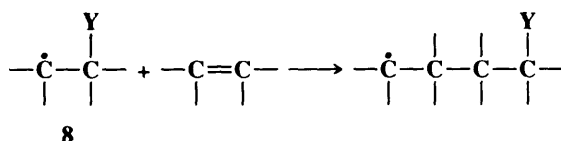
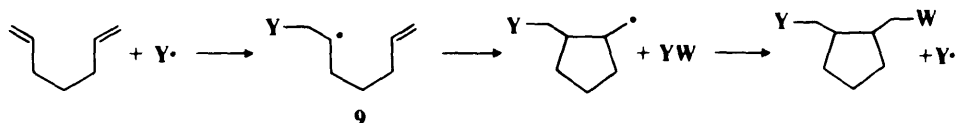


Step 2 is an abstraction, so W is nearly always univalent, either hydrogen or halogen (p. 683). Termination of the chain can occur in any of the ways discussed in Chapter 14. If **8** adds to another olefin molecule,



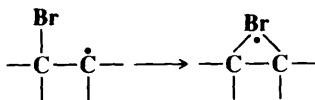
a dimer is formed. This can add to still another, and chains, long or short, may be built up. This is the mechanism of free-radical polymerization. Short polymeric molecules (called *telomers*), formed in this manner, are often troublesome side products in free-radical addition reactions.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical can add intramolecularly to the other bond, leading to a cyclic product, e.g.,<sup>50</sup>



Radicals of the type **9**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed in these reactions (see p. 752).

The free-radical addition mechanism just outlined predicts that the addition should be nonstereospecific, at least if **8** has any but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed for nucleophilic addition on p. 742. Not all free-radical additions have been found to be stereoselective, but many are. For example, addition of HBr to 1-bromocyclohexene gave only *cis*-1,2-dibromocyclohexane and none of the *trans* isomer (anti addition),<sup>51</sup> and propyne (at  $-78$  to  $-60^\circ\text{C}$ ) gave only *cis*-1-bromopropene (anti addition).<sup>52</sup> However, stereospecificity has been found only in a few cases. The most important of these is addition of HBr to 2-bromo-2-butene under free-radical conditions at  $-80^\circ\text{C}$ . Under these conditions, the *cis* isomer gave 92% of the meso product, while the *trans* isomer gave mostly the *dl* pair.<sup>53</sup> This stereospecificity disappeared at room temperature, where both olefins gave the same mixture of products (about 78% of the *dl* pair and 22% of the meso compound), so the addition was still stereoselective but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical, of the type mentioned on p. 682:



<sup>50</sup>For reviews of these and other free-radical cyclization reactions, see RajanBabu *Acc. Chem. Res.* **1991**, *24*, 139-145; Beckwith *Rev. Chem. Intermed.* **1986**, *7*, 143-154; Giese *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, 1986, pp. 141-209; Surzur *React. Intermed. (Plenum)* **1982**, *2*, 121-295; Julia *Acc. Chem. Res.* **1972**, *4*, 386-392; *Pure Appl. Chem.* **1974**, *40*, 553-567, **1967**, *15*, 167-183; Nonhebel; Walton, *Ref.* **49**, pp. 533-544; Wilt, in Kochi, *Ref.* **49**, vol. 1, pp. 418-446. For a review of cyclizations in general, see Thebtaranonth; Thebtaranonth *Tetrahedron* **1990**, *46*, 1385-1489.

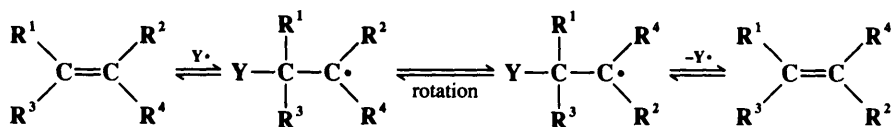
<sup>51</sup>Goering; Abell; Aycock *J. Am. Chem. Soc.* **1952**, *74*, 3588. See also LeBel; Czaja; DeBoer *J. Org. Chem.* **1969**, *34*, 3112.

<sup>52</sup>Skell; Allen *J. Am. Chem. Soc.* **1958**, *80*, 5997.

<sup>53</sup>Goering; Larsen *J. Am. Chem. Soc.* **1957**, *79*, 2653, **1959**, *81*, 5937. Also see Skell; Allen *J. Am. Chem. Soc.* **1959**, *81*, 5383; Skell; Freeman *J. Org. Chem.* **1964**, *29*, 2524.

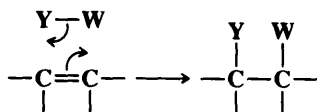
This species is similar to the bromonium ion that is responsible for stereospecific anti addition in the electrophilic mechanism. Further evidence for the existence of such bridged radicals was obtained by addition of  $\text{Br}^\bullet$  to olefins at 77 K. ESR spectra of the resulting species were consistent with bridged structures.<sup>54</sup>

For many radicals step 1 ( $\text{C}=\text{C} + \text{Y}^\bullet \rightarrow \bullet\text{C}-\text{C}-\text{Y}$ ) is reversible. In such cases free radicals can cause *cis*  $\rightarrow$  *trans* isomerization of a double bond by the pathway<sup>55</sup>



## Cyclic Mechanisms

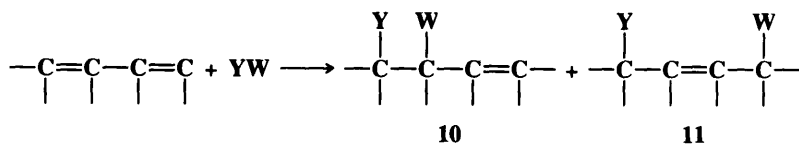
There are some addition reactions where the initial attack is not at one carbon of the double bond, but both carbons are attacked simultaneously. Some of these are four-center mechanisms, which follow this pattern:



In others there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be *syn*. The most important reaction of this type is the Diels-Alder reaction (5-47).

## Addition to Conjugated Systems

When electrophilic addition is carried out on a compound with two double bonds in conjugation, a 1,2-addition product (**10**) is often obtained, but in most cases there is also a 1,4-addition product (**11**), often in larger yield:<sup>55a</sup>



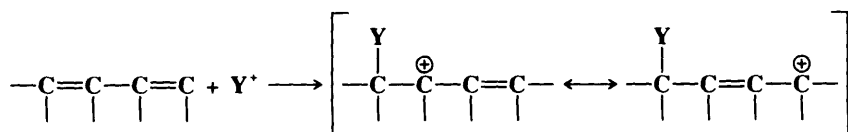
If the diene is unsymmetrical, there may be two 1,2-addition products. The competition between two types of addition product comes about because the carbocation resulting from

<sup>54</sup>Abell; Piette *J. Am. Chem. Soc.* **1962**, *84*, 916. See also Leggett; Kennerly; Kohl *J. Chem. Phys.* **1974**, *60*, 3264.

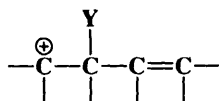
<sup>55</sup>Benson; Egger; Golden *J. Am. Chem. Soc.* **1965**, *87*, 468; Golden; Furuyama; Benson *Int. J. Chem. Kinet.* **1969**, *1*, 57.

<sup>55a</sup>For a review of electrophilic addition to conjugated dienes, see Khristov; Angelov; Petrov *Russ. Chem. Rev.* **1991**, *60*, 39-56.

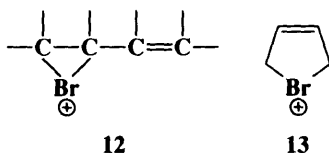
attack by  $Y^+$  is a resonance hybrid, with partial positive charges at the 2 and 4 positions:



$W^-$  may then attack either position. The original attack of  $Y^+$  is always at the end of the conjugated system because an attack at a middle carbon would give a cation unstabilized by resonance:



In the case of electrophiles like  $Br^+$ , which can form cyclic intermediates, both 1,2- and 1,4-addition products can be rationalized as stemming from an intermediate like **12**. Direct nucleophilic attack by  $W^-$  would give the 1,2-product, while the 1,4-product could be formed by attack at the 4 position, by an  $SN2'$ -type mechanism (see p. 329). Intermediates like **13**



have been postulated but ruled out for Br and Cl by the observation that chlorination or bromination of butadiene gives trans 1,4-products.<sup>56</sup> If an ion like **13** were the intermediate, the 1,4-products would have to have the cis configuration.

In most cases more 1,4- than 1,2-addition product is obtained. This may be a consequence of thermodynamic control of products, as against kinetic. In most cases, under the reaction conditions, **10** is converted to a mixture of **10** and **11** which is richer in **11**. That is, either isomer gives the same mixture of both, which contains more **11**. It was found that at low temperatures, butadiene and HCl gave only 20 to 25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4-product.<sup>57</sup> 1,2-Addition predominated over 1,4- in the reaction between DCl and 1,3-pentadiene, where the intermediate was the symmetrical (except for the D label)  $CH_3CH^+-CH-CHCH_2D$ .<sup>58</sup> Ion pairs were invoked to explain this result, since a free ion would be expected to be attacked by  $Cl^-$  equally well at both positions, except for the very small isotope effect.

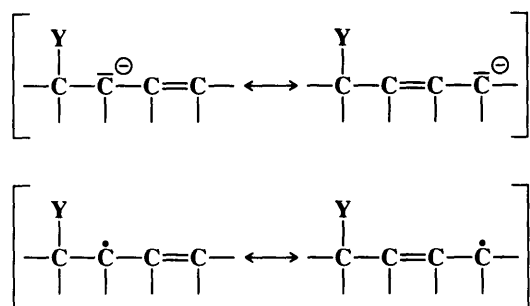
Addition to conjugated systems can also be accomplished by any of the other three mechanisms. In each case there is competition between 1,2 and 1,4 addition. In the case of

<sup>56</sup>Mislow; Hellman *J. Am. Chem. Soc.* **1951**, 73, 244; Mislow *J. Am. Chem. Soc.* **1953**, 75, 2512.

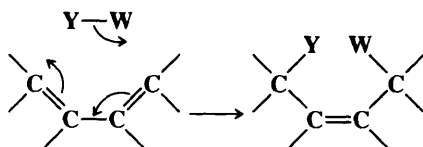
<sup>57</sup>Kharasch; Kritchevsky; Mayo *J. Org. Chem.* **1938**, 2, 489.

<sup>58</sup>Nordlander; Owuor; Haky *J. Am. Chem. Soc.* **1979**, 101, 1288.

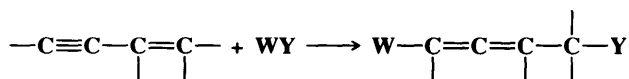
nucleophilic or free-radical attack,<sup>59</sup> the intermediates are resonance hybrids and behave



like the intermediate from electrophilic attack. Dienes can give 1,4 addition by a cyclic mechanism in this way:



Other conjugated systems, including trienes, enynes, diynes, etc., have been studied much less but behave similarly. 1,4 addition to enynes is an important way of making allenes:



## ORIENTATION AND REACTIVITY

### Reactivity

As with electrophilic aromatic substitution (Chapter 11), electron-donating groups increase the reactivity of a double bond toward electrophilic addition and electron-withdrawing groups decrease it. This is illustrated in Tables 15.1 and 15.2.<sup>60</sup> As a further illustration it may be mentioned that the reactivity toward electrophilic addition of a group of olefins increased in the order  $\text{CCl}_3\text{CH}=\text{CH}_2 < \text{Cl}_2\text{CHCH}=\text{CH}_2 < \text{ClCH}_2\text{CH}=\text{CH}_2 < \text{CH}_3\text{CH}_2=\text{CH}_2$ .<sup>61</sup> For nucleophilic addition the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being  $\text{F}_2\text{C}=\text{CF}_2$ <sup>62</sup> and  $(\text{NC})_2\text{C}=\text{C}(\text{CN})_2$ .<sup>63</sup> The effect of substituents is so great that it is

<sup>59</sup>For a review of free-radical addition to conjugated dienes, see Afanas'ev; Samokhvalov *Russ. Chem. Rev.* **1969**, 38, 318-329.

<sup>60</sup>Table 15.1 is from de la Mare *Q. Rev., Chem. Soc.* **1949**, 3, 126-145, p. 145. Table 15.2 is from Dubois; Mouvier *Tetrahedron Lett.* **1963**, 1325. See also Dubois; Mouvier *Bull. Soc. Chim. Fr.* **1968**, 1426; Grosjean; Mouvier; Dubois *J. Org. Chem.* **1976**, 41, 3869, 3872.

<sup>61</sup>Shelton; Lee *J. Org. Chem.* **1960**, 25, 428.

<sup>62</sup>For a review of additions to  $\text{F}_2\text{C}=\text{CF}_2$  and other fluoroolefins, see Chambers; Mobbs *Adv. Fluorine Chem.* **1965**, 4, 51-112.

<sup>63</sup>For reviews of additions to tetracyanoethylene, see Fatiadi *Synthesis* **1987**, 249-284, 749-789; Dhar *Chem. Rev.* **1967**, 67, 611-622.

**TABLE 15.1** Relative reactivity of some olefins toward bromine in acetic acid at 24°C<sup>60</sup>

Olefin	Relative rate
<b>PhCH=CH<sub>2</sub></b>	Very fast
<b>PhCH=CHPh</b>	18
<b>CH<sub>2</sub>=CHCH<sub>2</sub>Cl</b>	1.6
<b>CH<sub>2</sub>=CHCH<sub>2</sub>Br</b>	1.0
<b>PhCH=CHBr</b>	0.11
<b>CH<sub>2</sub>=CHBr</b>	0.0011

**TABLE 15.2** Relative reactivity of some olefins toward bromine in methanol<sup>60</sup>

Olefin	Relative rate
<b>CH<sub>2</sub>=CH<sub>2</sub></b>	$3.0 \times 10^1$
<b>CH<sub>3</sub>CH<sub>2</sub>CH=CH<sub>2</sub></b>	$2.9 \times 10^3$
<b>cis-CH<sub>3</sub>CH<sub>2</sub>CH=CHCH<sub>3</sub></b>	$1.3 \times 10^5$
<b>(CH<sub>3</sub>)<sub>2</sub>C=C(CH<sub>3</sub>)<sub>2</sub></b>	$2.8 \times 10^7$

possible to make the statement that *simple olefins do not react by the nucleophilic mechanism, and polyhalo or polycyano olefins do not generally react by the electrophilic mechanism*.<sup>64</sup> There are some reagents that attack only as nucleophiles, e.g., ammonia, and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example,  $F_2C=CF_2$  does not react with these. In still other cases, the same reagent reacts with a simple olefin by the electrophilic mechanism and with a polyhalo olefin by a nucleophilic mechanism. For example,  $Cl_2$  and  $HF$  are normally electrophilic reagents, but it has been shown that  $Cl_2$  adds to  $(NC)_2C=CHCN$  with initial attack by  $Cl^-$ <sup>65</sup> and that  $HF$  adds to  $F_2C=CClF$  with initial attack by  $F^-$ .<sup>66</sup> Compounds that have a double bond conjugated with a Z group (as defined on p. 741) nearly always react by a nucleophilic mechanism.<sup>67</sup> These are actually 1,4 additions, as discussed on p. 742. A number of studies have been made of the relative activating abilities of various Z groups.<sup>68</sup> On the basis of these studies, the following order of decreasing activating ability has been suggested:  $Z = NO_2, COAr, CHO, COR, SO_2Ar, CN, COOR, SOAr, CONH_2, CONHR$ .<sup>69</sup>

It seems obvious that electron-withdrawing groups enhance nucleophilic addition and inhibit electrophilic addition because they lower the electron density of the double bond. This is probably true, and yet similar reasoning does not always apply to a comparison between double and triple bonds.<sup>70</sup> There is a higher concentration of electrons between the carbons of a triple bond than in a double bond, and yet triple bonds are *less* subject to electrophilic attack and *more* subject to nucleophilic attack than double bonds.<sup>71</sup> This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds

<sup>64</sup>Such reactions can take place under severe conditions. For example, electrophilic addition could be accomplished with  $F_2C=CHF$  in super-acid solutions [Olah; *Mo J. Org. Chem.* **1972**, *37*, 1028] although  $F_2C=CF_2$  did not react under these conditions. For reviews of electrophilic additions to fluoroolefins, see Belen'kii; *German Sov. Sci. Rev. Sect. B* **1984**, *5*, 183-218; Dyatkin; Mochalina; Knunyants *Russ. Chem. Rev.* **1966**, *35*, 417-427; *Fluorine Chem. Rev.* **1969**, *3*, 45-71; Ref. 62, pp. 77-81.

<sup>65</sup>Dickinson; Wiley; McKusick *J. Am. Chem. Soc.* **1960**, *82*, 6132. For another example, see Atkinson; de la Mare; Larsen *J. Chem. Soc., Perkin Trans. 2* **1983**, 271.

<sup>66</sup>Miller; Fried; Goldwhite *J. Am. Chem. Soc.* **1960**, *82*, 3091.

<sup>67</sup>For a review of electrophilic reactions of such compounds, see Müllen; Wolf, in Patai; Rappoport, Ref. 37, pp. 513-558.

<sup>68</sup>See, for example, Friedman; Wall *J. Org. Chem.* **1966**, *31*, 2888; Ring; Tesoro; Moore *J. Org. Chem.* **1967**, *32*, 1091.

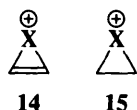
<sup>69</sup>Shenhav; Rappoport; Patai *J. Chem. Soc. B* **1970**, 469.

<sup>70</sup>For reviews of ionic additions to triple bonds, see, in Patai *The Chemistry of the Carbon-Carbon Triple Bond*; Wiley: New York, 1978, the articles by Schmid, pt. 1, pp. 275-341, and by Dickstein; Miller, pt. 2, pp. 813-955; Miller; Tanaka *Sel. Org. Transform.* **1970**, *1*, 143-238; Winterfeldt, in Viehe, Ref. 49, pp. 267-334. For comparisons of double and triple bond reactivity, see Melloni; Modena; Tonellato *Acc. Chem. Res.* **1981**, *14*, 227-233; Allen; Chiang; Kresge; Tidwell *J. Org. Chem.* **1982**, *47*, 775.

<sup>71</sup>For discussions, see Daniels; Bauer *J. Chem. Educ.* **1958**, *35*, 444; DeYoung; Ehrlich; Berliner *J. Am. Chem. Soc.* **1977**, *99*, 290; Strozier; Caramella; Houk *J. Am. Chem. Soc.* **1979**, *101*, 1340.

to the double bond.<sup>72</sup> In fact, all reagents that form bridged intermediates like **2** react faster with double than with triple bonds. On the other hand, addition of electrophilic  $H^+$  (acid-catalyzed hydration, **5-2**; addition of hydrogen halides, **5-1**) takes place at about the same rates for alkenes as for corresponding alkynes.<sup>73</sup> Furthermore, the presence of electron-withdrawing groups lowers the alkene/alkyne rate ratio. For example, while styrene  $PhCH=CH_2$  was brominated 3000 times faster than  $PhC\equiv CH$ , the addition of a second phenyl group ( $PhCH=CHPh$  vs.  $PhC\equiv CPh$ ) lowered the rate ratio to about 250.<sup>74</sup> In the case of *trans*- $MeOOCCH=CHCOOMe$  vs.  $MeOOC\equiv CCOOMe$ , the triple bond compound was actually brominated faster.<sup>75</sup>

Still, it is true that in general triple bonds are more susceptible to nucleophilic and less to electrophilic attack than double bonds, in spite of their higher electron density. One explanation is that the electrons in the triple bond are held more tightly because of the smaller carbon-carbon distance; it is thus harder for an attacking electrophile to pull out a pair. There is evidence from far-uv spectra to support this conclusion.<sup>76</sup> Another possible explanation has to do with the availability of the unfilled orbital in the alkyne. It has been shown that a  $\pi^*$  orbital of bent alkynes (such as cyclooctyne) has a lower energy than the  $\pi^*$  orbital of alkenes, and it has been suggested<sup>77</sup> that linear alkynes can achieve a bent structure in their transition states when reacting with an electrophile. Where electrophilic addition involves bridged-ion intermediates, those arising from triple bonds (**14**) are more strained than the corresponding **15** and furthermore are antiaromatic systems (see p. 56),



which **15** are not. This may be a reason why electrophilic addition by such electrophiles as  $Br$ ,  $I$ ,  $SR$ , etc., is slower for triple than for double bonds.<sup>78</sup> As might be expected, triple bonds connected to a  $Z$  group ( $C\equiv C-Z$ ) undergo nucleophilic addition especially well.<sup>79</sup>

Although alkyl groups in general increase the rates of electrophilic addition, we have already mentioned (p. 739) that there is a different pattern depending on whether the intermediate is a bridged ion or an open carbocation. For brominations and other electrophilic additions in which the first step of the mechanism is rate-determining, the rates for substituted alkenes correlate well with the ionization potentials of the alkenes, which means that steric effects are not important.<sup>80</sup> Where the second step is rate-determining [e.g., oxymercuration (**5-2**), hydroboration (**5-13**)], steric effects are important.<sup>80</sup>

Free-radical additions can occur with any type of substrate. The determining factor is the presence of a free-radical attacking species. Some reagents, e.g.,  $HBr$ ,  $RSH$ , attack by ionic mechanisms if no initiator is present, but in the presence of a free-radical initiator, the mechanism changes and the addition is of the free-radical type. Nucleophilic radicals

<sup>72</sup>Petrov *Russ. Chem. Rev.* **1960**, 29, 489-509.

<sup>73</sup>Melloni; Modena; Tonellato, *Ref.* 70, p. 228.

<sup>74</sup>Robertson; Dasent; Milburn; Oliver *J. Chem. Soc.* **1950**, 1628.

<sup>75</sup>Wolf; Ganguly; Berliner *J. Am. Chem. Soc.* **1985**, 50, 1053.

<sup>76</sup>Walsh *Q. Rev., Chem. Soc.* **1948**, 2, 73-91.

<sup>77</sup>Ng; Jordan; Krebs; Rüger *J. Am. Chem. Soc.* **1982**, 104, 7414.

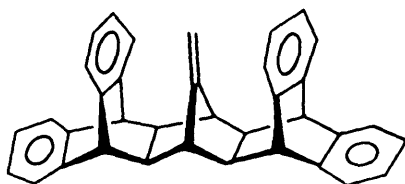
<sup>78</sup>Nevertheless, bridged ions **14** have been implicated in some additions to triple bonds. See, for example, Pincock; Yates, *Ref.* 14; Mauger; Berliner *J. Am. Chem. Soc.* **1972**, 94, 194; Bassi; Tonellato *J. Chem. Soc., Perkin Trans. 1* **1973**, 669; Schmid; Modro; Lenz; Garratt; Yates *J. Org. Chem.* **1976**, 41, 2331.

<sup>79</sup>For a review of additions to these substrates, see Winterfeldt *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 423-434 [*Angew. Chem.* 79, 389-400], *Newer Methods Prep. Org. Chem.* **1971**, 6, 243-279.

<sup>80</sup>Nelson; Cooper; Soundararajan *J. Am. Chem. Soc.* **1989**, 111, 1414; Nelson; Soundararajan *Tetrahedron Lett.* **1988**, 29, 6207.

(see p. 679) behave like nucleophiles in that the rate is increased by the presence of electron-withdrawing groups in the substrate. The reverse is true for electrophilic radicals.<sup>81</sup> However, nucleophilic radicals react with alkynes more slowly than with the corresponding alkenes,<sup>82</sup> which is contrary to what might have been expected.<sup>83</sup>

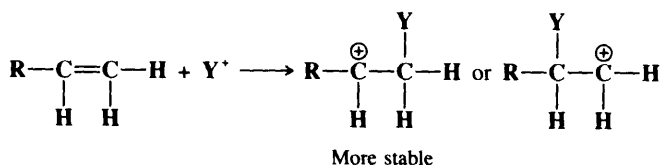
Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. The hydrocarbon **16**, in which the double bond is entombed

**16**

between the benzene rings, does not react with  $\text{Br}_2$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{O}_3$ ,  $\text{BH}_3$ ,  $\text{CBr}_2$ , or other reagents that react with most double bonds.<sup>84</sup> A similarly inactive compound is tetra-*t*-butylallene  $(t\text{-Bu})_2\text{C}=\text{C}=\text{C}(t\text{-Bu})_2$ , which is inert to  $\text{Br}_2$ ,  $\text{Cl}_2$ ,  $\text{O}_3$ , and catalytic hydrogenation.<sup>85</sup>

## Orientation

When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises: Which side of the reagent goes to which side of the double or triple bond? For electrophilic attack, the answer is given by *Markovnikov's rule: the positive portion of the reagent goes to the side of the double or triple bond that has more hydrogens*.<sup>86</sup> A number of explanations have been suggested for this regioselectivity, but the most probable is that  $\text{Y}^+$  adds to that side that will give the more stable carbocation. Thus, when an alkyl group is present, secondary carbocations are more stable than primary:



We may ask: How does  $\text{Y}^+$  "know" which side will give the more stable carbocation? As in the similar case of electrophilic aromatic substitution (p. 508), we invoke the Hammond postulate and say that the lower energy carbocation is preceded by the lower energy transition state. Markovnikov's rule also applies for halogen substituents because the halogen stabilizes

<sup>81</sup>For reviews of reactivity in free-radical additions, see Tedder *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 401-410 [*Angew. Chem.* 94, 433-442]; Tedder; Walton *Tetrahedron* **1980**, 36, 701-707.

<sup>82</sup>Giese; Lachhein *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 768 [*Angew. Chem.* 94, 780].

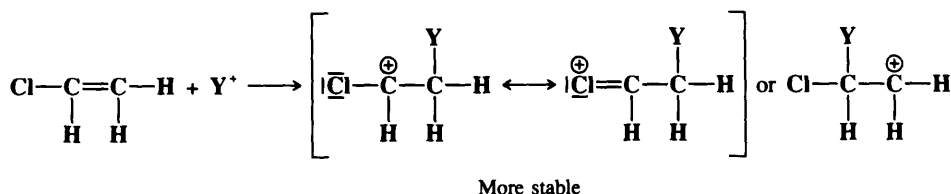
<sup>83</sup>For a discussion of reactivity and orientation of polar radicals, see Volovik; Dyadyusha; Staninets *J. Org. Chem. USSR* **1986**, 22, 1224.

<sup>84</sup>Butler; Gupta; Ng; Nyburg *J. Chem. Soc., Chem. Commun.* **1980**, 596.

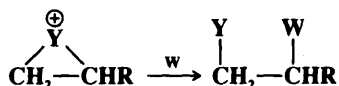
<sup>85</sup>Bolze; Eierdanz; Schlüter; Massa; Grahn; Berndt *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 924 [*Angew. Chem.* 94, 927].

<sup>86</sup>For discussions of Markovnikov's rule, see Isenberg; Grdinic *J. Chem. Educ.* **1969**, 46, 601; Grdinic; Isenberg, *Intra-Sci. Chem. Rep.* **1970**, 4, 145-162.

the carbocation by resonance:



Markovnikov's rule is also usually followed where bromonium ions or other three-membered rings are intermediates.<sup>87</sup> This means that in these cases attack by W must resemble the S<sub>N</sub>1 rather than the S<sub>N</sub>2 mechanism (see p. 369), though the overall stereospecific anti



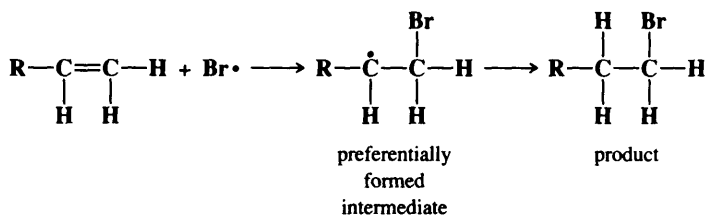
addition in these reactions means that the nucleophilic substitution step is taking place with inversion of configuration.

Olefins containing strong electron-withdrawing groups may violate Markovnikov's rule.

For example, attack at the Markovnikov position of  $\text{Me}_3\text{N}^+-\text{CH}=\text{CH}_2$  would give an ion with positive charges on adjacent atoms. The compound  $\text{CF}_3\text{CH}=\text{CH}_2$  has been reported to give electrophilic addition with acids in an anti-Markovnikov direction, but it has been shown<sup>88</sup> that, when treated with acids, this compound does not give simple electrophilic addition at all; the apparently anti-Markovnikov products are formed by other pathways.

For nucleophilic addition the direction of attack has been studied very little, except for Michael-type addition, with compounds of the type  $\text{C}=\text{C}-\text{Z}$ . Here the negative part of the reagent almost always attacks regioselectively at the carbon that does not carry the Z (see p. 742).

In free-radical addition<sup>89</sup> the main effect seems to be steric.<sup>90</sup> All substrates  $\text{CH}_2=\text{CHX}$  are preferentially attacked at the  $\text{CH}_2$ , regardless of the identity of X or of the attacking radical. With a reagent such as HBr, this means that the addition is anti-Markovnikov:



Thus the observed orientation in both kinds of HBr addition (Markovnikov electrophilic and anti-Markovnikov free radical) is caused by formation of the secondary intermediate.

<sup>87</sup>This has been graphically demonstrated by direct treatment of stabilized bromonium ions by nucleophiles: Dubois; Chréten J. *Am. Chem. Soc.* **1978**, *100*, 3506.

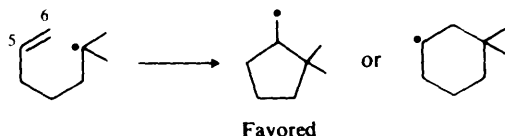
<sup>88</sup>Myhre; Andrews J. *Am. Chem. Soc.* **1970**, *92*, 7595, 7596. See also Newton J. *Chem. Educ.* **1987**, *64*, 531.

<sup>89</sup>For reviews of orientation in free-radical additions, see Tedder; Walton *Tetrahedron* **1980**, *36*, 701-707. *Adv. Phys. Org. Chem.* **1978**, *16*, 51-86. *Acc. Chem. Res.* **1976**, *9*, 183-191. See also Giese, Ref. 49; Tedder J. *Chem. Educ.* **1984**, *61*, 237.

<sup>90</sup>See, however, Riemenschneider; Bartels; Dornow; Drechsel-Grau; Eichel; Luthe; Matter; Michaelis; Boldt J. *Org. Chem.* **1987**, *52*, 205; Gleicher; Mahiou; Aretakis J. *Chem.* **1989**, *54*, 308.

In the electrophilic case it forms because it is more stable than the primary; in the free-radical case because it is sterically preferred. The stability order of the free-radical intermediates is also usually in the same direction:  $3^\circ > 2^\circ > 1^\circ$  (p. 188), but this factor is apparently less important than the steric factor. Internal olefins with no groups present to stabilize the radical usually give an approximately 1:1 mixture.

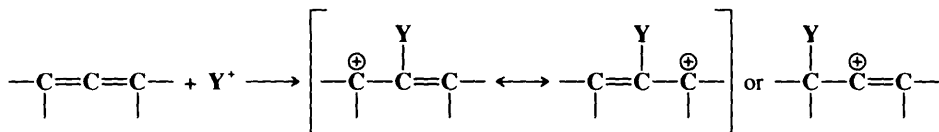
In *intramolecular* additions of radicals containing a 5,6 double bond,<sup>50</sup> both five- and six-membered rings can be formed, but in most cases<sup>91</sup> the five-membered rings are greatly preferred kinetically, even (as in the case shown) where five-membered ring closure means



generating a primary radical and six-membered ring closure a secondary radical. This phenomenon may be caused by more favorable entropy factors leading to a five-membered ring, as well as by stereoelectronic factors, but other explanations have also been offered.<sup>92</sup> Similar behavior is found when the double bond is in other positions (from the 3,4 to the 7,8 position). In each case the smaller ring (*Exo-Trig* addition) is preferred to the larger (*Endo-Trig* addition)<sup>93</sup> (see the Baldwin rules, p. 212). However, when a radical that is unsaturated in the 5,6 position contains an alkyl group in the 5 position, formation of the 6-membered ring is generally favored.<sup>94</sup>

For conjugated dienes, attack by a positive ion, a negative ion, or a free radical is almost always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more stable ion is formed. For example, isoprene  $\text{CH}_2=\text{CMeCH}=\text{CH}_2$ , treated with  $\text{HCl}$  gives only  $\text{Me}_2\text{CClCH}=\text{CH}_2$  and  $\text{Me}_2\text{C}=\text{CHCH}_2\text{Cl}$ , with none of the product arising from attack at the other end.  $\text{PhCH}=\text{CHCH}=\text{CH}_2$  gives only  $\text{PhCH}=\text{CHCHClCH}_3$  since it is the only one of the eight possible products that has a double bond in conjugation with the ring and that results from attack by  $\text{H}^+$  at an end of the conjugated system.

When allenes are attacked by electrophilic reagents,<sup>95</sup> Markovnikov's rule would predict that the attack should be at the end of the system, since there are no hydrogens in the middle. Attack at the center gives a carbocation stabilized by resonance, but not immediately.



<sup>91</sup>For an exception, see Wilt *Tetrahedron* **1985**, 41, 3979.

<sup>92</sup>For discussions, see Beckwith *Tetrahedron* **1981**, 37, 3073-3100; Verhoeven *Revl. Trav. Chim. Pays-Bas* **1980**, 99, 143. For molecular mechanics force-field approaches to this problem, see Beckwith; Schiesser *Tetrahedron* **1985**, 41, 3925; Spellmeyer; Houk *J. Org. Chem.* **1987**, 52, 959.

<sup>93</sup>See Beckwith; Easton; Serelis *J. Chem. Soc., Chem. Commun.* **1980**, 482.

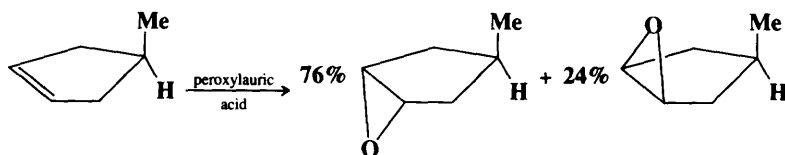
<sup>94</sup>See Chuang; Gallucci; Hart; Hoffman *J. Org. Chem.* **1988**, 53, 3218, and references cited therein.

<sup>95</sup>For a monograph on addition to allenes, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984. For reviews, see Pasto *Tetrahedron* **1984**, 40, 2805-2827; Smadja *Chem. Rev.* **1983**, 83, 263-320; in Landor *The Chemistry of Allenes*, vol. 2; Academic Press: New York, 1982, articles by Landor, Jacobs, and Hopf, pp. 351-577; Stang; Rappoport; Hanack; Subramanian, Ref. 34, pp. 152-167; Blake, in Patai *The Chemistry of Ketenes, Allenes and Related Compounds*, pt. 1; Wiley: New York, 1980; pp. 342-357; Modena; Tonellato, Ref. 34, pp. 215-231; Richey; Richey Ref. 34, pp. 917-922; Caserio *Sel. Org. Transform.* **1970**, 1, 239-299; Taylor *Chem. Rev.* **1967**, 67, 317-359, pp. 338-346; Mavrov; Kucherov *Russ. Chem. Rev.* **1967**, 36, 233-249; Griesbaum *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 933-946 [*Angew. Chem.* 78, 953-966].

In order for such stabilization to be in effect the three  $p$  orbitals must be parallel, and it requires a rotation about the C—C bond for this to happen.<sup>96</sup> Therefore, the stability of the allylic cation has no effect on the transition state, which still has a geometry similar to that of the original allene (p. 102). Probably because of this, attack on the unsubstituted  $\text{CH}_2=\text{C}=\text{CH}_2$  is most often at the end carbon, to give a vinylic cation, though center attack has also been reported. However, as alkyl or aryl groups are substituted on the allene carbons, attack at the middle carbon becomes more favorable because the resulting cation is stabilized by the alkyl or aryl groups (it is now a secondary, tertiary, or benzylic cation). For example, allenes of the form  $\text{RCH}=\text{C}=\text{CH}_2$  are still attacked most often at the end, but with  $\text{RCH}=\text{C}=\text{CHR}'$  center attack is more prevalent. Tetramethylallene is also attacked predominantly at the center carbon.<sup>97</sup> Free radicals<sup>98</sup> attack allenes most often at the end,<sup>99</sup> though attack at the middle has also been reported.<sup>100</sup> As with electrophilic attack and for the same reason, the stability of the allylic radical has no effect on the transition state of the reaction between a free radical and an allene. Again, as with electrophilic attack, the presence of alkyl groups increases the extent of attack by a radical at the middle carbon.<sup>101</sup>

## Stereochemical Orientation

It has already been pointed out that some additions are syn, with both groups, approaching from the same side, and that others are anti, with the groups approaching from opposite sides of the double or triple bond. For cyclic compounds there are further aspects of steric orientation. In syn addition to an unsymmetrical cyclic olefin, the two groups can come in from the more-hindered face or from the less-hindered face of the double bond. The rule is that syn addition is usually, though not always, from the less-hindered face. For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less-hindered and 24% from the more-hindered face.<sup>102</sup>



In anti addition to a cyclic substrate, the initial attack by the electrophile is also from the less-hindered face. However, many (though not all) electrophilic additions to norbornene and similar strained bicycloalkenes are syn additions.<sup>103</sup> In these cases attack is always from

<sup>96</sup>For evidence that this is so, see Okuyama; Izawa; Fueno *J. Am. Chem. Soc.* **1973**, 95, 6749.

<sup>97</sup>For example, see Bianchini; Guillemonat *Bull. Soc. Chim. Fr.* **1968**, 2120; Pittman *Chem. Commun.* **1969**, 122; Poutsma; Ibarbia *J. Am. Chem. Soc.* **1971**, 93, 440.

<sup>98</sup>For a review, see Jacobs, in Landor, Ref. 95, vol. 2, pp. 399-415.

<sup>99</sup>Griesbaum; Oswald; Quiram; Naegele *J. Org. Chem.* **1963**, 28, 1952.

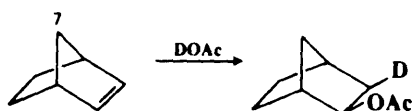
<sup>100</sup>See, for example, Pasto; L'Hermine *J. Org. Chem.* **1990**, 55, 685.

<sup>101</sup>For example, see Byrd; Caserio *J. Org. Chem.* **1972**, 37, 3881; Pasto; Warren; Morrison *J. Org. Chem.* **1981**, 46, 2837. See however Bartels; Boldt *Liebigs Ann. Chem.* **1981**, 40.

<sup>102</sup>Henbest; McCullough *Proc. Chem. Soc.* **1962**, 74.

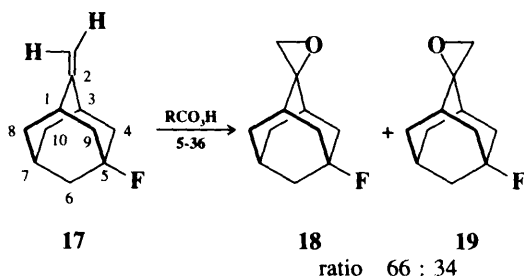
<sup>103</sup>For a discussion, see Traylor *Acc. Chem. Res.* **1969**, 2, 152-160.

the exo side, e.g.,<sup>104</sup>



unless the exo side is blocked by substituents in the 7 position, in which case endo attack may predominate; e.g., 7,7-dimethylnorbornene undergoes syn-endo epoxidation (**5-36**) and hydroboration<sup>105</sup> (**5-12**). However, addition of DCl and F<sub>3</sub>CCOOD to, and oxymercuration (**5-2**) of, 7,7-dimethylnorbornene proceed syn-exo in spite of the methyl groups in the 7 position.<sup>106</sup> Similarly, free-radical additions to norbornene and similar molecules are often syn-exo, though anti additions and endo attacks are also known.<sup>107</sup>

Electronic effects can also play a part in determining which face is attacked. In the adamantane derivative **17** steric effects are about the same for each face of the double bond. Yet epoxidation, dibromocarbene attack (**5-50**), and hydroboration (**5-12**) all predominantly



take place from the face that is syn to the electron-withdrawing fluorine.<sup>108</sup> In the case shown, about twice as much **18** was formed, compared to **19**. Similar results have been obtained on other substrates:<sup>109</sup> groups that are electron-withdrawing by the field effect ( $-I$ ) direct attack from the syn face;  $+I$  groups from the anti face, for both electrophilic and nucleophilic attack. These results are attributed<sup>110</sup> to hyperconjugation: For the adamantane case, there is overlap between the  $\sigma^*$  orbital of the newly-forming bond (between the attacking species and C-2 in **17**) and the filled  $\sigma$  orbitals of the C <sub>$\alpha$</sub> —C <sub>$\beta$</sub>  bonds on the opposite side. The four possible bonds are C-3—C-4 and C-1—C-9 on the syn side and C-3—C-10 and C-1—C-8 on the anti side. The preferred pathway is the one where the incoming group has the more electron-rich bonds on the side *opposite* to it (these are the ones it overlaps with). Since the electron-withdrawing F has its greatest effect on the bonds closest to it, the C-1—C-8 and C-3—C-10 bonds are more electron rich, and the group comes in on the face syn to the F.

<sup>104</sup>Cristol; Morrill; Sanchez *J. Org. Chem.* **1966**, *31*, 2719; Brown; Kawakami; Liu *J. Am. Chem. Soc.* **1970**, *92*, 5536; Alvernhe; Anker; Laurent; Haufe; Beguin *Tetrahedron* **1988**, *44*, 3551; Koga; Ozawa; Morokuma *J. Phys. Org. Chem.* **1990**, *3*, 519.

<sup>105</sup>Brown; Kawakami *J. Am. Chem. Soc.* **1970**, *92*, 201, 1990; Brown; Kawakami; Liu *J. Am. Chem. Soc.* **1973**, *95*, 2209.

<sup>106</sup>Brown; Liu *J. Am. Chem. Soc.* **1975**, *97*, 600, 2469; Brown; Kawakami *J. Am. Chem. Soc.* **1973**, *95*, 8665; Tidwell; Traylor *J. Org. Chem.* **1968**, *33*, 2614.

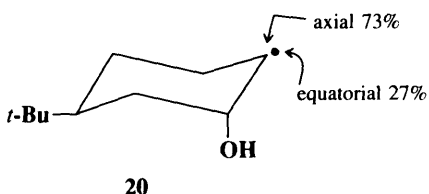
<sup>107</sup>For a review of free-radical addition to these systems, see Azovskaya; Prilezhaeva *Russ. Chem. Rev.* **1972**, *41*, 516-528.

<sup>108</sup>Srivastava; le Noble *J. Am. Chem. Soc.* **1987**, *109*, 5874. See also Bodepudi; le Noble *J. Am. Chem. Soc.* **1991**, *113*, 2001.

<sup>109</sup>Johnson; Tait; Cieplak *J. Am. Chem. Soc.* **1987**, *109*, 5875; Cieplak; Tait; Johnson *J. Am. Chem. Soc.* **1989**, *111*, 8447.

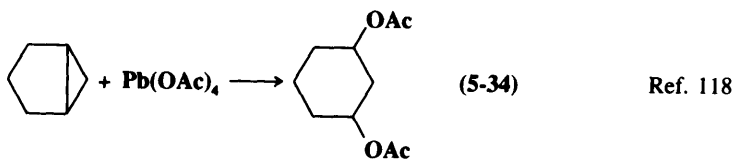
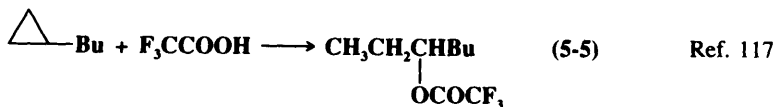
<sup>110</sup>Cieplak *J. Am. Chem. Soc.* **1981**, *103*, 4540. See also Jorgensen *Chemtracts: Org. Chem.* **1988**, *1*, 71.

It has been mentioned that additions of  $\text{Br}_2$  and  $\text{HOBr}$  are often anti because of formation of bromonium ions and that free-radical addition of  $\text{HBr}$  is also anti. When the substrate in any of these additions is a cyclohexene, the addition is not only anti but the initially formed product is conformationally specific too, being mostly diaxial.<sup>111</sup> This is so because diaxial opening of the three-membered ring preserves a maximum coplanarity of the participating centers in the transition state; indeed, on opening, epoxides also give diaxial products.<sup>112</sup> However, the initial diaxial product may then pass over to the diequatorial conformer unless other groups on the ring render the latter less stable than the former. In free-radical additions to cyclohexenes in which cyclic intermediates are not involved, the initial attack by the radical is also usually from the axial direction,<sup>113</sup> resulting in a diaxial initial product if the overall addition is anti. The direction from which unsymmetrical radicals attack has also been studied.<sup>114</sup> For example, when the radical **20** adds to a double bond it preferentially does so anti to the OH group, leading to a diaxial trans product.<sup>114</sup>



### Addition to Cyclopropane Rings<sup>115</sup>

We have previously seen (p. 152) that in some respects, cyclopropane rings resemble double bonds.<sup>116</sup> It is not surprising, therefore, that cyclopropanes undergo addition reactions analogous to those undergone by double-bond compounds, resulting in the opening of the three-membered rings, e.g. (the reaction numbers of the analogous addition reactions are given in parentheses),



<sup>111</sup>Barton, in *Theoretical Organic Chemistry, The Kekulé Symposium*; Butterworth: London, 1959, pp. 127-143; Goering; Abell; Aycok *J. Am. Chem. Soc.* **1952**, 74, 3588; Goering; Sims *J. Am. Chem. Soc.* **1955**, 77, 3465; Shoppee; Akhtar; Lack *J. Chem. Soc.* **1964**, 877; Readio; Skell *J. Org. Chem.* **1966**, 31, 753, 759.

<sup>112</sup>For example, see Anselmi; Berti; Catelani; Lecce; Monti *Tetrahedron* **1977**, 33, 2771.

<sup>113</sup>Huyser; Benson; Sinnige *J. Org. Chem.* **1967**, 32, 622; LeBel; Czaja; DeBoer, Ref. 51.

<sup>114</sup>For a review, see Giese *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 969-980 [*Angew. Chem.* **101**, 993-1004].

<sup>115</sup>For a review, see Charton, in *Zabicky The Chemistry of Alkenes*, vol 2.; Wiley: New York, 1970, pp. 569-592. For reviews of the use of cyclopropanes in organic synthesis, see Reissig *Top. Curr. Chem.* **1988**, 144, 73-135; Wong; Hon; Tse; Yip; Tanko; Hudlicky *Chem. Rev.* **1989**, 89, 165-198.

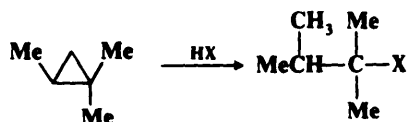
<sup>116</sup>The analogies are by no means complete: see Gordon *J. Chem. Educ.* **1967**, 44, 461.

<sup>117</sup>Peterson; Thompson *J. Org. Chem.* **1968**, 33, 968.

<sup>118</sup>Moon *J. Org. Chem.* **1964**, 39, 3456.

Other examples are discussed at 5-2, 5-11, and 5-49.

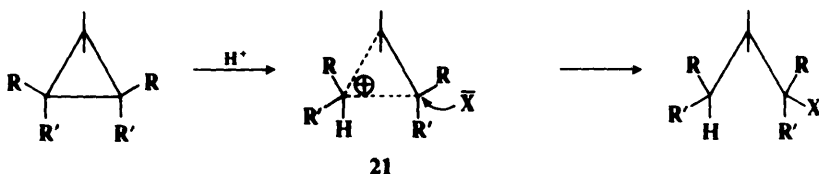
Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves electrophilic attack.<sup>119</sup> For substituted cyclopropanes, these reactions usually follow Markovnikov's rule, though exceptions are known and the degree of regioselectivity is often small. The application of Markovnikov's rule to these substrates can be illustrated by the reaction of 1,1,2-trimethylcyclopropane with HX.<sup>120</sup> The rule predicts that the electrophile (in this case H<sup>+</sup>)



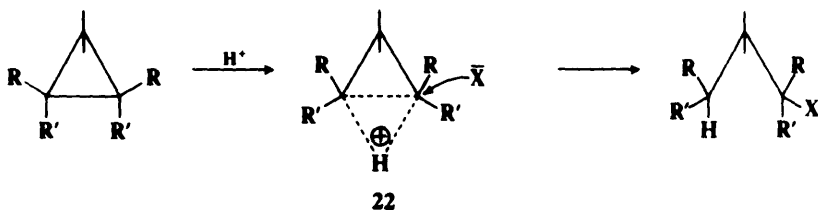
goes to the carbon with the most hydrogens and the nucleophile goes to the carbon that can best stabilize a positive charge (in this case the tertiary rather than the secondary carbon). The stereochemistry of the reaction can be investigated at two positions—the one that becomes connected to the electrophile and the one that becomes connected to the nucleophile. The results at the former position are mixed. Additions have been found to take place with 100% retention,<sup>121</sup> 100% inversion,<sup>122</sup> and with mixtures of retention and inversion.<sup>123</sup> At the carbon that becomes connected to the nucleophile the result is usually inversion, though retention has also been found,<sup>124</sup> and elimination, rearrangement, and racemization processes often compete, indicating that in many cases a positively charged carbon is generated at this position.

At least three mechanisms have been proposed for electrophilic addition (these mechanisms are shown for attack by HX, but analogous mechanisms can be written for other electrophiles).

#### Mechanism a



#### Mechanism b



<sup>119</sup>For a review, see DePuy *Top. Curr. Chem.* **1973**, *40*, 73-101. For a list of references to pertinent mechanistic studies, see Wiberg; Kass *J. Am. Chem. Soc.* **1985**, *107*, 988

<sup>120</sup>Kramer *J. Am. Chem. Soc.* **1970**, *92*, 4344.

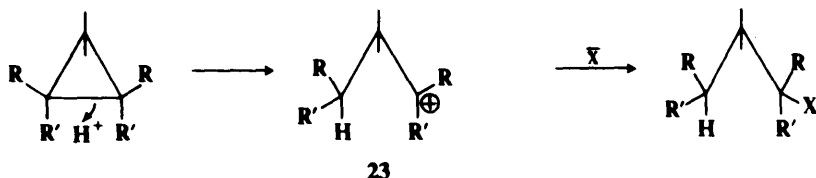
<sup>121</sup>For example, see DePuy; Breitbeil; DeBruin *J. Am. Chem. Soc.* **1966**, *88*, 3347; Hendrickson; Boeckman *J. Am. Chem. Soc.* **1969**, *91*, 3269.

<sup>122</sup>For example, see LaLonde; Ding; Tobias *J. Am. Chem. Soc.* **1967**, *89*, 6651; Warnet; Wheeler *Chem. Commun.* **1971**, 547; Hogeveen; Roobeek; Volger *Tetrahedron Lett.* **1972**, 221; Battiste; Mackiernan *Tetrahedron Lett.* **1972**, 4095. See also Jensen; Patterson; Dinizo *Tetrahedron Lett.* **1974**, 1315; Coxon; Steel; Whittington *J. Org. Chem.* **1990**, *55*, 4136.

<sup>123</sup>Nickon; Hammons *J. Am. Chem. Soc.* **1964**, *86*, 3322; Hammons; Probasco; Sanders; Whalen *J. Org. Chem.* **1968**, *33*, 4493; DePuy; Fünfschilling; Andrist; Olson *J. Am. Chem. Soc.* **1977**, *99*, 6297.

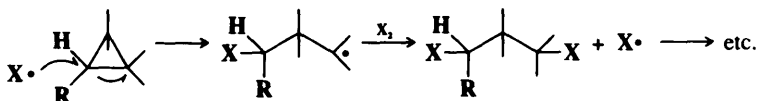
<sup>124</sup>Cristol; Lim; Dahl *J. Am. Chem. Soc.* **1970**, *92*, 4013; Hendrickson; Boeckman *J. Am. Chem. Soc.* **1971**, *93*, 4491.

## Mechanism c

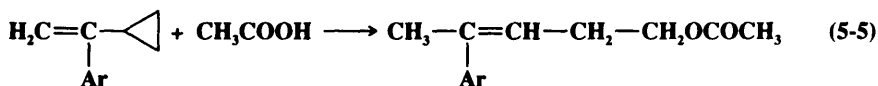


Mechanism *a* involves a corner-protonated cyclopropane<sup>125</sup> (**21**); we have already seen examples of such ions in the 2-norbornyl and 7-norbornenyl cations (pp. 321, 314). Mechanism *b* involves an edge-protonated cyclopropane (**22**). Mechanism *c* consists of a one-step S<sub>E</sub>2-type attack by H<sup>+</sup> to give the classical cation **23**, which then reacts with the nucleophile. Although the three mechanisms as we have drawn them show retention of configuration at the carbon that becomes attached to the proton, mechanisms *a* and *c* at least can also result in inversion at this carbon. Unfortunately, the evidence on hand at present does not allow us unequivocally to select any of these as the exclusive mechanism in all cases. Matters are complicated by the possibility that more than one edge-protonated cyclopropane is involved, at least in some cases. There is strong evidence for mechanism *b* with the electrophiles Br<sup>+</sup> and Cl<sup>+</sup>;<sup>126</sup> and for mechanism *a* with D<sup>+</sup> and Hg<sup>2+</sup>.<sup>127</sup> Ab initio studies show that the corner-protonated **21** is slightly more stable (about 1.4 kcal/mole, 6 kJ/mol) than the edge-protonated **22**.<sup>128</sup> There is some evidence against mechanism *c*.<sup>129</sup>

Free-radical additions to cyclopropanes have been studied much less, but it is known that Br<sub>2</sub> and Cl<sub>2</sub> add to cyclopropanes by a free-radical mechanism in the presence of uv light. The addition follows Markovnikov's rule, with the initial radical attacking the least-substituted carbon and the second group going to the most-substituted position. Several investigations have shown that the reaction is stereospecific at one carbon, taking place with inversion there, but nonstereospecific at the other carbon.<sup>130</sup> A mechanism that accounts for this behavior is<sup>131</sup>



In some cases conjugate addition has been performed on systems where a double bond is "conjugated" with a cyclopropyl ring. An example is<sup>132</sup>



<sup>125</sup>For reviews of protonated cyclopropanes, see Collins *Chem. Rev.* **1969**, 69, 543-550; Lee *Prog. Phys. Org. Chem.* **1970**, 7, 129-187.

<sup>126</sup>Coxon; Steel; Whittington; Battiste *J. Org. Chem.* **1989**, 54, 1383; Coxon; Steel; Whittington *J. Org. Chem.* **1989**, 54, 3702.

<sup>127</sup>Lambert; Chelius; Schulz; Carpenter *J. Am. Chem. Soc.* **1990**, 112, 3156; Lambert; Chelius; Bible; Hadju *J. Am. Chem. Soc.* **1991**, 113, 1331.

<sup>128</sup>Koch; Liu; Schleyer *J. Am. Chem. Soc.* **1989**, 111, 3479, and references cited therein.

<sup>129</sup>Wiberg; Kass, Ref. 119

<sup>130</sup>Maynes; Applequist *J. Am. Chem. Soc.* **1973**, 95, 856; Incremona; Upton *J. Am. Chem. Soc.* **1972**, 94, 301; Shea; Skell *J. Am. Chem. Soc.* **1973**, 95, 6728; Poutsma *J. Am. Chem. Soc.* **1965**, 87, 4293; Jarvis *J. Org. Chem.* **1970**, 35, 924; Upton; Incremona *J. Org. Chem.* **1976**, 41, 523.

<sup>131</sup>For free-radical addition to [1.1.1]propellane and bicyclo[1.1.0]butane, see Wiberg; Waddell; Laidig *Tetrahedron Lett.* **1966**, 27, 1553.

<sup>132</sup>Sarel; Ben-Shoshan *Tetrahedron Lett.* **1965**, 1053. See also Danishefsky *Acc. Chem. Res.* **1979**, 12, 66-72.

## REACTIONS

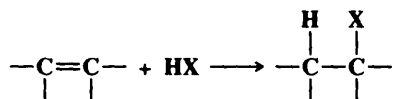
Reactions are classified by type of reagent. All reactions where hydrogen adds to one side of the double bond are treated first.

### Reactions in Which Hydrogen Adds to One Side

#### A. Halogen on the Other Side

##### 5-1 Addition of Hydrogen Halides

##### Hydro-halo-addition



Any of the four hydrogen halides can be added to double bonds.<sup>133</sup> HI, HBr, and HF<sup>134</sup> add at room temperature. The addition of HCl is more difficult and usually requires heat.<sup>22</sup> The reaction has been carried out with a large variety of double-bond compounds, including conjugated systems, where both 1,2 and 1,4 addition are possible. A convenient method for the addition of HF involves the use of a polyhydrogen fluoride-pyridine solution.<sup>135</sup> When the substrate is mixed with this solution in a solvent such as THF at 0°C, alkyl fluorides are obtained in moderate-to-high yields.

The addition of hydrogen halides to simple olefins, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with Markovnikov's rule.<sup>136</sup> When peroxides are added, the addition of HBr occurs by a free-radical mechanism and the orientation is anti-Markovnikov (p. 751).<sup>137</sup> It must be emphasized that this is true only for HBr. Free-radical addition of HF and HI has never been observed, even in the presence of peroxides, and of HCl only rarely. In the rare cases where free-radical addition of HCl was noted, the orientation was still Markovnikov, presumably because the more stable *product* was formed.<sup>138</sup> Free-radical addition of HF, HI, and HCl is energetically unfavorable (see the discussions on pp. 683, 693). It has often been found that anti-Markovnikov addition of HBr takes place even when peroxides have not been added. This happens because the substrate alkenes absorb oxygen from the air, forming small amounts of peroxides (4-9). Markovnikov addition can be ensured by rigorous purification of the substrate, but in practice this is not easy to achieve, and it is more common to add inhibitors, e.g., phenols or quinones, which suppress the free-radical pathway. The presence of free-radical precursors such as peroxides does not inhibit the ionic mechanism, but the radical reaction, being a chain process, is much more rapid than the electrophilic reaction. In most cases it is possible to control the mechanism (and hence the orientation) by adding peroxides

<sup>133</sup>For a list of references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 322-323.

<sup>134</sup>For reviews of addition of HF, see Sharts; Sheppard *Org. React.* **1974**, *21*, 125-406, pp. 192-198, 212-214; Hudlický *The Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976, pp. 36-41.

<sup>135</sup>Olah; Welch; Vankar; Nojima; Kerekes; Olah *J. Org. Chem.* **1979**, *44*, 3872. For related methods, see Yoneda; Abe; Fukuhara; Suzuki *Chem. Lett.* **1983**, 1135; Olah; Li *Synlett* **1990**, 267.

<sup>136</sup>For reviews of electrophilic addition of HX, see Ref. 22, and Dewar, Ref. 3.

<sup>137</sup>For reviews of free-radical addition of HX, see Thaler *Methods Free-Radical Chem.* **1969**, *2*, 121-227, pp. 182-195.

<sup>138</sup>Mayo *J. Am. Chem. Soc.* **1962**, *84*, 3964.

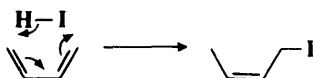
to achieve complete free-radical addition, or inhibitors to achieve complete electrophilic addition, though there are some cases where the ionic mechanism is fast enough to compete with the free-radical mechanism and complete control cannot be attained. Markovnikov addition of HBr, HCl, and HI has also been accomplished, in high yields, by the use of phase transfer catalysis.<sup>139</sup> For alternative methods of adding HBr (or HI) with anti-Markovnikov orientation, see 2-30.

It is also possible to add one<sup>140</sup> or two moles of any of the four hydrogen halides to triple bonds.

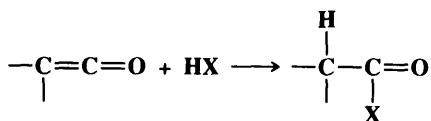


Markovnikov's rule ensures that *gem*-dihalides and not *vic*-dihalides are the products of the addition of two moles.

HX are electrophilic reagents, and many polyhalo and polycyano alkenes, e.g.,  $\text{Cl}_2\text{C=CHCl}$ , do not react with them at all in the absence of free-radical conditions. When such reactions do occur, however, they take place by a nucleophilic addition mechanism, i.e., initial attack is by  $\text{X}^-$ . This type of mechanism also occurs with Michael-type substrates  $\text{C=C—Z}$ ,<sup>141</sup> where the orientation is always such that the halogen goes to the carbon that does not bear the Z, so the product is of the form  $\text{X—C—CH—Z}$ , even in the presence of free-radical initiators. HI adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism:<sup>142</sup>



HX can be added to ketenes<sup>143</sup> to give acyl halides:

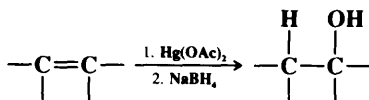


OS I, 166; II, 137, 336; III, 576; IV, 238, 543; VI, 273; VII, 59.

## B. Oxygen on the Other Side

### 5-2 Hydration of Double Bonds

#### Hydro-hydroxy-addition



<sup>139</sup>Landini; Rolla *J. Org. Chem.* **1980**, 45, 3527.

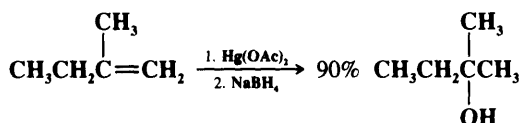
<sup>140</sup>For a convenient method of adding one mole of HCl or HBr to a triple bond, see Cousseau; Gouin *J. Chem. Soc., Perkin Trans. I* **1977**, 1797; Cousseau *Synthesis* **1980**, 805. For the addition of one mole of HI, see Kamiya; Chikami; Ishii *Synlett* **1990**, 675.

<sup>141</sup>For an example, see Marx *Tetrahedron* **1983**, 39, 1529.

<sup>142</sup>Gorton; Walsh *J. Chem. Soc., Chem. Commun.* **1972**, 782. For evidence that a pericyclic mechanism may be possible, even for an isolated double bond, see Sergeev; Stepanov; Leenson; Smirnov; Pupyshev; Tyurina; Mashyanov *Tetrahedron* **1982**, 38, 2585.

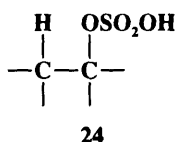
<sup>143</sup>For reviews of additions to ketenes, and their mechanisms, see Tidwell *Acc. Chem. Res.* **1990**, 23, 273-279; Seikaly; Tidwell *Tetrahedron* **1986**, 42, 2587-2613; Satchell; Satchell *Chem. Soc. Rev.* **1975**, 4, 231-250.

Olefins can be hydrated quickly under mild conditions in high yields without rearrangement products by the use of *oxymmercuration*<sup>144</sup> (addition of oxygen and mercury) followed by in situ treatment with sodium borohydride<sup>145</sup> (**2-24**). For example, 2-methyl-1-butene treated with mercuric acetate,<sup>146</sup> followed by NaBH<sub>4</sub>, gave 2-methyl-2-butanol:

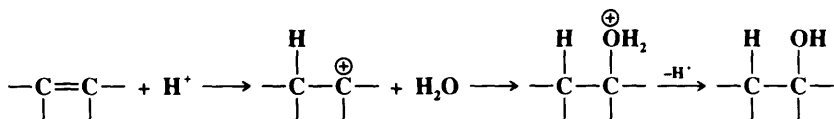


This method, which is applicable to mono-, di-, tri-, and tetraalkyl as well as phenyl-substituted olefins, gives almost complete Markovnikov addition. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate without, in general, causing difficulties.<sup>147</sup> When two double bonds are present in the same molecule, the use of ultrasound allows oxymmercuration of the less-substituted one without affecting the other.<sup>148</sup>

Double bonds can also be hydrated by treatment with water and an acid catalyst. The most common catalyst is sulfuric acid, but other acids, such as nitric or perchloric can also be used. The mechanism is electrophilic and begins with attack by a proton (see p. 739). The negative attacking species may be HSO<sub>4</sub><sup>-</sup> (or similar ion in the case of other acids) to give the initial product **24** which can be isolated, but under the conditions of the reaction,



is usually hydrolyzed to the alcohol (**0-4**). However, the conjugate base of the acid is not the only possible species that attacks the initial carbocation. The attack can also be by water:



When the reaction proceeds by this pathway, **24** and similar intermediates are not involved and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of E1 elimination of alcohols (**7-1**).<sup>149</sup> It is likely that the mechanism involves both pathways.

<sup>144</sup>For a monograph, see Larock *Solvation/Demercuration Reactions in Organic Synthesis*; Springer: New York, 1986. For reviews of this and other oxymetallation reactions, see Kitching *Organomet. React.* **1972**, *3*, 319-398; *Organomet. Chem. Rev.* **1968**, *3*, 61-134; Oullette, in Trahanovsky *Oxidation in Organic Chemistry*, pt. B; Academic Press: New York, 1973, pp. 140-166; House *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: New York, 1972, pp. 387-396; Zefirov *Russ. Chem. Rev.* **1965**, *34*, 527-536.

<sup>145</sup>Brown; Geoghegan *J. Am. Chem. Soc.* **1967**, *89*, 1522; *J. Org. Chem.* **1970**, *35*, 1844, **1972**, *37*, 1937; Brown; Geoghegan; Lynch; Kurek; *J. Org. Chem.* **1972**, *37*, 1941; Moon; Waxman *Chem. Commun.* **1967**, 1283; Moon; Takakis; Waxman *J. Org. Chem.* **1969**, *34*, 2951; Moon; Ganz; Waxman *Chem. Commun.* **1969**, 866; Johnson; Rickborn *Chem. Commun.* **1968**, 1073; Klein; Levene *Tetrahedron Lett.* **1969**, 4833; Chamberlain; Whitham *J. Chem. Soc. B* **1970**, 1382; Barrelle; Apparú *Bull. Soc. Chim. Fr.* **1972**, 2016.

<sup>146</sup>For a review of this reagent, see Butler, in Pizey *Synthetic Reagents*, vol. 4; Wiley: New York, 1981, pp. 1-145.

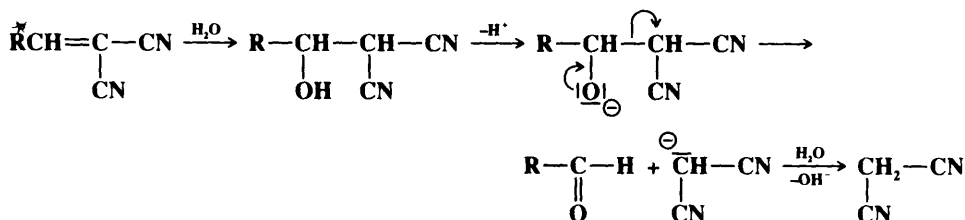
<sup>147</sup>See the extensive tables in Larock, Ref. 144, pp. 4-71.

<sup>148</sup>Einhorn; Einhorn; Luche *J. Org. Chem.* **1989**, *54*, 4479.

<sup>149</sup>For discussions of the mechanism, see Vinnik; Obratsov *Russ. Chem. Rev.* **1990**, *59*, 63-77; Liler *Reaction Mechanisms in Sulphuric Acid*; Academic Press: New York, 1971, pp. 210-225.

The initial carbocation occasionally rearranges to a more stable one. For example, hydration of  $\text{CH}_2=\text{CHCH}(\text{CH}_3)_2$  gives  $\text{CH}_3\text{CH}_2\text{COH}(\text{CH}_3)_2$ . With ordinary olefins the addition predominantly follows Markovnikov's rule. Another method for Markovnikov addition of water consists of simultaneously adding an oxidizing agent ( $\text{O}_2$ ) and a reducing agent (either  $\text{Et}_3\text{SiH}^{150}$  or a secondary alcohol such as 2-propanol<sup>151</sup>) to the olefin in the presence of a cobalt-complex catalyst. No rearrangement is observed with this method. The corresponding alkane and ketone are usually side products.

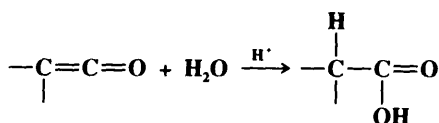
Water can be added indirectly, with anti-Markovnikov orientation, by treatment of the alkene with a 1:1 mixture of  $\text{PhCH}_2\text{NEt}_3^+ \text{BH}_4^-$  and  $\text{Me}_3\text{SiCl}$ , followed by addition of an aqueous solution of  $\text{K}_2\text{CO}_3$ .<sup>152</sup> For another method of anti-Markovnikov hydration, see 5-12. With substrates of the type  $\text{C}=\text{C}-\text{Z}$  ( $\text{Z}$  is as defined on p. 741) the product is almost always  $\text{HO}-\text{C}-\text{CH}-\text{Z}$  and the mechanism is usually nucleophilic,<sup>153</sup> though electrophilic addition gives the same product<sup>154</sup> since a cation  $\text{CH}-\overset{\oplus}{\text{C}}-\text{Z}$  would be destabilized by the positive charges (full or partial) on two adjacent atoms. However, the other product,  $\text{HC}-\text{CH}(\text{OH})\text{Z}$ , was obtained by treatment of the substrate with  $\text{O}_2$ ,  $\text{PhSiH}_3$ , and a manganese-complex catalyst.<sup>155</sup> When the substrate is of the type  $\text{RCH}=\text{CZZ}'$ , addition of water may result in cleavage of the adduct, to give an aldehyde and  $\text{CH}_2\text{ZZ}'$ , e.g.,<sup>156</sup>



The cleavage step is an example of **2-41**.

Conjugated dienes are seldom hydrated.

The addition of water to enol ethers causes hydrolysis to aldehydes or ketones (**0-6**). Ketenes add water to give carboxylic acids in a reaction catalyzed by acids:<sup>157</sup>



<sup>150</sup>Isayama; Mukaiyama *Chem. Lett.* **1989**, 569.

<sup>151</sup>Inoki; Kato; Takai; Isayama; Yamada; Mukaiyama *Chem. Lett.* **1989**, 515.

<sup>152</sup>Baskaran; Gupta; Chidambaram; Chandrasekaran *J. Chem. Soc., Chem. Commun.* **1989**, 903.

<sup>13</sup>For example, see Fedor; De; Gurwara *J. Am. Chem. Soc.* **1973**, *95*, 2905; Jensen; Hashtroudi *J. Org. Chem.* **1976**, *41*, 3299; Bernasconi; Leonarduzzi *J. Am. Chem. Soc.* **1982**, *104*, 5133, 5143.

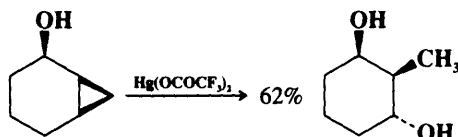
<sup>154</sup>For example, see Noyce; DeBruin *J. Am. Chem. Soc.* **1968**, *90*, 372.

<sup>155</sup>Inoki; Kato; Isayama; Mukaiyama *Chem. Lett.* **1990**, 1869.

<sup>156</sup>Bernasconi; Fox; Kanavarioti; Panda J. *Am. Chem. Soc.* **1986**, *108*, 2372; Bernasconi; Paschalis J. *Am. Chem. Soc.* **1989**, *111*, 5893, and other papers in this series.

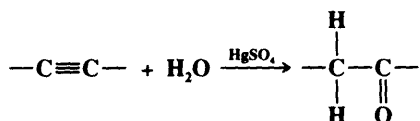
<sup>17</sup>For discussions of the mechanism, see Poon; Satchell *J. Chem. Soc., Perkin Trans. 2* **1983**, 1381; **1986**, 1485; Allen; Tidwell *J. Am. Chem. Soc.* **1987**, *109*, 2774; Allen; Stevenson; Tidwell *J. Org. Chem.* **1989**, *54*, 2843; Ref. 143.

The oxymercuration procedure (with mercuric trifluoroacetate) has been used to open cyclopropane rings, e.g.,<sup>158</sup>



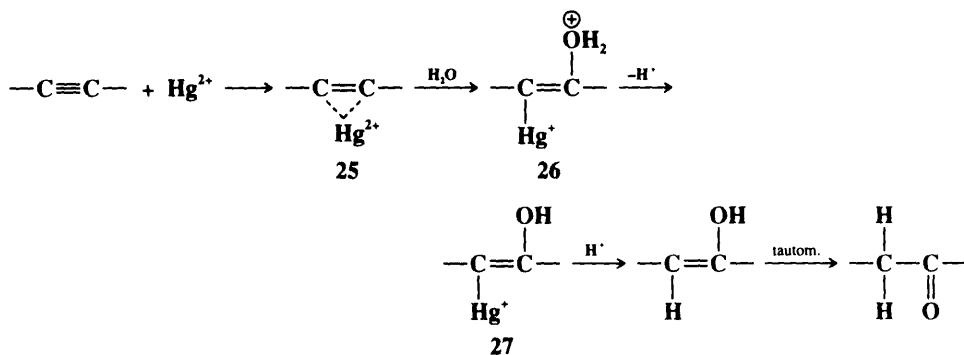
OS IV, 555, 560; VI, 766. Also see OS V, 818.

### 5-3 Hydration of Triple Bonds Dihydro-oxo-biaddition



The hydration of triple bonds is generally carried out with mercuric ion salts (often the sulfate or acetate) as catalysts.<sup>159</sup> Mercuric oxide in the presence of an acid is also a common reagent. Since the addition follows Markovnikov's rule, only acetylene gives an aldehyde. All other triple-bond compounds give ketones (for a method of reversing the orientation for terminal alkynes, see 5-12). With alkynes of the form  $\text{RC}\equiv\text{CH}$  methyl ketones are formed almost exclusively, but with  $\text{RC}\equiv\text{CR}'$  both possible products are usually obtained. The reaction can be conveniently carried out with a catalyst prepared by impregnating mercuric oxide onto Nafion-H (a superacidic perfluorinated resinsulfonic acid).<sup>160</sup>

The first step of the mechanism is formation of a complex (25) (ions like  $\text{Hg}^{2+}$  form complexes with alkynes—p. 80). Water then attacks in an  $\text{S}_\text{N}2$ -type process to give the intermediate 26, which loses a proton to give 27. Hydrolysis of 27 (an example of 2-24)



gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenylacetylene was hydrated photolytically.<sup>161</sup>

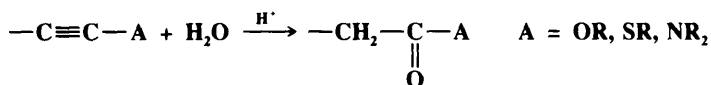
<sup>158</sup>Collum; Mohamadi; Hallock *J. Am. Chem. Soc.* **1983**, *105*, 6882; Collum; Still; Mohamadi *J. Am. Chem. Soc.* **1986**, *108*, 2094.

<sup>159</sup>For reviews, see Larock, Ref. 144, pp. 123-148; Khan; Martell *Homogeneous Catalysis by Metal Complexes*, vol. 2; Academic Press: New York, 1974, pp. 91-95. For a list of reagents, with references, see Ref. 133, pp. 596-597.

<sup>160</sup>Olah; Meidar *Synthesis* **1978**, 671.

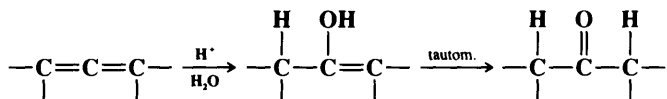
<sup>161</sup>Chiang; Kresge; Capponi; Wirz *Helv. Chim. Acta* **1986**, *69*, 1331.

Carboxylic esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,<sup>162</sup> and ynamines, without a mercuric catalyst.<sup>163</sup>



This is ordinary electrophilic addition, with rate-determining protonation as the first step.<sup>164</sup> Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts.<sup>165</sup> Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst.<sup>166</sup>

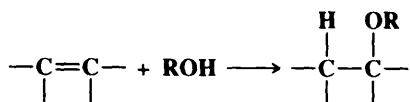
Allenes can also be hydrolyzed to ketones, with an acid catalyst.<sup>167</sup>



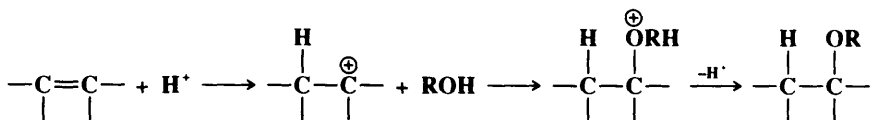
OS III, 22; IV, 13; V, 1024.

#### 5-4 Addition of Alcohols and Phenols

##### Hydro-alkoxy-addition



The addition of alcohols and phenols to double bonds is catalyzed by acids or bases. When the reactions are acid-catalyzed, the mechanism is electrophilic, with  $\text{H}^+$  as the attacking species. The resulting carbocation combines with a molecule of alcohol:



The addition, therefore, follows Markovnikov's rule. Primary alcohols give better results than secondary, and tertiary alcohols are very inactive. This is a convenient method for the preparation of tertiary ethers by the use of a suitable olefin such as  $\text{Me}_2\text{C}=\text{CH}_2$ .

For those substrates more susceptible to nucleophilic attack, e.g., polyhalo olefins and olefins of the type  $\text{C}=\text{C—Z}$ , it is better to carry out the reaction in basic solution, where the attacking species is  $\text{RO}^-$ .<sup>168</sup> The reactions with  $\text{C}=\text{C—Z}$  are of the Michael type, and OR goes to the side away from the Z. Since triple bonds are more susceptible to nucleophilic

<sup>162</sup>For a review of acetylenic ethers and thioethers, see Brandsma; Bos; Arens, in Viehe, Ref. 49, pp. 751-860.

<sup>163</sup>Arens *Adv. Org. Chem.* **1960**, 2, 163; Ref. 162, pp. 774-775.

