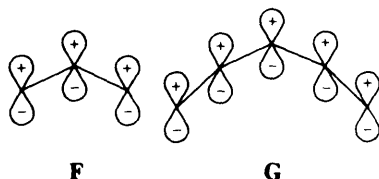
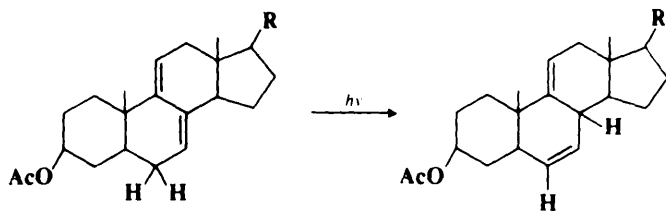


As expected, the Möbius-Hückel method leads to the same predictions. Here we look at the basis set of orbitals shown in **F** and **G** for [1,3] and [1,5] rearrangements, respectively.

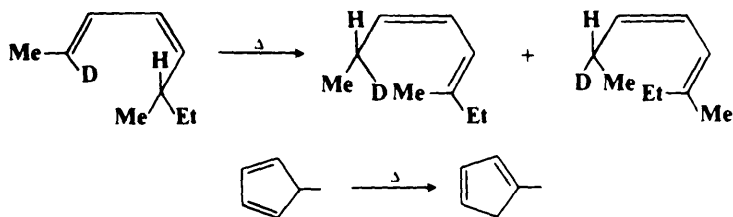


A [1,3] shift involves four electrons, so an allowed thermal pericyclic reaction must be a Möbius system (p. 1115) with one or an odd number of sign inversions. As can be seen in **F**, only an antarafacial migration can achieve this. A [1,5] shift, with six electrons, is allowed thermally only when it is a Hückel system with zero or an even number of sign inversions; hence it requires a suprafacial migration.

The actual reported results bear out this analysis. Thus a thermal [1,3] migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3] sigmatropic migrations of hydrogen are unknown.<sup>409</sup> On the other hand, the photochemical pathway allows suprafacial [1,3] shifts, and a few such reactions are known, an example being<sup>410</sup>



The situation is reversed for [1,5] hydrogen shifts. In this case the thermal rearrangements, being suprafacial, are quite common, while photochemical rearrangements are rare.<sup>411</sup> Examples of the thermal reaction are



Ref. 412

Ref. 413

<sup>409</sup>A possible [1,3] migration of hydrogen has been reported. See Yeh; Linder; Hoffman; Barton *J. Am. Chem. Soc.* **1986**, 108, 7849. See also Parto; Brophy *J. Org. Chem.* **1991**, 56, 4554.

<sup>410</sup>Dauben; Wipke *Pure Appl. Chem.* **1964**, 9, 539-553, p. 546. For another example, see Kropp; Fravel; Fields *J. Am. Chem. Soc.* **1976**, 98, 840.

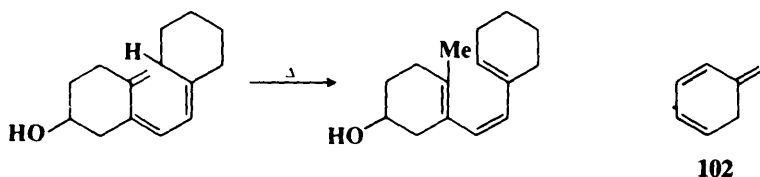
<sup>411</sup>For examples of photochemical [1,5] antarafacial reactions, see Kiefer; Tanna *J. Am. Chem. Soc.* **1969**, 91, 4478; Kiefer; Fukunaga *Tetrahedron Lett.* **1969**, 993; Dauben; Poulter; Suter *J. Am. Chem. Soc.* **1970**, 92, 7408.

<sup>412</sup>Roth; König; Stein *Chem. Ber.* **1970**, 103, 426.

<sup>413</sup>McLean; Haynes *Tetrahedron* **1965**, 21, 2329. For a review of such rearrangements, see Klärner *Top. Stereochem.* **1984**, 15 1-42.

Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed. In the second example, migration can continue around the ring. Migrations of this kind are called *circumambulatory rearrangements*.<sup>414</sup>

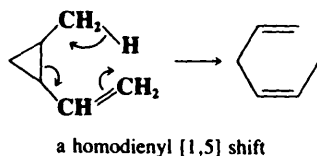
With respect to [1,7] hydrogen shifts, the rules predict the thermal reaction to be antarafacial. Unlike the case of [1,3] shifts, the transition state is not too greatly strained, and such rearrangements have been reported, e.g.,<sup>415</sup>



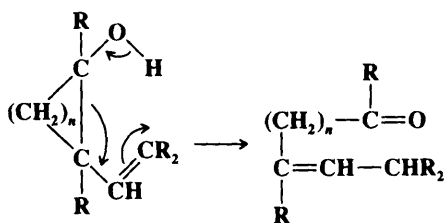
Photochemical [1,7] shifts are suprafacial and, not surprisingly, many of these have been observed.<sup>416</sup>

The orbital symmetry rules also help us to explain, as on pp. 865 and 1117, the unexpected stability of certain compounds. Thus, **102** could, by a thermal [1,3] sigmatropic rearrangement, easily convert to toluene, which of course is far more stable because it has an aromatic sextet. Yet **102** has been prepared and is stable at dry ice temperature and in dilute solutions.<sup>417</sup>

Analogous of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, e.g.,<sup>418</sup>



The reverse reaction has also been reported.<sup>419</sup> 2-Vinylcycloalkanols<sup>420</sup> undergo an analogous reaction, as do cyclopropyl ketones (see p. 1138 for this reaction).



<sup>414</sup>For a review, see Childs *Tetrahedron* **1982**, 38, 567-608. See also Minkin; Mikhailov; Dushenko; Yudilevich; Minyaev; Zschunke; Mügge *J. Phys. Org. Chem.* **1991**, 4, 31.

<sup>415</sup>Schlatmann; Pot; Havinga *Recl. Trav. Chim. Pays-Bas* **1964**, 83, 1173; Hoeger; Johnston; Okamura *J. Am. Chem. Soc.* **1987**, 109, 4690; Baldwin; Reddy *J. Am. Chem. Soc.* **1987**, 109, 8051, **1988**, 110, 8223.

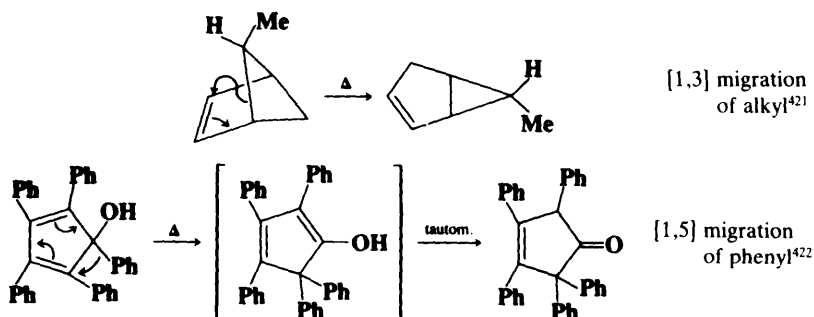
<sup>416</sup>See Murray; Kaplan *J. Am. Chem. Soc.* **1966**, 88, 3527; ter Borg; Kloosterziel *Recl. Trav. Chim. Pays-Bas* **1969**, 88, 266; Tezuka; Kimura; Sato; Mukai *Bull. Chem. Soc. Jpn.* **1970**, 43, 1120.

<sup>417</sup>Bailey; Baylouny *J. Org. Chem.* **1962**, 27, 3476.

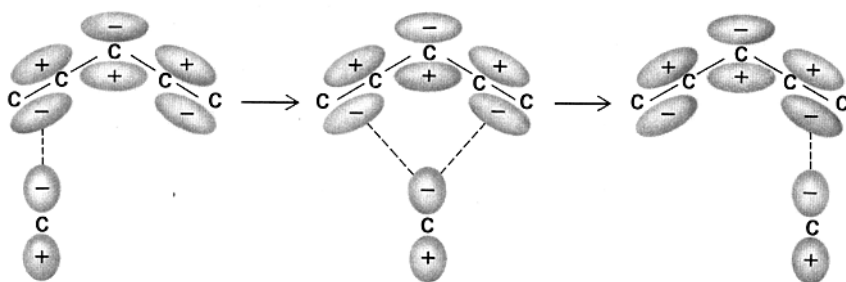
<sup>418</sup>Ellis; Frey *Proc. Chem. Soc.* **1964**, 221; Frey; Solly *Int. J. Chem. Kinet.* **1969**, 1, 473; Roth; König *Liebigs Ann. Chem.* **1965**, 688, 28; Ohloff *Tetrahedron Lett.* **1965**, 3795; Jorgenson; Thacher *Tetrahedron Lett.* **1969**, 4651; Corey; Yamamoto; Herron; Achiwa *J. Am. Chem. Soc.* **1970**, 92, 6635; Loncharich; Houk *J. Am. Chem. Soc.* **1988**, 110, 2089; Parziale; Berson *J. Am. Chem. Soc.* **1990**, 112, 1650; Pegg; Meehan *Aust. J. Chem.* **1990**, 43, 1009, 1071.

<sup>419</sup>Roth; König, Ref. 418. Also see Grimme *Chem. Ber.* **1965**, 98, 756.

<sup>420</sup>Arnold; Smolinsky *J. Am. Chem. Soc.* **1960**, 82, 4918; Lervierend; Conia *Tetrahedron Lett.* **1969**, 2681; Conia; Barnier *Tetrahedron Lett.* **1969**, 2679.

8-32 [1,*j*] Sigmatropic Migrations of Carbon

Sigmatropic migrations of alkyl or aryl groups<sup>423</sup> are less common than the corresponding hydrogen migrations.<sup>424</sup> When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a 1s orbital with only one lobe, a carbon free radical has its odd electron in a *p* orbital that has *two lobes of opposite sign*. Therefore, if we draw the imaginary transition states for this case (see p. 1123), we see that in a thermal suprafacial [1,5] process (Figure 18.5), symmetry can be conserved only if the migrating carbon moves in such a way that the lobe which was originally attached to the  $\pi$  system remains attached to the  $\pi$  system. This can happen only if configuration is *retained within the migrating group*. On the other hand, thermal suprafacial [1,3] migration (Figure 18.6) *can* take place if the migrating carbon switches lobes. If the migrating carbon was originally bonded by its minus lobe, it must now use its plus lobe to form the new C—C bond. Thus, configuration in the migrating group will be *inverted*. From these considerations we predict that suprafacial [1,*j*] sigmatropic rearrangements in which carbon is the migrating group are always allowed, both thermally and photochemically, but that thermal [1,3] migrations will proceed with inversion and thermal [1,5] migrations with retention of configuration within the migrating group.



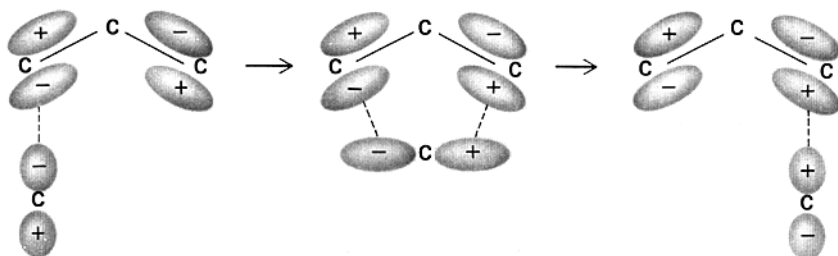
**FIGURE 18.5** Hypothetical orbital movement for a thermal [1,5] sigmatropic migration of carbon. To move from one — lobe to the other — lobe, the migrating carbon uses only its own — lobe, retaining its configuration.

<sup>421</sup>Roth; Friedrich *Tetrahedron Lett.* **1969**, 2607.

<sup>422</sup>Youssef; Ogliaruso *J. Org. Chem.* **1972**, 37, 2601.

<sup>423</sup>For reviews, see Mironov; Fedorovich; Akhrem, Ref. 404; Spangler, Ref. 404.

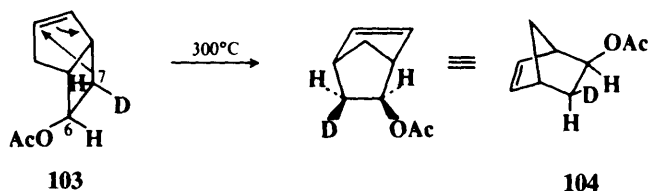
<sup>424</sup>It has been shown that methyl and phenyl have lower migratory aptitudes than hydrogen in thermal sigmatropic rearrangements: Shen; McEwen; Wolf *Tetrahedron Lett.* **1969**, 827; Miller; Greisinger; Boyer *J. Am. Chem. Soc.* **1969**, 91, 1578.



**FIGURE 18.6** Hypothetical orbital movement for a thermal [1,3] sigmatropic migration of carbon. The migrating carbon moves from a  $-$  to a  $+$  lobe, requiring it to switch its own bonding lobe from  $-$  to  $+$ , inverting its configuration.

More generally, we can say that suprafacial [1, $j$ ] migrations of carbon in systems where  $j = 4n - 1$  proceed with inversion thermally and retention photochemically, while systems where  $j = 4n + 1$  show the opposite behavior. Where antarafacial migrations take place, all these predictions are of course reversed.

The first laboratory test of these predictions was the pyrolysis of deuterated *endo*-bicyclo[3.2.0]hept-2-en-6-yl acetate (**103**), which gave the *exo*-deuterio-*exo*-norbornyl acetate



**104.**<sup>425</sup> Thus, as predicted by the orbital symmetry rules, this thermal suprafacial [1,3] sigmatropic reaction took place with complete inversion at C-7. Similar results have been obtained in a number of other cases.<sup>426</sup> However, similar studies of the pyrolysis of the parent hydrocarbon of **103**, labeled with D at C-6 and C-7, showed that while most of the product was formed with inversion at C-7, a significant fraction (11 to 29%) was formed with retention.<sup>427</sup> Other cases of lack of complete inversion are also known.<sup>428</sup> A diradical mechanism has been invoked to explain such cases.<sup>429</sup> There is strong evidence for a radical mechanism for some [1,3] sigmatropic rearrangements.<sup>430</sup> Photochemical suprafacial [1,3] migrations of carbon have been shown to proceed with retention, as predicted.<sup>431</sup>

<sup>425</sup>Berson; Nelson *J. Am. Chem. Soc.* **1967**, *89*, 5503; Berson *Acc. Chem. Res.* **1968**, *1*, 152-160.

<sup>426</sup>See Ref. 421; Berson *Acc. Chem. Res.* **1972**, *5*, 406-414; Bampfield; Brook; Hunt *J. Chem. Soc., Chem. Commun.* **1976**, 146; Franzus; Scheinbaum; Waters; Bowlin *J. Am. Chem. Soc.* **1976**, *98*, 1241; Klärner; Adamsky *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 674 [*Angew. Chem.* **91**, 738].

<sup>427</sup>Baldwin; Belfield *J. Am. Chem. Soc.* **1988**, *110*, 296; Klärner; Drewes; Hasselmann *J. Am. Chem. Soc.* **1988**, *110*, 297.

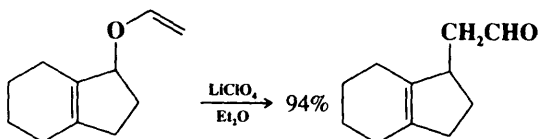
<sup>428</sup>See, for example, Berson; Nelson *J. Am. Chem. Soc.* **1970**, *92*, 1096; Berson; Holder *J. Am. Chem. Soc.* **1973**, *95*, 2037; Pikulin; Berson *J. Am. Chem. Soc.* **1988**, *110*, 8500.

<sup>429</sup>See Newman-Evans; Carpenter *J. Am. Chem. Soc.* **1984**, *106*, 7994; Pikulin; Berson, Ref. 428. See also Berson *Chemtracts: Org. Chem.* **1989**, *2*, 213-227.

<sup>430</sup>See, for example, Bates; Ramaswamy *Can. J. Chem.* **1985**, *63*, 745; Dolbier; Phanstiel *J. Am. Chem. Soc.* **1989**, *111*, 4907.

<sup>431</sup>Cookson; Hudec; Sharma *Chem. Commun.* **1971**, 107, 108.

Although allylic vinylic ethers generally undergo [3,3] sigmatropic rearrangements (8-35), they can be made to give the [1,3] kind, to give aldehydes, e.g.,

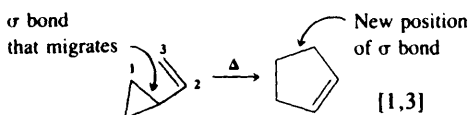


by treatment with  $\text{LiClO}_4$  in diethyl ether.<sup>431a</sup> In this case the C—O bond undergoes a 1,3 migration from the O to the end vinylic carbon. When the vinylic ether is of the type  $\text{ROCR}'=\text{CH}_2$ , ketones  $\text{RCH}_2\text{COR}'$  are formed. There is evidence that this [1,3] sigmatropic rearrangement is not concerted, but involves dissociation of the substrate into ions.<sup>431a</sup>

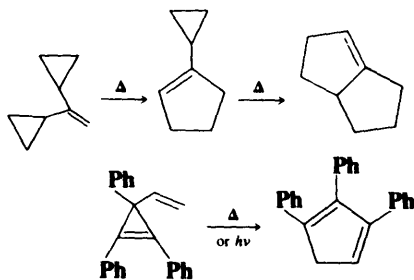
Thermal suprafacial [1,5] migrations of carbon have been found to take place with retention,<sup>432</sup> but also with inversion.<sup>433,434</sup> A diradical mechanism has been suggested for the latter case.<sup>433</sup>

Simple nucleophilic, electrophilic, and free-radical 1,2 shifts can also be regarded as sigmatropic rearrangements (in this case, [1,2] rearrangements). We have already (p. 1051) applied similar principles to such rearrangements to show that nucleophilic 1,2 shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair.

### 8-33 Conversion of Vinylcyclopropanes to Cyclopentenenes



The thermal expansion of a vinylcyclopropane to a cyclopentene ring<sup>435</sup> is a special case of a [1,3] sigmatropic migration of carbon, though it can also be considered an internal  $[\pi 2 + \sigma 2]$  cycloaddition reaction (see 5-49). The reaction has been carried out on many vinylcyclopropanes bearing various substituents in the ring or on the vinyl group and has been extended to 1,1-dicyclopropylenes<sup>436</sup>



<sup>431a</sup>Grieco; Clarke; Jagoe *J. Am. Chem. Soc.* **1991**, *113*, 5488.

<sup>432</sup>Boersma; de Haan; Kloosterziel; van de Ven *Chem. Commun.* **1970**, 1168.

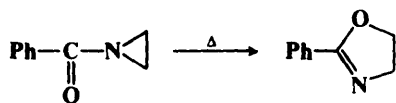
<sup>433</sup>Klärner; Yaslak; Wette *Chem. Ber.* **1979**, *112*, 1168; Klärner; Brassel *J. Am. Chem. Soc.* **1980**, *102*, 2469; Borden; Lee; Young *J. Am. Chem. Soc.* **1980**, *102*, 4841; Gajewski; Gortva; Borden *J. Am. Chem. Soc.* **1986**, *108*, 1083.

<sup>434</sup>Baldwin; Broline *J. Am. Chem. Soc.* **1982**, *104*, 2857.

<sup>435</sup>For reviews, see Wong et al., Ref. 114, pp. 169-172; Goldschmidt; Crammer *Chem. Soc. Rev.* **1988**, *17*, 229-267; Hudlický; Kutchan; Naqvi *Org. React.* **1985**, *33*, 247-335; Mil'vitskaya; Tarakanova; Plate *Russ. Chem. Rev.* **1976**, *45*, 469-478; DeWolfe, in Bamford; Tipper, Ref. 365, pp. 470-474; Gutsche; Redmore, Ref. 112, pp. 163-170; Frey *Adv. Phys. Org. Chem.* **1966**, *4*, 147-193, pp. 155-163, 175-176.

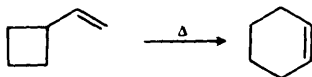
<sup>436</sup>Ketley *Tetrahedron Lett.* **1964**, 1687; Branton; Frey *J. Chem. Soc. A* **1966**, 1342.

and (both thermally<sup>437</sup> and photochemically<sup>438</sup>) to vinylcyclopropenes. Various heterocyclic analogs<sup>438a</sup> are also known, e.g.,<sup>439</sup>

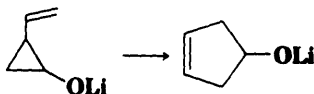


Two competing reactions are the homodienyl [1,5] shift (if a suitable H is available, see 8-31), and simple cleavage of the cyclopropane ring, leading in this case to a diene (see 8-3).

Vinylcyclobutanes can be similarly converted to cyclohexenes,<sup>440</sup> but larger ring compounds do not generally give the reaction.<sup>441</sup> Though high temperatures (as high as 500°C)



are normally required for the thermal reaction, the lithium salts of 2-vinylcyclopropanols rearrange at 25°C.<sup>442</sup>



Salts of 2-vinylcyclobutanols behave analogously.<sup>443</sup>

The reaction rate has also been greatly increased by the addition of a one-electron oxidant tris-(4-bromophenyl)aminium hexafluoroantimonate  $\text{Ar}_3\text{N}^+ \text{SbF}_6^-$  ( $\text{Ar} = p$ -bromophenyl).<sup>444</sup> This reagent converts the substrate to a cation radical, which undergoes ring expansion much faster.<sup>445</sup>

The mechanisms of these ring expansions are not certain. Both concerted<sup>446</sup> and diradical<sup>447</sup> pathways have been proposed, and it is possible that both pathways operate, in different systems.

<sup>437</sup>Small; Breslow, cited in Breslow, in Mayo, Ref. 114, vol. 1, p. 236.

<sup>438</sup>Padwa; Blacklock; Getman; Hatanaka; Loza *J. Org. Chem.* **1978**, *43*, 1481; Zimmerman; Aasen *J. Org. Chem.* **1978**, *43*, 1493; Zimmerman; Kreil *J. Org. Chem.* **1982**, *47*, 2060.

<sup>438a</sup>For a review of a nitrogen analog, see Boeckman; Walters *Adv. Heterocycl. Nat. Prod. Synth.* **1990**, *1*, 1-41.

<sup>439</sup>For reviews of ring expansions of aziridines, see Heine *Mech. Mol. Migr.* **1971**, *3*, 145-176; Dermer; Ham *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969, pp. 282-290. See also Wong et al., Ref. 114, pp. 190-192.

<sup>440</sup>See, for example, Overberger; Borchert *J. Am. Chem. Soc.* **1960**, *82*, 1007; Gruseck; Heuschmann *Chem. Ber.* **1990**, *123*, 1911.

<sup>441</sup>For an exception, see Thies *J. Am. Chem. Soc.* **1972**, *94*, 7074.

<sup>442</sup>Danheiser; Martinez-Davila; Morin *J. Org. Chem.* **1980**, *45*, 1340; Danheiser; Bronson; Okano *J. Am. Chem. Soc.* **1985**, *107*, 4579.

<sup>443</sup>Danheiser; Martinez-Davila; Sard *Tetrahedron* **1981**, *37*, 3943.

<sup>444</sup>Dinnocenzo; Conlan *J. Am. Chem. Soc.* **1988**, *110*, 2324.

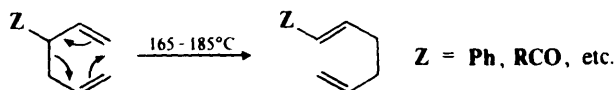
<sup>445</sup>For a review of ring expansion of vinylcyclobutane cation radicals, see Bauld *Tetrahedron* **1989**, *45*, 5307-5363.

<sup>446</sup>For evidence favoring the concerted mechanism, see Shields; Billups; Lepely *J. Am. Chem. Soc.* **1968**, *90*, 4749; Billups; Leavell; Lewis; Vanderpool *J. Am. Chem. Soc.* **1973**, *95*, 8096; Berson; Dervan; Malherbe; Jenkins *J. Am. Chem. Soc.* **1976**, *98*, 5937; Andrews; Baldwin *J. Am. Chem. Soc.* **1976**, *98*, 6705, 6706; Dolbier; Al-Sader; Sellers; Koroniak *J. Am. Chem. Soc.* **1981**, *103*, 2138; Gajewski; Olson *J. Am. Chem. Soc.* **1991**, *113*, 7432.

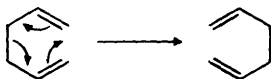
<sup>447</sup>For evidence favoring the diradical mechanism, see Willcott; Cargle *J. Am. Chem. Soc.* **1967**, *89*, 723; Doering; Schmidt *Tetrahedron* **1971**, *27*, 2005; Roth; Schmidt *Tetrahedron Lett.* **1971**, 3639; Simpson; Richey *Tetrahedron Lett.* **1973**, 2545; Gilbert; Higley *Tetrahedron Lett.* **1973**, 2075; Caramella; Huisgen; Schmolke *J. Am. Chem. Soc.* **1974**, *96*, 2997, 2999; Mazzocchi; Tamburin *J. Am. Chem. Soc.* **1975**, *97*, 555; Zimmerman; Fleming *J. Am. Chem. Soc.* **1983**, *105*, 622; Klumpp; Schakel *Tetrahedron Lett.* **1983**, *24*, 4595; McGaffin; de Meijere; Walsh *Chem. Ber.* **1991**, *124*, 939. A "continuous diradical transition state" has also been proposed: Doering; Sachdev *J. Am. Chem. Soc.* **1974**, *96*, 1168, **1975**, *97*, 5512; Roth; Lennartz; Doering; Birladeanu; Guyton; Kitagawa *J. Am. Chem. Soc.* **1990**, *112*, 1722.

For the conversion of a vinylcyclopropane to a cyclopentene in a different way, see OS 68, 220.

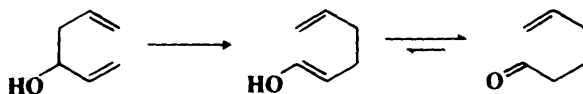
### 8-34 The Cope Rearrangement (3/4)→(1/6)-sigma-Migration



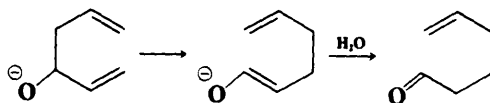
When 1,5-dienes are heated, they isomerize, in a [3,3] sigmatropic rearrangement known as the *Cope rearrangement* (not to be confused with the Cope elimination reaction, 7-8).<sup>448</sup> When the diene is symmetrical about the 3,4 bond, we have the unusual situation where a reaction gives a product identical with the starting material.<sup>449</sup>



Therefore, a Cope rearrangement can be detected only when the diene is not symmetrical about this bond. Any 1,5-diene gives the rearrangement; for example, 3-methyl-1,5-hexadiene heated to 300°C gives 1,5-heptadiene.<sup>450</sup> However, the reaction takes place more easily (lower temperature required) when there is a group on the 3- or 4-carbon with which the new double bond can conjugate. The reaction is obviously reversible and produces an equilibrium mixture of the two 1,5-dienes, which is richer in the thermodynamically more stable isomer. However, the reaction is not generally reversible<sup>451</sup> for 3-hydroxy-1,5-dienes, because the product tautomerizes to the ketone or aldehyde:



This reaction, called the *oxy-Cope rearrangement*,<sup>452</sup> has proved highly useful in synthesis.<sup>453</sup> The oxy-Cope rearrangement is greatly accelerated (by factors of  $10^{10}$  to  $10^{17}$ ) if the alkoxide is used rather than the alcohol.<sup>454</sup> In this case the direct product is the enolate ion, which is hydrolyzed to the ketone.



<sup>448</sup>For reviews, see Bartlett *Tetrahedron* **1980**, 36, 2-72, pp. 28-39; Rhoads; Raulins *Org. React.* **1975**, 22, 1-252; Smith; Kelly *Prog. Phys. Org. Chem.* **1971**, 8, 75-234, pp. 153-201; DeWolfe, in Bamford; Tipper, Ref. 365, pp. 455-461.

<sup>449</sup>Note that the same holds true for [1,j] sigmatropic reactions of symmetrical substrates (8-31, 8-32).

<sup>450</sup>Levy; Cope *J. Am. Chem. Soc.* **1944**, 66, 1684.

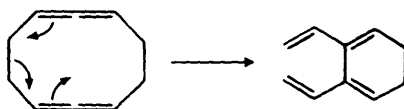
<sup>451</sup>For an exception, see Elmore; Paquette *Tetrahedron Lett.* **1991**, 32, 319.

<sup>452</sup>Berson; Jones *J. Am. Chem. Soc.* **1964**, 86, 5017, 5019; Viola; Levasseur *J. Am. Chem. Soc.* **1965**, 87, 1150; Berson; Walsh *J. Am. Chem. Soc.* **1968**, 90, 4729; Viola; Padilla; Lennox; Hecht; Proverb *J. Chem. Soc., Chem. Commun.* **1974**, 491; For reviews, see Paquette *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 609-626 [*Angew. Chem.* 102, 642-660], Synlett **1990**, 67-73; Marvell; Whalley, in Patai *The Chemistry of the Hydroxyl Group*, pt. 2; Wiley: New York, 1971, pp. 738-743.

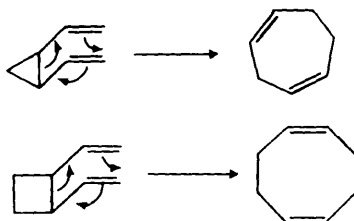
<sup>453</sup>For a list of references, see Ref. 106, pp. 639-640.

<sup>454</sup>Evans; Golub *J. Am. Chem. Soc.* **1975**, 97, 4765; Evans; Nelson *J. Am. Chem. Soc.* **1980**, 102, 774; Miyashi; Hazato; Mukai *J. Am. Chem. Soc.* **1978**, 100, 1008; Paquette; Pegg; Toops; Maynard; Rogers *J. Am. Chem. Soc.* **1990**, 112, 277; Gajewski; Gee *J. Am. Chem. Soc.* **1991**, 113, 967. See also Wender; Ternansky; Sieburth *Tetrahedron Lett.* **1985**, 26, 4319.

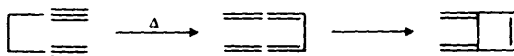
The 1,5-diene system may be inside a ring or part of an allenic system (this example illustrates both of these situations):<sup>455</sup>



but the reaction does not take place when one of the double bonds is part of an aromatic system, e.g., 1-phenyl-1-butene.<sup>456</sup> When the two double bonds are in vinylic groups attached to adjacent ring positions, the product is a ring four carbons larger. This has been applied to divinylcyclopropanes and cyclobutanes:<sup>457</sup>



Indeed, *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly that they generally cannot be isolated at room temperature,<sup>458</sup> though exceptions are known.<sup>459</sup> When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes.<sup>460</sup> A rate-determining Cope rearrangement is followed by a very rapid electrocyclic (**8-29**) reaction. The interconversion of



1,3,5-trienes and cyclohexadienes (in **8-29**) is very similar to the Cope rearrangement, though in **8-29**, the 3,4 bond goes from a double bond to a single bond rather than from a single bond to no bond.

Like 2 + 2 cycloadditions (p. 863), Cope rearrangements of simple 1,5-dienes can be catalyzed by certain transition-metal compounds. For example, the addition of  $\text{PdCl}_2(\text{PhCN})_2$  causes the reaction to take place at room temperature.<sup>461</sup> This can be quite useful synthetically, because of the high temperatures required in the uncatalyzed process.

<sup>455</sup>Harris *Tetrahedron Lett.* **1965**, 1359.

<sup>456</sup>See, for example, Lambert; Fabricius; Hoard *J. Org. Chem.* **1979**, *44*, 1480; Marvell; Almond *Tetrahedron Lett.* **1979**, 2777, 2779; Newcomb; Vieta *J. Org. Chem.* **1980**, *45*, 4793. For exceptions in certain systems, see Doering; Bragole *Tetrahedron* **1966**, *22*, 385; Jung; Hudspeth *J. Am. Chem. Soc.* **1978**, *100*, 4309; Yasuda; Harano; Kanematsu *J. Org. Chem.* **1980**, *45*, 2368.

<sup>457</sup>Vogel; Ott; Gajek *Liebigs Ann. Chem.* **1961**, *644*, 172. For reviews, see Wong et al., Ref. 114, pp. 172-174; Mil'vitskaya et al., Ref. 435, pp. 475-476.

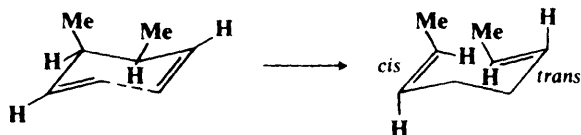
<sup>458</sup>Unsubstituted *cis*-1,2-divinylcyclopropane is fairly stable at  $-20^\circ$ : Brown; Golding; Stofko *J. Chem. Soc., Chem. Commun.* **1973**, 319; Schneider; Rebell *J. Chem. Soc., Chem. Commun.* **1975**, 283.

<sup>459</sup>See, for example, Brown *Chem. Commun.* **1965**, 226; Schönleber *Chem. Ber.* **1969**, *102*, 1789; Bolesov; li-hsein; Levina *J. Org. Chem. USSR* **1970**, *6*, 1791; Schneider; Rau *J. Am. Chem. Soc.* **1979**, *101*, 4426.

<sup>460</sup>For reviews of Cope rearrangements involving triple bonds, see Viola, Collins, and Filipp *Tetrahedron* **1981**, *37*, 3765-3811; Théron; Verny; Vessière, in Patai *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1; Wiley: New York, 1978, pp. 381-445, pp. 428-430; Huntsman *Intra-Sci. Chem. Rep.* **1972**, *6*, 151-159.

<sup>461</sup>Overman; Knoll *J. Am. Chem. Soc.* **1980**, *102*, 865; Hamilton; Mitchell; Rooney *J. Chem. Soc., Chem. Commun.* **1981**, 456. For reviews of catalysis of Cope and Claisen rearrangements, see Overman *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579-586 [*Angew. Chem.* *96*, 565-573]; Lutz *Chem. Rev.* **1984**, *84*, 205-247. For a study of the mechanism, see Overman; Renaldo *J. Am. Chem. Soc.* **1990**, *112*, 3945.

As we have indicated with our arrows, the mechanism of the uncatalyzed Cope rearrangement is a simple six-centered pericyclic process. Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form. For the case of 3,4-dimethyl-1,5-hexadiene it was demonstrated conclusively that the transition state is in the chair form. This was shown by the stereospecific nature of the reaction: The meso isomer gave the cis-trans product, while the ( $\pm$ ) compound gave the trans-trans diene.<sup>462</sup> If the transition state is in the chair form (taking the meso isomer, for example), one methyl must be "axial" and the other "equatorial" and the product must be the cis-trans olefin:



There are two possible boat forms for the transition state of the meso isomer. One leads to a trans-trans product;



the other to a cis-cis olefin. For the ( $\pm$ ) pair the predictions are just the opposite: There is just one boat form, and it leads to the cis-trans olefin, while one chair form ("diaxial" methyls) leads to the cis-cis product and the other ("diequatorial" methyls) predicts the trans-trans product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.<sup>463</sup> However, 3,4-dimethyl-1,5-hexadiene is free to assume either the chair or boat (it prefers the chair), but other compounds are not so free. Thus 1,2-divinylcyclopropane (p. 1131) can react *only* in the boat form, demonstrating that such reactions are not impossible.<sup>464</sup>

Because of the nature of the transition state in the pericyclic mechanism, optically active substrates with a chiral carbon at C-3 or C-4 transfer the chirality to the product, making this an enantioselective synthesis (see p. 1139 for an example in the mechanistically similar Claisen rearrangement).<sup>465</sup>

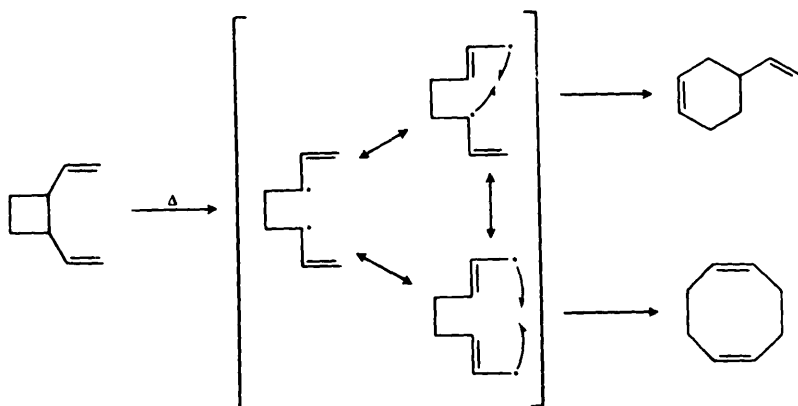
Not all Cope rearrangements proceed by the cyclic six-centered mechanism. Thus *cis*-1,2-divinylcyclobutane (p. 1131) rearranges smoothly to 1,5-cyclooctadiene, since the geometry is favorable. The trans isomer also gives this product, but the main product is 4-vinylcyclohexene (resulting from **8-33**). This reaction can be rationalized as proceeding by

<sup>462</sup>Doering; Roth *Tetrahedron* **1962**, *18*, 67. See also Hill; Gilman *Chem. Commun.* **1967**, 619; Goldstein; DeCamp *J. Am. Chem. Soc.* **1974**, *96*, 7356; Hansen; Schmid *Tetrahedron* **1974**, *30*, 1959; Gajewski; Benner; Hawkins *J. Org. Chem.* **1987**, *52*, 5198; Paquette; DeRussy; Cottrell *J. Am. Chem. Soc.* **1988**, *110*, 890.

<sup>463</sup>Preference for the chair transition state is a consequence of orbital-symmetry relationships: Hoffmann; Woodward *J. Am. Chem. Soc.* **1965**, *87*, 4389; Fukui; Fujimoto *Tetrahedron Lett.* **1966**, 251.

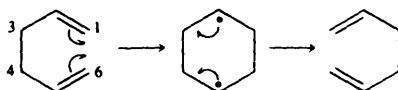
<sup>464</sup>For other examples of Cope rearrangements in the boat form, see Goldstein; Benzon *J. Am. Chem. Soc.* **1972**, *94*, 7147; Shea; Phillips *J. Am. Chem. Soc.* **1980**, *102*, 3156; Wiberg; Matturro; Adams *J. Am. Chem. Soc.* **1981**, *103*, 1600; Gajewski; Jimenez *J. Am. Chem. Soc.* **1986**, *108*, 468.

<sup>465</sup>For a review of Cope and Claisen reactions as enantioselective syntheses, see Hill, in Morrison *Asymmetric Synthesis*, vol. 3; Academic Press: New York, 1984, pp. 503-572, pp. 503-545.

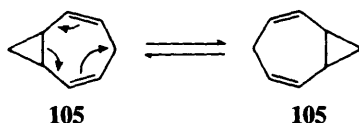


a diradical mechanism,<sup>466</sup> though it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by Cope rearrangement of the latter.<sup>467</sup>

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.<sup>468</sup> In this pathway,<sup>469</sup> the 1,6 bond is formed before the 3,4 bond breaks:



It was pointed out earlier that a Cope rearrangement of 1,5-hexadiene gives 1,5-hexadiene. This is a *degenerate Cope rearrangement* (p. 1054). Another molecule that undergoes it is bicyclo[5.1.0]octadiene (**105**).<sup>470</sup> At room temperature the nmr spectrum of this com-



pound is in accord with the structure shown on the left. At 180°C it is converted by a Cope reaction to a compound equivalent to itself. The interesting thing is that at 180°C the nmr spectrum shows that what exists is an equilibrium mixture of the two structures. That is, at

<sup>466</sup>Hammond; De Boer *J. Am. Chem. Soc.* **1964**, *86*, 899; Trecker; Henry *J. Am. Chem. Soc.* **1964**, *86*, 902. Also see Dolbier; Mancini *Tetrahedron Lett.* **1975**, 2141; Kessler; Ott *J. Am. Chem. Soc.* **1976**, *98*, 5014. For a discussion of diradical mechanisms in Cope rearrangements, see Berson, in Mayo, Ref. 1, pp. 358-372.

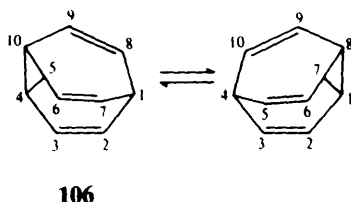
<sup>467</sup>See, for example, Berson; Dervan *J. Am. Chem. Soc.* **1972**, *94*, 8949; Baldwin; Gilbert *J. Am. Chem. Soc.* **1976**, *98*, 8283. For a similar result in the 1,2-divinylcyclopropane series, see Baldwin; Ullenius *J. Am. Chem. Soc.* **1974**, *96*, 1542.

<sup>468</sup>Doering; Toscano; Beasley *Tetrahedron* **1971**, *27*, 5299; Dewar; Wade *J. Am. Chem. Soc.* **1977**, *99*, 4417; Padwa; Blacklock *J. Am. Chem. Soc.* **1980**, *102*, 2797; Dollinger; Henning; Kirmse *Chem. Ber.* **1982**, *115*, 2309; Kaufmann; de Meijere *Chem. Ber.* **1984**, *117*, 1128; Dewar; Jie *J. Am. Chem. Soc.* **1987**, *109*, 5893; *J. Chem. Soc., Chem. Commun.* **1989**, 98. For evidence against this view, see Gajewski; Conrad *J. Am. Chem. Soc.* **1978**, *100*, 6268, 6269, **1979**, *101*, 6693; Gajewski *Acc. Chem. Res.* **1980**, *13*, 142-148; Morokuma; Borden; Hrovat *J. Am. Chem. Soc.* **1988**, *110*, 4474; Berson *Chemtracts: Org. Chem.* **1989**, *2*, 213-227; Halevi; Rom *Isr. J. Chem.* **1989**, *29*, 311; Owens; Berson *J. Am. Chem. Soc.* **1990**, *112*, 5973.

<sup>469</sup>For a report of still another mechanism, featuring a diionic variant of the diradical, see Gompper; Ulrich *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 299 [*Angew. Chem.* **88**, 298].

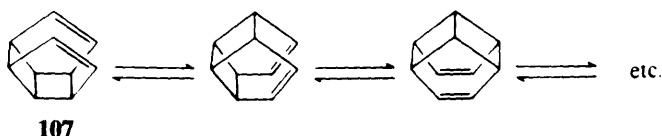
<sup>470</sup>Doering; Roth *Tetrahedron* **1963**, *19*, 715.

this temperature the molecule rapidly (faster than  $10^3$  times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons shift.<sup>471</sup> The positions of the nuclei are not the same in the two structures. Molecules like **105** that exhibit valence tautomerism (in this case, at  $180^\circ\text{C}$ ) are said to have *fluxional* structures. It may be recalled that *cis*-1,2-divinylcyclopropane does not exist at room temperature because it rapidly rearranges to 1,4-cycloheptadiene (p. 1131), but in **105** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Several other compounds with this structural feature are also known. Of these, *bullvalene* (**106**) is especially interesting. The Cope rearrangement shown



changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7. Any of these could then undergo several Cope rearrangements. In all, there are  $10! / 3$ , or more than 1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons that are adjacent. Since each of these tautomers is equivalent to all the others, this has been called an infinitely degenerate Cope rearrangement. Bullvalene has been synthesized and its proton nmr spectrum determined.<sup>472</sup> At  $-25^\circ\text{C}$  there are two peaks with an area ratio of 6:4. This is in accord with a single nontautomeric structure. The six are the vinylic protons and the four are the allylic ones. But at  $100^\circ\text{C}$  the compound shows only one nmr peak, indicating that we have here a truly unusual situation where the compound rapidly interchanges its structure among 1.2 million equivalent forms.<sup>473</sup> The  $^{13}\text{C}$  nmr spectrum of bullvalene also shows only one peak at  $100^\circ\text{C}$ .<sup>474</sup>

Another compound for which degenerate Cope rearrangements result in equivalence for all the carbons is *hypostrophene* (**107**).<sup>475</sup> In the case of the compound *barbaralane* (**108**)



<sup>471</sup>For reviews of valence tautomerizations, see Decock-Le Révérend; Goudmand *Bull. Soc. Chim. Fr.* **1973**, 389-407; Gajewski *Mech. Mol. Migr.* **1971**, 4, 1-53, pp. 32-49; Paquette *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 11-20 [*Angew. Chem.* 83, 11-20]; Domareva-Mandel'shtam; D'yakonov *Russ. Chem. Rev.* **1966**, 35, 559, 568; Schröder; Oth; Merényi *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 752-761 [*Angew. Chem.* 77, 774-784].

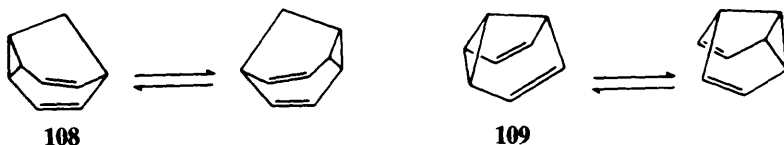
<sup>472</sup>Schröder *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 481 [*Angew. Chem.* 75, 772], *Chem. Ber.* **1964**, 97, 3140; Merényi; Oth; Schröder *Chem. Ber.* **1964**, 97, 3150. For a review of bullvalenes, see Schröder; Oth *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 414-423 [*Angew. Chem.* 79, 458-467].

<sup>473</sup>A number of azabullvalenes (**106** containing heterocyclic nitrogen) have been synthesized. They also have fluxional structures when heated, though with fewer tautomeric forms than bullvalene itself: Paquette; Barton *J. Am. Chem. Soc.* **1967**, 89, 5480; Wegener *Tetrahedron Lett.* **1967**, 4985; Paquette; Malpass; Krow; Barton *J. Am. Chem. Soc.* **1969**, 91, 5296.

<sup>474</sup>Oth; Müllen; Gilles; Schröder *Helv. Chim. Acta* **1974**, 57, 1415; Nakanishi; Yamamoto *Tetrahedron Lett.* **1974**, 1803; Günther; Ulmen *Tetrahedron* **1974**, 30, 3781. For deuterium nmr spectra see Poupko; Zimmermann; Luz *J. Am. Chem. Soc.* **1984**, 106, 5391. For a crystal structure study, see Luger; Buschmann; McMullan; Ruble; Matias; Jeffrey *J. Am. Chem. Soc.* **1986**, 108, 7825.

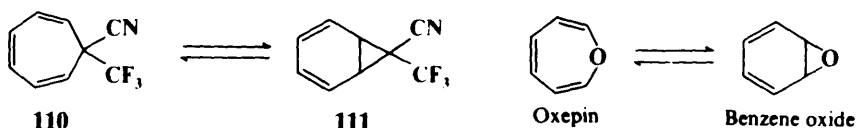
<sup>475</sup>McKennis; Brener; Ward; Pettit *J. Am. Chem. Soc.* **1971**, 93, 4957; Paquette; Davis; James *Tetrahedron Lett.* **1974**, 1615.

(bullvalene in which one  $\text{CH}=\text{CH}$  has been replaced by a  $\text{CH}_2$ ):



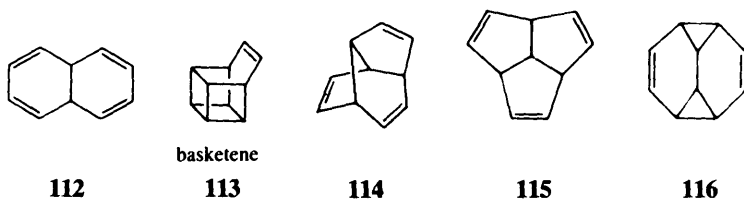
there are only two equivalent tautomers.<sup>476</sup> However, nmr spectra indicate that even at room temperature a rapid interchange of both tautomers is present, though by about  $-100^\circ\text{C}$  this has slowed to the point where the spectrum is in accord with a single structure. In the case of *semibullvalene* (**109**) (barbaralane in which the  $\text{CH}_2$  has been removed), not only is there a rapid interchange at room temperature, but even at  $-110^\circ\text{C}$ .<sup>477</sup> **109** has the lowest energy barrier of any known compound capable of undergoing the Cope rearrangement.<sup>478</sup>

The molecules taking part in a valence tautomerization need not be equivalent. Thus, nmr spectra indicate that a true valence tautomerization exists at room temperature between the cycloheptatriene **110** and the norcaradiene **111**.<sup>479</sup> In this case one isomer (**111**) has the



*cis*-1,2-divinylcyclopropane structure, while the other does not. In an analogous interconversion, benzene oxide<sup>480</sup> and oxepin exist in a tautomeric equilibrium at room temperature.<sup>481</sup>

Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol  $(\text{CH})_{10}$ .<sup>482</sup> Many other members of this group are known, including **112** to **116** and the [10]annulenes (p. 58). All these compounds represent



<sup>476</sup>Barbaralane was synthesized by Biethan; Klusacek; Musso *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 176 [*Angew. Chem.* 79, 152]; by Tsuruta; Kurabayashi; Mukai *Tetrahedron Lett.* **1965**, 3775; by Doering; Ferrier; Fossel; Hartenstein; Jones; Klumpp; Rubin; Saunders *Tetrahedron* **1967**, 23, 3943; and by Henkel; Hane *J. Org. Chem.* **1983**, 48, 3858.

<sup>477</sup>Zimmerman; Grunewald *J. Am. Chem. Soc.* **1966**, 88, 183; Meinwald; Schmidt *J. Am. Chem. Soc.* **1969**, 91, 5877; Zimmerman; Binkley; Givens; Grunewald; Sherwin *J. Am. Chem. Soc.* **1969**, 91, 3316.

<sup>478</sup>Cheng; Anet; Mioduski; Meinwald *J. Am. Chem. Soc.* **1974**, 96, 2887; Moskau; Aydin; Leber; Günther; Quast; Martin; Hassenrück; Miller; Grohmann *Chem. Ber.* **1989**, 122, 925.

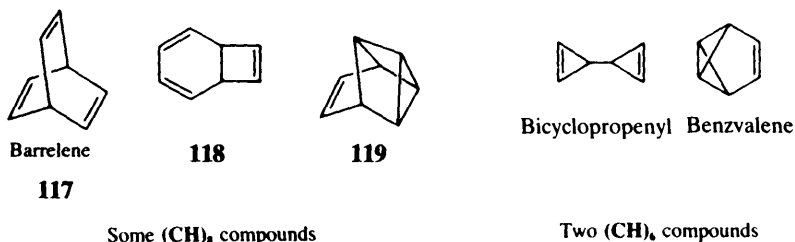
<sup>479</sup>Ciganek *J. Am. Chem. Soc.* **1965**, 87, 1149. For other examples of norcaradiene-cycloheptatriene valence tautomerizations, see Görlitz; Günther *Tetrahedron* **1969**, 25, 4467; Ciganek *J. Am. Chem. Soc.* **1965**, 93, 2207; Dürr; Kober *Chem. Ber.* **1973**, 106, 1565; Betz; Daub *Chem. Ber.* **1974**, 107, 2095; Maas; Regitz *Chem. Ber.* **1976**, 109, 2039; Warner; Lu *J. Am. Chem. Soc.* **1980**, 102, 331; Neidlein; Radke *Helv. Chim. Acta* **1983**, 66, 2626; Takeuchi; Kitagawa; Ueda; Senzaki; Okamoto *Tetrahedron* **1985**, 41, 5455.

<sup>480</sup>For a review of arene oxides, see Shirwaiker; Bhatt *Adv. Heterocycl. Chem.* **1984**, 37, 67-165.

<sup>481</sup>For reviews, see Ref. 363. See also Boyd; Stubbs *J. Am. Chem. Soc.* **1983**, 105, 2554.

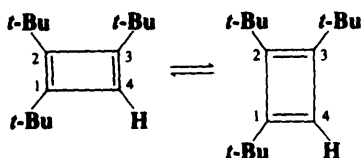
<sup>482</sup>For reviews of rearrangements and interconversions of  $(\text{CH})_n$  compounds, see Balaban; Banciu *J. Chem. Educ.* **1984**, 61, 766-770; Greenberg; Liebman, Ref. 89, pp. 203-215; Scott; Jones *Chem. Rev.* **1972**, 72, 181-202; Balaban *Rev. Roum. Chim.* **1966**, 11, 1097-1116. See also Maier; Wiegand; Baum; Wüllner *Chem. Ber.* **1989**, 122, 781.

positions of minimum energy on the  $(\text{CH})_{10}$  energy surface, and many have been interconverted by electrocyclic or Cope rearrangements. Similar groups of  $(\text{CH})_n$  compounds exist for other even-numbered values of  $n$ .<sup>482</sup> For example, there are 20 possible  $(\text{CH})_8$ <sup>483</sup> compounds,<sup>484</sup> including semibullvalene (**109**), cubane (p. 154), cuneane (p. 1149), octabisvalene (p. 154), cyclooctatetraene (p. 57), **117** to **119**, and five possible  $(\text{CH})_6$  compounds,<sup>485</sup> all



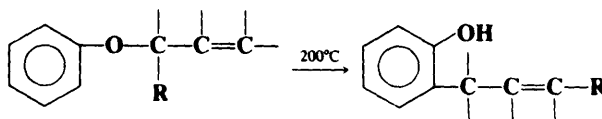
of which are known: benzene, prismane (p. 154), Dewar benzene (p. 1117), bicyclopropenyl,<sup>486</sup> and benzvalene.<sup>487</sup>

An interesting example of a valence tautomerism is the case of 1,2,3-tri-*t*-butylcyclobutadiene (p. 54). There are two isomers, both rectangular, and  $^{13}\text{C}$  nmr spectra show that



they exist in a dynamic equilibrium, even at  $-185^\circ\text{C}$ .<sup>488</sup>

### 8-35 The Claisen Rearrangement



Allylic aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.<sup>489</sup> If both ortho positions are filled, the allylic group migrates to the para

<sup>483</sup>For a review of strain in  $(\text{CH})_n$  compounds, see Hassenrück; Martin; Walsh *Chem. Rev.* **1989**, 89, 1125-1146.

<sup>484</sup>The structures of all possible  $(\text{CH})_n$  compounds, for  $n = 4, 6, 8$ , and  $10$ , are shown in Balaban, Ref. 482. For a review of  $(\text{CH})_{12}$  compounds, see Banciu; Popa; Balaban *Chem. Scr.* **1984**, 24, 28.

<sup>485</sup>For reviews of valence isomers of benzene and some related compounds, see Kobayashi; Kumadaki *Top. Curr. Chem.* **1984**, 123, 103-150; Bickelhaupt; de Wolf *Recl. Trav. Chim. Pays-Bas* **1988**, 107, 459-478.

<sup>486</sup>For a study of how this compound isomerizes to benzene, see Davis, Shea; Bergman *J. Am. Chem. Soc.* **1977**, 99, 1499.

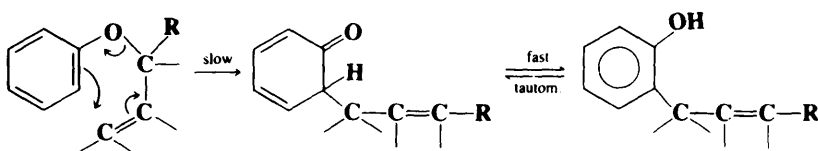
<sup>487</sup>For reviews of benzvalenes, see Christl *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 529-546 [*Angew. Chem.* 93, 515-531]; Burger *Chimia* **1979**, 147-152.

<sup>488</sup>Maier; Kalinowski; Euler *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 693 [*Angew. Chem.* 94, 706].

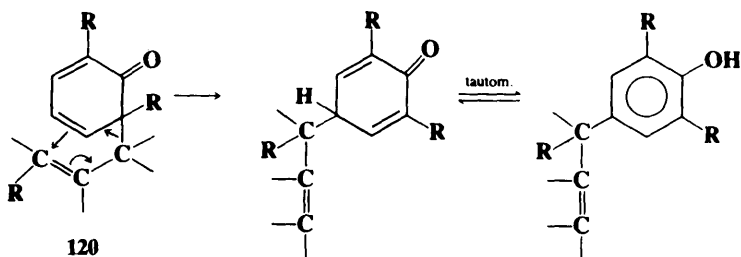
<sup>489</sup>For reviews, see Moody *Adv. Heterocycl. Chem.* **1987**, 42, 203-244; Bartlett, Ref. 448, pp. 28-39; Ziegler *Acc. Chem. Res.* **1977**, 10, 227-232; Bennett *Synthesis* **1977**, 589-606; Rhoads; Raulins, Ref. 448; Shine *Aromatic Rearrangements*; Elsevier: New York, 1969, pp. 89-120; Smith; Kelly *Prog. Phys. Org. Chem.* **1971**, 8, 75-234, pp. 153-201; Hansen; Schmid *Chimia* **1970**, 24, 89-99, *Chem. Br.* **1969**, 5, 111-116; Jefferson; Scheinmann *Q. Rev., Chem. Soc.* **1968**, 22, 391-421; Thyagarajan *Adv. Heterocycl. Chem.* **1967**, 8, 143-163; Dalrymple; Kruger; White, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 635-660.

position (this is often called the *para*-Claisen rearrangement). There is no reaction when the para and both ortho positions are filled. Migration to the meta position has not been observed. In the ortho migration the allylic group always undergoes an allylic shift. That is, as shown above, a substituent  $\alpha$  to the oxygen is now  $\gamma$  to the ring (and vice versa). On the other hand, in the para migration there is never an allylic shift: the allylic group is found exactly as it was in the original ether. Compounds with propargylic groups (i.e., groups with a triple bond in the appropriate position) do not generally give the corresponding products.

The mechanism is a concerted pericyclic [3,3] sigmatropic rearrangement<sup>490</sup> and accounts for all these facts. For the ortho rearrangement:

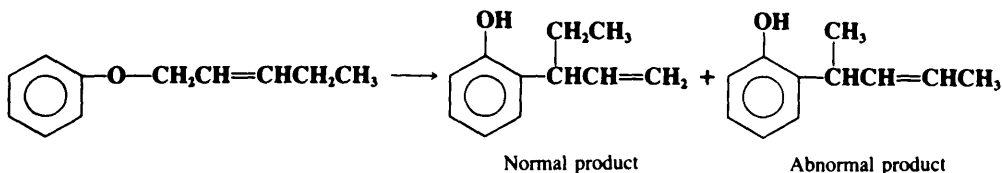


Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of crossover products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. The allylic shift for the ortho rearrangement (and the absence of one for the para) has been demonstrated by  $^{14}\text{C}$  labeling, even when no substituents are present. Studies of the transition-state geometry have shown that, like the Cope rearrangement, the Claisen rearrangement usually prefers a chairlike transition state.<sup>491</sup> When the ortho positions have no hydrogen, a second [3,3] sigmatropic migration (a Cope reaction) follows:



and the migrating group is restored to its original structure. Intermediates of structure **120** have been trapped by means of a Diels-Alder reaction.<sup>492</sup>

Ethers with an alkyl group in the  $\gamma$  position ( $\text{ArO}-\text{C}=\text{C}-\text{C}-\text{R}$  systems) sometimes give abnormal products, with the  $\beta$  carbon becoming attached to the ring.<sup>493</sup>



<sup>490</sup>For isotope effect evidence regarding the nature of the concerted transition state, see McMichael; Korver *J. Am. Chem. Soc.* **1979**, *101*, 2746; Gajewski; Conrad *J. Am. Chem. Soc.* **1979**, *101*, 2747; Kupczyk-Subotkowska; Saunders; Shine *J. Am. Chem. Soc.* **1988**, *110*, 7153.

<sup>491</sup>Vittorelli; Winkler; Hansen; Schmid *Helv. Chim. Acta* **1968**, *51*, 1457; Wunderli; Winkler; Hansen *Helv. Chim. Acta* **1977**, *60*, 2436; Copley; Knowles *J. Am. Chem. Soc.* **1985**, *107*, 5306.

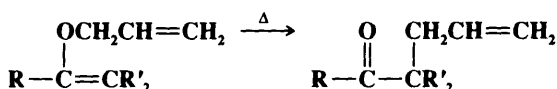
<sup>492</sup>Conroy; Firestone *J. Am. Chem. Soc.* **1956**, *78*, 2290.

<sup>493</sup>For reviews of these abnormal Claisen rearrangements, see Hansen *Mech. Mol. Migr.* **1971**, *3*, 177-236; Marvel; Whalley, in Patai, Ref. 452, pt. 2, pp. 743-750.

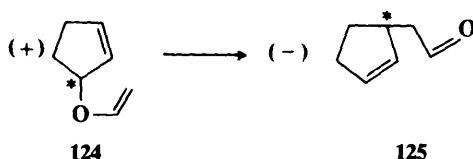


used.<sup>499</sup> In this case it may become a Friedel–Crafts reaction, with the mechanism no longer cyclic,<sup>500</sup> and ortho, meta, and para products may be obtained.

Allylic ethers of enols (allylic vinylic ethers) also undergo the Claisen rearrangement;<sup>501</sup> in fact, it was discovered with these compounds first:<sup>502</sup>

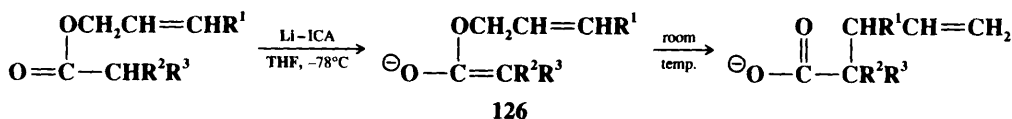


In these cases of course the final tautomerization does not take place even when  $\text{R}' = \text{H}$ , since there is no aromaticity to restore, and ketones are more stable than enols.<sup>503</sup> The use of water as solvent accelerates the reaction.<sup>504</sup> The mechanism is similar to that with allylic aryl ethers.<sup>505</sup> One experiment that demonstrated this was the conversion of optically active



**124** to **125**, which was still optically active.<sup>506</sup> This is another example of asymmetric induction (p. 117).<sup>465</sup>

It is possible to treat ketones with allyl alcohol and an acid catalyst to give  $\gamma,\delta$ -unsaturated ketones directly, presumably by initial formation of the vinylic ethers, and then Claisen rearrangement.<sup>507</sup> In an analogous procedure, the enolates (**126**) of allylic esters [formed by treatment of the esters with lithium isopropylcyclohexylamide (ICA)] rearrange to  $\gamma,\delta$ -unsaturated acids.<sup>508</sup>



<sup>499</sup>For a review, see Lutz, Ref. 461.

<sup>500</sup>For example, crossover experiments have demonstrated that the  $\text{ZnCl}_2$ -catalyzed reaction is intermolecular: Yagodin; Bunina-Krivukova; Bal'yan *J. Org. Chem. USSR* **1971**, 7, 1491.

<sup>501</sup>For a review, see Ziegler *Chem. Rev.* **1988**, 88, 1423-1452.

<sup>502</sup>Claisen *Ber.* **1912**, 45, 3157.

<sup>503</sup>However, it has proved possible to reverse the reaction, with a Lewis acid catalyst. See Boeckman; Flann; Poss *J. Am. Chem. Soc.* **1985**, 107, 4359.

<sup>504</sup>Grieco; Brandes; McCann; Clark *J. Org. Chem.* **1989**, 54, 5849.

<sup>505</sup>For discussions of the transition state, see Burrows; Carpenter *J. Am. Chem. Soc.* **1981**, 103, 6983, 6984; Gajewski; Jurayj; Kimbrough; Gande; Ganem; Carpenter *J. Am. Chem. Soc.* **1987**, 109, 1170. For mo calculations, see Vance; Rondan; Houk; Jensen; Borden; Komornicki; Wimmer *J. Am. Chem. Soc.* **1988**, 110, 2314; Dewar; Jie *J. Am. Chem. Soc.* **1989**, 111, 511.

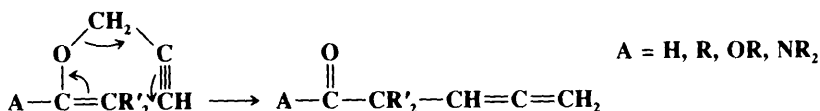
<sup>506</sup>Hill; Edwards *Tetrahedron Lett* **1964**, 3239.

<sup>507</sup>Lorette *J. Org. Chem.* **1961**, 26, 4855. See also Saucy; Marbet *Helv. Chim. Acta* **1967**, 50, 2091; Marbet; Saucy *Helv. Chim. Acta* **1967**, 50, 2095; Thomas *J. Am. Chem. Soc.* **1969**, 91, 3281; Johnson; Werthemann; Bartlett; Brocksom; Li; Faulkner; Petersen *J. Am. Chem. Soc.* **1970**, 92, 741; Pitteloud; Petrzilka; *Helv. Chim. Acta* **1979**, 62, 1319; Daub; Sanchez; Cromer; Gibson *J. Org. Chem.* **1982**, 47, 743; Bartlett; Tanzella; Barstow *J. Org. Chem.* **1982**, 47, 3941.

<sup>508</sup>Ireland; Mueller; Willard *J. Am. Chem. Soc.* **1976**, 98, 2868; Gajewski; Emrani *J. Am. Chem. Soc.* **1984**, 106, 5733; Cameron; Knight *J. Chem. Soc., Perkin Trans. I* **1986**, 161. See also Wilcox; Babston *J. Am. Chem. Soc.* **1986**, 108, 6636.

Alternatively, the silylketene acetal  $R^3R^2C=C(OSiR_3)OCH_2CH=CHR^1$  is often used instead of **126**.<sup>509</sup> This rearrangement also proceeds at room temperature. By either procedure, the reaction is called the *Ireland-Claisen rearrangement*. Note the presence of the negative charge in **126**. As with the oxy-Cope rearrangement (in **8-34**), negative charges generally accelerate the Claisen reaction,<sup>510</sup> though the extent of the acceleration can depend on the identity of the positive counterion.<sup>511</sup> The Ireland-Claisen rearrangement has been made enantioselective by converting **126** to an enol borinate in which the boron is attached to a chiral group.<sup>512</sup>

A number of expected analogs of the Claisen rearrangement are known, e.g., rearrangement of  $ArNHCH_2CH=CH_2$ ,<sup>513</sup> of N-allylic enamines  $R_2C=CRNRCR_2CR=CR_2$ ,<sup>514</sup> of allylic imino esters  $RC(OCH_2CH=CH_2)=NR$ <sup>515</sup> (these have often been rearranged with transition metal catalysts<sup>516</sup>), and of  $RCH=NRCHRCH_2CH=CH_2$ . These rearrangements of nitrogen-containing compounds are often called *aza-Cope rearrangements*.<sup>517</sup> An *azo-Cope* rearrangement:  $CH_2=CHCR_1CR_2N=NAr \rightarrow R_1CH=CHCH_2NArN=CR_2$  has been reported.<sup>518</sup> Propargylic vinylic compounds give allenic aldehydes, ketones, esters, or amides:<sup>519</sup>



The conversion of allylic aryl thioethers  $ArSCH_2CH=CH_2$  to *o*-allylic thiophenols (the *thio-Claisen rearrangement*) is not feasible, because the latter are not stable<sup>520</sup> but react to give bicyclic compounds.<sup>521</sup> However, many allylic vinylic sulfides do give the rearrangement.<sup>522</sup> Allylic vinylic sulfones, e.g.,  $H_2C=CRCH_2-SO_2-CH=CH_2$ , rearrange, when

<sup>509</sup>Ref. 508; Ireland; Wipf; Armstrong *J. Org. Chem.* **1991**, 56, 650.

<sup>510</sup>See, for example, Denmark; Harmata *Tetrahedron Lett.* **1984**, 25, 1543; Denmark; Harmata; White *J. Am. Chem. Soc.* **1989**, 111, 8878.

<sup>511</sup>Korceda; Luengo *J. Am. Chem. Soc.* **1985**, 107, 5572; Kirchner; Pratt; Hopkins *Tetrahedron Lett.* **1988**, 29, 4229.

<sup>512</sup>Corey; Lee *J. Am. Chem. Soc.* **1991**, 113, 4026.

<sup>513</sup>Marcinkiewicz; Green; Mamalis *Tetrahedron* **1961**, 14, 208; Inada; Ikado; Okazaki *Chem. Lett.* **1973**, 1213; Schmid; Hansen; Schmid *Helv. Chim. Acta* **1973**, 56, 105; Jolidon; Hansen *Helv. Chim. Acta* **1977**, 60, 978.

<sup>514</sup>Ficini; Barbara *Tetrahedron Lett.* **1966**, 6425; Hill; Gilman *Tetrahedron Lett.* **1967**, 1421; Ireland; Willard *J. Org. Chem.* **1974**, 39, 421; Hill; Khatri *Tetrahedron Lett.* **1978**, 4337. For the reverse of this rearrangement, see Wu; Fowler *J. Org. Chem.* **1988**, 53, 5998.

<sup>515</sup>For examples, see Synerholm; Gilman; Morgan; Hill *J. Org. Chem.* **1968**, 33, 1111; Black; Eastwood; Okraglik; Poynton; Wade; Welker *Aust. J. Chem.* **1972**, 25, 1483; Overman *J. Am. Chem. Soc.* **1974**, 96, 597; Metz; Mues *Tetrahedron* **1988**, 44, 6841.

<sup>516</sup>See Schenck; Bosnich *J. Am. Chem. Soc.* **1985**, 107, 2058, and references cited therein.

<sup>517</sup>For a review, see Przheval'skii; Grandberg *Russ. Chem. Rev.* **1987**, 56, 477-491. For reviews of [3,3] sigmatropic rearrangements with hetero atoms present, see Blechert *Synthesis* **1989**, 71-82; Winterfeldt *Fortschr. Chem. Forsch.* **1970**, 16, 75-102. For a review of [3,3] rearrangements of iminium salts, see Heimgartner; Hansen; Schmid *Adv. Org. Chem.* **1979**, 9, pt. 2, 655-731.

<sup>518</sup>Mitsuhashi *J. Am. Chem. Soc.* **1986**, 108, 2400.

<sup>519</sup>For reviews of Claisen rearrangements involving triple bonds, see Schuster; Coppola, Ref. 124, pp. 337-343; Viola et al., Ref. 460; Théron et al., Ref. 460, pp. 421-428. See also Henderson; Heathcock *J. Org. Chem.* **1988**, 53, 4736.

<sup>520</sup>They have been trapped: See, for example, Mortensen; Hedegaard; Lawesson *Tetrahedron* **1971**, 27, 3831; Kwart; Schwartz *J. Org. Chem.* **1974**, 39, 1575.

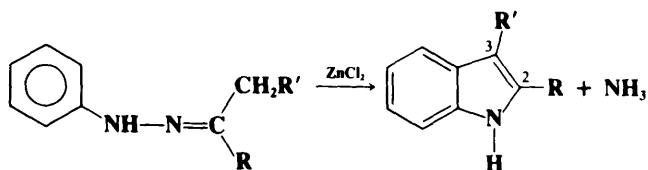
<sup>521</sup>Kwart; Hackett *J. Am. Chem. Soc.* **1962**, 84, 1754; Meyers; Rinaldi; Banoli *J. Org. Chem.* **1963**, 28, 2440; Makisumi *Tetrahedron Lett.* **1966**, 6399; Kwart; Cohen *J. Org. Chem.* **1967**, 32, 3135, *Chem. Commun.* **1968**, 319; Makisumi; Murabayashi *Tetrahedron Lett.* **1969**, 1971, 2449.

<sup>522</sup>See, for example, Schuijl; Brandsma *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 929, **1969**, 88, 1201; Corey; Shulman *J. Am. Chem. Soc.* **1970**, 92, 5522; Kondo; Ojima *Chem. Commun.* **1972**, 62; Meijer; Vermeer; Bos; Brandsma *Recl. Trav. Chim. Pays-Bas* **1974**, 93, 26; Morin; Paquer; Smadja *Recl. Trav. Chim. Pays-Bas* **1976**, 95, 179; Schaumann; Grabley *Liebigs Ann. Chem.* **1979**, 1746; Metzner; Pham; Vialle *Tetrahedron* **1986**, 42, 2025; Beslin; Perrio *Tetrahedron* **1991**, 47, 6275.

heated in the presence of ethanol and pyridine, to unsaturated sulfonate salts  $\text{CH}_2=\text{CRCH}_2\text{CH}_2\text{CH}_2\text{SO}_3^-$ , produced by reaction of the reagents with the unstable sulfene intermediates  $\text{CH}_2=\text{CRCH}_2\text{CH}_2\text{CH}=\text{SO}_2$ .<sup>523</sup> Allylic vinylic sulfoxides rapidly rearrange at room temperature or below.<sup>524</sup>

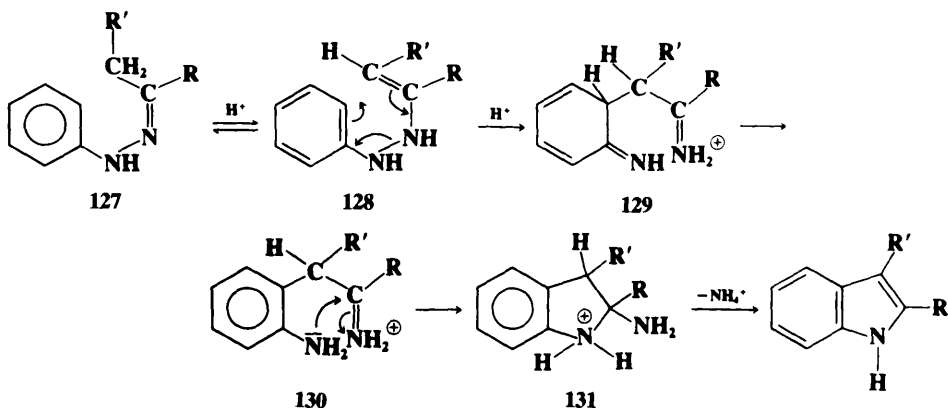
OS III, 418; V, 25; VI, 298, 491, 507, 584, 606; VII, 177; 66, 22, 29.

### 8-36 The Fischer Indole Synthesis



When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place and an indole is formed, in the *Fischer indole synthesis*.<sup>525</sup> Zinc chloride is the catalyst most frequently employed, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition-metals have also been used. Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (6-2) or by aliphatic diazonium coupling (2-7). However, it is not necessary to isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; this is now common practice. In order to obtain an indole, the aldehyde or ketone must be of the form  $\text{RCOCH}_2\text{R}'$  (R = alkyl, aryl, or hydrogen).

At first glance the reaction does not seem to be a rearrangement. However, the key step of the mechanism is a [3,3] sigmatropic rearrangement:<sup>526</sup>



<sup>523</sup>King; Harding *J. Am. Chem. Soc.* **1976**, 98, 3312.

<sup>524</sup>Block; Ahmad *J. Am. Chem. Soc.* **1985**, 107, 6731.

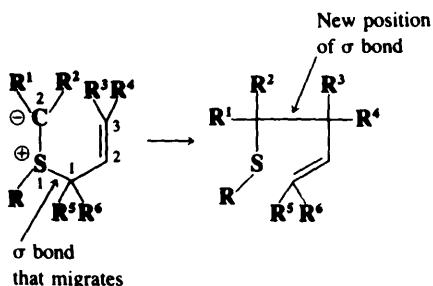
<sup>525</sup>For a monograph, see Robinson *The Fischer Indole Synthesis*; Wiley: New York, 1983. For reviews, see Grandberg; Sorokin *Russ. Chem. Rev.* **1974**, 43, 115-128; Shine *Aromatic Rearrangements*, Ref. 489, pp. 190-207; Sundberg *The Chemistry of Indoles*; Academic Press: New York, 1970, pp. 142-163; Robinson *Chem. Rev.* **1969**, 69, 227-250. For reviews of some abnormal Fischer indole syntheses, see Ishii *Acc. Chem. Res.* **1981**, 14, 275-283; Fusco; Sannicolo *Tetrahedron* **1980**, 36, 161-170.

<sup>526</sup>This mechanism was proposed by Robinson; Robinson *J. Chem. Soc.* **1918**, 113, 639.

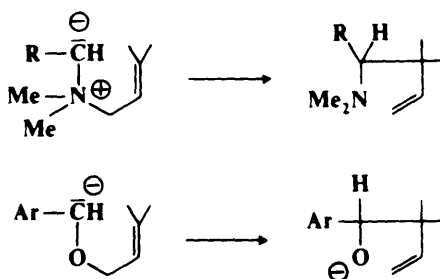
There is much evidence for this mechanism, e.g., (1) the isolation of **131**,<sup>527</sup> (2) the detection of **130** by <sup>13</sup>C and <sup>15</sup>N nmr,<sup>528</sup> (3) the isolation of side products that could only have come from **129**,<sup>529</sup> and (4) <sup>15</sup>N labeling experiments that showed that it was the nitrogen farther from the ring that is eliminated as ammonia.<sup>530</sup> The main function of the catalyst seems to be to speed the conversion of **127** to **128**. The reaction can be performed without a catalyst.

OS **III**, 725; **IV**, 884. Also see OS **IV**, 657.

### 8-37 [2,3] Sigmatropic Rearrangements (2/*S*3/) $\rightarrow$ (1/5/)-*sigma*-Migration



Sulfur ylides bearing an allylic group are converted on heating to unsaturated sulfides.<sup>531</sup> This is a concerted [2,3] sigmatropic rearrangement<sup>532</sup> and has also been demonstrated for the analogous cases of nitrogen ylides<sup>533</sup> and the conjugate bases of allylic ethers (in the last



<sup>527</sup>Southwick; McGrew; Engel; Milliman; Owellen *J. Org. Chem.* **1963**, 28, 3058; Southwick; Vida; Fitzgerald; Lee *J. Org. Chem.* **1968**, 33, 2051; Forrest; Chen *J. Chem. Soc., Chem. Commun.* **1972**, 1067.

<sup>528</sup>Douglas *J. Am. Chem. Soc.* **1978**, 100, 6463, **1979**, 101, 5676.

<sup>529</sup>Robinson; Brown *Can. J. Chem.* **1964**, 42, 1940; Bajwa; Brown *Can. J. Chem.* **1968**, 46, 1927, 3105, **1969**, 47, 785, **1970**, 48, 2293.

<sup>530</sup>Clausius; Weisser *Helv. Chim. Acta* **1952**, 35, 400.

