reagent,[850] but many oxidizing agents give the reaction, among them $KMnO_4$/$CuSO_4$,[851] Me_2SO—I_2,[852] Br_2 under phase-transfer conditions,[853] Br_2 on hydrated silica,[854] sodium perborate,[855] NaI/air,[856] *t*-BuOOH/VO(acac)$_2$,[857] SmI_2,[858] PPh_3 with a rhodium catalyst,[859] dibromohydantoin,[860] cetyltrimethylammonium dichromate,[861] and NO. It can also be done electrochemically.[862] Hydrogen peroxide 30% in hexafluoroisopropanol converts thiols to disulfides,[863] on Clayan with microwave irradiation,[864] and solventless reactions on MnO_2,[865] PCC (p. 1716)[866] or SO_2Cl_2[867] are also effective. However, strong oxidizing agents may give **19-26**. Even the oxygen in the air oxidizes thiols on standing, if a small amount of base is present. The reaction is reversible (see **19-75**), and the interconversion between cysteine and cystine is an important one in biochemistry.

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[849] For a review, see Capozzi, G.; Modena, G., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 785–839. For a list of reagents, with references, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.

[850] It has been pointed out that, nevertheless, H2O2 is not a very good reagent for this reaction, since it gives sulfonic acids (**19-30**) as well as disulfides: Evans, B.J.; Doi, J.T.; Musker, W.K. *J. Org. Chem.* ***1990***, *55*, 2337.

[851] Noureldin, N.A.; Caldwell, M.; Hendry, J.; Lee, D.G. *Synthesis* ***1998***, 1587.

[852] Aida, T.; Akasaka, T.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 1441. See also, Fristad, W.E.; Peterson, J.R. *Synth. Commun.* ***1985***, *15*, 1.

[853] Drabowicz, J.; Mikołajczyk, M. *Synthesis* ***1980***, 32.

[854] Ali, M.H.; McDermott, M. *Tetrahedron Lett.* ***2002***, *43*, 6271.

[855] McKillop, A.; Koyunçu, D. *Tetrahedron Lett.* ***1990***, *31*, 5007.

[856] Iranpoor, N.; Zeynizadeh, B. *Synthesis* ***1999***, 49.

[857] Raghavan, S.; Rajender, A.; Joseph, S.C.; Rasheed, M.A. *Synth. Commun.* ***2001***, *31*, 1477.

[858] Zhan, Z.-P.; Lang, K.; Liu, F.; Hu, L.-m. *Synth. Commun.* ***2004***, *34*, 3203.

[859] Tanaka, K.; Ajiki, K. *Tetahedron Lett.* ***2004***, *45*, 25.

[860] Khazaei, A.; Zolfigol, M.A.; Rostami, A. *Synthesis* ***2004***, 2959.

[861] Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004***, *45*, 1371. See also Tajbakhsh, M.; Hosseinzadeh, R.; Shakoori, A. *Tetrahedron Lett.* ***2004***, *45*, 1889.

[862] See, for example, Leite, S.L.S.; Pardini, V.L.; Viertler, H. *Synth. Commun.* ***1990***, *20*, 393. For a review, see Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 38–43.

[863] Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Synthesis* ***2000***, 223.

[864] Meshram, H.M.; Bandyopadhyay, A.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***2000***, *30*, 701.

[865] Firouzabadi, H.; Abbassi, M.; Karimi, B. *Synth. Commun.* ***1999***, *129*, 2527.

[866] Salehi, P.; Farrokhi, A.; Gholizadeh, M. *Synth. Commun.* ***2001***, *31*, 2777.

[867] Leino, R.; Lönnqvist, J.-E. *Tetrahedron Lett.* ***2004***, *45*, 8489.

The mechanism has been studied for several oxidizing agents and varies with the agent.[868] For oxygen it is[869]

$$RSH + B^- \rightleftharpoons RS^- + BH$$

$$RS^- + O_2 \longrightarrow RS\bullet + \bullet O_2^-$$

$$RS^- + \bullet O_2^- \longrightarrow RS\bullet + O_2^{2-}$$

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

With respect to the sulfur, this mechanism is similar to that of **14-16**, involving as it does loss of a proton, oxidation to a free radical, and radical coupling.

Unsymmetrical disulfides can be prepared[870] 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′.[871]

OS **III**, 86, 116.

REDUCTIONS

For the most part, reductions have been grouped into this chapter, with a few notable exceptions. Catalytic hydrogenation of alkenes and alkynes in **15-11** and **15-12**, hydrogenation of aromatic rings in **15-13** and reductive cleavage of cyclopropanes in **15-15** were placed in Chapter 15 to coincide with addition reactions, and protonolysis of alkyl boranes in **15-16** was placed there also for continuity. In general, reductions of functional groups encompass a variety of reaction types. The reactions in this section are classified into groups depending on the type of bond change involved. These groups are (*1*) attack at carbon (C—O and C=O), (*2*) attack at noncarbonyl multiple bonds to heteroatoms, (*3*) reactions in which a heteroatom is removed from the substrate, (*4*) reduction with cleavage, (*5*) reductive coupling, and (*6*) reactions in which an organic substrate is both oxidized and reduced. Most of the reagents in this section are metal hydrides, metals with an acid or a protic solvent, hydrogen gas with a catalyst, and so on. Other reducing agents are available, and will be introduced in the appropriate section. Note that plants can be used as reducing agents.[872]

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[868] See Tarbell, D.S. in Kharasch, N. *Organic Sulfur Compounds*, Pergamon, Elmsford, NY, ***1961***, pp. 97–102.

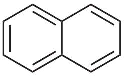
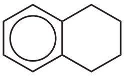
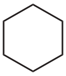
[869] Wallace, T.J.; Schriesheim, A.; Bartok, W. *J. Org. Chem.* ***1963***, *28*, 1311.

[870] Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.* ***1968***, 5907.

[871] For other methods, see Boustany, K.S.; Sullivan, A.B. *Tetrahedron Lett.* ***1970***, 3547; Harpp, D.N.; Ash, D.K.; Back, T.G.; Gleason, J.G.; Orwig, B.A.; VanHorn, W.F.; Snyder, J.P. *Tetrahedron Lett.* ***1970***, 3551; Oae, S.; Fukushima, D.; Kim, Y.H. *J. Chem. Soc. Chem. Commun.* ***1977***, 407.

[872] Bruni, R.; Fantin, G.; Medici, A.; Pedrini, P.; Sacchetti, G. *Tetrahedron Lett.* ***2002***, *43*, 3377.

TABLE 19.2. The Ease of Reduction of Various Functional Groups Toward Catalytic Hydrogenation.[876]

Reaction	Substrate[a]	Product	
19-39	$RCOCl$	$RCHO$	Easiest
19-45	RNO_2	RNH_2	
15-11	$RC\equiv CR$	$RCH=CHR$	
19-36	$RCHO$	RCH_2OH	
15-11	$RCH=CHR$	RCH_2CH_2R	
19-36	$RCOR$	$RCHOHR$	
19-56	$ArCH_2OR$	$ArCH_3 + ROH$	
19-43	$RC\equiv N$	RCH_2NH_2	
15-14			
19-38	$RCOOR'$	$RCH_2OH + R'OH$	
19-64	$RCOHNR'$	RCH_2NHR	
15-13			Most difficult
19-37	$RCOO^-$		Inert

[a] The groups are listed in approximate order of ease of reduction.

Selectivity[873]

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[874] and hydrogen (with a catalyst).[875] 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 19.2–19.4 list the reactivity of various functional groups toward catalytic hydrogenation, $LiAlH_4$, and BH_3, respectively.[876]

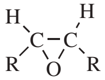
[873] For monographs on reductions in general, see Hudlický, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***; Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***. For a review, see Candlin, J.P.; Rennie, R.A.C., in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 77–135.

[874] For discussions of selectivity with metal hydride reducing agents, see Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979***, *35*, 567; Walker, E.R.H. *Chem. Soc. Rev.* ***1976***, *5*, 23; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 209–251; Rerick, M.N., in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***. For books, see, in Ref. 10, the works by Seyden-Penne, J.; Strouf, O. et al., and Hajós, A.

[875] For a discussion of catalyst selectivity for hydrogenations, see Rylander, P.N. *Aldrichimica Acta* ***1979***, *12*, 53. See also, Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***.

[876] Table 19.2 is from House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 9. Tables 19.3 and 19.4 are from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 213 and 232, respectively.

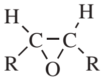
TABLE 19.3. The Ease of Reduction of Various Functional Groups with $LiAlH_4$ in Ether[876]

Reaction	Substrate[a]	Product	
19-36	RCHO	RCH_2OH	Easiest
19-36	RCOR	RCHOHR	
19-63	RCOCl	RCH_2OH	
19-38	Lactone	Diol	
19-35		RCH_2CHOHR	
19-38	RCOOR′	RCH_2OH + R′OH	
19-37	RCOOH	RCH_2OH	
19-37	$RCOO^-$	RCH_2OH	
19-64	$RCONR'_2$	$RCH_2NR'_2$	
19-43	RC≡N	RCH_2NH_2	
19-45	RNO_2	RNH_2	
19-80	$ArNO_2$	ArN=NAr	Most difficult
15-11	$RCH{=}CHR^-$		Inert

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

Table 19.5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.[877] 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 which

TABLE 19.4. The Ease of Reduction of Various Functional Groups With Borane[876]

Reaction	Substrate[a]	Product	
19-37	RCOOH	RCH_2OH	Easiest
15-16	RCH=CHR	$(RCH_2CHR)_3B$	
19-36	RCOR	RCHOHR	
19-43	RCN	RCH_2NH_2	
19-35		RCH_2CHOHR	
19-38	RCOOR′	RCH_2OH + R′OH	Most difficult
19-39,**19-63**	RCOCl		Inert

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

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[877]The first 10 columns are from Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979***, *35*, 567, p. 604. The column on (*i*-Bu)2AlH is from Yoon, N.M.; Gyoung, Y.S. *J. Org. Chem.* ***1985***, *50*, 2443; the one on NaAlEt2H2 from Stinson, S.R. *Chem. Eng. News, Nov. 3*, ***1980***, *58*, No. 44, 19; and the one on LiBEt3H from Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 1. For similar tables that show additional reducting agents, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 129; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***, pp. 16–17. For tables showing which agents reduce a wide variety of functional groups, see Hudlický, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***, pp. 177–200.

groups.[878] Lithium aluminium hydride is a very powerful and unselective reagent.[879] Consequently, other metal hydrides are generally used when chemoselectivity is required. As will be seen on p. 1794, 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).[880] Most of the metal hydrides are nucleophilic reagents and attack the carbon atom of a carbon-hetero single or multiple bond. Another useful reagent is LiAlHSeH.[881] However, BH$_3$[882,883] and AlH$_3$[884] are electrophiles (Lewis acids) and attack the heteroatom. This accounts for the different patterns of selectivity shown in the tables.

TABLE 19.5. Reactivity of Various Functional Groups With Some Metal Hydrides and Toward Catalytic Hydrogenation.[872]

Reaction[a]				A	B	C	D[374]	E[885]	F[886]	G	H	I	J[887]	K[888]	L	M	N
19-36	**RCHO**	⟶	**RCH$_2$OH**	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-36	**RCOR**	⟶	**RCHOHR**	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-39			**RCHO**														
	RCOCl	↗															
19-63		↘	**RCH$_2$OH**	+[889]	+	+	−	−	+	+	+	+	+	+	+	+	+
19-63	**lactone**	⟶	**diol**	−	+	+	+	+	+	±	+	+	+	+	+	+	+
19-35	**epoxide**	⟶	**alcohol**	−	+	+	+	±	±	±	+	+	+	+	+	+	+
19-38	**RCOOR′**	⟶	**RCH$_2$OH**														
			+R′OH	−	+	+	±	−	±	±	+	+	+	+	+	+	+
19-37	**RCOOH**	⟶	**RCH$_2$OH**	−	−	+	+	−	±	−	+	+	+	−	+	+	−

(*Continued*)

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[878] See also, the table in Hudlický, M. *J. Chem. Educ.* ***1977***, *54*, 100.

[879] For a review of LiAlH4, see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–194.

[880] For reviews of reductions by these reagents, see Málek, J. *J. Org. Chem.* ***1988***, *36*, 249; ***1985***, *34*, 1; Málek, J.; Č erny, M. *Synthesis* ***1972***, 217.

[881] Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. *J. Am. Chem. Soc.* ***2001***, *123*, 8408.

[882] See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. For reviews of reductions with BH3, see Wade, R.C. *J. Mol. Catal.* ***1983***, *18*, 273 (BH3 and a catalyst); Lane, C.F. *Chem. Rev.* ***1976***, *76*, 773; *Aldrichimica Acta* ***1977***, *10*, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979***, *12*, 3. For reviews of reduction with borane derivatives, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

[883] Reacts with solvent, reduced in aprotic solvents.

[884] Reduced to aldehyde (**19-44**)

[885] Brown, H.C.; Bigley, D.B.; Arora, S.K.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 7161. For reductions with thexylborane, see Brown, H.C.; Heim, P.; Yoon, N.M. *J. Org. Chem.* ***1972***, *37*, 2942.

[886] Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. *J. Org. Chem.* ***1976***, *41*, 1778.

[887] See Yoon, N.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1968***, *90*, 2927.

[888] Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 1. For a review of the synthesis of alkyl-substituted borohydrides, see Brown, H.C.; Singaram, B.; Singaram, S. *J. Organomet. Chem.* ***1982***, *239*, 43.

[889] See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. For reviews of reductions with BH3, see Wade, R.C. *J. Mol. Catal.*, ***1983***, *18*, 273 (BH3 and a catalyst); Lane, C.F. *Chem. Rev.* ***1976***, *76*, 773; *Aldrichimica Acta* ***1977***, *10*, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979***, *12*, 3. For reviews of reduction with borane derivatives, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

TABLE 19.5. (*Continued*)

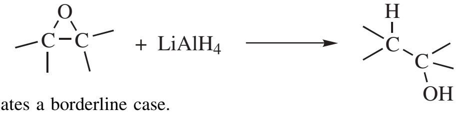
Reaction[a]	A	B	C	D[374]	E[885]	F[886]	G	H	I	J[887]	K[888]	L	M	N
19-37 **$RCOO^-$** ⟶ **RCH_2OH**	−	−	+	−	−	−	−	+	+	+	−	−		−
19-64 ⟶ **RCH_2NR_2'**														
$RCNR_2'$ ↗														
19-41 ↘ **RCHO**	−	−	−	+	+	+	−	+	+	+	+	+	+	+
19-43 **RC≡N** ⟶ **RCH_2NH_2**	−	−	−	+	−	±	−	+	+	+	±	+[384]	+	+
19-45 ⟶ **RCH_2NH_2'**														
$RCONR_2'$ ↗														
19-80 ↘ **RCHO**	−	−	−	−	−	−	−	+	+	−	−	+[890]	+	+
15-11 **RCH=CHR** ⟶ **RCH_2CH_2R**	−	−	−	+	+	+	−	−	−	−	+	−	−	+

A = $NaBH_4$ in EtOH. B = $NaBH_4$ + LiCl in diglyme. C = $NaBH_4$ + $AlCl_3$ in diglyme. D = BH_3–THF. E = bis-3-methyl-2-butylborane (disiamylborane) in THF. F = 9-BBN. G = $LiAlH(Ot\text{-}Bu)_3$ in THF. H = $LiAlH(OMe)_3$ in THF. I = $LiAlH_4$ in ether. J = AlH_3 in THF. K = $LiBEt_3H$. L = $(i\text{Bu})_2AlH$ [DIBALH). M = $NaAlEt_2H_2$. N = catalytic hydrogenation.

19-53 RX + $LiAlH_4$ ⟶ RH

19-57 R–OSO_2R' + $LiAlH_4$ ⟶ RH

19-35

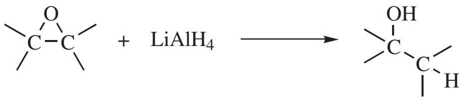


±indicates a borderline case.

A. Attack at Carbon (C–O and C=O)

19-35 Reduction of Epoxides

(3)*OC-seco*-Hydro-de-alkoxylation



Reduction of epoxides is a special case of **19-56** and is easily carried out.[891] The most common reagent is $LiAlH_4$,[892] which reacts by the S_N2-type mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an S_N2 mechanism, cleavage usually occurs so that a tertiary alcohol is formed if possible. If not, a secondary alcohol is preferred. However, for certain substrates, the epoxide ring can be opened the other way by reduction with $NaBH_4$–$ZrCl_4$,[893] Pd/C and

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[890] Reduced to hydroxylamine (**19-46**).

[891] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1019–1027.

[892] See Healy, E.F.; Lewis, J.D.; Minniear, A.B. *Tetrahedron Lett.* ***1994***, *35*, 6647 for a discussion of the LiAlH4 reduction of unsaturated cyclic epoxides.

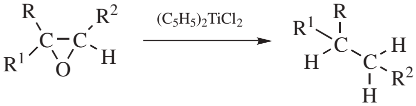
[893] Laxmi, Y.R.S.; Iyengar, D.S. *Synth. Commun.* ***1997***, *27*, 1731 (addition of L-proline to this reaction leads to moderate asymmetric induction).

$HCOONH_4$,[894] SiO_2–$Zn(BH_4)_2$,[895] or with BH_3 in THF.[896] The reaction has also been carried out with other reagents, for example, sodium amalgam in EtOH, Li in ethylenediamine,[897] Bu_3SnH–NaI,[898] and by catalytic hydrogenolysis.[899] Chemoselective and regioselective ring opening (e.g., of allylic epoxides and of epoxy ketones and esters) has been achieved with SmI_2,[900] HCOOH–NEt_3 and a palladium catalyst,[901] and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al).[902] Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride.[903]

Epoxy ketones are selectively reduced with lithium naphthalenide[904] or Cp_2TiCl in THF/MeOH[905] to the β-hydroxyketone. Other reduction methods can lead to the epoxy alcohol (see p.$$$). Reduction of epoxy amides with SmI_2 in methanol gave the α-hydroxyamide.[906]

Epi-sulfides can be reduced to give the alkene using Bu_3SnH in the presence of BEt_3.[907]

Epoxides can be reductively halogenated (the product is the alkyl bromide or iodide rather than the alcohol) with Me_3SiCl–NaX–$(Me_2SiH)_2O$ (1,1,3,3-tetramethyldisiloxane).[908]



The usual product of epoxide reductions is the alcohol, but epoxides are reduced all the way to the alkane by titanocene dichloride[909] and by Et_3SiH–BH_3.[910]

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[894] Dragovich, P.S.; Prins, T.J.; Zhou, R. *J. Org. Chem.* ***1995***, *60*, 4922. For reduction with a palladium catalyst in formic acid see Ley, S.V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.Q.; Zhou, W. *Org. Lett.* ***2003***, *5*, 4665.

[895] Ranu, B.C.; Das, A.R. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 1881.

[896] For a review of epoxide reduction with BH3, see Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 345–348. See also Yamamoto, Y.; Toi, H.; Sonoda, A.; Murahashi, S. *J. Chem. Soc. Chem. Commun.* ***1976***, 672.

[897] Brown, H.C.; Ikegami, S.; Kawakami, J.H. *J. Org. Chem.* ***1970***, *35*, 3243.

[898] Bonini, C.; Di Fabio, R. *Tetrahedron Lett.* ***1988***, *29*, 819.

[899] For a review, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 478–485. See Oshima, M.; Yamazaki, H.; Shimizu, I.; Nizar, M.; Tsuji, J. *J. Am. Chem. Soc.* ***1989***, *111*, 6280.

[900] Molander, G.A.; La Belle, B.E.; Hahn, G. *J. Org. Chem.* ***1986***, *51*, 5259; Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1987***, *28*, 4437. See also, Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* ***1988***, 507.

[901] Noguchi, Y.; Yamada, T.; Uchiro, H.; Kobayashi, S. *Tetrahedron Lett.* ***2000***, *41*, 7493, 7499.

[902] Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4081.

[903] Krishnamurthy, S.; Schubert, R.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1973***, *95*, 8486.

[904] Jankowska, R.; Liu, H.-J.; Mhehe, G.L. *Chem. Commun.* ***1999***, 1581.

[905] Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* ***2001***, *66*, 1046.

[906] Concellón, J.M.; Bardales, E. *Org. Lett.* ***2003***, *5*, 4783.

[907] Uenishi, J.; Kubo, Y. *Tetrahedron Lett.* ***1994***, *35*, 6697.

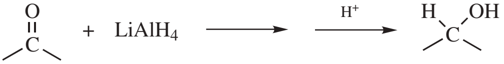
[908] Aizpurua, J.M.; Palomo, C. *Tetrahedron Lett.* ***1984***, *25*, 3123.

[909] van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974***, *96*, 5290.

[910] Fry, J.L.; Mraz, T.J. *Tetrahedron Lett.* ***1979***, 849.

19-36 Reduction of Aldehydes and Ketones to Alcohols[911]

***C,O*-Dihydro-addition**



Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents,[912] of which $LiAlH_4$ and other metallic hydrides are the most commonly used.[913] These reagents have two main advantages over many other reducing agents: They do not reduce carbon–carbon double or triple bonds (with the exception of propargylic alcohols),[914] and with $LiAlH_4$ all four hydrogens are usable for reduction. The reaction is broad and general. Lithium aluminum hydride easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes, containing double or triple bonds and/or nonreducible groups, such as NR_3, OH, OR, and F. If the molecule contains a group reducible by $LiAlH_4$ (e.g., NO_2, CN, COOR), then it is also reduced. Since $LiAlH_4$ reacts readily with water and alcohols, these compounds must be excluded. Common solvents are ether and THF. The compound $NaBH_4$ has a similar scope, but is more selective and so may be used with NO_2, Cl, COOR, CN, and so on in the molecule. Another advantage of $NaBH_4$ is that it can be used in water or alcoholic solvents and so reduces compounds, such as sugars that are not soluble in ethers.[915] Other solvents can be used with some modification of the borohydride. For example, butyltriphenylphosphonium borohydride reduces aldehydes to alcohols in dichloromethane.[916] A polymer-bound phase-transfer material with $NaBH_4$ in wet THF has also been used.[917] Sodium borohydride on alumina, under microwave irradiation, is also an effective reagent.[918] Sodium borohydride has been used on silica gel.[919] The scope of these reagents with ketones is similar to that with aldehydes. Lithium aluminum hydride reduces even sterically hindered ketones.

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[911] See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 306–368.

[912] For a review, see Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 96–129. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1075–1113.

[913] For books on metal hydrides, see Abdel-Magid, A.F., Ed., *Reductions in Organic Synthesis*, American Chemical Society, Washington, DC, ***1996***; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajos, A. *Complex Hydrides*, Elsevier, NY, ***1979***. For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 49–71; Wheeler, O.H., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, **1966**, pp. 507–566.

[914] See Meta, C.T.; Koide, K. *Org. Lett.* ***2004***, *6*, 1785; Naka, T.; Koide, K. *Tetrahedron Lett.* ***2003***, *44*, 443.

[915] The compound NaBH4 reduces solid ketones in the absence of any solvent (by mixing the powders): Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 320.

[916] Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* ***2001***, *31*, 1177.

[917] Tamami, B.; Mahdavi, H. *Tetrahedron* ***2003***, *59*, 821.

[918] Varma, R.S.; Saini, R.K. *Tetrahedron Lett.* ***1997***, *38*, 4337.

[919] Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Commun.* ***1999***, *29*, 295; Liu, W.-y.; Xu, Q.-h.; Ma, Y.-x. *Org. Prep. Proceed. Int.* ***2000***, *32*, 596.

The double bonds that are generally not affected by metallic hydrides may be isolated or conjugated, but double bonds that are conjugated with the C=O group may or may not be reduced, depending on the substrate, reagent, and reaction conditions.[920] Some reagents that reduce only the C=O bonds of α,β-unsaturated aldehydes and ketones are AlH_3,[921] $NaBH_4$, or $LiAlH_4$ in the presence of lanthanide salts,[922] cobalt complexes,[923] nickel compounds,[924] I_2,[925] $NaBH_3(OAc)$,[926] $Zn(BH_4)_2$[927] on Y-zeolite,[928] and Et_3SiH.,[929] Also, both $LiAlH_4$[930] and $NaBH_4$[931] predominantly reduce only the C=O bonds of C=C–C=O systems in most cases, although substantial amounts of fully saturated alcohols have been found in some cases[930] (**15-14**). For some reagents that reduce only the C=C bonds of conjugated aldehydes and ketones, see **15-11**. A mixture of $InCl_3$ and $NaBH_4$ reduced both the C=C and C=O units of conjugated ketones.[932]

When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be *chemoselective*.[933] A number of reagents have been found to reduce aldehydes much faster than ketones. Among these[934] are sodium triacetoxyborohydride[935] ($NaBH_4$–HCOOH),[936] zinc borohydride in THF,[937] bis-(isopropoxytitanium borohydride),[938] a complex of $LialH_4$ and *N*-methyl-2-pyrrolidinone (of particular interest since it is stable in air and to heating),[939] and Raney nickel.[940] On

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[920] For a review of the reduction of α,β-unsaturated carbonyl compounds, see Keinan, E.; Greenspoon, N., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 923–1022.

[921] Jorgenson, M.J. *Tetrahedron Lett.* ***1962***, 559; Dilling, W.L.; Plepys, R.A. *J. Org. Chem.* ***1970***, *35*, 2971.

[922] Gemal, A.L.; Luche, J. *J. Am. Chem. Soc.* ***1981***, *103*, 5454; Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1929. See also Chênevert, R.; Ampleman, G. *Chem. Lett.* ***1985***, 1489; Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985***, *15*, 985.

[923] Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* ***2001***, *3*, 2543.

[924] Khurana, J.M.; Chauhan, S. *Synth. Commun.* ***2001***, *31*, 3485.

[925] Singh, J.; Kaur, I.; Kaur, J.; Bhalla, A.; Kad, G.L. *Synth. Commun.* ***2003***, *33*, 191.

[926] Nutaitis, C.F.; Bernardo, J.E. *J. Org. Chem.* ***1989***, *54*, 5629.

[927] For a review of the reactivity of this reagent, see Ranu, B. *Synlett* ***1993***, 885.

[928] Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Tetrahedron Lett.* ***1998***, *39*, 5151.

[929] Ojima, I.; Kogure, T. *Organometallics* ***1982***, *1*, 1390.

[930] Johnson, M.R.; Rickborn, B. *J. Org. Chem.* ***1970***, *35*, 1041.

[931] Chaikin, S.W.; Brown, W.G. *J. Am. Chem. Soc.* ***1949***, *71*, 122.

[932] Ranu, B.C.; Samanta, S. *Tetrahedron* ***2003***, *59*, 7901.

[933] See Luibrand, R.T.; Taigounov, I.R.; Taigounov, A.A. *J. Org. Chem.* ***2001***, *66*, 7254.

[934] For some others (not all of them metal hydrides), see Hutchins, R.O.; Kandasamy, D. *J. Am. Chem. Soc.* ***1973***, *95*, 6131; Risbood, P.A.; Ruthven, D.M. *J. Org. Chem.* ***1979***, *44*, 3969; Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* ***1981***, *22*, 621; Fleet, G.W.J.; Harding, P.J.C. *Tetrahedron Lett.* ***1981***, *22*, 675; Yamaguchi, S.; Kabuto, K.; Yasuhara, F. *Chem. Lett.* ***1981***, 461; Kim, S.; Kang, H.J.; Yang, S. *Tetrahedron Lett.* ***1984***, *25*, 2985; Kamitori, Y.; Hojo, M.; Masuda, R.; Yamamoto, M. *Chem. Lett.* ***1985***, 253; Borbaruah, M.; Barua, N.C.; Sharma, R.P. *Tetrahedron Lett.* ***1987***, *28*, 5741.

[935] Gribble, G.W.; Ferguson, D.C. *J. Chem. Soc. Chem. Commun.* ***1975***, 535. See also, Nutaitis, C.F.; Gribble, G.W. *Tetrahedron Lett.* ***1983***, *24*, 4287.

[936] Blanton, J.R. *Synth. Commun.* ***1997***, *27*, 2093.

[937] Ranu, B.C.; Chakraborty, R. *Tetrahedron Lett.* ***1990***, *31*, 7663; See Ranu, B. *Synlett* ***1993***, 885.

[938] Ravikumar, K.S.; Chandrasekaran, S. *Tetrahedron* ***1996***, *52*, 9137.

[939] Fuller, J.C.; Stangeland, E.L.; Jackson, T.C.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 1515. See also, Mogali, S.; Darville, K.; Pratt, L.M. *J. Org. Chem.* ***2001***, *66*, 2368.

[940] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***2000***, 197.

the other hand, ketones can be chemoselectively reduced in the presence of aldehydes with $NaBH_4$ in aq. EtOH at $-15°C$ in the presence of cerium trichloride $CeCl_3$.[941] The reagent lithium *n*-dihydropyridylaluminum hydride reduces diaryl ketones much better than dialkyl or alkyl aryl ketones.[942] Most other hydrides reduce diaryl ketones more slowly than other types of ketones. Saturated ketones can be reduced in the presence of α,β-unsaturated ketones with $NaBH_4$-50% MeOH—CH_2Cl_2 at $-78°C$[943] and with zinc borohydride.[944]

In general, $NaBH_4$ reduces carbonyl compounds in this order: aldehydes > α,β-unsaturated aldehydes > ketones > α,β-unsaturated ketones, and a carbonyl group of one type can be selectively reduced in the presence of a carbonyl group of a less reactive type.[945] A number of reagents will preferentially reduce the less sterically hindered of two carbonyl compounds, but by the use of DIBALH in the presence of the Lewis acid methylaluminum bis(2,16-di-*tert*-butyl-4-methylphenoxide), it was possible selectively to reduce the *more hindered* of a mixture of two ketones.[946] It is obvious that reagents can often be found to reduce one kind of carbonyl function in the presence of another.[947] For a discussion of selectivity in reduction reactions, see p. 1787. A syn-selective reduction of β-hydroxy ketones was achieved using $(i\text{PrO})_2TiBH_4$.[948]

Quinones are reduced to hydroquinones by $LiAlH_4$, $SnCl_2$—HCl, or sodium hydrosulfite ($Na_2S_2O_4$), as well as by other reducing agents.

The reagent lithium tri-*sec*-butylborohydride $LiBH(sec\text{-Bu})_3$ (L-Selectride) reduces cyclic and bicyclic ketones in a highly stereoselective manner,.[949] For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity >99%. Both L-Selectride and the potassium salt (K-Selectride) reduce carbonyls in cyclic and acyclic molecules with high diastereoselectivity.[950] The more usual reagents, for example, $LiAlH_4$, $NaBH_4$, reduce relatively unhindered cyclic ketones either with little or no stereoselectivity[951] or give predominant formation of the more stable isomer (axial attack).[952] Mixed reagents, such as

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[941] See Gemal, A.L.; Luche, J. *Tetrahedron Lett.* ***1981***, *22*, 4077; Li, K.; Hamann, L.G.; Koreeda, M. *Tetrahedron Lett.* ***1992***, *33*, 6569.

[942] Lansbury, P.T.; Peterson, J.O. *J. Am. Chem. Soc.* ***1962***, *84*, 1756.

[943] Ward, D.E.; Rhee, C.K.; Zoghaib, W.M. *Tetrahedron Lett.* ***1988***, *29*, 517.

[944] Sarkar, D.C.; Das, A.R.; Ranu, B.C. *J. Org. Chem.* ***1990***, *55*, 5799.

[945] Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989***, *67*, 1206.

[946] Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 2650.

[947] For lists of some of these chemoselective reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1089–1092, and references given in Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989***, *67*, 1206.

[948] Ravikumar, K.S.; Sinha, S.; Chandrasekaran, S. *J. Org. Chem.* ***1999***, *64*, 5841.

[949] Brown, H.C.; Krishnamurthy, S. *J. Am. Chem. Soc.* ***1972***, *94*, 7159; Krishnamurthy, S.; Brown, H.C. *J. Am. Chem. Soc.* ***1976***, *98*, 3383.

[950] K-Selectride: Lawson, E.C.; Zhang, H.-C.; Maryanoff, B.E. *Tetrahedron Lett.* ***1999***, *40*, 593.

[951] For reviews of the stereochemistry and mechanism, see Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979***, *11*, 53; Wigfield, D.C. *Tetrahedron* ***1979***, *35*, 449. For a review of stereoselective synthesis of amino alcohols by this method, see Tramontini, M. *Synthesis* ***1982***, 605.

[952] For a discussion of why this isomer is predominantly formed, see Mukherjee, D.; Wu, Y.; Fronczek, F.R.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 3328.

$LiBH_3[N(C_3H_7)_2]$, gives high selectivity for axial attack.[953] Reduction of cyclohexanone derivatives with the very hindered $LiAlH(CEt_2CMe_3)_3$ gave primarily the cis-alcohol.[954] Cyclohexanones that have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the less stable alcohol, even with $LiAlH_4$ and $NaBH_4$.

Other reagents reduce aldehydes and ketones to alcohols,[955] including:

1. *Hydrogen and a Catalyst.*[956] The most common catalysts are platinum and ruthenium, but homogeneous catalysts have also been used,[957] including copper on silica gel[958] and a ruthenium catalyst on mesoporous silica.[959] Before the discovery of the metal hydrides this was one of the most common ways of effecting this reduction, but it suffers from the fact that C=C, C≡C, C=N, and C≡N bonds are more susceptible to attack than C=O bonds.[960] For aromatic aldehydes and ketones, reduction to the hydrocarbon (**19-61**) is a side reaction, stemming from hydrogenolysis of the alcohol initially produced (**19-54**).
2. *Sodium in Ethanol.*[961] This is called the *Bouveault–Blanc procedure* and was more popular for the reduction of carboxylic esters (**19-38**) than of aldehydes or ketones before the discovery of $LiAlH_4$.

   For the reaction with sodium in ethanol the following mechanism[962] has been suggested:[963]

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[953] Harrison, J.; Fuller, J.C.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 5201.

[954] Boireau, G.; Deberly, A.; Toneva, R. *Synlett* ***1993***, 585. In this study, reduction with LiAlH(O*t*-Bu)3 was shown to give primarily the trans-alcohol.

[955] This can also be done electrochemically. For a review, see Feoktistov, L.G.; Lund, H., in Baizer, M.M.; Lund, H. *Organic Electochemistry*, Marcel Dekker, NY, ***1983***, pp. 315–358, 315–326. See also, Coche, L.; Moutet, J. *J. Am. Chem. Soc.* ***1987***, *109*, 6887.

[956] For reviews, see Abdel-Magid, A.F., Ed., *Reductions in Organic Synthesis*, American Chemical Society Washington, DC, ***1996***, pp. 31–50; Parker, D., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 979–1047; Tanaka, K., in Červený, l. *Catalytic Hydrogenation*, Elsevier, NY, ***1986***, pp. 79–104; Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 66–77; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY., ***1967***, pp. 238–290.

[957] For a review, see Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 65–70.