<sup>164</sup>Hogeveen; Drenth *Recl. Trav. Chim. Pays-Bas* **1963**, 82, 375, 410; Verhelst; Drenth *J. Am. Chem. Soc.* **1974**, 96, 6692; Banait; Hojatti; Findlay; Kresge *Can. J. Chem.* **1987**, 65, 441.

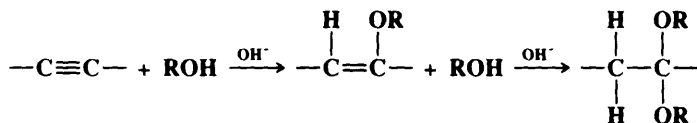
<sup>165</sup>See, for example, Noyce; Schiavelli *J. Org. Chem.* **1968**, 33, 845, *J. Am. Chem. Soc.* **1968**, 90, 1020, 1023.

<sup>166</sup>Menashe; Reshef; Shvo *J. Org. Chem.* **1991**, 56, 2912.

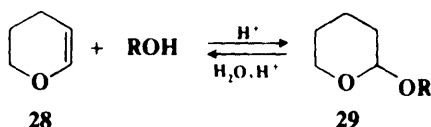
<sup>167</sup>For example, see Fedorova; Petrov *J. Gen. Chem. USSR* **1962**, 32, 1740; Mühlstadt; Graef *Chem. Ber.* **1967**, 100, 223; Cramer; Tidwell *J. Org. Chem.* **1981**, 46, 2683.

<sup>168</sup>For a review with respect to fluoroolefins, see Ref. 62, pp. 53-61.

attack than double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and enol ethers and acetals can be produced by this reaction:<sup>169</sup>



Because enol ethers are more susceptible than triple bonds to electrophilic attack, the addition of alcohols to enol ethers can also be catalyzed by acids.<sup>170</sup> One utilization of this reaction involves the compound dihydropyran (**28**), which is often used to protect the OH



groups of primary and secondary<sup>171</sup> alcohols and phenols.<sup>172</sup> The tetrahydropyranyl acetal formed by this reaction (**29**) is stable to bases, Grignard reagents,  $\text{LiAlH}_4$ , and oxidizing agents, any of which can be used to react with functional groups located within the R group. When the reactions are completed, **29** is easily cleaved by treatment with dilute acids (**0-6**). The addition of alcohols to enol ethers is also catalyzed by  $\text{CoCl}_2$ .<sup>173</sup>

In base-catalyzed addition to triple bonds the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions. Other catalysts, namely,  $\text{BF}_3$  and mercuric salts, have also been used in addition of ROH to triple bonds.

Alcohols can be added to certain double-bond compounds (cyclohexenes, cycloheptenes) photochemically<sup>174</sup> in the presence of a photosensitizer such as benzene. The mechanism is electrophilic and Markovnikov orientation is found. The olefins react in their first excited triplet states.<sup>175</sup>

The oxymercuration–demercuration procedure mentioned in 5-2 can be adapted to the preparation of ethers (Markovnikov orientation) if the oxymercuration is carried out in an alcohol ROH as solvent,<sup>176</sup> e.g., 2-methyl-1-butene in ethanol gives  $\text{EtMe}_2\text{COEt}$ .<sup>177</sup> Primary alcohols give good yields when mercuric acetate is used, but for secondary and tertiary alcohols it is necessary to use mercuric trifluoroacetate.<sup>178</sup> However, even with this reagent the method fails where the product would be a ditertiary ether. Alkynes generally give acetals. If the oxymercuration is carried out in the presence of a hydroperoxide instead of an alcohol, the product (after demercuration with  $\text{NaBH}_4$ ) is an alkyl peroxide (peroxymercuration).<sup>179</sup>

<sup>169</sup>For a review, see Shostakovskii; Trofimov; Atavin; Lavrov *Russ. Chem. Rev.* **1968**, 37, 907-919.

<sup>170</sup>For discussions of the mechanism, see Toullec; El-Alaoui; Bertrand *J. Chem. Soc., Perkin Trans. 2* **1987**, 1517; Kresge; Yin *J. Phys. Org. Chem.* **1989**, 2, 43.

<sup>171</sup>Tertiary alcohols can also be protected in this way if triphenylphosphine hydrobromide is used as a catalyst: Bolitt; Mioskowski; Shin; Falck *Tetrahedron Lett.* **1988**, 29, 4583.

<sup>172</sup>For useful catalysts for this reaction, some of which are also applicable to tertiary alcohols, see Miyashita; Yoshikoshi; Grieco *J. Org. Chem.* **1977**, 42, 3772; Olah; Husain; Singh *Synthesis* **1985**, 703; Johnston; Marston; Krieger; Goe *Synthesis* **1988**, 393.

<sup>173</sup>Iqbal; Srivastava; Gupta; Khan *Synth. Commun.* **1989**, 19, 901.

<sup>174</sup>For a review of the photochemical protonation of double and triple bonds, see Wan; Yates *Rev. Chem. Intermed.* **1984**, 5, 157-181.

<sup>175</sup>Marshall *Acc. Chem. Res.* **1969**, 2, 33-40.

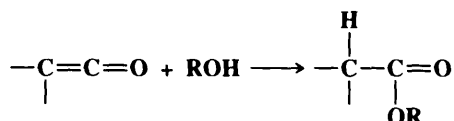
<sup>176</sup>For a review, with tables of many examples, see Larock, Ref. 144, pp. 162-345.

<sup>177</sup>Brown; Rei *J. Am. Chem. Soc.* **1969**, 91, 5646.

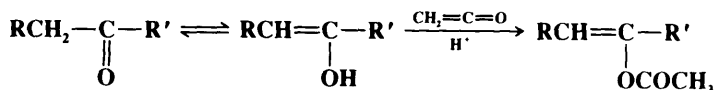
<sup>178</sup>Brown; Kurek; Rei; Thompson *J. Org. Chem.* **1984**, 49, 2551, **1985**, 50, 1171.

<sup>179</sup>Ballard; Bloodworth *J. Chem. Soc. C* **1971**, 945; Sokolov; Reutov *J. Org. Chem. USSR* **1969**, 5, 168. For a review, see Larock, Ref. 144, pp. 346-366.

Both alcohols and phenols add to ketenes to give carboxylic esters:<sup>180</sup>



This has been done intramolecularly (with the ketene end of the molecule generated and used in situ) to form medium- and large-ring lactones.<sup>181</sup> In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates:

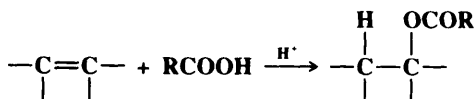


Alcohols can also add to olefins in a different way (see 5-22).

OS III, 371, 774, 813; IV, 184, 558; VI, 916; VII, 66, 160, 304, 334, 381; 67, 52; 69, 238.

## 5-5 Addition of Carboxylic Acids

### Hydro-acyloxy-addition



Carboxylic esters are produced by the addition of carboxylic acids to olefins, a reaction that is usually acid-catalyzed (by proton or Lewis acids<sup>182</sup>) and similar in mechanism to 5-4. Since Markovnikov's rule is followed, hard-to-get esters of tertiary alcohols can be prepared from olefins of the form  $\text{R}_2\text{C}=\text{CHR}$ .<sup>183</sup> When a carboxylic acid that contains a double bond in the chain is treated with a strong acid, the addition occurs internally and the product is a  $\gamma$ - and/or a  $\delta$ -lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double bond shifts (2-2).<sup>184</sup> The double bond always migrates to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. Carboxylic esters have also been prepared by the acyloxymercuration-demercuration of olefins (similar to the procedures mentioned in 5-2 and 5-4).<sup>185</sup>

Triple bonds can give enol esters or acylals when treated with carboxylic acids. Mercuric

<sup>180</sup>Quadbeck *Newer Methods Prep. Org. Chem.* **1963**, 2, 133-161. See also Chihara; Teratini; Ogawa *J. Chem. Soc., Chem. Commun.* **1981**, 1120. For discussions of the mechanism see Tille; Pracejus *Chem. Ber.* **1967**, 100, 196-210; Brady; Vaughn; Hoff *J. Org. Chem.* **1969**, 34, 843; Ref. 143; Jähme; Rüchardt *Tetrahedron Lett.* **1982**, 23, 4011; Poon; Satchell *J. Chem. Soc., Perkin Trans. 2* **1984**, 1083; **1985**, 1551.

<sup>181</sup>Boeckman; Pruitt *J. Am. Chem. Soc.* **1989**, 111, 8286.

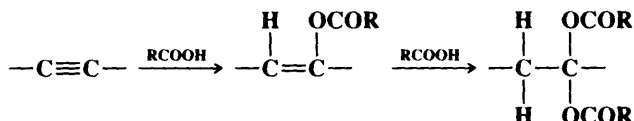
<sup>182</sup>See, for example, Guenzet; Camps *Bull. Soc. Chim. Fr.* **1973**, 3167, *Tetrahedron* **1974**, 30, 849; Ballantine; Davies; Purnell; Rayanakorn; Thomas; Williams *J. Chem. Soc., Chem. Commun.* **1981**, 8.

<sup>183</sup>See, for example, Peterson; Tao *J. Org. Chem.* **1964**, 29, 2322.

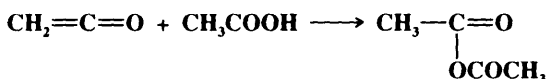
<sup>184</sup>For a review of such lactonizations, see Ansell; Palmer *Q. Rev., Chem. Soc.* **1964**, 18, 211-225.

<sup>185</sup>For a review, see Larock, Ref. 144, pp. 367-442.

salts are usually catalysts,<sup>186</sup> and vinylic mercury compounds  $\begin{array}{c} | \\ \text{---C=C---OCOR} \\ | \\ \text{HgX} \end{array}$  are intermediates.<sup>187</sup> Terminal alkynes  $\text{RC}\equiv\text{CH}$  react with  $\text{CO}_2$ , a secondary amine  $\text{R}_2\text{NH}$ , and a



ruthenium complex catalyst, to give enol carbamates  $\text{RCH}=\text{CHOC}(=\text{O})\text{NR}_2$ .<sup>188</sup> This reaction has also been performed intramolecularly, to produce unsaturated lactones.<sup>189</sup> With ketenes, carboxylic acids give anhydrides<sup>190</sup> and acetic anhydride is prepared industrially in this manner:



Carboxylic esters can also be obtained by the addition to olefins of diacyl peroxides.<sup>191</sup> These reactions are catalyzed by copper and are free-radical processes.

OS III, 853; IV, 261, 417, 444; V, 852, 863; VII, 30, 411. Also see OS I, 317.

## C. Sulfur on the Other Side

### 5-6 Addition of $\text{H}_2\text{S}$ and Thiols Hydro-alkylthio-addition



$\text{H}_2\text{S}$  and thiols add to olefins by electrophilic, nucleophilic, or free-radical mechanisms.<sup>192</sup> In the absence of initiators the addition to simple olefins is by an electrophilic mechanism, similar to that in 5-4, and Markovnikov's rule is followed. However, this reaction is usually very slow and often cannot be done or requires very severe conditions unless a proton or Lewis acid catalyst is used. For example, the reaction can be performed in concentrated

<sup>186</sup>For the use of rhodium complex catalysts, see Bianchini; Meli; Peruzzini; Zanobini; Bruneau; Dixneuf *Organometallics* **1990**, 9, 1155.

<sup>187</sup>See for example, Bach; Woodard; Anderson; Glick *J. Org. Chem.* **1982**, 47, 3707; Alekseeva; Chalov; Temkin *J. Org. Chem. USSR* **1983**, 19, 431; Bassetti; Floris *J. Org. Chem.* **1986**, 51, 4140, *J. Chem. Soc., Perkin Trans. 2* **1988**, 227; Grishin; Bazhenov; Ustynyuk; Zefirov; Kartashov; Sokolova; Skorobogatova; Chernov *Tetrahedron Lett.* **1988**, 29, 4631; Camps; Monthéard; Benzaid *Bull. Soc. Chim. Fr.* **1989**, 123. Ruthenium complexes have also been used as catalysts; Rotem; Shvo *Organometallics*, **1983**, 2, 1689; Rupp; Dixneuf *Tetrahedron Lett.* **1986**, 27, 6323; Mitsudo; Hori; Yamakawa; Watanabe *J. Org. Chem.* **1987**, 52, 2230.

<sup>188</sup>Mitsudo; Hori; Yamakawa; Watanabe *Tetrahedron Lett.* **1987**, 28, 4417; Mahé; Sasaki; Bruneau; Dixneuf *J. Org. Chem.* **1989**, 54, 1518.

<sup>189</sup>See, for example, see Sofia; Katzenellenbogen *J. Org. Chem.* **1985**, 50, 2331. For a list of other examples, see Ref. 133, p. 950.

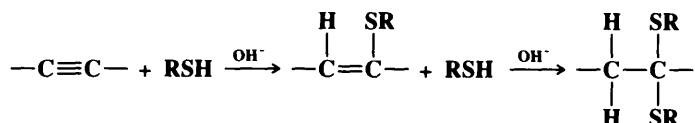
<sup>190</sup>For discussions of the mechanism, see Briody; Lillford; Satchell *J. Chem. Soc. B* **1968**, 885; Corriu; Guenzet; Camps; Rey *Bull. Soc. Chim. Fr.* **1970**, 3679; Blake; Vayjooee *J. Chem. Soc., Perkin Trans. 2* **1976**, 1533.

<sup>191</sup>Kharasch; Fono *J. Org. Chem.* **1959**, 24, 606; Kochi *J. Am. Chem. Soc.* **1962**, 84, 1572.

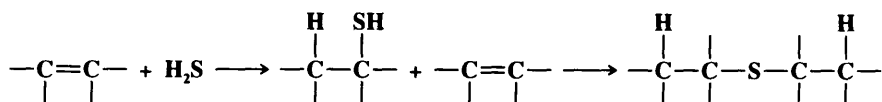
<sup>192</sup>For a review, see Wardell, In Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 169-178.

$\text{H}_2\text{SO}_4$ <sup>193</sup> or together with  $\text{AlCl}_3$ .<sup>194</sup> In the presence of free-radical initiators,  $\text{H}_2\text{S}$  and thiols add to double and triple bonds by a free-radical mechanism and the orientation is anti-Markovnikov.<sup>195</sup> In fact, the orientation can be used as a diagnostic tool to indicate which mechanism is operating. Free-radical addition can be done with  $\text{H}_2\text{S}$ ,  $\text{RSH}$  (R may be primary, secondary, or tertiary),  $\text{ArSH}$ , or  $\text{RCOSH}$ .<sup>196</sup> R may contain various functional groups. The olefins may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, COOH, COOR,  $\text{NO}_2$ ,  $\text{RSO}_2$ , etc. With alkynes it is possible to add 1 or 2 moles of  $\text{RSH}$ .

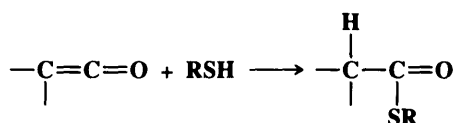
When thiols are added to substrates susceptible to nucleophilic attack, bases catalyze the reaction and the mechanism is nucleophilic. These substrates may be of the Michael type<sup>197</sup> or may be polyhalo olefins or alkynes.<sup>169</sup> As with the free-radical mechanism, alkynes can give either vinylic thioethers or dithioacetals:



By any mechanism, the initial product of addition of  $\text{H}_2\text{S}$  to a double bond is a thiol, which is capable of adding to a second molecule of olefin, so that sulfides are often produced:



Ketenes add thiols to give thiol esters:



OS III, 458; IV, 669; 65, 215. See also OS 69, 169.

<sup>193</sup>Shostakovskii; Kul'bovskaia; Gracheva; Laba; Yakushina *J. Gen. Chem. USSR* **1962**, 32, 707.

<sup>194</sup>Belley; Zamboni *J. Org. Chem.* **1989**, 54, 1230.

<sup>195</sup>For reviews of free-radical addition of  $\text{H}_2\text{S}$  and  $\text{RSH}$ , see Voronkov; Martynov; Mirskova *Sulfur Rep.* **1986**, 6, 77-95; Griesbaum *Angew. Chem. Int. Ed. Engl.* **1970**, 9, 273-287 [*Angew. Chem.* 82, 276-290]; Oswald; Griesbaum, in Kharasch; Meyers *Organic Sulfur Compounds*, vol. 2; Pergamon: Elmsford, NY, 1966, pp. 233-256; Stacey; Harris *Org. React.* **1963**, 13, 150-376, pp. 165-196, 247-324.

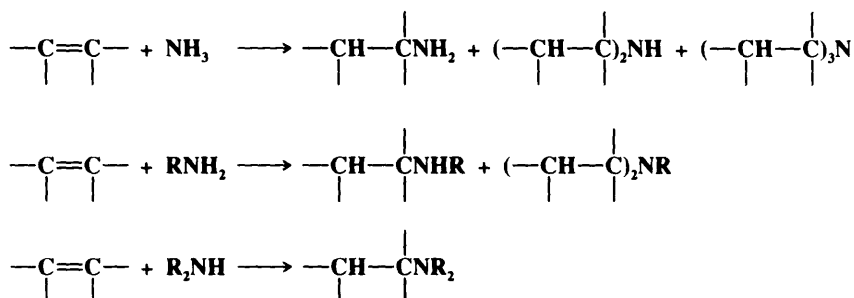
<sup>196</sup>For a review of the addition of thio acids, see Janssen, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 720-723.

<sup>197</sup>Michael substrates usually give the expected orientation. For a method of reversing the orientation for RS groups (the RS group goes  $\alpha$  to the  $\text{C}=\text{O}$  bond of a  $\text{C}=\text{C}-\text{C}=\text{O}$  system), see Gassman; Gilbert; Cole *J. Org. Chem.* **1977**, 42, 3233.

## D. Nitrogen on the Other Side

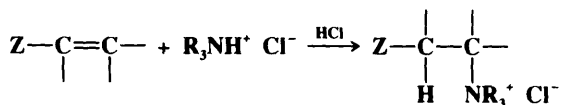
## 5-7 Addition of Ammonia and Amines

## Hydro-amino-addition



Ammonia and primary and secondary amines add to olefins that are susceptible to nucleophilic attack.<sup>198</sup> Ammonia gives three possible products, since the initial product is a primary amine, which may add to a second molecule of olefin, etc. Similarly, primary amines give both secondary and tertiary products. In practice it is usually possible to control which product predominates. Since ammonia and amines are much weaker acids than water, alcohols, and thiols (see 5-2, 5-4, 5-6) and since acids could hardly catalyze the reaction (because they would turn  $\text{NH}_3$  into  $\text{NH}_4^+$ ), this reaction does not occur by an electrophilic mechanism and so gives very low yields, if any, with ordinary olefins, unless extreme conditions are used (e.g., 178–200°C, 800–1000 atm, and the presence of metallic Na, for the reaction between  $\text{NH}_3$  and ethylene<sup>199</sup>). The mechanism is nearly always nucleophilic, and the reaction is generally performed on polyhalo olefins,<sup>200</sup> Michael-type substrates, and alkynes. As expected, on Michael-type substrates the nitrogen goes to the carbon that does not carry the Z. With substrates of the form  $\text{RCH}=\text{CZZ}'$ , the same type of cleavage of the adduct can take place as in 5-2.<sup>201</sup>

Other nitrogen compounds, among them hydroxylamine, hydrazines, amides ( $\text{RCONH}_2$  and  $\text{RCONHR}'$  including imides and lactams), and sulfonamides, also add to olefins. In the case of amides, basic catalysts are required, since amides are not good enough nucleophiles for the reaction and must be converted to  $\text{RCONH}^-$ . Even with amines, basic catalysts are sometimes used, so that  $\text{RNH}^-$  or  $\text{R}_2\text{N}^-$  is the actual nucleophile. Tertiary amines (except those that are too bulky) add to Michael-type substrates in a reaction that is catalyzed by acids like  $\text{HCl}$  or  $\text{HNO}_3$  to give the corresponding quaternary ammonium salts.<sup>202</sup>



The tertiary amine can be aliphatic, cycloalkyl, or heterocyclic (including pyridine).

<sup>198</sup>For reviews, see Gasc; Lattes; Périé *Tetrahedron* **1983**, 39, 703-731; Pines; Stalick *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*; Academic Press: New York, 1977, pp. 423-454; Suminov; Kost *Russ. Chem. Rev.* **1969**, 38, 884-899; Gibson, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 61-65.

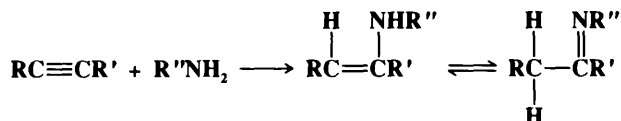
<sup>199</sup>Howk; Little; Scott; Whitman *J. Am. Chem. Soc.* **1954**, 76, 1899.

<sup>200</sup>For a review with respect to fluoroolefins, see Chambers; Mobbs *Adv. Fluorine Chem.* **1965**, 4, 51-112, pp. 62-68.

<sup>201</sup>See, for example, Bernasconi; Murray *J. Am. Chem. Soc.* **1986**, 108, 5251, 5257; Bernasconi; Bunnell *J. Org. Chem.* **1988**, 53, 2001.

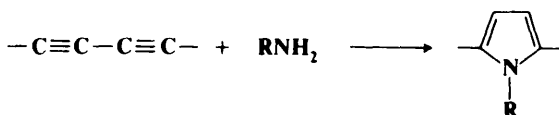
<sup>202</sup>Le Berre; Delacroix *Bull. Soc. Chim. Fr.* **1973**, 640, 647. See also Vogel; Büchi *Org. Synth.* 66, 29.

Primary amines add to triple bonds<sup>203</sup> to give enamines that have a hydrogen on the nitrogen and (analogously to enols) tautomerize to the more stable imines:



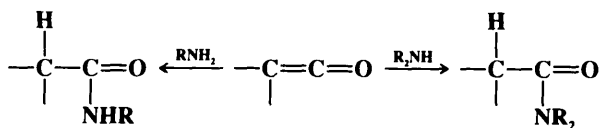
These are often stable enough for isolation.<sup>204</sup> When ammonia is used instead of a primary

amine, the corresponding  $\text{RCH}_2-\text{CR}'$  is not stable enough for isolation, but polymerizes. Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles:<sup>205</sup>

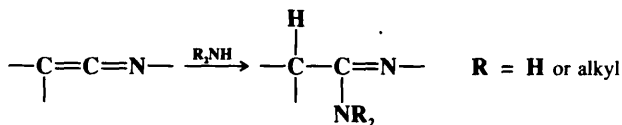


This is not 1,4 addition but 1,2 addition twice.

Primary and secondary amines add to ketenes to give, respectively, N-substituted and N,N-disubstituted amides:<sup>206</sup>



and to ketenimines to give amidines:<sup>207</sup>



Secondary amines can be added to certain nonactivated olefins if palladium(II) complexes are used as catalysts.<sup>208</sup> The complexation lowers the electron density of the double bond, facilitating nucleophilic attack.<sup>209</sup> Markovnikov orientation is observed and the addition is anti.<sup>210</sup>

<sup>203</sup>For a review of addition of ammonia and amines to triple bonds, see Chekulaeva; Kondrat'eva *Russ. Chem. Rev.* **1965**, 34, 669-680.

<sup>204</sup>For example, see Kruse; Kleinschmidt *J. Am. Chem. Soc.* **1961**, 83, 213, 216.

<sup>205</sup>Schulte; Reisch; Walker *Chem. Ber.* **1965**, 98, 98.

<sup>206</sup>For discussions of the mechanism of this reaction, see Briody; Satchell *Tetrahedron* **1966**, 22, 2649; Lillford; Satchell *J. Chem. Soc. B* **1967**, 360, **1968**, 54; Ref. 143.

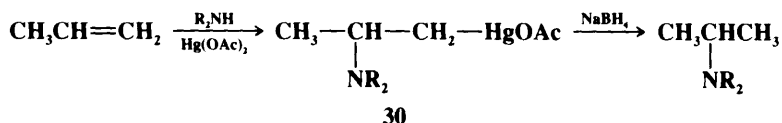
<sup>207</sup>Stevens; Freeman; Noll *J. Org. Chem.* **1965**, 30, 3718.

<sup>208</sup>See, for example, Walker; Manyik; Atkins; Farmer *Tetrahedron Lett.* **1970**, 3817; Takahashi; Miyake; Hata *Bull. Chem. Soc. Jpn.* **1972**, 45, 1183; Baker; Cook; Halliday; Smith *J. Chem. Soc., Perkin Trans. 2* **1974**, 1511; Hegedus; Allen; Waterman *J. Am. Chem. Soc.* **1976**, 98, 2674. For a review, see Gasc et al., Ref. 198. For a review of metal-catalyzed nucleophilic addition, see Bäckvall *Adv. Met.-Org. Chem.* **1989**, 1, 135-175.

<sup>209</sup>For a discussion of the mechanism, see Hegedus; Åkermark; Zetterberg; Olsson *J. Am. Chem. Soc.* **1984**, 106, 7122.

<sup>210</sup>Åkermark; Zetterberg *J. Am. Chem. Soc.* **1984**, 106, 5560.

$\text{NH}_3$  can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (5-12) followed by treatment with  $\text{NH}_2\text{Cl}$  or  $\text{NH}_2\text{OSO}_2\text{OH}$  (2-31). This produces a primary amine with anti-Markovnikov orientation. An indirect way of adding a primary or secondary amine to a double bond consists of aminomercuration followed by reduction (see 5-2 for the analogous oxymercuration-demercuration procedure), e.g.,<sup>211</sup>

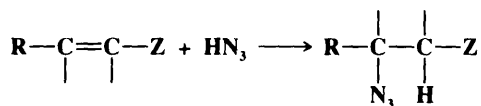


The addition of a secondary amine (shown above) produces a tertiary amine, while addition of a primary amine gives a secondary amine. The overall orientation follows Markovnikov's rule. Amido- and sulfamidomercuration-demercuration<sup>212</sup> and nitromercuration<sup>213</sup> have also been accomplished (see also 6-55). For conversion of **30** to other products, see 5-40 and 5-41.

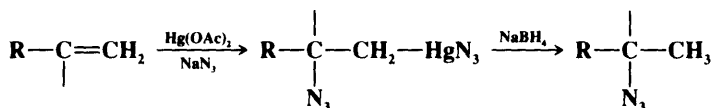
OS **I**, 196; **III**, 91, 93, 244, 258; **IV**, 146, 205; **V**, 39, 575, 929; **VI**, 75, 943; **66**, 29; **67**, 44, 48. See also OS **VI**, 932.

## 5-8 Addition of Hydrazoic Acid

### Hydro-azido-addition



Hydrazoic acid can be added to certain Michael-type substrates (Z is as defined on p. 741) to give  $\beta$ -azido compounds.<sup>214</sup> The reaction apparently fails if R is phenyl.  $\text{HN}_3$  also adds to enol ethers  $\text{CH}_2=\text{CHOR}$  to give  $\text{CH}_3-\text{CH}(\text{OR})\text{N}_3$ , and to silyl enol ethers,<sup>215</sup> but it does not add to ordinary alkenes unless a Lewis acid catalyst, such as  $\text{TiCl}_4$ , is used, in which case good yields of azide can be obtained.<sup>215</sup>  $\text{HN}_3$  can also be added indirectly to ordinary olefins by azidomercuration, followed by demercuration,<sup>216</sup> analogous to the similar



procedures mentioned in 5-2, 5-4, 5-5, and 5-7. The method can be applied to terminal alkenes or strained cycloalkenes (e.g., norbornene) but fails for unstrained internal alkenes.

<sup>211</sup>For a review, see Larock, Ref. 144, pp. 443-504. See also Barluenga; Percz-Prieto; Asensio *Tetrahedron* **1990**, 46, 2453.

<sup>212</sup>For a review, see Larock, Ref. 144, pp. 505-521.

<sup>213</sup>Bachman; Whitehouse *J. Org. Chem.* **1967**, 32, 2303. For a review, see Larock, Ref. 144, pp. 528-531.

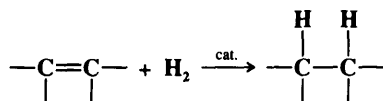
<sup>214</sup>Boyer *J. Am. Chem. Soc.* **1951**, 73, 5248; Harvey; Ratts *J. Org. Chem.* **1966**, 31, 3907. For a review, see Biffin; Miller; Paul, in Patai *The Chemistry of the Azido Group*; Wiley: New York, 1971, pp. 120-136.

<sup>215</sup>Hassner; Fibiger; Andisik *J. Org. Chem.* **1984**, 49, 4237.

<sup>216</sup>Heathcock *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 134 [*Angew. Chem.* 81, 148]. For a review, see Larock, Ref. 144, pp. 522-527.

## E. Hydrogen on Both Sides

### 5-9 Hydrogenation of Double and Triple Bonds<sup>217</sup> Dihydro-addition



Most carbon-carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.<sup>218</sup> Almost all known alkenes added hydrogen at temperatures between 0 and 275°C. Many functional groups may be present in the molecule, e.g., OH, COOH, NH<sub>2</sub>, CHO, COR, COOR, or CN. Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions under which double bonds can be reduced selectively<sup>219</sup> (see Table 19.2). The catalysts used can be divided into two broad classes, both of which mainly consist of transition metals and their compounds: (1) catalysts insoluble in the reaction medium (*heterogeneous catalysts*). Among the most effective are Raney nickel,<sup>220</sup> palladium-on-charcoal (perhaps the most common), NaBH<sub>4</sub>-reduced nickel<sup>221</sup> (also called nickel boride), platinum metal or its oxide, rhodium, ruthenium, and zinc oxide.<sup>222</sup> (2) Catalysts soluble in the reaction medium (*homogeneous catalysts*).<sup>223</sup> The most important is chlorotris(triphenylphosphine)rhodium RhCl(PH<sub>3</sub>)<sub>3</sub>,<sup>224</sup> (*Wilkinson's catalyst*),<sup>225</sup> which catalyzes the hydrogenation of many olefinic compounds without disturbing such groups as COOR, NO<sub>2</sub>, CN, or COR present in the same molecule.<sup>226</sup> Even unsaturated

<sup>217</sup>For a review, see Mitsui; Kasahara, in Zabicky, Ref. 115, vol. 2, pp. 175-214.

<sup>218</sup>For books on catalytic hydrogenation, see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; Červený *Catalytic Hydrogenation*; Elsevier: New York, 1986 (this book deals mostly with industrial aspects); Freifelder *Catalytic Hydrogenation in Organic Synthesis*; Wiley: New York, 1978. *Practical Catalytic Hydrogenation*; Wiley: New York, 1971; Augustine *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965. For reviews, see Parker, in Hartley *The Chemistry of the Metal-carbon Bond*, vol. 4; Wiley: New York, 1987, pp. 979-1047; Carruthers *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University Press: Cambridge, 1986, pp. 411-431; Colquhoun; Holton; Thompson; Twigg *New Pathways for Organic Synthesis*; Plenum: New York, 1984, pp. 266-300, 325-334; Kalinkin; Kolomnikova; Parnes; Kursanov *Russ. Chem. Rev.* **1979**, 48, 332-342; Candlin; Rennie, in Bentley; Kirby *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (vol. 4 of Weissberger *Techniques of Chemistry*), pt. 2; Wiley: New York, 1973, pp. 97-117; House, Ref. 144, pp. 1-34.

<sup>219</sup>For a discussion, see Rylander *Catalytic Hydrogenation over Platinum Metals*, Ref. 218, pp. 59-120.

<sup>220</sup>For a review of Raney nickel, see Pizey, Ref. 146, vol. 2, 1974, pp. 175-311. Double bonds have been reduced with Raney nickel alone; with no added H<sub>2</sub>. The hydrogen normally present in this reagent was sufficient: *Pojer Chem. Ind. (London)* **1986**, 177.

<sup>221</sup>Paul; Buisson; Joseph *Ind. Eng. Chem.* **1952**, 44, 1006; Brown *Chem. Commun.* **1969**, 952; *J. Org. Chem.* **1970**, 35, 1900. For a review of reductions with nickel boride and related catalysts, see Ganem; Osby *Chem. Rev.* **1986**, 86, 763-780.

<sup>222</sup>For reviews of hydrogenation with metal oxides, see Minachev; Khodakov; Nakhshunov *Russ. Chem. Rev.* **1976**, 45, 142-154; Kokes; Dent *Adv. Catal.* **1972**, 22, 1-50 (ZnO).

<sup>223</sup>For a monograph, see James *Homogeneous Hydrogenation*; Wiley: New York, 1973. For reviews, see Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987, pp. 523-564; Birch; Williamson *Org. React.* **1976**, 24, 1-186; James *Adv. Organomet. Chem.* **1979**, 17, 319-405; Harmon; Gupta; Brown *Chem. Rev.* **1973**, 73, 21-52; Strohmeier *Fortschr. Chem. Forsch.* **1972**, 25, 71-104; Heck *Organotransition Metal Chemistry*; Academic Press: New York, 1974, pp. 55-65; Rylander *Organic Syntheses with Noble Metal Catalysts*; Academic Press: New York, 1973, pp. 60-76; Lyons; Rennick; Burmeister *Ind. Eng. Chem., Prod. Res. Dev.* **1970**, 9, 2-20; Vol'pin; Kolomnikov *Russ. Chem. Rev.* **1969**, 38, 273-289.

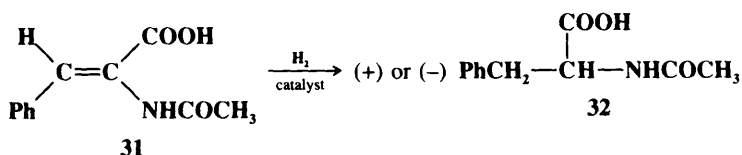
<sup>224</sup>Young; Osborn; Jardine; Wilkinson *Chem. Commun.* **1965**, 131; Osborn; Jardine; Young; Wilkinson *J. Chem. Soc. A* **1966**, 1711; Osborn; Wilkinson *Inorg. Synth.* **1967**, 10, 67; Biellmann *Bull. Soc. Chim. Fr.* **1968**, 3055; van Bekkum; van Rantwijk; van de Putte *Tetrahedron Lett.* **1969**, 1.

<sup>225</sup>For a review of Wilkinson's catalyst, see Jardine, *Prog. Inorg. Chem.* **1981**, 28, 63-202.

<sup>226</sup>Harmon; Parsons; Cooke; Gupta; Schoonenberg *J. Org. Chem.* **1969**, 34, 3684. See also Mohrig; Dabora; Foster; Schultz *J. Org. Chem.* **1984**, 49, 5179.

aldehydes can be reduced to saturated aldehydes,<sup>227</sup> though in this case decarbonylation (4-41) may be a side reaction. Among other homogeneous catalysts are chlorotris(triphenylphosphine)hydridoruthenium(II)  $(\text{Ph}_3\text{P})_3\text{RuClH}$ ,<sup>228</sup> which is specific for terminal double bonds (other double bonds are hydrogenated slowly or not at all), and pentacyanocobaltate(II)  $\text{Co}(\text{CN})_5^{3-}$ , which is effective for double and triple bonds only when they are part of conjugated systems<sup>229</sup> (the conjugation may be with  $\text{C}=\text{C}$ ,  $\text{C}=\text{O}$ , or an aromatic ring). Homogeneous catalysts often have the advantages of better catalyst reproducibility and better selectivity. They are also less susceptible to catalyst poisoning<sup>230</sup> (heterogeneous catalysts are usually poisoned by small amounts of sulfur, often found in rubber stoppers, or by sulfur-containing compounds such as thiols and sulfides).<sup>231</sup> On the other hand, heterogeneous catalysts are usually easier to separate from the reaction mixture.

Optically active homogeneous (as well as heterogeneous) catalysts have been used to achieve partially asymmetric (enantioselective) hydrogenations of certain prochiral substrates.<sup>232</sup> For example,<sup>233</sup> hydrogenation of **31** with a suitable catalyst gives (+) or (–) **32**



(depending on which enantiomer of the catalyst is used) with an enantiomeric excess as high as 96%.<sup>234</sup> Prochiral substrates that give such high optical yields generally contain functional groups similar to those in **31**.<sup>235</sup> The catalyst in such cases<sup>236</sup> is usually a ruthenium- or rhodium-phosphine in which the phosphine is optically active either because of an asymmetric phosphorus atom, e.g., **33**,<sup>237</sup> or because of a chiral group connected to the phosphorus,

<sup>227</sup>Jardine; Wilkinson *J. Chem. Soc. C* **1967**, 270.

<sup>228</sup>Hallman; Evans; Osborn; Wilkinson *Chem. Commun.* **1967**, 305; Hallman; McGarvey; Wilkinson *J. Chem. Soc. A* **1968**, 3143; Jardine; McQuillin *Tetrahedron Lett.* **1968**, 5189.

<sup>229</sup>Kwiatek; Mador; Seyler *J. Am. Chem. Soc.* **1962**, 84, 304; Jackman; Hamilton; Lawlor *J. Am. Chem. Soc.* **1968**, 90, 1914; Funabiki; Matsumoto; Tarama *Bull. Chem. Soc. Jpn.* **1972**, 45, 2723; Reger; Habib; Fauth *Tetrahedron Lett.* **1979**, 115.

<sup>230</sup>Birch *Tetrahedron Lett.* **1967**, 1935.

<sup>231</sup>For a review of catalyst poisoning by sulfur, see Barbier; Lamy-Pitara; Marecot; Boitiaux; Cosyns; Verna *Adv. Catal.* **1990**, 37, 279-318.

<sup>232</sup>For reviews, see, in Morrison *Asymmetric Synthesis*, vol. 5; Academic Press: New York, 1985, the reviews by Halpern, pp. 41-69; Koenig, pp. 71-101; Harada, pp. 345-383; Ojima; Clos; Bastos *Tetrahedron* **1989**, 45, 6901-6939, pp. 6902-6916; Jardine, in Hartley, Ref. 218, pp. 751-775; Nógrádi *Stereoselective Synthesis*; VCH: New York, 1986, pp. 53-87; Knowles *Acc. Chem. Res.* **1983**, 16, 106-112; Brunner *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 897-907 [*Angew. Chem.* 95, 921-931]; Klabunovskii *Russ. Chem. Rev.* **1982**, 51, 630-643; Čaplar; Comisso; Šunjić *Synthesis* **1981**, 85-116; Morrison; Masler; Neuberger *Adv. Catal.* **1976**, 25, 81-124; Kagan *Pure Appl. Chem.* **1975**, 43, 401-421; Bogdanović *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 954-964 [*Angew. Chem.* 85, 1013-1023]. See also Ref. 94 in Chapter 4.

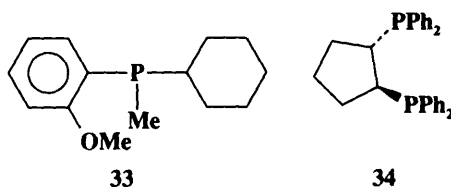
<sup>233</sup>For some other recent examples, see Hayashi; Kawamura; Ito *Tetrahedron Lett.* **1988**, 29, 5969; Muramatsu; Kawano; Ishii; Saburi; Uchida *J. Chem. Soc., Chem. Commun.* **1989**, 769; Amrani; Lecomte; Sinou; Bakos; Toth; Heil *Organometallics* **1989**, 8, 542; Yamamoto; Ikeda; Lin *J. Organomet. Chem.* **1989**, 370, 319; Waymouth; Pino *J. Am. Chem. Soc.* **1990**, 112, 4911; Ohta; Takaya; Noyori *Tetrahedron Lett.* **1990**, 31, 7189; Ashby; Halpern *J. Am. Chem. Soc.* **1991**, 113, 589; Heiser; Broger; Cramer *Tetrahedron: Asymmetry* **1991**, 2, 51; Burk *J. Am. Chem. Soc.* **1991**, 113, 8518.

<sup>234</sup>Koenig, in Morrison, Ref. 232, p. 74.

<sup>235</sup>For tables of substrates that have been enantioselectively hydrogenated, see Koenig, in Morrison, Ref. 232, pp. 83-101.

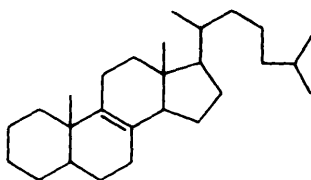
<sup>236</sup>For a list of these, with references, see Ref. 133, p. 7. For reviews of optically active nickel catalysts, see Izumi *Adv. Catal.* **1983**, 32, 215-271. *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 871-881 [*Angew. Chem.* 83, 956-966]. For a review of the synthesis of some of these phosphines, see Mortreux; Petit; Buono; Peiffer *Bull. Soc. Chim. Fr.* **1987**, 631-639.

<sup>237</sup>Knowles; Sabacky; Vineyard *J. Chem. Soc., Chem. Commun.* **1972**, 10. See also Vineyard; Knowles; Sabacky; Bachman; Weinkauff *J. Am. Chem. Soc.* **1977**, 99, 5946.



e.g., **34**.<sup>238</sup> Other types of catalysts, for example, titanocenes with chiral cyclopentadienyl ligands, have given enantioselective hydrogenation of olefins that lack functional groups such as COOH or NHCOCH<sub>3</sub>, for example, 2-phenyl-1-butene.<sup>239</sup> Enantioselective reduction of certain olefins has also been achieved by reducing with baker's yeast.<sup>240</sup>

Hydrogenations in most cases are carried out at room temperature and just above atmospheric pressure, but some double bonds are more resistant and require higher temperatures and pressures. The resistance is usually a function of increasing substitution and is presumably caused by steric factors. Trisubstituted double bonds require, say, 25°C and 100 atm, while tetrasubstituted double bonds may require 275°C and 1000 atm. Among the double bonds most difficult to hydrogenate or which cannot be hydrogenated at all are those common to two rings, as in the steroid shown. Hydrogenations, even at about atmospheric



pressure, are ordinarily performed in a special hydrogenator, but this is not always necessary. Both the catalyst and the hydrogen can be generated in situ, by treatment of H<sub>2</sub>PtCl<sub>6</sub> or RhCl<sub>3</sub> with NaBH<sub>4</sub>;<sup>241</sup> ordinary glassware can then be used. The great variety of catalysts available often allows an investigator to find one that is highly selective. For example, the catalyst Pd(salen) encapsulated in zeolites permitted the catalytic hydrogenation of 1-hexene in the presence of cyclohexene.<sup>242</sup>

Although catalytic hydrogenation is the method most often used, double bonds can be reduced by other reagents, as well. Among these are sodium in ethanol, sodium and *t*-butyl alcohol in HMPA,<sup>243</sup> lithium and aliphatic amines<sup>244</sup> (see also **5-10**), chromous ion,<sup>245</sup> zinc and acids, sodium hypophosphate and Pd-C,<sup>246</sup> (EtO)<sub>3</sub>SiH-Pd(OAc)<sub>2</sub>,<sup>247</sup> trifluoroacetic acid

<sup>238</sup> Allen; Gibson; Green; Skinner; Bashkin; Grebenik *J. Chem. Soc., Chem. Commun.* **1983**, 895.

<sup>239</sup> Halterman; Vollhardt; Welker; Bläser; Boese *J. Am. Chem. Soc.* **1987**, 109, 8105.

<sup>240</sup> See, for example, Gramatica; Manitto; Monti; Speranza *Tetrahedron* **1988**, 44, 1299; Ohta; Kobayashi; Ozaki *J. Org. Chem.* **1989**, 54, 1802. For reviews of baker's yeast, see Csuk; Glänzer *Chem. Rev.* **1991**, 91, 49-97; Servi *Synthesis* **1990**, 1-25.

<sup>241</sup> Brown; Sivasankaran *J. Am. Chem. Soc.* **1962**, 84, 2828; Brown; Brown *J. Am. Chem. Soc.* **1962**, 84, 1494, 1945, 2829, *J. Org. Chem.* **1966**, 31, 3989.

<sup>242</sup> Kowalak; Weiss; Balkus *J. Chem. Soc., Chem. Commun.* **1991**, 57.

<sup>243</sup> Angibeaud; Larchevêque; Normant; Tchoubar *Bull. Soc. Chim. Fr.* **1968**, 595; Whitesides; Ehmman *J. Org. Chem.* **1970**, 35, 3565.

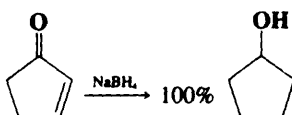
<sup>244</sup> Benkeser; Schroll; Sauve *J. Am. Chem. Soc.* **1955**, 77, 3378.

<sup>245</sup> For example, see Castro; Stephens *J. Am. Chem. Soc.* **1964**, 86, 4358; Castro; Stephens; Mojé *J. Am. Chem. Soc.* **1966**, 88, 4964.

<sup>246</sup> Sala; Doria; Passarotti *Tetrahedron Lett.* **1984**, 25, 4565.

<sup>247</sup> Tour; Pendalwar *Tetrahedron Lett.* **1990**, 31, 4719.

and triethylsilane  $\text{Et}_3\text{SiH}$ ,<sup>248</sup> hydrazine (if a small amount of oxidizing agent, such as air,  $\text{H}_2\text{O}_2$ , or cupric ion is present),<sup>249</sup> hydroxylamine and ethyl acetate,<sup>250</sup> and  $\text{NH}_2\text{OSO}_3\text{H}$ .<sup>251</sup> However, metallic hydrides, such as lithium aluminum hydride and sodium borohydride, do not in general reduce carbon-carbon double bonds, although this can be done in special cases where the double bond is polar, as in 1,1-diarylethenes<sup>252</sup> and in enamines.<sup>253</sup> In certain cases<sup>254</sup> these metallic hydride reagents may also reduce double bonds in conjugation with  $\text{C}=\text{O}$  bonds, as well as reducing the  $\text{C}=\text{O}$  bonds, e.g.,<sup>255</sup>



$\text{NaBH}_4$  has a greater tendency than  $\text{LiAlH}_4$  to effect this double reduction, though even with  $\text{NaBH}_4$  the product of single reduction (of the  $\text{C}=\text{O}$  bond) is usually formed in larger amount than the doubly reduced product.  $\text{LiAlH}_4$  gives significant double reduction only in cinnamyl systems, e.g., with  $\text{PhCH}=\text{CHCOOH}$ .<sup>256</sup>

Reduction of only the  $\text{C}=\text{C}$  bond of conjugated  $\text{C}=\text{C}-\text{C}=\text{O}$  and  $\text{C}=\text{C}-\text{C}\equiv\text{N}$  systems<sup>257</sup> has been achieved by many reducing agents,<sup>258</sup> a few of which are  $\text{H}_2$  and a Rh catalyst,<sup>259</sup>  $\text{Bu}_3\text{SnH}-\text{Pd}(\text{PPh}_3)_4$ ,<sup>260</sup>  $\text{Bu}_3\text{SnH}-\text{CuI}-\text{LiCl}$ ,<sup>261</sup>  $\text{Zn}-\text{Cu}$  in boiling  $\text{MeOH}$ ,<sup>262</sup>  $\text{Mg}-\text{MeOH}$ ,<sup>263</sup> diisobutylaluminum hydride- $\text{MeCu}-\text{HMPA}$ ,<sup>264</sup>  $\text{PhSiH}_3-\text{Mo}(\text{CO})_6$ ,<sup>265</sup>  $[(\text{Ph}_3\text{P})\text{CuH}]_6$ ,<sup>266</sup>  $\text{Zn}-\text{NiCl}_2$  in the presence of ultrasound,<sup>267</sup>  $\text{Al}-\text{NiCl}_2$ ,<sup>268</sup> potassium triphenylborohydride,<sup>269</sup>  $\text{CO}-\text{Se}-\text{H}_2\text{O}$ ,<sup>270</sup> and catecholborane.<sup>271</sup> See 6-25 for methods of re-

<sup>248</sup>Kursanov; Parnes; Bassova; Loim; Zdanovich *Tetrahedron* **1967**, 23, 2235; Doyle; McOsker *J. Org. Chem.* **1978**, 43, 693. For a monograph, see Kursanov; Parnes; Kalinkin; Loim *Ionic Hydrogenation and Related Reactions*; Harwood Academic Publishers: Chur, Switzerland, 1985. For a review, see Kursanov; Parnes; Loim *Synthesis* **1974**, 633-651.

<sup>249</sup>Corey; Mock; Pasto *Tetrahedron Lett.* **1961**, 347; Hünig; Müller; Thier *Tetrahedron Lett.* **1961**, 353; Furst; Berlo; Hooton *Chem. Rev.* **1965**, 65, 51-68, pp. 64-65; Kondo; Murai; Sonoda *Tetrahedron Lett.* **1977**, 3727.

<sup>250</sup>Wade; Amin *Synth. Commun.* **1982**, 12, 287.

<sup>251</sup>Appel; Büchner *Liebigs Ann. Chem.* **1962**, 654, 1; Dürckheimer *Liebigs Ann. Chem.* **1969**, 721, 240. For a review of the reagent hydroxylamine-O-sulfonic acid, see Wallace *Org. Prep. Proced. Int.* **1982**, 14, 265-307.

<sup>252</sup>See Granoth; Segall; Leader; Alkabetz *J. Org. Chem.* **1976**, 41, 3682.

<sup>253</sup>For a review of the reduction of enamines and indoles with  $\text{NaBH}_4$  and a carboxylic acid, see Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985**, 17, 317-384. Enamines can also be reduced by formic acid; see Nilsson; Carlson *Acta Chem. Scand. Sect. B* **1985**, 39, 187.

<sup>254</sup>For discussion, see Meyer *J. Chem. Educ.* **1981**, 58, 628.

<sup>255</sup>Brown; Hess *J. Org. Chem.* **1969**, 34, 2206. For other methods of reducing both double bonds, see Ref. 133, p. 540.

<sup>256</sup>Nystrom; Brown *J. Am. Chem. Soc.* **1947**, 69, 2548, **1948**, 70, 3738; Gammill; Gold; Mizsak *J. Am. Chem. Soc.* **1980**, 102, 3095.

<sup>257</sup>For a review of the reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds, see Keinan; Greenspoon, in Patai; Rappoport, Ref. 37, pt. 2, pp. 923-1022. For a review of the stereochemistry of catalytic hydrogenation of  $\alpha,\beta$ -unsaturated ketones, see Augustine *Adv. Catal.* **1976**, 25, 56-80.

<sup>258</sup>For a long list of these, with references, see Ref. 133, pp. 8-17.

<sup>259</sup>Djerassi; Gutzwiller *J. Am. Chem. Soc.* **1966**, 88, 4537; Cabello; Campelo; Garcia; Luna; Marinas *J. Org. Chem.* **1986**, 51, 1786; Ref. 226.

<sup>260</sup>Keinan; Gleize *Tetrahedron Lett.* **1982**, 23, 477; Four; Guibe *Tetrahedron Lett.* **1982**, 23, 1825.

<sup>261</sup>Lipshutz; Ung; Sengupta *Synlett* **1989**, 64.

<sup>262</sup>Sondengam; Fomum; Charles; Akam *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1219.

<sup>263</sup>Youn; Yon; Pak *Tetrahedron Lett.* **1986**, 27, 2409; Hudlicky; Sinai-Zingde; Natchus *Tetrahedron Lett.* **1987**, 28, 5287.

<sup>264</sup>Tsuda; Hayashi; Satomi; Kawamoto; Saegusa *J. Org. Chem.* **1986**, 51, 537.

<sup>265</sup>Keinan; Perez *J. Org. Chem.* **1987**, 52, 2576.

<sup>266</sup>Mahoney; Brestensky; Stryker *J. Am. Chem. Soc.* **1988**, 110, 291.

<sup>267</sup>Petrier; Luche *Tetrahedron Lett.* **1987**, 28, 2347, 2351.

<sup>268</sup>Hazarika; Barua *Tetrahedron Lett.* **1989**, 30, 6567.

<sup>269</sup>Kim; Park; Yoon *Synth. Commun.* **1988**, 18, 89.

<sup>270</sup>Nishiyama; Makino; Hamanaka; Ogawa; Sonoda *Bull. Chem. Soc. Jpn.* **1989**, 62, 1682.

<sup>271</sup>Evans; Fu *J. Org. Chem.* **1990**, 55, 5678.

ducing C=O bonds in the presence of conjugated C=C bonds.  $\text{LiAlH}_4$  also reduces the double bonds of allylic alcohols<sup>272</sup> and  $\text{NaBH}_4$  in MeOH-THF reduces  $\alpha,\beta$ -unsaturated nitro compounds to nitroalkanes.<sup>273</sup> Furthermore, both  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ , as well as  $\text{NaH}$ , reduce ordinary alkenes and alkynes when complexed with transition metal salts, such as  $\text{FeCl}_2$  or  $\text{CoBr}_2$ .<sup>274</sup>

The inertness of ordinary double bonds toward metallic hydrides is quite useful, since it permits reduction of, say, a carbonyl or nitro group, without disturbing a double bond in the same molecule (see Chapter 19 for a discussion of selectivity in reduction reactions). Sodium in liquid ammonia also does not reduce ordinary double bonds,<sup>275</sup> although it does reduce alkynes, allenes, conjugated dienes,<sup>276</sup> and aromatic rings (5-10).

Another hydrogenation method is called *transfer hydrogenation*.<sup>277</sup> In this method the hydrogen comes from another organic molecule, which is itself oxidized. A transition-metal catalyst, heterogeneous or homogeneous, is frequently employed. A common reducing agent is cyclohexene, which, when a palladium catalyst is used, is oxidized to benzene, losing 2 moles of hydrogen.

Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned. The comparative reactivity of triple and double bonds depends on the catalyst. With most catalysts, e.g., Pd, triple bonds are hydrogenated more easily, and therefore it is possible to add just 1 mole of hydrogen and reduce a triple bond to a double bond (usually a stereoselective syn addition) or to reduce a triple bond without affecting a double bond present in the same molecule.<sup>278</sup> A particularly good catalyst for this purpose is the Lindlar catalyst ( $\text{Pd}-\text{CaCO}_3-\text{PbO}$ ).<sup>279</sup> Triple bonds can also be selectively reduced to double bonds with diisobutylaluminum hydride (DIBALH),<sup>280</sup> with tetramethyldihydrodisiloxane-HOAc and a Pd(0) catalyst,<sup>281</sup> with activated zinc (see 2-38),<sup>282</sup> with a zinc-copper couple,<sup>283</sup> or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low-molecular-weight amine.<sup>284</sup> Terminal alkynes are not reduced by the  $\text{Na}-\text{NH}_3$  procedure because they are converted to acetylide ions under these conditions. However, terminal triple bonds can be reduced to double bonds by the addition to the  $\text{Na}-\text{NH}_3$  solution of  $(\text{NH}_4)_2\text{SO}_4$ , which liberates the free ethynyl group.<sup>285</sup>

An indirect method<sup>286</sup> of double-bond reduction involves hydrolysis of boranes (prepared

<sup>272</sup>For discussions of the mechanism of this reaction, see Snyder *J. Org. Chem.* **1967**, 32, 3531; Borden *J. Am. Chem. Soc.* **1968**, 90, 2197; Blunt; Hartshorn; Soong; Munro *Aust. J. Chem.* **1982**, 35, 2519; Vincens; Fadel; Vidal *Bull. Soc. Chim. Fr.* **1987**, 462.

<sup>273</sup>Varma; Kabalka *Synth. Commun.* **1985**, 15, 151.

<sup>274</sup>See for example Sato; Sato; Sato *J. Organomet. Chem.* **1976**, 122, C25, **1977**, 131, C26; Fujisawa; Sugimoto; Ohta *Chem. Lett.* **1976**, 581; Ashby; Lin *J. Org. Chem.* **1978**, 43, 2567; Chung *J. Org. Chem.* **1979**, 44, 1014. See also Osby; Heinzman; Ganem *J. Am. Chem. Soc.* **1986**, 108, 67.

<sup>275</sup>There are some exceptions. See, for example, Butler *Synth. Commun.* **1977**, 7, 441, and references cited therein.

<sup>276</sup>For a review of reductions of  $\alpha,\beta$ -unsaturated carbonyl compounds with metals in liquid  $\text{NH}_3$ , see Caine, *Org. React.* **1976**, 23, 1-258.

<sup>277</sup>For reviews, see Johnstone; Wilby; Entwistle *Chem. Rev.* **1985**, 85, 129; Brieger; Nestrick *Chem. Rev.* **1974**, 74, 567-580.

<sup>278</sup>For reviews of the hydrogenation of alkynes, see Hutchins; Hutchins, in Patai; Rappoport, Ref. 49, pt. 1, pp. 571-601; Marvell; Li *Synthesis* **1973**, 457-468; Gutmann; Lindlar, in Viehe, Ref. 70, pp. 355-363.

<sup>279</sup>Lindlar; Dubuis *Org. Synth.* V, 880. See also Rajaram; Narula; Chawla; Dev *Tetrahedron* **1983**, 39, 2315; McEwen; Guttieri; Maier; Laine; Shvo *J. Org. Chem.* **1983**, 48, 4436.

<sup>280</sup>Wilke; Müller *Chem. Ber.* **1956**, 89, 444, *Liebigs Ann. Chem.* **1960**, 629, 224; Gensler; Bruno *J. Org. Chem.* **1963**, 28, 1254; Eisch; Kaska *J. Am. Chem. Soc.* **1966**, 88, 2213. For a catalyst with even better selectivity for triple bonds, see Ulan; Maier; Smith *J. Org. Chem.* **1987**, 52, 3132.

<sup>281</sup>Trost; Braslaw *Tetrahedron Lett.* **1989**, 30, 4657.

<sup>282</sup>Aerssens; van der Heiden; Heus; Brandsma *Synth. Commun.* **1990**, 20, 3421; Chou; Clark; White *Tetrahedron Lett.* **1991**, 32, 299.

<sup>283</sup>Sondengam; Charles; Akam *Tetrahedron Lett.* **1980**, 21, 1069.

<sup>284</sup>For a list of methods of reducing triple to double bonds, with syn or anti addition, see Ref. 133, pp. 212-214.

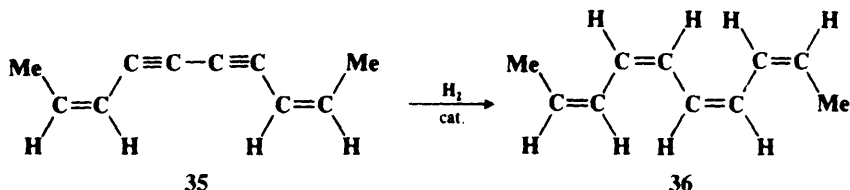
<sup>285</sup>Henne; Greenlee *J. Am. Chem. Soc.* **1943**, 65, 2020.

<sup>286</sup>For a review, see Zweifel *Intra-Sci. Chem. Rep.* **1973**, 7(2), 181-189.

by 5-12). Trialkylboranes can be hydrolyzed by refluxing with carboxylic acids,<sup>287</sup> while monoalkylboranes  $\text{RBH}_2$  can be hydrolyzed with base.<sup>288</sup> Triple bonds can be similarly reduced, to cis olefins.<sup>289</sup>

Conjugated dienes can add hydrogen by 1,2 or 1,4 addition. Selective 1,4 addition can be achieved by hydrogenation in the presence of carbon monoxide, with bis(cyclopentadienyl)chromium as catalyst.<sup>290</sup> With allenes<sup>291</sup> catalytic hydrogenation usually reduces both double bonds, but reduction of just one double bond, to give an olefin, has been accomplished by treatment with  $\text{Na-NH}_3$ <sup>292</sup> or with DIBALH,<sup>293</sup> and by hydrogenation with  $\text{RhCl}(\text{PPh}_3)_3$  as catalyst.<sup>294</sup>

Most catalytic reductions of double or triple bonds, whether heterogeneous or homogeneous, have been shown to be syn, with the hydrogens entering from the less-hindered side of the molecule.<sup>295</sup> Stereospecificity can be investigated only for tetrasubstituted olefins (except when the reagent is  $\text{D}_2$ ), which are the hardest to hydrogenate, but the results of these investigations show that the addition is usually 80 to 100% syn, though some of the anti addition product is normally also found and in some cases predominates. Catalytic hydrogenation of alkynes is nearly always stereoselective, giving the cis olefin (usually at least 80%), even when it is thermodynamically less stable. For example, **35** gave **36**, even though the steric hindrance is such that a planar molecule is impossible.<sup>296</sup> This is thus a



useful method for preparing cis olefins.<sup>297</sup> However, when steric hindrance is too great, the trans olefin may be formed. One factor that complicates the study of the stereochemistry of heterogeneous catalytic hydrogenation is that exchange of hydrogens takes place, as can be shown by hydrogenation with deuterium.<sup>298</sup> Thus deuterogenation of ethylene produced all the possible deuterated ethylenes and ethanes (even  $\text{C}_2\text{H}_6$ ), as well as HD.<sup>299</sup> With 2-butene, it was found that double-bond migration, cis-trans isomerization, and even exchange of hydrogen with groups not on the double bond could occur; e.g.,  $\text{C}_4\text{H}_2\text{D}_8$  and  $\text{C}_4\text{HD}_9$  were detected on treatment of *cis*-2-butene with deuterium and a catalyst.<sup>300</sup> Indeed, *alkanes*

<sup>287</sup>Brown; Murray *Tetrahedron* **1986**, 42, 5497; Kabalka; Newton; Jacobus *J. Org. Chem.* **1979**, 44, 4185.

<sup>288</sup>Weinheimer; Marisco *J. Org. Chem.* **1962**, 27, 1926.

<sup>289</sup>Brown; Zweifel *J. Am. Chem. Soc.* **1959**, 81, 1512.

<sup>290</sup>Miyake; Kondo *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 631 [*Angew. Chem.* 80, 663]. For other methods, with references, see Ref. 133, p. 211.

<sup>291</sup>For a review, see Schuster; Coppola, Ref. 95, pp. 57-61.

<sup>292</sup>Gardner; Narayana *J. Org. Chem.* **1961**, 26, 3518; Vaidyanathaswamy; Joshi; Devaprabhakara *Tetrahedron Lett.* **1971**, 2075.

<sup>293</sup>Montury; Goré *Tetrahedron Lett.* **1980**, 21, 51.

<sup>294</sup>Bhagwat; Devaprabhakara *Tetrahedron Lett.* **1972**, 1391.

<sup>295</sup>For a review of homogeneous hydrogenation directed to only one face of a substrate molecule, see Brown *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 190-203 [*Angew. Chem.* 99, 169-182].

<sup>296</sup>Holme; Jones; Whiting *Chem. Ind. (London)* **1956**, 928.

<sup>297</sup>For a catalyst that leads to trans olefins, see Burch; Muettterties; Teller; Williams *J. Am. Chem. Soc.* **1982**, 104, 4257.

<sup>298</sup>For a review of the use of deuterium to study the mechanism of heterogeneous organic catalysis, see Gudkov *Russ. Chem. Rev.* **1986**, 55, 259-270.

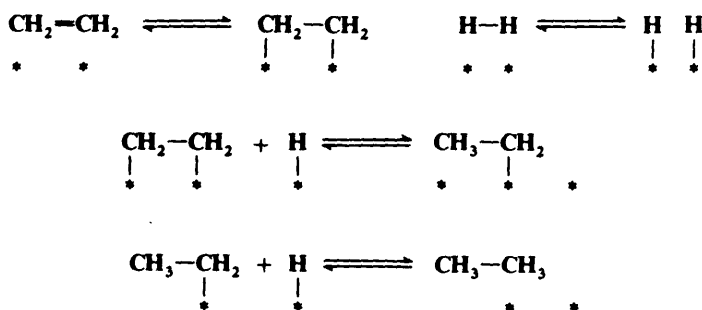
<sup>299</sup>Turkevich; Schissler; Irsa *J. Phys. Chem.* **1951**, 55, 1078.

<sup>300</sup>Wilson; Otvos; Stevenson; Wagner *Ind. Eng. Chem.* **1953**, 45, 1480.

have been found to exchange with deuterium over a catalyst,<sup>301</sup> and even without deuterium, e.g.,  $\text{CH}_4 + \text{CD}_4 \rightarrow \text{CHD}_3 + \text{CH}_3\text{D}$  in the gas phase, with a catalyst. All this makes it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.

Catalytic hydrogenation of triple bonds and the reaction with DIBALH usually give the cis olefin. Most of the other methods of triple-bond reduction lead to the more thermodynamically stable trans olefin. However, this is not the case with the method involving hydrolysis of boranes or with the reductions with activated zinc, hydrazine, or  $\text{NH}_2\text{OSO}_3\text{H}$ , which also give the cis products.

The mechanism of the heterogenous catalytic hydrogenation of double bonds is not thoroughly understood because it is a very difficult reaction to study.<sup>302</sup> Because the reaction is heterogeneous, kinetic data, though easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret. Furthermore, there are the difficulties caused by the aforementioned hydrogen exchange. The currently accepted mechanism for the common two-phase reaction was originally proposed in 1934.<sup>303</sup> According to this, the olefin is adsorbed onto the surface of the metal, though the nature of the actual bonding is unknown,<sup>304</sup>



despite many attempts to elucidate it.<sup>305</sup> The metallic site is usually indicated by an asterisk. For steric reasons it is apparent that adsorption of the olefin takes place with its less-hindered side attached to the catalyst surface. The fact that addition of hydrogen is generally also from the less-hindered side indicates that the hydrogen too is probably adsorbed on the catalyst surface before it reacts with the olefin. It is likely that the  $\text{H}_2$  molecule is cleaved to hydrogen atoms in the act of being adsorbed. It has been shown that platinum catalyzes homolytic cleavage of hydrogen molecules.<sup>306</sup> In the second step one of the adsorbed hydrogen atoms becomes attached to a carbon atom, creating in effect, an alkyl radical (which is still bound to the catalyst though only by one bond) and two vacant catalyst sites. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical to give the reaction product, freed from the catalyst surface, and two more vacant sites. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of process. For example, Figure 15.1 shows the

<sup>301</sup>For a review, see Gudkov; Balandin *Russ. Chem. Rev.* **1966**, 35, 756-761. For an example of intramolecular exchange, see Lebrilla; Maier *Tetrahedron Lett.* **1983**, 24, 1119. See also Poretti; Gäumann *Helv. Chim. Acta* **1985**, 68, 1160.

<sup>302</sup>For reviews, see Webb, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 20; Elsevier: New York, 1978, pp. 1-121; Clarke; Rooney *Adv. Catal.* **1976**, 25, 125-183; Siegel *Adv. Catal.* **1966**, 16, 123-177; Burwell *Chem. Eng. News* **1966**, 44(34), 56-67.

<sup>303</sup>Horiuti; Polanyi *Trans. Faraday Soc.* **1934**, 30, 1164.

<sup>304</sup>See, for example, Burwell; Schrage *J. Am. Chem. Soc.* **1965**, 87, 5234.

<sup>305</sup>See, for example, McKee *J. Am. Chem. Soc.* **1962**, 84, 1109; Ledoux *Nouv. J. Chim.* **1978**, 2, 9; Bautista; Campelo; Garcia; Guardoño; Luna; Marinas *J. Chem. Soc., Perkin Trans. 2* **1989**, 493.

<sup>306</sup>Krasna *J. Am. Chem. Soc.* **1961**, 83, 289.

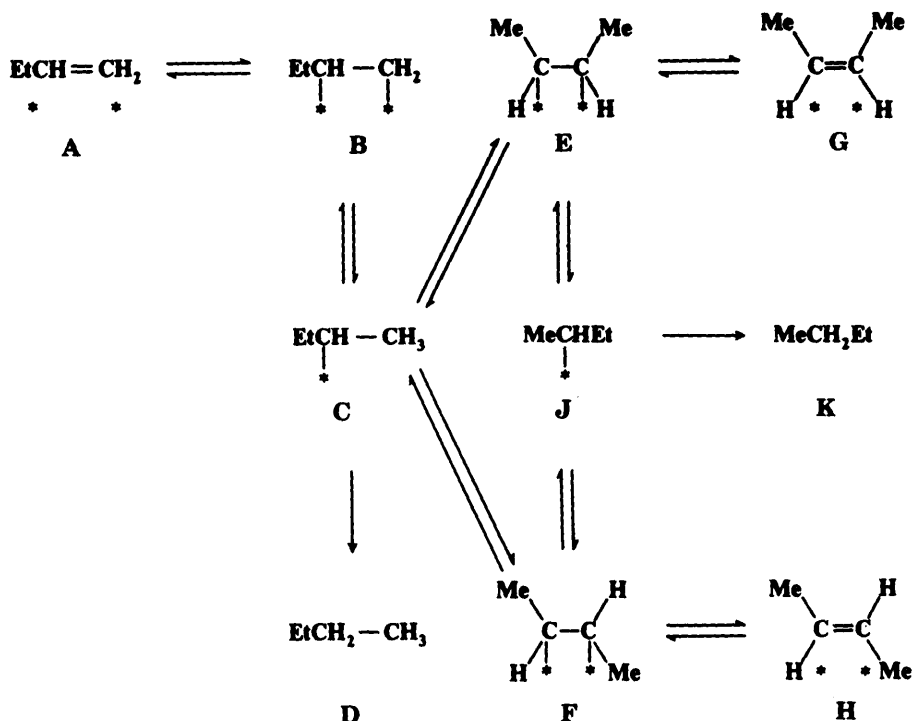
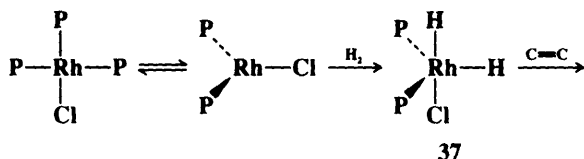


FIGURE 15.1 Steps in the hydrogenation of 1-butene.

steps that may be occurring in hydrogenation of 1-butene.<sup>307</sup> In this scheme the normal reaction is represented by  $A \rightarrow B \rightarrow C \rightarrow D$ , double-bond migration by  $A \rightarrow B \rightarrow C \rightarrow E \rightarrow G$ , cis-trans isomerization by  $H \rightarrow F \rightarrow C \rightarrow E \rightarrow G$ , and hydrogen exchange by  $A \rightarrow B \rightarrow C \rightarrow E \rightarrow J \rightarrow K$ . Although this mechanism is satisfactory as far as it goes,<sup>308</sup> there are still questions it does not answer, among them questions<sup>309</sup> involving the nature of the asterisk, the nature of the bonding, and the differences caused by the differing nature of each catalyst.<sup>310</sup>

The mechanism of homogeneous hydrogenation<sup>311</sup> catalyzed by  $\text{RhCl}(\text{PH}_3)_3$ <sup>312</sup> involves



<sup>307</sup>Smith; Burwell *J. Am. Chem. Soc.* **1962**, *84*, 925.

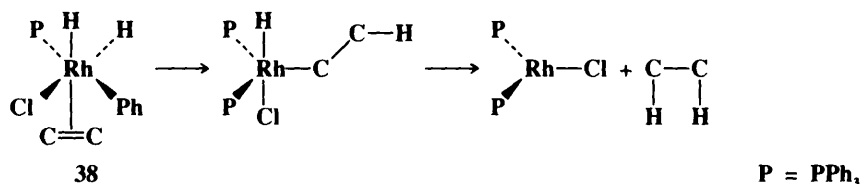
<sup>308</sup>A different mechanism has been proposed by Zaera; Somorjai *J. Am. Chem. Soc.* **1984**, *106*, 2288, but there is evidence against it: Beebe; Yates *J. Am. Chem. Soc.* **1986**, *108*, 663. See also Thomson; Webb *J. Chem. Soc., Chem. Commun.* **1976**, 526.

<sup>309</sup>For discussions, see Augustine; Yaghmaie; Van Peppen *J. Org. Chem.* **1984**, *49*, 1865; Maier *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 135-145 [*Angew. Chem.* **101**, 135-146].

<sup>310</sup>For a study of the detailed structure of Lindlar catalysts (which were shown to consist of seven distinct chemical phases), see Schlögl; Noack; Zbinden; Reller *Helv. Chim. Acta* **1987**, *70*, 627.

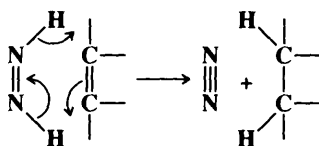
<sup>311</sup>For reviews, see Crabtree *Organometallic Chemistry of the Transition Metals*; Wiley: New York, 1988, pp. 190-200; Jardine, in Hartley, Ref. 218, vol. 4, pp. 1049-1071.

<sup>312</sup>Osborn; Jardine; Young; Wilkinson, Ref. 224; Jardine; Osborn; Wilkinson *J. Chem. Soc. A* **1967**, 1574; Montelatici; van der Ent; Osborn; Wilkinson *J. Chem. Soc. A* **1968**, 1054; Wink; Ford *J. Am. Chem. Soc.* **1985**, *107*, 1794; Koga; Daniel; Han; Fu; Morokuma *J. Am. Chem. Soc.* **1987**, *109*, 3455.



reaction of the catalyst with hydrogen to form a metal hydride  $(\text{PPh}_3)_2\text{RhH}_2\text{Cl}$  (**37**), which rapidly transfers two hydrogen atoms to the alkene. The intermediate **37** can be isolated. If a mixture of  $\text{H}_2$  and  $\text{D}_2$  is used, the product contains only dideuterated and nondeuterated compounds; no monodeuterated products are found, indicating that (unlike the case of heterogeneous catalysis)  $\text{H}_2$  or  $\text{D}_2$  has been added to one olefin molecule and that no exchange takes place.<sup>312</sup> Although conversion of **38** to the products takes place in two steps,<sup>313</sup> the addition of  $\text{H}_2$  to the double bond is syn.

In the above-mentioned reactions with hydrazine and hydroxylamine, the actual reducing species is diimide  $\text{NH}=\text{NH}$ , which is formed from  $\text{N}_2\text{H}_4$  by the oxidizing agent and from  $\text{NH}_2\text{OH}$  by the ethyl acetate.<sup>314</sup> Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,<sup>315</sup> at least in part by a cyclic mechanism:<sup>316</sup>



The addition is therefore stereospecifically syn<sup>317</sup> and, like catalytic hydrogenation, generally takes place from the less-hindered side of a double bond, though not much discrimination in this respect is observed where the difference in bulk effects is small.<sup>318</sup> Diimide reductions are most successful with symmetrical multiple bonds ( $\text{C}=\text{C}$ ,  $\text{C}\equiv\text{C}$ ,  $\text{N}=\text{N}$ ) and are not useful for those inherently polar ( $\text{C}\equiv\text{N}$ ,  $\text{C}=\text{N}$ ,  $\text{C}=\text{O}$ , etc.). Diimide is not stable enough for isolation at ordinary temperatures, though it has been prepared<sup>319</sup> as a yellow solid at  $-196^\circ\text{C}$ .

When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the Birch reduction (**5-10**).<sup>320</sup> The reduction with trifluoroacetic acid and  $\text{Et}_3\text{SiH}$  has an ionic mechanism, with  $\text{H}^+$  coming in from the acid and  $\text{H}^-$  from the silane.<sup>248</sup> In accord with this mechanism, the reaction can be applied only to those olefins which when

<sup>313</sup>Biellmann; Jung *J. Am. Chem. Soc.* **1968**, *90*, 1673; Hussey; Takeuchi *J. Am. Chem. Soc.* **1969**, *91*, 672; Heathcock; Poulter *Tetrahedron Lett.* **1969**, 2755; Smith; Shuford *Tetrahedron Lett.* **1970**, 525; Atkinson; Luke *Can. J. Chem.* **1970**, *48*, 3580.

<sup>314</sup>For reviews of hydrogenations with diimide, see Pasto; Taylor *Org. React.* **1991**, *40*, 91-155; Miller *J. Chem. Educ.* **1965**, *42*, 254-259; House, Ref. 144, pp. 248-256. For reviews of diimides, see Back *Rev. Chem. Intermed.* **1984**, *5*, 293-323; Hünig; Müller; Thier *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 271-280 [*Angew. Chem.* **77**, 368-377].

<sup>315</sup>Aylward; Sawistowska *J. Chem. Soc.* **1964**, 1435.

<sup>316</sup>Ref. 249; van Tamelen; Dewey; Lease; Pirkle *J. Am. Chem. Soc.* **1961**, *83*, 4302; Willis; Back; Parsons; Purdon *J. Am. Chem. Soc.* **1977**, *99*, 4451.

<sup>317</sup>Corey; Pasto; Mock *J. Am. Chem. Soc.* **1961**, *83*, 2957.

<sup>318</sup>van Tamelen; Timmons *J. Am. Chem. Soc.* **1962**, *84*, 1067.

<sup>319</sup>Wiberg; Fischer; Bachhuber *Chem. Ber.* **1974**, *107*, 1456, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 780 [*Angew. Chem.* **89**, 828]. See also Trombetti *Can. J. Phys.* **1968**, *46*, 1005; Bondybey; Nibler *J. Chem. Phys.* **1973**, *58*, 2125; Craig; Klierer; Shih *J. Am. Chem. Soc.* **1979**, *101*, 2480.

<sup>320</sup>For a review of the steric course of this reaction, see Toromanoff *Bull. Soc. Chim. Fr.* **1987**, 893-901. For a review of this reaction as applied to  $\alpha,\beta$ -unsaturated ketones, see Russell, in Patai; Rappoport, Ref. 37, pt. 2, pp. 471-512.