<sup>531</sup>For example, see Blackburn; Ollis; Plackett; Smith; Sutherland; *Chem. Commun.* **1968**, 186; Trost; LaRochelle *Tetrahedron Lett.* **1968**, 3327; Baldwin; Hackler; Kelly *Chem. Commun.* **1968**, 537, 538, 1083; Bates; Feld *Tetrahedron Lett.* **1968**, 417; Kirmse; Kapps *Chem. Ber.* **1968**, 101, 994, 1004; Biellmann; Ducep *Tetrahedron Lett.* **1971**, 33; Ceré; Paolucci; Pollicino; Sandri; Fava *J. Org. Chem.* **1981**, 46, 3315; Kido; Sinha; Abiko; Yoshikoshi *Tetrahedron Lett.* **1989**, 30, 1575. For a review as applied to ring expansions, see Vedejs *Acc. Chem. Res.* **1984**, 17, 358-364.

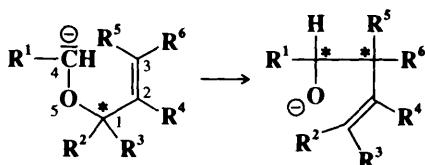
<sup>532</sup>For a review of the stereochemistry of these reactions, see Hoffmann *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 563-572 [*Angew. Chem.* 91, 625-634].

<sup>533</sup>For example, see Jemison; Ollis *Chem. Commun.* **1969**, 294; Rautenstrauch *Helv. Chim. Acta* **1972**, 55, 2233; Mageswaran; Ollis; Sutherland; Thebtaranonth *J. Chem. Soc., Chem. Commun.* **1973**, 651; Ollis; Sutherland; Thebtaranonth *J. Chem. Soc., Chem. Commun.* **1973**, 657; Mander; Turner *J. Org. Chem.* **1973**, 38, 2915; Stévenart-De Mesmaeker; Merényi; Viehe *Tetrahedron Lett.* **1987**, 28, 2591; Honda; Inoue; Sato *J. Am. Chem. Soc.* **1990**, 112, 1999.

case it is called the [2,3] Wittig rearrangement).<sup>534</sup> The reaction has been extended to certain other systems,<sup>535</sup> even to an all-carbon system.<sup>536</sup>

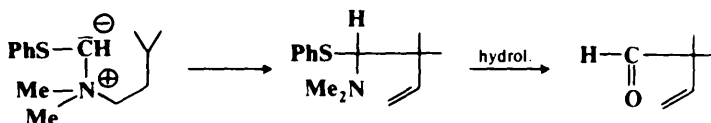
Since the reactions involve migration of an allylic group from a sulfur, nitrogen, or oxygen atom to an adjacent negatively charged carbon atom, they are special cases of the Stevens or Wittig rearrangements (8-22, 8-23). However, in this case the migrating group *must* be allylic (in 8-22 and 8-23 other groups can also migrate). Thus, when the migrating group is allylic, there are two possible pathways: (1) the radical-ion or ion-pair mechanisms (8-22, 8-23) and (2) the concerted pericyclic [2,3] sigmatropic rearrangement. These can easily be told apart, since the latter always involves an allylic shift (as in the Claisen rearrangement), while the former pathway does not.

Of these reactions, the [2,3] Wittig rearrangement in particular has often been used as a means of transferring chirality. The product of this reaction has potential chiral centers at C-3 and C-4 (if  $R^5 \neq R^6$ ), and if the starting ether is optically active because of a chiral



center at C-1, the product may be optically active as well. Many examples are known in which an optically active ether was converted to a product that was optically active because of chirality at C-3, C-4, or both.<sup>537</sup> If a suitable chiral center is present in  $R^1$  (or if a functional group in  $R^1$  can be so converted), then stereocontrol over three contiguous chiral centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.

If an OR or SR group is attached to the negative carbon, the reaction becomes a method for the preparation of  $\beta,\gamma$ -unsaturated aldehydes, because the product is easily hydrolyzed.<sup>538</sup>



Another [2,3] sigmatropic rearrangement converts allylic sulfoxides to allylicly rearranged alcohols by treatment with a thiophilic reagent such as trimethyl phosphite.<sup>539</sup> In this

<sup>534</sup>See, for example, Makisumi; Notzumoto *Tetrahedron Lett.* **1966**, 6393; Schöllkopf; Fellenberger; Rizk *Liebigs Ann. Chem.* **1970**, 734, 106; Rautenstrauch *Chem. Commun.* **1970**, 4. For a review, see Nakai; Mikami *Chem. Rev.* **1986**, 86, 885-902. For a list of references, see Ref. 106, pp. 521-522.

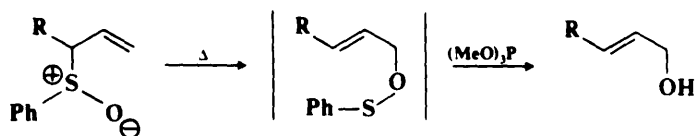
<sup>535</sup>See, for example, Baldwin; Brown; Höfle *J. Am. Chem. Soc.* **1971**, 93, 788; Yamamoto; Oda; Inouye *J. Chem. Soc., Chem. Commun.* **1973**, 848; Ranganathan; Ranganathan; Sidhu; Mehrotra *Tetrahedron Lett.* **1973**, 3577; Murata; Nakai *Chem. Lett.* **1990**, 2069. For reviews with respect to selenium compounds, see Reich, in *Liotta Organoselenium Chemistry*; Wiley: New York, 1987, pp. 365-393; Reich, in *Trahanovsky Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 102-111.

<sup>536</sup>Baldwin; Urban *Chem. Commun.* **1970**, 165.

<sup>537</sup>For reviews of stereochemistry in this reaction, see Mikami; Nakai *Synthesis* **1991**, 594-604; Nakai; Mikami, Ref. 534, pp. 888-895. See also Nakai; Nakai *Tetrahedron Lett.* **1988**, 29, 4587; Balestra; Kallmerten *Tetrahedron Lett.* **1988**, 29, 6901; Brückner *Chem. Ber.* **1989**, 122, 193, 703; Scheuplein; Kusche; Brückner; Harms *Chem. Ber.* **1990**, 123, 917; Wu; Houk; Marshall *J. Org. Chem.* **1990**, 55, 1421; Marshall; Wang *J. Org. Chem.* **1990**, 55, 2995.

<sup>538</sup>Huynh; Julia; Lorne; Michelot *Bull. Soc. Chim. Fr.* **1972**, 4057.

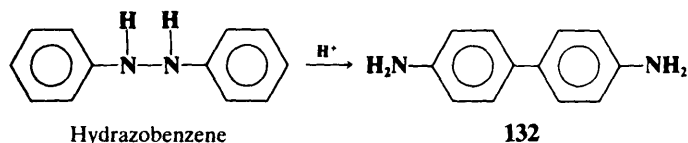
<sup>539</sup>Bickart; Carson; Jacobus; Miller; Mislow *J. Am. Chem. Soc.* **1968**, 90, 4869; Tang; Mislow *J. Am. Chem. Soc.* **1970**, 92, 2100; Grieco *J. Chem. Soc., Chem. Commun.* **1972**, 702; Evans; Andrews *Acc. Chem. Res.* **1974**, 7, 147-155; Isobe; Iio; Kitamura; Goto *Chem. Lett.* **1978**, 541; Hoffmann; Goldmann; Maak; Gerlach; Frickel; Steinbach *Chem. Ber.* **1980**, 113, 819; Sato; Otera; Nozaki *J. Org. Chem.* **1989**, 54, 2779.



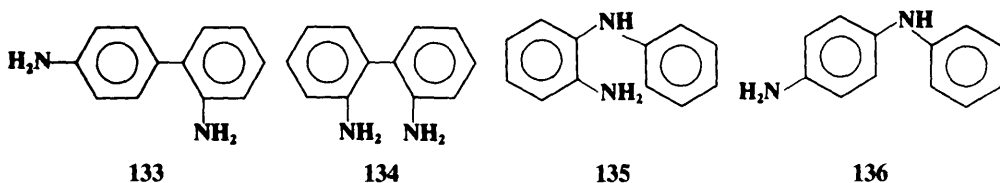
case the migration is from sulfur to oxygen. [2,3] oxygen-to-sulfur migrations are also known.<sup>540</sup> The Sommelet-Hauser rearrangement (**3-26**) is also a [2,3] sigmatropic arrangement.

OS 65, 159.

### 8-38 The Benzidine Rearrangement



When hydrazobenzene is treated with acids, it rearranges to give about 70% 4,4'-diaminobiphenyl (**132**, benzidine) and about 30% 2,4'-diaminobiphenyl (**133**). This reaction is called the *benzidine rearrangement* and is general for N,N'-diarylhydrazines.<sup>541</sup> Usually, the major product is the 4,4'-diaminobiaryl, but four other products may also be produced. These are the 2,4'-diaminobiaryl (**133**), already referred to, the 2,2'-diaminobiaryl (**134**), and the *o*- and *p*-arylaminoanilines (**135** and **136**), called *semidines*. The **134** and **136** com-



pounds are formed less often and in smaller amounts than the other two side products. Usually, the 4,4'-diaminobiaryl predominates, except when one or both para positions of the diarylhydrazine are occupied. However, the 4,4'-diamine may still be produced even if the para positions are occupied. If SO<sub>3</sub>H, COOH, or Cl (but not R, Ar, or NR<sub>2</sub>) is present in the para position, it may be ejected. With dinaphthylhydrazines, the major products are not the 4,4'-diaminobinaphthyls, but the 2,2' isomers. Another side reaction is disproportionation to ArNH<sub>2</sub> and ArN=NAr. For example, *p,p'*-PhC<sub>6</sub>H<sub>4</sub>NHNHC<sub>6</sub>H<sub>4</sub>Ph gives 88% disproportionation products at 25°C.<sup>542</sup>

<sup>540</sup>Braverman; Mechoulam *Isr. J. Chem.* **1967**, 5, 71, Braverman; Stabinsky *Chem. Commun.* **1967**, 270; Rautenstrauch *Chem. Commun.* **1970**, 526; Smith; Stirling *J. Chem. Soc. C* **1971**, 1530; Tamaru; Nagao; Bando; Yoshida *J. Org. Chem.* **1990**, 55, 1823.

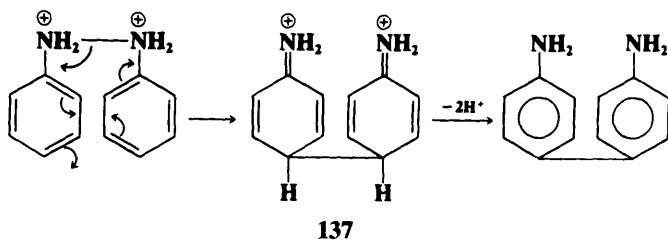
<sup>541</sup>For reviews, see, in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2; Wiley: New York, 1975, the reviews by Cox; Buncl, pp. 775-807; Koga; Koga; Anselme, pp. 914-921; Williams, in Bamford; Tipper, Ref. 365, vol. 13, 1972, pp. 437-448; Shine *Mech. Mol. Migr.* **1969**, 2, 191-247, *Aromatic Rearrangements*, Ref. 489, pp. 126-179; Banthorpe *Top. Carbocyclic Chem.* **1969**, 1, 1-62; Lukashevich *Russ. Chem. Rev.* **1967**, 36, 895-902.

<sup>542</sup>Shine; Stanley *J. Org. Chem.* **1967**, 32, 905. For investigations of the mechanism of the disproportionation reactions, see Shine; Haddas; Kwart; Brechbiel; Horgan; San Filippo *J. Am. Chem. Soc.* **1983**, 105, 2823; Rhee; Shine *J. Am. Chem. Soc.* **1986**, 108, 1000, **1987**, 109, 5052.

The mechanism has been exhaustively studied and several mechanisms have been proposed.<sup>543</sup> At one time it was believed that  $\text{NHAr}$  broke away from  $\text{ArNHNHAr}$  and became attached to the para position to give the semidine (**136**), which then went on to product. The fact that semidines could be isolated lent this argument support, as did the fact that this would be analogous to the rearrangements considered in Chapter 11 (**1-32** to **1-36**). However, this theory was killed when it was discovered that semidines could not be converted to benzidines under the reaction conditions. Cleavage into two independent pieces (either ions or radicals) has been ruled out by many types of crossover experiments, which always showed that the two rings of the starting material are in the product; that is,  $\text{ArNHNHAr'}$  gives no molecules (of any of the five products) containing two Ar groups or two Ar' groups, and mixtures of  $\text{ArNHNHAr}$  and  $\text{Ar'NHNHAr'}$  give no molecules containing both Ar and Ar'. An important discovery was the fact that, although the reaction is always first order in substrate, it can be either first<sup>544</sup> or second<sup>545</sup> order in  $[\text{H}^+]$ . With some substrates the reaction is entirely first order in  $[\text{H}^+]$ , while with others it is entirely second order in  $[\text{H}^+]$ , regardless of the acidity. With still other substrates, the reaction is first order in  $[\text{H}^+]$  at low acidities and second order at higher acidities. With the latter substrates fractional orders can often be observed,<sup>546</sup> because at intermediate acidities, both processes take place simultaneously. These kinetic results seem to indicate that the actual reacting species can

be either the monoprotonated substrate  $\text{ArNHNH}_2^+\text{Ar}$  or the diprotonated  $\text{ArNH}_2^+\text{NH}_2^+\text{Ar}$ .

Most of the proposed mechanisms<sup>547</sup> attempted to show how all five products could be produced by variations of a single process. An important breakthrough was the discovery that the two main products, **132** and **133**, are formed in entirely different ways, as shown by isotope-effect studies.<sup>548</sup> When the reaction was run with hydrazobenzene labeled with  $^{15}\text{N}$  at both nitrogen atoms, the isotope effect was 1.022 for formation of **132**, but 1.063 for formation of **133**. This showed that the N—N bond is broken in the rate-determining step in both cases, but the steps themselves are obviously different. When the reaction was run with hydrazobenzene labeled with  $^{14}\text{C}$  at a para position, there was an isotope effect of 1.028 for formation of **132**, but essentially no isotope effect (1.001) for formation of **133**. This can only mean that for **132** formation of the new C—C bond *and* breaking of the N—N bond both take place in the rate-determining step; in other words, the mechanism is concerted. The following [5.5] sigmatropic rearrangement accounts for this:<sup>549</sup>



<sup>543</sup>For a history of the mechanistic investigations and controversies, see Shine *J. Phys. Org. Chem.* **1989**, 2, 491.

<sup>544</sup>Banthorpe; Hughes; Ingold *J. Chem. Soc.* **1962**, 2386, 2402, 2407, 2413, 2418, 2429; Shine; Chamness *J. Org. Chem.* **1963**, 28, 1232; Banthorpe; O'Sullivan *J. Chem. Soc. B* **1968**, 627.

<sup>545</sup>Hammond; Shine *J. Am. Chem. Soc.* **1950**, 72, 220; Banthorpe; Cooper *J. Chem. Soc. B* **1968**, 618; Banthorpe; Cooper; O'Sullivan *J. Chem. Soc. B* **1971**, 2054.

<sup>546</sup>Carlin; Odioso *J. Am. Chem. Soc.* **1954**, 76, 100; Banthorpe; Ingold; Roy *J. Chem. Soc. B* **1968**, 64; Banthorpe; Ingold; O'Sullivan *J. Chem. Soc. B* **1968**, 624.

<sup>547</sup>For example, see the "polar-transition-state mechanism:" Banthorpe, Hughes; Ingold *J. Chem. Soc.* **1964**, 2864, and the " $\pi$ -complex mechanism:" Dewar, in Mayo, Ref. 114, vol. 1, pp. 323-344.

<sup>548</sup>Shine; Zmuda; Park; Kwart; Horgan; Collins; Maxwell *J. Am. Chem. Soc.* **1981**, 103, 955; Shine; Zmuda; Park; Kwart; Horgan; Brechbiel *J. Am. Chem. Soc.* **1982**, 104, 2501.

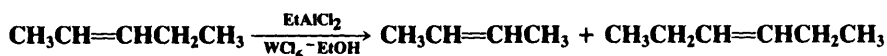
<sup>549</sup>This step was also part of the "polar-transition-state mechanism"; see Ref. 547.

The diion **137** was obtained as a stable species in super-acid solution at  $-78^{\circ}\text{C}$  by treatment of hydrazobenzene with  $\text{FSO}_3\text{H}-\text{SO}_2$  ( $\text{SO}_2\text{ClF}$ ).<sup>550</sup> Though the results just given were obtained with hydrazobenzene, which reacts by the diprotonated pathway, monoprotonated substrates have been found to react by the same [5,5] sigmatropic mechanism.<sup>551</sup> Some of the other rearrangements in this section are also sigmatropic. Thus, formation of the *p*-semidine **136** takes place by a [1,5] sigmatropic rearrangement,<sup>552</sup> and the conversion of 2,2'-hydrazonaphthalene to 2,2'-diamino-1,1'-binaphthyl by a [3,3] sigmatropic rearrangement.<sup>553</sup>

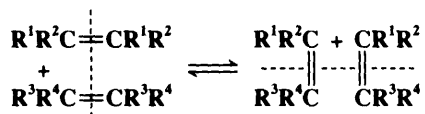
**133** is formed by a completely different mechanism, though the details are not known. There is rate-determining breaking of the N—N bond, but the C—C bond is not formed during this step.<sup>554</sup> The formation of the *o*-semidine **135** also takes place by a nonconcerted pathway.<sup>555</sup> Under certain conditions, benzidine rearrangements have been found to go through radical cations.<sup>556</sup>

## C. Other Cyclic Rearrangements

### 8-39 Metathesis of Olefins Alkene metathesis



When olefins are treated with certain catalysts (most often tungsten, molybdenum, or rhenium complexes), they are converted to other olefins in a reaction in which the alkylidene groups ( $\text{R}^1\text{R}^2\text{C}=\text{}$ ) have become interchanged by a process schematically illustrated by the equation:



The reaction is called *metathesis* of olefins.<sup>557</sup> In the example shown above, 2-pentene (either *cis*, *trans*, or a *cis-trans* mixture) is converted to a mixture of about 50% 2-pentene, 25% 2-butene, and 25% 3-hexene. The reaction is an equilibrium and the same mixture can be obtained by starting with equimolar quantities of 2-butene and 3-hexene.<sup>558</sup> In general, the

<sup>550</sup>Olah; Dunne; Kelly; Mo *J. Am. Chem. Soc.* **1972**, *94*, 7438.

<sup>551</sup>Shine; Park; Brownawell; San Filippo *J. Am. Chem. Soc.* **1984**, *106*, 7077.

<sup>552</sup>Heising; Schinke *Chem. Ber.* **1977**, *110*, 3319; Shine; Zmuda; Kwart; Horgan; Brechbiel *J. Am. Chem. Soc.* **1982**, *104*, 5181.

<sup>553</sup>Shine; Gruszecka; Subotkowski; Brownawell; San Filippo *J. Am. Chem. Soc.* **1985**, *107*, 3218.

<sup>554</sup>See Rhee; Shine, Ref. 542.

<sup>555</sup>Rhee; Shine *J. Org. Chem.* **1987**, *52*, 5633.

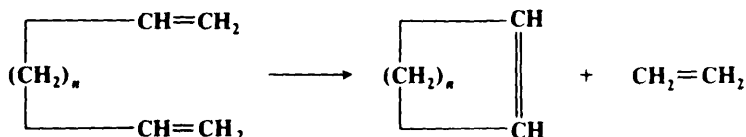
<sup>556</sup>See, for example, Nojima; Ando; Tokura *J. Chem. Soc., Perkin Trans. 1* **1976**, 1504.

<sup>557</sup>For monographs, see Drăguțan; Balaban; Dimonic *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*; Wiley: New York, 1985; Ivin *Olefin Metathesis*; Academic Press: New York, 1983. For reviews, see Feast; Gibson, in Hartley, Ref. 313, vol. 5, 1989, pp. 199-228; Streck *CHEMTECH* **1989**, 498-503; Schrock *J. Organomet. Chem.* **1986**, *300*, 249-262; Grubbs, in Wilkinson *Comprehensive Organometallic Chemistry*, vol. 8; Pergamon: Elmsford, NY, 1982, pp. 499-551; Basset; Leconte, *CHEMTECH* **1980**, 762-767; Banks, *CHEMTECH* **1979**, 494-500, *Fortschr. Chem. Forsch.* **1972**, *25*, 39-69; Calderon; Lawrence; Ofstead *Adv. Organomet. Chem.* **1979**, *17*, 449-492; Grubbs *Prog. Inorg. Chem.* **1978**, *24*, 1-50; Calderon, in Patai *The Chemistry of Functional Groups: Supplement A*, pt. 2; Wiley: New York, 1977, pp. 913-964, *Acc. Chem. Res.* **1972**, *5*, 127-132; Katz *Adv. Organomet. Chem.* **1977**, *16*, 283-317; Haines; Leigh *Chem. Soc. Rev.* **1975**, *4*, 155-188; Hocks *Bull. Soc. Chim. Fr.* **1975**, 1893-1903; Mol; Moulijn *Adv. Catal.* **1974**, *24*, 131-171; Hughes *Organomet. Chem. Synth.* **1972**, *1*, 341-374; Khidekel', Shebaldova; Kalechits *Russ. Chem. Rev.* **1971**, *40*, 669-678; Bailey, *Catal. Rev.* **1969**, *3*, 37-60.

<sup>558</sup>Calderon; Chen; Scott *Tetrahedron Lett.* **1967**, 3327; Wang; Menapace *J. Org. Chem.* **1968**, *33*, 3794; Hughes *J. Am. Chem. Soc.* **1970**, *92*, 532.

reaction can be applied to a single unsymmetrical olefin, giving a mixture of itself and two other olefins, or to a mixture of two olefins, in which case the number of different molecules in the product depends on the symmetry of the reactants. As in the case above, a mixture of  $R^1R^2C=CR^1R^2$  and  $R^3R^4C=CR^3R^4$  gives rise to only one new olefin ( $R^1R^2C=CR^3R^4$ ), while in the most general case, a mixture of  $R^1R^2C=CR^3R^4$  and  $R^5R^6C=CR^7R^8$  gives a mixture of ten olefins: the original two plus eight new ones. With simple alkenes the proportions of products are generally statistical,<sup>559</sup> which limits the synthetic utility of the reaction since the yield of any one product is low. However, in some cases one alkene may be more or less thermodynamically stable than the rest, so that the proportions are not statistical. Furthermore, it may be possible to shift the equilibrium. For example, 2-methyl-1-butene gives rise to ethylene and 3,4-dimethyl-3-hexene. By allowing the gaseous ethylene to escape, the yield of 3,4-dimethyl-3-hexene can be raised to 95%.<sup>560</sup>

Many catalysts, both homogeneous<sup>561</sup> and heterogeneous,<sup>562</sup> have been used for this reaction. Some of the former<sup>563</sup> are  $WCl_6$ -EtOH-EtAlCl<sub>2</sub>,<sup>559</sup>  $MoCl_2(NO)_2(Ph_3P)_2$ -Et-AlCl<sub>2</sub>,<sup>564</sup>  $WCl_6$ -BuLi,<sup>565</sup> and  $WCl_6$ -LiAlH<sub>4</sub>,<sup>566</sup> while among the latter are oxides of Mo, W, and Re deposited on alumina or silica gel.<sup>567</sup> In general, the former group are more useful for synthetic purposes. By choice of the proper catalyst, the reaction has been applied to terminal and internal alkenes, straight chain or branched. The effect of substitution on the ease of reaction is  $CH_2= > RCH_2CH= > R_2CHCH= > R_2C=$ .<sup>568</sup> Dienes can react intermolecularly or intramolecularly,<sup>569</sup> e.g.,



Cyclic olefins give dimeric dienes,<sup>570</sup> e.g.,



However, the products can then react with additional monomers and with each other, so that polymers are generally produced, and the cyclic dienes are obtained only in low yield.

<sup>559</sup>Calderon; Ofstead; Ward; Judy; Scott *J. Am. Chem. Soc.* **1968**, *90*, 4133.

<sup>560</sup>Knoche, Ger. Pat.(Offen.) 2024835, 1970 [*Chem. Abstr.* **1971**, *74*, 44118b]. See also Chevalier; Sinou; Descotes *Bull. Soc. Chim. Fr.* **1976**, 2254; Bessalova; Babich; Vdovin; Nametkin *Doklad. Chem.* **1975**, 225, 668; Ichikawa; Fukuzumi *J. Org. Chem.* **1976**, *41*, 2633; Baker; Crimmin *Tetrahedron Lett* **1977**, 441.

<sup>561</sup>First reported by Calderon; Chen; Scott, Ref. 558.

<sup>562</sup>First reported by Banks; Bailey *Ind. Eng. Chem., Prod. Res. Dev.* **1964**, *3*, 170. See also Banks *CHEMTECH* **1986**, 112-117.

<sup>563</sup>For a lengthy list, see Hughes *Organomet. Chem. Synth.*, Ref. 557, pp. 362-368. For a homogeneous rhenium catalyst, see Toreki; Schrock *J. Am. Chem. Soc.* **1990**, *112*, 2448.

<sup>564</sup>Zuech; Hughes; Kubicek; Kittleman *J. Am. Chem. Soc.* **1970**, *92*, 528; Hughes, Ref. 558.

<sup>565</sup>Wang; Menapace, Ref. 558.

<sup>566</sup>Chatt; Haines; Leigh *J. Chem. Soc., Chem. Commun.* **1972**, 1202; Matlin; Sammes *J. Chem. Soc., Perkin Trans. I* **1978**, 624.

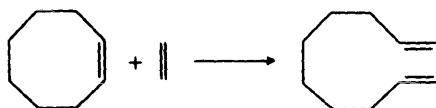
<sup>567</sup>For a list of heterogeneous catalysts, see Banks, *Fortschr. Chem. Forsch.*, Ref. 557, pp. 41-46.

<sup>568</sup>For an explanation for this order, see McGinnis; Katz; Hurwitz *J. Am. Chem. Soc.* **1976**, *98*, 605; Casey; Tuinstra; Saeman *J. Am. Chem. Soc.* **1976**, *98*, 608.

<sup>569</sup>Kroll; Doyle *Chem. Commun.* **1971**, 839; Zuech et al., Ref. 564.

<sup>570</sup>Calderon; Ofstead; Judy *J. Polym. Sci., Part A-1* **1967**, *5*, 2209; Wasserman; Ben-Efraim; Wolovsky *J. Am. Chem. Soc.* **1968**, *90*, 3286; Wolovsky; Nir *Synthesis* **1972**, 134.

The reaction between a cyclic and a linear olefin can give an ring-opened diene:<sup>571</sup>



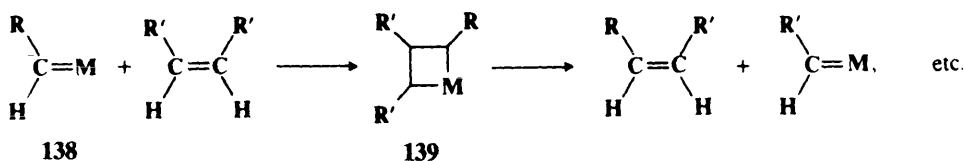
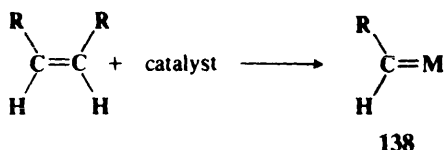
Olefins containing functional groups<sup>572</sup> do not give the reaction with most of the common catalysts, but some success has been reported with WCl<sub>6</sub>-SnMe<sub>4</sub><sup>573</sup> and with certain other catalysts.

The reaction has also been applied to internal triple bonds:<sup>574</sup>



but it has not been successful for terminal triple bonds.<sup>575</sup> An intramolecular reaction of a double bond with a triple bond has been reported.<sup>576</sup>

The generally accepted mechanism is a chain mechanism, involving the intervention of a metal-carbene complex (138)<sup>577</sup> and a four-membered ring containing a metal<sup>578</sup> (139).<sup>579</sup>



<sup>571</sup>Wasserman; Ben-Efraim; Wolovsky, Ref. 570; Ray; Crain, Fr. Pat. 1511381, 1968 [*Chem. Abstr.* **1969**, 70, 114580q]; Mango, U.S. Pat. 3424811, 1969 [*Chem. Abstr.* **1969**, 70, 106042a]; Rossi; Diversi; Lucherini; Porri *Tetrahedron Lett.* **1974**, 879; Lal; Smith *J. Org. Chem.* **1975**, 40, 775.

<sup>572</sup>For a review, see Mol *CHEMTECH* **1983**, 250-255. See also Bosma; van den Aardweg; Mol *J. Organomet. Chem.* **1983**, 255, 159, **1985**, 280, 115; Xiaoding; Mol *J. Chem. Soc., Chem. Commun.* **1985**, 631; Crisp; Collis *Aust. J. Chem.* **1988**, 41, 935.

<sup>573</sup>First shown by van Dam; Mittelmeijer; Boelhouwer *J. Chem. Soc., Chem. Commun.* **1972**, 1221.

<sup>574</sup>Pennella; Banks; Bailey *Chem. Commun.* **1968**, 1548; Mortreux; Petit; Blanchard *Tetrahedron Lett.* **1978**, 4967; Devarajan; Walton; Leigh *J. Organomet. Chem.* **1979**, 181, 99; Wengrovius; Sancho; Schrock *J. Am. Chem. Soc.* **1981**, 103, 3932; Villemain; Cadot *Tetrahedron Lett.* **1982**, 23, 5139; McCullough; Schrock *J. Am. Chem. Soc.* **1984**, 106, 4067.

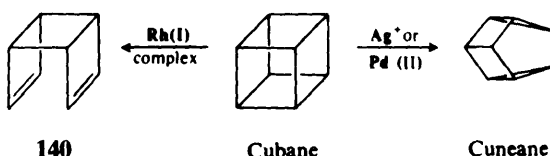
<sup>575</sup>McCullough; Listemann; Schrock; Churchill; Ziller *J. Am. Chem. Soc.* **1983**, 105, 6729.

<sup>576</sup>Trost; Trost *J. Am. Chem. Soc.* **1991**, 113, 1850.

<sup>577</sup>For a review of these complexes and their role in this reaction, see Crabtree *The Organometallic Chemistry of the Transition Metals*; Wiley: New York, 1988, pp. 244-267.

<sup>578</sup>For reviews of metallocycles, see Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA; 1987, pp. 459-520; Lindner *Adv. Heterocycl. Chem.* **1986**, 39, 237-279.

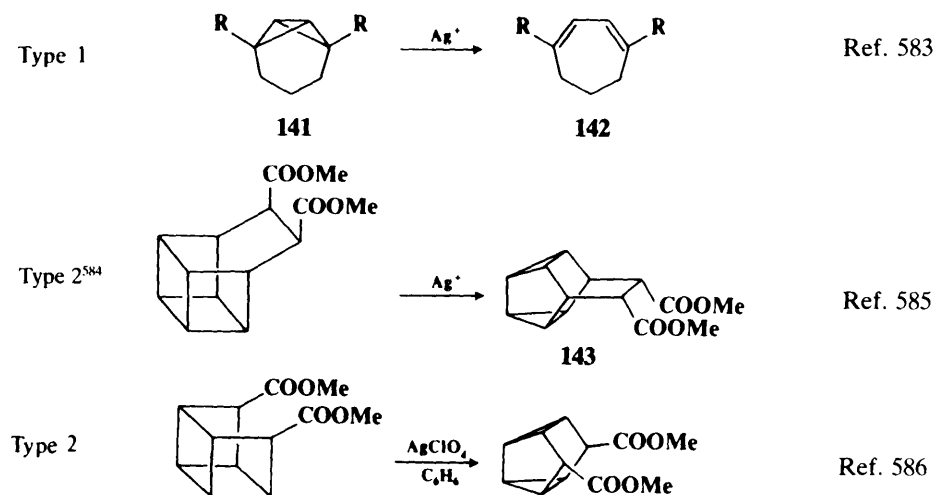
<sup>579</sup>For reviews of the mechanism, see Grubbs, *Prog. Inorg. Chem.*, Ref. 557; Katz, Ref. 557; Calderon; Ofstead; Judy *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 401-409 [*Angew. Chem.* **88**, 443-442]. See also McLain; Wood; Schrock *J. Am. Chem. Soc.* **1977**, 99, 3519; Casey; Polichnowski *J. Am. Chem. Soc.* **1977**, 99, 6097; Mango *J. Am. Chem. Soc.* **1977**, 99, 6117; Stevens; Beauchamp *J. Am. Chem. Soc.* **1979**, 101, 6449; Lee; Ott; Grubbs *J. Am. Chem. Soc.* **1982**, 104, 7491; Levisalles; Rudler; Villemain *J. Organomet. Chem.* **1980**, 193, 235; Iwasawa; Hamamura *J. Chem. Soc., Chem. Commun.* **1983**, 130; Rappé; Upton *Organometallics* **1984**, 3, 1440; Kress; Osborn; Greene; Ivin; Rooney *J. Am. Chem. Soc.* **1987**, 109, 899; Feldman; Davis; Schrock *Organometallics* **1989**, 8, 2266.

8-40 Metal-Ion-Catalyzed  $\sigma$ -Bond Rearrangements

Many highly strained cage molecules undergo rearrangement when treated with metallic ions such as  $\text{Ag}^+$ ,  $\text{Rh(I)}$ , or  $\text{Pd(II)}$ .<sup>580</sup> The bond rearrangements observed can be formally classified into two main types: (1) 2 + 2 ring openings of cyclobutanes and (2) conversion



of a bicyclo[2.2.0] system to a bicyclopropyl system. The molecule cubane supplies an example of each type (see above). Treatment with  $\text{Rh(I)}$  complexes converts cubane to tricyclo[4.2.0.0<sup>2,5</sup>]octa-3,7-diene (**140**),<sup>581</sup> an example of type 1, while  $\text{Ag}^+$  or  $\text{Pd(II)}$  causes the second type of reaction, producing cuneane.<sup>582</sup> Other examples are:



<sup>580</sup>For reviews, see Halpern, in Wender; Pino *Organic Syntheses via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 705-721; Bishop *Chem. Rev.* **1976**, 76, 461-486; Cardin; Cetinkaya; Doyle; Lappert *Chem. Soc. Rev.* **1973**, 2, 99-144, pp. 132-139; Paquette *Synthesis* **1975**, 347-357, *Acc. Chem. Res.* **1971**, 4, 280-287.

<sup>581</sup>Cassar; Eaton; Halpern *J. Am. Chem. Soc.* **1970**, 92, 3515; Eaton; Chakraborty *J. Am. Chem. Soc.* **1978**, 100, 3634.

<sup>582</sup>Cassar; Eaton; Halpern *J. Am. Chem. Soc.* **1970**, 92, 6336.

<sup>583</sup>Paquette; Allen; Henzel *J. Am. Chem. Soc.* **1970**, 92, 7002; Gassman; Atkins *J. Am. Chem. Soc.* **1971**, 93, 4579, **1972**, 94, 7748; Sakai; Westberg; Yamaguchi; Masamune *J. Am. Chem. Soc.* **1972**, 93, 4611; Paquette; Wilson; Henzel *J. Am. Chem. Soc.* **1972**, 94, 7771.

<sup>584</sup>The starting compound here is a derivative of basketane, or 1,8-bishomocubane. For a review of homo-, bis-homo-, and trishomocubanes, see Marchand *Chem. Rev.* **1989**, 89, 1011-1033.

<sup>585</sup>See, for example, Furstoss; Lehn *Bull. Soc. Chim. Fr.* **1966**, 2497; Paquette; Stowell *J. Am. Chem. Soc.* **1970**, 92, 2584, **1971**, 93, 2459; Dauben; Kielbasa *J. Am. Chem. Soc.* **1971**, 93, 7345; Paquette; Beckley; Farnham *J. Am. Chem. Soc.* **1975**, 97, 1089.

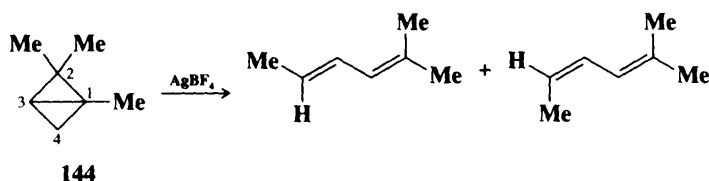
<sup>586</sup>Paquette; Beckley; McCreedy *Tetrahedron Lett.* **1971**, 775; Dauben; Schallhorn; Whalen *J. Am. Chem. Soc.* **1971**, 93, 1446.

**143** is the 9,10-dicarbomethoxy derivative of *snoutane* (pentacyclo[3.3.2.0<sup>2,4</sup>.0<sup>3,7</sup>.0<sup>6,8</sup>]-decane).

The mechanisms of these reactions are not completely understood, although relief of strain undoubtedly supplies the driving force. The reactions are thermally forbidden by the orbital-symmetry rules, and the role of the catalyst is to provide low-energy pathways so that the reactions can take place. The type 1 reactions are the reverse of the catalyzed 2 + 2 ring closures discussed at 5-49. The following mechanism, in which  $\text{Ag}^+$  attacks one of the edge bonds, has been suggested for the conversion of **141** to **142**.<sup>587</sup>



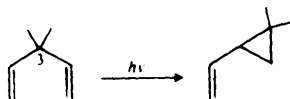
Simpler bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.<sup>588</sup> For example, treatment of **144** with  $\text{AgBF}_4$ ,<sup>589</sup>  $(\text{C}_6\text{F}_5\text{Cu})_4$ ,<sup>590</sup> or  $[(\pi\text{-allyl})\text{PdCl}]_2$ <sup>591</sup> gives a mixture of the



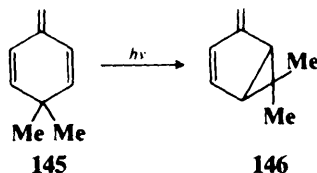
two dienes shown, resulting from a formal cleavage of the  $\text{C}_1\text{—C}_3$  and  $\text{C}_1\text{—C}_2$  bonds (note that a hydride shift has taken place).

### 8-41 The Di- $\pi$ -methane and Related Rearrangements

#### Di- $\pi$ -methane rearrangement



1,4-Dienes carrying alkyl or aryl substituents on C-3<sup>592</sup> can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di- $\pi$ -methane rearrangement*.<sup>593</sup> An example is conversion of **145** to **146**.<sup>594</sup> For most 1,4-dienes it is only the singlet excited states that



<sup>587</sup>Gassman; Atkins, Ref. 583; Sakai et al., Ref. 583.

<sup>588</sup>**141** can also be cleaved in this manner, giving a 3-methylenecyclohexene. See, for example, Gassman; Atkins *J. Am. Chem. Soc.* **1971**, 93, 1042; Dauben; Kielbasa *J. Am. Chem. Soc.* **1972**, 94, 3669; Gassman; Reitz *J. Am. Chem. Soc.* **1973**, 95, 3057; Paquette; Zon *J. Am. Chem. Soc.* **1974**, 96, 203, 224.

<sup>589</sup>Paquette; Henzel; Wilson *J. Am. Chem. Soc.* **1971**, 93, 2335.

<sup>590</sup>Gassman; Williams *Tetrahedron Lett.* **1971**, 1409.

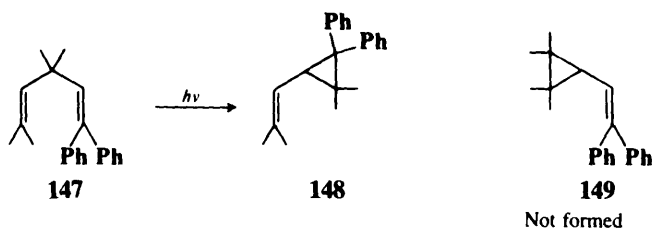
<sup>591</sup>Gassman; Meyer; Williams *Chem. Commun.* **1971**, 842.

<sup>592</sup>Zimmerman; Pincock *J. Am. Chem. Soc.* **1973**, 95, 2957.

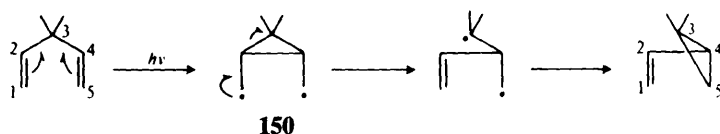
<sup>593</sup>For reviews, see Zimmerman *Org. Photochem.* **1991**, 11, 1-36; Zimmerman, in Mayo, Ref. 1, vol. 3, pp. 131-166; Hixson; Mariano; Zimmerman *Chem. Rev.* **1973**, 73, 531-551.

<sup>594</sup>Zimmerman; Hackett; Juers; McCall; Schröder *J. Am. Chem. Soc.* **1971**, 93, 3653.

give the reaction; triplet states generally take other pathways.<sup>595</sup> For unsymmetrical dienes, the reaction is regioselective. For example, **147** gave **148**, not **149**.<sup>596</sup>

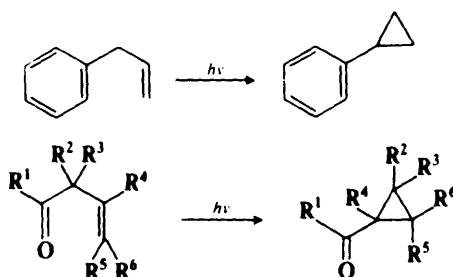


The mechanism can be described by the diradical pathway given<sup>597</sup> (the C-3 substituents act to stabilize the radical), though the species shown are not necessarily intermediates, but



may be transition states. It has been shown, for the case of certain substituted substrates, that configuration is retained at C-1 and C-5 and inverted at C-3.<sup>598</sup>

The reaction has been extended to allylic benzenes<sup>599</sup> (in this case C-3 substituents are not required), to  $\beta,\gamma$ -unsaturated ketones<sup>600</sup> (the latter reaction, which is called the *oxa-di-*



$\pi$ -methane rearrangement,<sup>601</sup> generally occurs only from the triplet state), to  $\beta,\gamma$ -unsaturated imines,<sup>602</sup> and to triple-bond systems.<sup>603</sup>

<sup>595</sup>However, some substrates, generally rigid bicyclic molecules, (e.g., barrelene, p. 1136, which is converted to semi-bullvalene) give the di- $\pi$ -methane rearrangement only from triplet states.

<sup>596</sup>Zimmerman; Pratt *J. Am. Chem. Soc.* **1970**, *92*, 6259, 6267; Zimmerman; Baum *J. Am. Chem. Soc.* **1971**, *93*, 3646. See also Zimmerman; Welter *J. Am. Chem. Soc.* **1978**, *100*, 4131; Alexander; Pratt; Rowley; Tipping *J. Chem. Soc., Chem. Commun.* **1978**, 101; Paquette; Bay; Ku; Rondan; Houk *J. Org. Chem.* **1982**, *47*, 422.

<sup>597</sup>See Zimmerman; Werthemann; Kamm *J. Am. Chem. Soc.* **1974**, *96*, 439; Zimmerman; Little *J. Am. Chem. Soc.* **1974**, *96*, 5143; Zimmerman; Boettcher; Buehler; Keck *J. Am. Chem. Soc.* **1975**, *97*, 5635. For an argument against the intermediacy of **150**, see Adam; De Lucchi; Dörr *J. Am. Chem. Soc.* **1989**, *111*, 5209.

<sup>598</sup>Zimmerman; Robbins; McKelvey; Samuel; Sousa *J. Am. Chem. Soc.* **1974**, *96*, 4630.

<sup>599</sup>For example, see Griffin; Covell; Petterson; Dodson; Klose *J. Am. Chem. Soc.* **1965**, *87*, 1410; Hixson *J. Am. Chem. Soc.* **1972**, *94*, 2507; Cookson; Ferreira; Salisbury *J. Chem. Soc., Chem. Commun.* **1974**, 665; Fasel; Hansen *Chimia* **1982**, *36*, 193; Paquette; Bay *J. Am. Chem. Soc.* **1984**, *106*, 6693; Zimmerman; Swafford *J. Org. Chem.* **1984**, *49*, 3069.

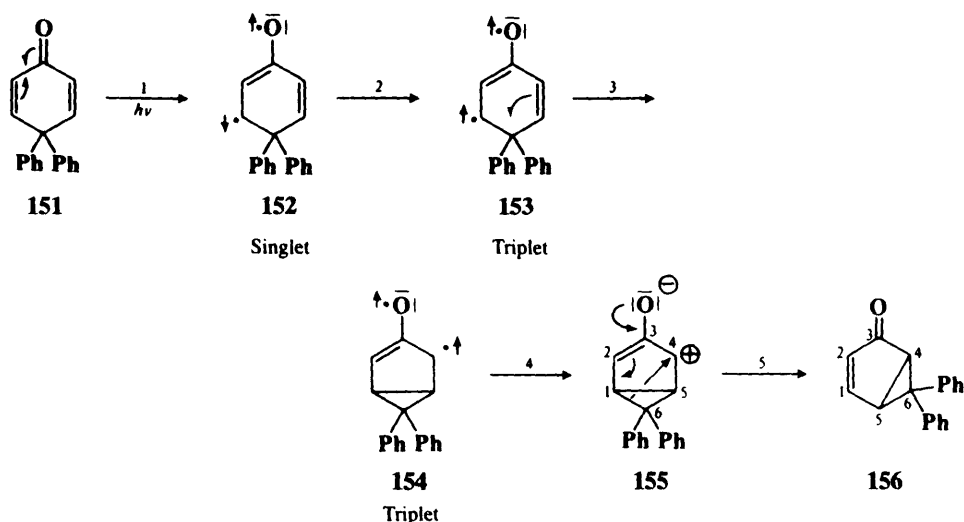
<sup>600</sup>For reviews of photochemical rearrangements of unsaturated ketones, see Schuster, in Mayo, Ref. 1, vol. 3, pp. 167-279; Houk *Chem. Rev.* **1976**, *76*, 1-74; Schaffner *Tetrahedron* **1976**, *32*, 641-653; Dauben; Lodder; Ipaktschi *Top. Curr. Chem.* **1975**, *54*, 73-114.

<sup>601</sup>For a review, see Demuth *Org. Photochem.* **1991**, *11*, 37-109.

<sup>602</sup>See Armesto; Horspool; Langa; Ramos *J. Chem. Soc., Perkin Trans. 1* **1991**, 223.

<sup>603</sup>See Griffin; Chihal; Perreten; Bhacca *J. Org. Chem.* **1976**, *41*, 3931.

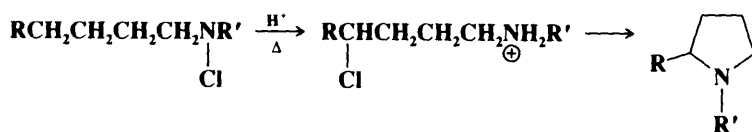
When photolyzed, 2,5-cyclohexadienones can undergo a number of different reactions, one of which is formally the same as the di- $\pi$ -methane rearrangement.<sup>604</sup> In this reaction, photolysis of the substrate **151** gives the bicyclo[3.1.0]hexenone **156**. Though the reaction is formally the same (note the conversion of **145** to **146** above), the mechanism is different



from that of the di- $\pi$ -methane rearrangement, because irradiation of a ketone can cause an  $n \rightarrow \pi^*$  transition, which is of course not possible for a diene lacking a carbonyl group. The mechanism<sup>605</sup> in this case has been formulated as proceeding through the excited triplet states **153** and **154**. In step 1, the molecule undergoes an  $n \rightarrow \pi^*$  excitation to the singlet species **152**, which cross to the triplet **153**. Step 3 is a rearrangement from one excited state to another. Step 4 is a  $\pi^* \rightarrow n$  electron demotion (an intersystem crossing from  $T_1 \rightarrow S_0$ , see p. 239). The conversion of **155** to **156** consists of two 1,2 alkyl migrations (a one-step process would be a 1,3 migration of alkyl to a carbocation center, see p. 1062): The old  $C_6-C_5$  bond becomes the new  $C_6-C_4$  bond and the old  $C_6-C_1$  bond becomes the new  $C_6-C_5$  bond.<sup>606</sup>

2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.<sup>607</sup>

## 8-42 The Hofmann-Löffler and Related Reactions



<sup>604</sup>For reviews of the photochemistry of 2,5-cyclohexadienones and related compounds, see Schaffner; Demuth, in Mayo, Ref. 1, vol. 3, pp. 281-348; Zimmerman *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 1-11 [*Angew. Chem.* **81**, 45-55]; Kropp *Org. Photochem.* **1967**, *1*, 1-90; Schaffner *Adv. Photochem.* **1966**, *4*, 81-112. For synthetic use, see Schultz; Lavieri; Macielag; Plummer *J. Am. Chem. Soc.* **1987**, *109*, 3991, and references cited therein.

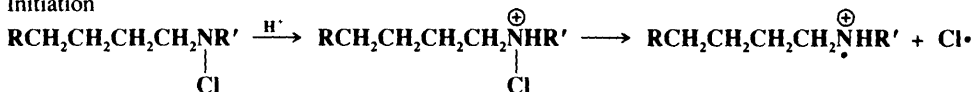
<sup>605</sup>Zimmerman; Schuster *J. Am. Chem. Soc.* **1961**, *83*, 4486; Schuster; Patel *J. Am. Chem. Soc.* **1968**, *90*, 5145; Schuster *Acc. Chem. Res.* **1978**, *11*, 65-73; Zimmerman; Pasteris *J. Org. Chem.* **1980**, *45*, 4864, 4876; Schuster; Liu *Tetrahedron* **1981**, *37*, 3329.

<sup>606</sup>Zimmerman; Crumine; Döpp; Huyffer *J. Am. Chem. Soc.* **1969**, *91*, 434.

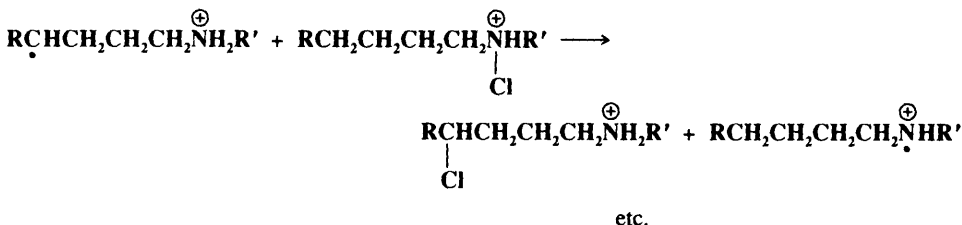
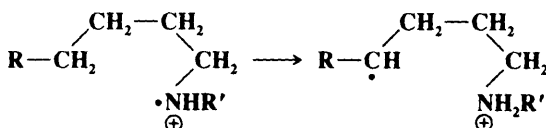
<sup>607</sup>For reviews, see Schaffner; Demuth, Ref. 604; Quinkert *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1072-1087 [*Angew. Chem.* **84**, 1157-1173]; Kropp, Ref. 604.

A common feature of the reactions in this section<sup>608</sup> is that they serve to introduce functionality at a position remote from functional groups already present. As such, they have proved very useful in synthesizing many compounds, especially in the steroid field (see also 9-2 and 9-16). When N-haloamines in which one alkyl group has a hydrogen in the 4 or 5 position are heated with sulfuric acid, pyrrolidines or piperidines are formed, in a reaction known as the *Hofmann-Löffler reaction* (also called the *Hofmann-Löffler-Freytag reaction*).<sup>609</sup> R' is normally alkyl, but the reaction has been extended to R' = H by the use of concentrated sulfuric acid solution and ferrous salts.<sup>610</sup> The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4 or 5 position of the alkyl group. It is possible to isolate the resulting haloamine salt, but usually this is not done, and the second step, the ring closure (0-43), takes place. Though the reaction is most often induced by heat, this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free-radical type, with the main step involving an internal hydrogen abstraction.<sup>611</sup>

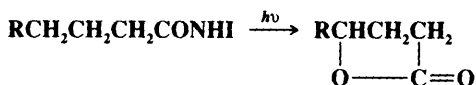
Initiation



Propagation



A similar reaction has been carried out on N-halo amides, which give  $\gamma$ -lactones:<sup>612</sup>



Another related reaction is the *Barton Reaction*,<sup>613</sup> by which a methyl group in the  $\delta$  position to an OH group can be oxidized to a CHO group. The alcohol is first converted

<sup>608</sup>For a review of the reactions in this section, see Carruthers *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University Press: Cambridge, 1986, pp. 263-279.

<sup>609</sup>For reviews, see Stella *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 337-350 [*Angew. Chem.* 95, 368-380]; Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972**, 4, 203-284, pp. 249-259; Deno *Methods Free-Radical Chem.* **1972**, 3, 135-154, pp. 136-143.

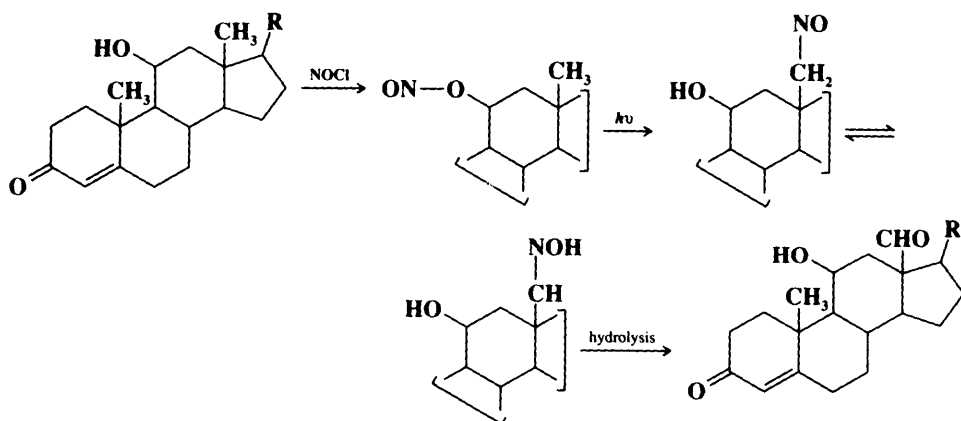
<sup>610</sup>Schmitz; Murawski *Chem. Ber.* **1966**, 99, 1493.

<sup>611</sup>Wawzonek; Thelan *J. Am. Chem. Soc.* **1950**, 72, 2118.

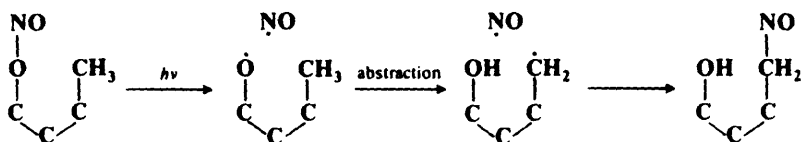
<sup>612</sup>Barton; Beckwith; Goosen *J. Chem. Soc.* **1965**, 181; Petterson; Wambsgans *J. Am. Chem. Soc.* **1964**, 86, 1648; Neale; Marcus; Schepers *J. Am. Chem. Soc.* **1966**, 88, 3051. For a review of N-halo amide rearrangements, see Neale *Synthesis* **1971**, 1-15.

<sup>613</sup>For reviews, see Hesse *Adv. Free-Radical Chem.* **1969**, 3, 83-137; Barton *Pure Appl. Chem.* **1968**, 16, 1-15.

to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group and nitrosation of the methyl group. Hydrolysis of the oxime tautomer gives the aldehyde, e.g.,<sup>614</sup>



This reaction takes place only when the methyl group is in a favorable steric position.<sup>615</sup> The mechanism is similar to that of the Hofmann-Löffler reaction.<sup>616</sup>

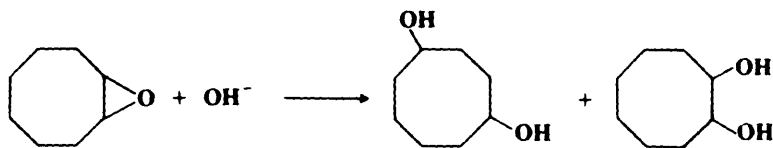


This is one of the few known methods for effecting substitution at an angular methyl group. Not only CH<sub>3</sub> groups but also alkyl groups of the form RCH<sub>2</sub> and R<sub>2</sub>CH can give the Barton reaction if the geometry of the system is favorable. An RCH<sub>2</sub> group is converted to the oxime R(C=NOH) (which is hydrolyzable to a ketone) or to a nitroso dimer, while an R<sub>2</sub>CH group gives a nitroso compound R<sub>2</sub>C(NO). With very few exceptions, the only carbons that become nitrosated are those in the position δ to the original OH group, indicating that a six-membered transition state is necessary for the hydrogen abstraction.<sup>617</sup>

OS III, 159.

## D. Noncyclic Rearrangements

### 8-43 Hydride Shifts



<sup>614</sup>Barton; Beaton *J. Am. Chem. Soc.* **1961**, *83*, 4083. Also see Barton; Beaton; Geller; Peckett *J. Am. Chem. Soc.* **1960**, *82*, 2640.

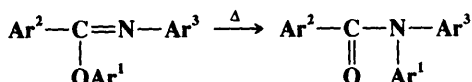
<sup>615</sup>For a discussion of which positions are favorable, see Burke; Silks; Strickland *Tetrahedron Lett.* **1968**, *29*, 2761.

<sup>616</sup>Kabasakalian; Townley *J. Am. Chem. Soc.* **1962**, *84*, 2711; Akhtar; Barton; Sammes *J. Am. Chem. Soc.* **1965**, *87*, 4601. See also Nickon; Ferguson; Bosch; Iwadare *J. Am. Chem. Soc.* **1977**, *99*, 4518; Barton; Hesse; Pechet; Smith *J. Chem. Soc., Perkin Trans. I* **1979**, 1159; Green; Boyle; Vairamani; Mukhopadhyay; Saunders; Bowen; Allinger *J. Am. Chem. Soc.* **1986**, *108*, 2381.

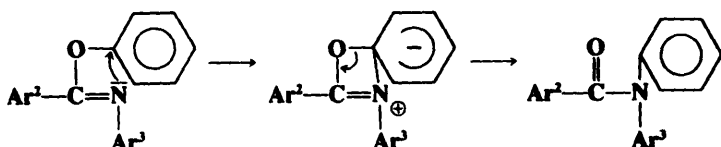
<sup>617</sup>For a discussion, see Nickon et al., Ref. 616.

The above is a typical example of a transannular hydride shift. The 1,2-diol is formed by a normal epoxide hydrolysis reaction (0-7). For a discussion of 1,3 and longer hydride shifts, see p. 1062.

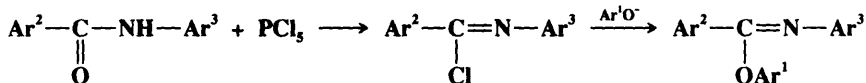
**8-44** The Chapman Rearrangement  
1/O→3/N-Aryl-migration



In the *Chapman rearrangement*, N,N-diaryl amides are formed when aryl imino esters are heated.<sup>618</sup> Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),<sup>619</sup> though the reaction can also be carried out without any solvent at all. Many groups may be present in the rings, e.g., alkyl, halo, OR, CN, COOR, etc. Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar<sup>2</sup> or Ar<sup>3</sup> decrease the reactivity. The products can be hydrolyzed to diarylamines, and this is a method for preparing these compounds. The mechanism probably involves an intramolecular<sup>620</sup> aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen

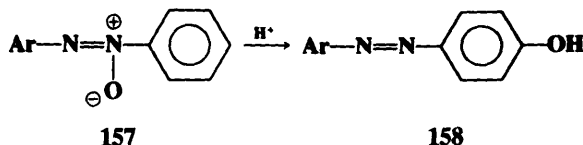


shift. Aryl imino esters can be prepared from N-aryl amides by reaction with PCl<sub>5</sub>, followed by treatment of the resulting imino chloride with an aroxide ion.<sup>621</sup> Imino esters with any



or all of the three groups being alkyl also rearrange, but they require catalysis by H<sub>2</sub>SO<sub>4</sub> or a trace of methyl iodide or methyl sulfate.<sup>622</sup> The mechanism is different, involving an intermolecular process.<sup>623</sup> This is also true for derivatives for formamide (Ar<sup>2</sup> = H).

**8-45** The Wallach Rearrangement



<sup>618</sup>For reviews, see Schulenberg; Archer *Org. React.* **1965**, *14*, 1-51; McCarty, in Patai, Ref. 237, pp. 439-447; McCarty; Garner, in Patai *The Chemistry of Amidines and Imidates*; Wiley: New York, 1975, pp. 189-240. For a review of 1,3 migrations of R in general, see Landis *Mech. Mol. Migr.* **1969**, *2*, 43-63.

<sup>619</sup>Wheeler; Roman; Santiago; Quiles *Can. J. Chem.* **1969**, *47*, 503.

<sup>620</sup>For evidence for the intramolecular character of the reaction, see Wiberg; Rowland *J. Am. Chem. Soc.* **1955**, *77*, 2205; Wheeler; Roman; Rosado *J. Org. Chem.* **1969**, *34*, 966; Kimura *J. Chem. Soc., Perkin Trans. 2* **1967**, 205.

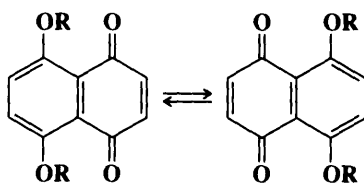
<sup>621</sup>For a review of the formation and reactions of imino chlorides, see Bonnett, in Patai, Ref. 237, pp. 597-662.

<sup>622</sup>Landis, Ref. 618.

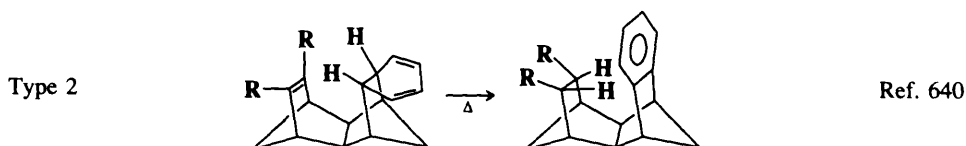
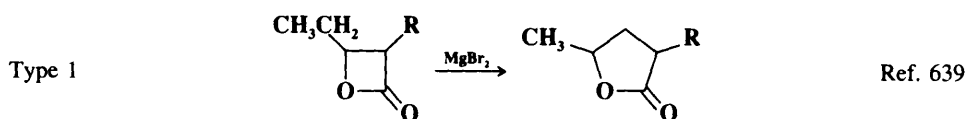
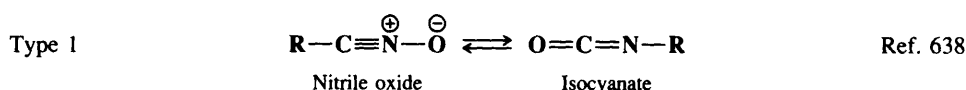
<sup>623</sup>See Challis; Frenkel *J. Chem. Soc., Perkin Trans. 2* **1978**, 192.



A *dyotropic rearrangement*<sup>636</sup> is an uncatalyzed process in which two  $\sigma$  bonds simultaneously migrate intramolecularly.<sup>637</sup> There are two types. The above is an example of Type 1, which consists of reactions in which the two  $\sigma$  bonds interchange positions. In Type 2, the two  $\sigma$  bonds do not interchange positions. An example is



Some other examples are



<sup>636</sup>Reetz *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 129, 130 [*Angew. Chem.* **84**, 161, 163].

<sup>637</sup>For reviews, see Minkin; Olekhovich; Zhdanov *Molecular Design of Tautomeric Compounds*; D. Reidel Publishing Co.: Dordrecht, 1988, pp. 221-246; Minkin *Sov. Sci. Rev., Sect. B* **1985**, *7*, 51-98; Reetz *Adv. Organomet. Chem.* **1977**, *16*, 33-65.

<sup>638</sup>See, for example, Taylor *J. Chem. Soc., Perkin Trans. 1* **1985**, 1181.

<sup>639</sup>See Black; Hall; Sheu *J. Org. Chem.* **1988**, *53*, 2371; Black; Fields *Synth. Commun.* **1988**, *18*, 125.

<sup>640</sup>See Mackenzie; Proctor; Woodnutt *Tetrahedron* **1987**, *43*, 5981, and references cited therein.

# 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  $\text{CH}_4$  is  $-4$ , in most cases attempts to apply the concept lead to fractional values or to apparent absurdities. Thus carbon in propane has an oxidation number of  $-2.67$  and in butane of  $-2.5$ , though organic chemists seldom think of these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (e.g., the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure. The practice in organic chemistry has been to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one*. Reduction is the opposite. For the simple functional groups this series is shown in Table 19.1.<sup>1</sup> It should be noted that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as chloromethane, but 1,2-dichloropropane is in a higher one. Obviously, such distinctions are somewhat arbitrary, and if we attempt to carry them too far, we shall find ourselves painted into a corner. Nevertheless, the basic idea has served organic chemistry well. It should be noted that conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen (Lavoisier's original definition of oxidation). The reverse is true for reductions.

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

### MECHANISMS

It must be noted that our definition of oxidation has nothing to do with mechanism. Thus the conversion of bromomethane to methanol with  $\text{KOH}$  (0-1) and to methane with  $\text{LiAlH}_4$  (0-76) have the same  $\text{S}_\text{N}2$  mechanisms, but one is a reduction (according to our definition)

<sup>1</sup>For more extensive tables, with subclassifications, see Soloveichik; Krakauer *J. Chem. Educ.* **1966**, *43*, 532-535.

**TABLE 19.1** Categories or simple functional groups arranged according to oxidation state

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

RH	$\begin{array}{c}   \quad   \\ -C=C- \\   \quad   \\ ROH \\ RCl \\ RNH_2 \\ \text{etc.} \end{array}$	$\begin{array}{c} -C\equiv C- \\   \quad   \\ R-C-R \\    \\ O \\   \\ -C-Cl \\   \\ Cl \\   \\ -C-C- \\   \quad   \\ Cl \quad Cl \\   \quad   \\ -C-C- \\   \quad   \\ OH \quad OH \\ \text{etc.} \end{array}$	$\begin{array}{c} R-C-OH \\    \\ O \\ R-C-NH_2 \\    \\ O \\   \\ Cl \\   \\ -C-Cl \\   \\ Cl \\ \text{etc.} \end{array}$	$\begin{array}{c} CO_2 \\ CCl_4 \end{array}$
<b>Approximate oxidation number</b>				
-4	-2	0	+2	+4

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

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

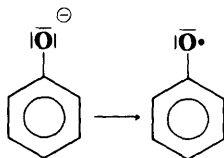
**1. Direct electron transfer.<sup>4</sup>** We have already met some reactions in which the reduction is a direct gain of electrons or the oxidation a direct loss of them. An example is the Birch reduction (5-10), where sodium directly transfers an electron to an aromatic ring. An example from this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

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

<sup>3</sup>Wiberg *Surv. Prog. Chem.* **1963**, 1, 211-248.

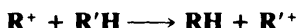
<sup>4</sup>For a monograph on direct electron-transfer mechanisms, see Eberson *Electron Transfer Reactions in Organic Chemistry*; Springer: New York, 1987. For a review, see Eberson *Adv. Phys. Org. Chem.* **1982**, 18, 79-185. For a review of multistage electron-transfer mechanisms, see Deuchert;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

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



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

**2. Hydride transfer.**<sup>7</sup> In some reactions a hydride ion is transferred to or from the substrate. The reduction of epoxides with  $\text{LiAlH}_4$  is an example (0-80). Another is the Cannizzaro reaction (9-69). Reactions in which a carbocation abstracts a hydride ion belong in this category:<sup>8</sup>

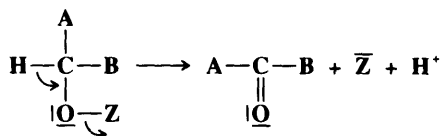


**3. Hydrogen-atom transfer.** Many oxidation and reduction reactions are free-radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of 4-1 involves abstraction of hydrogen:



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  $\text{CrO}_3\text{H}$ ,  $\text{MnO}_3$ , or a similar inorganic acid moiety. One example of this mechanism was seen in 4-6, where A was an alkyl or aryl group, B was OH, and Z was  $\text{CrO}_3\text{H}$ .

<sup>5</sup>Littler; Sayce *J. Chem. Soc.* **1964**, 2545.

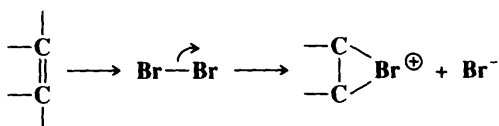
<sup>6</sup>For a review of the oxidation of phenols, see Mihailović; Čeković, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 505-592.

<sup>7</sup>For a review, see Watt *Adv. Phys. Org. Chem.* **1968**, 24, 57-112.

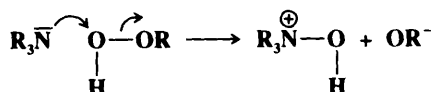
<sup>8</sup>For a review of these reactions, see Nenitzescu, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 463-520.

Another is the oxidation of a secondary alcohol to a ketone (9-3), where A and B are alkyl or aryl groups and Z is also  $\text{CrO}_3\text{H}$ . In the lead tetraacetate oxidation of glycols (9-7) the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. It should be noted that the cleavage shown is an example of an E2 elimination.

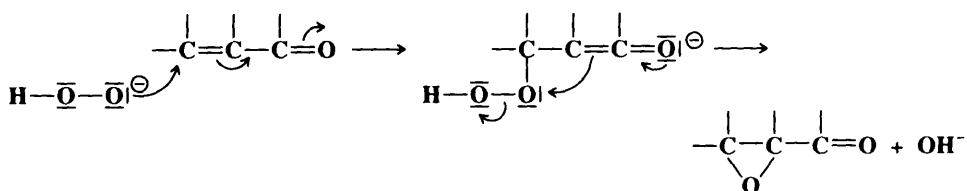
**5. Displacement mechanisms.** In these reactions the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an olefin (5-26).



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



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



In this case the oxygen of the oxidizing agent is in oxidation state  $-1$  and the  $\text{OH}^{-}$  departs with its oxygen in the  $-2$  state, so it is reduced and the substrate oxidized. There are several reactions that follow this pattern of addition of an oxidizing agent and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with  $\text{SeO}_2$  (9-16). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these six categories are not mutually exclusive.

## REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with our practice in the other chapters.<sup>9</sup> This means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent, e.g., acid dichromate or  $\text{LiAlH}_4$  (except for a discussion of selectivity of reducing agents, p. 1206). Some oxidizing or reducing agents are fairly specific in their action, attacking only

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

one or a few types of substrate. Others, like acid dichromate, permanganate,  $\text{LiAlH}_4$ , and catalytic hydrogenation, are much more versatile.<sup>10</sup>

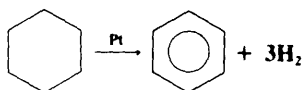
When an oxidation or a reduction could be considered in a previous chapter, this was done. For example, the catalytic hydrogenation of olefins is a reduction, but it is also an addition to the  $\text{C}=\text{C}$  bond and was treated in Chapter 15. In this chapter are discussed only those reactions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

## Oxidations<sup>11</sup>

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

### A. Eliminations of Hydrogen

#### 9-1 Aromatization of Six-Membered Rings Hexahydro-terelimination



<sup>10</sup>For books on certain oxidizing agents, see Mijs; de Jonge *Organic Synthesis by Oxidation with Metal Compounds*; Plenum: New York, 1986; Cainelli; Cardillo *Chromium Oxidations in Organic Chemistry*; Springer: New York, 1984; Arndt *Manganese Compounds as Oxidizing Agents in Organic Chemistry*; Open Court Publishing Company: La Salle, IL, 1981; Lee *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*; Open Court Publishing Company: La Salle, IL, 1980. For some reviews, see Curci *Adv. Oxygenated Processes* **1990**, 2, 1-59 (dioxiranes); Adam; Curci; Edwards *Acc. Chem. Res.* **1989**, 22, 205-211 (dioxiranes); Murray *Chem. Rev.* **1989**, 89, 1187-1201, *Mol. Struct. Energ.* **1988**, 5, 311-351 (dioxiranes); Kafafi; Martinez; Herron *Mol. Struct. Energ.* **1988**, 5, 283-310 (dioxiranes); Krief; Hevesi *Organoselenium Chemistry I*; Springer: New York, 1988, pp. 76-103 (seleninic anhydrides and acids); Ley, in Liotta *Organoselenium Chemistry*; Wiley: New York, 1987, pp. 163-206 (seleninic anhydrides and acids); Barton; Finet *Pure Appl. Chem.* **1987**, 59, 937-946 [bismuth(V)]; Fatiadi *Synthesis* **1987**, 85-127 ( $\text{KMnO}_4$ ); Rubottom, in Trahanovsky, Ref. 2, pt. D, 1982, pp. 1-145 (lead tetraacetate); Fatiadi, in Pizey *Synthetic Reagents*, vol. 4; Wiley: New York, 1981, pp. 147-335, *Synthesis* **1974**, 229-272 ( $\text{HIO}_4$ ); Fatiadi *Synthesis* **1976**, 65-104, 133-167 ( $\text{MnO}_2$ ); Ogata, in Trahanovsky, Ref. 2, pt. C, pp. 295-342, 1978 (nitric acid and nitrogen oxides); McKillop, *Pure Appl. Chem.* **1975**, 43, 463-479 (thallium nitrate); Pizey *Synthetic Reagents*, vol. 2; Wiley: New York, 1974, pp. 143-174 ( $\text{MnO}_2$ ); George; Balachandran *Chem. Rev.* **1975**, 75, 491-519 (nickel peroxide); Courtney; Swansborough *Rev. Pure Appl. Chem.* **1972**, 22, 47-54 (ruthenium tetroxide); Ho *Synthesis* **1973**, 347-354 (ceric ion); Aylward *Q. Rev., Chem. Soc.* **1971**, 25, 407-429 (lead tetraacetate); Meth-Cohn; Suschitzky *Chem. Ind. (London)* **1969**, 443-450 ( $\text{MnO}_2$ ); Sklarz *Q. Rev. Chem. Soc.* **1967**, 21, 3-28 ( $\text{HIO}_4$ ); Korshunov; Vereshchagin *Russ. Chem. Rev.* **1966**, 35, 942-957 ( $\text{MnO}_2$ ); Weinberg; Weinberg *Chem. Rev.* **1968**, 68, 449-523 (electrochemical oxidation). For reviews of the behavior of certain reducing agents, see Keefer; Lunn *Chem. Rev.* **1989**, 89, 459-502 (Ni-Al alloy); Málek *Org. React.* **1988**, 36, 249-590, **1985**, 34, 1-317 (metal alkoxylaluminum hydrides); Alpatova; Zabusova; Tomilov *Russ. Chem. Rev.* **1986**, 55, 99-112 (solvated electrons generated electrochemically); Caubère *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 599-613 [*Angew. Chem.* 95, 597-611] (modified sodium hydride); Nagai *Org. Prep. Proced. Int.* **1980**, 12, 13-48 (hydrosilanes); Pizey *Synthetic Reagents*, vol. 1; Wiley: New York, 1974, pp. 101-294 ( $\text{LiAlH}_4$ ); Winterfeldt *Synthesis* **1975**, 617-630 (diisobutylaluminum hydride and triisobutylaluminum); Hüchel *Fortschr. Chem. Forsch.* **1966**, 6, 197-250 (metals in ammonia or amines). For books on reductions with metal hydrides, see Seyden-Penne *Reductions by the Almino- and Borohydrides*; VCH: New York, 1991; Štrouf; Časenský; Kubánek *Sodium Dihydrido-bis(2-methoxyethoxy)aluminate (SDMA)*; Elsevier: New York, 1985; Hajós *Complex Hydrides*; Elsevier: New York, 1979. Also see House *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972; Refs. 9 and 11.

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

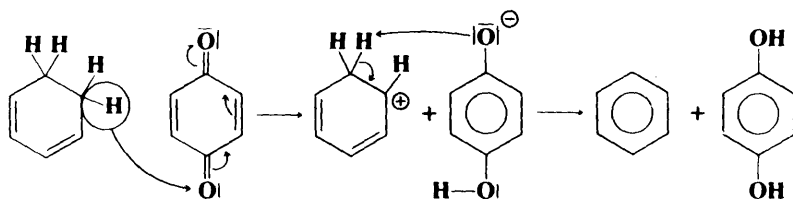
Six-membered alicyclic rings can be aromatized in a number of ways.<sup>12</sup> Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction can also be applied to heterocyclic five- and six-membered rings.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

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

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

2. The elements sulfur and selenium, which combine with the hydrogen evolved to give, respectively, H<sub>2</sub>S and H<sub>2</sub>Se. Little is known about this mechanism either.<sup>17</sup>

3. Quinones,<sup>18</sup> 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).<sup>19</sup> 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:<sup>20</sup>



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

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

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

<sup>15</sup>Land; Pettiette-Hall; McIver; Hemminger *J. Am. Chem. Soc.* **1989**, 111, 5970.

<sup>16</sup>Marshall; Müller; Ihrig *Tetrahedron Lett.* **1973**, 3491.

<sup>17</sup>House; Orchin *J. Am. Chem. Soc.* **1960**, 82, 639; Silverwood; Orchin *J. Org. Chem.* **1962**, 27, 3401.

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

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

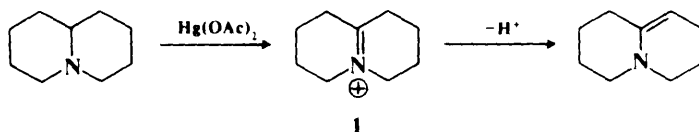
<sup>20</sup>Braude; Jackman; Linstead; Lowe *J. Chem. Soc.* **1960**, 3123, 3133; Trost *J. Am. Chem. Soc.* **1967**, 89, 1847; Ref. 18. See also Stoos; Roček *J. Am. Chem. Soc.* **1972**, 94, 2719; Hashish; Hoodless *Can. J. Chem.* **1976**, 54, 2261; Müller; Joly; Mermoud *Helv. Chim. Acta* **1984**,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

Among other reagents<sup>21</sup> that have been used are atmospheric oxygen,  $\text{MnO}_2$ ,<sup>22</sup>  $\text{SeO}_2$ , various strong bases,<sup>23</sup> chromic acid,<sup>24</sup> and activated charcoal.<sup>25</sup> The last-mentioned reagent also dehydrogenates cyclopentanes to cyclopentadienes. In some instances the hydrogen is not released as  $\text{H}_2$  or transferred to an external oxidizing agent but instead serves to reduce another molecule of substrate. This is a disproportionation reaction and can be illustrated by the conversion of cyclohexene to cyclohexane and benzene.