[958] Ravasio, N.; Psaro, R.; Zaccheria, F. *Tetrahedron Lett.* ***2002***, *43*, 3943.

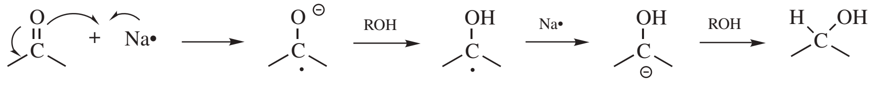
[959] Kesanli, B.; Lin, W. *Chem. Commun.* ***2004***, 2284.

[960] For catalysts that allow hydrogenation of only the C=O bond of α,β-unsaturated aldehydes, see Galvagno, S.; Poltarzewski, Z.; Donato, A.; Neri, G.; Pietropaolo, R. *J. Chem. Soc. Chem. Commun.* ***1986***, 1729; Farnetti, E.; Pesce, M.; Kaspar, J.; Spogliarich, R.; Graziani, M. *J. Chem. Soc. Chem. Commun.* ***1986***, 746; Narasimhan, C.S.; Deshpande, V.M.; Ramnarayan, K. *J. Chem. Soc. Chem. Commun.* ***1988***, 99.

[961] For a discussion, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 152–160.

[962] For reviews of the mechanisms of these reactions, see Pradhan, S.K. *Tetrahedron* ***1986***, *42*, 6351; Huffman, J.W. *Acc. Chem. Res.* ***1983***, *16*, 399. For discussions of the mechanism in the absence of protic solvents, see Huffman, J.W.; Liao, W.; Wallace, R.H. *Tetrahedron Lett.* ***1987***, *28*, 3315; Rautenstrauch, V. *Tetrahedron* ***1988***, *44*, 1613; Song, W.M.; Dewald, R.R. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 269. For a review of the stereochemistry of these reactions in liquid NH3, see Rassat, A. *Pure Appl. Chem.* ***1977***, *49*, 1049.

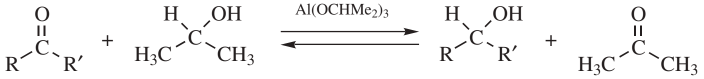
[963] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 151. See, however, Giordano, C.; Perdoncin, G.; Castaldi, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 499.



A ketyl

The ketyl intermediate can be isolated.[964]

3. *Isopropyl Alcohol and Aluminum Isopropoxide*. This is called the *Meerwein–Ponndorf–Verley reduction*.[965] It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (see **19-3**):



The equilibrium is shifted by removal of the acetone by distillation. There is a report of the reduction of benzaldehyde to benzyl alcohol by heating with Z-propanol at 225°C for 1 day.[966] The reaction takes place under very mild conditions and is highly specific for aldehydes and ketones, so that C=C bonds (including those conjugated with the C=O bonds) and many other functional groups can be present without themselves being reduced.[967] This includes acetals, so that one of two carbonyl groups in a molecule can be specifically reduced if the other is first converted to an acetal. β-Keto esters, β-diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction. A SmI_3-assisted version of this reduction has been reported.[968] Zeolites have been used as a medium for this reduction.[969] This reduction can be done catalytically[970] and an aluminum-free, zirconium zeolite catalyst has been developed.[971] A combination of Z-propanol with BINOL and $AlMe_3$ leads to reduction of α-chloroketones to the chlorohydrin with good enantioselectivity.[972] Microwave irradiation of a ketone with Z-propanol, KOH, and activated alumina gives good yields of the alcohol.[973]

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[964] For example, see Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* ***1976***, *98*, 5035; ***1977***, *99*, 6280.

[965] For other catalysts, see Akamanchi, K.G.; Noorani, V.R. *Tetrahedron Lett.* ***1995***, *36*, 5085; Akamanchi, K.G.; Varalakshmy, N.R. *Tetrahedron Lett.* ***1995***, *36*, 3571; Maruoka, K.; Saito, S.; Concepcion, A.B.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 1183. For a microwave-induced version of this reaction, see Barbry, D.; Torchy, S. *Tetrahedron Lett.* ***1997***, *38*, 2959.

[966] Bagnell, L.; Strauss, C.R. *Chem. Commun.* ***1999***, 287.

[967] Diisobornyloxyaluminum isopropoxide gives higher yields under milder conditions than aluminum isopropoxide: Hutton, J. *Synth. Commun.* ***1979***, *9*, 483. For other substitutes for aluminum isopropoxide, see Namy, J.L.; Souppe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* ***1984***, *49*, 2045; Okano, T.; Matsuoka, M.; Konishi, H.; Kiji, J. *Chem. Lett.* ***1987***, 181.

[968] Evans, D.A.; Nelson, S.G.; Gagné, M.R.; Muci, A.R. *J. Am. Chem. Soc.* ***1993***, *115*, 9800.

[969] Corma, A.; Domine, M.E.; Nemeth, L.; Valencia, S. *J. Am. Chem. Soc.* ***2002***, *124*, 3194.

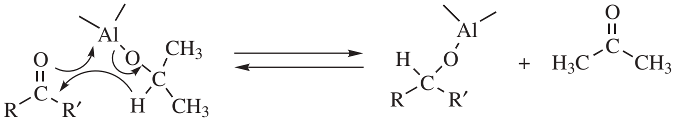
[970] Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Org. Lett.* ***2001***, *3*, 2391. See Albrecht, M.; Crabtree, R.H.; Mata, J.; Peris, E. *Chem. Commun.* ***2002***, 32.

[971] Zhu, Y.; Chuah, G.; Jaenicke, S. *Chem. Commun.* ***2003***, 2734.

[972] Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1020.

[973] Kazemi, F.; Kiasat, A.R. *Synth. Commun.* ***2002***, *32*, 2255.

The Meerwein–Ponndorf–Verley reaction usually[974] involves a cyclic transition state:[975]



but in some cases 2 equivalents of aluminum alkoxide are involved: one attacking the carbon and the other the oxygen, a conclusion that stems from the finding that in these cases the reaction was 1.5 order in alkoxide.[976] Although, for simplicity, we have shown the alkoxide as a monomer, it actually exists as trimers and tetramers, and it is these that react.[977]

4. *Metal Reductions*. A single carbonyl group of an α-diketone can be reduced (to give an α-hydroxy ketone) by heating with zinc powder in aq. DMF[978] or zinc in methanol in the presence of benzyltriethylammonium chloride.[979] This has also been accomplished with aq. VCl_2[980] and with Zn—$ZnCl_2$—EtOH.[981] Aluminum and NaOH in aqueous methanol reduces ketones.[982] β-Hydroxy ketones are reduced with good anti-selectivity using an excess of SmI_2 in water,[983] and other ketones or aldehydes are reduced with SmI_2[984] in aq. THF,[985] in Z-propanol,[986] or methanol.[987] Other metals can be used, including $FeCl_3$/Zn in aq. DMF[988] or DME/MeOH.[989] 1,2-Diketones were reduced to the α-hydroxy ketone with TiI_4 in acetonitrile, followed by hydrolysis.[990] Ammonia and aq. $TiCl_3$ in methanol reduces ketones.[991]

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[974] It has been that shown in some cases reduction with metal alkoxides, including aluminum isopropoxide, involves free-radical intermediates (SET mechanism): Screttas, C.G.; Cazianis, C.T. *Tetrahedron* ***1978***, *34*, 933; Nasipuri, D.; Gupta, M.D.; Banerjee, S. *Tetrahedron Lett.* ***1984***, *25*, 5551; Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986***, *51*, 3593; Yamataka, H.; Hanafusa, T. *Chem. Lett.* ***1987***, 643.

[975] See, for example, Shiner, Jr., V.J.; Whittaker, D. *J. Am. Chem. Soc.* ***1963***, *85*, 2337; Warnhoff, E.W.; Reynolds-Warnhoff, P.; Wong, M.Y.H. *J. Am. Chem. Soc.* ***1980***, *102*, 5956.

[976] Moulton, W.N.; Van Atta, R.E.; Ruch, R.R. *J. Org. Chem.* ***1961***, *26*, 290.

[977] Williams, E.D.; Krieger, K.A.; Day, A.R. *J. Am. Chem. Soc.* ***1953***, *75*, 2404; Shiner, Jr., V.J.; Whittaker, D. *J. Am. Chem. Soc.* ***1969***, *91*, 394.

[978] Kreiser, W. *Liebigs Ann. Chem.* ***1971***, *745*, 164.

[979] Kardile, G.B.; Desai, D.G.; Swami, S.S. *Synth. Commun.* ***1999***, *29*, 2129.

[980] Ho, T.; Olah, G.A. *Synthesis* ***1976***, 815.

[981] Toda, F.; Tanaka, K.; Tange, H. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1555.

[982] Bhar, S.; Guha, S. *Tetrahedron Lett.* ***2004***, *45*, 3775.

[983] Keck, G.E.; Wager, C.A.; Sell, T.; Wager, T.T. *J. Org. Chem.* ***1999***, *64*, 2172.

[984] See Prasad, E.; Flowers II, R.A. *J. Am. Chem. Soc.* ***2002***, *124*, 6895.

[985] Fukuzawa, S.-i.; Miura, M.; Matsuzawa, H. *Tetrahedron Lett.* ***2000***, *42*, 4167; Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2002***, *43*, 7197.

[986] Fukuzawa, S.-i.; Nakano, N.; Saitoh, T. *Eur. J. Org. Chem.* ***2004***, 2863.

[987] Keck, G.E.; Wager, C.A. *Org. Lett.* ***2000***, *2*, 2307.

[988] Sadavarte, V.S.; Swami, S.S.; Desai, D.G. *Synth. Commun.* ***1998***, *28*, 1139.

[989] Chopade, P.R.; Davis, T.A.; Prasad, E.; Flowers II, R.A. *Org. Lett.* ***2004***, *6*, 2685.

[990] Hayakawa, R.; Sahara, T.; Shimizu, M. *Tetrahedron Lett.* ***2000***, *41*, 7939.

[991] Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* ***2001***, 2235.

5. *Boranes.* Borane (BH_3) and substituted boranes reduce aldehydes and ketones in a manner similar to their addition to C=C bonds (**15-16**).[992] That is, the boron adds to the oxygen and the hydrogen to the carbon:[993]

The borate is then hydrolyzed to the alcohol. Both 9-BBN[994] (p. 1077) and BH_3—Me_2S[995] reduce only the C=O group of conjugated aldehydes and ketones. A variety of alkylboranes can be used for reduction.[996] Borane reduction of a titanium complex of a 1,3-diketone gives the syn-diol.[997] Reduction occurs with $B_{10}H_{14}$ with $CeCl_3$,[998] Alane (AlH_3) derivatives can also be used, including diisobutylaluminum hydride.[999] Tributylborane in ionic solvents reduces aldehydes to alcohols.[1000]

6. *Tin Hydrides.* Tributyltin hydride reduces aldehydes to primary alcohols by simply heating in methanol.[1001] A mixture of Bu_3SnH and phenylboronic acid (p. 815) reduces aldehydes in dichloromethane.[1002] Reduction of ketones was achieved with Bu_2SnH_2 and a palladium catalyst.[1003] Using triaryltin hydrides with BF_3•OEt_2, where aryl is 2,6-diphenylbenzyl, selective reduction of aliphatic aldehydes in the presence of a conjugated aldehyde was achieved.[1004]

7. *Cannizzaro Reaction.* In the Cannizzaro reaction (**19-81**), aldehydes without an α hydrogen are reduced to alcohols.

8. *Silanes.* In the presence of bases, certain silanes can selectively reduce carbonyls. Epoxy-ketones are reduced to epoxy-alcohols, for example, with

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[992] For a review, see Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 324–335. See Cha, J.S.; Moon, S.J.; Park, J.H. *J. Org. Chem.* ***2001***, *66*, 7514.

[993] Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc. 1960, 82*, 681; Brown, H.C.; Korytnyk, W. *J. Am. Chem. Soc.* ***1960***, *82*, 3866.

[994] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1975***, *40*, 1864; Lane, C.F. *Aldrichimica Acta* ***1976***, *9*, 31.

[995] Mincione, E. *J. Org. Chem.* ***1978***, *43*, 1829.

[996] Smith, K.; El-Hiti, G.A.; Hou, D.; De Boos, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2807.

[997] Bartoli, G.; Bosco, M.; Bellucci, M.C.; Daplozzo, R., Marcantoni, E.; Sambri, L. *Org. Lett.* ***2000***, *2*, 45.

[998] Bae, J.W.; Lee, S.H.; Jung, Y.J.; Yoon, C.-O.M.; Yoon, C.M. *Tetrahedron Lett.* ***2001***, *42*, 2137.

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[1000] In bmim PF_6, 1-butyl-3-methylimidazoliium hexafluorophosphate and in emim PF_6, 1-ethyl-3-methylimidazolium hexafluorophosphate: Kabalka, G.W.; Malladi, R.R. *Chem. Commun.* ***2000***, 2191.

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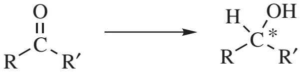
$(MeO)_3SiH$ and LiOMe.[1005] Controlling temperature and solvent leads to different ratios of syn- and anti- products.[1006] Silanes reduce ketones in the presence of $BF_3{\bullet}OEt_2$[1007] and transition-metal compounds catalyze this reduction.[1008] Ketones are reduced with Cl_3SiH in the presence of pyrrolidine carboxaldehyde[1009] or under photochemical conditions.[1010] Polymethylhydrosiloxane with tetrabutylammonium fluoride reduces α-amino ketones to give the syn-amino alcohol.[1011]

9. *Ammonium Formates*. Sodium formate and trialkylammonium formates can be used to reduce aldehydes and ketones to the corresponding alcohol. Decanal was reduced to decanol, for example, using sodium formate in *N*-methyl-2-pyrrolidinone as a solvent.[1012] A mixture of formic acid and ethyl magnesium bromide was used to reduce decanal to decanol in 70% yield.[1013]

Unsymmetrical ketones are prochiral (p. 193); that is, reduction creates a new stereogenic center:



Much effort has been put into finding optically active reducing agents that will produce one enantiomer of the alcohol enantioselectively, and considerable success has been achieved,.[1014] Each reagent tends to show a specificity for certain types of ketones.[1015] H.C. Brown and co-workers[1016] reduced various types of ketone with a number of reducing agents. These workers also determined the relative effectiveness of various reagents for reduction of eight other types of ketone, including heterocyclic, aralkyl, β-keto esters, β-keto acids,[1017] and so on.[1016] In most cases, good enantioselectivity can be obtained with the proper reagent.[1018] Substituents that are

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[1006] See Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 4475.

[1007] Smonou, I. *Tetrahedron Lett.* ***1994***, *35*, 2071.

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[1012] Babler, J.H.; Sarussi, S.J. *J. Org. Chem.* ***1981***, *46*, 3367.

[1013] Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* ***1981***, *22*, 621.

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[1015] For a list of many of these reducing agents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1097–1111.

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[1018] See Brown, H.C.; Ramachandran, P.V.; Weissman, S.A.; Swaminathan, S. *J. Org. Chem.* ***1990***, *55*, 6328; Rama Rao, A.V.; Gurjar, M.K.; Sharma, P.A.; Kaiwar, V. *Tetrahedron Lett.* ***1990***, *31*, 2341; Midland, M.M.; Kazubski, A.; Woodling, R.E. *J. Org. Chem.* ***1991***, *56*, 1068.

remote to the carbonyl group can play a role in facial selectivity of the reduction.[1019] Successful asymmetric reductions have been achieved with biologically derived reducing agents,[1020] such as baker's yeast,[1021] enzymes from other organisms,[1022] or with biocatalysts.[1023] Immobilized bakers yeast has been used in an ionic liquid.[1024]

Asymmetric reduction with very high enantioselectivity has also been achieved with achiral reducing agents and optically active catalysts.[1025] Two approaches are represented by (*1*) homogeneous catalytic hydrogenation with the catalyst 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl-ruthenium acetate, BINAP—Ru(OAc)$_2$,[1026] which reduces

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[1022] See Wei, Z.-L.; Li, Z.-Y.; Lin, G.-Q. *Tetrahedron* ***1998***, *54*, 13059; Guarna, A.; Occhiato, E.G.; Spinetti, L.M.; Vallecchi, M.E.; Scarpi, D. *Tetrahedron* ***1995***, *51*, 1775; Medson, C.; Smallridge, A.J.; Trewhella, M.A. *Tetrahedron Asymmetry*, ***1997***, *8*, 1049; Nakamura, K.; Inoue, Y.; Ohno, A. *Tetrahedron Lett.* ***1995***, *36*, 265; Casy, G.; Lee, T.V.; Lovell, H. *Tetrahedron Lett.* ***1992***, *33*, 817; Heiss, C.; Phillips, R.S. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 2821; Gotor, V.; Rebolledo, F.; Liz, R. *Tetrahedron Asymmetry* ***2001***, *12*, 513; Hage, A.; Petra, D.G.I.; Field, J.A.; Schipper, D.; Wijnberg, J.B.P.A.; Kamer, P.C.J.; Reek, J.N.H.; van Leeuwen, P.W.N.M.; Wever, R.; Schoemaker, H.E. *Tetrahedron Asymmetry* ***2001***, *12*, 1025; Yasohara, Y.; Kizaki, N.; Hasegawa, J.; Wada, M.; Kataoka, M.; Shimizu, S. *Tetrahedron Asymmetry* ***2001***, *12*, 1713; Tsujigami, T.; Sugai, T.; Ohta, H. *Tetrahedron Asymmetry* ***2001***, *12*, 2543; Yadav, J.S.; Nanda, S.; Reddy, P.T.; Rao, A.B. *J. Org. Chem.* ***2002***, *67*, 3900; Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. *J. Org. Chem.* ***2003***, *68*, 402; Gröger, H.; Hummel, W.; Buchholz, S.; Drauz, K.; Nguyen, T.V.; Rollmann, C.; Hüsken, H.; Abokitse, K. *Org. Lett.* ***2003***, *5*, 173; Matsuda, T.; Nakajima, Y.; Harada, T.; Nakamura, K. *Tetrahedron Asymmetry* ***2002***, *13*, 971; Nakamura, K.; Yamanaka, R. *Tetrahedron Asymmetry* ***2002***, *13*, 2529, and references cited therein; Carballeira, J.D.; Álvarez, E.; Campillo, M.; Pardo, L.; Sinisterra, J.V. *Tetrahedron Asymmetry* ***2004***, *15*, 951; Shkmoda, K.; Kubota, N.; Hamada, H.; Kaji, M.; Hirata, T. *Tetrahedron Asymmetry* ***2004***, *15*, 1677; Salvi, N.A.; Chattopadhyay, S. *Tetrahedron Asymmetry* ***2004***, *15*, 3397. For enzymatic reduction of thio ketones, see Nielsen, J.K.; Madsen, J.Ø. *Tetrahedron Asymmetry* ***1994***, *5*, 403.

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[1024] In bmim PF6, 1-butyl-3-methylimidazolium hexafluorophosphate: Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett.* ***2001***, *42*, 7517.

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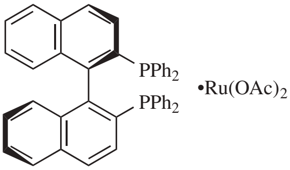
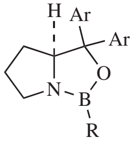


(*R*)(+)-BINAP



41

β-keto esters with high enantioselectivity.[1027] A variety of chiral additives and/or ligands have been used with catalytic hydrogenation reactions, and many functional groups can be tolerated.[1028] Asymmetric catalytic hydrogenation has been done in ionic liquids.[1029]

A second approach is reduction with BH_3—THF or catecholborane,[1030] using an oxazaborolidine **41** (R = H, Me, or *n*-Bu; Ar = Ph or β-naphthyl)[1031] or other chiral compounds[1032] as a catalyst. Both a polymer-bound oxazaborolidine[1033] and a

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[1029] In bmim BF4, 1-butyl-3-methylimidazolium tetrafluoroborate: Ngo, H.L.; Hu, A.; Lin, W. *Chem. Commun.* ***2003***, 1912.

[1030] For an example using catecholborane and a chiral gallium complex, see Ford, A.; Woodward, S. *Angew. Chem. Int. Ed.* ***1999***, *38*, 335.

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dendritic chiral catalyst has been used in conjunction with borane,[1034] as well as other chiral additives can be used.[1035]

A third important method is the combination of $LiAlH_4$ or $NaBH_4$ with a chiral ligand, often in the presence of a transition-metal complex.[1036] Examples include $LiBH_4/NiCl_2$ and a chiral amino alcohol,[1037] $NaBH_4$ with chiral Lewis acid complexes,[1038] or $NaBH_4/Me_3SiCl$ and a chiral ligand.[1039] A mixture of $NaBH_4$ and Me_3SiCl with a catalytic amount of a chiral, polymer-bound sulfonamide leads to asymmetric reduction.[1040]

Enantioselective reduction is possible with the other methods mentioned above. Reduction with silanes and transition-metal catalysts, such as ruthenium compounds, is also very effective.[1041] This method gives high enantioselectivity with various types of ketone, especially α,β-unsaturated ketones. Chiral ruthenium catalysts have been used with triethylammonium formate for the enantioselective reduction.[1042] A ruthenium catalyst with a polymer-supported chiral ligand has been used with Bu_4NBr and HCO_2Na in water.[1043] Chiral additives mixed with surfactants have been used with sodium formate.[1044] Enantioselective reduction was observed with $PhSiH_3$ and copper compounds with a chiral ligand,[1045] with a mixture of ruthenium and silver catalysts,[1046] or with $Mn(dpm)_3$ and oxygen (dpm = diphenylmethylene).[1047] Asymmetric reduction was achieved using an

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[1043] Liu, P.N.; Deng, J.G.; Tu, Y.Q.; Wang, S.H. *Chem. Commun.* ***2004***, 2070.

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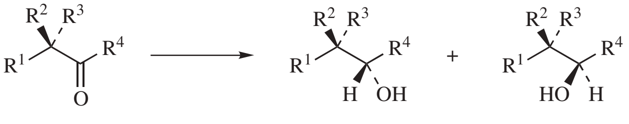
[1046] Gade, L.H.; César, V.; Bellemin-Laponnaz, S. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1014.

[1047] Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* ***2001***, *42*, 6651.

alkoxide or hydroxide base with a chiral rhodium,[1048] ruthenium,[1049] or iridium complex.[1050] A chiral samarium complex has been used in conjunction with Z-propanol.[1051] Chiral mercapto alcohols have also been used for asymmetric reduction.[1052]

Enantioselective reduction is not possible for aldehydes, since the products are primary alcohols in which the reduced carbon is not chiral, but deuterated aldehydes RCDO give a chiral product, and these have been reduced enantioselectively with B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Alpine-Borane) with almost complete optical purity.[1053] Other chiral boranes can be used to reduce aldehydes or ketones.[1054]

In the above cases, an optically active reducing agent or catalyst interacts with a prochiral substrate. Asymmetric reduction of ketones has also been achieved with an achiral reducing agent, if the ketone is complexed to an optically active transition-metal Lewis acid.[1055]



Diastereomers

There are other stereochemical aspects to the reduction of aldehydes and ketones. If there is a stereogenic center α to the carbonyl group,[1056] even an achiral reducing agent can give more of one diastereomer than of the other. Such

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[1048] Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* ***1999***, *64*, 2186.

[1049] With Yb(OTf)3 as a co-reagent, see Matsunaga, H.; Yoshioka, N.; Kunieda, T. *Tetrahedron Lett.* ***2001***, *42*, 8857. With microwave irradiation, see Lutsenko, S.; Moberg, C. *Tetrahedron Asymmetry* ***2001***, *12*, 2529.

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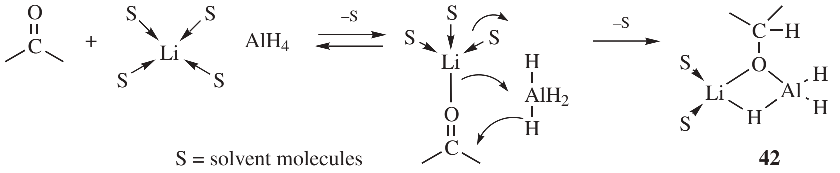
[1054] Wang, Z.; Zhao, C.; Pierce, M.E.; Fortunak, J.M. *Tetrahedron Asymmetry* ***1999***, *10*, 225; Ramachandran, P.V.; Pitre, S.; Brown, H.C. *J. Org. Chem.* ***2002***, *67*, 5315. For a discussion of the sources of stereoselectivity, see Rogic, M.M. *J. Org. Chem.* ***2000***, *65*, 6868; Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* ***2004***, *69*, 6860.

[1055] Dalton, D.M.; Gladysz, J.A. *J. Organomet. Chem.* ***1989***, *370*, C17.

[1056] In theory, the chiral center can be anywhere in the molecule, but in practice, reasonable diastereoselectivity is most often achieved when it is in the α position. For examples of high diastereoselectivity when the chiral center is further away, especially in reduction of β-hydroxy ketones, see Narasaka, K.; Pai, F. *Tetrahedron* ***1984***, *40*, 2233; Hassine, B.B.; Gorsane, M.; Pecher, J.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 597; Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* ***1988***, *53*, 1021; Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J. Am. Chem. Soc.* ***1988***, *110*, 3560.

diastereoselective reductions have been carried out with considerable success.[1057] In most such cases Cram's rule (p. 168) is followed, but exceptions are known.[1058]

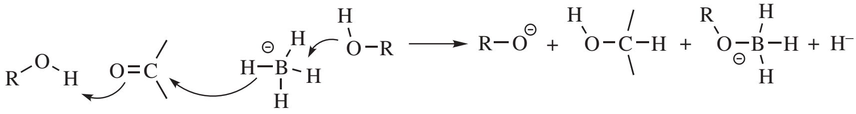
With most reagents there is an initial attack on the carbon of the carbonyl group by a hydride equivalent (H^-) although with BH_3[1059] the initial attack is on the oxygen. Detailed mechanisms are not known in most cases.[1060] With tetrahydroaluminate or borohydride compounds, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the carbon. The following mechanism has been proposed for $LiAlH_4$:[1061]



S = solvent molecules

42

Evidence that the cation plays an essential role, at least in some cases, is that when the Li^+ was effectively removed from $LiAlH_4$ (by the addition of a crown ether), the reaction did not take place.[1062] The complex **42** must now be hydrolyzed to the alcohol. For $NaBH_4$, the Na^+ does not seem to participate in the transition state, but kinetic evidence shows that an OR group from the solvent does participate and remains attached to the boron:[1063]



Free H^- cannot be the attacking entity in most reductions with boron or aluminum hydrides because the reactions are frequently sensitive to the size of the MH_4^- [or MR_mHn- or $M(OR)_mH_n^-$- etc.].

[1057] For reviews, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 131–148; Oishi, T.; Nakata, T. *Acc. Chem. Res.* ***1984***, *17*, 338.

[1058] One study showed that the Cram's rule product predominates with metal hydride reducing agents, but the other product with Bouveault-Blanc and dissolving metal reductions: Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 4475.

[1059] For a discussion of the mechanism with boranes, see Brown, H.C.; Wang, K.K.; Chandrasekharan, J. *J. Am. Chem. Soc.* ***1983***, *105*, 2340.

[1060] For reviews of the stereochemistry and mechanism, see Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979***, *11*, 53; Wigfield, D.C. *Tetrahedron* ***1979***, *35*, 449.

[1061] Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5524.

[1062] Pierre, J.; Handel, H. *Tetrahedron Lett.* ***1974***, 2317. See also Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* ***1976***, 1677; Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5524.

[1063] Wigfield, D.C.; Gowland, F.W. *J. Org. Chem.* ***1977***, *42*, 1108; *Tetrahedron Lett.* ***1976***, 3373. See however Adams, C.; Gold, V.; Reuben, D.M.E. *J. Chem. Soc. Chem. Commun.* ***1977***, 182; *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1466, 1472; Kayser, M.M.; Eliev, S.; Eisenstein, O. *Tetrahedron Lett.* ***1983***, *24*, 1015.

The question of whether the initial complex in the $LiAlH_4$ reduction (**42**, which can be written as $\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}O\overset{\ominus}{Al}H_3}$ = **43**) can reduce another carbonyl to give $\mathrm{H{-}\overset{|}{\underset{|}{C}}{\cdot}O_2\overset{\ominus}{Al}H_4}$ and so on has been controversial. It has been shown[1064] that this is probably not the case but that, more likely, **43** disproportionates to $\mathrm{(H{-}\overset{|}{\underset{|}{C}}{-}O)_4Al^{\ominus}}$ and AlH_4^-, which is the only attacking species. Disproportionation has also been reported in the $NaBH_4$ reaction.[1065]

Aluminate, **43**, is essentially $LiAlH_4$ with one of the hydrogens replaced by an alkoxy group, that is, $LiAlH_3OR$. The fact that **43** and other alkoxy derivatives of $LiAlH_4$ are less reactive than $LiAlH_4$ itself has led to the use of such compounds as reducing agents that are less reactive and more selective than $LiAlH_4$.[1066] We have already met some of these, for example, LiAlH(O—*t*-Bu)$_3$ (reactions **19-39–19-41**; see also, Table 19.5). As an example of chemoselectivity in this reaction it may be mentioned that LiAlH(O-*t*-Bu)$_3$ has been used to reduce only the keto group in a molecule containing both keto and carboxylic ester groups.[1067] However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause $LiAlH_4$ to be the active species, even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.[1068]

The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **15-11**, although not much is known about it.[1069]

For other reduction reactions of aldehydes and ketones (see **19-61**, **19-76**, and **19-81**).

OS **I**, 90, 304, 554; **II**, 317, 545, 598; **III**, 286; **IV**, 15, 25, 216, 660; **V**, 175, 294, 595, 692; **VI**, 215, 769, 887; **VII**, 129, 215, 241, 402, 417; **VIII**, 302, 312, 326, 527; **IX**, 58, 362, 676.

19-37 Reduction of Carboxylic Acids to Alcohols

Dihydro-de-oxo-bisubstitution

$$\mathrm{RCOOH} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH}$$

[1064] Haubenstock, H.; Eliel, E.L. *J. Am. Chem. Soc.* ***1962***, *84*, 2363; Malmvik, A.; Obenius, U.; Henriksson, U. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1899, 1905.

[1065] Malmvik, A.; Obenius, U.; Henriksson, U. *J. Org. Chem.* ***1988***, *53*, 221.

[1066] For reviews of reductions with alkoxyaluminum hydrides, see Málek, J. *Org. React.* ***1988***, *36*, 249; ***1985***, *34*, 1; Málek, J.; Černý, M. *Synthesis* ***1972***, 217.

[1067] Levine, S.G.; Eudy, N.H. *J. Org. Chem.* ***1970***, *35*, 549; Heusler, K.; Wieland, P.; Meystre, C. *Org. Synth. V*, 692.

[1068] Brown, C.A.; Krishnamurthy, S.; Kim, S.C. *J. Chem. Soc. Chem. Commun.* ***1973***, 391.

[1069] For a review of the mechanism of gas-phase hydrogenation, see Pavlenko, N.V. *Russ. Chem. Rev.* ***1989***, *58*, 453.

Carboxylic acids are easily reduced to primary alcohols by $LiAlH_4$.[1070] The reaction does not stop at the aldehyde stage (but see **19-40**). The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used,[1071] but not $NaBH_4$ (see Table 19.5).[1072] Note, however, that complexion of the carboxylic acid with cyanuric chloride (2,4,6-trichlorotriazine) also smooth reduction to the alcohol.[1073] A combination of $NaBH_4$ and an arylboronic acid (p. 815) is also effective.[1074] Benzyltriethylammonium borohydride is dichloromethane also reduces carboxylic acids to the alcohol.[1075] Catalytic hydrogenation is also generally ineffective.[1076] Borane is particularly good for carboxyl groups (Table 19.4) and permits selective reduction of them in the presence of many other groups (although the reaction with double bonds takes place at about the same rate in ether solvents).[1077] Borane also reduces carboxylic acid salts.[1078] 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[1079] or aq. H_3PO_4,[1080] or simply with SmI_2 in water.[1081] A mixture of $NaBH_4$ and I_2 has been used to reduced amino acids to amino alcohols.[1082]

OS **III**, 60; **VII**, 221; 530; **VIII**, 26, 434, 528.

19-38 Reduction of Carboxylic Esters to Alcohols

Dihydro,hydroxy-de-oxo,alkoxy-tersubstitution

$$RCOOR' \xrightarrow{LiAlH_4} RCH_2OH + R'OH$$

[1070] For a review, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 322–373.

[1071] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1114–1116. Zinc borohydride has also been used; see Narashimhan, S.; Madhavan, S.; Prasad, K.G. *J. Org. Chem.* ***1995***, *60*, 5314.

[1072] NaBH4 in the presence of Me2N=$CHCl^+$ Cl^- reduces carboxylic acids to primary alcohols chemoselectively in the presence of halide, ester, and nitrile groups: Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* ***1983***, 835.

[1073] Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* ***1999***, *40*, 4395.

[1074] Tale, R.H.; Patil, K.M.; Dapurkar, S.E. *Tetrahedron Lett.* ***2003***, *44*, 3427.

[1075] Narashimhan, S.; Swarnalakshmi, S.; Balakumar, R. *Synth. Commun.* ***2000***, *30*, 941.

[1076] See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 78–79.

[1077] Brown, H.C.; Korytnyk, W. *J. Am. Chem. Soc.* ***1960***, *82*, 3866; Batrakov, S.G.; Bergel'son, L.D. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1965***, 348; Pelter, A.; Hutchings, M.G.; Levitt, T.E.; Smith, K. *Chem. Commun.* ***1970***, 347; Brown, H.C.; Stocky, T.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8218; Chen, M.H.; Kiesten, E.I.S.; Magano, J.; Rodriguez, D.; Sexton, K.E.; Zhang, J.; Lee, H.T. *Org. Prep. Proceed. Int.* ***2002***, *34*, 665.

[1078] Yoon, N.M.; Cho, B.T. *Tetrahedron Lett.* ***1982***, *23*, 2475.

[1079] Kamochi, Y.; Kudo, T. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3049.

[1080] Kamochi, Y.; Kudo, T. *Tetrahedron* ***1992***, *48*, 4301.

[1081] Kamochi, Y.; Kudo, T. *Chem. Lett.* ***1993***, 1495.

[1082] McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* ***1993***, *58*, 3568.

Lithium aluminum hydride reduces carboxylic esters to give 2 equivalents of alcohol.[1083] 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 that is often a working equivalent of ‘‘hydrolyzing’’ esters. Lactones yield diols. Among the reagents that give the same products[1084] are DIBALH, lithium triethylborohydride, LiAlH(O*t*-Bu)$_3$,[1085] and BH_3—SMe_2 in refluxing THF.[1086] Although $NaBH_4$ reduces phenolic esters, especially those containing electron-withdrawing groups,[1087] its reaction with other esters is usually so slow that it is not the reagent of choice (exceptions are known[1088]), and it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. Note that $NaBH_4$ in DMF—MeOH reduces aryl carboxylic esters to benzylic alcohols,[1089] and $NaBH_4$—LiCl with microwave irradiation also reduces esters to primary alcohols.[1090] However, $NaBH_4$ reduces esters in the presence of certain compounds (see Table 19.5).[1091] Carboxylic esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,[1092] although 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, **19-62**, **19-65**, and **19-59**).