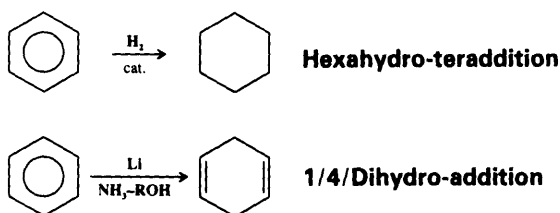
protonated can form a tertiary carbocation or one stabilized in some other way, e.g., by  $\alpha$  OR substitution.<sup>321</sup> It has been shown, by the detection of CIDNP, that reduction of  $\alpha$ -methylstyrene by hydridopentacarbonylmanganese(I)  $\text{HMn(CO)}_5$  involves free-radical addition.<sup>322</sup>

The occurrence of hydrogen exchange and double-bond migration in heterogeneous catalytic hydrogenation means that the hydrogenation does not necessarily take place by straightforward addition of two hydrogen atoms at the site of the original double bond. Consequently, this method is not synthetically useful for adding  $\text{D}_2$  to a double or triple bond in a regioselective or stereospecific manner. However, this objective can be achieved (with syn addition) by a homogeneous catalytic hydrogenation, which usually adds  $\text{D}_2$  without scrambling<sup>323</sup> or by the use of one of the diimide methods.<sup>317</sup> Deuterium can also be regioselectively added by the hydroboration-reduction procedure previously mentioned.

Reductions of double and triple bonds are found at OS **I**, 101, 311; **II**, 191, 491; **III**, 385, 586, 742, 794; **IV**, 136, 298, 302, 304, 408, 887; **V**, 16, 96, 277, 281, 993; **VI**, 68, 459; **VII**, 226, 287, 524; **68**, 64, 182.

Catalysts and apparatus for hydrogenation are found at OS **I**, 61, 463; **II**, 142; **III**, 176, 181, 685; **V**, 880.

### 5-10 Hydrogenation of Aromatic Rings



Aromatic rings can be reduced by catalytic hydrogenation,<sup>324</sup> but higher temperatures (100 to 200°C) are required than for ordinary double bonds.<sup>325</sup> Though the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.<sup>326</sup> Mild conditions are also successful in hydrogenations with phase transfer catalysts.<sup>327</sup> Many functional groups, such as OH,  $\text{O}^-$ , COOH, COOR,  $\text{NH}_2$ , etc., do not interfere with the reaction, but some groups may be preferentially reduced. Among these are  $\text{CH}_2\text{OH}$  groups, which undergo hydrogenolysis to  $\text{CH}_3$  (**0-78**). Phenols may be reduced to cyclohexanones, presumably through the enol. Heterocyclic compounds are often reduced. Thus furan gives tetrahydrofuran. With benzene rings it is usually impossible to stop the reaction after only one or two bonds have been reduced, since olefins are more easily reduced than aromatic rings.<sup>328</sup> Thus, 1 mole of benzene, treated with 1

<sup>321</sup>Parnes; Bolestova; Kursanov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1972**, 21, 1927.

<sup>322</sup>Sweany; Halpern *J. Am. Chem. Soc.* **1977**, 99, 8335. See also Thomas; Shackleton; Wright; Gillis; Colpa; Baird *J. Chem. Soc., Chem. Commun.* **1986**, 312; Garst; Bockman; Batlaw *J. Am. Chem. Soc.* **1986**, 108, 1689; Bullock; Samsel *J. Am. Chem. Soc.* **1987**, 109, 6542.

<sup>323</sup>Biellmann; Liesenfelt *Bull. Soc. Chim. Fr.* **1966**, 4029; Birch; Walker *Tetrahedron Lett.* **1966**, 4939; *J. Chem. Soc. C* **1966**, 1894; Morandi; Jensen *J. Org. Chem.* **1969**, 34, 1889. See, however, Atkinson; Luke, Ref. 313.

<sup>324</sup>For reviews, see Karakhanov; Dedov; Loktev *Russ. Chem. Rev.* **1985**, 54, 171-184; Weitkamp *Adv. Catal.* **1968**, 18, 1-110 (for naphthalenes).

<sup>325</sup>For a highly active heterogeneous Rh catalyst, see Timmer; Thewissen; Meinema; Bulten *Recl. Trav. Chim. Pays-Bas* **1990**, 109, 87.

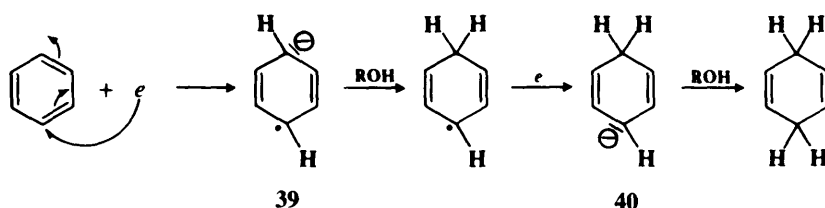
<sup>326</sup>For reviews, see Bennett *CHEMTECH* **1980**, 10, 444-446; Muetterties; Bleeke *Acc. Chem. Res.* **1979**, 12, 324-331.

<sup>327</sup>Januszkiewicz; Alper *Organometallics* **1983**, 2, 1055.

<sup>328</sup>For an indirect method of hydrogenating benzene to cyclohexene, see Harman; Taube *J. Am. Chem. Soc.* **1988**, 110, 7906.

mole of hydrogen, gives no cyclohexadiene or cyclohexene but  $\frac{1}{2}$  mole of cyclohexane and  $\frac{1}{2}$  mole of recovered benzene. This is not true for all aromatic systems. With phenanthrene, for example, it is easy to stop after only the 9,10-bond has been reduced (see p. 43).

When aromatic rings are reduced by lithium (or potassium or sodium) in liquid ammonia (such reductions are known as *dissolving metal reductions*), usually in the presence of an alcohol (often ethyl, isopropyl, or *t*-butyl alcohol), 1,4 addition of hydrogen takes place and nonconjugated cyclohexadienes are produced.<sup>329</sup> This reaction is called the *Birch reduction*.<sup>330</sup> Ammonia obtained commercially often has iron salts as impurities that lower the yield in the Birch reduction. Therefore it is often necessary to distill the ammonia. When substituted aromatic compounds are subjected to the Birch reduction, electron-donating groups such as alkyl or alkoxy decrease the rate of the reaction and are generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene, not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups such as COOH or CONH<sub>2</sub> increase the reaction rate and are found on the reduced positions of the product.<sup>331</sup> The mechanism involves solvated electrons,<sup>332</sup> which are transferred from the metal to the solvent and thence to the ring:<sup>333</sup>



The sodium becomes oxidized to Na<sup>+</sup> and creates a radical ion (39).<sup>334</sup> There is a great deal of evidence from esr spectra for these species.<sup>335</sup> The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, 40 accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of 39 are frequently obtained. There is evidence<sup>336</sup> at least with some substrates, e.g., biphenyl, that the radical ion corresponding to 39 is converted to the carbanion corresponding to 40 by a different pathway, in which the order of the steps is reversed: first a second electron is gained to give a dianion,<sup>334</sup> which then acquires a proton, producing the intermediate corresponding to 40.

<sup>329</sup>For a procedure that converts benzene to pure 1,4-cyclohexadiene, see Brandsma; van Soolingen; Andringa *Synth. Commun.* **1990**, 20, 2165.

<sup>330</sup>For a monograph, see Akhrem; Reshotova; Titov *Birch Reduction of Aromatic Compounds*; Plenum: New York, 1972. For reviews, see Rabideau *Tetrahedron* **1989**, 45, 1579-1603; Birch; Subba Rao *Adv. Org. Chem.* **1972**, 8, 1-65; Kaiser *Synthesis* **1972**, 391-415; Harvey *Synthesis* **1970**, 161-172; House, Ref. 144, pp. 145-150, 173-209; Hückel *Fortschr. Chem. Forsch.* **1966**, 6, 197-250; Smith, in *Augustine Reduction Techniques and Applications in Organic Synthesis*; Marcel Dekker: New York, 1968, pp. 95-170.

<sup>331</sup>These regioselectivities have generally been explained by molecular-orbital considerations regarding the intermediates involved. For example, see Birch; Hinde; Radom *J. Am. Chem. Soc.* **1980**, 102, 3370, 4074, 6430; **1981**, 103, 284; Zimmerman; Wang *J. Am. Chem. Soc.* **1990**, 112, 1280. For methods of reversing the regioselectivities, see Epling; Florio *Tetrahedron Lett.* **1986**, 27, 1469; Rabideau; Karrick *Tetrahedron Lett.* **1987**, 28, 2481.

<sup>332</sup>For reviews of solvated electrons and related topics, see Dye *Prog. Inorg. Chem.* **1984**, 32, 327-441; Alpatova; Kristalik; Pleskov *Top. Curr. Chem.* **1987**, 138, 149-219.

<sup>333</sup>Birch; Nasipuri *Tetrahedron* **1959**, 6, 148.

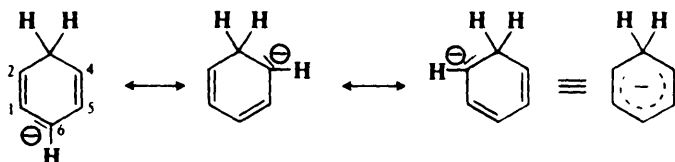
<sup>334</sup>For a review of radical ions and diions generated from aromatic compounds, see Holy *Chem. Rev.* **1974**, 74, 243-277.

<sup>335</sup>For example, see Jones, in Kaiser; Kevan *Radical Ions*; Wiley: New York, 1968, pp. 245-274; Bowers *Adv. Magn. Reson.* **1965**, 1, 317-396; Carrington *Q. Rev., Chem. Soc.* **1963**, 17, 67-99.

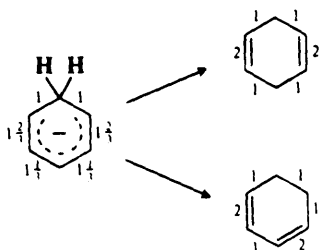
<sup>336</sup>Lindow; Cortez; Harvey *J. Am. Chem. Soc.* **1972**, 94, 5406; Rabideau; Peters; Huser *J. Org. Chem.* **1981**, 46, 1593.

Ordinary olefins are usually unaffected by Birch-reduction conditions, and double bonds may be present in the molecule if they are not conjugated with the ring. However, phenylated olefins, internal alkynes (p. 775), and conjugated olefins (with  $C=C$  or  $C=O$ ) are reduced under these conditions.

It may be noted that **40** is a resonance hybrid; i.e., we can write two additional canonical forms:



The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position to give the 1,3-diene?<sup>337</sup> An answer to this question has been proposed by Hine, who has suggested that this case is an illustration of the operation of the *principle of least motion*.<sup>338</sup> According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."<sup>338</sup> The principle can be applied to the case at hand in the following manner (simplified): The valence-bond bond orders (p. 26) for the six carbon-carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring)  $1\frac{1}{2}$ , 1, 1,  $1\frac{1}{2}$ ,  $1\frac{1}{2}$ , and  $1\frac{1}{2}$ . When the carbanion is converted to the diene, these bond orders change as follows:



It can be seen that the two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is  $\frac{1}{2} + \frac{1}{2} + \frac{1}{2} + \frac{1}{2}$ , while formation of the 1,3-diene requires a change of  $\frac{1}{2} + \frac{1}{2} + \frac{1}{2} + \frac{1}{2}$ . Since a greater change is required to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene. This may not be the only factor, because the  $^{13}\text{C}$  nmr spectrum of **40** shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.<sup>339</sup>

Reduction of aromatic rings with lithium<sup>340</sup> or calcium<sup>341</sup> in amines (instead of ammonia)

<sup>337</sup>For a discussion of this question, see Rabideau; Huser *J. Org. Chem.* **1983**, 48, 4266.

<sup>338</sup>Hine *J. Org. Chem.* **1966**, 31, 1236. For a review of this principle, see Hine *Adv. Phys. Org. Chem.* **1977**, 15, 1-61. See also Tee *J. Am. Chem. Soc.* **1969**, 91, 7144; Jochum; Gasteiger; Ugi *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 495-505 [*Angew. Chem.* 92, 503-513].

<sup>339</sup>Bates; Brenner; Cole; Davidson; Forsythe; McCombs; Roth *J. Am. Chem. Soc.* **1973**, 95, 926.

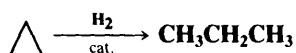
<sup>340</sup>Benkeser; Robinson; Sauve; Thomas *J. Am. Chem. Soc.* **1955**, 77, 3230; Reggel; Friedel; Wender *J. Org. Chem.* **1957**, 22, 891; Benkeser; Agnihotri; Burrous; Kaiser; Mallan; Ryan *J. Org. Chem.* **1964**, 29, 1313; Kwart; Conley *J. Org. Chem.* **1973**, 38, 2011.

<sup>341</sup>Benkeser; Kang *J. Org. Chem.* **1979**, 44, 3737; Benkeser; Belmonte; Kang *J. Org. Chem.* **1983**, 48, 2796. See also Benkeser; Laugal; Rappa *Tetrahedron Lett.* **1984**, 25, 2089.

proceeds further and cyclohexenes are obtained. It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced.<sup>342</sup>

OS **I**, 99, 499; **II**, 566; **III**, 278, 742; **IV**, 313, 887, 903; **V**, 398, 400, 467, 591, 670, 743, 989; **VI**, 371, 395, 461, 731, 852, 856, 996; **VII**, 249.

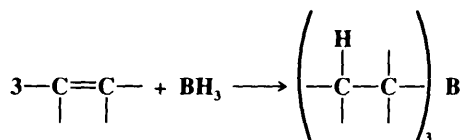
### 5-11 Reductive Cleavage of Cyclopropanes



Cyclopropanes can be cleaved by catalytic hydrogenolysis.<sup>343</sup> Among the catalysts used have been Ni, Pd, and Pt. The reaction can often be run under mild conditions.<sup>344</sup> Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,<sup>345</sup> can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.<sup>346</sup>

### F. A Metal on the Other Side

### 5-12 Hydroboration



When olefins are treated with borane<sup>347</sup> in ether solvents,  $\text{BH}_3$  adds across the double bond.<sup>348</sup> Borane cannot be prepared as a stable pure compound<sup>349</sup> (it dimerizes to diborane  $\text{B}_2\text{H}_6$ ), but it is commercially available in the form of complexes with THF,  $\text{Me}_2\text{S}$ ,<sup>350</sup> phosphines, or tertiary amines. The olefins can be treated with a solution of one of these complexes ( $\text{THF-BH}_3$  reacts at  $0^\circ\text{C}$  and is the most convenient to use;  $\text{R}_3\text{N-BH}_3$  generally require temperatures of about  $100^\circ\text{C}$ ; however, the latter can be prepared as air-stable liquids or solids, while the former can only be used as relatively dilute solutions in THF and are decomposed by moisture in air) or with a mixture of  $\text{NaBH}_4$  and  $\text{BF}_3$  etherate, which generates borane in situ.<sup>351</sup> Ordinarily, the process cannot be stopped with the addition of one molecule of  $\text{BH}_3$  because the resulting  $\text{RBH}_2$  adds to another molecule of olefin to give  $\text{R}_2\text{BH}$ , which in turn adds to a third olefin molecule, so that the isolated product is a trialkylborane  $\text{R}_3\text{B}$ . The reaction can be performed on alkenes with one to four substituents,

<sup>342</sup>One, two, or all three double bonds of certain aromatic nitrogen heterocycles can be reduced with metallic hydrides such as  $\text{NaBH}_4$  or  $\text{LiAlH}_4$ . For a review, see Keay *Adv. Heterocycl. Chem.* **1986**, 39, 1-77.

<sup>343</sup>For reviews, see Charton, Ref. 115, pp. 588-592; Newham *Chem. Rev.* **1963**, 63, 123-137; Rylander *Catalytic Hydrogenation over Platinum Metals*, Ref. 218, pp. 469-474.

<sup>344</sup>See, for example, Woodworth; Buss; Schleyer *Chem. Commun.* **1968**, 569.

<sup>345</sup>See, for example, Walborsky; Pierce *J. Org. Chem.* **1968**, 33, 4102; Walborsky; Aronoff; Schulman *J. Org. Chem.* **1970**, 36, 1036.

<sup>346</sup>For a review, see Staley *Sel. Org. Transform.* **1972**, 2, 309-348.

<sup>347</sup>For a review of this reagent, see Lane, in Pizey, Ref. 146, vol. 3, 1977, pp. 1-191.

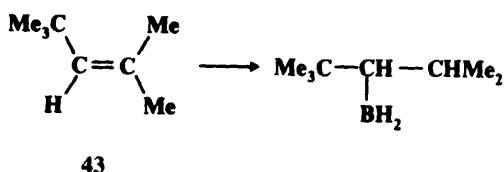
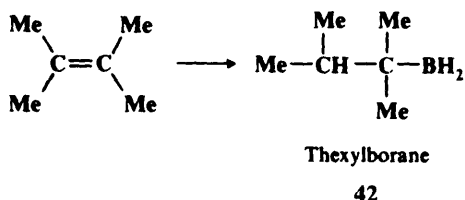
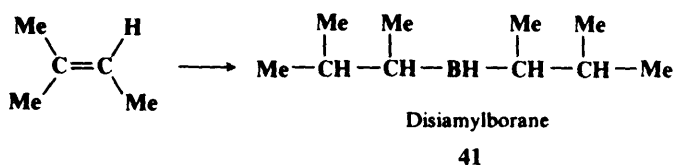
<sup>348</sup>For books on this reaction and its manifold applications, see Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972; *Organic Syntheses Via Boranes*; Wiley: New York, 1975; Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973. For reviews, see Matteson, in Hartley, Ref. 218, vol. 4, pp. 307-409, pp. 315-337; Smith *Chem. Ind. (London)* **1987**, 603-611; Brown; Vara Prasad *Heterocycles* **1987**, 25, 641-567; Suzuki; Dhillon *Top. Curr. Chem.* **1986**, 130, 23-88.

<sup>349</sup>Mappes; Fehlner *J. Am. Chem. Soc.* **1970**, 92, 1562; Fehlner *J. Am. Chem. Soc.* **1971**, 93, 6366.

<sup>350</sup>For a review of  $\text{BH}_3\text{SMe}_2$ , see Hutchins; Cistone *Org. Prep. Proced. Int.* **1981**, 13, 225-240.

<sup>351</sup>For a list of hydroborating reagents, with references, see Ref. 133, pp. 497-499.

including cyclic olefins, but when the olefin is moderately hindered, the product is the dialkylborane  $R_2BH$  or even the monoalkylborane  $RBH_2$ .<sup>352</sup> For example, **41** (*disiamylborane*), **42** (*thexylborane*),<sup>353</sup> and **44** have been prepared in this manner. Monoalkylboranes



$RBH_2$  (which can be prepared from hindered olefins, as above) and dialkylboranes  $R_2BH$  also add to olefins, to give the mixed trialkylboranes  $RR'_2B$  and  $R_2R'B$ , respectively. Surprisingly, when methylborane  $MeBH_2$ ,<sup>354</sup> which is not a bulky molecule, adds to olefins in the solvent THF, the reaction can be stopped with one addition to give the dialkylboranes  $RMeBH$ .<sup>355</sup> Reaction of this with a second olefin produces the trialkylborane  $RR'R'B$ .<sup>356</sup> Other monoalkylboranes, *i*-PrBH<sub>2</sub>, *n*-BuBH<sub>2</sub>, *s*-BuBH<sub>2</sub>, and *t*-BuBH<sub>2</sub>, behave similarly with internal olefins, but not with olefins of the type  $RCH=CH_2$ .<sup>357</sup>

In all cases the boron goes to the side of the double bond that has more hydrogens, whether the substituents are aryl or alkyl.<sup>358</sup> Thus the reaction of **43** with  $BH_3$  gives 98% **44** and only 2% of the other product. This actually follows Markovnikov's rule, since boron is more positive than hydrogen. However, the regioselectivity is caused mostly by steric factors, though electronic factors also play a part. Studies of the effect of ring substituents on rates and on the direction of attack in hydroboration of substituted styrenes showed that the attack by boron has electrophilic character.<sup>359</sup> When both sides of the double bond are

<sup>352</sup>Unless coordinated with a strong Lewis base such as a tertiary amine, mono and dialkylboranes actually exist as dimers e.g.,  $\begin{array}{c} \text{H} \\ \diagdown \quad \diagup \\ \text{R}_2\text{B} \quad \text{BR}_2 \\ \diagup \quad \diagdown \\ \text{H} \end{array}$ ; Brown; Klender *Inorg. Chem.* **1962**, *1*, 204.

<sup>353</sup>For a review of the chemistry of thexylborane, see Negishi; Brown *Synthesis* **1974**, 77-89.

<sup>354</sup>Prepared from lithium methylborohydride and HCl; Brown; Cole; Srebnik; Kim *J. Org. Chem.* **1986**, *51*, 4925.

<sup>355</sup>Srebnik; Cole; Brown *Tetrahedron Lett.* **1987**, *28*, 3771; *J. Org. Chem.* **1990**, *55*, 5051.

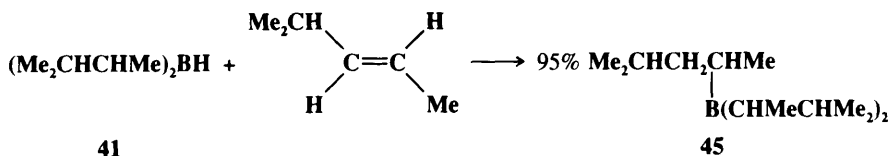
<sup>356</sup>For a method of synthesis of  $RR'R'B$ , see Kulkarni; Basavaiah; Zaidlewicz; Brown *Organometallics* **1982**, *1*, 212.

<sup>357</sup>Srebnik; Cole; Ramachandran; Brown *J. Org. Chem.* **1989**, *54*, 6085.

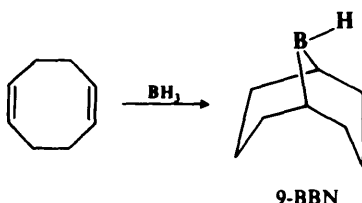
<sup>358</sup>For a thorough discussion of the regioselectivity with various types of substrate and hydroborating agents, see Cragg, Ref. 348, pp.63-84, 137-197. See also Brown; Vara Prasad; Zee *J. Org. Chem.* **1986**, *51*, 439.

<sup>359</sup>Brown; Sharp *J. Am. Chem. Soc.* **1966**, *88*, 5851; Klein; Dunkelblum; Wolff *J. Organomet. Chem.* **1967**, *7*, 377. See also Marshall; Prager *Aust. J. Chem.* **1979**, *32*, 1251.

monosubstituted or both disubstituted, about equal amounts of each isomer are obtained. However, it is possible in such cases to make the addition regioselective by the use of a large attacking molecule. For example, treatment of  $\text{iso-PrCH=CHMe}$  with borane gave 57% of product with boron on the methyl-bearing carbon and 43% of the other, while treatment with **41** gave 95% **45** and only 5% of the other isomer.<sup>360</sup>



Another reagent with high regioselectivity is 9-borabicyclo[3.3.1]nonane (9-BBN), which is prepared by hydroboration of 1,5-cyclooctadiene:<sup>361</sup>



9-BBN has the advantage that it is stable in air. Borane is quite unselective and attacks all sorts of double bonds. Disiamylborane, 9-BBN, and similar molecules are far more selective and preferentially attack less-hindered bonds, so it is often possible to hydroborate one double bond in a molecule and leave others unaffected or to hydroborate one olefin in the presence of a less reactive olefin.<sup>362</sup> For example, 1-pentene can be removed from a mixture of 1- and 2-pentenenes, and a cis olefin can be selectively hydroborated in a mixture of the cis and trans isomers.

A hydroboration reagent with greater regioselectivity than  $\text{BH}_3$  (for terminal alkenes or those of the form  $\text{R}_2\text{C=CHR}$ ) is monochloroborane<sup>363</sup>  $\text{BH}_2\text{Cl}$  coordinated with dimethyl sulfide (the hydroboration product is a dialkylchloroborane  $\text{R}_2\text{BCl}$ ).<sup>364</sup> For example, 1-hexene gave 94% of the anti-Markovnikov product with  $\text{BH}_3\text{-THF}$ , but 99.2% with  $\text{BH}_2\text{Cl-SMe}_2$ . Treatment of alkenes with dichloroborane–dimethyl sulfide  $\text{BHCl}_2\text{-SMe}_2$  in the presence of  $\text{BF}_3$ <sup>365</sup> or with  $\text{BCl}_3$  and  $\text{Me}_3\text{SiH}$ <sup>366</sup> gives alkyl dichloroboranes  $\text{RBCl}_2$ .

An important use of the hydroboration reaction is that alkylboranes, when oxidized with hydrogen peroxide and  $\text{NaOH}$ , are converted to alcohols (**2-28**). This is therefore an indirect way of adding  $\text{H}_2\text{O}$  across a double bond in an anti-Markovnikov manner. However, boranes undergo many other reactions as well. Among other things, they react with  $\alpha$ -halo carbonyl compounds to give alkylated products (**0-99**), with  $\alpha,\beta$ -unsaturated carbonyl compounds to give Michael-type addition of R and H (**5-19**), with CO to give alcohols and ketones (**8-24**

<sup>360</sup>Brown; Zweifel *J. Am. Chem. Soc.* **1961**, 83, 1241.

<sup>361</sup>See Knights; Brown *J. Am. Chem. Soc.* **1968**, 90, 5280, 5281; Brown; Chen *J. Org. Chem.* **1981**, 46, 3978; Soderquist; Brown *J. Org. Chem.* **1981**, 46, 4599.

<sup>362</sup>Brown; Mocrikofer *J. Am. Chem. Soc.* **1963**, 85, 2063; Zweifel; Brown *J. Am. Chem. Soc.* **1963**, 85, 2066; Zweifel; Ayyangar; Brown *J. Am. Chem. Soc.* **1963**, 85, 2072; Ref. 359.

<sup>363</sup>For a review of haloboranes, see Brown; Kulkarni *J. Organomet. Chem.* **1982**, 239, 23-41.

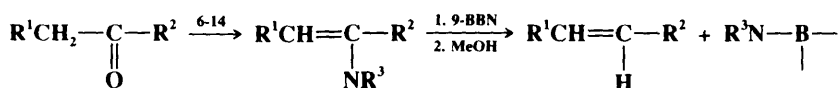
<sup>364</sup>Brown; Ravindran; Kulkarni *J. Org. Chem.* **1979**, 44, 2417.

<sup>365</sup>Brown; Ravindran; Kulkarni *J. Org. Chem.* **1980**, 45, 384; Brown; Racherla *J. Org. Chem.* **1986**, 51, 895.

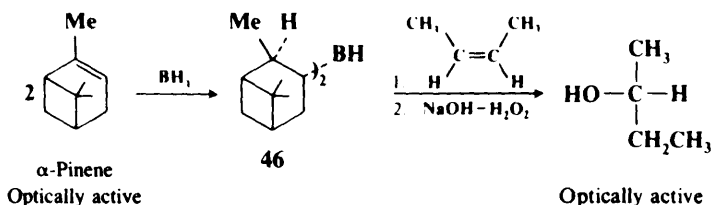
<sup>366</sup>undararajan; Matteson *J. Org. Chem.* **1990**, 55, 2274.

to **8-26**); they can be reduced with carboxylic acids, providing an indirect method for reduction of double bonds (**5-9**), or they can be oxidized with chromic acid or pyridinium chlorochromate to give ketones<sup>367</sup> or aldehydes (from terminal olefins),<sup>368</sup> dimerized with silver nitrate and NaOH (**4-34**), isomerized (**8-11**), or converted to amines (**2-31**) or halides (**2-30**). They are thus useful intermediates for the preparation of a wide variety of compounds.

Such functional groups as OR, OH, NH<sub>2</sub>, SMe, halogen, and COOR may be present in the molecule,<sup>369</sup> but not groups that are reducible by borane. Hydroboration of enamines with 9-BBN provides an indirect method for reducing an aldehyde or ketone to an alkene, e.g.,<sup>370</sup>



Use of the reagent diisopinocampheylborane **46** (prepared by treating optically active  $\alpha$ -pinene with BH<sub>3</sub>) results in enantioselective hydroboration-oxidation.<sup>371</sup> Alcohols with op-



tical purities as high as 98% have been obtained in this way.<sup>372</sup> However, **46** does not give good results with even moderately hindered alkenes; a better reagent for these compounds is isopinocampheylborane<sup>373</sup> though optical yields are lower. Limonylborane,<sup>374</sup> 2- and 4-dicaranylboranes,<sup>375</sup> a myrtanylborane,<sup>376</sup> and dilongifolylborane<sup>377</sup> have also been used. The method has been improved<sup>378</sup> by synthesizing the chiral isopinocampheylborane in the presence of tetramethylenediamine (TMED), whereupon a TMED-isopinocampheylborane adduct is formed. This adduct,<sup>379</sup> in Et<sub>2</sub>O, reacts with a prochiral alkene to give a dialkylborane RBHR' (R' = isocampheyl). The RBHR' crystallizes from THF in 99–100% optical

<sup>367</sup>Brown; Garg *J. Am. Chem. Soc.* **1961**, *83*, 2951; *Tetrahedron* **1986**, *42*, 5511; Rao; Devaprabhakara; Chandrasekaran *J. Organomet. Chem.* **1978**, *162*, C9; Parish; Parish; Honda *Synth. Commun.* **1990**, *20*, 3265.

<sup>368</sup>Brown; Kulkarni; Rao; Patil *Tetrahedron* **1986**, *42*, 5515.

<sup>369</sup>See, for example, Brown; Unni *J. Am. Chem. Soc.* **1968**, *90*, 2902; Brown; Gallivan *J. Am. Chem. Soc.* **1968**, *90*, 2906; Brown; Sharp *J. Am. Chem. Soc.* **1968**, *90*, 2915.

<sup>370</sup>Singaram; Rangaishenvi; Brown; Goralski; Hasha *J. Org. Chem.* **1991**, *56*, 1543.

<sup>371</sup>Brown; Ayyangar; Zweifel *J. Am. Chem. Soc.* **1964**, *86*, 397; Brown; Singaram *J. Org. Chem.* **1984**, *49*, 945; Brown; Vara Prasad *J. Am. Chem. Soc.* **1986**, *108*, 2049.

<sup>372</sup>For reviews of enantioselective syntheses with organoboranes, see Brown *Chemtracts: Org. Chem.* **1988**, *1*, 77–88; Brown; Singaram *Acc. Chem. Res.* **1988**, *21*, 287–293; *Pure Appl. Chem.* **1987**, *59*, 879–894; Srebnik; Ramachandran *Aldrichimica Acta* **1987**, *20*, 9–24; Matteson, Ref. 348, pp. 381–395; Brown; Jadhav; Singaram *Mod. Synth. Methods* **1986**, *4*, 307–356; Matteson *Synthesis* **1986**, 973–985; Brown; Jadhav, in Morrison, Ref. 232, vol. 2, 1983, pp. 1–43; Brown; Jadhav; Mandal *Tetrahedron* **1981**, *37*, 3547–3587.

<sup>373</sup>Brown; Jadhav; Mandal *J. Org. Chem.* **1982**, *47*, 5074. See also Brown; Weissman; Perumal; Dhokte *J. Org. Chem.* **1990**, *55*, 1217.

<sup>374</sup>Jadhav; Kulkarni *Heterocycles* **1982**, *18*, 169.

<sup>375</sup>Brown; Vara Prasad; Zaidlewicz *J. Org. Chem.* **1988**, *53*, 2911.

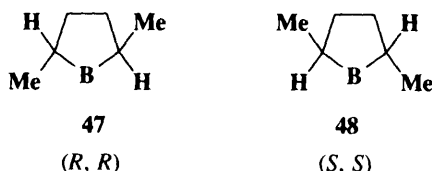
<sup>376</sup>Kiesgen de Richter; Bonato; Follet; Kamenka *J. Org. Chem.* **1990**, *55*, 2855.

<sup>377</sup>Jadhav; Brown *J. Org. Chem.* **1981**, *46*, 2988.

<sup>378</sup>Brown; Singaram *J. Am. Chem. Soc.* **1984**, *106*, 1797; Brown; Gupta; Vara Prasad *Bull. Chem. Soc. Jpn.* **1988**, *61*, 93.

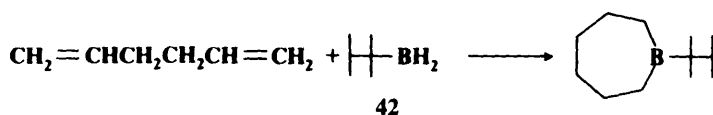
<sup>379</sup>For the crystal structure of this adduct, see Soderquist; Hwang-Lee; Barnes *Tetrahedron Lett.* **1988**, *29*, 3385.

purity (the other diastereomer remains in solution). The optically pure  $\text{RBHR}'$  is treated with acetaldehyde to produce  $\alpha$ -pinene and optically pure  $\text{R}_2\text{BH}$ , which can be converted to optically pure alcohols or to other products.<sup>380</sup> Since both (+) and (−)  $\alpha$ -pinene are readily available, both enantiomers can be prepared. The chiral cyclic boranes *trans*-2,5-dimethylborolanes (**47** and **48**) also add enantioselectively to olefins (except olefins of the

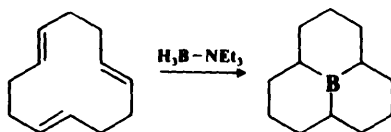


form  $\text{RR}'\text{C}=\text{CH}_2$ ) to give boranes of high optical purity.<sup>381</sup> When chiral boranes are added to trisubstituted olefins of the form  $\text{RR}'\text{C}=\text{CHR}''$ , two new chiral centers are created, and, with **47** or **48**, only one of the four possible diastereomers is predominantly produced, in yields greater than 90%.<sup>381</sup> This has been called *double-asymmetric synthesis*.<sup>382</sup>

The double bonds in a conjugated diene are hydroborated separately, i.e., there is no 1,4 addition. However, it is not easy to hydroborate just one of a conjugated system, since conjugated double bonds are less reactive than isolated ones. The xylborane<sup>353</sup> (**42**) is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or nonconjugated,<sup>383</sup> e.g.,



Rings of five, six, or seven members can be formed in this way. Similar cyclization can also be accomplished with other monoalkylboranes and, in some instances, with  $\text{BH}_3$  itself.<sup>384</sup> One example is the formation of 9-BBN, shown above. Another is conversion of 1,5,9-cyclododecatriene to perhydro-9*b*-boraphenylene:<sup>385</sup>



Triple bonds<sup>386</sup> can be monohydroborated to give vinylic boranes, which can be reduced with carboxylic acids to cis alkenes or oxidized and hydrolyzed to aldehydes or ketones. Terminal alkynes give aldehydes by this method, in contrast to the mercuric or acid-catalyzed addition of water discussed at 5-3. However, terminal alkynes give vinylic boranes<sup>387</sup> (and

<sup>380</sup>For another method of preparing optically pure mono- and dialkylboranes, see Brown; Singaram; Cole *J. Am. Chem. Soc.* **1985**, *107*, 460.

<sup>381</sup>Masamune; Kim; Petersen; Sato; Veenstra; Imai *J. Am. Chem. Soc.* **1985**, *107*, 4549.

<sup>382</sup>For another enantioselective hydroboration method, see p. 788.

<sup>383</sup>Brown; Pfaffenberger *J. Am. Chem. Soc.* **1967**, *89*, 5475; Brown; Negishi *J. Am. Chem. Soc.* **1972**, *94*, 3567.

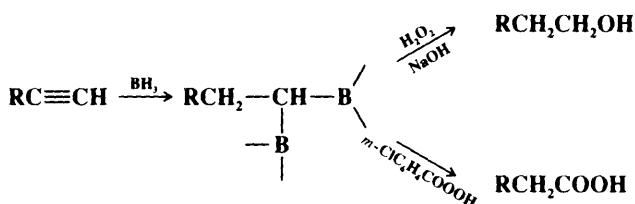
<sup>384</sup>For a review of cyclic hydroboration, see Brown; Negishi *Tetrahedron* **1977**, *33*, 2331-2357. See also Brown; Pai; Naik *J. Org. Chem.* **1984**, *49*, 1072.

<sup>385</sup>Rotermund; Köster *Liebigs Ann. Chem.* **1965**, *686*, 153; Brown; Negishi; Dickason *J. Org. Chem.* **1985**, *50*, 520.

<sup>386</sup>For a review of hydroboration of triple bonds, see Hudlik; Hudlik, in Patai, Ref. 70, pt. 1, pp. 203-219.

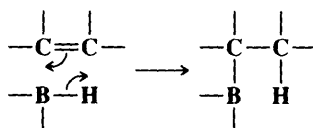
<sup>387</sup>For a review of the preparation and reactions of vinylic boranes, see Brown; Campbell *Aldrichimica Acta* **1981**, *14*, 1-11.

hence aldehydes) only when treated with a hindered borane such as **41**, **42**, or catecholborane (p. 615),<sup>388</sup> or with  $\text{BHBr}_2\text{-SMe}_2$ .<sup>389</sup> The reaction between terminal alkynes and  $\text{BH}_3$  produces 1,1-dibora compounds, which can be oxidized either to primary alcohols (with



$\text{NaOH-H}_2\text{O}_2$ ) or to carboxylic acids (with *m*-chloroperbenzoic acid).<sup>390</sup> Double bonds can be hydroborated in the presence of triple bonds if the reagent is 9-BBN.<sup>391</sup> On the other hand, dimesitylborane selectively hydroborates triple bonds in the presence of double bonds.<sup>392</sup> Furthermore, it is often possible to hydroborate selectively one particular double bond of a nonconjugated diene.<sup>393</sup> When the reagent is catecholborane, hydroboration is catalyzed by rhodium complexes, such as Wilkinson's catalyst.<sup>394</sup> Enantioselective hydroboration-oxidation has been achieved by the use of optically active rhodium complexes.<sup>395</sup>

For most substrates, the addition in hydroboration is stereospecific and syn, with attack taking place from the less-hindered side.<sup>396</sup> The mechanism<sup>397</sup> may be a cyclic four-center one:<sup>398</sup>



When the substrate is an allylic alcohol or amine, the addition is generally anti,<sup>399</sup> though the stereoselectivity can be changed to syn by the use of catecholborane and the rhodium complexes mentioned above.<sup>400</sup> Because the mechanism is different, use of this pro-

<sup>388</sup>Brown; Gupta *J. Am. Chem. Soc.* **1972**, *94*, 4370, **1975**, *97*, 5249. For a review of catecholborane, see Lane; Kabalka *Tetrahedron* **1976**, *32*, 981-990.

<sup>389</sup>Brown; Campbell *J. Org. Chem.* **1980**, *45*, 389.

<sup>390</sup>Zweifel; Arzoumanian *J. Am. Chem. Soc.* **1967**, *89*, 291.

<sup>391</sup>Brown; Coleman *J. Org. Chem.* **1979**, *44*, 2328.

<sup>392</sup>Pelter; Singaram; Brown *Tetrahedron Lett.* **1983**, *24*, 1433.

<sup>393</sup>For a list of references, see Gautam; Singh; Dhillon *J. Org. Chem.* **1988**, *53*, 187. See also Suzuki; Dhillon, Ref. 348.

<sup>394</sup>Männig; Nöth *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 878 [*Angew. Chem.* *97*, 854]. For a review, see Burgess; Ohlmeyer *Chem. Rev.* **1991**, *91*, 1179-1191.

<sup>395</sup>Burgess; Ohlmeyer *J. Org. Chem.* **1988**, *53*, 5178; Hayashi; Matsumoto; Ito *J. Am. Chem. Soc.* **1989**, *111*, 3426; Sato; Miya; Suzuki *Tetrahedron Lett.* **1990**, *31*, 231; Brown; Lloyd-Jones *Tetrahedron: Asymmetry* **1990**, *1*, 869.

<sup>396</sup>Kabalka; Bowman *J. Org. Chem.* **1973**, *38*, 1607; Brown; Zweifel *J. Am. Chem. Soc.* **1961**, *83*, 2544; Bergbreiter; Rainville *J. Org. Chem.* **1976**, *41*, 3031; Kabalka; Newton; Jacobus *J. Org. Chem.* **1978**, *43*, 1567.

<sup>397</sup>For kinetic studies, see Wang; Brown *J. Org. Chem.* **1980**, *45*, 5303, *J. Am. Chem. Soc.* **1982**, *104*, 7148; Vishwakarma; Fry *J. Org. Chem.* **1980**, *45*, 5306; Brown; Chandrasekharan; Wang *J. Org. Chem.* **1983**, *48*, 2901. *Pure Appl. Chem.* **1983**, *55*, 1387-1414; Chandrasekharan; Brown *J. Org. Chem.* **1985**, *50*, 518; Nelson; Cooper *Tetrahedron Lett.* **1986**, *27*, 4693; Brown; Chandrasekharan *J. Org. Chem.* **1988**, *53*, 4811.

<sup>398</sup>Brown; Zweifel *J. Am. Chem. Soc.* **1959**, *81*, 247; Pasto; Lepeska; Balasubramanian *J. Am. Chem. Soc.* **1972**, *94*, 6090; Pasto; Lepeska; Cheng *J. Am. Chem. Soc.* **1972**, *94*, 6083; Narayana; Periasamy *J. Chem. Soc., Chem. Commun.* **1987**, 1857. See, however, Jones *J. Org. Chem.* **1972**, *37*, 1886.

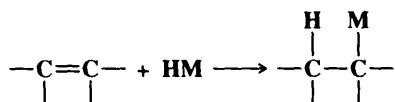
<sup>399</sup>See Still; Barrish *J. Am. Chem. Soc.* **1983**, *105*, 2487.

<sup>400</sup>See Evans; Fu; Hoveyda *J. Am. Chem. Soc.* **1988**, *110*, 6917; Burgess; Cassidy; Ohlmeyer *J. Org. Chem.* **1991**, *56*, 1020; Burgess; Ohlmeyer *J. Org. Chem.* **1991**, *56*, 1027.

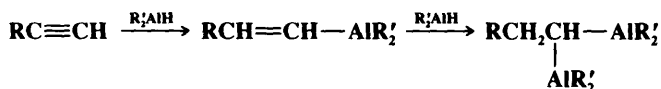
cedure can result in a change in regioselectivity as well, e.g., styrene  $\text{PhCH=CH}_2$  gave  $\text{PhCH(OH)CH}_3$ .<sup>401</sup>

OS VI, 719, 852, 919, 943; VII, 164, 339, 402, 427; 68, 130.

### 5-13 Other Hydrometalation Hydro-metallo-addition



Metal hydrides of groups 13 and 14 of the periodic table (e.g.,  $\text{AlH}_3$ ,  $\text{GaH}_3$ ) as well as many of their alkyl and aryl derivatives (e.g.,  $\text{R}_2\text{AlH}$ ,  $\text{Ar}_3\text{SnH}$ ) add to double bonds to give organometallic compounds.<sup>402</sup> The hydroboration reaction (5-12) is the most important example, but other important metals in this reaction are aluminum,<sup>403</sup> silicon, tin,<sup>404</sup> and zirconium<sup>405</sup> (a group 4 metal). Some of these reactions are uncatalyzed, but in other cases various types of catalyst have been used.<sup>406</sup> Hydrozirconation is most commonly carried out with  $\text{Cp}_2\text{ZrHCl}$  ( $\text{Cp}$  = cyclopentadienyl),<sup>407</sup> known as *Schwartz's reagent*. The mechanism with group 13 hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with group 14 hydrides a mechanism involving free radicals seems more likely. Dialkylmagnesiums have been obtained by adding  $\text{MgH}_2$  to double bonds.<sup>408</sup>  $\text{RMgX}$  can be added to an alkene  $\text{R'CH=CH}_2$  to give  $\text{R'CH}_2\text{CH}_2\text{MgX}$ , with  $\text{TiCl}_4$  as a catalyst (see also 8-12).<sup>409</sup> With some reagents triple bonds<sup>410</sup> can add 1 or 2 moles, e.g.,<sup>411</sup>



<sup>401</sup>Hayashi; Matsumoto; Ito, Ref. 395; Zhang; Lou; Guo; Dai *J. Org. Chem.* **1991**, 56, 1670.

<sup>402</sup>Negishi *Adv. Met.-Org. Chem.* **1989**, 1, 177-207; Eisch *The Chemistry of Organometallic Compounds*; Macmillan: New York, 1967, pp. 107-111. See also Eisch; Fichter *J. Organomet. Chem.* **1983**, 250, 63.

<sup>403</sup>For reviews of organoaluminums in organic synthesis, see Dzhemilev; Vostrikova; Tolstikov *Russ. Chem. Rev.* **1990**, 59, 1157-1173; Maruoka; Yamamoto *Tetrahedron* **1988**, 44, 5001-5032.

<sup>404</sup>For a review with respect to Al, Si, and Sn, see Negishi *Organometallics in Organic Synthesis*, vol. 1; Wiley: New York, 1980, pp. 45-48, 357-363, 406-412. For reviews of hydrosilylation, see Ojima, in Patai; Rappoport *The Chemistry of Organic Silicon Compounds*, pt. 2; Wiley: New York, 1989, pp. 1479-1526; Alberti; Pedulli *Rev. Chem. Intermed.* **1987**, 8, 207-246; Speier *Adv. Organomet. Chem.* **1979**, 17, 407-447; Andrianov; Souček; Khananashvili *Russ. Chem. Rev.* **1979**, 48, 657-668.

<sup>405</sup>For reviews of hydrozirconation, and the uses of organozirconium compounds, see Negishi; Takahashi *Synthesis* **1988**, 1-19; Dzhemilev; Vostrikova; Tolstikov *J. Organomet. Chem.* **1986**, 304, 17-39; Schwartz; Labinger *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 333-340 [*Angew. Chem.* 88, 402-409].

<sup>406</sup>See, for example, Oertle; Wettter *Tetrahedron Lett.* **1985**, 26, 5511; Randolph; Wrighton *J. Am. Chem. Soc.* **1986**, 108, 3366; Maruoka; Sano; Shinoda; Nakai; Yamamoto *J. Am. Chem. Soc.* **1986**, 108, 6036; Miyake; Yamamura *Chem. Lett.* **1989**, 981; Doyle; High; Nesloney; Clayton; Lin *Organometallics* **1991**, 10, 1225.

<sup>407</sup>For a method of preparing this reagent (which is also available commercially), see Buchwald; LaMaire; Nielsen; Watson; King *Tetrahedron Lett.* **1987**, 28, 3895. It can also be generated in situ: Lipshutz; Keil; Ellsworth *Tetrahedron Lett.* **1990**, 31, 7257.

<sup>408</sup>For a review, see Bogdanović *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 262-273 [*Angew. Chem.* 97, 253-264].

<sup>409</sup>For a review, see Sato *J. Organomet. Chem.* **1985**, 285, 53-64. For another catalyst, see Hoveyda; Xu *J. Am. Chem. Soc.* **1991**, 113, 5079.

<sup>410</sup>For a review of the hydrometalation of triple bonds, see Ref. 386, pp. 219-232.

<sup>411</sup>Wilke; Müller *Liebigs Ann. Chem.* **1960**, 629, 222; Eisch; Kaska *J. Am. Chem. Soc.* **1966**, 88, 2213; Eisch; Rhee *Liebigs Ann. Chem.* **1975**, 565.

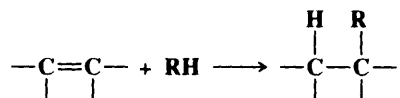
When 2 moles are added, electrophilic addition generally gives 1,1-dimetallic products (as with hydroboration), while free-radical addition usually gives the 1,2-dimetallic products.

OS VII, 456; **66**, 60; **67**, 86; **69**, 106. See also OS **66**, 43, 75.

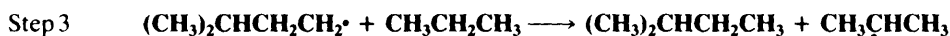
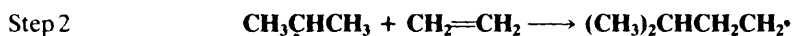
## G. Carbon on the Other Side

### 5-14 Addition of Alkanes

#### Hydro-alkyl-addition

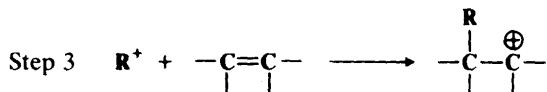
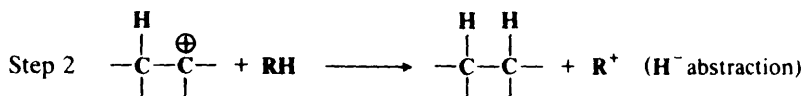
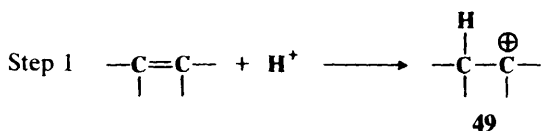


There are two important ways of adding alkanes to olefins—the thermal method and the acid-catalysis method.<sup>412</sup> Both give chiefly mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method the reactants are heated to high temperatures (about 500°C) at high pressures (150 to 300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.<sup>413</sup> The mechanism is undoubtedly of a free-radical type and can be illustrated by one possible sequence in the reaction between propane and ethylene:



There is kinetic evidence that the initiation takes place primarily by steps like 1, which are called *symproportionation* steps<sup>414</sup> (the opposite of disproportionation, p. 194).

In the acid-catalysis method, a proton or Lewis acid is used as the catalyst and the reaction is carried out at temperatures between -30 and 100°C. This is a Friedel-Crafts process with a carbocation mechanism<sup>415</sup> (illustrated for a proton acid catalyst):

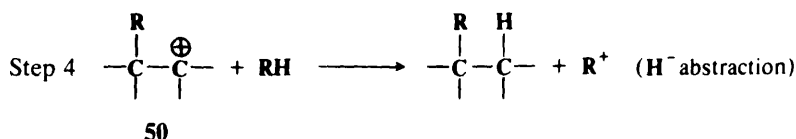


<sup>412</sup>For reviews, see Shuikin; Lebedev *Russ. Chem. Rev.* **1966**, 35, 448-455; Schmerling, in Olah *Friedel-Crafts and Related Reactions*, vol. 2; Wiley: New York, 1964, pp. 1075-1111, 1121-1122.

<sup>413</sup>Frey; Hepp *Ind. Eng. Chem.* **1936**, 28, 1439.

<sup>414</sup>Metzger *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 889 [*Angew. Chem.* 95, 914]; Hartmanns; Klenke; Metzger *Chem. Ber.* **1986**, 119, 488.

<sup>415</sup>For a review, see Mayr *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1371-1384 [*Angew. Chem.* 102, 1415-1428].



**50** often rearranges before it abstracts a hydride ion, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane. It is also possible for **49** (or **50**) instead of abstracting a hydride ion, to add to another mole of olefin, so that not only rearrangement products but also dimeric and polymeric products are frequent. If the tri- or tetrasubstituted olefins are treated with  $\text{Me}_4\text{Si}$ ,  $\text{HCl}$ , and  $\text{AlCl}_3$ , they become protonated to give a tertiary carbocation, which reacts with the  $\text{Me}_4\text{Si}$  to give a product that is the result of addition of  $\text{H}$  and  $\text{Me}$  to the original alkene.<sup>416</sup> (For a free-radical hydro-methyl-addition, see **5-20**.)

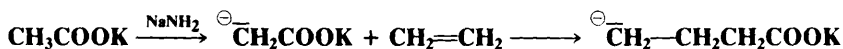
The addition of secondary or tertiary cations (generated from the corresponding alcohols, esters, or alkenes) to 1,1-dichloroethene gives carboxylic acids by hydrolysis of the intermediate ions (see **0-3**):<sup>417</sup>



The reaction can also be base-catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.<sup>418</sup> Carbanions most often used are those stabilized by one or more  $\alpha$ -aryl groups. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane:<sup>419</sup>



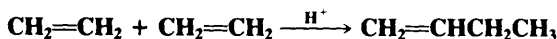
Conjugated dienes give 1,4 addition.<sup>420</sup> This reaction has also been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids<sup>421</sup> (see also **0-96**).



OS I, 229; IV, 665; VII, 479.

## 5-15 Addition of Alkenes and/or Alkynes to Alkenes and/or Alkynes

### Hydro-alkenyl-addition



<sup>416</sup>Bolestova; Parnes; Kursanov *J. Org. Chem. USSR* **1983**, 19, 2175.

<sup>417</sup>For reviews, see Bott *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 171-178 [*Angew. Chem.* 92, 169-176]; Bott; Hellmann *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 870-874 [*Angew. Chem.* 78, 932-936]. *Newer Methods Prep. Org. Chem.* **1971**, 6, 67-80.

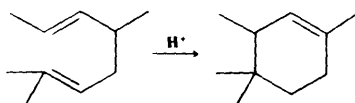
<sup>418</sup>For reviews, see Pines; Stalick, Ref. 198, pp. 240-422; Pines *Acc. Chem. Res.* **1974**, 7, 155-162; Pines; Schaap *Adv. Catal.* **1960**, 12, 117-148, pp. 126-146.

<sup>419</sup>Pines; Wunderlich *J. Am. Chem. Soc.* **1958**, 80, 6001.

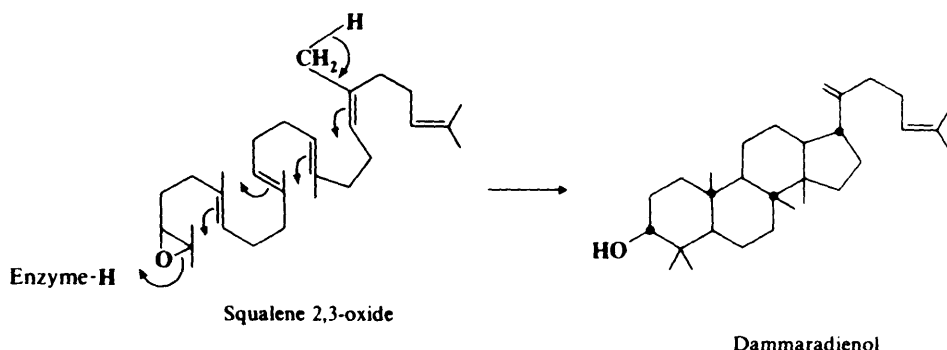
<sup>420</sup>Eberhardt; Peterson *J. Org. Chem.* **1965**, 30, 82; Pines; Stalick *Tetrahedron Lett.* **1968**, 3723.

<sup>421</sup>Schmerling; Toekelt *J. Am. Chem. Soc.* **1962**, 84, 3694.

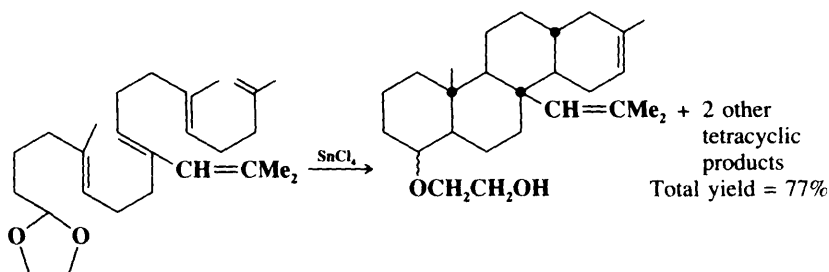
With certain substrates, alkenes can be dimerized by acid catalysts, so that the product is a dimer that contains one double bond.<sup>422</sup> This reaction is more often carried out internally, e.g.,



Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes. For example, squalene 2,3-oxide is converted by enzymic catalysis to dammaradienol.



The squalene  $\rightarrow$  lanosterol biosynthesis (which is a key step in the biosynthesis of cholesterol) is similar. The idea that the biosynthesis of such compounds involves this type of multiple ring closing was proposed in 1955 and is known as the *Stork–Eschenmoser hypothesis*.<sup>423</sup> Such reactions can also be carried out in the laboratory, without enzymes.<sup>424</sup> By putting cation-stabilizing groups at positions at which positive charges develop, Johnson and co-workers have been able to close as many as four rings stereoselectively and in high yield, in one operation.<sup>425</sup> An example is



which uses the  $\text{CH}=\text{CHMe}_2$  group as the cation-stabilizing auxilliary.

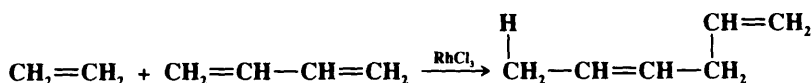
<sup>422</sup>For a review, see Onsager; Johansen, in Hartley; Patai *The Chemistry of the Metal–Carbon Bond*, vol. 3; Wiley: New York, 1985, pp. 205–257.

<sup>423</sup>Stork; Burgstahler *J. Am. Chem. Soc.* **1955**, *77*, 5068; Eschenmoser; Ruzicka; Jeger; Arigoni *Helv. Chim. Acta* **1955**, *38*, 1890.

<sup>424</sup>For reviews, see Gnonlonfon *Bull. Soc. Chim. Fr.* **1988**, 862–869; Sutherland *Chem. Soc. Rev.* **1980**, *9*, 265–280; Johnson *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9–17 [*Angew. Chem.* **88**, 33–40], *Bioorg. Chem.* **1976**, *5*, 51–98. *Acc. Chem. Res.* **1968**, *1*, 1–8; van Tamelen *Acc. Chem. Res.* **1975**, *8*, 152–158. For a review of the stereochemical aspects, see Bartlett, in Morrison, Ref. 232, vol. 3, pp. 341–409.

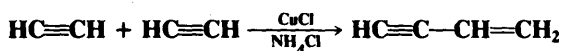
<sup>425</sup>Johnson; Telfer; Cheng; Schubert *J. Am. Chem. Soc.* **1987**, *109*, 2517; Johnson; Lindell; Steele *J. Am. Chem. Soc.* **1987**, *109*, 5852; Guay; Johnson; Schubert *J. Org. Chem.* **1989**, *54*, 4731.

The addition of olefins to olefins<sup>426</sup> can also be accomplished by bases<sup>427</sup> as well as by the use of catalyst systems<sup>428</sup> consisting of nickel complexes and alkylaluminum compounds (known as *Ziegler catalysts*),<sup>429</sup> catalysts derived from rhodium chloride,<sup>430</sup> and other transition metal catalysts. These and similar catalysts also catalyze the 1,4-addition of olefins to conjugated dienes,<sup>431</sup> e.g.,



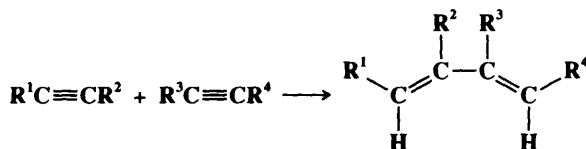
and the dimerization of 1,3-butadienes to octatrienes.<sup>432</sup>

In the presence of cuprous chloride and ammonium chloride, acetylene adds to another molecule of itself to give vinylacetylene.



This type of alkyne dimerization is also catalyzed by certain nickel complexes, as well as other catalysts<sup>433</sup> and has been carried out internally to convert diynes to large-ring cycloalkynes with an exocyclic double bond.<sup>434</sup>

In another type of alkyne dimerization, two molecules of alkyne, the same or different, can be coupled to give a 1,3-diene<sup>435</sup>



In this method, one alkyne is treated with Schwartz's reagent (see 5-13) to produce a vinylic zirconium intermediate. Addition of MeLi or MeMgBr, followed by the second alkyne, gives another intermediate, which, when treated with aqueous acid, gives the diene in moderate-to-good yields. The stereoisomer shown is the one formed in usually close to 100% purity. If the second intermediate is treated with I<sub>2</sub> instead of aqueous acid, the 1,4-diiodo-1,3-diene is obtained instead, in comparable yield and isomeric purity. This reaction can

<sup>426</sup>For a review of olefin dimerization and oligomerization with all catalysts, see Fel'dblyum; Obeshchalova *Russ. Chem. Rev.* **1968**, 37, 789-797.

<sup>427</sup>For a review, see Pines *Synthesis* **1974**, 309-327.

<sup>428</sup>For reviews, see Pillai; Ravindranathan; Sivaram *Chem. Rev.* **1986**, 86, 353-399; Jira; Freiesleben *Organomet. React.* **1972**, 3, 1-190, pp. 117-130; Heck, Ref. 223, pp. 84-94, 150-157; Khan; Martell, Ref. 159, vol. 2, pp. 135-15; Rylander Ref. 223, pp. 175-196; Tsuji *Adv. Org. Chem.* **1969**, 6, 109-255, pp. 213-220.

<sup>429</sup>See for example, Onsager; Wang; Blindheim *Helv. Chim. Acta* **1969**, 52, 187, 230; Fischer; Jonas; Misbach; Stabba; Wilke *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 943 [*Angew. Chem.* **85**, 1002].

<sup>430</sup>Cramer *J. Am. Chem. Soc.* **1965**, 87, 4717; Acc. Chem. Res. **1968**, 1, 186-191; Kobayashi; Taira *Tetrahedron* **1968**, 24, 5763; Takahashi; Okura; Keii *J. Am. Chem. Soc.* **1975**, 97, 7489.

<sup>431</sup>Alderson; Jenner; Lindsey *J. Am. Chem. Soc.* **1965**, 87, 5638. For a review see Su *Adv. Organomet. Chem.* **1979**, 17, 269-318.

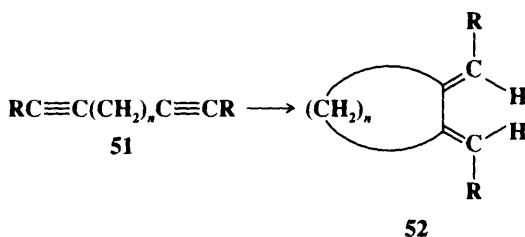
<sup>432</sup>See, for example, Denis; Jean; Croizy; Mortreux; Petit *J. Am. Chem. Soc.* **1990**, 112, 1292.

<sup>433</sup>See for example, Carlton; Read *J. Chem. Soc., Perkin Trans. 1* **1978**, 1631; Schmitt; Singer *J. Organomet. Chem.* **1978**, 153, 165; Selimov; Rutman; Dzhemilev *J. Org. Chem. USSR* **1983**, 19, 1621.

<sup>434</sup>Trost; Matsubara; Carinji *J. Am. Chem. Soc.* **1989**, 111, 8745.

<sup>435</sup>Buchwald; Nielsen *J. Am. Chem. Soc.* **1989**, 111, 2870.

also be done intramolecularly: Diynes **51** can be cyclized to *E,E* exocyclic dienes **52** by treatment with a zirconium complex.<sup>436</sup>



Rings of 4, 5, and 6 members were obtained in high yield; 7-membered rings in lower yield. When the reaction is applied to enynes, compounds similar to **52** but with only one double bond are obtained.<sup>437</sup>

In a conversion that is formally similar, substituted alkenes ( $\text{CH}_2=\text{CH}-\text{Y}$ ;  $\text{Y} = \text{R}, \text{COOMe}, \text{OAc}, \text{CN}, \text{etc.}$ ) can be dimerized to substituted alkanes  $\text{CH}_3\text{CHYCHYCH}_3$  by photolysis in an  $\text{H}_2$  atmosphere, using  $\text{Hg}$  as a photosensitizer.<sup>438</sup> Still another procedure involves palladium-catalyzed addition of vinylic halides to triple bonds to give 1,3-dienes.<sup>439</sup>

Olefins and alkynes can also add to each other to give cyclic products in other ways (see **5-49** and **5-51**).

OS **65**, **42**; **66**, **52**, **75**; **67**, **48**.

## 5-16 The Ene Synthesis

### Hydro-allyl-addition



Olefins can add to double bonds in a reaction different from those discussed in **5-15**, which, however, is still formally the addition of  $\text{RH}$  to a double bond. This reaction is called the *ene synthesis*<sup>440</sup> and bears a certain similarity to the Diels–Alder reaction (**5-47**). For the reaction to proceed without a catalyst, one of the components must be a reactive dienophile (see **5-47** for a definition of this word) such as maleic anhydride, but the other (which supplies the hydrogen) may be a simple alkene such as propene. There has been much discussion of the mechanism of this reaction, and both concerted pericyclic (as shown above) and stepwise mechanisms have been suggested. The reaction between maleic anhydride and optically active  $\text{PhCHMeCH}=\text{CH}_2$  gave an optically active product,<sup>441</sup> which is strong evi-

<sup>436</sup>Nugent; Thorn; Harlow *J. Am. Chem. Soc.* **1987**, *109*, 2788. See also Trost; Lee *J. Am. Chem. Soc.* **1988**, *110*, 7255; Tamao; Kobayashi; Ito *J. Am. Chem. Soc.* **1989**, *111*, 6478.

<sup>437</sup>RajanBabu; Nugent; Taber; Fagan *J. Am. Chem. Soc.* **1988**, *110*, 7128.

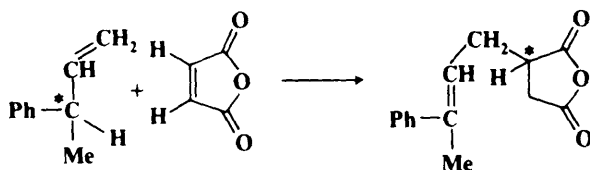
<sup>438</sup>Muedas; Ferguson; Crabtree *Tetrahedron Lett.* **1989**, *30*, 3389.

<sup>439</sup>Arcadi; Bernocchi; Burini; Cacchi; Marinelli; Pietroni *Tetrahedron Lett.* **1989**, *30*, 3465.

<sup>440</sup>Alder; Brachel *Liebigs Ann. Chem.* **1962**, *651*, 141. For a monograph, see Carruthers *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Elmsford, NY, 1990. For reviews, see Boyd, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 477-525; Keung; Alper *J. Chem. Educ.* **1972**, *49*, 97-100; Hoffmann *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 556-577 [*Angew. Chem.* *81*, 597-618]. For reviews of intramolecular ene reactions see Taber *Intramolecular Diels–Alder and Alder Ene Reactions*; Springer: New York, 1984; pp. 61-94; Oppolzer; Snieckus *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476-486 [*Angew. Chem.* *90*, 506-507]. Conia; Le Perchec *Synthesis* **1975**, 1-19. For a review of ene reactions in which one of the reactants bears a Si atom, see Dubac; Laporterie *Chem. Rev.* **1987**, *87*, 319-334.

Rabinovitz *J. Am. Chem. Soc.* **1964**, *86*, 965. See also Garsky; Koster; Arnold *J. Am. Chem. Soc.* **1974**, *96*, 1300; Mattern *J. Org. Chem.* **1976**, *41*, 3614; Nahm; Cheng *J. Org. Chem.* **1986**, *51*, 5093.

dence for a concerted rather than a stepwise mechanism.<sup>442</sup> The reaction can be extended

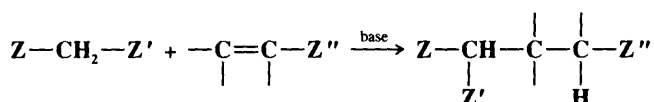


to less-reactive enophiles by the use of Lewis-acid catalysts, especially alkylaluminum halides.<sup>443</sup> The Lewis-acid catalyzed reaction probably has a stepwise mechanism.<sup>444</sup>

OS IV, 766; V, 459. See also OS 65, 159.

## 5-17 The Michael Reaction

**Hydro-bis(ethoxycarbonyl)methyl-addition,** etc.



Compounds containing electron-withdrawing groups (Z is defined on p. 741) add, in the presence of bases, to olefins of the form  $\text{C}=\text{C}-\text{Z}$  (including quinones). This is called the *Michael reaction* and involves conjugate addition.<sup>445</sup> The base removes the acidic proton and then the mechanism is as outlined on p. 741. The reaction has been carried out with malonates, cyanoacetates, acetoacetates, other  $\beta$ -keto esters, and compounds of the form  $\text{ZCH}_3$ ,  $\text{ZCH}_2\text{R}$ ,  $\text{ZCHR}_2$ , and  $\text{ZCHRZ}'$ , including carboxylic esters, ketones, aldehydes, nitriles, nitro compounds,<sup>446</sup> and sulfones, as well as other compounds with relatively acidic hydrogens, such as indenes and fluorenes. These reagents do not add to ordinary double bonds, except in the presence of free-radical initiators (5-22). 1,2 addition (to the  $\text{C}=\text{O}$  or  $\text{C}\equiv\text{N}$  group) often competes and sometimes predominates (6-41).<sup>447</sup> In particular,  $\alpha,\beta$ -unsaturated aldehydes seldom give 1,4 addition.<sup>448</sup> The Michael reaction has traditionally been performed in protic solvents, with catalytic amounts of base, but more recently better yields with fewer side reactions have been obtained in some cases by using an equimolar amount of base to convert the nucleophile to its enolate form (*preformed enolate*). In particular, preformed enolates are often used where stereoselective reactions are desired.<sup>449</sup>

<sup>442</sup>For other evidence for a concerted mechanism see Benn; Dwyer; Chappell *J. Chem. Soc., Perkin Trans. 2* **1977**, 533; Jenner; Salem; El'yanov; Gonikberg *J. Chem. Soc., Perkin Trans. 2* **1989**, 1671.

<sup>443</sup>For reviews, see Chaloner, in Hartley, Ref. 218, vol. 4, pp. 456-460; Snider *Acc. Chem. Res.* **1980**, 13, 426-432.

<sup>444</sup>See Snider; Ron *J. Am. Chem. Soc.* **1985**, 107, 8160.

<sup>445</sup>For reviews, see Yanovskaya; Kryshnal; Kulganek *Russ. Chem. Rev.* **1984**, 53, 744-756; Bergmann; Ginsburg; Pappo *Org. React.* **1959**, 10, 179-560; House, Ref. 144, pp. 595-623. The subject is also discussed at many places in *Stowell Carbanions in Organic Synthesis*; Wiley: New York, 1979.

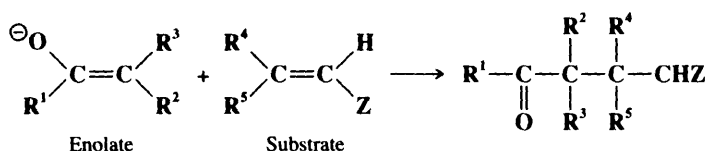
<sup>446</sup>For reviews of Michael reactions where Z or Z' is nitro see Yoshikoshi; Miyashita *Acc. Chem. Res.* **1985**, 18, 284-290; Baer; Urbas, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, pt. 2; Wiley: New York, 1970, pp. 130-148.

<sup>447</sup>For a discussion of 1,2 vs. 1,4 addition, see Oare; Heathcock, *Top. Stereochem.* **1989**, Ref. 449, pp. 232-236.

<sup>448</sup>For reports of successful 1,4 additions to  $\alpha,\beta$ -unsaturated aldehydes, see Kryshnal; Kulganek; Kucherov; Yanovskaya *Synthesis* **1979**, 107; Yamaguchi; Yokota; Minami *J. Chem. Soc., Chem. Commun.* **1991**, 1088.

<sup>449</sup>For reviews of stereoselective Michael additions, see Oare; Heathcock *Top. Stereochem.* **1991**, 20, 87-170. **1989**, 19, 227-407.

In a Michael reaction with suitably different R groups, two new chiral centers are created:

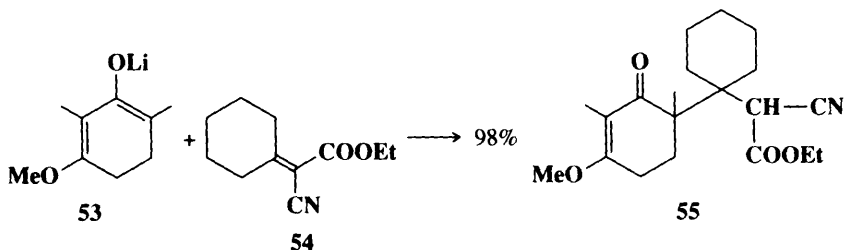


Thus the product in such cases can exist as two pairs of enantiomers.<sup>450</sup> In a diastereoselective process one of the two pairs is formed exclusively or predominantly, as a racemic mixture. Many such examples have been reported.<sup>449</sup> In many of these cases, both the enolate and substrate can exist as *Z* or *E* isomers. With enolates derived from ketones or carboxylic esters, *E* enolates gave the syn pair of enantiomers (p. 115), while *Z* enolates gave the anti pair.<sup>451</sup>

When either or both of the reaction components has a chiral substituent, the reaction can be enantioselective (only one of the four diastereomers formed predominantly), and this has been accomplished a number of times.<sup>452</sup> Enantioselective addition has also been achieved by the use of a chiral catalyst<sup>453</sup> and by using optically active enamines instead of enolates.<sup>454</sup>

Mannich bases (see 6-16) and  $\beta$ -halo carbonyl compounds can also be used as substrates; these are converted to the  $\text{C}=\text{C}-\text{Z}$  compounds in situ by the base (6-16, 7-13).<sup>455</sup> Substrates of this kind are especially useful in cases where the  $\text{C}=\text{C}-\text{Z}$  compound is unstable. The reaction of  $\text{C}=\text{C}-\text{Z}$  compounds with enamines (2-19) can also be considered a Michael reaction. Michael reactions are reversible (7-20).

When the substrate contains *gem*-Z groups, e.g., 54, bulky groups can be added, if the



reaction is carried out under aprotic conditions. For example, addition of enolate 53 to 54 gave 55 in which two adjacent quaternary centers have been formed.<sup>456</sup>

In certain cases, Michael reactions can take place under acidic conditions.<sup>457</sup>

<sup>450</sup>For a more extended analysis, see Oare; Heathcock *Top. Stereochem.* **1989**, Ref. 449, pp. 237-242.

<sup>451</sup>For example, see Oare; Heathcock *J. Org. Chem.* **1990**, 55, 157.

<sup>452</sup>See, for example, Corey; Peterson *Tetrahedron Lett.* **1985**, 26, 5025; Calderari; Seebach *Helv. Chim. Acta* **1985**, 68, 1592; Tomioka; Ando; Yasuda; Koga *Tetrahedron Lett.* **1986**, 27, 715; Posner; Switzer *J. Am. Chem. Soc.* **1986**, 108, 1239; Enders; Demir; Rendenbach *Chem. Ber.* **1987**, 120, 1731.

<sup>453</sup>Yura; Iwasaka; Mukaiyama *Chem. Lett.* **1988**, 1021; Yura; Iwasaka; Narasaka; Mukaiyama *Chem. Lett.* **1988**, 1025; Desimoni; Quadrelli; Righetti *Tetrahedron* **1990**, 46, 2927.

<sup>454</sup>See d'Angelo; Revial; Volpe; Pfau *Tetrahedron Lett.* **1988**, 29, 4427.

<sup>455</sup>Mannich bases react with ketones without basic catalysts to give 1,5-diketones, but this process, known as the thermal-Michael reaction, has a different mechanism: Brown; Buchanan; Curran; McLay *Tetrahedron* **1968**, 24, 4565; Gill; James; Lions; Potts *J. Am. Chem. Soc.* **1952**, 74, 4923.

<sup>456</sup>Holton; Williams; Kennedy *J. Org. Chem.* **1986**, 51, 5480.

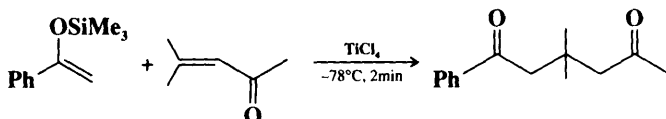
<sup>457</sup>See Hajos; Parrish *J. Org. Chem.* **1974**, 39, 1612; *Org. Synth. VII*, 363.

Michael reactions are sometimes applied to substrates of the type  $\text{C}\equiv\text{C}-\text{Z}$ , e.g.,

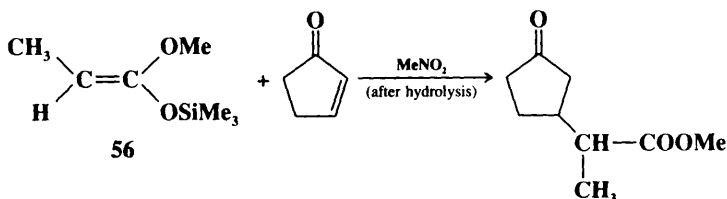


Indeed, because of the greater susceptibility of triple bonds to nucleophilic attack, it is even possible for nonactivated alkynes, e.g., acetylene, to be substrates in this reaction.<sup>458</sup>

In a closely related reaction, silyl enol ethers add to  $\alpha,\beta$ -unsaturated ketones and esters when catalyzed<sup>459</sup> by  $\text{TiCl}_4$ , e.g.,<sup>460</sup>

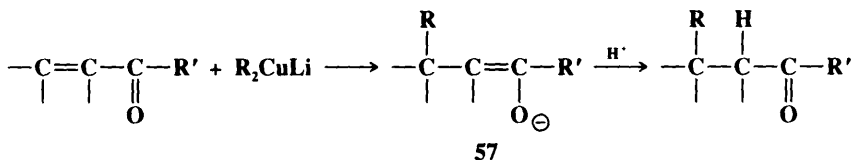


This reaction, also, has been performed diastereoselectively.<sup>461</sup> Allylic silanes  $\text{R}_2\text{C}=\text{CHCH}_2\text{SiMe}_3$  can be used instead of silyl enol ethers (the *Sakurai reaction*).<sup>462</sup> Similarly, silyl ketene acetals, e.g., **56**, give  $\delta$ -keto esters, in  $\text{MeNO}_2$  as solvent, for example,<sup>463</sup>



OS I, 272; II, 200; III, 286; IV, 630, 652, 662, 776; V, 486, 1135; VI, 31, 648, 666, 940; VII, 50, 363, 368, 414, 443; **65**, 12, 98; **66**, 37; **69**, 173, 226. See also OS **65**, 236.