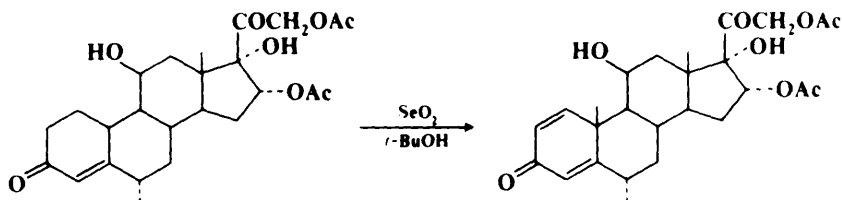
OS II, 214, 423; III, 310, 358, 729, 807; IV, 536; VI, 731. Also see OS III, 329.

## 9-2 Dehydrogenations Yielding Carbon–Carbon Double Bonds

### Dihydro-elimination



Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, though industrially mixtures of olefins are obtained in this way from mixtures of alkanes (generally by heating with chromia–alumina catalysts). There are, however, some notable exceptions, and it is not surprising that these generally involve cases where the new double bond can be in conjugation with a double bond or with an unshared pair of electrons already present.<sup>26</sup> One example is the synthesis developed by Leonard and co-workers,<sup>27</sup> in which tertiary amines give enamines when treated with mercuric acetate<sup>28</sup> (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  $\text{SeO}_2$  can in certain cases convert a carbonyl compound to an  $\alpha,\beta$ -unsaturated carbonyl compound by removing  $\text{H}_2$ <sup>30</sup> (though this reagent more often gives **9-16**). This reaction has been most often applied in the steroid series, an example being<sup>31</sup>



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

<sup>22</sup>See, for example, Leffingwell; Blum *Chem. Commun.* **1969**, 1151.

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

<sup>24</sup>Müller; Pautex; Hagemann *Chimia* **1988**, 42, 414.

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

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

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

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

<sup>29</sup>This reaction can also be accomplished with  $\text{I}_2$ ; Wadsworth; Detty; Murray; Weidner; Haley *J. Org. Chem.* **1984**, 49, 2676.

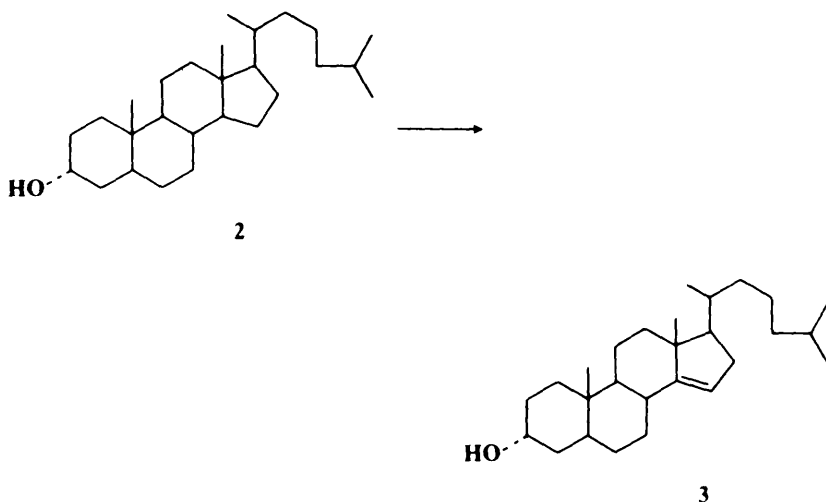
<sup>30</sup>For reviews, see Back, in Patai *The Chemistry of Organic Selenium and Tellurium Compounds*, pt. 2; Wiley: New York, 1987, pp. 91-213, pp. 110-114; Jerussi *Sel. Org. Transform.* **1970**, 1, 301-326, pp. 315-321; Trachtenberg, in Augustine, Ref. 11, pp. 166-174.

<sup>31</sup>Bernstein; Littell *J. Am. Chem. Soc.* **1960**, 82, 1235.

Similarly,  $\text{SeO}_2$  has been used to dehydrogenate 1,4-diketones<sup>32</sup> ( $\text{RCOCH}_2\text{CH}_2\text{COR} \rightarrow \text{RCOCH}=\text{CHCOR}$ ) and 1,2-diarylalkanes ( $\text{ArCH}_2\text{CH}_2\text{Ar} \rightarrow \text{ArCH}=\text{CHAr}$ ). These conversions can also be carried out by certain quinones, most notably DDQ (see 9-1).<sup>19</sup> Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone  $\rightarrow$  cyclopentenone) by  $\text{PdCl}_2$ ,<sup>33</sup> by  $\text{FeCl}_3$ ,<sup>34</sup> and by benzeneseleninic anhydride<sup>35</sup> (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<sup>36</sup> or with triphenylmethyl cation<sup>37</sup> (for another indirect method, see 7-12). Simple linear alkanes have been converted to alkenes by treatment with certain transition metal compounds.<sup>38</sup>

An entirely different approach to specific dehydrogenation has been reported by R. Breslow<sup>39</sup> and by J. E. Baldwin.<sup>40</sup> By means of this approach it was possible, for example, to convert 3 $\alpha$ -cholestanol (**2**) to 5 $\alpha$ -cholest-14-en-3 $\alpha$ -ol (**3**), thus introducing a double bond



at a specific site remote from any functional group.<sup>41</sup> This was accomplished by conversion of **2** to the ester **4**, followed by irradiation of **4**, which gave 55% **6**, which was then hydrolyzed

<sup>32</sup>For example, see Barnes; Barton *J. Chem. Soc.* **1953**, 1419.

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

<sup>34</sup>Cardinale; Laan; Russell; Ward *Recl. Trav. Chim. Pays-Bas* **1982**, 101, 199.

<sup>35</sup>Barton; Hui; Ley; Williams *J. Chem. Soc., Perkin Trans. 1* **1982**, 1919; Barton; Godfrey; Morzycki; Motherwell; Ley *J. Chem. Soc., Perkin Trans. 1* **1982**, 1947.

<sup>36</sup>Jung; Pan; Rathke; Sullivan; Woodbury *J. Org. Chem.* **1977**, 42, 3961.

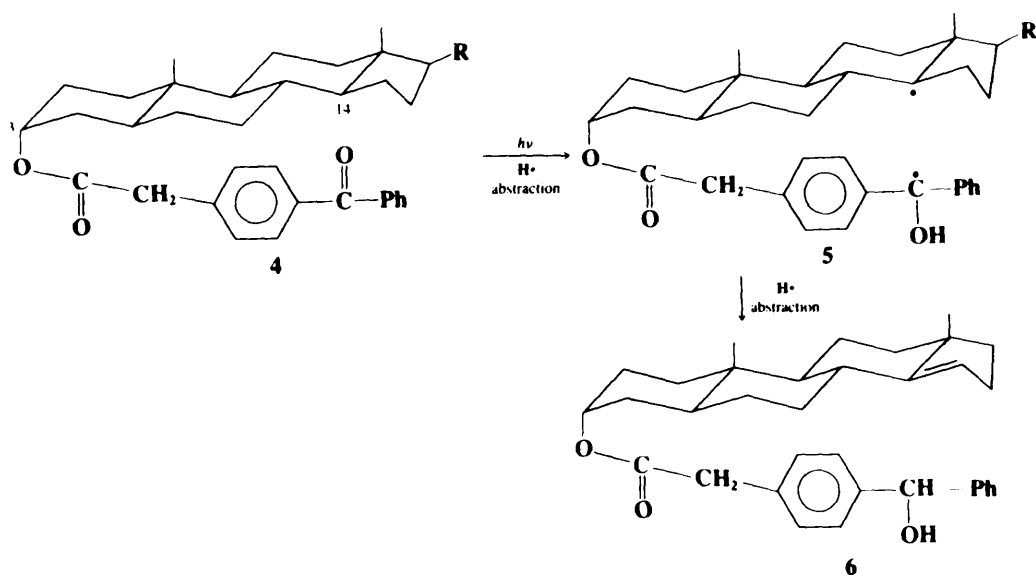
<sup>37</sup>Ryu; Murai; Hatayama; Sonoda *Tetrahedron Lett.* **1978**, 3455. For another method, which can also be applied to enol acetates, see Tsuji; Minami; Shimizu *Tetrahedron Lett.* **1983**, 24, 5635, 5639.

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

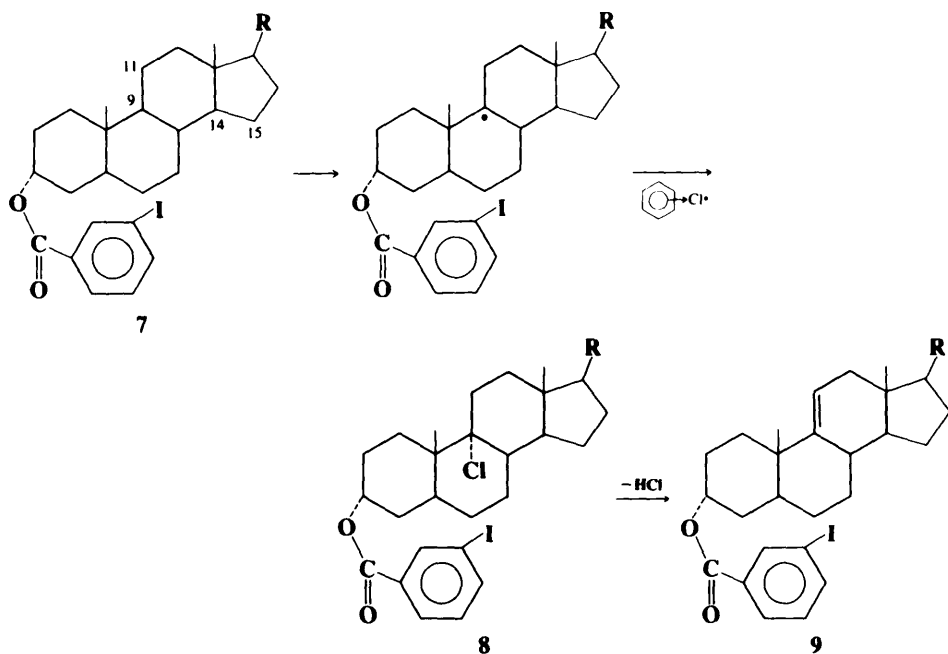
<sup>39</sup>Breslow; Baldwin *J. Am. Chem. Soc.* **1970**, 92, 732. For reviews, see Breslow *Chemtracts: Org. Chem.* **1988**, 1, 333-348; *Acc. Chem. Res.* **1980**, 13, 170-177; *Isr. J. Chem.* **1979**, 18, 187-191; *Chem. Soc. Rev.* **1972**, 1, 553-580.

<sup>40</sup>Baldwin; Bhatnagar; Harper *Chem. Commun.* **1970**, 659.

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



to **3**. The radiation excites the benzophenone portion of **4** (p. 246), which then abstracts hydrogen from the 14 position to give the diradical **5** which undergoes another internal abstraction to give **6**. In other cases, diradicals like **5** can close to a macrocyclic lactone (**9-16**). In an alternate approach,<sup>42</sup> a 9(11) double bond was introduced into a steroid nucleus by reaction of the *m*-iodo ester **7** with  $\text{PhICl}_2$  and uv light, which results in hydrogen being

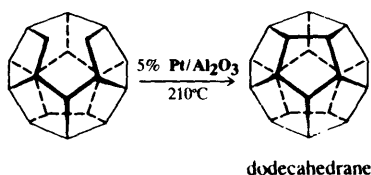


<sup>42</sup>Breslow; Corcoran; Snider; Doll; Khanna; Kaleya *J. Am. Chem. Soc.* **1977**, 99, 905. For related approaches, see Wolner *Tetrahedron Lett.* **1979**, 4613; Breslow; Heyer *J. Am. Chem. Soc.* **1982**, 104, 2045; Breslow; Guo *Tetrahedron Lett.* **1987**, 28, 3187; Breslow; Brandl; Hunger;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

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

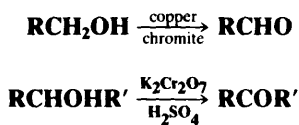
Certain 1,2-diarylalkenes  $\text{ArCH}=\text{CHAr}'$  have been converted to the corresponding alkynes  $\text{ArC}\equiv\text{CAr}'$  by treatment with *t*-BuOK in DMF.<sup>42a</sup>

A different kind of dehydrogenation was used in the final step of Paquette's synthesis of dodecahedrane:<sup>43</sup>



OS V, 428, VII, 4, 473.

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



Primary alcohols can be converted to aldehydes and secondary alcohols to ketones in four main ways:<sup>44</sup>

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

<sup>42a</sup>Akiyama; Nakatsuji; Nomura; Matsuda; Nakashima *J. Chem. Soc., Chem. Commun.* **1991**, 948.

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

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

<sup>45</sup>For thorough discussions, see Lee, Ref. 28, pp. 56-81; and (with respect to chromium and manganese reagents) House, Ref. 10, pp. 257-273.

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

<sup>47</sup>For a review, see Lee; van den Engh, in Trahanovsky, Ref. 2, pt. B, pp. 197-222.

<sup>48</sup>Bowden; Heilbron; Jones; Weedon *J. Chem. Soc.* **1946**, 39; Bowers; Halsall; Jones; Lemin *J. Chem. Soc.* **1953**, 2548.

chiral center.<sup>49</sup> The Jones reagent also oxidizes primary allylic alcohols to the corresponding aldehydes.<sup>50</sup> Three other Cr(VI) reagents commonly used<sup>51</sup> are dipyridine Cr(VI) oxide (Collins's reagent),<sup>52</sup> pyridinium chlorochromate (Corey's reagent),<sup>53</sup> and pyridinium dichromate.<sup>54</sup> MnO<sub>2</sub> is also a fairly specific reagent for OH groups and is often used to oxidize allylic alcohols to  $\alpha,\beta$ -unsaturated aldehydes or ketones. For acid-sensitive compounds CrO<sub>3</sub> in HMPA,<sup>55</sup> a CrO<sub>3</sub>-pyridine complex,<sup>56</sup> or trimethylsilyl chromates<sup>57</sup> can be used. Sodium hypochlorite in acetic acid is useful for oxidizing larger amounts of secondary alcohols.<sup>58</sup> The oxidizing agent can be supported on a polymer.<sup>59</sup> Both chromic acid<sup>60</sup> and permanganate<sup>61</sup> have been used in this way (see p. 421). Phase transfer catalysis has also been used with permanganate,<sup>62</sup> chromic acid,<sup>63</sup> and ruthenium tetroxide.<sup>64</sup> Phase transfer catalysis is particularly useful because the oxidizing agents are insoluble in most organic solvents, while the substrates are generally insoluble in water (see p. 362). Ultrasound has been used for KMnO<sub>4</sub> oxidations.<sup>65</sup>

Most of these oxidizing agents have also been used to convert primary alcohols to aldehydes, but precautions must be taken that the aldehyde is not further oxidized to the carboxylic acid (9-22).<sup>66</sup> 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:<sup>67</sup> dimethyl sulfoxide (see 9-20), Collins's reagent, Corey's reagent, pyridinium dichromate, tetrapropylammonium perruthenate Pr<sub>4</sub>N<sup>+</sup> RuO<sub>4</sub><sup>-</sup>, ceric ammonium nitrate (CAN),<sup>69</sup> Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> in water,<sup>70</sup> Ag<sub>2</sub>CO<sub>3</sub>-on-celite,<sup>71</sup> hot

<sup>49</sup>For example, see Djerassi; Hart; Warawa *J. Am. Chem. Soc.* **1964**, 86, 78.

<sup>50</sup>Harding; May; Dick *J. Org. Chem.* **1975**, 40, 1664.

<sup>51</sup>For a comparative study of Jones's, Collins's, and Corey's reagents, see Warrenner; Lee; Russell; Paddon-Row *Aust. J. Chem.* **1978**, 31, 1113.

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

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

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

<sup>55</sup>Cardillo; Orena; Sandri *Synthesis* **1976**, 394.

<sup>56</sup>Poos; Arth; Beyler; Saret *J. Am. Chem. Soc.* **1953**, 75, 422.

<sup>57</sup>Moiseenkov; Cheskis; Veselovskii; Veselovskii; Romanovich; Chizhov *J. Org. Chem. USSR* **1987**, 23, 1646.

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

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

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

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

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

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

<sup>64</sup>Morris; Kiely *J. Org. Chem.* **1987**, 52, 1149.

<sup>65</sup>Yamawaki; Sumi; Ando; Hanfusa *Chem. Lett.* **1983**, 379.

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

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

<sup>68</sup>Griffith; Ley; Whitcombe; White *J. Chem. Soc., Chem. Commun.* **1987**, 1625; Griffith; Ley *Aldrichimica Acta* **1990**, 23, 13-19.

<sup>69</sup>Trahanovsky; Young *J. Chem. Soc.* **1965**, 5777; Trahanovsky; Young; Brown *J. Org. Chem.* **1967**, 32, 3865.

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

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

$\text{HNO}_3$  in aqueous glyme,<sup>72</sup>  $\text{O}_2$ -pyridine-CuCl,<sup>73</sup>  $\text{Pb}(\text{OAc})_4$ -pyridine,<sup>74</sup> and benzoyl peroxide-NiBr<sub>2</sub>.<sup>75</sup> 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<sup>76</sup> are  $\text{Cl}_2$ -pyridine,<sup>77</sup>  $\text{H}_2\text{O}_2$ -ammonium molybdate,<sup>78</sup>  $\text{NaBrO}_3$ -CAN,<sup>79</sup> and  $\text{NaOCl}$  in  $\text{HOAc}$ ,<sup>80</sup> while  $\text{RuCl}_2(\text{PPh}_3)_3$ -benzene,<sup>81</sup> osmium tetroxide,<sup>82</sup> 2,2'-bipyridylchromium peroxide,<sup>83</sup> and  $\text{Br}_2$ -Ni(OBz)<sub>2</sub><sup>84</sup> oxidize primary OH groups in the presence of a secondary OH group.<sup>85</sup> Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in the presence of saturated alcohols by the use of potassium manganate  $\text{K}_2\text{MnO}_4$  under phase transfer conditions.<sup>86</sup> On the other hand, Fremy's salt (see 9-4) selectively oxidizes benzylic alcohols and not allylic or saturated ones.<sup>87</sup> Benzylic alcohols can also be oxidized to aldehydes by  $\text{NH}_4\text{NO}_3$  or  $\text{NaNO}_2$  in aqueous  $\text{F}_3\text{CCOOH}$ ,<sup>88</sup> by  $\text{H}_2\text{O}_2$ -HBr,<sup>89</sup> and by *m*-chloroperbenzoic acid-HCl-DMF,<sup>90</sup> among other reagents. Certain zirconocene complexes can selectively oxidize only one OH group of a diol, even if both are primary.<sup>91</sup>

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

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

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

<sup>72</sup>McKillop; Ford *Synth. Commun.* **1972**, 2, 307.

<sup>73</sup>Jallibert; Riviere *Tetrahedron Lett.* **1977**, 1215.

<sup>74</sup>Partch *Tetrahedron Lett.* **1964**, 3071; Partch; Monthey *Tetrahedron Lett.* **1967**, 4427. See also Brocksom; Ferreira *J. Chem. Res. (S)* **1980**, 412; Mihailović; Konstantinović; Vukićević *Tetrahedron Lett.* **1986**, 27, 2287.

<sup>75</sup>Doyle; Patric; Williams *J. Org. Chem.* **1979**, 44, 2955.

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

<sup>77</sup>Wicha; Zarecki *Tetrahedron Lett.* **1974**, 3059.

<sup>78</sup>Trost; Masuyama *Isr. J. Chem.* **1984**, 24, 134. For a method involving  $\text{H}_2\text{O}_2$  and another catalyst, see Sakata; Ishii *J. Org. Chem.* **1991**, 56, 6233.

<sup>79</sup>Tomioka; Oshima; Nozaki *Tetrahedron Lett.* **1982**, 23, 539.

<sup>80</sup>Stevens; Chapman; Stubbs; Tam; Albizzati *Tetrahedron Lett.* **1982**, 23, 4647.

<sup>81</sup>Tomioka; Takai; Oshima; Nozaki *Tetrahedron Lett.* **1981**, 22, 1605.

<sup>82</sup>Maione; Romeo *Synthesis* **1984**, 955.

<sup>83</sup>Firouzabadi; Iranpoor; Kiaeezadeh; Toofan *Tetrahedron* **1986**, 42, 719.

<sup>84</sup>Doyle; Bagheri *J. Org. Chem.* **1981**, 46, 4806; Doyle; Dow; Bagheri; Patric *J. Org. Chem.* **1983**, 48, 476.

<sup>85</sup>For a list of references to the selective oxidation of various types of alcohol, see Kulkarni; Mathew *Tetrahedron* **1990**, 31, 4497.

<sup>86</sup>Kim; Chung; Cho; Hahn *Tetrahedron Lett.* **1989**, 30, 2559. See also Kim; Song; Lee; Hahn *Tetrahedron Lett.* **1986**, 27, 2875.

<sup>87</sup>Morey; Dzielenziak; Saa *Chem. Lett.* **1985**, 263.

<sup>88</sup>Rodkin; Shtern; Cheprakov; Makhon'kov; Mardaleishvili; Beletskaya *J. Org. Chem. USSR* **1988**, 24, 434.

<sup>89</sup>Dakka; Sasson *Bull. Soc. Chim. Fr.* **1988**, 756.

<sup>90</sup>Kim; Jung; Kim; Ryu *Synth. Commun.* **1990**, 20, 637.

<sup>91</sup>Nakano; Terada; Ishii; Ogawa *Synthesis* **1986**, 774.

<sup>92</sup>Sheikh; Eadon *Tetrahedron Lett.* **1972**, 257.

<sup>93</sup>Krafft; Zorc *J. Org. Chem.* **1986**, 51, 5482.

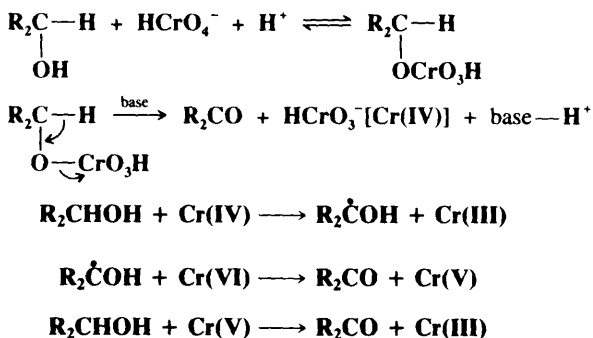
<sup>94</sup>Choudary; Reddy; Kantam; Jamil *Tetrahedron Lett.* **1985**, 26, 6257.

<sup>95</sup>For a review, see Djerassi *Org. React.* **1951**, 6, 207-272.

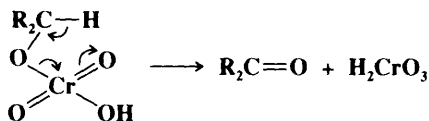
lective oxidizing agents and often oxidize OH groups without disturbing other oxidizable groups.<sup>96</sup> N-Bromosuccinimide does not oxidize aliphatic primary alcohols, but N-chlorosuccinimide does. With these reagents it is often possible to oxidize only one of several OH groups that may be present in a molecule. The combination of N-iodosuccinimide and  $\text{Bu}_4\text{N}^+ \text{I}^-$  oxidizes primary (to aldehydes) and secondary alcohols in high yields.<sup>97</sup>

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

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



The base in the second step may be water, though it is also possible<sup>100</sup> that in some cases no external base is involved and that the proton is transferred directly to one of the  $\text{CrO}_3\text{H}$



oxygens in which case the Cr(IV) species produced would be  $\text{H}_2\text{CrO}_3$ . Part of the evidence for this mechanism was the isotope effect of about 6 found on use of  $\text{MeCDOHMe}$ , showing that the  $\alpha$  hydrogen is removed in the rate-determining step.<sup>101</sup> Note that, as in 4-6, the substrate is oxidized by three different oxidation states of chromium.<sup>102</sup>

<sup>96</sup>For a review, see Filler *Chem. Rev.* **1963**, 63, 21-43, pp. 22-28.

<sup>97</sup>Hanessian; Wong; Therien *Synthesis* **1981**, 394.

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

<sup>99</sup>Westheimer *Chem. Rev.* **1949**, 45, 419-451, p. 434; Holloway; Cohen; Westheimer *J. Am. Chem. Soc.* **1951**, 73, 65.

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

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

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

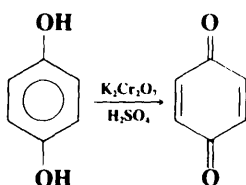
With other oxidizing agents, mechanisms are less clear.<sup>103</sup> It seems certain that some oxidizing agents operate by a hydride-shift mechanism,<sup>104</sup> e.g., dehydrogenation with triphenylmethyl cation<sup>105</sup> and the Oppenauer oxidation, and some by a free-radical mechanism, e.g., oxidation with  $\text{S}_2\text{O}_8^{2-}$ <sup>106</sup> and with  $\text{VO}_2^+$ .<sup>107</sup> A summary of many proposed mechanisms is given by Littler.<sup>108</sup>

Secondary alkyl ethers can be oxidized to ketones by bromine (e.g.,  $\text{Me}_2\text{CHOCHMe}_2 + \text{Br}_2 \rightarrow \text{Me}_2\text{CO}$ ).<sup>109</sup> Primary alkyl ethers give carboxylic acids (**9-22**) with bromine, but can be cleaved to aldehydes with 1-chlorobenzotriazole.<sup>110</sup>

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

## 9-4 Oxidation of Phenols and Aromatic Amines to Quinones

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



Ortho and para diols are easily oxidized to *ortho*- and *para*-quinones, respectively.<sup>111</sup> Either or both OH groups can be replaced by  $\text{NH}_2$  groups to give the same products, though for the preparation of *ortho*-quinones only OH groups are normally satisfactory. The reaction has been successfully carried out with other groups para to OH or  $\text{NH}_2$ ; halogen, OR, Me, *t*-Bu, and even H, though with the last yields are poor. Many oxidizing agents have been used: acid dichromate,<sup>112</sup> silver oxide, silver carbonate, lead tetraacetate,  $\text{HIO}_4$ , and atmospheric oxygen, to name a few. A particularly effective reagent for rings with only one OH or  $\text{NH}_2$  group is  $(\text{KSO}_3)_2\text{N}-\text{O}^\bullet$  (dipotassium nitrosodisulfonate; Fremy's salt), which is a stable free radical.<sup>113</sup> Phenols, even some whose para positions are unoccupied, can be oxidized to *ortho*-quinones with diphenylseleninic anhydride.<sup>114</sup>

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

<sup>104</sup>See Barter; Littler *J. Chem. Soc. B* **1967**, 205. For evidence that oxidation by  $\text{HNO}_2$  involves a hydride shift, see Moodie; Richards *J. Chem. Soc., Perkin Trans. 2* **1986**, 1833; Ross; Gu; Hum; Malhotra *Int. J. Chem. Kinet.* **1986**, 18, 1277.

<sup>105</sup>Bonthrone; Reid *J. Chem. Soc.* **1959**, 2773.

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

<sup>107</sup>Littler; Waters *J. Chem. Soc.* **1959**, 4046.

<sup>108</sup>Littler *J. Chem. Soc.* **1962**, 2190.

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

<sup>110</sup>Pojer *Aust. J. Chem.* **1980**, 32, 2787.

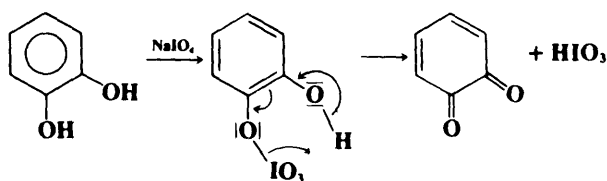
<sup>111</sup>For reviews, see Haines-1988, Ref. 11, pp. 305-323, 438-447; Naruta; Maruyama in Patai, Rappoport, Ref. 18, pt. 1, pp. 247-276; Thomson, in Patai, Ref. 18, pt. 1, pp. 112-132.

<sup>112</sup>For a review of this oxidation with chromium reagents, see Cainelli; Cardillo, Ref. 10, pp. 92-117.

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

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

Less is known about the mechanism than is the case for **9-3**, but, as in that case, it seems to vary with the oxidizing agent. For oxidation of catechol with  $\text{NaIO}_4$ , it was found that the reaction conducted in  $\text{H}_2^{18}\text{O}$  gave unlabeled quinone,<sup>115</sup> so the following mechanism<sup>116</sup> was proposed:

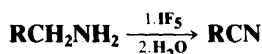


When catechol was oxidized with  $\text{MnO}_4^-$  under aprotic conditions, a semiquinone radical ion intermediate was involved.<sup>117</sup> For autoxidations (i.e., with atmospheric oxygen) a free-radical mechanism is known to operate.<sup>118</sup>

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

## 9-5 Dehydrogenation of Amines

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



Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out with a variety of reagents, among others,  $\text{IF}_5$ ,<sup>119</sup> lead tetraacetate,<sup>120</sup> nickel peroxide,<sup>121</sup>  $\text{NaOCl}$  in micelles,<sup>122</sup>  $\text{K}_2\text{S}_2\text{O}_8\text{-NiSO}_4$ ,<sup>123</sup> and  $\text{CuCl-O}_2\text{-pyridine}$ .<sup>124</sup> Several methods have been reported for the dehydrogenation of secondary amines to imines.<sup>125</sup> Among them<sup>126</sup> are treatment with (1) iodosylbenzene  $\text{PhIO}$  alone or in the presence of a ruthenium complex,<sup>127</sup> (2)  $\text{Me}_2\text{SO}$  and oxalyl chloride,<sup>128</sup> and (3)  $t\text{-BuOOH}$  and a rhenium catalyst.<sup>129</sup>

A reaction that involves dehydrogenation to an imine which then reacts further is the reaction of primary or secondary amines with palladium black.<sup>130</sup> The imine initially formed by the dehydrogenation reacts with another molecule of the same or a different amine to give an aminal, which loses  $\text{NH}_3$  or  $\text{RNH}_2$  to give a secondary or tertiary amine. An example

<sup>115</sup>Adler; Falkehag; Smith *Acta Chem. Scand.* **1962**, 16, 529.

<sup>116</sup>This mechanism is an example of category 4 (p. 1160).

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

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

<sup>119</sup>Stevens *J. Org. Chem.* **1961**, 26, 2531.

<sup>120</sup>Stojiljković; Andrejević; Mihailović *Tetrahedron* **1967**, 23, 721.

<sup>121</sup>Nakagawa; Tsuji *Chem. Pharm. Bull.* **1963**, 11, 296. See also Xu; Yamaguchi; Tanabe *Chem. Lett.* **1988**, 281.

<sup>122</sup>Juršić *J. Chem. Res. (S)* **1988**, 168.

<sup>123</sup>Yamazaki; Yamazaki *Bull. Chem. Soc. Jpn.* **1990**, 63, 301.

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

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

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

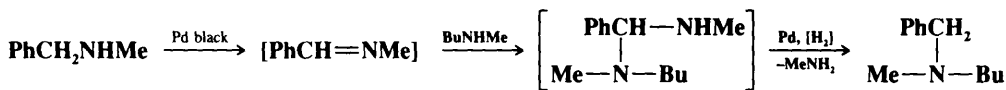
<sup>127</sup>Müller; Gilbert *Tetrahedron* **1988**, 44, 7171.

<sup>128</sup>Keirs; Overton *J. Chem. Soc., Chem. Commun.* **1987**, 1660.

<sup>129</sup>Murahashi; Naota; Taki *J. Chem. Soc., Chem. Commun.* **1985**, 613.

<sup>130</sup>Murahashi; Yoshimura; Tsumiyama; Kojima *J. Am. Chem. Soc.* **1983**, 105, 5002. See also Wilson; Laine *J. Am. Chem. Soc.* **1985**, 107, 361.

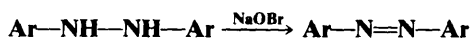
is the reaction between N-methylbenzylamine and butylmethylamine, which produces 95% N-methyl-N-butylbenzylamine.



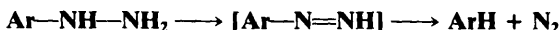
Another method for the conversion of primary to secondary amines ( $2\text{RNH}_2 \rightarrow \text{R}_2\text{NH}$ ) involves treatment with a catalytic amount of sodium hydride.<sup>131</sup> This reaction also involves an imine intermediate.

## 9-6 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines

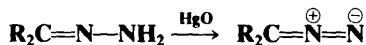
### 1/N,2/N-Dihydro-elimination



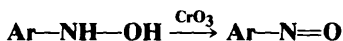
N,N'-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, HgO,<sup>132</sup>  $\text{K}_3\text{Fe}(\text{CN})_6$  under phase transfer conditions,<sup>133</sup> benzeneseleninic anhydride,<sup>134</sup>  $\text{MnO}_2$  (this reagent yields cis azobenzenes),<sup>135</sup>  $\text{CuCl}_2$ , and air and NaOH.<sup>136</sup> 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,<sup>137</sup> but these are unstable and decompose to nitrogen and the hydrocarbon:



When hydrazones are oxidized with HgO,  $\text{Ag}_2\text{O}$ ,  $\text{MnO}_2$ , lead tetraacetate, or certain other oxidizing agents, diazo compounds are obtained<sup>138</sup> (see also 7-28):



Hydrazones of the form  $\text{ArCH}=\text{NNH}_2$  react with HgO in solvents such as diglyme or ethanol to give nitriles  $\text{ArCN}$ .<sup>139</sup> Aromatic hydroxylamines are easily oxidized to nitroso compounds, most commonly by acid dichromate.<sup>140</sup>



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.

<sup>131</sup>Richey; Erickson *Tetrahedron Lett.* **1972**, 2807; Erickson; Richey *Tetrahedron Lett.* **1972**, 2811.

<sup>132</sup>For a review, see Newbold, in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1; Wiley: New York, 1975, pp. 543-557, 564-573.

<sup>133</sup>Dimroth; Tüncher *Synthesis* **1977**, 339.

<sup>134</sup>Barton; Lester; Ley *J. Chem. Soc., Chem. Commun.* **1978**, 276; Back *J. Chem. Soc., Chem. Commun.* **1978**, 278.

<sup>135</sup>Hyatt *Tetrahedron Lett.* **1977**, 141.

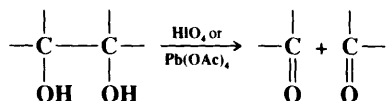
<sup>136</sup>For a review, see Newbold, in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1; Wiley: New York, 1975, pp. 543-557, 564-573.

<sup>137</sup>See Mannen; Itano *Tetrahedron* **1973**, 29, 3497.

<sup>138</sup>For a review, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 233-256.

<sup>139</sup>Mobbs; Suschitzky *Tetrahedron Lett.* **1971**, 361.

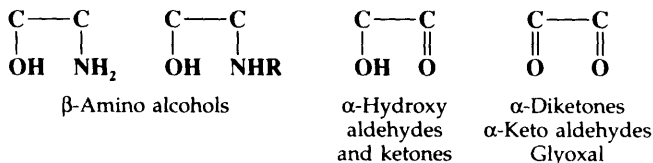
<sup>140</sup>For a review, see Hudlicky. Ref. 11, pp. 231-232.

**B. Oxidations Involving Cleavage of Carbon–Carbon Bonds<sup>141</sup>****9-7 Oxidative Cleavage of Glycols and Related Compounds****2/O-De-hydrogen-uncoupling**

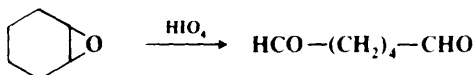
1,2-Glycols are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.<sup>142</sup> The products are 2 moles of aldehyde, or 2 moles of ketone, or 1 mole of each, depending on the groups attached to the two carbons. The yields are so good that olefins are often converted to glycols (**5-35**) and then cleaved with  $\text{HIO}_4$  or  $\text{Pb(OAc)}_4$  rather than being cleaved directly with ozone (**9-9**) or dichromate or permanganate (**9-10**). A number of other oxidizing agents also give the same products, among them<sup>143</sup> activated  $\text{MnO}_2$ ,<sup>144</sup> thallium(III) salts,<sup>145</sup> pyridinium chlorochromate,<sup>146</sup> and  $\text{O}_2$  catalyzed by  $\text{Co(III)}$  salts.<sup>147</sup> Permanganate, dichromate, and several other oxidizing agents<sup>148</sup> 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.<sup>149</sup>

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

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



$\alpha$ -Diketones and  $\alpha$ -hydroxy ketones are also cleaved by alkaline  $\text{H}_2\text{O}_2$ .<sup>150</sup>  $\text{HIO}_4$  has been used to cleave epoxides to aldehydes,<sup>151</sup> e.g.,



<sup>141</sup>For a review, see Bentley, in Bentley; Kirby, Ref. 12, pp. 137-254.

<sup>142</sup>For reviews covering both reagents, see Haines-1988, Ref. 11, pp. 277-301, 432-437; House, Ref. 10, pp. 3353-363; Perlin, in Augustine *Oxidation*, vol. 1; Marcel Dekker: New York, 1969, pp. 189-212; Bunton, in Wiberg, Ref. 2, pp. 367-407. For reviews of lead tetraacetate, see Rubottom, Ref. 10; Aylward, Ref. 10. For reviews of  $\text{HIO}_4$ , see Fatiadi, Ref. 10; Sklarz, Ref. 10.

<sup>143</sup>For a list of reagents, with references, see Ref. 21, pp. 615-616.

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

<sup>145</sup>McKillop; Raphael; Taylor *J. Org. Chem.* **1972**, 37, 4204.

<sup>146</sup>Cisneros; Fernández; Hernández *Synth. Comm.* **1982**, 12, 833.

<sup>147</sup>de Vries; Schors *Tetrahedron Lett.* **1968**, 5689.

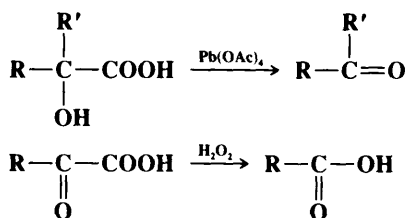
<sup>148</sup>For a list of reagents, with references, see Ref. 21, pp. 836-837.

<sup>149</sup>For a review, see Shono *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer: New York, 1984, pp. 31-37. See also Ruhoff; Schäfer *Synthesis* **1988**, 54.

<sup>150</sup>See, for example, Ogata; Sawaki; Shiroyama *J. Org. Chem.* **1977**, 42, 4061.

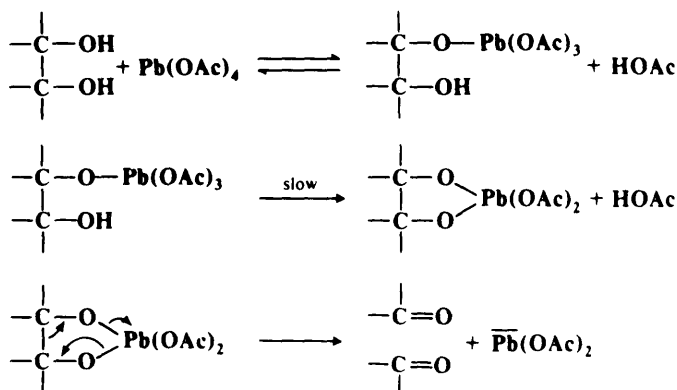
<sup>151</sup>Nagarkatti; Ashley *Tetrahedron Lett.* **1973**, 4599.

$\alpha$ -Hydroxy acids and  $\alpha$ -keto acids are not cleaved by  $\text{HIO}_4$  but are cleaved by  $\text{Pb}(\text{OAc})_4$ , alkaline  $\text{H}_2\text{O}_2$ , and other reagents. These are oxidative decarboxylations.  $\alpha$ -Hydroxy acids give aldehydes or ketones, and  $\alpha$ -keto acids give carboxylic acids:

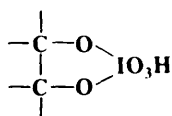


Also see 9-13 and 9-14.

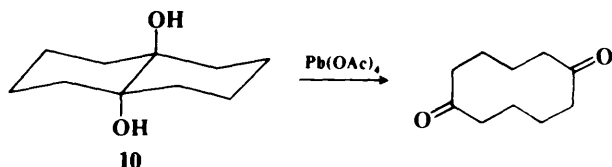
The mechanism of glycol oxidation with  $\text{Pb}(\text{OAc})_4$  was proposed by Criegee:<sup>152</sup>



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.<sup>153</sup> For periodic acid the mechanism is similar, with the intermediate<sup>154</sup>



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

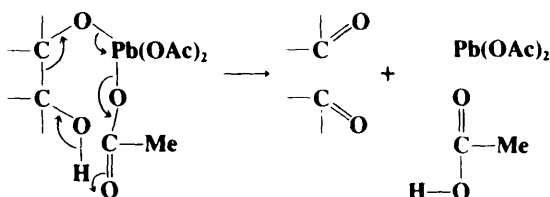


<sup>152</sup>Criegee; Kraft; Rank *Liebigs Ann. Chem.* **1933**, 507, 159. For reviews, see Waters, Ref. 2, pp. 72-81; Stewart, Ref. 2, pp. 97-106.

<sup>153</sup>For example, see Criegee; Höger; Huber; Kruck; Marktscheffel; Schellenberger *Liebigs Ann. Chem.* **1956**, 599, 81.

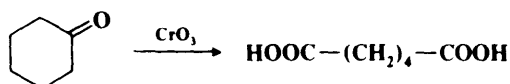
<sup>154</sup>Buist; Bunton; Miles *J. Chem. Soc.* **1959**, 743; Buist; Bunton; Hipperson *J. Chem. Soc. B* **1971**, 2128.

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



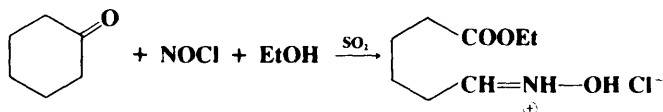
OS IV, 124; VII, 185; **68**, 162.

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

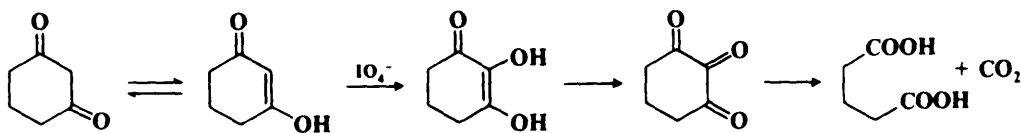


Oxidative cleavage of open-chain ketones or alcohols<sup>156</sup> is seldom a useful preparative procedure, not because these compounds do not undergo oxidation (they do, except for diaryl ketones) but because the result is generally a hopeless mixture. However, the reaction is quite useful for cyclic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

Cyclic ketones can also be cleaved by treatment with NOCl and an alcohol in liquid SO<sub>2</sub> to give an  $\omega$ -oximinocarboxylic ester, e.g.,<sup>159</sup>



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



<sup>155</sup>Angyal; Young *J. Am. Chem. Soc.* **1959**, *81*, 5251.

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

<sup>157</sup>Wallace; Pobiner; Schriesheim *J. Org. Chem.* **1965**, *30*, 3768. See also Osowska-Pacwicka; Alper *J. Org. Chem.* **1988**, *53*, 808.

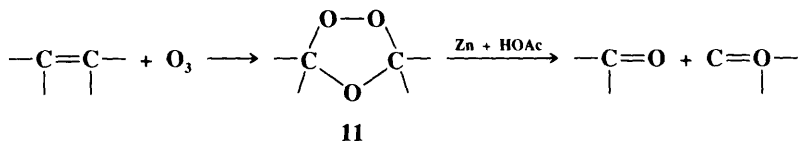
<sup>158</sup>Lissel; Dehmloew *Tetrahedron Lett.* **1978**, 3689; Sotiriou; Lee; Giese *J. Org. Chem.* **1990**, *55*, 2159.

<sup>159</sup>Rogić; Vitrone; Swerdloff *J. Am. Chem. Soc.* **1977**, *99*, 1156; Moorhoff; Paquette *J. Org. Chem.* **1991**, *56*, 703.

<sup>160</sup>Wolfrom; Bobbitt *J. Am. Chem. Soc.* **1956**, *78*, 2489.

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

### 9-9 Ozonolysis Oxo-uncoupling



When compounds containing double bonds are treated with ozone, usually at low temperatures, they are converted to compounds called *ozonides* (**11**) that can be isolated but, because some of them are explosive, are more often decomposed with zinc and acetic acid or catalytic hydrogenation to give 2 moles of aldehyde, or 2 moles of ketone, or 1 mole of each, depending on the groups attached to the olefin.<sup>161</sup> The decomposition of **11** has also been carried out with many other reducing agents, among them trimethyl phosphite,<sup>162</sup> thiourea,<sup>163</sup> and dimethyl sulfide.<sup>164</sup> However, ozonides can also be *oxidized* with oxygen, peracids, or H<sub>2</sub>O<sub>2</sub> to give ketones and/or carboxylic acids or *reduced* with LiAlH<sub>4</sub>, NaBH<sub>4</sub>, BH<sub>3</sub>, or catalytic hydrogenation with excess H<sub>2</sub> to give 2 moles of alcohol.<sup>165</sup> Ozonides can also be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines,<sup>166</sup> or with an alcohol and anhydrous HCl to give the corresponding carboxylic esters.<sup>167</sup> Ozonolysis is therefore an important synthetic reaction.

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

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

<sup>162</sup>Knowles; Thompson *J. Org. Chem.* **1960**, *25*, 1031.

<sup>163</sup>Gupta; Soman; Dev *Tetrahedron* **1982**, *38*, 3013.

<sup>164</sup>Pappas; Keaveney; Gancher; Berger *Tetrahedron Lett.* **1966**, 4273.

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

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

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

<sup>168</sup>Pryor; Giamalva; Church *J. Am. Chem. Soc.* **1983**, *105*, 6858, **1985**, *107*, 2793.

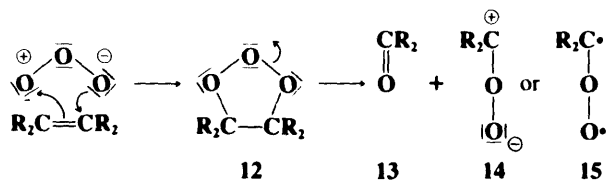
<sup>169</sup>See, for example, Bailey; Lane *J. Am. Chem. Soc.* **1967**, *89*, 4473; Gillies *J. Am. Chem. Soc.* **1975**, *97*, 1276; Bailey; Hwang; Chiang *J. Org. Chem.* **1985**, *50*, 231.

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

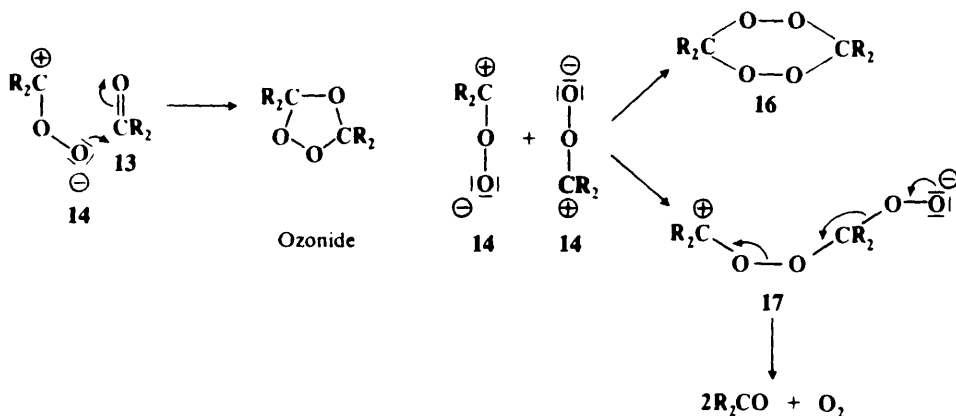
<sup>171</sup>See, for example, Wibaut; Sixma *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 761; Williamson; Cvetanović *J. Am. Chem. Soc.* **1968**, *90*, 4248; Razumovskii; Zaikov *J. Org. Chem. USSR* **1972**, *8*, 468, 473; Klutsch; Fliszár *Can. J. Chem.* **1972**, *50*, 2841.

and prefers double to triple bonds (p. 748). Compounds that contain triple bonds generally give carboxylic acids, though sometimes ozone oxidizes them to  $\alpha$ -diketones (**9-27**). Aromatic compounds are also attacked less readily than olefins, but have often been cleaved. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives 3 moles of glyoxal ( $\text{HCOCHO}$ ), 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.<sup>172</sup>

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



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



<sup>172</sup>Dobinson; Bailey *Tetrahedron Lett.* **1960** (No. 13) 14; O'Murchu *Synthesis* **1989**, 880.

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

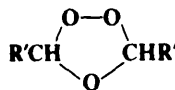
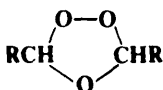
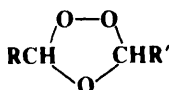
<sup>174</sup>Gillies; Gillies; Suenram; Lovas *J. Am. Chem. Soc.* **1988**, *110*, 7991. See also Criegee; Schröder *Chem. Ber.* **1960**, *93*, 689; Durham; Greenwood *J. Org. Chem.* **1968**, *33*, 1629; Bailey; Carter; Fischer; Thompson *Can. J. Chem.* **1973**, *51*, 1278; Hisatsune; Shinoda; Heicklen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

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

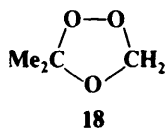
kind of dimerization to **17**.<sup>176</sup> If the first path is taken (this is normally possible only if **13** is an aldehyde; most ketones do not do this<sup>177</sup>), hydrolysis of the ozonide gives the normal products. If **16** is formed, hydrolysis of it gives one of the products, and of course **13**, which then does not undergo further reaction, is the other. **17**, if formed, can decompose directly, as shown, to give the normal products and oxygen. In protic solvents, **14** is converted to a hydroperoxide, and these have been isolated, for example,  $\text{Me}_2\text{C}(\text{OOH})\text{OMe}$  from  $\text{Me}_2\text{C}=\text{CMe}_2$



in methanol. Further evidence for the mechanism is that **16** can be isolated in some cases, e.g., from  $\text{Me}_2\text{C}=\text{CMe}_2$ . But perhaps the most impressive evidence comes from the detection of cross products. In the Criegee mechanism, the two parts of the original olefin break apart and then recombine to form the ozonide. In the case of an unsymmetrical olefin  $\text{RCH}=\text{CHR}'$  there should be three ozonides:



since there are two different aldehydes **13** and two different species **14**, and these can recombine in the three ways shown. Actually six ozonides, corresponding to the cis and trans forms of these three, were isolated and characterized for methyl oleate.<sup>178</sup> Similar results have been reported for smaller olefins, e.g., 2-pentene, 4-nonene, and even 2-methyl-2-pentene.<sup>179</sup> The last-mentioned case is especially interesting, since it is quite plausible that this compound would cleave in only one way, so that only one ozonide (in cis and trans versions) would be found; but this is not so, and three were found for this case too. However, terminal olefins give little or no cross ozonide formation.<sup>180</sup> In general, the less alkylated end of the olefin tends to go to **13** and the other to **14**. Still other evidence<sup>181</sup> for the Criegee mechanism is: (1) When  $\text{Me}_2\text{C}=\text{CMe}_2$  was ozonized in the presence of  $\text{HCHO}$ , the ozonide **18** could be isolated;<sup>182</sup> (2) **14** prepared in an entirely different manner (photooxidation of



diazo compounds), reacted with aldehydes to give ozonides;<sup>183</sup> and (3) cis and trans olefins generally give the same ozonide, which would be expected if they cleave first.<sup>184</sup> However,

<sup>176</sup>Fliszár; Gravel; Cavalieri *Can. J. Chem.* **1966**, *44*, 67, 1013; Fliszár; Chylińska *Can. J. Chem.* **1967**, *45*, 29, 1968, 46, 783.

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

<sup>178</sup>Riezbos; Grimmelikhuisen; van Dorp *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1234; Privett; Nickell *J. Am. Oil Chem. Soc.* **1964**, *41*, 72.

<sup>179</sup>Loan; Murray; Story *J. Am. Chem. Soc.* **1965**, *87*, 737; Lorenz; Parks *J. Org. Chem.* **1965**, *30*, 1976.

<sup>180</sup>Murray; Williams *J. Org. Chem.* **1969**, *34*, 1891.

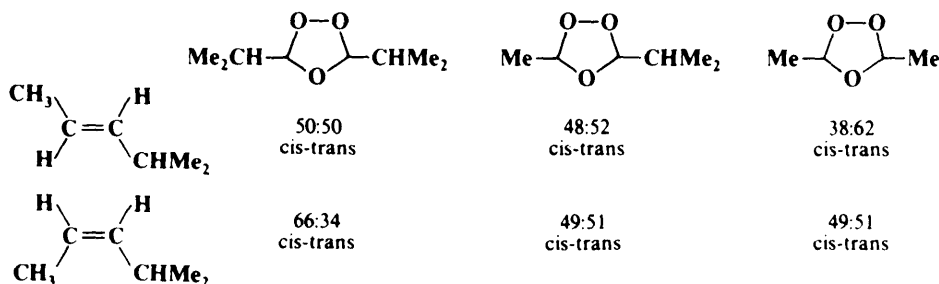
<sup>181</sup>For further evidence, see Keul; Choi; Kuczkowski *J. Org. Chem.* **1985**, *50*, 3365; Mori; Nojima; Kusabayashi *J. Am. Chem. Soc.* **1987**, *109*, 4407; Pierrot; El Idrissi; Santelli *Tetrahedron Lett.* **1989**, *30*, 461; Wojciechowski; Chiang; Kuczkowski *J. Org. Chem.* **1990**,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

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

<sup>183</sup>Murray; Suzui *J. Am. Chem. Soc.* **1973**, *95*, 3343; Higley; Murray *J. Am. Chem. Soc.* **1974**, *96*, 3330.

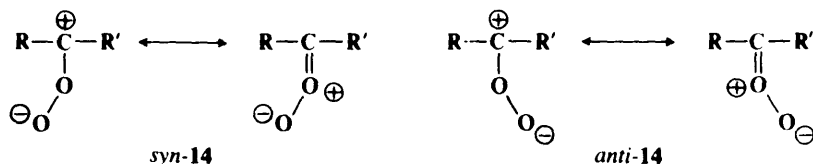
<sup>184</sup>See, for example, Murray; Williams *J. Org. Chem.* **1969**, *34*, 1896.

this was not true for  $\text{Me}_3\text{CCH}=\text{CHCMe}_3$ , where the *cis* olefin gave the *cis* ozonide (chiefly), and the *trans* gave the *trans*.<sup>185</sup> 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.<sup>186</sup>



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

The above stereochemical results have been explained<sup>187</sup> on the basis of the Criegee mechanism with the following refinements: (1) The formation of **12** is stereospecific, as expected from a 1,3 dipolar cycloaddition. (2) Once they are formed, **14** and **13** remain attracted to each other, much like an ion pair. (3) **14** exists in *syn* and *anti* forms, which are produced in different amounts and can hold their shapes, at least for a time. This is



plausible if we remember that a  $\text{C}=\text{O}$  canonical form contributes to the structure of **14**. (4) The combination of **14** and **13** is also a 1,3 dipolar cycloaddition, so configuration is retained in this step too.<sup>188</sup>

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

<sup>185</sup>Schröder *Chem. Ber.* **1962**, 95, 733; Kolsaker *Acta Chem. Scand., Ser. B* **1978**, 32, 557.

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

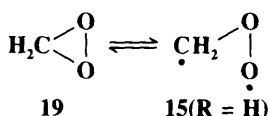
<sup>187</sup>Bauld; Thompson; Hudson; Bailey *J. Am. Chem. Soc.* **1968**, 90, 1822; Bailey; Ferrell *J. Am. Chem. Soc.* **1978**, 100, 899; Keul; Kuczkowski *J. Am. Chem. Soc.* **1985**, 50, 3371.

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

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

<sup>190</sup>Mile; Morris *J. Chem. Soc., Chem. Commun.* **1978**, 263.

The ozonolysis of ethylene in the liquid phase (without a solvent) was shown to take place by the Criegee mechanism.<sup>191</sup> This reaction has been used to study the structure of the intermediate **14** or **15**. The compound dioxirane (**19**) was identified in the reac-



tion mixture<sup>192</sup> at low temperatures and is probably in equilibrium with the biradical **15** (R = H).

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

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

## 9-10 Oxidative Cleavage of Double Bonds and Aromatic Rings

**Oxo-de-alkylidene-bisubstitution**, etc.



Double bonds can be cleaved by many oxidizing agents,<sup>195</sup> the most common of which are neutral or acid permanganate and acid dichromate. The products are generally 2 moles of ketone, 2 moles of carboxylic acid, or 1 mole of each, depending on what groups are attached to the olefin. With ordinary solutions of permanganate or dichromate yields are generally low, and the reaction is seldom a useful synthetic method; but high yields can be obtained by oxidizing with KMnO<sub>4</sub> dissolved in benzene containing the crown ether dicyclohexano-18-crown-6 (see p. 82).<sup>196</sup> The crown ether coordinates with K<sup>+</sup>, permitting the KMnO<sub>4</sub> to dissolve in benzene. Another reagent frequently used for synthetic purposes is the *Lemieux-von Rudloff reagent*: HIO<sub>4</sub> containing a trace of MnO<sub>4</sub><sup>-</sup>.<sup>197</sup> The MnO<sub>4</sub><sup>-</sup> is the actual oxidizing agent, being reduced to the manganate stage, and the purpose of the HIO<sub>4</sub> is to reoxidize the manganate back to MnO<sub>4</sub><sup>-</sup>. Another reagent that behaves similarly is NaIO<sub>4</sub>-ruthenium tetroxide.<sup>198</sup>

<sup>191</sup>Fong; Kuczkowski *J. Am. Chem. Soc.* **1980**, 102, 4763.

<sup>192</sup>Sucram; Lovas *J. Am. Chem. Soc.* **1978**, 100, 5117. See, however, Ishiguro; Hirano; Sawaki *J. Org. Chem.* **1988**, 53, 5397.

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

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

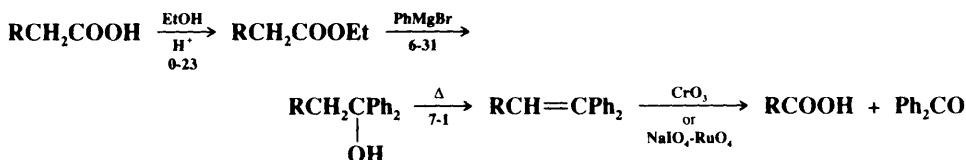
<sup>195</sup>For a review of the oxidation of C=C and C=N bonds, see Henry; Lange, in Patai, Ref. 103, pp. 965-1098. For a review of oxidative cleavages of C=C double bonds and aromatic rings, see Hudlický, Ref. 11, pp. 77-84, 96-98. For reviews with respect to chromium reagents, see Badanyan; Minasyan;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

<sup>196</sup>Sam; Simmons *J. Am. Chem. Soc.* **1972**, 94, 4024. See also Lee; Chang *J. Org. Chem.* **1978**, 43, 1532.

<sup>197</sup>Lemicux; Rudloff *Can. J. Chem.* **1955**, 33, 1701, 1710; Rudloff *Can. J. Chem.* **1955**, 33, 1714, **1956**, 34, 1413, **1965**, 43, 1784.

<sup>198</sup>For a review, see Lee; van den Engh, in Trahanovsky, Ref. 2, pt. B, pp. 186-192. For the use of NaIO<sub>4</sub>-OsO<sub>4</sub>, see Cainelli; Contento; Manescalchi; Plessi *Synthesis* **1989**, 47.

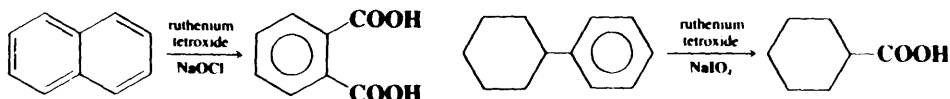
The *Barbier–Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage by acid dichromate ( $\text{NaIO}_4$ –ruthenium tetroxide has also been used), but this is cleavage of a 1,1-diphenyl olefin, which generally gives good yields:



With certain reagents, the oxidation of double bonds can be stopped at the aldehyde stage, and in these cases the products are the same as in the ozonolysis procedure. Among these reagents are chromyl trichloroacetate,<sup>199</sup> *t*-butyl iodoxybenzene,<sup>200</sup>  $\text{KMnO}_4$  in  $\text{THF-H}_2\text{O}$ ,<sup>201</sup> and  $\text{NaIO}_4$ – $\text{OsO}_4$ .<sup>202</sup> Enol ethers  $\text{RC(OR')=CH}_2$  have been cleaved to carboxylic esters  $\text{RC(OR')=O}$  by atmospheric oxygen.<sup>203</sup>

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (5-35) or cyclic ester,<sup>204</sup> and then further oxidation as in 9-7.<sup>205</sup> In line with the electrophilic attack on the olefin, triple bonds are more resistant to oxidation than double bonds. Terminal triple-bond compounds can be cleaved to carboxylic acids ( $\text{RC}\equiv\text{CH} \rightarrow \text{RCOOH}$ ) with thallium(III) nitrate<sup>206</sup> or with [bis(trifluoroacetoxy)iido]pentafluorobenzene  $\text{C}_6\text{F}_5\text{I(OCOCF}_3)_2$ ,<sup>207</sup> among other reagents.

Aromatic rings can be cleaved with strong enough oxidizing agents. An important laboratory reagent for this purpose is ruthenium tetroxide along with a cooxidant such as  $\text{NaIO}_4$  or  $\text{NaOCl}$  (household bleach can be used).<sup>208</sup> Examples<sup>209</sup> are the oxidation of naphthalene to phthalic acid<sup>210</sup> and, even more remarkably, of cyclohexylbenzene to cyclohexanecar-



boxylic acid<sup>211</sup> (note the contrast with 9-11). The latter conversion was also accomplished with ozone.<sup>212</sup> Another reagent that oxidizes aromatic rings is air catalyzed by  $\text{V}_2\text{O}_5$ . The

<sup>199</sup>Schildknecht; Föttinger *Liebigs Ann. Chem.* **1962**, 659, 20.

<sup>200</sup>Ranganathan; Ranganathan; Singh *Tetrahedron Lett.* **1985**, 26, 4955.

<sup>201</sup>Viski; Szeverényi; Simándi *J. Org. Chem.* **1986**, 51, 3213.

<sup>202</sup>Pappo; Allen; Lemieux; Johnson *J. Org. Chem.* **1956**, 21, 478.

<sup>203</sup>Taylor *J. Chem. Res. (S)* **1987**, 178. For a similar oxidation with  $\text{RuO}_4$ , see Torii; Inokuchi; Kondo *J. Org. Chem.* **1985**, 50, 4980.

<sup>204</sup>See, for example, Lee; Spitzer *J. Org. Chem.* **1976**, 41, 3644; Lee; Chang; Helliwell *J. Org. Chem.* **1976**, 41, 3644, 3646.

<sup>205</sup>There is evidence that oxidation with  $\text{Cr(VI)}$  in aqueous acetic acid involves an epoxide intermediate: Awasthy; Roček *J. Am. Chem. Soc.* **1969**, 91, 991; Roček; Drozd *J. Am. Chem. Soc.* **1970**, 92, 6668.

<sup>206</sup>McKillop; Oldenzel; Swann; Taylor; Robey *J. Am. Chem. Soc.* **1973**, 95, 1296.

<sup>207</sup>Moriarty; Penmasta; Awasthi; Prakash *J. Org. Chem.* **1988**, 53, 6124.

<sup>208</sup>Ruthenium tetroxide is an expensive reagent, but the cost can be greatly reduced by the use of an inexpensive cooxidant such as  $\text{NaOCl}$ , the function of which is to oxidize  $\text{RuO}_2$  back to ruthenium tetroxide.

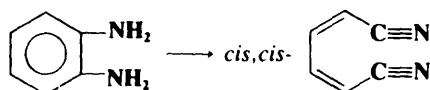
<sup>209</sup>For other examples, see Piatak; Herbst; Wicha Caspi *J. Org. Chem.* **1969**, 34, 116; Wolfe; Hasan; Campbell *Chem. Commun.* **1970**, 1420; Ayres; Hossain *Chem. Commun.* **1972**, 428; Nuñez; Martín *J. Org. Chem.* **1990**, 55, 1928.

<sup>210</sup>Spitzer; Lee *J. Org. Chem.* **1974**, 39, 2468.

<sup>211</sup>Caputo; Fuchs *Tetrahedron Lett.* **1967**, 4729.

<sup>212</sup>Klein; Steinmetz *Tetrahedron Lett.* **1975**, 4249. For other reagents that convert an aromatic ring to  $\text{COOH}$  and leave alkyl groups untouched, see Deno; Greigiger; Messer; Meyer; Stroud *Tetrahedron Lett.* **1977**, 1703; Liotta; Hoff *J. Org. Chem.* **1980**, 45, 2887; Chakraborti; Ghatak *J. Chem. Soc., Perkin Trans. 1* **1985**, 2605.

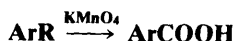
oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride (p. 794) by this reagent are important industrial procedures.<sup>213</sup> *o*-Diamines have been oxidized with nickel peroxide, with lead tetraacetate,<sup>214</sup> and with O<sub>2</sub> catalyzed by CuCl.<sup>215</sup>



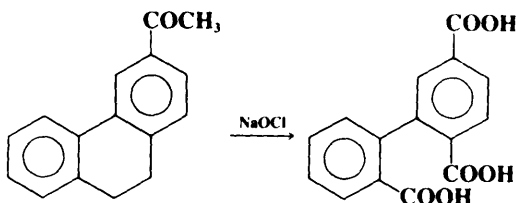
The last-named reagent also cleaves *o*-dihydroxybenzenes (catechols) to give, in the presence of MeOH, the monomethylated dicarboxylic acids  $\text{HOOC}-\text{C}=\text{C}-\text{C}=\text{C}-\text{COOMe}$ .<sup>216</sup>

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

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



Alkyl chains on aromatic rings can be oxidized to COOH groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate.<sup>218</sup> The method is most often applied to the methyl group, though longer side chains can also be cleaved. However, tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.<sup>219</sup> It is usually difficult to oxidize an R group on a fused aromatic system without cleaving the ring or oxidizing it to a quinone (9-19). However, this has been done (e.g., 2-methylnaphthalene was converted to 2-naphthoic acid) with aqueous Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>.<sup>220</sup> Functional groups can be present anywhere on the side chain and, if in the α position, greatly increase the ease of oxidation. An exception is an α phenyl group. In such cases the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each ring gets one carbon atom, e.g.,



It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity<sup>221</sup> toward most reagents is  $\text{CH}_2\text{Ar} > \text{CHR}_2 > \text{CH}_2\text{R} > \text{CH}_3$ .<sup>222</sup> Groups

<sup>213</sup>For a review, see Pyatnitskii *Russ. Chem. Rev.* **1976**, 45, 762-776.

<sup>214</sup>Nakagawa; Onoue *Tetrahedron Lett.* **1965**, 1433. *Chem. Commun.* **1966**, 396.

<sup>215</sup>Kajimoto; Takahashi; Tsuji *J. Org. Chem.* **1976**, 41, 1389.

<sup>216</sup>Tsuji; Takayanagi *Tetrahedron* **1978**, 34 641; Bankston *Org. Synth.* 66, 180.

<sup>217</sup>This is the name if R = ethyl. The IUPAC names will obviously differ, depending on the R group.

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

<sup>219</sup>Brandenberger; Maas; Dvoretzky *J. Am. Chem. Soc.* **1961**, 83, 2146.

<sup>220</sup>Friedman; Fishel; Shechter *J. Org. Chem.* **1965**, 30, 1453.

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

<sup>222</sup>For example, see Foster; Hickinbottom *J. Chem. Soc.* **1960**, 680; Ferguson; Wims *J. Org. Chem.* **1960**, 25, 668.

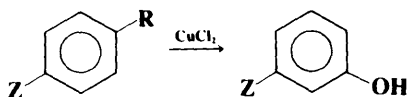
on the ring susceptible to oxidation (OH, NHR, NH<sub>2</sub>, etc.) must be protected. The oxidation can be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in 4-9, with a hydroperoxide intermediate. With this procedure it is possible to isolate ketones from ArCH<sub>2</sub>R, and this is often done.<sup>223</sup>

The mechanism has been studied for the closely related reaction: Ar<sub>2</sub>CH<sub>2</sub> + CrO<sub>3</sub> → Ar<sub>2</sub>C=O.<sup>224</sup> A deuterium isotope effect of 6.4 was found, indicating that the rate-determining step is either Ar<sub>2</sub>CH<sub>2</sub> → Ar<sub>2</sub>CH• or Ar<sub>2</sub>CH<sub>2</sub> → Ar<sub>2</sub>CH<sup>+</sup>. Either way this explains why tertiary groups are not converted to COOH and why the reactivity order is CHR<sub>2</sub> > CH<sub>2</sub>R > CH<sub>3</sub>, as mentioned above. Both free radicals and carbocations exhibit this order of stability (Chapter 5). The two possibilities are examples of categories 2 and 3 (p. 1160). Just how the radical or the cation goes on to the product is not known.

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

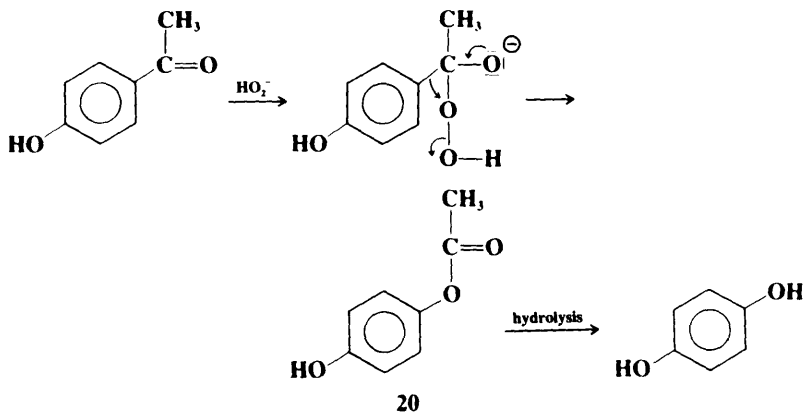
## 9-12 Oxidative Cleavage of Alkyl Groups from Rings

### Hydroxy-de-alkyl-*cine*-substitution



It is possible to replace an alkyl group on a ring by an OH group. When the alkyl group is one oxidizable to COOH (9-11), cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.<sup>225</sup> 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<sub>2</sub>O<sub>2</sub>,<sup>226</sup> but there must be an OH or NH<sub>2</sub> group in the ortho or para position. This is called the *Dakin reaction*.<sup>227</sup> The mechanism may be similar to that of the Baeyer-Villiger reaction (8-20):<sup>228</sup>



<sup>223</sup>For a review, see Pines; Stalick, Ref. 23, pp. 508-543.

<sup>224</sup>Wiberg; Evans *Tetrahedron* **1960**, 8, 313.

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

<sup>226</sup>For a convenient procedure, see Hocking *Can. J. Chem.* **1973**, 51, 2384.

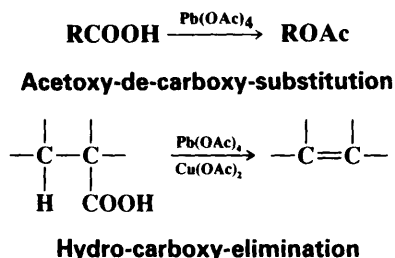
<sup>227</sup>See Schubert; Kintner, in Patai *The Chemistry of the Carbonyl Group*, Ref. 44, pp. 749-752.

<sup>228</sup>For a discussion, see Hocking; Bhandari; Shell; Smyth *J. Org. Chem.* **1982**, 47, 4208.

The intermediate **20** has been isolated.<sup>229</sup> The reaction has been performed on aromatic aldehydes with an alkoxy group in the ring, and no OH or NH<sub>2</sub>. In this case acidic H<sub>2</sub>O<sub>2</sub> was used.<sup>230</sup>

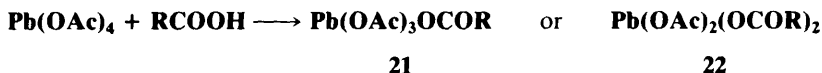
OS I, 149; III, 759.

### 9-13 Oxidative Decarboxylation



Carboxylic acids can be decarboxylated<sup>231</sup> with lead tetraacetate to give a variety of products, among them the ester ROAc (formed by replacement of COOH by an acetoxy group), the alkane RH (see 2-40), and, if a β hydrogen is present, the alkene formed by elimination of H and COOH, as well as numerous other products arising from rearrangements, internal cyclizations,<sup>232</sup> 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)<sub>2</sub> along with the Pb(OAc)<sub>4</sub>.<sup>233</sup> In the absence of Cu(OAc)<sub>2</sub>, primary acids give mostly alkanes (though yields are generally low) and secondary acids may give carboxylic esters or alkenes. Carboxylic esters have been obtained in good yields from some secondary acids, from β,γ-unsaturated acids, and from acids in which R is a benzylic group. Other oxidizing agents,<sup>234</sup> including Co(III), Ag(II), Mn(III), and Ce(IV), have also been used to effect oxidative decarboxylation.<sup>235</sup>

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



<sup>229</sup>Hocking; Ko; Smyth *Can. J. Chem.* **1978**, 56, 2646.

<sup>230</sup>Matsumoto; Kobayashi; Hotta *J. Org. Chem.* **1984**, 49, 4740.

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

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

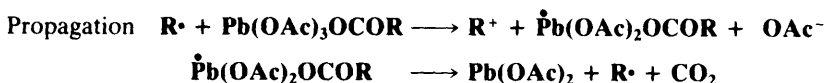
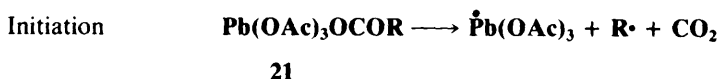
<sup>233</sup>Bacha; Kochi *Tetrahedron* **1968**, 24, 2215; Ogibin; Katzin; Nikishin *Synthesis* **1974**, 889.

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

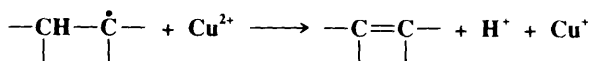
<sup>235</sup>For another method, see Barton; Bridon; Zard *Tetrahedron* **1989**, 45, 2615.

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

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



Products can then be formed either from  $\text{R}\cdot$  or  $\text{R}^+$ . Primary  $\text{R}\cdot$  abstract H from solvent molecules to give  $\text{RH}$ .  $\text{R}^+$  can lose  $\text{H}^+$  to give an alkene, react with  $\text{HOAc}$  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.  $\text{R}\cdot$  can also dimerize to give  $\text{RR}$ . The effect of  $\text{Cu}^{2+}$  ions<sup>237</sup> is to oxidize the radicals to alkenes,



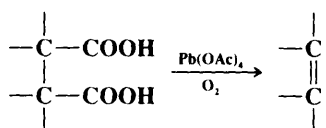
thus producing good yields of alkenes from primary and secondary substrates.  $\text{Cu}^{2+}$  has no effect on tertiary radicals, because these are efficiently oxidized to alkenes by lead tetraacetate.

In another type of oxidative decarboxylation, arylacetic acids can be oxidized to aldehydes with one less carbon ( $\text{ArCH}_2\text{COOH} \rightarrow \text{ArCHO}$ ) by tetrabutylammonium periodate.<sup>238</sup> Simple aliphatic carboxylic acids were converted to nitriles with one less carbon ( $\text{RCH}_2\text{COOH} \rightarrow \text{RC}\equiv\text{N}$ ) by treatment with trifluoroacetic anhydride and  $\text{NaNO}_2$  in  $\text{F}_3\text{CCOOH}$ .<sup>239</sup>

See also **4-39**.

## 9-14 Bisdecarboxylation

### Dicarboxy-elimination



Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bisdecarboxylated with lead tetraacetate in the presence of  $\text{O}_2$ .<sup>231</sup> The reaction is of wide scope. The elimination is stereoselective, but not stereospecific (both *meso*- and *dl*-2,3-diphenylsuccinic acid gave *trans*-stilbene);<sup>240</sup> a concerted mechanism is thus unlikely. The

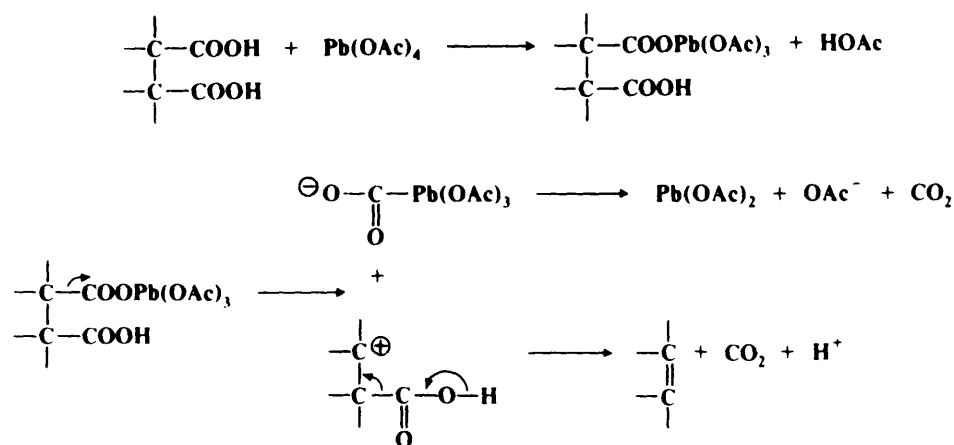
<sup>237</sup>Bacha; Kochi *J. Org. Chem.* **1968**, 33, 83; Kochi; Bacha *J. Org. Chem.* **1968**, 33, 2746; Torssell *Ark. Kemi* **1970**, 31, 401.

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

<sup>239</sup>Smushkevich; Usorov; Suvorov *J. Org. Chem. USSR* **1975**, 11, 653.

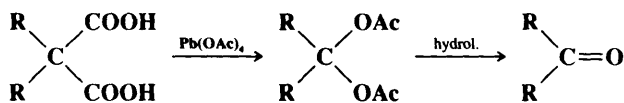
<sup>240</sup>Corey; Casanova *J. Am. Chem. Soc.* **1963**, 85, 165.

following mechanism is not inconsistent with the data:

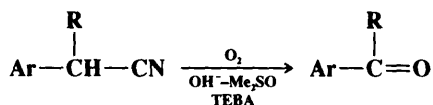


though a free-radical mechanism seems to hold in some cases. Bisdecarboxylation of succinic acid derivatives to give alkenes<sup>241</sup> has also been carried out by other methods, including treatment of the corresponding anhydrides with nickel, iron, or rhodium complexes,<sup>242</sup> by decomposition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

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



### 9-15 Oxidative Decyanation Oxo-de-hydro,cyano-bisubstitution



$\alpha$ -Substituted aryl nitriles having a sufficiently acidic  $\alpha$  hydrogen can be converted to ketones by oxidation with air under phase transfer conditions.<sup>247</sup> The nitrile is added to NaOH in benzene or Me<sub>2</sub>SO containing a catalytic amount of triethylbenzylammonium chloride

<sup>241</sup>For a review, see De Lucchi; Modena *Tetrahedron* **1984**, *40*, 2585-2632, pp. 2591-2608.