Silanes, such as Ph_2SiH_2, with a catalytic amount of triphenylphosphine and a rhodium catalyst reduced esters to primary alcohols.[1093] Aliphatic silanes such as $EtMe_2SiH$, also reduced esters with a ruthenium catalyst.[1094]

OS **II**, 154, 325, 372, 468; **III**, 671; **IV**, 834; **VI**, 781; **VII**, 356; **VIII**, 155; **IX**, 251.

[1083] For a review, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 391–531.

[1084] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1116–1120.

[1085] Ayers, T.A. *Tetrahedron Lett.* ***1999***, *40*, 5467.

[1086] Brown, H.C.; Choi, Y.M. *Synthesis* ***1981***, 439; Brown, H.C.; Choi,Y.M.; Narasimhan, S. *J. Org. Chem.* ***1982***, *47*, 3153.

[1087] Takahashi, S.; Cohen, L.A. *J. Org. Chem.* ***1970***, *35*, 1505.

[1088] For example, see Brown, M.S.; Rapoport, H. *J. Org. Chem.* ***1963***, *28*, 3261; Bianco, A.; Passacantilli, P.; Righi, G. *Synth. Commun.* ***1988***, *18*, 1765; Boechat, N.; da Costa, J.C.S.; Mendonç a, J.de S.; de Oliveira, P.S.M.; DeSouza, M.V.N. *Tetrahedron Lett.* ***2004***, *45*, 6021.

[1089] Zanka, A.; Ohmori, H.; Okamoto, T. *Synlett* ***1999***, 1636.

[1090] Feng, J.-C.; Liu, B.; Dai, L.; Yang, X.-L.; Tu, S.-J. *Synth. Commun.* ***2001***, *31*, 1875.

[1091] See also Kikugawa, Y. *Chem. Lett.* ***1975***, 1029; Santaniello, E.; Ferraboschi, P.; Sozzani, P. *J. Org. Chem.* ***1981***, *46*, 4584; Brown, H.C.; Narasimhan, S.; Choi,Y.M. *J. Org. Chem.* ***1982***, *47*, 4702; Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 1948; Guida, W.C.; Entreken, E.E.; Guida, W.C. *J. Org. Chem.* ***1984***, *49*, 3024.

[1092] For a review, see Adkins, H. *Org. React.* ***1954***, *8*, 1.

[1093] Ohta, T.; Kamiya, M.; Kusui, K.; Michibata, T.; Nobutomo, M.; Furukawa, I. *Tetrahedron Lett.* ***1999***, *40*, 6963.

[1094] Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* ***2002***, *67*, 4985.

19-39 Reduction of Acyl Halides

Hydro-de-halogenation or Dehalogenation

$$\mathrm{RCOCl} \xrightarrow[-78^\circ\mathrm{C}]{\mathrm{LiAlH}(\mathrm{O}t\text{-Bu})_3} \mathrm{RCHO}$$

Acyl halides can be reduced to aldehydes[1095] by treatment with lithium tri-*tert*-butoxyaluminum hydride in diglyme at −78°C.[1096] The R group may be alkyl or aryl and may contain many types of substituents, including NO_2, CN, and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction under these conditions. Acyl halides can also be reduced to aldehydes by hydrogenolysis with palladium-on-barium sulfate as catalyst. This is called the *Rosenmund reduction.*[1097] A more convenient hydrogenolysis procedure involves palladium-on-charcoal as the catalyst, with ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.[1098] The reduction of acyl halides to aldehydes has also been carried out[1099] with Bu_3SnH,[1100] with the $InCl_3$-catalyzed reaction with Bu_3SnH,[1101] with $NaBH_4$ in a mixture of DMF and THF,[1102] and with formic acid/NH_4OH.[1103] In some of these cases, the mechanisms are free-radical. There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see **19-41**). There is also a method in which the COOH group is replaced by a completely different CHO group (**16-87**).

OS **III**, 551, 627; **VI**, 529, 1007. Also see, OS **III**, 818; **VI**, 312.

[1095] For a review of the formation of aldehydes from acid derivatives, see Fuson, R.C., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 211–232. For a review of the reduction of acyl halides, see Wheeler, O.H., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251.

[1096] Cha, J.S.; Brown, H.C. *J. Org. Chem.* ***1993***, *58*, 4732, and references cited therein.

[1097] For a review, see Rylander, P.N. *Catalytic Hydrogenation Over Platinum Metals*, Academic Press, NY, ***1967***, pp. 398–404. For a discussion of the Pt catalyst, see Maier, W.F.; Chettle, S.J.; Rai, R.S.; Thomas, G. *J. Am. Chem. Soc.* ***1986***, *108*, 2608.

[1098] Peters, J.A.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1323; ***1981***, *100*, 21. See also, Burgstahler, A.W.; Weigel, L.O.; Shaefer, C.G. *Synthesis* ***1976***, 767.

[1099] For some other methods, see Wagenknecht, J.H. *J. Org. Chem.* ***1972***, *37*, 1513; Smith, D.G.; Smith, D.J.H. *J. Chem. Soc. Chem. Commun.* ***1975***, 459; Leblanc, J.C.; Moise, C.; Tirouflet, J. *J. Organomet. Chem.* ***1985***, *292*, 225; Corriu, R.J.P.; Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1988***, *29*, 1271. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1265–1266.

[1100] Kuivila, H.G. *J. Org. Chem.* ***1960***, *25*, 284; Walsh, Jr., E.J.; Stoneberg, R.L.; Yorke, M.; Kuivila, H.G. *J. Org. Chem.* ***1969***, *34*, 1156; Four, P.; Guibe, F. *J. Org. Chem.* ***1981***, *46*, 4439; Lusztyk, J.; Lusztyk, E.; Maillard, B.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 2923.

[1101] Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* ***2000***, *41*, 113.

[1102] Babler, J.H. *Synth. Commun.* ***1982***, *12*, 839. For the use of NaBH4 and metal ions, see Entwistle, I.D.; Boehm, P.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 27.

[1103] Shamsuddin, K.M.; Zubairi, Md.O.; Musharraf, M.A. *Tetrahedron Lett.* ***1998***, *39*, 8153.

19-40 Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes[1104]

Hydro-de-hydroxylation or Dehydroxylation (overall transformation)

$$\mathrm{RCOOH} \longrightarrow \mathrm{RCHO}$$
$$\mathrm{RCOOR'} \longrightarrow \mathrm{RCHO}$$

With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (**19-37**) and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes[1105] by treatment with Li in $\mathrm{MeNH_2}$ or $\mathrm{NH_3}$ followed by hydrolysis of the resulting imine,[1106] with

$$\mathrm{RCOOH} \xrightarrow[\mathrm{MeNH_2}]{\mathrm{Li}} \mathrm{RCH{=}N{-}Me} \xrightarrow{\mathrm{H_2O}} \mathrm{RCHO}$$

with thexylchloro(or bromo)borane-$\mathrm{Me_2S}$[1107] (see **15-16** for the thexyl group), $\mathrm{Me_2N{=}CHCl^+\ Cl^-}$ in pyridine,[1108] and with diaminoaluminum hydrides.[1109] Benzoic acid derivatives were reduced to benzaldehyde derivatives with $\mathrm{NaH_2PO_2}$ and a diacylperoxide and a palladium catalyst.[1110] Caproic and isovaleric acids have been reduced to aldehydes in 50% yields or better with DIBALH (i-$\mathrm{Bu_2AlH}$) at −75 to −70°C.[1111] Carboxylic acids can be reduced directly on Claycop–$\mathrm{H_2O_2}$ using microwave irradiation.[1112]

Carboxylic esters have been reduced to aldehydes with DIBALH at −70°C, with diaminoaluminum hydrides,[1113] with $\mathrm{LiAlH_4{-}Et_2NH}$,[1114] and for phenolic esters with $\mathrm{LiAlH(O{-}}t\mathrm{{-}Bu)_3}$ at 0°C.[1115] Aldehydes have also been prepared by reducing ethyl thiol esters (RCOSEt) with $\mathrm{Et_3SiH}$ and a Pd—C catalyst.[1116] Pretreatment of

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[1104] For a review, see Cha, J.S. *Org. Prep. Proced. Int.* ***1989***, *21*, 451.

[1105] For other reagents, see Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1987***, *28*, 3941; Cha, J.S.; Kim, J.E.; Yoon, M.S.; Kim, Y.S. *Tetrahedron Lett.* ***1987***, *28*, 6231. See also, the lists, in Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1265–1268.

[1106] Bedenbaugh, A.O.; Bedenbaugh, J.H.; Bergin, W.A.; Adkins, J.D. *J. Am. Chem. Soc.* ***1970***, *92*, 5774.

[1107] Chloro - see Brown, H.C.; Cha, J.S.; Yoon, N.M.; Nazer, B. *J. Org. Chem.* ***1987***, *52*, 5400; Bromo, see Cha, J.S.; Kim, J.E.; Lee, K.W. *J. Org. Chem.* ***1987***, *52*, 5030.

[1108] Fujisawa, T.; Mori, T.; Tsuge, S.; Sato, T. *Tetrahedron Lett.* ***1983***, *24*, 1543.

[1109] Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1974***, 1447; ***1975***, 215; Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.

[1110] Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2002***, 836.

[1111] Zakharkin, L.I.; Sorokina, L.P. *J. Gen. Chem. USSR* ***1967***, *37*, 525.

[1112] Varma, R.S.; Dahiya, R. *Tetrahedron Lett.* ***1998***, *39*, 1307.

[1113] Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1974***, 1447; ***1975***, 215; Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.

[1114] Cha, J.S.; Kwon, S.S. *J. Org. Chem.* ***1987***, *52*, 5486.

[1115] Zakharkin, L.I.; Khorlina, I.M. *Tetrahedron Lett.* ***1962***, 619, *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 288; ***1964***, 435; Zakharkin, L.I.; Gavrilenko, V.V.; Maslin, D.N.; Khorlina, I.M. *Tetrahedron Lett.* ***1963***, 2087; Zakharkin, L.I.; Gavrilenko, V.V.; Maslin, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1964***, 867; Weissman, P.M.; Brown, H.C. *J. Org. Chem.* ***1966***, *31*, 283.

[1116] Fukuyama, T.; Lin, S.; Li, L. *J. Am. Chem. Soc.* ***1990***, *112*, 7050.

the acid with Me_3SiCl followed by reduction with DIBALH also gives the aldehyde.[1117] Thioesters have been reduced to the aldehyde with lithium metal in THF at −78°C, followed by quenching with methanol.[1118]

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracarbonylferrate, $Na_2Fe(CO)_4$.[1119] Heating a carboxylic acid, presumably to form the anhydride, and then reaction with Na/EtOH leads to the aldehyde.[1120]

Acid chlorides are reduced to aldehydes with Bu_3SnH and a nickel catalyst.[1121]

Also see, **19-62** and **19-38**.

OS **VI**, 312; **VIII**, 241, 498.

19-41 Reduction of Amides to Aldehydes

Hydro-de-dialkylamino-substitution

$$RCONR_2' + LiAlH_4 \longrightarrow RCHO + NHR_2'$$

N,N-Disubstituted amides can be reduced to amines with $LiAlH_4$ (see **19-64**), but also to aldehydes.[1122] Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction and primary alcohols are obtained instead. Other reagents[1123] that give good yields of aldehydes are DIBALH,[1124] $LiAlH(O\text{—}t\text{-}Bu)_3$, diaminoaluminum hydrides,[1125] disiamylborane (see **15-16** for the disiamyl group), [1126] and $Cp_2Zr(H)Cl$.[1127]

Aldehydes have been prepared from carboxylic acids or acyl halides by first converting them to certain types of amides that are easily reducible. There are several examples:[1128]

[1117] Chandrasekhar, S.; Kumar, M.S.; Muralidhar, B. *Tetrahedron Lett.* ***1998***, *39*, 909.

[1118] Penn, J.H.; Owens, W.H. *Tetrahedron Lett.* ***1992***, *33*, 3737.

[1119] Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 2490; Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Tomi, K.; Takegami, Y. *Tetrahedron Lett.* ***1975***, 1063.

[1120] Shi, Z.; Gu, H. *Synth. Commun.* ***1997***, *27*, 2701.

[1121] Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron Lett.* ***1997***, *38*, 8093.

[1122] For a review, see Fuson, R.C., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 220–225.

[1123] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.1269–1271.

[1124] Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 2046.

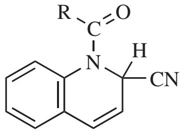
[1125] Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1975***, 875.

[1126] Godjoian, G.; Singaram, B. *Tetrahedron Lett.* ***1997***, *38*, 1717.

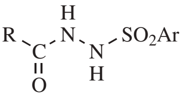
[1127] White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* ***2000***, *122*, 11995.

[1128] For other examples, see Doleschall, G. *Tetrahedron* ***1976***, *32*, 2549; Atta-ur-Rahman; Basha, A. *J. Chem. Soc. Chem. Commun.* ***1976***, 594; Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 555; Craig, J.C.; Ekwurieb, N.N.; Fu, C.C.; Walker, K.A.M. *Synthesis* ***1981***, 303.

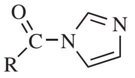
1. *Reissert Compounds.*[1129] Compounds such as **44** are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **44** with sulfuric acid gives the corresponding aldehyde.



44



45



46

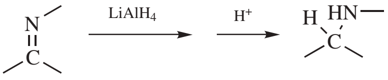
2. *Acyl Sulfonylhydrazides.* Compounds such as **45** are cleaved with base to give aldehydes. This is known as the *McFadyen–Stevens reduction* and is applicable only to aromatic aldehydes or aliphatic aldehydes with no a hydrogen.[1130] RCON=NH (see **19-67**) has been proposed as an intermediate in this reaction.[1131]
3. *Imidazoles.* Compounds **46**[1132] can be reduced to aldehydes with $LiAlH_4$.
4. *See Also the Sonn–Müller Method.* (**19-44**).

OS **VIII**, 68. See OS **IV**, 641, **VI**, 115 for the preparation of Reissert compounds.

B. Attack at Non-Carbonyl Multiple-Bonded Heteroatoms

19-42 Reduction of the Carbon–Nitrogen Double Bond

C,*N*-Dihydro-addition



Imines and Schiff bases,[1133] hydrazones,[1134] and other C=N compounds can be reduced with $LiAlH_4$, $NaBH_4$,[1135] Na–EtOH, hydrogen and a catalyst, as well as

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[1129] For reviews of Reissert compounds, see Popp, F.D.; Uff, B.C. *Heterocycles* ***1985***, *23*, 731; Popp, F.D. *Bull. Soc. Chim. Belg.* ***1981***, *90*, 609; *Adv. Heterocycl. Chem.* ***1979***, *24*, 187; ***1968***, *9*, 1. See Bridge, A.W.; Hursthouse, M.B.; Lehmann, C.W.; Lythgoe, D.J.; Newton, C.G. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1839 for isoquinoline Reissert salts.

[1130] Babad, H.; Herbert, W.; Stiles, A.W. *Tetrahedron Lett.* ***1966***, 2927; Dudman, C.C.; Grice, P.; Reese, C.B. *Tetrahedron Lett.* ***1980***, *21*, 4645.

[1131] For discussions, see Cacchi, S.; Paolucci, G. *Gazz. Chem. Ital.* ***1974***, *104*, 221; Matin, S.B.; Craig, J.C.; Chan, R.P.K. *J. Org. Chem.* ***1974***, *39*, 2285.

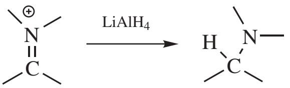
[1132] For a review, see Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61.

[1133] See Ranu, B.C.; Sarkar, A.; Majee, A. *J. Org. Chem.* ***1997***, *62*, 1841; Verdaguer, X.; Lange, U.E.W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1103; Amin, Sk.R.; Crowe, W.E. *Tetrahedron Lett.* ***1997***, *38*, 7487; Vetter, A.H.; Berkessel, A. *Synthesis* ***1995***, 419.

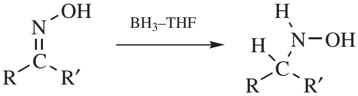
[1134] For an enantioselective reduction of hydrazone derivatives, see Burk, M.J.; Feaster, J.E. *J. Am. Chem. Soc.* ***1992***, *114*, 6266.

[1135] Bhattacharyya, S.; Neidigh, K.A.; Avery, M.A.; Williamson, J.S. *Synlett* ***1999***, 1781.

with other reducing agents.[1136] A mixture of Sm/I_2[1137] or In/NH_4Cl[1138] reduces imines. Reduction with Bu_2SnClH in HMPA has been shown to be chemoselective for imines.[1139] Iminium salts are also reduced by $LiAlH_4$, although here there is no "addition" to the nitrogen:[1140] Silanes[1141] with a triarylborane catalyst reduces *N*-sulfonyl imines[1142] as does TiI_4.[1143] Imines are reduced with Cl_3SiH and pyrrolidine carboxaldehyde,[1144] Samarium bromide in HMPA,[1145] Z-propanol with a ruthenium catalyst,[1146] and with triethylammonium formate with microwave irradiation.[1147] Oximes are reduced with hydrogen gas an a catalytic amount of 48% HBr.[1148]



Oximes are generally reduced to amines (**19-48**),[1149] but simple reduction to give hydroxylamines can be accomplished with borane[1150] or sodium cyanoborohydride.[1151] Oxime *O*-ethers are reduced with Bu_3SnH and BF_3•OEt_2.[1152] Diazo compounds (ArN=NAr) are reductively cleaved to aniline derivatives with Zn and ammonium formate in methanol.[1153]



[1136] For a review, see Harada, K., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 276–293. For a review with respect to catalytic hydrogenation, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 123–138.

[1137] Banik, B.K.; Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F.F. *Tetrahedron Lett.* ***1999***, *40*, 6731.

[1138] Banik, B.K.; Hackfeld, L.; Becker, F.F. *Synth. Commun.* ***22001***, *31*, 1581.

[1139] Shibata, I.; Moriuchi-Kawakami, T.; Tanizawa, D.; Suwa, T.; Sugiyama, E.; Matsuda, H.; Baba, A. *J. Org. Chem.* ***1998***, *63*, 383.

[1140] For a review of nucleophilic addition to iminium salts, see Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 275–356.

[1141] For a discussion of noncovalent interactions in the reduction of imines, see Malkov, A.V.; Mariani, A.; MacDougall, K.N.; Koč ovský, P. *Org. Lett.* ***2004***, *6*, 2253.

[1142] Blackwell, J.M.; Sonmor, E.R.; Scoccitti, T.; Piers, W.E. *Org. Lett.* ***2000***, *2*, 3921.

[1143] Shimizu, M.; Sahara, T.; Hayakawa, R. *Chem. Lett.* ***2001***, 792.

[1144] Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* ***2001***, *42*, 2525.

[1145] Knettle, B.W.; Flowers II, R.A. *Org. Lett.* ***2001***, *3*, 2321.

[1146] Samec, J.S.M.; Bäckvall, J.-E. *Chem. Eur. J.* ***2002***, *8*, 2955.

[1147] Moghaddam, F.M.; Khakshoor, O.; Ghaffarzadeh, M. *J. Chem. Res. (S)* ***2001***, 525.

[1148] Davies, I.W.; Taylor, M., Marcoux, J.-F.; Matty, L.; Wu, J.; Hughes, D.; Reider, P.J. *Tetrahedron Lett.* ***2000***, *41*, 8021.

[1149] For examples, see Bolm, C.; Felder, M. *Synlett* ***1994***, 655; Williams, D.R.; Osterhout, M.H.; Reddy, J.P. *Tetrahedron Lett.* ***1993***, *34*, 3271.

[1150] Feuer, H.; Vincent Jr., B.F.; Bartlett, R.S. *J. Org. Chem.* ***1965***, *30*, 2877; Kawase, M.; Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 643.

[1151] For reviews of $NaBH_3CN$, see Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* ***1979***, *11*, 201; Lane, C.F. *Synthesis* ***1975***, 135.

[1152] Ueda, M.; Miyabe, H.; Namba, M.; Nakabayashi, T.; Naito, T. *Tetrahedron Lett.* ***2002***, *43*, 4369.

[1153] Gowda, S.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2002***, *43*, 1329.

Reduction of imines has been carried out enantioselectively.[1154] Catalytic hydrogenation with a chiral iridium[1155] or palladium[1156] catalyst has been used. Catalytic hydrogenation of iminium salts with a chiral ruthenium catalyst gives the amine.[1157] In a related reaction, enamines were reduced by hydrogenation over a chiral rhodium catalyst.[1158] An ammonium formate with a chiral ruthenium complex was used with imines.[1159] Hydrogenation of oximes with Pd/C and a nickel complex gives the imine, and in the presence of a lipase and ethyl acetate the final product was an acetamide, formed with high enantioselectivity.[1160] Conjugated *N*-sulfonyl imines are reduced to the conjugated sulfonamide with good enantioselectivity using a chiral rhodium catalyst in the presence of LiF and $PhSnMe_3$.[1161] Phosphinyl imines, $R_2C{=}N{-}P({=}O)Ar_2$, are reduced with high enantioselectivity using a chiral copper catalyst.[1162] Silanes, such as $PhSiH_3$, can be used for the reduction of imines, and in the presence of a chiral titanium catalyst the resulting amine was formed with excellent enantioselectivity.[1163]

Isocyanates have been catalytically hydrogenated to *N*-substituted formamides: RNCO → R–NH–CHO.[1164] Isothiocyanates were reduced to thioformamides with SmI_2 in HMPA/*t*-BuOH.[1165]

OS **III**, 328, 827; **VI**, 905; **VIII**, 110, 568. Also see, OS **IV**, 283.

19-43 The Reduction of Nitriles to Amines

***CC*,*NN*-Tetrahydro-biaddition**

$$R{-}C{\equiv}N + LiAlH_4 \longrightarrow R{-}CH_2{-}NH_2$$

Nitriles can be reduced to primary amines with many reducing agents,[1166] including $LiAlH_4$, and $H_3B{\bullet}SMe_2{\bullet}$.[1167] The reagent $NaBH_4$ does not generally

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[1154] See Denmark, S.E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* ***1994***, *116*, 8797; Fuller, J.C.; Belisle, C.M.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 5389; Willoughby, C.A.; Buchwald, S.L. *J. Org. Chem.* ***1993***, *58*, 7627; *J. Am. Chem. Soc.* ***1992***, *114*, 7562; Kawate, T.; Nakagawa, M.; Kakikawa, T.; Hino, T. *Tetrahedron Asymmetry* ***1992***, *3*, 227. For a review of asymmetric reductions involving the C=N unit, see Zhu, Q.-C.; Hutchins, R.O. *Org. Prep. Proceed. Int.* ***1994***, *26*, 193.

[1155] Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* ***1999***, *121*, 6421; Xiao, D.; Zhang, X. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3425; Trifonova, A.; Diesen, J.S.; Chapman, C.J.; Andersson, P.G. *Org. Lett.* ***2004***, *6*, 3825.

[1156] Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* ***2001***, *3*, 313.

[1157] Magee, M.P.; Norton, J.R. *J. Am. Chem. Soc.* ***2001***, *123*, 1778.

[1158] Tararov, V.I.; Kadyrov, R.; Riermeier, T.H.; Holz, J.; Börner, A. *Tetrahedron Lett.* ***2000***, *41*, 2351.

[1159] Mao, J.; Baker, D.C. *Org. Lett.* ***1999***, *1*, 841.

[1160] Choi, Y.K.; Kim, M.J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* ***2001***, *3*, 4099.

[1161] Hayashi, T.; Ishigedani, M. *Tetrahedron* ***2001***, *57*, 2589.

[1162] Lipshutz, B.H.; Shimizu, H. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2228.

[1163] Hansen, M.C.; Buchwald, S.L. *Org. Lett.* ***2000***, *2*, 713.

[1164] Howell, H.G. *Synth. Commun.* ***1983***, *13*, 635.

[1165] Park, H.S.; Lee, I.S.; Kim, Y.H. *Chem. Commun.* ***1996***, 1805.

[1166] For a review, see Rabinovitz, M., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 307–340. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 875–878.

[1167] See Brown, H.C.; Choi, Y.M.; Narasimhan, S. *Synthesis* ***1981***, 605.

reduce nitriles except in alcoholic solvents with a catlayst, such as $CoCl_2$,[1168] $NiCl_2$,[1169] or Raney nickel.[1170] A mixture of $NaBH_4/NiCl_2$ in acetic anhydride reduces the nitrile to the amine, which is trapped as the acetamide.[1171] Lithium dimethylamino- borohydride ($LiBH_3NMe_2$) reduces aryl nitriles to the corresponding benzylamines.[1172]

The reduction of nitriles is of wide scope and has been applied to many nitriles. When catalytic hydrogenation is used, secondary amines, $(RCH_2)_2NH$, are often side products.[1173] These can be avoided by adding a compound, such as acetic anhydride, which removes the primary amine as soon as it is formed,[1174] or by the use of excess ammonia to drive the equilibria backward.[1175] Sponge nickel[1176] or nickel on silica gel[1177] have been used for the catalytic hydrogenation of aryl nitriles to amines.

Attempts to stop with the addition with only 1 equivalent of hydrogen, have failed that is, to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (**19-44**).

N-Alkylnitrilium ions are reduced to secondary amines by $NaBH_4$.[1178]

$$RCN \xrightarrow{R'_3O^+BF_4^-} R{-}C{\equiv}N^{\oplus}{-}R' \xrightarrow[\text{diglyme}]{NaBH_4} RCH_2{-}NH{-}R'$$

Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see **16-8**), this is a method for the conversion of nitriles to secondary amines.

Note that the related compounds, the isonitriles ($R{-}^{\oplus}N{\equiv}C^{\ominus}$, also called isocyanides) have been reduced to *N*-methylamines with $LiAlH_4$, as well as with other reducing agents.

OS **III**, 229, 358, 720; **VI**, 223.

[1168] Satoh, T.; Suzuki, S. *Tetrahedron Lett.* ***1969***, 4555. For a discussion of the mechanism, see Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1982***, *104*, 6801.

[1169] Khurana, J.M.; Kukreja, G. *Synth. Commun.* ***2002***, *32*, 1265.

[1170] Egli, R.A. *Helv. Chim. Acta* ***1970***, *53*, 47.

[1171] Caddick, S.; de K. Haynes, A.K.; Judd, D.B.; Williams, M.R.V. *Tetrahedron Lett.* ***2000***, *41*, 3513.

[1172] Thomas, S.; Collins, C.J.; Cuzens, J.R.; Spieciarich, D.; Goralski, C.T.; Singaram, B. *J. Org. Chem.* ***2001***, *66*, 1999.

[1173] For a method of making secondary amines the main products, see Galán, A.; de Mendoza, J.; Prados, P.; Rojo, J.; Echavarren, A.M. *J. Org. Chem.* ***1991***, *56*, 452.

[1174] For example, see Carothers, W.H.; Jones, G.A. *J. Am. Chem. Soc.* ***1925***, *47*, 3051; Gould, F.E.; Johnson, G.S.; Ferris, A.F. *J. Org. Chem.* ***1960***, *25*, 1658.

[1175] For example, see Freifelder, M. *J. Am. Chem. Soc.* ***1960***, *82*, 2386.

[1176] Tanaka, K.; Nagasawa, M.; Kasuga, Y.; Sakamura, H.; Takuma, Y.; Iwatani, K. *Tetrahedron Lett.* ***1999***, *40*, 5885.

[1177] Takamizawa, S.; Wakasa, N.; Fuchikami, T. *Synlett* ***2001***, 1623.

[1178] Borch, R.F. *Chem. Commun.* ***1968***, 442.

19-44 The Reduction of Nitriles to Aldehydes

Hydro,oxy-de-nitrilo-tersubstitution

$$\mathrm{R{-}C{\equiv}N} \xrightarrow[\text{2. hydrolysis}]{\text{1. HCl, SnCl}_2} \mathrm{RCH{=}O}$$

There are two principal methods for the reduction of nitriles to aldehydes.[1179] In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form an iminium salt, **47**.

$$\mathrm{RCCl} = \overset{\oplus}{\mathrm{N}}\mathrm{H_2} \quad \overset{\ominus}{\mathrm{Cl}}$$

47

Iminium salt **47** is reduced with anhydrous $SnCl_2$ to RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (**16-2**) to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[1180] It is also possible to prepare **47** in a different way, by treating ArCONHPh with PCl_5, which can then be converted to the aldehyde. This is known as the *Sonn–Müller method.* Aqueous formic acid in the presence of PtO_2, followed by treatment with aqueous acid, converts aryl nitriles to aryl aldehydes.[1181]

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 equivalent of hydrogen and hydrolysis, *in situ*, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$,[1182] $LiAlH(NR_2)_3$,[1183] and DIBALH.[1184] The metal hydride method is useful for aliphatic and aromatic nitriles.

OS **III**, 626, 818; **VI**, 631.

19-45 Reduction of Nitro Compounds to Amines

$$\mathrm{RNO_2} \xrightarrow[\text{HCl}]{\text{Zn}} \mathrm{RNH_2}$$

Both aliphatic[1185] and aromatic nitro compounds can be reduced to amines, although the reaction has been applied much more often to aromatic nitro

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[1179] For a review, see Rabinovitz, M., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, p. 307. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1271–1272.

[1180] Zil'berman, E.N.; Pyryalova, P.S. *J. Gen. Chem. USSR* ***1963***, *33*, 3348.

[1181] Xi, F.; Kamal, F.; Schenerman, M.A. *Tetrahedron Lett.* ***2002***, *43*, 1395.

[1182] Brown, H.C.; Shoaf, C.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1079. For a review of reductions with this and related reagents, see Málek, J. *Org. React.* ***1988***, *36*, 249, see pp. 287–289, 438–448.

[1183] Cha, J.S.; Lee, S.E.; Lee, H.S. *Org. Prep. Proceed. Int.* ***1992***, *24*, 331. Also see, Cha, J.S.; Jeoung, M.K.; Kim, J.M.; Kwon, O.O.; Lee, J.C. *Org. Prep. Proceed. Int.* ***1994***, *26*, 583.

[1184] Miller, A.E.G.; Biss, J.W.; Schwartzman, L.H. *J. Org. Chem.* ***1959***, *24*, 627; Marshall, J.A.; Andersen, N.H.; Schlicher, J.W. *J. Org. Chem.* ***1970***, *35*, 858.

[1185] For a review of selective reduction of aliphatic nitro compounds without disturbance of other functional groups, see Ioffe, S.L.; Tartakovskii, V.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1966***, *35*, 19.

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.[1186] Indium metal in aqueous ethanol with ammonium chloride[1187] or with water in aq. THF[1188] also reduces aromatic nitro compounds to the corresponding aniline derivative. Indium metal in methanol, with acetic anhydride and acetic acid, converts aromatic nitro compounds to the acetanilide.[1189] Samarium and a catalytic amount of iodine also accomplishes this reduction,[1190] as does Sm with a bipyridinium dibromide in methanol.[1191] Samarium metal in methanol with ultrasound also reduces aryl nitro compounds.[1192] Sodium sulfide (NaHS) on alumina with microwave irradiation reduces aryl nitro compounds to aniline derivatives.[1193] A mild reduction uses Al(Hg) in aq. THF with ultrasound.[1194] An Al/$NiCl_2$ reagent was used to reduced the nitro group of a polymer-bound $CH_2OCH_2C_6H_4NO_2$ moiety.[1195] Some other reagents used[1196] were $Et_3SiH/RhCl(PPh_3)_3$,[1197] AlH_3—$AlCl_3$, Mn with $CrCl_2$,[1198] nanoparticulate iron in water at 210°C,[1199] formic acid and Pd—C[1200] for formic acid with Raney nickel in methanol,[1201] and sulfides, such as NaHS, $(NH_4)_2S$, or polysulfides. The reaction with sulfides or polysulfides is called the *Zinin reduction*.[1202] Amines are also the products when nitro compounds, both alkyl and aryl, are reduced with $HCOONH_4$—Pd—C.[1203] Many other functional groups (e.g., COOH, COOR, CN, amide) are not affected by this reagent (although ketones are reduced, see **19-33**). With optically active alkyl substrates this method gives

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[1186] For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 104–116, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 168–202. See Deshpande, R.M.; Mahajan, A.N.; Diwakar, M.M.; Ozarde, P.S.; Chaudhari, R.V. *J. Org. Chem.* ***2004***, *69*, 4835; Wu, G.; Huang, M.; Richards, M.; Poirer, M.; Wen, X.; Draper, R.W. *Synthesis* ***2003***, 1657.

[1187] Moody, C.J.; Pitts, M.R. *Synlett* ***1998***, 1028; Banik, B.K.; Suhendra, M.; Banik, I.; Becker, F.F. *Synth. Commun.* ***2000***, *30*, 3745.

[1188] Lee, J.G.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Kang, Y.; Cho, Y.S. *Synthesis* ***2001***, 81.

[1189] Kim, B.H.; Han, R.; Piao, F.; Jun, Y.M.; Baik, W.; Lee, B.M. *Tetrahedron Lett.* ***2003***, *44*, 77.

[1190] Banik, B.K.; Mukhopadhyay, C.; Venkatraman, M.S.; Becker, F.F. *Tetrahedron Lett.* ***1998***, *39*, 7243; Wang, L.; Zhou, L.; Zhang, Y. *Synlett* ***1999***, 1065.

[1191] Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* ***2001***, *66*, 919.

[1192] Basu, M.K.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 5603.

[1193] Kanth, S.R.; Reddy, G.V.; Rao, V.V.V.N.S.R.; Maitraie, P.; Narsaiah, B.; Rao, P.S. *Synth. Commun.* ***2002***, *32*, 2849.

[1194] Fitch, R.W.; Luzzio, F.A. *Tetrahedron Lett.* ***1994***, *35*, 6013.

[1195] Kamal, A.; Reddy, K.L.; Devaiah, V.; Reddy, G.S.K. *Tetrahedron Lett.* ***2003***, *44*, 4741.

[1196] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 821–828.

[1197] Brinkman, H.R. *Synth. Commun.* ***1996***, *26*, 973.

[1198] Hari, A.; Miller, B.L. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2777.

[1199] Wang, L.; Li, P.; Wu, Z.; Yan, J.; Wang, M.; Ding, Y. *Synthesis* ***2003***, 2001.

[1200] Entwistle, I.D.; Jackson, A.E.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 443. See also, Terpko, M.O.; Heck, R.F. *J. Org. Chem.* ***1980***, *45*, 4992; Babler, J.H.; Sarussi, S.J. *Synth. Commun.* ***1981***, *11*, 925.

[1201] Gowda, D.C.; Gowda, A.S.P.; Baba, A.R.; Gowda, S. *Synth. Commun.* ***2000***, *30*, 2889.

[1202] For a review of the Zinin reduction, see Porter, H.K. *Org. React.* ***1973***, *20*, 455.