## 5-18 1,4 Addition of Organometallic Compounds to Activated Double Bonds Hydro-alkyl-addition



<sup>458</sup>See, for example, Makosza *Tetrahedron Lett.* **1966**, 5489.

<sup>459</sup>Other catalysts have also been used. For a list of catalysts, with references, see Ref. 133, pp. 793-795. See also Mukaiyama; Kobayashi; Tamura; Sagawa *Chem. Lett.* **1987**, 491; Mukaiyama; Kobayashi *J. Organomet. Chem.* **1990**, 382, 39.

<sup>460</sup>Narasaka; Soai; Aikawa; Mukaiyama *Bull. Chem. Soc. Jpn.* **1976**, 49, 779; Saigo; Osaki; Mukaiyama *Chem. Lett.* **1976**, 163; Matsuda *J. Organomet. Chem.* **1987**, 321, 307; Narasaka *Org. Synth.* 65, 12. See also Yoshikoshi; Miyashita. Ref. 446.

<sup>461</sup>See Heathcock; Uehling *J. Org. Chem.* **1986**, 51, 279; Mukaiyama; Tamura; Kobayashi *Chem. Lett.* **1986**, 1017, 1817, 1821, **1987**, 743.

<sup>462</sup>Hosomi; Sakurai *J. Am. Chem. Soc.* **1977**, 99, 1673; Jellal; Santelli *Tetrahedron Lett.* **1980**, 21, 4487; Sakurai; Hosomi; Hayashi *Org. Synth. VII*, 443. For a review, see Fleming; Dunoguès; Smithers *Org. React.* **1989**, 37, 57-575, pp. 127-132, 335-370. For a review of intramolecular additions, see Schinzer *Synthesis* **1988**, 263-273.

<sup>463</sup>RajanBabu *J. Org. Chem.* **1984**, 49, 2083.

Lithium dialkylcopper reagents (see 0-87) add to  $\alpha,\beta$ -unsaturated aldehydes<sup>464</sup> and ketones ( $R' = H, R, Ar$ ) to give conjugate addition products<sup>465</sup> in a reaction closely related to the Michael reaction.  $\alpha,\beta$ -Unsaturated esters are less reactive,<sup>466</sup> and the corresponding acids do not react at all. R can be primary alkyl, vinylic, or aryl. If  $Me_3SiCl$  is present, the reaction takes place much faster and with higher yields; in this case the product is the silyl enol ether of 57 (see 2-23).<sup>467</sup> The use of  $Me_3SiCl$  also permits good yields with allylic R groups.<sup>468</sup>

Various functional groups such as OH and unconjugated C=O groups may be present in the substrate.<sup>469</sup> A characteristic of the reaction is that only one of the R groups of  $R_2CuLi$  adds to the substrate; the other is wasted. This can be a limitation where the precursor (RLi or RCu, see 2-35) is expensive or available in limited amounts. The difficulty can be overcome by using one of the mixed reagents  $R(R'C\equiv C)CuLi$ ,<sup>470</sup>  $R(O-t-Bu)CuLi$ ,<sup>471</sup> or  $R(PhS)CuLi$ ,<sup>472</sup> each of which transfers only the R group. These reagents are easily prepared by the reaction of RLi with  $R'C\equiv CCu$  ( $R' = n-Pr$  or  $t-Bu$ ),  $t-BuOCu$ , or  $PhSCu$ , respectively. A further advantage of the mixed reagents is that good yields of addition product are achieved when R is tertiary, so that use of one of them permits the introduction of a tertiary alkyl group. The mixed reagents  $R(CN)CuLi$ <sup>473</sup> (prepared from RLi and  $CuCN$ ) and  $R_2Cu(CN)Li_2$ <sup>474</sup> also selectively transfer the R group.<sup>475</sup> The reaction has also been carried out with  $\alpha,\beta$ -acetylenic ketones, esters, and nitriles.<sup>476</sup> Conjugate addition to  $\alpha,\beta$ -unsaturated and acetylenic acids and esters, as well as ketones, can be achieved by the use of the coordinated reagents  $RCu\cdot BF_3$  (R = primary).<sup>477</sup> Alkylcopper compounds  $RCu$  (R = primary or secondary alkyl) have also been used with tetramethylethylenediamine and  $Me_3SiCl$  to give silyl enol ethers from  $\alpha,\beta$ -unsaturated ketones in high yield.<sup>478</sup>

There is generally little or no competition from 1,2 addition (to the C=O). However, when R is allylic, 1,4 addition is observed with some substrates and 1,2 addition with others.<sup>479</sup>  $R_2CuLi$  also add to  $\alpha,\beta$ -unsaturated sulfones<sup>480</sup> but not to simple  $\alpha,\beta$ -unsaturated nitriles.<sup>481</sup>

<sup>464</sup>Chuit; Foulon; Normant *Tetrahedron* **1980**, 36, 2305, **1981**, 37, 1385. For a review, see Alexakis; Chuit; Comerçon-Bourgain; Foulon; Jabri; Mangeney; Normant *Pure Appl. Chem.* **1984**, 56, 91-98. A better reagent for the addition of a methyl group to an  $\alpha,\beta$ -unsaturated aldehyde is  $Me_3Cu_3Li_2$ ; Clive; Farina; Beaulieu, *J. Org. Chem.* **1982**, 47, 2572.

<sup>465</sup>House; Respass; Whitesides *J. Org. Chem.* **1966**, 31, 3128. For reviews, see Posner *Org. React.* **1972**, 19, 1-113; House *Acc. Chem. Res.* **1976**, 9, 59-67. For examples of the use of this reaction in the synthesis of natural products, see Posner *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York 1980, pp. 10-67. For a list of organocopper reagents that give this reaction, with references, see Ref. 133, pp. 805-809, 916-920.

<sup>466</sup> $R_2CuLi$  also add to N-tosylated  $\alpha,\beta$ -unsaturated amides: Nagashima; Ozaki; Washiyama; Itoh *Tetrahedron Lett.* **1985**, 26, 657.

<sup>467</sup>Corey; Boaz *Tetrahedron Lett.* **1985**, 26, 6019; Alexakis; Berlan; Besace *Tetrahedron Lett.* **1986**, 27, 1047; Matsuzaki; Horiguchi; Nakamura; Kuwajima *Tetrahedron* **1989**, 45, 349; Horiguchi; Komatsu; Kuwajima *Tetrahedron Lett.* **1989**, 30, 7087; Linderman; McKenzie *J. Organomet. Chem.* **1989**, 361, 31; Bertz; Smith *Tetrahedron* **1990**, 46, 4091. For a list of references, see Ref. 133, p. 748.

<sup>468</sup>Lipshutz; Ellsworth; Dimock; Smith *J. Am. Chem. Soc.* **1990**, 112, 4404.

<sup>469</sup>For the use of enol tosylates of 1,2-diketones as substrates, see Charonnat; Mitchell; Keogh *Tetrahedron Lett.* **1990**, 31, 315.

<sup>470</sup>Corey; Beames *J. Am. Chem. Soc.* **1972**, 94, 7210; House; Umen *J. Org. Chem.* **1973**, 38, 3893; Corey; Floyd; Lipshutz *J. Org. Chem.* **1978**, 43, 3419.

<sup>471</sup>Posner; Whitten *Tetrahedron Lett.* **1973**, 1815.

<sup>472</sup>Posner; Whitten; Sterling *J. Am. Chem. Soc.* **1973**, 95, 7788.

<sup>473</sup>Gorlier; Hamon; Levisalles; Wagnon *J. Chem. Soc., Chem. Commun.* **1973**, 88. For another useful mixed reagent see Leddic; Miller *J. Org. Chem.* **1979**, 44, 1006.

<sup>474</sup>Lipshutz; Wilhelm; Kozlowski *Tetrahedron Lett.* **1982**, 23, 3755; Lipshutz *Tetrahedron Lett.* **1983**, 24, 127.

<sup>475</sup>When the two R groups of  $R_2Cu(CN)Li_2$  are different, one can be selectively transferred: Lipshutz; Wilhelm; Kozlowski *J. Org. Chem.* **1984**, 49, 3938.

<sup>476</sup>For a list of references, see Ref. 133, pp. 237-238.

<sup>477</sup>For a review, see Yamamoto *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 947-959 [*Angew. Chem.* 98, 945-957]. For a discussion of the role of the  $BF_3$ , see Lipshutz; Ellsworth; Siahaan *J. Am. Chem. Soc.* **1988**, 110, 4834, **1989**, 111, 1351.

<sup>478</sup>Johnson; Marren *Tetrahedron Lett.* **1987**, 28, 27.

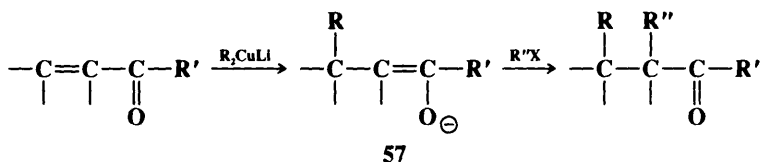
<sup>479</sup>House; Fischer *J. Org. Chem.* **1969**, 34, 3615. See also Daviaud; Miginiac *Tetrahedron Lett.* **1973**, 3345.

<sup>480</sup>Posner; Brunelle *Tetrahedron Lett.* **1973**, 935.

<sup>481</sup>House; Umen Ref. 470.

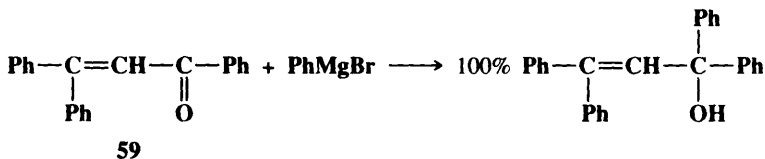
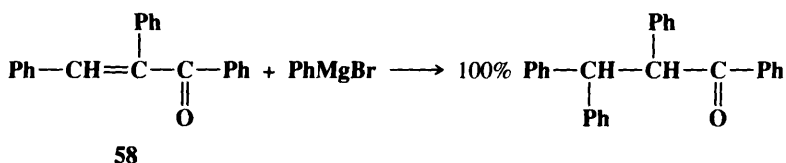
Organocopper reagents  $\text{RCu}$  (as well as certain  $\text{R}_2\text{CuLi}$ ) add to  $\alpha,\beta$ -unsaturated and acetylenic sulfoxides.<sup>482</sup>

Usually, after an enolate ion is generated from an  $\alpha,\beta$ -unsaturated ketone, it is converted to the  $\beta$ -alkylated product as shown above. But it is often possible to have the enolate react with some other electrophile (*tandem vicinal difunctionalization*), in some cases at the O and in other cases at the C.<sup>483</sup> For example, if an alkyl halide  $\text{R}''\text{X}$  is present ( $\text{R}''$  = primary alkyl or allylic), and the solvent is 1,2-dimethoxyethane, the enolate **57** can be alkylated



directly.<sup>484</sup> Thus, by this method, both the  $\alpha$  and  $\beta$  positions of a ketone are alkylated in one synthetic operation (see also 5-53).

Grignard reagents also add to these substrates, but with these reagents, 1,2 addition may seriously compete:<sup>485</sup> The product is often controlled by steric factors. Thus **58** with phenylmagnesium bromide gives 100% 1,4 addition, while **59** gives 100% 1,2 addition. In general,



substitution at the carbonyl group increases 1,4 addition, while substitution at the double bond increases 1,2 addition. In most cases both products are obtained, but  $\alpha,\beta$ -unsaturated *aldehydes* nearly always give exclusive 1,2 addition when treated with Grignard reagents. However, the extent of 1,4 addition of Grignard reagents can be increased by the use of a copper ion catalyst, e.g.,  $\text{CuCl}$ ,  $\text{Cu}(\text{OAc})_2$ .<sup>486</sup> It is likely that alkylcopper reagents, formed from  $\text{RMgX}$  and  $\text{Cu}^+$  (cupric acetate is reduced to cuprous ion by excess  $\text{RMgX}$ ), are the actual attacking species in these cases.<sup>465</sup> Alkylolithiums,<sup>487</sup> treated with compounds of the form  $\text{C}=\text{C}-\text{COCH}_3$  and  $\text{C}=\text{C}-\text{COOC}_2\text{H}_5$ , gave only 1,2 addition,<sup>488</sup> but 1,4 addition was achieved with esters of the form  $\text{C}=\text{C}-\text{COOAr}$ , where Ar was a bulky group such as 2,6-

<sup>482</sup>Truce; Lusch *J. Org. Chem.* **1974**, 39,3174, **1978**, 43, 2252.

<sup>483</sup>For reviews of such reactions, see Chapdelaine; Hulce *Org. React.* **1990**, 38, 225-653; Taylor *Synthesis* **1985**, 364-392. For a list of references, see Ref. 133, pp. 810-811, 922.

<sup>484</sup>Coates; Sandefur *J. Org. Chem.* **1974**, 39, 275; Posner; Lentz *Tetrahedron Lett.* **1977**, 3215.

<sup>485</sup>For a discussion of the factors affecting 1,2 vs. 1,4 addition, see Negishi, Ref. 404, pp. 127-133.

<sup>486</sup>Posner, Ref. 465.

<sup>487</sup>For a review of addition of organolithium compounds to double bonds, see Hunt *Org. Prep. Proced. Int.* **1989**, 21, 705-749.

<sup>488</sup>Rozhkov; Makin *J. Gen. Chem. USSR* **1964**, 34, 57. For a discussion of 1,2 vs. 1,4 addition with organolithiums, see Cohen; Abraham; Myers *J. Am. Chem. Soc.* **1987**, 109, 7923.

di-*t*-butyl-4-methoxyphenyl.<sup>489</sup> Also, alkyllithiums can be made to give 1,4 addition with  $\alpha,\beta$ -unsaturated ketones<sup>490</sup> and aldehydes<sup>491</sup> if the reactions are conducted in the presence of HMPA. Among alkyllithiums that have been found to add 1,4 in this manner are 2-lithio-1,3-dithianes (see 0-97).<sup>492</sup> 1,4 Addition of alkyllithiums to  $\alpha,\beta$ -unsaturated aldehydes can also be achieved by converting the aldehyde to a benzothiazole derivative (masking the aldehyde function),<sup>493</sup> from which the aldehyde group can be regenerated.

However, neither Grignard reagents nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds.<sup>494</sup> Grignard reagents in general add only to double bonds susceptible to nucleophilic attack, e.g., fluoroolefins and tetracyanoethylene.<sup>495</sup> However, active Grignard reagents (benzylic, allylic) also add to the double bonds of allylic amines,<sup>496</sup> and of allylic and homoallylic alcohols,<sup>497</sup> as well as to the triple bonds of propargyl alcohols and certain other alkynols.<sup>498</sup> It is likely that cyclic intermediates are involved in these cases, in which the magnesium coordinates with the hetero atom. Organolithium reagents (primary, secondary, and tertiary alkyl and in some cases aryl) also add to the double and triple bonds of allylic and propargylic alcohols<sup>499</sup> (in this case tetramethylethylenediamine is a catalyst) and to certain other olefins containing hetero groups such as OR, NR<sub>2</sub>, or SR. Allylic, benzylic, and tertiary alkyl Grignard reagents also add to 1-alkenes and strained internal alkenes, e.g., norbornene, if the reaction is carried out not in ether but in a hydrocarbon solvent such as pentane or in the alkene itself as solvent, heated, under pressure if necessary, to 60 to 130°C.<sup>500</sup> Yields are variable. *Intramolecular* addition of RMgX to completely unactivated double and triple bonds has been demonstrated,<sup>501</sup> e.g., refluxing of 6-chloro-1-heptene with Mg for 5 hr gave, after hydrolysis, an 88% yield of 1,2-dimethylcyclopentane.<sup>502</sup>

An alkynyl group can be added to the double bond of an  $\alpha,\beta$ -unsaturated ketone by use of the diethylalkynylalane reagents Et<sub>2</sub>AlC $\equiv$ CR.<sup>503</sup> In a similar manner, the alkenyl reagents R<sub>2</sub>AlCH=CR<sub>2</sub> transfer an alkenyl group.<sup>504</sup> Trialkylalanes R<sub>3</sub>Al also add 1,4 to such ketones

<sup>489</sup>Cooke *J. Org. Chem.* **1986**, 51, 1637.

<sup>490</sup>Sauvêtre; Seyden-Penne *Tetrahedron Lett.* **1976**, 3949; Roux; Wartski; Seyden-Penne *Tetrahedron* **1981**, 37, 1927. *Synth. Commun.* **1981**, 11, 85.

<sup>491</sup>El-Bouz; Wartski *Tetrahedron Lett.* **1980**, 21, 2897.

<sup>492</sup>Lucchetti; Dumont; Krief *Tetrahedron Lett.* **1979**, 2695; Brown; Yamaichi *J. Chem. Soc., Chem. Commun.* **1979**, 100; Ref. 491. See also Bürstinghaus; Seebach *Chem. Ber.* **1977**, 110, 841.

<sup>493</sup>Corey; Boger *Tetrahedron Lett.* **1978**, 9. For another indirect method, see Sato; Okazaki; Otera; Nozaki *Tetrahedron Lett.* **1988**, 29, 2979.

<sup>494</sup>For reviews of the addition of RM to isolated double bonds see Wardell; Paterson, in Hartley; Patai, Ref. 422, vol. 2, 1985, pp. 219-338, pp. 268-296; Vara Prasad; Pillai *J. Organomet. Chem.* **1983**, 259, 1-30.

<sup>495</sup>Gardner; Kochi *J. Am. Chem. Soc.* **1976**, 98, 558.

<sup>496</sup>Richey; Moses; Domalski; Erickson; Heyn *J. Org. Chem.* **1981**, 46, 3773.

<sup>497</sup>Eisch; Husk *J. Am. Chem. Soc.* **1965**, 87, 4194; Felkin; Kaeseberg *Tetrahedron Lett.* **1970**, 4587; Richey; Szucs *Tetrahedron Lett.* **1971**, 3785; Eisch; Merkley *J. Am. Chem. Soc.* **1979**, 101, 1148; Kang *Organometallics* **1984**, 3, 525.

<sup>498</sup>Eisch; Merkley Ref. 497; Von Rein; Richey *Tetrahedron Lett.* **1971**, 3777; Miller; Reichenbach *Synth. Commun.* **1976**, 6, 319. See also Duboudin; Jousseau *J. Organomet. Chem.* **1979**, 168, 1. *Synth. Commun.* **1979**, 9, 53.

<sup>499</sup>For a review of the addition of organolithium compounds to double or triple bonds, see Wardell, in Zuckerman *Inorganic Reactions and Methods*, vol. 11; VCH: New York, 1988, pp. 129-142.

<sup>500</sup>Lehmkuhl; Reinehr *J. Organomet. Chem.* **1970**, 25, C47; **1973**, 57, 29; Lehmkuhl; Janssen *Liebigs Ann. Chem.* **1978**, 1854. This is actually a type of ene reaction. For a review of the intramolecular version of this reaction, see Oppolzer *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 38-52 [*Angew. Chem.* **101**, 39-53].

<sup>501</sup>See, for example, Richey; Rees *Tetrahedron Lett.* **1966**, 4297; Drozd; Ustynyuk; Tsel'eva; Dmitriev *J. Gen. Chem. USSR* **1969**, 39, 1951; Felkin; Umpleby; Hagaman; Wenkert *Tetrahedron Lett.* **1972**, 2285; Hill; Myers *J. Organomet. Chem.* **1979**, 173, 1.

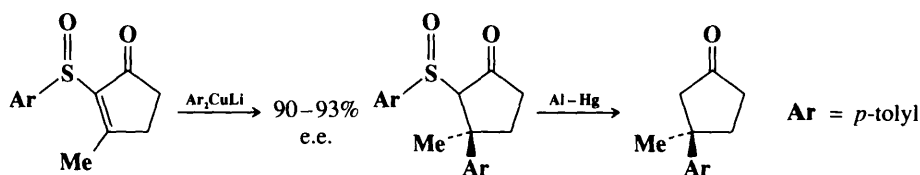
<sup>502</sup>For intramolecular addition of RLi and R<sub>2</sub>CuLi, see Wender; White *J. Am. Chem. Soc.* **1988**, 110, 2218; Bailey; Nurmi; Patricia; Wang *J. Am. Chem. Soc.* **1987**, 109, 2442.

<sup>503</sup>Hooz; Layton *J. Am. Chem. Soc.* **1971**, 93, 7320; Schwartz; Carr; Hansen; Dayrit *J. Org. Chem.* **1980**, 45, 3053.

<sup>504</sup>Hooz; Layton *Can. J. Chem.* **1973**, 51, 2098. For a similar reaction with an alkenylzirconium reagent, see Schwartz; Loots; Kosugi *J. Am. Chem. Soc.* **1980**, 102, 1333; Dayrit; Schwartz *J. Am. Chem. Soc.* **1981**, 103, 4466.

in the presence of nickel acetylacetonate.<sup>505</sup> Also used for 1,4 addition to these ketones are trialkylzinc lithium reagents  $R_3ZnLi$  (reagents of the type  $RMe_2ZnLi$  transfer only  $R$ ),<sup>506</sup> alkyl- and arylmanganese chlorides, catalyzed by  $CuCl$  (this reagent is successful for  $\alpha,\beta$ -unsaturated aldehydes and esters also),<sup>507</sup> arylpalladium compounds,<sup>508</sup> and arylmercury compounds with phase transfer catalysts.<sup>509</sup> Diarylzinc compounds (prepared with the aid of ultrasound) in the presence of nickel acetylacetonate, undergo 1,4 addition not only to  $\alpha,\beta$ -unsaturated ketones, but also to  $\alpha,\beta$ -unsaturated aldehydes.<sup>510</sup> An allyl group can be added, to  $\alpha,\beta$ -unsaturated carboxylic esters, amides and nitriles, with  $CH_2=CHCH_2SiMe_3$  and  $F^-$  ion.<sup>511</sup> This reagent gave better results than lithium diallylcuprate. Functionalized allylic groups can be added to terminal alkynes with allylic halides, zinc, and ultrasound, to give 1,4-dienes.<sup>512</sup> An alkyl group can be added to nitroolefins with  $RCu(CN)ZnI$ <sup>513</sup> or with a trialkylalane; when one of the  $R$  groups of the latter is alkenyl, it is the one transferred.<sup>514</sup> Trialkylalanes and dialkylzinc compounds add to triple bonds in the presence of a zirconium complex.<sup>515</sup> An aryl group can be added to a triple bond with an aryl iodide and a  $Pd-HCOOH-R_3N$  catalyst.<sup>516</sup>

As with the Michael reaction (5-17) the 1,4 addition of organometallic compounds has been performed diastereoselectively<sup>517</sup> and enantioselectively.<sup>518</sup> In one example of the latter,<sup>519</sup>  $\alpha,\beta$ -unsaturated sulfoxides that are optically active because of chirality at sulfur (p. 100) have given high enantiomeric excesses, e.g.,<sup>520</sup>



<sup>505</sup>Jeffery; Meisters; Mole *J. Organomet. Chem.* **1974**, 74, 365; Bagnell; Meisters; Mole *Aust. J. Chem.* **1975**, 28, 817; Ashby; Heinsohn *J. Org. Chem.* **1974**, 39, 3297. See also Sato; Oikawa; Sato *Chem. Lett.* **1979**, 167; Kunz; Pecs *J. Chem. Soc., Perkin Trans. I* **1989**, 1168.

<sup>506</sup>Isobe; Kondo; Nagasawa; Goto *Chem. Lett.* **1977**, 679; Watson; Kjonaas *Tetrahedron Lett.* **1986**, 27, 1437; Tückmantel; Oshima; Nozaki *Chem. Ber.* **1986**, 119, 1581; Kjonaas; Vawter *J. Org. Chem.* **1986**, 51, 3993.

<sup>507</sup>Cahiez; Alami *Tetrahedron Lett.* **1989**, 30, 3541, 7365, **1990**, 31, 7423.

<sup>508</sup>Cacchi; Arcadi *J. Org. Chem.* **1983**, 48, 4236.

<sup>509</sup>Cacchi; Misiti; Palmieri *Tetrahedron* **1981**, 37, 2941.

<sup>510</sup>de Souza Barboza; Pétrier; Luche *Tetrahedron Lett.* **1985**, 26, 829; Pétrier; de Souza Barboza; Dupuy; Luche *J. Org. Chem.* **1985**, 50, 5761.

<sup>511</sup>Majetich; Casares; Chapman; Behnke *J. Org. Chem.* **1986**, 51, 1745.

<sup>512</sup>Knochel; Normant *J. Organomet. Chem.* **1986**, 309, 1.

<sup>513</sup>Retherford; Yeh; Schipor; Chen; Knochel *J. Org. Chem.* **1989**, 54, 5200.

<sup>514</sup>Pecunioso; Menicagli *Tetrahedron* **1987**, 43, 5411, *J. Org. Chem.* **1988**, 53, 45.

<sup>515</sup>Negishi; Van Horn; Yoshida; Rand *Organometallics* **1983**, 2, 563.

<sup>516</sup>Cacchi; Felici; Pietroni *Tetrahedron Lett.* **1984**, 25, 3137.

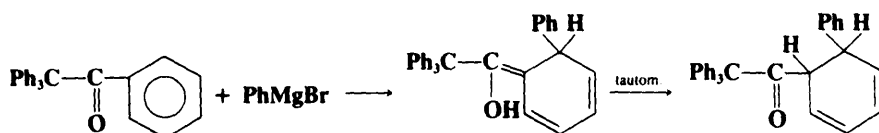
<sup>517</sup>For some examples, see Isobe; Funabashi; Ichikawa; Mio; Goto *Tetrahedron Lett.* **1984**, 25, 2021; Kawasaki; Tomioka; Koga *Tetrahedron Lett.* **1985**, 26, 3031; Yamamoto; Nishii; Ibuka *J. Chem. Soc., Chem. Commun.* **1987**, 464, 1572; Smith; Dunlap; Sulikowski *Tetrahedron Lett.* **1988**, 29, 439; Smith; Trumper *Tetrahedron Lett.* **1988**, 29, 443; Alexakis; Sedrani; Mangeney; Normant *Tetrahedron Lett.* **1988**, 29, 4411; Larchevêque; Tamagnan; Petit *J. Chem. Soc., Chem. Commun.* **1989**, 31; Page; Procter; Hursthouse; Mazid *J. Chem. Soc., Perkin Trans. I* **1990**, 167; Corey; Hannon *Tetrahedron Lett.* **1990**, 31, 1393.

<sup>518</sup>For reviews, see Posner *Acc. Chem. Res.* **1987**, 20, 72-78; in Morrison, Ref. 232, vol. 2, 1983, the articles by Tomioka; Koga pp. 201-224; Posner, pp. 225-241.

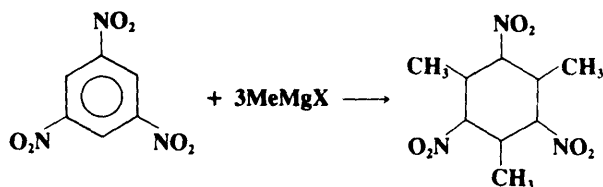
<sup>519</sup>For other examples, see Oppolzer; Moretti; Godel; Meunier; Löhrer *Tetrahedron Lett.* **1983**, 24, 4971; Helmchen; Wegner *Tetrahedron Lett.* **1985**, 26, 6051; Corey; Naef; Hannon *J. Am. Chem. Soc.* **1986**, 108, 7114; Dieter; Tokles *J. Am. Chem. Soc.* **1987**, 109, 2040; Ahn; Klassen; Lippard *Organometallics* **1990**, 9, 3178; Alexakis; Sedrani; Mangeney *Tetrahedron Lett.* **1990**, 31, 345; Rossiter; Eguchi *Tetrahedron Lett.* **1990**, 31, 965; Bolm; Ewald *Tetrahedron Lett.* **1990**, 31, 5011; Jansen; Feringa *J. Org. Chem.* **1990**, 55, 4168; Soai; Okudo; Okamoto *Tetrahedron Lett.* **1991**, 32, 95.

<sup>520</sup>Posner; Kogan; Hulce *Tetrahedron Lett.* **1984**, 25, 383.

In certain cases, Grignard reagents add 1,4 to aromatic systems, e.g.,<sup>521</sup>

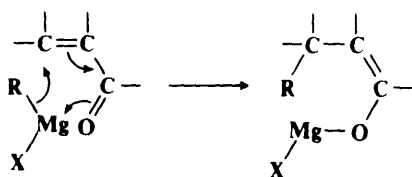


Such cyclohexadienes are easily oxidizable to benzenes (often by atmospheric oxygen), so this reaction becomes a method of alkylating and arylating suitably substituted (usually hindered) aryl ketones. A similar reaction has been reported for aromatic nitro compounds:<sup>522</sup>



Both Grignard and  $R_2CuLi$  reagents<sup>523</sup> have also been added to triple-bond systems of the form  $C\equiv C-C=O$ .<sup>524</sup>

The mechanisms of most of these reactions are not well known. The 1,4 uncatalyzed Grignard reaction has been postulated to proceed by a cyclic mechanism



but there is evidence against it.<sup>525</sup> The  $R_2CuLi$  and copper-catalyzed Grignard additions may involve a number of mechanisms, since the actual attacking species and substrates are so diverse.<sup>526</sup> A free-radical mechanism of some type (perhaps SET) has been suggested<sup>527</sup>

<sup>521</sup>This example is from Schmidlin; Wohl *Ber.* **1910**, 43, 1145; Mosher; Huber *J. Am. Chem. Soc.* **1953**, 75, 4604. For a review of such reactions see Fuson *Adv. Organomet. Chem.* **1964**, 1, 221-238.

<sup>522</sup>Severin; Schmitz *Chem. Ber.* **1963**, 96, 3081. See also Bartoli; Bosco; Baccolini *J. Org. Chem.* **1980**, 45, 522; Bartoli *Acc. Chem. Res.* **1984**, 17, 109-115; Bartoli; Dalpozzo; Grossi *J. Chem. Soc., Perkin Trans. 2* **1989**, 573. For a study of the mechanism, see Bartoli; Bosco; Cantagalli; Dalpozzo; Ciminale *J. Chem. Soc., Perkin Trans. 2* **1985**, 773.

<sup>523</sup>For example see Corey; Kim; Chen; Takeda *J. Am. Chem. Soc.* **1972**, 94, 4395; Anderson; Corbin; Cotterrell; Cox; Henrick; Schaub; Siddall *J. Am. Chem. Soc.* **1975**, 97, 1197.

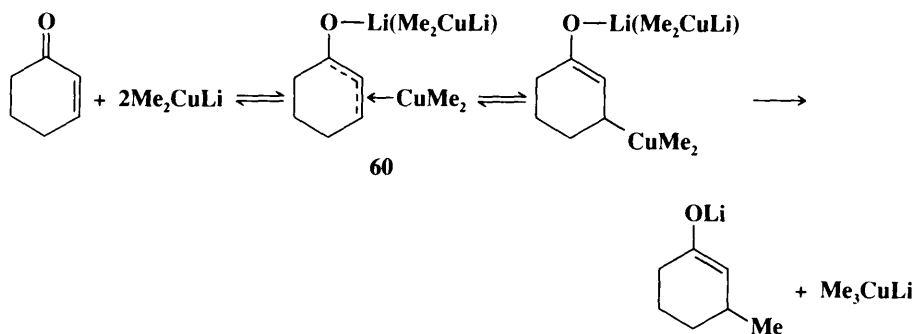
<sup>524</sup>For a review of the addition of organometallic reagents to conjugated enynes see Miginiac *J. Organomet. Chem.* **1982**, 238, 235-266.

<sup>525</sup>House; Thompson *J. Org. Chem.* **1963**, 28, 360; Klein *Tetrahedron* **1964**, 20, 465. See however Marets; Rivière *Bull. Soc. Chim. Fr.* **1970**, 4320.

<sup>526</sup>For some mechanistic investigations see Berlan; Battioni; Koosha *J. Organomet. Chem.* **1978**, 152, 359; *Bull. Soc. Chim. Fr.* **1979**, II-183; Four; Riviere; Tang *Tetrahedron Lett.* **1977**, 3879; Casey; Cesa *J. Am. Chem. Soc.* **1979**, 101, 4236; Smith; Hannah *Tetrahedron* **1979**, 35, 1183; Krauss; Smith *J. Am. Chem. Soc.* **1981**, 103, 141; Bartoli; Bosco; Dal Pozzo; Ciminale *J. Org. Chem.* **1982**, 47, 5227; Corey; Boaz *Tetrahedron Lett.* **1985**, 26, 6015; Yamamoto; Yamada; Uyehara *J. Am. Chem. Soc.* **1987**, 109, 5820; Ullenius; Christenson *Pure Appl. Chem.* **1988**, 60, 57; Christenson; Olsson; Ullenius *Tetrahedron* **1989**, 45, 523; Krause *Tetrahedron Lett.* **1989**, 30, 5219.

<sup>527</sup>See, for example, House; Umen *J. Am. Chem. Soc.* **1972**, 94, 5495; Ruden; Litterer *Tetrahedron Lett.* **1975**, 2043; House; Snoble *J. Org. Chem.* **1976**, 41, 3076; Wigal; Grunwell; Hershberger; *J. Org. Chem.* **1991**, 56, 3759.

though the fact that retention of configuration at R has been demonstrated in several cases rules out a completely free R• radical.<sup>528</sup> For simple  $\alpha,\beta$ -unsaturated ketones, such as 2-cyclohexenone, and  $\text{Me}_2\text{CuLi}$ , there is evidence<sup>529</sup> for this mechanism:

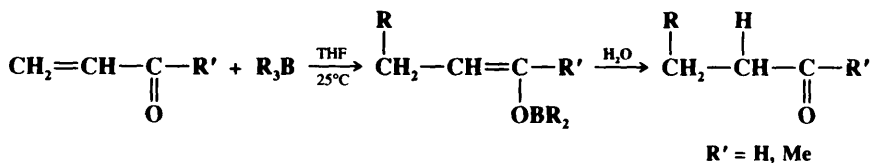


**60** is a  $d, \pi^*$  complex, with bonding between copper, as a base supplying a pair of  $d$  electrons, and the enone as a Lewis acid using the  $\pi^*$  orbital of the allylic system.<sup>529</sup> The  $^{13}\text{C}$  nmr spectrum of an intermediate similar to **60** has been reported.<sup>530</sup> The addition of  $\text{R}_3\text{Al}$  takes place by a free-radical mechanism.<sup>505</sup>

For the addition of organocopper reagents to alkynes and conjugated dienes, see 5-53. OS IV, 93; V, 762; VI, 442, 666, 762, 786; **65**, 203; **66**, 43, 52, 95.

### 5-19 The Addition of Boranes to Activated Double Bonds

#### Hydro-alkyl-addition (overall transformation)



Trialkylboranes rapidly add to the double bonds of acrolein, methyl vinyl ketone, and certain of their derivatives in THF at  $25^\circ\text{C}$  to give enol borinates, which can be hydrolyzed to aldehydes or ketones.<sup>531</sup> The water may be present from the beginning, so the reaction can be run in one laboratory step. Since the boranes can be prepared from olefins (5-12), this reaction provides a means of lengthening a carbon chain by three or four carbons, respectively. Compounds containing a terminal alkyl group, such as crotonaldehyde  $\text{CH}_3\text{CH}=\text{CHCHO}$  and 3-penten-2-one, fail to react under these conditions, as does acrylonitrile, but these compounds can be induced to react by the slow and controlled addition of  $\text{O}_2$  or by initiation with peroxides or uv light.<sup>532</sup> A disadvantage is that only one of the

<sup>528</sup>Näf; Degen *Helv. Chim. Acta* **1971**, 54, 1939; Whitesides; Kendall *J. Org. Chem.* **1972**, 37, 3718. See also Ref. 465.

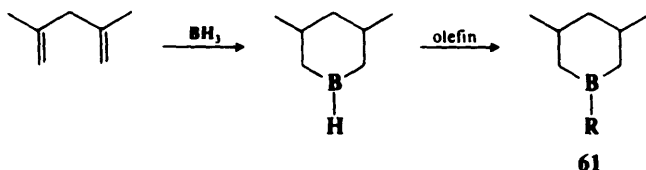
<sup>529</sup>Corey; Hannon; Boaz *Tetrahedron* **1989**, 45, 545.

<sup>530</sup>Bertz; Smith *J. Am. Chem. Soc.* **1989**, 111, 8276.

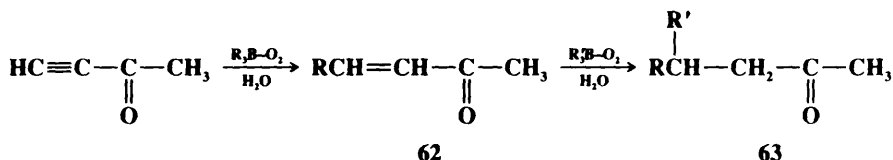
<sup>531</sup>Suzuki; Arase; Matsumoto; Itoh; Brown; Rogić; Rathke *J. Am. Chem. Soc.* **1967**, 89, 5708; Köster; Zimmermann; Fenzl *Liebigs Ann. Chem.* **1976**, 1116. For reviews see Pelter; Smith; Brown; Ref. 348, pp. 301-305, 318-323; Brown; Midland *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 692-700, pp. 694-698 [*Angew. Chem.* **84**, 702-710]; Kabalka *Intra-Sci. Chem. Rep.* **1973**, 7(1), 57-64; Brown *Boranes in Organic Chemistry*, Ref. 348, pp. 413-433.

<sup>532</sup>Brown; Kabalka *J. Am. Chem. Soc.* **1970**, 92, 712, 714. See also Utimoto; Tanaka; Furubayashi; Nozaki *Tetrahedron Lett.* **1973**, 787; Miyaoura; Kashiwagi; Itoh; Suzuki *Chem. Lett.* **1974**, 395.

three R groups of  $R_3B$  adds to the substrate, so that the other two are wasted. This difficulty is overcome by the use of a B-alkyl borinate such as **61**,<sup>533</sup> which can be prepared as shown.



**61** (R = *t*-butyl) can be made by treatment of **61** (R = OMe) with *t*-BuLi. The use of this reagent permits *t*-butyl groups to be added. B-1-Alkenyl-9-BBN compounds  $B-RCH=CR'$ -9-BBN (prepared by treatment of alkynes with 9-BBN or of  $RCH=CR'Li$  with B-methoxy-9-BBN<sup>534</sup>) add to methyl vinyl ketones to give, after hydrolysis,  $\gamma,\delta$ -unsaturated ketones,<sup>535</sup> though B-R-9-BBN, where R = a saturated group, are not useful here, because the R group of these reagents does not preferentially add to the substrate.<sup>533</sup> The corresponding B-1-alkynyl-9-BBN compounds also give the reaction.<sup>536</sup> Like the three substrates mentioned above, 3-butyne-2-one fails to react in the absence of air but undergoes the reaction when exposed to a slow stream of air.<sup>537</sup>

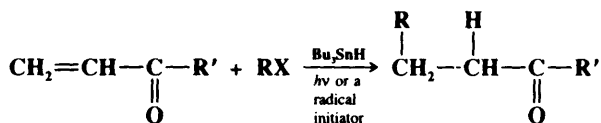


Since the product, **62**, is an  $\alpha,\beta$ -unsaturated ketone, it can be made to react with another  $BR_3$ , the same or different, to produce a wide variety of ketones **63**.

The fact that these reactions are catalyzed by free-radical initiators and inhibited by galvinoxyl<sup>538</sup> (a free-radical inhibitor) indicates that free-radical mechanisms are involved.

## 5-70 The Addition of Tin and Mercury Hydrides to Activated Double Bonds

### Hydro-alkyl-addition



In a reaction similar to **5-19**, alkyl groups can be added to olefins activated by such groups as  $COR'$ ,  $COOR'$ , CN, and even Ph.<sup>539</sup> In the method illustrated above, the R group comes

<sup>533</sup>Brown; Negishi *J. Am. Chem. Soc.* **1971**, 93, 3777.

<sup>534</sup>Brown; Bhat; Rajagopalan *Organometallics* **1986**, 5, 816.

<sup>535</sup>Jacob; Brown *J. Am. Chem. Soc.* **1976**, 98, 7832; Satoh; Serizawa; Hara; Suzuki *J. Am. Chem. Soc.* **1985**, 107, 5225. See also Molander; Singaram; Brown *J. Org. Chem.* **1984**, 49, 5024. Alkenyldialkoxyboranes, together with  $BF_3$ -etherate, also transfer vinylic groups; Hara; Hyuga; Aoyama; Sato; Suzuki *Tetrahedron Lett.* **1990**, 31, 247.

<sup>536</sup>Sinclair; Molander; Brown *J. Am. Chem. Soc.* **1977**, 99, 954. See also Molander; Brown *J. Org. Chem.* **1977**, 42, 3106.

<sup>537</sup>Suzuki; Nozawa; Itoh; Brown; Kabalka; Holland *J. Am. Chem. Soc.* **1970**, 92, 3503.

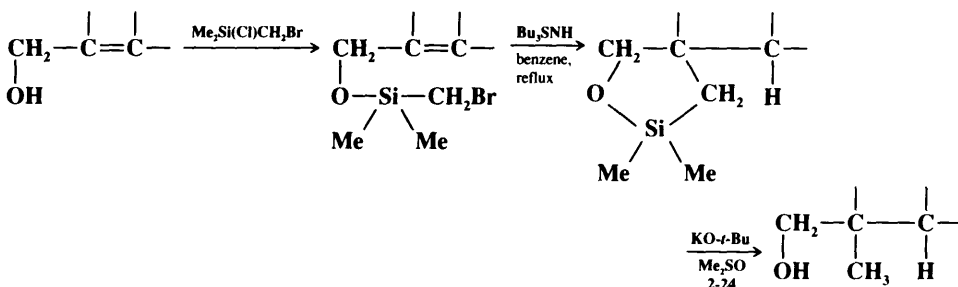
<sup>538</sup>Kabalka; Brown; Suzuki; Honma; Arase; Itoh *J. Am. Chem. Soc.* **1970**, 92, 710. See also Arase; Masuda; Suzuki *Bull. Chem. Soc. Jpn.* **1976**, 49, 2275.

<sup>539</sup>For reviews, see Giese, Ref. 50, pp. 36-68; Giese *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 553-565 [*Angew. Chem.* 97, 555-567]; Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 263-273. The last review includes a table with many examples of the mercury method. For a list of reagents, with references, see Ref. 133, pp. 915-916.

from an alkyl halide (R = primary, secondary, or tertiary alkyl; X = Br or I) and the hydrogen from the tin hydride. Organomercury hydrides  $\text{RHgH}$ , generated in situ from  $\text{RHgX}$  and  $\text{NaBH}_4$ , can also be used.<sup>540</sup> When the tin method is used,  $\text{Bu}_3\text{SnH}$  can also be generated in a similar way, from  $\text{R}_3\text{SnX}$  and  $\text{NaBH}_4$ . The tin method has a broader scope (e.g., it can be used on  $\text{CH}_2=\text{CCl}_2$ ), but the mercury method uses milder reaction conditions. Like **5-19**, these additions have free-radical mechanisms. The reaction has been used for free-radical cyclizations of the type discussed on p. 752.<sup>541</sup> Such cyclizations normally give predominant formation of 5-membered rings, but large rings (11 to 20 members) have also been synthesized by this reaction.<sup>542</sup>

Free-radical addition of an aryl group and a hydrogen has been achieved by treatment of activated olefins with a diazonium salt and  $\text{TiCl}_3$ .<sup>543</sup>

In a related reaction, a methyl group and a hydrogen can be added indirectly to the double bond of an otherwise unactivated allylic alcohol in this manner:<sup>544</sup>

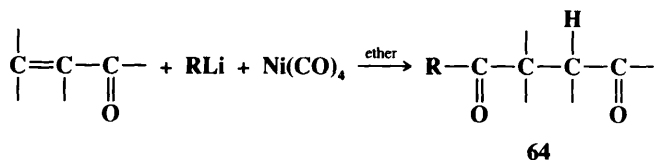


This procedure has been used to introduce angular methyl groups (methyl groups at the bridgeheads of fused rings).<sup>545</sup>

OS VII, 105.

## 5-21 Acylation of Activated Double Bonds and of Triple Bonds

### Hydro-acyl-addition



An acyl group can be introduced into the 4 position of an  $\alpha,\beta$ -unsaturated ketone by treatment with an organolithium compound and nickel carbonyl.<sup>546</sup> The product is a 1,4-

<sup>540</sup>For the use of tris(trimethylsilyl)silane instead, see Giese; Koppong; Chatgililoglu *Tetrahedron Lett.* **1989**, 30, 681.

<sup>541</sup>For reviews, see Jasperse; Curran; Fevig *Chem. Rev.* **1991**, 91, 1237-1286; Curran *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, 1, 121-157; Giese, Ref. 50, pp. 151-169. For a list of references, see Ref. 133, pp. 215-216.

<sup>542</sup>See Porter; Chang *J. Am. Chem. Soc.* **1987**, 109, 4976.

<sup>543</sup>Citterio; Vismara *Synthesis* **1980**, 291. For other methods of adding an alkyl or aryl group and a hydrogen to activated double bonds by free-radical processes, see Cacchi; Palmieri *Synthesis* **1984**, 575; Lebedev; Lopatina; Berestova; Petrov; Beletskaya *J. Org. Chem. USSR* **1986**, 22, 1238; Barton; Crich *J. Chem. Soc., Perkin Trans. I* **1986**, 1603; Luche; Allavena *Tetrahedron Lett.* **1988**, 29, 5369; Varea; González-Núñez; Rodrigo-Chiner; Asensio *Tetrahedron Lett.* **1989**, 30, 4709; Barton; Sarma *Tetrahedron Lett.* **1990**, 31, 1965.

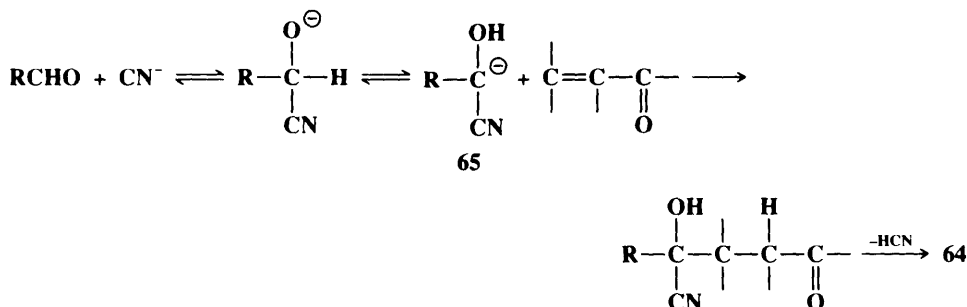
<sup>544</sup>Stork; Sofia *J. Am. Chem. Soc.* **1986**, 108, 6826. See also Stork *Bull. Chem. Soc. Jpn.* **1988**, 61, 149.

<sup>545</sup>Stork; Mah *Tetrahedron Lett.* **1989**, 30, 3609.

<sup>546</sup>Corey; Hegedus *J. Am. Chem. Soc.* **1969**, 91, 4926.

diketone. R may be aryl or primary alkyl. The reaction can also be applied to alkynes (which need not be activated), in which case 2 moles add and the product is also a 1,4-diketone, e.g.,  $R'C\equiv CH \rightarrow RCOCHR'CH_2COR$ .<sup>547</sup> In a different procedure,  $\alpha,\beta$ -unsaturated ketones and aldehydes are acylated by treatment at  $-110^\circ\text{C}$  with  $R_2(\text{CN})\text{CuLi}_2$  and CO. This method is successful for R = primary, secondary, and tertiary alkyl.<sup>548</sup> For secondary and tertiary groups,  $R(\text{CN})\text{CuLi}$  (which does not waste an R group) can be used instead.<sup>549</sup>

Another method involves treatment with an aldehyde and cyanide ion (see 6-49) in a polar aprotic solvent such as DMF or  $\text{Me}_2\text{SO}$ .<sup>550</sup>



This method has been applied to  $\alpha,\beta$ -unsaturated ketones, esters, and nitriles to give the corresponding 1,4-diketones,  $\gamma$ -keto esters, and  $\gamma$ -keto nitriles, respectively (see also 6-54).

The ion **65** is a synthon for the unavailable  $\text{RC}^\ominus=\text{O}$  anion (see also p. 471); it is a masked  $\text{RC}^\ominus=\text{O}$  anion. Other masked carbanions that have been used in this reaction are the  $\text{RC}^\ominus(\text{CN})\text{NR}'_2$  ion,<sup>551</sup> the  $\text{EtS}^\ominus\text{CRSOEt}$  ion<sup>552</sup> (see p. 475), the  $\text{CH}_2=\text{C}^\ominus\text{OEt}$  ion,<sup>553</sup>  $\text{CH}_2=\text{C}(\text{OEt})\text{Cu}_2\text{Li}$ ,<sup>554</sup>  $\text{CH}_2=\text{CMe}(\text{SiMe}_3)$ ,<sup>554</sup> and the  $\text{RC}^\ominus(\text{OCHMeOEt})\text{CN}$  ion<sup>555</sup> (see p. 471). In the last case, best results are obtained when R is a vinylic group. Anions of 1,3-dithianes (**0-97**) do not give 1,4 addition to these substrates (except in the presence of HMPA, see 5-18) but add 1,2 to the  $\text{C}=\text{O}$  group instead (**6-41**).

In another procedure, acyl radicals derived from phenyl selenoesters  $\text{ArCOSePh}$  (by treatment of them with  $\text{Bu}_3\text{SnH}$ ) add to  $\alpha,\beta$ -unsaturated esters and nitriles to give  $\gamma$ -keto esters and  $\gamma$ -keto nitriles, respectively.<sup>556</sup> Hydroacylation has also been done by electrochemical reaction of the substrate with an anhydride.<sup>557</sup>

OS VI, 866; **65**, 26.

<sup>547</sup>Sawa; Hashimoto; Ryang; Tsutsumi *J. Org. Chem.* **1968**, 33, 2159.

<sup>548</sup>Seyferth; Hui *J. Am. Chem. Soc.* **1985**, 107, 4551. See also Lipshutz; Elworthy *Tetrahedron Lett.* **1990**, 31, 477.

<sup>549</sup>Seyferth; Hui *Tetrahedron Lett.* **1986**, 27, 1473.

<sup>550</sup>For reviews, see Stetter; Kuhlmann *Org. React.* **1991**, 40, 407-496; Stetter *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 639-647 [*Angew. Chem.* 88, 695-704]. For a similar method involving thiazolium salts, see Stetter; Kuhlmann *Chem. Ber.* **1976**, 109, 2890; Stetter; Skobel *Chem. Ber.* **1987**, 120, 643; Stetter; Kuhlmann; Haese *Org. Synth.* 65, 26.

<sup>551</sup>Enders; Gerdes; Kipphardt *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 179 [*Angew. Chem.* 102, 226].

<sup>552</sup>Herrmann; Richman; Schlessinger *Tetrahedron Lett.* **1973**, 3271, 3275.

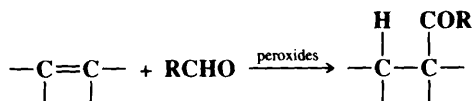
<sup>553</sup>Boeckman; Bruza; Baldwin; Lever *J. Chem. Soc., Chem. Commun.* **1975**, 519.

<sup>554</sup>Boeckman; Bruza *J. Org. Chem.* **1979**, 44, 4781.

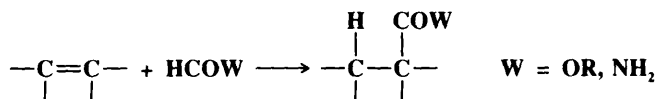
<sup>555</sup>Stork; Maldonado *J. Am. Chem. Soc.* **1974**, 96, 5272.

<sup>556</sup>Boger; Mathvink *J. Org. Chem.* **1989**, 54, 1777.

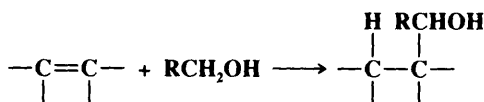
<sup>557</sup>Shono; Nishiguchi; Ohmizu *J. Am. Chem. Soc.* **1977**, 99, 7396; Lund; Degrand *Tetrahedron Lett.* **1977**, 3593.

**5-22** Addition of Alcohols, Amines, Carboxylic Esters, Aldehydes, etc.**Hydro-acyl-addition**, etc.

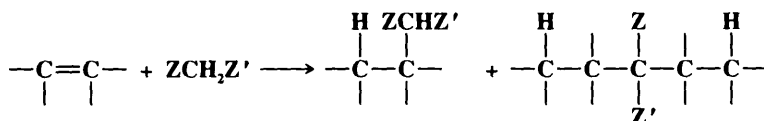
Aldehydes, formates, primary, and secondary alcohols, amines, ethers, alkyl halides, compounds of the type  $\text{Z---CH}_2\text{---Z'}$ , and a few other compounds add to double bonds in the presence of free-radical initiators.<sup>558</sup> This is formally the addition of  $\text{RH}$  to a double bond, but the "R" is not just any carbon but one connected to an oxygen or a nitrogen, a halogen, or to two Z groups (defined as on p. 464). The addition of aldehydes is illustrated above. Formates and formamides<sup>559</sup> add similarly:



Alcohols, ethers, amines, and alkyl halides add as follows (shown for alcohols):



$\text{ZCH}_2\text{Z'}$  compounds react at the carbon bearing the active hydrogen:<sup>560</sup>



Similar additions have been successfully carried out with carboxylic acids, anhydrides,<sup>561</sup> acyl halides, carboxylic esters, nitriles, and other types of compounds.<sup>562</sup>

These reactions are not successful when the olefin contains electron-withdrawing groups such as halo or carbonyl groups. A free-radical initiator is required, usually peroxides or

<sup>558</sup>For reviews see Giese, Ref. 50, pp. 69-77; Vogel *Synthesis* **1970**, 99-140; Huyser, Ref. 49, pp.152-159; Elad *Fortschr. Chem. Forsch.* **1967**, 7, 528-558.

<sup>559</sup>Elad, Ref. 558, pp. 530-543.

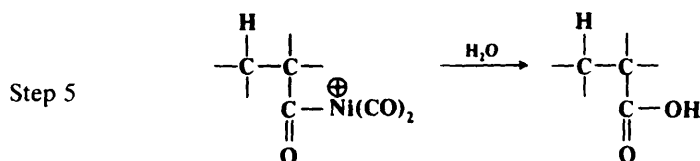
<sup>560</sup>For example, see Cadogan; Hey; Sharp *J. Chem. Soc. C* **1966**, 1743; *J. Chem. Soc. B* **1967**, 803; Hájek; Málek *Coll. Czech. Chem. Commun.* **1979**, 44, 3695.

<sup>561</sup>de Klein *Recl. Trav. Chim. Pays-Bas* **1975**, 94, 48.

<sup>562</sup>Allen; Cadogan; Hey *J. Chem. Soc.* **1965**, 1918; Cadogan *Pure Appl. Chem.* **1967**, 15, 153-165, pp. 153-158. See also Giese; Zwick *Chem. Ber.* **1982**, 115, 2526; Giese; Erfort *Chem. Ber.* **1983**, 116, 1240.





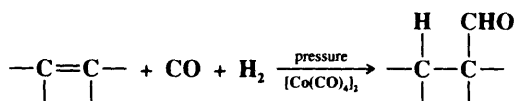


Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

In either the acid catalysis or the nickel carbonyl (or other metallic catalyst) method, if alcohols, thiols, amines, etc. are used instead of water, the product is the corresponding ester, thiol ester, or amide, instead of the carboxylic acid.

## 5-24 Hydroformylation

### Hydro-formyl-addition



Olefins can be hydroformylated<sup>574</sup> by treatment with carbon monoxide and hydrogen over a catalyst. The most common catalysts are cobalt carbonyls and rhodium complexes<sup>575</sup> [e.g., hydridocarbonyltris(triphenylphosphine)rhodium], but other transition metal compounds have also been used. Cobalt catalysts are less active than the rhodium type, and catalysts of other metals are less active still.<sup>576</sup> Commercially, this is called the *oxo process*, but it can be carried out in the laboratory in an ordinary hydrogenation apparatus. The order of reactivity is straight-chain terminal olefins > straight-chain internal olefins > branched-chain olefins. Conjugated dienes give dialdehydes when rhodium catalysts are used<sup>577</sup> but saturated monoaldehydes (the second double bond is reduced) with cobalt carbonyls. 1,4- and 1,5-dienes may give cyclic ketones.<sup>578</sup> Many functional groups, e.g., OH, CHO, COOR, CN, can be present in the molecule, though halogens usually interfere. Hydroformylation of triple bonds proceeds very slowly, and few examples have been reported.<sup>579</sup> Among the side

<sup>574</sup>For reviews, see Kalck; Peres; Jenck *Adv. Organomet. Chem.* **1991**, 32, 121-146; Davies, in Hartley; Patai, Ref. 422, vol. 3, pp. 361-389; Pino; Piacenti; Bianchi, in Wender; Pino, Ref. 565, pp. 43-231; Cornils, in Falbe *New Syntheses with Carbon Monoxide*, Ref. 565, pp. 1-225; Collman et al., Ref. 223, pp. 621-632; Pino *J. Organomet. Chem.* **1980**, 200, 223-242; Pruett *Adv. Organomet. Chem.* **1979**, 17, 1-60; Stille; James, in Patai, Ref. 1, pt. 2, pp. 1099-1166; Heck, Ref. 223, pp. 215-224; Khan; Martell, Ref. 159, vol. 2, pp. 39-60; Falbe *Carbon Monoxide in Organic Synthesis*, Ref. 565, pp. 3-77; Chalk; Harrod *Adv. Organomet. Chem.* **1968**, 6, 119-170. For a review with respect to fluoroolefins, see Ohshiro; Hirao, Ref. 571.

<sup>575</sup>For example, see Osborn; Wilkinson; Young *Chem. Commun.* **1965**, 17; Brown; Wilkinson *Tetrahedron Lett.* **1969**, 1725; *J. Chem. Soc. A* **1970**, 2753; Stefani; Consiglio; Botteghi; Pino *J. Am. Chem. Soc.* **1973**, 95, 6504; Bott *Chem. Ber.* **1975**, 108, 997; van Leeuwen; Roobeek *J. Organomet. Chem.* **1983**, 258, 343; Salvadori; Vitulli; Raffaelli; Lazzaroni *J. Organomet. Chem.* **1983**, 258, 351; Collman; Belmont; Brauman *J. Am. Chem. Soc.* **1983**, 105, 7288; Brown; Kent *J. Chem. Soc., Perkin Trans. 1* **1987**, 1597; Hanson; Davis *J. Chem. Educ.* **1987**, 64, 928; Jackson; Perlmutter; Suh *J. Chem. Soc., Chem. Commun.* **1987**, 724; Hendriksen; Oswald; Ansell; Leta; Kastrup *Organometallics* **1989**, 8, 1153; Lazzaroni; Uccello-Barretta; Benetti *Organometallics* **1989**, 8, 2323; Amer; Alper *J. Am. Chem. Soc.* **1990**, 112, 3674. For a review of the rhodium-catalyzed process, see Jardine, in Hartley, Ref. 218, vol. 4, pp. 733-818, pp. 778-784.

<sup>576</sup>Collman et al., Ref. 223, p. 630.

<sup>577</sup>Fell; Rupilius *Tetrahedron Lett.* **1969**, 2721.

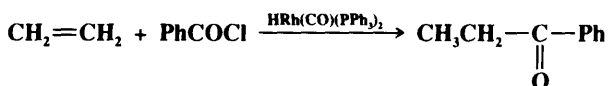
<sup>578</sup>For a review of ring closure reactions with CO, see Mullen, in Falbe *New Syntheses with Carbon Monoxide*, Ref. 565, pp. 414-439. See also Eilbracht; Hüttmann; Deussen *Chem. Ber.* **1990**, 123, 1063, and other papers in this series.

<sup>579</sup>For examples with rhodium catalysts, see Fell; Beutler *Tetrahedron Lett.* **1972**, 3455; Botteghi; Salomon *Tetrahedron Lett.* **1974**, 4285. For an indirect method, see Campi; Fitzmaurice; Jackson; Perlmutter; Smalldridge *Synthesis* **1987**, 1032.

reactions are the aldol reaction (6-39), acetal formation, the Tishchenko reaction (9-70), and polymerization. Stereoselective syn addition has been reported.<sup>580</sup> Asymmetric hydroformylation has been accomplished with a chiral catalyst.<sup>581</sup>

When dicobalt octacarbonyl  $[\text{Co}(\text{CO})_4]_2$  is the catalyst, the species that actually adds to the double bond is tricarbonylhydrocobalt  $\text{HCo}(\text{CO})_3$ .<sup>582</sup> Carbonylation  $\text{RCo}(\text{CO})_3 + \text{CO} \rightarrow \text{RCo}(\text{CO})_4$  takes place, followed by a rearrangement and a reduction of the C—Co bond, similar to steps 4 and 5 of the nickel carbonyl mechanism shown in 5-23. The reducing agent in the reduction step is tetracarbonylhydrocobalt  $\text{HCo}(\text{CO})_4$ ,<sup>583</sup> or, under some conditions,  $\text{H}_2$ .<sup>584</sup> When  $\text{HCo}(\text{CO})_4$  was the agent used to hydroformylate styrene, the observation of CIDNP indicated that the mechanism is different, and involves free radicals.<sup>585</sup> Alcohols can be obtained by allowing the reduction to continue after all the carbon monoxide is used up. It has been shown<sup>586</sup> that the formation of alcohols is a second step, occurring after the formation of aldehydes, and that  $\text{HCo}(\text{CO})_3$  is the reducing agent.

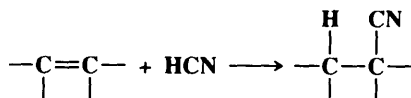
An indirect method for the hydroformylation of olefins involves formation of the trialkylborane (5-12) and treatment of this with carbon monoxide and a reducing agent (see 8-26). *Hydroacylation* of alkenes has been accomplished, in variable yields, by treatment with an acyl halide and a rhodium complex catalyst, e.g.,<sup>587</sup>



OS VI, 338.

## 5-25 Addition of HCN

### Hydro-cyano-addition



Ordinary olefins do not react with HCN, but polyhalo olefins and olefins of the form  $\text{C}=\text{C}-\text{Z}$  add HCN to give nitriles.<sup>588</sup> The reaction is therefore a nucleophilic addition and is base-

<sup>580</sup>See, for example, Haelg; Consiglio; Pino *Helv. Chim. Acta* **1981**, 64, 1865.

<sup>581</sup>For reviews, see Ojima; Hirai, in Morrison, Ref. 232, vol. 5, 1985, pp. 103-145, pp. 125-139; Consiglio; Pino *Top. Curr. Chem.* **1982**, 105, 77-123. See also Kollár; Bakos; Tóth; Heil *J. Organomet. Chem.* **1988**, 350, 277, **1989**, 370, 257; Pottier; Mortreux; Petit *J. Organomet. Chem.* **1989**, 370, 333; Stille; Su; Brechot; Parrinello; Hegedus *Organometallics* **1991**, 10, 1183; Consiglio; Nefkens; Borer *Organometallics* **1991**, 10, 2046.

<sup>582</sup>Heck; Breslow, *Chem. Ind. (London)* **1960**, 467, *J. Am. Chem. Soc.* **1961**, 83, 4023; Karapinka; Orchin *J. Org. Chem.* **1961**, 26, 4187; Whyman *J. Organomet. Chem.* **1974**, 81, 97; Mirbach *J. Organomet. Chem.* **1984**, 265, 205. For discussions of the mechanism see Orchin *Acc. Chem. Res.* **1981**, 14, 259-266; Versluis; Ziegler; Baerends; Ravenek *J. Am. Chem. Soc.* **1989**, 111, 2018.

<sup>583</sup>Alemдарoglu; Penninger; Oltay *Monatsh. Chem.* **1976**, 107, 1153; Ungváry; Markó *Organometallics* **1982**, 1, 1120.

<sup>584</sup>See Kovács; Ungváry; Markó *Organometallics* **1986**, 5, 209.

<sup>585</sup>Bockman; Garst; King; Markó; Ungváry *J. Organomet. Chem.* **1985**, 279, 165.

<sup>586</sup>Aldridge; Jonassen *J. Am. Chem. Soc.* **1963**, 85, 886.

<sup>587</sup>Schwartz; Cannon *J. Am. Chem. Soc.* **1974**, 96, 4721. For some other hydroacylation methods see Cooke; Parlman *J. Am. Chem. Soc.* **1977**, 99, 5222; Larock; Bernhardt *J. Org. Chem.* **1978**, 43, 710; Suggs *J. Am. Chem. Soc.* **1979**, 101, 489; Isnard; Denise; Sneed; Cognion; Durual *J. Organomet. Chem.* **1982**, 240, 285; Zudin; Il'inich; Likholobov; Yermakov *J. Chem. Soc., Chem. Commun.* **1984**, 545; Kondo; Akazome; Tsuji; Watanabe *J. Org. Chem.* **1990**, 55, 1286.

<sup>588</sup>For reviews see Friedrich, in Patai; Rappoport, Ref. 49, pt. 2, pp. 1345-1390; Nagata; Yoshioka *Org. React.* **1977**, 25, 255-476; Brown, in Wender; Pino, Ref. 565, pp. 655-672; Friedrich; Wallenfels, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 68-72.

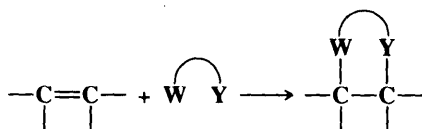
catalyzed. When Z is COR or, more especially, CHO, 1,2 addition (**6-51**) is an important competing reaction and may be the only reaction. Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH<sub>4</sub>Cl, and HCl or by Ni or Pd compounds.<sup>589</sup> The HCN can be generated in situ from acetone cyanohydrin (see **6-49**), avoiding the use of the poisonous HCN.<sup>590</sup> One or two moles of HCN can be added to a triple bond, since the initial product is a Michael-type substrate. Acrylonitrile is commercially prepared this way, by the addition of HCN to acetylene. Alkylaluminum cyanides, e.g., Et<sub>2</sub>AlCN, or mixtures of HCN and trialkylalanes R<sub>3</sub>Al are especially good reagents for conjugate addition of HCN<sup>591</sup> to α,β-unsaturated ketones and α,β-unsaturated acyl halides. HCN can be added to ordinary olefins in the presence of dicobalt octacarbonyl<sup>592</sup> or certain other transition-metal compounds.<sup>593</sup> An indirect method for the addition of HCN to ordinary olefins uses an isocyanide RNC and Schwartz's reagent (see **5-13**); this method gives anti-Markovnikov addition.<sup>594</sup> *t*-Butyl isocyanide and TiCl<sub>4</sub> have been used to add HCN to C=C—Z olefins.<sup>595</sup>

OS I, 451; II, 498; III, 615; IV, 392, 393, 804; V, 239, 572; VI, 14.

For addition of ArH, see **1-12** (Friedel–Crafts alkylation).

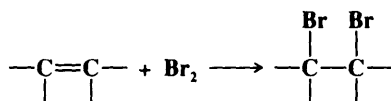
## Reactions in Which Hydrogen Adds to Neither Side

Some of these reactions are *cycloadditions* (reactions **5-36**, **5-37**, **5-42**, and **5-45** to **5-52**). In such cases addition to the multiple bond closes a ring:



## A. Halogen on One or Both Sides

### 5-26 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen) Dihalo-addition



<sup>589</sup>Jackson; Lovel *Aust. J. Chem.* **1983**, 36, 1975.

<sup>590</sup>Jackson; Perlmutter *Chem. Br.* **1986**, 338.

<sup>591</sup>For a review, see Nagata; Yoshioka Ref. 588.

<sup>592</sup>Arthur; England; Pratt; Whitman *J. Am. Chem. Soc.* **1954**, 76, 5364.

<sup>593</sup>For a review, see Brown, Ref. 588, pp. 658-667. For a review of the nickel-catalyzed process, see Tolman; McKinney; Seidel; Druliner; Stevens *Adv. Catal.* **1985**, 33, 1-46. For studies of the mechanism see Tolman; Seidel; Druliner; Domaille *Organometallics* **1984**, 3, 33; Druliner *Organometallics* **1984**, 3, 205; Bäckvall; Andell *Organometallics* **1986**, 5, 2350; McKinney; Roe *J. Am. Chem. Soc.* **1986**, 108, 5167; Funabiki; Tatsami; Yoshida *J. Organomet. Chem.* **1990**, 384, 199. See also Jackson; Lovel; Perlmutter; Smalridge *Aust. J. Chem.* **1988**, 41, 1099.

<sup>594</sup>Buchwald; LeMaire *Tetrahedron Lett.* **1987**, 28, 295.

<sup>595</sup>Ito; Kato; Imai; Saegusa *J. Am. Chem. Soc.* **1982**, 104, 6449.

Most double bonds are easily halogenated<sup>596</sup> with bromine, chlorine, or interhalogen compounds.<sup>597</sup> Iodination has also been accomplished, but the reaction is slower.<sup>598</sup> Under free-radical conditions, iodination proceeds more easily.<sup>599</sup> However, vic-diiodides are generally unstable and tend to revert to iodine and the olefin. The order of activity for some of the reagents is  $\text{BrCl} > \text{ICl}^{600} > \text{Br}_2 > \text{IBr} > \text{I}_2$ .<sup>601</sup> Mixed halogenations have also been achieved by other methods. Mixtures of  $\text{Br}_2$  and  $\text{Cl}_2$  have been used to give bromochlorination,<sup>602</sup> as has tetrabutylammonium dichlorobromate  $\text{Bu}_4\text{NBrCl}_2$ ,<sup>603</sup> iodochlorination has been achieved with  $\text{CuCl}_2$  and either  $\text{I}_2$ ,  $\text{HI}$ ,  $\text{CdI}_2$ , or other iodine donors;<sup>604</sup> iodoiodofluorination<sup>605</sup> with mixtures of  $\text{AgF}$  and  $\text{I}_2$ ,<sup>606</sup> and mixtures of N-bromo amides in anhydrous HF give bromofluorination.<sup>607</sup> Bromo-, iodo-, and chlorofluorination have also been achieved by treatment of the substrate with a solution of  $\text{Br}_2$ ,  $\text{I}_2$ , or an N-halo amide in polyhydrogen fluoride-pyridine;<sup>608</sup> while addition of I along with Br, Cl, or F has been accomplished with the reagent bis(pyridine)iodyl tetrafluoroborate  $\text{I(Py)}_2\text{BF}_4$  and  $\text{Br}^-$ ,  $\text{Cl}^-$ , or  $\text{F}^-$ , respectively.<sup>609</sup> This reaction (which is also successful for triple bonds<sup>610</sup>) can be extended to addition of I and other nucleophiles, e.g.,  $\text{NCO}$ ,  $\text{OH}$ ,  $\text{OAc}$ , and  $\text{NO}_2$ .<sup>609</sup>

Under ordinary conditions fluorine itself is too reactive to give simple addition; it attacks other bonds and mixtures are obtained.<sup>611</sup> However,  $\text{F}_2$  has been successfully added to certain double bonds in an inert solvent at low temperatures ( $-78^\circ\text{C}$ ), usually by diluting the  $\text{F}_2$  gas with Ar or  $\text{N}_2$ .<sup>612</sup> Addition of fluorine has also been accomplished with other reagents, e.g.,  $\text{CoF}_3$ ,<sup>613</sup>  $\text{XeF}_2$ ,<sup>614</sup> and a mixture of  $\text{PbO}_2$  and  $\text{SF}_4$ .<sup>615</sup>

<sup>596</sup>For a list of reagents that have been used for di-halo-addition, with references, see Ref. 133, pp. 319-321.

<sup>597</sup>For a monograph, see de la Mare *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976. For a review, see House, Ref. 144, pp. 422-431.

<sup>598</sup>Sumrell; Wyman; Howell; Harvey *Can. J. Chem.* **1964**, *42*, 2710; Zanger; Rabinowitz *J. Org. Chem.* **1975**, *40*, 248.

<sup>599</sup>Skell; Pavlis *J. Am. Chem. Soc.* **1964**, *86*, 2956; Ayres; Michejda; Rack *J. Am. Chem. Soc.* **1971**, *93*, 1389.

<sup>600</sup>For a review of  $\text{ICl}$ , see McClelland, in Pizey, Ref. 146, vol. 5, 1983, pp. 85-164.

<sup>601</sup>White; Robertson *J. Chem. Soc.* **1939**, 1509.

<sup>602</sup>Buckles; Forrester; Burham; McGee *J. Org. Chem.* **1960**, *25*, 24.

<sup>603</sup>Negoro; Ikeda *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3519.

<sup>604</sup>Baird; Surridge; Buza *J. Org. Chem.* **1971**, *36*, 2088, 3324.

<sup>605</sup>For a review of mixed halogenations where one side is fluorine, see Sharts; Sheppard *Org. React.* **1974**, *21*, 125-406, pp. 137-157. See also German; Zemskov, Ref. 612. For a review of halogen fluorides in organic synthesis, see Boguslavskaya *Russ. Chem. Rev.* **1984**, *53*, 1178-1194.

<sup>606</sup>Hall; Jones *Can. J. Chem.* **1973**, *51*, 2902. See also Zupan; Pollak *J. Org. Chem.* **1976**, *41*, 2179. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1745; Rozen; Brand *Tetrahedron Lett.* **1980**, *21*, 4543; Evans; Schauble *Synthesis* **1987**, 551; Kuroboshi; Hiyama *Synlett* **1991**, 185.

<sup>607</sup>Robinson; Finckenor; Oliveto; Gould *J. Am. Chem. Soc.* **1959**, *81*, 2191; Bowers *J. Am. Chem. Soc.* **1959**, *81*, 4107; Pattison; Peters; Dean *Can. J. Chem.* **1965**, *43*, 1689. For other methods, see Boguslavskaya; Chuvatkin; Kartashov; Ternovskoi *J. Org. Chem. USSR* **1987**, *23*, 230; Shimizu; Nakahara; Yoshioka *J. Chem. Soc., Chem. Commun.* **1989**, 1881.

<sup>608</sup>Olah; Nojima; Kerekes *Synthesis* **1973**, 780; Ref. 135. For other halofluorination methods, see Rozen; Brand *J. Org. Chem.* **1985**, *50*, 3342, **1986**, *51*, 222; Alvernhe; Laurent; Haufe *Synthesis* **1987**, 562; Camps; Chamorro; Gasol; Guerrero *J. Org. Chem.* **1989**, *54*, 4294; Ichihara; Funabiki; Hanafusa *Tetrahedron Lett.* **1990**, *31*, 3167.

<sup>609</sup>Barluenga; González; Campos; Asensio *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 319 [*Angew. Chem.* **97**, 341].

<sup>610</sup>Barluenga; Rodríguez; González; Campos; Asensio *Tetrahedron Lett.* **1986**, *27*, 3303.

<sup>611</sup>See, for example, Fuller; Stacey; Tatlow; Thomas *Tetrahedron* **1962**, *18*, 123.

<sup>612</sup>Merritt; Stevens *J. Am. Chem. Soc.* **1966**, *88*, 1822; Merritt *J. Am. Chem. Soc.* **1967**, *89*, 609; Barton; Lister-James; Hesse; Pechet; Rozen *J. Chem. Soc., Perkin Trans. 1* **1982**, 1105; Rozen; Brand *J. Org. Chem.* **1986**, *51*, 3607. For reviews of the use of  $\text{F}_2$  in organic synthesis, see Haas; Lieb *Chimia* **1985**, *39*, 134-140; Purrington; Kagen; Patrick *Chem. Rev.* **1986**, *86*, 997-1018. See also German; Zemskov *New Fluorinating Agents in Organic Synthesis*; Springer: New York, 1989.

<sup>613</sup>Rausch; Davis; Osborne *J. Org. Chem.* **1963**, *28*, 494.

<sup>614</sup>Zupan; Pollak *J. Org. Chem.* **1974**, *39*, 2646, **1976**, *41*, 4002, **1977**, *42*, 1559, *Tetrahedron Lett.* **1974**, 1015; Gregorić; Zupan *J. Org. Chem.* **1979**, *44*, 1255; Shackelford *J. Org. Chem.* **1979**, *44*, 3485; Filler *Isr. J. Chem.* **1978**, *17*, 71-79. For a review of fluorination with xenon fluorides see Zupan, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 657-679.

<sup>615</sup>Bissell; Fields *J. Org. Chem.* **1964**, *29*, 1591.

The reaction with bromine is very rapid and is easily carried out at room temperature. Bromine is often used as a test, qualitative or quantitative, for unsaturation.<sup>616</sup> The vast majority of double bonds can be successfully brominated. Even when aldehyde, ketone, amine, etc. functions are present in the molecule, they do not interfere, since the reaction with double bonds is faster.