<sup>242</sup>Trost; Chen *Tetrahedron Lett.* **1971**, 2603.

<sup>243</sup>Cain; Vukov; Masamune *Chem. Commun.* **1969**, 98.

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

<sup>245</sup>For a similar reaction with ceric ammonium nitrate, see Salomon; Roy; Salomon *Tetrahedron Lett.* **1988**, 29, 769.

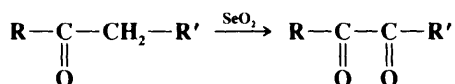
<sup>246</sup>Tufariello; Kissel *Tetrahedron Lett.* **1966**, 6145.

<sup>247</sup>For other methods of achieving this conversion, with references, see Ref. 21, p. 618.

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

### C. Reactions Involving Replacement of Hydrogen by Oxygen

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



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

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

<sup>249</sup>Büchi; Liang; Wüest *Tetrahedron Lett.* **1978**, 2763.

<sup>250</sup>Chuang; Yang; Chang; Fang *Synlett* **1990**, 733.

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

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

<sup>253</sup>For example, see Harms; Eisenbraun *Org. Prep. Proced. Int.* **1972**, 4, 67.

<sup>254</sup>Rangarajan; Eisenbraun *J. Org. Chem.* **1985**, 50, 2435.

<sup>255</sup>Rathore; Saxena; Chandrasekaran *Synth. Commun.* **1986**, 16, 1493.

<sup>256</sup>Syper *Tetrahedron Lett.* **1966**, 4493.

<sup>257</sup>Barton; Hui; Ley *J. Chem. Soc., Perkin Trans. 1* **1982**, 2179.

<sup>258</sup>Daniher *Org. Prep. Proced.* **1970**, 2, 207; Bhatt; Perumal *Tetrahedron Lett.* **1981**, 22, 2605.

<sup>259</sup>Lee; Harvey *J. Org. Chem.* **1988**, 53, 4587.

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

<sup>261</sup>Holland; Daum; Riemland *Tetrahedron Lett.* **1981**, 22, 5127.

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

<sup>263</sup>Barton; Crich *Tetrahedron* **1985**, 41, 4359.

<sup>264</sup>Dauben; Lorber; Fullerton *J. Org. Chem.* **1969**, 34, 3587; Fullerton; Chen *Synth. Commun.* **1976**, 6, 217.

<sup>265</sup>Arzoumanian; Metzger *Synthesis* **1971**, 527-536; Charavel; Metzger *Bull. Soc. Chim. Fr.* **1968**, 4102.

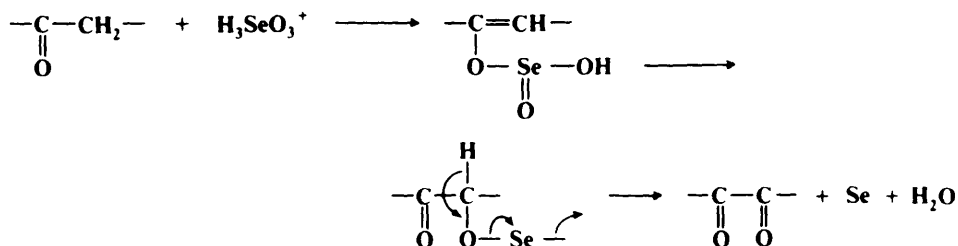
<sup>266</sup>Madurro; Chiericato; De Giovanni; Romero *Tetrahedron Lett.* **1988**, 29, 765.

<sup>267</sup>Shaw; Sherry *Tetrahedron Lett.* **1971**, 4379; Sheats; Olli; Stout; Lundeen; Justus; Nigh *J. Org. Chem.* **1979**, 44, 4075.

<sup>268</sup>Muzart; Piva *Tetrahedron Lett.* **1988**, 29, 2321.

disulfate  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  and a catalytic amount of diphenyl diselenide in MeOH to give  $\alpha$ -keto acetals  $\text{RCOCH}(\text{OMe}_2)$ .<sup>269</sup>

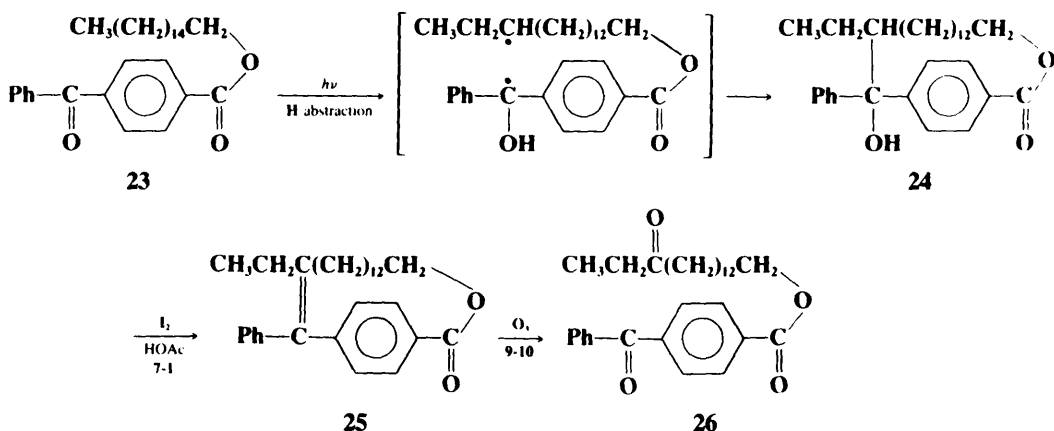
Two mechanisms have been suggested for the reaction with  $\text{SeO}_2$ . One of these involves a selenate ester of the enol:<sup>270</sup>



In the other proposed mechanism,<sup>271</sup> the principal intermediate is a  $\beta$ -ketoseleninic acid



It has proved possible to convert  $\text{CH}_2$  to  $\text{C}=\text{O}$  groups, even if they are not near any functional groups, indirectly, by the remote oxidation method of Breslow<sup>39</sup> (see 9-2). In a typical example, the keto ester **23** was irradiated to give the hydroxy lactone **24**, which was



dehydrated to **25**. Ozonolysis of **25** gave the diketo ester **26**, in which the C-14  $\text{CH}_2$  group of **23** has been oxidized to a  $\text{C}=\text{O}$  group.<sup>272</sup> The reaction was not completely regioselective: **26** comprised about 60% of the product, with the remainder consisting of other compounds in which the keto group was located at C-12, C-15, and other positions along the carbon chain. Greater regioselectivity was achieved when the aromatic portion was connected to the chain at two positions.<sup>273</sup> In the method so far described, the reaction takes place because one portion of a molecule (the benzophenone moiety) abstracts hydrogen from another

<sup>269</sup>Tiecco; Testaferri; Tingoli; Bartoli *J. Org. Chem.* **1990**, 55, 4523.

<sup>270</sup>Corey; Schaefer *J. Am. Chem. Soc.* **1960**, 82, 918.

<sup>271</sup>Sharpless; Gordon *J. Am. Chem. Soc.* **1976**, 98, 300.

<sup>272</sup>Breslow; Winnik *J. Am. Chem. Soc.* **1969**, 91, 3083; Breslow; Rothbard; Herman; Rodriguez *J. Am. Chem. Soc.* **1978**, 100, 1213.

<sup>273</sup>Breslow; Rajagopalan; Schwarz *J. Am. Chem. Soc.* **1981**, 103, 2905.

portion of the same molecule, i.e., the two portions are connected by a series of covalent bonds. However, the reaction can also be carried out where the two reacting centers are actually in different molecules, providing the two molecules are held together by hydrogen bonding. For example, one of the  $\text{CH}_2$  groups of *n*-hexadecanol monosuccinate  $\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{OCOCH}_2\text{CH}_2\text{COOH}$  was oxidized to a  $\text{C}=\text{O}$  group by applying the above procedure to a mixture of it and benzophenone-4-carboxylic acid *p*- $\text{PhCOC}_6\text{H}_4\text{COOH}$  in  $\text{CCl}_4$ .<sup>274</sup>

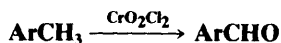
Other remote oxidations<sup>275</sup> have also been reported. Among these are conversion of aryl ketones  $\text{ArCO}(\text{CH}_2)_3\text{R}$  to 1,4-diketones  $\text{ArCO}(\text{CH}_2)_2\text{COR}$  by photoirradiation in the presence of such oxidizing agents as  $\text{K}_2\text{Cr}_2\text{O}_7$  or  $\text{KMnO}_4$ ,<sup>276</sup> and conversion of alkyl ketones  $\text{RCO}(\text{CH}_2)_3\text{R}'$  to 1,3- and 1,4-diketones with  $\text{Na}_2\text{S}_2\text{O}_8$  and  $\text{FeSO}_4$ .<sup>277</sup>

It is possible to perform the conversion  $\text{CH}_2 \rightarrow \text{C}=\text{O}$  on an alkane, with no functional groups at all, though the most success has been achieved with substrates in which all  $\text{CH}_2$  groups are equivalent, such as unsubstituted cycloalkanes. One method uses  $\text{H}_2\text{O}_2$  and bis(picolinato)iron(II). With this method, cyclohexane was converted with 72% efficiency to give 95% cyclohexanone and 5% cyclohexanol.<sup>278</sup> The same type of conversion, with lower yields (20-30%), has been achieved with the *Gif system*.<sup>279</sup> There are several variations. One consists of pyridine-acetic acid, with  $\text{H}_2\text{O}_2$  as oxidizing agent and tris(picolinato)iron(III) as catalyst.<sup>280</sup> Other *Gif* systems use  $\text{O}_2$  as oxidizing agent and zinc as a reductant.<sup>281</sup> The selectivity of the *Gif* systems towards alkyl carbons is  $\text{CH}_2 > \text{CH} \geq \text{CH}_3$ , which is unusual, and shows that a simple free-radical mechanism (see p. 683) is not involved.<sup>282</sup> Another reagent that can oxidize the  $\text{CH}_2$  of an alkane is methyl(trifluoromethyl)dioxirane, but this produces  $\text{CH}-\text{OH}$  more often than  $\text{C}=\text{O}$  (see 4-4).<sup>283</sup>

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

## 9-17 Oxidation of Arylmethanes

### Oxo-de-dihydro-bisubstitution



Methyl groups on an aromatic ring can be oxidized to the aldehyde stage by several oxidizing agents. The reaction is a special case of 9-16. When the reagent is chromyl chloride ( $\text{CrO}_2\text{Cl}_2$ ), the reaction is called the *Étard reaction*<sup>284</sup> and the yields are high.<sup>285</sup> Another oxidizing agent is a mixture of  $\text{CrO}_3$  and  $\text{Ac}_2\text{O}$ . In this case the reaction stops at the aldehyde stage because

<sup>274</sup>Breslow; Scholl *J. Am. Chem. Soc.* **1971**, 93, 2331. See also Breslow; Heyer *Tetrahedron Lett.* **1983**, 24, 5039.

<sup>275</sup>See also Beckwith; Duong *J. Chem. Soc., Chem. Commun.* **1978**, 413.

<sup>276</sup>Mitani; Tamada; Uehara; Koyama *Tetrahedron Lett.* **1984**, 25, 2805.

<sup>277</sup>Nikishin; Troyansky; Lazareva *Tetrahedron Lett.* **1984**, 25, 4987.

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

<sup>279</sup>Named for Gif-sur-Yvette, France, where it was discovered.

<sup>280</sup>About-Jaudet; Barton; Cshai; Ozbalik *Tetrahedron Lett.* **1990**, 31, 1657.

<sup>281</sup>See Barton; Boivin; Gastiger; Morzycki; Hay-Motherwell; Motherwell; Ozbalik; Schwartzentruber *J. Chem. Soc., Perkin Trans. I* **1986**, 947; Barton; Cshai; Ozbalik *Tetrahedron* **1990**, 46, 3743.

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

<sup>283</sup>Mello; Fiorentino; Fusco; Curci *J. Am. Chem. Soc.* **1989**, 111, 6749.

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

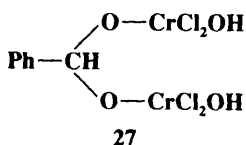
<sup>285</sup>For a review, see Hartford; Darrin *Chem. Rev.* **1958**, 58, 1-61, pp. 25-53.

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

Among other oxidizing agents<sup>286</sup> that have been used to accomplish the conversion of  $\text{ArCH}_3$  to  $\text{ArCHO}$  are ceric ammonium nitrate,<sup>287</sup> ceric trifluoroacetate,<sup>288</sup> benzeneseleninic anhydride,<sup>257</sup>  $\text{KMnO}_4\text{-Et}_3\text{N}$ ,<sup>289</sup> and silver(II) oxide.<sup>290</sup> Oxidation of  $\text{ArCH}_3$  to carboxylic acids is considered at 9-11.

Conversion of  $\text{ArCH}_3$  to  $\text{ArCHO}$  can also be achieved indirectly by bromination to give  $\text{ArCHBr}_2$  (4-1), followed by hydrolysis (0-2).

The mechanism of the Étard reaction is not completely known.<sup>291</sup> An insoluble complex is formed on addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but what the structure is is not fully settled, though many proposals have been made as to its structure and as to how it is hydrolyzed. It is known that  $\text{ArCH}_2\text{Cl}$  is not an intermediate (see 9-20), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements<sup>292</sup> indicate that the complex from toluene is **27**, a structure first proposed by Étard. According to this proposal the reaction stops after

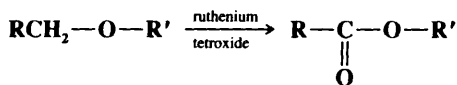


only two hydrogens have been replaced because of the insolubility of **27**. There is a disagreement on how **27** is formed, assuming that the complex has this structure. Both an ionic<sup>293</sup> and a free-radical<sup>294</sup> process have been proposed. An entirely different structure for the complex was proposed by Nenitzescu and co-workers.<sup>295</sup> On the basis of esr studies they proposed that the complex is  $\text{PhCH}_2\text{OCrCl}_2\text{OCrOCl}_2\text{OH}$ , which is isomeric with **27**. However, this view has been challenged by Wiberg and Eisenthal,<sup>294</sup> who interpret the esr result as being in accord with **27**. Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.<sup>296</sup>

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

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

### Oxo-de-dihydro-bisubstitution



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

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

<sup>288</sup>Marrocco; Brilmyer *J. Org. Chem.* **1983**, 48, 1487. See also Kreh; Spotnitz; Lundquist *J. Org. Chem.* **1989**, 54, 1526.

<sup>289</sup>Li; Liu *Synthesis* **1989**, 293.

<sup>290</sup>Syper *Tetrahedron Lett.* **1967**, 4193.

<sup>291</sup>For a review, see Nenitzescu *Bull. Soc. Chim. Fr.* **1968**, 1349-1357.

<sup>292</sup>Wheeler *Can. J. Chem.* **1960**, 38, 2137. See also Makhija; Stairs *Can. J. Chem.* **1968**, 46, 1255.

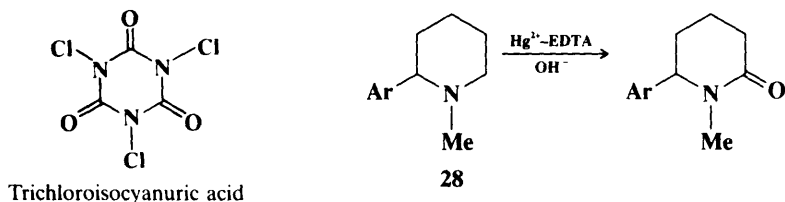
<sup>293</sup>Stairs *Can. J. Chem.* **1964**, 42, 550.

<sup>294</sup>Wiberg; Eisenthal *Tetrahedron* **1964**, 20, 1151. See also Gragerov; Ponomarchuk *J. Org. Chem. USSR* **1969**, 6, 1125.

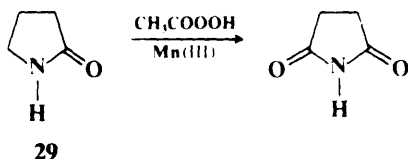
<sup>295</sup>Necşoiu; Balaban; Pascaru; Sliam; Elian; Nenitzescu *Tetrahedron* **1963**, 19, 1133; Necşoiu; Przemetchi; Ghenculescu; Rentea; Nenitzescu *Tetrahedron* **1966**, 22, 3037.

<sup>296</sup>Duffin; Tucker *Chem. Ind. (London)* **1966**, 1262, *Tetrahedron* **1968**, 24, 6999.

Ethers in which at least one group is primary alkyl can be oxidized to the corresponding carboxylic esters in high yields with ruthenium tetroxide.<sup>297</sup> Cyclic ethers give lactones. The reaction, a special case of **9-16**, has also been accomplished with  $\text{CrO}_3$  in sulfuric acid,<sup>298</sup> with benzyltrihethylammonium permanganate,<sup>299</sup> and with trichloroisocyanuric acid in the presence of an excess of water.<sup>300</sup> In a similar reaction, cyclic tertiary amines (e.g., **28**) can



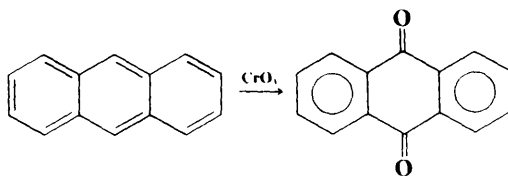
be converted to lactams by oxidation with  $\text{Hg(II)}$ -EDTA complex in basic solution.<sup>301</sup> Lactams, which need not be N-substituted (e.g., **29**), can be converted to cyclic imides by



oxidation with a hydroperoxide or peracid and an  $\text{Mn(II)}$  or  $\text{Mn(III)}$  salt.<sup>302</sup> Certain tertiary amines containing a methyl group can be oxidized<sup>303</sup> to formamides ( $\text{R}_2\text{NCH}_3 \rightarrow \text{R}_2\text{NCHO}$ ) by  $\text{MnO}_2$ ,<sup>304</sup>  $\text{CrO}_3$ -pyridine,<sup>305</sup>  $\text{O}_2$  and platinum,<sup>306</sup> or other oxidizing agents, but the reaction is not general.

## 9-19 Oxidation of Aromatic Hydrocarbons to Quinones

### Arene-quinone transformation



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

<sup>298</sup>Henbest; Nicholls *J. Chem. Soc.* **1959**, 221, 227; Harrison; Harrison *Chem. Commun.* **1966**, 752.

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

<sup>300</sup>Juenge; Beal *Tetrahedron Lett.* **1968**, 5819; Juenge; Corey; Beal *Tetrahedron* **1971**, *27*, 2671.

<sup>301</sup>Wenkert; Angell *Synth. Commun.* **1988**, *18*, 1331.

<sup>302</sup>Doumaux; McKeon; Trecker *J. Am. Chem. Soc.* **1969**, *91*, 3992; Doumaux; Trecker *J. Org. Chem.* **1970**, *35*, 2121.

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

<sup>304</sup>See, for example, Henbest; Thomas *J. Chem. Soc.* **1957**, 3032; Henbest; Stratford *J. Chem. Soc. C* **1966**, 995.

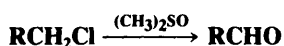
<sup>305</sup>Cavé; Kan-Fan; Potier; Le Men; Janot *Tetrahedron* **1967**, *23*, 4691.

<sup>306</sup>Davis; Rosenblatt *Tetrahedron Lett.* **1968**, 4085.

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

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

## 9-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes<sup>310</sup> Oxo-de-hydro,halo-bisubstitution



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

Similar oxidation of alcohols has been carried out with dimethyl sulfoxide and other reagents<sup>317</sup> in place of DCC: acetic anhydride,<sup>318</sup>  $\text{SO}_3$ -pyridine-triethylamine,<sup>319</sup> trifluoroacetic anhydride,<sup>320</sup> oxalyl chloride,<sup>321</sup> tosyl chloride,<sup>322</sup> chlorine,<sup>323</sup> bromine,<sup>324</sup>  $\text{AgBF}_4$ - $\text{Et}_3\text{N}$ ,<sup>325</sup>  $\text{P}_2\text{O}_5$ - $\text{Et}_3\text{N}$ ,<sup>326</sup> phenyl dichlorophosphate,<sup>327</sup> trichloromethyl chloroformate,<sup>328</sup> tri-

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

<sup>308</sup>Periasamy; Bhatt *Synthesis* **1977**, 330; Balanikas; Hussain; Amin; Hecht *J. Org. Chem.* **1988**, 53, 1007.

<sup>309</sup>See, for example, Ito; Katayama; Kunai; Sasaki *Tetrahedron Lett.* **1989**, 30, 205.

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

<sup>311</sup>Nace; Monagle *J. Org. Chem.* **1959**, 24, 1792; Kornblum; Jones; Anderson *J. Am. Chem. Soc.* **1959**, 81, 4113.

<sup>312</sup>Kornblum; Jones; Anderson, Ref. 311.

<sup>313</sup>Epoxides can be converted to  $\alpha$ -halo ketones by treatment with bromodimethylsulfonium bromide: Olah; Vankar; Arvanaghi *Tetrahedron Lett.* **1979**, 3653.

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

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

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

<sup>317</sup>For a review of activated  $\text{Me}_2\text{SO}$  reagents and their use in this reaction, see Mancuso; Swern *Synthesis* **1981**, 165-185.

<sup>318</sup>Albright; Goldman *J. Am. Chem. Soc.* **1967**, 89, 2416.

<sup>319</sup>Parikh; Doering *J. Am. Chem. Soc.* **1967**, 89, 5507.

<sup>320</sup>Huang; Omura; Swern *Synthesis* **1978**, 297.

<sup>321</sup>Omura; Swern *Tetrahedron* **1978**, 34, 1651. See also Marx; Tidwell *J. Org. Chem.* **1984**, 49, 788.

<sup>322</sup>Albright *J. Org. Chem.* **1974**, 39, 1977.

<sup>323</sup>Corey; Kim *Tetrahedron Lett.* **1973**, 919.

<sup>324</sup>Munavu *J. Org. Chem.* **1980**, 45 3341.

<sup>325</sup>Ganem; Boeckman *Tetrahedron Lett.* **1974**, 917.

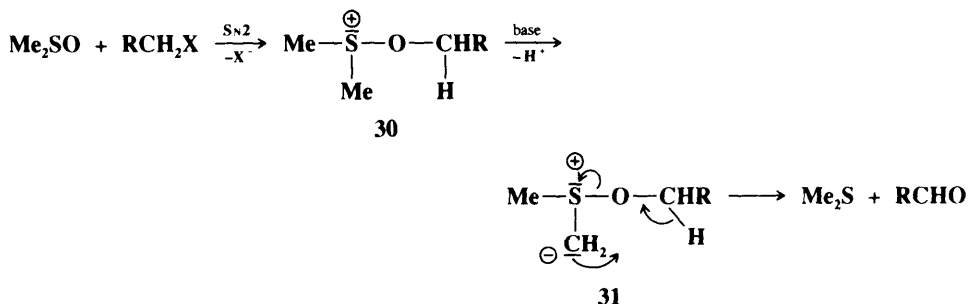
<sup>326</sup>Taber; Amedeo; Jung *J. Org. Chem.* **1987**, 52, 5621.

<sup>327</sup>Liu; Nyangulu *Tetrahedron Lett.* **1988**, 29, 3167.

<sup>328</sup>Takano; Inomata; Tomita; Yanase; Samizu; Ogasawara *Tetrahedron Lett.* **1988**, 29, 6619.

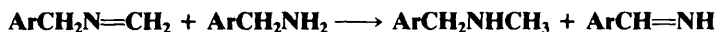
methylamine oxide,<sup>329</sup> KI and NaHCO<sub>3</sub>,<sup>330</sup> and methanesulfonic anhydride,<sup>322</sup> among others. When oxalyl chloride is used, the method is called *Swern oxidation*.

The mechanism of these dimethyl sulfoxide oxidations is probably as follows:<sup>331</sup>



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

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*,<sup>335</sup> is limited to benzylic halides. The reaction is seldom useful when the R in RCH<sub>2</sub>Cl is alkyl. The first part of the reaction is conversion to the amine ArCH<sub>2</sub>NH<sub>2</sub> (**0-44**), which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step that is the actual Sommelet reaction, though the entire process can be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine (ArCH<sub>2</sub>N=CH<sub>2</sub>) 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.

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

<sup>329</sup>Godfrey; Ganem *Tetrahedron Lett.* **1990**, 31, 4825.

<sup>330</sup>Bauer; Macomber *J. Org. Chem.* **1975**, 40, 1990.

<sup>331</sup>Pfitzner; Moffatt *J. Am. Chem. Soc.* **1965**, 87, 5661; Johnson; Phillips *J. Org. Chem.* **1967**, 32, 1926; Torrsell *Acta Chem. Scand.* **1967**, 21, 1.

<sup>332</sup>Torrsell *Tetrahedron Lett.* **1966**, 4445; Johnson; Phillips, Ref. 331; Khuddus; Swern *J. Am. Chem. Soc.* **1973**, 95, 8393.

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

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

<sup>335</sup>For a review, see Angyal *Org. React.* **1954**, 8, 197-217.

<sup>336</sup>Hass; Bender *J. Am. Chem. Soc.* **1949**, 71, 1767.

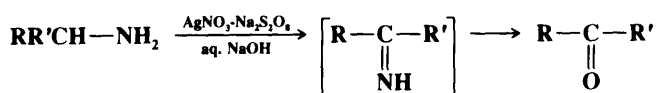
<sup>337</sup>McKillop; Ford *Synth. Commun.* **1974**, 4, 45.

<sup>338</sup>Franzen; Otto *Chem. Ber.* **1961**, 94, 1360.

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

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

**9-21 Oxidation of Amines or Nitro Compounds to Aldehydes, Ketones, or Dihalides**  
**Oxo-de-hydro,amino-bisubstitution** (overall transformation)



Primary aliphatic amines can be oxidized to aldehydes or ketones<sup>342</sup> by reaction with Ag(II) prepared in situ by treatment of silver nitrate with sodium persulfate.<sup>343</sup> The reaction consists of dehydrogenation to the imine (9-5) followed by hydrolysis. Other reagents used<sup>344</sup> have been nitrosobenzene<sup>345</sup> or N-bromoacetamide<sup>346</sup> (for benzylic amines), 3,5-di-*t*-butyl-1,2-benzoquinone,<sup>347</sup> *m*-trifluoromethylbenzenesulfonyl peroxide,<sup>348</sup> diphenylseleninic anhydride,<sup>349</sup>  $PdCl_2$  or  $AuCl_3$ ,<sup>350</sup> and aqueous NaOCl with phase-transfer catalysts.<sup>351</sup> Benzylic amine salts  $PhCHNR_2^+H^+ Cl^-$  ( $R, R' = H$  or alkyl) give benzaldehydes or aryl ketones when heated in  $Me_2SO$ .<sup>352</sup> Several indirect methods for achieving the conversion  $RR'CHNH_2 \rightarrow RR'C=O$  ( $R' = \text{alkyl, aryl, or H}$ ) have been reported.<sup>353</sup>

Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aqueous bromine<sup>354</sup> and with neutral permanganate.<sup>355</sup> 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.<sup>356</sup>

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

<sup>339</sup>Mukaiyama; Inanaga; Yamaguchi *Bull. Chem. Soc. Jpn.* **1981**, 54, 2221.

<sup>340</sup>Suzuki; Onishi; Fujita; Misawa; Otera *Bull. Chem. Soc. Jpn.* **1986**, 59, 3287.

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

<sup>342</sup>For a review, see Haines-1988, Ref. 11, pp. 200-220, 411-415.

<sup>343</sup>Bacon; Stewart *J. Chem. Soc. C* **1966**, 1384. See also Lee; Clarke *Tetrahedron Lett.* **1967**, 415.

<sup>344</sup>For lists of reagents, with references, see Ref. 21, pp. 601-602; Hudlický, Ref. 11, p. 240.

<sup>345</sup>Suzuki; Weisburger *Tetrahedron Lett.* **1966**, 5409, *J. Chem. Soc. C* **1968**, 199.

<sup>346</sup>Banerji *Bull. Chem. Soc. Jpn.* **1988**, 61, 3717.

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

<sup>348</sup>Hoffman; Kumar *J. Org. Chem.* **1984**, 49, 4011.

<sup>349</sup>Czarny *J. Chem. Soc., Chem. Commun.* **1976**, 81. See also Czarny *Synth. Commun.* **1976**, 6, 285.

<sup>350</sup>Kuehne; Hall *J. Org. Chem.* **1976**, 41, 2742.

<sup>351</sup>Lee; Freedman *Tetrahedron Lett.* **1976**, 1641.

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

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

<sup>354</sup>Deno; Fruit *J. Am. Chem. Soc.* **1968**, 90, 3502.

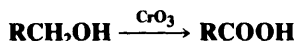
<sup>355</sup>Rawalay; Shechter *J. Org. Chem.* **1967**, 32, 3129. For another procedure, see Monković; Wong; Bachand *Synthesis* **1985**, 770.

<sup>356</sup>Doyle; Siegfried *J. Chem. Soc., Chem. Commun.* **1976**, 433.

<sup>357</sup>Ballini; Petrini *Tetrahedron Lett.* **1989**, 30, 5329.

<sup>358</sup>For a list of reagents, with references, see Ref. 21, p. 603.

### 9-22 Oxidation of Primary Alcohols to Carboxylic Acids or Carboxylic Esters Oxo-de-dihydro-bisubstitution

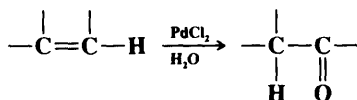


Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents including chromic acid, permanganate, and nitric acid.<sup>359</sup> The reaction can be looked on as a combination of **9-3** and **4-6**. When acidic conditions are used, a considerable amount of carboxylic ester  $\text{RCOOCH}_2\text{R}$  is often isolated, though this is probably not formed by a combination of the acid with unreacted alcohol, but by a combination of intermediate aldehyde with unreacted alcohol to give an acetal or hemiacetal, which is oxidized to the ester.<sup>360</sup>  $\text{RCOOCH}_2\text{R}$  can be made the main product by treating the alcohol with (1)  $\text{Ru}_3(\text{CO})_{12}$  and diphenylacetylene, or with a complex formed from these two reagents;<sup>361</sup> (2) Pd salts and  $\text{CCl}_4$  in the presence of  $\text{K}_2\text{CO}_3$ ;<sup>362</sup> or (3)  $\text{RuH}_2(\text{PPh}_3)_4$ .<sup>363</sup> Primary alcohols  $\text{RCH}_2\text{OH}$  can be directly oxidized to acyl fluorides  $\text{RCOF}$  with cesium fluoroxy sulfate.<sup>364</sup> Lactones can be prepared by oxidizing diols in which at least one OH is primary.<sup>365</sup>

Primary alkyl ethers can be selectively cleaved to carboxylic acids by aqueous  $\text{Br}_2$  ( $\text{RCH}_2\text{OR}' \rightarrow \text{RCOOH}$ ).<sup>109</sup> Aldehydes  $\text{RCHO}$  can be directly converted to carboxylic esters  $\text{RCOOR}'$  by treatment with  $\text{Br}_2$  in the presence of an alcohol.<sup>366</sup>

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

### 9-23 Oxidation of Olefins to Aldehydes and Ketones 1/Oxo-(1/→2/hydro)-migr-attachment



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

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

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

<sup>361</sup>Blum; Shvo *J. Organomet. Chem.* **1984**, 263, 93, *Isr. J. Chem.* **1984**, 24, 144.

<sup>362</sup>Nagashima; Sato; Tsuji *Tetrahedron* **1985**, 41, 5645.

<sup>363</sup>Murahashi; Naota; Ito; Maeda; Taki *J. Org. Chem.* **1987**, 52, 4319. For another method, see Markó; Mekhafia; Ollis *Synlett* **1990**, 347.

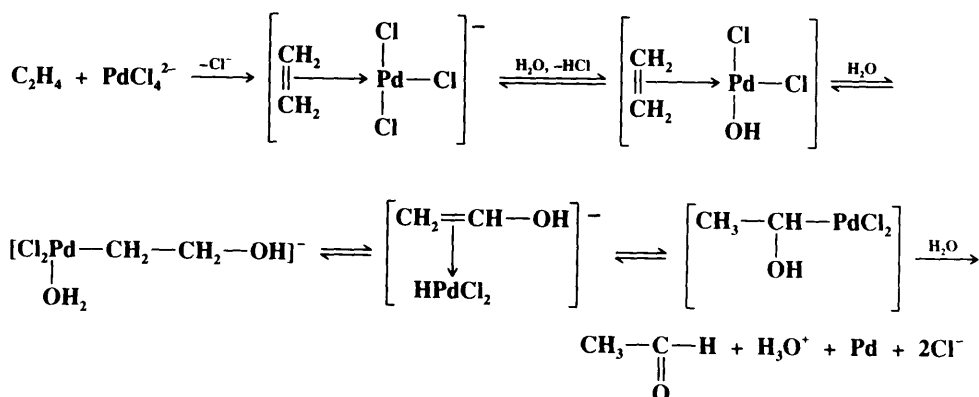
<sup>364</sup>Stavber; Planinšek; Zupan *Tetrahedron Lett.* **1989**, 30, 6095.

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

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

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

(the *Wacker process*), but it is also suitable for laboratory preparations. The palladium chloride is reduced to palladium. Because the reagent is expensive, the reaction is usually carried out with a cooxidant, most often  $\text{CuCl}_2$ , whose function is to reoxidize the Pd to Pd(II). The  $\text{CuCl}_2$  is reduced to Cu(I), which itself is reoxidized to Cu(II) by air, so that atmospheric oxygen is the only oxidizing agent actually used up. Many other cooxidants have been tried, among them  $\text{O}_3$ ,  $\text{Fe}^{3+}$ , and  $\text{PbO}_2$ . The principal product is an aldehyde only from ethylene: With other olefins Markovnikov's rule is followed, and ketones are formed predominantly. The generally accepted mechanism involves  $\pi$  complexes of palladium.<sup>368</sup>



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

Similar reactions have been carried out with other oxidizing agents. An example involving migration of an alkyl group instead of hydrogen is oxidation of  $\text{Me}_2\text{C}=\text{CMe}_2$  with peroxytrifluoroacetic acid–boron trifluoride to give  $\text{Me}_3\text{COME}$  (pinacolone).<sup>369</sup> This reaction consists of epoxidation (5-36) followed by pinacol rearrangement of the epoxide (8-2). A migration is also involved in the conversion of  $\text{ArCH}=\text{CHCH}_3$  to  $\text{ArCH}(\text{CH}_3)\text{CHO}$  by treatment with  $\text{I}_2\text{--Ag}_2\text{O}$  in aqueous dioxane.<sup>370</sup>

Other reagents used have been chromyl chloride<sup>371</sup> (e.g.,  $\text{Me}_3\text{CCH}_2\text{CMe}=\text{CH}_2 \rightarrow \text{Me}_3\text{CCH}_2\text{CHMeCHO}$ ),  $\text{Pb}(\text{OAc})_4\text{--F}_3\text{CCOOH}$ <sup>372</sup> (e.g.,  $\text{PhCH}=\text{CH}_2 \rightarrow \text{PhCH}_2\text{CHO}$ ), thallium(III) nitrate–methanol<sup>373</sup> (e.g., cyclohexene  $\rightarrow$  cyclopentanecarboxaldehyde),  $\text{Cl}_2$  or  $\text{Br}_2$  and  $\text{AgNO}_3$ ,<sup>374</sup> disiamylborane followed by pyridinium chlorochromate,<sup>375</sup>  $\text{H}_2\text{O}_2$  and a Pd catalyst,<sup>376</sup>  $\text{H}_2\text{O--PdCl}_2$ –polyethylene glycol,<sup>377</sup>  $\text{O}_2$  and a catalyst,<sup>378</sup>  $\text{CrO}_3\text{--H}_2\text{SO}_4\text{--Hg(II)}$

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

<sup>369</sup>Hart; Lerner J. *Org. Chem.* **1967**, 32, 2669.

<sup>370</sup>Kikuchi; Kogure; Toyoda *Chem. Lett.* **1984**, 341.

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

<sup>372</sup>Lethbridge; Norman; Thomas J. *Chem. Soc., Perkin Trans. 1* **1973**, 35.

<sup>373</sup>McKillop; Hunt; Kienzle; Bigham; Taylor J. *Am. Chem. Soc.* **1973**, 95, 3635. See also Grant; Liao; Low *Aust. J. Chem.* **1975**, 28, 903.

<sup>374</sup>Kakis; Brase; Oshima J. *Org. Chem.* **1971**, 36, 4117.

<sup>375</sup>Brown; Kulkarni; Rao *Synthesis* **1980**, 151.

<sup>376</sup>Roussel; Mimoun J. *Org. Chem.* **1980**, 45, 5387.

<sup>377</sup>Alper; Januszkiwicz; Smith *Tetrahedron Lett.* **1985**, 26, 2263.

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

salts,<sup>379</sup>  $\text{HgSO}_4\text{-H}_2\text{O}$ ,<sup>380</sup> and  $\text{Hg}(\text{OAc})_2$  followed by  $\text{PdCl}_2$ .<sup>381</sup> The reaction has also been accomplished electrochemically.<sup>382</sup>

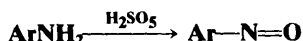
Alkenes have also been converted to more-highly-oxidized products. Examples are: (1) Treatment with  $\text{KMnO}_4$  in aqueous acetone containing acetic acid gives  $\alpha$ -hydroxy ketones.<sup>383</sup> (2) 1,2-Disubstituted and trisubstituted alkenes give  $\alpha$ -chloro ketones when oxidized with chromyl chloride in acetone:  $\text{RCH}=\text{CR}'\text{R}'' \rightarrow \text{RCOCClR}'\text{R}''$ .<sup>384</sup> (3)  $\alpha$ -Iodo ketones can be prepared by treating alkenes with bis(sym-collidine)iodine(I) tetrafluoroborate.<sup>385</sup> (4)  $\text{KMnO}_4$  in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.<sup>386</sup>

Enol ethers are oxidized to carboxylic esters ( $\text{RCH}=\text{CHOR}' \rightarrow \text{RCH}_2\text{COOR}'$ ) with pyridinium chlorochromate<sup>387</sup> and enamines to  $\alpha$ -amino ketones ( $\text{R}^1\text{CH}=\text{CR}^2\text{NR}^3 \rightarrow \text{R}^1\text{COCR}^2\text{NR}^3$ ) with N-sulfonyloxaziridines.<sup>388</sup> Enamines  $\text{R}^1\text{R}^4\text{C}=\text{CR}^2\text{NR}^3$  ( $\text{R}^4 \neq \text{H}$ ) do not give these products, but lose the amino group to give  $\alpha$ -hydroxy ketones  $\text{R}^1\text{R}^4\text{C}(\text{OH})\text{COR}^2$ .<sup>388</sup> Carboxylic acids can be prepared from terminal alkynes ( $\text{RC}\equiv\text{CH} \rightarrow \text{RCH}_2\text{COOH}$ ) by conversion of the alkyne to its thiophenyl ether ( $\text{RC}\equiv\text{CSPh}$ ) and treatment of this with  $\text{HgSO}_4$  in  $\text{HOAc-H}_2\text{SO}_4$ .<sup>389</sup>

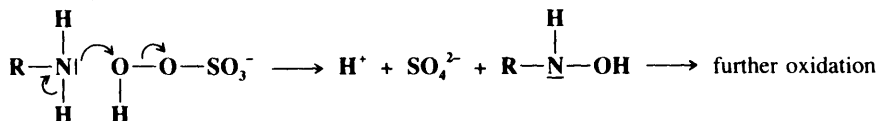
OS VI, 1028; VII, 137; 67, 121.

## 9-24 Oxidation of Amines to Nitroso Compounds and Hydroxylamines

### N-Oxo-de-dihydro-bisubstitution



Primary aromatic amines can be oxidized<sup>390</sup> to nitroso compounds. Most often the conversion is accomplished by Caro's acid ( $\text{H}_2\text{SO}_5$ ) or with  $\text{H}_2\text{O}_2$  in  $\text{HOAc}$ .<sup>391</sup> 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  $\alpha$  hydrogen. If there is an  $\alpha$  hydrogen, the compound tautomerizes to the oxime.<sup>392</sup> Among the reagents used for this oxidation are sodium perborate<sup>393</sup> and  $\text{Na}_2\text{WO}_4\text{-H}_2\text{O}_2$ .<sup>394</sup> The mechanism with  $\text{H}_2\text{SO}_5$  has been postulated to be an example of category 5 (p. 1161).<sup>395</sup>



<sup>379</sup>Rogers; McDermott; Whitesides *J. Org. Chem.* **1975**, *40*, 3577.

<sup>380</sup>Arzoumanian; Aune; Guitard; Metzger *J. Org. Chem.* **1974**, *39*, 3445.

<sup>381</sup>Rodeheaver; Hunt *Chem. Commun.* **1971**, 818. See also Hunt; Rodeheaver *Tetrahedron Lett.* **1972**, 3595.

<sup>382</sup>See Tsuji; Minato *Tetrahedron Lett.* **1987**, *28*, 3683.

<sup>383</sup>Srinivasan; Lee *Synthesis* **1979**, 520. See also Baskaran; Das; Chandrasekaran *J. Org. Chem.* **1989**, *54*, 5182.

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

<sup>385</sup>Evans; Schauble *Synthesis* **1986**, 727.

<sup>386</sup>Sharpless; Lauer; Repić; Teranishi; Williams, *J. Am. Chem. Soc.* **1971**, *93*, 3303; Jensen; Sharpless *J. Org. Chem.* **1974**, *39*, 2314.

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

<sup>388</sup>Davis; Sheppard *Tetrahedron Lett.* **1988**, *29*, 4365.

<sup>389</sup>Abrams *Can. J. Chem.* **1983**, *61*, 2423.

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

<sup>391</sup>Holmes; Bayer *J. Am. Chem. Soc.* **1960**, *82*, 3454.

<sup>392</sup>For example, see Kahr; Berther *Chem. Ber.* **1960**, *93*, 132.

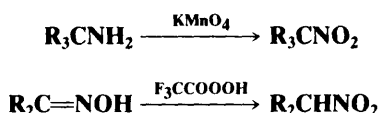
<sup>393</sup>Zajac; Darcy; Subong; Buzby *Tetrahedron Lett.* **1989**, *30*, 6495.

<sup>394</sup>Corey; Gross *Org. Synth.* **65**, 166.

<sup>395</sup>Gragerov; Levit *J. Gen. Chem. USSR* **1960**, *30*, 3690.

Secondary amines  $R_2NH$  are oxidized to hydroxylamines  $R_2NHOH$  (which are resistant to further oxidation) by dimethyldioxirane<sup>396</sup> and by benzoyl peroxide and  $Na_2HPO_4$ .<sup>397</sup>  
OS III, 334; 65, 166.

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

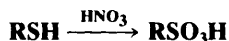


Tertiary alkyl primary amines can be oxidized to nitro compounds in excellent yields with  $KMnO_4$ .<sup>398</sup> This type of nitro compound is not easily prepared in other ways. All classes of primary amine (including primary, secondary, and tertiary alkyl as well as aryl) are oxidized to nitro compounds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

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

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

**9-26** Oxidation of Thiols and Other Sulfur Compounds to Sulfonic Acids  
**Thiol-sulfonic acid oxidation**



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

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

<sup>397</sup>Biloski; Ganem *Synthesis* **1983**, 537.

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

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

<sup>400</sup>Keinan; Mazur *J. Org. Chem.* **1977**, *42* 844; Bachman; Strawn *J. Org. Chem.* **1968**, *33*, 313.

<sup>401</sup>Emmons *J. Am. Chem. Soc.* **1957**, *79*, 5528; Gilbert; Borden *J. Org. Chem.* **1979**, *44*, 659.

<sup>402</sup>Howe; Hiatt *J. Org. Chem.* **1970**, *35*, 4007. See also Nielsen; Atkins; Norris; Coon; Sitzmann *J. Org. Chem.* **1980**, *45*, 2341.

<sup>402a</sup>Kol; Rozen *J. Chem. Soc., Chem. Commun.* **1991**, 567.

<sup>403</sup>McKillop; Tarbin *Tetrahedron* **1987**, *43*, 1753.

<sup>404</sup>Eaton; Wicks *J. Org. Chem.* **1988**, *53*, 5353.

<sup>405</sup>Corey; Samuelsson; Luzzio *J. Am. Chem. Soc.* **1984**, *106*, 3682.

<sup>406</sup>See Boyer, in Feuer, Ref. 398, pp. 264-265.

<sup>407</sup>For a review of the oxidation of disulfides, see Savage; Maclaren, in Kharasch; Meyers *Organic Sulfur Compounds*, vol. 2; pp. 367-402, Pergamon, New York, 1966.

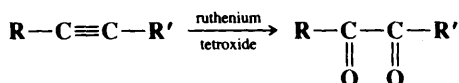
<sup>408</sup>For a general review of the oxidation of thiols, see Capozzi; Modena, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 785-839. For a review specifically on the oxidation to sulfonic acids, see Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965,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

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

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

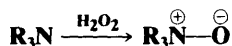
## D. Reactions in Which Oxygen is Added to the Substrate

### 9-27 The Oxidation of Alkynes to $\alpha$ -Diketones Dioxo-biaddition



Internal alkynes have been oxidized<sup>411</sup> to  $\alpha$ -diketones by several oxidizing agents,<sup>412</sup> including ruthenium tetroxide,<sup>413</sup> neutral  $\text{KMnO}_4$ ,<sup>414</sup>  $\text{SeO}_2$  with a small amount of  $\text{H}_2\text{SO}_4$ ,<sup>415</sup> bis(trifluoroacetoxy)iodobenzene,<sup>416</sup>  $\text{NaIO}_4$ - $\text{RuO}_2$ ,<sup>417</sup>  $\text{I}_2$ - $\text{Me}_2\text{SO}$ ,<sup>418</sup> and thallium(III) nitrate,<sup>206</sup> as well as by electrooxidation.<sup>419</sup> Ozone generally oxidizes triple-bond compounds to carboxylic acids (9-9), but  $\alpha$ -diketones are sometimes obtained instead.  $\text{SeO}_2$  with a small amount of  $\text{H}_2\text{SO}_4$  oxidizes arylacetylenes to  $\alpha$ -keto acids ( $\text{ArC}\equiv\text{CH} \rightarrow \text{ArCOCO}_2\text{H}$ ),<sup>415</sup> while  $\text{H}_2\text{O}_2$ - $\text{Hg}(\text{OAc})_2$  together with a molybdenate salt oxidizes them to  $\alpha$ -keto aldehydes, though yields are not high.<sup>420</sup>

### 9-28 Oxidation of Tertiary Amines to Amine Oxides N-Oxygen-attachment



Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peracids are also important reagents for this purpose. Pyridine and its derivatives are oxidized only by peracids.<sup>421</sup> In the attack by hydrogen peroxide there is first formed a trialkylammonium peroxide, a hydrogen-bonded complex represented as  $\text{R}_3\text{N}\cdot\text{H}_2\text{O}_2$ , which can be isolated.<sup>422</sup> The decomposition of this complex probably involves an attack by the

<sup>409</sup>Wallace; Schriesheim *Tetrahedron* **1965**, 21, 2271.

<sup>410</sup>For a review, see Gilbert, Ref. 408, pp. 202-214.

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

<sup>412</sup>For a list of reagents, with references, see Hudlický, Ref. 11, p. 92.

<sup>413</sup>Gopal; Gordon *Tetrahedron Lett.* **1971**, 2941.

<sup>414</sup>Khan; Newman *J. Org. Chem.* **1952**, 17, 1063; Srinivasan; Lee *J. Org. Chem.* **1979**, 44, 1574; Lee; Lee; Chandler *J. Org. Chem.* **1985**, 50, 4306.

<sup>415</sup>Sonoda; Yamamoto; Murai; Tsutsumi *Chem. Lett.* **1972**, 229.

<sup>416</sup>Vasil'eva; Khalfina; Karpitskaya; Merkushev *J. Org. Chem. USSR* **1987**, 23, 1967.

<sup>417</sup>Zibuck; Seebach *Helv. Chim. Acta* **1988**, 71, 237.

<sup>418</sup>Yusubov; Filimonov *Synthesis* **1991**, 131.

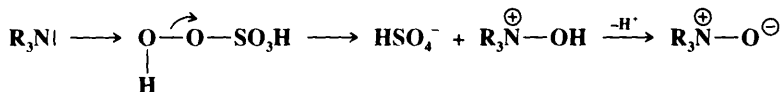
<sup>419</sup>Torii; Inokuchi; Hirata *Synthesis* **1987**, 377.

<sup>420</sup>Ballistreri; Failla; Tomaselli *J. Org. Chem.* **1988**, 53, 830.

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

<sup>422</sup>Oswald; Guertin *J. Org. Chem.* **1963**, 28, 651.

OH<sup>+</sup> moiety of the H<sub>2</sub>O<sub>2</sub>. Oxidation with Caro's acid has been shown to proceed in this manner:<sup>423</sup>

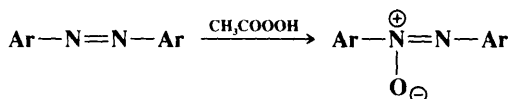


This mechanism is the same as that of **9-24**; the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peracids is probably the same. Racemic β-hydroxy tertiary amines have been resolved by oxidizing them with *t*-BuOOH and a chiral catalyst—one enantiomer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

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

### 9-29 Oxidation of Azobenzenes to Azoxybenzenes

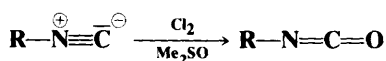
#### N-Oxygen-attachment



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

### 9-30 Oxidation of Isocyanides to Isocyanates

#### Oxygen-attachment

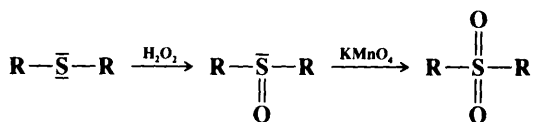


Isocyanides have been oxidized to isocyanates with HgO and with O<sub>3</sub>, as well as with a halogen and dimethyl sulfoxide (or pyridine N-oxide).<sup>428</sup> In the latter case the oxidizing agent is the halogen, which converts the isocyanide to R–N=CCl<sub>2</sub> which is hydrolyzed to the isocyanate.<sup>429</sup> Cyanide ion has been oxidized to cyanate ion with many oxidizing agents.

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

### 9-31 Oxidation of Thioethers to Sulfoxides and Sulfones

#### S-Oxygen-attachment



<sup>423</sup>Ogata; Tabushi *Bull. Chem. Soc. Jpn.* **1958**, 31, 969.

<sup>424</sup>Miyano; Lu; Viti; Sharpless *J. Org. Chem.* **1985**, 50, 4350.

<sup>425</sup>For reviews, see Yandovskii; Gidasov; Tselinskii *Russ. Chem. Rev.* **1981**, 50, 164-179; Newbold, *Ref. 136*, pp. 557-563, 573-593.

<sup>426</sup>Johnson; Gould *J. Org. Chem.* **1974**, 39, 407.

<sup>427</sup>Mitsuhashi; Simamura; Tezuka *Chem. Commun.* **1970**, 1300.

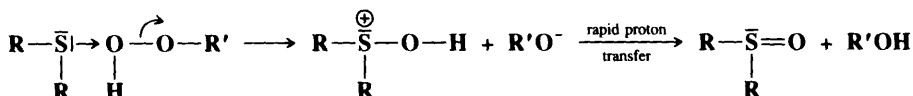
<sup>428</sup>For a review, see Simándi, *Ref. 411*, pp. 559-562.

<sup>429</sup>Johnson; Daughhetee *J. Org. Chem.* **1964**, 29, 246; Johnson; Krutzsch *J. Org. Chem.* **1967**, 32, 1939.

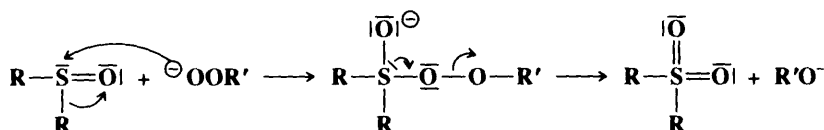
<sup>430</sup>Tanaka; Uemura; Okano *Bull. Chem. Soc. Jpn.* **1977**, 50, 2785.

Thioethers can be oxidized to sulfoxides by 1 mole of 30%  $\text{H}_2\text{O}_2$  or by many other oxidizing agents,<sup>431</sup> including  $\text{NaIO}_4$ ,<sup>432</sup>  $t\text{-BuOCl}$ ,<sup>433</sup> calcium hypochlorite  $\text{Ca}(\text{OCl})_2$ ,<sup>434</sup> sodium chlorite  $\text{NaClO}_2$ ,<sup>434</sup> sodium hypochlorite  $\text{NaOCl}$ ,<sup>435</sup> dioxiranes,<sup>436</sup>  $\text{HNO}_3$  and an  $\text{AuCl}_4^-$  catalyst,<sup>437</sup>  $\text{O}_2$  and a ceric ammonium nitrate catalyst,<sup>438</sup> acyl nitrites,<sup>439</sup> sodium perborate,<sup>403</sup> and peracids.<sup>440</sup> Sulfoxides can be further oxidized to sulfones by another mole of  $\text{H}_2\text{O}_2$ ,  $\text{KMnO}_4$ , sodium perborate, potassium hydrogen persulfate  $\text{KHSO}_5$ ,<sup>441</sup> or a number of other agents. If enough oxidizing agent is present, thioethers can be directly converted to sulfones without isolation of the sulfoxides.<sup>442</sup> These reactions give high yields, and many functional groups do not interfere.<sup>443</sup> As with tertiary amines (9-28), racemic thioethers can be kinetically resolved by oxidation to sulfoxides with an optically active reagent, and this has often been done.<sup>444</sup> Selenides  $\text{R}_2\text{Se}$  can be oxidized to selenoxides and selenones.<sup>445</sup>

When the oxidizing agent is a peroxide, the mechanism<sup>446</sup> of oxidation to the sulfoxide is similar to that of 9-28.<sup>447</sup>



The second oxidation, which is normally slower than the first<sup>448</sup> (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 ( $\text{R}'\text{OO}^-$ ) also attacks the SO group as a nucleophile:<sup>449</sup>



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

<sup>432</sup>Leonard; Johnson *J. Org. Chem.* **1962**, 27, 282; Hiskey; Harpold *J. Org. Chem.* **1967**, 32, 3191.

<sup>433</sup>Walling; Mintz *J. Org. Chem.* **1967**, 32, 1286; Skattebøl; Boulette; Solomon *J. Org. Chem.* **1967**, 32, 3111.

<sup>434</sup>Weber; Scheider; Salami; Paquer *Recl. Trav. Chim. Pays-Bas* **1986**, 105, 99.

<sup>435</sup>Ramsden; Drago; Riley *J. Am. Chem. Soc.* **1989**, 111, 3958.

<sup>436</sup>Colonna; Gaggero *Tetrahedron Lett.* **1989**, 30, 6233.

<sup>437</sup>Gasparrini; Giovannoli; Misiti; Natile; Palmieri *J. Org. Chem.* **1990**, 55, 1323.

<sup>438</sup>Riley; Smith; Correa *J. Am. Chem. Soc.* **1988**, 110, 177.

<sup>439</sup>Louw; Vermeeren; van Asten; Ullée *J. Chem. Soc., Chem. Commun.* **1976**, 496.

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

<sup>441</sup>Trost; Curran *Tetrahedron Lett.* **1981**, 22, 1287.

<sup>442</sup>For a review, see Schank, in Patai; Rappoport; Stirling, Ref. 431, pp. 165-231, pp. 205-213.

<sup>443</sup>For a review of the oxidation of  $\alpha$ -halo sulfides, see Venier; Barager *Org. Prep. Proced. Int.* **1974**, 6, 77-102, pp. 85-86.

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

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

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

<sup>447</sup>Modena; Todesco *J. Chem. Soc.* **1962**, 4920, 1962, and references cited therein.

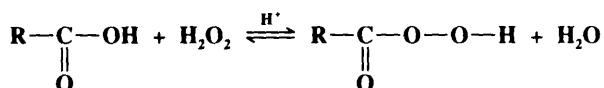
<sup>448</sup>There are some reagents that oxidize sulfoxides in preference to sulfides, e.g.,  $\text{NaMnO}_4$ ; see Henbest; Khan *Chem. Commun.* **1968**, 1036.

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

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

### 9-32 Oxidation of Carboxylic Acids to Peroxy Acids

#### Peroxy-de-hydroxy-substitution

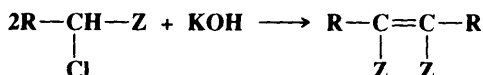


The oxidation of carboxylic acids with  $\text{H}_2\text{O}_2$  and an acid catalyst is the best general method for the preparation of peroxy acids.<sup>450</sup> The most common catalyst for aliphatic R is concentrated sulfuric acid. The reaction is an equilibrium and is driven to the right by removal of water or by the use of excess reagents. For aromatic R the best catalyst is methanesulfonic acid, which is also used as the solvent.

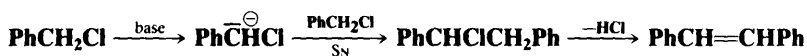
### E. Oxidative Coupling

#### 9-33 Coupling Involving Carbanions

#### De-hydro,chloro-coupling



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



$\alpha,\alpha$ -Dibromotoluenes  $\text{ArCHBr}_2$  give tolanes  $\text{ArC}\equiv\text{CAr}$ , by debromination of the intermediates  $\text{ArCBr}=\text{CBrAr}$ .<sup>453</sup> In a related reaction, diarylmethane dihalides  $\text{Ar}_2\text{CX}_2$  have been dimerized to tetraaryl alkenes  $\text{Ar}_2\text{C}=\text{CAr}_2$  with sodium selenide,<sup>454</sup> with copper,<sup>455</sup> with iron(II) oxalate dihydrate,<sup>456</sup> and with iron pentacarbonyl.<sup>457</sup>

A somewhat different type of coupling is observed when salts of  $\beta$ -keto esters, aryl-acetonitriles  $\text{ArCH}_2\text{CN}$ , and other compounds of the form  $\text{ZCH}_2\text{Z}'$  are treated with an

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

<sup>451</sup>For discussion, see Saunders; Cockerill *Mechanisms of Elimination Reactions*; Wiley: New York, 1973, pp. 548-554.

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

<sup>453</sup>Vernigor; Shalaev; Luk'yanets *J. Org. Chem. USSR* **1981**, 17, 317.

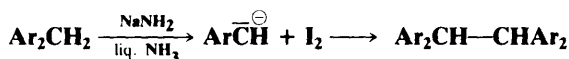
<sup>454</sup>Okamoto; Yano *J. Org. Chem.* **1969**, 34, 1492.

<sup>455</sup>Buckles; Matlack *Org. Synth. IV*, 914.

<sup>456</sup>Khurana; Maikap; Mehta *Synthesis* **1990**, 731.

<sup>457</sup>Coffey *J. Am. Chem. Soc.* **1961**, 83, 1623.

oxidizing agent such as iodine,<sup>458</sup>  $\text{PbO}_2$ ,<sup>459</sup>  $\text{Ag}_2\text{O}$ ,<sup>460</sup>  $\text{Cu(II)}$  salts,<sup>461</sup> or a  $\text{Cu}$ -amine- $\text{O}_2$  system,<sup>462</sup> e.g.,

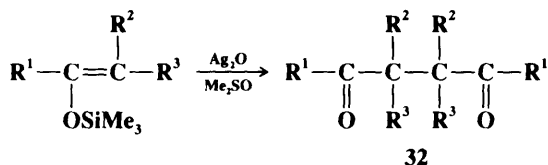


In this case the product is a substituted alkane rather than an alkene. This reaction has been used to close rings.<sup>463</sup> Arylmethanesulfonyl chlorides  $\text{ArCH}_2\text{SO}_2\text{Cl}$  couple to give  $\text{ArCH}=\text{CHAr}$  when treated with  $\text{Et}_3\text{N}$ .<sup>464</sup>

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

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

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



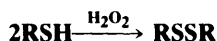
Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with  $\text{Ag}_2\text{O}$  in dimethyl sulfoxide or certain other polar aprotic solvents.<sup>465</sup> The reaction has been performed with  $\text{R}^2, \text{R}^3 = \text{hydrogen or alkyl}$ , though best yields are obtained when  $\text{R}^2 = \text{R}^3 = \text{H}$ . 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- $\text{BF}_3\text{-Et}_2\text{O}$ ,<sup>466</sup> ceric ammonium nitrate,<sup>467</sup> and lead tetraacetate.<sup>468</sup> If  $\text{R}^1 = \text{OR}$  (in which case the substrate is a ketene silyl acetal), dimerization with  $\text{TiCl}_4$  leads to a dialkyl succinate (32,  $\text{R}^1 = \text{OR}$ ).<sup>469</sup>

In a similar reaction, lithium enolates  $\text{RC(Li)}=\text{CH}_2$  were dimerized to 1,4-diketones  $\text{RCOCH}_2\text{CH}_2\text{COR}$  with  $\text{CuCl}_2$ ,  $\text{FeCl}_3$ , or copper(II) triflate, in a nonprotic solvent.<sup>470</sup>

OS 69, 173.

### 9-35 Oxidation of Thiols to Disulfides

#### S-De-hydrogen-coupling



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

<sup>459</sup>Brettell; Seddon *J. Chem. Soc., C* **1970**, 1320.

<sup>460</sup>Ito; Fujii; Konoike; Saegusa *Synth. Commun.* **1976**, 6, 429.

<sup>461</sup>Rathke; Lindert *J. Am. Chem. Soc.* **1971**, 93, 4605; Baudin; Julia; Rolando; Verpeaux *Bull. Soc. Chim. Fr.* **1987**, 493.

<sup>462</sup>de Jongh; de Jonge; Mijs *J. Org. Chem.* **1971**, 36, 3160.

<sup>463</sup>Chung; Dunn *J. Org. Chem.* **1983**, 48, 1125.

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

<sup>465</sup>Ito; Konoike; Saegusa *J. Am. Chem. Soc.* **1975**, 97, 649.

<sup>466</sup>Moriarty; Prakash; Duncan *J. Chem. Soc., Perkin Trans. I* **1987**, 559.

<sup>467</sup>Baclocchi; Casu; Ruzziconi *Tetrahedron Lett.* **1989**, 30, 3707.

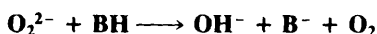
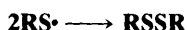
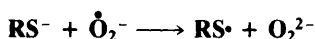
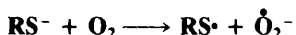
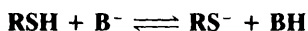
<sup>468</sup>Moriarty; Penmasta; Prakash *Tetrahedron Lett.* **1987**, 28, 873.

<sup>469</sup>Inaba; Ojima *Tetrahedron Lett.* **1977**, 2009. See also Totten; Wenke; Rhodes *Synth. Commun.* **1985**, 15, 291, 301.

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

Thiols are easily oxidized to disulfides.<sup>471</sup> Hydrogen peroxide is the most common reagent,<sup>472</sup> but many oxidizing agents give the reaction, among them thallium(III) acetate,<sup>473</sup>  $\text{Me}_2\text{SO}-\text{I}_2$ ,<sup>474</sup>  $\text{Br}_2$  under phase transfer conditions,<sup>475</sup> methoxytributyltin- $\text{FeCl}_3$ ,<sup>476</sup> sodium perborate,<sup>477</sup>  $\text{NO}$ ,<sup>478</sup> and  $\text{NO}_2$ .<sup>478</sup> It can also be done electrochemically.<sup>479</sup> However, strong oxidizing agents may give **9-26**. Even the oxygen in the air oxidizes thiols on standing, if a small amount of base is present. The reaction is reversible (see **9-61**), and the interconversion between cysteine and cystine is an important one in biochemistry.

The mechanism has been studied for several oxidizing agents and varies with the agent.<sup>480</sup> For oxygen it is<sup>481</sup>

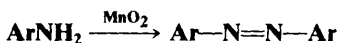


With respect to the sulfur, this mechanism is similar to that of **4-17**, involving as it does loss of a proton, oxidation to a free radical, and radical coupling.

Unsymmetrical disulfides can be prepared<sup>482</sup> by treatment of a thiol  $\text{RSH}$  with diethyl azodicarboxylate  $\text{EtOOCN}=\text{NCOOEt}$  to give an adduct, to which another thiol  $\text{R}'\text{SH}$  is then added, producing the disulfide  $\text{RSSR}'$ .<sup>483</sup>

OS **III**, 86, 116.

### 9-36 Oxidation of Amines to Azo or Azoxy Compounds N-De-bishydrogen-coupling



Primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them  $\text{MnO}_2$ , lead tetraacetate,  $\text{O}_2$  and a base, barium permanganate,<sup>484</sup> and sodium perborate in acetic acid. *t*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.<sup>485</sup>

OS **V**, 341.

<sup>471</sup>For a review, see Capozzi; Modena, Ref. 408, pp. 785-839. For a list of reagents, with references, see Block, Ref. 440.

<sup>472</sup>It has been pointed out that, nevertheless,  $\text{H}_2\text{O}_2$  is not a very good reagent for this reaction, since it gives sulfonic acids (**9-26**) as well as disulfides: Evans; Doi; Musker *J. Org. Chem.* **1990**, 55, 2337.

<sup>473</sup>Uemura; Tanaka; Okano *Bull. Chem. Soc. Jpn.* **1977**, 50, 220.

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

<sup>475</sup>Drabowicz; Mikołajczyk *Synthesis* **1980**, 32.

<sup>476</sup>Sato; Otera; Nozaki *Tetrahedron Lett.* **1990**, 31, 3591.

<sup>477</sup>McKillop; Koyuncu *Tetrahedron Lett.* **1990**, 31, 5007.

<sup>478</sup>Pryor; Church; Govindan; Crank *J. Org. Chem.* **1982**, 47, 156.

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

<sup>480</sup>See Tarbell, in Kharasch, *Organic Sulfur Compounds*; Pergamon: Elmsford, NY, 1961, pp. 97-102.

<sup>481</sup>Wallace; Schriesheim; Bartok *J. Org. Chem.* **1963**, 28, 1311.

<sup>482</sup>Mukaiyama; Takahashi *Tetrahedron Lett.* **1968**, 5907.

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

<sup>484</sup>Firouzabadi; Mostafavipoor *Bull. Chem. Soc. Jpn.* **1983**, 56, 914.

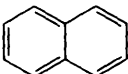
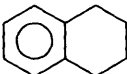


<sup>485</sup>Kosswig *Liebigs Ann. Chem.* **1971**, 749, 206.

**Reductions: Selectivity**<sup>486</sup>

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<sup>487</sup> and hydrogen (with a catalyst).<sup>488</sup> Many different metal-hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced chemoselectively. Tables 19.2, 19.3, and 19.4 list the reactivity of various functional groups toward catalytic hydrogenation,  $\text{LiAlH}_4$ , and  $\text{BH}_3$ , respectively.<sup>489</sup> Table 19.5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.<sup>490</sup> Of course, the tables cannot be exact, because the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce

**TABLE 19.2** The ease of reduction of various functional groups toward catalytic hydrogenation<sup>489</sup>

The groups are listed in approximate order of ease of reduction

Reaction	Substrate	Product	
0-83	$\text{RCOCl}$	$\text{RCHO}$	Easiest
9-47	$\text{RNO}_2$	$\text{RNH}_2$	
5-9	$\text{RC}\equiv\text{CR}$	$\text{RCH=CHR}$	
6-25	$\text{RCHO}$	$\text{RCH}_2\text{OH}$	
5-9	$\text{RCH=CHR}$	$\text{RCH}_2\text{CH}_2\text{R}$	
6-25	$\text{RCOR}$	$\text{RCHOHR}$	
0-79	$\text{ArCH}_2\text{OR}$	$\text{ArCH}_3 + \text{ROH}$	
6-27	$\text{RC}\equiv\text{N}$	$\text{RCH}_2\text{NH}_2$	
5-10			
9-42	$\text{RCOOR}'$	$\text{RCH}_2\text{OH} + \text{R}'\text{OH}$	
9-39	$\text{RCONHR}'$	$\text{RCH}_2\text{NHR}'$	
5-10			Most difficult
9-38	$\text{RCOO}^-$		
			Inert

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

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


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

<sup>489</sup>Table 19.2 is from House, Ref. 10, p. 9. Tables 19.3 and 19.4 are from Brown, Ref. 487, pp. 213 and 232, respectively.

<sup>490</sup>The first ten columns are from Brown; Krishnamurthy, Ref. 487, p. 604. The column on  $(i\text{-Bu})_2\text{AlH}$  is from Yoon; Gyoung *J. Org. Chem.* **1985**, 50, 2443; the one on  $\text{NaAlEt}_2\text{H}_2$  from Stinson, *Chem. Eng. News* Nov. 3, **1980**, 58, No. 44, 19; and the one on  $\text{LiBEt}_3\text{H}$  from Brown; Kim; Krishnamurthy *J. Org. Chem.* **1980**, 45, 1. For similar tables that show additional reducing agents, see Pelter; Smith; Brown, Ref. 494, p. 129; Hajós, Ref. 10, pp. 16-17. For tables showing which agents reduce a wide variety of functional groups, see Hudlický, Ref. 486, pp. 177-200.

**TABLE 19.3** The ease of reduction of various functional groups with  $\text{LiAlH}_4$  in ether<sup>489</sup>


However,  $\text{LiAlH}_4$  is a very powerful reagent, and much less chemoselectivity is possible here than with most of the other metal hydrides

Reaction	Substrate	Product	
6-25	<b>RCHO</b>	<b>RCH<sub>2</sub>OH</b>	Easiest
6-25	<b>RCOR</b>	<b>RCHOHR</b>	
9-45	<b>RCOCl</b>	<b>RCH<sub>2</sub>OH</b>	
9-42	Lactone	Diol	
0-80	<b>RCH—CHR</b> 	<b>RCH<sub>2</sub>CHOHR</b>	
9-42	<b>RCOOR'</b>	<b>RCH<sub>2</sub>OH + R'OH</b>	Most difficult Inert
9-38	<b>RCOOH</b>	<b>RCH<sub>2</sub>OH</b>	
9-38	<b>RCOO<sup>-</sup></b>	<b>RCH<sub>2</sub>OH</b>	
9-39	<b>RCONR'<sub>2</sub></b>	<b>RCH<sub>2</sub>NR'<sub>2</sub></b>	
6-27	<b>RC≡N</b>	<b>RCH<sub>2</sub>NH<sub>2</sub></b>	
9-47	<b>RNO<sub>2</sub></b>	<b>RNH<sub>2</sub></b>	
9-67	<b>ArNO<sub>2</sub></b>	<b>ArN=NAr</b>	
5-9	<b>RCH=CHR</b>		

which groups.<sup>491</sup>  $\text{LiAlH}_4$  is very powerful and unselective reagent.<sup>492</sup> Consequently, other metal hydrides are generally used when chemoselectivity is required. As mentioned on p. 917, a number of less reactive (and more selective) reagents have been prepared by replacing some of the hydrogens of  $\text{LiAlH}_4$  with alkoxy groups (by treatment of  $\text{LiAlH}_4$  with  $\text{ROH}$ ).<sup>493</sup> Most of the metal hydrides are nucleophilic reagents and attack the carbon atom of a carbon-hetero single or multiple bond. However,  $\text{BH}_3$ <sup>494</sup> and  $\text{AlH}_3$ <sup>495</sup> are electrophiles (Lewis acids)

**TABLE 19.4** The ease of reduction of various functional groups with borane<sup>489</sup>

It is evident that this reagent and  $\text{LiAlH}_4$  (Table 19.3) complement each other

Reaction	Substrate	Product	
9-38	<b>RCOOH</b>	<b>RCH<sub>2</sub>OH</b>	Easiest
5-12	<b>RCH=CHR</b>	<b>(RCH<sub>2</sub>CHR)<sub>3</sub>B</b>	
6-25	<b>RCOR</b>	<b>RCHOHR</b>	
6-27	<b>RCN</b>	<b>RCH<sub>2</sub>NH<sub>2</sub></b>	
0-80	<b>RCH—CHR</b> 	<b>RCH<sub>2</sub>CHOHR</b>	
9-42	<b>RCOOR'</b>	<b>RCH<sub>2</sub>OH + R'OH</b>	Most difficult Inert
0-83, 9-45	<b>RCOCl</b>		

<sup>491</sup>See also the table in Ref. 9.

<sup>492</sup>For a review of  $\text{LiAlH}_4$ , see Pizey, Ref. 10, vol. 1 pp. 101-194.

<sup>493</sup>For reviews of reductions by these reagents, see Málek Ref. 10; Málek; Černý *Synthesis* **1972**, 217-234.

<sup>494</sup>See Brown; Heim; Yoon *J. Am. Chem. Soc.* **1970**, 92, 1637; Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 319-371. For reviews of reductions with  $\text{BH}_3$ , see Wade *J. Mol. Catal.* **1983**, 18, 273-297 ( $\text{BH}_3$  and a catalyst); Lane *Chem. Rev.* **1976**, 76, 773-799, *Aldrichimica Acta* **1977**, 10, 41-51; Brown; Krishnamurthy *Aldrichimica Acta* **1979**, 12, 3-11. For reviews of reduction with borane derivatives, see Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 125-164; Pelter *Chem. Ind. (London)* **1976**, 888-896.

<sup>495</sup>See Brown; Yoon *J. Am. Chem. Soc.* **1966**, 88, 1464; Yoon; Brown *J. Am. Chem. Soc.* **1968**, 90, 2927.

**TABLE 19.5** Reactivity of various functional groups with some metal hydrides and toward catalytic hydrogenation.<sup>490</sup> ± indicates a borderline case.

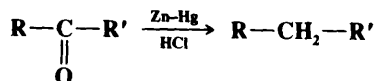
Reaction	NbH <sub>5</sub> in EtOH	NbH <sub>5</sub> + LiCl in diglyme	NbH <sub>5</sub> + AlCl <sub>3</sub> in diglyme	BH <sub>3</sub> -THF <sup>487</sup>	Bis-3-methyl-2-butyl-borane (disiamylborane) in THF <sup>498</sup>	9-BBN <sup>499</sup>	LiAlH(O- <i>i</i> -Bu) <sub>3</sub> in THF	LiAlH(OMe) <sub>3</sub> in THF	LiAlH <sub>4</sub> in ether	AlH <sub>3</sub> in THF <sup>495</sup>	LiBEt <sub>3</sub> H <sup>501</sup>	( <i>i</i> -Bu) <sub>2</sub> AlH(DIBALH)	NaAlEt <sub>2</sub> H <sub>2</sub>	Catalytic hydrogenation
6-25 RCHO → RCH <sub>2</sub> OH														
6-25 RCOR → RCHOHR														
0-83 RCHO														
9-45 RCOCl → RCH <sub>2</sub> OH	+ <sup>496</sup>													
9-42 Lactone → diol														
0-80 Epoxide → alcohol														
9-42 RCOOR' → RCH <sub>2</sub> OH + R'OH														
9-38 RCOOH → RCH <sub>2</sub> OH														
9-38 RCOO <sup>-</sup> → RCH <sub>2</sub> OH														
9-39 RCONR <sub>2</sub> ' → RCH <sub>2</sub> NR <sub>2</sub> '														
0-85 RCHO														
6-27 RC≡N → RCH <sub>2</sub> NH <sub>2</sub>														
9-47 RNH <sub>2</sub>														
9-67 RN=NR														
5-9 RCH=CHR → RCH <sub>2</sub> CH <sub>2</sub> R														

and attack the hetero atom. This accounts for the different patterns of selectivity shown in the tables.

The reactions in this section are grouped into classifications based on bond changes, similar to those used for the oxidation reactions. These sections are: (A) reactions involving replacement of oxygen by hydrogen, (B) reactions in which oxygen is removed from the substrate, (C) reduction with cleavage, and (D) reductive coupling.

**A. Reactions Involving Replacement of Oxygen by Hydrogen.** In reactions 9-37 to 9-41, a C=O is reduced to a CH<sub>2</sub> group.

**9-37 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<sub>2</sub>.<sup>502</sup> The two oldest, but still very popular, methods are the *Clemmensen reduction* and the *Wolff-Kishner reduction*. The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam and aqueous HCl.<sup>503</sup> Ketones are reduced more often than aldehydes. In the Wolff-Kishner reduction,<sup>504</sup> the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The *Huang-Minlon modification*<sup>505</sup> of the Wolff-Kishner reaction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. The reaction can also be carried out under more moderate conditions (room temperature) in dimethyl sulfoxide with potassium *t*-butoxide as base.<sup>506</sup> 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.<sup>507</sup> 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,<sup>508</sup> α-hydroxy ketones give either ketones (hydrogenolysis of the OH, 0-78) or olefins, and 1,3-diones usually

<sup>502</sup>Reacts with solvent, reduced in aprotic solvents.

<sup>503</sup>Reduced to aldehyde (6-28).

<sup>504</sup>Brown; Bigley; Arora; Yoon *J. Am. Chem. Soc.* **1970**, 92, 7161. For reductions with triethylborane, see Brown; Heim; Yoon *J. Org. Chem.* **1972**, 37, 2942.

<sup>505</sup>Brown; Krishnamurthy; Yoon *J. Org. Chem.* **1976**, 41, 1778.

<sup>506</sup>Reduced to hydroxylamine (9-49).

<sup>507</sup>Brown; Kim; Krishnamurthy, Ref. 490. For a review of the synthesis of alkyl-substituted borohydrides, see Brown; Singaram; Singaram *J. Organomet. Chem.* **1982**, 239, 43-64.

<sup>508</sup>For a review, see Reusch, in Augustine, Ref. 486, pp. 171-211.

<sup>509</sup>For a review, see Vedejs *Org. React.* **1975**, 22, 401-422. For a discussion of experimental conditions, see Fieser; Fieser, Ref. 46, vol. 1, pp. 1287-1289.

<sup>510</sup>For a review, see Todd *Org. React.* **1948**, 4, 378-422.