[1203] Ram, S.; Ehrenkaufer, R.E. *Tetrahedron Lett.* ***1984***, *25*, 3415.

retention of configuration.[1204] Ammonium formate in methanol reduces aromatic nitro compounds.[1205] Lithium aluminum hydride reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (**19-80**). Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, although both aliphatic and aromatic nitro compounds have been reduced to amines with $NaBH_4$ and various catalysts, such as $NiCl_2$ or $CoCl_2$[1206] phthalocyanine iron (II),[1207] and $ZrCl_4$.[1208] Borohydride exchange resin in the presence of $Ni(OAc)_2$, however, gives the amine.[1209] 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[1210] or in cleavage of the nitro group from the ring.[1211] 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.[1212] The nitro groups of *N*-nitro compounds can also be reduced to amino groups, for example, nitrourea $NH_2CONHNO_2$ gives semicarbazide $NH_2CONHNH_2$. Bakers yeast reduces aromatic nitro compounds to aniline derivatives.[1213] A combination of $NaH_2PO_2/FeSO_4$ with microwave irradiation reduces aromatic nitro compounds to aniline derivatives.[1214] Hydrazine on alumina, with $FeCl_3$ and microwave irradiation accomplishes this reduction.[1215] Hydrazine–formic acid with Raney nickel in methanol reduces aromatic nitro compounds.[1216] Heating aromatic nitro compounds with 57% HI reduces the nitro group to the amino group.[1217]

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (**19-46**), hydrazobenzenes, azobenzenes (**19-80**), and azoxybenzenes (**19-79**) 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. Reduction by metals in mineral acids cannot be stopped, but always produces the amine.

[1204] Barrett, A.G.M.; Spilling, C.D. *Tetrahedron Lett.* ***1988***, *29*, 5733.

[1205] Gowda, D.C.; Mahesh, B. *Synth. Commun.* ***2000***, *30*, 3639.

[1206] See, for example, Osby, J.O.; Ganem, B. *Tetrahedron Lett.* ***1985***, *26*, 6413; Petrini, M.; Ballini, R.; Rosini, G. *Synthesis* ***1987***, 713; He, Y.; Zhao, H.; Pan, X.; Wang, S. *Synth. Commun.* ***1989***, *19*, 3047. See also, references cited therein.

[1207] Wilkinson, H.S.; Tanoury, G.J.; Wald, S.A.; Senanayake, C.H. *Tetrahedron Lett.* ***2001***, *42*, 167.

[1208] Chary, K.P.; Ram, S.R.; Iyengar, D.S. *Synlett* ***2000***, 683.

[1209] Yoon, N.M.; Choi, J. *Synlett* ***1993***, 135.

[1210] Severin, T.; Schmitz, R. *Chem. Ber.* ***1962***, *95*, 1417; Severin, T.; Adam, M. *Chem. Ber.* ***1963***, *96*, 448.

[1211] Kaplan, L.A. *J. Am. Chem. Soc.* ***1964***, *86*, 740. See also, Swanwick, M.G.; Waters, W.A. *Chem. Commun.* ***1970***, 63.

[1212] This result has also been achieved by hydrogenation with certain catalysts [Lyle, R.E.; LaMattina, J.L. *Synthesis* ***1974***, 726; Knifton, J.F. *J. Org. Chem.* ***1976***, *41*, 1200; Ono, A.; Terasaki, S.; Tsuruoka, Y. *Chem. Ind. (London) 1983*, 477], and with hydrazine hydrate and Raney nickel: Ayyangar, N.R.; Kalkote, U.R.; Lugad, A.G.; Nikrad, P.V.; Sharma, V.K. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3159.

[1213] Baik, W.; Han, J.L.; Lee, K.C.; Lee, N.H.; Kim, B.H.; Hahn, J.-T. *Tetrahedron Lett.* ***1994***, *35*, 3965.

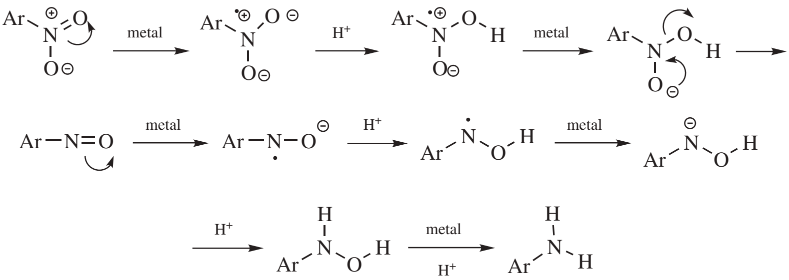
[1214] Meshram, H.M.; Ganesh, Y.S.S.; Sekhar, K.C.; Yadav, J.S. *Synlett* ***2000***, 993.

[1215] Vass, A.; Dudás, J.; Tóth, J.; Varma, R.S. *Tetrahedron Lett.* ***2001***, *42*, 5347.

[1216] Gowda, S.; Gowda, D.C. *Tetrahedron* ***2002***, *58*, 2211.

[1217] Kumar, J.S.D.; Ho, M.M.; Toyokuni, T. *Tetrahedron Lett.* ***2001***, *42*, 5601.

The mechanisms of these reductions have not been studied much, although 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 (**19-47**), and hydroxylamines can be isolated (**19-46**). With metals and acid the following path has been suggested:[1218]



Certain aromatic nitroso compounds (Ar—NO) can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 *M* aq. KCN with uv light.[1219] The reaction has also been performed electrochemically.[1220] 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.

Reductive alkylation of aromatic nitro compounds is possible. The reaction of nitrobenzene with allylic or benzyl halides in the presence of an excess of tin metal in methanol, leads to the *N,N*-diallyl or dibenzyl aniline.[1221] A similar reaction occurs with nitrobenzene, allyl bromide, and indium metal in aq. acetonitrile.[1222]

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; **81**, 188.

19-46 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,[1223] hydroxylamines are formed. Among other reagents used for this

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[1218] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 211.

[1219] Petersen, W.C.; Letsinger, R.L. *Tetrahedron Lett.* ***1971***, 2197; Vink, J.A.J.; Cornelisse, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1333.

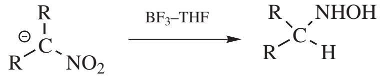
[1220] Lamoureux, C.; Moinet, C. *Bull. Soc. Chim. Fr.* ***1988***, 59.

[1221] Bieber, L.W.; da Costa, R.C.; da Silva, M.F. *Tetahedron Lett.* ***2000***, *41*, 4827.

[1222] Kang, K.H.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Chung, B.Y.; Cho, Y.S. *Synth. Commun.* ***2001***, *31*, 2277.

[1223] For some other methods of accomplishing this conversion, see Rondestvedt Jr., C.S.; Johnson, T.A. *Synthesis* ***1977***, 850; Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P. *Tetrahedron* ***1978***, *34*, 213.

purpose have been SmI_2,[1224] N_2H_4–Rh–C,[1225] and $KBH_4/BiCl_3$.[1226] Borane in THF reduces aliphatic nitro enolate anions to hydroxylamines:[1227]



Nitro compounds have been reduced electrochemically, to hydroxylamines, as well as to other products.[1228]

OS **I**, 445; **III**, 668; **IV**, 148; **VI**, 803; **VIII**, 16.

19-47 Reduction of Nitroso Compounds and Hydroxylamines to Amines

***N*-Dihydro-de-oxo-bisubstitution**

$$\mathrm{RNO} \xrightarrow[\mathrm{HCl}]{\mathrm{Zn}} \mathrm{RNH_2}$$

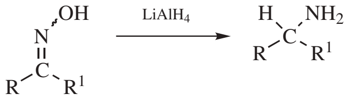
***N*-Hydro-de-hydroxylation or *N*-Dehydroxylation**

$$\mathrm{RNHOH} \xrightarrow[\mathrm{HCl}]{\mathrm{Zn}} \mathrm{RNH_2}$$

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents that reduce nitro compounds (**19-45**). Reaction with CuCl, and then phenylboronic acid (p. 815), also reduces nitroso compounds to the amine.[1229] A hydroxylamine can be reduced to the amine with CS_2 in acetonitrile.[1230] Indium metal in EtOH/aq. NH_4Cl reduces hydroxylamines to the amine.[1231] *N*-Nitroso compounds are similarly reduced to hydrazinesm $R_2N–NO \rightarrow R_2N–NH_2$.[1232]

OS **I**, 511; **II**, 33, 202, 211, 418; **III**, 91; **IV**, 247. See also, OS **VIII**, 93.

19-48 Reduction of Oximes to Primary Amines or Aziridines



[1224] Kende, A.S.; Mendoza, J.S. *Tetrahedron Lett.* ***1991***, *32*, 1699.

[1225] Oxley, P.W.; Adger, B.M.; Sasse, M.J.; Forth, M.A. *Org. Synth.* ***67***, 187.

[1226] Ren, P.D-D.; Pan, X.-W.; Jin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997***, *27*, 3497.

[1227] Feuer, H.; Bartlett, R.S.; Vincent Jr., B.F.; Anderson, R.S. *J. Org. Chem.* ***1965***, *31*, 2880.

[1228] For reviews of the electroreduction of nitro compounds, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 188–198; Lund, H. in Baizer; Lund *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 285–313.

[1229] Yu, Y.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2004***, *6*, 2631.

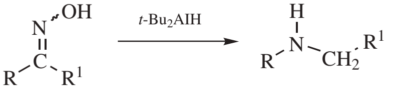
[1230] Schwartz, M.A..; Gu, J.; Hu, X. *Tetrahedron Lett.* ***1992***, *33*, 1687.

[1231] Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* ***2003***, *5*, 1773.

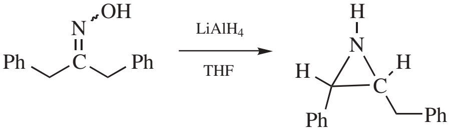
[1232] For examples of this reduction, accomplished with titanium reagents, see Entwistle, I.D.; Johnstone, R.A.W.; Wilby, A.H. *Tetrahedron* ***1982***, *38*, 419; Lunn, G.; Sansone, E.B.; Keefer, L.K. *J. Org. Chem.* ***1984***, *49*, 3470.

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% PhCHOHCH=NOH.[1233] Among other reducing agents that give this reduction[1234] are zinc and acetic acid, BH_3,[1235] $NaBH_3CN$—$TiCl_3$,[1236] polymethylhydrosiloxane (PMHS) with Pd-C,[1237] and sodium and an alcohol.[1238] Catalytic hydrogenation is also effective.[1239] The reduction has been performed enantioselectively with Baker's yeast[1240] and with Ph_2SiH_2 and an optically active rhodium complex catalyst.[1241] Reduction of oximes with indium metal in acetic anhydride/acetic acid–THF leads to the acetamide.[1242] Oxime *O*-ethers are reduced to the amine with modest enantioselectivity using a chiral oxazaboroline.[1243]

When the reducing agent is DIBALH, the product is a secondary amine, arising from a rearrangement:[1244]



With certain oximes (e.g., those of the type $ArCH_2CR$=NOH), treatment with $LiAlH_4$ gives aziridines,[1245] for example,



Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including Zn—HCl and H_2 and Raney nickel.

[1233] Felkin, H. *C. R. Acad. Sci.* ***1950***, *230*, 304.

[1234] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 845–846.

[1235] Feuer, H.; Braunstein, D.M. *J. Org. Chem.* ***1969***, *34*, 1817.

[1236] Leeds, J.P.; Kirst, H.A. *Synth. Commun.* ***1988***, *18*, 777.

[1237] Chandrasekhar, S.; Reddy, M.V.; Chandraiah, L. *Synlett* ***2000***, 1351.

[1238] For example, see Sugden, J.K.; Patel, J.J.B. *Chem. Ind. (London)* ***1972***, 683.

[1239] For a review, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 139–159.

[1240] Gibbs, D.E.; Barnes, D. *Tetrahedron Lett.* ***1990***, *31*, 5555.

[1241] Brunner, H.; Becker, R.; Gauder, S. *Organometallics* ***1986***, *5*, 739; Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* ***2001***, 2360.

[1242] Harrison, J.R.; Moody, C.J.; Pitts, M.R. *Synlett* ***2000***, 1601.

[1243] Fontaine, E.; Namane, C.; Meneyrol, J.; Geslin, M.; Serva, L.; Russey, E.; Tissandié, S.; Maftouh, M.; Roger, P. *Tetrahedron Asymmetry* ***2001***, *12*, 2185.

[1244] Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* ***1983***, *24*, 4711; Graham, S.H.; Williams, A.J.S. *Tetrahedron* ***1965***, *21*, 3263.

[1245] For a review, see Kotera, K.; Kitahonoki, K. *Org. Prep. Proced.* ***1969***, *1*, 305. For examples, see Tatchell, A.R. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 1294; Ferrero, L.; Rouillard, M.; Decouzon, M.; Azzaro, M. *Tetrahedron Lett.* ***1974***, 131; Diab, Y.; Laurent, A.; Mison, P. *Tetrahedron Lett.* ***1974***, 1605.

Oximes have been reduced in a different way, to give imines ($RR'C{=}NOH \rightarrow RR'C{=}NH$), which are generally unstable but which can be trapped to give useful products. Among reagents used for this purpose have been $Bu_3P{-}SPh_2$[1246] and $Ru_3(CO)_{12}$.[1247] Oximes can also be reduced to hydroxylamines (**19-42**). Nitrones have been reduced to imines using $AlCl_3{\bullet}6\ H_2O/KI$ followed by $Na_2S_2O_3{-}H_2O$.[1248]

OS **II**, 318; **III**, 513; **V**, 32, 83, 373, 376.

19-49 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles

$$RCH_2NO_2 \xrightarrow[HOAc]{Zn} RCH{=}NOH$$

Nitro compounds that contain an α hydrogen can be reduced to oximes with zinc dust in acetic acid[1249] or with other reagents, among them $CS_2{-}NEt_3$,[1250] $CrCl_2$,[1251] and (for α-nitro sulfones) $NaNO_2$.[1252] α-Nitro alkenes have been converted to oximes

$$-\overset{|}{C}{=}\overset{|}{C}-NO_2 \longrightarrow -\overset{|}{C}H-\overset{|}{C}{=}NOH$$

with sodium hypophosphite, indium with aq. $NH_4Cl/MeOH$,[1253] and with Pb—HOAc—DMF, as well as with certain other reagents.[1254]

$$RCH_2NO_2 \xrightarrow{NaBH_2S_3} RC{\equiv}N$$

Primary aliphatic nitro compounds can be reduced to aliphatic nitriles with sodium dihydro(trithio)borate[1087] or with t-$BuN{\equiv}C/BuN{=}C{=}O$.[1255] Secondary compounds give mostly ketones (e.g., nitrocyclohexane gave 45% cyclohexanone, 30% cyclohexanone oxime, and 19% *N*-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent (see also, **19-45**).

OS **IV**, 932.

[1246] Barton, D.H.R.; Motherwell, W.B.; Simon, E.S.; Zard, S.Z. *J. Chem. Soc. Chem. Commun.* ***1984***, 337.

[1247] Akazome, M.; Tsuji, Y.; Watanabe, Y. *Chem. Lett.* ***1990***, 635.

[1248] Boruah, M.; Konwar, D. *Synlett* ***2001***, 795.

[1249] Johnson, K.; Degering, E.F. *J. Am. Chem. Soc.* ***1939***, *61*, 3194.

[1250] Barton, D.H.R.; Fernandez, I.; Richard, C.S.; Zard, S.Z. *Tetrahedron* ***1987***, *43*, 551; Albanese, D.; Landini, D.; Penso, M. *Synthesis* ***1990***, 333.

[1251] Hanson, J.R. *Synthesis* ***1974***, 1, pp. 7-8.

[1252] Zeilstra, J.J.; Engberts, J.B.F.N. *Synthesis* ***1974***, 49.

[1253] Yadav, J.S.; Subba Reddy, B.V.; Srinivas, R.; Ramalingam, T. *Synlett* ***2000***, 1447.

[1254] See Kabalka, G.W.; Pace, E.D.; Wadgaonkar, P.P. *Synth. Commun.* ***1990***, *20*, 2453; Sera, A.; Yamauchi, H.; Yamada, H.; Itoh, K. *Synlett* ***1990***, 477.

[1255] El Kaim, L.; Gacon, A. *Tetrahedron Lett.* ***1997***, *38*, 3391.

19-50 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,[1256] including $NaBH_4$, $NaBH_4/LiCl$,[1257] $NaBH_4/CoCl_2/H_2O$,[1258] $NaBH_4/ZrCl_4$,[1259] $BHCl_2{\bullet}SMe_2$,[1260] H_2 and a catalyst, $Bu_3SnH/PhSiH_3$/AIBN,[1261] Mg or Ca in MeOH,[1262] $Sm/NiCl_2$,[1263] Zn-$FeCl_3$/EtOH,[1264] Zn/NH_4Cl/aq. EtOH,[1265] $FeCl_3/NaI$,[1266] $FeSO_4/NH_3/MeOH$,[1267] baker's yeast,[1268] Sm/I_2,[1269] Indium metal in EtOH,[1270] $LiMe_2NBH_3$,[1271] and tin complexes prepared from $SnCl_2$ or $Sn(SR)_2$.[1272] Reaction with PPh_3 leads to a phosphazide, $Ph_3P{=}N{-}N{=}N{-}R$, which loses nitrogen in what is called the *Staudinger reaction*[1273] a method to prepare phosphazo compounds, but in this case leads to reduction. Alkylation is possible, and the reaction of an alkyl azide with PMe_3, and then an excess of iodomethane leads to the *N*-methylated amine.[1274] This reaction, combined with RX → RN_3 (**10-43**), 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.[1275] Sulfonyl azides RSO_2N_3

[1256] For a review, see Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297, see pp. 321–327. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 815–820; Rolla, F. *J. Org. Chem.* ***1982***, *47*, 4327.

[1257] Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 4495.

[1258] Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* ***2000***, 646.

[1259] Chary, K.P.; Ram, S.R.; Salahuddin, S.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3559.

[1260] Salunkhe, A.M.; Ramachandran, P.V.; Brown, H.C. *Tetrahedron* ***2002***, *58*, 10059.

[1261] Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998***, *63*, 2796.

[1262] Maiti, S.N.; Spevak, P.; Narender Reddy, A.V. *Synth. Commun.* ***1988***, *18*, 1201.

[1263] Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* ***2002***, *32*, 189.

[1264] Pathak, D.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2000***, 816.

[1265] Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* ***2002***, *32*, 3279.

[1266] Kamal, A.; Ramana, K.V.; Ankati, H.B.; Ramana, A.V. *Tetrahedron Lett.* ***2002***, *43*, 6861.

[1267] Kamal, A.; Laxman, E.; Arifuddin, M. *Tetrahedron Lett.* ***2000***, *41*, 7743.

[1268] Kamal, A.; Damayanthi, Y.; Reddy, B.S.N.; Lakminarayana, B.; Reddy, B.S.P. *Chem. Commun.* ***1997***, 1015; Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synlett* ***1996***, 1193.

[1269] Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* ***1997***, *38*, 1065.

[1270] Reddy, G.V.; Rao, G.V.; Iyengar, D.S. *Tetrahedron Lett.* ***1999***, *40*, 3937.

[1271] Alvarez, S.G.; Fisher, G.B.; Singaram, B. *Tetrahedron Lett.* ***1995***, *36*, 2567.

[1272] Bartra, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* ***1990***, *46*, 587. See also, Bosch, I.; Costa, A.M.; Martín, M.; Urpí, F.; Vilarrasa, J. *Org. Lett.* ***2000***, *2*, 397.

[1273] First reported by Staudinger, H.; Meyer, J. *Helv. Chim. Acta* ***1919***, *2*, 635. For a review, see Golobov, Y.G.; Zhmurova, I.N.; Kasukhin, L.F. *Tetrahedron* ***1981***, *37*, 437. For a discussion of the mechanism, see Tian, W.Q.; Wang, Y.A. *J. Org. Chem.* ***2004***, *69*, 4299. For a modification that leads to β-lactams, see Krishnaswamy, D.; Bhawal, B.M.; Deshmukh, A.R.A.S. *Tetrahedron Lett.* ***2000***, *41*, 417; Wack, H.; Drury III, W.J.; Taggi, A.E.; Ferraris, D.; Lectka, T. *Org. Lett.* ***1999***, *1*, 1985.

[1274] Kato, H.; Ohmori, K.; Suzuki, K. *Synlett* ***2001***, 1003.

[1275] See, for example, Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* ***1985***, 202; ***1987***, 487. The reactions **10-48**, **10-43**, and **19-50** have also been accomplished in one laboratory step: Koziara, A. *J. Chem. Res. (S)* ***1989***, 296.

have been reduced to sulfonamides RSO_2NH_2 by irradiation in isopropyl alcohol[1276] and with NaH.[1277]

OS **V**, 586; **VII**, 433.

19-51 Reduction of Miscellaneous Nitrogen Compounds

Isocyanate–methylamine transformation $R{—}N{=}C{=}O \xrightarrow{LiAlH_4} R{—}NH{—}CH_3$

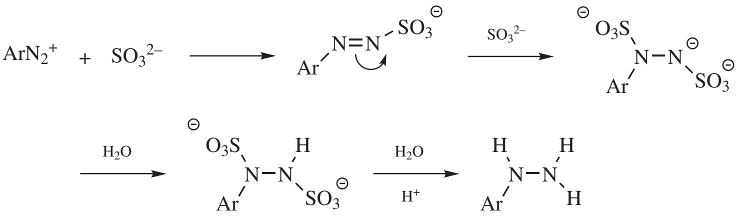
Isothiocyanate–methylamine transformation $R{—}N{=}C{=}S \xrightarrow{LiAlH_4} R{—}NH{—}CH_3$

***N,N*-Dihydro-addition** $Ar{—}N{=}N{—}Ar \xrightarrow[\text{catalyst}]{H_2} Ar{—}NH{—}NH{—}Ar$

Diazonium–arylhydrazone reduction $ArN_2{}^+\ Cl^- \xrightarrow{Na_2SO_3} ArNHNH_2$

***N*-Hydro-de-nitroso-substitution** $R_2N{—}NO \xrightarrow[Ni]{H_2} R_2NH$

Isocyanates and isothiocyanates are reduced to methylamines on treatment with $LiAlH_4$. $LiAlH_4$ does not usually reduce azo compounds[1278] (indeed these are the products from $LiAlH_4$ reduction of nitro compounds, **19-80**), but these can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide[1279] (see **15-11**). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism.[1280]



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 (**19-69**). *N*-Nitrosoamines can be denitrosated to secondary amines by a number of reducing agents, including H_2 and a catalyst,[1281] BF_3—THF—$NaHCO_3$,[1282] and $NaBH_4$—$TiCl_4$,[1283] as well as by hydrolysis.[1284]

[1276] Reagen, M.T.; Nickon, A. *J. Am. Chem. Soc.* ***1968***, *90*, 4096.

[1277] Lee, Y.; Closson, W.D. *Tetrahedron Lett.* ***1974***, 381.

[1278] For a review see Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 601, 604–614.

[1279] For example, see Ioffe, B.V.; Sergeeva, Z.I.; Dumpis,Yu.Ya. *J. Org. Chem. USSR* ***1969***, *5*, 1683.

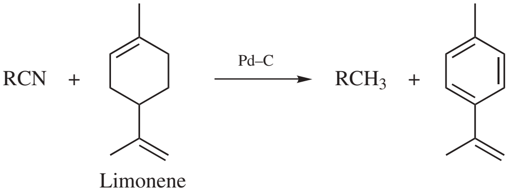
[1280] Huisgen, R.; Lux, R. *Chem. Ber.* ***1960***, *93*, 540.

[1281] Enders, D.; Hassel, T.; Pieter, R.; Renger, B.; Seebach, D. *Synthesis* ***1976***, 548.

[1282] Jeyaraman, R.; Ravindran, T. *Tetrahedron Lett.* ***1990***, *31*, 2787.

[1283] Kano, S.; Tanaka, Y.; Sugino, E.; Shibuya, S.; Hibino, S. *Synthesis* ***1980***, 741.

[1284] Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34, pp. 41–42.



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.[1285] Hydrogen gas (H_2) is also effective,[1286] although higher temperatures are required. The group 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.[1287]

Aryl nitro compounds are reduced to diaryl hydrazines with Al—KOH in methanol.[1288]

OS **I**, 442; **III**, 475. Also see, OS **V**, 43.

C. Reactions in Which a Heteroatom Is Removed from the Substrate

19-52 Reduction of Silanes to Methylene Compounds

Si-Hydrogen-uncoupling

$$\text{R–SiR}'_3 \longrightarrow \text{R–H}$$

In certain cases, the C—Si bond of silanes can be converted to C—H. α-Silyl esters are reduced to esters with mercuric acetate and tetrabutylammonium fluoride, for example.[1289]

19-53 Reduction of Alkyl Halides

Hydro-de-halogenation or Dehalogenation

$$\text{RX} \longrightarrow \text{RH}$$

This type of reduction can be accomplished with many reducing agents.[1290] A powerful, but highly useful reagent is $LiAlH_4$,[1291] which reduces almost all types of

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[1285] Kindler, K.; Lührs, K. *Chem. Ber.* ***1966***, *99*, 227; *Liebigs Ann. Chem.* ***1967***, *707*, 26.

[1286] See also Andrade, J.G.; Maier, W.F.; Zapf, L.; Schleyer, P.v.R. *Synthesis* ***1980***, 802; Brown, G.R.; Foubister, A.J. *Synthesis* ***1982***, 1036.

[1287] Takahashi, K.; Shibagaki, M.; Matsushita, H. *Chem. Lett.* ***1990***, 311.

[1288] Khurana, J.M.; Singh, *S. J. Chem. Soc., Perkin Trans. 1* ***1999***, 1893.

[1289] Poliskie, G.M.; Mader, M.M.; van Well, R. *Tetrahedron Lett.* ***1999***, *40*, 589.

[1290] For reviews, see Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181; Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 29–39.

[1291] For a review of LiAlH4, see Pizey, J.S. *Synthetic reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–294. For monographs on complex metal hydrides, see Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***.

alkyl halide, including vinylic, bridgehead, and cyclopropyl halides.[1292] Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. An even more powerful reducing agent, is lithium triethylborohydride ($LiEt_3BH$), which rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl halides.[1293] Another powerful reagent, which reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides, is a complex formed from lithium trimethoxyaluminum hydride, $LiAlH(OMe)_3$, and CuI.[1294] A milder reducing agent is $NaBH_4$ in a dipolar aprotic solvent, such as Me_2SO, DMF, or sulfolane,[1295] which at room temperature or above reduces primary, secondary, and some tertiary[1296] halides in good yield without affecting other functional groups that would be reduced by $LiAlH_4$, for example, COOH, COOR, CN.[1297] A mixture of $NaBH_4$ and $InCl_3$ efficiently reduces secondary bromides.[1298] Borohydride exchange resin is also an effective reducing agent in the presence of metal catalysts, such as $Ni(OAc)_2$,[1299] and Bu_4NBH_4, is also effective.[1300]

Other reducing agents[1301] include zinc (with acid or base), $SnCl_2$, SmI_2—THF—HMPA,[1302] and Et_3SiH in the presence of $AlCl_3$.[1303] Diethyl phosphonate–Et_3N,[1304] phosphorus tris(dimethylamide) $(Me_2N)_3P$,[1305] and organotin hydrides R_nSnH_{4-n}[1306] (chiefly Bu_3SnH) usually used in conjunction with a radical

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[1292] Jefford, C.W.; Kirkpatrick, D.; Delay, F. *J. Am. Chem. Soc.* ***1972***, *94*, 8905; Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1982***, *47*, 276.

[1293] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1980***, *45*, 849; ***1983***, *48*, 3085.

[1294] Masamune, S.; Rossy, P.A.; Bates, G.S. *J. Am. Chem. Soc.* ***1973***, *95*, 6452; Masamune, S.; Bates, G.S.; Georghiou, P.E. *J. Am. Chem. Soc.* ***1974***, *96*, 3686.

[1295] Bell, H.M.; Vanderslice, C.W.; Spehar, A. *J. Org. Chem.* ***1969***, *34*, 3923; Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* ***1969***, 3495; Vol'pin, M.E.; Dvolaitzky, M.; Levitin, I. *Bull. Soc. Chim. Fr.* ***1970***, 1526; Hutchins, R.O.; Kandasamy, D.; Dux III, F.; Maryanoff, C.A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* ***1978***, *43*, 2259.

[1296] Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971***, *36*, 1568.

[1297] For the use of $NaBH_4$ under phase-transfer conditions, see Bergbreiter, D.E.; Blanton, J.R. *J. Org. Chem.* ***1987***, *52*, 472.

[1298] Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* ***2002***, *124*, 906.

[1299] Yoon, N.M.; Lee, H.J.; Ahn, J.H.; Choi, J. *J. Org. Chem.* ***1994***, *59*, 4687.

[1300] Narasimhan, S.; Swarnalakshmi, S.; Balakumar, R.; Velmathi, S. *Synth. Commun.* ***1999***, *29*, 685.

[1301] For some other reducing agents, not mentioned here, see Akiba, K.; Shimizu, A.; Ohnari, H.; Ohkata, K. *Tetrahedron Lett.* ***1985***, *26*, 3211; Kim, S.; Yi, K.Y. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 789; Cole, S.J.; Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *J. Chem. Soc. Perkin Trans. 1* ***1991***, 103; Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181, Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 29–39.

[1302] For discussions of mechansims related to SmI_2 reduction of halides. Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* ***1987***, 1485; Shabangi, M.; Kuhlman, M.L.; Flowers II, R.A. *Org. Lett.* ***1999***, *1*, 2133. See also, Molander, G.A.; Hahn, G. *J. Org. Chem.* ***1986***, *51*, 1135. See Ogawa, A.; Ohya, S.; Hirao, T. *Chem. Lett.* ***1997***, 275 for reduction with $SmI_2/h\nu$.

[1303] Doyle, M.P.; McOsker, C.C.; West, C.T. *J. Org. Chem.* ***1976***, *41*, 1393; Parnes, Z.N.; Romanova, V.S.; Vol'pin, M.E. *J. Org. Chem. USSR* ***1988***, *24*, 254.

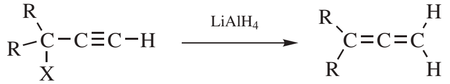
[1304] Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1881.

[1305] Downie, I.M.; Lee, J.B. *Tetrahedron Lett.* ***1968***, 4951.

[1306] Seyferth, D.; Yamazaki, H.; Alleston, D.L. *J. Org. Chem.* ***1963***, *28*, 703. For a novel trialkyltin hydride, see Gastaldi, S.; Stein, D. *Tetrahedron Lett.* ***2002***, *43*, 4309.

initiator, such as AIBN.[1307] Tributyltin hydride can be used in conjunction with transition-metal salts, such as $InCl_3$.[1308] The organotin hydride ($MeOCH_2CH_2OCH_2CH_2CH_2)_3SnH$ reduces alkyl halides and is water soluble, unlike Bu_3SnH.[1309] In a related area, silylated cyclohexadienes have been used with AIBN as radical-chain reducing reagents, effective for tertiary halides.[1310] Other transition metal-based reducing agents include $NiCl_2$,[1311] $Ni(OAc)_2/Al(acac)_3/NaH$.[1312] Raney nickel in Z-propanol reduces primary iodides in the presence of a lactone moiety.[1313] Aluminum amalgam efficiently reduced an iodohydrin to the alcohol.[1314] A polymer-bound dialkyltin halide has been used in conjunction with $NaBH_4$ to reduce alkyl bromides.[1315]

Reduction, especially of bromides and iodides, can also be effected by catalytic hydrogenation,[1316] and electrochemically.[1317] Raney nickel by itself can reduce alkyl halides.[1318] A good reducing agent for the removal of all halogen atoms in a polyhalo compound (including vinylic, allylic, geminal, and even bridgehead halogens) is lithium[1319] or sodium[1320] and *t*-BuOH in THF. Propargylic halides can often be reduced with allylic rearrangement to give allenes.[1321]



The choice of a reducing agent usually depends on what other functional groups are present. Each reducing agent reduces certain groups and not others. This type of

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[1307] For reviews of organotin hydrides, see Neumann, W.P. *Synthesis* ***1987***, 665; Kuivila, H.G. *Synthesis* ***1970***, 499, *Acc. Chem. Res.* ***1968***, *1*, 299. Tributyltin hydride also reduces vinyl halides in the prescence of a palladium catalyst. See Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* ***1996***, *37*, 6759.

[1308] Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* ***2001***, *42*, 4661; Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* ***2004***, *6*, 4981.

[1309] Light, J.; Breslow, R. *Tetrahedron Lett.* ***1990***, *31*, 2957.

[1310] Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J.C. *J. Am. Chem. Soc.* ***2003***, *125*, 5726.

[1311] Alonso, F.; Radivoy, G.; Yus, M. *Tetrahedron* ***1999***, *55*, 4441.

[1312] Massicot, F.; Schneider, R.; Fort, Y.; Illy-Cherry, S.; Tillement, O. *Tetrahedron* ***2000***, *56*, 4765.

[1313] Mebane, R.C.; Grimes, K.D.; Jenkins, S.R.; Deardorff, J.D.; Gross, B.H. *Synth. Commun.* ***2002***, *32*, 2049.

[1314] Wang, Y.-C.; Yan, T.-H. *Chem. Commun.* ***2000***, 545.

[1315] Enholm, E.J.; Schulte II, J.P. *Org. Lett.* ***1999***, *1*, 1275.

[1316] For a discussion, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***. See also, Kantam, M.L.; Rahman, A.; Bandyopadhyay, T.; Haritha, Y. *Synth. Commun.* ***1999***, *29*, 691.

[1317] For reviews, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 136–151; Feoktistov, L.G., in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 259–284.

[1318] For an example see Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.

[1319] For example, see Gassman, P.G.; Pape, P.G. *J. Org. Chem.* ***1964***, *29*, 160; Fieser, L.F.; Sachs, D.H. *J. Org. Chem.* ***1964***, *29*, 1113; Berkowitz, D.B. *Synthesis* ***1990***, 649.

[1320] For example, see Gassman, P.G.; Aue, D.H.; Patton, D.S. *J. Am. Chem. Soc.* ***1968***, *90*, 7271; Gassman, P.G.; Marshall, J.L. *Org. Synth.* *V*, 424.

[1321] For examples, see Crandall, J.K.; Keyton, D.J.; Kohne, J. *J. Org. Chem.* ***1968***, *33*, 3655; Claesson, A.; Olsson, L. *J. Am. Chem. Soc.* ***1979***, *101*, 7302.

selectivity is called *chemoselectivity.* A chemoselective reagent is one that reacts with one functional group (e.g., halide), but not another (e.g., C=O). For example, there are several reagents that reduce only the halogen of α-halo ketones, leaving the carbonyl group intact.[1322] Among them are polymer-supported triphenylphosphine,[1323] decaborane with 10% Pd/C,[1324] Bi in aq. THF[1325] or In metal in water,[1326] and *i*-Bu_2AlH—$SnCl_2$.[1327] In a similar chemoselective reaction, the halogen in α-haloimines has been reduced with $SnCl_2$/MeOH without reducing the C=N bond.[1328]

Both $NaBH_3CN$—$SnCl_2$.[1329] and the *n*-butyllithium ate complex of B-*n*-butyl-9-BBN[1330] (see p. 1077) reduce tertiary alkyl, benzylic, and allylic halides, but do not react with primary or secondary alkyl or aryl halides. Another highly selective reagent, in this case for primary and secondary iodo and bromo groups, is sodium cyanoborohydride, $NaBH_3CN$, in HMPA.[1331] Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides.[1332] See p. 1787 for a discussion of selectivity in reduction reactions.