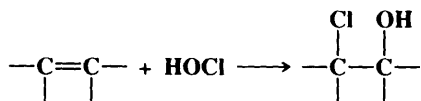
Several other reagents add  $\text{Cl}_2$  to double bonds, among them  $\text{SO}_2\text{Cl}_2$ ,<sup>617</sup>  $\text{PCl}_5$ ,<sup>618</sup>  $\text{Me}_3\text{SiCl-MnO}_2$ ,<sup>619</sup>  $\text{MoCl}_5$ ,<sup>620</sup>  $\text{KMnO}_4$ -oxalyl chloride,<sup>620a</sup> and iodobenzene dichloride  $\text{PhICl}_2$ .<sup>621</sup> A convenient reagent for the addition of  $\text{Br}_2$  to a double bond on a small scale is the commercially available pyridinium bromide perbromide  $\text{C}_5\text{H}_5\text{NH}^+ \text{Br}_3^-$ .<sup>622</sup>  $\text{Br}_2$  or  $\text{Cl}_2$  can also be added with  $\text{CuBr}_2$  or  $\text{CuCl}_2$  in the presence of a compound such as acetonitrile, methanol, or triphenylphosphine.<sup>623</sup>

The mechanism is usually electrophilic (see p. 737), but when free-radical initiators (or uv light) are present, addition can occur by a free-radical mechanism.<sup>624</sup> Once  $\text{Br}^\bullet$  or  $\text{Cl}^\bullet$  radicals are formed, however, substitution may compete (4-1 and 4-2). This is especially important when the olefin has allylic hydrogens. Under free-radical conditions (uv light) bromine or chlorine adds to the benzene ring to give, respectively, hexabromo- and hexachlorocyclohexane. These are mixtures of stereoisomers (see p. 131).<sup>625</sup>

Conjugated systems give both 1,2 and 1,4 addition.<sup>625</sup> Triple bonds add bromine, though generally more slowly than double bonds (see p. 748). Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Two moles of bromine can be added to triple bonds to give tetrabromo products. There is evidence that the addition of the first mole of bromine to a triple bond may take place by a nucleophilic mechanism.<sup>626</sup>  $\text{I}_2$  on  $\text{Al}_2\text{O}_3$  adds to triple bonds to give good yields of 1,2-diiodoalkenes.<sup>627</sup> With allenes it is easy to stop the reaction after only 1 mole has added, to give  $\text{X}-\text{C}-\text{CX}=\text{C}$ .<sup>628</sup> Addition of halogen to ketenes gives  $\alpha$ -halo acyl halides, but the yields are not good.

OS I, 205, 521; II, 171, 177, 270, 408; III, 105, 123, 127, 209, 350, 526, 531, 731, 785; IV, 130, 195, 748, 851, 969; V, 136, 370, 403, 467; VI, 210, 422, 675, 862, 954.

## 5-27 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen) Hydroxy-chloro-addition, etc.<sup>629</sup>



<sup>616</sup>For a review of this, see Kuchar, in Patai, Ref. 36, pp. 273-280.

<sup>617</sup>Kharasch; Brown *J. Am. Chem. Soc.* **1939**, *61*, 3432.

<sup>618</sup>Spiegler; Tinker *J. Am. Chem. Soc.* **1939**, *61*, 940.

<sup>619</sup>Bellesia; Ghelfi; Pagnoni; Pinetti *J. Chem. Res. (S)* **1989**, *108*, 360.

<sup>620</sup>Uemura; Onoe; Okano *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3121; San Filippo; Sowinski; Romano *J. Am. Chem. Soc.* **1975**, *97*, 1599. See also Nugent *Tetrahedron Lett.* **1978**, 3427.

<sup>620a</sup>Markó; Richardson *Tetrahedron Lett.* **1991**, *32*, 1831.

<sup>621</sup>See, for example, Tanner; Gidley *J. Org. Chem.* **1968**, *33*, 38; Masson; Thuillier *Bull. Soc. Chim. Fr.* **1969**, 4368; Lasne; Thuillier *Bull. Soc. Chim. Fr.* **1974**, 249.

<sup>622</sup>Fieser; Fieser *Reagents for Organic Synthesis*, vol. 1; Wiley: New York, 1967, pp. 967-970. For a discussion of the mechanism with  $\text{Br}_3^-$ , see Bellucci; Bianchini; Vecchiani *J. Org. Chem.* **1986**, *51*, 4224.

<sup>623</sup>Koyano *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1439, 3501; Uemura; Tabata; Kimura; Ichikawa *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1973; Or; Levy; Asscher; Vofsi *J. Chem. Soc., Perkin Trans. 2* **1974**, 857; Uemura; Okazaki; Onoe; Okano *J. Chem. Soc., Perkin Trans. 1* **1977**, 676; Ref. 604.

<sup>624</sup>For example, see Poutsma *J. Am. Chem. Soc.* **1965**, *87*, 2161, 2172; *J. Org. Chem.* **1966**, *31*, 4167; Dessau, *J. Am. Chem. Soc.* **1979**, *101*, 1344.

<sup>625</sup>For a review, see Cais, in Patai, Ref. 36, pp. 993-999.

<sup>626</sup>Sinn; Hopferditzel; Sauermann *Monatsh. Chem.* **1965**, *96*, 1036.

<sup>627</sup>Hondrogianis; Lee; Kabalka; Pagni *Tetrahedron Lett.* **1989**, *30*, 2069.

<sup>628</sup>For a review of additions of halogens to allenes, see Jacobs, in Landor, Ref. 95, vol. 2, pp. 466-483.

<sup>629</sup>Addends are listed in order of priority in the Cahn-Ingold-Prelog system (p. 109).

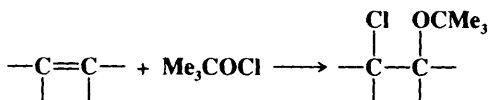
HOCl, HOBr, and HOI can be added to olefins<sup>630</sup> to produce halohydrins.<sup>631</sup> HOBr and HOCl are often generated in situ by the reaction between water and Br<sub>2</sub> or Cl<sub>2</sub> respectively. HOI, generated from I<sub>2</sub> and H<sub>2</sub>O, also adds to double bonds, if the reaction is carried out in tetramethylene sulfone-CHCl<sub>3</sub><sup>632</sup> or if an oxidizing agent such as HIO<sub>3</sub> is present.<sup>633</sup> HOF has also been added, but this reagent is difficult to prepare in a pure state and detonations occur.<sup>634</sup> HOBr can also be conveniently added by the use of a reagent consisting of an N-bromo amide [e.g., N-bromosuccinimide (NBS) or N-bromoacetamide] and a small amount of water in a solvent such as Me<sub>2</sub>SO or dioxane.<sup>635</sup> An especially powerful reagent for HOCl addition is *t*-butyl hydroperoxide (or di-*t*-butyl peroxide) along with TiCl<sub>4</sub>. This reaction is generally complete within 15 min at -78°C.<sup>636</sup> Chlorohydrins can be conveniently prepared by treatment of the alkene with Chloramine T (TsNCl<sup>-</sup> Na<sup>+</sup>)<sup>637</sup> in acetone-water.<sup>638</sup> HOI can be added by treatment of alkenes with periodic acid and NaHSO<sub>3</sub>.<sup>639</sup>

The mechanism of HOX addition is electrophilic, with initial attack by the positive halogen end of the HOX dipole. Following Markovnikov's rule, the positive halogen goes to the side of the double bond that has more hydrogens. The resulting carbocation (or bromonium or iodonium ion) reacts with OH<sup>-</sup> or H<sub>2</sub>O to give the product. If the substrate is treated with Br<sub>2</sub> or Cl<sub>2</sub> (or another source of positive halogen such as NBS) in an

alcohol or a carboxylic acid solvent, it is possible to obtain, directly  $\text{X}-\text{C}(\text{OR})_2-\text{C}(\text{OR})_2-\text{OR}$  or  $\text{X}-\text{C}(\text{OR})_2-\text{C}(\text{OR})_2-\text{OCOR}$ , respectively (see also 5-35).<sup>640</sup> Even the weak nucleophile CF<sub>3</sub>SO<sub>2</sub>O<sup>-</sup>

can participate in the second step: The addition of Cl<sub>2</sub> or Br<sub>2</sub> to olefins in the presence of this ion resulted in the formation of some β-haloalkyl triflates.<sup>641</sup> There is evidence that the mechanism with Cl<sub>2</sub> and H<sub>2</sub>O is different from that with HOCl.<sup>642</sup> HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds —CX<sub>2</sub>—CO—.

*t*-Butyl hypochlorite, hypobromite, and hypoiodite<sup>643</sup> add to double bonds to give halogenated *t*-butyl ethers, e.g.,



This is a convenient method for the preparation of tertiary ethers. When Me<sub>3</sub>COCl or Me<sub>3</sub>COBr is added to olefins in the presence of excess ROH, the ether produced is

<sup>630</sup>For a list of reagents used to accomplish these additions, with references, see Ref. 133, pp. 325-327.

<sup>631</sup>For a review, see Boguslavskaya *Russ. Chem. Rev.* **1972**, *41*, 740-749.

<sup>632</sup>Cambie; Noall; Potter; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1977**, 266.

<sup>633</sup>See, for example, Cornforth; Green *J. Chem. Soc. C* **1970**, 846; Furrow *Int. J. Chem. Kinet.* **1982**, *14*, 927; Antonioletti; D'Auria; De Mico; Piancatelli; Scettri *Tetrahedron* **1983**, *39*, 1765.

<sup>634</sup>Migliorese; Appelman; Tsangaris *J. Org. Chem.* **1979**, *44*, 1711.

<sup>635</sup>For examples, see Dalton; Hendrickson; Jones *Chem. Commun.* **1966**, 591; Dalton; Dutta *J. Chem. Soc. B* **1971**, 85; Sisti *J. Org. Chem.* **1970**, *35*, 2670.

<sup>636</sup>Klunder; Caron; Uchiyama; Sharpless *J. Org. Chem.* **1985**, *50*, 912.

<sup>637</sup>For reviews of this reagent, see Bremner, in Pizey, Ref. 146, vol. 6, 1985, pp. 9-59; Campbell; Johnson *Chem. Rev.* **1978**, *78*, 65-79.

<sup>638</sup>Damin; Garapon; Sillion *Synthesis* **1981**, 362.

<sup>639</sup>Ohta; Sakata; Takeuchi; Ishii *Chem. Lett.* **1990**, 733.

<sup>640</sup>For a list of reagents that accomplish alkoxy-halo-addition, with references, see Ref. 133, pp. 327-328.

<sup>641</sup>Zefirov; Koz'min; Sorokin; Zhdankin *J. Org. Chem. USSR* **1982**, *18*, 1546. For reviews of this and related reactions, see Zefirov; Koz'min *Acc. Chem. Res.* **1985**, *18*, 154, *Sov. Sci. Rev., Sect. B* **1985**, *7*, 297-339.

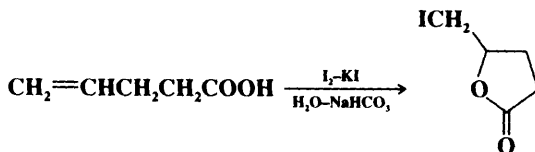
<sup>642</sup>Buss; Rockstuhl; Schnurpfel *J. Prakt. Chem.* **1982**, 324, 197.

<sup>643</sup>Glover; Goosen *Tetrahedron Lett.* **1980**, 21, 2005.

$\text{X}-\text{C}=\text{C}-\text{OR}$ .<sup>644</sup> Vinylic ethers give  $\beta$ -halo acetals.<sup>645</sup> A mixture of  $\text{Cl}_2$  and  $\text{SO}_3$  at  $-78^\circ\text{C}$

converts alkenes to 2-chloro chlorosulfates  $\text{ClCH}_2\text{CH}(\text{OR})\text{OSO}_2\text{Cl}$ , which are stable compounds.<sup>646</sup> Chlorine acetate [solutions of which are prepared by treating  $\text{Cl}_2$  with  $\text{Hg}(\text{OAc})_2$  in an appropriate solvent] adds to olefins to give acetoxy chlorides.<sup>647</sup> The latter are also produced<sup>648</sup> by treatment of olefins with a mixture of  $\text{PdCl}_2$  and  $\text{CuCl}_2$  in acetic acid<sup>649</sup> or with chromyl chloride  $\text{CrO}_2\text{Cl}_2$  in acetyl chloride.<sup>650</sup> Acetoxy fluorides have been obtained by treatment of olefins with  $\text{CH}_3\text{COOF}$ .<sup>651</sup>

An internal example of the addition of X and OCOR is called *halolactonization*;<sup>652</sup> e.g.,



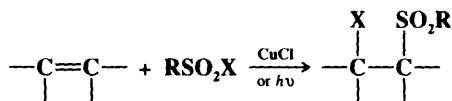
This reaction has been used mostly to prepare iodo lactones, but bromo lactones and, to a lesser extent, chloro lactones, have also been prepared. In the case of  $\gamma,\delta$ -unsaturated acids, 5-membered rings ( $\gamma$ -lactones) are predominantly formed (as shown above; note that Markovnikov's rule is followed), but 6-membered and even 4-membered lactones have also been made by this procedure. Thallium reagents, along with the halogen, have also been used.<sup>653</sup>

For a method of iodoacetyl addition, see 5-35.

OS I, 158; IV, 130, 157; VI, 184, 361, 560; VII, 164; 67, 105; 69, 38.

## 5-28 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)

**Alkylsulfonyl-chloro-addition**, etc.<sup>654</sup>



Sulfonyl halides add to double bonds, to give  $\beta$ -halo sulfones, in the presence of free-radical initiators or uv light. A particularly good catalyst is cuprous chloride.<sup>655</sup> Triple bonds behave

<sup>644</sup>Bresson; Dauphin; Geneste; Kergomard; Lacourt *Bull. Soc. Chim. Fr.* **1970**, 2432, **1971**, 1080.

<sup>645</sup>Weissermel; Lederer *Chem. Ber.* **1963**, 96, 77.

<sup>646</sup>Zefirov; Koz'min; Sorokin *J. Org. Chem.* **1984**, 49, 4086.

<sup>647</sup>de la Mare; Wilson; Rosser *J. Chem. Soc., Perkin Trans. 2* **1973**, 1480; de la Mare; O'Connor; Wilson *J. Chem. Soc., Perkin Trans. 2* **1975**, 1150. For the addition of bromine acetate see Wilson; Woodgate *J. Chem. Soc., Perkin Trans. 2* **1976**, 141.

<sup>648</sup>For a list of reagents that accomplish acyloxy-halo-addition, with references, see Ref. 133, pp. 328-329.

<sup>649</sup>Henry *J. Org. Chem.* **1967**, 32, 2575, **1973**, 38, 1681. For a 1,4 example of this addition, see Bäckvall; Nystrom; Nordberg *J. Am. Chem. Soc.* **1985**, 107, 3676; Nyström; Rein; Bäckvall *Org. Synth.* 67, 105.

<sup>650</sup>Bäckvall Young; Sharpless *Tetrahedron Lett.* **1977**, 3523.

<sup>651</sup>Rozen; Lerman; Kol; Hebel *J. Org. Chem.* **1985**, 50, 4753.

<sup>652</sup>For reviews, see Cardillo; Orena *Tetrahedron* **1990**, 46, 3321-3408; Dowle; Davies *Chem. Soc. Rev.* **1979**, 8, 171-197. For a list of reagents that accomplish this, with references, see Ref. 133, pp. 945-946. For a review with respect to the stereochemistry of the reaction, see Bartlett, in Morrison, Ref. 232, vol. 3, 1984, pp. 411-454, pp. 416-425.

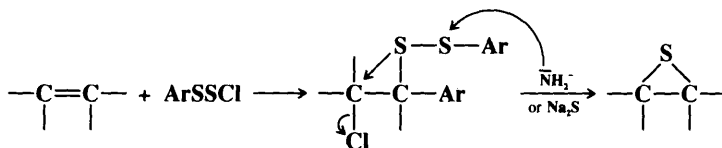
<sup>653</sup>See Cambie; Rutledge; Somerville; Woodgate *Synthesis* **1988**, 1009, and references cited therein.

<sup>654</sup>When a general group (such as halo) is used, its priority is that of the lowest member of its group (see footnote 629). Thus the general name for this transformation is halo-alkylsulfonyl-addition because "halo" has the same priority as "fluoro," its lowest member.

<sup>655</sup>Asscher; Vofsi *J. Chem. Soc.* **1964**, 4962; Truce; Goralski; Christensen; Bavry *J. Org. Chem.* **1970**, 35, 4217; Sinnreich; Asscher *J. Chem. Soc., Perkin Trans. 1* **1972**, 1543.

similarly, to give  $\beta$ -halo- $\alpha,\beta$ -unsaturated sulfones.<sup>656</sup> In a similar reaction, sulfenyl chlorides,  $\text{RSCl}$ , give  $\beta$ -halo thioethers.<sup>657</sup> The latter may be free-radical or electrophilic additions, depending on conditions. The addition of  $\text{MeS}$  and  $\text{Cl}$  has also been accomplished by treating the olefin with  $\text{Me}_3\text{SiCl}$  and  $\text{Me}_2\text{SO}$ .<sup>658</sup> The use of  $\text{Me}_3\text{SiBr}$  and  $\text{Me}_2\text{SO}$  does not give this result; dibromides (**5-26**) are formed instead.  $\text{MeS}$  and  $\text{F}$  have been added by treatment of the olefin with dimethyl(methylthio)sulfonium fluoroborate  $\text{Me}_2\text{SSMe}^+\text{BF}_4^-$  and triethylamine tris-hydrofluoride  $\text{Et}_3\text{N}\cdot 3\text{HF}$ .<sup>659</sup>  $\beta$ -Iodo thiocyanates can be prepared from alkenes by treatment with  $\text{I}_2$  and isothiocyanatotributylstannane  $\text{Bu}_3\text{SnNCS}$ .<sup>660</sup> Bromothiocyantation can be accomplished with  $\text{Br}_2$  and thallium(I) thiocyanate.<sup>661</sup>

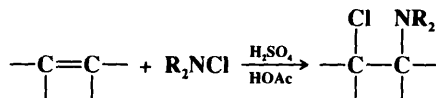
$\beta$ -Halo disulfides, formed by addition of arenethiosulfonyl chlorides to double-bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.<sup>662</sup>



The overall episulfidation is a stereospecific syn addition.

OS 65, 90. See also OS VII, 251.

## 5-29 Addition of Halogen and an Amino Group (Addition of Halogen, Nitrogen) Dialkylamino-chloro-addition



The groups  $\text{R}_2\text{N}$  and  $\text{Cl}$  can be added directly to olefins, allenes, conjugated dienes, and alkynes, by treatment with dialkyl-N-chloroamines and acids.<sup>663</sup> These are free-radical additions, with initial attack by the  $\text{R}_2\text{NH}\cdot$  radical ion.<sup>664</sup> N-Halo amides  $\text{RCONHX}$  add  $\text{RCONH}$  and  $\text{X}$  to double bonds under the influence of uv light or chromous chloride.<sup>665</sup> For an indirect way of adding  $\text{NH}_2$  and  $\text{I}$  to a double bond, see 5-32.

<sup>656</sup>Truce; Wolf *J. Org. Chem.* **1971**, 36, 1727; Amiel *J. Org. Chem.* **1971**, 36, 3691, 3697, **1974**, 39, 3867; Zakharkin; Zhigareva *J. Org. Chem. USSR* **1973**, 9, 918; Okuyama; Izawa; Fueno *J. Org. Chem.* **1974**, 39, 351.

<sup>657</sup>For reviews, see Rasteikiene; Greiciute; Lin'kova; Knunyants *Russ. Chem. Rev.* **1977**, 46, 548-564; Kühle *Synthesis* **1971**, 563-586.

<sup>658</sup>Bellesia; Ghelfi; Pagnoni; Pinetti *J. Chem. Res. (S)* **1987**, 238. See also Liu; Nyangulu *Tetrahedron Lett.* **1988**, 29, 5467.

<sup>659</sup>Haufe; Alvernhe; Anker; Laurent; Saluzzo *Tetrahedron Lett.* **1988**, 29, 2311.

<sup>660</sup>Woodgate; Janssen; Rutledge; Woodgate; Cambie *Synthesis* **1984**, 1017, and references cited therein. See also Watanabe; Uemura; Okano *Bull. Chem. Soc. Jpn.* **1983**, 56, 2458.

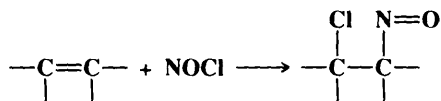
<sup>661</sup>Cambie; Larsen; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans. I* **1981**, 58.

<sup>662</sup>Fujisawa; Kobori *Chem. Lett.* **1972**, 935. For another method of olefin-thiirane conversion, see Capozzi; Capozzi; Menichetti *Tetrahedron Lett.* **1988**, 29, 4177.

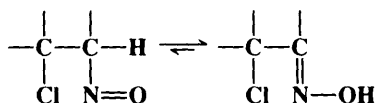
<sup>663</sup>Neale; Hinman *J. Am. Chem. Soc.* **1963**, 85, 2666; Neale; Marcus *J. Org. Chem.* **1967**, 32, 3273; Minisci; Galli; Cecere *Tetrahedron Lett.* **1966**, 3163. For reviews see Mirskova; Drozdova; Levkovskaya; Voronkov *Russ. Chem. Rev.* **1989**, 58, 250-271; Neale *Synthesis* **1971**, 1-15; Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972**, 4, 203-284, pp. 238-249.

<sup>664</sup>For a review of these species, see Chow; Danen; Nelson; Rosenblatt *Chem. Rev.* **1978**, 78, 243-274.

<sup>665</sup>Tuaillon; Couture; Lessard *Can. J. Chem.* **1987**, 65, 2194, and other papers in this series. For a review, see Labeish; Petrov *Russ. Chem. Rev.* **1989**, 58, 1048-1061.

**5-30 Addition of NOX and NO<sub>2</sub>X (Addition of Halogen, Nitrogen)****Nitroso-chloro-addition**

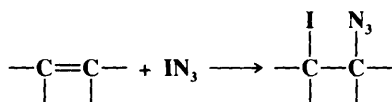
There are three possible products when NOCl is added to olefins.<sup>666</sup> The initial product is always the β-halo nitroso compound, but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime:



With some olefins, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound.<sup>667</sup> Many functional groups can be present without interference, e.g., COOH, COOR, CN, OR. The mechanism in most cases is probably simple electrophilic addition, and the addition is usually anti, though syn addition has been reported in some cases.<sup>668</sup> Markovnikov's rule is followed, the positive NO going to the carbon that has more hydrogens.

Nitryl chloride NO<sub>2</sub>Cl also adds to olefins, to give β-halo nitro compounds, but this is a free-radical process. The NO<sub>2</sub> goes to the less-substituted carbon.<sup>669</sup> Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro olefins.<sup>670</sup> FNO<sub>2</sub> can be added to olefins<sup>671</sup> by treatment with HF in HNO<sub>3</sub><sup>672</sup> or by addition of the olefin to a solution of nitronium tetrafluoroborate NO<sub>2</sub><sup>+</sup> BF<sub>4</sub><sup>-</sup> (see 1-2) in 70% polyhydrogen fluoride-pyridine solution<sup>673</sup> (see also 5-26).

OS IV, 711; V, 266, 863.

**5-31 Addition of XN<sub>3</sub> (Addition of Halogen, Nitrogen)****Azido-iodo-addition**

The addition of iodine azide to double bonds gives β-iodo azides.<sup>674</sup> The addition is stereospecific and anti, suggesting that the mechanism involves a cyclic iodonium ion interme-

<sup>666</sup>For a review, see Kadzyauskas; Zefirov *Russ. Chem. Rev.* **1968**, 37, 543-550.

<sup>667</sup>For a review of the preparation of halo nitro compounds see Shvekhgeimer; Smirnyagin; Sadykov; Novikov *Russ. Chem. Rev.* **1968**, 37, 351-363.

<sup>668</sup>For example, see Meinwald; Meinwald; Baker *J. Am. Chem. Soc.* **1964**, 86, 4074.

<sup>669</sup>Shechter *Rec. Chem. Prog.* **1964**, 25, 55-76.

<sup>670</sup>Schlubach; Braun *Liebigs Ann. Chem.* **1959**, 627, 28.

<sup>671</sup>For a review, see Sharts; Sheppard *Org. React.* **1974**, 21, 125-406, pp. 236-243.

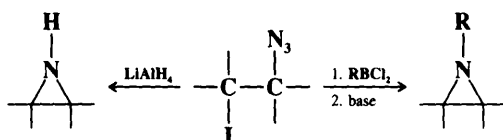
<sup>672</sup>Knunyants; German; Rozhkov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, 1794.

<sup>673</sup>Olah; Nojima *Synthesis* **1973**, 785.

<sup>674</sup>For reviews, see Dehnicke *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 507-514 [*Angew. Chem.* 91, 527-534]; Hassner *Acc. Chem. Res.* **1971**, 4, 9-16; Biffin; Miller; Paul, *Ref.* 214, pp. 136-147.

diate.<sup>675</sup> The reaction has been performed on many double-bond compounds, including allenes<sup>676</sup> and  $\alpha,\beta$ -unsaturated ketones. Similar reactions can be performed with  $\text{BrN}_3$ <sup>677</sup> and  $\text{ClN}_3$ . 1,4 addition has been found with acyclic conjugated dienes.<sup>678</sup> In the case of  $\text{BrN}_3$  both electrophilic and free-radical mechanisms are important,<sup>679</sup> while with  $\text{ClN}_3$  the additions are chiefly free-radical.<sup>680</sup>  $\text{IN}_3$  also adds to triple bonds to give  $\beta$ -iodo- $\alpha,\beta$ -unsaturated azides.<sup>681</sup>

$\beta$ -Iodo azides can be reduced to aziridines with  $\text{LiAlH}_4$ <sup>682</sup> or converted to N-alkyl- or N-arylaziridines by treatment with an alkyl- or arylchloroborane followed by a base.<sup>683</sup> In



both cases the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (**0-43**) follows.

OS VI, 893.

### 5-32 Addition of INCO (Addition of Halogen, Nitrogen)

#### Isocyanato-iodo-addition



In a reaction similar to **5-31**, iodine isocyanate adds to double bonds to give  $\beta$ -iodo isocyanates.<sup>684</sup> The addition is stereospecific and anti; the mechanism similar to that shown in **5-31**. The reaction has been applied to mono-, di-, and some trisubstituted olefins. The orientation generally follows Markovnikov's rule, the positive iodine adding to the less highly substituted side.  $\alpha,\beta$ -Unsaturated carbonyl compounds do not react. Triple bonds give  $\beta$ -iodo- $\alpha,\beta$ -unsaturated isocyanates in low yields.<sup>685</sup> Allenes add 1 mole of INCO to give  $\beta$ -iodo- $\beta,\gamma$ -unsaturated isocyanates.<sup>686</sup> Since an isocyanate group can be hydrolyzed to an amino group ( $\text{RNCO} \rightarrow \text{RNH}_2$ , **6-3**), the method is an indirect way of adding  $\text{H}_2\text{N}$  and I to double bonds.

OS VI, 795.

<sup>675</sup>See, however, Cambie; Hayward; Rutledge; Smith-Palmer; Swedlund; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1979**, 180.

<sup>676</sup>Hassner; Keogh *J. Org. Chem.* **1986**, 51, 2767.

<sup>677</sup>Azido-bromo-addition has also been done with another reagent: Olah; Wang; Li; Prakash *Synlett* **1990**, 487.

<sup>678</sup>Hassner; Keogh *Tetrahedron Lett.* **1975**, 1575.

<sup>679</sup>Hassner; Boerwinkle *J. Am. Chem. Soc.* **1968**, 90, 217; Hassner; Teeter *J. Org. Chem.* **1971**, 36, 2176.

<sup>680</sup>Even  $\text{IN}_3$  can be induced to add by a free-radical mechanism [see, for example, Cambie; Jurlina; Rutledge; Swedlund; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1982**, 327]. For a review of free-radical additions of  $\text{XN}_3$ , see Hassner *Intra-Sci. Chem. Rep.* **1970**, 4, 109-114.

<sup>681</sup>Hassner; Isbister; Friederang *Tetrahedron Lett.* **1969**, 2939.

<sup>682</sup>Hassner; Matthews; Fowler *J. Am. Chem. Soc.* **1969**, 91, 5046.

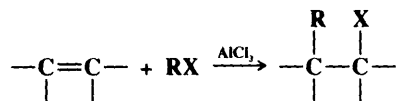
<sup>683</sup>Levy; Brown *J. Am. Chem. Soc.* **1973**, 95, 4067.

<sup>684</sup>Heathcock; Hassner *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 213 [*Angew. Chem.* 75, 344]; Birckenbach; Linhard *Ber.* **1931**, 64B, 961, 1076; Drehfahl; Ponsold *Chem. Ber.* **1960**, 93, 519; Hassner; Hoblitt; Heathcock; Kropp; Lorber *J. Am. Chem. Soc.* **1970**, 92, 1326; Gebelein; Rosen; Swern *J. Org. Chem.* **1969**, 34, 1677; Cambie; Hume; Rutledge; Woodgate *Aust. J. Chem.* **1983**, 36, 2569.

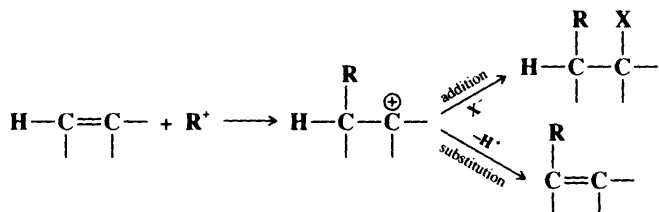
<sup>685</sup>Grimwood; Swern *J. Org. Chem.* **1967**, 32, 3665.

<sup>686</sup>Greibrokk *Acta Chem. Scand.* **1973**, 27, 3368.

## 5-33 Addition of Alkyl Halides (Addition of Halogen, Carbon)

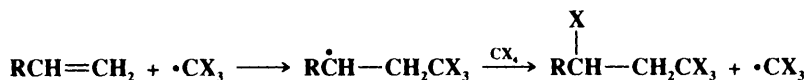
**Alkyl-halo-addition<sup>684</sup>**

Alkyl halides can be added to olefins in the presence of a Friedel-Crafts catalyst, most often  $AlCl_3$ .<sup>687</sup> The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with **1-12**). Methyl and ethyl halides, which cannot rearrange, give no reaction at all. The attacking species is the carbocation formed from the alkyl halide and the catalyst (see **1-12**).<sup>688</sup> The addition therefore follows Markovnikov's rule, with the cation going to the carbon with more hydrogens. Substitution is a side reaction, arising from loss of hydrogen from the carbocation formed when the original carbocation attacks the double bond:



Conjugated dienes can add 1,4.<sup>689</sup> Triple bonds also undergo the reaction, to give vinylic halides.<sup>690</sup>

$CCl_4$ ,  $BrCCl_3$ ,  $ICF_3$ , and similar simple polyhalo alkanes add to olefins in good yield.<sup>691</sup> These are free-radical additions and require initiation, e.g.,<sup>692</sup> by peroxides, metal halides (e.g.,  $FeCl_2$ ,  $CuCl$ ),<sup>693</sup> or uv light. The initial attack is by the carbon, and it goes to the carbon with more hydrogens, as in most free-radical attack:



This type of polyhalo alkane adds to halogenated olefins in the presence of  $AlCl_3$  by an electrophilic mechanism. This is called the *Prins reaction* (not to be confused with the other Prins reaction, **6-53**).<sup>694</sup>

$ArX$  can be added across double bonds, in a free-radical process, by treatment of olefins

<sup>687</sup>For a review, see Schmerling, in Olah, Ref. 412, vol. 2, pp. 1133-1174. See also Mayr; Striepe *J. Org. Chem.* **1983**, *48*, 1159; Mayr; Schade; Rubow; Schneider *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1029 [*Angew. Chem.* *99*, 1059]. For a list of references, see Ref. 133, p. 342.

<sup>688</sup>For a discussion of the mechanism, see Pock; Mayr; Rubow; Wilhelm *J. Am. Chem. Soc.* **1986**, *108*, 7767.

<sup>689</sup>Kolyaskina; Petrov *J. Gen. Chem. USSR* **1962**, *32*, 1067.

<sup>690</sup>See, for example, Maroni; Melloni; Modena *J. Chem. Soc., Perkin Trans. I* **1973**, 2491, **1974**, 353.

<sup>691</sup>For reviews, see Freidlina; Velichko *Synthesis* **1977**, 145-154; Freidlina; Chukovskaya *Synthesis* **1974**, 477-488.

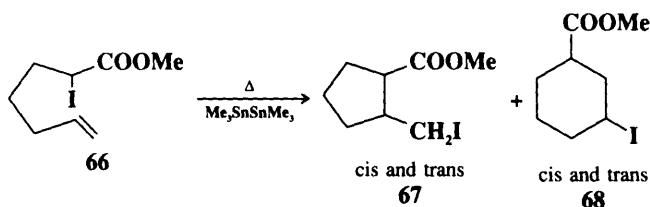
<sup>692</sup>For other initiators, see Matsumoto; Nakano; Takasu; Nagai *J. Org. Chem.* **1978**, *43*, 1734; Tsuji; Sato; Nagashima *Tetrahedron* **1985**, *41*, 393; Bland; Davis; Durrant *J. Organomet. Chem.* **1985**, *280*, 397; Phelps; Bergbreiter; Lee; Villani; Weinreb *Tetrahedron Lett.* **1989**, *30*, 3915.

<sup>693</sup>For example, see Asscher; Vofsi *J. Chem. Soc.* **1963**, 1887, 3921, *J. Chem. Soc. B* **1968**, 947; Murai; Tsutsumi *J. Org. Chem.* **1966**, *31*, 3000; Martin; Steiner; Streith; Winkler; Bellus *Tetrahedron* **1985**, *41*, 4057. For the addition of  $CH_2Cl_2$  and  $PhBr$ , see Mitani; Nakayama; Koyama *Tetrahedron Lett.* **1980**, *21*, 4457.

<sup>694</sup>For a review with respect to fluoroolefins, see Paleta *Fluorine Chem. Rev.* **1977**, *8*, 39-71.

with diazonium salts, although Meerwein arylation (substitution) (**4-19**) competes.<sup>695</sup> This addition can be either 1,2 or 1,4 with conjugated dienes.<sup>696</sup> Addition of  $\text{ArX}$  can also be accomplished by treatment with an arylmercury halide  $\text{ArHgX}$  in the presence of  $\text{CuX}_2$ ,  $\text{LiX}$ , and a palladium compound catalyst, usually  $\text{Li}_2\text{PdCl}_4$ .<sup>697</sup> In this case also, substitution (**4-20**) is a side reaction. Yields of addition product are increased by increasing the concentration of  $\text{CuX}_2$ . Palladium compounds also catalyze the addition of allylic halides to alkynes.<sup>698</sup>

A variant of the free-radical addition method has been used for ring closure. For example, treatment of **66** with the free-radical initiator hexamethylditin gave a mixture of *cis*- and



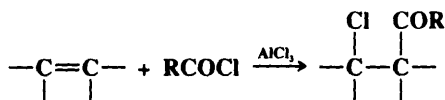
*trans*-**67**, with a small amount of *cis*- and *trans*-**68** (total yield 83%).<sup>699</sup> The reaction has been performed with  $\alpha$ -iodo esters, ketones, and malonates.

For another method of adding R and I to a triple bond, see **5-53**.

OS II, 312; IV, 727; V, 1076; VI, 21; VII, 290.

### 5-34 Addition of Acyl Halides (Addition of Halogen, Carbon)

#### Acyl-halo-addition



Acyl halides have been added to many olefins, in the presence of Friedel–Crafts catalysts. The reaction has been applied to straight-chain, branched, and cyclic olefins, but to very few containing functional groups, other than halogen.<sup>700</sup> The mechanism is similar to that of **5-33**, and, as in that case, substitution competes (**2-15**). Increasing temperature favors substitution,<sup>701</sup> and good yields of addition products can be achieved if the temperature is kept under  $0^\circ\text{C}$ . The reaction usually fails with conjugated dienes, since polymerization predominates.<sup>702</sup> The reaction can be performed on triple-bond compounds, producing com-

<sup>695</sup>For example, see Iurkevich; Dombrovskii; Terent'ev *J. Gen. Chem. USSR* **1958**, 28, 226; Fedorov; Pribytkova; Kanishchev; Dombrovskii *J. Org. Chem. USSR* **1973**, 9, 1517; Cleland *J. Org. Chem.* **1961**, 26, 3362, **1969**, 34, 744; Doyle; Siegfried; Elliott; Dellaria *J. Org. Chem.* **1977**, 42, 2431; Ganushchak; Obushak; Polishchuk *J. Org. Chem. USSR* **1986**, 22, 2291.

<sup>696</sup>For example, see Dombrovskii; Ganushchak *J. Gen. Chem. USSR* **1961**, 31, 1191, **1962**, 32, 1867; Ganushchak; Golik; Migaichuk *J. Org. Chem. USSR* **1972**, 8, 2403.

<sup>697</sup>Heck *J. Am. Chem. Soc.* **1968**, 90, 5538. See also Bäckvall; Nordberg *J. Am. Chem. Soc.* **1980**, 102, 393.

<sup>698</sup>Kaneda; Uchiyama; Fujiwara; Imanaka; Teranishi *J. Org. Chem.* **1979**, 44, 55.

<sup>699</sup>Curran; Chang *J. Org. Chem.* **1989**, 54, 3140; Curran; Chen; Spletzer; Seong; Chang *J. Am. Chem. Soc.* **1989**, 111, 8872. See also Ichinose; Matsunaga; Fugami; Oshima; Utimoto *Tetrahedron Lett.* **1989**, 30, 3155.

<sup>700</sup>For reviews, see Groves *Chem. Soc. Rev.* **1972**, 1, 73-97; House, Ref. 144, pp. 786-797; Nenitzescu; Balaban, in Olah, Ref. 412, vol. 3, 1964, pp. 1033-1152.

<sup>701</sup>Jones; Taylor; Rudd *J. Chem. Soc.* **1961**, 1342.

<sup>702</sup>For examples of 1,4 addition at low temperatures, see Melikyan; Babayan; Atanesyan; Badanyan *J. Org. Chem. USSR* **1984**, 20, 1884.

pounds of the form  $\text{RCO}-\text{C}=\text{C}-\text{Cl}$ .<sup>703</sup> A *formyl* group and a halogen can be added to

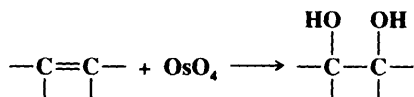
triple bonds by treatment with N,N-disubstituted formamides and  $\text{POCl}_3$  (Vilsmeier conditions, see 1-15).<sup>704</sup>

OS IV, 186; VI, 883; 69, 238.

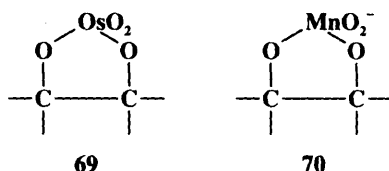
## B. Oxygen, Nitrogen, or Sulfur on One or Both Sides

### 5-35 Hydroxylation (Addition of Oxygen, Oxygen)

#### Dihydroxy-addition



There are many reagents that add two OH groups to a double bond.<sup>705</sup>  $\text{OsO}_4$ <sup>706</sup> and alkaline  $\text{KMnO}_4$ <sup>707</sup> give syn addition, from the less-hindered side of the double bond. Osmium tetroxide adds rather slowly but almost quantitatively. The cyclic ester 69 is an intermediate and can be isolated,<sup>708</sup> but is usually decomposed in solution, with sodium sulfite in ethanol



or other reagents. Bases catalyze the reaction by coordinating with the ester. The chief drawback to this reaction is that  $\text{OsO}_4$  is expensive and highly toxic, so that its use has been limited to small-scale preparations of scarce materials. However, the same result (syn addition) can be accomplished more economically by the use of  $\text{H}_2\text{O}_2$ , with  $\text{OsO}_4$  present in catalytic amounts.<sup>709</sup> *t*-Butyl hydroperoxide in alkaline solution,<sup>710</sup> N-methylmorpholine-N-oxide,<sup>711</sup> and  $\text{K}_3\text{Fe}(\text{CN})_6$ <sup>712</sup> have been substituted for  $\text{H}_2\text{O}_2$  in this procedure. Another method uses polymer-bound  $\text{OsO}_4$ .<sup>713</sup>

<sup>703</sup>For example see Nifant'ev; Grachev; Bakinovskii; Kara-Murza; Kochetkov *J. Appl. Chem. USSR* **1963**, 36, 646; Savenkov; Khokhlov; Nazarova; Mochalkin *J. Org. Chem. USSR* **1973**, 9, 914; Martens; Janssens; Hoornaert *Tetrahedron* **1975**, 31, 177; Brownstein; Morrison; Tan *J. Org. Chem.* **1985**, 50, 2796.

<sup>704</sup>*Yen Ann. Chim. (Paris)* **1962**, [13] 7, 785.

<sup>705</sup>For reviews, see Hudlický *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990, pp. 67-73; Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1985, pp. 73-98, 278-294; Sheldon; Kochi *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981, pp. 162-171, 294-296. For a list of reagents, with references, see Ref. 133, pp. 494-496.

<sup>706</sup>For a review, see Schröder *Chem. Rev.* **1980**, 80, 187-213.  $\text{OsO}_4$  was first used for this purpose by Criegee *Liebigs Ann. Chem.* **1936**, 522, 75.

<sup>707</sup>For a review, see Fatiadi *Synthesis* **1987**, 85-127, pp. 86-96.

<sup>708</sup>For a molecular orbital study of the formation of 69, see Jørgensen; Hoffmann *J. Am. Chem. Soc.* **1986**, 108, 1867.

<sup>709</sup>Milas; Sussman *J. Am. Chem. Soc.* **1936**, 58, 1302, **1937**, 59, 2345. For a review, see Rylander, Ref. 223, pp. 121-133. For another procedure that uses  $\text{H}_2\text{O}_2$ , see Venturello; Gambaro *Synthesis* **1989**, 295.

<sup>710</sup>Akashi; Palermo; Sharpless *J. Org. Chem.* **1978**, 43, 2063.

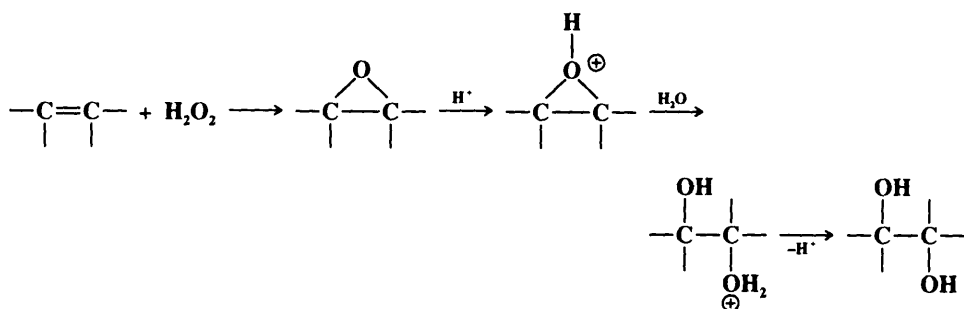
<sup>711</sup>VanRheenen; Kelly; Cha *Tetrahedron Lett.* **1976**, 1973; Iwasawa; Kato; Narasaka *Chem. Lett.* **1988**, 1721. See also Ray; Matteson *Tetrahedron Lett.* **1980**, 449.

<sup>712</sup>Minato; Yamamoto; Tsuji *J. Org. Chem.* **1990**, 55, 766.

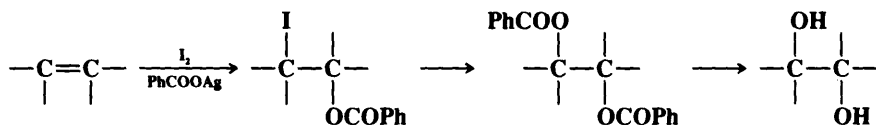
<sup>713</sup>Cainelli; Contento; Manescalchi; Plessi *Synthesis* **1989**, 45.

Potassium permanganate is a strong oxidizing agent and can oxidize the glycols<sup>714</sup> that are the products of this reaction (see 9-7 and 9-10). In acid and neutral solution it always does so; hence it is not feasible to prepare glycols in this manner. Glycols can be prepared with alkaline<sup>715</sup> permanganate, but the conditions must be mild. Even so, yields are seldom above 50%, though they can be improved with phase transfer catalysis<sup>716</sup> or increased stirring.<sup>717</sup> There has been much speculation that, as with OsO<sub>4</sub>, cyclic esters (70) are intermediates, and there is evidence for them.<sup>718</sup> This reaction is the basis of the *Baeyer test* for the presence of double bonds.

Anti hydroxylation can be achieved by treatment with H<sub>2</sub>O<sub>2</sub> and formic acid. In this case, epoxidation (5-36) occurs first, followed by an S<sub>N</sub>2 reaction, which results in overall anti addition:



The same result can be achieved in one step with *m*-chloroperoxybenzoic acid and water.<sup>719</sup> Overall anti addition can also be achieved by the method of Prevost. In this method the olefin is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is anti and results in a β-halo benzoate (71). These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism (p. 308), so the groups are still anti:



Hydrolysis of the ester does not change the configuration. Woodward's method is similar, but results in overall syn hydroxylation. The olefin is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-

<sup>714</sup>Or give more-highly-oxidized products such as α-hydroxy ketones without going through the glycols. See, for example, Wolfe; Ingold; Lemieux *J. Am. Chem. Soc.* **1981**, 103, 938; Wolfe; Ingold *J. Am. Chem. Soc.* **1981**, 103, 940.

<sup>715</sup>The role of the base seems merely to be to inhibit acid-promoted oxidations. The base does not appear to play any part in the mechanism: Taylor; Green *Can. J. Chem.* **1985**, 63, 2777.

<sup>716</sup>See, for example, Weber; Shepherd *Tetrahedron Lett.* **1972**, 4907; Ogino; Mochizuki *Chem. Lett.* **1979**, 443.

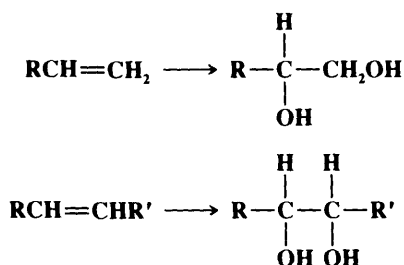
<sup>717</sup>Taylor; Williams; Edwards; Otonnaa; Samanich *Can. J. Chem.* **1984**, 62, 11; Taylor *Can. J. Chem.* **1984**, 62, 2641.

<sup>718</sup>For some recent evidence, see Ogino; Kikuri *J. Am. Chem. Soc.* **1989**, 111, 6174; Lee; Chen *J. Am. Chem. Soc.* **1989**, 111, 7534; Ogino; Hasegawa; Hoshino *J. Org. Chem.* **1990**, 55, 2653. See however Freeman; Chang; Kappos; Sumarta *J. Org. Chem.* **1987**, 52, 1461; Freeman; Kappos *J. Org. Chem.* **1989**, 54, 2730, and other papers in this series; Perez-Benito; Lee *Can. J. Chem.* **1985**, 63, 3545.

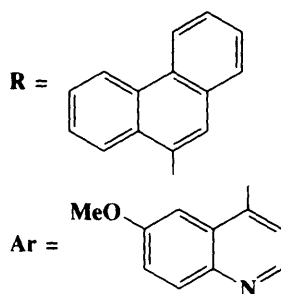
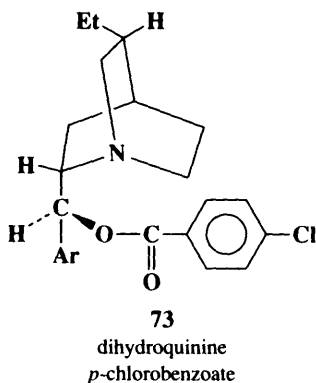
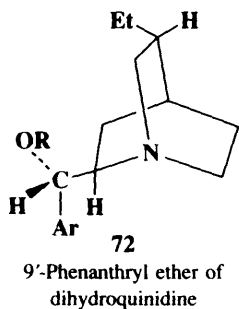
<sup>719</sup>Fringuelli; Germani; Pizzo; Savelli *Synth. Commun.* **1989**, 19, 1939.

halo ester; the addition is anti and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal  $S_N2$  process,<sup>720</sup> so the monoacetate is syn and hydrolysis gives the glycol that is the product of overall syn addition. Although the Woodward method results in overall syn addition, the product may be different from that with  $OsO_4$  or  $KMnO_4$ , since the overall syn process is from the more-hindered side of the olefin.<sup>721</sup> Both the Prevost and the Woodward methods<sup>722</sup> have also been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.<sup>723</sup>

With suitable substrates, addition of two OH groups creates either one or two new chiral centers:



Addition to olefins of the form  $\text{RCH=CH}_2$  has been made enantioselective, and addition to  $\text{RCH=CHR}'$  both diastereoselective<sup>724</sup> and enantioselective, by using optically active amines, such as **72**, **73** (derivatives of the naturally occurring quinine and quinidine),



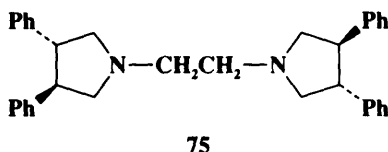
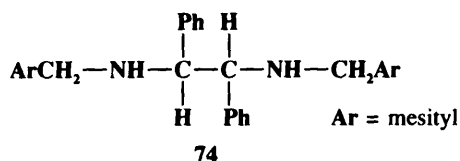
<sup>720</sup>For another possible mechanism that accounts for the stereochemical result of the Woodward method, see Woodward; Brucher *J. Am. Chem. Soc.* **1958**, *80*, 209.

<sup>721</sup>For another method of syn hydroxylation, which can be applied to either face, see Corey; Das *Tetrahedron Lett.* **1982**, *23*, 4217.

<sup>722</sup>For some related methods, see Jasserand; Girard; Rossi; Granger *Tetrahedron Lett.* **1976**, 1581; Ogata; Aoki *J. Org. Chem.* **1966**, *31*, 1625; Mangoni; Adinolfi; Barone; Parrilli *Tetrahedron Lett.* **1973**, 4485; *Gazz. Chim. Ital.* **1975**, *105*, 377; Horiuchi; Satoh *Chem. Lett.* **1988**, 1209; Campi; Deacon; Edwards; Fitzroy; Giunta; Jackson; Trainor *J. Chem. Soc., Chem. Commun.* **1989**, 407.

<sup>723</sup>Cambie; Hayward; Roberts; Rutledge *J. Chem. Soc., Chem. Commun.* **1973**, 359; *J. Chem. Soc., Perkin Trans. I* **1974**, 1858, 1864; Cambie; Rutledge *Org. Synth.* *VI*, 348.

<sup>724</sup>For diastereoselective, but not enantioselective, addition of  $OsO_4$ , see Cha; Christ; Kishi *Tetrahedron Lett.* **1983**, *24*, 3943, 3947; *Tetrahedron* **1984**, *40*, 2247; Stork; Kahn *Tetrahedron Lett.* **1983**, *24*, 3951; Vedejs; McClure *J. Am. Chem. Soc.* **1986**, *108*, 1094; Evans; Kaldor *J. Org. Chem.* **1990**, *55*, 1698.



**74**,<sup>725</sup> or **75**,<sup>726</sup> along with OsO<sub>4</sub>.<sup>727</sup> These amines bind to the OsO<sub>4</sub> in situ as chiral ligands, causing it to add asymmetrically.<sup>728</sup> This has been done both with the stoichiometric and with the catalytic method.<sup>729</sup> The catalytic method has been extended to conjugated dienes, which give tetrahydroxy products diastereoselectively.<sup>730</sup>

Ligands **72** and **73** not only cause enantioselective addition, but also accelerate the reaction, so that they may be useful even where enantioselective addition is not required.<sup>731</sup> Although **72** and **73** are not enantiomers, they give enantioselective addition to a given olefin in the opposite sense; e.g., styrene predominantly gave the (*R*) diol with **72**, and the (*S*) diol with **73**.<sup>732</sup> Enantioselective and diastereoselective addition have also been achieved by using preformed derivatives of OsO<sub>4</sub>, already containing chiral ligands,<sup>733</sup> and by the use of OsO<sub>4</sub> on olefins that have a chiral group elsewhere in the molecule.<sup>734</sup>

Olefins can also be oxidized with metallic acetates such as lead tetraacetate<sup>735</sup> or thallium(III) acetate<sup>736</sup> to give bisacetates of glycols.<sup>737</sup> Oxidizing agents such as benzoquinone, MnO<sub>2</sub>, or O<sub>2</sub>, along with palladium acetate, have been used to convert conjugated dienes to 1,4-diacetoxy-2-alkenes (1,4 addition).<sup>738</sup>

OS II, 307; III, 217; IV, 317; V, 647; VI, 196, 342, 348.

<sup>725</sup>Corey; Jardine; Virgil; Yuen; Connell *J. Am. Chem. Soc.* **1989**, *111*, 9243; Corey; Lotto *Tetrahedron Lett.* **1990**, *31*, 2665.

<sup>726</sup>Tomioka; Nakajima; Koga *J. Am. Chem. Soc.* **1987**, *109*, 6213, *Tetrahedron Lett.* **1990**, *31*, 1741; Tomioka; Nakajima; Iitaka; Koga *Tetrahedron Lett.* **1988**, *29*, 573.

<sup>727</sup>Wai; Marko; Svendsen; Finn; Jacobsen; Sharpless *J. Am. Chem. Soc.* **1989**, *111*, 1123; Lohray; Kalantar; Kim; Park; Shibata; Wai; Sharpless *Tetrahedron Lett.* **1989**, *30*, 2041; Kwong; Sorato; Ogina; Chen; Sharpless *Tetrahedron Lett.* **1990**, *31*, 2999; Shibata; Gilheany; Blackburn; Sharpless *Tetrahedron Lett.* **1990**, *31*, 3817; Sharpless et al., *J. Org. Chem.* **1991**, *56*, 4585.

<sup>728</sup>For discussions of the mechanism of the enantioselectivity, see Jørgensen *Tetrahedron Lett.* **1990**, *31*, 6417; Ogino; Chen; Kwong; Sharpless *Tetrahedron Lett.* **1991**, *32*, 3965.

<sup>729</sup>For other examples of asymmetric dihydroxylation, see Yamada; Narasaka *Chem. Lett.* **1986**, 131; Tokles; Snyder *Tetrahedron Lett.* **1986**, *27*, 3951; Annunziata; Cinquini; Cozzi; Raimondi; Stefanelli *Tetrahedron Lett.* **1987**, *28*, 3139; Hirama; Oishi; Itô *J. Chem. Soc., Chem. Commun.* **1989**, 665.

<sup>730</sup>Park; Kim; Sharpless *Tetrahedron Lett.* **1991**, *32*, 1003.

<sup>731</sup>Sharpless et al., Ref. 727. See also Jacobsen; Marko; France; Svendsen; Sharpless *J. Am. Chem. Soc.* **1989**, *111*, 737.

<sup>732</sup>Jacobsen; Marko; Mungall; Schröder; Sharpless *J. Am. Chem. Soc.* **1988**, *110*, 1968.

<sup>733</sup>Kokubo; Sugimoto; Uchida; Tanimoto; Okano *J. Chem. Soc., Chem. Commun.* **1983**, 769.

<sup>734</sup>Hauser; Ellenberger; Clardy; Bass *J. Am. Chem. Soc.* **1984**, *106*, 2458; Johnson; Barbachyn *J. Am. Chem. Soc.* **1984**, *106*, 2459.

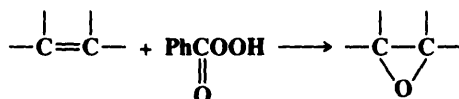
<sup>735</sup>For a review, see Moriarty *Sel. Org. Transform.* **1972**, *2*, 183-237.

<sup>736</sup>See, for example, Uemura; Miyoshi; Tabata; Okano *Tetrahedron* **1981**, *37*, 291. For a review of the reactions of thallium(III) compounds with olefins, see Uemura, in Hartley, Ref. 218, vol. 4, pp. 473-538, pp. 497-513. For a review of thallium(III) acetate and trifluoroacetate, see Uemura, in Pizey, Ref. 146, vol. 5, 1983, pp. 165-187.

<sup>737</sup>For another method see Fristad; Peterson *Tetrahedron* **1984**, *40*, 1469.

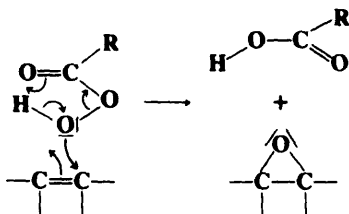
<sup>738</sup>See Bäckvall; Nordberg *J. Am. Chem. Soc.* **1981**, *103*, 4959; Bäckvall; Byström; Nordberg *J. Org. Chem.* **1984**, *49*, 4619; Bäckvall; Awasthi; Renko *J. Am. Chem. Soc.* **1987**, *109*, 4750. For articles on this and related reactions, see Bäckvall *Bull. Soc. Chim. Fr.* **1987**, 665-670, *New J. Chem.* **1990**, *14*, 447-452. For another method, see Uemura; Fukuzawa; Patil; Okano *J. Chem. Soc., Perkin Trans. 1* **1985**, 499.

### 5-36 Epoxidation (Addition of Oxygen, Oxygen) epi-Oxy-addition



Olefins can be epoxidized with any of a number of peracids,<sup>739</sup> of which *m*-chloroperbenzoic has been the most often used. The reaction, called the *Prilezhaev reaction*, has wide utility.<sup>740</sup> Alkyl, aryl, hydroxyl, ester, and other groups may be present, though not amino groups, since these are affected by the reagent. Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkyl olefins. Conditions are mild and yields are high. Other peracids, especially peracetic and perbenzoic, are also used; trifluoroperacetic acid<sup>741</sup> and 3,5-dinitroperoxybenzoic acid<sup>742</sup> are particularly reactive ones.

The following one-step mechanism<sup>743</sup> was proposed by Bartlett:<sup>744</sup>



Evidence for this mechanism is as follows:<sup>745</sup> (1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peracid. (2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited. (3) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.<sup>746</sup> (4) The addition is stereospecific (i.e., a trans olefin gives a trans epoxide and a cis olefin a cis epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate. However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both cis and trans isomers giving predominantly or exclusively the product where the incoming oxygen is syn to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxy acid.<sup>747</sup>

<sup>739</sup>For a list of reagents, including peracids and others, used for epoxidation, with references, see Ref. 133, pp. 456-461.

<sup>740</sup>For reviews, see Hudlický, Ref. 705, pp. 60-64; Haines, Ref. 705, pp. 98-117, 295-303; Dryuk *Russ. Chem. Rev.* **1985**, *54*, 986-1005; Plesničar, in Trahanovsky *Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 211-252; Swern, in Swern *Organic Peroxides*, vol. 2; Wiley: New York, 1971, pp. 355-533; Metelitsa *Russ. Chem. Rev.* **1972**, *41*, 807-821; Hiatt, in Augustine; Trecker *Oxidation*, vol. 2; Marcel Dekker: New York, 1971, pp. 113-140; House, Ref. 144, pp. 292-321. For a review pertaining to the stereochemistry of the reaction, see Berti *Top. Stereochem.* **1973**, *7*, 93-251, pp. 95-187.

<sup>741</sup>Emmons; Pagano *J. Am. Chem. Soc.* **1955**, *77*, 89.

<sup>742</sup>Rastetter; Richard; Lewis *J. Org. Chem.* **1978**, *43*, 3163.

<sup>743</sup>For discussions of the mechanism, see Dryuk *Tetrahedron* **1976**, *32*, 2855-2866; Finn; Sharpless, in Morrison, Ref. 232, vol. 5, pp. 247-308. For a review of polar mechanisms involving peroxides, see Plesničar in Patai *The Chemistry of Peroxides*; Wiley: New York, 1983, pp. 521-584.

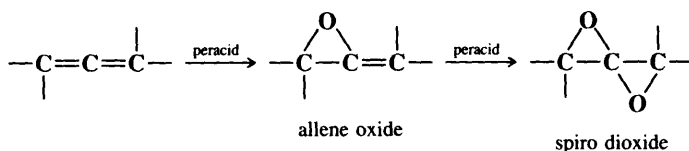
<sup>744</sup>Bartlett *Rec. Chem. Prog.* **1957**, *18*, 111. For other proposed mechanisms see Kwart; Hoffman *J. Org. Chem.* **1966**, *31*, 419; Hanzlik; Shearer *J. Am. Chem. Soc.* **1975**, *97*, 5231.

<sup>745</sup>Ogata; Tabushi *J. Am. Chem. Soc.* **1961**, *83*, 3440. See also Woods; Beak *J. Am. Chem. Soc.* **1991**, *113*, 6281.

<sup>746</sup>Khalil; Pritzkow *J. Prakt. Chem.* **1973**, *315*, 58; Schneider; Becker; Philipp *Chem. Ber.* **1961**, *114*, 1562; Batog; Savenko; Batrak; Kucher *J. Org. Chem. USSR* **1961**, *17*, 1860.

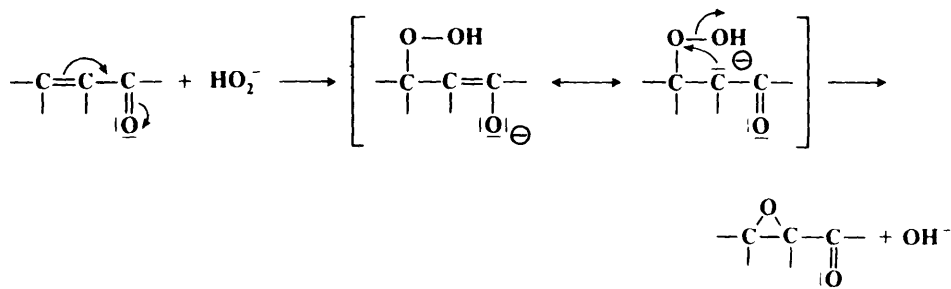
<sup>747</sup>See Berti, Ref. 740, pp. 130-162.

Conjugated dienes can be epoxidized (1,2 addition), though the reaction is slower than for corresponding olefins, but  $\alpha,\beta$ -unsaturated ketones do not generally give epoxides when treated with peracids.<sup>748</sup> However,  $\alpha,\beta$ -unsaturated esters react normally, to give glycidic esters.<sup>749</sup> When a carbonyl group is in the molecule but not conjugated with the double bond, the Baeyer–Villiger reaction (8-20) may compete. Allenes<sup>750</sup> are converted by peracids to allene oxides<sup>751</sup> or spiro dioxides, both of which species can in certain cases be isolated<sup>752</sup>



but more often are unstable under the reaction conditions and react further to give other products.<sup>753</sup>

$\alpha,\beta$ -Unsaturated ketones (including quinones), aldehydes, and sulfones can be epoxidized with alkaline  $\text{H}_2\text{O}_2$ .<sup>754</sup> This is a nucleophilic addition by a Michael-type mechanism, involving attack by  $\text{HO}_2^-$ :<sup>755</sup>



$\alpha,\beta$ -Unsaturated carboxylic acids can be epoxidized with  $\text{H}_2\text{O}_2$  and heteropoly acids,<sup>756</sup> and  $\alpha,\beta$ -unsaturated esters, amides, and sulfones with *t*-BuOOH and an alkyl lithium in THF.<sup>757</sup> Epoxides can also be prepared by treating olefins with oxygen or with an alkyl peroxide,<sup>758</sup>

<sup>748</sup>A few exceptions are known. For example see Hart; Verma; Wang *J. Org. Chem.* **1973**, 38, 3418.

<sup>749</sup>MacPeck; Starcher; Phillips *J. Am. Chem. Soc.* **1959**, 81, 680.

<sup>750</sup>For a review of epoxidation of allenes, see Jacobs, in Landor, Ref. 95, vol. 2, pp. 417-510, pp. 483-491.

<sup>751</sup>For a review of allene oxides see Chan; Ong *Tetrahedron* **1980**, 36, 2269-2289.

<sup>752</sup>Crandall; Machleder; Thomas *J. Am. Chem. Soc.* **1968**, 90, 7346; Camp; Greene *J. Am. Chem. Soc.* **1968**, 90, 7349; Crandall; Conover; Komin; Machleder *J. Org. Chem.* **1974**, 39, 1723; Crandall; Batal *J. Org. Chem.* **1988**, 53, 1338.

<sup>753</sup>For example see Crandall; Machleder; Sojka *J. Org. Chem.* **1973**, 38, 1149; Crandall; Rambo *J. Org. Chem.* **1990**, 55, 5929.

<sup>754</sup>For example, see Payne *J. Am. Chem. Soc.* **1959**, 81, 4901; Payne; Williams *J. Org. Chem.* **1961**, 26, 651; Zwanenburg; ter Wiel *Tetrahedron Lett.* **1970**, 935.

<sup>755</sup>Bunton; Minkoff *J. Chem. Soc.* **1949**, 665; Temple *J. Org. Chem.* **1970**, 35, 1275; Apeloig; Karni; Rappoport *J. Am. Chem. Soc.* **1983**, 105, 2784. For a review, see Patai; Rappoport in Patai, Ref. 36, pt. 1, pp. 512-517.

<sup>756</sup>Oguchi; Sakata; Takeuchi; Kaneda; Ishii; Ogawa *Chem. Lett.* **1989**, 2053.

<sup>757</sup>Meth-Cohn; Moore; Taljaard *J. Chem. Soc., Perkin Trans. 1* **1988**, 2663; Bailey; Clegg; Jackson; Meth-Cohn *J. Chem. Soc., Perkin Trans. 1* **1990**, 200.

<sup>758</sup>For example, see Gould; Hiatt; Irwin *J. Am. Chem. Soc.* **1968**, 90, 4573; Sharpless; Michaelson *J. Am. Chem. Soc.* **1973**, 95, 6136; Hart; Lavrik *J. Org. Chem.* **1974**, 39, 1793; Beg; Ahmad *J. Org. Chem.* **1977**, 42, 1590; Kochi *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978, pp. 69-73; Mihelich *Tetrahedron Lett.* **1979**, 4729; Ledon; Durbut; Varescon *J. Am. Chem. Soc.* **1981**, 103, 3601; Mimoun; Mignard; Brechot; Saussine *J. Am. Chem. Soc.* **1986**, 108, 3711; Kato; Ota; Matsukawa; Endo *Tetrahedron Lett.* **1988**, 29, 2843; Laszlo; Levart; Singh *Tetrahedron Lett.* **1991**, 32, 3167.

catalyzed by a complex of a transition metal such as V, Mo, Ti, or Co.<sup>759</sup> The reaction with oxygen, which can also be carried out without a catalyst, is probably a free-radical process.<sup>760</sup>

In the *Sharpless asymmetric epoxidation*,<sup>761</sup> allylic alcohols are converted to optically active epoxides in better than 90% enantiomeric excess, by treatment with *t*-BuOOH, titanium tetrakispropoxide and optically active diethyl tartrate.<sup>762</sup> The Ti(OCHMe)<sub>4</sub> and diethyl tartrate can be present in catalytic amounts (5-10 mole %) if molecular sieves are present.<sup>763</sup> Since both (+) and (−) diethyl tartrate are readily available, and the reaction is stereospecific, either enantiomer of the product can be prepared. The method has been successful for a wide range of primary allylic alcohols, where the double bond is mono-, di-, tri-, and tetrasubstituted.<sup>764</sup> This procedure, in which an optically active catalyst is used to induce asymmetry, has proved to be one of the most important methods of asymmetric synthesis, and has been used to prepare a large number of optically active natural products and other compounds. Among these are the 8 L-aldohexoses (the unnatural isomers), which were totally synthesized with the aid of this method, starting from a common precursor, 4-benzhydryloxy-(*E*)-but-2-en-ol.<sup>765</sup> The mechanism of the Sharpless epoxidation is believed to involve attack on the substrate by a compound<sup>766</sup> formed from the titanium alkoxide and the diethyl tartrate to produce a complex that also contains the substrate and the *t*-BuOOH.<sup>767</sup> Ordinary alkenes (without an allylic OH group) have been enantioselectively epoxidized with sodium hypochlorite (commercial bleach) and an optically active manganese-complex catalyst.<sup>768</sup>

Among other reagents for converting olefins to epoxides<sup>769</sup> are H<sub>2</sub>O<sub>2</sub>, catalyzed by tungstic acid or its derivatives,<sup>770</sup> F<sub>2</sub>-H<sub>2</sub>O-MeCN,<sup>771</sup> and magnesium monoperoxyphthalate.<sup>772</sup> The last reagent, which is commercially available, has been shown to be a good substitute for *m*-chloroperbenzoic acid in a number of reactions.<sup>773</sup>

<sup>759</sup>For a review, see Jørgensen *Chem. Rev.* **1989**, *89*, 431-458.

<sup>760</sup>For reviews, see Van Santen; Kuipers *Adv. Catal.* **1987**, *35*, 265-321; Filippova; Blyumberg *Russ. Chem. Rev.* **1982**, *51*, 582-591.

<sup>761</sup>For reviews, see Pfenninger *Synthesis* **1986**, 89-116; Rossiter, in Morrison, Ref. 232, vol. 5, pp. 193-246. For histories of its discovery, see Sharpless *Chem. Br.* **1986**, 38-44, *CHEMTECH* **1985**, 692-700.

<sup>762</sup>Katsuki; Sharpless *J. Am. Chem. Soc.* **1980**, *102*, 5974; Rossiter; Katsuki; Sharpless *J. Am. Chem. Soc.* **1981**, *103*, 464; Sharpless; Woodard; Finn *Pure Appl. Chem.* **1983**, *55*, 1823-1836.

<sup>763</sup>Gao; Hanson; Klunder; Ko; Masamune; Sharpless *J. Am. Chem. Soc.* **1987**, *109*, 5765. For another improvement, see Wang; Zhou *Tetrahedron* **1987**, *43*, 2935.

<sup>764</sup>See the table in Finn; Sharpless, Ref. 743, pp. 249-250. See also Schweiter; Sharpless *Tetrahedron Lett.* **1985**, 26, 2543.

<sup>765</sup>Ko; Lee; Masamune; Reed; Sharpless; Walker *Tetrahedron* **1990**, *46*, 245. For other stereospecific syntheses of monosaccharides, see Mukaiyama; Suzuki; Yamada; Tabusa *Tetrahedron* **1990**, *46*, 265, and references cited therein.

<sup>766</sup>Very similar compounds have been prepared and isolated as solids whose structures have been determined by x-ray crystallography: Williams; Pedersen; Sharpless; Lippard *J. Am. Chem. Soc.* **1984**, *106*, 6430.

<sup>767</sup>For a review of the mechanism, see Finn; Sharpless, Ref. 743. For other mechanistic studies, see Jørgensen; Wheeler; Hoffmann *J. Am. Chem. Soc.* **1987**, *109*, 3240; Hawkins; Sharpless *Tetrahedron Lett.* **1987**, 28, 2825; Carlier; Sharpless *J. Org. Chem.* **1989**, *54*, 4016; Corey *J. Org. Chem.* **1990**, *55*, 1693; Woodard; Finn; Sharpless *J. Am. Chem. Soc.* **1991**, *113*, 106; Finn; Sharpless *J. Am. Chem. Soc.* **1991**, *113*, 113; Takano; Iwebuchi; Ogasawara *J. Am. Chem. Soc.* **1991**, *113*, 2786.

<sup>768</sup>Jacobsen; Zhang; Muci; Ecker; Deng *J. Am. Chem. Soc.* **1991**, *113*, 7063. See also Irie; Noda; Ito; Katsuki *Tetrahedron Lett.* **1991**, 32, 1055; Irie; Ito; Katsuki *Synlett* **1991**, 265; Halterman; Jan *J. Org. Chem.* **1991**, *56*, 5253.

<sup>769</sup>For other methods of converting olefins to epoxides, see Balavoine; Eskenazi; Meunier; Rivière *Tetrahedron Lett.* **1984**, 25, 3187; Tezuka; Iwaki *J. Chem. Soc., Perkin Trans. 1* **1984**, 2507; Samsel; Srinivasan; Kochi *J. Am. Chem. Soc.* **1985**, *107*, 7606; Xie; Xu; Hu; Ma; Hou; Tao *Tetrahedron Lett.* **1988**, 29, 2967; Bruice *Aldrichimica Acta* **1988**, 21, 87-94; Adam; Curci; Edwards *Acc. Chem. Res.* **1989**, *22*, 205-211; Troisi; Cassidei; Lopez; Mello; Curci *Tetrahedron Lett.* **1989**, 30, 257; Rodriguez; Dulcère *J. Org. Chem.* **1991**, *56*, 469.

<sup>770</sup>See, for example, Bortolini; Di Furia; Modena; Seraglia *J. Org. Chem.* **1985**, *50*, 2688; Prat; Lett *Tetrahedron Lett.* **1986**, 27, 707; Prandi; Kagan; Mimoun *Tetrahedron Lett.* **1986**, 27, 2617; Venturello; D'Aloisio *J. Org. Chem.* **1988**, *53*, 1553.

<sup>771</sup>Rozen; Kol *J. Org. Chem.* **1990**, *55*, 5155.

<sup>772</sup>Brougham; Cooper; Cumerson; Heaney; Thompson *Synthesis* **1987**, 1015; Querci; Ricci *J. Chem. Soc., Chem. Commun.* **1989**, 889.

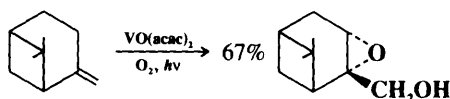
<sup>773</sup>Brougham et al., Ref. 772.

It would be useful if triple bonds could be similarly epoxidized to give oxirenes. However, oxirenes are not stable compounds.<sup>774</sup> Two of them have been trapped in solid argon matrices



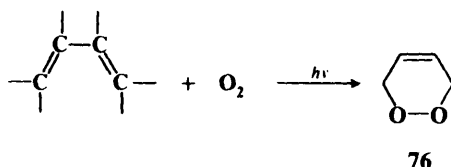
at very low temperatures, but they decayed on warming to 35 K.<sup>775</sup> Oxirenes probably form in the reaction,<sup>776</sup> but react further before they can be isolated. Note that oxirenes bear the same relationship to cyclobutadiene that furan does to benzene and may therefore be expected to be antiaromatic (see p. 55).

In a different type of reaction, olefins are photooxygenated (with singlet O<sub>2</sub>, see 4-9) in the presence of a Ti, V, or Mo complex to give epoxy alcohols formally derived from allylic hydroxylation followed by epoxidation, e.g.,<sup>777</sup>

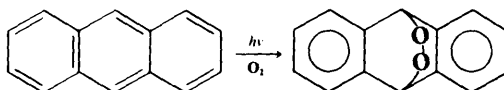


OS I, 494; IV, 552, 860; V, 191, 414, 467, 1007; VI, 39, 320, 679, 862; VII, 121, 126, 461; 66, 203.

### 5-37 Photooxidation of Dienes (Addition of Oxygen, Oxygen) (2 + 4)OC,OC-cyclo-Peroxy-1/4/addition



Conjugated dienes react with oxygen under the influence of light to give cyclic peroxides 76.<sup>778</sup> The reaction has mostly<sup>779</sup> been applied to cyclic dienes.<sup>780</sup> The scope extends to certain aromatic compounds,<sup>781</sup> e.g.,



<sup>774</sup>For a review of oxirenes, see Lewars *Chem. Rev.* **1983**, 83, 519-534.

<sup>775</sup>Torres; Bourdelande; Clement; Strausz *J. Am. Chem. Soc.* **1983**, 105, 1698. See also Laganis; Janik; Curphey; Lemal *J. Am. Chem. Soc.* **1983**, 105, 7457.

<sup>776</sup>McDonald; Schwab *J. Am. Chem. Soc.* **1964**, 86, 4866; Ibne-Rasa; Pater; Ciabattioni; Edwards *J. Am. Chem. Soc.* **1973**, 95, 7894; Ogata; Sawaki; Inoue *J. Org. Chem.* **1973**, 38, 1044.

<sup>777</sup>Adam; Braun; Griesbeck; Lucchini; Staab; Will *J. Am. Chem. Soc.* **1989**, 111, 203.

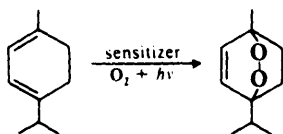
<sup>778</sup>For reviews, see Ciennan *Tetrahedron* **1991**, 47, 1343-1382. *Adv. Oxygenated Processes* **1988**, 1, 85-122; Wasserman; Ives *Tetrahedron* **1981**, 37, 1825-1852; Denny; Nickon *Org. React.* **1973**, 20, 133-336; Adams in Augustine; Trecker, Ref. 740, vol. 2, pp. 65-112; Gollnick *Adv. Photochem.* **1968**, 6, 1-122; Schönberg, Ref. 49, pp. 382-397; Gollnick; Schenck in Hamer *1,4-Cycloaddition Reactions*; Academic Press: New York, 1967, pp. 255-344; Arbuzov *Russ. Chem. Rev.* **1965**, 34, 558-574.

<sup>779</sup>For many examples with acyclic dienes, see Matsumoto; Dobashi; Kuroda; Kondo *Tetrahedron* **1985**, 41, 2147.

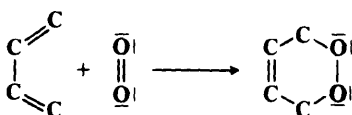
<sup>780</sup>For reviews of cyclic peroxides, see Saito; Nittala, in Patai, Ref. 743, pp. 311-374; Balci *Chem. Rev.* **1981**, 81, 91-108; Adam; Bloodworth *Top. Curr. Chem.* **1981**, 97, 121-158.