<sup>511</sup>Huang-Minlon *J. Am. Chem. Soc.* **1946**, 68, 2487, **1949**, 71, 3301.

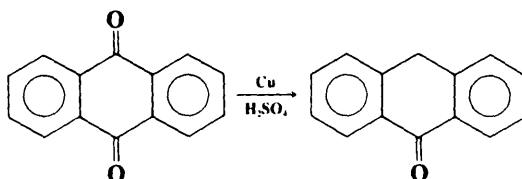
<sup>512</sup>Cram; Sahyun; Knox *J. Am. Chem. Soc.* **1962**, 84, 1734.

<sup>513</sup>Yamamura; Ueda; Hirata *Chem. Commun.* **1967**, 1049; Toda; Hayashi; Hirata; Yamamura *Bull. Chem. Soc. Jpn.* **1972**, 45, 264.

<sup>514</sup>For a review of Clemmensen reduction of diketones and unsaturated ketones, see Buchanan; Woodgate *Q. Rev. Chem. Soc.* **1969**, 23, 522-536.

undergo rearrangement, e.g.,  $\text{MeCOCH}_2\text{COMe} \rightarrow \text{MeCOCHMe}_2$ .<sup>509</sup> Neither method is suitable for  $\alpha,\beta$ -unsaturated ketones. These give pyrazolines<sup>510</sup> 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  $\text{C}=\text{C}$  bond.<sup>511</sup> Sterically hindered ketones are resistant to both the Clemmensen and Huang-Minlon procedures but can be reduced by vigorous treatment with anhydrous hydrazine.<sup>512</sup> In the Clemmensen reduction, pinacols (9-62) are often side products.

Other reagents have also been used to reduce the  $\text{C}=\text{O}$  of aldehydes and ketones to  $\text{CH}_2$ .<sup>513</sup> Among these are  $\text{H}_2$  and a catalyst at 180 to 250°C,<sup>514</sup> triisopropyl phosphite  $\text{P}(\text{O}-i\text{-Pr})_3$ ,<sup>515</sup> and, for aryl ketones ( $\text{ArCOR}$  and  $\text{ArCOAr}$ ),  $\text{LiAlH}_4\text{-AlCl}_3$ ,<sup>516</sup>  $\text{LiAlH}_4\text{-P}_2\text{I}_4$ ,<sup>517</sup>  $\text{Li-NH}_3$ ,<sup>518</sup>  $\text{NaBH}_4\text{-F}_3\text{CCOOH}$ ,<sup>519</sup>  $\text{NaBH}_4\text{-AlCl}_3$ ,<sup>520</sup>  $\text{BH}_3\text{-}t\text{-BuNH}_2\text{-AlCl}_3$ ,<sup>521</sup>  $\text{CO-Se-H}_2\text{O}$ ,<sup>522</sup>  $\text{HCOONH}_4\text{-Pd-C}$ ,<sup>523</sup> or trialkylsilanes in  $\text{F}_3\text{CCOOH}$ .<sup>524</sup> Most of these reagents also reduce aryl aldehydes  $\text{ArCHO}$  to methylbenzenes  $\text{ArCH}_3$ .<sup>525</sup> Aliphatic aldehydes  $\text{RCHO}$  can be reduced to  $\text{RCH}_3$  with titanocene dichloride  $(\text{C}_5\text{H}_5)_2\text{TiCl}_2$ .<sup>526</sup> One carbonyl group of 1,2-diketones can be selectively reduced by  $\text{H}_2\text{S}$  with an amine catalyst<sup>527</sup> or by  $\text{HI}$  in refluxing acetic acid.<sup>528</sup> One carbonyl group of quinones can be reduced with copper and sulfuric acid or with tin and  $\text{HCl}$ :<sup>529</sup>



One carbonyl group of 1,3-diketones was selectively reduced by catalytic hydrogenolysis.<sup>530</sup>

An indirect method of accomplishing the reaction is reduction of tosylhydrazones ( $\text{R}_2\text{C}=\text{N-NHTs}$ ) to  $\text{R}_2\text{CH}_2$  with  $\text{NaBH}_4$ ,  $\text{BH}_3$ , catecholborane, bis(benzyloxy)borane,

<sup>509</sup>Cusack; Davis *J. Org. Chem.* **1965**, 30, 2062; Wenkert; Kariv *Chem. Commun.* **1965**, 570; Galton; Kalafer; Beringer *J. Org. Chem.* **1970**, 35, 1.

<sup>510</sup>Pyrazolines can be converted to cyclopropanes; see 7-46.

<sup>511</sup>See, however, Banerjee; Álvarez; Santana; Carrasco *Tetrahedron* **1986**, 42, 6615.

<sup>512</sup>Barton; Ives; Thomas *J. Chem. Soc.* **1955**, 2056.

<sup>513</sup>For a list, with references, see Ref. 21, pp. 35-38.

<sup>514</sup>See for example, Maier; Bergmann; Bleicher; Schleyer *Tetrahedron Lett.* **1981**, 22, 4227. For a review of the mechanism, see Pavlenko *Russ. Chem. Rev.* **1989**, 58, 453-469.

<sup>515</sup>Olah; Wu *Synlett* **1990**, 54.

<sup>516</sup>Nystrom; Berger *J. Am. Chem. Soc.* **1958**, 80, 2896. See also Volod'kin; Ershov; Portnykh *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1967**, 384.

<sup>517</sup>Suzuki; Masuda; Kubota; Osuka *Chem. Lett.* **1983**, 909.

<sup>518</sup>Hall; Lipsky; McEnroe; Bartels *J. Org. Chem.* **1971**, 36, 2588.

<sup>519</sup>Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985**, 17, 317-384.

<sup>520</sup>Ono; Suzuki; Kamimura *Synthesis* **1987**, 736.

<sup>521</sup>Lau; Tardif; Dufresne; Scheigetz *J. Org. Chem.* **1989**, 54, 491.

<sup>522</sup>Nishiyama; Hamanaka; Ogawa; Kambe; Sonoda *J. Org. Chem.* **1988**, 53, 1326.

<sup>523</sup>Ram; Spicer *Tetrahedron Lett.* **1988**, 29, 3741.

<sup>524</sup>Kursanov; Parnes; Loim *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1966**, 1245; West; Donnelly; Kooistra; Doyle *J. Org. Chem.* **1973**, 38, 2675. See also Fry; Orfanopoulos; Adlington; Dittman; Silverman *J. Org. Chem.* **1978**, 43, 374; Olah; Arvanaghi; Ohannesian *Synthesis* **1986**, 770.

<sup>525</sup>See, for example, Hall; Bartels; Engman *J. Org. Chem.* **1972**, 37, 760; Kursanov; Parnes; Loim; Bakalova *Doklad. Chem.* **1968**, 179, 328; Zahalka; Alper *Organometallics* **1986**, 5, 1909.

<sup>526</sup>van Tamelen; Gladys *J. Am. Chem. Soc.* **1974**, 96, 5290.

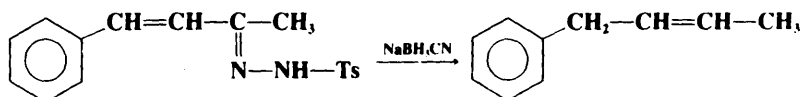
<sup>527</sup>Mayer; Hiller; Nitzschke; Jentzsch *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 370-373 [*Angew. Chem.* 75, 1011-1014].

<sup>528</sup>Reusch; LeMahieu *J. Am. Chem. Soc.* **1964**, 86, 3068.

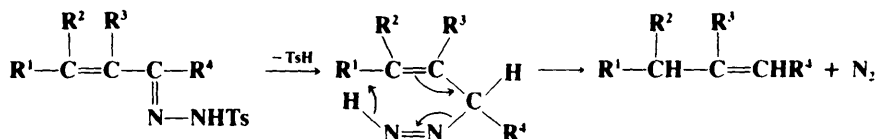
<sup>529</sup>Meyer *Org. Synth. I*, 60; Macleod; Allen *Org. Synth. II*, 62.

<sup>530</sup>Cormier; McCauley *Synth. Commun.* **1988**, 18, 675.

$\text{NaBH}_3\text{CN}$ , or bis(triphenylphosphine)copper(I) tetrahydroborate.<sup>531</sup> The reduction of  $\alpha,\beta$ -unsaturated tosylhydrazones with  $\text{NaBH}_3\text{CN}$ , with  $\text{NaBH}_4\text{-HOAc}$ , 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,<sup>532</sup> e.g.,



A cyclic mechanism is apparently involved:

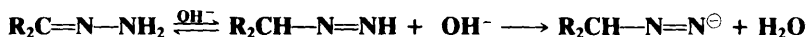


Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization of this (4-36).

The first step in the mechanism<sup>533</sup> of the Wolff-Kishner reaction consists of formation of the hydrazone (6-20).



It is this species that undergoes reduction in the presence of base, most likely in the following manner:



Not much is known about the mechanism of the Clemmensen reduction. Several mechanisms have been proposed,<sup>534</sup> including one going through a zinc-carbene intermediate.<sup>535</sup> 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.

<sup>531</sup>Caglioti; Magi *Tetrahedron* **1963**, 19, 1127; Fischer; Pelah; Williams; Djerassi *Chem. Ber.* **1965**, 98, 3236; Elphimoff-Felkin; Verrier *Tetrahedron Lett.* **1968**, 1515; Hutchins; Milewski; Maryanoff *J. Am. Chem. Soc.* **1973**, 95, 3662; Cacchi; Caglioti; Paolucci *Bull. Chem. Soc. Jpn.* **1974**, 47, 2323; Lane *Synthesis* **1975**, 135-146, pp. 145-146; Kabalka; Yang; Chandler; Baker *Synthesis* **1977**, 124; Kabalka; Summers *J. Org. Chem.* **1981**, 46, 1217; Fleet; Harding; Whitcombe *Tetrahedron Lett.* **1980**, 21, 4031; Miller; Yang; Weigel; Han; Liu *J. Org. Chem.* **1989**, 54, 4175.

<sup>532</sup>Hutchins; Kacher; Rua *J. Org. Chem.* **1975**, 40, 923; Kabalka; Yang; Baker *J. Org. Chem.* **1976**, 41, 574; Taylor; Djerassi *J. Am. Chem. Soc.* **1976**, 98, 2275; Hutchins; Natale *J. Org. Chem.* **1978**, 43, 2299; Greene *Tetrahedron Lett.* **1979**, 63.

<sup>533</sup>For a review of the mechanism, see Szmant *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 120-128 [*Angew. Chem.* **80**, 141-149].

<sup>534</sup>See, for example, Horner; Schmitt *Liebigs Ann. Chem.* **1978**, 1617; Poutsma; Wolthuis *J. Org. Chem.* **1959**, 24, 875; Nakabayashi *J. Am. Chem. Soc.* **1960**, 82, 3900, 3906; Di Vona; Rosnati *J. Org. Chem.* **1991**, 56, 4269.

<sup>535</sup>Burdon; Price *J. Chem. Soc., Chem. Commun.* **1986**, 893.

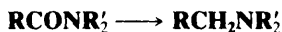
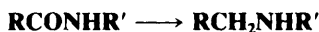
**9-38 Reduction of Carboxylic Acids to Alcohols****Dihydro-de-oxo-bisubstitution**

Carboxylic acids are easily reduced to primary alcohols by  $\text{LiAlH}_4$ .<sup>536</sup> The reaction does not stop at the aldehyde stage (but see 0-84). The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used,<sup>537</sup> but not  $\text{NaBH}_4$  (see Table 19.5).<sup>538</sup> Catalytic hydrogenation is also generally ineffective.<sup>539</sup> Borane is particularly good for carboxyl groups (Table 19.4) and permits selective reduction of them in the presence of many other groups (though the reaction with double bonds takes place at about the same rate).<sup>540</sup> Borane also reduces carboxylic acid salts.<sup>541</sup> Aluminum hydride reduces  $\text{COOH}$  groups without affecting carbon-halogen bonds in the same molecule. The reduction has also been carried out with  $\text{SmI}_2$  in basic media.<sup>541a</sup>

OS III, 60; VII, 221; 530; 65, 173; 66, 160; 68, 77.

**9-39 Reduction of Amides to Amines****Dihydro-deoxo-bisubstitution**

Amides can be reduced<sup>542</sup> to amines with  $\text{LiAlH}_4$  or by catalytic hydrogenation, though high temperatures and pressures are usually required for the latter. Even with  $\text{LiAlH}_4$  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.  $\text{NaBH}_4$  by itself does not reduce amides, though it does so in the presence of certain other reagents.<sup>543</sup> Substituted amides can be similarly reduced:



Borane<sup>544</sup> and sodium in 1-propanol<sup>545</sup> are good reducing agents for all three types of amides. Another reagent that reduces disubstituted amides to amines is trichlorosilane.<sup>546</sup> Sodium

<sup>536</sup>For a review, see Gaylord *Reduction with Complex Metal Hydrides*; Wiley: New York, 1956, pp. 322-373.

<sup>537</sup>For a list of reagents, with references, see Ref. 21, pp. 548-549.

<sup>538</sup> $\text{NaBH}_4$  in the presence of  $\text{Me}_2\text{N}=\text{CHCl}^+ \text{Cl}^-$  reduces carboxylic acids to primary alcohols chemoselectively in the presence of halide, ester, and nitrile groups; Fujisawa; Mori; Sato *Chem. Lett.* **1983**, 835.

<sup>539</sup>See Rylander *Hydrogenation Methods*, Ref. 488, pp. 78-79.

<sup>540</sup>Brown; Korytnyk *J. Am. Chem. Soc.* **1960**, 82, 3866; Batrakov; Bergel'son *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965**, 348; Pelter; Hutchings; Levitt; Smith *Chem. Commun.* **1970**, 347; Brown; Stocky *J. Am. Chem. Soc.* **1977**, 99, 8218.

<sup>541</sup>Yoon; Cho *Tetrahedron Lett.* **1982**, 23, 2475.

<sup>541a</sup>Kamochi; Kudo *Chem. Lett.* **1991**, 893.

<sup>542</sup>For a review, see Challis; Challis, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 795-801. For a review of the reduction of amides, lactams, and imides with metallic hydrides, see Gaylord, Ref. 536, pp. 544-636. For a list of reagents, with references, see Ref. 21, pp. 432-433.

<sup>543</sup>See, for example, Satoh; Suzuki; Miyaji; Imai *Tetrahedron Lett.* **1969**, 4555; Rahman; Basha; Waheed; Ahmed *Tetrahedron Lett.* **1976**, 219; Kuehne; Shannon *J. Org. Chem.* **1977**, 42, 2082; Wann; Thorsen; Kreevoy *J. Org. Chem.* **1981**, 46, 2579; Mandal; Giri; Pakrashi *Synthesis* **1987**, 1128; Akaboro; Takanohashi *Chem. Lett.* **1990**, 251.

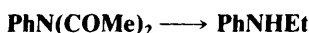
<sup>544</sup>Brown; Heim *J. Org. Chem.* **1973**, 38, 912; Brown; Narasimhan; Choi *Synthesis* **1981**, 441, 996; Krishnamurthy *Tetrahedron Lett.* **1982**, 23, 3315; Bonnat; Hercouet; Le Corre *Synth. Commun.* **1991**, 21, 1579.

<sup>545</sup>Bhandari; Sharma; Chatterjee *Chem. Ind. (London)* **1990**, 547.

<sup>546</sup>Nagata; Dohmaru; Tsurugi *Chem. Lett.* **1972**, 989. See also Benkeser; Li; Mozden *J. Organomet. Chem.* **1979**, 178, 21.

(dimethylamino)borohydride reduces unsubstituted and disubstituted, but not monosubstituted amides.<sup>547</sup>

With some  $\text{RCONR}'_2$ ,  $\text{LiAlH}_4$  causes cleavage, and the aldehyde (0-85) or alcohol is obtained. Lithium triethylborohydride produces the alcohol with most N,N-disubstituted amides, though not with unsubstituted or N-substituted amides.<sup>548</sup> Lactams are reduced to cyclic amines in high yields with  $\text{LiAlH}_4$ , though cleavage sometimes occurs here too. Imides are generally reduced on both sides, though it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, though with acyclic imides cleavage is often obtained, e.g.,<sup>549</sup>

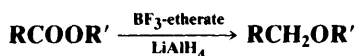


Acyl sulfonamides have been reduced ( $\text{RCONHSO}_2\text{Ph} \rightarrow \text{RCH}_2\text{NHSO}_2\text{Ph}$ ) with  $\text{BH}_3\text{-SMe}_2$ .<sup>550</sup>

OS IV, 339, 354, 564; VI, 382; VII, 41.

#### 9-40 Reduction of Carboxylic Esters to Ethers

##### Dihydro-de-oxo-bisubstitution

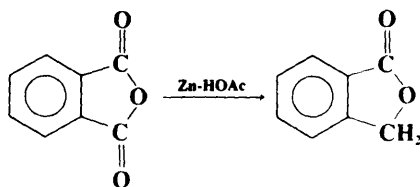


Carboxylic esters and lactones have been reduced to ethers, though the more usual course is the obtention of 2 moles of alcohol (9-42). Reduction to ethers has been accomplished with a reagent prepared from  $\text{BF}_3$ -etherate and either  $\text{LiAlH}_4$ ,  $\text{LiBH}_4$ , or  $\text{NaBH}_4$ .<sup>551</sup> with trichlorosilane and uv light,<sup>552</sup> and with catalytic hydrogenation. The reaction with the  $\text{BF}_3$  reagent apparently succeeds with secondary  $\text{R}'$ , but not with primary  $\text{R}'$ , which give 9-42. Lactones give cyclic ethers.<sup>553</sup> Thiono esters  $\text{RCSOR}'$  can be reduced to ethers  $\text{RCH}_2\text{OR}'$  with Raney nickel (4-36).<sup>554</sup> Since the thiono esters can be prepared from carboxylic esters (6-11), this provides an indirect method for the conversion of carboxylic esters to ethers. Thiol esters  $\text{RCOSR}'$  have been reduced to thioethers  $\text{RCH}_2\text{SR}'$ .<sup>555</sup>

See also 9-43, 0-81.

#### 9-41 Reduction of Cyclic Anhydrides to Lactones

##### Dihydro-de-oxo-bisubstitution



<sup>547</sup>Hutchins; Learn; El-Telbany; Stercho *J. Org. Chem.* **1984**, 49, 2438.

<sup>548</sup>Brown; Kim *Synthesis* **1977**, 635.

<sup>549</sup>Witkop; Patrick *J. Am. Chem. Soc.* **1952**, 74, 3861.

<sup>550</sup>Belletire; Fry *Synth. Commun.* **1988**, 18, 29.

<sup>551</sup>Pettit; Ghatak; Green; Kasturi; Piatak *J. Org. Chem.* **1961**, 26, 1685; Pettit; Green; Kasturi; Ghatak *Tetrahedron* **1962**, 18, 953; Ager; Sutherland *J. Chem. Soc., Chem. Commun* **1982**, 248. See also Dias; Pettit *J. Org. Chem.* **1971**, 36, 3485.

<sup>552</sup>Tsurugi; Nakao; Fukumoto *J. Am. Chem. Soc.* **1969**, 91, 4587; Nagata; Dohmaru; Tsurugi *J. Org. Chem.* **1973**, 38, 795; Baldwin; Doll; Haut *J. Org. Chem.* **1974**, 39, 2470; Baldwin; Haut *J. Org. Chem.* **1975**, 40, 3885. See also Kraus; Frazier; Roth; Taschner; Neuenschwander *J. Org. Chem.* **1981**, 46, 2417.

<sup>553</sup>See, for example, Pettit; Kasturi; Green; Knight *J. Org. Chem.* **1961**, 26, 4773; Edward; Ferland *Chem. Ind. (London)* **1964**, 975.

<sup>554</sup>Baxter; Bradshaw *J. Org. Chem.* **1981**, 46, 831.

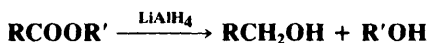
<sup>555</sup>Eliel; Daignault *J. Org. Chem.* **1964**, 29, 1630; Bublitz *J. Org. Chem.* **1967**, 32, 1630.

Cyclic anhydrides can give lactones if reduced with Zn–HOAc, with hydrogen and platinum or  $\text{RuCl}_2(\text{Ph}_3\text{P})_3$ ,<sup>556</sup> with  $\text{NaBH}_4$ ,<sup>557</sup> or even with  $\text{LiAlH}_4$ , though with the last-mentioned reagent diols are the more usual product (9-44). With some reagents the reaction can be accomplished regioselectively, i.e., only a specific one of the two  $\text{C}=\text{O}$  groups of an unsymmetrical anhydride is reduced.<sup>558</sup> Open-chain anhydrides either are not reduced at all (e.g., with  $\text{NaBH}_4$ ) or give 2 moles of alcohol.

There are no *Organic Syntheses* references, but see OS II, 526, for a related reaction.

## 9-42 Reduction of Carboxylic Esters to Alcohols

### Dihydro,hydroxy-de-oxo,alkoxy-tersubstitution

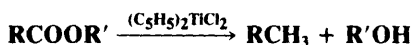


$\text{LiAlH}_4$  reduces carboxylic esters to give 2 moles of alcohol.<sup>559</sup> The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining  $\text{R}'\text{OH}$ , this is a method of “hydrolyzing” esters. Lactones yield diols. Among the reagents that give the same products<sup>560</sup> are DIBALH, lithium triethylborohydride, and  $\text{BH}_3\text{-SMe}_2$  in refluxing THF.<sup>561</sup>  $\text{NaBH}_4$  reduces phenolic esters, especially those containing electron-withdrawing groups,<sup>562</sup> but its reaction with other esters is usually so slow that such reactions are seldom feasible (though exceptions are known<sup>563</sup>), and it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. However,  $\text{NaBH}_4$  reduces esters in the presence of certain compounds (see Table 19.5).<sup>564</sup> Carboxylic esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,<sup>565</sup> though high pressures and temperatures are required. Ester functions generally survive low-pressure catalytic hydrogenations. Before the discovery of  $\text{LiAlH}_4$ , the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault–Blanc procedure*. This procedure is still sometimes used where selectivity is necessary. See also 9-40, 9-43, and 0-81.

OS II, 154, 325, 372, 468; III, 671; IV, 834; VI, 781; VII, 356; 68, 92.

## 9-43 Reduction of Carboxylic Acids and Esters to Alkanes

### Trihydro-de-alkoxy,oxo-tersubstitution, etc.



The reagent titanocene dichloride reduces carboxylic esters in a different manner from that of 0-81, 9-40, or 9-42. The products are the alkane  $\text{RCH}_3$  and the alcohol  $\text{R}'\text{OH}$ .<sup>526</sup> 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

<sup>556</sup>Lyons *J. Chem. Soc., Chem. Commun.* **1975**, 412; Morand; Kayser *J. Chem. Soc., Chem. Commun.* **1976**, 314. See also Hara; Wada *Chem. Lett.* **1991**, 553.

<sup>557</sup>Bailey; Johnson *J. Org. Chem.* **1970**, 35, 3574.

<sup>558</sup>See, for example, Kayser; Salvador; Morand *Can. J. Chem.* **1983**, 61, 439; Ikariya; Osakada; Ishii; Osawa; Saburi; Yoshikawa *Bull. Chem. Soc. Jpn.* **1984**, 57, 897; Soucy; Favreau; Kayser *J. Org. Chem.* **1987**, 52, 129.

<sup>559</sup>For a review, see Gaylord, Ref. 536, pp. 391-531.

<sup>560</sup>For a list of reagents, with references, see Ref. 21, pp. 549-551.

<sup>561</sup>Brown; Choi *Synthesis* **1981**, 439; Brown; Choi; Narasimhan *J. Org. Chem.* **1982**, 47, 3153.

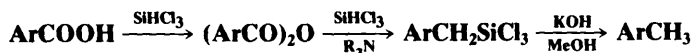
<sup>562</sup>Takahashi; Cohen *J. Org. Chem.* **1970**, 35, 1505.

<sup>563</sup>For example, see Brown; Rapoport *J. Org. Chem.* **1963**, 28, 3261; Bianco; Passacantilli; Righi *Synth. Commun.* **1988**, 18, 1765.

<sup>564</sup>See also Kikugawa *Chem. Lett.* **1975**, 1029; Santaniello; Ferraboschi; Sozzani *J. Org. Chem.* **1981**, 46, 4584; Brown; Narasimhan; Choi *J. Org. Chem.* **1982**, 47, 4702; Soai; Oyamada; Takase; Ookawa *Bull. Chem. Soc. Jpn.* **1984**, 57, 1948; Guida; Entreken; Guida *J. Org. Chem.* **1984**, 49, 3024.

<sup>565</sup>For a review, see Adkins, *Org. React.* **1954**, 8, 1-27.

with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).<sup>566</sup> The following sequence has been suggested:<sup>566</sup>



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.<sup>567</sup> However, it is also possible to reduce aromatic ester groups, by a variation of the trichlorosilane procedure.<sup>568</sup> *o*- and *p*-hydroxybenzoic acids and their esters have been reduced to cresols  $\text{HOC}_6\text{H}_4\text{CH}_3$  with sodium bis(2-methoxyethoxy)aluminum hydride  $\text{NaAlH}_2(\text{OC}_2\text{H}_4\text{OMe})_2$  (*Red-Al*).<sup>569</sup>

Carboxylic acids can also be converted to alkanes, indirectly,<sup>570</sup> by reduction of the corresponding tosylhydrazides  $\text{RCONHNH}_2$  with  $\text{LiAlH}_4$  or borane.<sup>571</sup>

OS VI, 747.

#### 9-44 Reduction of Anhydrides to Alcohols



$\text{LiAlH}_4$  usually reduces open-chain anhydrides to give 2 moles of alcohol. With cyclic anhydrides the reaction with  $\text{LiAlH}_4$  can be controlled to give either diols or lactones<sup>572</sup> (see 9-41).  $\text{NaBH}_4$  in THF, with dropwise addition of methanol, reduces open-chain anhydrides to one mole of primary alcohol and one mole of carboxylic acid.<sup>573</sup>

OS VI, 482.

#### 9-45 Reduction of Acyl Halides to Alcohols

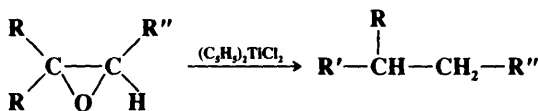
**Dihydro,hydroxy-de-halo,oxo-tersubstitution**



Acyl halides are reduced<sup>574</sup> to alcohols by  $\text{LiAlH}_4$  or  $\text{NaBH}_4$ , as well as by other metal hydrides (Table 19.5), but not by borane. The reaction may be regarded as a combination of 9-37 and 0-76.

OS IV, 271.

#### 9-46 Complete Reduction of Epoxides



<sup>566</sup>Benkeser; Foley; Gaul; Li *J. Am. Chem. Soc.* **1970**, *92*, 3232.

<sup>567</sup>Benkeser; Ehler *J. Org. Chem.* **1973**, *38*, 3660.

<sup>568</sup>Benkeser; Mozdzen; Muth *J. Org. Chem.* **1979**, *44*, 2185.

<sup>569</sup>Černý; Málek *Tetrahedron Lett.* **1969**, 1739, *Collect. Czech. Chem. Commun.* **1970**, *35*, 2030.

<sup>570</sup>For another indirect method, which can also be applied to acid derivatives, see Degani; Fochi *J. Chem. Soc., Perkin Trans. 1* **1978**, 1133. For a direct method, see Le Deit; Cron; Le Corre *Tetrahedron Lett.* **1991**, *32*, 2759.

<sup>571</sup>Attanasi; Caglioti; Gasparrini; Misiti *Tetrahedron* **1975**, *31*, 341, and references cited therein.

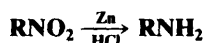
<sup>572</sup>Bloomfield; Lee *J. Org. Chem.* **1967**, *32*, 3919.

<sup>573</sup>Soai; Yokoyama; Mochida *Synthesis* **1987**, 647.

<sup>574</sup>For a review of the reduction of acyl halides, see Wheeler, in Patai *The Chemistry of Acyl Halides*; Wiley: New York, 1972, pp. 231-251. For a list of reagents, with references, see Ref. 21, p. 549.

Though the usual product of epoxide reductions is the alcohol (**0-80**), epoxides are reduced all the way to the alkane by titanocene dichloride<sup>526</sup> and by  $\text{Et}_3\text{SiH}-\text{BH}_3$ .<sup>575</sup>

### 9-47 Reduction of Nitro Compounds to Amines



Both aliphatic<sup>576</sup> and aromatic nitro compounds can be reduced to amines, though the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn, or Fe (or sometimes other metals) and acid, and catalytic hydrogenation.<sup>577</sup> Among other reagents used<sup>578</sup> have been  $\text{AlH}_3-\text{AlCl}_3$ , hydrazine and a catalyst,<sup>579</sup>  $\text{TiCl}_3$ ,<sup>580</sup>  $\text{Al}-\text{NiCl}_2-\text{THF}$ ,<sup>581</sup> formic acid and  $\text{Pd}-\text{C}$ ,<sup>582</sup> and sulfides such as  $\text{NaHS}$ ,  $(\text{NH}_4)_2\text{S}$ , or polysulfides. The reaction with sulfides or polysulfides is called the *Zinin reduction*.<sup>583</sup> The reagent sodium dihydro(trithio)borate  $\text{NaBH}_2\text{S}_3$  reduces aromatic nitro compounds to amines,<sup>584</sup> but aliphatic nitro compounds give other products (see **9-58**). In contrast,  $\text{LiAlH}_4$  reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (**9-67**). Most metal hydrides, including  $\text{NaBH}_4$  and  $\text{BH}_3$ , do not reduce nitro groups at all, though both aliphatic and aromatic nitro compounds have been reduced to amines with  $\text{NaBH}_4$  and various catalysts, such as  $\text{NiCl}_2$  or  $\text{CoCl}_2$ .<sup>585</sup> Treatment of aromatic nitro compounds with  $\text{NaBH}_4$  alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact<sup>586</sup> or in cleavage of the nitro group from the ring.<sup>587</sup> With  $(\text{NH}_4)_2\text{S}$  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.<sup>588</sup> The nitro groups of N-nitro compounds can also be reduced to amino groups, e.g., nitrourea  $\text{NH}_2\text{CONHNO}_2$  gives semicarbazide  $\text{NH}_2\text{CONHNH}_2$ .

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (**9-49**), hydrazobenzenes (**9-68**),

<sup>575</sup>Fry; Mraz *Tetrahedron Lett.* **1979**, 849.

<sup>576</sup>For a review of selective reduction of aliphatic nitro compounds without disturbance of other functional groups, see Ioffe; Tartakovskii; Novikov *Russ. Chem. Rev.* **1966**, 35, 19-32.

<sup>577</sup>For reviews, see Rylander *Hydrogenation Methods*, Ref. 488, pp. 104-116, *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967, pp. 168-202.

<sup>578</sup>For a list of reagents, with references, see Ref. 21, pp. 411-415.

<sup>579</sup>An explosion has been reported with *o*-chloronitro compounds: Rondestvedt; Johnson *Synthesis* **1977**, 851. For a review of the use of hydrazine, see Furst; Berlo; Hooton *Chem. Rev.* **1965**, 65, 51-68, pp. 52-60. See also Yuste; Saldaña; Walls *Tetrahedron Lett.* **1982**, 23, 147; Adger; Young *Tetrahedron Lett.* **1984**, 25, 5219.

<sup>580</sup>Ho; Wong *Synthesis* **1974**, 45. See also George; Chandrasekaran *Synth. Commun.* **1983**, 13, 495.

<sup>581</sup>Sarmah; Barua *Tetrahedron Lett.* **1990**, 31, 4065.

<sup>582</sup>Entwistle; Jackson; Johnstone; Telford *J. Chem. Soc., Perkin Trans. 1* **1977**, 443. See also Terpkio; Heck *J. Org. Chem.* **1980**, 45, 4992; Babler; Sarussi *Synth. Commun.* **1981**, 11, 925.

<sup>583</sup>For a review of the Zinin reduction, see Porter *Org. React.* **1973**, 20, 455-481.

<sup>584</sup>Lalancette; Brindle *Can. J. Chem.* **1971**, 49, 2990. See also Maki; Sugiyama; Kikuchi; Seto *Chem. Lett.* **1975**, 1093.

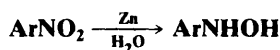
<sup>585</sup>See, for example, Jardine; McQuillin *Chem. Commun.* **1970**, 626; Hanaya; Muramatsu; Kudo; Chow *J. Chem. Soc., Perkin Trans. 1* **1979**, 2409; Ono; Sasaki; Yaginuma *Chem. Ind. (London)* **1983**, 480; Osby; Ganem *Tetrahedron Lett.* **1985**, 26, 6413; Petrini; Ballini; Rosini *Synthesis* **1987**, 713; He; Zhao; Pan; Wang *Synth. Commun.* **1989**, 19, 3047.

<sup>586</sup>Severin; Schmitz *Chem. Ber.* **1962**, 95, 1417; Severin; Adam *Chem. Ber.* **1963**, 96, 448.

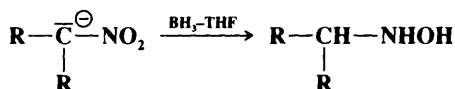
<sup>587</sup>Kaplan *J. Am. Chem. Soc.* **1964**, 86, 740. See also Swanwick; Waters *Chem. Commun.* **1970**, 63.

<sup>588</sup>This result has also been achieved by hydrogenation with certain catalysts [Lyle; LaMattina, *Synthesis* **1974**, 726; Knifton *J. Org. Chem.* **1976**, 41, 1200; Ono; Terasaki; Tsuruoka *Chem. Ind. (London)* **1983**, 477], and with hydrazine hydrate and Raney nickel: Ayyangar; Kalkote; Lugade; Nikrad; Sharma *Bull. Chem. Soc. Jpn.* **1983**, 56, 3159.



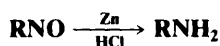
**9-49** Reduction of Nitro Compounds to Hydroxylamines

When aromatic nitro compounds are reduced with zinc and water under neutral conditions,<sup>595</sup> hydroxylamines are formed. Among other reagents used for this purpose have been  $\text{SmI}_2$ ,<sup>596</sup>  $\text{N}_2\text{H}_4\text{-Rh-C}$ ,<sup>597</sup> and  $\text{NaBH}_4\text{-Se}$ .<sup>598</sup> Borane in THF reduces aliphatic nitro compounds (in the form of their salts) to hydroxylamines:<sup>599</sup>

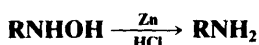


Nitro compounds have been reduced electrochemically, to hydroxylamines as well as to other products.<sup>600</sup>

OS **I**, 445; **III**, 668; **IV**, 148; **VI**, 803; **67**, 187.

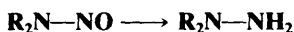
**9-50** Reduction of Nitroso Compounds and Hydroxylamines to Amines

**N-Dihydro-de-oxo-bisubstitution**



**N-Hydro-de-hydroxylation** or **N-Dehydroxylation**

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents that reduce nitro compounds (**9-47**). N-Nitroso compounds are similarly reduced to hydrazines:<sup>601</sup>



OS **I**, 511; **II**, 33, 202, 211, 418; **III**, 91; **IV**, 247. See also OS **65**, 166.

**9-51** Reduction of Oximes to Primary Amines or Aziridines

Both aldioximes and ketoximes can be reduced to primary amines with  $\text{LiAlH}_4$ . The reaction is slower than with ketones, so that, for example,  $\text{PhCOCH=NOH}$  gave 34% Ph-

<sup>595</sup>For some other methods of accomplishing this conversion, see Rondestvedt; Johnson *Synthesis* **1977**, 850; Entwistle; Gilkerson; Johnstone; Telford *Tetrahedron* **1978**, 34, 213.

<sup>596</sup>Kende; Mendoza *Tetrahedron Lett.* **1991**, 32, 1699.

<sup>597</sup>Oxley; Adger; Sasse; Forth *Org. Synth.* 67, 187.

<sup>598</sup>Yanada; Yamaguchi; Meguri; Uchida *J. Chem. Soc., Chem. Commun.* **1986**, 1655.

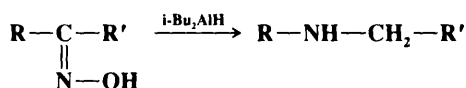
<sup>599</sup>Feuer; Bartlett; Vincent; Anderson *J. Org. Chem.* **1965**, 31, 2880.

<sup>600</sup>For reviews of the electroreduction of nitro compounds, see Fry, Ref. 244, pp. 188-198; Lund, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 285-313.

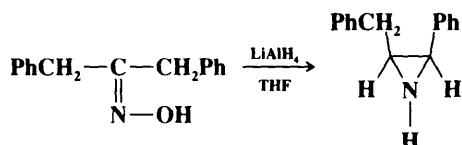
<sup>601</sup>For examples of this reduction, accomplished with titanium reagents, see Entwistle; Johnstone; Wilby *Tetrahedron* **1982**, 38, 419; Lunn; Sansone; Keefer *J. Org. Chem.* **1984**, 49, 3470.

$\text{CHOHCH=NOH}$ .<sup>602</sup> Among other reducing agents that give this reduction<sup>603</sup> are zinc and acetic acid, sodium ethoxide,  $\text{BH}_3$ ,<sup>604</sup>  $\text{NaBH}_3\text{CN-TiCl}_3$ ,<sup>605</sup> and sodium and an alcohol.<sup>606</sup> Catalytic hydrogenation is also effective.<sup>607</sup> The reduction has been performed enantioselectively with baker's yeast<sup>608</sup> and with  $\text{Ph}_2\text{SiH}_2$  and an optically active rhodium complex catalyst.<sup>609</sup>

When the reducing agent is DIBALH, the product is a secondary amine, arising from a rearrangement:<sup>610</sup>



With certain oximes (e.g., those of the type  $\text{ArCH}_2\text{CR=NOH}$ ), treatment with  $\text{LiAlH}_4$  gives aziridines,<sup>611</sup> e.g.,



Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including  $\text{Zn-HCl}$  and  $\text{H}_2$  and Raney nickel.

Oximes have been reduced in a different way, to give imines ( $\text{RR}'\text{C=NOH} \rightarrow \text{RR}'\text{C=NH}$ ), which are generally unstable but which can be trapped to give useful products. Among reagents used for this purpose have been  $\text{Bu}_3\text{P-SPh}_2$ <sup>612</sup> and  $\text{Ru}_3(\text{CO})_{12}$ .<sup>613</sup>

Oximes can also be reduced to hydroxylamines (6-26).

OS II, 318; III, 513; V, 32, 83, 373, 376.

## 9-52 Reduction of Azides to Primary Amines

### N-Dihydro-de-diazo-bisubstitution



Azides are easily reduced to primary amines by  $\text{LiAlH}_4$ , as well as by a number of other reducing agents,<sup>614</sup> including  $\text{NaBH}_4$ ,  $\text{PPh}_3$  (with this reagent, the process is called the

<sup>602</sup>Felkin C. R. *Acad. Sci.* **1950**, 230, 304.

<sup>603</sup>For a list of reagents, with references, see Ref. 21, p. 424.

<sup>604</sup>Feuer; Braunstein *J. Org. Chem.* **1969**, 34, 1817.

<sup>605</sup>Leeds; Kirst *Synth. Commun.* **1988**, 18, 777.

<sup>606</sup>For example, see Sugden; Patel *Chem. Ind. (London)* **1972**, 683.

<sup>607</sup>For a review, see Rylander *Catalytic Hydrogenation over Platinum Metals*, Ref. 577, pp. 139-159.

<sup>608</sup>Gibbs; Barnes *Tetrahedron Lett.* **1990**, 31, 5555.

<sup>609</sup>Brunner; Becker; Gauder *Organometallics* **1986**, 5, 739.

<sup>610</sup>Sasatani; Miyazaki; Maruoka; Yamamoto *Tetrahedron Lett.* **1983**, 24, 4711. See also Rerick; Trotter; Daigault; DeFoe *Tetrahedron Lett.* **1963**, 629; Petrarca; Emery *Tetrahedron Lett.* **1963**, 635; Graham; Williams *Tetrahedron* **1965**, 21, 3263.

<sup>611</sup>For a review, see Kotera; Kitahonoki *Org. Prep. Proced.* **1969**, 1, 305-324. For examples, see Shandala; Solomon; Waight *J. Chem. Soc.* **1965**, 892; Kitahonoki; Takano; Matsuura; Kotera *Tetrahedron* **1969**, 25, 335; Landor; Sonola; Tatchell *J. Chem. Soc., Perkin Trans. I* **1974**, 1294; Ferrero; Rouillard; Decouzon; Azzaro *Tetrahedron Lett.* **1974**, 131; Diab; Laurent; Mison *Tetrahedron Lett.* **1974**, 1605.

<sup>612</sup>Barton; Motherwell; Simon; Zard *J. Chem. Soc., Chem. Commun.* **1984**, 337.

<sup>613</sup>Akazome; Tsuji; Watanabe *Chem. Lett.* **1990**, 635.

<sup>614</sup>For a review, see Scriven; Turnbull *Chem. Rev.* **1988**, 88, 297-368, pp. 321-327. For lists of reagents, with references, see Ref. 21, pp. 409-410; Rolla *J. Org. Chem.* **1982**, 47, 4327.

*Staudinger reaction*),<sup>615</sup>  $\text{H}_2$  and a catalyst, Mg or Ca in MeOH,<sup>616</sup>  $\text{N}_2\text{H}_4\text{-Pd}$ ,<sup>617</sup> and tin complexes prepared from  $\text{SnCl}_2$  or  $\text{Sn}(\text{SR})_2$ .<sup>618</sup> This reaction, combined with  $\text{RX} \rightarrow \text{RN}_3$  (**0-61**), is an important way of converting alkyl halides  $\text{RX}$  to primary amines  $\text{RNH}_2$ ; in some cases the two procedures have been combined into one laboratory step.<sup>619</sup> Sulfonyl azides  $\text{RSO}_2\text{N}_3$  have been reduced to sulfonamides  $\text{RSO}_2\text{NH}_2$  by irradiation in isopropyl alcohol<sup>620</sup> and with  $\text{NaH}$ .<sup>621</sup>

OS V, 586; VII, 433.

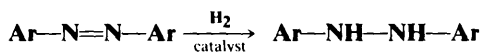
### 9-53 Reduction of Miscellaneous Nitrogen Compounds



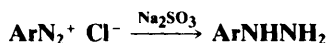
**Isocyanate-methylamine transformation**



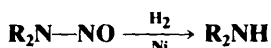
**Isothiocyanate-methylamine transformation**



***N,N*-Dihydro-addition**

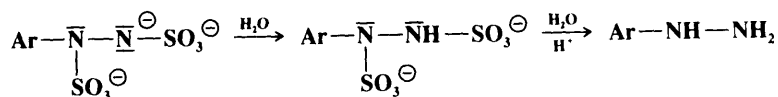
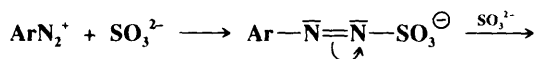


**Diazonium-arylhydrazone reduction**



***N*-Hydro-de-nitroso-substitution**

Isocyanates and isothiocyanates are reduced to methylamines on treatment with  $\text{LiAlH}_4$ .  $\text{LiAlH}_4$  does not usually reduce azo compounds<sup>622</sup> (indeed these are the products from  $\text{LiAlH}_4$  reduction of nitro compounds, **9-67**), but these can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide<sup>623</sup> (see **5-9**). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism.<sup>624</sup>



The initial product is a salt of hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment. Diazonium salts can also be reduced to arenes (**4-24**). *N*-Nitrosoamines

<sup>615</sup>First reported by Staudinger; Meyer *Helv. Chim. Acta* **1919**, 2, 635.

<sup>616</sup>Maiti; Spevak; Narendra Reddy *Synth. Commun.* **1988**, 18, 1201.

<sup>617</sup>Malik; Preston; Archibald; Cohen; Baum *Synthesis* **1989**, 450.

<sup>618</sup>Bartra; Romea; Urpi; Vilarrasa *Tetrahedron* **1990**, 46, 587.

<sup>619</sup>See, for example, Koziara; Osowska-Paciewicka; Zawadzki; Zwierzak *Synthesis* **1985**, 202, **1987**, 487. The reactions **0-67**, **0-61**, and **9-52** have also been accomplished in one laboratory step: Koziara *J. Chem. Res. (S)* **1989**, 296.

<sup>620</sup>Reagen; Nickon *J. Am. Chem. Soc.* **1968**, 90, 4096.

<sup>621</sup>Lee; Closson *Tetrahedron Lett.* **1974**, 381.

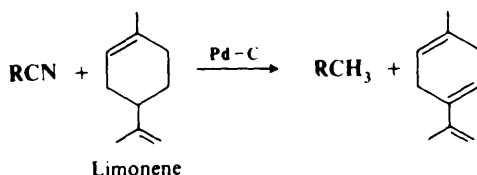
<sup>622</sup>For a review see Newbold, in Patai, Ref. 136, pt. 2, pp. 601, 604-614.

<sup>623</sup>For example, see Ioffe; Sergeeva; Dumpis *J. Org. Chem. USSR* **1969**, 5, 1683.

<sup>624</sup>Huisgen; Lux *Chem. Ber.* **1960**, 93, 540.

can be denitrosated to secondary amines by a number of reducing agents, including  $\text{H}_2$  and a catalyst,<sup>625</sup>  $\text{BF}_3\text{-THF-NaHCO}_3$ ,<sup>626</sup> and  $\text{NaBH}_4\text{-TiCl}_4$ ,<sup>627</sup> as well as by hydrolysis.<sup>628</sup>

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.<sup>629</sup>  $\text{H}_2$  is also



effective,<sup>630</sup> though higher temperatures are required. R may be alkyl or aryl. Cyano groups CN have also been reduced to  $\text{CH}_2\text{OH}$ , in the vapor phase, with 2-propanol and zirconium oxide.<sup>631</sup>

OS I, 442; III, 475. Also see OS V, 43.

### 9-54 Reduction of Sulfonyl Halides and Sulfonic Acids to Thiols



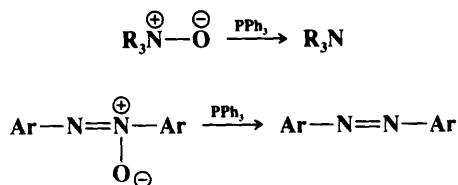
Thiols can be prepared by the reduction of sulfonyl halides<sup>632</sup> with  $\text{LiAlH}_4$ . Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Sulfonic acids have been reduced to thiols with a mixture of triphenylphosphine and either  $\text{I}_2$  or a diaryl disulfide.<sup>633</sup> Disulfides  $\text{RSSR}$  can also be produced.<sup>634</sup> For the reduction of sulfonyl chlorides to sulfinic acids, see 0-118.

OS I, 504; IV, 695; V, 843.

## B. Reactions in Which an Oxygen Is Removed from the Substrate

### 9-55 Reduction of Amine Oxides and Azoxy Compounds

#### N-Oxygen-detachment



<sup>625</sup>Enders; Hassel; Pieter; Renger; Seebach *Synthesis* **1976**, 548.

<sup>626</sup>Jeyaraman; Ravindran *Tetrahedron Lett.* **1990**, 31, 2787.

<sup>627</sup>Kano; Tanaka; Sugino; Shibuya; Hibino *Synthesis* **1980**, 741.

<sup>628</sup>Fridman; Mukhametshin; Novikov *Russ. Chem. Rev.* **1971**, 40, 34-50, pp. 41-42.

<sup>629</sup>Kindler; Lührs *Chem. Ber.* **1966**, 99, 227, *Liebigs Ann. Chem.* **1967**, 707, 26.

<sup>630</sup>See also Andrade; Maier; Zapf; Schleyer *Synthesis* **1980**, 802; Brown; Foubister *Synthesis* **1982**, 1036.

<sup>631</sup>Takahashi; Shibagaki; Matsushita *Chem. Lett.* **1990**, 311.

<sup>632</sup>For a review, see Wardell, in Patai, Ref. 408, pp. 216-220.

<sup>633</sup>Oae; Togo *Bull. Chem. Soc. Jpn.* **1983**, 56, 3802, **1984**, 57, 232.

<sup>634</sup>For example, see Alper *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 677 [*Angew. Chem.* **81**, 706]; Chan; Montillier; Van Horn; Harpp *J. Am. Chem. Soc.* **1970**, 92, 7224. See also Olah; Narang; Field; Karpeles *J. Org. Chem.* **1981**, 46, 2408; Oae; Togo *Synthesis* **1982**, 152, *Bull. Chem. Soc. Jpn.* **1983**, 56, 3813; Suzuki; Tani; Osuka *Chem. Lett.* **1984**, 139; Babu; Bhatt *Tetrahedron Lett.* **1986**, 27, 1073; Narayana; Padmanabhan; Kabalka *Synlett* **1991**, 125.

Amine oxides<sup>635</sup> and azoxy compounds (both alkyl and aryl)<sup>636</sup> can be reduced practically quantitatively with triphenylphosphine.<sup>637</sup> Other reducing agents, e.g.,  $\text{LiAlH}_4$ ,  $\text{H}_2$ -Ni,  $\text{PCl}_3$ ,  $\text{CS}_2$ ,<sup>638</sup>  $\text{NaHTe}$ ,<sup>639</sup>  $\text{TiCl}_3$ ,<sup>640</sup>  $\text{TiCl}_4$  with  $\text{LiAlH}_4$ ,  $\text{SbCl}_2$ , or  $\text{NaI}$ ,<sup>641</sup> and sulfur have also been used. Nitrile oxides<sup>642</sup>  $\text{R}-\text{C}\equiv\text{N}-\overset{+}{\text{N}}-\overset{-}{\text{O}}$  can be reduced to nitriles with trialkylphosphines,<sup>643</sup> and isocyanates  $\text{RNCO}$  to isocyanides  $\text{RNC}$  with  $\text{Cl}_3\text{SiH}-\text{Et}_3\text{N}$ .<sup>644</sup>

OS IV, 166. See also OS 67, 20.

## 9-56 Reduction of Sulfoxides and Sulfones

### S-Oxygen-detachment



Sulfoxides can be reduced to sulfides by many reagents,<sup>645</sup> among them  $\text{LiAlH}_4$ ,  $\text{HI}$ ,  $\text{Bu}_3\text{SnH}$ ,<sup>646</sup>  $\text{TiCl}_2$ ,<sup>647</sup>  $\text{MeSiCl}_3-\text{NaI}$ ,<sup>648</sup>  $\text{H}_2$ -Pd-C,<sup>649</sup>  $\text{NaBH}_4-\text{FeCl}_3$ ,<sup>650</sup>  $\text{NaBr}$ ,<sup>651</sup>  $\text{TiCl}_4-\text{NaI}$ ,<sup>652</sup>  $\text{Ph}_3\text{P}$ ,<sup>653</sup> and  $t\text{-BuBr}$ .<sup>654</sup> Sulfones, however, are usually stable to reducing agents, though they have been reduced to sulfides with DIBALH ( $i\text{-Bu}$ )<sub>2</sub>AlH.<sup>655</sup> A less general reagent is  $\text{LiAlH}_4$ , which reduces some sulfones to sulfides, but not others.<sup>656</sup> Both sulfoxides and sulfones can be reduced by heating with sulfur (which is oxidized to  $\text{SO}_2$ ), though the reaction with sulfoxides proceeds at a lower temperature. It has been shown by using substrate labeled with <sup>35</sup>S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since about 75% of the original radioactivity of the sulfone is lost.<sup>657</sup> This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*. There is no direct general method for the reduction of sulfones to sulfoxides.

<sup>635</sup>For reviews of the reduction of heterocyclic amine oxides, see Albini; Pietra, Ref. 421, pp. 120-134; Katritzky; Lagowski, Ref. 421, pp. 166-231.

<sup>636</sup>For a review, see Newbold, in Patai, Ref. 136, pt. 2, pp. 602-603, 614-624.

<sup>637</sup>For a review, see Rowley, in Cadogan *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979, pp. 295-350.

<sup>638</sup>Yoshimura; Asada; Oae *Bull. Chem. Soc. Jpn.* **1982**, 55, 3000.

<sup>639</sup>Barton; Fekih; Lusinci *Tetrahedron Lett.* **1985**, 26, 4603.

<sup>640</sup>Kuz'min; Mizhiritskii; Kogan *J. Org. Chem. USSR* **1989**, 25, 596.

<sup>641</sup>Malinowski; Kaczmarek *Synthesis* **1987**, 1013; Kaczmarek; Malinowski; Balicki *Bull. Soc. Chim. Belg.* **1988**, 97, 787.

<sup>642</sup>For reviews of the chemistry of nitrile oxides, see Torrsell *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988, pp. 55-74; Grundmann *Fortschr. Chem. Forsch.* **1966**, 7, 62-127.

<sup>643</sup>Grundmann; Frommelt *J. Org. Chem.* **1965**, 30, 2077.

<sup>644</sup>Baldwin; Derome; Riordan *Tetrahedron* **1983**, 39, 2989.

<sup>645</sup>For reviews, see Kukushkin *Russ. Chem. Rev.* **1990**, 59, 844-852; Madesclaire *Tetrahedron* **1988**, 44, 6537-6580; Drabowicz; Togo; Mikołajczyk; Oae *Org. Prep. Proced. Int.* **1984**, 16, 171-198; Drabowicz; Numata; Oae *Org. Prep. Proced. Int.* **1977**, 9, 63-83. For a list of reagents, with references, see Block, Ref. 440.

<sup>646</sup>Kozuka; Furumai; Akasaka; Oae *Chem. Ind. (London)* **1974**, 496.

<sup>647</sup>Drabowicz; Mikołajczyk *Synthesis* **1978**, 138. For the use of  $\text{TiCl}_3$ , see Ho; Wong *Synth. Commun.* **1973**, 3, 37.

<sup>648</sup>Olah; Husain; Singh; Mehrotra *J. Org. Chem.* **1983**, 48, 3667. See also Schmidt; Russ *Chem. Ber.* **1981**, 114, 822.

<sup>649</sup>Ogura; Yamashita; Tsuchihashi *Synthesis* **1975**, 385.

<sup>650</sup>Lin; Zhang *Synth. Commun.* **1987**, 17, 1403.

<sup>651</sup>Bernard; Caredda; Piras; Serra *Synthesis* **1990**, 329.

<sup>652</sup>Balicki *Synthesis* **1991**, 155.

<sup>653</sup>For a review, see Ref. 637, pp. 301-304.

<sup>654</sup>Tenca; Dossena; Marchelli; Casnati *Synthesis* **1981**, 141.

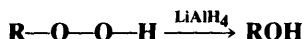
<sup>655</sup>Gardner; Kaiser; Krubiner; Lucas *Can. J. Chem.* **1973**, 51, 1419.

<sup>656</sup>Bordwell; McKellin *J. Am. Chem. Soc.* **1951**, 73, 2251; Whitney; Cram *J. Org. Chem.* **1970**, 35, 3964; Weber; Stromquist; Ito *Tetrahedron Lett.* **1974**, 2595.

<sup>657</sup>Oae; Kawamura *Bull. Chem. Soc. Jpn.* **1963**, 36, 163; Kiso; Oae *Bull. Chem. Soc. Jpn.* **1967**, 40, 1722. See also Oae; Nakai; Tsuchida; Furukawa *Bull. Chem. Soc. Jpn.* **1971**, 44, 445.

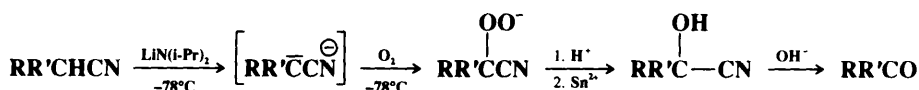
but an indirect method has been reported.<sup>658</sup> Selenoxides can be reduced to selenides with a number of reagents.<sup>659</sup>

### 9-57 Reduction of Hydroperoxides



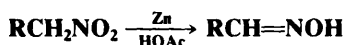
Hydroperoxides can be reduced to alcohols with  $\text{LiAlH}_4$  or  $\text{Ph}_3\text{P}$ <sup>660</sup> or by catalytic hydrogenation. This functional group is very susceptible to catalytic hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.<sup>661</sup>

The reaction is an important step in a method for the oxidative decyanation of nitriles containing an  $\alpha$  hydrogen.<sup>662</sup> The nitrile is first converted to the  $\alpha$ -hydroperoxy nitrile by treatment with base at  $-78^\circ\text{C}$  followed by  $\text{O}_2$ . The hydroperoxy nitrile is then reduced to



the cyanohydrin, which is cleaved (the reverse of 6-49) to the corresponding ketone. The method is not successful for the preparation of aldehydes ( $\text{R}' = \text{H}$ ).

### 9-58 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles



Nitro compounds that contain an  $\alpha$  hydrogen can be reduced to oximes with zinc dust in  $\text{HOAc}$ <sup>663</sup> or with other reagents, among them  $\text{Co-Cu(II)}$  salts in alkanediamines,<sup>664</sup>  $\text{CS}_2\text{-Et}_3\text{N}$ ,<sup>665</sup>  $\text{CrCl}_2$ ,<sup>666</sup> and (for  $\alpha$ -nitro sulfones)  $\text{NaNO}_2$ .<sup>667</sup>  $\alpha$ -Nitro alkenes have been converted

to oximes ( $\text{—C=C—NO}_2 \rightarrow \text{—CH—C=NOH}$ ) with sodium hypophosphite and with  $\text{Pb-HOAc-DMF}$ , as well as with certain other reagents.<sup>668</sup>

Primary aliphatic nitro compounds can be reduced to nitriles with sodium dihydro(trithio)borate.<sup>584</sup> Secondary compounds give mostly ketones (e.g., nitrocyclohexane



<sup>658</sup>Still; Ablenas *J. Org. Chem.* **1983**, *48*, 1617.

<sup>659</sup>See for example, Sakaki; Oae *Chem. Lett.* **1977**, 1003; Still; Hasan; Turnbull *Can. J. Chem.* **1978**, *56*, 1423; Denis; Krief *J. Chem. Soc., Chem. Commun.* **1980**, 544.

<sup>660</sup>For a review, see Ref. 637, pp. 318-320.

<sup>661</sup>Rebeller; Clément *Bull. Soc. Chim. Fr.* **1964**, 1302.

<sup>662</sup>Freerksen; Selikson; Wroble; Kyler; Watt *J. Org. Chem.* **1983**, *48*, 4087. This paper also reports several other methods for achieving this conversion.

<sup>663</sup>Johnson; Degering *J. Am. Chem. Soc.* **1939**, *61*, 3194.

<sup>664</sup>Knifton *J. Org. Chem.* **1973**, *38*, 3296.

<sup>665</sup>Barton; Fernandez; Richard; Zard *Tetrahedron* **1987**, *43*, 551; Albanese; Landini; Penso *Synthesis* **1990**, 333.

<sup>666</sup>Hanson; Organ *J. Chem. Soc. C* **1970**, 1182; Hanson *Synthesis* **1974**, 1-8, pp. 7-8.

<sup>667</sup>Zeilstra; Engberts *Synthesis* **1974**, 49.

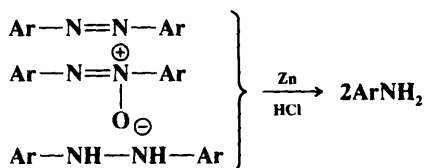
<sup>668</sup>See Varma; Varma; Kabalka *Synth. Commun.* **1986**, *16*, 91; Kabalka; Pace; Wadgaonkar *Synth. Commun.* **1990**, 20, 2453; Sera; Yamauchi; Yamada; Itoh *Synlett* **1990**, 477.

gave 45% cyclohexanone, 30% cyclohexanone oxime, and 19% N-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent. See also 9-47.

OS IV, 932.

### C. Reduction with Cleavage

#### 9-59 Reduction of Azo, Azoxy, and Hydrazo Compounds to Amines



Azo, azoxy, and hydrazo compounds can all be reduced to amines.<sup>669</sup> Metals (notably zinc) and acids, and  $\text{Na}_2\text{S}_2\text{O}_4$ , are frequently used as reducing agents. Borane reduces azo compounds to amines, though it does not reduce nitro compounds.<sup>670</sup>  $\text{LiAlH}_4$  does not reduce hydrazo compounds or azo compounds, though with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds,  $\text{LiAlH}_4$  gives only azo compounds (9-55).

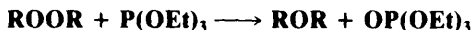
OS I, 49; II, 35, 39; III, 360. Also see OS II, 290.

#### 9-60 Reduction of Peroxides

##### O-Hydrogen-uncoupling



Peroxides are cleaved to 2 moles of alcohols by  $\text{LiAlH}_4$  or by catalytic hydrogenation. Peroxides can be reduced to ethers with  $\text{P}(\text{OEt})_3$ .<sup>671</sup>

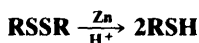


In a similar reaction, disulfides  $\text{RSSR}'$  can be converted to sulfides  $\text{RSR}'$  by treatment with tris(diethylamino)phosphine  $(\text{Et}_2\text{N})_3\text{P}$ .<sup>672</sup>

OS VI, 130.

#### 9-61 Reduction of Disulfides to Thiols

##### S-Hydrogen-uncoupling



Disulfides can be reduced to thiols by mild reducing agents,<sup>673</sup> such as zinc and dilute acid or  $\text{Ph}_3\text{P}$  and  $\text{H}_2\text{O}$ .<sup>674</sup> The reaction can also be accomplished simply by heating with alkali.<sup>675</sup>

<sup>669</sup>For a review, see Newbold, in Patai, Ref. 136, pt. 2, pp. 629-637.

<sup>670</sup>Brown; Subba Rao *J. Am. Chem. Soc.* **1960**, 82, 681.

<sup>671</sup>Horner; Jurgeleit *Liebigs Ann. Chem.* **1955**, 591, 138. See also Ref. 637, pp. 320-322.

<sup>672</sup>Harpp; Gleason; Snyder *J. Am. Chem. Soc.* **1968**, 90, 4181; Harpp; Gleason *J. Am. Chem. Soc.* **1971**, 93, 2437. For another method, see Comassetto; Lang; Ferreira; Simonelli; Correia *J. Organomet. Chem.* **1987**, 334, 329.

<sup>673</sup>For a review, see Wardell, in Patai, Ref. 408, pp. 220-229.

<sup>674</sup>Overman; Smoot; Overman *Synthesis* **1974**, 59.

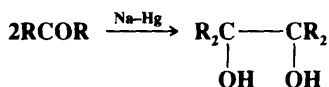
<sup>675</sup>For discussions, see Danchy; Hunter *J. Org. Chem.* **1967**, 32, 2047; Danchy, in Ref. 407, pp. 337-349.

Among other reagents used have been  $\text{LiAlH}_4$ ,  $\text{KBH}(\text{O}-i\text{-Pr})_3$ ,<sup>676</sup> and hydrazine or substituted hydrazines.<sup>678</sup>

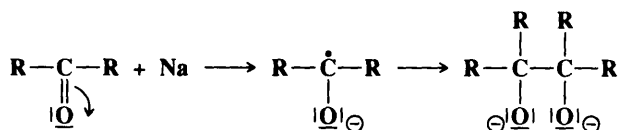
OS II, 580. Also see OS IV, 295.

## D. Reductive Coupling

### 9-62 Bimolecular Reduction of Aldehydes and Ketones to 1,2-Diols 2/O-Hydrogen-coupling



1,2-Diols (pinacols) can be synthesized by reduction of aldehydes and ketones with active metals such as sodium, magnesium, or aluminum.<sup>679</sup> Aromatic ketones give better yields than aliphatic ones. The use of a  $\text{Mg-MgI}_2$  mixture has been called the *Gomberg-Bachmann pinacol synthesis*. As with a number of other reactions involving sodium, there is a direct electron transfer here, converting the ketone or aldehyde to a ketyl, which dimerizes.



Other reagents have been used,<sup>680</sup> including  $\text{SmI}_2$ ,<sup>681</sup>  $\text{Ce-I}_2$ ,<sup>682</sup>  $\text{Yb}$ ,<sup>683</sup> and a reagent prepared from  $\text{TiCl}_4$  and  $\text{Mg}$  amalgam<sup>684</sup> (a low-valent titanium reagent; see 9-64). Dialdehydes have been cyclized by this reaction (with  $\text{TiCl}_3$ ) to give cyclic 1,2-diols in good yield.<sup>685</sup> Unsymmetrical coupling between two different aldehydes has been achieved by the use of a vanadium complex,<sup>686</sup> while  $\text{TiCl}_3$  in aqueous solution has been used to couple two different ketones.<sup>687</sup>

The dimerization of ketones to 1,2-diols can also be accomplished photochemically; indeed, this is one of the most common photochemical reactions.<sup>688</sup> The substrate, which

<sup>676</sup>Brown; Nazer; *Ch. Synthesis* **1984**, 498.

<sup>677</sup>Krishnamurthy; Aimino *J. Org. Chem.* **1989**, *54*, 4458.

<sup>678</sup>Maiti; Spevak; Singh; Micetich; Narendra Reddy *Synth. Commun.* **1988**, *18*, 575.

<sup>679</sup>For efficient methods, see Schreibmann *Tetrahedron Lett.* **1970**, 4271; Fürstner; Csuk; Rohrer; Weidmann *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729.

<sup>680</sup>For a list of reagents, with references, see Ref. 21, pp. 547-548.

<sup>681</sup>Namy; Soupe; Kagan *Tetrahedron Lett.* **1983**, *24*, 765.

<sup>682</sup>Imamoto; Kusumoto; Hatanaka; Yokoyama *Tetrahedron Lett.* **1982**, *23*, 1353.

<sup>683</sup>Hou; Takamine; Fujiwara; Taniguchi *Chem. Lett.* **1987**, 2061.

<sup>684</sup>Corey; Danheiser; Chandrasekaran *J. Org. Chem.* **1976**, *41*, 260; Pons; Zahra; Santelli *Tetrahedron Lett.* **1981**, *22*, 3965. For some other titanium-containing reagents, see Clerici; Porta *J. Org. Chem.* **1985**, *50*, 76; Handa; Inanaga *Tetrahedron Lett.* **1987**, *28*, 5717. For a review of such coupling with Ti and V halides, see Lai *Org. Prep. Proced. Int.* **1980**, *12*, 363-391.

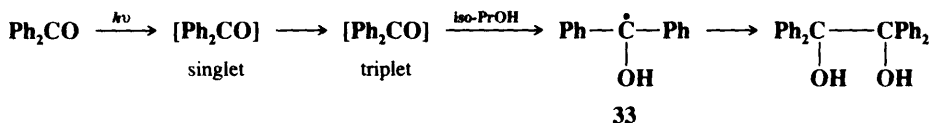
<sup>685</sup>McMurry; Rico *Tetrahedron Lett.* **1989**, *30*, 1169. For other cyclization reactions of dialdehydes and ketoaldehydes, see Molander; Kenny *J. Am. Chem. Soc.* **1989**, *111*, 8236; Raw; Pedersen *J. Org. Chem.* **1991**, *56*, 830; Chiara; Cabri; Hanessian *Tetrahedron Lett.* **1991**, *32*, 1125.

<sup>686</sup>Freudenberger; Konradi; Pedersen *J. Am. Chem. Soc.* **1989**, *111*, 8014.

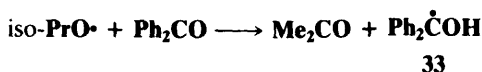
<sup>687</sup>Clerici; Porta *J. Org. Chem.* **1982**, *47*, 2852, *Tetrahedron* **1983**, *39*, 1239. For some other unsymmetrical couplings, see Hou; Takamine; Aoki; Shiraishi; Fujiwara; Taniguchi *J. Chem. Soc., Chem. Commun.* **1988**, 668; Delair; Luche *J. Chem. Soc., Chem. Commun.* **1989**, 398; Takahara; Freudenberger; Konradi; Pedersen *Tetrahedron Lett.* **1989**, *30*, 7177.

<sup>688</sup>For reviews, see Schönberg *Preparative Organic Photochemistry*; Springer: New York, 1968, pp. 203-217; Neckers *Mechanistic Organic Photochemistry*; Reinhold: New York, 1967, pp. 163-177; Calvert; Pitts *Photochemistry*; Wiley: New York, 1966, pp. 532-536; Turro *Modern Molecular Photochemistry*; W.A. Benjamin: New York, 1978, pp. 363-385; Kan *Organic Photochemistry*; McGraw-Hill: New York, 1966, pp. 222-229.

is usually a diaryl or aryl alkyl ketone (though a few aromatic aldehydes and dialkyl ketones have been dimerized), is irradiated with uv light in the presence of a hydrogen donor such as isopropyl alcohol, toluene, or an amine.<sup>689</sup> 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  $T_1$

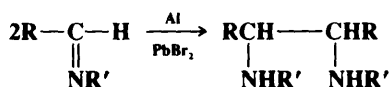


species abstracts hydrogen from the alcohol (p. 246) and then dimerizes. The iso-PrO• radical, which is formed by this process, donates H• to another molecule of ground-state benzophenone, producing acetone and another molecule of 33. This mechanism<sup>690</sup> predicts that the quantum yield for the disappearance of benzophenone should be 2, since each quantum

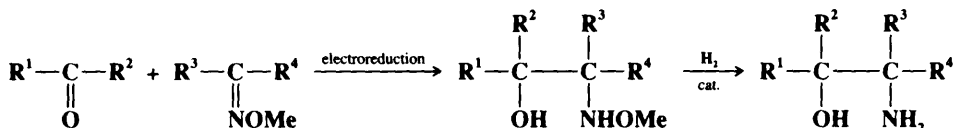


of light results in the conversion of 2 moles of benzophenone to 33. Under favorable experimental conditions the observed quantum yield does approach 2. Benzophenone abstracts hydrogen with very high efficiency. Other aromatic ketones are dimerized with lower quantum yields, and some (e.g., *p*-aminobenzophenone, *o*-methylacetophenone) cannot be dimerized at all in 2-propanol (though *p*-aminobenzophenone, for example, can be dimerized in cyclohexane<sup>691</sup>). The reaction has also been carried out electrochemically.<sup>692</sup>

In a similar type of process, imines have been dimerized to give 1,2-diamines, by a number of procedures, including treatment with Al-PbBr<sub>2</sub>,<sup>693</sup> with TiCl<sub>4</sub>-Mg,<sup>694</sup> with SmI<sub>2</sub>,<sup>695</sup>



and (for silylated imines) NbCl<sub>4</sub>(THF)<sub>2</sub>.<sup>696</sup> When electroreduction was used, it was even possible to obtain cross products, by coupling a ketone to an O-methyl oxime:<sup>697</sup>



<sup>689</sup>For a review of amines as hydrogen donors in this reaction, see Cohen; Parola; Parsons *Chem. Rev.* **1973**, 73, 141-161.

<sup>690</sup>For some of the evidence for this mechanism, see Pitts; Letsinger; Taylor; Patterson; Recktenwald; Martin *J. Am. Chem. Soc.* **1959**, 81, 1068; Hammond; Moore *J. Am. Chem. Soc.* **1959**, 81, 6334; Moore; Hammond; Foss *J. Am. Chem. Soc.* **1961**, 83, 2789; Huyser; Neckers *J. Am. Chem. Soc.* **1963**, 85, 3641.

<sup>691</sup>Porter; Suppan *Proc. Chem. Soc.* **1964**, 191.

<sup>692</sup>For reviews, see Fry, Ref. 244, pp. 174-180; Shono, Ref. 149, pp. 137-140; Baizer; Petrovich *Prog. Phys. Org. Chem.* **1970**, 7, 189-227. For a review of electrolytic reductive coupling, see Baizer, in Baizer, Lund, Ref. 600, pp. 639-689.

<sup>693</sup>Tanaka; Dhiman; Fujita; Ikemoto; Torii *Tetrahedron Lett.* **1988**, 29, 3811.

<sup>694</sup>Betschart; Seebach *Helv. Chim. Acta* **1987**, 70, 2215; Betschart; Schmidt; Seebach *Helv. Chim. Acta* **1988**, 71, 1999; Mangeney; Tejero; Alexakis; Grosjean; Normant *Synthesis* **1988**, 255.

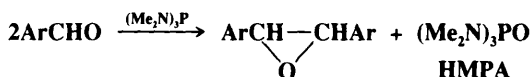
<sup>695</sup>Enholm; Forbes; Holub *Synth. Commun.* **1990**, 20, 981; Imamoto; Nishimura *Chem. Lett.* **1990**, 1141.

<sup>696</sup>Roskamp; Pedersen *J. Am. Chem. Soc.* **1987**, 109, 3152.

<sup>697</sup>Shono; Kise; Fujimoto *Tetrahedron Lett.* **1991**, 32, 525.

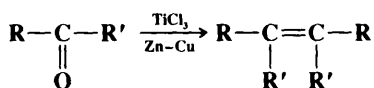
The N-methoxyamino alcohol could then be reduced to the amino alcohol.<sup>697</sup>  
OS I, 459; II, 71.

### 9-63 Bimolecular Reduction of Aldehydes and Ketones to Epoxides Aldehyde-oxirane transformation



Aromatic aldehydes can be dimerized to epoxides by treatment with hexamethylphosphorus triamide.<sup>698</sup> The reagent<sup>699</sup> is converted to hexamethylphosphoric triamide (HMPA). The reaction can be used for the preparation of mixed epoxides by the use of a mixture of two aldehydes in which the less reactive aldehyde predominates. Epoxides have also been prepared by treatment of aromatic aldehydes or ketones with the anions  $(\text{Me}_2\text{N})_2\text{P}^{\ominus}=\text{O}$  and  $(\text{EtO})_2\text{P}^{\ominus}=\text{O}$  (derived, respectively, by treatment with an alkali metal of HMPA or triethyl phosphite).<sup>700</sup>  
OS V, 358.

### 9-64 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 with  $\text{TiCl}_3$  and a zinc-copper couple.<sup>701</sup> This is called the *McMurry reaction*.<sup>702</sup> The reagent produced in this way is called a *low-valent titanium reagent*, and the reaction has also been accomplished<sup>703</sup> with low-valent titanium reagents prepared in other ways, e.g., from Mg and a  $\text{TiCl}_3$ -THF complex,<sup>704</sup> from  $\text{TiCl}_4$  and Zn or Mg,<sup>705</sup> from  $\text{TiCl}_3$  and  $\text{LiAlH}_4$ ,<sup>706</sup> from  $\text{TiCl}_3$  and lamellar potassium graphite,<sup>707</sup> from  $\text{TiCl}_3$  and K or Li,<sup>708</sup> as well as with  $\text{Zn-Me}_3\text{SiCl}$ <sup>709</sup> and with certain compounds prepared from  $\text{WCl}_6$  and either lithium, lithium iodide,  $\text{LiAlH}_4$ , or an

<sup>698</sup>Mark J. *Am. Chem. Soc.* **1963**, 85, 1884; Newman; Blum J. *Am. Chem. Soc.* **1964**, 86, 5598.

<sup>699</sup>For the preparation of the reagent, see Mark *Org. Synth.* V, 602.

<sup>700</sup>Normant *Bull. Soc. Chim. Fr.* **1966**, 3601.

<sup>701</sup>McMurry; Fleming J. *Org. Chem.* **1978**, 43, 3255. For an optimized procedure, see McMurry; Lectka; Rico J. *Org. Chem.* **1989**, 54, 3748.

<sup>702</sup>For reviews, see McMurry *Chem. Rev.* **1989**, 89, 1513-1524, *Acc. Chem. Res.* **1983**, 16, 405-511; Lenoir *Synthesis* **1989**, 883-897; Betschart; Seebach *Chimia* **1989**, 43, 39-49; Lai, Ref. 684. For related reviews, see Kahn; Rieke *Chem. Rev.* **1988**, 88, 733-745; Pons; Santelli *Tetrahedron* **1988**, 44, 4295-4312.

<sup>703</sup>For a list of reagents, with references, see Ref. 21, pp. 160-161.

<sup>704</sup>Tyrlik; Wolochowicz *Bull. Soc. Chim. Fr.* **1973**, 2147.

<sup>705</sup>Mukaiyama; Sato; Hanna *Chem. Lett.* **1973**, 1041; Lenoir *Synthesis* **1977**, 553; Lenoir; Burghard J. *Chem. Res. (S)* **1980**, 396; Carroll; Taylor *Aust. J. Chem.* **1990**, 43, 1439.

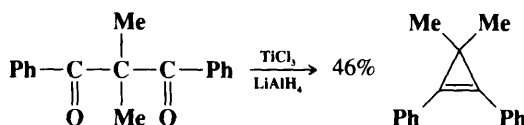
<sup>706</sup>McMurry; Fleming J. *Am. Chem. Soc.* **1974**, 96, 4708; Dams; Malinowski; Geise *Bull. Soc. Chim. Belg.* **1982**, 91, 149, 311; Bottino; Finocchiaro; Libertini; Reale; Recca J. *Chem. Soc., Perkin Trans. 2* **1982**, 77. This reagent has been reported to give capricious results; see McMurry; Fleming, Ref. 708.

<sup>707</sup>Fürstner; Weidmann *Synthesis* **1987**, 1071.

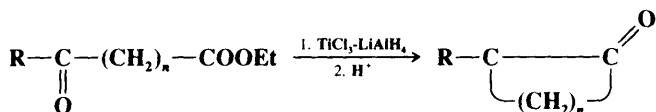
<sup>708</sup>McMurry; Fleming J. *Org. Chem.* **1976**, 41, 896; Richardson *Synth. Commun.* **1981**, 11, 895.

<sup>709</sup>Banerjee; Sulbaran de Carrasco; Frydrych-Houge; Motherwell J. *Chem. Soc., Chem. Commun.* **1986**, 1803.

alkyllithium<sup>710</sup> (see 7-21). The reaction has been used to convert dialdehydes and diketones to cycloalkenes.<sup>711</sup> Rings of 3 to 16 and 22 members have been closed in this way, e.g.,<sup>712</sup>



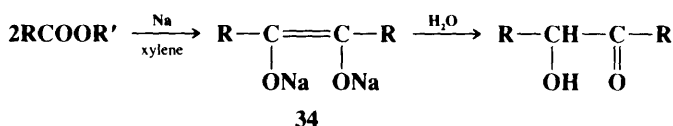
The same reaction on a keto ester gives a cycloalkanone.<sup>713</sup>



Unsymmetrical alkenes can be prepared from a mixture of two ketones, if one is in excess.<sup>714</sup> The mechanism consists of initial coupling of two radical species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated.<sup>715</sup>

OS VII, 1.