Vinyl halides can be reduced to the corresponding alkene is some cases.[1333] As mentioned above, electrochemical reduction of aryl and vinyl halides is well known.[1334] When vinyl dibromides, such as $RCH{=}CBr_2$, are treated with $(MeO)_2P({=}O)H$ and triethylamine, for example, the product is the vinyl bromide $RCH{=}HBr$.[1335] Indium in ethanol accomplishes the same transformation.[1336] Similar reduction occurs when vinyl diiodides are treated with Zn–Cu in acetic acid.[1337]

[1322] For a review of reductive dehalogenation of polyhalo ketones, see Noyori, R.; Hayakawa, Y. *Org. React.* ***1983***, *29*, 163.

[1323] Dhuru, S.P.; Padiya, K.J.; Salunkhe, M.M. *J. Chem. Res. (S)* ***1998***, 56.

[1324] Lee, S.H.; Jung, Y.J.; Cho, Y.J.; Yoon, C.-O.M.; Hwang, H.-J.; Yoon, C.M. *Synth. Commun.* ***2001***, *31*, 2251.

[1325] Ren, P.-D.; Hin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997***, *27*, 2577.

[1326] Park, L.; Keum, G.; Kang, S.B.; Kim, K.S.; Kim, Y. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 4462.

[1327] Oriyama, T.; Mukaiyama, T. *Chem. Lett.* ***1984***, 2069.

[1328] Aelterman, W.; Eeckhaut, A.; De Kimpe, N. *Synlett* ***2000***, 1283.

[1329] Kim, S.; Ko, J.S. *Synth. Commun.* ***1985***, *15*, 603.

[1330] Toi, H.; Yamamoto, Y.; Sonoda, A.; Murahashi, S. *Tetrahedron* ***1981***, *37*, 2261.

[1331] Hutchins, R.O.; Kandasamy, D.; Maryanoff, C.A.; Masilamani, D.; Maryanoff, B.E. *J. Org. Chem.* ***1977***, *42*, 82.

[1332] Fluorides can also be reduced by a solution of K and dicyclohexano-18-crown-6 in toluene or diglyme: Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* ***1981***, *22*, 2583. See also, Brandänge, S.; Dahlman, O.; Ölund, J. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 141.

[1333] For a general discussion that includes reduction of vinyl halides with tin compounds, see Curran, D.P. *Synthesis* ***1988***, 417, 489.

[1334] Fry, A.; Mitnick, M.A.; Reed, R.G. *J. Org. Chem.* ***1970***, *35*, 1232; Bhuvaneswari, N.; Venkatachalam, C.S.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1992***, *33*, 1499; Urove, G.A.; Peters, D.G.; Mubarak, M.S. *J. Org. Chem.* ***1992***, *57*, 786; Miller, L.L.; Rienkena, E. *J. Org. Chem.* ***1969***, *34*, 3359; Fry, A.J.; Mitnick, M.A. *J. Am. Chem. Soc.* ***1969***, *91*, 6207.

[1335] Abbas, S.; Hayes, C.J.; Worden, S. *Tetrahedron Lett.* ***2000***, *41*, 3215.

[1336] Ranu, B.C.; Samanta, S.; Guchhait, S.K. *J. Org. Chem.* ***2001***, *66*, 4102.

[1337] Kdota, I.; Ueno, H.; Ohno, A.; Yamamoto, Y. *Tetrhaedron Lett.* ***2003***, *44*, 8645.

With $LiAlH_4$ and most other metallic hydrides, the mechanism usually consists of simple nucleophilic substitution with attack by hydride ion that may or may not be completely free. The mechanism is S_N2 rather than S_N1, since primary halides react better than secondary or tertiary (tertiary generally give alkenes or do not react at all) and since Walden inversion has been demonstrated. However, rearrangements found in the reduction of bicyclic tosylates with $LiAlH_4$ indicate that the S_N1 mechanism can take place.[1338] There is evidence that $LiAlH_4$ and other metal hydrides can also reduce halides by an SET mechanism,[1339] especially those, such as vinylic,[1340] cyclopropyl,[1341] or bridgehead halides, that are resistant to nucleophilic substitution. Reduction of halides by $NaBH_4$ in 80% aqueous diglyme[1342] and by BH_3 in nitromethane[1343] takes place by an S_N1 mechanism. It is known that $NaBH_4$ in sulfolane reduces tertiary halides possessing a β-hydrogen by an elimination-addition mechanism.[1344]

The mechanism for reduction of alkyl halides is not always nucleophilic substitution. For example, reductions with organotin hydrides generally[1345] take place by free-radical mechanisms,[1346] as do those with $Fe(CO)_5$. Alkyl halides, including fluorides and polyhalides, can be reduced with magnesium and a secondary or tertiary alcohol (most often 2-propanol).[1347] This is actually an example of the occurrence in one step of the sequence:

$$RX \longrightarrow RMgX \longrightarrow H^+RH$$

More often the process is carried out in two separate steps (**12-36** and **12-22**).

OS **I**, 357, 358, 548; **II**, 320, 393; **V**, 424; **VI**, 142, 376, 731; **VIII**, 82. See also, OS **VIII**, 583.

[1338] Appleton, R.A.; Fairlie, J.C.; McCrindle, R. *Chem. Commun.* ***1967***, 690; Kraus, W.; Chassin, C. *Tetrahedron Lett.* ***1970***, 1443. See Omoto, M.; Kato, N.; Sogon, T.; Mori, A. *Tetrahedron Lett.* ***2001***, *42*, 939.

[1339] Singh, P.R.; Khurana, J.M.; Nigam, A. *Tetrahedron Lett.* ***1981***, *22*, 2901; Srivastava, S.; le Noble, W.J. *Tetrahedron Lett.* ***1984***, *25*, 4871; Ashby, E.C.; Pham, T.N. *J. Org. Chem.* ***1986***, *51*, 3598; Hatem, J.; Meslem, J.M.; Waegell, B. *Tetrahedron Lett.* ***1986***, *27*, 3723; Ashby, E.C.; Deshpande, A.K. *J. Org. Chem.* ***1994***, *59*, 3798; Ashby, E.C.; Welder, C.; Doctorovich, F. *Tetrahedron Lett.* ***1993***, *34*, 7235. See, however, Hirabe, T.; Takagi, M.; Muraoka, K.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* ***1985***, *50*, 1797; Park, S.; Chung, S.; Newcomb, M. *J. Org. Chem.* ***1987***, *52*, 3275.

[1340] Chung, S. *J. Org. Chem.* ***1980***, *45*, 3513.

[1341] McKinney, M.A.; Anderson, S.W.; Keyes, M.; Schmidt, R. *Tetrahedron Lett.* ***1982***, *23*, 3443; Hatem, J.; Waegell, B. *Tetrahedron* ***1990***, *46*, 2789.

[1342] Bell, H.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1966***, *88*, 1473.

[1343] Matsumura, S.; Tokura, N. *Tetrahedron Lett.* ***1969***, 363.

[1344] Jacobus, J. *Chem. Commun.* ***1970***, 338; Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971***, *36*, 1568.

[1345] For an exception, see Carey, F.A.; Tramper, H.S. *Tetrahedron Lett.* ***1969***, 1645.

[1346] Menapace, L.W.; Kuivila, H.G. *J. Am. Chem. Soc.* ***1964***, *86*, 3047; Tanner, D.D.; Singh, H.K. *J. Org. Chem.* ***1986***, *51*, 5182.

[1347] Bryce-Smith, D.; Wakefield, B.J.; Blues, E.T. *Proc. Chem. Soc.* ***1963***, 219.

19-54 Reduction of Alcohols[1348]

Hydro-de-hydroxylation or Dehydroxylation

$$\mathrm{ROH} + \mathrm{H_2} \xrightarrow{\text{catalyst}} \mathrm{RH}$$

The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily and have often been reduced.[1349] Diaryl and triarylcarbinols are similarly easy to reduce and this has been accomplished with $LiAlH_4$—$AlCl_3$,[1350] with $NaBH_4$ in F_3CCOOH,[1351] and with iodine, water, and red phosphorus (OS **I**, 224). Other reagents have been used,[1352] among them PPh_3/diethyl-azo-dicarboxylate and arylsulfonyl hydrazine,[1353] PPh_3 and electrolysis,[1354] Me_3SiCl—MeI—MeCN,[1355] Me_3SiCl—NaI,[1356] Et_3SiH—BF_3,[1357] SmI_2—THF—HMPA,[1358] and tin and HCl. The reduction of secondary alcohols was accomplished using Ph_2SiClH and $InCl_3$.[1359] 1,3-Diols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is Raney nickel.[1360] Allylic alcohols (and ethers and acetates) can be reduced (often with accompanying allylic rearrangement) with Zn amalgam and HCl, as well as with certain other reagents.[1361] α-Acetylenic alcohols are converted to alkynes by reduction of their cobalt carbonyl complexes with $NaBH_4$ and CF_3COOH.[1362] Reagents that reduce the OH group

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[1348] For a review, see Müller, P., in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 515–522.

[1349] For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 157–163, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 449–468. For a review of the stereochemistry of hydrogenolysis, see Klabunovskii, E.I. *Russ. Chem. Rev.* ***1966***, *35*, 546.

[1350] Blackwell, J.; Hickinbottom, W.J. *J. Chem. Soc.* ***1961***, 1405; Avendaño, C.; de Diego, C.; Elguero, J. *Monatsh. Chem.* ***1990***, *121*, 649.

[1351] For a review, see Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317. Also see, Nutaitis, C.F.; Bernardo, J.E. *Synth. Commun.* ***1990***, *20*, 487.

[1352] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 44–46.

[1353] Myers, A.G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* ***1997***, *119*, 8572.

[1354] Maeda, H.; Maki, T.; Eguchi, K.; Koide, T.; Ohmori, H. *Tetrahedron Lett.* ***1994***, *35*, 4129.

[1355] Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* ***1987***, *28*, 3817.

[1356] Cain, G.A.; Holler, E.R. *Chem. Commun.* ***2001***, 1168.

[1357] Orfanopoulos, M.; Smonou, I. *Synth. Commun.* ***1988***, *18*, 833; Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* ***1988***, *29*, 5793. See Wustrow, D.J.; Smith III, W.J.; Wise, L.D. *Tetrahedron Lett.* ***1994***, *35*, 61 for reduction with $Et_3SiH/LiClO_4$.

[1358] Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2945.

[1359] Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* ***2001***, *66*, 7741.

[1360] Krafft, M.E.; Crooks III, W.J. *J. Org. Chem.* ***1988***, *53*, 432. For another catalyst, see Parnes, Z.N.; Shaapuni, D.Kh.; Kalinkin, M.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 1592.

[1361] For discussion, see Elphimoff-Felkin, I.; Sarda, P. *Org. Synth.* ***VI***, 769; *Tetrahedron* ***1977***, *33*, 511. For another reagent, see Lee, J.; Alper, H. *Tetrahedron Lett.* ***1990***, *31*, 4101.

[1362] Nicholas, K.M.; Siegel, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4999.

of α-hydroxy ketones without affecting the C=O group include lithium diphenylphosphide, Ph_2PLi,[1363] red phosphorus–iodine,[1364] and Me_3SiI.[1365]

Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (**19-57**). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine–SO_3 in THF, and $LiAlH_4$ then added.[1366] Another indirect reduction that can be done in one step involves treatment of the alcohol (primary, secondary, or benzylic) with NaI, Zn, and Me_3SiCl.[1367] In this case, the alcohol is first converted to the iodide, which is reduced. For other indirect reductions of OH, see **19-59**.

The mechanisms of most alcohol reductions are obscure.[1368] Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.[1369] The mechanism of electroreduction of allylic alcohols in acidic aqueous media has been examined.[1370]

Note that tertiary benzylic alcohols are cleaved to give the aromatic compound [$ArC(OH)Ar'_2 \rightarrow Ar\text{-}H$] by heating with cesium carbonate and $Pd(OAc)_2$.[1371]

OS **I**, 224; **IV**, 25, 218, 482; **V**, 339; **VI**, 769.

19-55 Reduction of Phenolic and Other Hydroxyaryl Compunds

Hydro-de-hydroxylation or Dehydroxylation, etc.

$$\mathrm{ArOH} \xrightarrow{\mathrm{Zn}} \mathrm{ArH}$$

Oxygenated compounds, such as phenols, phenolic esters, and ethers, can be reduced.[1372] Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see **15-13**) is a side product.[1373]

[1363] Leone-Bay, A. *J. Org. Chem.* ***1986***, *51*, 2378.

[1364] Ho, T.L.; Wong, C.M. *Synthesis* ***1975***, 161.

[1365] Ho, T.L. *Synth. Commun.* ***1979***, *9*, 665.

[1366] Corey, E.J.; Achiwa, K. *J. Org. Chem.* ***1969***, *34*, 3667.

[1367] Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* ***1981***, 32.

[1368] For discussions of the mechanisms of the hydrogenolysis of benzyl alcohols, see Khan, A.M.; McQuillin, F.J.; Jardine, I. *Tetrahedron Lett.* ***1966***, 2649; *J. Chem. Soc. C* ***1967***, 136; Garbisch, Jr., E.W.; Schreader, L.; Frankel, J.J. *J. Am. Chem. Soc.* ***1967***, *89*, 4233; Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.

[1369] Mitsui, S.; Kudo, Y.; Kobayashi, M. *Tetrahedron* ***1969***, *25*, 1921; Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.

[1370] Shukun, H.; Yougun, S.; Jindong, Z.; Jian, S. *J. Org. Chem.* ***2001***, *66*, 4487.

[1371] Terao, Y.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* ***2004***, *69*, 6942.

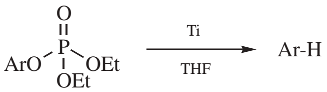
[1372] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 44–52ff.

[1373] Shuikin, N.I.; Erivanskaya, L.A. *Russ. Chem. Rev.* ***1960***, *29*, 309, see pp. 313–315. See also, Bagnell, L.J.; Jeffery, E.A. *Aust. J. Chem.* ***1981***, *34*, 697.

Much better results have been obtained by conversion of phenols to certain esters or ethers and reduction of the latter:

$$ArOSO_2CF_3 \xrightarrow[\text{Pd(OAc)}_2\text{, Ph}_3\text{P, DMF}]{\text{HCOOH, Et}_3\text{N}} ArH \qquad \text{Ref.}^{1374}$$

$$ArOTs + NaBH_4/NiCl_2 \longrightarrow ArH \qquad \text{Ref.}^{1375}$$



Ref.[1376]

OS **VI**, 150. See also, OS **VII**, 476.

19-56 Replacement of Alkoxyl by Hydrogen

Hydro-de-alkoxylation or Dealkoxylation

$$R\text{–}O\text{–}R' \longrightarrow R\text{–}H + R'\text{–}H$$

R, R′ = allyl, aryl, vinyl, benzylic

Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported[1377] (e.g., THF treated with $LiAlH_4$—$AlCl_3$[1378] or with a mixture of $LiAlH(O\text{—}t\text{-Bu})_3$ and Et_3B[1379] gave 1-butanol; the latter reagent also cleaves methyl alkyl ethers).[1380] Certain types of ethers can be cleaved quite well by reducing agents.[1381] Among these are allyl aryl,[1382] vinyl aryl,[1383] benzylic ethers,[1349,1384] and anisole[1385] (for epoxides, see **19-35**). 7-Oxobicyclo[2.2.1]heptanes

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[1374] Cacchi, S.; Ciattini. P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1986***, *27*, 5541. See also, Peterson, G.A.; Kunng, F.; McCallum, J.S.; Wulff, W.D. *Tetrahedron Lett.* ***1987***, *28*, 1381; Chen, Q.; He, Y. *Synthesis* ***1988***, 896; Cabri, W.; De Bernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* ***1990***, *55*, 350.

[1375] Wang, F.; Chiba, K.; Tada, M. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 1897.

[1376] Welch, S.C.; Walters, M.E. *J. Org. Chem.* ***1978***, *43*, 4797. See also, Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1973***, *38*, 2314.

[1377] Ranu, B.C.; Bhar, S. *Org. Prep. Proceed. Int.* ***1996***, *28*, 371.

[1378] Bailey, W.J.; Marktscheffel, F. *J. Org. Chem.* ***1960***, *25*, 1797.

[1379] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1979***, *44*, 3678.

[1380] For a review of ether reduction, see Müller, P., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 522–528.

[1381] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1013–1019.

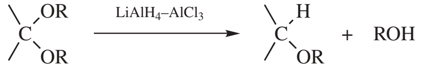
[1382] Tankguchi, T.; Ogasawara, K. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1136; Rao, G.V.; Reddy, D.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3565.

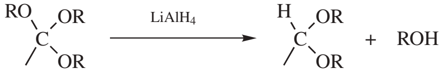
[1383] Tweedie, V.L.; Barron B.G. *J. Org. Chem.* ***1960***, *25*, 2023. See also, Hutchins, R.O.; Learn, K. *J. Org. Chem.* ***1982***, *47*, 4380.

[1384] Bouzide, A.; Sauvé, G. *Synlett* ***1997***, 1153; Thomas, R.M.; Mohan, G.H.; Iyengar, D.S. *Tetrahedron Lett.* ***1997***, *38*, 4721; Shi, L.; Xia, W.J.; Zhang, F.M.; Tu, Y.Q. *Synlett* ***2002***, 1505. See also Olivero, S.; Duñach, E. *Tetrahedron Lett.* ***1997***, *38*, 6193.

[1385] Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* ***1994***, *35*, 8727.

can be reductively cleaved with DIBAL and nickel catalysts.[1386] α-Methoxy ketones are demethoxylated (O=C—COMe → O=C—CH) with SmI_2.[1387]





Acetals and ketals are resistant to $LiAlH_4$ and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection (**16-5**). However, a combination of $LiAlH_4$ and $AlCl_3$[1388] does reduce acetals and ketals, removing one group, as shown above.[1389] The actual reducing agents in this case are primarily chloroaluminum hydride (AlH_2Cl) and dichloroaluminum hydride ($AlHCl_2$), which are formed from the reagents.[1390] This conversion can also be accomplished with DIBALH,[1391] as well as with other reagents.[1392] Ortho esters are easily reduced to acetals by $LiAlH_4$ alone, offering a route to aldehydes, which are easily prepared by hydrolysis of the acetals (**10-6**). Mixed ketals [R(OMe)OR′] can be demethoxylated (to give RHOR′) with $Bn_3SnCl/NaCHBH_3$ in the presence of AIBN.[1393]

OS **III**, 693; **IV**, 798; **V**, 303. Also see, OS **III**, 742; **VII**, 386.

19-57 Reduction of Tosylates and Similar Compounds

Hydro-de-sulfonyloxy-substitution

$$RCH_2OTs \; + \; LiAlH_4 \longrightarrow RCH_3$$

Tosylates and other sulfonates can be reduced[1394] with $LiAlH_4$,[1395] with $NaBH_4$ in a dipolar aprotic solvent,[1396] with $LiEt_3BH$, with *i*-Bu_2AlH (DIBALH),[1397] or with Bu_3SnH—NaI.[1398] The scope of the reaction seems to be similar to that of **19-53**.

[1386] Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem.Soc.* ***1995***, *117*, 532.

[1387] Mikami, K.; Yamaoka, M.; Yoshida, A. *Synlett* ***1998***, 607.

[1388] For a review of reductions by metal hydride–Lewis acid combinations, see Rerick, M.N., in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***, pp. 1–94.

[1389] Eliel, E.L.; Badding, V.G.; Rerick, M.N. *J. Am. Chem. Soc.* ***1962***, *84*, 2371.

[1390] Ashby, E.C.; Prather, J. *J. Am. Chem. Soc.* ***1966***, *88*, 729; Diner, U.E.; Davis, H.A.; Brown, R.K. *Can. J. Chem.* ***1967***, *45*, 207.

[1391] See, for example, Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 2156; Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* ***1983***, 1593.

[1392] For other reagents that accomplish this conversion, see Kotsuki, H.; Ushio, Y.; Yoshimura, N.; Ochi, M. *J. Org. Chem.* ***1987***, *52*, 2594; Hojo, M.; Ushioda, N.; Hosomi, A. *Tetrahedron Lett.* ***2004***, *45*, 4499; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 931–942.

[1393] Srikrishna, A.; Viswajanani, R. *Synlett* ***1995***, 95.

[1394] For a list of substrate types and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 46–52.

[1395] For examples, see Dimitriadis, E.; Massy-Westropp, R.A. *Aust. J. Chem.* ***1982***, *35*, 1895; Goodenough, K.M.; Moran, W.J.; Raubo, P.; Harrity, J.P.A. *J. Org. Chem.* ***2005***, *70*, 207.

[1396] Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* ***1969***, 3495.

[1397] Janssen, C.G.M.; Hendriks, A.H.M.; Godefroi, E.F. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 220.

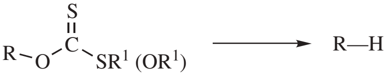
[1398] Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* ***1983***, 795.

When the reagent is $LiAlH_4$, alkyl tosylates are reduced more rapidly than iodides or bromides if the solvent is Et_2O, but the order is reversed in diglyme.[1399] The reactivity difference is great enough so that a tosylate function can be reduced in the presence of a halide and vice versa. Tertiary allylcyclopropyl tosylates have been reduced with BuZnCl and a palladium catalyst.[1400]

OS **VI**, 376, 762; **VIII**, 126. See also, OS **VII**, 66.

19-58 Hydrogenolysis of esters (Barton–McCombie Reaction)

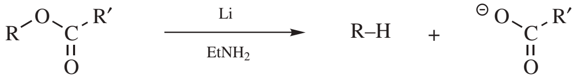
Hydro-de-thioacetoxylation



Alcohols can readily be converted to carbonate and thiocarbonate derivatives. Under radical conditions,[1401] using *azobis*-isobutyronitrile (AIBN, p. 935) and Bu_3SnH, the carbonate or thiocarbonate unit is reduced and replaced with hydrogen. The overall process is reduction of the ROH unit to RH. This is called the *Barton–McCombie reaction.*[1402] When R is cyclododecane (OCSOR), for example, this reduction yields the parent cyclododecane in 76% yield.[1403] When R = cyclododecane (OCSSMe), treatment with $Bu_3P{=}O$ and AIBN, gives the alkane in 94% yield.[1404] Both $PhSiH_3$/AIBN[1405] and $PhSiH_2$—BEt_3•O_2 can be used.[1406] This reaction can be catalytic in Bu_3SnH.[1407] Variations include reduction of ROCSNHPh derivatives using Ph_3SiH/BEt_3.[1408]

19-59 Reductive Cleavage of Carboxylic Esters

Hydro-de-acyloxylation or Deacyloxylation



[1399] Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 2550.

[1400] Ollivier, J.; Piras, P.P.; Stolle, A.; Aufranc, P.; de Meijere, A.; Salaün, J. *Tetrahedron Lett.* ***1992***, *33*, 3307.

[1401] Barton, D.H.R.; Jaszberenyi, J.Cs.; Tang, D. *Tetrahedron Lett.* ***1993***, *34*, 3381.

[1402] Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 1574; Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* ***1983***, *105*, 4059.

[1403] Jang, D.O.; Cho, D.H.; Kim, J. *Synth. Commun*, ***1998***, *28*, 3559. Also see Gimisis, T.; Ballestri, M.; Ferreri, C.; Chatgilialoglu, C.; Boukherroub, R.; Manuel, G. *Tetrahedron Lett.* ***1995***, *36*, 3897; Crimmins, M.T.; Dudek, C.M.; Cheung, A.W-H. *Tetrahedron Lett.* ***1992***, *33*, 181.

[1404] Jang, D.O.; Cho, D.H.; Barton, D.H.R. *Synlett* ***1998***, 39; Barton, D.H.R.; Parekh, S.I.; Tse, C.-L. *Tetrahedron Lett.* ***1993***, *34*, 2733.

[1405] Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 2793.

[1406] Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 7193.

[1407] Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* ***1997***, *119*, 6949.

[1408] Oba, M.; Nishiyama, K. *Tetrahedron* ***1994***, *50*, 10193.

The alkyl group R of certain carboxylic esters can be reduced to RH[1409] by treatment with lithium in ethylamine.[1410] The reaction is successful when R is a tertiary or a sterically hindered secondary alkyl group. A free-radical mechanism is likely.[1411] Similar reduction, also by a free-radical mechanism, has been reported with sodium in HMPA—*t*-BuOH.[1412] In the latter case, tertiary R groups give high yields of RH, but primary and secondary R are converted to a mixture of RH and ROH. Both of these methods provide an indirect method of accomplishing **19-54** for tertiary R.[1413] The same thing can be done for primary and secondary R by treating alkyl chloroformates, ROCOCl, with tri-*n*-propylsilane in the presence of *tert*-butylperoxide[1414] and by treating thiono ethers ROC(=S)W (where W can be OAr or other groups) with Ph_2SiH_2[1415] or Ph_3SiH[1416] and a free-radical initiator. Allylic acetates can be reduced with $NaBH_4$ and a palladium complex,[1417] and with $SmI_2Pd(0)$.[1418] The last reagent converts propargylic acetates to allenes $R^1C{=}C{=}CR^2R^3OAc \rightarrow R^1CH{=}C{=}CR^2R^3$.[1418] For other carboxylic ester reductions, see **19-62**, **19-38**, and **19-65**.

Note that acid chlorides can be reduced (R—COCl → R—H) using $(Me_3Si)_3SiH$/AIBN.[1419]

OS **VII**, 139.

19-60 Reduction of Hydroperoxides and Peroxides

$$\text{R—O—O—H} \xrightarrow{\text{LiAlH}_4} \text{ROH}$$

Hydroperoxides can be reduced to alcohols with $LiAlH_4$ or Ph_3P[1420] or by catalytic hydrogenation. This functional group is very susceptible to catalytic

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[1409] For a review of some of the reactions in this section and some others, see Hartwig, W. *Tetrahedron* ***1983***, *39*, 2609.

[1410] Barrett, A.G.M.; Godfrey, C.R.A.; Hollinshead, D.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; Joukhadar, L.; McGhie, J.F.; Misra, S.C. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 1501. See Garst, M.E.; Dolby, L.J.; Esfandiari, S.; Fedoruk, N.A.; Chamberlain, N.C.; Avey, A.A. *J. Org. Chem.* ***2000***, *65*, 7098.

[1411] Barrett, A.G.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; McGhie, J.F. *J. Chem. Soc. Chem. Commun.* ***1979***, 1173.

[1412] Deshayes, H.; Pete, J. *Can. J. Chem.* ***1984***, *62*, 2063.

[1413] Also see Barton, D.H.R.; Crich, D. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1603.

[1414] Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1207.

[1415] See Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.C. *Tetrahedron Lett.* ***1990***, *31*, 4681, and references cited therein. For similar methods, see Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2578; Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *Tetrahedron Lett.* ***1990***, *31*, 5093.

[1416] Oba, M.; Nishiyama, K. *Synthesis* ***1994***, 624.

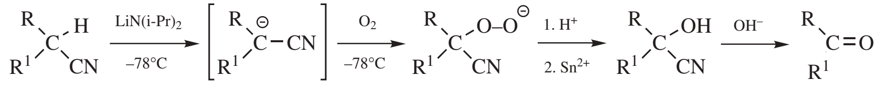
[1417] Hutchins, R.O.; Learn, K.; Fulton, R.P. *Tetrahedron Lett.* ***1980***, *21*, 27. See also Ipaktschi, J. *Chem. Ber.* ***1984***, *117*, 3320.

[1418] Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1986***, *27*, 601, 5237. See also, Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2945.

[1419] Ballestri, M.; Chatgilialoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* ***1992***, *33*, 1787.

[1420] For a review, see Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 318–320.

hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.[1421]



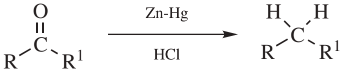
The reaction is an important step in a method for the oxidative decyanation of nitriles containing an α hydrogen.[1422] The nitrile is first converted to the α-hydroperoxy nitrile by treatment with base at −78°C followed by O_2. The hydroperoxy nitrile is then reduced to the cyanohydrin, which is cleaved (the reverse of **16-52**) to the corresponding ketone. The method is not successful for the preparation of aldehydes (R′ = H).

Peroxides are cleaved to 2 equivalents of alcohols by $LiAlH_4$, Mg/MeOH,[1423] or by catalytic hydrogenation. Peroxides can be reduced to ethers with $P(OEt)_3$.[1424] In a similar reaction, disulfides (RSSR′) can be converted to sulfides RSR′ by treatment with tris(diethylamino)phosphine, $(Et_2N)_3P$.[1425]

OS **VI**, 130.

19-61 Reduction of Carbonyl to Methylene in Aldehydes and Ketones

Dihydro-de-oxo-bisubstitution



There are various ways of reducing the C=O group of aldehydes and ketones to CH_2.[1426] The two oldest, but still very popular, methods are the *Clemmensen reduction*[1427] and the *Wolff–Kishner reduction*. The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam and aq. HCl.[1428] Ketones are reduced more often than aldehydes. In the Wolff–Kishner reduction,[1429] the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH

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[1422] Freerksen, R.W.; Selikson, S.J.; Wroble, R.R.; Kyler, K.S.; Watt, D.S. *J. Org. Chem.* ***1983***, *48*, 4087. This paper also reports several other methods for achieving this conversion.

[1423] Dai, P.; Dussault, P.H.; Trullinger, T.K. *J. Org. Chem.* ***2004***, *69*, 2851.

[1424] Horner, L.; Jurgeleit, W. *Liebigs Ann. Chem.* ***1955***, *591*, 138. See also, Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 320–322.

[1425] Harpp, D.N.; Gleason, J.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2437. For another method, see Comasseto, J.V.; Lang, E.S.; Ferreira, J.T.B.; Simonelli, F.; Correi, V.R. *J. Organomet. Chem.* ***1987***, *334*, 329.

[1426] For a review, see Reusch, W. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***, pp. 171–211.

[1427] Fragmentation reactions sometimes accompany Clemmenson reduction. See Bailey, K.E.; Davis, B.R. *Aust. J. Chem.* ***1995***, *48*, 1827. Also see Rosnati, V. *Tetrahedron Lett.* ***1992***, *33*, 4791.

[1428] For a review, see Vedejs, E. *Org. React.* ***1975***, *22*, 401. For a discussion of experimental conditions, see Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 1287–1289.

[1429] For a review, see Todd, D. *Org. React.* ***1948***, *4*, 378.

or KOH). The *Huang–Minlon modification*[1430] of the Wolff–Kishner reaction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. A microwave-assisted Huang–Minlon procedure has been reported.[1431] The reaction can also be carried out under more moderate conditions (room temperature) in DMSO with potassium *tert*-butoxide as base.[1432] A new modification of the reduction treats a ketone with hydrazine in toluene with microwave irradiation, and subsequent reaction with KOH with microwave irradiation completes the Wolff–Kishner reduction.[1433] 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.[1434] 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,[1435] α-hydroxy ketones give either ketones (hydrogenolysis of the OH, **19-54**) or alkenes, and 1,3-diones usually undergo rearrangement (e.g., $MeCOCH_2$-$COMe \rightarrow MeCOCHMe_2$).[1436] Neither method is suitable for α,β-unsaturated ketones. These give pyrazolines[1437] 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.[1438] Sterically hindered ketones are resistant to both the Clemmensen and Huang–Minlon procedures, but can be reduced by vigorous treatment with anhydrous hydrazine.[1439] In the Clemmensen reduction, pinacols (**19-76**) are often side products.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2.[1440] Among these are Me_3SiCl followed by $Et_3SiH/TiCl_4$,[1441] $Ni(OAc)_2$ on borohydride exchange resin,[1442] Et_3SiH on pyridinium poly(hydrogen fluoride),

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[1430] Huang-Minlon *J. Am. Chem. Soc.* ***1946***, *68*, 2487; ***1949***, *71*, 3301.

[1431] Jaisankar, P.; Pal, B.; Giri, V.S. *Synth. Commun.* ***2002***, *32*, 2569.

[1432] Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* ***1962***, *84*, 1734.

[1433] Gadhwal, S.; Baruah, M.; Sandhu, J.S. *Synlett* ***1999***, 1573.

[1434] Toda, M.; Hayashi, M.; Hirata, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 264.

[1435] For a review of Clemmensen reduction of diketones and unsaturated ketones, see Buchanan, J.G.S.; Woodgate, P.D. *Q. Rev. Chem. Soc.* ***1969***, *23*, 522.

[1436] Cusack, N.J.; Davis, B.R. *J. Org. Chem.* ***1965***, *30*, 2062; Wenkert, E.; Kariv, E. *Chem. Commun.* ***1965***, 570; Galton, S.A.; Kalafer, M.; Beringer, F.M. *J. Org. Chem.* ***1970***, *35*, 1.

[1437] Pyrazolines can be converted to cyclopropanes; see **17-34**.

[1438] See, however, Banerjee, A.K.; Alvárez, J.; Santana, M.; Carrasco, M.C. *Tetrahedron* ***1986***, *42*, 6615.

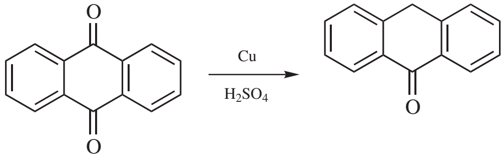
[1439] Barton, D.H.R.; Ives, D.A.J.; Thomas, B.R. *J. Chem. Soc.* ***1955***, 2056.

[1440] For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 61–66.

[1441] Yato, M.; Homma, K.; Ishida, A. *Heterocycles* ***1995***, *41*, 17.

[1442] Bandgar, B.P.; Nikat, S.M.; Wadgaonkar, P.P. *Synth. Commun.* ***1995***, *25*, 863.