<sup>781</sup>For reviews, see in Wasserman; Murray *Singlet Oxygen*; Academic Press: New York, 1979, the articles by Wasserman; Lipshutz, pp. 429-509; Saito; Matsuura, pp. 511-574; Rigaudy *Pure Appl. Chem.* **1968**, 16, 169-186.

Besides those dienes and aromatic rings that can be photooxidized directly, there is a larger group that give the reaction in the presence of a photosensitizer such as eosin (see p. 241). Among these is  $\alpha$ -terpinene, which is converted to ascaridole:

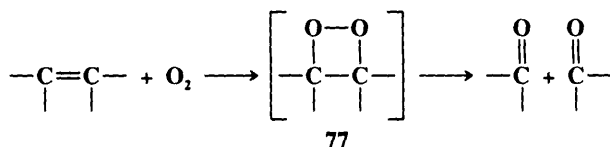


As in **4-9**, it is not the ground-state oxygen (the triplet), that reacts, but the excited singlet state,<sup>782</sup> so the reaction is actually a Diels-Alder reaction (see **5-47**) with singlet oxygen as dienophile:<sup>783</sup>



Like **5-47**, this reaction is reversible.

We have previously discussed the reaction of singlet oxygen with double-bond compounds to give hydroperoxides (**4-9**), but singlet oxygen can also react with double bonds in another way to give a dioxetane intermediate<sup>784</sup> (**77**), which usually cleaves to aldehydes or ketones<sup>785</sup>



but has been isolated.<sup>786</sup> Both the 6-membered cyclic peroxides **76**<sup>787</sup> and the 4-membered **77**<sup>788</sup> have been formed from oxygenation reactions that do not involve singlet oxygen. If **77** are desired, better reagents<sup>789</sup> are triphenyl phosphite ozonide  $(\text{PhO})_3\text{PO}_3$  and triethylsilyl hydrotrioxide  $\text{Et}_3\text{SiOOOH}$ , though yields are not high.<sup>790</sup>

<sup>782</sup>For books and reviews on singlet oxygen, see Ref. 216 in Chapter 14.

<sup>783</sup>Footo; Wexler *J. Am. Chem. Soc.* **1964**, *86*, 3880; Corey; Taylor *J. Am. Chem. Soc.* **1964**, *86*, 3881; Foote; Wexler; Ando *Tetrahedron Lett.* **1965**, 4111; Monroe *J. Am. Chem. Soc.* **1981**, *103*, 7253. See also Hathaway; Paquette *Tetrahedron Lett.* **1985**, *41*, 2037; O'Shea; Foote *J. Am. Chem. Soc.* **1988**, *110*, 7167.

<sup>784</sup>For reviews, see Adam; Cilento *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 529-542 [*Angew. Chem.* *95*, 525-538]; Schaap; Zaklika in Wasserman; Murray, Ref. 781, pp. 173-242; Bartlett *Chem. Soc. Rev.* **1976**, *5*, 149-163. For discussions of the mechanisms see Frimer *Chem. Rev.* **1979**, *79*, 359-387; Clennan; Nagraba *J. Am. Chem. Soc.* **1988**, *110*, 4312.

<sup>785</sup>For discussions see Kearns *Chem. Rev.* **1971**, *71*, 395-427, pp. 422-424; Foote *Pure Appl. Chem.* **1971**, *27*, 635-645.

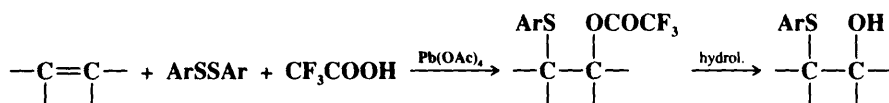
<sup>786</sup>For reviews of 1,2-dioxetanes see Adam, in Patai, Ref. 743, pp. 829-920; Bartlett; Landis, in Wasserman; Murray Ref. 781, pp. 243-286; Adam *Adv. Heterocycl. Chem.* **1977**, *21*, 437-481. See also Inoue; Hakushi; Turro *Kokagaku Toronkai Koen Yoshishu* **1979**, 150 [C.A. *92*, 214798q]; Adam; Encarnación *Chem. Ber.* **1982**, *115*, 2592; Adam; Baader *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 166 [*Angew. Chem.* *96*, 156].

<sup>787</sup>See Nelson; Teasley; Kapp *J. Am. Chem. Soc.* **1986**, *108*, 5503.

<sup>788</sup>For a review, see Nelson *Acc. Chem. Res.* **1987**, *20*, 269-276.

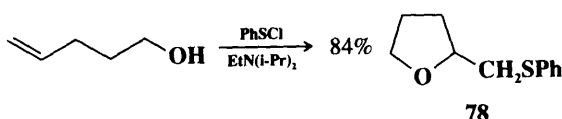
<sup>789</sup>For another reagent, see Curci; Lopez; Troisi; Rashid; Schaap *Tetrahedron Lett.* **1987**, *28*, 5319.

<sup>790</sup>Posner; Weitzberg; Nelson; Murr; Seliger *J. Am. Chem. Soc.* **1987**, *109*, 278.

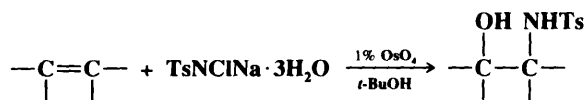
**5-38** Hydroxysulfenylation (Addition of Oxygen, Sulfur)**Hydroxy-arylthio-addition** (overall transformation)

A hydroxy and an arylthio group can be added to a double bond by treatment with an aryl disulfide and lead tetraacetate in the presence of trifluoroacetic acid.<sup>791</sup> Manganese and copper acetates have been used instead of  $\text{Pb(OAc)}_4$ .<sup>792</sup> Addition of the groups OH and RSO has been achieved by treatment of olefins with  $\text{O}_2$  and a thiol RSH.<sup>793</sup> Two RS groups were added, to give *vic*-dithiols, by treatment of the alkene with a disulfide RSSR and  $\text{BF}_3$ -etherate.<sup>794</sup>

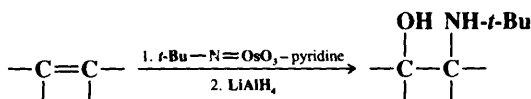
In a number of cases, addition of an ether group and a thioether group has been carried



out internally. For example, 4-penten-1-ol, treated with benzenesulfonyl chloride and ethyldiisopropylamine, gave the tetrahydrofuran **78**.<sup>795</sup>

**5-39** Oxyamination (Addition of Oxygen, Nitrogen)**Tosylamino-hydroxy-addition**

N-Tosylated  $\beta$ -hydroxy alkylamines (which can be easily hydrolyzed to  $\beta$ -hydroxyamines<sup>796</sup>) can be prepared<sup>797</sup> by treatment of alkenes with the trihydrate of Chloramine-T<sup>637</sup> and a catalytic amount of  $\text{OsO}_4$ . In some cases yields can be improved by the use of phase-transfer catalysis.<sup>798</sup> The reaction has been carried out enantioselectively.<sup>799</sup> In another procedure, certain  $\beta$ -hydroxy secondary alkylamines can be prepared by treatment of alkenes with the osmium compounds  $\text{t-Bu-N=OsO}_3$ , followed by reductive cleavage with  $\text{LiAlH}_4$  of the



<sup>791</sup>Trost; Ochiai; McDougal *J. Am. Chem. Soc.* **1978**, *100*, 7103. For a related reaction, see Zefirov; Zyk; Kutateladze; Kolbasenko; Lapin *J. Org. Chem. USSR* **1986**, *22*, 190.

<sup>792</sup>Bewick; Mellor; Owton *J. Chem. Soc., Perkin Trans. I* **1985**, 1039; Bewick; Mellor; Milano; Owton *J. Chem. Soc., Perkin Trans. I* **1985**, 1045; Samii; Ashmawy; Mellor *Tetrahedron Lett.* **1986**, *27*, 5289.

<sup>793</sup>Chung; D'Souza; Szmant *J. Org. Chem.* **1987**, *52*, 1741, and other papers in this series.

<sup>794</sup>Caserio; Fisher; Kim *J. Org. Chem.* **1985**, *50*, 4390.

<sup>795</sup>Tuladhar; Fallis *Tetrahedron Lett.* **1987**, *28*, 523. For a list of other examples, with references, see Ref. 133, pp. 451-452.

<sup>796</sup>For some reactions of the oxyamination products, see Bäckvall; Oshima; Palermo; Sharpless *J. Org. Chem.* **1979**, *44*, 1953.

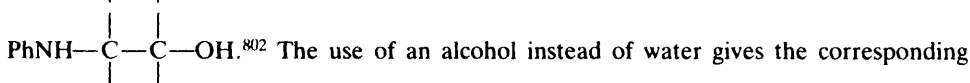
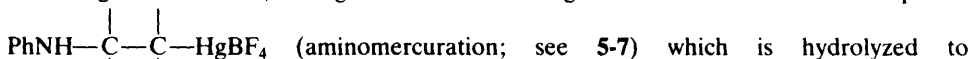
<sup>797</sup>Sharpless; Chong; Oshima *J. Org. Chem.* **1976**, *41*, 177.

<sup>798</sup>Herranz; Sharpless *J. Org. Chem.* **1978**, *43*, 2544.

<sup>799</sup>Hassine; Gorsane; Pecher; Martin *Bull. Soc. Chim. Belg.* **1985**, *94*, 759.

initially formed osmic esters.<sup>800</sup> It is presumed that  $\text{Ts}-\text{N}=\text{OsO}_3$  is an intermediate in the Chloramine-T reaction. Another oxyamination reaction involves treatment of a palladium complex of the olefin with a secondary or primary amine, followed by lead tetraacetate or another oxidant.<sup>801</sup>

$\beta$ -Amino alcohols can be prepared by treatment of an olefin with a reagent prepared from  $\text{HgO}$  and  $\text{HBF}_4$  along with aniline to give an aminomercurial compound

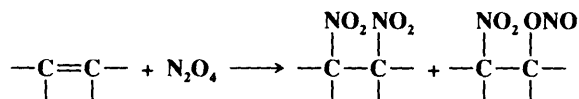


The use of an alcohol instead of water gives the corresponding amino ether.

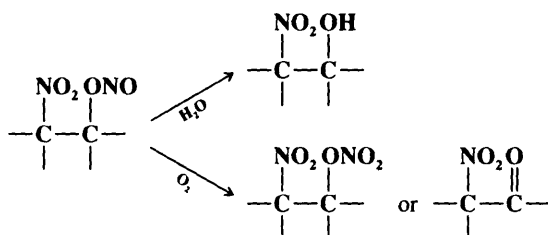
OS VII, 223, 375.

#### 5-40 Addition of $\text{N}_2\text{O}_4$ and Related Reactions (Addition of Nitrogen, Nitrogen or Nitrogen, Oxygen)

##### Dinitro-addition; Nitro-nitrosooxy-addition



When olefins are treated with  $\text{N}_2\text{O}_4$  in an ether, ester, or alkane as solvent, *vic*-dinitro compounds and  $\beta$ -nitro alkyl nitrites are produced.<sup>803</sup> The reaction can be successfully performed with all kinds of olefins and acetylenes. Generally, both products are produced. The dinitro compound is usually stable, but the ester is quite reactive. Upon addition of water or alcohol it is hydrolyzed to a  $\beta$ -nitro alcohol. If oxygen is added, it is oxidized to a  $\beta$ -nitro alkyl nitrate or an  $\alpha$ -nitro aldehyde or ketone.



The nitrate is stable. Even without deliberate addition of oxygen, it is not uncommon to find some nitrate or ketone. It is therefore possible to prepare four types of compound in this reaction, not counting the nitrite.

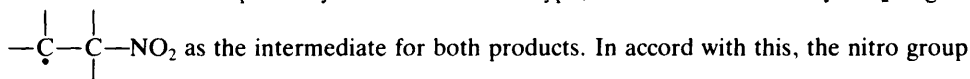
<sup>800</sup>Sharpless; Patrick; Truesdale; Biller *J. Am. Chem. Soc.* **1975**, 97, 2305; Hentges; Sharpless *J. Org. Chem.* **1980**, 45, 2257. For another method, in which the NH in the product is connected to an easily removable protecting group, see Herranz; Biller; Sharpless *J. Am. Chem. Soc.* **1978**, 100, 3596; Herranz; Sharpless *J. Org. Chem.* **1980**, 45, 2710.

<sup>801</sup>Bäckvall; Björkman *J. Org. Chem.* **1980**, 45, 2893, *Acta Chem. Scand., Ser. B* **1984**, 38, 91; Bäckvall; Bystrom *J. Org. Chem.* **1982**, 47, 1126.

<sup>802</sup>Barluenga; Alonso-Cires; Asensio *Synthesis* **1981**, 376.

<sup>803</sup>For reviews, see Ogata, in Trahanovsky, Ref. 740, pt. C pp. 309-313; Larson, in Feuer, Ref. 446, pt. 1, 1969, pp. 316-323.

The mechanism is probably of the free-radical type,<sup>804</sup> with initial attack by NO<sub>2</sub> to give



(in the nitrite derivatives) is found on the side with more hydrogens. An NO<sub>2</sub> and an acetamido (AcNH) group can be added to arylalkenes (with the NHAc going to the side closer to the aryl group) with nitronium tetrafluoroborate in MeCN.<sup>805</sup> Unsubstituted alkenes give poor yields.

OS VI, 837.

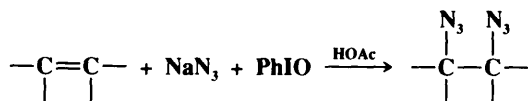
#### 5-41 Diamination (Addition of Nitrogen, Nitrogen)

##### Di(alkylaryl-amino)-addition



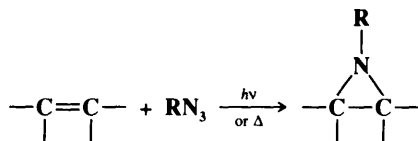
Primary (R = H) and secondary aromatic amines react with alkenes in the presence of thallium(III) acetate to give *vic*-diamines in good yields.<sup>806</sup> The reaction is not successful for primary aliphatic amines. In another procedure, olefins can be diaminated by treatment with the osmium compounds R<sub>2</sub>NOsO<sub>2</sub> and R<sub>3</sub>NOsO (R = *t*-Bu),<sup>807</sup> analogous to the osmium compound mentioned at 5-39. The palladium-promoted method of 5-39 has also been extended to diamination.<sup>808</sup> Alkenes can also be diaminated<sup>809</sup> indirectly by treatment of the aminomercurial compound mentioned in 5-39 with a primary or secondary aromatic amine.<sup>810</sup>

Two azido groups can be added to double bonds by treatment with sodium azide and iodosobenzene in acetic acid.<sup>811</sup>



#### 5-42 Formation of Aziridines (Addition of Nitrogen, Nitrogen)

##### *epi*-Arylimino-addition, etc.



<sup>804</sup>Shechter; Gardikes; Pagano *J. Am. Chem. Soc.* **1959**, *81*, 5420; Shechter; Gardikes; Cantrell; Tiers *J. Am. Chem. Soc.* **1967**, *89*, 3005.

<sup>805</sup>Bloom; Fleischmann; Mellor *J. Chem. Soc., Perkin Trans. I* **1984**, 2357.

<sup>806</sup>Gómez Aranda; Barluenga; Aznar *Synthesis* **1974**, 504.

<sup>807</sup>Chong; Oshima; Sharpless *J. Am. Chem. Soc.* **1977**, *99*, 3420. See also Sharpless; Singer *J. Org. Chem.* **1976**, *41*, 2504.

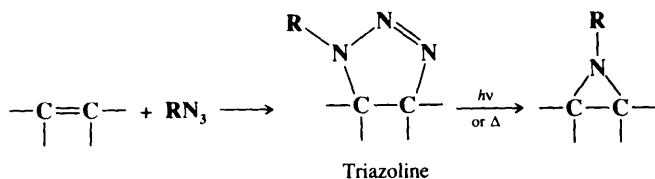
<sup>808</sup>Bäckvall *Tetrahedron Lett.* **1978**, 163.

<sup>809</sup>For other diamination methods, see Michejda; Campbell *J. Am. Chem. Soc.* **1979**, *101*, 7687; Becker; White; Bergman *J. Am. Chem. Soc.* **1980**, *102*, 5676; Becker; Bergman *Organometallics* **1983**, *2*, 787; Jung; Kohn *Tetrahedron Lett.* **1984**, *25*, 399; *J. Am. Chem. Soc.* **1985**, *107*, 2931; Osowska-Pacewicz; Zwierzak *Synthesis* **1990**, 505.

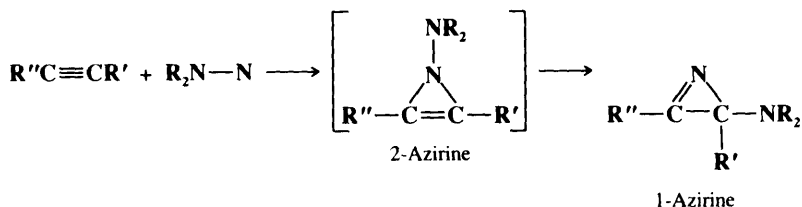
<sup>810</sup>Barluenga; Alonso-Cires; Asensio *Synthesis* **1979**, 962.

<sup>811</sup>Moriarty; Khosrowshahi *Tetrahedron Lett.* **1986**, *27*, 2809. For other methods, see Minisci; Galli *Tetrahedron Lett.* **1962**, 533; Fristad; Brandvold; Peterson; Thompson *J. Org. Chem.* **1985**, *50*, 3647.

Aziridines can be prepared directly from double-bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.<sup>812</sup> The reaction has been carried out with R = aryl, cyano, EtOOC, and RSO<sub>2</sub>, as well as other groups. The reaction can take place by at least two pathways. In one, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to that of carbene addition (5-50). In the other pathway a 1,3 dipolar addition (5-46) takes place to give a triazoline (which can be isolated), followed by extrusion of nitrogen (7-46). Evidence for the nitrene pathway is most compelling for



R = acyl groups. As discussed on p. 202, singlet nitrenes add stereospecifically while triplet nitrenes do not. Diphenyl sulfimide Ph<sub>2</sub>SNH converts Michael-type substrates to the corresponding aziridines.<sup>813</sup> Aminonitrenes R<sub>2</sub>NN have been shown to add to triple bonds to

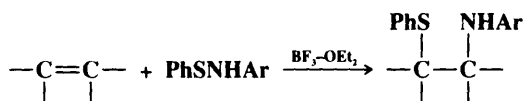


give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.<sup>814</sup> Like oxirenes (see 5-36), 2-azirines are unstable, probably because of antiaromaticity.

Nitrenes can also add to aromatic rings to give ring-expansion products analogous to those mentioned in 5-50.<sup>815</sup>

OS VI, 56.

#### 5-43 Aminosulfenylation (Addition of Nitrogen, Sulfur) Arylamino-arylthio-addition



An amino group and an arylthio group can be added to a double bond by treatment with a sulfenamide PhSNHAr in the presence of BF<sub>3</sub>-etherate.<sup>816</sup> The addition is anti, and the

<sup>812</sup>For reviews, see Dermer; Ham *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969, pp. 68-79; Muller; Hamer *1,2-Cycloaddition Reactions*; Wiley: New York, 1967.

<sup>813</sup>Furukawa; Yoshimura; Ohtsu; Akasaka; Oae *Tetrahedron* **1980**, 36, 73. For other methods see Groves; Takahashi *J. Am. Chem. Soc.* **1983**, 105, 2073; Mahy; Bedi; Battioni; Mansuy *J. Chem. Soc., Perkin Trans. 2* **1988**, 1517; Atkinson; Kelly *J. Chem. Soc., Perkin Trans. 1* **1989**, 1515.

<sup>814</sup>Anderson; Gilchrist; Rees *Chem. Commun.* **1969**, 147.

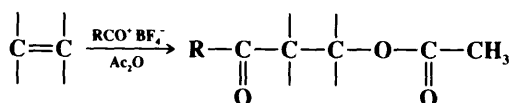
<sup>815</sup>For example, see Hafner; König *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 96 [*Angew. Chem.* 75, 89]; Lwowski; Johnson *Tetrahedron Lett.* **1967**, 891.

<sup>816</sup>Benati; Montavocchi; Spagnolo *Tetrahedron Lett.* **1984**, 25, 2039. See also Brownbridge *Tetrahedron Lett.* **1984**, 25, 3759.

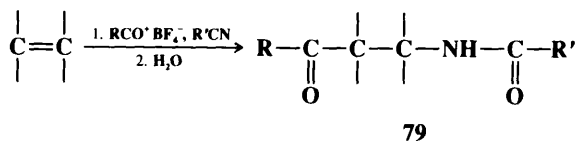
mechanism probably involves a thiiranium ion.<sup>817</sup> In another aminosulfonylation procedure, the substrate is treated with dimethyl(methylthio)sulfonium fluoroborate  $\text{MeSSMe}_2^+ \text{BF}_4^-$  and ammonia or an amine,<sup>818</sup> the latter acting as a nucleophile. This reaction was extended to other nucleophiles:<sup>819</sup>  $\text{N}_3^-$ ,  $\text{NO}_2^-$ ,  $\text{CN}^-$ ,  $\text{OH}^-$ , and  $\text{OAc}^-$  to give  $\text{MeS}-\text{C}(\text{Me})_2-\text{C}(\text{Me})_2-\text{A}$ , where  $\text{A} = \text{N}_3, \text{NO}_2, \text{CN}, \text{OH}, \text{and OAc}$ , respectively. An RS ( $\text{R} = \text{alkyl or aryl}$ ) and an NHCOMe group have been added in an electrochemical procedure.<sup>820</sup>

#### 5-44 Acylacyloxylation and Acylamidation (Addition of Oxygen, Carbon, or Nitrogen, Carbon)

##### Acyl-acyloxy-addition

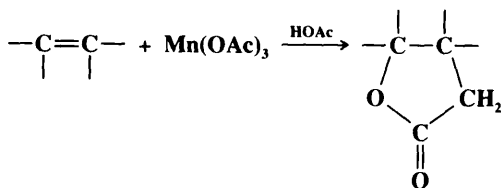


An acyl and an acyloxy group can be added to a double bond by treatment with an acyl fluoroborate and acetic anhydride.<sup>821</sup> As expected, the addition follows Markovnikov's rule, with the electrophile  $\text{Ac}^+$  going to the carbon with more hydrogens. In an analogous reaction, an acyl and an amido group can be added, if a nitrile is used in place of the anhydride:



This reaction has also been carried out on triple bonds, to give the unsaturated analogs of **79** (syn addition).<sup>823</sup>

#### 5-45 The Conversion of Olefins to $\gamma$ -Lactones (Addition of Oxygen, Carbon)



<sup>817</sup>See Ref. 20.

<sup>818</sup>Trost; Shibata *J. Am. Chem. Soc.* **1982**, 104, 3225; Caserio; Kim. *J. Am. Chem. Soc.* **1982**, 104, 3231.

<sup>819</sup>Trost; Shibata; Martin *J. Am. Chem. Soc.* **1982**, 104, 3228; Trost; Shibata, Ref. 818. For an extension that allows A to be  $\text{C}\equiv\text{CR}$ , see Trost; Martin *J. Am. Chem. Soc.* **1984**, 106, 4263.

<sup>820</sup>Bewick; Coe; Mellor; Owton *J. Chem. Soc., Perkin Trans. 1* **1985**, 1033.

<sup>821</sup>Shastin; Balenkova *J. Org. Chem. USSR* **1984**, 20, 870.

<sup>822</sup>Shastin; Balenkova *J. Org. Chem. USSR* **1984**, 20, 1235; Gridnev; Shastin; Balenkova *J. Org. Chem. USSR* **1987**, 23, 1389; Gridnev; Buevich; Sergeyev; Balenkova *Tetrahedron Lett.* **1989**, 30, 1987.

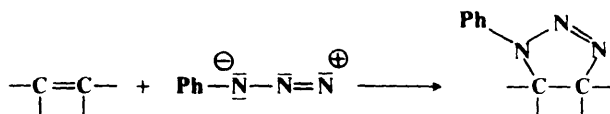
<sup>823</sup>Gridnev; Balenkova *J. Org. Chem. USSR* **1988**, 24, 1447.

Olefins react with manganese(III) acetate to give  $\gamma$ -lactones.<sup>824</sup> The mechanism is probably free-radical, involving addition of  $\cdot\text{CH}_2\text{COOH}$  to the double bond. Lactone formation has also been accomplished by treatment of olefins with lead tetraacetate,<sup>825</sup> with  $\alpha$ -bromo carboxylic acids in the presence of benzoyl peroxide as catalyst,<sup>826</sup> and with dialkyl malonates and iron(III) perchlorate  $\text{Fe}(\text{ClO}_4)_3 \cdot 9\text{H}_2\text{O}$ .<sup>827</sup> Olefins can also be converted to  $\gamma$ -lactones by indirect routes.<sup>828</sup>

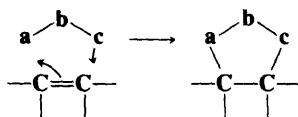
OS VII, 400.

For addition of aldehydes and ketones, see the Prins reaction (6-53), and reactions 6-63 and 6-64.

#### 5-46 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)



Azides add to double bonds to give triazolines. This is one example of a large group of reactions (2 + 3 cycloadditions) in which five-membered heterocyclic compounds are prepared by addition of 1,3-dipolar compounds to double bonds (see Table 15.3).<sup>829</sup> These are compounds that have a sequence of three atoms a—b—c, of which a has a sextet of electrons in the outer shell and c an octet with at least one unshared pair. The reaction can then be formulated as



<sup>824</sup>Bush; Finkbeiner *J. Am. Chem. Soc.* **1968**, *90*, 5903; Heiba; Dessau; Koehl *J. Am. Chem. Soc.* **1968**, *90*, 5905; Heiba; Dessau; Rodewald *J. Am. Chem. Soc.* **1974**, *96*, 7977; Midgley; Thomas *J. Chem. Soc., Perkin Trans. 2* **1984**, 1537; Ernst; Fristad *Tetrahedron Lett.* **1985**, *26*, 3761; Shundo; Nishiguchi; Matsubara; Hirashima *Tetrahedron* **1991**, *47*, 831. See also Corey; Gross *Tetrahedron Lett.* **1985**, *26*, 4291.

<sup>825</sup>Heiba; Dessau; Koehl *J. Am. Chem. Soc.* **1968**, *90*, 2706.

<sup>826</sup>Nakano; Kayama; Nagai *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1049. See also Kraus; Landgrebe *Tetrahedron Lett.* **1984**, *25*, 3939.

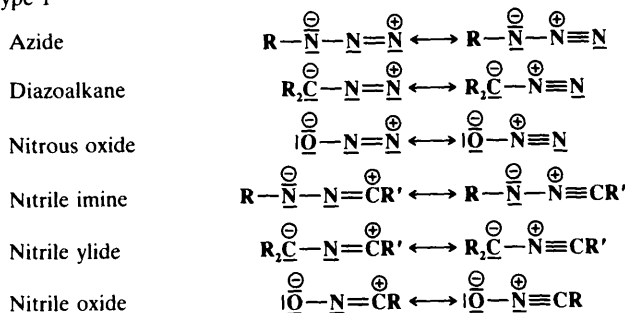
<sup>827</sup>Citterio; Sebastiano; Nicolini; Santi *Synlett* **1990**, 42.

<sup>828</sup>See, for example, Boldt; Thielecke; Etzemüller *Chem. Ber.* **1969**, *102*, 4157; Das Gupta; Felix; Kempe; Eschenmoser *Helv. Chim. Acta* **1972**, *55*, 2198; Bäuml; Tscheschlok; Pock; Mayr *Tetrahedron Lett.* **1988**, *29*, 6925.

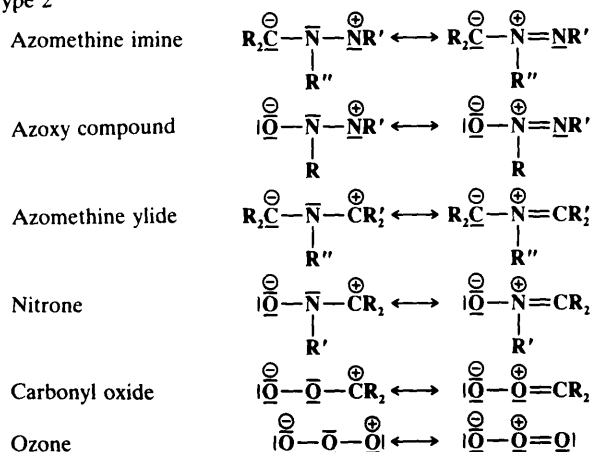
<sup>829</sup>For a treatise, see Padwa *1,3-Dipolar Cycloaddition Chemistry*, 2 vols.; Wiley: New York, 1984. For general reviews, see Carruthers, Ref. 440; Drygina; Garnovskii *Russ. Chem. Rev.* **1986**, *55*, 851-866; Samuilov; Kononov *Russ. Chem. Rev.* **1984**, *53*, 332-342; Beltrame, in Bamford; Tipper, Ref. 1, vol. 9, pp. 117-131; Huisgen; Grashey; Sauer, in Patai, Ref. 36, vol. 1, pp. 806-878; Huisgen *Helv. Chim. Acta* **1967**, *50*, 2421-2439, *Bull. Soc. Chim. Fr.* **1965**, 3431-3440, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565-598, 633-645 [*Angew. Chem.* *75*, 604-637, 742-754]. For specific monographs and reviews, see Torssell *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988; Scriven *Azides and Nitrenes*; Academic Press: New York, 1984; Stanovnik *Tetrahedron* **1991**, *47*, 2925-2945 (diazalkanes); Kanemasa; Tsuge *Heterocycles* **1990**, *30*, 719-736 (nitrile oxides); Paton *Chem. Soc. Rev.* **1989**, *18*, 33-52 (nitrile sulfides); Terao; Aono; Achiwa *Heterocycles* **1988**, *27*, 981-1008 (azomethine ylides); Vedejs *Adv. Cycloaddit.* **1988**, *1*, 33-51 (azomethine ylides); DeShong; Lander; Leguin; Dicken *Adv. Cycloaddit.* **1988**, *1*, 87-128 (nitrones); Balasubramanian *Org. Prep. Proced. Int.* **1985**, *17*, 23-47 (nitrones); Confalone; Huie *Org. React.* **1988**, *36*, 1-173 (nitrones); Padwa, in *Horspool Synthetic Organic Photochemistry*; Plenum: New York, 1984, pp. 313-374 (nitrile ylides); Bianchi; Gandolfi; Grünanger in Patai; Rappoport, Ref. 49, pp. 752-784 (nitrile oxides); Black; Crozier; Davis *Synthesis* **1975**, 205-221 (nitrones); Stuckwisch *Synthesis* **1973**, 469-483 (azomethine ylides, azomethine imines). For reviews of intramolecular 1,3-dipolar additions see Padwa, in Padwa, treatise cited above, vol. 2, pp. 277-406; Padwa; Schoffstall *Adv. Cycloaddit.* **1990**, *2*, 1-89; Tsuge; Hattai; Hisano, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 345-475; Padwa *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 123-136 [*Angew. Chem.* *88*, 131-144]. For a review of azomethine ylides, see Tsuge; Kanemasa *Adv. Heterocycl. Chem.* **1989**, *45*, 231-349. For reviews of 1,3-dipolar cycloreversions, see Bianchi; Gandolfi, in Padwa, treatise cited above, vol. 2, pp. 451-542; Bianchi; De Micheli; Gandolfi *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 721-738 [*Angew. Chem.* *91*, 781-798]. For a related review, see Petrov; Petrov *Russ. Chem. Rev.* **1987**, *56*, 152-162. For the use of this reaction to synthesize natural products, see papers in *Tetrahedron* **1985**, *41*, 3447-3568.

**TABLE 15.3** Some common 1,3-dipolar compounds

## Type 1

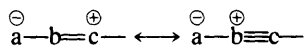


## Type 2



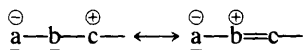
Since compounds with six electrons in the outer shell of an atom are usually not stable, the  $\text{a}-\text{b}-\text{c}$  system is actually one canonical form of a resonance hybrid, for which at least one other form can be drawn (see Table 15.3). 1,3-Dipolar compounds can be divided into two main types:

1. Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form has a triple bond on that atom:



If we limit ourselves to the first row of the periodic table, b can only be nitrogen, c can be carbon or nitrogen, and a can be carbon, oxygen, or nitrogen; hence there are six types. Among these are azides ( $\text{a} = \text{b} = \text{c} = \text{N}$ ), illustrated above, and diazoalkanes.

2. Those in which the dipolar canonical form has a single bond on the sextet atom and the other form has a double bond:

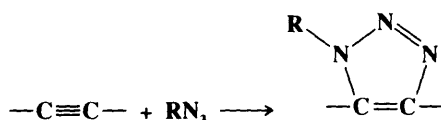


Here b can be nitrogen or oxygen, and a and c can be nitrogen, oxygen, or carbon, but there are only 12 types, since, for example, N—N—C is only another form of C—N—N. Examples are shown in Table 15.3.

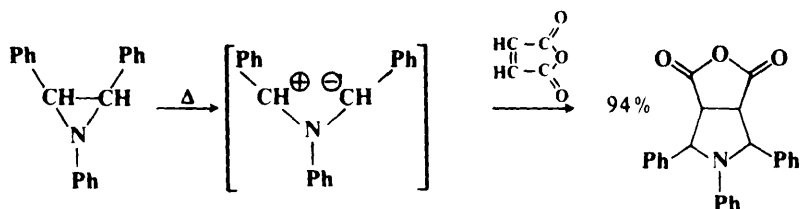
Of the 18 systems, some of which are unstable and must be generated in situ,<sup>830</sup> the reaction has been accomplished for at least 15, though not in all cases with a carbon-carbon double bond (the reaction also can be carried out with other double bonds<sup>831</sup>). Not all olefins undergo 1,3-dipolar addition equally well. The reaction is most successful for those that are good dienophiles in the Diels-Alder reaction (5-47). The addition is stereospecific and syn, and the mechanism is probably a one-step concerted process, as illustrated above.<sup>832</sup> As expected for this type of mechanism, the rates do not vary much with changes in solvent.<sup>833</sup> There are no simple rules covering orientation in 1,3-dipolar additions. Regioselectivities are complicated but have been explained by molecular-orbital treatments.<sup>834</sup> When the 1,3-dipolar compound is a thiocarbonyl ylide ( $R_2C=S^+-CH_2^-$ ) the addition has been shown to be nonstereospecific with certain substrates (though stereospecific with others), indicating a nonsynchronous mechanism in these cases, and in fact, a diionic intermediate (see mechanism c on p. 857) has been trapped in one such case.<sup>835</sup>

Conjugated dienes generally give exclusive 1,2 addition, though 1,4 addition (a 3 + 4 cycloaddition) has been reported.<sup>836</sup>

Carbon-carbon triple bonds can also undergo 1,3-dipolar addition.<sup>837</sup> For example, azides give triazoles:



The 1,3-dipolar reagent can in some cases be generated by the in situ opening of a suitable three-membered ring system. For example, aziridines can add to activated double bonds to give pyrrolidines, e.g.,<sup>838</sup>



<sup>830</sup>For a review of some aspects of this, see Grigg *Chem. Soc. Rev.* **1987**, 16, 89-121.

<sup>831</sup>For a review of 1,3-dipolar addition to other double bonds, see Bianchi; De Micheli; Gandolfi, in Patai, Ref. 1, pt. 1, pp. 369-532. For a review of such addition to the C=S bond, see Dunn; Rudolf *Carbon Disulfide in Organic Chemistry*; Wiley: New York, 1989, pp. 97-119.

<sup>832</sup>For a review, see Huisgen *Adv. Cycloaddit.* **1988**, 1, 1-31. For discussions, see Huisgen *J. Org. Chem.* **1976**, 41, 403; Firestone *Tetrahedron* **1977**, 33, 3009-3039; Harcourt *Tetrahedron* **1978**, 34, 3125; Haque *J. Chem. Educ.* **1984**, 61, 490; Al-Sader; Kadri *Tetrahedron Lett.* **1985**, 26, 4661; Houk; Firestone; Munchausen; Mueller; Arison; Garcia *J. Am. Chem. Soc.* **1985**, 107, 7227; Majchrzak; Warkentin *J. Phys. Org. Chem.* **1990**, 3, 339.

<sup>833</sup>For a review of the role of solvents in this reaction, see Kadaba *Synthesis* **1973**, 71-84.

<sup>834</sup>For a review, see Houk; Yamaguchi, in Padwa *1,3-Dipolar Cycloaddition Chemistry*, Ref. 829, vol. 2, pp. 407-450. See also Burdisso; Gandolfi; Quartieri; Rastelli *Tetrahedron* **1987**, 159.

<sup>835</sup>Huisgen; Mloston; Langhals *J. Am. Chem. Soc.* **1986**, 108, 6401; *J. Org. Chem.* **1986**, 51, 4085; Mloston; Langhals; Huisgen *Tetrahedron Lett.* **1989**, 30, 5373; Huisgen; Mloston *Tetrahedron Lett.* **1989**, 30, 7041.

<sup>836</sup>Baran; Mayr *J. Am. Chem. Soc.* **1987**, 109, 6519.

<sup>837</sup>For reviews, see Bastide; Hamelin; Texier; Quang *Bull. Soc. Chim. Fr.* **1973**, 2555-2579; 2871-2887; Fuks; Viehe in Viehe Ref. 49, p. 460-477.

<sup>838</sup>For a review, see Lown, in Padwa, Ref. 834, vol 1, pp. 653-732.

Aziridines also add to  $\text{C}\equiv\text{C}$  triple bonds as well as to other unsaturated linkages, including  $\text{C}=\text{O}$ ,  $\text{C}=\text{N}$ , and  $\text{C}\equiv\text{N}$ .<sup>839</sup> In some of these reactions it is a  $\text{C}-\text{N}$  bond of the aziridine that opens rather than the  $\text{C}-\text{C}$  bond.

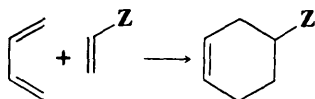
For other 2 + 3 cycloadditions, see 5-48.

OS V, 957, 1124; VI, 592, 670; 67, 133. Also see OS IV, 380.

**C. Carbon on Both Sides.** Reactions 5-47 to 5-52 are cycloaddition reactions.<sup>840</sup>

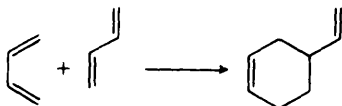
### 5-47 The Diels–Alder Reaction

(2 + 4)cyclo-Ethylene-1/4/addition or (4 + 2)cyclo-[But-2-ene-1,4-diyl]-1/2/addition, etc.



In the *Diels–Alder reaction* a double bond adds 1,4 to a conjugated diene (a 2 + 4 cycloaddition),<sup>841</sup> so the product is always a six-membered ring. The double-bond compound is called a *dienophile*. The reaction is easy and rapid and of very broad scope.<sup>842</sup> Ethylene and simple olefins make poor dienophiles, although the reaction has been carried out with these compounds. Most dienophiles are of the form  $-\text{C}=\text{C}-\text{Z}$  or  $\text{Z}-\text{C}=\text{C}-\text{Z}'$ , where Z and

Z' are CHO, COR,<sup>843</sup> COOH, COOR, COCl, COAr, CN,<sup>844</sup> NO<sub>2</sub>,<sup>845</sup> Ar, CH<sub>2</sub>OH, CH<sub>2</sub>Cl, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>CN, CH<sub>2</sub>COOH, halogen, or  $\text{C}=\text{C}$ . In the last case, the dienophile is itself a diene:



When two dienes react, mixtures are quite possible. Thus, butadiene and isoprene ( $\text{CH}_2=\text{CH}-\text{CMe}=\text{CH}_2$ ) gave all nine possible Diels–Alder adducts, as well as eight-mem-

<sup>839</sup>For reviews, see Lown *Rec. Chem. Prog.* **1971**, 32, 51-83; Gladysheva; Sineokov; Etlis *Russ. Chem. Rev.* **1970**, 39, 118-129.

<sup>840</sup>For a system of classification of cycloaddition reactions, see Huisgen *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 321-328 [*Angew. Chem.* 80, 329-337]. For a review of certain types of cycloadditions leading to 3- to 6-membered rings involving 2, 3, or 4 components, see Posner *Chem. Rev.* **1986**, 86, 831-844. See also the series *Advances in Cycloaddition*.

<sup>841</sup>For a monograph, see Wasserman *Diels–Alder Reactions*; Elsevier: New York, 1965. For reviews, see Roush *Adv. Cycloaddit.* **1990**, 2, 91-146; Carruthers, Ref. 440; Brieger; Bennett *Chem. Rev.* **1980**, 80, 63-97; Oppolzer *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 10-23 [*Angew. Chem.* 89, 10-24]; Beltrame, in Bamford; Tipper, Ref. 1, vol. 9, pp. 94-117; Huisgen; Grashey; Sauer, in Patai, Ref. 36, vol. 1, pp. 878-929; Carruthers, Ref. 218, pp. 183-244; Sauer *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 211-230, **1967**, 6, 16-33 [*Angew. Chem.* 78, 233-252, 79, 76-94]. For a monograph on intramolecular Diels–Alder reactions see Taber, Ref. 440. For reviews, see Deslongchamps *Aldrichimica Acta* **1991**, 24, 43-56; Craig *Chem. Soc. Rev.* **1987**, 16, 187-238; Salakhov; Ismailov *Russ. Chem. Rev.* **1986**, 55, 1145-1163; Fallis *Can. J. Chem.* **1984**, 62, 183-234. For a long list of references to various aspects of the Diels–Alder reaction, see Ref. 133, pp. 263-272.

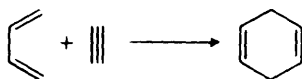
<sup>842</sup>For a review of reactivity in the Diels–Alder reaction, see Konovalov *Russ. Chem. Rev.* **1983**, 52, 1064-1080.

<sup>843</sup>For a review of Diels–Alder reactions with cyclic enones, see Fringuelli; Taticchi; Wenkert *Org. Prep. Proced. Int.* **1990**, 22, 131-165.

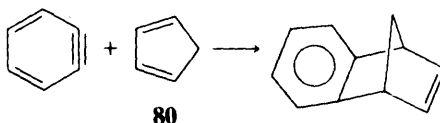
<sup>844</sup>For a review of the Diels–Alder reaction with acrylonitrile, see Butskus *Russ. Chem. Rev.* **1962**, 31, 283-294. For a review of tetracyanoethylene as a dienophile, see Ciganek; Linn; Webster, in Rappoport, Ref. 588, pp. 449-453.

<sup>845</sup>For a review of the Diels–Alder reaction with nitro compounds, see Novikov; Shuekhgeimer; Dudinskaya *Russ. Chem. Rev.* **1960**, 29, 79-94.

bered rings and trimers.<sup>846</sup> Particularly common dienophiles are maleic anhydride<sup>847</sup> and quinones.<sup>848</sup> Triple bond compounds ( $-\text{C}\equiv\text{C}-\text{Z}$  or  $\text{Z}-\text{C}\equiv\text{C}-\text{Z}'$ ) may be dienophiles<sup>849</sup>



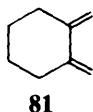
as may allenes, though allenes without activating groups are very poor dienophiles.<sup>850</sup> Ketenes, however, do not undergo Diels-Alder reactions.<sup>851</sup> Benzyne, although not isolable, act as dienophiles and can be trapped with dienes,<sup>852</sup> e.g.,



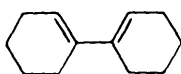
The low reactivity of ethylene can be overcome by using phenyl vinyl sulfone  $\text{PhSO}_2\text{CH}=\text{CH}_2$  instead.<sup>853</sup> The  $\text{PhSO}_2$  group can be easily removed with  $\text{Na-Hg}$  after the ring-closure reaction. Similarly, phenyl vinyl sulfoxide  $\text{PhSOCH}=\text{CH}_2$  can be used as a synthon for acetylene.<sup>854</sup> In this case  $\text{PhSOH}$  is lost from the sulfoxide product (7-12).

Besides carbon-carbon multiple bonds, other double- and triple-bond compounds can be dienophiles, giving rise to heterocyclic compounds. Among these are  $\text{N}\equiv\text{C}-$ ,  $-\text{N}=\text{C}-$ ,  $-\text{N}=\text{N}-$ ,  $\text{O}=\text{N}-$ , and  $-\text{C}=\text{O}$  compounds<sup>855</sup> and, as we have seen (5-37), even molecular oxygen.

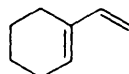
Dienes can be open-chain, inner-ring (e.g., 80), outer-ring<sup>856</sup> (e.g., 81), across rings (e.g., 82), or inner-outer (e.g., 83), except that they may not be frozen into a transoid conformation



81



82



83

<sup>846</sup>Johnstone; Quan *J. Chem. Soc.* **1963**, 935.

<sup>847</sup>For a review of Diels-Alder reactions with maleic anhydride see Klotzel *Org. React.* **1948**, 4, 1-59.

<sup>848</sup>For reviews of Diels-Alder reactions with quinones, see Finley, in Patai *Ref.* 38, vol. 1, pt. 2, pp. 986-1018, vol. 2, pt. 1 (edited by Patai; Rappoport), 1988, pp. 537-717, pp. 614-645. For a review of the synthesis of quinones using Diels-Alder reactions, see Naruta; Maruyama, in the same treatise, vol. 2, pt. 1, pp. 241-402, pp. 277-303.

<sup>849</sup>For reviews of triple bonds in cycloaddition reactions, see Bastide; Henri-Rousseau, in Patai, *Ref.* 70, pt. 1, pp. 447-522, Fuks; Viehe, in Viehe, *Ref.* 49, pp. 477-508.

<sup>850</sup>For a review of allenes as dienes or dienophiles, see Hopf, in Landor, *Ref.* 95, vol. 2, pp. 563-577.

<sup>851</sup>Ketenes react with conjugated dienes to give 1,2 addition (see 5-49).

<sup>852</sup>For a review of benzyne as dienophiles, see Hoffmann *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967, pp. 200-239. For a review of the reactions of benzyne with heterocyclic compounds see Bryce; Vernon *Adv. Heterocycl. Chem.* **1981**, 28, 183-229.

<sup>853</sup>Carr; Williams; Paquette *J. Org. Chem.* **1983**, 48, 4976; Kinney; Crouse; Paquette *J. Org. Chem.* **1983**, 48, 4986.

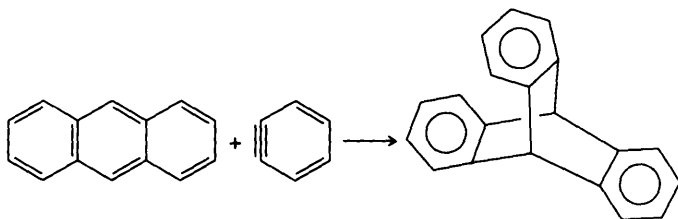
<sup>854</sup>Paquette; Moerck; Harichian; Magnus *J. Am. Chem. Soc.* **1978**, 100, 1597. For other acetylene synthons see De Lucchi; Lucchini; Pasquato; Modena *J. Org. Chem.* **1984**, 49, 596; Hermeling; Schäfer *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 233 [*Angew. Chem.* 96, 238]. For a review, see De Lucchi; Modena *Tetrahedron* **1984**, 40, 2585-2632. For a review of 2 + 2 and 2 + 4 cycloadditions of vinylic sulfides, sulfoxides, and sulfones, see De Lucchi; Pasquato *Tetrahedron* **1988**, 44, 6755-6794.

<sup>855</sup>For monographs on dienes and dienophiles with hetero atoms, see Boger; Weinreb *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; Hamer, *Ref.* 778. For reviews, see Weinreb; Scola *Chem. Rev.* **1989**, 89, 1525-1534; Boger, in Lindberg *Strategies and Tactics in Organic Synthesis*, vol. 2; Academic Press: New York, 1989, pp. 1-56; Kametani; Hibino *Adv. Heterocycl. Chem.* **1987**, 42, 245-333; Boger *Tetrahedron* **1983**, 39, 2869-2939; Weinreb; Staib *Tetrahedron* **1982**, 38, 3087-3128; Weinreb; Levin *Heterocycles* **1979**, 12, 949-975; Desimoni; Tacconi *Chem. Rev.* **1975**, 75, 651-692; Kresze; Firl *Fortschr. Chem. Forsch.* **1969**, 11, 245-284. See also *Ref.* 862.

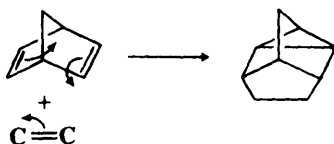
<sup>856</sup>For reviews of Diels-Alder reactions of some of these compounds, see Charlton; Alauddin *Tetrahedron* **1987**, 43, 2873-2889; Oppolzer *Synthesis* **1978**, 793-802.

(see p. 842). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.<sup>857</sup>

Aromatic compounds can also behave as dienes.<sup>858</sup> Benzene is very unreactive toward dienophiles; very few dienophiles (one of them is benzyne) have been reported to give Diels–Alder adducts with it.<sup>859</sup> Naphthalene and phenanthrene are also quite resistant, though naphthalene has given Diels–Alder addition at high pressures.<sup>860</sup> However, anthracene and other compounds with at least three linear benzene rings give Diels–Alder reactions readily. The interesting compound triptycene can be prepared by a Diels–Alder reaction between benzyne and anthracene:<sup>861</sup>



Certain heterocyclic aromatic rings (among them furans)<sup>862</sup> can also behave as dienes in the Diels–Alder reaction. Some hetero dienes that give the reaction are  $\text{—C=C—C=O}$ ,  $\text{O=C—C=O}$ , and  $\text{N=C—C=N}$ .<sup>854</sup> For both all-carbon and hetero systems, the “diene” can be a conjugated enyne. If the geometry of the molecule is suitable, the diene can even be nonconjugated, e.g.,<sup>863</sup>



This last reaction is known as the *homo-Diels–Alder reaction*.

<sup>857</sup>For a monograph on dienes, with tables showing more than 800 types, see Fringuelli; Taticchi *Dienes in the Diels–Alder Reaction*; Wiley: New York, 1990. For a review of Diels–Alder reactions with 2-pyrones, see Shusherina *Russ. Chem. Rev.* **1974**, 43, 851–861. For reviews of dienes with hetero substituents, see Danishefsky *Chemtracts: Org. Chem.* **1989**, 2, 273–297; Petrzilka; Grayson *Synthesis* **1981**, 753–786. For a review of dienes containing a 1-CONR<sub>2</sub> group, see Smith *Org. Prep. Proced. Int.* **1990**, 22, 315–397.

<sup>858</sup>For a review, see Wagner–Jauregg *Synthesis* **1980**, 165–214, 769–798. See also Balaban; Biermann; Schmidt *Nouv. J. Chim.* **1985**, 9, 443.

<sup>859</sup>Miller; Stiles *J. Am. Chem. Soc.* **1963**, 85, 1798; Meyerson; Fields *Chem. Ind. (London)* **1966**, 1230; Ciganek *Tetrahedron Lett.* **1967**, 3321; Friedman *J. Am. Chem. Soc.* **1967**, 89, 3071; Liu; Krespan *J. Org. Chem.* **1969**, 34, 1271.

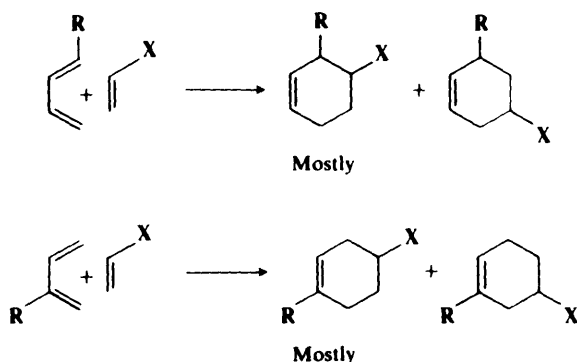
<sup>860</sup>Jones; Mangold; Plieninger *Tetrahedron* **1962**, 18, 267; Plieninger; Wild; Westphal *Tetrahedron* **1969**, 25, 5561.

<sup>861</sup>Wittig; Niethammer *Chem. Ber.* **1960**, 93, 944; Wittig; Härle; Knauss; Niethammer *Chem. Ber.* **1960**, 93, 951. For a review of triptycene, see Skvarchenko; Shalaev; Klabunovskii *Russ. Chem. Rev.* **1974**, 43, 951–966.

<sup>862</sup>For reviews, see Katritzky; Dennis *Chem. Rev.* **1989**, 89, 827–861; Schmidt *Acc. Chem. Res.* **1986**, 19, 250–259; Boger *Chem. Rev.* **1986**, 86, 781–793.

<sup>863</sup>See, for example, Fickes; Metz *J. Org. Chem.* **1978**, 43, 4057; Paquette; Kesselmayr; Künzer *J. Org. Chem.* **1988**, 53, 5183.

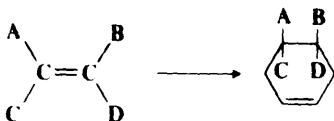
When an unsymmetrical diene adds to an unsymmetrical dienophile, there are two possible products (not counting stereoisomers):



Although mixtures are often obtained, usually one predominates, the one indicated above. This regioselectivity, in which the “ortho” or “para” product is favored over the “meta,” has been explained by molecular-orbital considerations.<sup>864</sup> When  $X = \text{NO}_2$ , regioselectivity to give the “ortho” or “para” product was very high at room temperature, and this method, combined with subsequent removal of the  $\text{NO}_2$  (see 0-82) has been used to perform regioselective Diels-Alder reactions.<sup>865</sup>

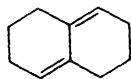
The stereochemistry of the Diels-Alder reaction can be considered from several aspects:

1. With respect to the dienophile, the addition is stereospecifically syn, with very few exceptions.<sup>866</sup> This means that groups that are *cis* in the olefin will be *cis* in the cyclohexene ring:



2. With respect to 1,4-disubstituted dienes, fewer cases have been investigated, but here too the reaction is stereospecific and syn. Thus, *trans,trans*-1,4-diphenylbutadiene gives *cis*-1,4-diphenylcyclohexene derivatives.

3. The diene must be in the cisoid conformation. If it is frozen into the transoid conformation, as in **84**, the reaction does not take place. The diene either must be frozen into the cisoid conformation or must be able to achieve it during the reaction.



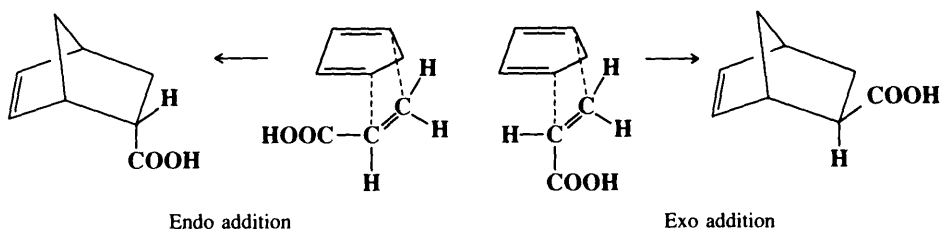
**84**

<sup>864</sup>Feuer; Herndon; Hall *Tetrahedron* **1968**, 24, 2575; Inukai; Sato; Kojima *Bull. Chem. Soc. Jpn.* **1972**, 45, 891; Epiotis *J. Am. Chem. Soc.* **1973**, 95, 5624; Sustmann *Pure Appl. Chem.* **1974**, 40, 569-593; Trost; Vladuchick; Bridges *J. Am. Chem. Soc.* **1980**, 102, 3554; Alston; Gordon; Ottenbrite; Cohen *J. Org. Chem.* **1983**, 48, 5051; Kahn; Pau; Overman; Hehre *J. Am. Chem. Soc.* **1986**, 108, 7381.

<sup>865</sup>Danishefsky; Hershenson *J. Org. Chem.* **1979**, 44, 1180; Ono; Miyake; Kamimura; Kaji *J. Chem. Soc., Perkin Trans. 1* **1987**, 1929. For another method of controlling regioselectivity, see Kraus; Liras *Tetrahedron Lett.* **1989**, 30, 1907.

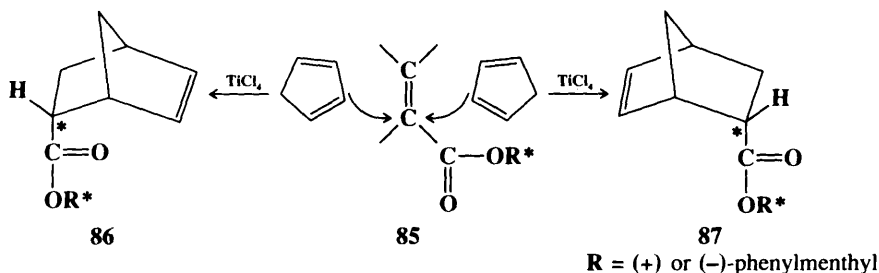
<sup>866</sup>For an exception, see Meier; Eckes; Niedermann; Kolshorn *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1046 [*Angew. Chem.* 99, 1040].

**4.** When the diene is cyclic, there are two possible ways in which addition can occur if the dienophile is not symmetrical. The larger side of the dienophile may be under the ring (*endo* addition), or it may be the smaller side (*exo* addition):



Most of the time, the addition is predominantly endo; i.e., the more bulky side of the olefin is under the ring, and this is probably true for open-chain dienes also.<sup>867</sup> However, exceptions are known, and in many cases mixtures of exo and endo addition products are found.<sup>868</sup>

5. In some cases, the Diels-Alder reaction can be made enantioselective.<sup>869</sup> Most such work has used a chiral dienophile (e.g., **85**) and an achiral diene,<sup>870</sup> along with a Lewis acid catalyst (see below). In such cases addition of the diene to the two faces of **85** takes place at different rates, and **86** and **87** are formed in different amounts.<sup>871</sup> In the case illustrated,



hydrolysis of the product removes the chiral R group, making it a chiral auxiliary in this reaction. Asymmetric Diels–Alder reactions have also been carried out with achiral dienes and dienophiles, but with an optically active catalyst.<sup>872</sup>

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it. For the dienophile it is just the reverse: donating groups decrease the rate,

<sup>867</sup>See, for example, Baldwin; Reddy *J. Org. Chem.* **1989**, *54*, 5264.

<sup>26a</sup> See, for example, Alder; Günzl *Chem. Ber.* **1960**, 93, 809; Stockmann *J. Org. Chem.* **1961**, 26, 2025; Jones; Wifc *J. Chem. Soc., Chem. Commun.* **1973**, 421; Lindsay Smith; Norman; Stillings *Tetrahedron* **1978**, 34, 1381; Müller; Bernardinelli; Rodriguez; Pfyffer; Schaller *Chimia* **1987**, 41, 244.

<sup>869</sup>For reviews, see Taschner *Org. Synth. Theory Appl.* **1989**, *1*, 1-101; Helmchen; Karge; Weetman *Mod. Synth. Methods* **1986**, *4*, 261-306; Paquette, in Morrison, Ref. 232, vol. 3, pp. 455-501; Oppolzer *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876-889 [*Angew. Chem.* **96**, 840-854]. See also the list of references in Macaulay; Fallis *J. Am. Chem. Soc.* **1990**, *112*, 1136.

<sup>67a</sup>For the use of chiral dienes, see Fisher; Hehre; Kahn; Overman *J. Am. Chem. Soc.* **1988**, *110*, 4625; Menezes; Zezza; Sheu; Smith *Tetrahedron Lett.* **1989**, *30*, 3295; Charlton; Plourde; Penner *Can. J. Chem.* **1989**, *67*, 1010; Tripathy; Carroll; Thornton *J. Am. Chem. Soc.* **1990**, *112*, 6743, **1991**, *113*, 7630; Rieger; Breitmaier *Synthesis* **1990**, 697.

<sup>71</sup>Oppolzer; Kurth; Reichlin; Moffatt *Tetrahedron Lett.* **1981**, 22, 2545. See also Walborsky; Barash; Davis *Tetrahedron* **1963**, 19, 2333; Furuta; Iwanaga; Yamamoto *Tetrahedron Lett.* **1986**, 27, 4507; Evans; Chapman; Bisaha *J. Am. Chem. Soc.* **1988**, 110, 1238; Mattay; Mertes; Maas *Chem. Ber.* **1989**, 122, 327; Alonso; Carretero; Garcia Ruano *Tetrahedron Lett.* **1989**, 30, 3853; Tomioka; Hamada; Suenaga; Koga *J. Chem. Soc., Perkin Trans. 1* **1990**, 426; Cativiela; López; Mayor *Tetrahedron: Asymmetry* **1990**, 1, 61.

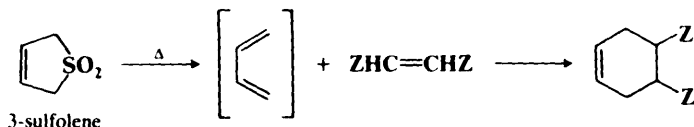
<sup>72</sup>For a review, see Narasaka *Synthesis* **1991**, 1-11. For some recent examples, see Bir; Kaufmann *J. Organomet. Chem.* **1990**, 390, 1; Rebieri; Riant; Kagan *Tetrahedron: Asymmetry* **1990**, 1, 199; Terada; Mikami; Nakai *Tetrahedron Lett.* **1991**, 32, 935; Corey; Imai; Zhang *J. Am. Chem. Soc.* **1991**, 113, 728; Narasaka; Tanaka; Kanai *Bull. Chem. Soc. Jpn.* **1991**, 64, 387; Hawkins; Loren *J. Am. Chem. Soc.* **1991**, 113, 7794.

and withdrawing groups increase it. Cyclic dienes, in which the cisoid conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the cisoid conformation by rotation.<sup>873</sup>

As should be apparent from the foregoing, many interesting compounds can be prepared by the Diels–Alder reaction, some of which would be hard to make in any other way. It has thus been exceedingly useful. Competing reactions are polymerization of the diene or dienophile, or both, and 1,2 cycloaddition (5-49). However, yields are usually quite high. No catalyst is needed, though it has been found that Lewis acids catalyze some Diels–Alder reactions,<sup>874</sup> usually those in which Z in the dienophile is a C=O or C=N group. A Lewis acid catalyst usually increases both the regioselectivity of the reaction (in the sense given above) and the extent of endo addition,<sup>875</sup> and, in the case of enantioselective reactions, the extent of enantioselectivity. Some Diels–Alder reactions can also be catalyzed by the addition of a stable cation radical, e.g., tris(4-bromophenyl)aminium hexachloroantimonate  $\text{Ar}_3\text{N}^+ \text{SbCl}_6^-$ .<sup>876</sup>

A number of other methods have been reported for the acceleration of Diels–Alder reactions, including the use of a microwave oven,<sup>877</sup> water as a solvent (a hydrophobic effect),<sup>878</sup> 5 M  $\text{LiClO}_4$  in  $\text{Et}_2\text{O}$  as solvent,<sup>879</sup> absorption of the reactants on chromatographic absorbents,<sup>880</sup> and the use of an ultracentrifuge<sup>881</sup> (one of several ways to achieve reaction at high pressures).<sup>882</sup>

The Diels–Alder reaction is usually reversible and has been used to protect double bonds.<sup>883</sup> A convenient substitute for butadiene in the Diels–Alder reaction is the compound



3-sulfolene since the latter is a solid which is easy to handle while the former is gas.<sup>884</sup> Butadiene is generated in situ by a reverse Diels–Alder reaction (see 7-25).

There are, broadly speaking, three possible mechanisms that have been considered for

<sup>873</sup>Sauer; Lang; Mielert *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 268 [*Angew. Chem.* **74**, 352]; Sauer; Wiest *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 269 [*Angew. Chem.* **74**, 353]. See, however, Scharf; Plum; Fleischhauer; Schleker *Chem. Ber.* **1979**, *112*, 862.

<sup>874</sup>Yates; Eaton *J. Am. Chem. Soc.* **1960**, *82*, 4436; Fray; Robinson *J. Am. Chem. Soc.* **1961**, *83*, 249; Inukai; Kojima *J. Org. Chem.* **1967**, *32*, 869, 872; Laszlo; Lucchetti *Tetrahedron Lett.* **1984**, *25*, 4387; Bonnesen; Puckett; Honeychuck; Hersh *J. Am. Chem. Soc.* **1989**, *111*, 6070. For review of the role of the catalyst in increasing reactivity, see Kiselev; Kononov *Russ. Chem. Rev.* **1989**, *58*, 230-249.

<sup>875</sup>For discussions see Houk; Strozier *J. Am. Chem. Soc.* **1973**, *95*, 4094; Alston; Ottenbrite *J. Org. Chem.* **1975**, *40*, 1111.

<sup>876</sup>For a review, see Bauld; *Tetrahedron* **1989**, *45*, 5307-5363.

<sup>877</sup>Giguere; Bray; Duncan; Majetich *Tetrahedron Lett.* **1986**, *27*, 4945; Berlan; Giboreau; Lefevre; Marchand *Tetrahedron Lett.* **1991**, *32*, 2363.

<sup>878</sup>Rideout; Breslow *J. Am. Chem. Soc.* **1980**, *102*, 7816. For a review, see Breslow *Acc. Chem. Res.* **1991**, *24*, 159-164. See also Grieco; Garner; He *Tetrahedron Lett.* **1983**, 1897; Blokzijl; Blandamer; Engberts *J. Am. Chem. Soc.* **1991**, *113*, 4241; Breslow; Rizzo *J. Am. Chem. Soc.* **1991**, *113*, 4340.

<sup>879</sup>Grieco; Nunes; Gaul *J. Am. Chem. Soc.* **1990**, *112*, 4595. See also Braun; Sauer *Chem. Ber.* **1986**, *119*, 1269; Forman; Dailey *J. Am. Chem. Soc.* **1991**, *113*, 2761.

<sup>880</sup>Veselsky; Gybin; Lozanova; Moiseenkova; Smit; Caple *Tetrahedron Lett.* **1988**, *29*, 175.

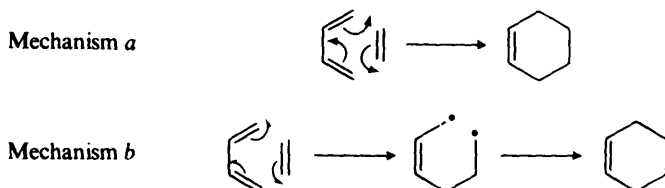
<sup>881</sup>Dolata; Bergman *Tetrahedron Lett.* **1987**, *28*, 707.

<sup>882</sup>For reviews, see Isaacs; George *Chem. Br.* **1987**, 47-54; Asano; le Noble *Chem. Rev.* **1978**, *78*, 407-489. See also Firestone; Smith *Chem. Ber.* **1989**, *122*, 1089.

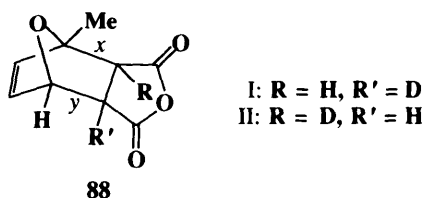
<sup>883</sup>For reviews of the reverse Diels–Alder reaction, see Ichihara *Synthesis* **1987**, 207-222; Lasne; Ripoll *Synthesis* **1985**, 121-143; Ripoll; Rouessac; Rouessac *Tetrahedron* **1978**, *34*, 19-40; Brown *Pyrolytic Methods in Organic Chemistry*; Academic Press: New York, 1980, pp. 259-281; Kwart; King *Chem. Rev.* **1968**, *68*, 415-447.

<sup>884</sup>Sample; Hatch *Org. Synth.* **VI**, 454. For a review, see Chou; Tso *Org. Prep. Proced. Int.* **1989**, *21*, 257-296.

the uncatalyzed Diels–Alder reaction.<sup>885</sup> In mechanism *a* there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step. In



mechanism *b* one end of the diene fastens to one end of the dienophile first to give a diradical, and then, in a second step, the other ends become fastened. A diradical formed in this manner must be a singlet; i.e., the two unpaired electrons must have opposite spins, by an argument similar to that outlined on p. 196. The third mechanism (*c*, not shown) is similar to mechanism *b*, but the initial bond and the subsequent bond are formed by movements of electron pairs and the intermediate is a diion. There have been many mechanistic investigations of the Diels–Alder reaction. The bulk of the evidence suggests that most Diels–Alder reactions take place by the one-step cyclic mechanism *a*,<sup>886</sup> although it is possible that a diradical<sup>887</sup> or even a diion<sup>888</sup> mechanism may be taking place in some cases. The main evidence in support of mechanism *a* is as follows: (1) The reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration. (2) In general, the rates of Diels–Alder reactions depend very little on the nature of the solvent. This would rule out a diion intermediate because polar solvents increase the rates of reactions that develop charges in the transition state. (3) It was shown that, in the decomposition of **88**, the isotope effect  $k_I/k_{II}$  was equal to 1.00 within experimental error.<sup>889</sup> If bond *x* broke before bond *y*, there should surely be a



secondary isotope effect. This result strongly indicates that the bond breaking of *x* and *y* is simultaneous. This is the reverse of a Diels–Alder reaction, and by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds *x* and *y*. Subsequently, a similar experiment was carried out on the forward reaction<sup>890</sup> and the result was the same. There is also other evidence for mechanism

<sup>885</sup>For reviews, see Sauer; Sustmann *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779-807 [*Angew. Chem.* **92**, 773-801]; Houk *Top. Curr. Chem.* **1979**, *79*, 1-40; Seltzer *Adv. Alicyclic Chem.* **1968**, *2*, 1-57; Ref. 841. For a review of the application of quantum-chemical methods to the study of this reaction, see Babichev; Kovtunencko; Voitenko; Tytilin *Russ. Chem. Rev.* **1988**, *57*, 397-405.

<sup>886</sup>For a contrary view, see Dewar; Pierini *J. Am. Chem. Soc.* **1984**, *106*, 203; Dewar; Olivella; Stewart *J. Am. Chem. Soc.* **1986**, *108*, 5771. For arguments against this view, see Houk; Lin; Brown *J. Am. Chem. Soc.* **1986**, *108*, 554; Hancock; Wood *J. Chem. Soc., Chem. Commun.* **1988**, 351; Gajewski; Peterson; Kagel; Huang *J. Am. Chem. Soc.* **1989**, *111*, 9078.

<sup>887</sup>See, for example, Bartlett; Mallet *J. Am. Chem. Soc.* **1976**, *98*, 143; Jenner; Rimmelin *Tetrahedron Lett.* **1980**, *21*, 3039; Van Mele; Huybrechts *Int. J. Chem. Kinet.* **1987**, *19*, 363, **1989**, *21*, 967.

<sup>888</sup>For a reported example, see Gassman; Gorman *J. Am. Chem. Soc.* **1990**, *112*, 8624.

<sup>889</sup>Seltzer *J. Am. Chem. Soc.* **1963**, *85*, 1360, **1965**, *87*, 1534. For a review of isotope effect studies of Diels–Alder and other pericyclic reactions, see Gajewski *Isot. Org. Chem.* **1987**, *7*, 115-176.

<sup>890</sup>Van Sickle; Rodin *J. Am. Chem. Soc.* **1964**, *86*, 3091.

*a.*<sup>891</sup> However, the fact that the mechanism is concerted does not necessarily mean that it is synchronous. In the transition state of a synchronous reaction both new  $\sigma$  bonds would be formed to the same extent, but a Diels–Alder reaction with non-symmetrical components might very well be non-synchronous; i.e., it could have a transition state in which one bond has been formed to a greater degree than the other.<sup>671</sup>

In another aspect of the mechanism, the effects of electron-donating and electron-withdrawing substituents (p. 843) indicate that the diene is behaving as a nucleophile and the dienophile as an electrophile. However, this can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride and not at all with tetracyanoethylene, though the latter is normally the most reactive dienophile known. It is apparent, then, that this diene is the electrophile in its Diels–Alder reactions.<sup>893</sup> Reactions of this type are said to proceed with *inverse electron demand*.<sup>894</sup>

We have emphasized that the Diels–Alder reaction generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of olefins to cyclobutanes (5-49) gives very poor results in most cases, except when photochemically induced. Fukui, Woodward, and Hoffmann have shown that these contrasting results can be explained by the *principle of conservation of orbital symmetry*.<sup>895</sup> which predicts that certain reactions are allowed and others forbidden. The orbital-symmetry rules (also called the Woodward–Hoffmann rules) apply *only to concerted reactions*, e.g., mechanism *a*, and are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction. There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, three of which are used more frequently than others.<sup>896</sup> Of these three we will discuss two: the frontier-orbital method and the Möbius–Hückel method. The third, called the correlation diagram method,<sup>897</sup> is less convenient to apply than the other two.

<sup>891</sup>See, for example, Dewar; Pyron *J. Am. Chem. Soc.* **1970**, *92*, 3098; Brun; Jenner *Tetrahedron* **1972**, *28*, 3113; Doering; Franck-Neumann; Hasselmann; Kaye *J. Am. Chem. Soc.* **1972**, *94*, 3833; McCabe; Eckert *Acc. Chem. Res.* **1974**, *7*, 251-257; Berson; Dervan; Malherbe; Jenkins *J. Am. Chem. Soc.* **1976**, *98*, 5937; Rücker; Lang; Sauer; Friege; Sustmann *Chem. Ber.* **1980**, *113*, 1663; Tolbert; Ali *J. Am. Chem. Soc.* **1981**, *103*, 2104.

<sup>892</sup>Woodward; Katz *Tetrahedron* **1959**, *5*, 70; Liu; Schmidt *Tetrahedron* **1971**, *27*, 5289; Dewar; Pyron, Ref. 891; Papadopoulos; Jenner *Tetrahedron Lett.* **1982**, *23*, 1889; Houk; Loncharich; Blake; Jorgensen *J. Am. Chem. Soc.* **1989**, *111*, 9172; Lehd; Jensen *J. Org. Chem.* **1990**, *55*, 1034.

<sup>893</sup>Sauer; Wiest *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 269 [*Angew. Chem.* **74**, 353].

<sup>894</sup>For a review, see Boger; Patel *Prog. Heterocycl. Chem.* **1989**, *1*, 30-64.

<sup>895</sup>For monographs, see Gilchrist; Storr *Organic Reactions and Orbital Symmetry*, 2nd ed.; Cambridge University Press: Cambridge, 1979; Fleming *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; Woodward; Hoffmann *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970 [the text of this book also appears in *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781-853; *Angew. Chem.* **81**, 797-869]; Lehr; Marchand *Orbital Symmetry*; Academic Press, New York, 1972. For reviews, see Pearson *J. Chem. Educ.* **1981**, *58*, 753-757; in Klopman *Chemical Reactivity and Reaction Paths*; Wiley: New York, 1974, the articles by Fujimoto; Fukui, pp. 23-54. Klopman, pp. 55-165. Herndon; Feuer; Giles; Otteson; Silber, pp. 275-299; Michl, pp. 301-338; Simonetta *Top. Curr. Chem.* **1973**, *42*, 1-47; Houk *Surv. Prog. Chem.* **1973**, *6*, 113-208; Vollmer; Servis *J. Chem. Educ.* **1970**, *47*, 491-500; Gill *Essays Chem.* **1970**, *1*, 43-76. *Q. Rev., Chem. Soc.* **1968**, *22*, 338-389; Seebach *Fortschr. Chem. Forsch.* **1969**, *11*, 177-215; Miller *Adv. Phys. Org. Chem.* **1968**, *6*, 185-332; Millie *Bull. Soc. Chim. Fr.* **1966**, 4031-4038. For a review of applications to inorganic chemistry, see Pearson *Top. Curr. Chem.* **1973**, *41*, 75-112.

<sup>896</sup>For other approaches see Epiotis *Theory of Organic Reactions*; Springer: New York, 1978; Epiotis; Shaik *J. Am. Chem. Soc.* **1978**, *100*, 1, 9; Halevi *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 593-607 [*Angew. Chem.* **88**, 664-679]; Shen *J. Chem. Educ.* **1973**, *50*, 238-242; Salem *J. Am. Chem. Soc.* **1968**, *90*, 543, 553; Trindle *J. Am. Chem. Soc.* **1970**, *92*, 3251, 3255; Mulder; Oosterhoff *Chem. Commun.* **1970**, 305, 307; Goddard *J. Am. Chem. Soc.* **1970**, *92*, 7520, **1972**, *94*, 793; Herndon *Chem. Rev.* **1972**, *72*, 157-179; Perrin *Chem. Br.* **1972**, *8*, 163-173; Langlet; Malrieu *J. Am. Chem. Soc.* **1972**, *94*, 7254; Pearson *J. Am. Chem. Soc.* **1972**, *94*, 8287; Mathieu, *Bull. Soc. Chim. Fr.* **1973**, 807; Silver; Karplus *J. Am. Chem. Soc.* **1975**, *97*, 2645; Day *J. Am. Chem. Soc.* **1975**, *97*, 2431; Mok; Nye *J. Chem. Soc., Perkin Trans. 2* **1975**, 1810; Ponc *Collect. Czech. Chem. Commun.* **1984**, *49*, 455, **1985**, *50*, 1121; Hua-ming; De-xiang *Tetrahedron* **1986**, *42*, 515; Bernardi; Olivucci; Robb *Res. Chem. Intermed.* **1989**, *12*, 217, *Acc. Chem. Res.* **1990**, *23*, 405.