### 9-65 Acyloin Ester Condensation



When carboxylic esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place, and the product is an  $\alpha$ -hydroxy ketone (called an acyloin).<sup>716</sup> The reaction, called the *acyloin ester condensation*, is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way, for example, R = C<sub>17</sub>H<sub>35</sub>, but for high-molecular-weight esters, toluene or xylene is used as the solvent. The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.<sup>717</sup> The yields are 50 to 60% for the preparation of 6- and 7-membered rings, 30 to 40% for 8- and 9-membered, and 60 to 95% for rings of 10 to 20 members. Even larger rings have been closed in this manner. This is one of the best ways of closing rings of 10 members or more. The reaction has been used to close 4-membered rings,<sup>718</sup> though this is generally not

<sup>710</sup>Sharpless; Umbreit; Nieh; Flood *J. Am. Chem. Soc.* **1972**, *94*, 6538; Fujiwara; Ishikawa; Akiyama; Teranishi *J. Org. Chem.* **1978**, *43*, 2477; Dams; Malinowski; Geise, Ref. 706. See also Petit; Mortreux; Petit *J. Chem. Soc., Chem. Commun.* **1984**, 341; Chisholm; Klang *J. Am. Chem. Soc.* **1989**, *111*, 2324.

<sup>711</sup>Baumstark; Bechara; Semigran *Tetrahedron Lett.* **1976**, 3265; McMurry; Fleming; Kees; Krepski, Ref. 701.

<sup>712</sup>Baumstark; McCloskey; Witt *J. Org. Chem.* **1978**, *43*, 3609.

<sup>713</sup>McMurry; Miller *J. Am. Chem. Soc.* **1983**, *105*, 1660.

<sup>714</sup>McMurry; Fleming; Kees; Krepski, Ref. 701; Nishida; Kataoka *J. Org. Chem.* **1978**, *43*, 1612; Coe; Scriven *J. Chem. Soc., Perkin Trans. 1* **1986**, 475; Chisholm; Klang, Ref. 710.

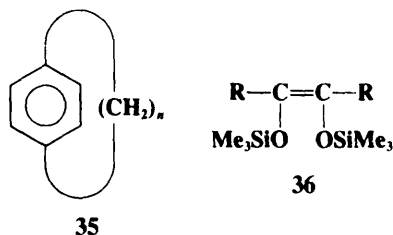
<sup>715</sup>McMurry; Fleming; Kees; Krepski, Ref. 701; Dams; Malinowski; Westdorp; Geise *J. Org. Chem.* **1982**, *47*, 248.

<sup>716</sup>For a review, see Bloomfield; Owsley; Nelke *Org. React.* **1976**, *23*, 259-403. For a list of reactions, with references, see Ref. 21, pp. 645-646.

<sup>717</sup>For a review of cyclizations by means of the acyloin condensation, see Finley, *Chem. Rev.* **1964**, *64*, 573-589.

<sup>718</sup>Cope; Herrick *J. Am. Chem. Soc.* **1950**, *72*, 983; Bloomfield; Irelan *J. Org. Chem.* **1966**, *31*, 2017.

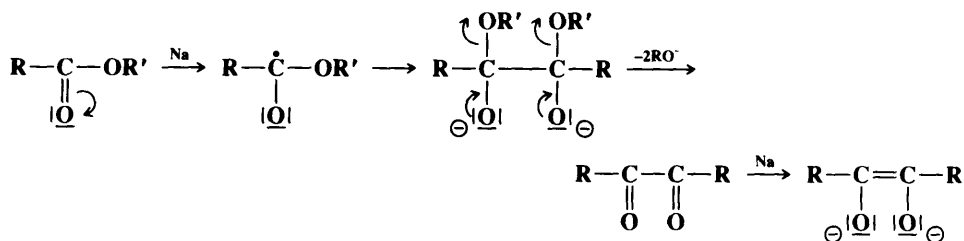
successful. The presence of double or triple bonds does not interfere.<sup>719</sup> Even a benzene ring can be present, and many paracyclophane derivatives (**35**) with  $n = 9$  or more have



been synthesized in this manner.<sup>720</sup>

Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane  $\text{Me}_3\text{SiCl}$ , in which case the dianion **34** is converted to the bis silyl enol ether **36**, which can be isolated and subsequently hydrolyzed to the acyloin with aqueous acid.<sup>721</sup> This is now the standard way to conduct the acyloin condensation. Among other things, this method inhibits the Dieckmann condensation<sup>722</sup> (**0-108**), which otherwise competes with the acyloin condensation when a 5-, 6-, or 7-membered ring can be closed (note that the ring formed by a Dieckmann condensation is always one carbon atom smaller than that formed by an acyloin condensation of the same substrate). The  $\text{Me}_3\text{SiCl}$  method is especially good for the closing of four-membered rings.<sup>723</sup> Yields of 4-, 5-, and 6-membered rings are improved by the use of ultrasound.<sup>724</sup>

The mechanism is not known with certainty, but it is usually presumed that the diketone RCOCOR is an intermediate,<sup>725</sup> since small amounts of it are usually isolated as side products, and when it is resistant to reduction (e.g., *t*-Bu-COCO-*t*-Bu), it is the major product. A possible sequence (analogous to that of 9-62) is



In order to account for the ready formation of large rings, which means that the two ends of the chain must approach each other even though this is conformationally unfavorable for

<sup>719</sup>Cram; Gaston *J. Am. Chem. Soc.* **1960**, *82*, 6386.

<sup>72b</sup>For a review, see Cram *Rec. Chem. Prog.* **1959**, 20, 71.

<sup>71</sup>Schräpler; Rühlmann *Chem. Ber.* **1964**, 97, 1383. For a review of the  $\text{Me}_3\text{SiCl}$  method, see Rühlmann *Synthesis* **1971**, 236-253.

<sup>722</sup>Bloomfield *Tetrahedron Lett.* **1968**, 591.

<sup>723</sup>Bloomfield *Tetrahedron Lett.* **1968**, 587; Gream; Worthley *Tetrahedron Lett.* **1968**, 3319; Wynberg; Reiffers; Strating *Recl. Trav. Chim. Pays-Bas* **1970**, 89, 982; Bloomfield; Martin; Nelke *J. Chem. Soc., Chem. Commun.* **1972**, 96.

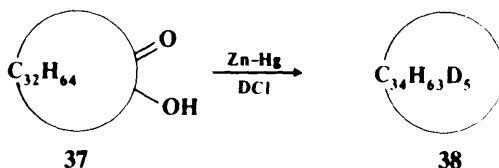
<sup>724</sup>Fadel; Canet; Salaün *Synlett* 1990, 89.

<sup>75</sup> Another mechanism, involving addition of the ketyl to another molecule of ester (rather than a dimerization of two ketyl radicals), in which a diketone is not an intermediate, has been proposed: Bloomfield; Owsley; Ainsworth; Robertson *J. Org. Chem.* **1975**, *40*, 393.

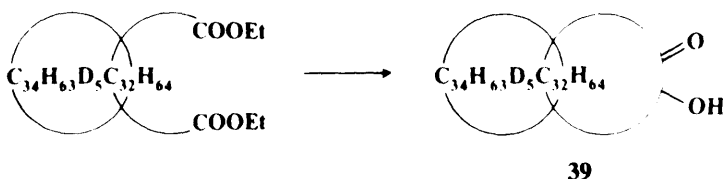
long chains, it may be postulated that the two ends become attached to nearby sites on the surface of the sodium.

In a related reaction, aromatic carboxylic acids were condensed to  $\alpha$ -diketones ( $2\text{ArCOOH} \rightarrow \text{ArCOCOAr}$ ) on treatment with excess Li in dry THF in the presence of ultrasound.<sup>726</sup>

The acyloin condensation was used in an ingenious manner to prepare the first reported catenane (see p. 91).<sup>727</sup> The catenane (**39**) was prepared by a statistical synthesis (p. 91) in the following manner: An acyloin condensation was performed on the diethyl ester of the  $\text{C}_{34}$  dicarboxylic acid (tetratriacontadioic acid) to give the cyclic acyloin **37**. This was reduced by a Clemmensen reduction with DCl in  $\text{D}_2\text{O}$  instead of HCl in  $\text{H}_2\text{O}$ , thus producing a  $\text{C}_{34}$  cycloalkane containing deuterium (**38**):<sup>728</sup>



**38** contained about five atoms of deuterium per molecule. The reaction was then repeated, this time in a 1:1 mixture of xylene and **38** as solvent. It was hoped that some of the molecules of ester would be threaded through **38** before they closed:



The first thing that was done with the product was to remove by chromatography the **38** that had been used as the solvent. The remaining material still contained deuterium, as determined by ir spectra, even with all the **38** gone. This was strong evidence that the material consisted not only of **37**, but also of **39**. As further evidence, the mixture was oxidized to open up the acyloin rings (9-7). From the oxidation product was isolated the  $\text{C}_{34}$  diacid (as expected) containing no deuterium, and **38**, containing deuterium. The total yield of **39** and **37** was 5 to 20%, but the percentage of **39** in this mixture was only about 1 to 2%.<sup>728</sup> This synthesis of a catenane produced only a small yield and relied on chance, on the probability that a diester molecule would be threaded through **38** before it closed.

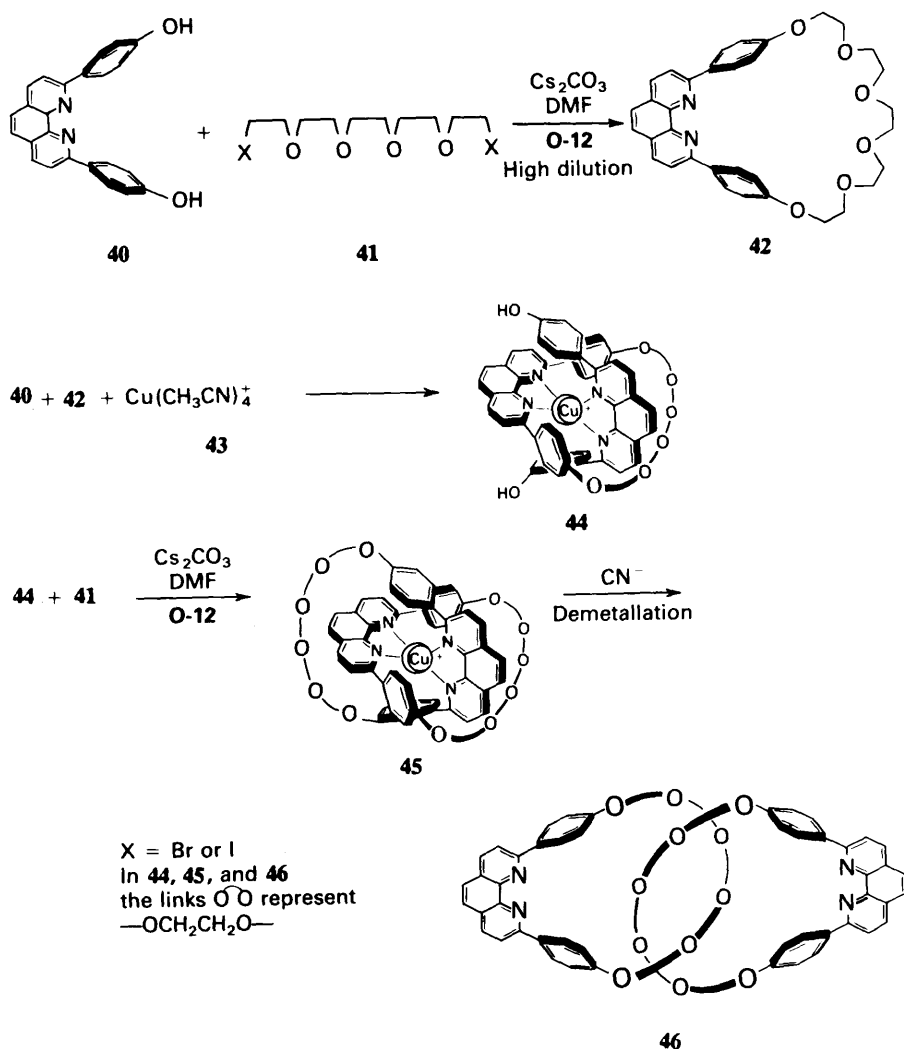
Several *directed* syntheses of catenanes have also been reported. One of these relies upon coordination of ligands to a metallic ion to achieve the proper geometry. An example is shown in Figure 19.1.<sup>729</sup> 2,9-Bis(*p*-hydroxyphenyl)-1,10-phenanthroline **40** is converted to the macrocycle **42** by treatment with the polyether **41**, in a Williamson reaction, under

<sup>726</sup>Karaman; Fry *Tetrahedron Lett.* **1989**, 30, 6267.

<sup>727</sup>For reviews of the synthesis of catenanes, see Sauvage *Acc. Chem. Res.* **1990**, 23, 319-327; *Nouv. J. Chim.* **1985**, 9, 299-310; Dietrich-Buchecker; Sauvage *Chem. Rev.* **1987**, 87, 795-810.

<sup>728</sup>This work was done by Wasserman *J. Am. Chem. Soc.* **1960**, 82, 4433. For other statistical syntheses, see Wolovsky *J. Am. Chem. Soc.* **1970**, 92, 2132; Ben-Efraim; Batich; Wasserman *J. Am. Chem. Soc.* **1970**, 92, 2133; Agam; Zilkha *J. Am. Chem. Soc.* **1976**, 98, 5214; Schill; Schweickert; Fritz; Vetter *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 889 [*Angew. Chem.* 95, 909].

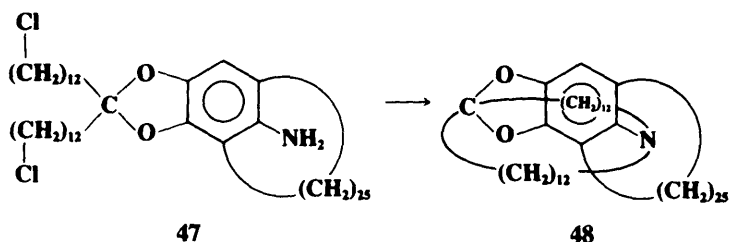
<sup>729</sup>Dietrich-Buchecker; Sauvage; Kintzinger *Tetrahedron Lett.* **1983**, 24, 5095; Dietrich-Buchecker; Sauvage; Kern *J. Am. Chem. Soc.* **1984**, 106, 3043; Dietrich-Buchecker; Sauvage *Tetrahedron* **1990**, 46, 503.

FIGURE 19.1 Synthesis of the catenane 46.<sup>729</sup>

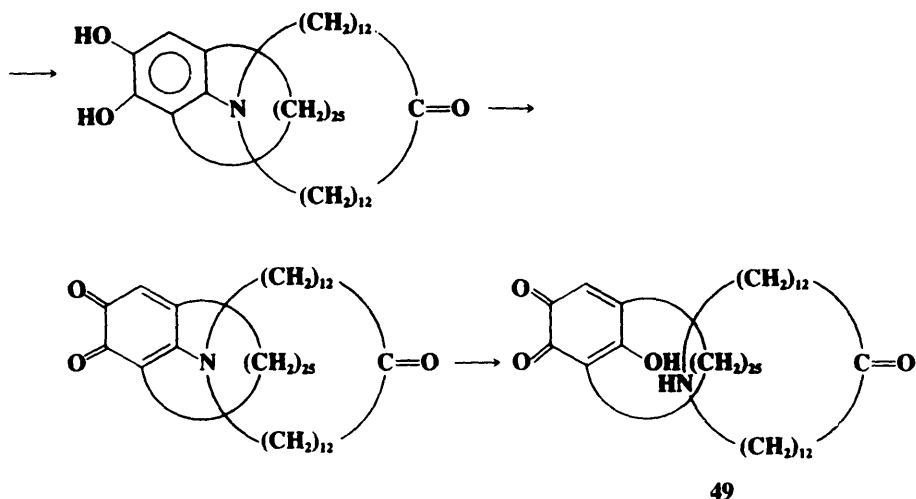
high dilution conditions. 42, combined with another molecule of 40, forms a coordination compound 44 when a mixture of 40 and 42 is treated with a copper complex 43. The two phenolic OH groups of 44 are in proper positions so that when combined with additional 41, the interlocking copper complex 45 (called a *catenate*) is formed. In the final step, the copper is removed by treatment with  $\text{CN}^-$  (which preferentially coordinates with  $\text{Cu}^+$ ) to give the catenane 46. 45 was obtained in 42% yield from 42. 45 was also obtained more directly, by treatment of 40 with the complex 43, which forms another complex in which the two molecules of 40 coordinate with the copper. This, treated with two moles of 41, generates 45. A similar strategy was used to prepare [3]catenanes.<sup>730</sup>

<sup>729</sup>Sauvage; Weiss *J. Am. Chem. Soc.* **1985**, *107*, 6108. For other preparations of [3]catenanes, see Dietrich-Buchecker; Hemmert; Khémiss; Sauvage *J. Am. Chem. Soc.* **1990**, *112*, 8002; Ashton et al. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1039 [*Angew. Chem.* *103*, 1055]. See also Guilhem; Pascard; Sauvage; Weiss *J. Am. Chem. Soc.* **1988**, *110*, 8711.

Another directed synthesis of catenanes<sup>731</sup> does not use a metallic ion. The key step in this approach<sup>732</sup> was formation of a tertiary amine by **0-43**. Sterically, one of the halide groups of **47** is above the plane, and the other below it, so that ring closure must occur



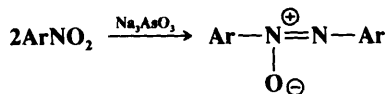
through the 28-membered ring. After **48** was formed, the acetal was cleaved (**0-6**). It was then necessary to cleave the remaining bond holding the two rings together, i.e., the C—N bond. This was done by oxidation to the *ortho*-quinone (**9-4**), which converted the amine function to an enamine, which was hydrolyzable (**6-2**) with acid to give the catenane (**49**):



OS II, 114; IV, 840; VI, 167.

## 9-66 Reduction of Nitro to Azoxy Compounds

### Nitro-azoxy reductive transformation



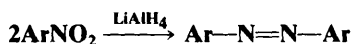
<sup>731</sup>For still others, see Schill; Schweickert; Fritz; Vetter *Chem. Ber.* **1988**, 121, 961; Ashton; Goodnow; Kaifer; Reddington; Slawin; Spencer; Stoddart; Vicent; Williams *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1396 [*Angew. Chem.* 101, 1404]; Brown; Philp; Stoddart *Synlett* **1991**, 459.

<sup>732</sup>Schill; Lüttringhaus *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 546 [*Angew. Chem.* 76, 567]; Schill *Chem. Ber.* **1965**, 98, 2906, **1966**, 99, 2689, **1967**, 100, 2021; Logemann; Rissler; Schill; Fritz *Chem. Ber.* **1981**, 114, 2245. For the preparation of [3]catenanes by a similar approach, see Schill; Zürcher *Chem. Ber.* **1977**, 110, 2046; Rissler; Schill; Fritz; Vetter *Chem. Ber.* **1986**, 119, 1374.

Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide,  $\text{NaTeH}$ ,<sup>733</sup> lead,<sup>734</sup>  $\text{NaBH}_4\text{-PhTeTePh}$ ,<sup>735</sup> and glucose. The most probable mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (9-49), and these combine (2-53). The combination step is rapid compared to the reduction process.<sup>736</sup> Nitroso compounds can be reduced to azoxy compounds with triethyl phosphite or triphenylphosphine<sup>737</sup> or with an alkaline aqueous solution of an alcohol.<sup>738</sup>

OS II, 57.

**9-67 Reduction of Nitro to Azo Compounds**  
***N*-De-bisoxxygen-coupling**



Nitro compounds can be reduced to azo compounds with various reducing agents, of which  $\text{LiAlH}_4$  and zinc and alkali are the most common. With many of these reagents, slight differences in conditions can lead either to the azo or azoxy (9-66) compound. Analogously to 9-66, this reaction may be looked on as a combination of  $\text{ArN=O}$  and  $\text{ArNH}_2$  (2-52). However, when the reducing agent was  $\text{HOCH}_2\text{CH}_2\text{ONa}$ <sup>739</sup> or  $\text{NaBH}_4$ ,<sup>740</sup> it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with  $\text{LiAlH}_4$ .

OS III, 103.

**9-68 Reduction of Nitro to Hydrazo Compounds**  
***N*-Hydrogen-de-bisoxxygen-coupling**



Nitro compounds can be reduced to hydrazo compounds with zinc and sodium hydroxide, with hydrazine hydrate and Raney nickel,<sup>741</sup> or with  $\text{LiAlH}_4$  mixed with a metal chloride such as  $\text{TiCl}_4$  or  $\text{VCl}_3$ .<sup>742</sup> The reduction has also been accomplished electrochemically.

**Reactions in Which an Organic Substrate is Both Oxidized and Reduced**

Some reactions that belong in this category have been considered in earlier chapters. Among these are the Tollens' condensation (6-46), the benzil-benzilic acid rearrangement (8-6), and the Wallach rearrangement (8-45).

**9-69 The Cannizzaro Reaction**  
**Cannizzaro Aldehyde Disproportionation**



<sup>733</sup>Osuka; Shimizu; Suzuki *Chem. Lett.* **1983**, 1373.

<sup>734</sup>Azoo; Grimshaw *J. Chem. Soc. C* **1968**, 2403.

<sup>735</sup>Ohe; Uemura; Sugita; Masuda; Taga *J. Org. Chem.* **1989**, 54, 4169.

<sup>736</sup>Ogata; Mibae *J. Org. Chem.* **1962**, 27, 2048.

<sup>737</sup>Bunyan; Cadogan *J. Chem. Soc.* **1963**, 42.

<sup>738</sup>See, for example, Hutton; Waters *J. Chem. Soc. B* **1968**, 191. See also Porta; Pizzotti; Cenini *J. Organomet. Chem.* **1981**, 222, 279.

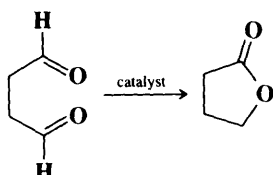
<sup>739</sup>Tadros; Ishak; Bassili *J. Chem. Soc.* **1959**, 627.

<sup>740</sup>Hutchins; Lamson; Rufa; Milewski; Maryanoff *J. Org. Chem.* **1971**, 36, 803.

<sup>741</sup>Furst; Moore *J. Am. Chem. Soc.* **1957**, 79, 5492.

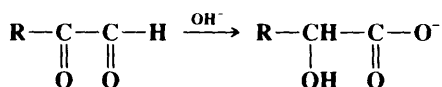
<sup>742</sup>Olah *J. Am. Chem. Soc.* **1959**, 81, 3165.

Aromatic aldehydes, and aliphatic ones with no  $\alpha$  hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.<sup>743</sup> In this reaction one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an  $\alpha$  hydrogen do not give the reaction, because when these compounds are treated with base the aldol reaction (6-39) is much faster.<sup>744</sup> Normally, the best yield of acid or alcohol is 50% each, but this can be altered in certain cases. When the aldehyde contains a hydroxide group in the ring, excess base oxidizes the alcohol formed and the acid can be prepared in high yield (the  $\text{OH}^-$  is reduced to  $\text{H}_2$ ). On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde. In this case the formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed Cannizzaro reaction*. The Tollens' condensation (6-46) includes a crossed Cannizzaro reaction as its last step. A Cannizzaro reaction run on 1,4-dialdehydes (note that  $\alpha$  hydrogens are present here) with a rhodium phosphine complex catalyst gives ring closure, e.g.,<sup>745</sup>



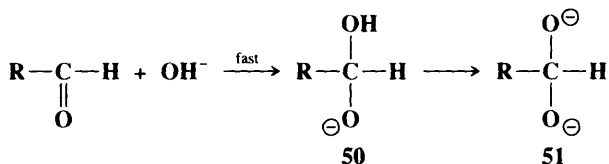
The product is the lactone derived from the hydroxy acid that would result from a normal Cannizzaro reaction.

$\alpha$ -Keto aldehydes give internal Cannizzaro reactions:



This product is also obtained on alkaline hydrolysis of compounds of the formula  $\text{RCOCHX}_2$ . Similar reactions have been performed on  $\alpha$ -keto acetals<sup>746</sup> and  $\gamma$ -keto aldehydes.

The mechanism<sup>747</sup> of the Cannizzaro reaction<sup>748</sup> involves a hydride shift (an example of mechanism type 2, p. 1160). First  $\text{OH}^-$  adds to the  $\text{C}=\text{O}$  to give **50**, which may lose a proton in the basic solution to give the diion **51**.



<sup>743</sup>For a review, see Geissman *Org. React.* **1944**, 2, 94-113.

<sup>744</sup>An exception is cyclopropanecarboxaldehyde: van der Maeden; Steinberg; de Boer *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 221.

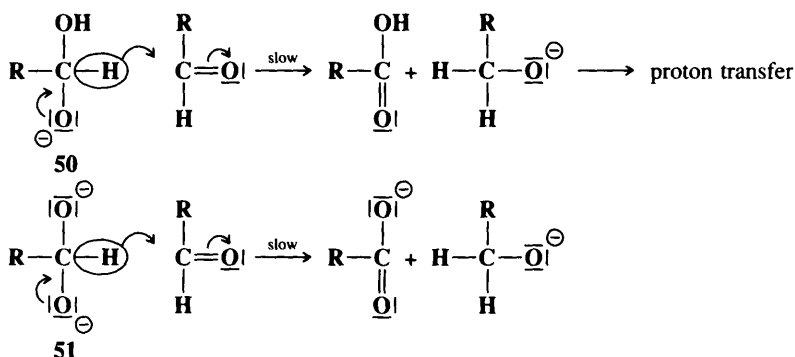
<sup>745</sup>Bergens; Fairlie; Bosnich *Organometallics* **1990**, 9, 566.

<sup>746</sup>Thompson *J. Org. Chem.* **1967**, 32, 3947.

<sup>747</sup>For evidence that an SET pathway may intervene, see Ashby; Coleman; Gamasa *J. Org. Chem.* **1987**, 52, 4079; Fuentes; Marinas; Sinisterra *Tetrahedron Lett.* **1987**, 28, 2947.

<sup>748</sup>See for example, Swain; Powell; Sheppard; Morgan *J. Am. Chem. Soc.* **1979**, 101, 3576; Watt *Adv. Phys. Org. Chem.* **1988**, 24, 57-112, pp. 81-86.

The strong electron-donating character of  $\text{O}^-$  greatly facilitates the ability of the aldehydic hydrogen to leave with its electron pair. Of course, this effect is even stronger in **51**. When the hydride does leave, it attacks another molecule of aldehyde. The hydride can come from **50** or **51**:

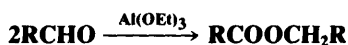


If the hydride ion comes from **50**, the final step is a rapid proton transfer. In the other case, the acid salt is formed directly, and the alkoxide ion acquires a proton from the solvent. Evidence for this mechanism is: (1) The reaction can be first order in base and second order in substrate (thus going through **50**) or, at higher base concentrations, second order in each (going through **51**); and (2) when the reaction was run in  $\text{D}_2\text{O}$ , the recovered alcohol contained no  $\alpha$  deuterium,<sup>749</sup> indicating that the hydrogen comes from another mole of aldehyde and not from the medium.<sup>750</sup>

OS I, 276; II, 590; III, 538; IV, 110.

## 9-70 The Tishchenko Reaction

### Tishchenko aldehyde-ester disproportionation



When aldehydes, with or without  $\alpha$  hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another reduced, as in **9-69**, but here they are found as the ester. The process is called the *Tishchenko reaction*. Crossed Tishchenko reactions are also possible. With more strongly basic alkoxides, such as magnesium or sodium alkoxides, aldehydes with an  $\alpha$  hydrogen give the aldol reaction. Like **9-69**, this reaction has a mechanism that involves hydride transfer.<sup>751</sup> The Tishchenko reaction can also be catalyzed<sup>752</sup> by ruthenium complexes,<sup>753</sup> by boric acid,<sup>754</sup> and, for aromatic aldehydes, by disodium tetracarbonylferrate  $\text{Na}_2\text{Fe}(\text{CO})_4$ .<sup>755</sup>

OS I, 104.

<sup>749</sup>Fredenhagen; Bonhoeffer *Z. Phys. Chem., Abt. A* **1938**, 181, 379; Hauser; Hamrick; Stewart *J. Org. Chem.* **1956**, 21, 260.

<sup>750</sup>When the reaction was run at  $100^\circ\text{C}$  in  $\text{MeOH}-\text{H}_2\text{O}$ , isotopic exchange was observed (the product from PhCDO had lost some of its deuterium): Swain; Powell; Lynch; Alpha; Dunlap *J. Am. Chem. Soc.* **1979**, 101, 3584. Side reactions were postulated to account for the loss of deuterium. See, however, Chung *J. Chem. Soc., Chem. Commun.* **1982**, 480.

<sup>751</sup>See, for example, Zakharkin; Sorokina *J. Gen. Chem. USSR* **1967**, 37, 525; Saegusa; Ueshima; Kitagawa *Bull. Chem. Soc. Jpn.* **1969**, 42, 248; Ogata; Kishi *Tetrahedron* **1969**, 25, 929.

<sup>752</sup>For a list of reagents, with references, see Ref. 21, p. 840.

<sup>753</sup>Ito; Horino; Koshiro; Yamamoto *Bull. Chem. Soc. Jpn.* **1982**, 55, 504.

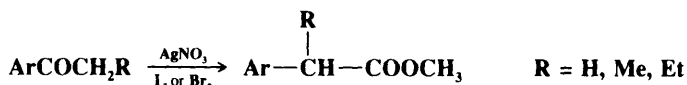
<sup>754</sup>Stapp *J. Org. Chem.* **1973**, 38, 1433.

<sup>755</sup>Yamashita; Watanabe; Mitsudo; Takegami *Bull. Chem. Soc. Jpn.* **1976**, 49, 3597.

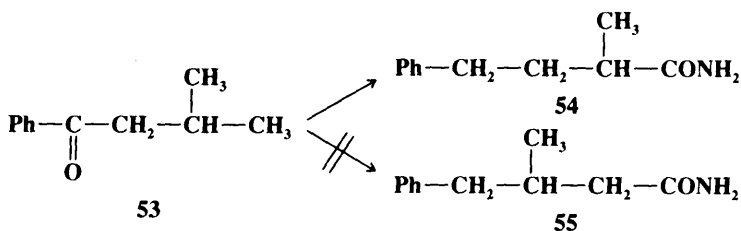


In the *Willgerodt reaction* a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid by heating with ammonium polysulfide.<sup>765</sup> The carbonyl group of the product is always at the end of the chain. Thus  $\text{ArCOCH}_2\text{CH}_3$  gives the amide and the salt of  $\text{ArCH}_2\text{CH}_2\text{COOH}$ , and  $\text{ArCOCH}_2\text{CH}_2\text{CH}_3$  gives derivatives of  $\text{ArCH}_2\text{CH}_2\text{CH}_2\text{COOH}$ . However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinylic and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. The use of sulfur and a dry primary or secondary amine (or ammonia) as the reagent is called the *Kindler modification* of the Willgerodt reaction.<sup>766</sup> The product in this case is  $\text{Ar}(\text{CH}_2)_n\text{CSNR}_2$ ,<sup>767</sup> 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  $100^\circ\text{C}$ .<sup>768</sup> Dimethylamine has also been used in the form of dimethylammonium dimethylcarbamate  $\text{Me}_2\text{NCOO}^- \text{Me}_2\text{NH}_2^+$ .<sup>769</sup> The Kindler modification has also been applied to aliphatic ketones.<sup>770</sup>

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  $\text{I}_2$  or  $\text{Br}_2$ ,<sup>771</sup> or with thallium nitrate, MeOH, and trimethyl orthoformate adsorbed on K-10, an acidic clay.<sup>772</sup>



The mechanism of the Willgerodt reaction is not completely known, but some conceivable mechanisms can be excluded. Thus, one might suppose that the alkyl group becomes completely detached from the ring and then attacks it with its other end. However, this possibility is ruled out by experiments such as the following: When isobutyl phenyl ketone (**53**) is subjected to the Willgerodt reaction, the product is **54**, not **55**, which would arise if the end carbon of the ketone became bonded to the ring in the product.<sup>773</sup>



<sup>765</sup>For a review, see Brown *Synthesis* **1975**, 358-375.

<sup>766</sup>For a review, see Mayer, in Oae, Ref. 431, pp. 58-63. For a study of the optimum conditions for this reaction, see Lundstedt; Carlson; Shabana *Acta Chem. Scand., Ser. B* **1987**, *41*, 157, and other papers in this series. See also Carlson; Lundstedt *Acta Chem. Scand., Ser. B* **1987**, *41*, 164.

<sup>767</sup>The reaction between ketones, sulfur, and ammonia can also lead to heterocyclic compounds. For a review, see Asinger; Offermanns *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 907-919 [*Angew. Chem.* **79**, 953-965].

<sup>768</sup>Amupitan *Synthesis* **1983**, 730.

<sup>769</sup>Schroth; Andersch *Synthesis* **1989**, 202.

<sup>770</sup>See Dutron-Woitrin; Merényi; Viehe *Synthesis* **1985**, 77.

<sup>771</sup>Higgins; Thomas *J. Chem. Soc., Perkin Trans. I* **1982**, 235. See also Higgins; Thomas *J. Chem. Soc., Perkin Trans. I* **1983**, 1483.

<sup>772</sup>Taylor; Chiang; McKillop; White *J. Am. Chem. Soc.* **1976**, *98*, 6750; Taylor; Conley; Katz; McKillop *J. Org. Chem.* **1984**, *49*, 3840.

<sup>773</sup>King; McMillan *J. Am. Chem. Soc.* **1946**, *68*, 632.

This also excludes a cyclic-intermediate mechanism similar to that of the Claisen rearrangement (8-35). Another important fact is that the reaction is successful for singly branched side chains, such as **53**, but not for doubly branched side chains, as in  $\text{PhCOCMe}_3$ .<sup>773</sup> Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus  $\text{PhCOCH}_2\text{CH}_3$ ,  $\text{PhCH}_2\text{COMe}$ , and  $\text{PhCH}_2\text{CH}_2\text{CHO}$  all give  $\text{Ph-CH}_2\text{CH}_2\text{CONH}_2$ .<sup>774</sup> All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain, though just what form these take is not certain. Initial reduction to the hydrocarbon can be ruled out, since alkylbenzenes do not give the reaction. In certain cases imines<sup>775</sup> or enamines<sup>776</sup> 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.

<sup>774</sup>For an example of this type of behavior, see Asinger, Saus; Mayer *Monatsh. Chem.* **1967**, 98, 825.

<sup>775</sup>Asinger; Halcour *Monatsh. Chem.* **1964**, 95, 24. See also Nakova; Tolkachev; Evstigneeva *J. Org. Chem. USSR* **1975**, 11, 2660.

<sup>776</sup>Mayer, in Janssen *Organosulfur Chemistry*; Wiley: New York, 1967, pp. 229-232.

# Appendix A

## THE LITERATURE OF ORGANIC CHEMISTRY

All discoveries in the laboratory must be published somewhere if the information is to be made generally available. A new experimental result that is not published might as well not have been obtained, insofar as it benefits the entire chemical world. The total body of chemical knowledge (called *the literature*) is located on the combined shelves of all the chemical libraries in the world. Anyone who wishes to learn whether the answer to any chemical question is known, and, if so, what the answer is, has only to turn to the contents of these shelves. Indeed the very expressions "is known," "has been done," etc., really mean "has been published." To the uninitiated, the contents of the shelves may appear formidably large, but fortunately the process of extracting information from the literature of organic chemistry is usually not difficult. In this appendix we shall examine the literature of organic chemistry, confining our attention chiefly to the results of laboratory work, rather than those of industrial organic chemistry.<sup>1</sup> The literature can be divided into two broad categories: primary sources and secondary sources. A *primary source* publishes the original results of laboratory investigations. Books, indexes, and other publications that cover material that has previously been published in primary sources are called *secondary sources*. It is because of the excellence of the secondary sources in organic chemistry (especially *Chemical Abstracts* and Beilstein) that literature searching is comparatively not difficult. The two chief kinds of primary source are journals and patents. There are several types of secondary source.

### PRIMARY SOURCES

#### Journals

For well over a hundred years, nearly all new work in organic chemistry (except for that disclosed in patents) has been published in journals. There are thousands of journals that publish chemical papers, in many countries and in many languages. Some print papers covering all fields of science; some are restricted to chemistry; some to organic chemistry; and some are still more specialized. Fortunately for the sanity of organic chemists, the vast majority of important papers in "pure" organic chemistry (as opposed to "applied") are published in relatively few journals, perhaps 50 or fewer. Of course, this is still a large number, especially since some are published weekly and some semimonthly, but it is considerably smaller than the total number of journals (perhaps as high as 10,000) that publish chemical articles.

<sup>1</sup>For books on the chemical literature, see Wolman *Chemical Information*, 2nd ed.; Wiley: New York, 1988; Maizell *How to Find Chemical Information*, 2nd ed.; Wiley: New York, 1987; Mellon *Chemical Publications*, 5th ed.; McGraw-Hill: New York, 1982; Skolnik *The Literature Matrix of Chemistry*; Wiley: New York, 1982; Antony *Guide to Basic Information Sources in Chemistry*; Jeffrey Norton Publishers: New York, 1979; Bottle *Use of the Chemical Literature*; Butterworth: London, 1979; Woodburn *Using the Chemical Literature*; Marcel Dekker: New York, 1974. For a three-part article on the literature of organic chemistry, see Hancock *J. Chem. Educ.* **1968**, 45, 193-199, 260-266, 336-339.

In addition to ordinary papers, there are two other types of publications in which original work is reported: *notes* and *communications*. A note is a brief paper, often without a summary (nearly all papers are published with summaries or abstracts prepared by the author). Otherwise, a note is similar to a paper.<sup>2</sup> Communications (also called *letters*) are also brief and usually without summaries (though some journals now publish summaries along with their communications, a welcome trend). However, communications differ from notes and papers in three respects:

1. They are brief, not because the work is of small scope, but because they are condensed. Usually they include only the most important experimental details or none at all.
2. They are of immediate significance. Journals that publish communications make every effort to have them appear as soon as possible after they are received. Some papers and notes are of great importance, and some are of lesser importance, but all communications are supposed to be of high importance.
3. Communications are preliminary reports, and the material in them may be republished as papers at a later date, in contrast to the material in papers and notes, which cannot be republished.

Although papers (we use the term in its general sense, to cover notes and communications also) are published in many languages, the English-speaking chemist is in a fairly fortunate position. At present well over half of the important papers in organic chemistry are published in English. Not only are American, British, and British Commonwealth journals published almost entirely in English, but so are many others around the world. There are predominantly English-language journals published in Japan, Italy, Czechoslovakia, Sweden, the Netherlands, Israel, and other countries, and even such traditionally German or French journals as *Chemische Berichte*, *Liebigs Annalen der Chemie*, and *Bulletin de la Société Chimique de France* now publish some papers in English. Most of the articles published in other languages have summaries printed in English also. Furthermore, the second most important language (in terms of the number of organic chemical papers published) is Russian, and most of these papers are available in English translation, though in most cases, six months to a year later. A considerable number of important papers are published in German and French; these are generally not available in translation, so that the organic chemist should have at least a reading knowledge of these languages. An exception is the journal *Angewandte Chemie*, which in 1962 became available in English under the title *Angewandte Chemie International Edition in English*. Of course, a reading knowledge of French and German (especially German) is even more important for the older literature. Before about 1920, more than half of the important chemical papers were in these languages. It must be realized that the original literature is never obsolete. Secondary sources become superseded or outdated, but nineteenth century journals are found in most chemical libraries and are still consulted. Table A.1 presents a list of the more important current journals that publish original papers<sup>3</sup> and communications in organic chemistry. Some of them also publish review articles, book reviews, and other material. Changes in journal title have not been infrequent; footnotes to the table indicate some of the more important, but some of the other journals listed have also undergone title changes.

The primary literature has grown so much in recent years that attempts have been made to reduce the volume. One such attempt is the *Journal of Chemical Research*, begun in 1977. The main section of this journal, called the "Synopsis," publishes synopses, which are essentially long abstracts, with references. The full texts of most of the papers are published only in microfiche and miniprint versions. For some years, the American Chemical

<sup>2</sup>In some journals notes are called "short communications," an unfortunate practice, because they are not communications as that term is defined in the text.

<sup>3</sup>In Table A.1 notes are counted as papers.

**TABLE A.1** A list of the more important current journals that publish original papers in organic chemistry, listed in alphabetical order of *Chemical Abstracts* abbreviations, which are indicated in boldface. Also given are the year of founding, number of issues per year as of 1991, and whether the journal primarily publishes papers (P), communications (C), or both

No.	Name	Papers or communications	Issues per year
1	<b>Acta Chemica Scandinavica</b> (1947)	P	10
2	<b>Angewandte Chemie</b> (1888) <sup>4</sup>	C <sup>5</sup>	12
3	<b>Australian Journal of Chemistry</b> (1948)	P	12
4	<b>Bioorganic Chemistry</b> (1971)	P <sup>5</sup>	4
5	<b>Bioorganic &amp; Medicinal Chemistry Letters</b> (1991)	C	12
6	<b>Bulletin of the Chemical Society of Japan</b> (1926)	P	12
7	<b>Bulletin des Sociétés Chimique Belges</b> (1887)	P	12
8	<b>Bulletin de la Société Chimique de France</b> (1858)	P <sup>5</sup>	6
9	<b>Canadian Journal of Chemistry</b> (1929)	PC	12
10	<b>Carbohydrate Research</b> (1965)	PC	22
11	<b>Chemische Berichte</b> (1868) <sup>6</sup>	P	12
12	<b>Chemistry and Industry (London)</b> (1923)	C	24
13	<b>Chemistry Letters</b> (1972)	C	12
14	<b>Chimia</b> (1947)	C <sup>5</sup>	12
15	<b>Collection of Czechoslovak Chemical Communications</b> (1929)	P	12
16	<b>Doklady Akademii Nauk SSSR</b> (1922) <sup>4</sup>	C	36
17	<b>Gazzetta Chimica Italiana</b> (1871)	P	12
18	<b>Helvetica Chimica Acta</b> (1918)	P	8
19	<b>Heteroatom Chemistry</b> (1990)	P	6
20	<b>Heterocycles</b> (1973)	C <sup>5</sup>	12
21	<b>International Journal of Chemical Kinetics</b> (1969)	P	12
22	<b>Israel Journal of Chemistry</b> (1963)	P <sup>7</sup>	4
23	<b>Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya</b> (1936) <sup>4</sup>	PC	12
24	<b>Journal of the American Chemical Society</b> (1879)	PC	26
25	<b>Journal of Chemical Research, Synopses</b> (1977)	P	12
26	<b>Journal of the Chemical Society, Chemical Communications</b> (1965)	C	24
27	<b>Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry</b> (1841) <sup>8</sup>	PC	12
28	<b>Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry</b> (1841) <sup>8</sup>	P	12

<sup>4</sup>These journals are available in English translation; see Table A.2.

<sup>5</sup>These journals also publish review articles regularly.

<sup>6</sup>Former title: **Berichte der deutschen chemischen Gesellschaft**.

<sup>7</sup>Each issue of this journal is devoted to a specific topic.

<sup>8</sup>Beginning with 1966 and until 1971, *J. Chem. Soc.* was divided into three sections: A, B, and C. Starting with 1972, Section B became *Perkin Trans. 2* and Section C became *Perkin Trans. 1*. Section A (Physical and Inorganic Chemistry) was further divided into *Faraday* and *Dalton Transactions*.

TABLE A.1 (Continued)

No.	Name	Papers or communications	Issues per year
29	<b>Journal of Fluorine Chemistry</b> (1971)	PC	12
30	<b>Journal of Heterocyclic Chemistry</b> (1964)	PC	12
31	<b>Journal of the Indian Chemical Society</b> (1924)	P	12
32	<b>Journal of Medicinal Chemistry</b> (1958)	PC	12
33	<b>Journal of Molecular Structure</b> (1967)	PC	16
34	<b>Journal of Organometallic Chemistry</b> (1963)	PC	48
35	<b>Journal of Organic Chemistry</b> (1936)	PC	26
36	<b>Journal of Photochemistry and Photobiology, A: Chemistry</b> (1972)	P	12
37	<b>Journal of Physical Organic Chemistry</b> (1988)	P	12
38	<b>Journal für Praktische Chemie</b> (1834)	P	6
39	<b>Khimiya Geterotsiklicheskikh Soedinenii</b> (1965) <sup>4</sup>	P	12
40	<b>Liebigs Annalen der Chemie</b> (1832)	P	12
41	<b>Mendeleev Communications</b> (1991)	C	8
42	<b>Metalloorganicheskaya Khimiya</b> (1988) <sup>4</sup>	PC	6
43	<b>Monatshefte für Chemie</b> (1870)	P	12
44	<b>New Journal of Chemistry</b> (1977) <sup>9</sup>	P	11
45	<b>Organometallics</b> (1982)	PC	12
46	<b>Organic Mass Spectrometry</b> (1968)	PC	12
47	<b>Organic Preparations and Procedures International</b> (1969)	P <sup>5</sup>	6
48	<b>Photochemistry and Photobiology</b> (1962)	P <sup>5</sup>	12
49	<b>Polish Journal of Chemistry</b> (1921) <sup>10</sup>	PC	12
50	<b>Pure and Applied Chemistry</b> (1960)	<sup>11</sup>	12
51	<b>Recueil des Travaux Chimiques des Pays-Bas</b> (1882)	PC	12
52	<b>Research on Chemical Intermediates</b> (1973) <sup>12</sup>	P <sup>5</sup>	6
53	<b>Sulfur Letters</b> (1982)	C	6
54	<b>Synlett</b> (1989)	C <sup>5</sup>	12
55	<b>Synthetic Communications</b> (1971)	C	22
56	<b>Synthesis</b> (1969)	P <sup>5</sup>	12
57	<b>Tetrahedron</b> (1958)	P <sup>5</sup>	48
58	<b>Tetrahedron: Asymmetry</b> (1990)	PC	12
59	<b>Tetrahedron Letters</b> (1959)	C	52
60	<b>Zhurnal Obshchei Khimii</b> (1869) <sup>4</sup>	PC	12
61	<b>Zhurnal Organicheskoi Khimii</b> (1965) <sup>4</sup>	PC	12

Society journals, including *J. Am. Chem. Soc.* and *J. Org. Chem.*, have provided supplementary material for some of their papers. This material is available from the Microforms and Back Issues Office at the ACS Washington office, either on microfiche or as a photocopy. These practices have not yet succeeded in substantially reducing the total volume of the world's primary chemical literature.

<sup>9</sup>Before 1987 this journal was called **Nouveau Journal de Chimie**.

<sup>10</sup>Before 1978 this journal was called **Roczniki Chemii**.

<sup>11</sup>*Pure Appl. Chem.* publishes IUPAC reports and lectures given at IUPAC meetings.

<sup>12</sup>Before 1989 this journal was called **Reviews of Chemical Intermediates**.

**TABLE A.2** Journals from Table A.1 available in English translation. The numbers are keyed to those of Table A.1. The year of first translation is given

2	<b>Angewandte Chemie, International Edition in English</b> (1962)
16	<b>Doklady Chemistry (English Translation)</b> (1956)
23	<b>Bulletin of the Academy of Sciences of the USSR, Division of Chemical Science</b> (1952)
39	<b>Chemistry of Heterocyclic Compounds (English Translation)</b> (1965)
42	<b>Organometallic Chemistry in the USSR</b> (1988)
60	<b>Journal of General Chemistry of the USSR</b> (1949)
61	<b>Journal of Organic Chemistry of the USSR</b> (1949)

## Patents

In many countries, including the United States, it is possible to patent a new compound or a new method for making a known compound (either laboratory or industrial procedures), as long as the compounds are useful. It comes as a surprise to many to learn that a substantial proportion of the patents granted (perhaps 20 to 30%) are chemical patents. Chemical patents are part of the chemical literature, and both U.S. and foreign patents are regularly abstracted by *Chemical Abstracts*. In addition to learning about the contents of patents from this source, chemists may consult the *Official Gazette* of the U.S. Patent Office, which, published weekly and available in many libraries, lists titles of all patents issued that week. Bound volumes of all U.S. patents are kept in a number of large libraries, including the New York Public Library, which also has an extensive collection of foreign patents. Photocopies of any U.S. patent and most foreign patents can be obtained at low cost from the U.S. Patent and Trademark Office, Washington, D.C., 20231. In addition, *Chemical Abstracts* lists, in the introduction to the first issue of each volume, instructions for obtaining patents from 26 countries.

Although patents are often very useful to the laboratory chemist, and no literature search is complete that neglects relevant patents, as a rule they are not as reliable as papers. There are two reasons for this:

1. It is in the interest of the inventor to claim as much as possible. Therefore he or she may, for example, actually have carried out a reaction with ethanol and with 1-propanol, but will claim all primary alcohols, and perhaps even secondary and tertiary alcohols, glycols, and phenols. An investigator repeating the reaction on an alcohol that the inventor did not use may find that the reaction gives no yield at all. In general, it is safest to duplicate the actual examples given, of which most chemical patents contain one or more.

2. Although legally a patent gives an inventor a monopoly, any alleged infringements must be protected in court, and this may cost a good deal of money. Therefore some patents are written so that certain essential details are concealed or entirely omitted. This practice is not exactly cricket, because a patent is supposed to be a full disclosure, but patent attorneys are generally skilled in the art of writing patents, and procedures given are not always sufficient to duplicate the results.

Fortunately, the above statements do not apply to all chemical patents: many make full disclosures and claim only what was actually done. It must also be pointed out that it is not always possible to duplicate the work reported in every paper in a journal. In general, however, the laboratory chemist must be more wary of patents than of papers.

## SECONDARY SOURCES

Journal articles and patents contain virtually all of the original work in organic chemistry. However, if this were all—if there were no indexes, abstracts, review articles, and other secondary sources—the literature would be unusable, because it is so vast that no one could hope to find anything in particular. Fortunately, the secondary sources are excellent. There are various kinds and the categories tend to merge. Our classification is somewhat arbitrary.

### Listings of Titles

The profusion of original papers is so great that publications that merely list the titles of current papers find much use. Such lists are primarily methods of alerting the chemist to useful papers published in journals that he or she does not normally read. There are two "title" publications covering the whole of chemistry. One of these, *Current Contents Physical, Chemical & Earth Sciences*,<sup>13</sup> which began in 1967 and appears weekly, contains the contents pages of all issues of about 800 journals in chemistry, physics, earth sciences, mathematics, and allied sciences. Each issue contains an index of important words taken from the titles of the papers listed in that issue, and an author index, which, however, lists only the first-named author of each paper. The author's address is also given, so that one may write for reprints. *Current Contents* is also available on computer discs, with "keywords"—words taken from the title and the interior of the paper. The discs can be searched for the keywords, allowing the user to find papers containing specific topics of interest.

The other "title" publication is *Chemical Titles*, published by Chemical Abstracts Service. This biweekly publication, begun in 1961, lists, in English, all titles from more than 700 journals, all in the field of chemistry. The most useful aspect of this publication is the way the titles are given. They are listed in alphabetical order of *every word in the title*, except for such words as "the," "of," "investigation," "synthesis," etc. (each issue contains a list of words prevented from indexing). This means that a title containing seven significant words is listed seven times. These words are also called "keywords". Furthermore, at each listing are given the words that immediately precede and follow the keyword. In the second section of each issue (called the Bibliography) the complete titles and the authors are given. Incidentally, this Bibliography duplicates, for the journals they both cover, the listings in *Current Contents Physical, Chemical, & Earth Sciences*, since the complete contents of journals are given in order of page number. Each issue of *Chemical Titles* has an author index, covering all authors, not just the first author. Addresses are not given.

### Abstracts

Listings of titles are valuable, as far as they go, but they do not tell what is in the paper, beyond the implications carried by the titles. From the earliest days of organic chemistry, abstracts of papers have been widely available, often as sections of journals whose principal interests lay elsewhere.<sup>14</sup> At the present time there are only two publications entirely devoted to abstracts covering the whole field of chemistry. One of these, *Referativnyi Zhurnal, Khimiya*, which began in 1953, is published in Russian and is chiefly of interest to Russian-

<sup>13</sup>Title pages of organic chemistry journals are also carried by *Current Contents Life Sciences*, which is a similar publication covering biochemistry and medicine.

<sup>14</sup>For example, *Chem. Ind. (London)* publishes abstracts of papers that appear in other journals. In the past, journals such as *J. Am. Chem. Soc.*, *J. Chem. Soc.*, and *Ber.* also did so.

speaking chemists. The other is *Chemical Abstracts*. This publication, which appears weekly, prints abstracts in English of virtually every paper containing original work in pure or applied chemistry published anywhere in the world.<sup>15</sup> Approximately 18,000 journals are covered, in many languages. In addition, *CA* publishes abstracts of every patent of chemical interest from 18 countries, including the United States, United Kingdom, Germany, and Japan, as well as many patents from eight additional countries. *CA* lists and indexes but does not abstract review articles and books. The abstracts currently appear in 80 sections, of which sections 21 to 34 are devoted to organic chemistry, under such headings as Alicyclic Compounds, Alkaloids, Physical Organic Chemistry, Heterocyclic Compounds (One Hetero Atom), etc. Each abstract of a paper begins with a heading that gives (1) the abstract number;<sup>16</sup> (2) the title of the paper; (3) the authors' names as fully as given in the paper; (4) the authors' address; (5) the abbreviated name of the journal (see Table A.1);<sup>17</sup> (6) the year, volume, issue, and page numbers; and (7) the language of the paper. In earlier years *CA* gave the language only if it differed from the language of the journal title. Abstracts of patents begin with the abstract number, title, inventor and company (if any), patent number, patent class number, date patent issued, country of priority, patent application number, date patent applied for, and number of pages in the patent. The body of the abstract is a concise summary of the information in the paper. For many common journals the author's summary (if there is one) is used in *CA* as it appears in the original paper, with perhaps some editing and additional information. Each issue of *CA* contains an author index, a patent index, and an index of keywords taken from the titles and the texts or contexts of the abstracts. The patent index lists all patents in order of number. The same compound or method is often patented in several countries. *CA* abstracts only the first patent, but does list the patent numbers of the duplicated patents in the patent index along with all previous patent numbers that correspond to it. Before 1981 there were separate Patent Number Indexes and Patent Concordances (the latter began in 1963).

At the end of each section of *CA* there is a list of cross-references to related papers in other sections.

*Chemical Abstracts* is, of course, highly used for "current awareness"; it allows one to read, in one place, abstracts of virtually all new work in chemistry, though its large size puts a limit on the extent of this type of usefulness.<sup>18</sup> *CA* is even more useful as a repository of chemical information, a place for finding out what was done in the past. This value stems from the excellent indexes, which enable the chemist in most cases to ascertain quickly where information is located. From the time of its founding in 1907 until 1961, *CA* published annual indexes. Since 1962 there are two volumes published each year, and a separate index is issued for each volume. For each volume there is an index of subjects, authors, formulas, and patent numbers. Beginning in 1972 the subject index has been issued in two parts, a chemical substance index and a general subject index, which includes all entries that are not the names of single chemical substances. However, the indexes to each volume become essentially superseded as collective indexes are issued. The first collective indexes are ten-year (decennial) indexes, but the volume of information has made five-year indexes necessary since 1956. Collective indexes so far published are shown in Table A.3. Thus a user of the indexes at the time of this writing would consult the collective indexes through 1986 and the semiannual indexes thereafter. The 12th collective index (covering 1987 through 1991) is scheduled to appear in 1992.

<sup>15</sup>For a guide to the use of *CA*, see Schulz *From CA to CAS ONLINE*; VCH: New York, 1988.

<sup>16</sup>Beginning in 1967. See p. 1247.

<sup>17</sup>These abbreviations are changed from time to time. Therefore the reader may notice inconsistencies.

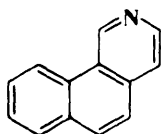
<sup>18</sup>It is possible to subscribe to *CA Selects*, which provides copies of all abstracts within various narrow fields, such as organofluorine chemistry, organic reaction mechanisms, organic stereochemistry, etc.

TABLE A.3 CA collective indexes so far published

Coll. index	Subject General subject	Chemical substance	Author	Formula	Patents
1	1907-1916		1907-1916		
2	1917-1926		1917-1926		1907-1936
3	1927-1936		1927-1936	1920-1946	
4	1937-1946		1937-1946		1937-1946
5	1947-1956		1947-1956	1947-1956	1947-1956
6	1957-1961		1957-1961	1957-1961	1957-1961
7	1962-1966		1962-1966	1962-1966	1962-1966
8	1967-1971		1967-1971	1967-1971	1967-1971
9	1972-1976	1972-1976	1972-1976	1972-1976	1972-1976
10	1977-1981	1977-1981	1977-1981	1977-1981	1977-1981
11	1982-1986	1982-1986	1982-1986	1982-1986	1982-1986

Beginning with the eighth collective index period, *CA* has published an *Index Guide*. This publication gives structural formulas and/or alternate names for thousands of compounds, as well as many other cross-references. It is designed to help the user efficiently and rapidly to find *CA* references to subjects of interest in the general subject, formula, and chemical substance indexes. Each collective index contains its own *Index Guide*. A new *Index Guide* is issued every 18 months. The *Index Guide* is necessary because the *CA* general subject index is a "controlled index", meaning it restricts its entries only to certain terms. For example, anyone who looks for the term "refraction" in the general subject index will not find it. The *Index Guide* includes this term, and directs the reader to "Electromagnetic wave, refraction of", "Sound and ultrasound, refraction of", and other terms, all of which will be found in the general subject index. Similarly, the chemical substance index usually lists a compound only under one name—the approved *CA* name. Trivial and other names will be found in the *Index Guide*. For example, the term "*methyl carbonate*" is not in the chemical substance index, but the *Index Guide* does have this term, and tells us to look for it in the chemical substance index under the headings "Carbonic acid, esters, dimethyl ester" (for  $\text{Me}_2\text{CO}_3$ ) and "Carbonic acid, esters, monomethyl ester" (for  $\text{MeHCO}_3$ ). Furthermore, the *Index Guide* gives terms related to the chosen term, helping users to broaden a search. For example, one who looks for "Atomic orbital" in the *Index Guide* will find the terms "Energy level", "Molecular orbital", "Atomic integral", and "Exchange, quantum mechanical, integrals for", all of which are controlled index terms.

Along with each index (annual, semiannual, or collective) appears an index of ring systems. This valuable index enables the user to ascertain immediately if any ring system appears in the corresponding subject or chemical substance index and under what names. For example, someone wishing to determine whether any compounds containing this ring system



Benz(h)isoquinoline

are reported in the 1982-1986 collective index (even if he or she did not know the name) would locate, under the heading "3-ring systems," the listing **6, 6, 6** (since the compound

has three rings of six members each), under which he or she would find the sublisting  $C_5N-C_6-C_6$  (since one ring contains five carbons and a nitrogen while the others are all-carbon), under which is listed the name benz(h)isoquinoline, as well as the names of 30 other systems  $C_5N-C_6-C_6$ . A search of the chemical substance index under these names will give all references to these ring systems that have appeared in *CA* from 1982 to 1986.

Before 1967, *CA* used a two-column page, with each column separately numbered. A row of letters from *a* to *h* appeared down the center of the page. These letters are for the guidance of the user. Thus an entry 7337*b* refers to the *b* section of column 7337. In early years superscript numbers, e.g., 4327<sup>5</sup>, were used in a similar manner. In very early years these numbers were not printed on the page at all, though they are given in the decennial indexes, so that the user must mentally divide the page into nine parts. Beginning with 1967, abstracts are individually numbered and column numbers are discarded. Therefore, beginning with 1967, index entries give abstract number rather than column number. The abstract numbers are followed by a letter that serves as a check character to prevent miscopying errors in computer handling. To use the *CA* general subject, chemical substance, and formula indexes intelligently requires practice, and the student should become familiar with representative volumes of these indexes and with the introductory sections to them, as well as with the *Index Guides*.

In the *CA* formula indexes formulas are listed in order of (1) number of carbon atoms; (2) number of hydrogen atoms; (3) other elements in alphabetic order. Thus, all  $C_3$  compounds are listed before any  $C_4$  compound; all  $C_5H_7$  compounds before any  $C_5H_8$  compound;  $C_7H_{11}Br$  before  $C_7H_{11}N$ ;  $C_9H_6N_4S$  before  $C_9H_6O$ , etc. Deuterium and tritium are represented by *D* and *T* and treated alphabetically, e.g.,  $C_2H_5DO$  after  $C_2H_5Cl$  and before  $C_2H_5F$  or  $C_2H_6$ .

Since 1965, *CA* has assigned a Registry Number to each unique chemical substance. This is a number of the form [766-51-8] that remains invariant, no matter what names are used in the literature. More than 10 million numbers have already been assigned and thousands are added each week. Registry Numbers are primarily for computer use. All numbers so far have been published with the *CA* preferred names in a multivolume "Registry Handbook."

For abstracts printed since 1967 (the eighth collective period and later) *CA* can be searched by computer online. For a discussion of online searching see pp. 1260-1266.

Although *CA* and *Referativnyi Zhurnal, Khimya* are currently the only chemical abstracting publications that cover the entire field of chemistry, there were a number of earlier abstracting publications now defunct. The most important are *Chemisches Zentralblatt* and *British Abstracts*. These publications are still valuable because they began before *CA* and can therefore supply abstracts for papers that appeared before 1907. Furthermore, even for papers published after 1907, *Zentralblatt* and *British Abstracts* are often more detailed. *Zentralblatt* was published, under various names, from 1830 to 1969.<sup>19</sup> *British Abstracts* was a separate publication from 1926 to 1953, but earlier abstracts from this source are available in the *Journal of the Chemical Society* from 1871 to 1925.

## Beilstein

This publication is so important to organic chemistry that it deserves a section by itself. Beilstein's "Handbuch der organischen Chemie," usually referred to as *Beilstein*, lists all the known organic compounds reported in the literature during its period of coverage. For

<sup>19</sup>An "obituary" of *Zentralblatt* by Weiske, which gives its history and statistical data about its abstracts and indexes, was published in the April 1973 issue of *Chem. Ber.* (pp. I-XVI).

each compound are given: all names; the molecular formula; the structural formula; all methods of preparation (briefly, e.g., "by refluxing 1-butanol with NaBr and sulfuric acid"); physical constants such as melting point, refractive index, etc.; other physical properties; chemical properties including reactions; occurrence in nature (i.e., which species it was isolated from); biological properties, if any; derivatives with melting points; analytical data, and any other information that has been reported in the literature.<sup>20</sup> Equally important, for every piece of information, a reference is given to the original literature. Furthermore, the data in Beilstein have been critically evaluated. That is, all information is carefully researched and documented, and duplicate and erroneous results are eliminated. Some compounds are discussed in two or three lines and others require several pages. The value of such a work should be obvious.

The first three editions of Beilstein are obsolete. The fourth edition (*vierte Auflage*) covers the literature from its beginnings through 1909. This edition, called *das Hauptwerk*, consists of 27 volumes. The compounds are arranged in order of a system too elaborate to discuss fully here.<sup>21</sup> The compounds are divided into three divisions which are further subdivided into "systems":

Division	Volumes	System numbers
I. Acyclic compounds	1-4	1-449
II. Carbocyclic compounds	5-16	450-2359
III. Heterocyclic compounds	17-27	2360-4720

*Das Hauptwerk* is still the basis of Beilstein and has not been superseded. The later literature is covered by supplements that have been arranged to parallel *das Hauptwerk*. The same system is used, so that the compounds are treated in the same order. The first supplement (*erstes Ergänzungswerk*) covers 1910-1919; the second supplement (*zweites Ergänzungswerk*) covers 1920-1929; the third supplement (*drittes Ergänzungswerk*) covers 1930-1949; the fourth supplement (*viertes Ergänzungswerk*) covers 1950-1959, and the fifth supplement covers 1960-1979. Like *das Hauptwerk*, each supplement contains 27 volumes,<sup>22</sup> except that supplements 3 and 4 are combined for vols. 17 to 27, so that for these volumes the combined third and fourth supplement covers the years 1930-1959. Each supplement has been divided into volumes in the same way as *das Hauptwerk*, and, for example, compounds found in vol. 3, system number 199 of *das Hauptwerk* will also be found in vol. 3, system number 199 of each supplement. To make cross-referencing even easier, each supplement gives, for each compound, the page numbers at which the same compound can be found in the earlier books. Thus, on page 554 of vol. 6 of the fourth supplement, under the listing phenetole are found the symbols (H 140; E I 80; E II 142; E III 545) indicating that earlier information on phenetole is given on page 140 of vol. 6 of *das Hauptwerk*, on page 80 of the first, page 142 of the second, and page 545 of the third supplement. Furthermore, each page of the

<sup>20</sup>For a discussion of how data are processed for inclusion in Beilstein, see Luckenbach; Ecker; Sunkel *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 841-849 [*Angew. Chem.* 93, 876-885].

<sup>21</sup>For descriptions of the Beilstein system and directions for using it, see Sunkel; Hoffmann; Luckenbach *J. Chem. Educ.* **1981**, 58, 982; Luckenbach *CHEMTECH* **1979**, 612-621. The Beilstein Institute has also published two English-language guides to the system. One, available free, is *How to Use Beilstein*; Beilstein Institute: Frankfurt/Main, 1979. The other is by Weissbach *A Manual for the Use of Beilstein's Handbuch der Organischen Chemie*; Springer: New York, 1976. An older work, which many students will find easier to follow, is by Huntress *A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie*, 2nd ed.; Wiley: New York, 1938.

<sup>22</sup>In some cases, to keep the system parallel and to avoid books that are too big or too small, volumes are issued in two or more parts, and, in other cases, two volumes are bound as one.

supplements contains, at the top center, the corresponding page numbers of *das Hauptwerk*. Since the same systematic order is followed in all six series, location of a compound in any one series gives its location in the other five. If a compound is found, for example, in vol. 5 of *das Hauptwerk*, one has but to note the page number and scan vol. 5 of each supplement until that number appears in the top center of the page (the same number often covers several pages). Of course, many compounds are found in only one, two, three, four, or five of the series, since no work may have been published on that compound during a particular period covered.

From *das Hauptwerk* to the fourth supplement, Beilstein is in German, though it is not difficult to read since most of the words are the names of compounds (a Beilstein German-English Dictionary, available free from the publisher, is in many libraries). For the fifth supplement (covering 1960-1979), which is in English, publication of Division III began before the earlier divisions. At the time of this writing, vols. 17 to 22 (totaling 70 separate parts exclusive of index volumes) of this supplement have been published, as well as a combined index for volumes 17-19. This index covers only the fifth supplement. The subject portion of this index, which lists compound names only, gives these names in English.

Volumes 28 and 29 of Beilstein are subject and formula indexes, respectively. The most recent complete edition of these volumes is part of the second supplement and covers only *das Hauptwerk* and the first two supplements (though complete indexes covering *das Hauptwerk* and the first four supplements have been announced to appear in the next few years). For vol. 1 there is a cumulative subject and a cumulative formula index, which combine *das Hauptwerk* and the first four supplements.<sup>23</sup> Similar index volumes, covering all four supplements, have been issued for the other volumes, 2 to 27. Some of these are combined, e.g., 2-3, 12-14, and 23-25. For English-speaking chemists (and probably for many German-speaking chemists) the formula indexes are more convenient. Of course (except for the fifth supplement indexes), one must still know some German, because most formula listings contain the names of many isomers. If a compound is found only in *das Hauptwerk*, the index listing is merely the volume and page numbers, e.g., 1, 501. Roman numbers are used to indicate the supplements, for example, 26, 15, I 5, II 7. Thus the subject and formula indexes lead at once to locations in *das Hauptwerk* and the first four supplements. The Beilstein formula indexes are constructed the same way as the CA indexes (p. 1247).

There is also a fourth division of Beilstein (systems 4721 to 4877) that covers natural products of uncertain structure: rubbers, sugars, etc. These are treated in vols. 30 and 31, which do not go beyond 1935 and which are covered in the collective indexes. These volumes will not be updated. All such compounds are now included in the regular Beilstein volumes.

Like CA, Beilstein is available online.

## Compendia and Tables of Information

In addition to Beilstein, there are many other reference works in organic chemistry that are essentially compilations of data. These books are very useful and often save the research worker a great deal of time. In this section we discuss some of the more important of such works.

1. The fifth edition of "Heilbron's Dictionary of Organic Compounds," J. Buckingham, Ed., 7 vols., Chapman and Hall, London, 1982, contains brief listings of more than 150,000

<sup>23</sup>Most page number entries in the combined indexes contain a letter, e.g., CHBr<sub>2</sub>Cl 67f, II 33a, III 87d, IV, 81. These letters tell where on the page to find the compound and are useful because the names given in the index are not necessarily those used in the earlier series. The letter "a" means the compound is the first on its page, "b" is the second, etc. No letters are given for the fourth supplement.

organic compounds, giving names, structural formulas, physical properties, and derivatives, with references. For many entries additional data concerning occurrence, biological activity, and toxicity hazard information are also given. The arrangement is alphabetical. The dictionary contains indexes of names, formulas, hetero atoms, and CA Registry Numbers. Annual supplements, with cumulative indexes, have appeared since 1983. A similar work, devoted to organometallic compounds, is "Dictionary of Organometallic Compounds," 3 vols. with supplements, published by Chapman and Hall beginning in 1984. Another, "Dictionary of Steroids," 2 vols., 1991, is also published by Chapman and Hall.

2. A multivolume compendium of physical data is Landolt-Börnstein's "Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik," 6th ed., Springer, Berlin, 1950-. There is also a "New Series," for which the volumes are given the English title "Numerical Data and Functional Relationships in Science and Technology," as well as the German title. This compendium, which is not yet complete, lists a great deal of data, some of which are of interest to organic chemists, e.g., indexes of refraction, heats of combustion, optical rotations, and spectral data. Literature references are given for all data.

3. "The Handbook of Chemistry and Physics," CRC Press, Boca Raton, FL (called the "rubber handbook"), which is revised annually (71st ed., 1990-91), is a valuable repository of data quickly found. For organic chemists the most important table is "Physical Constants of Organic Compounds," which lists names, formulas, color, solubilities, and physical properties of thousands of compounds. However, there are many other useful tables. A similar work is Lange's "Handbook of Chemistry," 13th ed., McGraw-Hill, New York, 1985. Another such handbook, but restricted to data of interest to organic chemists, is Dean, "Handbook of Organic Chemistry," McGraw-Hill, New York, 1987. This book also contains a long table of "Physical Constants of Organic Compounds," and has much other information including tables of thermodynamic properties, spectral peaks,  $pK_a$  values, bond distances, and dipole moments.

4. A list of most of the known natural compounds, e.g., terpenes, alkaloids, carbohydrates, to which structures have been assigned, along with structural formulas, melting points, optical rotations, and references, is provided in Devon and Scott, "Handbook of Naturally Occurring Compounds," 3 vols., Academic Press, New York, 1972.

5. Dreisbach, "Physical Properties of Chemical Compounds," Advances in Chemistry Series nos. 15, 22, 29, American Chemical Society, Washington, 1955-1961 lists many physical properties of more than 1000 organic compounds.

6. Physical properties of thousands of organometallic compounds, with references, are collected in four large compendia: the "Dictionary of Organometallic Compounds," mentioned under item 1, above; Dub, "Organometallic Compounds," 2nd ed., 3 vols. with supplements and index, Springer, New York, 1966-1975; Hagihara, Kumada, and Okawara, "Handbook of Organometallic Compounds," W. A. Benjamin, New York, 1968; and Kaufman, "Handbook of Organometallic Compounds," Van Nostrand, Princeton, NJ, 1961.

7. The "Merck Index," 11th ed., Merck and Company, Rahway, NJ, 1989, is a good source of information about chemicals of medicinal importance. Many drugs are given three types of name: *chemical name* (which is the name an organic chemist would give it; of course, there may well be more than one); *generic name*, which must be placed on all containers of the drug; and *trade names*, which are different for each company that markets the drug. For example, the generic name for 1-(4-chlorobenzhydryl)-4-methylpiperazine is chlorcyclazine. Among the trade names for this drug, which is an antihistamine, are Trihistan, Perazyl, and Alergicide. The "Merck Index" is especially valuable because it gives all known names of all three types for each compound and the names are cross-indexed. Also given, for each compound, are the structural formula, CA preferred name and Registry Number,

physical properties, medicinal and other uses, toxicity indications, and references to methods of synthesis. There are indexes of formulas and Registry Numbers, and miscellaneous tables. The 10th edition of the "Merck Index" (1983) also includes a lengthy list of organic name reactions, with references, but the 11th edition omits this list.

8. There are two publications that list properties of azeotropic mixtures. Timmermans, "The Physico-Chemical Constants of Binary Systems in Concentrated Solutions," 4 vols., Interscience, New York, 1959-1960, is by far the more comprehensive. The other is "Azeotropic Data," 2 vols., Advances in Chemistry Series no. 6 and no. 35, American Chemical Society, Washington, 1952, 1962.

9. Thousands of dipole moments, with references, are collected in McClellan, "Tables of Experimental Dipole Moments," vol. 1, W.H. Freeman, San Francisco, CA, 1963; vol. 2, Rahara Enterprises, El Cerrita, CA, 1974.

10. "Tables of Interatomic Distances and Configurations in Molecules and Ions," London Chemical Society Special Publication no. 11, 1958, and its supplement, Special Publication no. 18, 1965, include bond distances and angles for hundreds of compounds, along with references.

11. The "Ring Systems Handbook," published in 1988 by the Chemical Abstracts Service, provides the names and formulas of ring and cage systems that have been published in *CA*. The ring systems are listed under a system essentially the same as that used for the *CA* index of ring systems (p. 1246). Each entry gives the *CA* index name and Registry Number for that ring system. In many cases a *CA* reference is also given. There is a separate Formula Index (for the parent ring systems) and a Ring Name Index. Cumulative supplements are issued twice a year. The "Ring Systems Handbook" supersedes earlier publications called "The Parent Compound Handbook" and "The Ring Index".

12. The Sadtler Research Laboratories publish large collections of ir, uv, nmr, and other spectra, in loose-leaf form. Indexes are available.

13. Infrared, uv, nmr, Raman, and mass spectral data, as well as melting-point, boiling-point, solubility, density, and other data for more than 30,000 organic compounds are collected in the "CRC Handbook of Data on Organic Compounds," 2nd ed., 9 vols., CRC Press, Boca Raton, FL, 1988, edited by Weast and Grasselli. It differs from the Sadtler collection in that the data are given in tabular form (lists of peaks) rather than reproduction of the actual spectra, but this book has the advantage that all the spectral and physical data for a given compound appear at one place. References are given to the Sadtler and other collections of spectra. Volumes 7 to 9 contain indexes of spectral peaks for ir, uv, nmr,  $^{13}\text{C}$  nmr, mass, and Raman spectra, as well as indexes of other names, molecular formulas, molecular weights, and physical constants. Annual updates began appearing in 1990 (the first one is called volume 10).

14. The "Aldrich Library of Infrared Spectra," 3rd ed., Aldrich Chemical Company, Milwaukee, WI, 1981, by Pouchert contains more than 12,000 ir spectra so arranged that the user can readily see the change that takes place in a given spectrum when a slight change is made in the structure of a molecule. The same company also publishes the "Aldrich Library of FT-IR Spectra" and the "Aldrich Library of NMR Spectra", both also by Pouchert. A similar volume, which has ir and Raman spectra of about 1000 compounds, is "Raman/Infrared Atlas of Organic Compounds," 2nd ed., VCH, New York, 1989, by Schrader.

15. An extensive list of visible and uv peaks is given in "Organic Electronic Spectral Data," Wiley, New York. Twenty-six volumes have appeared so far, covering the literature through 1984.

16. A collection of 500  $^{13}\text{C}$  nmr spectra is found in Johnson and Jankowski, "Carbon-13 NMR Spectra," Wiley, New York, 1972.

## Reviews

A review article is an intensive survey of a rather narrow field; e.g., the titles of some recent reviews are "Preparation, Properties, and Reactions of Carbonyl Oxides,"<sup>24</sup> "Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds: Chirality Transfer, Multiplication, and Amplification,"<sup>25</sup> "1,3-Dipolar Cycloadditions of Diazoalkanes to some Nitrogen Containing Heteroaromatic Systems,"<sup>26</sup> and "Alkyl and Aryl-Substituted Main-Group Metal Amides."<sup>27</sup> A good review article is of enormous value, because it is a thorough survey of all the work done in the field under discussion. Review articles are printed in review journals and in certain books. The most important review journals in organic chemistry (though most are not exclusively devoted to organic chemistry) are shown in Table A.4. Some of the journals listed in Table A.1, for example, the *Bull. Soc. Chim. Fr.* and *J. Organomet. Chem.* also publish occasional review articles.

There are several open-ended serial publications that are similar in content to the review journals but are published irregularly (seldom more often than once a year) and are hard-bound. Some of these publish reviews in all fields of chemistry; some cover only organic chemistry; some specialize further. The coverage is indicated by the titles. Table A.5 shows some of the more important such publications, with *CA* abbreviations.

There are several publications that provide listings of review articles in organic chemistry. The most important is the *J. Org. Chem.*, which began to list review articles in 1978 (the first list is at *J. Org. Chem.* 43, 3085), suspended the listings in 1985, and resumed them in 1990 (at *J. Org. Chem.* 55, 398). These lists, which appear about four times a year, give the titles and reference sources of virtually all review articles in the field of organic chemistry that have appeared in the preceding three months, including those in the review journals and serials mentioned above, as well as those in monographs and treatises. There is also a listing of new monographs on a single subject. Each list includes a subject index.

**TABLE A.4** Review journals, with year of founding and issues per year as of 1991

<b>Accounts of Chemical Research</b> (1968)	12
<b>Aldrichimica Acta</b> (1968)	4
<b>Angewandte Chemie</b> (1888)	12
and its English Translation:	
<b>Angewandte Chemie, International Edition in English</b> (1962)	12
<b>Chemical Reviews</b> (1924)	8
<b>Chemical Society Reviews</b> (1947) <sup>28</sup>	4
<b>Heterocycles</b> (1973)	12
<b>Natural Product Reports</b> (1984)	6
<b>Soviet Scientific Reviews, Section B, Chemistry Reviews</b> (1979)	Irreg.
<b>Sulfur Reports</b> (1980)	6
<b>Synthesis</b> (1969)	12
<b>Tetrahedron</b> (1958)	48
<b>Topics in Current Chemistry</b> (1949) <sup>29</sup>	Irreg.
<b>Uspekhi Khimii</b> (1932)	12
and its English translation: <b>Russian Chemical Reviews</b> (1960)	12

<sup>24</sup>Bunnelle *Chem. Rev.* **1991**, 91, 335-362.