[PPHF],[1443] and, for aryl ketones (ArCOR and ArCOAr), $NaBH_4$–F_3CCOOH,[1444] $NaBH_4$–$AlCl_3$,[1445] $NaBH_3CN$ in THF–aq. HCl,[1446] Ni–Al in H_2O,[1447] HCOO-NH_4–Pd–C,[1448] H_3PO_2/AcOH and an I_2 catalyst,[1449] or trialkylsilanes in F_3CC-OOH.[1450] Silanes, such as Et_3SiH and a triarylborane catalyst, reduce aliphatic aldehydes to the alkane, $-CHO \rightarrow -CH_3$.[1451] Chlorosilanes, such as Me_2SiClH, with an $InCl_3$ catalyst reduced ketones to the methylene compound.[1452] Polymethylhydroxysiloxane and a triarylborane catalyst deoxygenates ketones.[1453] Most of these reagents also reduce aryl aldehydes (ArCHO) to methylbenzenes ($ArCH_3$).[1454] Aliphatic aldehydes (RCHO) can be reduced to RCH_3 with titanocene dichloride, $(C_5H_5)_2TiCl_2$.[1455] One carbonyl group of 1,2-diketones can be selectively reduced by H_2S with an amine catalyst[1456] or by HI in refluxing acetic acid.[1457] One carbonyl group of quinones, such as **48**, can be reduced with copper and sulfuric acid or with tin and HCl.[1458] One carbonyl group of 1,3-diketones was selectively reduced by catalytic hydrogenolysis.[1459] Catalytic hydrogenation at 170°C with Pt/K10 removes oxygen from the molecule.[1460] Simply heating a ketone in supercritical Z-propanol reduces the ketone to the methylene compound.[1461]



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[1443] Olah, G.A.; Wang, Q.; Prakash, G.K.S. *Synlett* ***1992***, 647.

[1444] Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317.

[1445] Ono, A.; Suzuki, N.; Kamimura, J. *Synthesis* ***1987***, 736.

[1446] Pashkovsky, F.S.; Lokot, I.P.; Lakhvich, F.A. *Synlett* ***2001***, 1391.

[1447] Ishimoto, K.; Mitoma, Y.; Negashima, S.; Tashiro, H.; Prakash, G.K.S.; Olah, G.A.; Tahshiro, M. *Chem. Commun.* ***2003***, 514.

[1448] Ram, S.; Spicer, L.D. *Tetrahedron Lett.* ***1988***, *29*, 3741.

[1449] Hicks, L.D.; Han, J.K.; Fry, A.J. *Tetrahedron Lett.* ***2000***, *41*, 7817; Gordon, P.E.; Fry, A.J. *Tetrahdron Lett.* ***2001***, *42*, 831.

[1450] Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1966***, 1245; West, C.T.; Donnelly, S.J.; Kooistra, D.A.; Doyle, M.P. *J. Org. Chem.* ***1973***, *38*, 2675. See also, Fry, J.L.; Orfanopoulos, M.; Adlington, M.G.; Dittman, Jr., W.R.; Silverman, S.B. *J. Org. Chem.* ***1978***, *43*, 374; Olah, G.A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* ***1986***, 770.

[1451] Gevorgyan, V.; Rubin, M.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 1672.

[1452] Miyai, T.; Ueba, M.; Baba, A. *Synlett* ***1999***, 182.

[1453] Chandrasekar, S.; Reddy, Ch.R.; Babu, B.N. *J. Org. Chem.* ***2002***, *67*, 9080.

[1454] See, for example, Hall, S.S.; Bartels, A.P.; Engman, A.M. *J. Org. Chem.* ***1972***, *37*, 760; Kursanov, D.N.; Parnes, Z.N.; Loim, N.M.; Bakalova, G.V. *Doklad. Chem.* ***1968***, *179*, 328; Zahalka, H.A.; Alper, H. *Organometallics* ***1986***, *5*, 1909.

[1455] van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974***, *96*, 5290.

[1456] Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 370.

[1457] Reusch, W.; LeMahieu, R. *J. Am. Chem. Soc.* ***1964***, *86*, 3068.

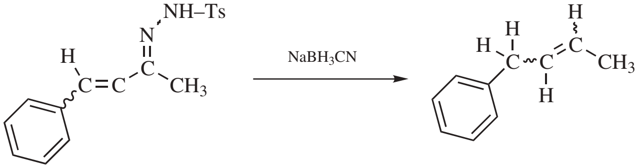
[1458] Meyer, K.H. *Org. Synth.* ***I***, 60; Macleod, L.C.; Allen, C.F.H. *Org. Synth.* ***II***, 62.

[1459] Cormier, R.A.; McCauley, M.D. *Synth. Commun.* ***1988***, *18*, 675.

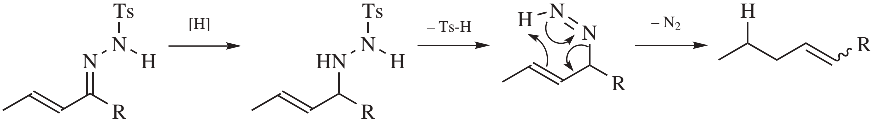
[1460] Török, B.; London, G. Bartók, M. *Synlett* ***2000***, 631.

[1461] Hatano, B.; Tagaya, H. *Tetraehedron Lett.* ***2003***, *44*, 6331.

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, or $NaBH_3CN$. The reduction of α,β-unsaturated tosylhydrazones with $NaBH_3CN$, 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,[1462] for example,



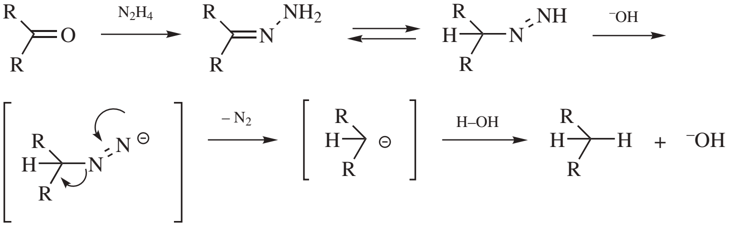
A cyclic mechanism is apparently involved:



Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization of using Raney nickel or another reagent (**14-27**).

It is interesting to see that amines can be deaminated to give the corresponding methylene compounds with low-valent titanium ($TiCl_3$/Li/THF).[1463]

The first step in the mechanism[1464] of the Wolff–Kishner reaction consists of formation of the hydrazone (**16-14**). It is this species that undergoes reduction in the presence of base, most likely in the following manner:



[1462] Kabalka, G.W.; Yang, D.T.C.; Baker, Jr., J.D. *J. Org. Chem.* ***1976***, *41*, 574; Taylor, E.J.; Djerassi, C. *J. Am. Chem. Soc.* ***1976***, *98*, 2275; Hutchins, R.O.; Natale, N.R. *J. Org. Chem.* ***1978***, *43*, 2299; Greene, A.E. *Tetrahedron Lett.* ***1979***, 63.

[1463] Talukdar, S.; Banerji, A. *Synth. Commun*, ***1996***, *26*, 1051.

[1464] For a review of the mechanism, see Szmant, H.H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 120. Also see, Taber, D.F.; Stachel, S.J. *Tetrahedron Lett.* ***1992***, *33*, 903.

Not much is known about the mechanism of the Clemmensen reduction. Several mechanisms have been proposed,[1465] including one going through a zinc–carbene intermediate.[1466] 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.

19-62 Reduction of Carboxylic Esters to Ethers

Dihydro-de-oxo-bisubstitution

$$\mathrm{RCOOR'} \xrightarrow[\mathrm{LiAlH_4}]{\mathrm{BF_3\text{–}etherate}} \mathrm{RCH_2OR'}$$

Carboxylic esters and lactones have been reduced to ethers, although 2 equivalents of alcohol are more commonly obtained (**19-38**). Reduction to ethers has been accomplished with a reagent prepared from BF_3–etherate and either $LiAlH_4$, $LiBH_4$, or $NaBH_4$,[1467] with trichlorosilane and uv light,[1468] and with catalytic hydrogenation. The reaction with the BF_3 reagent apparently succeeds with secondary R′, but not with primary R′, which give **19-38**. Lactones give cyclic ethers.[1469] Acyloxy groups are reduced by cleavage of the C—C=O bond, R(Ar)COO—C → C—H) with an excess of Ph_2SiH_2 and di-*tert*-butyl peroxide.[1470] Esters are reduced to ethers using Et_3SiH and $TiCl_4$.[1471] Lactones are converted to cyclic ethers by treatment with Cp_2TiCl_2 followed by Et_3SiH on Amberlyst 15.[1472]

Thiono esters RCSOR′ can be reduced to ethers RCH_2OR' with Raney nickel (**14-27**).[1473] Reaction of thio esters, such as C—OC(=O)Ph with Ph_2SiH_2 and Ph_3SnH with BEt_3, followed by AIBN (p. 935) leads to reduction of the C=S unit to give an ether.[1474] Since the thiono esters can be prepared from carboxylic

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[1465] See, for example, Horner, L.; Schmitt, E. *Liebigs Ann. Chem.* ***1978***, 1617; Poutsma, M.L.; Wolthius, E. *J. Org. Chem.* ***1959***, *24*, 875; Nakabayashi, T. *J. Am. Chem. Soc.* ***1960***, *82*, 3900, 3906; Di Vona, M.L.; Rosnati, V. *J. Org. Chem.* ***1991***, *56*, 4269.

[1466] Burdon, J.; Price, R.C. *J. Chem. Soc. Chem. Commun.* ***1986***, 893.

[1467] Pettit, G.R.; Green, B.; Kasturi, T.R.; Ghatak, U.R. *Tetrahedron* ***1962***, *18*, 953; Ager, D.J.; Sutherland, I.O. *J. Chem. Soc. Chem. Commun.* ***1982***, 248. See also, Dias, J.R.; Pettit, G.R. *J. Org. Chem.* ***1971***, *36*, 3485.

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[1469] See, for example, Pettit, G.R.; Kasturi, T.R.; Green, B.; Knight, J.C. *J. Org. Chem.* ***1961***, *26*, 4773; Edward, J.T.; Ferland, J.M. *Chem. Ind. (London)* ***1964***, 975.

[1470] Kim, J.-G.; Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004***, *45*, 3031; Jiang, D.O.; Kim, J.; Cho, D.H.; Chung, C.-M. *Tetrahedron Lett.* ***2001***, *42*, 1073.

[1471] Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* ***2001***, *57*, 5353.

[1472] Hansen, M.C.; Verdaguer, X.; Buchwald, S.L. *J. Org. Chem.* ***1998***, *63*, 2360.

[1473] Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.

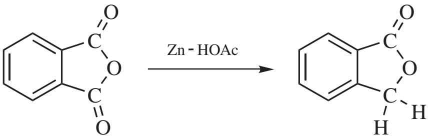
[1474] Jang, D.O.; Song, S.H. *Synlett* ***2000***, 811; Jang, D.O.; Song, S.H.; Cho, D.H. *Tetrahedron* ***1999***, *55*, 3479.

esters (**16-11**), this provides an indirect method for the conversion of carboxylic esters to ethers. Thiol esters (RCOSR′) have been reduced to thioethers (RCH_2SR').[1475]

See also, **19-65**, **19-59**.

19-63 Reduction of Cyclic Anhydrides to Lactones and Acid Derivatives to Alcohols

Dihydro-de-oxo-bisubstitution



Cyclic anhydrides can give lactones if reduced with Zn—HOAc, with hydrogen and platinum or $RuCl_2(Ph_3P)_3$,[1476] with $NaBH_4$,[1477] or even with $LiAlH_4$, although with the last-mentioned reagent diols are the more usual product. With a BINOL–AlHOEt complex, however, reduction to the lactone proceeds smoothly.[1478] With some reagents the reaction can be accomplished regioselectively, that is, only a specific one of the two C=O groups of an unsymmetrical anhydride is reduced.[1479] Open-chain anhydrides either are not reduced at all (e.g., with $NaBH_4$) or give 2 equivalents of alcohol. The $LiAlH_4$ usually reduces open-chain anhydrides to give 2 equivalents of alcohol. With cyclic anhydrides the reaction with $LiAlH_4$ can be controlled to give either diols or lactones.[1480] The $NaBH_4$ in THF, with dropwise addition of methanol, reduces open-chain anhydrides to 1 equivalent of primary alcohol and 1 equivalent of carboxylic acid.[1481]

Acyl halides are reduced[1482] to alcohols by $LiAlH_4$ or $NaBH_4$, as well as by other metal hydrides (Table 19.5), but not by borane.

In general, reduction of amides to alcohols is difficult. More commonly the amide is reduced to an amine. An exception uses LiH_2NBH_3 to give the alcohol.[1483] Reduction with sodium metal in propanol also gives the alcohol.[1484] Acyl

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[1475] Eliel, E.L.; Daignault, R.A. *J. Org. Chem.* ***1964***, *29*, 1630; Bublitz, D.E. *J. Org. Chem.* ***1967***, *32*, 1630.

[1476] Lyons, J.E. *J. Chem. Soc. Chem. Commun.* ***1975***, 412; Morand, P.; Kayser, M.M. *J. Chem. Soc. Chem. Commun.* ***1976***, 314. See also Hara, Y.; Wada, K. *Chem. Lett.* ***1991***, 553.

[1477] Bailey, D.M.; Johnson, R.E. *J. Org. Chem.* ***1970***, *35*, 3574.

[1478] Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* ***1993***, *34*, 1167.

[1479] See, for example, Kayser, M.M.; Salvador, J.; Morand, P. *Can. J. Chem.* ***1983***, *61*, 439; Ikariya, T.; Osakada, K.; Ishii, Y.; Osawa, S.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 897; Soucy, C.; Favreau, D.; Kayser, M.M. *J. Org. Chem.* ***1987***, *52*, 129.

[1480] Bloomfield, J.J.; Lee, S.L. *J. Org. Chem.* ***1967***, *32*, 3919.

[1481] Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* ***1987***, 647.

[1482] For a review of the reduction of acyl halides, see Wheeler, O.H., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1263–1264.

[1483] Myers, A.G.; Yang, B.H.; Kopecky, D.J. *Tetrahedron Lett.* ***1996***, *37*, 3623.

[1484] Moody, H.M.; Kaptein, B.; Broxterman, Q.B.; Boesten, W.H.J.; Kamphuis, J. *Tetrahedron Lett.* ***1994***, *35*, 1777.

imidazoles are also reduced to the corresponding alcohol with $NaBH_4$ in aq. HCl.[1485]

There are no *Organic Syntheses* references, but see OS **II**, 526, for a related reaction. See OS **VI**, 482 for reduction to alcohols and OS **IV**, 271 for reduction of acyl halides.

19-64 Reduction of Amides to Amines

Dihydro-deoxo-bisubstitution

$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

Amides can be reduced[1486] to amines with $LiAlH_4$ or by catalytic hydrogenation, but 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. Although $NaBH_4$ by itself does not reduce amides, it does so in the presence of certain other reagents[1487] including iodine.[1488] Lithium borohydride reduces acetamides.[1489] Substituted amides can be reduced with these powerful reagents; secondary amides to secondary amine and tertiary amides to tertiary amines. Borane[1490] and sodium in 1-propanol[1491] are good reducing agents for all three types of amides. Another reagent that reduces disubstituted amides to amines is trichlorosilane.[1492] Other silanes, such as Et_3SiH in the presence of a rhenium catalyst, reduce amides to amines.[1493] Sodium (dimethylamino)borohydride reduces unsubstituted and disubstituted, but not monosubstituted amides.[1494] Electrolytic reduction of carbamates to give an amine are possible.[1495]

[1485] Sharma, R.; Voynov, G.H.; Ovaska, T.V.; Marquez, V.E. *Synlett* ***1995***, 839.

[1486] For a review, see Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 795–801. For a review of the reduction of amides, lactams, and imides with metallic hydrides, see Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, p. 544. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 869–872.

[1487] See, for example, Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* ***1969***, 4555; Rahman, A.; Basha, A.; Waheed, N.; Ahmed, S. *Tetrahedron Lett.* ***1976***, 219; Kuehne, M.E.; Shannon, P.J. *J. Org. Chem.* ***1977***, *42*, 2082; Wann, S.R.; Thorsen, P.T.; Kreevoy, M.M. *J. Org. Chem.* ***1981***, *46*, 2579; Mandal, S.B.; Giri, V.S.; Pakrashi, S.C. *Synthesis* ***1987***, 1128; Akabori, S.; Takanohashi, Y. *Chem. Lett.* ***1990***, 251.

[1488] Prasad, A.S.B.; Kanth, J.V.B.; Periasamy, M. *Tetrahedron* ***1992***, *48*, 4623.

[1489] Tanaka, H.; Ogasawara, K. *Tetrahedron Lett.* ***2002***, *43*, 4417.

[1490] Brown, H.C.; Narasimhan, S.; Choi, Y.M. *Synthesis* ***1981***, 441, 996; Krishnamurthy, S. *Tetrahedron Lett.* ***1982***, *23*, 3315; Bonnat, M.; Hercourt, A.; Le Corre, M. *Synth. Commun.* ***1991***, *21*, 1579.

[1491] Bhandari, K.; Sharma, V.L.; Chatterjee, S.K. *Chem. Ind. (London)* ***1990***, 547.

[1492] Nagata, Y.; Dohmaru, T.; Tsurugi, J. *Chem. Lett.* ***1972***, 989. See also, Benkeser, R.A.; Li, G.S.; Mozdzen, E.C. *J. Organomet. Chem.* ***1979***, *178*, 21.

[1493] Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* ***2001***, *42*, 1945.

[1494] Hutchins, R.O.; Learn, K.; El-Telbany, F.; Stercho, Y.P. *J. Org. Chem.* ***1984***, *49*, 2438.

[1495] Franco, D.; Duñach, E. *Tetrahedron Lett.* ***2000***, *41*, 7333.

With some RCONR, $LiAlH_4$ causes cleavage, and the aldehyde (**10-41**) or alcohol is obtained. Lithium triethylborohydride produces the alcohol with most *N,N*-disubstituted amides, but not with unsubstituted or *N*-substituted amides.[1496] Lactams are reduced to cyclic amines in high yields with $LiAlH_4$, although cleavage sometimes occurs here too. A mixture of $LiBHEt_3/Et_3SiH$ is also effective.[1497] Lactams are also reduced to cyclic amines with 9-BBN[1498] (p. 1077) or $LiBH_3NMe_2$.[1499] Imides are generally reduced on both sides,[1500] although it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, although with acyclic imides cleavage is often obtained, for example,[1501]

$$PhN(COMe)_2 \longrightarrow PhNHEt$$

Acyl sulfonamides have been reduced ($RCONHSO_2Ph \rightarrow RCH_2NHSO_2Ph$) with $BH_3{-}SMe_2$[1502] and with SmI_2/DMPU.[1503]

OS **IV**, 339, 354, 564; **VI**, 382; **VII**, 41.

19-65 Reduction of Carboxylic Acids and Esters to Alkanes

Trihydro-de-alkoxy,oxo-tersubstitution, and so on.

$$RCOOR' \xrightarrow{(C_5H_5)_2TiCl_2} RCH_3 + R'OH$$

The reagent titanocene dichloride reduces carboxylic esters in a different manner from that of **19-59**, **19-62**, or **19-38**. The products are the alkane RCH_3 and the alcohol R′OH.[909] 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 with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).[1504] The following sequence has been suggested:[1504]

$$ArCOOH \xrightarrow{SiHCl_3} (ArCO)_2O \xrightarrow[R_3N]{SiHCl_3} ArCH_2SiCl_3 \xrightarrow[MeOH]{KOH} ArCH_3$$

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.[1505] However, it is also

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[1496] Brown, H.C.; Kim, S.C. *Synthesis* ***1977***, 635.

[1497] Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M.C.; García Ruano, J.L.G. *Tetrahedron Lett.* ***1994***, *35*, 2053.

[1498] Colllins, C.J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* ***1999***, *40*, 3673.

[1499] Flaniken, J.M.; Collins, C.J.; Lanz, M.; Singaram, B. *Org. Lett.* ***1999***, *1*, 799.

[1500] For a reduction with borane•THF, see Akula, M.R.; Kabalka, G.W. *Org. Prep. Proceed. Int.* ***1999***, *31*, 214.

[1501] Witkop, B.; Patrick, J.B. *J. Am. Chem. Soc.* ***1952***, *74*, 3861.

[1502] Belletire, J.L.; Fry, D.F. *Synth. Commun.* ***1988***, *18*, 29.

[1503] Vedejs, E.; Lin, S. *J. Org. Chem.* ***1994***, *59*, 1602.

[1504] Benkeser, R.A.; Foley, K.M.; Gaul, J.M.; Li, G.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3232.

[1505] Benkeser, R.A.; Ehler, D.F. *J. Org. Chem.* ***1973***, *38*, 3660.

possible to reduce aromatic ester groups, by a variation of the trichlorosilane procedure.[1506] Both *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).[1507] Heating a 2-pyridylbenzyl ester with ammonium formate and a rutheniumc atlyst leads to reduction of the CH_2COO unit to the the alkane.[1508]

Carboxylic acids can also be converted to alkanes, indirectly,[1509] by reduction of the corresponding tosylhydrazides $RCONHNH_2$ with $LiAlH_4$ or borane.[1510]

OS **VI**, 747.

19-66 Hydrogenolysis of Nitriles

Hydro-de-cyanation

$$R\text{—}CN \longrightarrow R\text{—}H$$

This transformation is not common, but given the proliferation of nitriles in organic chemistry, it is potentially quite useful. In the presence of mercuric compounds, tertiary nitriles can be reduced to the hydrocarbon with sodium cyanoborohydride.[1511] *gem*-Dinitriles can be reduced to the corresponding mononitrile with SmI_2.[1512]

19-67 Reduction of the C—N Bond

Hydro-de-amination or Deamination

$$RNH_2 \longrightarrow RH$$

Benzylic amines are particularly susceptible to hydrogenolysis by catalytic hydrogenation[1513] or dissolving metal reduction.[1514] Note that the Wolff–Kishner reduction in **19-61** involved formation of a hydrazone and deprotonation by base led to loss of nitrogen and reduction. Ceric ammonium nitrate in aqueous acetonitrile has also been shown to reductively cleave the *N*-benzyl group.[1515] Primary amines have been reduced to RH with hydroxylamine-*O*-sulfonic acid and

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[1506] Benkeser, R.A.; Mozdzen, E.C.; Muth, C.L. *J. Org. Chem.* ***1979***, *44*, 2185.

[1507] Černý, M.; Málek, J. *Collect. Czech. Chem. Commun.* ***1970***, *35*, 2030.

[1508] Chatani, N.; Tatamidani, H.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* ***2001***, *123*, 4849.

[1509] For another indirect method, which can also be applied to acid derivatives, see Degani, I.; Fochi, R. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 1133. For a direct method, see Le Deit, H.; Cron S.; Le Corre, M. *Tetrahedron Lett.* ***1991***, *32*, 2759.

[1510] Attanasi, O.; Caglioti, L.; Gasparrini, F.; Misiti, D. *Tetrahedron* ***1975***, *31*, 341, and references cited therein.

[1511] Sassaman, M.B. *Tetrahedron* ***1996***, *52*, 10835.

[1512] Kang, H.-Y.; Hong, W.S.; Cho, Y.S.; Koh, H.Y. *Tetrahedron Lett.* ***1995***, *36*, 7661.

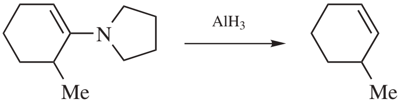
[1513] Hartung, W.H.; Simonoff, R. *Org. React.* ***1953***, *7*, 263.

[1514] du Vigneaud, V.; Behrens, O.K. *J. Biol. Chem.* ***1937***, *117*, 27.

[1515] Bull, S.D.; Davies, S.G.; Fenton, G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3765.

aq. NaOH to give the hydrocarbon, nitrogen gas, and the sulfate anion.[1516] It is postulated that R—N=N—H is an intermediate that decomposes to the carbocation. The reaction has also been accomplished with difluoroamine HNF_2;[1517] the same intermediates are postulated in this case. Treatment of aniline with 20 equivalents of NO gave benzene.[1518] An indirect means of achieving the same result is the conversion of the primary amine to the sulfonamide, $RNHSO_2R'$ (**16-102**), and treatment of this with NH_2OSO_2OH[1519] or NaOH, and then NH_2Cl.[1520] Tosylaziridines derived from terminal alkenes are reduced to the corresponding primary tosylamine with polymethylhydrosiloxane/Pd—C.[1521]

Other indirect methods involve reduction of *N,N*-ditosylates (p. 497) with $NaBH_4$ in HMPA[1522] and modifications of the Katritzky pyrylium–pyridinium method.[1523] Allylic and benzylic amines[1349] can be reduced by catalytic hydrogenolysis. Aziridines can be reductively opened with SmI_2[1524] or with Bu_3SnH and AIBN.[1525] The C—N bond of enamines is reductively cleaved to give an alkene with alane (AlH_3).[1526]



and with 9-BBN (p. 1077) or borane methyl sulfide (BMS).[1527] Since enamines can be prepared from ketones (**16-13**), this is a way of converting ketones to alkenes. In the latter case, BMS gives retention of configuration [an (*E*) isomer gives the (*E*) product], while 9-BBN gives the other isomer.[1527] Diazo ketones are reduced to methyl ketones by HI: $RCOCHN_2 + HI \rightarrow RCOCH_3$.[1528]

Quaternary ammonium salts can be cleaved with $LiAlH_4$, $R_4N^+ + LiAlH_4 \rightarrow R_3N + R^-$, as can quaternary phosphonium salts R_4P^+. Other reducing agents have also been used, for example, lithium triethylborohydride (which preferentially cleaves methyl groups)[1529] and sodium in liquid ammonia. When quaternary salts

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[1516] Doldouras, G.A.; Kollonitsch, J. *J. Am. Chem. Soc.* ***1978***, *100*, 341.

[1517] Bumgardner, C.L.; Martin, K.J.; Freeman, J.P. *J. Am. Chem. Soc.* ***1963***, *85*, 97.

[1518] Itoh, T.; Matsuya, Y.; Nagata, K.; Ohsawa, A. *Tetrahedron Lett.* ***1996***, *37*, 4165.

[1519] Nickon, A.; Hill, R.H. *J. Am. Chem. Soc.* ***1964***, *86*, 1152.

[1520] Guziec Jr., F.S.; Wei, D. *J. Org. Chem.* ***1992***, *57*, 3772.

[1521] Chandrasekhar, S.; Ahmed, M. *Tetahedron Lett.* ***1999***, *40*, 9325.

[1522] Hutchins, R.O.; Cistone, F.; Goldsmith, B.; Heuman, P. *J. Org. Chem.* ***1975***, *40*, 2018.

[1523] See Katritzky, A.R.; Bravo-Borja, S.; El-Mowafy, A.M.; Lopez-Rodriguez, G. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1671.

[1524] Molander, G.A.; Stengel, P.J. *Tetrahedron*, ***1997***, *53*, 8887.

[1525] Schwan, A.L.; Refvik, M.D. *Tetrahedron Lett.* ***1993***, *34*, 4901.

[1526] Coulter, J.M.; Lewis, J.W.; Lynch, P.P. *Tetrahedron* ***1968***, *24*, 4489.

[1527] Singaram, B.; Goralski, C.T.; Rangaishenvi, M.V.; Brown, H.C. *J. Am. Chem. Soc.* ***1989***, *111*, 384.

[1528] For example, see Pojer, P.M.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* ***1968***, *21*, 1375.

[1529] Cooke Jr., M.P.; Parlman, R.M. *J. Org. Chem.* ***1975***, *40*, 531.

are reduced with sodium amalgam in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups. Of course, aziridines[899] can be reduced in the same way as epoxides (**19-35**).

Nitro compounds, RNO_2, can be reduced to RH[1530] by sodium methylmercaptide, CH_3SNa, in an aprotic solvent[1531] or by Bu_3SnH.[1532] Both reactions have free-radical mechanisms.[1533] Tertiary nitro compounds can be reduced to RH by NaHTe.[1534] Hydrogenolysis with a Pt catalyst in the gas phase has been reported to reduce nitro compounds, as well as primary and secondary amines.[1535] The nitro group of aromatic nitro compounds has been removed with sodium borohydride.[1536] This reaction involves an addition–elimination mechanism. Reduction of the C—N bond on aromatic amines with Li metal in THF generates the aryl compounds.[1537] Sodium nitrite, sodium bisulfite in EtOH/water/acetic acid does a similar reduction.[1538] Conversion of the aniline derivative to the methanesulfonamide and subsequent treatment with NaH and NH_2Cl gives the same result.[1539] The Bu_3SnH reagent also reduces isocyanides, RNC (prepared from RNH_2 by formylation followed by **17-31**), to RH,[1540] a reaction that can also be accomplished with Li or Na in liquid NH_3,[1541] or with K and a crown ether in toluene.[1542] α-Nitro ketones can be reduced to ketones with $Na_2S_2O_4$—Et_3SiH in HMPA—H_2O.[1543]

OS **III**, 148; **IV**, 508; **VIII**, 152.

[1530] For a method of reducing allylic nitro groups, see Ono, N.; Hamamoto, I.; Kamimura, A.; Kaji, A. *J. Org. Chem.* ***1986***, *51*, 3734.

[1531] Kornblum, N.; Carlson, S.C.; Smith, R.G. *J. Am. Chem. Soc.* ***1979***, *101*, 647; Kornblum, N.; Widmer, J.; Carlson, S.C. *J. Am. Chem. Soc.* ***1979***, *101*, 658.

[1532] For reviews, see Ono, N., in Feuer, H.; Nielsen, A.T. *Nitro Compounds; Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135, 1–45; Rosini, G.; Ballini, R. *Synthesis* ***1988***, 833, see pp. 835–837; Ono, N.; Kaji, A. *Synthesis* ***1986***, 693. For discussions of the mechanism, see Korth, H.; Sustmann, R.; Dupuis, J.; Geise, B. *Chem. Ber.* ***1987***, *120*, 1197; Kamimura, A.; Ono, N. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3629.

[1533] For a discussion of the mechanism with Bu_3SnH, see Tanner, D.D.; Harrison, D.J.; Chen, J.; Kharrat, A.; Wayner, D.D.M.; Griller, D.; McPhee, D.J. *J. Org. Chem.* ***1990***, *55*, 3321. If an α substituent is present, it may be reduced instead of the NO_2. For a mechanistic discussion, see Bowman, W.R.; Crosby, D.; Westlake, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 73.

[1534] Suzuki, H.; Takaoka, K.; Osuka, A. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 1067.

[1535] Guttieri, M.J.; Maier, W.F. *J. Org. Chem.* ***1984***, *49*, 2875.

[1536] Severin, T.; Schmitz, R.; Temme, H. *Chem. Ber.* ***1963***, *96*, 2499; Kniel, P. *Helv. Chim. Acta* ***1968***, *51*, 371. For another method, see Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* ***1983***, *105*, 4017.

[1537] Azzena, U.; Dessanti, F.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* ***1999***, *40*, 8291.

[1538] Geoffroy, O.J.; Morinelli, T.A.; Meier, G.B. *Tetrahedron Lett.* ***2001***, *42*, 5367.

[1539] Wang, Y.; Guziec, Jr., F.S. *J. Org. Chem.* ***2001***, *66*, 8293.

[1540] Barton, D.H.R.; Bringmann, G.; Motherwell, W.B. *Synthesis* ***1980***, 68.

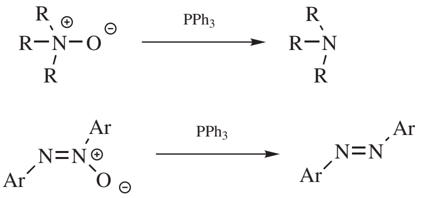
[1541] See Niznik, G.E.; Walborsky, H.M. *J. Org. Chem.* ***1978***, *43*, 2396; Yadav, J.S.; Reddy, P.S.; Joshi, B.V. *Tetrahedron Lett.* ***1988***, *44*, 7243.

[1542] Ohsawa, T.; Mitsuda, N.; Nezu, J.; Oishi, T. *Tetrahedron Lett.* ***1989***, *30*, 845.

[1543] Kamimura, A.; Kurata, K.; Ono, N. *Tetrahedron Lett.* ***1989***, *30*, 4819.

19-68 Reduction of Amine Oxides and Azoxy Compounds

N-Oxygen-detachment



Amine oxides[1544] and azoxy compounds (both alkyl and aryl)[1545] can be reduced practically quantitatively with triphenylphosphine.[1546] Other reducing agents, for example, $LiAlH_4$, $NaBH_4/LiCl$,[1547] H_2—Ni, PCl_3, $TiCl_3$,[1548] Ga/H_2O,[1549] In/$TiCl_4$,[1550] $LiAlH_4/TiCl_4$, or $SbCl_2$ have also been used. Indium metal with aqueous ammonium chloride in methanol gives good yields of pyridine from pyridine *N*-oxide.[1551] Similar results are obtained using ammonium formate and Raney nickel[1552] or zinc.[1553] Indium (III) chloride has been used for the reduction of quinoline *N*-oxide to quinoline.[1554] Polymethylhydrosiloxane with Pd—C is also an effective reducing agent for amino oxides.[1555] Nitrile oxides[1556] ($R—C{\equiv}N^+–O^-$) can be reduced to nitriles with trialkylphosphines,[1557] and isocyanates (RNCO) to isocyanides (RNC) with $Cl_3SiH—Et_3N$.[1558]

Analogous to amino *N*-oxides, phosphine oxides ($R_3P{=}O$) are reduced to phosphines (R_3P). Treatment of a phosphine oxide with MeOTf followed by reduced

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[1544] For reviews of the reduction of heterocyclic amine oxides, see Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 120–134; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 166–231.

[1545] For a review, see Newbold, B.T., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 602–603, 614–624.

[1546] For a review, see Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 295–350.

[1547] Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30, 3*511.

[1548] Kuz'min, S.V.; Mizhiritskii, M.D.; Kogan, L.M. *J. Org. Chem. USSR* ***1989***, *25*, 596.

[1549] Han, J.H.; Choi, K.I.; Kim, J.H.; Yoo, B.W. *Synth. Commun.* ***2004***, *34*, 3197.

[1550] Yoo, B.W.; Choi, K.H.; Choi, K.I.; Kim, J.H. *Synth. Commun.* ***2003***, *33*, 4185.

[1551] Yadav, J.S.; Reddy, B.V.S.; Reddy, M.M. *Tetrahedron Lett.* ***200***, *41*, 2663.

[1552] Balicki, R.; Maciejewski, G. *Synth. Commun.* ***2002***, *32*, 1681.

[1553] Balicki, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* ***2003***, *33*, 4137.

[1554] Ilias, Md.; Barman, D.C.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***2002***, *43*, 1877.

[1555] Chandrasekhar, S.; Reddy, Ch.R.; Rao, R.J.; Rao, J.M. *Synlett* ***2002***, 349.

[1556] For reviews of the chemistry of nitrile oxides, see Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 55–74; Grundmann, C. *Fortschr. Chem. Forsch.* ***1966***, *7*, 62.

[1557] Grundmann, C.; Frommeld, H.D. *J. Org. Chem.* ***1965***, *30*, 2077.

[1558] Baldwin, J.E.; Derome, A.E.; Riordan, P.D. *Tetrahedron* ***1983***, *39*, 2989.

with $LiAlH_4$ gives the phosphine.[1559] Chiral phosphine oxides are reduced to the phosphine with excellent enantioselectivity using PPh_3 and Cl_3SiH.[1560]

OS **IV**, 166. See also, OS **VIII**, 57.