<sup>897</sup>For excellent discussions of this method see Woodward; Hoffmann, Ref. 895; Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 352-366; Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 378-389; Yates *Hückel Molecular Orbital Theory*; Academic Press: New York, 1978, pp. 263-276.

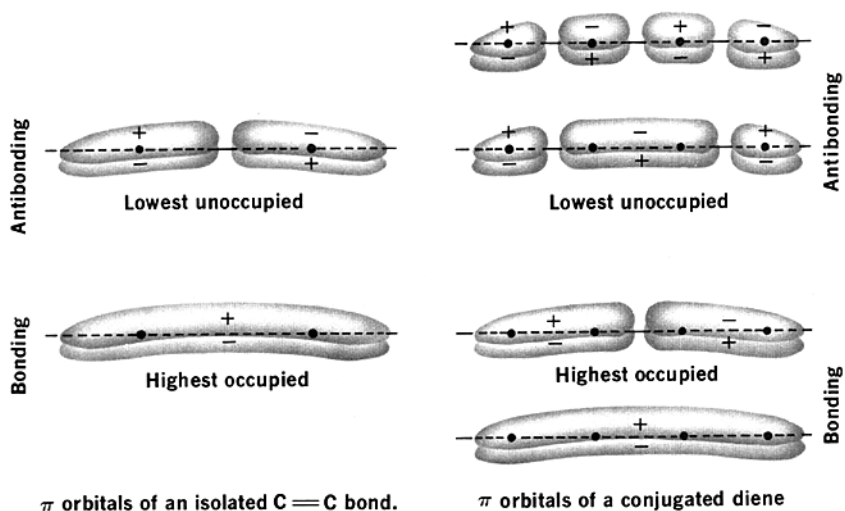
### The Frontier-Orbital Method<sup>898</sup>

As applied to cycloaddition reactions the rule is that *reactions are allowed only when all overlaps between the highest-occupied molecular orbital (HOMO) of one reactant and the lowest-unoccupied molecular orbital (LUMO) of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*. We may recall that monoolefins have two  $\pi$  molecular orbitals (p. 9) and that conjugated dienes have four (p. 31), as shown in Figure 15.2. A concerted cyclization of two monoolefins (a  $2 + 2$  reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe (Figure 15.3). On the other hand, the Diels-Alder reaction (a  $2 + 4$  reaction) is allowed, whether considered from either direction (Figure 15.4).

These considerations are reversed when the ring closures are photochemically induced since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the  $2 + 2$  reaction is now allowed (Figure 15.5) and the  $2 + 4$  reaction disallowed. The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, Diels-Alder adducts are usually cleaved quite readily, while cyclobutanes, despite the additional strain, require more strenuous conditions.

### The Möbius-Hückel Method<sup>899</sup>

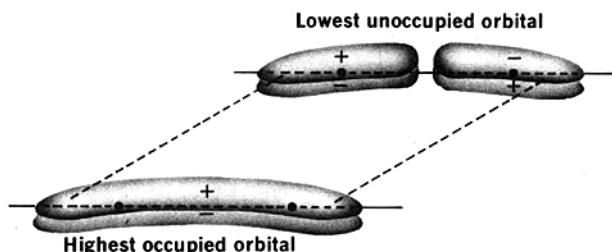
In this method, the orbital symmetry rules are related to the Hückel aromaticity rule discussed in Chapter 2. Hückel's rule, which states that a cyclic system of electrons is aromatic (hence, stable) when it consists of  $4n + 2$  electrons, applies of course to molecules in their ground states. In applying the orbital symmetry principle we are not concerned with ground states, but with transition states. In the present method we do not examine the molecular



**FIGURE 15.2** Schematic drawings of the  $\pi$  orbitals of an isolated  $C=C$  bond and a conjugated diene.

<sup>898</sup>Fukui; Fujimoto *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2018, **1969**, *42*, 3399; Fukui *Fortschr. Chem. Forsch.* **1970**, *15*, 1-85; *Acc. Chem. Res.* **1971**, *4*, 57-64; Houk *Acc. Chem. Res.* **1975**, *8*, 361-369. See also Chu *Tetrahedron* **1978**, *34*, 645. For a monograph on frontier orbitals see Fleming, Ref. 895. For reviews, see Fukui *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 801-809 [*Angew. Chem.* **94**, 852-861]; Houk, in Marchand; Lehr, *Pericyclic Reactions*, vol. 2; Academic Press: New York, 1977, pp. 181-271.

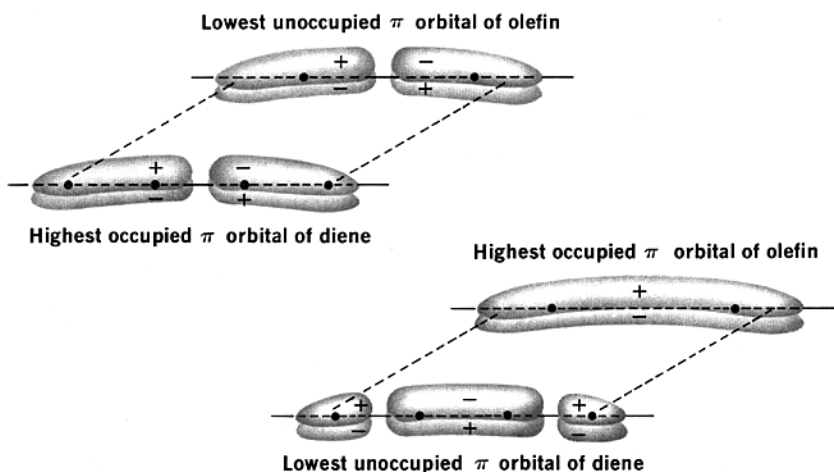
<sup>899</sup>Zimmerman, in Marchand; Lehr, Ref. 898, pp. 53-107; *Acc. Chem. Res.* **1971**, *4*, 272-280; *J. Am. Chem. Soc.* **1966**, *88*, 1564, 1566; Dewar *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 761-775 [*Angew. Chem.* **83**, 859-875]; Jefford; Burger *Chimia* **1971**, *25*, 297-307; Herndon *J. Chem. Educ.* **1981**, *58*, 371-376.



**FIGURE 15.3** Overlap of orbitals in a thermal  $2 + 2$  cycloaddition.

orbitals themselves, but rather the  $p$  orbitals before they overlap to form the molecular orbitals. Such a set of  $p$  orbitals is called a *basis set* (Figure 15.6). In investigating the possibility of a concerted reaction, we put the basis sets into the position they would occupy in the transition state. Figure 15.7 shows this for both the  $2 + 2$  and the  $2 + 4$  ring closures. What we look for are *sign inversions*. In Figure 15.7 we can see that there are no sign inversions in either case. That is, the dashed line connects only lobes with a minus sign. Systems with *zero or an even number of sign inversions* are called *Hückel systems*. Because they have no sign inversions, both of these systems are Hückel systems. Systems with *an odd number of sign inversions* are called *Möbius systems* (because of the similarity to the Möbius strip, which is a mathematical surface, shown in Figure 15.8). Möbius systems do not enter into either of these reactions, but an example of such a system is shown on p. 1114.

The rule may then be stated: *A thermal pericyclic reaction involving a Hückel system is allowed only if the total number of electrons is  $4n + 2$ . A thermal pericyclic reaction involving a Möbius system is allowed only if the total number of electrons is  $4n$ .* For photochemical reactions these rules are reversed. Since both the  $2 + 4$  and  $2 + 2$  cycloadditions are Hückel systems, the Möbius–Hückel method predicts that the  $2 + 4$  reaction, with 6 electrons, is thermally allowed, but the  $2 + 2$  reaction is not. On the other hand, the  $2 + 2$  reaction is allowed photochemically, while the  $2 + 4$  reaction is forbidden.



**FIGURE 15.4** Two ways for orbitals to overlap in a thermal  $2 + 4$  cycloaddition.

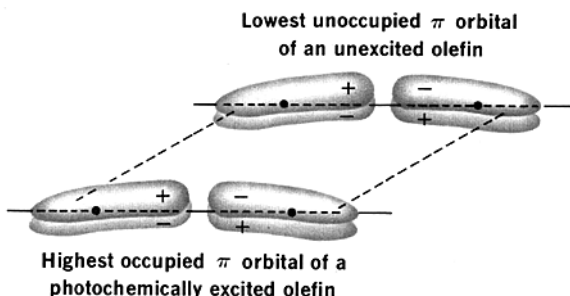


FIGURE 15.5 Overlap of orbitals in a photochemical  $2 + 2$  cycloaddition.

Note that both the  $2 + 2$  and  $2 + 4$  transition states are Hückel systems no matter what basis sets we chose. For example, Figure 15.9 shows other basis sets we might have chosen. In every case there will be zero or an even number of sign inversions.

Thus, the frontier-orbital and Hückel-Möbius methods (and the correlation-diagram method as well) lead to the same conclusions: thermal  $2 + 4$  cycloadditions and photochemical  $2 + 2$  cycloadditions (and the reverse ring openings) are allowed, while photochemical  $2 + 4$  and thermal  $2 + 2$  ring closings (and openings) are forbidden. Application of the same procedures to other ring closures shows that  $4 + 4$  and  $2 + 6$  ring closures and openings require photochemical induction while the  $4 + 6$  and  $2 + 8$  reactions can take place only thermally (see 5-52). In general, cycloaddition reactions allowed thermally are those with  $4n + 2$  electrons, while those allowed photochemically have  $4n$  electrons.

It must be emphasized once again that the rules apply only to cycloaddition reactions that take place by cyclic mechanisms, i.e., where two  $\sigma$  bonds are formed (or broken) at about the same time.<sup>900</sup> The rule does not apply to cases where one bond is clearly formed (or broken) before the other. It must further be emphasized that the fact that the thermal Diels-Alder reaction (mechanism *a*) is allowed by the principle of conservation of orbital symmetry does not constitute proof that any given Diels-Alder reaction proceeds by this mechanism. The principle merely says the mechanism is allowed, not that it must go by this pathway. However, the principle does say that thermal  $2 + 2$  cycloadditions in which the molecules assume a face-to-face geometry cannot<sup>901</sup> take place by a cyclic mechanism because

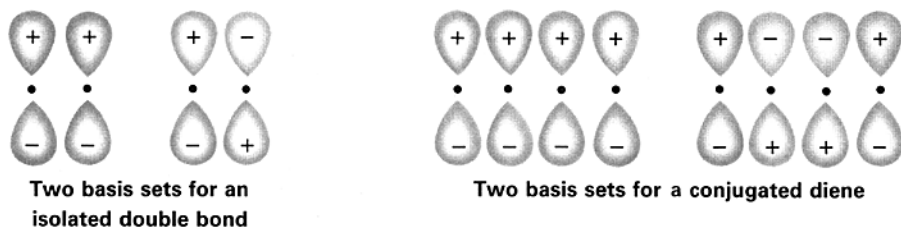


FIGURE 15.6 Some basis sets.

<sup>900</sup>For a discussion of concertedness in these reactions see Lehr; Marchand, in Marchand; Lehr, Ref. 898, vol. 1, pp. 1-51.

<sup>901</sup>The possibility has been raised that some disallowed reactions may nevertheless proceed by concerted mechanisms: see Schmidt *Helv. Chim. Acta* **1971**, *54*, 862, *Tetrahedron Lett.* **1972**, 581; Muszkat; Schmidt *Helv. Chim. Acta* **1971**, *54*, 1195; Baldwin; Andrist; Pinschmidt *Acc. Chem. Res.* **1972**, *5*, 402-406; Berson *Acc. Chem. Res.* **1972**, *5*, 406-414; Baldwin, in Marchand; Lehr, Ref. 898, vol. 2, pp. 273-302.

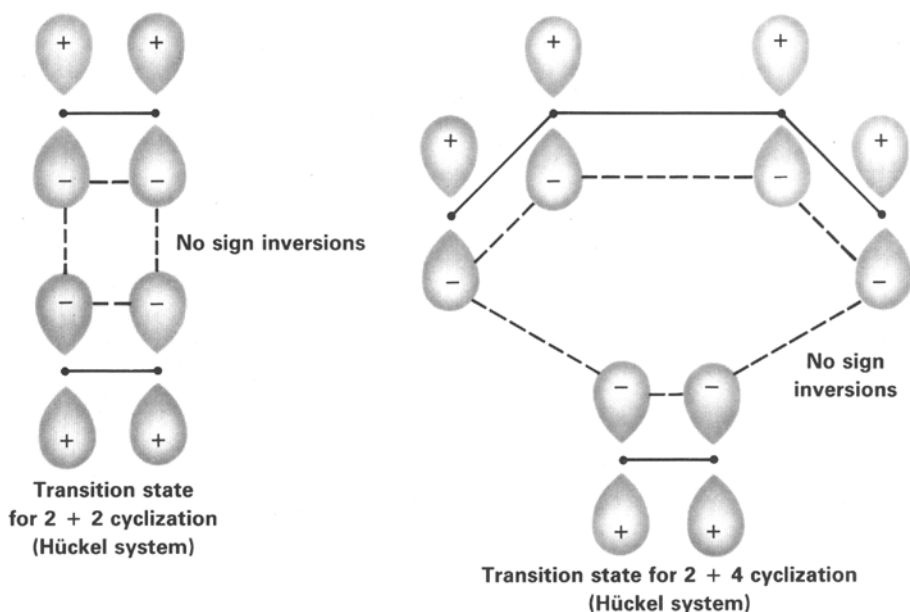


FIGURE 15.7 Transition states illustrating Hückel-Möbius rules for cycloaddition reactions.

their activation energies would be too high (however, see below). As we shall see (5-49), such reactions largely occur by two-step mechanisms. Similarly, 2 + 4 photochemical cycloadditions are also known, but the fact that they are not stereospecific indicates that they also take place by the two-step diradical mechanism (mechanism *b*).<sup>902</sup>

In all of the above discussion we have assumed that a given molecule forms both the new  $\sigma$  bonds from the same face of the  $\pi$  system. This manner of bond formation, called *suprafacial*, is certainly most reasonable and almost always takes place. The subscript *s* is used to designate this geometry, and a normal Diels-Alder reaction would be called a [ $\pi_2$  +  $\pi_4$ ] cycloaddition (the subscript  $\pi$  indicates that  $\pi$  electrons are involved in the

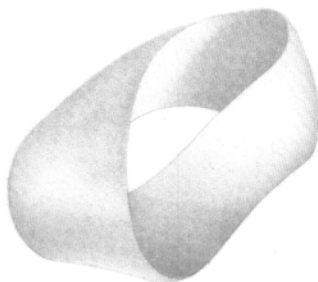


FIGURE 15.8 A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together.

<sup>902</sup>For example, see Sieber; Heimgartner; Hansen; Schmid *Helv. Chim. Acta* **1972**, *55*, 3005. For discussions see Bartlett; Helgeson; Wersel *Pure Appl. Chem.* **1968**, *16*, 187-200; Seeley *J. Am. Chem. Soc.* **1972**, *94*, 4378; Kaupp *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 313, 718 [*Angew. Chem.* **84**, 259, 718].

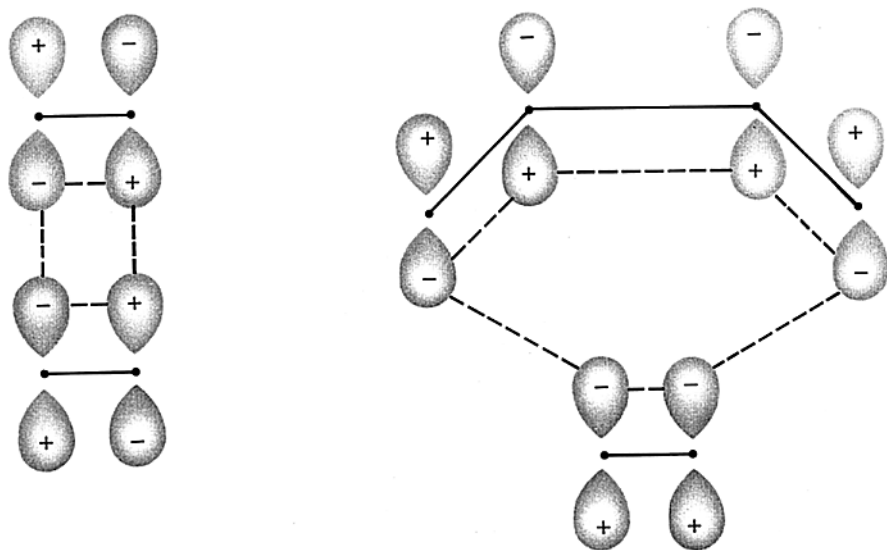
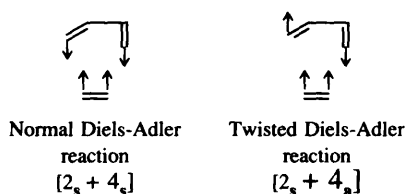


FIGURE 15.9 Transition states for 2 + 2 and 2 + 4 cyclizations involving other basis sets.

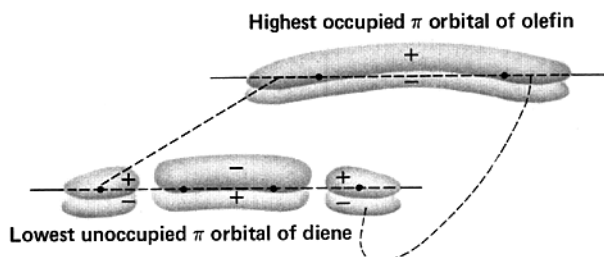
cycloaddition). However, we can conceive of another approach in which the newly forming bonds of the diene lie on *opposite* faces of the  $\pi$  system, i.e., they point in opposite directions.



This type of orientation of the newly formed bonds is called *antarafacial*, and the reaction would be a [ $\pi 2_s + \pi 4_a$ ] cycloaddition (a stands for antarafacial). We can easily show by the frontier-orbital method that this reaction (and consequently the reverse ring-opening reactions) are thermally forbidden and photochemically allowed. Thus in order for a [ $\pi 2_s + \pi 4_a$ ] reaction to proceed, overlap between the highest occupied  $\pi$  orbital of the olefin and the lowest unoccupied  $\pi$  orbital of the diene would have to occur as shown in Figure 15.10, with a + lobe overlapping a - lobe. Since like signs are no longer overlapping, the thermal reaction is now forbidden. Similarly, thermal [ $\pi 2_a + \pi 4_s$ ] and [ $\pi 2_a + \pi 2_a$ ] cyclizations are forbidden, while thermal [ $\pi 2_a + \pi 4_a$ ] and [ $\pi 2_s + \pi 2_a$ ] cyclizations are allowed, and these considerations are reversed for the corresponding photochemical processes. Of course, an antarafacial approach is highly unlikely in a 2 + 4 cyclization,<sup>903</sup> but larger ring closures could take place by such a pathway, and 2 + 2 thermal cyclizations, where the [ $\pi 2_s + \pi 2_s$ ] pathway is forbidden, can also do so in certain cases (see 5-49). We therefore see that whether a given cycloaddition is allowed or forbidden depends on the geometry of approach of the two molecules involved.

Symmetry considerations have also been advanced to explain predominant endo addi-

<sup>903</sup>A possible photochemical [ $\pi 2_a + \pi 4_s$ ] cycloaddition has been reported: Hart; Miyashi; Buchanan; Sasson *J. Am. Chem. Soc.* **1974**, *96*, 4857.

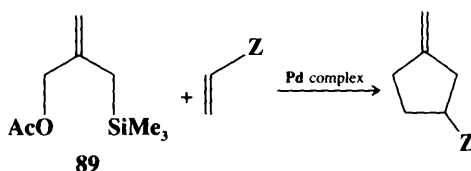


**FIGURE 15.10** Overlap of orbitals in an antarafacial thermal 2 + 4 cycloaddition.

tion.<sup>904</sup> In the case of 2 + 4 addition of butadiene to itself, the approach can be exo or endo. It can be seen (Figure 15.11) that whether the highest-occupied molecular orbital of the diene overlaps with the lowest-unoccupied molecular orbital of the olefin or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals<sup>905</sup> of like sign (dashed lines between heavy dots). Addition from the exo direction has no such stabilization. Evidence for secondary orbital overlap as the cause of predominant endo orientation, at least in some cases, is that 4 + 6 cycloaddition is predicted by similar considerations to proceed with predominant exo orientation, and that is what is found.<sup>906</sup> However, this explanation does not account for endo orientation in cases where the dienophile does not possess additional  $\pi$  orbitals, and a number of alternative explanations have been offered.<sup>907</sup>

OS II, 102; III, 310, 807; IV, 238, 311, 738, 890, 964; V, 60, 96, 414, 424, 604, 985, 1037; VI, 82, 196, 422, 427, 445, 454; VII, 4, 312, 485; **65**, 98; **66**, 142; **67**, 163; **68**, 198, 206; **69**, 31. For a reverse Diels–Alder reaction, see OS VII, 339. See also OS VII, 326.

#### 5-48 All-Carbon 2 + 3 Cycloadditions



Several methods have been reported for the formation of cyclopentanes by 2 + 3 cycloadditions.<sup>908</sup> One type involves reagents that produce intermediates **90** or **91**.<sup>909</sup> A synthetically useful example<sup>910</sup> uses 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**89**) (which is com-

<sup>904</sup>Hoffmann; Woodward *J. Am. Chem. Soc.* **1965**, 87, 4388.

<sup>905</sup>For reviews of secondary orbital interactions, see Ginsburg *Tetrahedron* **1983**, 39, 2095-2135; Gleiter; Paquette *Acc. Chem. Res.* **1983**, 16, 328-334.

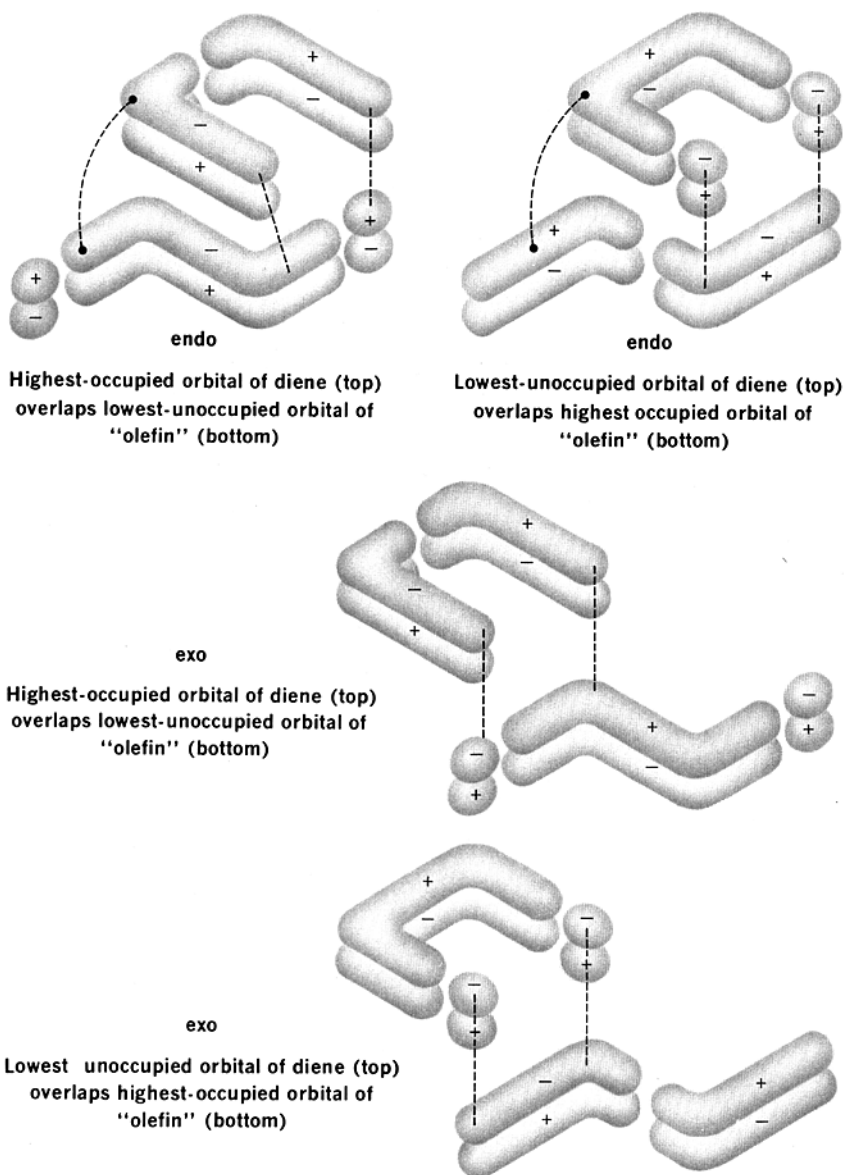
<sup>906</sup>See, for example, Cookson; Drake; Hudec; Morrison *Chem. Commun.* **1966**, 15; Itô; Fujise; Okuda; Inoue *Bull. Chem. Soc. Jpn.* **1966**, 39, 1351; Paquette; Barrett *J. Am. Chem. Soc.* **1966**, 88, 2590; Paquette; Barrett; Kuhla *J. Am. Chem. Soc.* **1969**, 91, 3616; Houk; Woodward *J. Am. Chem. Soc.* **1970**, 92, 4143, 4145; Jones; Kncen *J. Chem. Soc., Chem. Commun.* **1973**, 420.

<sup>907</sup>See, for example, Houk; Luskus *J. Am. Chem. Soc.* **1971**, 93, 4606; Kobuke; Sugimoto; Furukawa; Fueno *J. Am. Chem. Soc.* **1972**, 94, 3633; Jacobson *J. Am. Chem. Soc.* **1973**, 95, 2579; Mellor; Webb *J. Chem. Soc., Perkin Trans. 2* **1974**, 17, 26; Fox; Cardona; Kiwi *J. Org. Chem.* **1987**, 52, 1469.

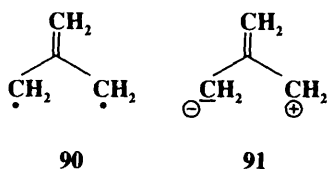
<sup>908</sup>For a list of methods, with references, see Trost; Seoane; Mignani; Acemoglu *J. Am. Chem. Soc.* **1989**, 111, 7487.

<sup>909</sup>For reviews, see Trost *Pure Appl. Chem.* **1988**, 60, 1615-1626; *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 1-20 [*Angew. Chem.* 98, 1-20].

<sup>910</sup>See, for example, Trost; Lynch; Renaut; Steinman *J. Am. Chem. Soc.* **1986**, 108, 284.

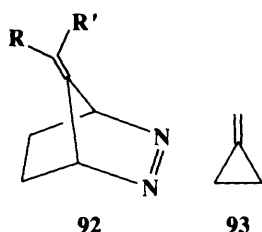


**FIGURE 15.11** Overlap of orbitals in 2 + 4 cycloaddition of dienes.

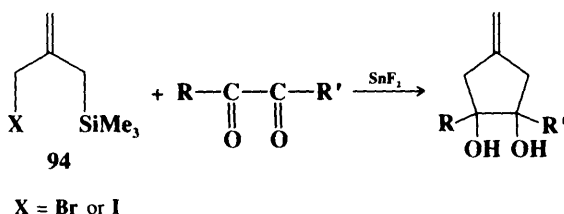


mercially available) and a palladium or other transition metal catalyst to generate **90** or **91**, which adds to double bonds, to give, in good yields, cyclopentanes with an exocyclic double

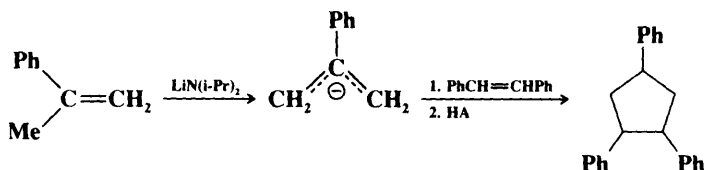
bond. Similar or identical intermediates generated from bicyclo azo compounds **92** (see



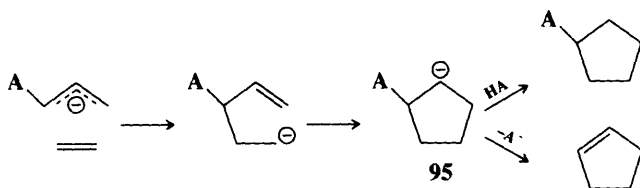
**7-46**)<sup>911</sup> or methylenecyclopropane **93**<sup>912</sup> also add to activated double bonds. With suitable substrates the addition can be enantioselective.<sup>913</sup> The reagent **94**, similar to **89**, forms cis 5-membered cyclic unsaturated diols when treated with  $\alpha$ -diketones in the presence of  $\text{SnF}_2$ .



In a different type of procedure, 2 + 3 cycloadditions are performed with allylic anions. Such reactions are called 1,3-anionic cycloadditions.<sup>915</sup> For example,  $\alpha$ -methylstyrene adds to stilbene on treatment with the strong base lithium diisopropylamide.<sup>916</sup>



The mechanism can be outlined as



<sup>911</sup>For a review, see Little *Chem. Rev.* **1986**, *86*, 875-884.

<sup>912</sup>See Yamago; Nakamura *J. Am. Chem. Soc.* **1989**, *111*, 7285.

<sup>913</sup>See Binger; Schäfer *Tetrahedron Lett.* **1988**, *29*, 529; Chaigne; Gotteland; Malacria *Tetrahedron Lett.* **1989**, *30*, 1803.

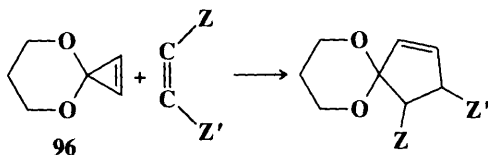
<sup>914</sup>Molander; Shubert *J. Am. Chem. Soc.* **1986**, *108*, 4683.

<sup>915</sup>For reviews, see Kauffmann *Top. Curr. Chem.* **1980**, *92*, 109-147, pp. 111-116; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 627-639 [*Angew. Chem.* *86*, 715-727].

<sup>916</sup>Eidenschink; Kauffmann *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 292 [*Angew. Chem.* *84*, 292].

In the case above, **95** is protonated in the last step by the acid HA, but if the acid is omitted and a suitable nucleofuge is present, it may leave, resulting in a cyclopentene.<sup>917</sup> In these cases the reagent is an allylic anion, but similar 2 + 3 cycloadditions involving allylic cations have also been reported.<sup>918</sup>

In a third type of procedure,<sup>919</sup> cyclopropene ketal **96** reacts with olefins bearing two

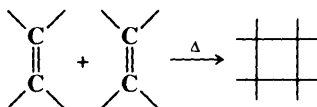


electron-withdrawing groups Z to give cyclopentenenes.<sup>920</sup>

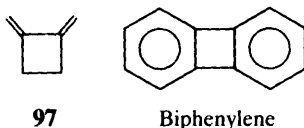
OS **65**, 32; **66**, 8.

#### 5-49 Dimerization of Olefins

##### (2 + 2)cyclo-Ethylene-1/2/addition



The thermal reaction between two molecules of olefin to give cyclobutane derivatives (a 2 + 2 cycloaddition) can be carried out where the olefins are the same or different, but the reaction is not a general one for olefins.<sup>921</sup> Dimerization of like olefins occurs with the following compounds: F<sub>2</sub>C=CX<sub>2</sub> (X = F or Cl) and certain other fluorinated alkenes (though not F<sub>2</sub>C=CH<sub>2</sub>), allenes (to give derivatives of **97**),<sup>922</sup> benzynes (to give biphenylene deriv-



atives), activated olefins (e.g., styrene, acrylonitrile, butadiene), and certain methylene-cyclopropanes.<sup>923</sup> Substituted ketenes dimerize to give cyclobutene derivatives (**98**) as the

<sup>917</sup>See, for example, Padwa; Yeske *J. Am. Chem. Soc.* **1988**, *110*, 1617; Beak; Burg *J. Org. Chem.* **1989**, *54*, 1647.

<sup>918</sup>For example, see Hoffmann; Vathke-Ernst *Chem. Ber.* **1981**, *114*, 2208, 2898; Klein; Mayr *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1027 [*Angew. Chem.* **93**, 1069]; Noyori; Hayakawa *Tetrahedron* **1985**, *41*, 5879.

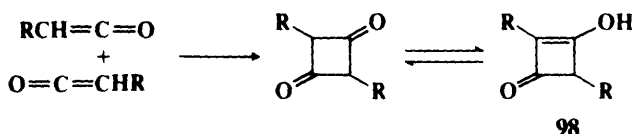
<sup>919</sup>For some other methods of making cyclopentanes or cyclopentenenes by 2 + 3 cycloadditions, see Danheiser; Carini; Fink; Basak *Tetrahedron* **1983**, *39*, 935; Shimizu; Ohashi; Tsuji *Tetrahedron Lett.* **1985**, *26*, 3825; Marino; Laborde *J. Org. Chem.* **1987**, *52*, 1; Curran; Chen *J. Am. Chem. Soc.* **1987**, *109*, 6558; Feldman; Romanelli; Ruckle; Miller *J. Am. Chem. Soc.* **1988**, *110*, 3300; Herndon; Turner; Schnatter *J. Am. Chem. Soc.* **1988**, *110*, 3334; Ghera; Yechezkel; Hassner *Tetrahedron Lett.* **1990**, *31*, 3653; Crimmins; Nantermet *J. Org. Chem.* **1990**, *55*, 4235. For a review of a 2 + 2 + 1 method (the Pauson-Khand reaction), see Schore *Org. React.* **1991**, *40*, 1-90.

<sup>920</sup>Boger; Brotherton *J. Am. Chem. Soc.* **1986**, *108*, 6695, 6713; Boger; Wysocki *J. Org. Chem.* **1988**, *53*, 3408.

<sup>921</sup>For reviews, see Carruthers, Ref. 440; Reinholdt *Adv. Heterocycl. Chem.* **1977**, *21*, 253-321; Roberts; Sharts *Org. React.* **1962**, *12*, 1-56; Gilchrist; Storr, Ref. 895, pp. 173-212; Beltrame, in Bamford; Tipper, Ref. 1, vol. 9, pp. 131-152; Huisgen; Grashey; Sauer, in Patai, Ref. 36, pp. 779-802. For a review of the use of 2 + 2 cycloadditions in polymerization reactions see Dilling, *Chem. Rev.* **1983**, *83*, 1-47. For a list of references, see Ref. 133, pp. 82-83, 659-660.

<sup>922</sup>For a review, see Fischer, in Patai, Ref. 36, pp. 1064-1067.

<sup>923</sup>Dolbier; Lomas; Garza; Harmon; Tarrant *Tetrahedron* **1972**, *28*, 3185.



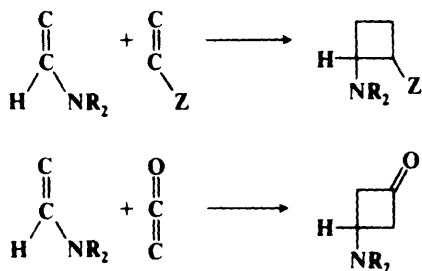
major primary products, though ketene itself dimerizes in a different manner, to give an unsaturated  $\beta$ -lactone (6-63).<sup>924</sup>

Different olefins combine as follows:

1.  $\text{F}_2\text{C}=\text{CX}_2$  ( $\text{X} = \text{F}$  or  $\text{Cl}$ ), especially  $\text{F}_2\text{C}=\text{CF}_2$ , form cyclobutanes with many olefins. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal Diels-Alder reactions.<sup>925</sup>

2. Allenes<sup>926</sup> and ketenes<sup>927</sup> react with activated olefins and alkynes. Ketenes give 1,2 addition, even with conjugated dienes.<sup>928</sup> Ketenes also add to unactivated olefins if sufficiently long reaction times are used.<sup>929</sup> Allenes and ketenes also add to each other.<sup>930</sup>

3. Enamines<sup>931</sup> form four-membered rings with Michael-type olefins<sup>932</sup> and ketenes.<sup>933</sup> In both cases, only enamines from aldehydes give stable four-membered rings:



The reaction of enamines with ketenes can be conveniently carried out by generating the ketene in situ from an acyl halide and a tertiary amine.

4. Olefins with electron-withdrawing groups may form cyclobutanes with olefins containing electron-donating groups. The enamine reactions, mentioned above, are examples

<sup>924</sup>Farnum; Johnson; Hess; Marshall; Webster *J. Am. Chem. Soc.* **1965**, 87, 5191; Dehmlow; Pickardt; Slopianka; Fastabend; Drechsler; Soufi *Liebigs Ann. Chem.* **1987**, 377.

<sup>925</sup>Bartlett; Montgomery; Seidel *J. Am. Chem. Soc.* **1964**, 86, 616; De Cock; Piettre; Lahousse; Janousek; Merényi; Viehe *Tetrahedron* **1985**, 41, 4183.

<sup>926</sup>For reviews of 2 + 2 cycloadditions of allenenes, see Schuster; Coppola, Ref. 95, pp. 286-317; Hopf, in Landor, Ref. 95, vol. 2, pp. 525-562; Ghosez; O'Donnell, in Marchand; Lehr, Ref. 898, vol. 2, pp. 79-140; Baldwin; Fleming *Fortschr. Chem. Forsch.* **1970**, 15, 281-310.

<sup>927</sup>For reviews of cycloadditions of ketenes, see Ghosez; O'Donnell, Ref. 926; Brady *Synthesis* **1971**, 415-422; Luknitskii; Vovsi *Russ. Chem. Rev.* **1969**, 38, 487-494; Ulrich *Cycloaddition Reactions of Heterocumulenes*; Academic Press: New York, 1967, pp. 38-121; Holder *J. Chem. Educ.* **1976**, 53, 81-85. For a review of intramolecular cycloadditions of ketenes to alkenes, see Snider *Chem. Rev.* **1988**, 88, 793-811.

<sup>928</sup>See, for example, Martin; Gott; Goodlett; Hasek *J. Org. Chem.* **1965**, 30, 4175; Brady; O'Neal *J. Org. Chem.* **1967**, 32, 2704; Huisgen; Feiler; Otto *Tetrahedron Lett.* **1968**, 4491, *Chem. Ber.* **1969**, 102, 3475. For indirect methods of the 1,4 addition of the elements of ketene to a diene see Freeman; Balls; Brown *J. Org. Chem.* **1968**, 33, 2211; Corey; Ravindranathan; Terashima *J. Am. Chem. Soc.* **1971**, 93, 4326. For a review of ketene equivalents see Ranganathan; Ranganathan; Mehrotra *Synthesis* **1977**, 289-296.

<sup>929</sup>Huisgen; Feiler *Chem. Ber.* **1969**, 102, 3391; Brady; Patel *J. Org. Chem.* **1973**, 38, 4106; Bak; Brady *J. Org. Chem.* **1979**, 44, 107.

<sup>930</sup>Bampfield; Brook; McDonald *J. Chem. Soc., Chem. Commun.* **1975**, 132; Gras; Bertrand *Nouv. J. Chim.* **1981**, 5, 521.

<sup>931</sup>For a review of cycloaddition reactions of enamines, see Cook, in *Cook Enamines*, 2nd ed.; Marcel Dekker: New York, 1988, pp. 347-440.

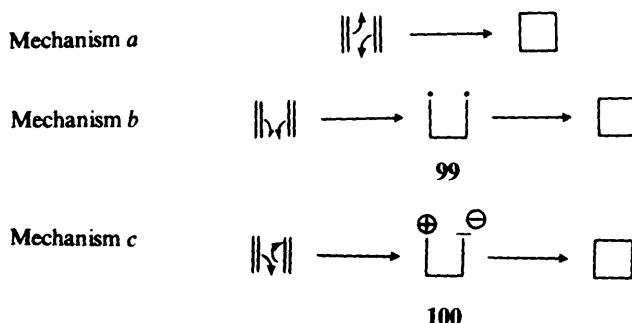
<sup>932</sup>Brannock; Bell; Goodlett; Thweatt *J. Org. Chem.* **1964**, 29, 813.

<sup>933</sup>Berchtold; Harvey; Wilson *J. Org. Chem.* **1961**, 26, 4776; Opitz; Kleeman *Liebigs Ann. Chem.* **1963**, 665, 114; Hasek; Gott; Martin *J. Org. Chem.* **1966**, 31, 1931.

of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with olefins of the form  $C=C-A$ , where  $A$  may be  $OR$ ,<sup>934</sup>  $SR$  (enol and thioenol ethers),<sup>935</sup> cyclopropyl,<sup>936</sup> or certain aryl groups.<sup>937</sup>

Solvents are not necessary for  $2 + 2$  cycloadditions. They are usually carried out at 100 to 225°C under pressure, although the reactions in group 4 occur under milder conditions.

The reaction is similar to the Diels–Alder (in action, not in scope), and if dienes are involved, the latter reaction may compete, though most olefins react with a diene either entirely by 1,2 or entirely by 1,4 addition. Three mechanisms can be proposed<sup>938</sup> analogous to those proposed for the Diels–Alder reaction. Mechanism *a* is a concerted pericyclic process, and mechanisms *b* and *c* are two-step reactions involving, respectively, a diradical (**99**) and a diion (**100**) intermediate. As in 5-47, a diradical intermediate must be a singlet.



In searching for ways to tell which mechanism is operating in a given case, we would expect mechanism *c* to be sensitive to changes in solvent polarity, while mechanisms *a* and *b* should be insensitive. We would also expect mechanism *a* to be stereospecific, while mechanisms *b* and *c* probably would not be stereospecific, though if the second step of these processes takes place very rapidly, before **99** or **100** has a chance to rotate about the newly formed single bond, stereospecificity might be observed. Because of entropy considerations such rapid ring closure might be more likely here than in a  $2 + 4$  cycloaddition.

There is evidence that the reactions can take place by all three mechanisms, depending on the structure of the reactants. A thermal  $[\pi 2_s + \pi 2_s]$  mechanism is ruled out for most of these substrates by the orbital symmetry rules, but a  $[\pi 2_s + \pi 2_a]$  mechanism is allowed (p. 851), and there is much evidence that ketenes and certain other linear molecules<sup>939</sup> in which the steric hindrance to such an approach is minimal can and often do react by this mechanism. In a  $[\pi 2_s + \pi 2_a]$  cycloaddition the molecules must approach each other in such a way (Figure 15.12a) that the + lobe of the HOMO of one molecule (I) overlaps with both + lobes of the LUMO of the other (II), even though these lobes are on opposite sides of the nodal plane of II. The geometry of this approach requires that the groups S and U of molecule II project *into* the plane of molecule I. This has not been found to happen for ordinary

<sup>934</sup>For a review with ketene acetals  $R_2C=C(OR')_2$ , see Scheeren *Recl. Trav. Chim. Pays-Bas* **1986**, 105, 71-84.

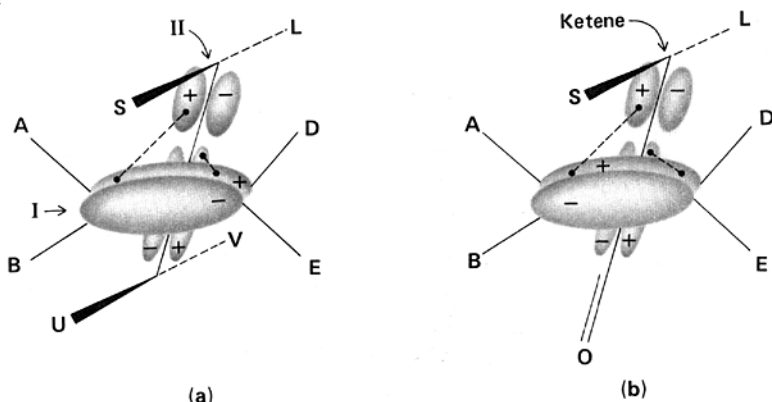
<sup>935</sup>Williams; Wiley; McKusick *J. Am. Chem. Soc.* **1962**, 84, 2210.

<sup>936</sup>Nishida; Moritani; Teraji *J. Org. Chem.* **1973**, 38, 1878.

<sup>937</sup>Nagata; Shiota; Nogami; Mikawa *Chem. Lett.* **1973**, 1087; Shiota; Yoshida; Nogami; Mikawa *Chem. Lett.* **1973**, 1271.

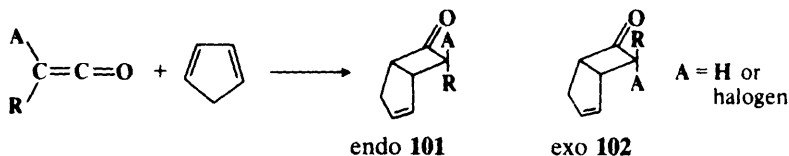
<sup>938</sup>For a review, see Bartlett *Q. Rev., Chem. Soc.* **1970**, 24, 473-497.

<sup>939</sup>There is evidence that a cyclopentyne (generated in situ) also adds to a double bond by an antarafacial process: Gilbert; Baze *J. Am. Chem. Soc.* **1984**, 106, 1885.



**FIGURE 15.12** Orbital overlap in  $\pi_{2s} + \pi_{2a}$  cycloaddition between (a) two olefin molecules and (b) a ketene and an olefin. S and L stand for small and large.

alkenes,<sup>940</sup> but if molecule II is a ketene (Figure 15.12b), the group marked U is not present and the  $[\pi_{2s} + \pi_{2a}]$  reaction can take place. Among the evidence<sup>941</sup> for this mechanism<sup>942</sup> is the following: (1) The reactions are stereospecific.<sup>943</sup> (2) The isomer that forms is the *more-hindered one*. Thus methylketene plus cyclopentadiene gave only the endo product (**101**, A = H, R = CH<sub>3</sub>).<sup>944</sup> Even more remarkably, when haloalkyl ketenes  $RXC=C=O$  were treated with cyclopentadiene, the endo-exo ratio of the product (**101**, **102**, A = halogen)



actually *increased* substantially when R was changed from Me to iso-Pr to *t*-Bu!<sup>945</sup> One would expect preferential formation of the exo products (**102**) from  $[\pi_{2s} + \pi_{2s}]$  cycloadditions where the molecules approach each other face-to-face, but a  $[\pi_{2s} + \pi_{2a}]$  process leads to endo products because the ketene molecule (which for steric reasons would approach with its smaller group directed toward the olefin) must twist as shown in Figure 15.13 (L = larger;

<sup>940</sup>See, for example, Padwa; Koehn; Masaracchia; Osborn; Trecker *J. Am. Chem. Soc.* **1971**, 93, 3633; Bartlett; Cohen; Elliott; Hummel; Minns; Sharts; Fukunaga *J. Am. Chem. Soc.* **1972**, 94, 2899.

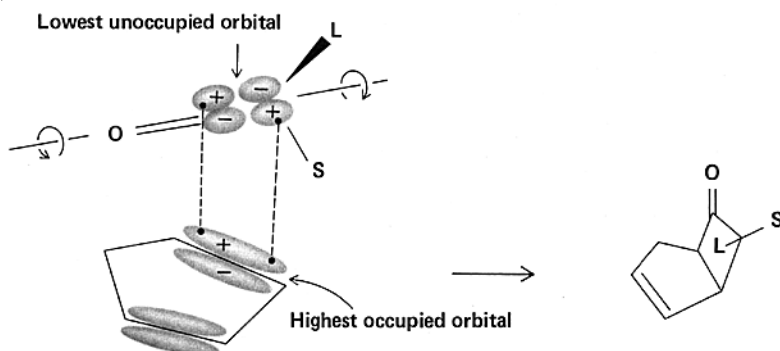
<sup>941</sup>For other evidence, see Baldwin; Kapecki *J. Am. Chem. Soc.* **1970**, 92, 4874; Brook; Griffiths *Chem. Commun.* **1970**, 1344; Frey; Isaacs *J. Chem. Soc. B* **1970**, 830; Egger *Int. J. Chem. Kinet.* **1973**, 5, 285; Moon; Kolesar *J. Org. Chem.* **1974**, 39, 995; Isaacs; Hatcher *J. Chem. Soc., Chem. Commun.* **1974**, 593; Hassner; Cory; Sartoris *J. Am. Chem. Soc.* **1976**, 98, 7698; Gheorghiu; Părvulescu; Drăghici; Elian *Tetrahedron* **1981**, 37 Suppl., 143. See, however, Holder; Graf; Duesler; Moss *J. Am. Chem. Soc.* **1983**, 105, 2929.

<sup>942</sup>On the other hand, molecular orbital calculations predict that the cycloaddition of ketenes to olefins does not take place by a  $[\pi_{2s} + \pi_{2a}]$  mechanism: Wang; Houk *J. Am. Chem. Soc.* **1990**, 112, 1754; Bernardi; Bottoni; Robb; Venturini *J. Am. Chem. Soc.* **1990**, 112, 2106; Valentí; Pericàs; Moyano *J. Org. Chem.* **1990**, 55, 3582.

<sup>943</sup>Huisgen; Feiler; Binsch *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 753 [*Angew. Chem.* 76, 892]; *Chem. Ber.* **1969**, 102, 3460; Martin; Goodlett; Burpitt *J. Org. Chem.* **1965**, 30, 4309; Montaigne; Ghosez *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 221 [*Angew. Chem.* 80, 194]; Bertrand; Gras; Gore *Tetrahedron* **1975**, 31, 857; Marchand-Brynaert; Ghosez *J. Am. Chem. Soc.* **1972**, 94, 2870; Huisgen; Mayr *Tetrahedron Lett.* **1975**, 2965, 2969.

<sup>944</sup>Brady; Hoff; Roe; Parry *J. Am. Chem. Soc.* **1969**, 91, 5679; Rey; Roberts; Dieffenbacher; Dreiding *Helv. Chim. Acta* **1970**, 53, 417. See also Brady; Parry; Stockton *J. Org. Chem.* **1971**, 36, 1486; DoMinh; Strausz *J. Am. Chem. Soc.* **1970**, 92, 1766; Isaacs; Stanbury *Chem. Commun.* **1970**, 1061; Brook; Harrison; Duke *Chem. Commun.* **1970**, 589; Dehmloew, *Tetrahedron Lett.* **1973**, 2573; Rey; Roberts; Dreiding; Roussel; Vanlierde; Toppet; Ghosez *Helv. Chim. Acta* **1982**, 65, 703.

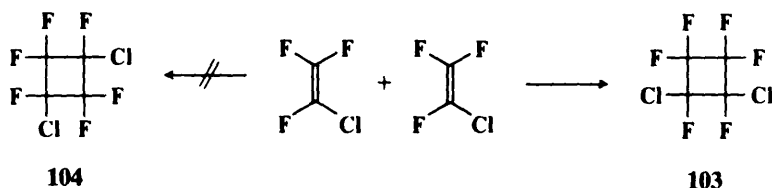
<sup>945</sup>Brady; Roe *J. Am. Chem. Soc.* **1970**, 92, 4618.



**FIGURE 15.13** Orbital overlap in the reaction of a ketene with cyclopentadiene. S and L stand for small and large.

S = smaller group) in order for the + lobes to interact and this swings the larger group into the endo position.<sup>946</sup> The experimental results in which the amount of endo isomer increases with the increasing size of the R group would seem to be contrary to what would be expected from considerations of steric hindrance (we may call them *masochistic steric effects*), but they are just what is predicted for a  $[\pi 2_s + \pi 2_a]$  reaction. (3) There is only moderate polar solvent acceleration.<sup>947</sup> (4) The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.<sup>948</sup> Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place by the  $[\pi 2_s + \pi 2_a]$  mechanism,<sup>949</sup> but the evidence in these cases is more consistent with the diradical mechanism *b*.<sup>950</sup>

The diradical mechanism *b* is most prominent in the reactions involving fluorinated alkenes.<sup>951</sup> These reactions are generally not stereospecific<sup>952</sup> and are insensitive to solvent effects. Further evidence that a diion is not involved is that head-to-head coupling is found when an unsymmetrical molecule is dimerized. Thus dimerization of  $F_2C=CFCl$  gives **103**,



<sup>946</sup>Brook; Harrison; Duke, Ref. 944.

<sup>947</sup>Brady; O'Neal *J. Org. Chem.* **1967**, 32, 612; Huisgen; Feiler; Otto *Tetrahedron Lett.* **1968**, 4485. *Chem. Ber.* **1969**, 102, 3444; Sterk *Z. Naturforsch., Teil B* **1972**, 27, 143.

<sup>948</sup>Baldwin; Kapecki *J. Am. Chem. Soc.* **1970**, 92, 4868; Isaacs; Stanbury *J. Chem. Soc., Perkin Trans. 2* **1973**, 166.

<sup>949</sup>For example, see Kiefer; Okamura *J. Am. Chem. Soc.* **1968**, 90, 4187; Baldwin; Roy *Chem. Commun.* **1969**, 1225; Moore; Bach; Ozretich *J. Am. Chem. Soc.* **1969**, 91, 5918.

<sup>950</sup>Muscio; Jacobs *Tetrahedron Lett.* **1969**, 2867; Taylor; Warburton; Wright *J. Chem. Soc. C* **1971**, 385; Dai; Dolbier *J. Am. Chem. Soc.* **1972**, 94, 3946; Duncan; Weyler; Moore *Tetrahedron Lett.* **1973**, 4391; Grimme; Rother *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 505 [*Angew. Chem.* 85, 512]; Levek; Kiefer *J. Am. Chem. Soc.* **1976**, 98, 1875; Pasto; Heid; Warren *J. Am. Chem. Soc.* **1982**, 104, 3676; Pasto; Yang *J. Org. Chem.* **1986**, 51, 1676; Dolbier; Seabury *Tetrahedron Lett.* **1987**, 28, 1491. *J. Am. Chem. Soc.* **1987**, 109, 4393; Dolbier; Weaver *J. Org. Chem.* **1990**, 55, 711.

<sup>951</sup>It has been argued that the mechanism here is not the diradical mechanism, but the  $[\pi 2_s + \pi 2_a]$  mechanism: Roberts *Tetrahedron* **1985**, 41, 5529.

<sup>952</sup>Montgomery; Schueller; Bartlett *J. Am. Chem. Soc.* **1964**, 86, 621; Bartlett; Hummel; Elliott; Minns *J. Am. Chem. Soc.* **1972**, 94, 2898.

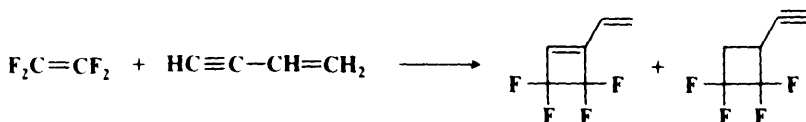
not **104**. If one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the negative end of the other.<sup>953</sup>

The diion mechanism<sup>954</sup> *c* has been reported for at least some of the reactions<sup>955</sup> in categories 3 and 4,<sup>956</sup> as well as some ketene dimerizations.<sup>957</sup> For example, the rate of the reaction between 1,2-bis(trifluoromethyl)-1,2-dicyanoethene and ethyl vinyl ether was strongly influenced by changes in solvent polarity.<sup>958</sup> Some of these reactions are nonsterEOSpecific, but others are stereospecific.<sup>959</sup> As previously indicated, it is likely that in the latter cases the diionic intermediate closes before rotation can take place. Such rapid ring closure is more likely for a diion than for a diradical because of the attraction between the opposite charges. Other evidence for the diion mechanism in these cases is that reaction rates are greatly dependent on the presence of electron-donating and electron-withdrawing groups and that it is possible to trap the diionic intermediates.

Whether a given olefin reacts by the diradical or diion mechanism depends, among other things, on the groups attached to it. For example, phenyl and vinyl groups at the  $\alpha$  positions of **99** or **100** help to stabilize a diradical, while donors such as oxygen and nitrogen favor a diion (they stabilize the positively charged end).<sup>960</sup> A table on p. 451 of reference 960 shows which mechanism is more likely for 2 + 2 cycloadditions of various pairs of olefins.

Thermal cleavage of cyclobutanes<sup>961</sup> to give two olefin molecules (*cycloreversion*),<sup>962</sup> the reverse of 2 + 2 cycloaddition) operates by the diradical mechanism, and the [<sub>o</sub>2<sub>s</sub> + <sub>o</sub>2<sub>a</sub>] pathway has not been found<sup>963</sup> (the subscripts  $\sigma$  indicate that  $\sigma$  bonds are involved in this reaction).

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds, e.g.,



About equal amounts

The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed, except where these rearrange before they can be isolated (see **5-51**)<sup>964</sup> or in the presence of a suitable coordination compound, so that the cyclobutadiene is produced in the form of a complex (p. 55).<sup>965</sup>

<sup>953</sup>For additional evidence based on radical stabilities, see Silversmith; Kitahara; Caserio; Roberts *J. Am. Chem. Soc.* **1958**, *80*, 5840; Ref. 925; Doering; Guyton *J. Am. Chem. Soc.* **1978**, *100*, 3229.

<sup>954</sup>For reviews of this mechanism, see Huisgen *Acc. Chem. Res.* **1977**, *10*, 117-124, 199-206; Huisgen; Schug; Steiner *Bull. Soc. Chim. Fr.* **1976**, 1813-1820.

<sup>955</sup>For a review of cycloadditions with polar intermediates, see Gompper *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 312-327 [*Angew. Chem.* **81**, 348-363].

<sup>956</sup>The reactions of ketenes with enamines are apparently not concerted but take place by the diionic mechanism: Otto; Feiler; Huisgen *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 737 [*Angew. Chem.* **80**, 759].

<sup>957</sup>See Moore; Wilbur *J. Am. Chem. Soc.* **1978**, *100*, 6523.

<sup>958</sup>Proskow; Simmons; Cairns *J. Am. Chem. Soc.* **1966**, *88*, 5254. See also Huisgen *Pure Appl. Chem.* **1980**, *52*, 2283-2302.

<sup>959</sup>Proskow; Simmons; Cairns, Ref. 958; Huisgen; Steiner *J. Am. Chem. Soc.* **1973**, *95*, 5054, 5055.

<sup>960</sup>Hall *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 440-455 [*Angew. Chem.* **95**, 448-464].

<sup>961</sup>See Frey *Adv. Phys. Org. Chem.* **1966**, *4*, 147-193, pp. 170-175, 180-183.

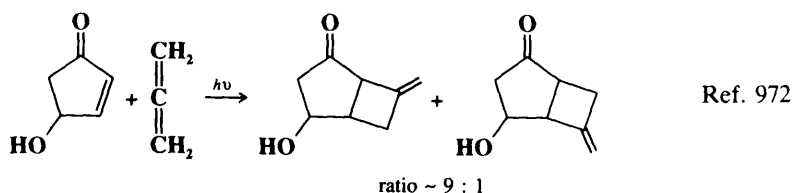
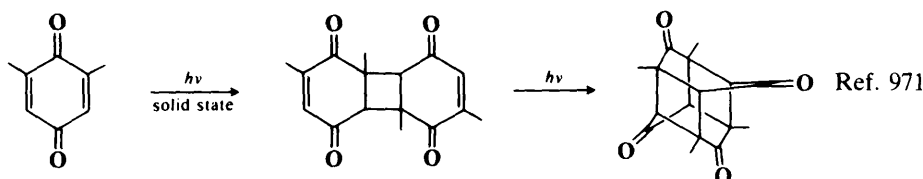
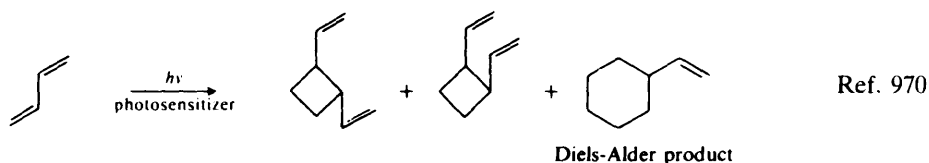
<sup>962</sup>For reviews of 2 + 2 cycloreversions, see Schaumann; Ketcham *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 225-247 [*Angew. Chem.* **94**, 231-253]; Brown, Ref. 883, pp. 247-259.

<sup>963</sup>See, for example, Cocks; Frey; Stevens *Chem. Commun.* **1969**, 458; Srinivasan; Hsu *J. Chem. Soc., Chem. Commun.* **1972**, 1213; Paquette; Kukla *Tetrahedron Lett.* **1973**, 1241; Paquette; Carmody *J. Am. Chem. Soc.* **1976**, *98*, 8175. See however Cant; Coxon; Hartshorn *Aust. J. Chem.* **1975**, *28*, 391; Doering; Roth; Breuckmann; Figge; Lennartz; Fessner; Prinzbach *Chem. Ber.* **1988**, *121*, 1.

<sup>964</sup>For a review of these cases, and of cycloadditions of triple bonds to double bonds, see Fuks; Viehe, in Viehe, Ref. 49, pp. 435-442.

<sup>965</sup>D'Angelo; Ficini; Martinon; Riche; Sevin *J. Organomet. Chem.* **1979**, *177*, 265. For a review, see Hogeveen; Kok in Patai; Rappoport, Ref. 49, pt. 2, pp. 981-1013.

Although thermal 2 + 2 cycloaddition reactions are essentially limited to the cases described above, many (though by no means all) double-bond compounds undergo such reactions *when photochemically excited* (either directly or by a photosensitizer—see p. 241), even if they are not in the above categories.<sup>966</sup> Simple alkenes absorb in the far uv (p. 235), which is difficult to reach experimentally, though this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to simple alkenes<sup>967</sup> (especially to strained compounds such as cyclopropenes and cyclobutenes), but more often the double-bond compounds involved are conjugated dienes,<sup>968</sup>  $\alpha,\beta$ -unsaturated ketones,<sup>969</sup> acids, or acid derivatives, or quinones, since these compounds, because they are conjugated, absorb at longer wavelengths (p. 234). Both dimerizations and mixed additions are common, some examples being (see also the example on p. 246):



<sup>966</sup>For reviews, see Demuth; Mikhail *Synthesis* **1989**, 145-162; Ninomiya; Naito *Photochemical Synthesis*; Academic Press: New York, 1989, pp. 58-109; Ramamurthy; Venkatesan *Chem. Rev.* **1987**, 87, 433-481; Lewis *Adv. Photochem.* **1986**, 13, 165-235; Wender, in Coyle *Photochemistry in Organic Synthesis*; Royal Society of Chemistry: London, 1986, pp. 163-188; Schreiber *Science* **1985**, 227, 857-863; Neckers; Tinnemans, in Horspool *Synthetic Organic Photochemistry*; Plenum: New York, 1984, pp. 285-311; Baldwin *Org. Photochem.* **1981**, 5, 123-225; Turro *Modern Molecular Photochemistry*; W.A. Benjamin: New York, 1978, pp. 417-425, 458-465; Kricka; Ledwith *Synthesis* **1974**, 539-549; Herndon *Top. Curr. Chem.* **1974**, 46, 141-179; Sammes *Q. Rev., Chem. Soc.* **1970**, 24, 37-68, pp. 46-55; Crowley; Mazzocchi, in Zabicky, Ref. 115, pp. 297-316; Turro; Dalton; Weiss *Org. Photochem.* **1969**, 2, 1-62; Trecker *Org. Photochem.* **1969**, 2, 63-116; Scharf *Fortschr. Chem. Forsch.* **1969**, 11, 216-244; Steinmetz *Fortschr. Chem. Forsch.* **1967**, 7, 445-527; Fonken *Org. Photochem.* **1967**, 1, 197-246; Chapman; Lenz *Org. Photochem.* **1967**, 1, 283-321; Schönberg, Ref. 49, pp. 70-96, 109-117; Warrener; Bremner *Rev. Pure Appl. Chem.* **1966**, 16, 117-173, pp. 122-128.

<sup>967</sup>For examples of nonphotosensitized dimerization of simple alkenes, see Arnold; Abraitys *Chem. Commun.* **1967**, 1053; Yamazaki; Cvetanović *J. Am. Chem. Soc.* **1969**, 91, 520.

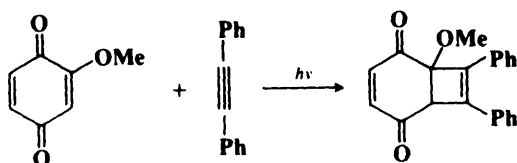
<sup>968</sup>For a review, see Dilling *Chem. Rev.* **1969**, 69, 845-877.

<sup>969</sup>For reviews of various aspects of this subject, see Cossy; Carrupt; Vogel, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 2; Wiley: New York, 1989, pp. 1369-1565; Kemernitskii; Ignatov; Levina *Russ. Chem. Rev.* **1988**, 57, 270-282; Weedon, in Horspool, Ref. 966, pp. 61-143; Lenz *Rev. Chem. Intermed.* **1981**, 4, 369-404; Margaretha *Chimia* **1975**, 29, 203-209; Bauslaugh *Synthesis* **1970**, 287-300; Eaton *Acc. Chem. Res.* **1968**, 1, 50-57.

<sup>970</sup>Hammond; Turro; Fischer *J. Am. Chem. Soc.* **1961**, 83, 4674; Liu; Turro; Hammond *J. Am. Chem. Soc.* **1965**, 87, 3406; Candall; Griffiths *Trans. Faraday Soc.* **1965**, 61, 1968; DeBoer; Turro; Hammond *Org. Synth. V*, 528.

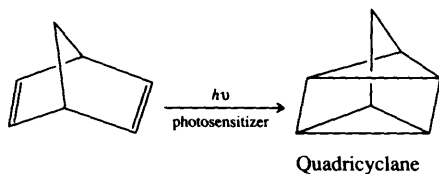
<sup>971</sup>Cookson; Cox; Hudec *J. Chem. Soc.* **1961**, 4499.

<sup>972</sup>Stensen; Svendsen; Hofer; Sydnæs *Acta Chem. Scand., Ser. B* **1968**, 42, 259.

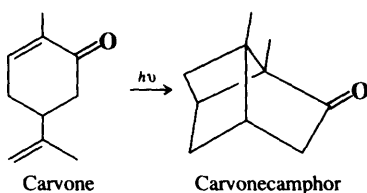


Ref. 973

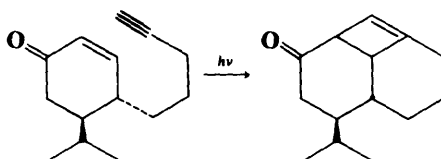
Photochemical 2 + 2 cycloadditions can also take place intramolecularly if a molecule has two double bonds that are properly oriented.<sup>974</sup> The cyclization of the quinone dimer shown above is one example. Other examples are



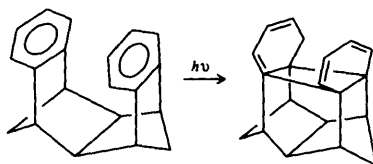
Ref. 975



Ref. 976



Ref. 977



Ref. 978

<sup>973</sup>Pappas; Pappas *Tetrahedron Lett.* **1967**, 1597.

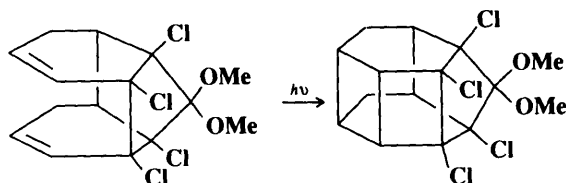
<sup>974</sup>For reviews, see Becker; Haddad *Org. Photochem.* **1989**, *10*, 1-162; Crimmins *Chem. Rev.* **1988**, *88*, 1453-1473; Oppolzer *Acc. Chem. Res.* **1982**, *15*, 135-141; Prinzbach *Pure Appl. Chem.* **1968**, *16*, 17-46; Dilling *Chem. Rev.* **1966**, *66*, 373-393.

<sup>975</sup>Hammond; Turro; Fischer, Ref. 970; Dauben; Cargill *Tetrahedron* **1961**, *15*, 197. See also Cristol; Snell *J. Am. Chem. Soc.* **1958**, *80*, 1950.

<sup>976</sup>Ciamician; Silber *Ber.* **1908**, *41*, 1928; Büchi; Goldman *J. Am. Chem. Soc.* **1957**, *79*, 4741.

<sup>977</sup>Koft; Smith *J. Am. Chem. Soc.* **1984**, *106*, 2115.

<sup>978</sup>Fessner; Prinzbach; Rihs *Tetrahedron Lett.* **1983**, *24*, 5857.



Ref. 979

It is obvious that many molecules can be constructed in this way that would be difficult to make by other procedures. However, attempted cyclizations of this kind are not always successful. In many cases polymeric or other side products are obtained instead of the desired product.

It is possible that some of these photochemical cycloadditions take place by a  $[\pi 2_s + \pi 2_s]$  mechanism (which is of course allowed by orbital symmetry); when and if they do, one of the molecules must be in the excited singlet state ( $S_1$ ) and the other in the ground state.<sup>980</sup> The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,<sup>981</sup> making it likely that the  $[\pi 2_s + \pi 2_s]$  mechanism is operating in these reactions. However, in most cases it is a triplet excited state that reacts with the ground-state molecule; in these cases the diradical (or in certain cases, the diionic) mechanism is taking place. In one intramolecular case, the intermediate diradical has been trapped.<sup>982</sup> Photosensitized  $2\pi + 2\pi$  cycloadditions almost always involve the triplet state and hence a diradical (or diionic) mechanism.

The photochemical diradical mechanism is not quite the same as the thermal diradical mechanism. In the thermal mechanism the initially formed diradical must be a singlet, but in the photochemical process a triplet excited state is adding to a ground state (which is of course a singlet). Thus, in order to conserve spin,<sup>983</sup> the initially formed diradical must be a triplet; i.e., the two electrons must have the same spin. Consequently the second, or ring-closing, step of the mechanism cannot take place at once, because a new bond cannot form from a combination of two electrons with the same spin, and the diradical has a reasonably long lifetime before collisions with molecules in the environment allow a spin inversion to take place and the diradical to cyclize. We would therefore predict nonstereospecificity, and that is what is found.<sup>984</sup> It has been believed that at least some  $2 + 2$  photocycloadditions take place by way of exciplex intermediates<sup>985</sup> [an *exciplex*<sup>986</sup> is an excited EDA complex (p. 79) which is dissociated in the ground state; in this case one double bond is the donor and the other the acceptor], but there is evidence against this.<sup>987</sup>

It has been found that certain  $2 + 2$  cycloadditions which do not occur thermally can be made to take place without photochemical initiation by the use of certain catalysts, usually

<sup>979</sup>Mehta; Padma; Ōsawa; Barbiric; Mochizuki *Tetrahedron Lett.* **1987**, 28, 1295.

<sup>980</sup>We have previously seen (p. 242) that reactions between two excited molecules are extremely rare.

<sup>981</sup>Yamazaki; Cvetanović, Ref. 967; Yamazaki; Cvetanović; Irwin *J. Am. Chem. Soc.* **1976**, 98, 2198. For other likely examples, see Lewis; Hoyle; Johnson *J. Am. Chem. Soc.* **1975**, 97, 3267; Lewis; Kojima *J. Am. Chem. Soc.* **1988**, 110, 8660.

<sup>982</sup>Becker; Haddad; Sahali *Tetrahedron Lett.* **1989**, 30, 2661.

<sup>983</sup>This is an example of the Wigner spin conservation rule (p. 241). Note that spin conservation is something entirely different from symmetry conservation.

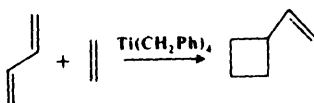
<sup>984</sup>See, for example, Liu; Hammond *J. Am. Chem. Soc.* **1967**, 89, 4936; Kramer; Bartlett *J. Am. Chem. Soc.* **1972**, 94, 3934.

<sup>985</sup>See, for example, Farid; Doty; Williams *J. Chem. Soc., Chem. Commun.* **1972**, 711; Mizuno; Pac; Sakurai *J. Am. Chem. Soc.* **1974**, 96, 2993; Caldwell; Creed *Acc. Chem. Res.* **1980**, 13, 45-50; Mattes; Farid *Acc. Chem. Res.* **1982**, 15, 80-86; Swapna; Lakshmi; Rao; Kunwar *Tetrahedron* **1989**, 45, 1777.

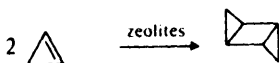
<sup>986</sup>For a review of exciplexes, see Davidson *Adv. Phys. Org. Chem.* **1983**, 19, 1-130.

<sup>987</sup>Schuster; Heibel; Brown; Turro; Kumar *J. Am. Chem. Soc.* **1988**, 110, 8261.

transition-metal compounds.<sup>988</sup> Examples are:



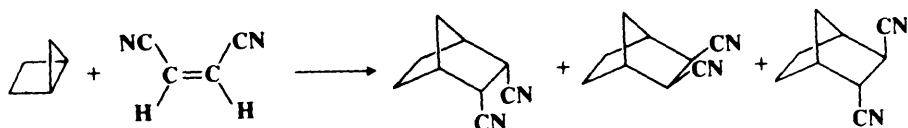
Ref. 989



Ref. 990

Among the catalysts used are Lewis acids<sup>991</sup> and phosphine-nickel complexes.<sup>992</sup> Certain of the reverse cyclobutane ring openings can also be catalytically induced (8-40). The role of the catalyst is not certain and may be different in each case. One possibility is that the presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the  $\pi$  or  $\sigma$  bonds of the substrate.<sup>993</sup> In such a case the reaction would of course be a concerted  $2_s + 2_s$  process. However, the available evidence is more consistent with nonconcerted mechanisms involving metal-carbon  $\sigma$ -bonded intermediates, at least in most cases.<sup>994</sup> For example, such an intermediate was isolated in the dimerization of norbornadiene, catalyzed by iridium complexes.<sup>995</sup>

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne<sup>996</sup> bearing electron-withdrawing groups.<sup>997</sup> These reactions are  $_{\pi}2 + _{\pi}2$  cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems such as bicyclo[1.1.0]butanes<sup>998</sup> and bicyclo[2.1.0]pentanes. For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fu-



maronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.<sup>999</sup> The lack of stereospecificity and the negligible effect of solvent on the rate indicate

<sup>988</sup>For reviews, see Dzhemilev; Khusnutdinov; Tolstikov *Russ. Chem. Rev.* **1987**, 56, 36-51; Kricka; Ledwith, *Ref.* 966.

<sup>989</sup>Cannell *J. Am. Chem. Soc.* **1972**, 94, 6867.

<sup>990</sup>Schipperijn; Lukas *Tetrahedron Lett.* **1972**, 231.

<sup>991</sup>West; Kwitowski *J. Am. Chem. Soc.* **1968**, 90, 4697; Lukas; Baardman; Kouwenhoven *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 369 [*Angew. Chem.* **88**, 412].

<sup>992</sup>See, for example, Hoover; Lindsey *J. Org. Chem.* **1969**, 34, 3051; Noyori; Ishigami; Hayashi; Takaya *J. Am. Chem. Soc.* **1973**, 95, 1674; Yoshikawa; Aoki; Kiji; Furukawa *Tetrahedron* **1974**, 30, 405.

<sup>993</sup>For discussions, see Labunskaya; Shebalova; Khidkel' *Russ. Chem. Rev.* **1974**, 43, 1-16; Mango *Top. Curr. Chem.* **1974**, 45, 39-91, *Tetrahedron Lett.* **1973**, 1509, *Intra-Sci. Chem. Rep.* **1972**, 6 (3), 171-187, *CHEMTECH* **1971**, 1, 758-765, *Adv. Catal.* **1969**, 20, 291-325; Mango; Schachtschneider *J. Am. Chem. Soc.* **1971**, 93, 1123, **1969**, 91, 2484; van der Lugt *Tetrahedron Lett.* **1970**, 2281; Wristers; Brener; Pettit *J. Am. Chem. Soc.* **1970**, 92, 7499.

<sup>994</sup>See, for example, Cassar; Halpern *Chem. Commun.* **1970**, 1082; Doyle; McMeeking; Binger *J. Chem. Soc., Chem. Commun.* **1976**, 376; Grubbs; Miyashita; Liu; Burk *J. Am. Chem. Soc.* **1977**, 99, 3863.

<sup>995</sup>Fraser; Bird; Bezman; Shapley; White; Osborn *J. Am. Chem. Soc.* **1973**, 95, 597.

<sup>996</sup>Gassman; Mansfield *J. Am. Chem. Soc.* **1968**, 90, 1517, 1524.

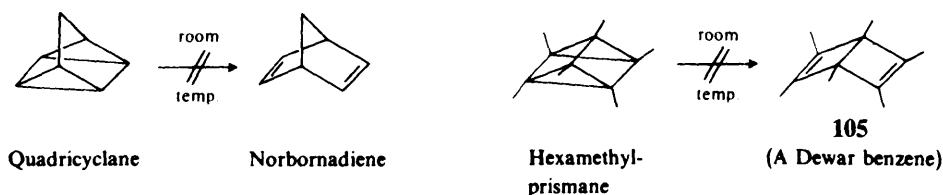
<sup>997</sup>For a review, see Gassman *Acc. Chem. Res.* **1971**, 4, 128-136.

<sup>998</sup>Cairncross; Blanchard *J. Am. Chem. Soc.* **1966**, 88, 496.

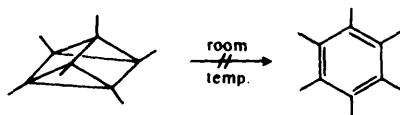
<sup>999</sup>Gassman; Mansfield; Murphy *J. Am. Chem. Soc.* **1969**, 91, 1684.

a diradical mechanism. Photochemical<sup>1000</sup> and metal-catalyzed<sup>1001</sup> „2 + „2 cycloadditions have also been reported.