<sup>25</sup>Noyori; Kitamura *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 49-69 [*Angew. Chem.* 103 34-55].

<sup>26</sup>Stanovnik *Tetrahedron* **1991**, 47, 2925-2945.

<sup>27</sup>Veith *Adv. Organomet. Chem.* **1990**, 31, 269-300.

<sup>28</sup>Successor to *Quarterly Reviews* (abbreviated as *Q. Rev., Chem. Soc.*).

<sup>29</sup>Formerly called *Fortschritte der Chemischen Forschung*.

**TABLE A.5** Irregularly Published Serial Publications

<b>Advances in Carbocation Chemistry</b>	<b>Fortschritte der Chemie Organischer Naturstoffe</b>
<b>Advances in Carbohydrate Chemistry and Biochemistry</b>	<b>Isotopes in Organic Chemistry</b>
<b>Advances in Catalysis</b>	<b>Molecular Structure and Energetics</b>
<b>Advances in Cycloaddition</b>	<b>Organic Photochemistry</b>
<b>Advances in Free Radical Chemistry</b>	<b>Organometallic Reactions</b>
<b>Advances in Heterocyclic Chemistry</b>	<b>Organic Reactions</b>
<b>Advances in Metal-Organic Chemistry</b>	<b>Organic Synthesis: Theory and Applications</b>
<b>Advances in Molecular Modeling</b>	<b>Progress in Heterocyclic Chemistry</b>
<b>Advances in Organometallic Chemistry</b>	<b>Progress in Macrocyclic Chemistry</b>
<b>Advances in Oxygenated Processes</b>	<b>Progress in Physical Organic Chemistry</b>
<b>Advances in Photochemistry</b>	<b>Reactive Intermediates (Plenum)</b>
<b>Advances in Physical Organic Chemistry</b>	<b>Reactive Intermediates (Wiley)</b>
<b>Advances in Protein Chemistry</b>	<b>Survey of Progress in Chemistry</b>
<b>Advances in Theoretically Interesting Molecules</b>	<b>Topics in Physical Organometallic Chemistry</b>
<b>Fluorine Chemistry Reviews</b>	<b>Topics in Stereochemistry</b>

Another publication is the "Index of Reviews in Organic Chemistry," compiled by Lewis, Chemical Society, London, a classified listing of review articles. The first volume, published in 1971, lists reviews from about 1960 (in some cases much earlier) to about 1970 in alphabetical order of topic. Thus four reviews are listed under "Knoevenagel condensation," five under "Inclusion compounds," and one under "Vinyl ketones." There is no index. A second volume (1977) covers the literature to 1976. Annual or biannual supplements appeared from 1979 until the publication was terminated in 1985. Classified lists of review articles on organometallic chemistry are found in articles by Smith and Walton<sup>30</sup> and by Bruce.<sup>31</sup> A similar list for heterocyclic chemistry is found in articles by Katritzky and others.<sup>32</sup> See also the discussion of the *Index of Scientific Reviews*, p. 1267.

## Annual Reviews

The review articles discussed in the previous section are each devoted to a narrow topic covering the work done in that area over a period of years. An annual review is a publication that covers a broad area but limits the period covered, usually to 1 or 2 years.

1. The oldest annual review publication still publishing is *Annual Reports on the Progress of Chemistry*, published by the Royal Society of Chemistry (formerly the Chemical Society), which began in 1905 and which covers the whole field of chemistry. Since 1967 it has been divided into sections. Organic chemistry is found in Section B.

2. Because the number of papers in chemistry has become so large, the Royal Society of Chemistry publishes annual-review-type volumes of smaller scope, called *Specialist Periodical Reports*. Among those of interest to organic chemists are "Carbohydrate Chemistry" (vol. 22 covers 1988); "Photochemistry" (vol. 21 covers 1988-1989); and "General and Synthetic Methods," (vol. 12 covers 1987).

<sup>30</sup>Smith; Walton *Adv. Organomet. Chem.* **1975**, *13*, 453-558.

<sup>31</sup>Bruce *Adv. Organomet. Chem.* **1972**, *10*, 273-346, **1973**, *11*, 447-471, **1974**, *12*, 380-407.

<sup>32</sup>Belen'kii *Adv. Heterocycl. Chem.* **1988**, *44*, 269-396; Katritzky; Jones *Adv. Heterocycl. Chem.* **1979**, *25*, 303-391; Katritzky; Weeds *Adv. Heterocycl. Chem.* **1966**, *7*, 225-299.

3. "Organic Reaction Mechanisms," published by Wiley, New York, is an annual survey that covers the latest developments in the field of mechanisms. The first volume, covering 1965, appeared in 1966.

4. There are two annual reviews devoted to progress in organic synthesis. Theilheimer, "Synthetic Methods of Organic Chemistry," S. Karger Verlag, Basel, is an annual compilation, beginning in 1946, of new methods for the synthesis of organic compounds, arranged according to a system based on bond closings and bond breakings. Equations, brief procedures, yields, and literature references are given. Volume 44 was issued in 1990. Volumes 3 and 4 are available only in German, but all the rest are in English. There is an index to each volume. Cumulative indexes appear in every fifth volume. Beginning with vol. 8, each volume includes a short summary of trends in synthetic organic chemistry. A more recent series is "Annual Reports in Organic Synthesis," Academic Press, New York, which has covered the literature of each year since 1970. Equations are listed with yields and references according to a fairly simple system.

5. The *Journal Of Organometallic Chemistry* several times a year publishes annual surveys arranged according to metallic element. For example, vol. 404, published in February 1991, contains annual surveys for 1989 of organic compounds containing Sb, Bi, and Fe, and the use of transition metals in organic synthesis, and surveys for 1988 covering B, Ru, and Os.

## Awareness Services

Besides the annual reviews and the title and abstract services previously mentioned, there exist a number of publications designed to keep readers aware of new developments in organic chemistry or in specific areas of it.

1. *Chemtracts: Organic Chemistry* is a bimonthly periodical, begun in 1988, that prints abstracts of certain recently published papers (those that the editors consider most important), with commentaries on these papers by distinguished organic chemists. Each issue deals with about 20 papers, and also includes a review article.

2. The Institute for Scientific Information (ISI), besides publishing *Current Contents* (p. 1244) and the *Science Citation Index* (p. 1266), also publishes *Index Chemicus* (formerly called *Current Abstracts of Chemistry and Index Chemicus*). This publication, begun in 1960 and appearing weekly, is devoted to printing structural formulas of all new compounds appearing in more than 100 journals, along with equations to show how they were synthesized and an author's summary of the work. Each issue contains five indexes: author, journal, biological activity, labeled compounds, and unisolated intermediates. These indexes are cumulated annually.

3. Theilheimer and the "Annual Reports on Organic Synthesis," mentioned in the previous section, list new synthetic methods once a year. There are several publications that do this monthly. Among these are *Current Chemical Reactions* (begun in 1979 and published by ISI), *Journal of Synthetic Methods* (begun in 1975 and published by Derwent Publications), and *Methods in Organic Synthesis*, begun in 1984 and published by the Royal Society of Chemistry. *Methods in Organic Synthesis* also lists books and review articles pertaining to organic synthesis.

4. *Natural Product Updates*, a monthly publication begun in 1987 and published by the Royal Society of Chemistry, lists recent results in the chemistry of natural products, along with structural formulas. It covers new compounds, structure determinations, new properties and total syntheses, among other topics.

## General Treatises

There are a number of large-scale multivolume treatises that cover the whole field of organic chemistry or large areas of it.

1. "Rodd's Chemistry of Carbon Compounds," edited by Coffey, Elsevier, Amsterdam, is a treatise consisting of five main volumes, each of which contains several parts. Publication began in 1964 and is not yet complete. The organization is not greatly different from most textbooks, but the coverage is much broader and deeper. Supplements to many of the volumes have appeared. An earlier edition, called "Chemistry of Carbon Compounds," edited by Rodd, was published in 10 parts from 1951 to 1962.

2. Houben-Weyl's "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, is a major treatise in German devoted to laboratory methods. The fourth edition, which was begun in 1952 and consists of 20 volumes, most of them in several parts, is edited by E. Muller. The series includes supplementary volumes. The first four volumes contain general laboratory methods, analytical methods, physical methods, and general chemical methods. The later volumes are devoted to the synthesis of specific types of compounds, e.g., hydrocarbons, oxygen compounds, nitrogen compounds, etc. Beginning in 1990 parts of the series have appeared in English.

3. "Comprehensive Organic Chemistry," Pergamon, Elmsford, NY, 1979, is a six-volume treatise on the synthesis and reactions of organic compounds. The first three volumes cover the various functional groups, vol. 4, heterocyclic compounds, and vol. 5, biological compounds such as proteins, carbohydrates, and lipids. Probably the most useful volume is vol. 6, which contains formula, subject, and author indexes, as well as indexes of reactions and reagents. The last two of these not only refer to pages within the treatise, but directly give references to review articles and original papers. For example, on p. 1129, under "Chromic acid-sulphuric acid (Jones reagent), oxidation, alcohols," are listed 13 references to original papers. Several similar treatises, including the nine-volume "Comprehensive Organometallic Chemistry" (1982), the eight-volume "Comprehensive Heterocyclic Chemistry" (1984), and the six-volume "Comprehensive Medicinal Chemistry" (1989) are also published by Pergamon. The indexes to these works also include references.

4. A major treatise devoted to experimental methods of chemistry is "Techniques of Chemistry," edited first by Weissberger and then by Saunders, Wiley, New York. This publication, which began in 1970, so far consists of 21 volumes, most of them in several parts, covering such topics as electrochemical and spectral methods, kinetic methods, photochromism, and organic solvents. "Techniques of Chemistry" is a successor to an earlier series, called "Techniques of Organic Chemistry," which appeared in 14 volumes, some of them in more than one edition, from 1945 to 1969.

5. "Comprehensive Chemical Kinetics," edited by Bamford and Tipper, 1969-, Elsevier, Amsterdam, is a multivolume treatise covering the area of reaction kinetics. Six of these volumes (not all published at the time of writing) deal with the kinetics and mechanisms of organic reactions in a thorough and comprehensive manner.

6. Three multivolume treatises that cover specific areas are Elderfield, "Heterocyclic Compounds," Wiley, New York, 1950-; Manske and Holmes, "The Alkaloids," Academic Press, New York, 1950-; and Simonson, Owen, Barton, and Ross, "The Terpenes," Cambridge University Press, London, 1947-1957.

## Monographs and Treatises on Specific Areas

Organic chemistry is blessed with a large number of books devoted to a thorough coverage of a specific area. Many of these are essentially very long review articles, differing from

ordinary review articles only in size and scope. Some of the books are by a single author, and others have chapters by different authors but all are carefully planned to cover a specific area. Many of these books have been referred to in footnotes in appropriate places in this book. There have been several series of monographs, one of which is worth special mention: "The Chemistry of Functional Groups," under the general editorship of Patai, published by Wiley, New York. Each volume deals with the preparation, reactions, and physical and chemical properties of compounds containing a given functional group. Volumes covering more than 20 functional groups have appeared so far, including books on alkenes, cyano compounds, amines, carboxylic acids and esters, quinones, etc.

## Textbooks

There are many excellent textbooks in the field of organic chemistry. We restrict ourselves to listing only a few of those published, mostly since 1985. Some of these are first-year texts and some are advanced (advanced texts generally give references; first-year texts do not, though they may give general bibliographies, suggestions for further reading, etc.); some cover the whole field, and others cover reactions, structure, and/or mechanism only. All the books listed here are not only good textbooks but valuable reference books for graduate students and practicing chemists.

Baker and Engel, "Organic Chemistry," West Publishing Co., St. Paul, MN, 1992.

Carey, "Organic Chemistry," 2nd ed., McGraw-Hill, New York, 1992.

Carey and Sundberg, "Advanced Organic Chemistry," 2 vols., Plenum, New York, 3rd ed., 1990.

Carruthers, "Some Modern Methods of Organic Synthesis," 3rd ed., Cambridge University Press, Cambridge, 1986.

Ege, "Organic Chemistry," 2nd ed., D.C. Heath, New York, 1989.

Fessenden and Fessenden, "Organic Chemistry," 4th ed., Brooks/Cole, Monterey, CA, 1990.

House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, New York, 1972.

Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed., Cornell University Press, Ithaca, NY, 1969.

Isaacs, "Physical Organic Chemistry," Wiley, New York, 1987.

Jones, "Physical and Mechanistic Organic Chemistry," 2nd ed., Cambridge University Press, Cambridge, 1984.

Loudon, "Organic Chemistry," 2nd ed., Benjamin/Cummings, Menlo Park, CA, 1988.

Lowry and Richardson, "Mechanism and Theory in Organic Chemistry," 3rd ed., Harper and Row, New York, 1987.

McMurry, "Organic Chemistry," 2nd ed., Brooks/Cole, Monterey, CA, 1988.

Maskill, "The Physical Basis of Organic Chemistry," Oxford University Press, Oxford, 1985.

Morrison and Boyd, "Organic Chemistry," 6th ed., Prentice-Hall, Englewood Cliffs, NJ, 1992.

Pine, "Organic Chemistry," 5th ed., McGraw-Hill, New York, 1987.

Ritchie, "Physical Organic Chemistry," 2nd ed., Marcel Dekker, New York, 1989.

Solomons, "Organic Chemistry," 5th ed., Wiley, New York, 1992.

Streitwieser, Heathcock, and Kosower, "Introduction to Organic Chemistry," 4th ed., Macmillan, New York, 1992.

Sykes, "A Guidebook to Mechanism in Organic Chemistry," 6th ed., Longmans Scientific and Technical, Essex, 1986.

Vollhardt, "Organic Chemistry," W.H. Freeman, San Francisco, 1987.

Wade, "Organic Chemistry," 2nd ed., Prentice-Hall, Englewood Cliffs, NJ, 1991.

## Other Books

In this section we mention several books that do not fit conveniently into the previous categories. All but the last have to do with laboratory synthesis.

1. *Organic Syntheses*, published by Wiley, New York is a collection of procedures for the preparation of specific compounds. The thin annual volumes have appeared each year since 1921. For the first 59 volumes, the procedures for each 10- (or 9-) year period are collected in cumulative volumes. Beginning with vol. 60, the cumulative volumes cover five-year periods. The cumulative volumes published so far are:

Annual volumes	Collective volumes
1-9	I
10-19	II
20-29	III
30-39	IV
40-49	V
50-59	VI
60-64	VII

The advantage of the procedures in *Organic Syntheses*, compared with those found in original journals, is that these procedures are *tested*. Each preparation is carried out first by its author and then by a member of the *Organic Syntheses* editorial board, and only if the yield is essentially duplicated is the procedure published. While it is possible to repeat most procedures given in journals, this is not always the case. All *Organic Syntheses* preparations are noted in Beilstein and in *CA*. In order to locate a given reaction in *Organic Syntheses*, the reader may use the OS references given in the present volume (through OS 69); the indexes in *Organic Syntheses* itself; Shriner and Shriner, "Organic Syntheses Collective Volumes I, II, III, IV, V Cumulative Indices," Wiley, New York, 1976, or Sugasawa and Nakai; "Reaction Index of Organic Syntheses," Wiley, New York, 1967 (through OS 45). Another book classifies virtually all the reactions in *Organic Syntheses* (collective vols. I to VII and annual vols. 65 to 68) into eleven categories: annulation, rearrangement, oxidation, reduction, addition, elimination, substitution, C—C bond formation, cleavage, protection/deprotection, and miscellaneous. This is "Organic Syntheses: Reaction Guide," by Liotta and Volmer, published by Wiley, New York, in 1991. Some of the categories are subdivided further, and some reactions are listed in more than one category. What is given under each entry are the equation and the volume and page reference to *Organic Syntheses*.

2. Volume 1 of "Reagents for Organic Synthesis," by Fieser and Fieser, Wiley, New York, 1967, is a 1457-page volume which discusses, in separate sections, some 1120 reagents and catalysts. It tells how each reagent is used in organic synthesis (with references) and, for each, tells which companies sell it, or how to prepare it, or both. The listing is alphabetical. Fourteen additional volumes have so far been published, which continue the format of vol. 1 and add more recent material. A cumulative index for vols. 1 to 12, by Smith and Fieser, was published in 1990.

3. "Comprehensive Organic Transformations," by Larock, VCH, New York, 1989, has been frequently referred to in footnotes in Part 2 of this book. This compendium is devoted to listings of methods for the conversion of one functional group into another, and covers the literature through 1987. It is divided into nine sections covering the preparation of alkanes and arenes, alkenes, alkynes, halides, amines, ethers, alcohols and phenols, aldehydes and ketones, and nitriles, carboxylic acids and derivatives. Within each section are given many methods for synthesizing the given type of compound, arranged in a logical system. A schematic equation is given for each method, and then a list of references (without author names, to save space) for locating examples of the use of that method. When different reagents are used for the same functional group transformation, the particular reagent is shown for each reference. There is a 164-page index of group transformations.

4. "Survey of Organic Synthesis," by Buehler and Pearson, Wiley, New York, 2 vols., 1970, 1977, discusses hundreds of reactions used to prepare the principal types of organic compounds. The arrangement is by chapters, each covering a functional group, e.g., ketones, acyl halides, amines, etc. Each reaction is thoroughly discussed and brief synthetic procedures are given. There are many references.

5. A similar publication is Sandler and Karo, "Organic Functional Group Preparations," 2nd ed., 3 vols., Academic Press, New York, 1983-1989. This publication covers more functional groups than Buehler and Pearson.

6. "Compendium of Organic Synthetic Methods," Wiley, New York, contains equations describing the preparation of thousands of monofunctional and difunctional compounds with references. Seven volumes have been published so far (1971 and 1974, edited by Harrison and Harrison; 1977, edited by Hegedus and Wade; 1980 and 1984, edited by Wade; 1988 and 1992, edited by Smith).

7. "The Vocabulary of Organic Chemistry," by Orchin, Kaplan, Macomber, Wilson, and Zimmer, Wiley, New York, 1980, presents definitions of more than 1000 terms used in many branches of organic chemistry, including stereochemistry, thermodynamics, wave mechanics, natural products, and fossil fuels. There are also lists of classes of organic compounds, types of mechanism, and name reactions (with mechanisms). The arrangement is topical rather than alphabetical, but there is a good index. "Compendium of Chemical Terminology," by Gold, Loening, McNaught, and Sehmi (the "Gold book"), published by Blackwell Scientific Publications, Oxford, in 1987, is an official IUPAC list of definitions of terms in several areas of chemistry, including organic.

## LITERATURE SEARCHING

Until recently searching the chemical literature meant looking only at printed materials (some of which might be on microfilm or microfiche). Now, however, much of the literature can be searched online, including some of the most important. Whether the search is online or uses only the printed material, there are two basic types of search, (1) searches for information about one or more specific compounds or classes of compounds, and (2) other types of searches. First we will discuss searches using only printed materials, and then online searching.<sup>32a</sup>

### Literature Searching Using Printed Materials

*Searching for specific compounds.* Organic chemists often need to know if a compound has ever been prepared and if so, how, and/or they may be seeking a melting point, an ir

<sup>32a</sup>For a monograph that covers both online searching and searches using printed materials, see Wiggins *Chemical Information Sources*; McGraw-Hill: New York, 1991.

spectrum, or some other property. Someone who wants all the information that has ever been published on any compound begins by consulting the formula indexes in Beilstein (p. 1249). At this time there are two ways to do this. (1) The formula index to the second supplement (Vol. 29, see p. 1249) will quickly show whether the compound is mentioned in the literature through 1929. If it is there, the searcher turns to the pages indicated, where all methods used to prepare the compound are given, as well as all physical properties, with references. Use of the page heading method described on p. 1249 will then show the locations, if any, in the third and later supplements. (2) If one has an idea which volume of Beilstein the compound is in (and the tables of contents at the front of the volumes may help), one may search the cumulative index for that volume. If not sure, one may consult several indexes. One of these two procedures will locate all compounds mentioned in the literature through 1959. If the compound is heterocyclic, it may be in the fifth supplement. If it is in vols. 17-19 (or in a later volume whose index has been published), the corresponding indexes may be consulted. If not, the page heading method will find it, if it was reported before 1960.<sup>33</sup> There is a way by which all of the above can be avoided. A computer program, called SANDRA (available from the Beilstein publisher), allows the user to find the Beilstein location by using a mouse to draw the structural formula of the compound sought. At this point the investigator will know (1) all information published through 1959 or 1979,<sup>34</sup> or (2) that the compound is not mentioned in the literature through 1959 or 1979.<sup>34</sup> In some cases, scrutiny of Beilstein will be sufficient, perhaps if only a boiling point or a refractive index is required. In other cases, especially where specific laboratory directions are needed, the investigator will have to turn to the original papers.

To carry the search past 1959 (or 1979), the chemist next turns to the collective formula indexes of *Chemical Abstracts*: 1957-1961; 1962-1966; 1967-1971; 1972-1976; 1977-1981; 1982-1986; such later collective indexes as have appeared; and the semiannual indexes thereafter. If a given formula index contains only a few references to the compound in question, the pages or abstract numbers will be given directly in the formula index. However, if there are many references, the reader will be directed to see the chemical substance index or (before 1972) the subject index for the same period; and here the number of page or abstract numbers may be very large indeed. Fortunately, numerous subheadings are given, and these often help the user to narrow the search to the more promising entries. Nevertheless, one will undoubtedly turn to many abstracts that do not prove to be helpful. In many cases, the information in the abstracts will be sufficient. If not, the original references must be consulted. In some cases (the index entry is marked by an asterisk or a double asterisk) the compound is not mentioned in the abstract, though it is in the original paper or patent. Incidentally, all entries in the *CA* indexes that refer to patents are prefixed by the letter P. Since 1967, the prefixes B and R have also been used, to signify books and reviews, respectively.

By the procedure outlined above, all information regarding a specific compound that has been published up to about a year before the search can be found by a procedure that is always straightforward and that in many cases is rapid (if the compound has been reported only a few times). Equally important, if the compound has not been reported, the investigator will know that, too. It should be pointed out that for common compounds, such as benzene, ether, acetone, etc., trivial mentions in the literature are not indexed (so they will not be found by this procedure), only significant ones. Thus, if acetone is converted to another compound, an index entry will be found, but not if it is used as a solvent or an eluent in a common procedure.

<sup>33</sup>Compounds newly reported in the fifth supplement that are in a volume whose index has not yet been published will not be found by this procedure. To find them in Beilstein it is necessary to know something about the system (see Ref. 21), but they may also be found by consulting *CA* indexes beginning with the sixth collective index, or by using Beilstein online.

<sup>34</sup>For those heterocyclic compounds that would naturally belong to a volume for which the fifth supplement has been published.

The best way to learn if a compound is mentioned in the literature after the period covered by the latest semiannual formula index of *CA* is to use the online services (p. 1261). However, if one lacks access to these, one may consult *Chemical Titles* and the keyword index (p. 1244) at the end of each issue of *CA*. In these cases, of course, it is necessary to know what name might be used for the compound. The name is not necessary for *Index Chemicus* (p. 1254); one consults the formula indexes. However, these methods are far from complete. *Index Chemicus* lists primarily new compounds, those which would not have been found in the earlier search. As for *Chemical Titles*, the compound can be found only if it is mentioned in the title. The keyword indexes in *CA* are more complete, being based on internal subject matter as well as title, but they are by no means exhaustive. Furthermore, all three of these publications lag some distance behind the original journals. To locate all references to a compound after the period covered by the latest semiannual formula index of *CA*, it is necessary to use *CA* online.

The complete procedure described above may not be necessary in all cases. Often all the information one needs about a compound will be found in one of the handbooks (p. 1250), in the "Dictionary of Organic Compounds" (p. 1249), or in one of the other compendia listed in this chapter, most of which give references to the original literature.

### Other Searches<sup>35</sup>

There is no definite procedure for making other literature searches using only printed materials. Any chemist who wishes to learn all that is known about the mechanism of the reaction between aldehydes and HCN, or which compounds of the general formula  $\text{Ar}_3\text{CR}$  have been prepared, or which are the best catalysts for Friedel-Crafts acylation of naphthalene derivatives with anhydrides, or where the group  $-\text{C}(\text{NH}_2)=\text{N}-$  absorbs in the ir, is dependent on his or her ingenuity and knowledge of the literature. If a specific piece of information is needed, it may be possible to find it in one of the compendia mentioned previously. If the topic is more general, the best procedure is often to begin by consulting one or more monographs, treatises, or textbooks that will give general background information and often provide references to review articles and original papers. In many cases this is sufficient, but when a complete search is required, it is necessary to consult the *CA* subject and/or chemical substance indexes, where the ingenuity of the investigator is most required, for now it must be decided which words to look under. If one is interested in the mechanism of the reaction between aldehydes and HCN, one might look under "aldehydes," or "hydrogen cyanide," or even under "acetaldehyde" or "benzaldehyde," etc., but then the search is likely to prove long. A better choice in this case would be "cyanohydrin," since these are the normal products and references there would be fewer. It would be a waste of time to look under "mechanism." In any case, many of the abstracts would not prove helpful. Literature searching of this kind is necessarily a wasteful process. Of course, the searcher would not consult the *CA* annual indexes but only the collective indexes as far as they go and the semiannual indexes thereafter. If it is necessary to search before 1907 (and even before 1920, since *CA* was not very complete from 1907 to about 1920), recourse may be made to *Chemisches Zentralblatt* (p. 1247) and the abstracts in the *Journal of the Chemical Society* (p. 1247).

### Literature Searching Online<sup>32a</sup>

Online searching means using a computer terminal to search a *database*. Although databases in chemistry are available from several organizations, by far the most important such or-

<sup>35</sup>This discussion is necessarily short. For much more extensive discussions, consult the books in Refs. 1 and 15.

ganization is STN International (The Scientific & Technical Information Network), which is available in many countries. STN has dozens of databases, including many that cover chemistry and chemical engineering. To access these databases a chemistry department, a library, or an individual subscribes to STN (for a nominal fee), and receives code numbers that will permit access to the system. Then all one needs is a computer and a modem. STN charges for each use, depending on which databases are used, for how long, and what kind of information is requested. One of the nice features of STN is that the same command language is used for all databases, so when one has mastered the language for one database, one can use it for all the others. In this section we will discuss literature searching using *CA* online, which is one of the databases available from STN. One thing that must be remembered is that *CA* online is complete only from 1967 to the present,<sup>36</sup> so that searches for earlier abstracts must use the printed volumes. However, for the period since 1967, not only is online searching a great deal faster than searching the printed *CA*, but, as we shall see, one can do kinds of searches online that are simply not possible using only the printed volumes. Furthermore, the online files are updated every two weeks, so that one will find all the abstracts online well past the appearance of the latest semiannual indexes, often even before the library has received the latest weekly printed issue of *CA*. *CA* online is extremely flexible; one can search in a great many ways. It is beyond the scope of this book to discuss the system in detail<sup>37</sup> (*CA* conducts workshops on its use), but even with the few commands we will give here, a user can often find all that he or she is looking for. *CA* online has two major files, the *CA File* and the *Registry File*.<sup>38</sup> These are so different that we discuss them separately.

### *The CA File*

This file is accessed with the command `FILE CA`. Once in the file, the user uses the command `SEARCH` (or `SEA` or `S`)<sup>39</sup> to look for references to specific terms. For example, one may type `SEA SEMIPINACOL`. On the screen will appear something like

L1 4 SEMIPINACOL

The L1 means that this is line one. Future answers from the system will number the lines in consecutive order. The 4 means that the system has four abstracts that contain the word semipinacol. The word may be in the title, an index entry, or a keyword. The search term may be the name of a compound, which means that individual compounds can be searched for in this way. If the name used is the *CA* indexing name, all the abstracts mentioning that compound will be retrieved. However, common names or other names can also be searched (e.g., catechol), and if they are mentioned in the title of the paper, or, for example as a keyword, those abstracts will be retrieved.

Compounds can also be searched for by using the Registry Number, e.g.,

SEARCH 126786-44-3

Let us return to the example of semipinacol. The system told us there were four abstracts for this term. We may now see these abstracts by using the display command (`DISPLAY` or `DIS` or `D`), e.g.,

D L1 1 BIB ABS

<sup>36</sup>There is also a file called CAOLD that has some papers earlier than 1967.

<sup>37</sup>For a discussion of *CA* online, see Ref. 15.

<sup>38</sup>There is also a file, LCA, which is used for learning the system. It includes only a small fraction of the papers in the *CA File*, and is not updated. There is no charge for using the LCA File, except for a small hourly fee.

<sup>39</sup>Most commands can be used in three ways, as shown here. When the full term is spelled out (`SEARCH`), the system assumes an unsophisticated user, and gives more help. If the command is `S`, the system assumes the user is knowledgeable about the system.

L1 means we are asking the system to display material pertaining to semipinacol, which is on line L1. If we fail to insert this information, the system will display items pertaining to the last L number shown.

1 means we are asking for information on the first of the four papers. The papers are listed in reverse chronological order, meaning paper 1 will be the latest of the four. Similarly, we can ask to see the information on any of the others.

BIB ABS means we are asking for bibliographic data (abstract number, title of paper, authors' names, journal, year, etc.) and for a display of the full abstract.<sup>40</sup> There are other choices. Instead of BIB ABS we could have typed CAN which would give us the abstract number only (we might then choose to find the other information in the printed CA). Or, we could have typed IND, which would give us the abstract number and the index terms for this paper, or ALL which would give everything we get from BIB ABS plus the index terms. In all, there are nine or ten ways to ask for display material. Our choice will depend on how much we need to know, and on the cost, since the more information requested, the higher the cost.

As so far described, online searching is faster than searching the printed CA, but gives us essentially the same information. The scope of the online method is much greater than that, for it allows us to combine words, in a number of ways. One such way is by the use of the terms AND, NOT, and OR. If we search AMBIDENT AND NUCLEOPHILE, we will get something like this:

332 AMBIDENT

3275 NUCLEOPHILE

L2 42 AMBIDENT AND NUCLEOPHILE

This means there are 42 entries that have the words AMBIDENT and NUCLEOPHILE somewhere in them; in the titles, keywords, or index entries. We can now, if we wish, display any or all of them. But a particular entry might have these two words in unrelated contexts, e.g., it might be a paper about ambident electrophiles, but which also has NUCLEOPHILE as an index term. We would presumably get fewer papers, but with a higher percentage of relevant ones, if we could ask for AMBIDENT NUCLEOPHILE, and in fact, the system does allow this. If we type S AMBIDENT(W)NUCLEOPHILE, we will get only those papers in which the term NUCLEOPHILE directly follows AMBIDENT, with no words in between.<sup>41</sup> This is called proximity searching, and there are other, similar commands. For example, the use of (4A) instead of (W) will give all instances in which the two words appear 4 or fewer words apart, in either order.

Another important option is a truncation symbol. If we ask for NUCLEOPHILE we will find all entries that contain the term nucleophile, but not those that contain a different form of this term, e.g., nucleophilic. We can take care of this by using NUCLEOPHIL? as a search term instead of NUCLEOPHILE. This will retrieve all terms that start with the letters NUCLEOPHIL, no matter what other letters follow, thus retrieving nucleophilic, nucleophilicity, nucleophiles, etc., as well as nucleophile. The question mark is one of several truncation symbols, each of which serves a different function.

The words AND, NOT, and OR are called *Boolean operators*. They may be combined in many ways, e.g.,

S ORTHO AND EFFECT AND HAMMETT

S (CARBON(W)DIOXIDE OR CARBON(W)DISULFIDE) AND CATALY? NOT ACID

S HYDANTOIN AND (METHYL OR ETHYL) NOT (VINYL? OR PHENYL)

<sup>40</sup>For some papers in the late 1960s only the bibliographic data, and not the abstracts, are available online.

<sup>41</sup>If we ask for AMBIDENT NUCLEOPHILE without the (W), the system treats it as if we asked for AMBIDENT(W)NUCLEOPHILE, and gives the same answers.

A particular search command can contain dozens of such terms. Obviously, if one is careful about choosing the proper search terms, one can focus in on just the relevant papers, and leave out those that will not be useful. However, there will often be far more papers than can conveniently be handled, and there are other ways to limit searches. One such way is by using a narrow field. For example, a synthetic chemist may wish to find references in which a given compound is synthesized, but find, when he or she searches for that compound, that most of the references concern biological or medicinal uses of the compound. By using the command

SEA 3489-26-7/ORG

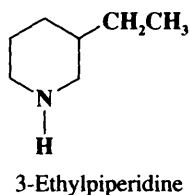
the search will retrieve only those papers for the compound of Registry Number 3489-26-7 that have been abstracted in the organic (ORG) sections of CA (Sections 21 to 34), and will not retrieve papers from the biochemical sections, which are more likely to stress biological or medicinal uses. There are many other ways to limit searches. It is possible to search only for papers in a single section of CA, only those that appeared in a given year or range of years, only those in which the search term appears in the title of the paper, only those by a given author, etc.

Besides subject terms, the CA File also contains bibliographical information, such as author names, location of the laboratory in which the work was done, language of the paper, etc., and these can be searched. For example, S ROBERTS, J?/AU will find all papers published by any authors named Roberts whose first name begins with J. These terms can be combined with subject terms in Boolean searches.

### *The Registry File*

The Registry File is entered with the command FILE REGISTRY. This can be done at any time, and it is possible to go back and forth between the CA and Registry Files at will. The Registry File uses the same commands (including Boolean) as the CA File, but instead of displaying abstracts and bibliographical information, it displays information about compounds. Its most useful feature is that it allows the user to build a structure, and then gives information about compounds that possess that structure, even if the structure is only part of a larger structure (see below).

The procedure for building a structure can be long and complex, if the structure is large and complex, but the commands are simple. We will illustrate by building the structure for 3-ethylpiperidine, which uses the most important commands. We begin with the command

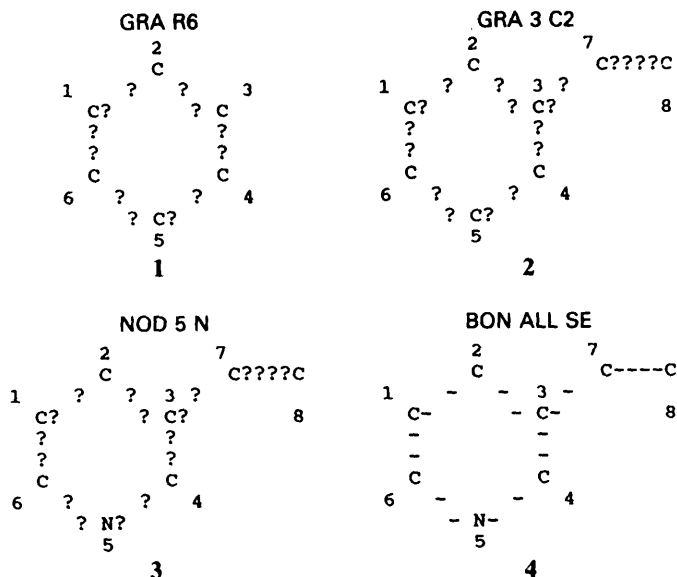


STRUCTURE. The system will ask if we wish to build on a structure previously used. If we say no, we will then get the prompt

ENTER (DIS), GRA, NOD, BON OR ?:

GRA is used for putting in chains or rings. We enter GRA R6, DIS (the DIS must be typed if the structure is to be displayed), and get the structure **1** shown in Figure A.1.<sup>42</sup> R6 specifies

<sup>42</sup>The structures shown in Figure A.1 are those received by ordinary computer terminals. Better-looking structures, more like those printed in books, are obtained with certain types of terminals. The system always asks the user to specify which type of terminal is being used.



**FIGURE A.1** Steps in building the structure of 3-ethylpiperidine in the Registry File. Above each structure is the command that gave that structure.

a 6-membered ring. If we had simply entered 6 we would have created a six-atom chain. The six numbers shown are purely arbitrary and have no connection with the way the positions are actually numbered in any nomenclature scheme. Immediately after this structure is displayed, the same prompt reappears, as it does after every structure. We wish to introduce a two-atom side chain (the ethyl group), so we enter `GRA 3 C2`, `DIS`, and get structure 2 in Figure A.1. The `C2` indicates a two-atom chain, and the 3 means that we want it attached to atom 3 (in this case the atom number is completely arbitrary, since attachment to any atom would give an equivalent result). Note that the system has numbered the new atoms 7 and 8. We will not be introducing any more atoms into our structure, but if we were they would be numbered consecutively, in the order in which they were introduced. We have all the atoms we need (we do not indicate the hydrogens because the system assumes that all nonspecified valences are connected to hydrogen, unless we tell it otherwise), but we still have not told the system about the nitrogen. Although the system uses `C` to specify all atoms, they will only remain carbon atoms until we instruct the system differently. To get 3-ethylpiperidine the atom in the 5 position must be nitrogen. A `C` can be changed to another element by using `NOD` (for node), so we now type `NOD 5 N`, `DIS`. This changes `C-5` to `N-5`, giving all the atoms in their final positions (3 in Figure A.1). However, the structure is still not complete because the bonds have not been specified. By using the `BON` command we can make any bond single, double, or triple, and can even indicate aromaticity or other resonance. In this case we want all the bonds to be single bonds, so we type `BON ALL SE`, `DIS` (`SE` is used for single bonds), and get our final structure 4 in Figure A.1.

At this point we type `END`, and get

## L1 STRUCTURE CREATED

The structure is now ready to be searched. At the command `SEARCH L1`, the system will give the prompts

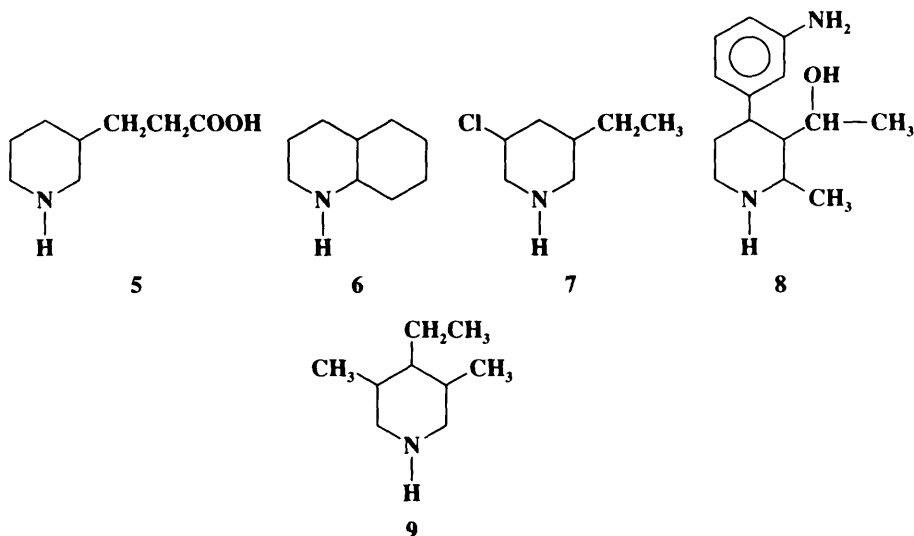
ENTER TYPE OF SEARCH (SSS), CSS, FAMILY, OR EXACT:

ENTER SCOPE OF SEARCH (SAMPLE), FULL, RANGE, OR SUBSET:

The system asks for the desired scope, because a full search (of the entire Registry File of more than 10 million substances) may cost a lot of money and may not be worth it if the desired answers can be obtained from a more limited search.

As shown by the first prompt there are four types of search, of which we will discuss two: exact and substructure (SSS). In an exact search, only information regarding exactly the structure given will be retrieved, but even so there may well be several answers, because CA treats stereoisomers and isotopically-substituted compounds as separate answers. At the conclusion of the search the system gives the number of answers, e.g., 4. We may now look at the four answers by using the display command. As in the CA File, there is a choice of display formats, but if we choose SUB we will get (1) the Registry Number, (2) the approved CA index name, (3) other names that have appeared in CA for that compound, (4) a structural formula, and (5) the number of CA references since 1967, along with a notation as to whether the compound is found in the CAOLD File. By using other display formats, we can also obtain the bibliographic information and abstracts for the latest 10 references. If there are more than 10 CA references, we can of course switch to the CA File, and use the Registry Number to search that file completely. If the exact structure search yields no answers, we know that no references to it have appeared in CA since 1967.

Although an exact search can be useful, in most cases it does not give any more information than can be obtained from the printed CA. Substructure searches (SSS) are far more important, because there is no other way to get this information. If we do a substructure search on **4** in Figure A.1, we not only get all the answers we would get in an exact search, but all substances that contain, anywhere within their structure, the arrangement of atoms and bonds shown in **4**. For example, **5**, **6**, **7**, and **8** would all be retrieved in this



search, but **9** would not be. SSS searches typically retrieve from tens to hundreds of times as many answers as exact searches of the same structure. Furthermore, the scope can be widened by the use of variable nodes. For example, the symbol X means any halogen, the symbol M any metal, and the symbol G allows the user to specify his or her own variable at that point (e.g.,  $\text{G} = \text{Cl}$  or  $\text{NO}_2$  or  $\text{Ph}$ ). As with an exact search, each answer can be displayed as described above.

As mentioned above, building structures can be very complicated, and, because there is great flexibility in the system, there are a great many ways to use the commands, but the

rewards are the retrieval of information that cannot be obtained in any other way. We have given here only a hint of the possibilities in using this system.

It is not necessary to build structures to use the Registry File. Compounds can also be searched for by using names, combinations of name fragments, Registry Numbers, molecular formulas, and in other ways. The display methods are the same.

### *Other Databases*

Several of the other databases carried by STN are of interest to organic chemists. Among these are BEILSTEIN, which allows Beilstein to be searched online (SSS and EXACT searches can also be done in this database); CASREACTS, in which the user can specify a starting compound and a product, usually by giving Registry Numbers, and the system tells whether that transformation has been reported in the literature (beginning in 1985), and if so gives reagents and references; and CJACS, which gives the complete texts (but not the display material, such as tables and displayed equations) of all papers published in about 20 journals published by the American Chemical Society (including *J. Am. Chem. Soc.*, *J. Org. Chem.*, and *Chem. Rev.*) since 1982. Chemical journals of several other publishers, including Elsevier (*J. Organomet. Chem.* etc.), VCH (*Angew. Chem. Int. Ed. Engl.*), and the Royal Society of Chemistry (*J. Chem. Soc.*, *Perkin Trans. 1* etc.), are also available online in a similar manner. Having these journals online is particularly useful because their texts can be searched for keywords, author's names, Registry Numbers, and other types of information.

## **Science Citation Index**

A publication that can greatly facilitate literature searching is *Science Citation Index (SCI)*, begun in 1961. This publication, which is quite different from any other mentioned in this chapter, gives a list of all papers in a given year that have cited a given paper, patent, or book. Its utility lies in the fact that it enables the user to search *forward* from a given paper or patent, rather than backward, as is usually the case. For example, suppose a chemist is familiar with a paper by Jencks and Gilchrist (*J. Am. Chem. Soc.* **1968**, 90, 2622) entitled "Nonlinear Structure-Reactivity Correlations. The Reactivity of Nucleophilic Reagents toward Esters." The chemist is easily able to begin a search for earlier papers by using references supplied in this paper and can then go further backward with the aid of references in those papers, etc. But for obvious reasons the paper itself supplies no way to locate *later* papers. *SCI* is designed to make up for this gap. The citation index of *SCI* lists all papers, patents, or books cited in a given year or 2-month period (by first author only) and then gives a list of papers that have done the citing. The index is published bimonthly and cumulated annually. For example, column 43901 of the 1989 citation index shows that the Jencks paper mentioned above was cited as a footnote in 16 papers published in 1989. It is reasonable to assume that most of the papers that cited the Jencks paper were on closely related subjects. For each of the 16 papers are listed the first author, journal abbreviation, volume and page numbers, and year. In a similar manner, if one consulted *SCI* for all the years from 1968 on, one would have a complete list of papers that cited that paper. One could obviously broaden the search by then consulting *SCI* (from 1989 on) for papers that cited these 16 papers and so on. Papers, patents, or books listed, for example, in the 1989 *SCI* may go back many years, e.g., papers published by Einstein in 1905 and 1906 are included. The only requirement is that a paper published in 1989 (or late 1988) has mentioned the earlier paper in a footnote. The arrangement of cited papers or books is alphabetical by cited first author and then by cited year. Cited patents are listed in a separate table, in order of patent number, though the inventor and country are also given.

*SCI* covers about 3200 journals in the physical and biological sciences, as well as in medicine, agriculture, and technology. In addition to the citation index, each bimonthly and annual *SCI* also includes three other indexes. One of these, called *Source Index*, is similar to the *CA* author index. It lists the titles, journal abbreviations, volume, issue, page numbers, and year of all papers published by a given author during that two-month period or year. All authors are listed; not just first authors. The second, called the *Corporate Index*, lists all publications that have been published from a given institution during that period, by first author. Thus, the corporate index for 1989 lists 63 papers by 45 different first authors emanating from the Department of Chemistry of Rutgers University, New Brunswick, NJ. The main section of the corporate index (the Geographic Section) lists institutions by country or (for the U.S.) by state. There is also an Organization Section, which lists the names of institutions alphabetically, and for each gives the location, so it can be found in the geographic section. The third index included in *SCI* is the *Permuterm*<sup>43</sup> *Subject Index*. This index alphabetically lists every significant word in the titles of all papers published in that year or bimonthly period, paired with all other significant words in the same title. Thus, for example, a title with seven significant words appears at 42 separate places in the index. Each of the seven words appears six times as the main word, each time paired with a different word as the co-word. The user is then led to the *Source Index*, where the full reference is given. *SCI* is also available online (though not through STN) and on CD-ROM discs. A version of *SCI* that is restricted to chemistry but also includes searchable abstracts, is available only in the CD-ROM format.

The publishers of *SCI* also produce another publication, called *Index to Scientific Reviews*, that appears semiannually. This publication, which began in 1974, is very similar to *SCI*, but confines itself to listing citations to review articles. The citations come from about 2500 journals in the same general areas as are covered by *SCI*. The review articles cited appeared in about 215 review journals and books, as well as in those journals that publish occasional review articles. Like *SCI*, the *Index to Scientific Reviews* contains citation, source, corporate, and Permuterm indexes. It also contains a "Research Front Specialty Index," which classifies reviews by subject.

## How to Locate Journal Articles

Having obtained a reference from Beilstein, *SCI*, *CA*, a treatise, or some other source, one often needs to consult the original journal (the location of patents is discussed on p. 1243). The first step is to ascertain the full name of the journal, since it is the abbreviation that is generally given. Of course, everyone should be familiar with the abbreviations of the very important journals, such as *J. Org. Chem.*, *Chem. Ber.*, etc., but references are often found to journals whose titles are not at all familiar (e.g., *K. Skogs Lantbruksakad. Tidskr.* or *Nauchn. Tr. Mosk. Lesotekh. Inst.*). In such cases, one consults the *Chemical Abstracts Service Source Index (CASSI)*, 1989 edition, which contains the names of all the journals covered by *CA* from 1907 to 1989 (even those no longer published), with the most recent abbreviations in bold print. CASSI also lists journals covered by *Chemisches Zentralblatt* and its predecessors from 1830 to 1969, and journals cited in Beilstein before 1907. The journals are listed in alphabetical order of the *abbreviations*, not of the titles. Journal title changes have not been infrequent, and CASSI also contains all former names, with cross-references to the current names. Quarterly supplements, cumulated annually, to CASSI have appeared since 1990 listing new journals and recent changes in journal titles. It should be pointed out that, while many publications use the *CA* abbreviations, not all do. The

<sup>43</sup>Registered trade name.

student will find that usages vary from country to country, and even from journal to journal within a country. Furthermore, the *CA* abbreviations have changed from time to time.

Once the complete title is known, the journal can easily be obtained if it is in the library customarily used by the chemist. If not, one must use another library, and the next step is to find out which libraries carry the journal. *CASSI* answers this question too, since it carries a list of some 360 libraries in the United States and other countries, and *for each journal it tells which of these libraries carries it*, and furthermore, if the holdings are incomplete, which volumes of that journal are carried by each library. It may be possible to visit the closest library personally. If not, a copy of the article can usually be obtained through interlibrary loan. *CASSI* also includes lists of journal publishers, sales agents, and document depositories. Photocopies of most documents cited in *CA* can be obtained from Chemical Abstracts Document Delivery Service, Customer Services, 2540 Olentangy River Road, Columbus OH, 43210, U.S.A. Orders for documents can be placed by mail, telephone, Telex, fax, or online through STN or other services.

# Appendix B

## CLASSIFICATION OF REACTIONS BY TYPE OF COMPOUND SYNTHESIZED

### Acetals and Ketals

- 0-12** Reaction between alkoxides and *gem*-dihalides (Williamson) or  $\alpha$ -halo ethers
- 0-15** Reaction between diazoalkanes and alcohols
- 0-17** Transesterification
- 0-79** Reduction of ortho esters
- 0-92** Reaction between Grignard reagents and ortho esters
- 4-7** Electrolytic alkoxylation of ethers
- 4-8** Cyclization of  $\beta$ -hydroxy ethers
- 5-4** Addition of alcohols or phenols to triple bonds
- 6-6** Addition of alcohols to aldehydes or ketones
- 6-53** Addition of aldehydes to olefins (Prins)
- 6-57** Trimerization and polymerization of aldehydes

### Acetoxy Sulfides

- 9-71** Pummerer rearrangement

### Acetylenes (*see* Alkynes)

**Acids** (*see* Carboxylic Acids, Sulfonic Acids)

### Acylals

- 5-5** Addition of carboxylic acids to alkynes
- 6-56** Acylation of aldehydes or ketones
- 9-14** Bisdecarboxylation of malonic acids
- 9-17** Oxidation of arylmethanes with  $\text{CrO}_3$  and  $\text{Ac}_2\text{O}$

### Acyl Halides

- 0-3** Reaction between 1,1,1-trihalides and  $\text{SO}_3$
- 0-74** From carboxylic acids
- 0-75** Conversion of acid derivatives to acyl halides
- 4-3** Halogenation of aldehydes
- 5-1** Addition of hydrogen halides to ketenes
- 5-22** Free-radical addition of acyl halides to olefins
- 9-22** Oxidation of alcohols

### Acyloxy Ketones

- 5-44** Addition of an acyl and an acyloxy group to a double bond

**Acyloins** (*see* Hydroxy Aldehydes and Ketones)

**Alcohols** (*see also* Diols, Hydroxy Esters, etc.)

- 0-1** Hydrolysis of alkyl halides
- 0-4** Hydrolysis of inorganic esters
- 0-6** Hydrolysis of enol ethers, acetals, or ortho esters
- 0-10** Hydrolysis of carboxylic esters
- 0-17** Transesterification
- 0-18** Payne rearrangement
- 0-23** Transesterification
- 0-55** Ammonolysis of carboxylic esters
- 0-68** Cleavage of ethers with concentrated acids
- 0-79** Reduction of acetals or ortho esters
- 0-80** Reduction of epoxides
- 0-92** Cleavage of acetals or ortho esters with Grignard reagents

## Alcohols (continued)

- 0-93** Reaction between organometallic compounds and epoxides  
**0-97** Alkylation of alcohols  
**0-114** Hydrolysis of sulfonic esters  
**1-12** Alkylation of aromatic rings with ethylene oxide  
**1-22** Hydroxyalkylation of aromatic rings  
**2-25** Reaction between organometallic reagents and oxygen  
**4-4** Hydroxylation at an aliphatic carbon  
**4-23** Free-radical hydroxymethylation of aromatic rings  
**5-2** Hydration of olefins and of cyclopropanes  
**5-12** Hydroboration-oxidation of alkenes  
**5-18** Addition of organometallic compounds to unsaturated alcohols  
**5-20** Addition of  $\text{CH}_3$  and H to allylic alcohols  
**5-22** Free-radical addition of alcohols to olefins  
**5-43** Addition of OH and SR to double bonds  
**6-25** Reduction of aldehydes or ketones  
**6-29** Addition of Grignard reagents to aldehydes or ketones  
**6-32** Addition of Grignard reagents to carboxylic esters or acyl halides  
**6-53** Reductive addition of alkenes to aldehydes  
**7-2** Alkaline cleavage of ethers  
**7-39** Reaction of N-substituted amides with certain catalysts  
**8-1** Rearrangement of alcohols or olefins (Wagner-Meerwein)  
**8-3** Expansion and contraction of rings (Demyanov)  
**8-20** Cleavage of methyl ketones with peracids (Baeyer-Villiger)  
**8-21** Cleavage of hydroperoxides  
**8-23** Rearrangement of ethers upon treatment with alkylolithiums (Wittig)  
**8-24** From boranes and CO, or  $\text{CN}^-$ , or  $\text{CHCl}_2\text{OMe}$   
**8-25** From boranes, CO, water, and NaOH  
**8-26** From boranes, CO, and  $\text{LiAlH}_4$   
**8-37** [2,3] Sigmatropic rearrangements of allylic ethers or allylic sulfoxides  
**9-9** Reduction of ozonides  
**9-38** Reduction of carboxylic acids  
**9-42** Reduction of carboxylic esters  
**9-43** Reduction of carboxylic esters with titanocene dichloride  
**9-44** Reduction of anhydrides  
**9-45** Reduction of acyl halides  
**9-53** Reduction of nitriles  
**9-57** Reduction of hydroperoxides  
**9-60** Reduction of peroxides  
**9-69** Reaction between aldehydes and base (Cannizzaro)

**Aldehydes** (*see also* Dicarbonyl Compounds, Unsaturated Carbonyl Compounds, etc.)

- 0-2** Hydrolysis of *gem*-dihalides  
**0-4** Hydrolysis of enol esters of inorganic acids  
**0-6** Hydrolysis of enol ethers, acetals, thioacetals, etc.  
**0-10** Hydrolysis of enol esters  
**0-83** Reduction of acyl halides  
**0-84** Reduction of carboxylic acids, esters, or anhydrides  
**0-85** Reduction of amides  
**0-95** Alkylation and hydrolysis of imines; alkylation of aldehydes  
**0-97** Alkylation and hydrolysis of dithianes  
**0-98** Alkylation and hydrolysis of oxazines and similar compounds  
**0-99** Reaction of diazo aldehydes with boranes  
**0-102** Carbonylation of alkyl halides  
**0-105** Reaction between formates or formamides and organometallic compounds  
**0-110** Formylation of carboxylic acid salts  
**0-113** Reaction between formic acid, another acid, and thorium oxide  
**1-15** Formylation of aromatic rings with formamides and  $\text{POCl}_3$  (Vilsmeier)  
**1-16** Formylation of aromatic rings with  $\text{Zn}(\text{CN})_2$  and HCl (Gatterman)  
**1-17** Formylation of aromatic rings with chloroform (Reimer-Tiemann)  
**1-18** Other formylations of aromatic rings  
**2-25** Oxidation of 1,1-dimetallic compounds  
**2-32** Carbonylation of organometallic compounds

## Aldehydes (continued)

- 2-40** Decarboxylation of glycidic acids
- 3-15** Carbonylation of aryl iodides
- 3-17** Vicarious substitution of aryl nitro compounds
- 4-16** Cross-coupling of alkanes with trioxane
- 4-20** Arylation of allylic alcohols
- 4-31** Reaction of diazonium salts with oximes, followed by hydrolysis
- 5-2** Cleavage of activated olefins with water
- 5-3** Hydration of acetylene
- 5-9** Selective reduction of unsaturated aldehydes
- 5-12** Oxidation of boranes; hydrolysis of unsaturated boranes
- 5-18** Addition of organometallic compounds to unsaturated aldehydes
- 5-19** Addition of boranes to unsaturated aldehydes
- 5-24** Hydroformylation of olefins (oxo process)
- 6-2** Hydrolysis of imines, oximes, hydrazones, or other C=N compounds
- 6-4** Hydrolysis of primary nitro compounds (Nef)
- 6-28** Reduction of nitriles
- 6-32** Addition of Grignard reagents to formamides
- 6-41** Reaction of aldehydes or ketones with boron methides
- 6-69** Hydrolysis of metalated aldimines
- 7-1** Dehydration of 1,2-diols
- 7-2** Pyrolysis of vinylic ethers
- 7-32** Fragmentation of  $\gamma$ -amino or  $\gamma$ -hydroxy halides
- 7-33** Fragmentation of 1,3-diols
- 7-38** Fragmentation of certain ketoximes
- 7-43** Pyrolysis of  $\beta$ -hydroxy olefins
- 7-44** Pyrolysis of allylic ethers
- 8-2** Rearrangements of diols (pinacol)
- 8-9** Homologation of aldehydes
- 8-14** Reaction between  $\alpha$ -hydroxy or  $\alpha$ -halo amides and NaOBr (Hofmann)
- 8-21** Cleavage of hydroperoxides
- 8-23** Rearrangement of allylic ethers
- 8-26** Treatment of boranes with CO and  $\text{LiAl(OMe)}_3$
- 8-32** [1,3] Sigmatropic rearrangements of allylic vinylic ethers

- 8-42** Photolysis of nitrites, followed by hydrolysis (Barton)
- 9-3** Oxidation of primary alcohols
- 9-7** Oxidative cleavage of glycols or related compounds
- 9-9** Ozonolysis of olefins
- 9-13** Oxidation of arylacetic acids
- 9-16** Oxidation of activated methyl groups
- 9-17** Oxidation of arylmethanes (Étard)
- 9-20** Oxidation of primary halides or esters of primary alcohols
- 9-21** Oxidation of amines or nitro compounds
- 9-23** Oxidation of olefins with noble-metal salts
- 9-71** Hydrolysis of  $\alpha$ -acetoxy sulfides

## Alicyclic Compounds

- 0-86** Internal coupling (Wurtz)
- 0-88** Cyclization of diallylic halides
- 0-90** Cyclization of 1,3-diols
- 0-94** Internal malonic ester synthesis
- 0-102** Carbonylation of 1,4-dihalides
- 0-108** Internal condensation of diesters (Dieckmann)
- 0-113** Ketonic decarboxylation of dicarboxylic acids
- 1-12** Intramolecular Friedel-Crafts alkylation
- 1-13** Scholl ring closure
- 1-14** Intramolecular Friedel-Crafts acylation
- 1-23** Cyclodehydration of aldehydes and ketones
- 2-16** Intramolecular insertion of carbocations
- 2-20** Intramolecular insertion of carbenes
- 3-16** Cyclization of dihalobiphenyls
- 4-17** Coupling of terminal diynes (cycloalkynes)
- 4-18** Intramolecular arylation (Pschorr)
- 4-33** Cyclization of dimagnesium compounds
- 5-10** Reduction of aromatic rings
- 5-15** Cyclization of dienes or diynes
- 5-18** Cyclization of unsaturated Grignard reagents
- 5-20** Free radical cyclization of alkenes with tin or mercury halides

## Alicyclic Compounds (continued)

- 5-22 Cyclization of unsaturated aldehydes
- 5-24 Carbonylation of dienes
- 5-33 Cyclization of halo olefins
- 5-47 Addition of olefins to dienes (Diels-Alder)
- 5-48 All-carbon 2 + 3 cycloadditions
- 5-49 Dimerization of olefins
- 5-50 Addition of carbenes or carbenoids to olefins or alkynes
- 5-51 Tetramerization of alkynes
- 5-52 Other cycloaddition reactions
- 6-29 Ring closure of halo carbonyl compounds
- 6-32 Reaction between carboxylic esters and dimagnesium compounds
- 6-39 Internal aldol reactions
- 6-47 Internal Wittig reactions
- 6-48 Cyclization of dinitriles (Thorpe-Ziegler)
- 7-46 Extrusion of N<sub>2</sub> from pyrazolines or pyrazoles
- 7-47 Extrusion of CO from cyclic ketones
- 7-48 Extrusion of SO<sub>2</sub> from cyclic sulfones
- 7-49 Decarboxylation of cyclic peroxides (Story)
- 8-1 Wagner-Meerwein rearrangements to give cyclic products
- 8-3 Expansion and contraction of rings
- 8-7 Ring contraction of halo ketones (Favorskii)
- 8-8 Ring contraction of cyclic diazo ketones (Wolff)
- 8-9 Ring expansion of cyclic ketones
- 8-24 Treatment of cyclic boranes with CO
- 8-29 Cyclization of conjugated dienes and trienes
- 8-32 [1, j] Sigmatropic migrations of carbon
- 8-33 Ring expansion of vinylcyclopropanes and cyclobutenes
- 8-34 Ring expansion of vinylcycloalkanes; cyclization of diynes
- 8-39 Metathesis of dienes
- 8-40 Metal-ion-catalyzed  $\sigma$ -bond rearrangements
- 8-41 The di- $\pi$ -methane rearrangement
- 9-2 Dehydrogenative ring closing
- 9-33 Oxidative cyclization
- 9-62 Reductive cyclization of dialdehydes
- 9-64 Cyclization of diketones or keto esters
- 9-65 Condensation of diesters (acyloin)

Alkanes (*see also* Alicyclic Compounds)

- 0-76 Reduction of alkyl halides
- 0-77 Reduction of tosylates and similar compounds
- 0-78 Hydrogenolysis of alcohols
- 0-81 Reductive cleavage of carboxylic esters
- 0-82 Reduction of the C—N bond
- 0-86 Coupling of alkyl halides (Wurtz)
- 0-87 Coupling of alkyl halides with organometallic reagents
- 0-89 Reaction between organometallic reagents and alkyl sulfates or sulfonates
- 0-90 Coupling of alcohols
- 0-92 Reaction between Grignard reagents and ethers
- 0-97 Reduction of dithianes
- 2-18 Alkylation of alkanes
- 2-20 Insertion of carbenes
- 2-24 Reaction between organometallic compounds and acids
- 2-40 Decarboxylation of carboxylic acids
- 2-41 Cleavage of tertiary alkoxides
- 2-45 Cleavage of nonenolizable ketones
- 2-46 Cleavage of ketones with amide ion (Haller-Bauer)
- 2-47 Cleavage of alkanes
- 2-48 Decyanation of nitriles
- 4-16 Coupling of alkanes
- 4-33 Coupling of Grignard reagents
- 4-34 Coupling of boranes
- 4-35 Coupling of other organometallic compounds
- 4-36 Desulfurization of sulfur compounds
- 4-38 Decarboxylative dimerization (Kolbe)
- 4-41 Decarbonylation of aldehydes or acyl halides
- 5-9 Reduction of olefins and alkynes
- 5-10 Reduction of aromatic rings
- 5-11 Reductive cleavage of cyclopropanes
- 5-14 Addition of alkanes to olefins
- 5-15 Dimerization of alkenes

## Alkanes (continued)

- 6-29** Reaction of ketones with trimethylaluminum
- 6-32** Reaction of carboxylic acids with trimethylaluminum
- 7-47** Extrusion of CO<sub>2</sub> from diacyl peroxides
- 9-6** Oxidation of hydrazines
- 9-13** Oxidative decarboxylation of carboxylic acids
- 9-37** Reduction of aldehydes or ketones (Wolff-Kishner; Clemmensen)
- 9-43** Reduction of carboxylic acids or esters
- 9-46** Reduction of epoxides
- 9-53** Reduction of cyano to methyl groups

**Alkenes** (*see also* Alicyclic Compounds, Unsaturated Acids, Unsaturated Alcohols, etc.)

- 0-76** Reduction of unsaturated halides
- 0-78** Reduction of allylic alcohols
- 0-82** Reductive cleavage of enamines
- 0-86** Coupling of vinylic halides
- 0-87** Coupling of unsaturated halides with organometallic reagents
- 0-88** Coupling of allylic halides, tosylates, or acetates
- 0-89** Coupling of vinylic triflates with organometallic reagents
- 0-90** Coupling of allylic alcohols with organometallic reagents
- 0-91** Coupling of allylic esters with organometallic reagents
- 0-92** Cleavage of allylic, vinylic or silyl ethers
- 2-2** Migration of double and triple bonds
- 2-40** Decarboxylation of unsaturated acids
- 4-19** Arylation of olefins (Meerwein)
- 4-20** Arylation of olefins by organopalladium compounds
- 4-30** Vinylation of diazonium salts
- 4-33** Dimerization of allylic Grignard reagents
- 4-34** Dimerization of vinylic chloroboranes
- 4-35** Dimerization of vinylic organometallic reagents
- 4-36** Desulfurization of thiophenes
- 4-38** Additive dimerization of olefins and carboxylic acids
- 5-9** Selective reduction of alkynes or alkenes
- 5-10** Reduction of aromatic rings
- 5-12** Reduction of vinylic boranes; hydroboration of enamines
- 5-15** Dimerization of olefins; dimerization of alkynes
- 5-16** The ene synthesis
- 5-18** Reaction of allylic halides, alkynes, and zinc
- 5-47** Addition of olefins to dienes (Diels-Alder)
- 5-50** Addition of carbenes to aromatic rings
- 5-51** Tetramerization of alkynes
- 5-52** Dimerization of dienes
- 5-53** Addition of two alkyl groups to an alkyne
- 5-55** Reaction of diphenylacetylene with methylsulfinyl carbanion
- 6-29** Reaction of *gem*-dimetallic compounds or organolithium compounds with aldehydes or ketones
- 6-30** Reformatsky reaction with Bu<sub>3</sub>P
- 6-34** Reaction of ketones with Tebbe's reagent
- 6-41** From tosylhydrazone salts
- 6-42** Addition to aldehydes or ketones of  $\alpha$ -sulfinyl carbanions or of  $\alpha$ -lithiosilanes (Peterson)
- 6-47** Reaction between phosphorus ylides and aldehydes or ketones (Wittig)
- 6-62** Reaction of sulfonyl halides with tertiary amines and diazoalkanes
- 7-1** Dehydration of alcohols
- 7-2** Alkaline cleavage of ethers
- 7-3** Pyrolysis of carboxylic esters
- 7-4** Pyrolysis of xanthates (Chugaev)
- 7-5** Cleavage of inorganic esters and sulfonates
- 7-6** Cleavage of quaternary ammonium hydroxides (Hofmann)
- 7-7** Cleavage of quaternary ammonium salts
- 7-8** Cleavage of amine oxides (Cope)
- 7-9** Cleavage of aliphatic diazonium salts
- 7-10** Decomposition of tosylhydrazones
- 7-11** Cleavage of sulfonium compounds

## Alkenes (continued)

- 7-12** Cleavage of sulfoxides, selenoxides, and sulfones  
**7-13** Dehydrohalogenation of alkyl halides  
**7-14** Reaction of sulfonyl halides with tertiary amines  
**7-15** Elimination of boranes  
**7-16** Elimination of HM from organometallic compounds  
**7-19** Decarbonylation of acyl halides  
**7-20** Cleavage of Michael adducts  
**7-21** Deoxygenation of *vic*-diols  
**7-22** Cleavage of cyclic thionocarbonates  
**7-23** Deoxidation of epoxides  
**7-24** Desulfurization of episulfides  
**7-25** Reaction of  $\alpha$ -halo sulfones with bases (Ramberg-Bäcklund)  
**7-26** Reaction of aziridines with nitrous acid  
**7-27** Denitration of *vic*-dinitro compounds  
**7-29** Dehalogenation of *vic*-dihalides  
**7-31** Elimination of a halo and a hetero group (Boord)  
**7-32** Fragmentation of  $\gamma$ -amino or  $\gamma$ -hydroxy halides  
**7-33** Fragmentation of 1,3-diols  
**7-34** Decarbonylation of  $\beta$ -hydroxy carboxylic acids and of  $\beta$ -lactones  
**7-36** Elimination of CO and CO<sub>2</sub> from bridged bicyclic compounds  
**7-43** Pyrolysis of  $\beta$ -hydroxy olefins  
**7-44** Pyrolysis of allylic ethers  
**7-51** Twofold extrusion from certain cyclic molecules  
**8-1** Rearrangement of alcohols and olefins (Wagner-Meerwein)  
**8-3** Expansion and contraction of rings (Demyanov)  
**8-8** Rearrangement of carbenes or carbenoids  
**8-27** Reaction between vinylic boranes and iodine or NaOMe  
**8-28** Reaction of lithium alkynyltrialkylborates with electrophiles  
**8-29** Electrocyclic rearrangements of cyclobutenes and cyclohexadienes  
**8-31** [1,*j*] Sigmatropic migrations of hydrogen  
**8-32** [1,*j*] Sigmatropic migrations of carbon  
**8-33** Rearrangement of vinylcyclopropanes  
**8-34** Rearrangement of 1,5-dienes (Cope)  
**8-39** Metathesis of olefins  
**8-40** Cyclobutane reversions  
**8-41** The di- $\pi$ -methane rearrangement  
**9-2** Dehydrogenation of diarylalkanes; remote dehydrogenation  
**9-13** Oxidative decarboxylation of carboxylic acids  
**9-14** Bisdecarboxylation of succinic acids  
**9-33** Oxidative coupling of halides  
**9-37** Reduction of  $\alpha$ -hydroxy ketones; of unsaturated tosylhydrazones  
**9-64** Bimolecular reduction of aldehydes or ketones

**Alkyl Halides** (*see also* Dihalides, Haloaldehydes, etc.)

- 0-65** Halide exchange (Finkelstein)  
**0-66** Reaction between inorganic esters and halide ions  
**0-67** Reaction between alcohols and hydrogen halides or inorganic acid halides  
**0-68** Cleavage of ethers with HI or HBr  
**0-70** Cleavage of carboxylic esters with LiI  
**0-72** Conversion of amines to halides  
**0-73** Cleavage of tertiary amines (von Braun)  
**0-76** Reduction of dihalides  
**0-80** Reductive halogenation of epoxides  
**0-92** Homologation of alkyl halides  
**0-97** Homologation of alkyl halides  
**1-12** Reaction between aromatic rings and carbon tetrachloride  
**1-24** Haloalkylation of aromatic rings  
**2-30** Halogenation of organometallic compounds  
**2-39** Exchange between halides and organometallic compounds  
**4-1** Free-radical halogenation  
**4-2** Allylic halogenation  
**4-39** Decarboxylative halogenation (Hunsdiecker)  
**5-1** Addition of hydrogen halides to alkenes or alkynes  
**5-22** Free-radical addition of alkyl halides to olefins

**Alkyl Halides (continued)**

- 5-26** Addition of halogens to olefins or alkynes
- 5-33** Addition of alkyl or aryl halides to olefins
- 6-24** Reductive halogenation of aldehydes
- 6-29** Addition of methyl niobium reagents to ketones
- 7-39** Reaction of N-substituted amides with  $\text{PCl}_5$  (von Braun)

**Alkynes** (*see also* Alkynyl Halides, Alkynyl Ethers)

- 0-78** Reduction of acetylenic alcohols
- 0-87** From allenic substrates, with organocopper reagents
- 0-88** Propargylation of alkyl halides
- 0-100** Alkylation at an alkynyl carbon
- 2-2** Triple-bond migration
- 2-40** Decarboxylation of acetylenic acids
- 3-13** Reaction between aryl iodides and copper acetylides
- 4-17** Coupling of alkynes (Eglinton)
- 4-20** Arylation of alkynes
- 4-33** Dimerization of alkynyl organometallic compounds
- 4-34** Coupling of alkynyl borates
- 7-6** Pyrolysis of bisquaternary ammonium hydroxides
- 7-12** Cleavage of selenoxides
- 7-13** Dehydrohalogenation of dihalides or vinylic halides
- 7-17** Elimination of the elements of  $\text{CH}_4$  from certain alkenes
- 7-25** Decomposition of thiiren-1,1-dioxides
- 7-28** Reaction of bistosylhydrazones with metallic oxides
- 7-29** Dehalogenation of tetrahalides
- 8-28** From boranes and lithium acetylides
- 8-39** Metathesis of alkynes
- 9-2** Dehydrogenation of certain diaryl alkenes
- 9-33** Oxidation of dihalotoluenes

**Alkynyl Ethers**

- 7-13** Reaction between vinylidene dihalides and amide ion

**Alkynyl Halides**

- 2-30** Reaction of acetylide ions with halogens

**Allenes**

- 0-76** Reduction of propargyl halides
- 0-81** Reduction of propargyl acetates
- 0-88** Alkylation of propargyl halides
- 0-89** Alkylation of propargyl tosylates
- 0-91** Reaction between propargyl esters and organometallic reagents
- 0-92** Cleavage of propargyl ethers by Grignard reagents
- 2-2** Rearrangement of alkynes
- 6-47** Reaction of phosphoranes with ketenes or  $\text{CO}_2$
- 7-13** Dehydrohalogenation of dihalides
- 7-29** Dehalogenation of tetrahalides or dihaloalkenes
- 7-43** Pyrolysis of  $\beta$ -hydroxy alkynes
- 8-3** Contraction of three-membered rings
- 8-35** Rearrangement of propargylic vinyl compounds

**Amidals** (*see* Bisamides)**Amides** (*see also* Bisamides)

- 0-11** Cleavage of an alkyl group from N-*t*-butyl amides
- 0-51** Reaction between secondary amines and chloroform
- 0-52** Amination of acyl halides
- 0-53** Amination of anhydrides
- 0-54** Amination of carboxylic acids
- 0-55** Amination of carboxylic esters
- 0-56** Amination of amides
- 0-57** Amination of other acid derivatives
- 0-58** N-Alkylation of amides
- 0-103** Carbonylation of alkyl halides
- 1-6** Amidation of aromatic rings with hydroxamic acids
- 1-19** Carbamoylation of aromatic rings (Gatterman)
- 1-21** Amidation of aromatic rings with isocyanates
- 1-25** Amidoalkylation of aromatic rings
- 1-35** Rearrangement of N-halo-N-acyl aromatic amines (Orton)
- 2-12** Insertion by nitrenes
- 2-31** Indirectly from aldehydes
- 2-32** From imines, CO, and a borane
- 2-42** Reaction between amino acids and anhydrides (Dakin-West)
- 2-46** Cleavage of ketones with amide ion (Haller-Bauer)

**Amides (continued)**

- 2-48** Decyanation of cyano amides
- 2-55** Carbonylation of amines
- 3-6** N-Arylation of amides
- 3-15** Carboamidation of aryl halides
- 4-14** Reaction of aldehydes with ammonia
- 4-15** Amidation at an alkyl carbon
- 4-23** Carboamidation of nitrogen heterocycles
- 5-3** Hydration of ynamines
- 5-7** Addition of amides to olefins; addition of amines to ketenes
- 5-22** Free-radical addition of amides to olefins
- 5-23** Hydrocarboxylation of olefins in the presence of amines
- 6-5** Partial hydrolysis of nitriles
- 6-15** Reductive alkylation of amines (Leuckart)
- 6-18** Addition of amines and water to nitriles
- 6-26** Reduction of isocyanates
- 6-36** Addition of Grignard reagents to isocyanates
- 6-55** Addition of alcohols or other carbocation sources to nitriles (Ritter)
- 6-65** Addition of water to isocyanides
- 8-7** Rearrangement of  $\alpha$ -halo ketones in the presence of amines (Favorskii)
- 8-8** Rearrangement of diazo ketones in the presence of amines (Arndt-Eistert)
- 8-14** Reaction between amides, lead tetraacetate, and acetic acid
- 8-17** Reaction between ketones and hydrazoic acid (Schmidt)
- 8-18** Rearrangement of oximes (Beckmann)
- 8-44** Rearrangement of aryl imidates (Chapman)
- 9-18** Oxidation of tertiary amines
- 9-72** Oxidation of aryl ketones with ammonium polysulfide (Willgerodt)

**Amidines**

- 0-55** Amination of imidates
- 5-7** Addition of amines to ketenimines
- 6-18** Addition of ammonia or amines to nitriles

**Amido Ketones**

- 5-44** Addition of an acyl group and an acylamino group to a double bond

**Aminals**

- 6-14** Addition of amines to aldehydes or ketones

**Amine Oxides**

- 9-28** Oxidation of tertiary amines

**Amines** (*see also* Cyanoamines, Amino Acids, etc.)

- 0-11** Hydrolysis of amides
- 0-36** Cleavage of amines or quaternary ammonium salts
- 0-43** Alkylation of ammonia or amines
- 0-44** Reaction between alkyl halides and hexamethylenetetramine (Delépine)
- 0-45** Reaction of alkyl halides with cyanamide
- 0-46** From alcohols or ethers
- 0-47** Transamination
- 0-48** Alkylation of amines with diazo compounds
- 0-50** Amination of alkanes
- 0-58** Hydrolysis of phthalimides (Gabriel); etc.
- 0-63** Hydrolysis of bis(trimethylsilyl)-amines
- 0-72** Cleavage of aromatic amines or quaternary ammonium salts
- 0-82** Reduction of quaternary ammonium salts or aziridines
- 0-92** Cleavage of amine ethers with organometallic compounds
- 0-93** Reaction of organometallic compounds with aziridines
- 0-97** Alkylation of amines
- 0-114** Hydrolysis of sulfonamides
- 1-6** Direct amination of aromatic rings
- 1-25** Aminoalkylation of aromatic rings
- 1-32** Rearrangement of N-nitroamines
- 1-33** Rearrangement of N-nitrosoamines (Fischer-Hepp)
- 1-34** Rearrangement of triazenes
- 1-36** Rearrangement of arylamines or aryl alkyl ammonium salts
- 2-11** Amination at an activated position