19-69 Replacement of the Diazonium Group by Hydrogen

Dediazoniation or **Hydro-de-diazoniation**

$$ArN_2^+ + H_3PO_2 \longrightarrow ArH$$

Reduction of the diazonium group (*dediazoniation*) provides an indirect method for the removal of an amino group from an aromatic ring.[1561] The best and most common way of accomplishing this is by use of hypophosphorous acid H_3PO_2, although many other reducing agents[1562] have been used, among them ethanol, HMPA,[1563] thiophenol,[1564] and sodium stannite. Ethanol was the earliest reagent used, and it frequently gives good yields, but often ethers (ArOEt) are side products. When H_3PO_2 is used, 5–15 equivalents of this reagent are required per equivalent of substrate. Diazonium salts can be reduced in nonaqueous media by several methods, including treatment with Bu_3SnH or Et_3SiH in ethers or MeCN[1565] and by isolation as the BF_4^- salt and reduction of this with $NaBH_4$ in DMF.[1566] Aromatic amines can be deaminated ($ArNH_2 \longrightarrow ArH$) in one laboratory step by treatment with an alkyl nitrite in DMF[1567] or boiling THF.[1568] The corresponding diazonium salt is an intermediate.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic (S_N1) mechanism while the reduction to ArH proceeds by a free-radical process.[1569] The reduction with H_3PO_2 is also believed to have a free-radical mechanism.[1570] In the reduction with $NaBH_4$, an aryldiazene intermediate

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[1559] Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* ***2001***, *3*, 87.

[1560] Wu, H.-C.; Yu, J.-Q.; Spencer, J.B. *Org. Lett.* ***2004***, *6*, 4675.

[1561] For a review, see Zollinger, H., in Patai, S.; Rappoport, Z. *The Chemistry of Functinal Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 603–669.

[1562] For lists of some of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 39–41; Tröndlin, F.; Rüchardt, C. *Chem. Ber.* ***1977***, *110*, 2494.

[1563] Shono, T.; Matsumura, Y.; Tsubata, K. *Chem. Lett.* ***1979***, 1051.

[1564] For a list of some of these, with references, see Korzeniowski, S.H.; Blum, L.; Gokel, G.W. *J. Org. Chem.* ***1977***, *42*, 1469.

[1565] Nakayama, J.; Yoshida, M.; Simamura, O. *Tetrahedron* ***1970***, *26*, 4609.

[1566] Hendrickson, J.B. *J. Am. Chem. Soc.* ***1961***, *83*, 1251. See also, Threadgill, M.D.; Gledhill, A.P. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 873.

[1567] Doyle, M.P.; Dellaria, Jr., J.F.; Siegfried, B.; Bishop, S.W. *J. Org. Chem.* ***1977***, *42*, 3494.

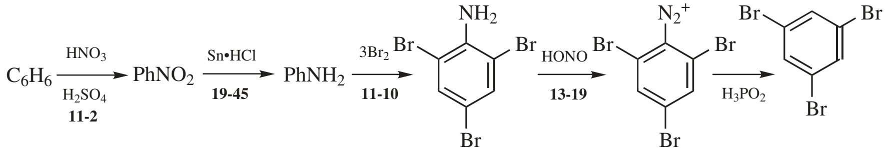
[1568] Cadogan, J.I.G.; Molina, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 541.

[1569] For examples, see DeTar, D.F.; Kosuge, T. *J. Am. Chem. Soc.* ***1958***, *80*, 6072; Lewis, E.S.; Chambers, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 3267; Broxton, T.J.; Bunnett, J.F.; Paik, C.H. *J. Org. Chem.* ***1977***, *42*, 643.

[1570] See, for example, Kornblum, N.; Cooper, G.D.; Taylor, J.E. *J. Am. Chem. Soc.* ***1950***, *72*, 3013; Beckwith, A.L.J. *Aust. J. Chem.* ***1972***, *25*, 1887; Levit, A.F.; Kiprianova, L.A.; Gragerov, I.P. *J. Org. Chem. USSR* ***1975***, *11*, 2395.

(ArN=NH) has been demonstrated,[1571] arising from nucleophilic attack by BH_4^- on the β nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution.[1572] It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical AR• or the corresponding anion Ar^- may be involved.[1573]

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



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

Unwanted dediazoniation can be suppressed by using hexasulfonated calix[6]arenes (see p. 122).[1574]

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

19-70 Desulfurization

Hydro-de-thio-substitution, and so on

$$\mathrm{RSH} \longrightarrow \mathrm{RH}$$

$$\mathrm{RSR'} \longrightarrow \mathrm{RH} + \mathrm{R'H}$$

$$\mathrm{RS(O)}_n\mathrm{R'} \longrightarrow \mathrm{RH} + \mathrm{R'H}$$

Thiols and thioethers,[1575] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[1576] The hydrogen is usually not applied externally, since

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[1571] König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 45; McKenna, C.E.; Traylor, T.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2313.

[1572] Huang, P.C.; Kosower, E.M. *J. Am. Chem. Soc.* ***1968***, *90*, 2354, 2362, 2367; Smith III, M.R.; Hillhouse, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 4066.

[1573] Rieker, A.; Niederer, P.; Leibfritz, D. *Tetrahedron Lett.* ***1969***, 4287; Kosower, E.M.; Huang, P.C.; Tsuji, T. *J. Am. Chem. Soc.* ***1969***, *91*, 2325; König, E.; Musso, H.; Záhorszky, U.I. König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 45; McKenna, C.E.; Traylor, T.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2313.; Broxton, T.J.; McLeish, M.J. *Aust. J. Chem.* ***1983***, *36*, 1031.

[1574] Shinkai, S.; Mori, S.; Araki, K.; Manabe, O. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3679.

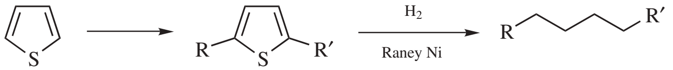
[1575] For a review of the reduction of thioethers, see Block, E., in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 585–600.

[1576] For reviews, see Belen'kii, L.I., in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962***, *12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962***, *62*, 347.

Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, including disulfides, thiono esters,[1577] thioamides, sulfoxides, and thioacetals.[1578] Reduction of thioacetals is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see **19-61**), and it can also give the alkene if a hydrogen is present.[1579] In most of the examples given, R can also be aryl. Other reagents[1580] have also been used.[1581]

Lithium aluminum hydride reduces most sulfur compounds with cleavage of the C—S bond, including thiols.[1582] Thioesters can be reduced with Ni_2B (from $NiBr_2$/$NaBH_4$).[1583] β-Ketosulfones are reduced with $TiCl_4$—Zn,[1584] $TiCl_4$—Sm,[1585] or Bu_3SnCl—$NaCNBH_3$/AIBN.[1586]

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene to **49**, followed by reduction to give **50**.



49 **50**

Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$ from **49**) with a nickel boride catalyst prepared from nickel(II) chloride and $NaBH_4$ in methanol.[1587] It is possible to reduce just one SR group of a dithioacetal by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[1588] Phenyl selenides RSePh can be reduced to RH with Ph_3SnH[1589] and with nickel boride.[1590] Cleavage of the C—Se bond can also be achieved with SmI_2.[1591]

[1577] See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.

[1578] For desulfurization of the mixed acetal PhCHC(OBu)SPh to $PhCH_2OBu$ see Nakata, D.; Kusaka, C.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* ***2001***, *42*, 415.

[1579] Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963***, *28*, 1443.

[1580] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 53–60. For a review with respect to transition-metal reagents, see Luh, T.; Ni, Z. *Synthesis* ***1990***, 89. For some very efficient nickel-containing reagents, see Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989***, *54*, 4848.

[1581] For example, diphosphorus tetraiodide by Suzuki, H.; Tani, H.; Takeuchi, S. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2421; Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* ***1989***, *30*, 1277; $NiBr_2$-Ph_3P-$LiAlH_4$ by Ho, K.M.; Lam, C.H.; Luh, T. *J. Org. Chem.* ***1989***, *54*, 4474.

[1582] Smith, M.B.; Wolinsky, J. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 1431.

[1583] Back, T.G.; Baron D.L.; Yang, K. *J. Org. Chem.* ***1993***, *58*, 2407.

[1584] Guo, H.; Ye, S.; Wang, J.; Zhang, Y. *J. Chem. Res. (S)* ***1997***, 114.

[1585] Wang, J.; Zhang, Y. *Synth. Commun.* ***1996***, *26*, 1931.

[1586] Giovannini, R.; Petrini, M. *Synlett* ***1995***, 973.

[1587] Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972***, *2*, 415.

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[1589] Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc. Chem. Commun.* ***1978***, 41.

[1590] Back, T.G. *J. Chem. Soc. Chem. Commun.* ***1984***, 1417.

[1591] Ogawa, A.; Ohya, S.; Doi, M.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* ***1998***, *39*, 6341.

The exact mechanism of the Raney nickel reactions are still in doubt, although they are probably of the free-radical type.[1592] It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds, that is, the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the alkenes and the failure to isolate any potential sulfur-containing intermediates.[1593]

Sulfonamides are reduced to the corresponding amine by heating with Me_3SiCl and NaI.[1594]

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

19-71 Reduction of Sulfonyl Halides and Sulfonic Acids to Thiols or Disulfides

$$RSO_2Cl \xrightarrow{LiAlH_4} RSH$$

Thiols can be prepared by the reduction of sulfonyl halides[1595] with $LiAlH_4$. Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Another reagent for this reduction is Me_2SiCl_2 and Zn with dimethyl acetamide.[1596] Sulfonic acids have been reduced to thiols with a mixture of triphenylphosphine and either I_2 or a diaryl disulfide.[1597] For the reduction of sulfonyl chlorides to sulfinic acids, see **16-104**.

Disulfides RSSR can also be produced.[1598] Other sulfonic acid derivatives can be converted to disulfides. Esters, such as PhSAc, are converted to disulfides PhS—SPh with Clayan and microwave irradiation.[1599] Thiobenzoate derivatives PhSBz are similarly converted to PhS—SPh with SmI_2.[1600] In a similar manner, RS—SO_3Na is converted to RS—SR when heated with samarium metal in water.[1601]

OS **I**, 504; **IV**, 695; **V**, 843.

[1592] For a review, see Bonner, W.A.; Grimm, R.A., in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, ***1966***, pp. 35–71, 410–413. For a review of the mechanism of desulfurization on molybdenum surfaces, see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* ***1988***, *21*, 394.

[1593] Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962***, *40*, 941.

[1594] Sabitha, G.; Reddy, B.V.S.; Abraham, S.; Yadav, J.S. *Tetrahedron Lett.* ***1999***, *40*, 1569.

[1595] For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 216–220.

[1596] Uchiro, H.; Kobayashi, S. *Tetrahedron Lett.* ***1999***, *40*, 3179.

[1597] Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3802; ***1984***, *57*, 232.

[1598] For example, see Alper, H. *Angew. Chem. Int. Ed.* ***1969***, *8*, 677; Chan, T.H.; Montillier, J.P.; Van Horn, W.F.; Harpp, D.N. *J. Am. Chem. Soc.* ***1970***, *92*, 7224. See also, Olah, G.A.; Narang, S.C.; Field, L.D.; Karpeles, R. *J. Org. Chem.* ***1981***, *46*, 2408; Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3813; Suzuki, H.; Tani, H.; Osuka, A. *Chem. Lett.* ***1984***, 139; Babu, J.R.; Bhatt, M.V. *Tetrahedron Lett.* ***1986***, *27*, 1073; Narayana, C.; Padmanabhan, S.; Kabalka, G.W. *Synlett* ***1991***, 125.

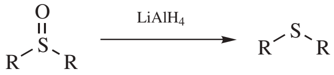
[1599] Meshram, H.M.; Bandyopadhyay, A.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***1999***, *29*, 2705.

[1600] Yoo, B.W.; Baek, H.S.; Keum, S.R.; Yoon, C.M.; Nam. G.S.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2000***, *30*, 4317.

[1601] Wang, L.; Li, P.; Zhou, L. *Tetrahedron Lett.* ***2002***, *43*, 8141.

19-72 Reduction of Sulfoxides and Sulfones

S-Oxygen-detachment



Sulfoxides can be reduced to sulfides by many reagents,[1602] among them Ph_3P,[1603] $LiAlH_4$, HI, Bu_3SnH,[1604] $MeSiCl_3$—NaI,[1605] H_2—Pd—C,[1606] $NaBH_4$—$NiCl_2$,[1607] $NaBH_4/I_2$,[1608] catecholborane,[1609] TiI_4,[1610] $TiCl_4$/In,[1611] Cp_2TiCl_2/In,[1612] Sm/methanolic NH_4Cl with ultrasound,[1613] $(EtO)_2PCl/NEt_3$,[1614] and $SiO_2/SOCl_2$. Sulfones, however, are usually stable to reducing agents, although they have been reduced to sulfides with DIBALH, $(i\text{Bu})_2AlH$.[1615] A less general reagent is $LiAlH_4$, which reduces some sulfones to sulfides, but not others.[1616] Heating sulfoxides with 2,6-dihydroxypyridine gives the corresponding sulfide.[1617] Both sulfoxides and sulfones can be reduced by heating with sulfur (which is oxidized to SO_2), although 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 ~ 75% of the original radioactivity of the sulfone is lost.[1618] This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*. There is no direct general

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[1602] For reviews, see Kukushkin, V.Yu. *Russ. Chem. Rev.* ***1990***, *59*, 844; Madesclaire, M. *Tetrahedron* ***1988***, *44*, 6537; Drabowicz, J.; Togo, H.; Mikołajczyk, M.; Oae, S. *Org. Prep. Proced. Int.* ***1984***, *16*, 171; Drabowicz, J.; Numata, T.; Oae, S. *Org. Prep. Proced. Int.* ***1977***, *9*, 63. For a list of reagents, with references, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.

[1603] For a review, see Rowley, A.G., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 301–304.

[1604] Kozuka, S.; Furumai; S.; Akasaka, T.; Oae, S. *Chem. Ind. (London)* ***1974***, 496.

[1605] Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667. See also, Schmidt, A.H. Russ *Chem. Ber.* ***1981***, *114*, 822.

[1606] Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Synthesis* ***1975***, 385.

[1607] Khurana, J.M.; Ray, A.; Singh, S. *Tetrahedron Lett.* ***1998***, *39*, 3829.

[1608] Karimi, B.; Zareyee, D. *Synthesis* ***2003***, 335.

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[1610] Shimizu, M.; Shibuya, K.; Hayakawa, R. *Synlett* ***2000***, 1437.

[1611] Yoo, B.W.; Choi, K.H.; Kim, D.Y.; Choi, K.I.; Kim, J.H. *Synth. Commun.* **2003**, 33, 53.

[1612] Yoo, B.W.; Choi, K.H.; Lee, S.J.; Yoon, C.M.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2002***, *32*, 63.

[1613] Yadav, J.S.; Subba Reddy, B.V.; Srinivas, C.; Srihari, P. *Synlett* ***2001***, 854.

[1614] Jie, Z.; Rammoorty, V.; Fischer, B. *J. Org. Chem.* ***2002***, *67*, 711.

[1615] Gardner, J.N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.* ***1973***, *51*, 1419.

[1616] Bordwell, F.G.; McKellin, W.H. *J. Am. Chem. Soc.* ***1951***, *73*, 2251; Whitney, T.A.; Cram, D.J. *J. Org. Chem.* ***1970***, *35*, 3964; Weber, W.P.; Stromquist, P.; Ito, T.I. *Tetrahedron Lett.* ***1974***, 2595.

[1617] Miller, S.J.; Collier, T.R.; Wu, W. *Tetrahedron Lett.* ***2000***, *41*, 3781.

[1618] Kiso, S.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 1722. See also, Oae, S.; Nakai, M.; Tsuchida, Y.; Furukawa, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 445.

method for the reduction of sulfones to sulfoxides, but an indirect method has been reported.[1619] Selenoxides can be reduced to selenides with a number of reagents.[1620]

OS IX, 446

D. Reduction With Cleavage

19-73 de-Alkylation of Amines and Amides

$$R'_2N\text{—}R \longrightarrow R'_2N\text{—}H$$

Certain amines can be dealkylated, usually under reductive conditions. *N*-Allyl amines, $R_2N\text{—}CH_2CH{=}CH_2$ are converted to the corresponding amine, $R_2N\text{—}H$, with Dibal/$NiCl_2$dppp,[1621] and with $Pd(dba)_2$dppb.[1622] A mixture of $TiCl_3$ and Li converts *N*-benzylamines to the amine ($R_2NCH_2Ph \rightarrow R_2NH$).[1623] In the case of *N,N*-dimethyl amines, $RuCl_3$ and H_2O_2 demethylate the amine ($ArNMe_2 \rightarrow ArNHMe$).[1624] Tribenzylamines are dealkylated to give the dibenzylamine with ceric ammonium nitrate in aqueous acetonitrile.[1625] *N*-Benzyl indoles are cleaved to indoles with O_2, DMSO/KO*t*-Bu[1626] or with tetrabutylammonium fluoride.[1627]

The process is not limited to amines. Amides can also be dealkylated. *N*-Benzyl amides are debenzylated in the presence of NBS and AIBN.[1628]

N-Alkyl sulfonamides are dealkylated with $PhI(OAc)_2$ and I_2 with ultrasound to give a primary sulfonamide.[1629] Similar results are obtained with H_5IO_6 and a chromium catalyst.[1630] *tert*-Butyl sulfonamides are cleaved to the primary sulfonamide with BCl_3.[1631]

[1619] Still, I.W.J.; Ablenas, F.J. *J. Org. Chem.* ***1983***, *48*, 1617.

[1620] See, for example, Sakaki, K.; Oae, S. *Chem. Lett.* ***1977***, 1003; Still, I.W.J.; Hasan, S.K.; Turnbull, K. *Can. J. Chem.* ***1978***, *56*, 1423; Denis, J.N.; Krief, A. *J. Chem. Soc. Chem. Commun.* ***1980***, 544.

[1621] Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* ***1998***, *39*, 4679.

[1622] Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* ***1995***, *132*, 1157; Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J.-M. *Tetrahedron Lett.* ***1995***, *36*, 1267.

[1623] Talukdar, S.; Banerji, A. *Synth. Commun.* ***1995***, *25*, 813.

[1624] Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* ***1992***, *33*, 6991.

[1625] Bull, S.D.; Davies, S.G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D.; Fenton, G. *Chem. Commun.* ***2000***, 337.

[1626] Haddach, A.A.; Kelleman, A.; Deaton-Rewoliwski, M.V. *Tetrahedron Lett.* ***2002***, *43*, 399.

[1627] Routier, S.; Saugé, L.; Ayerbe, N,; Couderet, G.; Mérour, J.-Y. *Tetrahedron Lett.* ***2002***, *43*, 589. For a related debenzylation see Meng, G.; He, Y.-P.; Chen, F.-E. *Synth. Commun.* ***2003***, *33*, 2593.

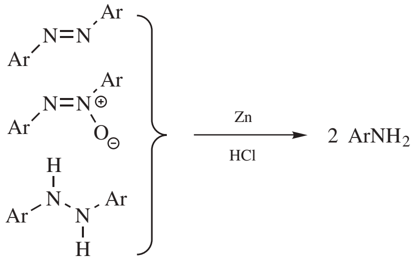
[1628] Baker, S.R.; Parsons, A.F.; Wilson, M. *Tetrahedron Lett.* ***1998***, *39*, 331.

[1629] Katohgi, M.; Yokoyama, M.; Togo, H. *Synlett* ***2000***, 1055; Katohgi, M.; Togo, H. *Tetrahedron* ***2001***, *57*, 7481.

[1630] Xu, L.; Zhang, S.; Trudell, M.L. *Synlett* ***2004***, 1901.

[1631] Wan, Y.; Wu, X.; Kannan, M.A.; Alterman, M. *Tetrahedron Lett.* ***2003***, *44*, 4523.

19-74 Reduction of Azo, Azoxy, and Hydrazo Compounds to Amines



Azo, azoxy, and hydrazo compounds can all be reduced to amines.[1632] Metals (notably zinc) and acids, and $Na_2S_2O_4$, are frequently used as reducing agents, and Bu_3SnH with a copper catalyst has been used.[1633] Borane reduces azo compounds to amines, although it does not reduce nitro compounds.[1634] $LiAlH_4$ does not reduce hydrazo compounds or azo compounds, although with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds, $LiAlH_4$ gives only azo compounds (**19-68**). Noted that azo compounds are reduced to the hydrazine by reaction with hydrazine hydrate in ethanol.[1635]

OS **I**, 49; **II**, 35, 39; **III**, 360; **X**, 327. Also see, OS **II**, 290.

19-75 Reduction of Disulfides to Thiols

S-Hydrogen-uncoupling

$$\mathrm{RSSR} \xrightarrow[\mathrm{H^+}]{\mathrm{Zn}} 2\ \mathrm{RSH}$$

Disulfides can be reduced to thiols by mild reducing agents,[1636] such as zinc and dilute acid, In and NH_4Cl/EtOH,[1637] or Ph_3P and H_2O.[1638] The reaction can also be accomplished simply by heating with alkali.[1639] Among other reagents used have been $LiAlH_4$, $NaBH_4/ZrCl_4$,[1640] Mg/MeOH,[1641] KBH(*O*—*i*Pr)$_3$,[1642] and hydrazine or substituted hydrazines.[1643]

[1632] For a review, see Newbold, B.T., in Patai, S. *The Chemistry of Hydrazo, Azo, and azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 629–637.

[1633] Tan, Z.; Qu, Z.; Chen, B.; Wang, J. *Tetrahedron* ***2000***, *56*, 7457.

[1634] Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* ***1960***, *82*, 681.

[1635] Zhang, C.-R.; Wang, Y.-L. *Synth. Commun.* ***2003***, *33*, 4205.

[1636] For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 220–229.

[1637] Reddy, G.V.S.; Rao, G.V.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 859.

[1638] Overman, L.E.; Smoot, J.; Overman, J.D. *Synthesis* ***1974***, 59.

[1639] For discussions, see Danehy, J.P.; Hunter, W.E. *J. Org. Chem.* ***1967***, *32*, 2047.

[1640] Chary, K.P.; Rajaram, S.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3905.

[1641] Sridhar, M.; Vadivel, S.K.; Bhalerao, U.T. *Synth. Commun.* ***1997***, *27*, 1347.

[1642] Brown, H.C.; Nazer, B.; Cha, J.S. *Synthesis* ***1984***, 498.

[1643] Maiti, S.N.; Spevak, P.; Singh, M.P.; Micetich, R.G.; Narender Reddy, A.V. *Synth. Commun.* ***1988***, *18*, 575.

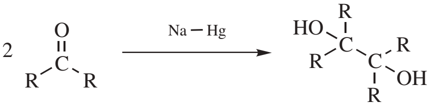
Aryl diselenides are similarly cleaved to selenols (ArSeH) with Cp_2TiH followed by $Ph_2I^+X^-$.[1644]

OS **II**, 580. Also see, OS **IV**, 295.

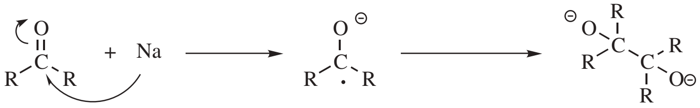
E. Reductive Coupling

19-76 Bimolecular Reduction of Aldehydes and Ketones to 1,2-Diols and Imines to 1,2-Diamines

2/*O*-Hydrogen-coupling and 2/*N*-Hydrogen-coupling



1,2-Diols (pinacols) can be synthesized by reduction of aldehydes and ketones with active metals, such as sodium, magnesium, or aluminum.[1645] Aromatic ketones give better yields than aliphatic ones. The use of a Mg—MgI_2 mixture has been called the *Gomberg–Bachmann pinacol synthesis*.[1646] 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,[1647] including Sm,[1648] Yb,[1649] Yb-Me_3SiCl,[1650] $InCl_3$ catalyst with Mg,[1651] Al/$TiCl_3$,[1652] $VOCl_3$ catalyst with Me_3SiCl,[1653]

[1644] Huang, X.; Wu, L.-L.; Xu, X.-H. *Synth. Commun.* ***2001***, *31*, 1871.

[1645] For efficient methods, see Schreibmann, A.A.P. *Tetrahedron Lett.* ***1970***, 4271; Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 1729. For an ultrasound promoted reaction with aluminum, see Bian, Y.-J.; Liu, S.-M.; Li, J.-T.; Li, T.-S. *Synth. Commun.* ***2002***, *32*, 1169.

[1646] For an ultrasound promoted reaction, see Li, J.-T.; Bian, Y.-J.; Zang, H.-J.; Li, T.-s. *Synth. Commun.* ***2002***, *32*, 547.

[1647] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.1111–1114.

[1648] Ghatak, A.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 3793; Talukdar, S.; Fang, J.-M. *J. Org. Chem.* ***2001***, *66*, 330; Yu, M.; Zhang, Y. *Org. Prep. Proceed. Int.* ***2001***, *33*, 187; Hélion, F.; Lannou, M.-I.; Namy, J.-L. *Tetrahedron Lett.* ***2003***, *44*, 5507.

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[1650] Ogawa, A.; Takeuchi, H.; Hirao, T. *Tetrahedron Lett.* ***1999***, *40*, 7113.

[1651] Mori, K.; Ohtaka, S.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1497.

[1652] Li, J.-T.; Lin, Z.-P.; Qi, N.; Li, T.-S. *Synth. Commun.* ***2004***, *34*, 4339.

[1653] Hirao, T.; Hatano, B.; Imamoto, Y.; Ogawa, A. *J. Org. Chem.* ***1999***, *64*, 7665.

activated Mn,[1654] In with ultrasound,[1655] Zn,[1656] and a reagent prepared from $TiCl_4$[1657] and Mg amalgam[1658] (a low-valent titanium reagent;[1659] see **19-76**). A mixture of $TiCl_4$[1660] or $TiCl_2$[1661] and Zn can also be used. Unsymmetrical coupling between two different aldehydes has been achieved by the use of a vanadium complex,[1662] while $TiCl_3$ in aqueous solution has been used to couple two different ketones.[1663] Two aldehydes have also been coupled using magnesium in water.[1664] Coupling leads to a mixture of syn- and anti-diols. "Syn-selective" reagents are Cp_2TiCl_2/Mn,[1665] $TiCl_4/Bu_4I$,[1666] TiI_4,[1667] $TiBr_2$+Cu,[1668] and $NbCl_3$.[1669] With SmI_2,[1670] coupling in the presence of a primary alkyl iodide leads to acyl addition using an excess of HMPA, but pinacol coupling with an excess of LiBr.[1671] "Anti-selective" coupling reactions are also known: Ti–salen,[1672] Mg with a $NiCl_2$ catalyst,[1673] $Sm/SmCl_3$,[1674] and $TiCl_4(thf)_2$ with a chiral Schiff base.[1675] Aryl

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[1656] Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y.S.; Heravi, M.M. *Monat. Chem.* ***2001***, *132*, 689.

[1657] For a discussion of pinacol versus reduction with this reagent, and mechanistic considerations, see Clerici, A.; Pastori, N.; Porta, O. *Tetrahaedron Lett.* ***2004***, *45*, 1825.

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[1659] For a discussion of the mechanism, see Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem Soc.* ***2001***, *123*, 1503.

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[1663] Clerici, A.; Porta, O. *J. Org. Chem.* ***1982***, *47*, 2852; *Tetrahedron* ***1983***, *39*, 1239. For some other unsymmetrical couplings, see Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Chem. Soc. Chem. Commun.* ***1988***, 668; Delair, P.; Luche, J. *J. Chem. Soc. Chem. Commun.* ***1989***, 398; Takahara, P.M.; Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *Tetrahedron Lett.* ***1989***, *30*, 7177.

[1664] Zhang, W.-C.; Li, C.-J. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3131.

[1665] Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* ***1998***, 2673. Also see, Barden, M.C.; Schwartz, J. *J. Am. Chem. Soc.* ***1996***, *118*, 5484; Gansäuer, A. *Chem. Commun.* ***1997***, 457; Gansäuer, A. *Synlett* ***1997***, 363; Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* ***1996***, *37*, 3035.

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[1670] Namy, J.L.; Souppe, J.; Kagan, H.B. *Tetrahedron Lett.* ***1983***, *24*, 765; Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc*, ***1996***, *118*, 11666; Honda, T.; Katoh, M. *Chem. Commun.* ***1997***, 369; Shiue, J.-S.; Lin, C.-C.; Fang, J.-M. *Tetrahedron Lett.* ***1993***, *34*, 335. Also see Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett.* ***1996***, *37*, 7755.

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[1675] Li, Y.-G.; Tian, Q.-S.; Zhao, J.; Feng, Y.; Li, M.-J.; You, T.-P. *Tetrahedron Asymmetry* ***2004***, *15*, 1707.

aldehydes are coupled to give the bis-trimethylsilyl ether using Mn, Me_3SiCl, and Cp_2TiCl_2.[1676]

A crossed-pinacol coupling was reported using Et_2Zn and with a BINOL catalyst gave good enantioselectivity.[1677] A combination of Mg and Me_3SiCl was also used to a crossed-pinacol.[1678]

Intramolecular pinacol coupling reactions are known, giving cyclic 1,2-diols.[1679] Dialdehydes have been cyclized by reaction with $TiCl_3$ to give cyclic 1,2-diols in good yield.[1680] A radical-induced coupling of an α,ω-dialdehyde led to *cis*-1,2-cyclopentanediol when treated with Bu_3SnH and AIBN.[1681] or induced photochemically.[1682]

Chiral additives with pinacol couplings lead to formation of a diol with moderate to good enantioselectivity.[1683] Chiral metal complexes in conjunction with a metal leads to diol formation with good enantioselectivity.[1684]

A variation of the pinacol coupling treats acyl nitriles with indium metal and ultrasound to give a 1,2-diketone.[1685] Another variation couples acetals to give 1,2-diols.[1686]

The dimerization of ketones to 1,2-diols can also be accomplished photochemically; indeed, this is one of the most common photochemical reactions.[1687] The substrate, which 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.[1688]

[1676] Dunlap, M.S.; Nicholas, K.M. *Synth. Commun.* ***1999***, *29*, 1097.

[1677] Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2169.

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[1679] **With a Ti catalyst + Zn**: Yamamoto, Y.; Hattori, R.; Itoh, K. *Chem. Commun.* ***1999***, 825; Yamamoto, Y.; Hattori, R.; Miwa, T.; Nakagai, Y.-I.; Kubota, T.; Yamamoto, C.; Okamoto, Y.; Itoh, K. *J. Org. Chem.* ***2001***, *66*, 3865. **With SmI_2/*t*-BuOH**: Handa, S.; Kachala, M.S.; Lowe, S.R. *Tetrahedron Lett.* ***2004***, *45*, 253.

[1680] McMurry, J.E.; Rico, J.G. *Tetrahedron Lett.* ***1989***, *30*, 1169. For the stereochemistry of this coupling, see McMurry, J.E.; Siemers, N.O. *Tetrahedron Lett.* ***1993***, *34*, 7891. For other cyclization reactions of dialdehydes and ketoaldehydes, see Molander, G.A.; Kenny, C. *J. Am. Chem. Soc.* ***1989***, *111*, 8236; Raw, A.S.; Pedersen, S.F. *J. Org. Chem.* ***1991***, *56*, 830; Chiara, J.L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* ***1991***, *32*, 1125.

[1681] Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998***, *63*, 6375.

[1682] Hays, D.S.; Fu. G.C. *J. Am. Chem. Soc.* ***1995***, *117*, 7283.

[1683] Enders, D.; Ullrich, E.C. *Tetrahedron Asymmetry* ***2000***, *11*, 3861.

[1684] See Bensari, A.; Renaud, J.-L.; Riant, O. *Org. Lett.* ***2001***, *3*, 3863; Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* ***2004***, *126*, 13198.

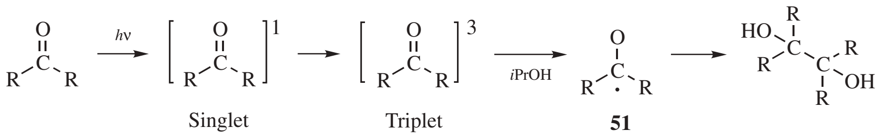
[1685] Baek, H.S. et al. *Tetrahedron Lett.* ***2000***, *41*, 8097.

[1686] Studer, A.; Curran, D.P. *Synlett* ***1996***, 255.

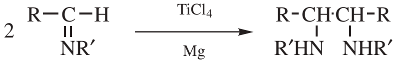
[1687] For reviews, see Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 203–217; Neckers, D.C. *Mechanistic Organic Photochemistry*, Reinhold, NY, ***1967***, pp. 163–177; Calvert, J.G.; Pitts Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 532–536; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***, pp. 363–385; Kan, R.O. *Organic Photochemistry*, McGraw-Hill, NY, ***1966***, pp. 222–229.

[1688] For a review of amines as hydrogen donors in this reaction, see Cohen, S.G.; Parola, A.; Parsons, Jr., G.H. *Chem. Rev.* ***1973***, *73*, 141.

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 species abstracts hydrogen from the alcohol (p. 347), and then dimerizes. The *i*PrO• radical, which is formed by this process, donates H• to another molecule of ground-state benzophenone, producing acetone and another molecule of **51**. This mechanism[1689] predicts that the quantum yield for the disappearance of benzophenone should be 2, since each quantum of light results in the conversion of 2 equivalents of benzophenone to **51**. 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 (although *p*-aminobenzophenone, e.g., can be dimerized in cyclohexane[1690]). The reaction has also been carried out electrochemically.[1691]



$$2\ \underset{\text{NR}'}{\overset{}{\text{R}-\underset{\|}{\text{C}}-\text{H}}} \xrightarrow[\text{Mg}]{\text{TiCl}_4} \text{R-}\underset{\text{R}'\text{HN}}{\text{CH}}\text{-}\underset{\text{NHR}'}{\text{CH}}\text{-R}$$

A coupling reaction similar to pinacol coupling has been used with imines, which dimerize to give 1,2-diamines. A number of reagents have been used, including treatment with $TiCl_4$—Mg,[1692] In/aq. EtOH,[1693] Zn/aq. NaOH,[1694] Cp_2VCl_2/Zn/

[1689] For some of the evidence for this mechanism, see Pitts, Jr., J.N.; Letsinger, R.L.; Taylor, R.; Patterson, S.; Recktenwald, G.; Martin, R.B. *J. Am. Chem. Soc.* ***1959***, *81*, 1068; Moore, W.M.; Hammond, G.S.; Foss, R.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2789; Huyser, E.S.; Neckers, D.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3641.

[1690] Porter, G.; Suppan, P. *Proc. Chem. Soc.* ***1964***, 191.

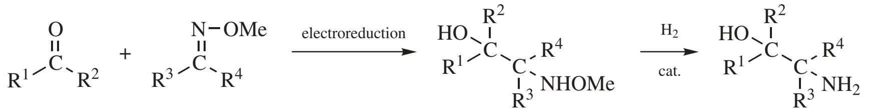
[1691] Elinson, M.N.; Feducovich, S.K.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron* ***2000***, *56*, 9999. For reviews, see Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 174–180; Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 137–140; Baizer, M.M.; Petrovich, J.P. *Prog. Phys. Org. Chem.* ***1970***, *7*, 189. For a review of electrolytic reductive coupling, see Baizer, M.M. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 639–689.