## Amines (continued)

- 2-31** Conversion of organometallic compounds to amines
- 2-40** Decarboxylation of amino acids
- 2-48** Decyanation of cyanoamines
- 3-6** Arylation of ammonia or amines
- 3-7** Reaction between naphthols, bisulfite ion, and ammonia or amines (Bucherer)
- 3-18** Amination of heterocyclic nitrogen compounds (Chichibabin)
- 3-19** Direct amination of activated aromatic rings
- 3-26** Rearrangement of benzylic quaternary ammonium salts (Sommelet-Hauser)
- 3-27** Rearrangement of aryl hydroxylamines
- 4-10** Demethylation of tertiary amines
- 4-36** Desulfurization of thioamides
- 5-7** Addition of ammonia or amines to olefins
- 5-18** Addition of organometallic compounds to allylic amines
- 5-22** Free-radical addition of amines to olefins
- 5-41** Diamination of alkenes
- 5-43** Addition of  $R_2N$  and  $SR$  to double bonds
- 6-2** Hydrolysis of imines, enamines, and iminium ions
- 6-3** Hydrolysis of isocyanates or isothiocyanates
- 6-5** Hydrolysis of cyanamides
- 6-13** Addition of ammonia to aldehydes
- 6-15** Reductive alkylation of ammonia or amines
- 6-16** Reaction between aldehydes, ammonia or amines, and an active hydrogen compound (Mannich)
- 6-26** Reduction of imines, hydrazones, or other compounds containing the  $C=N$  bond
- 6-27** Reduction of nitriles or nitrilium ions
- 6-29** Addition of organometallic compounds to amides
- 6-32** Addition of Grignard reagents to formamides
- 6-35** Addition of Grignard reagents to imines
- 6-66** Reduction of isocyanides
- 7-6** Cleavage of quaternary ammonium hydroxides (Hofmann)
- 7-7** Cleavage of quaternary ammonium salts
- 7-38** Fragmentation of certain ketoximes
- 8-14** Reaction between amides and  $NaOBr$  (Hofmann)
- 8-15** Rearrangement of acyl azides in the presence of water (Curtius)
- 8-16** Rearrangement of hydroxamic acids and acyl halides (Lossen)
- 8-17** Addition of hydrazoic acid to carboxylic acids (Schmidt)
- 8-19** Rearrangement of N-haloamines
- 8-22** Rearrangement of quaternary ammonium salts and tertiary benzylic amines (Stevens)
- 8-37** [2,3] Sigmatropic rearrangements of quaternary ammonium salts
- 8-38** Rearrangement of benzidines
- 8-42** Hofmann-Löffler and related reactions
- 9-5** Conversion of primary to secondary amines by dehydrogenation
- 9-9** Reaction between ozonides, ammonia, and hydrogen
- 9-21** Oxidative cleavage of amines
- 9-39** Reduction of amides
- 9-47** Reduction of nitro compounds
- 9-50** Reduction of nitroso compounds or hydroxylamines
- 9-51** Reduction of oximes
- 9-52** Reduction of azides
- 9-53** Reduction of isocyanates, isothiocyanates, or N-nitroso compounds
- 9-55** Reduction of amine oxides
- 9-59** Reduction of azo, azoxy, or hydrazo compounds
- 9-62** Bimolecular reduction of imines (1,2-diamines)

## Amino Acids and Esters

- 0-11** Hydrolysis of lactams
- 0-43** Amination of halo acids
- 0-55** Ammonolysis of  $\beta$ -lactones
- 0-94** Alkylation of N-acetylaminomalonic esters (Sorensen)
- 2-8** Nitrosation at a carbon bearing an active hydrogen and reduction of the

Amino Acids and Esters (continued)  
resulting oxime or nitroso compound

**2-11** From acyl halides and a dialkyl azodicarboxylate

**6-5** Hydrolysis of cyanohydrins

**6-16** Reaction between aldehydes, ammonia, and carboxylic acids or esters

**6-50** Addition of cyanide and ammonium ions to aldehydes or ketones, followed by hydrolysis (Strecker)

**8-14** Reaction between imides and NaOBr (Hofmann)

### Amino Carbonyl Compounds

**0-46** Amination of  $\alpha$ -hydroxy ketones

**0-47** Transamination of Mannich bases

**1-36** Photolysis of acylated arylamines

**6-16** Reaction between aldehydes, ammonia, and aldehydes, ketones, or esters (Mannich)

**8-13** Rearrangement of ketoxime tosylates (Neber)

**8-22** Rearrangement of quaternary ammonium salts (Stevens)

**9-23** Oxidation of certain enamines

### Amino Ethers

**0-18** Alcoholysis of aziridines

**5-39** Aminomercuration of alkenes, followed by alcoholysis

**6-16** Reaction between aldehydes, amines, and alcohols or phenols (Mannich)

### Amino Thiols

**0-49** Amination of episulfides

**1-9** Sulfurization of aromatic amines (Herz)

**6-16** Reaction between an aldehyde, ammonia, and a thiol (Mannich)

### Anhydrides

**0-27** Reaction of acyl halides with acid salts

**0-28** Dehydration of carboxylic acids

**0-33** Reaction of acid derivatives with inorganic acids

**3-15** From aryl halides and CO

**4-11** Acylation of aldehydes

**4-31** Reaction between diazonium fluoroborates, CO, and an acid salt

**5-5** Addition of carboxylic acids to ketenes

**5-22** Free-radical addition of anhydrides to olefins

**8-20** Reaction between  $\alpha$ -diketones and peroxy compounds (Baeyer-Villiger)

**9-10** Oxidation of aromatic rings

### Arenes

**0-76** Reduction of aryl and benzylic halides

**0-78** Hydrogenolysis of benzyl alcohols

**0-79** Reduction of benzylic ethers

**0-86** Coupling of halides containing aryl groups

**0-87** Coupling of aryl halides with organometallic reagents

**0-90** Coupling of benzylic alcohols

**1-12** Alkylation of aromatic rings (Friedel-Crafts)

**1-13** Arylation of aromatic rings (Scholl)

**1-22** Diarylation of ketones

**1-23** Ring closure of aryl-substituted carbonyl compounds

**1-37** Cleavage or rearrangement of alkyl arenes

**1-38** Decarbonylation of aromatic aldehydes or deacylation of aromatic ketones

**1-39** Decarboxylation of aromatic acids

**1-41** Desulfonation of aromatic sulfonic acids

**1-42** Dehalogenation of aryl halides

**1-44** Hydrolysis of organometallic compounds

**2-40** Decarboxylation of  $\alpha$ -aryl acids

**2-41** Cleavage of tertiary alkoxides

**2-45** Cleavage of aryl ketones

**2-46** Cleavage of aryl ketones with amide ions (Haller-Bauer)

**2-48** Decyanation of aryl nitriles

**3-9** Reduction of phenols, phenolic ethers, or phenolic esters

**3-10** Reduction of aromatic nitro compounds

**3-13** Coupling of organometallic compounds with aryl halides, ethers, and esters

## Arenes (continued)

- 3-16** Coupling of aryl iodides (Ullmann)
- 3-17** Alkylation with organometallic compounds
- 4-18** Free-radical arylation by diazonium salts (Gomberg–Bachmann, Pschorr)
- 4-21** Free-radical arylation by peroxides
- 4-22** Photochemical arylation
- 4-24** Reduction of diazonium salts
- 4-29** Dimerization of diazonium salts
- 4-30** Methylation of diazonium salts
- 4-33** Coupling of Grignard reagents
- 4-34** Coupling of arylboranes
- 4-35** Coupling of other organometallic compounds
- 4-36** Reduction of sulfur compounds
- 4-38** Coupling of aromatic acyl halides, with decarbonylation
- 4-41** Decarbonylation of aromatic aldehydes
- 5-20** Addition of tin and mercury hydrides to aryl alkenes
- 5-51** Trimerization of alkynes
- 6-29** Alkylation–reduction of aromatic aldehydes and ketones
- 7-36** Diels–Alder reactions of cyclopentadienones with alkynes
- 8-30** Photoconversion of stilbenes to phenanthrenes
- 9-1** Aromatization of six-membered rings
- 9-6** Oxidation of hydrazines
- 9-33** Dimerization of arenes
- 9-37** Reduction of aromatic aldehydes
- 9-43** Reduction of aromatic acids

## Aryl Halides

- 1-11** Halogenation of aromatic compounds
- 1-35** Rearrangement of N-haloamines (Orton)
- 1-39** Replacement of aromatic COOH by halogen
- 1-41** Replacement of aromatic SO<sub>2</sub>Br by halogen
- 1-42** Migration of halogen
- 2-30** Reaction of aryl organometallic compounds with halogens
- 3-8** Aryl halide exchange; halo-de-nitration; halo-de-hydroxylation

- 3-23** Reaction between diazonium salts and iodide ion
- 3-24** Heating of diazonium fluoroborates (Schiemann)
- 4-25** Reaction between diazonium salts and CuCl or CuBr (Sandmeyer)
- 4-39** Decarboxylative halogenation (Hunsdiecker)
- 4-41** Decarbonylation of acyl halides

## Azides

- 0-61** Alkylation or acylation of azide ion
- 2-10** Treatment of amides with tosyl azide
- 2-50** Reaction between hydrazines and nitrous acid
- 3-22** Reaction of diazonium salts with azide ion
- 4-39** Reaction of acyl peroxides with copper azide
- 5-8** Addition of hydrazoic acid to double bonds
- 5-31** Addition of halogen azides to double bonds
- 5-41** Treatment of olefins with sodium azide, ferrous ion, and hydrogen peroxide
- 5-43** Addition of SR and N<sub>3</sub> to double bonds
- 8-15** Reaction between hydrazides and nitrous acid
- 8-17** Reaction between alcohols or olefins and hydrazoic acid

## Azido Amides

- 2-10** Azidation of amides

## Azines

- 6-20** Addition of hydrazine to aldehydes or ketones

## Aziridines

- 0-43** Cyclization of haloamines
- 0-46** Cyclization of amino alcohols
- 0-61** Cyclization of β-azido alcohols
- 5-31** From β-iodo azides
- 5-42** Reaction of alkenes with azides
- 6-45** Reaction of imines with α-halo carbonyl compounds
- 7-46** Extrusion of N<sub>2</sub> from triazolines
- 9-51** Reduction of oximes

**Azo Compounds**

- 1-4 Coupling of diazonium salts with aromatic rings
- 1-34 Rearrangement of aryl triazenes
- 2-7 Aliphatic diazonium coupling
- 2-52 Reaction of amines with nitroso compounds (Mills)
- 2-53 From aromatic nitro compounds
- 4-29 Coupling of aryl diazonium salts
- 8-45 Rearrangement of azoxy compounds (Wallach)
- 9-6 Oxidation of hydrazines
- 9-36 Oxidation of amines
- 9-55 Reduction of azoxy compounds
- 9-67 Reduction of nitro compounds

**Azoxy Compounds**

- 0-64 Reaction between alkyl halides and alkanediazotates
- 2-53 Reaction of nitroso compounds with hydroxylamines
- 9-29 Oxidation of azo compounds
- 9-36 Oxidation of amines
- 9-66 Reduction of nitro or nitroso compounds; reaction between nitroso compounds and hydroxylamines

**Benzoin**s (*see* Hydroxy Aldehydes and Ketones)

**Bisamides**

- 4-16 Coupling of amides
- 6-14 Addition of amides to aldehydes or ketones
- 6-67 Reaction between isocyanides, acids, amines, and aldehydes or ketones (Ugi)

**Bis(trimethylsilyl)amines**

- 0-63 Reaction between halides or tosylates and  $(\text{Me}_3\text{Si})_2\text{NNa}$

**Bisulfite Addition Compounds** (*see* Hydroxy Sulfonic Acids)

**Boranes**

- 2-35 Reaction between boron halides and Grignard reagents
- 5-12 Hydroboration of olefins or alkynes
- 5-19 Reaction of borinates with organometallic compounds

- 7-15 Exchange reaction between boranes and olefins

- 8-11 Migration of boron

**Bunte Salts**

- 0-39 Reaction between alkyl halides and thiosulfate ion

**Carbamates**

- 0-24 Reaction between  $\text{K}_2\text{CO}_3$ , amines, and halides
- 0-52 Reaction between chloroformates and primary amines
- 0-62 Reaction between alkyl halides, ethanol, and thiocyanate ion
- 0-72 Cleavage of tertiary amines with  $\text{ClCOOPh}$
- 2-12 Insertion by nitrenes
- 2-55 Carbonylation of amines or nitro or nitroso compounds
- 6-8 Addition of alcohols to isocyanates
- 6-9 Reaction of alcohols with  $\text{ClCN}$
- 6-68 Addition of alkyl hypochlorites to isocyanides
- 8-14 Reaction between amides, bromine, and alkoxides (Hofmann), and similar rearrangement reactions
- 8-15 Rearrangement of acyl azides in the presence of alcohols (Curtius)

**Carbodiimides**

- 6-58 Addition of isocyanates to isocyanates
- 7-42 Dehydration of ureas and thioureas

**Carbonates**

- 0-20 Alcoholysis of phosgene
- 0-24 Reaction between alkyl halides and carbonate salts

**Carboxylic Acids**

- 0-3 Hydrolysis of 1,1,1-tri-halides
- 0-6 Hydrolysis of ortho esters
- 0-8 Hydrolysis of acyl halides
- 0-9 Hydrolysis of anhydrides
- 0-10 Hydrolysis of carboxylic esters
- 0-11 Hydrolysis of amides
- 0-70 Cleavage of carboxylic esters with  $\text{LiI}$
- 0-81 Reductive cleavage of carboxylic esters

## Carboxylic Acids (continued)

- 0-94** Malonic ester synthesis
- 0-96** Alkylation of carboxylate ions
- 0-98** Hydrolysis of oxazines
- 0-103** Carbonylation of alkyl halides and other substrates
- 1-19** Carboxylation of aromatic rings with carbonyl halides
- 1-20** Carboxylation of aromatic rings with carbon dioxide (Kolbe-Schmitt)
- 1-39** Rearrangement of aromatic carboxylate ions
- 2-40** Decarboxylation of dicarboxylic acids
- 2-43** Basic cleavage of  $\beta$ -keto esters or  $\beta$ -diketones
- 2-44** The haloform reaction
- 2-45** Cleavage of nonenolizable ketones
- 3-15** Carboxylation of aryl halides
- 3-25** Rearrangement of aromatic nitro compounds upon treatment with cyanide ion (von Richter)
- 4-6** Oxidation of aldehydes
- 4-31** Reaction of diazonium fluoroborates with CO
- 5-2** Addition of water to ketenes
- 5-12** Oxidation of 1,1-diboranes
- 5-14** Addition of carbocations to 1,1-dichloroethene; addition of carboxylates to olefins
- 5-18** Addition of alkylcopper reagents to unsaturated carboxylic acids
- 5-22** Free-radical addition of acids to olefins
- 5-23** Hydrocarboxylation of olefins
- 6-4** Hydrolysis of primary nitro compounds
- 6-5** Hydrolysis of nitriles
- 6-34** Addition of Grignard reagents to carbon dioxide
- 6-41** Reaction of ketones with tosylmethyl azide, followed by hydrolysis
- 6-47** Reaction of phosphoranes with CO<sub>2</sub>
- 7-3** Pyrolysis of carboxylic esters
- 7-38** Fragmentation of certain ketoximes
- 8-7** Rearrangement of  $\alpha$ -halo ketones (Favorskii)
- 8-8** Rearrangement of diazo ketones (Arndt-Eistert)
- 8-20** Oxidation of aldehydes
- 8-26** From boranes
- 9-7** Oxidative cleavage of  $\alpha$ -diketones and  $\alpha$ -keto acids
- 9-8** Oxidative cleavage of ketones and secondary alcohols
- 9-9** Oxidation of ozonides; ozonolysis of alkynes
- 9-10** Oxidative cleavage of olefins, terminal alkynes, or aromatic rings
- 9-11** Oxidation of aromatic side chains
- 9-21** Oxidation of amines
- 9-22** Oxidation of primary alcohols or ethers
- 9-23** Oxidation of arylthioalkynes
- 9-44** Reduction of anhydrides
- 9-69** Reaction between aldehydes and base (Cannizzaro)
- 9-72** Oxidation of aryl ketones by ammonium polysulfide (Willgerodt)

**Carboxylic Esters** (*see also* Dicarbonyl Compounds, Unsaturated Esters, etc.)

- 0-3** Alcoholysis of trihalides
- 0-6** Hydrolysis of ortho esters
- 0-20** Alcoholysis of acyl halides
- 0-21** Alcoholysis of anhydrides
- 0-22** Esterification of carboxylic acids
- 0-23** Transesterification
- 0-24** Alkylation of carboxylic acid salts
- 0-25** Cleavage of ethers with anhydrides
- 0-26** Alkylation of carboxylic acids with diazo compounds
- 0-95** Alkylation of carboxylic esters
- 0-97** Alkylation of aryl esters
- 0-98** Alkylation and alcoholysis of oxazines
- 0-99** Reaction of halo esters or diazo esters with boranes
- 0-103** Carbonylation of alkyl halides and other substrates
- 0-104** Reaction between Grignard reagents and chloroformates
- 2-32** Carbonylation of organometallic compounds
- 2-43** Base cleavage of  $\beta$ -keto esters
- 2-44** Haloform cleavage of methyl ketones
- 3-4** Reaction between aryl halides and carboxylic acid salts
- 3-14** Arylation of carboxylic esters
- 3-15** Carbalkoxylation of aryl halides and phenols

**Carboxylic Esters (continued)**

- 3-17** Vicarious substitution of aryl nitro compounds
- 4-11** Free-radical acyloxylation
- 4-23** Carbalkoxylation of nitrogen heterocycles
- 4-39** Reaction between silver salts and iodine (Simonini)
- 5-3** Hydration of acetylenic ethers
- 5-4** Addition of alcohols or phenols to ketenes
- 5-5** Addition of carboxylic acids or acyl peroxides to olefins
- 5-17** Addition of carboxylic esters to activated olefins (Michael)
- 5-18** Addition of organometallic compounds to unsaturated esters
- 5-20** Addition of tin and mercury hydrides to unsaturated ketones
- 5-22** Free-radical addition of carboxylic esters to olefins
- 5-23** Hydrocarboxylation of olefins in the presence of alcohols
- 5-35** Addition of carboxylic acid salts to olefins
- 5-43** Addition of OAc and SR to double bonds
- 5-54** Dicarbalkoxylation of olefins and acetylenes
- 6-7** Reductive acylation of ketones
- 6-9** Alcoholysis of nitriles
- 8-7** Rearrangement of  $\alpha$ -halo ketones (Favorskii)
- 8-8** Rearrangement of diazo ketones in the presence of alcohols (Arndt-Eistert)
- 8-20** Reaction between ketones and peroxy compounds (Baeyer-Villiger)
- 9-8** Cleavage of cyclic ketones with NOCl and an alcohol
- 9-9** From ozonides
- 9-10** Oxidative cleavage of enol ethers
- 9-13** Reaction between carboxylic acids and lead tetraacetate
- 9-18** Oxidation of ethers
- 9-22** Oxidation of primary alcohols or aldehydes
- 9-23** Oxidation of enol ethers
- 9-70** Reaction between aldehydes and aluminum ethoxide (Tishchenko)
- 9-72** Reaction of acetophenones with  $\text{AgNO}_3\text{-I}_2$  or other reagents

**Catenanes**

- 9-65** Acyloin condensation or other methods

**Cyanamides**

- 0-45** Reaction between alkyl halides and cyanamide
- 0-73** Cleavage of tertiary amines with cyanogen bromide (von Braun)
- 7-39** Dehydration of disubstituted ureas

**Cyanates**

- 0-12** Reaction of aroxides and cyanogen halides

**Cyanoamines**

- 0-46** Amination of cyanohydrins
- 1-28** Cyanation of aromatic amines
- 2-17** Cyanation of secondary amines
- 6-16** Reaction between aldehydes, ammonia, and nitriles (Mannich)
- 6-50** Addition of cyanide and ammonium ions to aldehydes or ketones (Strecker)
- 6-51** Addition of HCN to  $\text{C}=\text{N}$  or  $\text{C}\equiv\text{N}$  bonds

**Cyano Carbonyl Compounds**

- 0-94** Akylation of cyano carbonyl compounds
- 0-107** Acylation of nitriles by acyl halides
- 0-109** Acylation of nitriles by carboxylic esters
- 0-111** Reaction between acyl halides and CuCN
- 2-17** Cyanation of ketones
- 2-19** Cyanoethylation of enamines; reaction of enamines with cyanogen chloride
- 3-14** Arylation of cyano carbonyl compounds
- 5-17** Addition of olefins (Michael)
- 5-21** Acylation of unsaturated nitriles
- 5-25** Addition of HCN to unsaturated aldehydes, ketones, or carboxylic esters
- 6-41** Addition of cyano carbonyl compounds to aldehydes or ketones (Knoevenagel)
- 6-48** Condensation of nitriles (Thorpe)
- 9-33** Dimerization of cyano carbonyl compounds

**Cyanohydrins** (*see* Hydroxy Nitriles)

**Cycloalkanes and Alkenes** (*see* Alicyclic Compounds)

**Dialdehydes** (*see* Dicarboxyl Compounds)

### Diazo Compounds

- 0-112** Reaction between acyl halides and diazomethane
- 2-9** Reaction of active hydrogen compounds with tosyl azide
- 2-49** Diazotization of  $\alpha$ -amino esters and similar compounds
- 6-41** Addition of diazo esters to aldehydes
- 7-45** Elimination from N-nitroso-N-alkyl compounds
- 9-6** Oxidation of hydrazones

### Diazonium Salts

- 1-5** Direct diazotization of aromatic rings
- 2-49** Diazotization of primary amines

### 1,2-Dicarbonyl Compounds

- 0-103** Dicarboxylation of halides
- 0-106** Dimerization of acyl halides
- 0-109** Acylation of 1,3-dithianes, followed by hydrolysis
- 6-29** Addition of RLi and CO to carboxylic esters
- 6-69** Reaction of metalated aldimines with CO<sub>2</sub>
- 9-9** Ozonization of alkynes or aromatic rings
- 9-16** Oxidation of ketones with selenium dioxide
- 9-21** Oxidative cleavage of  $\alpha$ -amino ketones
- 9-23** Oxidation of olefins
- 9-27** Oxidation of alkynes
- 9-65** Reductive condensation of aromatic carboxylic acids

### 1,3-Dicarbonyl Compounds

- 0-94** Alkylation at a carbon bearing an active hydrogen
- 0-107** Acylation at a carbon bearing an active hydrogen
- 0-108** Acylation of carboxylic esters by carboxylic esters (Claisen; Dieckmann)
- 0-109** Acylation of ketones by carboxylic esters

**0-110** Acylation of carboxylic acid salts

- 1-22** Reaction between aromatic compounds and diethyl oxomalonate
- 2-15** Acylation of acetals or ketals followed by hydrolysis
- 2-16** Alkoxyacylalkylation of aldehydes
- 2-19** Acylation of enamines followed by hydrolysis (Stork)
- 3-14** Arylation at a carbon bearing an active hydrogen
- 5-2** Cleavage of activated olefins with water
- 5-17** Addition of active hydrogen compounds to olefins (Michael)
- 5-22** Free-radical addition of 1,3-dicarbonyl compounds to olefins
- 6-30** Reaction between nitriles, zinc, and  $\alpha$ -halo esters (Blaise)
- 6-41** Addition of 1,3-dicarbonyl compounds to aldehydes or ketones (Knoevenagel)
- 6-43** Carboxylation of ketones and carboxylic esters
- 7-20** Cleavage of Michael adducts
- 7-50** Extrusion of sulfur from  $\beta$ -keto thiol esters
- 8-2** Rearrangement of epoxy ketones
- 8-9** Reaction of ketones with ethyl diazoacetate
- 9-16** Remote oxidation of ketones
- 9-33** Dimerization of  $\beta$ -keto esters or similar compounds

### 1,4-Dicarbonyl Compounds

- 0-6** Cleavage of furans
- 1-14** Acylation of aromatic rings by succinic anhydride
- 4-16** Coupling of ketones, carboxylic acids, and esters
- 5-21** Acylation of unsaturated ketones or alkynes
- 5-54** Dicarboxylation of olefins and acetylenes
- 9-16** Remote oxidation of ketones
- 9-34** Dimerization of silyl enol ethers or of lithium enolates

### 1,5-Dicarbonyl Compounds

- 5-17** Addition of silyl enol ethers or silyl ketene acetals to unsaturated ketones or esters

**Dicarboxylic Acids** (*see* Dicarboxylic Compounds, Carboxylic Acids)

**Dicyano Compounds**

- 0-94 Alkylation of malononitriles
- 3-14 Arylation of malononitriles
- 5-17 Addition of nitriles to unsaturated nitriles (Michael)
- 5-25 Addition of HCN to triple bonds
- 6-41 Addition of malononitriles to aldehydes or ketones (Knoevenagel)
- 6-51 Addition of HCN to nitriles
- 9-10 Oxidation of *o*-diamines

**Diesters** (*see* Dicarboxylic Compounds)

**Dihalides and Polyhalides**

- 0-69 Treatment of epoxides with  $\text{SOCl}_2$ ,  $\text{Ph}_3\text{P}$  and  $\text{CCl}_4$  or  $\text{Ph}_3\text{PCl}_2$
- 0-76 Reduction of trihalides
- 0-87 Coupling of halides with trihalides
- 2-40 Decarboxylation of trihalo acids
- 2-44 The haloform reaction
- 3-17 Vicarious substitution of aryl nitro compounds
- 4-1 Free-radical halogenation
- 5-1 Addition of hydrogen halides to alkynes
- 5-26 Addition of halogens to olefins or alkynes
- 5-33 Free-radical addition of polyhalides to olefins
- 6-24 Reaction of  $\text{PCl}_5$ ,  $\text{SF}_4$ , or other reagents with aldehydes, ketones, or other  $\text{C}=\text{O}$  compounds
- 9-21 Treatment of amines with  $\text{CuX}$  and alkyl nitrites

**Diketones** (*see* Dicarboxylic Compounds)

**Dinitro Compounds**

- 4-13 Nitration of alkanes or nitro compounds
- 5-40 Addition of  $\text{N}_2\text{O}_4$  to olefins

**gem-Diols (Hydrates)**

- 6-1 Hydration of aldehydes

**1,2-Diols**

- 0-7 Hydrolysis of epoxides
- 4-16 Coupling of alcohols
- 5-35 Hydroxylation of olefins

- 6-29 Addition of a masked Grignard reagent to an aldehyde or ketone

- 6-41 From aromatic aldehydes and carbanions

- 9-62 Bimolecular reduction of aldehydes or ketones

**1,3-Diols**

- 6-46 Condensation between formaldehyde and aldehydes or ketones (Tollens)

- 6-53 Addition of aldehydes to olefins (Prins)

**Disulfides**

- 0-38 Reaction between alkyl halides and disulfide ion

- 3-5 Reaction between aryl halides and disulfide ion

- 3-28 The Smiles rearrangement

- 5-28 Addition of  $\text{ArSSCl}$  to alkenes

- 9-35 Oxidation of thiols

- 9-54 Reduction of sulfonyl halides

**Dithioacetals**

- 0-36 From *gem*-dihalides or acetals and thiolate ions

- 5-6 Addition of thiols to alkynes

- 6-11 Addition of thiols to aldehydes or ketones

**Dithiols**

- 5-38 Reaction of alkenes with a disulfide and  $\text{BF}_3$  etherate

- 6-11 Addition of  $\text{H}_2\text{S}$  to carbonyl compounds or imines

**Enamines**

- 0-97 Alkylation of enamines

- 5-7 Addition of amines to triple-bond compounds

- 6-14 Addition of amines to aldehydes or ketones

- 6-32 Reaction between Grignard reagents and formamides

- 6-47 Reaction of phosphonates with aldehydes or ketones

- 7-18 Dehydrocyanation of cyano amines

- 9-2 Dehydrogenation of tertiary amines

**Enolate Ions**

- 0-95** From enol acetates
- 2-3** Treatment of aldehydes or ketones with base
- 2-22** Treatment of active hydrogen compounds with base

**Enol Carbamates**

- 5-5** Reaction between alkynes, CO, and an amine

**Enol Ethers and Esters**

- 0-15** O-Alkylation of carbonyl compounds with diazo alkanes
- 0-17** Transesterification
- 0-20** Reaction between acyl halides and active hydrogen compounds
- 0-23** Transesterification
- 0-24** Acylation of vinylic halides
- 0-94** Alkylation with ortho esters
- 0-107** O-Acylation of 1,3-dicarbonyl compounds
- 5-4** Addition of alcohols or phenols to alkynes; addition of aldehydes or ketones to ketene
- 5-5** Addition of carboxylic acids to alkynes
- 6-6** Addition of alcohols or anhydrides to aldehydes or ketones
- 6-33** Reaction between carboxylic esters and Tebbe's reagent or metal carbene complexes
- 6-47** Reaction of  $\alpha$ -alkoxy phosphoranes with aldehydes or ketones
- 7-2** Cleavage of acetals
- 7-31** Elimination from  $\beta$ -halo acetals

**Enols** (*see* Unsaturated Alcohols and Phenols)

**Enol Thioethers**

- 5-6** Addition of thiols to alkynes
- 6-11** Reaction of aldehydes or ketones with thiols
- 9-2** Dehydrogenation and reduction of sulfoxides

**Enynes**

- 5-15** Dimerization of alkynes

**Episulfides**

- 0-36** Reaction between epoxides and phosphine sulfides
- 5-28** Cyclization of  $\beta$ -halo disulfides
- 6-62** Reaction of diazoalkanes with sulfur or thioketones

**Epoxides**

- 0-13** Cyclization of halohydrins
- 0-16** Cyclization of 1,2-diols
- 0-18** Payne rearrangement of 2,3-epoxy alcohols
- 4-8** Epoxidation of a secododecahedrane
- 5-36** Epoxidation of olefins
- 6-29** Reaction of carbonyl compounds with *gem*-dihalides and Li or BuLi
- 6-45** Condensation between aldehydes and  $\alpha$ -halo esters, ketones, or amides (Darzens)
- 6-61** Addition of sulfur ylides or diazomethane to aldehydes or ketones
- 9-63** Bimolecular reduction of aldehydes or ketones

**Esters** (*see* Carboxylic Esters, Inorganic Esters)

**Ethers** (*see also* Hydroxy Ethers, etc.)

- 0-6** Cleavage of oxonium ions
- 0-10** Reaction between carboxylic esters and alkoxide ion
- 0-12** Reaction between alkoxides or aroxides and alkyl halides (Williamson)
- 0-14** Reaction between alkoxides or aroxides and inorganic esters
- 0-15** Alkylation of alcohols or phenols with diazo compounds
- 0-16** Dehydration of alcohols
- 0-17** Transesterification
- 0-19** Alkylation of alcohols with onium salts
- 0-29** Exchange of ethers and oxonium salts
- 0-30** Reaction of halides with oxide ion
- 0-68** Cleavage of oxonium salts
- 0-79** Reduction of acetals or ketals
- 0-92** Reaction between Grignard reagents and acetals or ketals; dimerization of acetals

**Ethers (continued)**

- 2-23** Reaction between Grignard reagents and *t*-butyl peresters
- 3-4** Reaction between aryl halides and alkoxides or aroxides
- 4-8** Cyclization of alcohols with lead tetraacetate
- 4-36** Desulfurization of thiono esters
- 5-4** Addition of alcohols or phenols to olefins
- 5-22** Free-radical addition of ethers to olefins
- 6-7** Reductive alkylation of alcohols
- 9-40** Reduction of carboxylic esters
- 9-60** Reduction of peroxides

**Glycidic Esters**

- 5-36** Epoxidation of  $\alpha,\beta$ -unsaturated esters
- 6-45** Condensation between aldehydes or ketones and  $\alpha$ -halo esters (Darzens)

**Grignard Reagents** (*see* Organometallic Compounds)**Halo Acids, Esters, Aldehydes, Ketones** (*see* Halo Carbonyl Compounds)**Haloamines**

- 5-29** Addition of N-haloamines to unsaturated compounds

**N-Haloamines and Amides**

- 2-54** Halogenation of amines or amides

**Halo Carbonyl Compounds**

- 0-69** Reaction of acyl chlorides with ethylene oxide and NaI
- 0-71** Reaction of diazo ketones with hydrohalic acids
- 2-4** Halogenation of aldehydes or ketones
- 2-5** Halogenation of carboxylic acids (Hell-Volhard-Zelinskii) and acid derivatives
- 5-26** Addition of halogens to ketenes
- 5-27** Addition of HOBr or HOCl to triple bonds; addition of chlorine acetate or other reagents to olefins
- 5-34** Addition of acyl halides to olefins
- 8-10** Rearrangement of halo epoxides
- 9-23** Oxidation of certain alkenes

**Halo Ethers and Acetals**

- 5-27** Addition of hypohalites to double bonds
- 6-23** Addition of alcohols and hydrogen halides to aldehydes or ketones
- 6-24** Reaction of carboxylic esters with ClF or other reagents

**Haloformic Esters**

- 0-20** Alcoholysis of phosgene

**Halohydrins**

- 0-69** Cleavage of epoxides with hydrogen halides
- 5-27** Addition of hypohalous acids to olefins

**Halo Sulfides, Sulfoxides, and Sulfones**

- 2-6** Halogenation of sulfoxides and sulfones
- 5-29** Addition of sulfonyl halides to olefins
- 9-71** Pummerer rearrangements

**Hemiacetals**

- 4-4** Electrolytic oxidation of tetrahydrofuran
- 6-6** Addition of alcohols to aldehydes or ketones

**Hemiaminals**

- 6-13** Reaction between aldehydes or ketones and ammonia
- 6-14** Reaction between aldehydes or ketones and amines

**Hemimercaptals**

- 6-11** Addition of thiols to aldehydes or ketones

**Heterocyclic Compounds** (*see also* Anhydrides, Aziridines, Epoxides, Episulfides, Imides, Lactams, Lactones)

- 0-13** Cyclization of halohydrins (cyclic ethers)
- 0-16** Cyclization of glycols (cyclic ethers; furans)
- 0-17** Reaction of diols with acetals (cyclic acetals)
- 0-36** Reaction of dihalides with sulfide ion (cyclic sulfides)

## Heterocyclic Compounds (continued)

- 0-43** Cyclization of haloamines (cyclic amines); dealkylation of quaternary salts of nitrogen heterocycles
- 0-45** Reaction between dihalides and cyanamide (cyclic amines)
- 0-59** Reaction between ureas and malonic esters (cyclic ureides)
- 1-9** Sulfurization of aromatic rings (cyclic sulfides)
- 1-14** Intramolecular acylation
- 1-21** Intramolecular amidation of aromatic rings
- 1-23** Cyclization of amides with  $\text{POCl}_3$  (isoquinolines)
- 2-12** Intramolecular nitrene insertion
- 3-6** Intramolecular arylation of amines (cyclic amines)
- 3-14** Intramolecular arylation of active hydrogen compounds
- 3-17** Arylation of heterocyclic nitrogen compounds
- 3-18** Amination of heterocyclic nitrogen compounds
- 4-8** Cyclization of alcohols with lead tetraacetate (tetrahydrofurans)
- 4-15** Cyclization of N-tosyl malonic esters
- 4-18** Intramolecular arylation (Pschorr)
- 4-23** Alkylation, arylation, and carbalkoxylation of nitrogen heterocycles
- 5-7** Addition of ammonia or primary amines to conjugated diynes (pyrroles)
- 5-10** Hydrogenation of heterocyclic aromatic rings
- 5-12** Addition of boranes to dienes (cyclic boranes)
- 5-37** Photooxidation of dienes (cyclic peroxides)
- 5-38** Cyclization of unsaturated alcohols with sulfonyl chlorides (tetrahydrofurans)
- 5-42** Addition of aminonitrenes to triple bonds (1-azirines)
- 5-46** 1,3-Dipolar addition to double or triple bonds
- 5-47** Diels-Alder addition involving hetero atoms
- 5-50** Expansion of heterocyclic rings upon treatment with carbenes
- 5-52** Other cycloaddition reactions
- 6-6** Formation of cyclic acetals; reaction between diketones and acids (furans, pyrans)
- 6-11** Addition of  $\text{H}_2\text{S}$  to aldehydes or ketones (cyclic thioacetals)
- 6-13** Reaction between aldehydes and ammonia (cyclic amines)
- 6-14** Intramolecular addition of amines to carbonyl groups (cyclic imines)
- 6-18** Reaction of dinitriles with ammonia (cyclic imidines)
- 6-20** Reaction between hydrazines and  $\beta$ -diketones or  $\beta$ -keto esters (pyrazoles; pyrazolones)
- 6-38** Ring expansion of thiono lactones (cyclic ethers)
- 6-41** Reaction of ketones with tosylmethylisocyanide (oxazolines)
- 6-53** Reaction between alcohols and aldehydes (dioxanes)
- 6-57** Trimerization of aldehydes (trioxanes)
- 6-60** Trimerization of nitriles (triazines)
- 6-63** Addition of olefins to aldehydes or ketones (oxetanes)
- 7-25** Reaction of dichlorobenzyl sulfones with base (thiiren-1,1-dioxides)
- 7-47** Extrusion of  $\text{CO}_2$  from benzoxadiazepinones (indazoles)
- 7-51** Condensation of thiobenzilic acid with aldehydes or ketones (oxathiolan-5-ones)
- 8-15** Curtius rearrangement of cycloalkyl or aryl azides
- 8-19** Rearrangement of N-haloamines (cyclic amines)
- 8-22** Ring enlargement of cyclic quaternary ammonium salts (cyclic amines)
- 8-33** Ring expansion of N-acylaziridines (oxazoles)
- 8-36** Cyclization of arylhydrazones (Fischer indole synthesis)
- 8-42** Acid-catalyzed rearrangement of N-haloamines (pyrrolidines; piperidines—Hofmann-Löffler)
- 9-1** Aromatization of heterocyclic rings
- 9-37** Reduction of  $\alpha,\beta$ -unsaturated ketones (pyrazolones)
- 9-39** Reduction of lactams (cyclic amines)
- 9-40** Reduction of lactones (cyclic ethers)

**Hydrates** (*see gem-Diols*)**Hydrazides**

**0-52** Acylation of hydrazines with acyl halides

**0-55** Acylation of hydrazines with carboxylic esters

**Hydrazines**

**3-18** Hydrazination of heterocyclic nitrogen compounds

**5-7** Addition of hydrazines to olefins

**8-14** Reaction between ureas and NaOBr (Hofmann)

**9-47** Reduction of N-nitro compounds

**9-50** Reduction of N-nitroso compounds

**9-53** Reduction of azo compounds or diazonium salts

**9-68** Reduction of nitro compounds

**Hydrazo Compounds** (*see Hydrazines*)**Hydrazones**

**2-7** Aliphatic diazonium coupling

**6-20** Addition of hydrazines to aldehydes or ketones

**Hydroperoxides**

**0-31** Reaction between alkyl or acyl halides and hydrogen peroxide

**2-25** Reaction between organometallic reagents and oxygen

**4-9** Autoxidation; reaction of alkenes with singlet oxygen

**Hydroxamic Acids**

**0-52** Acylation of hydroxylamine with acyl halides

**0-55** Acylation of hydroxylamine with carboxylic esters

**6-4** Hydrolysis of aliphatic nitro compounds

**Hydroxy Acids**

**0-10** Hydrolysis of lactones

**0-103** Dicarboxylation of aryl iodides

**1-20** Carboxylation of phenols

**1-22** Reaction between aromatic compounds and diethyl oxomalonate

**2-25** Oxidation of dilithiated carboxylic acids

**6-5** Hydrolysis of cyanohydrins

**6-30** Reaction between aldehydes or ketones and zinc carboxylates

**6-41** Addition of dianions of carboxylic acids to ketones

**6-52** Addition of CO<sub>2</sub> to aldehydes and ketones

**8-6** Rearrangement of benzils

**8-7** Rearrangement of  $\alpha,\beta$ -epoxy ketones (Favorskii)

**9-69** Reaction between keto aldehydes and base

**Hydroxy Aldehydes and Ketones**

**0-5** Hydrolysis of diazo ketones

**0-97** Reaction between dithiane salts and epoxides

**0-98** Alkylation of oxazines with epoxides

**1-30** Rearrangement of phenolic esters (Fries)

**2-19** Alkylation of enamines with epoxides

**4-4** Hydroxylation of ketones

**6-25** Monoreduction of  $\alpha$ -diketones

**6-29** Addition of RLi and CO to ketones

**6-30** Reaction between aldehydes or ketones, zinc, and halo ketones

**6-39** Combination of aldehydes and/or ketones (aldol)

**6-41** Various Knoevenagel methods

**6-46** Condensation of formaldehyde with aldehydes or ketones (Tollens)

**6-54** Condensation of aromatic aldehydes (benzoin)

**6-69** Reaction of metalated aldimines with aldehydes or epoxides

**8-2** Rearrangement of epoxy silyl ethers

**8-4** Rearrangement of  $\alpha$ -hydroxy aldehydes or ketones

**9-20** Oxidation of epoxides

**9-23** Oxidation of alkenes

**9-65** Condensation of carboxylic esters (acyloin)

**Hydroxyamines and Amides**

**0-49** Amination of epoxides

**0-51** Hydrolysis of silyloxy isocyanides

**1-22** Hydroxymethylation of aromatic amines

**1-25** Aminoalkylation and amidoalkylation of phenols

**Hydroxyamines and Amides (continued)**

- 1-29** Hydroxylation of amines
- 3-27** Rearrangement of aryl hydroxylamines (Bamberger)
- 4-4** Hydroxylation of amides
- 5-39** Oxyamination of double bonds; aminomercuration of alkenes, followed by hydrolysis
- 6-13** Addition of ammonia to aldehydes or ketones
- 6-14** Addition of amines or amides to aldehydes or ketones
- 6-30** Reaction between aldehydes or ketones, zinc, and halo amides
- 6-41** Reaction of aldehydes with the conjugate base of formamide; reaction of ketones with imines
- 6-67** Reaction between isocyanides,  $\text{TiCl}_4$  and aldehydes or ketones, followed by hydrolysis
- 9-62** Coupling of ketones and O-methyl oximes

**Hydroxy Esters**

- 0-23** Transesterification of lactones
- 0-25** Acylation of epoxides
- 4-4** Hydroxylation of carboxylic esters
- 6-30** Reaction between aldehydes or ketones, zinc, and  $\alpha$ -halo esters (Reformatsky)
- 6-40** Condensation between carboxylic esters and aldehydes or ketones
- 6-41** Addition of  $\alpha$ -metalated esters to ketones

**Hydroxy Ethers**

- 0-18** Alcoholysis of epoxides

**Hydroxylamines**

- 5-7** Addition of hydroxylamine to olefins
- 6-26** Reduction of oximes
- 6-35** Addition of alkyllithium compounds to oximes
- 7-8** Cleavage of amine oxides (Cope)
- 8-22** Rearrangement of N-oxides (Meisenheimer)
- 9-24** Oxidation of amines
- 9-49** Reduction of nitro compounds

**Hydroxy Nitriles**

- 0-101** Reaction between epoxides and cyanide ion
- 4-4** Hydroxylation of nitriles
- 6-30** Reaction between aldehydes and ketones, zinc, and halo nitriles
- 6-41** Addition of nitriles to ketones
- 6-49** Addition of HCN to aldehydes or ketones

**Hydroxy Sulfonic Acids**

- 0-41** Reaction between epoxides and bisulfite ion
- 6-12** Addition of bisulfite ion to aldehydes or ketones

**Hydroxy Thiols and Thioethers**

- 0-35** Reaction between epoxides and NaSH
- 0-36** Reaction between epoxides and thiolate ions
- 1-26** Thioalkylation of phenols
- 5-38** Hydroxysulfenylation of alkenes
- 6-11** Addition of  $\text{H}_2\text{S}$  to aldehydes or ketones

**Imides (including Ureides)**

- 0-52** Reaction between acyl halides and lithium nitride
- 0-53** Amination of anhydrides
- 0-58** N-Alkylation of imides
- 0-59** N-Acylation of amides or imides
- 5-7** Addition of imides to olefins
- 5-23** Hydrocarboxylation of unsaturated amides
- 6-68** Addition of N-halo amides to isocyanides
- 8-14** Reaction between amides and NaOBr (Hofmann)
- 8-15** Rearrangement of acyl azides in the presence of water (Curtius)
- 9-18** Oxidation of lactams

**Imines**

- 2-8** Reaction between active hydrogen compounds and nitroso compounds
- 2-19** Treatment of enamines with nitrilium salts
- 5-7** Addition of amines to triple-bond compounds

**Imines (continued)**

- 6-13** Addition of ammonia to aldehydes or ketones
- 6-14** Addition of amines to aldehydes or ketones
- 6-37** Addition of Grignard reagents to nitriles
- 6-47** Addition of ylides to nitroso compounds
- 6-69** Reaction of isocyanides with organometallic compounds (metalated imines)
- 8-15** Pyrolysis of alkyl or aryl azides
- 8-18** Reaction between oxime sulfonates and organometallic compounds
- 8-19** Rearrangement of trityl N-haloamines and hydroxylamines (Stieglitz)
- 9-5** Dehydrogenation of secondary amines
- 9-51** Reduction of oximes

**Imino Esters (Imidates), Imino Thioesters, and Their Salts**

- 1-27** Reaction of phenols with nitriles
- 6-9** Alcoholysis of nitriles (Pinner)
- 8-18** Reaction between oxime sulfonates and organoaluminum sulfides
- 8-44** From amides

**Imino Nitriles**

- 8-18** Reaction between an oxime sulfonate, an organoaluminum compound, and  $\text{Me}_3\text{SiCN}$

**Inorganic Esters**

- 0-32** Reaction of alcohols or alkyl halides with inorganic acids or halides
- 2-28** Oxidation of trialkylboranes
- 3-8** Reaction between aryl halides and  $\text{POCl}_3$
- 3-20** Reaction between diazonium salts and  $\text{F}_3\text{CSO}_2\text{OH}$
- 5-27** Addition of  $\text{Cl}_2$  and  $\text{SO}_3$  to alkenes
- 5-40** Addition of  $\text{N}_2\text{O}_4$  to alkenes (nitro nitriles, nitro nitrates)

**Isocyanates**

- 0-52** Reaction between amines and phosphene
- 0-59** Reaction between oxalyl chloride and unsubstituted amides

- 0-62** Alkylation or acylation of cyanate ion
- 2-55** Carbonylation of amines
- 5-32** Addition of iodine isocyanate to double bonds
- 8-14** Reaction between amides and  $\text{NaOBr}$  (Hofmann)
- 8-15** Rearrangement of acyl azides (Curtius)
- 8-16** Rearrangement of hydroxamic acids (Lossen)
- 8-17** Addition of hydrazoic acid to carboxylic acids (Schmidt)
- 9-30** Oxidation of isocyanides

**Isocyanides**

- 0-51** Reaction between primary amines and chloroform, or  $\text{Me}_3\text{SiCN}$  and epoxides or oxetanes
- 0-101** Reaction between alkyl halides and cyanide ion
- 7-41** Elimination of water from N-alkylformamides
- 9-55** Reduction of isocyanates

**Isothiocyanates**

- 0-52** Reaction between amines and thiophosgene
- 0-62** Alkylation or acylation of thiocyanate ion
- 3-21** Reaction between diazonium salts and thiocyanate ion
- 6-19** Addition of amines to carbon disulfide
- 9-30** From isocyanides

**Isothiuronium Salts**

- 0-35** Reaction between alkyl halides and thiourea

**Ketals (see Acetals)****Ketenes**

- 7-1** Pyrolysis of carboxylic acids
- 7-14** Dehydrohalogenation of acyl halides
- 7-30** Dehalogenation of  $\alpha$ -halo acyl halides
- 8-8** Rearrangement of diazo ketones (Wolff)

**Ketenimines**

- 6-47** Reaction between phosphoranes and isocyanates
- 7-1** Dehydration of amides

**Keto Acids, Aldehydes, and Esters** (*see* Dicarboxyl Compounds)**Ketones** (*see also* Dicarboxyl Compounds, Unsaturated Carbonyl Compounds, etc.)

- 0-1** Hydrolysis of vinylic halides
- 0-2** Hydrolysis of *gem*-dihalides
- 0-4** Hydrolysis of enol esters of inorganic acids
- 0-6** Hydrolysis of enol ethers, ketals, thioketals, etc.
- 0-10** Hydrolysis of enol esters
- 0-76** Reduction of halo ketones
- 0-78** Reduction of hydroxy ketones
- 0-82** Reduction of diazo ketones or nitro ketones
- 0-87** Coupling of halo ketones with lithium alkylcopper reagents
- 0-94** Acetoacetic ester synthesis and similar reactions
- 0-95** Alkylation of ketones
- 0-97** Alkylation and hydrolysis of dithianes and similar compounds
- 0-98** Alkylation and hydrolysis of oxazines
- 0-99** Reaction of halo ketones or diazo ketones with boranes
- 0-102** Carbonylation of alkyl halides
- 0-104** Reaction between acyl halides and organometallic compounds
- 0-105** Reaction between other acid derivatives and organometallic compounds
- 0-107** Acylation of active hydrogen compounds followed by cleavage
- 0-109** Reduction of  $\beta$ -keto sulfoxides
- 0-110** Acylation of carboxylic acid salts followed by cleavage
- 0-113** Ketonic decarboxylation
- 1-14** Acylation of aromatic rings (Friedel-Crafts)
- 1-19** Reaction between aromatic rings and phosgene
- 1-27** Acylation of aromatic rings with nitriles (Hoesch)

- 1-30** Rearrangement of phenolic ethers (Fries)
- 1-36** Photolysis of acylated arylamines
- 2-2** Rearrangement of hydroxy olefins
- 2-16** Reaction between aldehydes and boron-stabilized carbanions
- 2-19** Alkylation of enamines followed by hydrolysis (Stork)
- 2-25** Oxidation of *gem*-dimetallic compounds
- 2-32** Carbonylation of organometallic compounds
- 2-40** Decarboxylation of  $\beta$ -keto acids or esters
- 2-41** Cleavage of tertiary alkoxides
- 2-42** Reaction between amino acids and anhydrides (Dakin-West)
- 2-43** Basic cleavage of  $\beta$ -diketones
- 3-14** Arylation of ketones
- 3-15** Acylation of aryl iodides
- 4-20** Arylation of allylic alcohols
- 4-23** Acylation of nitrogen heterocycles
- 4-31** Reaction of diazonium salts with oximes, followed by hydrolysis; or with  $R_4Sn$  and CO; or with silyl enol ethers
- 5-3** Hydration of alkynes or allenes
- 5-9** Selective reduction of unsaturated ketones
- 5-10** Reduction of phenols
- 5-12** Oxidation of boranes; hydrolysis of unsaturated boranes
- 5-17** Addition of ketones to activated olefins (Michael)
- 5-18** Addition of organometallic compounds to unsaturated ketones
- 5-19** Addition of boranes to unsaturated ketones
- 5-20** Addition of tin and mercury hydrides to unsaturated ketones
- 5-22** Free-radical addition of aldehydes or ketones to olefins
- 5-24** Hydroacylation of alkenes
- 5-50** Hydrolysis of bicyclo[4.1.0]heptanes
- 6-2** Hydrolysis of imines, oximes, hydrazones, and other  $C=N$  compounds
- 6-4** Hydrolysis of secondary aliphatic nitro compounds (Nef)
- 6-31** Reaction between lithium carboxylates and alkyllithium compounds

## Ketones (continued)

- 6-33 Indirectly, from carboxylic esters
- 6-37 Addition of Grignard reagents to nitriles
- 6-42 Hydrolysis of epoxy silanes
- 6-69 Reaction of alkyl halides with metalated aldimines
- 7-1 Dehydration of 1,2-diols
- 7-32 Fragmentation of  $\gamma$ -amino or  $\gamma$ -hydroxy halides
- 7-33 Fragmentation of 1,3-diols
- 7-38 Fragmentation of certain ketoximes
- 7-43 Pyrolysis of  $\beta$ -hydroxy olefins
- 7-44 Pyrolysis of allylic ethers
- 8-2 Rearrangement of glycols and related compounds (pinacol)
- 8-3 Ring expansion of certain hydroxyamines (Tiffeneu-Demyanov)
- 8-4 Acid-catalyzed ketone rearrangements
- 8-9 Homologation of aldehydes or ketones
- 8-14 Reaction between  $\alpha$ -hydroxy or  $\alpha$ -halo amides and NaOBr (Hofmann)
- 8-21 Cleavage of hydroperoxides
- 8-25 Treatment of boranes with CO and  $H_2O$ , followed by NaOH and  $H_2O_2$ ; or with  $CN^-$  followed by trifluoroacetic anhydride; from dialkylchloroboranes
- 8-28 Treatment of lithium alkynyltrialkylborates with electrophiles
- 8-32 [1,3] Sigmatropic rearrangements of allylic vinylic ethers
- 9-3 Oxidation of secondary alcohols
- 9-7 Oxidative cleavage of glycols and related compounds
- 9-9 Ozonolysis of olefins
- 9-10 Oxidative cleavage of olefins
- 9-11 Oxidation of diarylmethanes
- 9-14 Bisdecarboxylation of malonic acids
- 9-15 Oxidative decyanation of nitriles
- 9-16 Oxidation of activated or unactivated methylene groups
- 9-20 Oxidation of secondary alkyl halides and tosylates
- 9-21 Oxidation of amines or nitro compounds
- 9-23 Oxidation of olefins with noble-metal salts
- 9-37 Reduction of diketones or quinones

- 9-57 Indirect oxidative decyanation of nitriles

## Lactams

- 0-54 Cyclization of amino acids
- 0-55 Reaction between lactones and ammonia or amines; ring expansion of lactams
- 0-58 Cyclization of halo amides
- 5-7 Addition of lactams to olefins
- 5-23 Hydrocarboxylation of unsaturated amines
- 6-31 Reaction between imines, zinc, and halo esters
- 6-47 Reaction between imides and phosphoranes
- 6-64 Addition of ketenes to imines; addition of enamines to isocyanates
- 8-17 Reaction between cyclic ketones and hydrazoic acid (Schmidt)
- 8-18 Rearrangement of oximes of cyclic ketones (Beckmann)
- 8-19 Expansion of aminocyclopropanols
- 9-18 Oxidation of cyclic tertiary amines

## Lactones

- 0-22 Cyclization of hydroxy acids
- 0-24 Cyclization of halo acids
- 0-89 Intramolecular coupling
- 2-43 Cleavage of cyclic  $\alpha$ -cyano ketones
- 5-4 Internal addition of alcohols to a ketene function
- 5-5 Cyclization of olefinic acids
- 5-23 Hydrocarboxylation of unsaturated alcohols
- 5-27 Halolactonization
- 5-45 Reaction of alkenes with manganese(III) acetate
- 6-47 Reaction of anhydrides with phosphoranes
- 6-63 Addition of ketenes to aldehydes or ketones
- 7-47 Extrusion of  $CO_2$  from 1,2-dioxolane-3,5-diones
- 7-49 Decarboxylation of cyclic peroxides (Story)
- 8-20 Reaction between cyclic ketones and peroxy compounds (Baeyer-Villiger)
- 8-42 Rearrangement of N-halo amides
- 9-18 Oxidation of cyclic ethers

Lactones (continued)

- 9-22 Oxidation of diols
- 9-41 Reduction of cyclic anhydrides
- 9-69 Oxidative-reductive ring closure of dialdehydes

**Mercaptals** (*see* Thioacetals)

**Mercaptans** (*see* Thiols)

**Metalloenes**

- 2-35 Reaction between sodium cyclopentadienylide and metal halides

**Monoesters of Dicarboxylic Acids**

- 0-21 Alcoholysis of cyclic anhydrides
- 0-23 Equilibration of dicarboxylic acids and esters
- 6-9 Alcoholysis of cyano acids
- 9-10 Oxidative cleavage of catechols

**Nitrile Oxides**

- 7-40 Oxidation of nitro compounds

**Nitriles** (*see also* Dicyano Compounds, Cyano Carbonyl Compounds, etc.)

- 0-95 Alkylation of nitriles
- 0-99 Reaction of halo nitriles or diazo nitriles with boranes
- 0-101 Reaction between alkyl halides and cyanide ion
- 1-28 Cyanation of aromatic rings
- 2-17 Cyanation of ketones, nitro compounds, or benzylic compounds
- 2-33 Cyanation of organometallic compounds
- 2-40 Decarboxylation of  $\alpha$ -cyano acids
- 3-11 Reaction between aryl halides and CuCN (Rosenmund-von Braun)
- 3-12 Cyanide fusion of sulfonic acid salts
- 3-14 Arylation of nitriles
- 3-17 Vicarious substitution of aryl nitro compounds
- 4-28 Reaction between diazonium salts and CuCN (Sandmeyer)
- 4-39 Reaction of acyl peroxides with copper cyanide
- 4-41 Decarbonylation of aromatic acyl cyanides
- 5-17 Addition to activated olefins (Michael)
- 5-19 Addition of boranes to acrylonitrile

- 5-20 Addition of tin and mercury hydrides to unsaturated nitriles
- 5-22 Free-radical addition of nitriles to olefins
- 5-25 Addition of HCN to olefins
- 5-43 Addition of CN and SR to double bonds
- 6-22 From aldehydes or carboxylic esters
- 6-41 Reaction of ketones with tosylmethylisocyanide
- 6-51 Addition of KCN to sulfonyl hydrazones
- 6-59 Reaction between acid salts and BrCN
- 7-37 Dehydration of aldoximes and similar compounds
- 7-38 Fragmentation of ketoximes
- 7-39 Dehydration of amides
- 7-40 From primary nitro compounds or azides
- 8-22 Rearrangement of isocyanides
- 9-5 Dehydrogenation of amines
- 9-6 Oxidation of hydrazones
- 9-13 Treatment of carboxylic acids with trifluoroacetic anhydride and  $\text{NaNO}_2$
- 9-55 Reduction of nitrile oxides
- 9-58 Reduction of nitro compounds with  $\text{NaBH}_2\text{S}_3$

**Nitro Compounds**

- 0-60 Reaction between alkyl halides and nitrite ion
- 0-94 Alkylation of nitro compounds
- 1-2 Nitration of aromatic rings
- 1-32 Rearrangement of N-nitro aromatic amines
- 2-40 Decarboxylation of  $\alpha$ -nitro acids
- 2-51 N-Nitration of amines or amides
- 3-17 Alkylation of aromatic nitro compounds
- 4-13 Nitration of alkanes
- 4-26 Reaction between diazonium salts and sodium nitrite
- 5-7 Nitromercuration-reduction of alkenes
- 5-9 Reduction of unsaturated nitro compounds
- 5-17 Addition to activated olefins (Michael)

**Nitro Compounds (continued)**

- 5-18** Addition of organometallic reagents to nitroolefins
- 5-30** Addition of NOCl and other nitrogen compounds to olefins
- 5-40** Addition of  $\text{N}_2\text{O}_4$  and other nitrogen compounds to olefins
- 5-43** Addition of  $\text{NO}_2$  and SR to double bonds
- 6-41** Addition of nitro compounds to aldehydes or ketones; reaction of pyrylium salts with nitromethane
- 6-43** Carboxylation of nitro compounds
- 9-25** Oxidation of primary amines, oximes, azides, isocyanates, or nitroso compounds

**Nitrogen Ylides**

- 2-21** Treatment of quaternary ammonium salts with organometallic compounds

**Nitrones**

- 0-34** Alkylation of oximes

**Nitroso Compounds**

- 1-3** Nitrosation of aromatic rings
- 1-33** Rearrangement of N-nitroso aromatic amines (Fischer-Hepp)
- 1-39** Nitrosative decarboxylation of aromatic acids
- 2-8** Nitrosation at a carbon bearing an active hydrogen
- 2-51** Reaction between secondary amines or amides and nitrous acid
- 5-30** Addition of NOCl to olefins
- 8-42** Photolysis of nitrites (Barton)
- 9-6** Oxidation of hydroxylamines
- 9-24** Oxidation of primary amines
- 9-48** Reduction of nitro compounds

**Olefins (see Alkenes)****Organometallic Compounds (see also Boranes)**

- 1-39** Replacement of aromatic COOH with Hg
- 2-21** Metallation of susceptible positions with organometallic compounds
- 2-22** Metallation of susceptible positions with metals or strong bases

- 2-24** Cleavage of alkyl groups from di- or polyvalent organometallic compounds

- 2-34** Reaction between an organometallic compound and a metal

- 2-35** Reaction between an organometallic compound and a metal halide

- 2-36** Reaction between an organometallic compound and an organometallic compound (exchange)

- 2-38** Metallation of alkyl or aryl halides with metals

- 2-39** Metallation of alkyl or aryl halides with organometallic compounds

- 2-40** Decarboxylation of carboxylic acid salts

- 4-32** Reaction of diazonium salts with metals

- 4-37** Reaction between sulfides and lithium or lithium naphthalide

- 5-13** Hydrometallation of alkenes

- 5-18** Reaction between copper-containing compounds and organolithium compounds

- 5-53** Addition of allylic zinc compounds to vinylic Grignard and lithium reagents (*gem*-dimetallic compounds)

- 8-12** Rearrangement of Grignard reagents

**Ortho Esters**

- 0-12** Reaction of alkoxides with 1,1,1-tri-halides (Williamson)

- 0-17** Transesterification

- 4-7** Electrolytic alkoxylation of acetals

- 6-6** Addition of alcohols to formic acid

**Osazones**

- 6-20** Addition of hydrazines to  $\alpha$ -hydroxy aldehydes or ketones

**Oxime Ethers**

- 0-15** Alkylation of oximes with diazo compounds

- 0-34** Alkylation of oximes with alkyl sulfates

**Oximes**

- 2-8** Nitrosation at a carbon bearing an active hydrogen

- 5-30** Addition of NOCl to olefins

**Oximes (continued)**

- 6-21** Addition of hydroxylamine to aldehydes or ketones
- 6-35** Addition of Grignard reagents to the conjugate bases of nitro compounds
- 8-42** Photolysis of nitrites (Barton)
- 9-8** Cleavage of cyclic ketones with NOCl and an alcohol
- 9-24** Oxidation of aliphatic primary amines
- 9-58** Reduction of nitro compounds

**Oxiranes (see Epoxides)****Oxonium Salts**

- 0-29** Reaction between alkyl halides and ethers or ketones

**Ozonides**

- 9-9** Ozonolysis of olefins

**Peptides**

- 0-54** Coupling of amino acids

**Peroxides (see also Hydroperoxides, Peroxy acids)**

- 0-31** Reaction of alkyl and acyl halides with peroxide ion
- 4-10** Reaction between hydroperoxides and susceptible hydrocarbons
- 5-4** Oxymercuration–reduction of alkenes in the presence of a hydroperoxide
- 5-37** Photooxidation of dienes
- 7-49** Reaction of ketones with  $\text{H}_2\text{O}_2$

**Peroxy Acids**

- 9-32** Oxidation of carboxylic acids

**Phenols**

- 0-10** Hydrolysis of phenolic esters
- 0-32** Cleavage of phenolic ethers with sulfonic acids
- 0-36** Cleavage of phenolic ethers
- 0-46** Cleavage of phenolic ethers
- 0-68** Cleavage of phenolic ethers with HI or HBr
- 1-29** Electrophilic hydroxylation of aromatic rings
- 1-30** Rearrangement of phenolic esters (Fries)

- 1-31** Rearrangement of phenolic ethers
- 2-25** Oxidation of aryl organometallic compounds
- 2-26** Oxidation of arylthallium compounds
- 3-1** Hydrolysis of aryl halides and other compounds
- 3-2** Reaction between naphthylamines and bisulfite ion (Bucherer)
- 3-3** Alkali fusion of sulfonate ions
- 3-20** Hydrolysis of diazonium salts
- 3-27** Rearrangement of N-hydroxylamines
- 4-5** Free-radical hydroxylation of aromatic rings
- 4-21** Phenylation of phenols
- 5-50** Ortho methylation of phenols
- 6-25** Reduction of quinones
- 8-5** The dienone–phenol rearrangement
- 8-20** Cleavage of aryl ketones with peracids (Baeyer–Villiger)
- 8-21** Rearrangement of aralkyl peroxides
- 8-35** Rearrangement of allylic aryl ethers (Claisen)
- 8-45** Rearrangement of azoxy compounds (Wallach)
- 9-1** Aromatization of cyclic ketones
- 9-12** Oxidative cleavage of alkylbenzenes or aromatic aldehydes
- 9-42** Reduction of phenolic esters
- 9-43** Reduction of certain acids and esters

**Phosphines**

- 0-43** Reaction between alkyl halides and phosphine
- 0-82** Reduction of quaternary phosphonium salts
- 2-35** Reaction between phosphorus halides and Grignard reagents

**Phosphonates**

- 6-47** Reaction between alkyl halides and phosphites (Arbuzov)

**Phosphoranes**

- 6-47** Treatment of phosphonium ions with alkyllithiums

**Quaternary Ammonium and Phosphonium Salts**

- 0-43** Alkylation of amines (Menschutkin) or phosphines

**Quaternary Ammonium and Phosphonium Salts (continued)**

- 5-7** Addition of tertiary amines to alkenes  
**6-47** Reaction of phosphines with Michael olefins or with alkyl halides

**Quinones**

- 1-14** Intramolecular Friedel-Crafts acylation of diaryl ketones  
**9-4** Oxidation of phenols or aromatic amines  
**9-19** Oxidation of aromatic hydrocarbons

**Schiff Bases** (*see* Imines)**Selenides**

- 0-36** Selenylation of alkyl halides  
**2-13** Selenylation of aldehydes, ketones, and carboxylic esters  
**2-29** Selenylation of organometallic compounds  
**9-56** Reduction of selenoxides

**Semicarbazones**

- 6-20** Addition of semicarbazide to aldehydes or ketones

**Silyl Enol Ethers**

- 2-23** Trialkylsilylation of ketones or aldehydes  
**2-27** Reaction between vinylic lithium compounds and silyl peroxides  
**5-18** Michael-type reaction in the presence of  $\text{Me}_3\text{SiCl}$

**Sulfenyl Chlorides**

- 4-12** Chlorosulfonation

**Sulfides** (*see* Thioethers)**Sulfinic Acids and Esters**

- 0-118** Reduction of sulfonyl chlorides  
**2-29** Reaction of Grignard reagents with  $\text{SO}_2$   
**3-28** The Smiles rearrangement  
**4-27** Reaction of diazonium salts with  $\text{FeSO}_4$  and Cu  
**7-12** Cleavage of sulfones

**Sulfonamides**

- 0-58** N-Alkylation of sulfonamides  
**0-94** Alkylation of sulfonamides  
**0-99** Reaction of halo sulfonamides with boranes  
**0-116** Reaction between sulfonyl halides and ammonia or amines  
**3-17** Vicarious substitution of aryl nitro compounds  
**5-7** Addition of sulfonamides to olefins  
**9-39** Reduction of acyl sulfonamides  
**9-53** Reduction of sulfonyl azides

**Sulfones**

- 0-40** Reaction between alkyl halides and sulfinates  
**0-94** Alkylation of sulfones  
**0-95** Alkylation of sulfones  
**0-99** Reaction of halo sulfones with boranes  
**0-109** Reaction between carboxylic esters and methylsulfonyl carbanion  
**0-119** Reaction between sulfonic acid derivatives and organometallic compounds  
**1-10** Sulfonylation of aromatic rings  
**3-5** Reaction between aryl halides and sulfinate ions  
**3-17** Vicarious substitution of aryl nitro compounds  
**5-17** Addition of sulfones to activated olefins (Michael)  
**5-18** Addition of organometallic compounds to unsaturated sulfones  
**5-28** Addition of sulfonyl halides to olefins  
**6-41** Addition of sulfones to aldehydes or ketones (Knoevenagel)  
**9-31** Oxidation of thioethers or sulfoxides

**Sulfonic Acid Esters**

- 0-32** Reaction between alcohols or ethers and sulfonic acids  
**0-94** Alkylation of sulfonic acid esters  
**0-95** Alkylation of sulfonic acid esters  
**0-99** Reaction of halo sulfonic acid esters with boranes  
**0-115** Alcoholysis of sulfonic acid derivatives  
**3-17** Vicarious substitution of aryl nitro compounds

## Sulfonic Acid Esters (continued)

- 6-41** Addition of sulfonic acid esters to aldehydes or ketones (Knoevenagel)

## Sulfonic Acids

- 0-41** Reaction between alkyl halides and sulfite ion  
**0-114** Hydrolysis of sulfonic acid derivatives  
**1-7** Sulfonation of aromatic rings  
**1-40** Sulfonation with rearrangement (Jacobsen)  
**2-14** Sulfonylation of aldehydes, ketones, or carboxylic acids  
**3-5** Reaction between aryl halides and sulfite ion  
**9-26** Oxidation of thiols or other sulfur compounds

## Sulfonium Salts

- 0-36** Reactions between alkyl halides and thioethers

## Sulfonyl Azides

- 0-116** Reaction between sulfonyl halides and azide ion

## Sulfonyl Halides

- 0-117** From sulfonic acids and derivatives  
**1-8** Halosulfonation of aromatic rings  
**2-29** Reaction of Grignard reagents with sulfonyl chloride or with  $\text{SO}_2$  followed by  $\text{X}_2$   
**4-12** Free-radical halosulfonation (Reed)  
**4-27** Reaction of diazonium salts with  $\text{SO}_2$  and  $\text{CuCl}_2$

## Sulfoxides

- 0-94** Alkylation of sulfoxides  
**0-109** Reaction between carboxylic esters and methylsulfinyl anion  
**1-9** Sulfurization of aromatic rings with thionyl chloride  
**2-29** Reaction of Grignard reagents with sulfinic esters  
**5-18** Addition of organometallic compounds to unsaturated sulfoxides  
**5-38** Treatment of alkenes with  $\text{O}_2$  and RSH

- 6-41** Addition of sulfoxides to aldehydes or ketones (Knoevenagel)

- 9-31** Oxidation of thioethers

- 9-56** Indirectly, from sulfones

## Thioamides

- 1-21** Amidation of aromatic rings with isothiocyanates  
**4-14** From thioaldehydes generated in situ  
**6-36** Addition of Grignard reagents to isothiocyanates  
**9-72** Reaction of ketones with sulfur and ammonia or amines

## Thiocarbamates

- 6-5** Hydrolysis of thiocyanates  
**6-8** Addition of alcohols to isothiocyanates

## Thiocyanates

- 0-42** Reaction between alkyl halides and thiocyanate ion  
**3-5** Reaction between aryl halides and thiocyanate ion  
**3-21** Reaction between diazonium salts and thiocyanate ion  
**4-39** Reaction between acyl peroxides and copper thiocyanate  
**5-28** Addition of halogen and SCN to alkenes

## Thioethers

- 0-36** Reaction between alkyl halides and thiolate ions or  $\text{Na}_2\text{S}$   
**0-97** Alkylation of thioethers  
**1-9** Sulfurization of aromatic rings  
**1-26** Thioalkylation of aromatic rings  
**2-13** Sulfonylation of ketones, carboxylic esters, and amides  
**2-29** Reaction between Grignard reagents and sulfur or disulfides  
**3-5** Reaction between aryl halides and thiolate ions  
**3-21** Reaction between diazonium salts and thiolate ions or  $\text{Na}_2\text{S}$   
**4-36** Reduction of dithioacetals  
**5-6** Addition of thiols to olefins  
**5-28** Addition of sulfonyl chlorides to olefins

**Thioethers (continued)**

- 5-43** Diarylamino-arylthio-addition to double bonds
- 6-11** Reductive alkylation of thiols
- 7-11** Cleavage of sulfonium compounds
- 8-22** Rearrangement of sulfonium salts (Stevens)
- 8-37** [2,3] Sigmatropic rearrangements of sulfur ylides
- 9-40** Reduction of thiol esters
- 9-56** Reduction of sulfoxides or sulfones
- 9-60** Reduction of disulfides

**Thiol Acids and Esters**

- 0-36** Reaction between alcohols and thiol acids
- 0-37** Reaction between acid derivatives and thiols or  $\text{H}_2\text{S}$
- 1-27** Reaction between aromatic rings and thiocyanates
- 5-3** Hydration of acetylenic thioethers
- 5-6** Addition of thiol acids to olefins; addition of thiols to ketenes
- 5-23** Hydrocarboxylation of olefins in the presence of thiols
- 6-11** From carboxylic acids, alcohols, and  $\text{P}_4\text{S}_{10}$
- 6-38** Addition of Grignard reagents to carbon disulfide
- 7-50** From thiol acids and  $\alpha$ -halo ketones

**Thiols**

- 0-10** Hydrolysis of thiol esters
- 0-35** Reaction of alkyl halides with  $\text{NaSH}$ ; cleavage of isothiuronium salts
- 1-9** Sulfurization of aromatic compounds (Herz)
- 2-29** Reaction between Grignard reagents and sulfur
- 3-5** Reaction between aryl halides and  $\text{NaSH}$
- 3-21** Reaction between diazonium salts and  $\text{NaSH}$
- 5-6** Addition of  $\text{H}_2\text{S}$  to olefins
- 6-38** Addition of lithium dialkylcopper reagents to dithiocarboxylic esters
- 9-54** Reduction of sulfonic acids or sulfonyl halides
- 9-61** Reduction of disulfides

**Thioketones**

- 6-11** From ketones

**Thiono Esters and Thioamides**

- 6-11** From carboxylic esters or amides
- 6-64** Addition of imines to thioketenes ( $\beta$ -thiolactams)

**Thioureas (see Ureas)****Triazenes**

- 1-4** Reaction between aromatic amines and diazonium salts
- 2-51** Reaction between amines and diazonium salts

**Unsaturated Acids, Esters, Aldehydes, Ketones (see Unsaturated Carbonyl Compounds)****Unsaturated Alcohols and Phenols**

- 2-2** Isomerization of allylic alcohols (formation of enols)
- 4-4** Allylic hydroxylation
- 5-10** Selective reduction of  $\alpha,\beta$ -unsaturated aldehydes or ketones
- 5-18** Addition of organometallic compounds to propargylic alcohols
- 6-25** Selective reduction of  $\alpha,\beta$ -unsaturated aldehydes or ketones
- 6-29** Addition of vinylic or alkynyl organometallic compounds to aldehydes or ketones
- 6-41** Condensation of alkyne salts with aldehydes or ketones
- 6-47** Reaction of certain ylides with aldehydes (scoopy reactions)
- 6-53** Addition of aldehydes to olefins (Prins)
- 7-2** Reaction of epoxides with strong bases
- 7-12** From epoxides or alkenes via selenoxide cleavage
- 8-3** Ring opening of cycloalkyl carbocations
- 8-33** Rearrangement of Li salts of 2-vinylcyclopropanols
- 8-35** Rearrangement of allylic aryl ethers (Claisen)
- 8-37** [2,3] Sigmatropic rearrangements

**Unsaturated Carbonyl Compounds**

- 0-95** Vinylation of ketones or carboxylic esters
- 0-97** Hydrolysis of bis(methylthio)-alkenes
- 2-2** Isomerization of  $\alpha$ -hydroxy alkynes and alkynones
- 2-15** Acylation of olefins
- 2-27** From lithium acetylides
- 2-32** From vinylic organometallic compounds
- 2-55** From allylic amines and CO
- 4-6** Oxidation of unsaturated aldehydes
- 4-40** Decarboxylative allylation of keto acids
- 5-17** Addition to activated alkynes (Michael)
- 5-18** Addition of vinylic organometallic compounds to unsaturated carbonyl compounds; addition of organometallic compounds to acetylenic carbonyl compounds
- 5-19** Addition of unsaturated boranes to methyl vinyl ketones
- 5-23** Hydrocarboxylation of triple bonds
- 5-34** Addition of acyl halides to triple bonds
- 5-35** 1,4-Addition of acetals to dienes
- 6-16** Reaction between aldehydes, ammonia, and aldehydes, ketones, or carboxylic esters (Mannich)
- 6-30** Reaction between aldehydes or ketones, zinc, and  $\alpha$ -halo esters (Reformatsky)
- 6-39** Condensation of aldehydes and/or ketones (aldol)
- 6-40** Condensation between carboxylic esters and aldehydes or ketones
- 6-41** Condensation between active-hydrogen compounds and aldehydes or ketones (Knoevenagel)
- 6-44** Condensation between anhydrides and aldehydes (Perkin)
- 6-47** Condensation between  $\beta$ -carboxy phosphoranes and aldehydes or ketones
- 7-3** Pyrolysis of lactones
- 7-12** Cleavage of carbonyl-containing selenoxides and sulfones
- 7-35** Fragmentation of epoxy hydrazones

- 8-31** Rearrangement of vinylic hydroxy-cyclopropanes
- 8-34** Rearrangement of 3-hydroxy-1,5-dienes (oxy-Cope)
- 8-35** Rearrangement of allylic vinylic ethers (Claisen)
- 8-37** [2,3] Sigmatropic rearrangements
- 9-2** Dehydrogenation of aldehydes or ketones
- 9-16** Oxidation of a methylene group  $\alpha$  to a double or triple bond

**Unsaturated Ethers and Thioethers**

- 0-97** Alkylation of allylic ethers
- 7-31** Elimination of X and OR from  $\beta$ -halo acetals
- 8-37** [2,3] Sigmatropic rearrangement of allylic sulfur ylides

**Unsaturated Nitriles, Nitro Compounds, and Sulfonic Acids and Esters**

- 2-33** Cyanation of vinylic organometallic compounds
- 5-17** Addition to activated alkynes (Michael)
- 5-18** Addition of organometallic compounds to activated alkynes
- 5-25** Addition of HCN to alkynes
- 5-33** Addition of nitril chloride to triple bonds
- 6-41** Condensation between active hydrogen compounds and aldehydes or ketones (Knoevenagel)
- 7-18** Cleavage of H and HgCl from  $\beta$ -nitro mercuric halides
- 8-35** Rearrangement of allylic vinylic sulfones and sulfoxides

**Ureas and Thioureas**

- 0-56** Exchange of ureas
- 2-55** Carbonylation of amines
- 6-17** Addition of amines to isocyanates or isothiocyanates
- 6-19** Addition of amines to CO<sub>2</sub> or CS<sub>2</sub>
- 6-55** Addition of alcohols or other carbocation sources to cyanamides (Ritter)
- 8-14** Reaction between amides and lead tetraacetate

**Ureides (see Imides)**

**Urethanes** (*see* Carbamates)

**Vinyl Ethers** (*see* Enol Ethers)

**Vinyl Halides**

- 0-65** Halide exchange
- 2-30** Halogenation of alkenyl organometallic compounds
- 5-1** Addition of hydrogen halides to triple bonds
- 5-26** Halogenation of alkynes or allenes
- 5-33** Addition of alkyl halides to triple bonds
- 5-34** Addition of acyl halides to triple bonds

**6-24** Addition of  $\text{PCl}_5$  to aldehydes or ketones

**6-47** Reaction of halophosphoranes with aldehydes or ketones; reaction of certain ylides with halogen compounds (scoopy reactions)

**Xanthates**

**6-10** Addition of alcohols to carbon disulfide

**7-4** Reaction of alcohols with  $\text{NaOH}$  and  $\text{CS}_2$ , followed by methyl iodide

**Ylides** (*see* Nitrogen Ylides, Phosphoranes)

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