[1692] Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* ***1988***, *71*, 1999; Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* ***1988***, 255; Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* ***1998***, 873, 875.

[1693] Kalyanam, N.; Rao, G.V. *Tetrahedron Lett.* ***1993***, *34*, 1647.

[1694] Dutta, M.P.; Baruah, B.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett* ***1998***, 857.

$PhMe_2SiCl$,[1695] Et_2AlCl,[1696] SmI_2,[1697] and (for silylated imines) $NbCl_4(thf)_2$.[1698] When electroreduction was used, it was even possible to obtain cross-products, by coupling a ketone to an *O*-methyl oxime:[1699] *O*-Methyl oxime ethers are coupled to give 1,2-diamines using Zn and $TiCl_4$.[1700] Aldehydes are converted to 1,2-diamines by treatment with TMS_2NH, NaH, and Li metal in 5 *M* $LiClO_4$ in ether, with sonication.[1701] Hemiaminals are coupled to give 1,2-diamines with TiI_4/Zn.[1702] Amides are converted to 1,2-diamines with Cp_2TiF_2 and $PhMeSiH_2$.[1703] Samarium(II) iodide was used to couple iminium salts, giving the 1,2-diamine.[1704] Ketones can be treated with Yb, and then an imine to give amino alcohols.[1705]

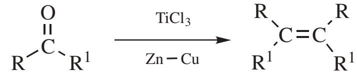


The *N*-methoxyamino alcohol could then be reduced to the amino alcohol.[1699] A photochemical coupling has also been reported.[1706] A variation of this reaction treats an imine with Yb in THF/HMPA and then an aldehyde to give a 1,2-bis(imine).[1707]

OS **I**, 459; **II**, 71; **X**, 312; **81**, 26.

19-77 Bimolecular Reduction of Aldehydes or Ketones to Alkenes

De-oxygen-coupling



Aldehydes and ketones, both aromatic and aliphatic (including cyclic ketones), can be converted in high yields to dimeric alkenes by treatment low valent titanium,[1708] initially generated with $TiCl_3$ and a zinc–copper couple.[1709] This is called

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[1695] Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* ***1998***, *63*, 9421.

[1696] This reaction proceeds with *N*-ethylation. See Shimizu, M.;Niwa, Y. *Tetrahedron Lett.* ***2001***, *42*, 2829.

[1697] Enholm, E.J.; Forbes, D.C.; Holub, D.P. *Synth. Commun.* ***1990***, *20*, 981; Imamoto, T.; Nishimura, S. *Chem. Lett.* ***1990***, 1141; Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* ***2004***, *6*, 4747.

[1698] Roskamp, E.J.; Pedersen, S.F. *J. Am. Chem. Soc.* ***1987***, *109*, 3152.

[1699] Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* ***1991***, *32*, 525.

[1700] Kise, N.; Ueda, N. *Tetrahedron Lett.* ***2001***, *42*, 2365.

[1701] Mojtahedi, M.M.; Saidi, M.R.; Shirzi, J.S.; Bolourtchian, M. *Synth. Commun.* ***2001***, *31*, 3587.

[1702] Yoshimura, N.; Mukaiyama, T. *Chem. Lett.* ***2001***, 1334.

[1703] Selvakumar, K.; Harrod, J.F. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2129.

[1704] Kim, M.; Knettle, B.W.; Dahlén, A.; Hilmersson, G.; Flowers III, R.A. *Tetrahedron* ***2003***, *59*, 10397.

[1705] Su, W.; Yang, B. *Synth. Commun.* ***2003***, *33*, 2613.

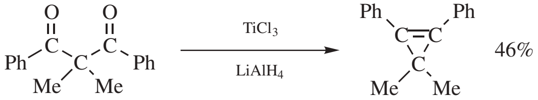
[1706] Campos, P.J.; Arranz, J.; Rodríguez, M.A. *Tetrahedron* ***2000***, *56*, 7285; Ortega, M.; Rodríguez, M.A.; Campos, P.J. *Tetrahedron* ***2004***, *60*, 6475.

[1707] Jin, W.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* ***2001***, *66*, 514.

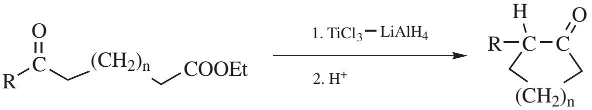
[1708] For a highly active reagent see Rele, S.; Chattopadhyay, S.; Nayak, S.K. *Tetrahedron Lett.* ***2001***, *42*, 9093.

[1709] McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255. For an optimized procedure, see McMurry, J.E.; Lectka, T.; Rico, J.G. *J. Org. Chem.* ***1989***, *54*, 3748.

the *McMurry reaction*.[1710] The reagent produced in this way is called a *low-valent titanium reagent*, and the reaction has also been accomplished[1711] with low-valent titanium reagents prepared in other ways, for example, from Mg and a $TiCl_3$–THF complex,[1712] from $TiCl_4$ and Zn or Mg,[1713] from $TiCl_3$ and $LiAlH_4$,[1714] from $TiCl_3$ and lamellar potassium graphite,[1715] from $TiCl_3$ and K or Li,[1716] as well as with $ZnMe_3SiCl$[1717] and with certain compounds prepared from WCl_6 and either lithium, lithium iodide, $LiAlH_4$, or an alkyllithium[1718] (see **17-18**). The reaction has been used to convert dialdehydes and diketones to cycloalkenes.[1719] Rings of 3–16 and 22 members have been closed in this way, for example,[1720]



The same reaction on a keto ester gives a cycloalkanone.[1721]



[1710] For reviews, see McMurry, J.E. *Chem. Rev.* ***1989***, *89*, 1513; *Acc. Chem. Res.* ***1983***, *16*, 405; Lenoir, D. *Synthesis* ***1989***, 883; Betschart, C.; Seebach, D. *Chimia* ***1989***, *43*, 39; Lai, Y. *Org. Prep. Proceed. Int.* ***1980***, *12*, 363. For related reviews, see Kahn, B.E.; Rieke, R.D. *Chem. Rev.* ***1988***, *88*, 733; Pons, J.; Santelli, M. *Tetrahedron* ***1988***, *44*, 4295. For the stereochemistry associated with this reaction, see Andersson, P.G. *Tetrahedron Lett.* ***1994***, *35*, 2609.

[1711] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 305–308.

[1712] Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* ***1973***, 2147.

[1713] Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* ***1973***, 1041; Lenoir, D. *Synthesis* ***1977***, 553; Lenoir, D.; Burghard, H. *J. Chem. Res. (S)* ***1980***, 396; Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* ***1990***, *43*, 1439.

[1714] McMurry, J.E.; Fleming, M.P. *J. Am. Chem. Soc.* ***1974***, *96*, 4708; Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* ***1982***, *91*, 149, 311; Bottino, F.A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 77. This reagent has been reported to give capricious results; see McMurry, J.E.; Fleming, M.P. *J. Org. Chem.* ***1976***, *41*, 896.

[1715] Fürstner, A.; Weidmann, H. *Synthesis* ***1987***, 1071.

[1716] McMurry, J.E.; Fleming, M.P. *J. Org. Chem.* ***1976***, *41*, 896; Richardson, W.H. *Synth. Commun.* ***1981***, *11*, 895; Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* ***2001***, *66*, 2990.

[1717] Banerjee, A.K.; Sulbaran de Carrasco, M.C.; Frydrych-Houge, C.S.V.; Motherwell, W.B. *J. Chem. Soc. Chem. Commun.* ***1986***, 1803.

[1718] Sharpless, K.B.; Umbreit, M.A.; Nieh, M.T.; Flood, T.C. *J. Am. Chem. Soc.* ***1972***, *94*, 6538; Fujiwara, Y.; Ishikawa, R.; Akiyama, F.; Teranishi, S. *J. Org. Chem.* ***1978***, *43*, 2477; Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* ***1982***, *19*, 149, 311. See also, Petit, M.; Mortreux, A.; Petit, F. *J. Chem. Soc. Chem. Commun.* ***1984***, 341; Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 2324.

[1719] Baumstark, A.L.; Bechara, E.J.H.; Semigran, M.J. *Tetrahedron Lett.* ***1976***, 3265; McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255.

[1720] Baumstark, A.L.; McCloskey, C.J.; Witt, K.E. *J. Org. Chem.* ***1978***, *43*, 3609.

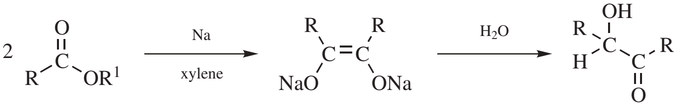
[1721] McMurry, J.E.; Miller, D.D. *J. Am. Chem. Soc.* ***1983***, *105*, 1660.

Indoles have been prepared form ortho-acyl amides with Ti(powder) and Me_3SiCl[1722] or with $TiCl_3$—C_8K.[1723] Benzofurans have been prepared by a closely related reaction.[1724]

Unsymmetrical alkenes can be prepared from a mixture of two ketones in a cross-coupling reaction, if one is in excess.[1725] An aldehyde and a ketone were cross-coupled using $Yb(OTf)_3$, for example.[1726] The mechanism consists of initial coupling of two radical species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated.[1727]

OS **VII**, 1.

19-78 Acyloin Ester Condensation



52

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).[1728] The reaction, called the *acyloin ester condensation*,[1729] 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. Modifications to this procedure have been reported, including an ultrasound-promoted acyloin condensation in ether,[1730] which imporvied the yields of four-, five-, and six-membered rings, and Olah's procedure, which was also done in ether.[1731]

The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.[1732] The yields are 50–60% for the preparation

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[1722] Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* ***1995***, *117*, 4468.

[1723] Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* ***1994***, *59*, 5215.

[1724] Fürstner, A.; Jumbam, D.N. *Tetrahedron* ***1992***, *48*, 5991.

[1725] McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255; Nishida, S.; Kataoka, F. *J. Org. Chem.* ***1978***, *43*, 1612; Coe, P.L.; Scriven, C.E. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 475; Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 2324.

[1726] Curini, M.; Epifano, F.; Maltese, F., Marcotullio, M.C. *Eur. J. Org. Chem.* ***2003***, 1631.

[1727] McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255; Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H.Y. *J. Org. Chem.* ***1982***, *47*, 248. See Villiers, C.; Ephritikhine, M. *Angew. Chem,. Int. Ed.* ***1997***, *36*, 2380; Stahl, M.; Pindur, U.; Frenking, G. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2234.

[1728] For a review, see Bloomfield, J.J.; Owsley, D.C.; Nelke, J.M. *Org. React.* ***1976***, *23*, 259. For a list of reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1313–1315.

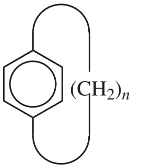
[1729] For reaction with tethered diesters, see Daynard, T.S.; Eby, P.S.; Hutchinson, J.H. *Can. J. Chem.* ***1993***, *71*, 1022.

[1730] Fadel, A.; Canet, J,-L.; Salaün, J. *Synlett* ***1990***, 89.

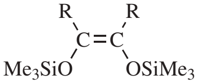
[1731] Olah, G.A.; Wu, A. *Synthesis* ***1991***, 1177.

[1732] For a review of cyclizations by means of the acyloin condensation, see Finley, K.T. *Chem. Rev.* ***1964***, *64*, 573.

of 6- and 7-membered rings, 30–40% for 8- and 19-membered, and 60–95% for rings of 10–20 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,[1733] although this is generally not successful. The presence of double or triple bonds does not interfere.[1734] Even a benzene ring can be present, and many paracyclophane derivatives (**53**) with $n = 9$ or more have been synthesized in this manner.[1735]



53



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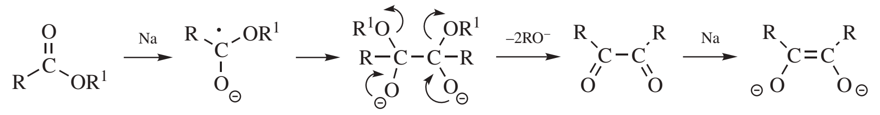
Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane Me_3SiCl, in which case the dianion **52** is converted to the bis silyl enol ether **54**, which can be isolated and subsequently hydrolyzed to the acyloin with aqueous acid.[1736] This is now the standard way to conduct the acyloin condensation. Among other things, this method inhibits the Dieckmann condensation[1737] (**16-85**), which otherwise competes with the acyloin condensation when a five-, six-, or seven-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.[1738]

The mechanism is not known with certainty, but it is usually presumed that the diketone RCOCOR is an intermediate,[1739] 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 **19-76**) is



[1733] Cope, A.C.; Herrick, E.C. *J. Am. Chem. Soc.* ***1950***, *72*, 983; Bloomfield, J.J.; Irelan, J.R.S. *J. Org. Chem.* ***1966***, *31*, 2017.

[1734] Cram, D.J.; Gaston, L.K. *J. Am. Chem. Soc.* ***1960***, *82*, 6386.

[1735] For a review, see Cram, D.J. *Rec. Chem. Prog.*, ***1959***, *20*, 71.

[1736] Schräpler, U.; Rühlmann, K. *Chem. Ber.* ***1964***, *97*, 1383. For a review of the Me_3SiCl method, see Rühlmann, K. *Synthesis* ***1971***, 236.

[1737] Bloomfield, J.J. *Tetrahedron Lett.* ***1968***, 591.

[1738] Gream, G.E.; Worthley, S. *Tetrahedron Lett.* ***1968***, 3319; Wynberg, H.; Reiffers, S.; Strating, J. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 982; Bloomfield, J.J.; Martin, R.A.; Nelke, J.M. *J. Chem. Soc. Chem. Commun.* ***1972***, 96.

[1739] 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, J.J.; Owsley, D.C.; Ainsworth, C.; Robertson, R.E. *J. Org. Chem.* ***1975***, *40*, 393.

A large surface area for the sodium is usually required for good results in this coupling, consistent with a surface reaction. 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 although this is conformationally unfavorable for long chains, it may be postulated that the two ends become attached to nearby sites on the surface[1740] of the sodium. Although high dilution techniques are not always necessary, effective stirring (high speed stirrer at 2000–2500 rpm) is usually required to generate "sodium sand". Highly pure sodium gives poorer results, and a small percentage of potassium is important. Up to 50% potassium (1:1 Na/K)[1741] has been used in acyloin condensations.

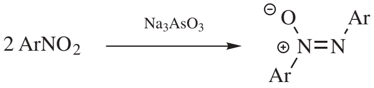
In a related reaction, aromatic carboxylic acids were condensed to α-diketones (2ArCOOH → ArCOCOAr) on treatment with excess Li in dry THF in the presence of ultrasound.[1742]

The acyloin condensation was used in an ingenious manner to prepare the first reported catenane (see p. 131).[1743] This synthesis of a catenane produced only a small yield and relied on chance for threading the molecules before ring closure.

OS **II**, 114; **IV**, 840; **VI**, 167.

19-79 Reduction of Nitro to Azoxy Compounds

Nitro-azoxy reductive transformation



Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, NaTeH,[1744] $NaBH_4$–PhTe-TePh,[1745] 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 (**19-46**), and these combine (**12-51**). The combination step is rapid compared to the reduction process.[1746] Nitroso compounds can be reduced to azoxy compounds with triethyl phosphite or triphenylphosphine[1747] or with an alkaline aqueous solution of an alcohol.[1748]

OS **II**, 57.

[1740] For the preparation of high-surface sodium, see Makosza, M.; Grela, K. *Synlett* ***1997***, 267.

[1741] Vogel, I.A. *A Textbook of Practical Organic Chemistry*, 3rd ed, Wiley, NY, ***1966***, p. 856.

[1742] Karaman, R.; Fry, J.L. *Tetrahedron Lett.* ***1989***, *30*, 6267.

[1743] For reviews of the synthesis of catenanes, see Sauvage, J. *Acc. Chem. Res.* ***1990***, *23*, 319; *Nouv. J. Chim.* ***1985***, *9*, 299; Dietrich-Buchecker, C.O.; Sauvage, J. *Chem. Rev.* ***1987***, *87*, 795.

[1744] Osuka, A.; Shimizu, H.; Suzuki, H. *Chem. Lett.* ***1983***, 1373.

[1745] Ohe, K.; Uemura, S.; Sugita, N.; Masuda, H.; Taga, T. *J. Org. Chem.* ***1989***, *54*, 4169.

[1746] Ogata, Y.; Mibae, J. *J. Org. Chem.* ***1962***, *27*, 2048.

[1747] Bunyan, P.J.; Cadogan, J.I.G. *J. Chem. Soc.* ***1963***, 42.

[1748] See, for example, Hutton, J.; Waters, W.A. *J. Chem. Soc. B* ***1968***, 191. See also, Porta, F.; Pizzotti, M.; Cenini, S. *J. Organomet. Chem.* ***1981***, *222*, 279.

19-80 Reduction of Nitro to Azo Compounds

***N*-De-bisoxygen-coupling**

$$2\,\mathrm{ArNO_2} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{Ar{-}N{=}N{-}Ar}$$

Nitro compounds can be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and zinc and alkali are the most common. A combination of triethylammonium formate and lead in methanol is also effective.[1749] With many of these reagents, slight differences in conditions can lead either to the azo or azoxy (**19-79**) compound. By analogy to **19-79**, this reaction may be looked on as a combination of ArN=O and $ArNH_2$ (**13-24**). However, when the reducing agent was $NaBH_4$,[1750] it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with $LiAlH_4$. Dicarborane, with a catalytic amount of acetic acid, reduces aromatic nitro compounds to the amine.[1751]

Nitro compounds can be further reduced to hydrazo compounds with zinc and sodium hydroxide, with hydrazine hydrate and Raney nickel,[1752] or with $LiAlH_4$ mixed with a metal chloride such as $TiCl_4$ or VCl_3.[1753] The reduction has also been accomplished electrochemically.

OS **III**, 103.

F. 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 (**16-43**), the benzil–benzilic acid rearrangement (**18-6**), and the Wallach rearrangement (**18-43**).

19-81 The Cannizzaro Reaction

Cannizzaro Aldehyde Disproportionation

$$2\,\mathrm{ArCHO} \xrightarrow{\mathrm{NaOH}} \mathrm{ArCH_2OH} + \mathrm{ArCOO^-}$$

Aromatic aldehydes, and aliphatic ones with no a hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.[1754] 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 (**16-34**) is much faster.[1755] Normally, the best yield of acid or alcohol is 50% each, but this can

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[1749] Srinavasa, G.R.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2003***, *44*, 5835.

[1750] Hutchins, R.O.; Lamson, D.W.; Rufa, L.; Milewski, C.; Maryanoff, B. *J. Org. Chem.* ***1971***, *36*, 803.

[1751] Bae, J.W.; Cho, Y.J.; Lee, S.H.; Yoon, C.M. *Tetrahedron Lett.* ***2000***, *41*, 175.

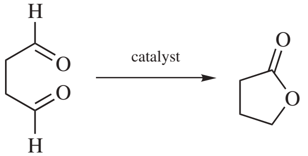
[1752] Furst, A.; Moore, R.E. *J. Am. Chem. Soc.* ***1957***, *79*, 5492.

[1753] Olah, G.A. *J. Am. Chem. Soc.* ***1959***, *81*, 3165.

[1754] For a review, see Geissman, T.A. *Org. React.* ***1944***, *2*, 94.

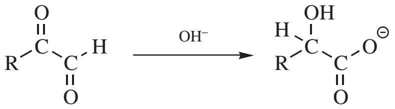
[1755] An exception is cyclopropanecarboxaldehyde: van der Maeden, F.P.B.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 221.

be altered in certain cases. Solvent-free reactions are known.[1756] On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde.[1757] 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*.[1758] The Tollens' condensation (**16-43**) 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 catalyst gives ring closure, for example,[1759]



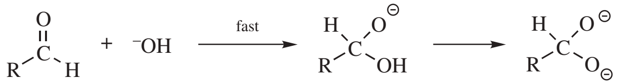
The product is the lactone derived from the hydroxy acid that would result from a normal Cannizzaro reaction. Chiral additives have been used, but with bis(oxazolidine) derivatives the reaction proceeded with poor enantioselectivity.[1760]

α-Keto aldehydes give internal Cannizzaro reactions:



This product is also obtained on alkaline hydrolysis of compounds of the formula $RCOCHX_2$. Similar reactions have been performed on α-keto acetals[1761] and γ-keto aldehydes.

The mechanism[1762] of the Cannizzaro reaction[1763] involves a hydride shift (an example of mechanism type 2, p. 1706). First $^{-}$OH adds to the C=O to give **55**, which may lose a proton in the basic solution to give the diion **56**.



55 **56**

[1756] Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001***, *42*, 7983.

[1757] For an example using microwave irradiation, see Thakuria, J.A.; Baruah, M.; Sandhu, J.S. *Chem. Lett.* ***1999***, 995.

[1758] For a microwave assisted crossed Cannizzaro reaction, see Varma, R.S.; Naicker, K.P.; Liesen, P.J. *Tetrahedron Lett.* ***1998***, *39*, 8437. See Reddy, B.V.S.; Srinivas, R.; Yadav, J.S.; Ramalingam, T. *Synth. Commun.* ***2002***, *32*, 219.

[1759] Bergens, S.H.; Fairlie, D.P.; Bosnich, B. *Organometallics* ***1990***, *9*, 566.

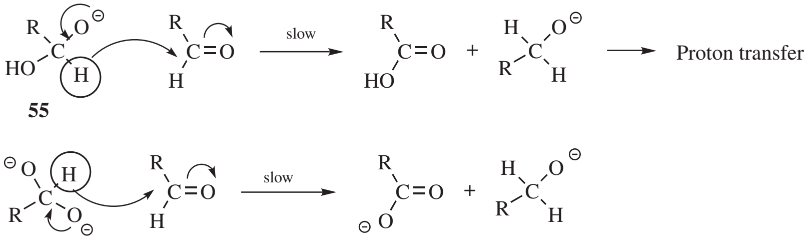
[1760] Russell, A.E.; Miller, S.P.; Morken, J.P. *J. Org. Chem.* ***2000***, *65*, 8381.

[1761] Thompson, J.E. *J. Org. Chem.* ***1967***, *32*, 3947.

[1762] For evidence that an SET pathway may intervene, see Ashby, E.C.; Coleman III, D.T.; Gamasa, M.P. *J. Org. Chem.* ***1987***, *52*, 4079; Fuentes, A.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett.* ***1987***, *28*, 2947.

[1763] See for example, Swain, C.G.; Powell, A.L.; Sheppard, W.A.; Morgan, C.R. *J. Am. Chem. Soc.* ***1979***, *101*, 3576; Watt, C.I.F. *Adv. Phys. Org. Chem.* ***1988***, *24*, 57, 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 **56**. Hydride is transferred to another molecule of aldehyde. The hydride can come from **55** or **56**:



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56

If the hydride ion comes from **55**, 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 **55**) or, at higher base concentrations, second order in each (going through **56**); and (*2*) when the reaction was run in D_2O, the recovered alcohol contained no α deuterium,[1764] indicating that the hydrogen comes from another equivalent of aldehyde and not from the medium.[1765]

OS **I**, 276; **II**, 590; **III**, 538; **IV**, 110.

19-82 The Tishchenko Reaction

Tishchenko aldehyde-ester disproportionation

$$2\,\text{ArCHO} \xrightarrow{\text{Al(OEt)}_3} \text{ROOCH}_2\text{R}$$

When aldehydes, with or without a hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another reduced, as in **19-81**, 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 a hydrogen give the aldol reaction. Treatment of a dialdehyde, such as phthalic dicarboxaldehyde (phthalaldehyde) with CaO, leads to a lactone.[1766] Like **19-81**, this reaction has a mechanism that

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[1764] Fredenhagen, H.; Bonhoeffer, K.F. *Z. Phys. Chem. Abt. A* ***1938***, *181*, 379; Hauser, C.R.; Hamrick, Jr., P.J.; Stewart, A.T. *J. Org. Chem.* ***1956***, *21*, 260.

[1765] 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, C.G.; Powell, A.L.; Lynch, T.J.; Alpha, S.R.; Dunlap, R.P. *J. Am. Chem. Soc.* ***1979***, *101*, 3584. Side reactions were postulated to account for the loss of deuterium. See, however, Chung, S. *J. Chem. Soc. Chem. Commun.* ***1982***, 480.

[1766] Seki, T.; Hattori, H. *Chem. Commun.* ***2001***, 2510.

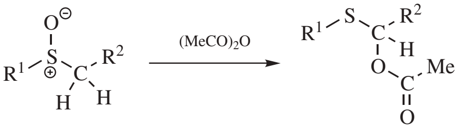
involves hydride transfer.[1767] The Tishchenko reaction can also be catalyzed[1768] by ruthenium complexes,[1769] by Cp_2ZrH_2[1770] or $BuTi(OiPr)_4Li$,[1771] and, for aromatic aldehydes, by disodium tetracarbonylferrate, $Na_2Fe(CO)_4$.[1772] Both CaO (noted above) and SrO have been used as catalysts.[1773] A bisphenylenedioxy bis-(aluminum) catalyst has been used to convert aliphatic aldehydes to the corresponding ester.[1774] The bis $Al(OiPr)_2$ derivative of catechol has also been used as a catalyst.[1775]

A Tishchenko–aldol-transfer reaction was reported using β-hydroxy ketones and an aldehydes with an $AlMe_3$ catalyst, giving a mono acyl diol.[1776]

OS **I**, 104.

19-83 The Pummerer Rearrangement[1777]

Pummerer methyl sulfoxide rearrangement



When sulfoxides bearing an a 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.[1778] The product is readily hydrolyzed (**10-6**) to the aldehyde R_2CHO.[1779] 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[1780] by other

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[1767] See, for example, Zakharkin, L.I.; Sorokina, L.P. *J. Gen. Chem. USSR* ***1967***, *37*, 525; Saegusa, T.; Ueshima, T.; Kitagawa, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 248; Ogata, Y.; Kishi, I. *Tetrahedron* ***1969***, *25*, 929.

[1768] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1653–1655.

[1769] Ito, T.; Horino, H.; Koshiro,Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 504.

[1770] DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* ***1997***, *62*, 6974.

[1771] Mahrwald, R.; Costisella, B. *Synthesis* ***1996***, 1087.

[1772] Yamashita, A.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 3597.

[1773] Seki, T.; Akutsu, K.; Hattori, H. *Chem. Commun.* ***2001***, 1000.

[1774] Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* ***1999***, *40*, 7695.

[1775] Simpura, I.; Nevalainen, V. *Tetrahedron* ***2001***, *57*, 9867.

[1776] Mascarenhas, C.M.; Duffey, M.O.; Liu, S.-Y.; Morken, J.P. *Org. Lett.* ***1999***, *1*, 1427; Simpura, I.; Nevalainen, V. *Tetrahedron Lett.* ***2001***, *42*, 3905; Cavazzini, M.; Pozzi, G.; Quici, S.; Maillard, D.; Sinou, D. *Chem. Commun.* ***2001***, 1220.

[1777] For a review of the Pummerer reaction for the synthesis of heterocyclic compounds, see Bur, S.K.; Padwa, A. *Chem. Rev.* ***2004***, *104*, 2401.

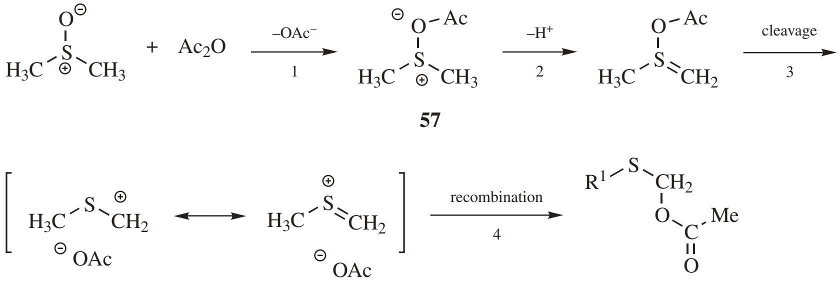
[1778] For reviews, see De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* ***1991***, *40*, 157; Warren, S. *Chem. Ind. (London)* ***1980***, 824; Oae, S.; Numata, T. *Isot. Org. Chem.* ***1980***, *5*, 45; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 154–162.

[1779] See, for example, Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* ***1978***, 881.

[1780] For a review of α-chloro sulfides, see Dilworth, B.M.; McKervey, M.A. *Tetrahedron* ***1986***, *42*, 3731.

reagents, including sulfuryl chloride, NBS, and NCS. Enantioselective Pummerer rearrangements are known.[1781] Uncatalyzed thermal rearrangements are also known.[1782]

The following four-step mechanism has been proposed for the reaction between acetic anhydride and DMSO:[1783]



For DMSO and acetic anhydride, step 4 is intermolecular, as shown by ^{18}O isotopic labeling studies.[1784] With other substrates, however, step 4 can be inter- or intramolecular, depending on the structure of the sulfoxide.[1785] 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 **57**[1786] could be isolated at low temperature, and on warming gave the expected product.[1787] There is much other evidence for this mechanism.[1788]

A sila-Pummerer rearrangement has been reported.[1789]

19-84 The Willgerodt Reaction

Willgerodt carbonyl transformation

$$ArCOCH_3 \xrightarrow{(NH_4)_2S_x} ArCH_2CONH_2 + ArCH_2COO^- NH_4^+$$

[1781] Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K. *Tetrahedron Lett.* ***1995***, *36*, 115; Kita, Y.; Shibata, N.; Fukui, S.; Fujita, S. *Tetrahedron Lett.* ***1994***, *35*, 9733; Kita, Y.; Shibata, N.; Kawano, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* ***1994***, *35*, 3575; Kita, Y.; Shibata, N.; Yoshida, N. *Tetrahedron Lett.* ***1993***, *34*, 4063.

[1782] Wladislaw, B.; Marzorati, L.; Biaggio, F.C. *J. Org. Chem.* ***1993***, *58*, 6132.

[1783] See, for example, Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 257; Kita, Y.; Shibata, N.; Yoshida, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* ***1994***, *35*, 2569.

[1784] Oae, S.; Kitao, T.; Kawamura, S.; Kitaoka, Y. *Tetrahedron* ***1963***, *19*, 817.

[1785] See, for example, Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 266; Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 270.

[1786] For a review of sulfur-containing cations, see Marino, J.P. *Top. Sulfur Chem.* ***1976***, *1*, 1.

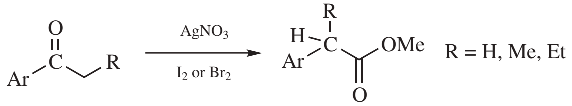
[1787] Sharma, A.K.; Swern, D. *Tetrahedron Lett.* ***1974***, 1503.

[1788] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 154–156; Oae, S.; Numata, T. *Isot. Org. Chem.* ***1980***, *5*, 45, 48; Wolfe, S.; Kazmaier, P.M. *Can. J. Chem.* ***1979***, *57*, 2388, 2397; Russell, G.A.; Mikol, G.J. *Mech. Mol. Migr.* ***1968***, *1*, 157.

[1789] Kirpichenko, S.V.; Suslova, E.N.; Albanov, A.I.; Shainyan, B.A. *Tetrahedron Lett.* ***1999***, *40*, 185.

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.[1790] 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. Unlike the Pummerer rearrangement (**19-83**), which involves transposition of an oxygen from S to C, the Willgerodt reaction involves oxygen migration *and* oxidation of the organic species. 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.[1791] The product in this case is $Ar(CH_2)_nCSNR_2$,[1792] 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.[1793] Dimethylamine has also been used in the form of dimethylammonium dimethylcarbamate, Me_2NCOO^- $Me_2NH_2^+$.[1794] The Kindler modification has also been applied to aliphatic ketones.[1795] Thioamides have been prepared from ketones in a base-catalyzed reaction.[1796]

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,[1797] or with thallium nitrate, MeOH, and trimethyl orthoformate adsorbed on Montmorillonite K10, an acidic clay.[1798]



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

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[1790] For a review, see Brown, E.V. *Synthesis* ***1975***, 358.

[1791] For a review, see Mayer, R., in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 58–63. For a study of the optimum conditions for this reaction, see Lundstedt, T.; Carlson, R.; Shabana, R. *Acta Chem. Scand. Ser. B* ***1987***, *41*, 157, and other papers in this series. See also, Carlson, R.; Lundstedt, T. *Acta Chem. Scand. Ser. B* ***1987***, *41*, 164; Kanyonyo, M.R.; Gozzo, A.; Lambert, D.M.; Lesieur, D.; Poupaert, J.H. *Bull. Soc. Chim. Belg.* ***1997***, *106*, 39.

[1792] The reaction between ketones, sulfur, and ammonia can also lead to heterocyclic compounds. For a review, see Asinger, F.; Offermanns, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 907.

[1793] Amupitan, J.O. *Synthesis* ***1983***, 730.

[1794] Schroth, W.; Andersch, J. *Synthesis* ***1989***, 202.

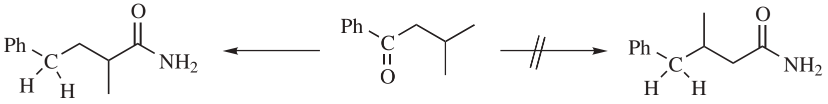
[1795] See Dutron-Woitrin, F.; Merényi, R.; Viehe, H.G. *Synthesis* ***1985***, 77.

[1796] For a review, see Poupaert, J.H.; Bouinidane, K.; Renard, M.; Lambert, D.; Isa, M. *Org. Prep. Proceed. Int.* ***2001***, *33*, 335.

[1797] Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 235. See also, Higgins, S.D.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1483.

[1798] Taylor, E.C.; Conley, R.A.; Katz, A.H.; McKillop, A. *J. Org. Chem.* ***1984***, *49*, 3840.

end. However, this possibility is ruled out by experiments such as the following: When isobutyl phenyl ketone (**58**) is subjected to the Willgerodt reaction, the product is **59**, not **60**, which would arise if the end carbon of the ketone became bonded to the ring in the product:[1799]



59 **58** **60**

This also excludes a cyclic-intermediate mechanism similar to that of the Claisen rearrangement (**18-33**). Another important fact is that the reaction is successful for singly branched side chains, such as **58**, but not for doubly branched side chains, as in $PhCOCMe_3$.[1799] 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 $PhCH_2CH_2CONH_2$.[1800] All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain, although 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[1801] or enamines[1802] 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.

[1799] King, J.A.; McMillan, F.H. *J. Am. Chem. Soc.* ***1946***, *68*, 632.

[1800] For an example of this type of behavior, see Asinger, F.; Saus, A.; Mayer, A. *Monatsh. Chem.* ***1967***, *98*, 825.

[1801] Asinger, F.; Halcour, K. *Monatsh. Chem.* ***1964***, *95*, 24. See also, Nakova, E.P.; Tolkachev, O.N.; Evstigneeva, R.P. *J. Org. Chem. USSR* ***1975***, *11*, 2660.

[1802] Mayer, R., in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 229–232.