In 5-47 we used the principle of conservation of orbital symmetry to explain why certain reactions take place readily and others do not. The orbital-symmetry principle can also explain why certain molecules are stable though highly strained. For example, quadricyclane and hexamethylprismane<sup>1002</sup> are thermodynamically much less stable (because much more strained) than their corresponding isomeric dienes, norbornadiene and hexamethylbicyclo[2.2.0]hexadiene (**105**).<sup>1003</sup> Yet the former two compounds can be kept indefinitely at



room temperature, although in the absence of orbital-symmetry considerations it is not easy to understand why the electrons simply do not move over to give the more stable diene isomers. The reason is that both these reactions involve the conversion of a cyclobutane ring to a pair of double bonds (a „2 + „2 process) and, as we have seen, a thermal process of this sort is forbidden by the Woodward–Hoffmann rules. The process is allowed photochemically, and we are not surprised to find that both quadricyclane and hexamethylprismane are photochemically converted to the respective dienes at room temperature or below.<sup>1004</sup> It is also possible to conceive of simple bond rearrangements whereby hexamethylprismane is converted to hexamethylbenzene, which of course is far more stable than either hexa-



methylprismane or **105**. It has been calculated that hexamethylbenzene is at least 90 kcal/mol (380 kJ/mol) more stable than hexamethylprismane. The fact that hexamethylprismane does not spontaneously undergo this reaction has prompted the observation<sup>1005</sup> that the prismane has “the aspect of an angry tiger unable to break out of a paper cage.” However, a correlation diagram for this reaction<sup>1005</sup> discloses that it too is a symmetry-forbidden process. All three of these “forbidden” reactions do take place when the compounds are heated, but the diradical mechanism is likely under these conditions.<sup>1006</sup>

<sup>1000</sup>Freeman; Balls *J. Org. Chem.* **1967**, 32, 2354; Wiskott; Schleyer *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 694 [*Angew. Chem.* 79, 680]; Prinzbach; Eberbach *Chem. Ber.* **1968**, 101, 4083; Prinzbach; Sedelmeier; Martin *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 103 [*Angew. Chem.* 89, 111].

<sup>1001</sup>See, for example, Volger; Hogeveen; Gaasbeek *J. Am. Chem. Soc.* **1969**, 91, 218; Katz; Cereface *J. Am. Chem. Soc.* **1969**, 91, 2405, 6519.

<sup>1002</sup>This compound can be prepared by photolysis of **105**, another example of an intramolecular photochemical 2 + 2 cycloaddition: Lemal; Lokensgard *J. Am. Chem. Soc.* **1966**, 88, 5934; Schäfer; Criegee; Askani; Grüner *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 78 [*Angew. Chem.* 79, 54].

<sup>1003</sup>For a review of this compound, see Schäfer; Hellmann *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 518-525 [*Angew. Chem.* 79, 566-573].

<sup>1004</sup>These conversions can also be carried out by the use of transition metal catalysts: Hogeveen; Volger *Chem. Commun.* **1967**, 1133; *J. Am. Chem. Soc.* **1967**, 89, 2486; Kaiser; Childs; Maitlis *J. Am. Chem. Soc.* **1971**, 93, 1270; Landis; Gremaud; Patrick *Tetrahedron Lett.* **1982**, 23, 375; Maruyama; Tamiaki *Chem. Lett.* **1987**, 683.

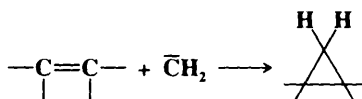
<sup>1005</sup>Woodward; Hoffmann *Ref.* 895, pp. 107-112.

<sup>1006</sup>See, for example, Oth *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 1185.

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.<sup>1007</sup> These compounds actually have the structures that were proposed for benzenes in the nineteenth century. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the Dewar formula. Because of this bicyclo[2.2.0]hexadiene is often called Dewar benzene. On p. 26 it was mentioned that Dewar formulas are canonical forms (though not very important) of benzenes. Yet they also exist as separate compounds in which the positions of the nuclei are different from those of benzenes.

OS V, 54, 235, 277, 297, 370, 393, 424, 459, 528; VI, 378, 571, 962, 1002, 1024, 1037; VII, 177, 256, 315; 68, 32, 41; 69, 199, 205. For the reverse reaction, see OS V, 734.

## 5-50 The Addition of Carbenes and Carbenoids to Double and Triple Bonds *epi-Methylene-addition*



Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives (1 + 2 cycloaddition).<sup>1008</sup> Many derivatives of carbene, e.g., PhCH, ROCH,<sup>1009</sup> Me<sub>2</sub>C=C, C(CN)<sub>2</sub>, have been added to double bonds, but the reaction is most often performed with CH<sub>2</sub> itself, with halo and dihalocarbenes,<sup>1010</sup> and with carbalkoxycarbenes<sup>1011</sup> (generated from diazoacetic esters). Alkylcarbenes HCR have been added to olefins,<sup>1012</sup> but more often these rearrange to give olefins (p. 201). The carbene can be generated in any of the ways normally used (p. 198). However, most reactions in which a cyclopropane is formed by treatment of an olefin with a carbene "precursor" do not actually involve free carbene intermediates. In some cases it is certain that free carbenes are not involved, and in other cases there is doubt. Because of this, the term *carbene transfer* is often used to cover all reactions in which a double bond is converted to a cyclopropane, whether a carbene or a carbenoid (p. 199) is actually involved.

Carbene itself is extremely reactive and gives many side reactions, especially insertion reactions (2-20), which greatly reduce yields. When it is desired to add CH<sub>2</sub> for preparative purposes, free carbene is not used, but the Simmons-Smith procedure (p. 870) or some other method that does not involve free carbenes is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere.<sup>1013</sup> A few of the many ways<sup>1014</sup> in which halocarbenes or carbenoids are

<sup>1007</sup>For reviews of valence isomers of benzene, see Kobayashi; Kumadaki *Adv. Heterocycl. Chem.* **1982**, 31, 169-206. *Acc. Chem. Res.* **1981**, 14, 76-82; van Tamelen *Acc. Chem. Res.* **1972**, 5, 186-192. *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 738-745 [*Angew. Chem.* 77, 759-767]; Bolesov *Russ. Chem. Rev.* **1968**, 37, 666-670; Viehe *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 746-751 [*Angew. Chem.* 77, 768-773]; Ref. 1003.

<sup>1008</sup>For reviews, see, in Rappoport *The Chemistry of the Cyclopropyl Group*; Wiley: New York, 1987, the reviews by Tsuji; Nishida, pt. 1, pp. 307-373; Verhé; De Kimpe, pt. 1, pp. 445-564; Marchand, in Patai, Ref. 1, pt. 1, pp. 534-607, 625-635; Bethell, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 101-113; in Patai, Ref. 36, the articles by Cadogan; Perkins, pp. 633-671; Huisgen; Grashey; Sauer, pp. 755-776; Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971, pp. 85-122, 267-406. For a review of certain intramolecular additions, see Burke; Grieco *Org. React.* **1979**, 26, 361-475. For a list of reagents, with references, see Ref. 133, pp. 71-79.

<sup>1009</sup>For a review, see Schöllkopf *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 588-598 [*Angew. Chem.* 80, 603-613].

<sup>1010</sup>For a review of the addition of halocarbenes, see Parham; Schweizer *Org. React.* **1963**, 13, 55-90.

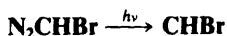
<sup>1011</sup>For a review, see Dave; Warnhoff *Org. React.* **1970**, 18, 217-401.

<sup>1012</sup>For example see Frey *J. Chem. Soc.* **1962**, 2293.

<sup>1013</sup>For reviews of carbene selectivity in this reaction, see Moss *Acc. Chem. Res.* **1989**, 22, 15-21, **1980**, 13, 58-64. For a review with respect to halocarbenes, see Kostikov; Molchanov; Khlebnikov *Russ. Chem. Rev.* **1989**, 58, 654-666.

<sup>1014</sup>Much of the work in this field has been carried out by Seyferth and co-workers; see, for example, Seyferth; Burlitch; Minasz; Mui; Simmons; Treiber; Dowd *J. Am. Chem. Soc.* **1965**, 87, 4259; Seyferth; Haas *J. Organomet. Chem.* **1972**, 46, C33, *J. Org. Chem.* **1975**, 40, 1620; Seyferth; Hopper *J. Org. Chem.* **1972**, 37, 4070, *J. Organomet. Chem.* **1973**, 51, 77; Seyferth; Haas; Dagani *J. Organomet. Chem.* **1976**, 104, 9.

generated for this reaction are the following,<sup>1015</sup> most of which involve formal elimination (the first two steps of the  $\text{S}_{\text{N}}1\text{CB}$  mechanism, p. 356):

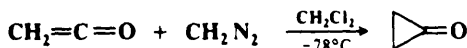


The reaction between  $\text{CHCl}_3$  and  $\text{OH}^-$  is often carried out under phase transfer conditions.<sup>1019</sup> It has been shown that the reaction between  $\text{PhCHCl}_2$  and  $t\text{-BuOK}$  produces a carbenoid, but when the reaction is run in the presence of a crown ether, the free  $\text{PhCCl}$  is formed instead.<sup>1020</sup> Dihalocyclopropanes are very useful compounds<sup>1021</sup> that can be reduced to cyclopropanes, treated with magnesium or sodium to give allenes (**8-3**), or converted to a number of other products.

Olefins of all types can be converted to cyclopropane derivatives by this reaction (though difficulty may be encountered with sterically hindered ones).<sup>1022</sup> Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.<sup>1023</sup> Conjugated dienes give 1,2 addition:<sup>1024</sup>



Addition of a second mole gives bicyclopentyl derivatives.<sup>1025</sup> 1,4 addition is rare but has been reported in certain cases.<sup>1026</sup> Carbene adds to ketene to give cyclopropanone.<sup>1027</sup>



<sup>1015</sup>A much longer list, with references, is given in Kirmse, *Carbene Chemistry*, Ref. 1008, pp. 313-319. See also Ref. 133, pp. 73-75.

<sup>1016</sup>For a review of the use of phenyl(trihalomethyl)mercury compounds as dihalocarbene or dihalocarbenoid precursors, see Seyferth *Acc. Chem. Res.* **1972**, *5*, 65-74. For a review of the synthesis of cyclopropanes with the use of organomercury reagents, see Larock, Ref. 539, pp. 341-380.

<sup>1017</sup>For reviews of fluorinated carbenes, see Seyferth in Moss; Jones *Carbenes*, vol. 2; Wiley: New York, 1975, pp. 101-158; Sheppard; Sharts *Organic Fluorine Chemistry*; W. A. Benjamin: New York, 1969, pp. 237-270.

<sup>1018</sup>Dolbier; Burkholder *Tetrahedron Lett.* **1988**, *29*, 6749.

<sup>1019</sup>For reviews of the use of phase-transfer catalysis in the addition of dihalocarbenes to  $\text{C}=\text{C}$  bonds, see Starks; Liotta *Phase Transfer Catalysis*; Academic Press: New York, 1978, pp. 224-268; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*; Springer: New York, 1977, pp. 18-43, 58-62. For a discussion of the mechanism, see Gol'dberg; Shimanskaya *J. Org. Chem. USSR* **1984**, *20*, 1212.

<sup>1020</sup>Moss; Pilkievicz *J. Am. Chem. Soc.* **1974**, *96*, 5632; Moss; Lawrynowicz *J. Org. Chem.* **1984**, *49*, 3828.

<sup>1021</sup>For reviews of dihalocyclopropanes, see Banwell; Reum *Adv. Strain Org. Chem.* **1991**, *1*, 19-64; Kostikov; Molchanov; Hopf *Top. Curr. Chem.* **1990**, *155*, 41-80; Weyerstahl, in Patai; Rappoport, Ref. 614, pt. 2, pp. 1451-1497; Barlet; Vo-Quang *Bull. Soc. Chim. Fr.* **1969**, 3729-3760.

<sup>1022</sup>Dehmlo; Eulenberger *Liebigs Ann. Chem.* **1979**, 1112.

<sup>1023</sup>Cairns; McKusick *Angew. Chem.* **1961**, *73*, 520.

<sup>1024</sup>Woodworth; Skell *J. Am. Chem. Soc.* **1957**, *79*, 2542.

<sup>1025</sup>Orchin; Herrick *J. Org. Chem.* **1959**, *24*, 139; Nakhapetyan; Safonova; Kazanskii *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1962**, 840; Skattebøl *J. Org. Chem.* **1964**, *29*, 2951.

<sup>1026</sup>Anastassiou; Cellura; Ciganek *Tetrahedron Lett.* **1970**, 5267; Jefford; Mareda; Gehret; Kabengele; Graham; Burger *J. Am. Chem. Soc.* **1976**, *98*, 2585; Mayr; Heigl *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 579 [*Angew. Chem.* **97**, 567]; Jenneskens; de Wolf; Bickelhaupt *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 585 [*Angew. Chem.* **97**, 568]; Le; Jones; Bickelhaupt; de Wolf *J. Am. Chem. Soc.* **1989**, *111*, 8491; Kraakman; de Wolf; Bickelhaupt *J. Am. Chem. Soc.* **1989**, *111*, 8534; Hudlicky; Seoane; Price; Gadamasetti *Synlett* **1990**, 433; Lambert; Ziernicka-Merchant *J. Org. Chem.* **1990**, *55*, 3460.

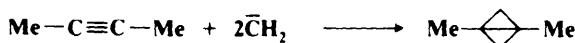
<sup>1027</sup>Turro; Hammond *Tetrahedron* **1968**, *24*, 6017; Rothgery; Holt; McGee *J. Am. Chem. Soc.* **1975**, *97*, 4971. For a review of cyclopropanones, see Wasserman; Berdahl; Lu, in Rappoport, Ref. 1008, pt. 2, pp. 1455-1532.

Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation:<sup>1028</sup>

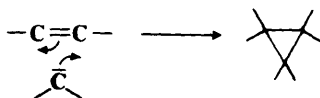


A second mole gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.<sup>1029</sup>

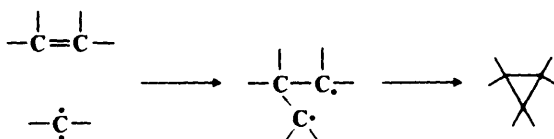
Triple-bond compounds<sup>1030</sup> react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they rearrange to allenes.<sup>1031</sup> Cyclopropenones (p. 53) are obtained by hydrolysis of dihalocyclopropenes.<sup>1032</sup> It has proved possible to add 2 moles of a carbene to an alkyne to give a bicyclobutane:<sup>1033</sup>



Most carbenes are electrophilic, and, in accord with this, electron-donating substituents on the olefin increase the rate of the reaction, and electron-withdrawing groups decrease it,<sup>1034</sup> though the range of relative rates is not very great.<sup>1035</sup> As discussed on p. 196, carbenes in the singlet state (which is the most common state) react stereospecifically and syn,<sup>1036</sup> probably by a one-step mechanism,<sup>1037</sup> similar to mechanism *a* of 5-47 and 5-49:



Infrared spectra of a carbene and the cyclopropane product have been observed in an argon matrix at 12 to 45 K.<sup>1038</sup> Carbenes in the triplet state react nonstereospecifically,<sup>1039</sup> probably by a diradical mechanism, similar to mechanism *b* of 5-47 and 5-49:



<sup>1028</sup>For reviews of the addition of carbenes and carbenoids to allenes, see Landor, in Landor, Ref. 95, vol. 2, pp. 351-360; Bertrand *Bull. Soc. Chim. Fr.* **1968**, 3044-3054. For a review of the synthetic uses of methylenecyclopropanes and cyclopropenes, see Binger; Büch *Top. Curr. Chem.* **1967**, 135, 77-151.

<sup>1029</sup>For a review of the preparation of spiro compounds by this reaction, see Krapcho *Synthesis* **1978**, 77-126.

<sup>1030</sup>For reviews, see Fuks; Viehe, in Viehe, Ref. 49, pp. 427-434; Closs *Adv. Alicyclic Chem.* **1966**, 1, 53-127, pp. 58-65.

<sup>1031</sup>Frey *Chem. Ind. (London)* **1960**, 1266.

<sup>1032</sup>Vol'pin; Koreschkov; Kursanov *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1959**, 535.

<sup>1033</sup>Doering; Coburn *Tetrahedron Lett.* **1965**, 991. Also see Mahler *J. Am. Chem. Soc.* **1962**, 84, 4600.

<sup>1034</sup>Skell; Garner *J. Am. Chem. Soc.* **1956**, 78, 5430; Doering; Henderson *J. Am. Chem. Soc.* **1958**, 80, 5274; Mitsch; Rodgers *Int. J. Chem. Kinet.* **1969**, 1, 439.

<sup>1035</sup>For a review of reactivity in this reaction, with many comprehensive tables of data, see Moss in Jones; Moss *Carbenes*, vol. 1; Wiley: New York, 1973, pp. 153-304. See also Cox; Gould; Hacker; Moss; Turro *Tetrahedron Lett.* **1983**, 24, 5313.

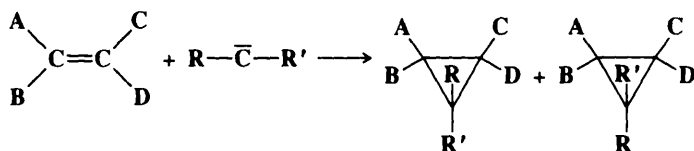
<sup>1036</sup>Woodworth; Skell *J. Am. Chem. Soc.* **1959**, 81, 3383; Jones; Ando; Hendrick; Kulczycki; Howley; Hummel; Malament *J. Am. Chem. Soc.* **1972**, 94, 7469.

<sup>1037</sup>For evidence that at least some singlet carbenes add by a two-step mechanism, see Giese; Lee; Neumann *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 310 [*Angew. Chem.* **94**, 320].

<sup>1038</sup>Nefedov; Zuev; Maltsev; Tomilov *Tetrahedron Lett.* **1989**, 30, 763.

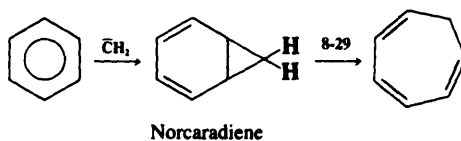
<sup>1039</sup>Skell; Klebe *J. Am. Chem. Soc.* **1960**, 82, 247. See also Jones; Tortorelli; Gaspar; Lambert *Tetrahedron Lett.* **1978**, 4257.

For carbenes or carbenoids of the type  $R-\bar{C}-R'$  there is another aspect of stereochemistry.<sup>1040</sup> When these species are added to all but symmetrical olefins, two isomers are possible, even if the four groups originally on the double-bond carbons maintain their configurations:



Which isomer is predominantly formed depends on  $R$ ,  $R'$ , and on the method by which the carbene or carbenoid is generated. Most studies have been carried out on monosubstituted species ( $R' = H$ ), and in these studies it is found that aryl groups generally prefer the more substituted side (syn addition) while carbethoxy groups usually show anti stereoselectivity. When  $R = \text{halogen}$ , free halocarbenes show little or no stereochemical preference, while halocarbenoids exhibit a preference for syn addition. Beyond this, it is difficult to make simple generalizations.

Carbenes are so reactive that they add to the "double bonds" of aromatic rings. The products are usually not stable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene.<sup>1041</sup>



but not all carbenes are reactive enough to add to benzene. The norcaradiene intermediate cannot be isolated in this case<sup>1042</sup> (it undergoes an electrocyclic rearrangement, 8-29), though certain substituted norcaradienes, e.g., the product of addition of  $\text{C}(\text{CN})_2$  to benzene,<sup>1043</sup> have been isolated.<sup>1044</sup> With  $\text{CH}_2$ , insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding  $\text{CH}_2$  to benzene rings without the use of free carbene is the catalytic decomposition of  $\text{CH}_2\text{N}_2$  in the aromatic compound as solvent with  $\text{CuCl}$  or  $\text{CuBr}$ .<sup>1045</sup> By this method better yields of cycloheptatrienes are obtained without insertion side products.  $\text{CHCl}$  is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density.

<sup>1040</sup>For reviews of the stereochemistry of carbene and carbenoid addition to double bonds, see Moss *Sel. Org. Transform.* **1970**, 1, 35-88; Closs *Top Stereochem.* **1968**, 3, 193-235. For a discussion of enantioselectivity in this reaction, see Nakamura *Pure App. Chem.* **1978**, 50, 37.

<sup>1041</sup>Doering; Knox *J. Am. Chem. Soc.* **1951**, 75, 297.

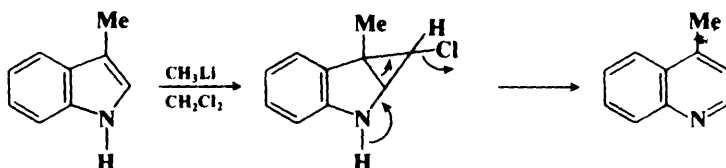
<sup>1042</sup>It has been detected by uv spectroscopy: Rubin *J. Am. Chem. Soc.* **1981**, 103, 7791.

<sup>1043</sup>Ciganek *J. Am. Chem. Soc.* **1967**, 89, 1454.

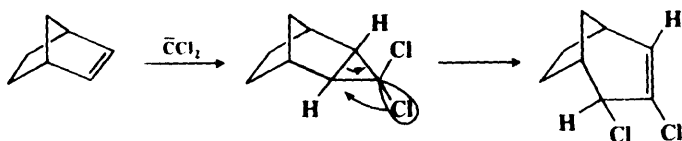
<sup>1044</sup>See, for example, Mukai; Kubota; Toda *Tetrahedron Lett.* **1967**, 3581; Maier; Heep *Chem. Ber.* **1968**, 101, 1371; Ciganek *J. Am. Chem. Soc.* **1971**, 93, 2207; Dürr; Kober *Tetrahedron Lett.* **1972**, 1255, 1259; Vogel; Wiedemann; Roth; Eimer; Günther *Liebigs Ann. Chem.* **1972**, 759, 1; Bannerman; Cadogan; Gosney; Wilson *J. Chem. Soc., Chem. Commun.* **1975**, 618; Takeuchi; Kitagawa; Senzaki; Okamoto *Chem. Lett.* **1983**, 73; Kawase; Iyoda; Oda *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 559 [*Angew. Chem.* 99, 572].

<sup>1045</sup>Wittig; Schwarzenbach *Liebigs Ann. Chem.* **1961**, 650, 1; Müller; Fricke *Liebigs Ann. Chem.* **1963**, 661, 38; Müller; Kessler; Fricke; Kiedaisch *Liebigs Ann. Chem.* **1961**, 675, 63.

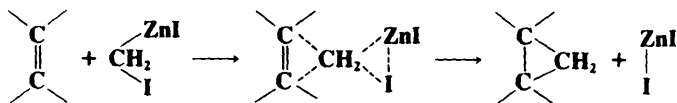
Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes,<sup>1046</sup> e.g.,



In such cases a side reaction that sometimes occurs is expansion of the *six-membered* ring. Ring expansion can occur even with nonaromatic compounds, when the driving force is supplied by relief of strain,<sup>1047</sup> e.g.,



As previously mentioned, free carbene is not very useful for additions to double bonds since it gives too many side products. The *Simmons-Smith procedure* accomplishes the same result without a free carbene intermediate and without insertion side products.<sup>1048</sup> This procedure involves treatment of the double-bond compound with  $\text{CH}_2\text{I}_2$  and a Zn-Cu couple and leads to cyclopropane derivatives in good yields.<sup>1049</sup> The Zn-Cu couple can be prepared in several ways,<sup>1050</sup> of which heating Zn dust with CuCl in ether under nitrogen<sup>1051</sup> is particularly convenient. The reaction has also been done with unactivated zinc and ultrasound.<sup>1052</sup> When  $\text{TiCl}_4$  is used along with Zn and CuCl,  $\text{CH}_2\text{I}_2$  can be replaced by the cheaper  $\text{CH}_2\text{Br}_2$ .<sup>1053</sup> The actual attacking species is an organozinc intermediate, probably  $(\text{ICH}_2)_2\text{Zn} \cdot \text{ZnI}_2$ . This intermediate is stable enough for solutions of it to be isolable.<sup>1054</sup> An x-ray crystallographic investigation of the intermediate, complexed with a diether, has been reported.<sup>1055</sup> The addition is stereospecifically syn, and a concerted mechanism is likely, perhaps<sup>1056</sup>



<sup>1046</sup>For a review of the reactions of heterocyclic compounds with carbenes, see Rees; Smithen *Adv. Heterocycl. Chem.* **1964**, 3, 57-78.

<sup>1047</sup>Jefford; Gunsher; Hill; Brun; Le Gras; Waegell *Org. Synth.* VI, 142. For a review of the addition of halocarbenes to bridged bicyclic olefins see Jefford *Chimia* **1970**, 24, 357-363.

<sup>1048</sup>For reviews, see Simmons; Cairns; Vladuchick; Hoiness *Org. React.* **1973**, 20, 1-131; Furukawa; Kawabata *Adv. Organomet. Chem.* **1974**, 12, 83-134, pp. 84-103.

<sup>1049</sup>Simmons; Smith *J. Am. Chem. Soc.* **1959**, 81, 4256.

<sup>1050</sup>Shank; Shechter *J. Org. Chem.* **1959**, 24, 1525; LeGoff *J. Org. Chem.* **1964**, 29, 2048. For the use of a Zn-Cu couple, see Denis; Girard; Conia *Synthesis* **1972**, 549.

<sup>1051</sup>Rawson; Harrison *J. Org. Chem.* **1970**, 35, 2057.

<sup>1052</sup>Repič; Vogt *Tetrahedron Lett.* **1982**, 23, 2729; Repič; Lee; Giger *Org. Prep. Proced. Int.* **1984**, 16, 25.

<sup>1053</sup>Friedrich; Lunetta; Lewis *J. Org. Chem.* **1989**, 54, 2388.

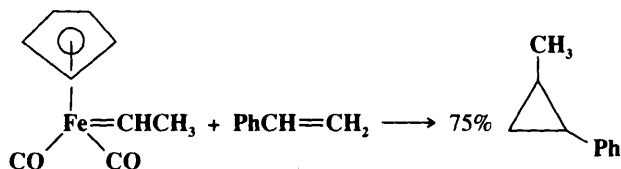
<sup>1054</sup>Blanchard; Simmons *J. Am. Chem. Soc.* **1964**, 86, 1337.

<sup>1055</sup>Denmark; Edwards; Wilson *J. Am. Chem. Soc.* **1991**, 113, 723.

<sup>1056</sup>Simmons; Blanchard; Smith *J. Am. Chem. Soc.* **1964**, 86, 1347.

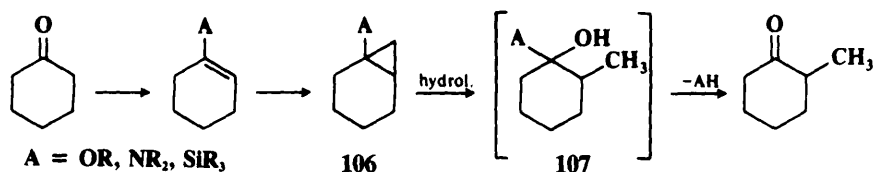
With the Simmons–Smith procedure, as with free carbenes, conjugated dienes give 1,2 addition,<sup>1057</sup> and allenes give methylenecyclopropanes or spiropentanes. An alternative way of carrying out the Simmons–Smith reaction is by treatment of the substrate with  $\text{CH}_2\text{I}_2$  or another dihalomethane and  $\text{Et}_2\text{Zn}$  in ether. This method can be adapted to the introduction of  $\text{RCH}$  and  $\text{ArCH}$  by the use of  $\text{RCH}_2\text{I}$  or  $\text{ArCH}_2\text{I}$  instead of the dihalomethane.<sup>1058</sup> In another method,  $\text{CH}_2\text{I}_2$  or  $\text{MeCH}_2\text{I}$  is used along with an alane  $\text{R}_3\text{Al}$  to transfer  $\text{CH}_2$  or  $\text{MeCH}$ .<sup>1059</sup> For the conversion of enolates to cyclopropanols,  $\text{CH}_2\text{I}_2$  has been used along with  $\text{SmI}_2$ .<sup>1060</sup>

Free carbenes can also be avoided by using transition metal–carbene complexes  $\text{L}_n\text{M}=\text{CRR}'$  ( $\text{L}$  = a ligand,  $\text{M}$  = a metal), which add the group  $\text{CRR}'$  to double bonds.<sup>1061</sup> An example is<sup>1062</sup>



These complexes can be isolated in some cases; in others they are generated in situ from appropriate precursors, of which diazo compounds are among the most important. These compounds, including  $\text{CH}_2\text{N}_2$  and others, react with metals or metal salts (copper, palladium, and rhodium are most commonly used) to give the carbene complexes that add  $\text{CRR}'$  to double bonds.<sup>1063</sup> Optically active complexes have been used for enantioselective cyclopropane synthesis.<sup>1064</sup>

The Simmons–Smith reaction has been used as the basis of a method for the indirect  $\alpha$  methylation of a ketone.<sup>1065</sup> The ketone (illustrated for cyclohexanone) is first converted to an enol ether, e.g., by **6-6**, or to an enamine (**6-14**) or silyl enol ether (**2-23**). Application of the Simmons–Smith reaction gives the norcarane derivative **106**, which is then cleaved



<sup>1057</sup>Overberger; Halek *J. Org. Chem.* **1963**, 28, 867.

<sup>1058</sup>Furukawa; Kawabata; Nishimura *Tetrahedron Lett.* **1968**, 24, 53, *Tetrahedron Lett.* **1968**, 3495; Nishimura; Kawabata; Furukawa *Tetrahedron* **1969**, 25, 2647; Miyano; Hashimoto *Bull. Chem. Soc. Jpn.* **1973**, 46, 892; Friedrich; Biresaw *J. Org. Chem.* **1982**, 47, 1615.

<sup>1059</sup>Maruoka; Fukutani; Yamamoto *J. Org. Chem.* **1985**, 50, 4412, *Org. Synth.* 67, 176.

<sup>1060</sup>Imamoto; Takiyama *Tetrahedron Lett.* **1987**, 28, 1307. See also Molander; Harring *J. Org. Chem.* **1989**, 54, 3525.

<sup>1061</sup>For reviews, see Helquist *Adv. Met.-Org. Chem.* **1991**, 2, 143-194; Brookhart; Studabaker *Chem. Rev.* **1987**, 87, 411-432; Syatkovskii; Babitskii *Russ. Chem. Rev.* **1984**, 53, 672-682.

<sup>1062</sup>Brookhart; Tucker; Husk *J. Am. Chem. Soc.* **1983**, 105, 258.

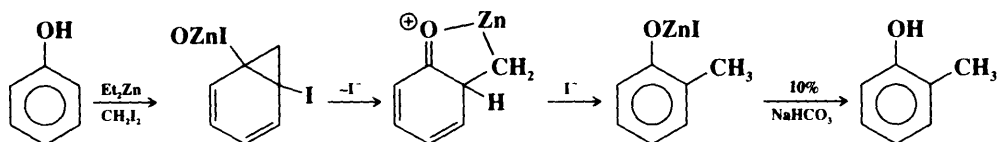
<sup>1063</sup>For reviews, see Adams; Spero *Tetrahedron* **1991**, 47, 1765-1808; Collman et al., Ref. 223, pp. 800-806; Maas *Top. Curr. Chem.* **1987**, 137, 75-253; Doyle *Chem. Rev.* **1986**, 86, 919-939, *Acc. Chem. Res.* **1986**, 19, 348-356; Heck, Ref. 568, pp. 401-407; Wulfsberg; Poling *React. Intermed. (Plenum)* **1980**, 1, 321-512; Müller; Kessler; Zeeh *Fortschr. Chem. Forsch.* **1966**, 7, 128-171.

<sup>1064</sup>Brookhart; Liu *Organometallics* **1989**, 8, 1572, *J. Am. Chem. Soc.* **1991**, 113, 939; Brookhart; Liu; Goldman; Timmers; Williams *J. Am. Chem. Soc.* **1991**, 113, 927; Lowenthal; Abiko; Masamune *Tetrahedron Lett.* **1990**, 31, 6005; Evans; Woerpel; Hinman; Faul *J. Am. Chem. Soc.* **1991**, 113, 726. For asymmetric Simmons–Smith reactions, see Mori; Arai; Yamamoto *Tetrahedron* **1986**, 42, 6447; Mash; Nelson; Heidt *Tetrahedron Lett.* **1987**, 28, 1865; Sugimura; Futagawa; Yoshikawa; Tai *Tetrahedron Lett.* **1989**, 30, 3807. See also Ojima; Clos; Bastos, Ref. 232, pp. 6919-6921.

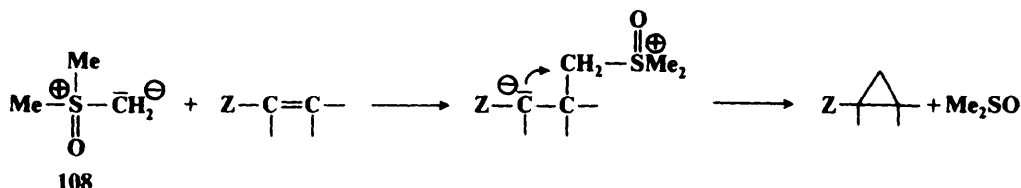
<sup>1065</sup>See Wenkert; Mueller; Reardon; Sathe; Scharf; Tosi *J. Am. Chem. Soc.* **1970**, 92, 7428 for the enol ether procedure; Kuehne; King *J. Org. Chem.* **1973**, 38, 304 for the enamine procedure; Conia *Pure Appl. Chem.* **1975**, 43, 317-326 for the silyl ether procedure.

(addition of water to a cyclopropane ring) to an intermediate **107**, which loses ROH, RNH<sub>2</sub>, or R<sub>3</sub>SiH, producing the methylated ketone. Cleavage of **106** is carried out by acid hydrolysis if A is OR, by basic hydrolysis if A is SiR<sub>3</sub>,<sup>1066</sup> and by neutral hydrolysis in aqueous methanol if A is NR<sub>2</sub>.

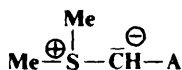
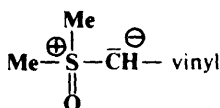
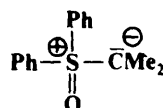
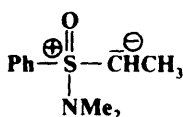
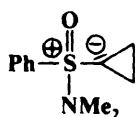
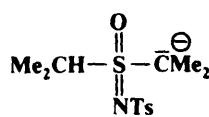
In another variation, phenols can be ortho-methylated in one laboratory step, by treatment with Et<sub>2</sub>Zn and CH<sub>2</sub>I<sub>2</sub>.<sup>1067</sup> The following mechanism was proposed:



Double-bond compounds that undergo the Michael reaction (5-17) can be converted to cyclopropane derivatives with sulfur ylides.<sup>1068</sup> Among the most common of these is dimethyloxosulfonium methylide (**108**),<sup>1069</sup> which is widely used to transfer CH<sub>2</sub> to activated



double bonds, but other sulfur ylides, e.g., **109** (A = acyl,<sup>1070</sup> carbethoxy<sup>1071</sup>), **110**,<sup>1072</sup> and **111**,<sup>1073</sup> which transfer CHA, CH—vinyl, and CMe<sub>2</sub>, respectively, have also been used. CHR

**109****110****111****112****113****114**

and CR<sub>2</sub> can be added in a similar manner with certain nitrogen-containing compounds. For example, the ylides<sup>1074</sup> **112** and **113** and the carbanion **114** can be used, respectively, to add

<sup>1066</sup>In the case of silyl enol ethers the inner bond can be cleaved with FeCl<sub>3</sub>, giving a ring-enlarged β-chloro ketone: Ito; Fujii; Saegusa *J. Org. Chem.* **1976**, *41*, 2073; *Org. Synth.* VI, 327.

<sup>1067</sup>Lehnert; Sawyer; Macdonald *Tetrahedron Lett.* **1989**, *30*, 5215.

<sup>1068</sup>For a monograph and reviews on sulfur ylides, see Chapter 2, Ref. 53.

<sup>1069</sup>Truce; Badiger *J. Org. Chem.* **1964**, *29*, 3277; Corey; Chaykovsky *J. Am. Chem. Soc.* **1965**, *87*, 1353; Agami; Prevost *Bull. Soc. Chim. Fr.* **1967**, 2299. For a review of this reagent, see Gololobov; Nesmeyanov; Lysenko; Boldeskul *Tetrahedron* **1987**, *43*, 2609-2651.

<sup>1070</sup>Trost *J. Am. Chem. Soc.* **1967**, *89*, 138. See also Nozaki; Takaku; Kondô *Tetrahedron* **1966**, *22*, 2145.

<sup>1071</sup>Payne *J. Org. Chem.* **1967**, *32*, 3351.

<sup>1072</sup>LaRochelle; Trost; Krepski *J. Org. Chem.* **1971**, *36*, 1126; Marino; Kaneko *Tetrahedron Lett.* **1973**, 3971, 3975.

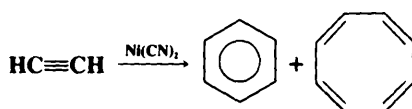
<sup>1073</sup>Corey; Jautelat *J. Am. Chem. Soc.* **1967**, *89*, 3912.

<sup>1074</sup>For a review of sulfoximides R<sub>2</sub>S(O)NR<sub>2</sub> and ylides derived from them, see Kennewell; Taylor *Chem. Soc. Rev.* **1980**, *9*, 477-498.

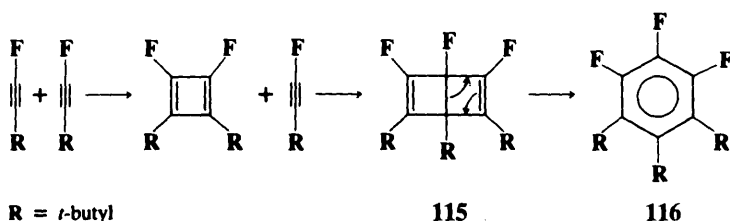
CHMe, cyclopropylidene, and CMe<sub>2</sub> to activated double bonds.<sup>1075</sup> Similar reactions have been performed with phosphorus ylides,<sup>1076</sup> with pyridinium ylides,<sup>1077</sup> and with the compounds (PhS)<sub>3</sub>CLi and Me<sub>3</sub>Si(PhS)<sub>2</sub>CLi.<sup>1078</sup> The reactions with ylides are of course nucleophilic addition.

OS V, 306, 855, 859, 874; VI, 87, 142, 187, 327, 731, 913, 974; VII, 12, 200, 203; 67, 176; 68, 220; 69, 144, 180.

### 5-51 Trimerization and Tetramerization of Alkynes



When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.<sup>1079</sup> It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes. This reaction has been used to prepare very crowded molecules. Diisopropylacetylene was trimerized over Co<sub>2</sub>(CO)<sub>8</sub> and over Hg[Co(CO)<sub>4</sub>]<sub>2</sub> to hexaisopropylbenzene.<sup>1080</sup> The six isopropyl groups are not free to rotate but are lined up perpendicular to the plane of the benzene ring. Even more interesting was the *spontaneous* (no catalyst) trimerization of *t*-BuC≡CF to give 1,2,3-tri-*t*-butyl-4,5,6-trifluorobenzene (**116**), the first time three adjacent *t*-butyl groups had been put onto a benzene ring.<sup>1081</sup> The fact that this is a head-to-head joining makes the following sequence likely:



The fact that **115** (a dewar benzene) was also isolated lends support to this scheme.<sup>1082</sup>

<sup>1075</sup>For reviews, see Johnson *Aldrichimica Acta* **1985**, 18, 1-10, *Acc. Chem. Res.* **1973**, 6, 341-347; Kennewell; Taylor *Chem. Soc. Rev.* **1975**, 4, 189-209; Trost *Acc. Chem. Res.* **1974**, 7, 85-92.

<sup>1076</sup>Bestmann; Seng *Angew. Chem. Int. Ed. Engl.* **1962**, 1, 116 [*Angew. Chem.* 74, 154]; Grieco; Finkelhor *Tetrahedron Lett.* **1972**, 3781.

<sup>1077</sup>Shestopalov; Sharanin; Litvinov; Nefedov *J. Org. Chem. USSR* **1969**, 25, 1000.

<sup>1078</sup>Cohen; Myers *J. Org. Chem.* **1968**, 53, 457.

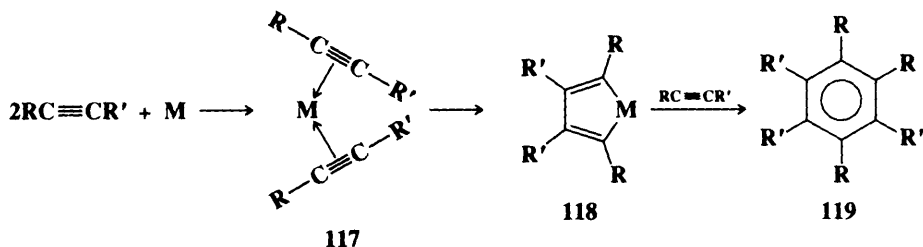
<sup>1079</sup>For reviews, see Winter, in Hartley; Patai, Ref. 422, vol. 3, pp. 259-294; Vollhardt *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 539-556 [*Angew. Chem.* 96, 525-541]; *Acc. Chem. Res.* **1977**, 10, 1-8; Maitlis *J. Organomet. Chem.* **1980**, 200, 161-176, *Acc. Chem. Res.* **1976**, 9, 93-99, *Pure Appl. Chem.* **1972**, 30, 427-448; Yur'eva *Russ. Chem. Rev.* **1974**, 43, 48-68; Khan; Martell, Ref. 159, pp. 163-168; Reppe; Kutepow; Magin *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 727-733 [*Angew. Chem.* 81, 717-723]; Fuks; Viehe, in Viehe, Ref. 49, pp. 450-460; Hoogzand; Hübel, in Wender; Pino *Organic Syntheses Via Metal Carbonyls*, vol. 1; Wiley: New York, 1968, pp. 343-371; Reikhsfel'd; Makovetskii *Russ. Chem. Rev.* **1966**, 35, 510-523. For a list of reagents, with references, see Ref. 133, pp. 100-101. For a review of metal-catalyzed cycloadditions of alkynes to give rings of all sizes, see Schore *Chem. Rev.* **1988**, 88, 1081-1119.

<sup>1080</sup>Arnett; Bollinger *J. Am. Chem. Soc.* **1964**, 86, 4729; Hopff *Chimia* **1964**, 18, 140; Hopff; Gati *Helv. Chim. Acta* **1965**, 48, 509.

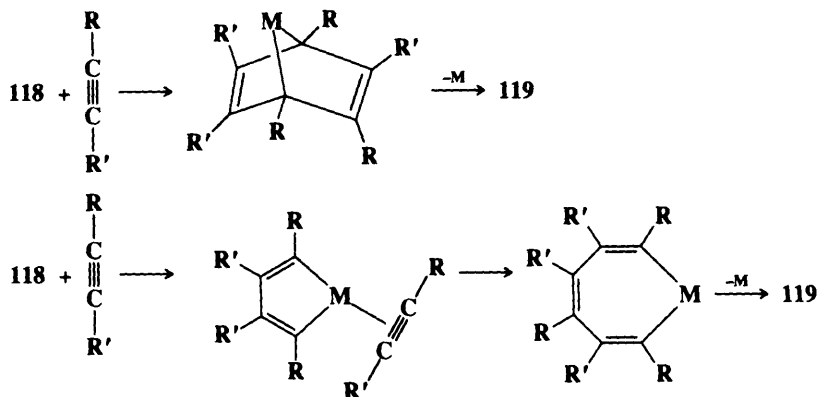
<sup>1081</sup>Viehe; Merényi; Oth; Valange *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 746 [*Angew. Chem.* 76, 888]; Viehe; Merényi; Oth; Senders; Valange *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 755 [*Angew. Chem.* 76, 923].

<sup>1082</sup>For other reactions between cyclobutadienes and triple bonds to give dewar benzenes, see Wingert; Regitz *Chem. Ber.* **1986**, 119, 244.

In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene  $\text{RC}\equiv\text{CH}$ . The chief product is usually the 1,2,4-isomer, with lesser amounts of the 1,3,5-isomer also generally obtained, but little if any of the 1,2,3-isomer. The mechanism of the catalyzed reaction to form benzenes<sup>1083</sup> is believed to go through a species **117** in which two molecules of alkyne coordinate with the



metal, and another species **118**, a five-membered heterocyclic intermediate.<sup>1084</sup> Such intermediates (where  $\text{M} = \text{Rh}$ ,  $\text{Ir}$ , or  $\text{Ni}$ ) have been isolated and shown to give benzenes when treated with alkynes.<sup>1085</sup> Note that this pathway accounts for the predominant formation of the 1,2,4-isomer. Two possibilities for the last step are a Diels-Alder reaction, and a ring expansion, each followed by extrusion of the metal.<sup>1085a</sup>



In at least one case the mechanism is different, going through a cyclobutadiene-nickel complex (p. 55), which has been isolated.<sup>1086</sup>

When benzene, in the gas phase, was adsorbed onto a surface of 10% rhodium-on-alumina, the reverse reaction took place, and acetylene was formed.<sup>1087</sup>

<sup>1083</sup>For studies of the mechanism of the reaction that produces cyclooctatetraenes, see Diercks; Stamp; Kopf; tom Dieck *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 893 [*Angew. Chem.* **96**, 891]; Colborn; Vollhardt *J. Am. Chem. Soc.* **1986**, 108, 5470; Lawrie; Gable; Carpenter *Organometallics* **1989**, 8, 2274.

<sup>1084</sup>See, for example, Colborn; Vollhardt *J. Am. Chem. Soc.* **1981**, 103, 6259; Kochi *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978, pp. 428-432; Collman et al., Ref. 223, pp. 870-877; Eisch; Sexsmith *Res. Chem. Intermed.* **1990**, 13, 149-192.

<sup>1085</sup>See, for example, Collman; Kang *J. Am. Chem. Soc.* **1967**, 89, 844; Collman *Acc. Chem. Res.* **1968**, 1, 136-143; Yamazaki; Hagihara *J. Organomet. Chem.* **1967**, 7, P22; Wakatsuki; Kuramitsu; Yamazaki *Tetrahedron Lett.* **1974**, 4549; Moseley; Maitlis *J. Chem. Soc., Dalton Trans.* **1974**, 169; Müller *Synthesis* **1974**, 761-774; Eisch; Galle *J. Organomet. Chem.* **1975**, 96, C23; McAlister; Bercaw; Bergman *J. Am. Chem. Soc.* **1977**, 99, 1666.

<sup>1085a</sup>There is evidence that the mechanism of the last step more likely resembles the Diels-Alder pathway than the ring expansion pathway: Bianchini et al. *J. Am. Chem. Soc.* **1991**, 113, 5127.

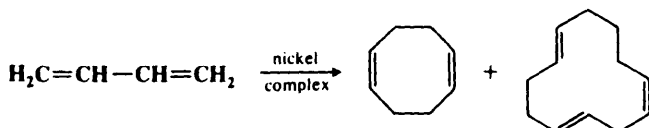
<sup>1086</sup>Mauret; Alphonse *J. Organomet. Chem.* **1984**, 276, 249. See also Pepermans; Willem; Gielen; Hoogzand *Bull. Soc. Chim. Belg.* **1988**, 97, 115.

<sup>1087</sup>Parker; Hexter; Siedle *J. Am. Chem. Soc.* **1985**, 107, 4584.

For addition of triple bonds to triple bonds, but not with ring formation, see 5-15.  
OS VII, 256.

## 5-52 Other Cycloaddition Reactions

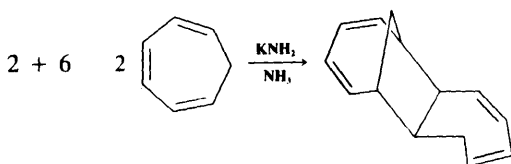
**cyclo-[But-2-en-1,4-diyl]-1/4/addition, etc.**



Conjugated dienes can be dimerized or trimerized at their 1,4 positions (formally, 4 + 4 and 4 + 4 + 4 cycloadditions) by treatment with certain complexes or other transition-metal compounds.<sup>1088</sup> Thus butadiene gives 1,5-cyclooctatriene and 1,5,9-cyclododecatriene.<sup>1089</sup> The relative amount of each product can be controlled by use of the proper catalyst. For example,  $\text{Ni}:\text{P}(\text{OC}_6\text{H}_4\text{-}o\text{-Ph})_3$  gives predominant dimerization, while  $\text{Ni}(\text{cyclooctatriene})_2$  gives mostly trimerization. The products arise, not by direct 1,4 to 1,4 attack, but by stepwise mechanisms involving metal-olefin complexes.<sup>1090</sup>

As we saw in 5-47, the Woodward-Hoffmann rules allow suprafacial concerted cycloadditions to take place thermally if the total number of electrons is  $4n + 2$  and photochemically if the number is  $4n$ . Furthermore, forbidden reactions become allowed if one molecule reacts antarafacially. It would thus seem that syntheses of many large rings could easily be achieved. However, when the newly formed ring is eight-membered or greater, concerted mechanisms, though allowed by orbital symmetry for the cases stated, become difficult to achieve because of the entropy factor (the two ends of one system must simultaneously encounter the two ends of the other), unless one or both components are cyclic, in which case the molecule has many fewer possible conformations. There have been a number of reports of cycloaddition reactions leading to eight-membered and larger rings, some thermally and some photochemically induced, but (apart from the dimerization and trimerization of butadienes mentioned above, which are known not to involve direct 4 + 4 or 4 + 4 + 4 cycloaddition) in most cases evidence is lacking to indicate whether they are concerted or stepwise processes.

Some examples are



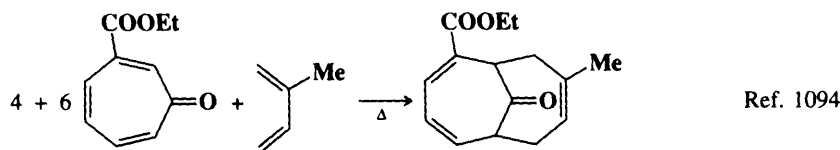
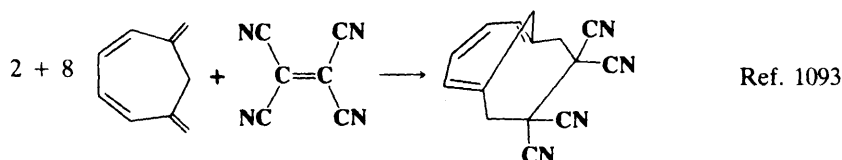
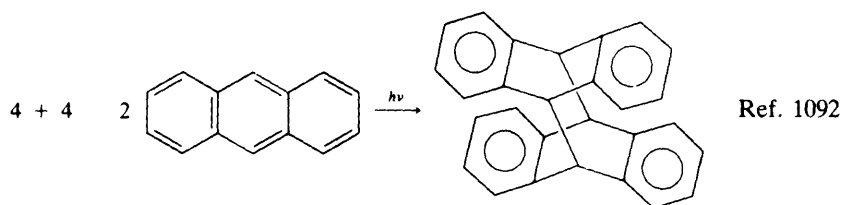
Ref. 1091

<sup>1088</sup>For reviews, see Wilke *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 186-206 [*Angew. Chem.* 100, 189-211], J. *Organomet. Chem.* **1980**, 200, 349-364; Tolstikov; Dzhemilev *Sov. Sci. Rev., Sect. B* **1985**, 7, 237-295, pp. 278-290; Heimbach; Schenklunn *Top. Curr. Chem.* **1980**, 92, 45-108; Heimbach *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 975-989 [*Angew. Chem.* 85, 1035-1049]; Baker *Chem. Rev.* **1973**, 73, 487-530, pp. 489-512; Semmelhack *Org. React.* **1972**, 19, 115-198, pp. 128-143; Heimbach; Jolly; Wilke *Adv. Organomet. Chem.* **1970**, 8, 29-86, pp. 48-83; Khan; Martell, Ref. 159, pp. 159-163; Heck, Ref. 223, pp. 157-164.

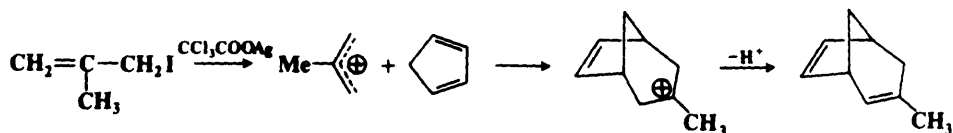
<sup>1089</sup>For a review of the 1,5,9-cyclododecatrienes (there are four stereoisomers, of which the *ttt* is shown above), see Rona *Intra-Sci. Chem. Rep.* **1971**, 5, 105-148.

<sup>1090</sup>For example, see Heimbach; Wilke *Liebigs Ann. Chem.* **1969**, 727, 183; Barnett; Büssemeyer; Heimbach; Jolly; Krüger; Tkatchenko; Wilke *Tetrahedron Lett.* **1972**, 1457; Barker; Green; Howard; Spencer; Stone *J. Am. Chem. Soc.* **1976**, 98, 3373; Graham; Stephenson *J. Am. Chem. Soc.* **1977**, 99, 7098.

<sup>1091</sup>Staley; Orvedal *J. Am. Chem. Soc.* **1974**, 96, 1618. In this case the reagent converted one molecule of cycloheptatriene to the cycloheptatrienyl anion (p. 46), which then added stepwise to the other molecule.

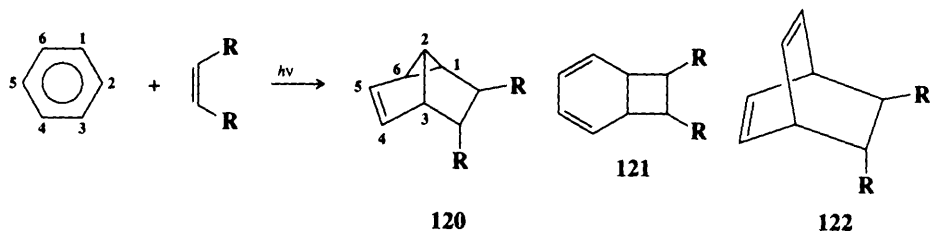


The suprafacial thermal addition of an allylic cation to a diene (a 3 + 4 cycloaddition) is allowed by the Woodward–Hoffmann rules (this reaction would be expected to follow the same rules as the Diels–Alder reaction<sup>1095</sup>). Such cycloadditions can be carried out<sup>1096</sup> by treatment of a diene with an allylic halide in the presence of a suitable silver salt, e.g.,<sup>1097</sup>



This reaction has even been carried out with benzene assuming the role of the diene.<sup>1098</sup>

Benzene rings can undergo photochemical cycloaddition with olefins.<sup>1099</sup> The major product is usually the 1,3 addition product **120** (in which a 3-membered ring has also been formed), though some of the 1,2 product **121** (**5-49**) is sometimes formed as well. (**121** is



<sup>1092</sup>Shönberg, Ref. 49, pp. 97-99.

<sup>1993</sup>Farrant; Feldmann *Tetrahedron Lett.* **1970**, 4979.

<sup>1994</sup>Garst; Roberts; Houk; Rondan *J. Am. Chem. Soc.* **1984**, *106*, 3882.

<sup>1095</sup>Because the HOMO of an allylic cation, p. 33, has the same symmetry as the HOMO of an alkene.

<sup>1984</sup>For reviews of 3 + 4 cycloadditions see Mann *Tetrahedron* **1986**, 42, 4611-4659; Hoffmann *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 1-19, **1973**, 12, 819-835 [*Angew. Chem.* 96, 29-48, 85, 877-894]; Noyori *Acc. Chem. Res.* **1979**, 12, 61-66.

<sup>1997</sup>Hoffmann; Joy; Suter *J. Chem. Soc. B* **1968**, 57.

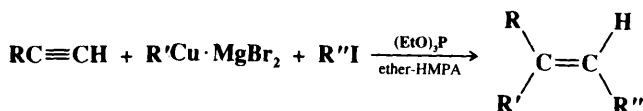
<sup>199</sup>Hoffmann; Hill *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 136 [*Angew. Chem.* **86**, 127].

<sup>1997</sup>For reviews, see Wender; Ternansky; deLong; Singh; Olivero; Rice *Pure Appl. Chem.* **1990**, 62, 1597-1602; Wender; Siggel; Nuss *Org. Photochem.* **1989**, 10, 357-473; Gilbert, in Horspool, Ref. 966, pp. 1-60. For a review of this and related reactions, see McCullough *Chem. Rev.* **1987**, 87, 811-860.

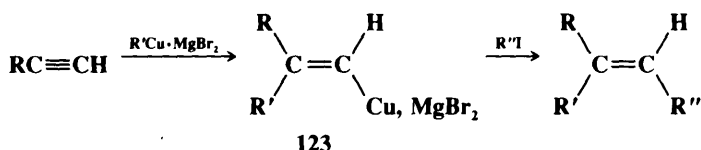
usually the main product where the olefin bears electron-withdrawing groups and the aromatic compound electron-donating groups, or vice versa.) The 1,4 product **122** is rarely formed. The reaction has also been run with benzenes substituted with alkyl, halo, OR, CN, and other groups, and with acyclic and cyclic olefins bearing various groups.<sup>1100</sup>

OS VI, 512; VII, 485.

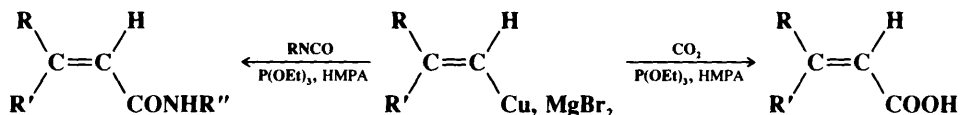
### 5-53 The Addition of Two Alkyl Groups to an Alkyne Dialkyl-addition



Two different alkyl groups can be added to a terminal alkyne<sup>1101</sup> in one laboratory step by treatment with an alkylcopper–magnesium bromide reagent (called *Normant reagents*)<sup>1102</sup> and an alkyl iodide in ether–HMPA containing triethyl phosphite.<sup>1103</sup> The groups add stereoselectively syn. The reaction, which has been applied to primary<sup>1104</sup> R' and to primary, allylic, benzylic, vinylic, and α-alkoxyalkyl R'', involves initial addition of the alkylcopper reagent,<sup>1105</sup> followed by a coupling reaction (0-87):



Acetylene itself (R = H) undergoes the reaction with R<sub>2</sub>CuLi instead of the Normant reagent.<sup>1106</sup> The use of R' containing functional groups has been reported.<sup>1107</sup> If the alkyl iodide is omitted, the vinylic copper intermediate **123** can be converted to a carboxylic acid by the addition of CO<sub>2</sub> (see 6-34) or to an amide by the addition of an isocyanate



(see 6-36), in either case in the presence of HMPA and a catalytic amount of triethyl phosphite.<sup>1108</sup> The use of I<sub>2</sub> results in a vinylic iodide.<sup>1109</sup>

<sup>1100</sup>See the table in Wender; Siggel; Nuss, Ref. 1099, pp. 384-415.

<sup>1101</sup>For reviews of this and related reactions, see Raston; Salem, in Hartley, Ref. 218, vol. 4, pp. 159-306, pp. 233-248; Normant; Alexakis *Synthesis* **1981**, 841-870; Hudrlik, in Patai, Ref. 70, pt. 1 pp. 233-238. For a list of reagents and references for this and related reactions, see Ref. 133, pp. 233-238.

<sup>1102</sup>For the composition of these reagents see Ashby; Smith; Goel *J. Org. Chem.* **1981**, 46, 5133; Ashby; Goel *J. Org. Chem.* **1983**, 48, 2125.

<sup>1103</sup>Normant; Cahiez; Chuit; Alexakis; Villieras *J. Organomet. Chem.* **1972**, 40, C49; Alexakis; Cahiez; Normant; Villieras *Bull. Soc. Chim. Fr.* **1977**, 693; Gardette; Alexakis; Normant *Tetrahedron* **1985**, 41, 5887. For an extensive list of references see Marfat; McGuirk; Helquist *J. Org. Chem.* **1979**, 44, 3888.

<sup>1104</sup>For a method of using secondary and tertiary R, see Rao; Periasamy *Tetrahedron Lett.* **1988**, 29, 4313.

<sup>1105</sup>The initial product, **123**, can be hydrolyzed with acid to give RR'C=CH<sub>2</sub>. See Westmijze; Kleijn; Meijer; Vermeer *Recl. Trav. Chim. Pays-Bas* **1981**, 100, 98, and references cited therein.

<sup>1106</sup>Alexakis; Normant; Villieras *Tetrahedron Lett.* **1976**, 3461; Alexakis; Cahiez; Normant *Synthesis* **1979**, 826, *Tetrahedron* **1980**, 36, 1961; Furber; Taylor; Burford *J. Chem. Soc., Perkin Trans. 1* **1986**, 1809.

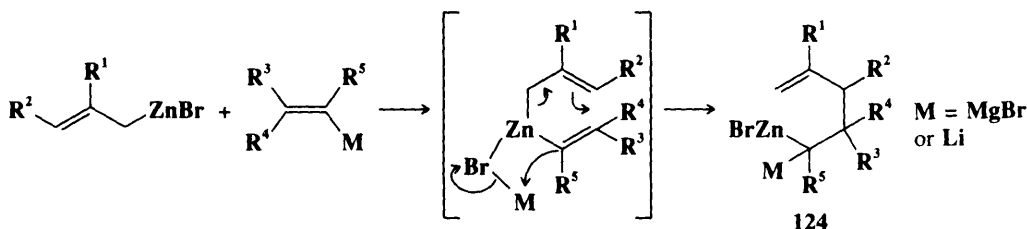
<sup>1107</sup>Rao; Knochel *J. Am. Chem. Soc.* **1991**, 113, 5735.

<sup>1108</sup>Normant; Cahiez; Chuit; Villieras *J. Organomet. Chem.* **1973**, 54, C53.

<sup>1109</sup>Alexakis; Cahiez; Normant *Org. Synth. VII*, 290.

Similar reactions, in which two alkyl groups are added to a triple bond, have been carried out with trialkylalanes  $R_3Al$ , with zirconium complexes as catalysts.<sup>1110</sup>

Allylic zinc bromides add to vinylic Grignard and lithium reagents to give the *gem*-

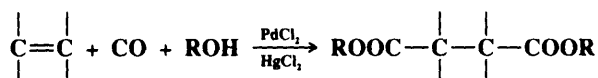


dimetallo compounds **124**. The two metallo groups can be separately reacted with various nucleophiles.<sup>1111</sup>

OS VII, 236, 245, 290.

### 5-54 Dicarboxylation of Olefins and Acetylenes

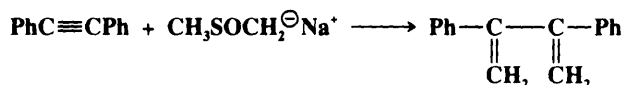
#### Dicarboxy-addition



Alkenes can be converted to succinic esters by reaction with carbon monoxide, an alcohol, and palladium chloride in the presence of mercuric chloride.<sup>1112</sup> The addition is mostly syn. In similar reaction, both terminal and internal alkynes can be converted to esters of maleic acid.

### 5-55 The Conversion of Diphenylacetylene to a Butadiene

#### Dimethylene-biaddition



Diphenylacetylene reacts with methylsulfinyl carbanion to give 2,3-diphenylbutadiene.<sup>1113</sup> Neither the scope nor the mechanism of the reaction seems to have been investigated.

OS VI, 531.

<sup>1110</sup>Yoshida; Negishi *J. Am. Chem. Soc.* **1981**, *103*, 4985; Rand; Van Horn; Moore; Negishi *J. Org. Chem.* **1981**, *46*, 4093; Negishi; Van Horn; Yoshida *J. Am. Chem. Soc.* **1985**, *107*, 6639. For reviews, see Negishi *Acc. Chem. Res.* **1987**, *20*, 65-72; *Pure Appl. Chem.* **1981**, *53*, 2333-2356; Negishi; Takahashi *Aldrichimica Acta* **1985**, *18*, 31-47.

<sup>1111</sup>Knochel; Normant *Tetrahedron Lett.* **1986**, *27*, 1039, 1043, 4427, 4431, 5727.

<sup>1112</sup>Heck *J. Am. Chem. Soc.* **1972**, *94*, 2712. See also Fenton; Steinwand *J. Org. Chem.* **1972**, *37*, 2034; Stille; Divakaruni *J. Org. Chem.* **1979**, *44*, 3474; Catellani; Chiusoli; Peloso *Tetrahedron Lett.* **1983**, *24*, 813; Deprés; Coelho; Greene *J. Org. Chem.* **1985**, *50*, 1972.

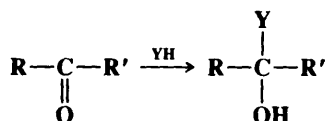
<sup>1113</sup>Iwai; Ide *Org. Synth.* VI, 531.

# 16

## ADDITION TO CARBON-HETERO MULTIPLE BONDS

### MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon-oxygen, carbon-nitrogen, and carbon-sulfur double bonds and the carbon-nitrogen triple bond. The mechanistic study of these reactions is much simpler than that of the additions to carbon-carbon multiple bonds considered in Chapter 15.<sup>1</sup> Most of the questions that concerned us there either do not arise here or can be answered very simply. Since  $C=O$ ,  $C=N$ , and  $C\equiv N$  bonds are strongly polar, with the carbon always the positive end (except for isocyanides, see p. 979), there is never any doubt about the *orientation* of unsymmetrical addition to these bonds. Nucleophilic attacking species always go to the carbon and electrophilic ones to the oxygen or nitrogen. Additions to  $C=S$  bonds are much less common,<sup>2</sup> but in these cases the addition can be in the other direction.<sup>3</sup> For example, thiobenzophenone  $Ph_2C=S$ , when treated with phenyllithium gives, after hydrolysis, benzhydryl phenyl sulfide  $Ph_2CHSPh$ .<sup>4</sup> The *stereochemistry* of addition is not generally a factor because it is not normally possible to determine whether the addition is syn or anti. In addition of  $YH$  to a ketone, e.g.,



the product has a chiral carbon, but unless there is chirality in  $R$  or  $R'$  or  $YH$  is optically active, the product must be a racemic mixture and there is no way to tell from its steric nature whether the addition of  $Y$  and  $H$  was syn or anti. The same holds true for  $C=N$  and  $C=S$  bonds, since in none of these cases can chirality be present at the hetero atom. The stereochemistry of addition of a single  $YH$  to the carbon-nitrogen triple bond could be investigated, since the product can exist in *E* and *Z* forms (p. 127), but these reactions are not very important. Of course, if  $R$  or  $R'$  is chiral, a racemic mixture will not always arise

<sup>1</sup>For a discussion, see Jencks *Prog. Phys. Org. Chem.* **1964**, 2, 63-118.

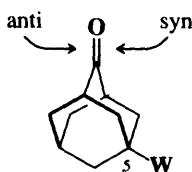
<sup>2</sup>For reviews of thioketones and other compounds with  $C=S$  bonds, see Schaumann, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 2; Wiley: New York, 1989, pp. 1269-1367; Ohno, in Oae *Organic Chemistry of Sulfur*; Plenum: New York, 1977, pp. 189-229; Mayer, in Janssen *Organosulfur Chemistry*; Wiley: New York, 1967, pp. 219-240; Campaigne, in Patai *The Chemistry of the Carbonyl Group*, pt. 1; Wiley: New York, 1966, pp. 917-959.

<sup>3</sup>For a review of additions of organometallic compounds to  $C=S$  bonds, both to the sulfur (*thiophilic addition*) and to the carbon (*carbophilic addition*), see Wardell; Paterson, in Hartley; Patai *The Chemistry of the Metal-Carbon Bond*, vol. 2; Wiley: New York, 1985, pp. 219-338, pp. 261-267.

<sup>4</sup>Beak; Worley *J. Am. Chem. Soc.* **1972**, 94, 597. For some other examples, see Schaumann; Walter *Chem. Ber.* **1974**, 107, 3562; Metzner; Vialle; Vibet *Tetrahedron* **1978**, 34, 2289.

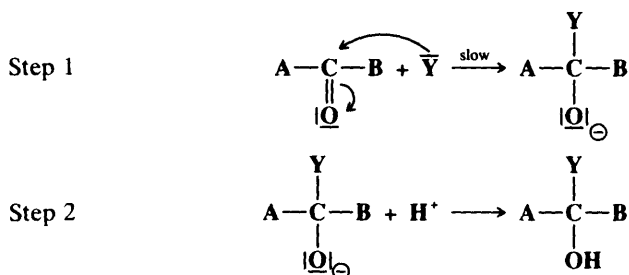
and the stereochemistry of addition can be studied in such cases. Cram's rule (p. 117) allows us to predict the direction of attack of Y in many cases.<sup>5</sup> However, even in this type of study, the relative directions of attack of Y and H are not determined, but only the direction of attack of Y with respect to the rest of the substrate molecule.

On p. 754 it was mentioned that electronic effects can play a part in determining which face of a carbon-carbon double bond is attacked. The same applies to additions to carbonyl groups. For example, in 5-substituted adamantanonones:



electron-withdrawing ( $-I$ ) groups W cause the attack to come from the syn face, while electron-donating groups cause it to come from the anti face.<sup>6</sup>

The mechanistic picture is further simplified by the fact that free-radical additions to carbon-hetero double bonds are rare.<sup>7</sup> The principal question remaining is which attacks first, the nucleophile or electrophile. In most cases it is the nucleophile, and these reactions are regarded as *nucleophilic additions*, which can be represented thus (for the  $C=O$  bond, analogously for the others):



The electrophile shown in step 2 is the proton. In almost all the reactions considered in this chapter the electrophilic attacking atom is either hydrogen or carbon. It may be noted that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (p. 331), and it might be expected that substitution would compete with addition. However, this is seldom the case. When A and B are H, R, or Ar, the substrate is an aldehyde or ketone and these almost never undergo substitution, owing to the extremely poor nature of H, R, and Ar as leaving groups. For carboxylic acids and their

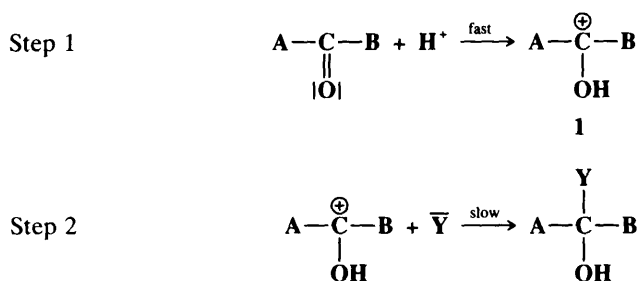
<sup>5</sup>For a discussion of such rules, see Eliel *The Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962, pp. 68-74. For reviews of the stereochemistry of addition to carbonyl compounds, see Bartlett *Tetrahedron* **1980**, *36*, 2-72, pp. 22-28; Ashby; Laemmle *Chem. Rev.* **1975**, *75*, 521-546; Goller *J. Chem. Educ.* **1974**, *51*, 182-185; Toromanoff *Top. Stereochem.* **1967**, *2*, 157-198.

<sup>6</sup>Cheung; Tseng; Lin; Srivastava; le Noble *J. Am. Chem. Soc.* **1986**, *108*, 1598; Laube; Stilz *J. Am. Chem. Soc.* **1987**, *109*, 5876.

<sup>7</sup>An example is found in 6-35. For other examples, see Kaplan *J. Am. Chem. Soc.* **1966**, *88*, 1833; Drew; Kerr *Int. J. Chem. Kinet.* **1983**, *15*, 281; Fraser-Reid; Vite; Yeung; Tsang *Tetrahedron Lett.* **1988**, *29*, 1645; Beckwith; Hay *J. Am. Chem. Soc.* **1989**, *111*, 2674; Clerici; Porta *J. Org. Chem.* **1989**, *54*, 3872; Cossy; Pete; Portella *Tetrahedron Lett.* **1989**, *30*, 7361.

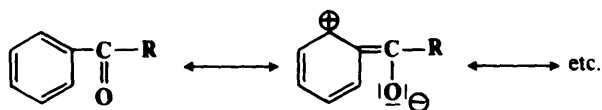
derivatives (B = OH, OR, NH<sub>2</sub>, etc.) addition is seldom found, because these are much better leaving groups. It is thus the nature of A and B that determines whether a nucleophilic attack at a carbon-hetero multiple bond will lead to substitution or addition.

As is the case in the tetrahedral mechanism, it is also possible for the electrophilic species to attack first, in which case it goes to the hetero atom. This species is most often a proton and the mechanism is



No matter which species attacks first, the rate-determining step is usually the one involving nucleophilic attack. It may be observed that many of these reactions can be catalyzed by both acids and bases.<sup>8</sup> Bases catalyze the reaction by converting a reagent of the form YH to the more powerful nucleophile Y<sup>-</sup> (see p. 348). Acids catalyze it by converting the substrate to an ion (e.g., **1**) in which the positive charge on the carbon is greatly increased, thus making it more attractive to nucleophilic attack. Similar catalysis can also be found with metallic ions, such as Ag<sup>+</sup>, which act here as Lewis acids.<sup>9</sup> We have mentioned before (p. 170) that ions of type **1** are comparatively stable carbocations because the positive charge is spread by resonance.

Reactivity factors in additions to carbon-hetero multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution.<sup>10</sup> If A and/or B are electron-donating groups, rates are decreased. Electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Aryl groups are somewhat deactivating compared to alkyl, because of resonance that stabilizes the substrate molecule but is lost on going to the intermediate:



Double bonds in conjugation with the carbon-hetero multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4 addition (p. 742). Steric factors are also quite important and contribute to the decreased reactivity of ketones compared with aldehydes. Highly hindered ketones like hexamethylacetone and dineopentyl ketone either do not undergo many of these reactions or require extreme conditions.

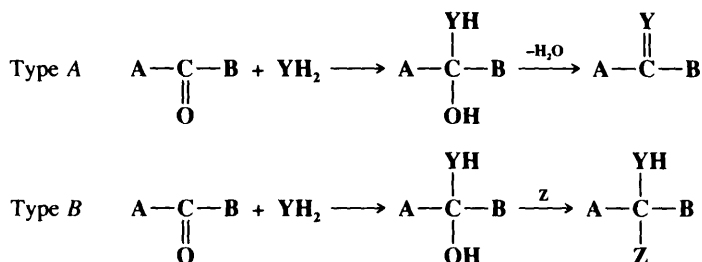
<sup>b</sup>For a discussion of acid and base catalysis in these reactions, see Jencks; Gilbert *Pure Appl. Chem.* **1977**, *49*, 1021-1027.

\*Toromanoff *Bull. Soc. Chim. Fr.* **1962**, 1190.

<sup>10</sup>For a review of the reactivity of nitriles, see Schaefer, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 239-305.

## REACTIONS

Many of the reactions in this chapter are simple additions to carbon-hetero multiple bonds, with the reaction ending when the two groups have been added. But in many other cases subsequent reactions take place. We shall meet a number of such reactions, but most are of two types:

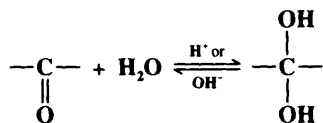


In type *A*, the adduct loses water (or, in the case of addition to  $\text{C}=\text{NH}$ , ammonia, etc.), and the net result of the reaction is the substitution of  $\text{C}=\text{Y}$  for  $\text{C}=\text{O}$  (or  $\text{C}=\text{NH}$ , etc.). In type *B* there is a rapid substitution, and the  $\text{OH}$  (or  $\text{NH}_2$ , etc.) is replaced by another group  $\text{Z}$ , which is often another  $\text{YH}$  moiety. This substitution is in most cases nucleophilic, since  $\text{Y}$  usually has an unshared pair and  $\text{S}_{\text{N}}1$  reactions occur very well on this type of compound (see p. 342), even when the leaving group is as poor as  $\text{OH}$  or  $\text{NH}_2$ . In this chapter we shall classify reactions according to what is initially adding to the carbon-hetero multiple bond, even if subsequent reactions take place so rapidly that it is not possible to isolate the initial adduct.

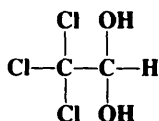
Most of the reactions considered in this chapter can be reversed. In many cases we shall consider the reverse reactions with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another, e.g., 6-2 and 6-14. For reactions that are reversible, the principle of microscopic reversibility (p. 215) applies.

We shall discuss first reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the hetero atom and then reactions in which carbon adds to the hetero atom. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, are treated at the end.

## Reactions in Which Hydrogen or a Metallic Ion Adds to the Hetero Atom

A. Attack by  $\text{OH}$  (Addition of  $\text{H}_2\text{O}$ )6-1 The Addition of Water to Aldehydes and Ketones. Formation of Hydrates  
**O-Hydro-C-hydroxy-addition**

The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or *gem*-diol.<sup>11</sup> These compounds are usually stable only in water solution and decompose on distillation; i.e., the equilibrium shifts back toward the carbonyl compound. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20°C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.<sup>12</sup> It has been found, by exchange with <sup>18</sup>O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.<sup>13</sup> Since methyl, a + I group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral<sup>14</sup> is a stable crystalline substance. In order for it to revert to chloral, OH<sup>-</sup> or H<sub>2</sub>O must leave; this is made difficult by the electron-withdrawing character of the Cl<sub>3</sub>C group. Some other<sup>15</sup> polychlorinated and



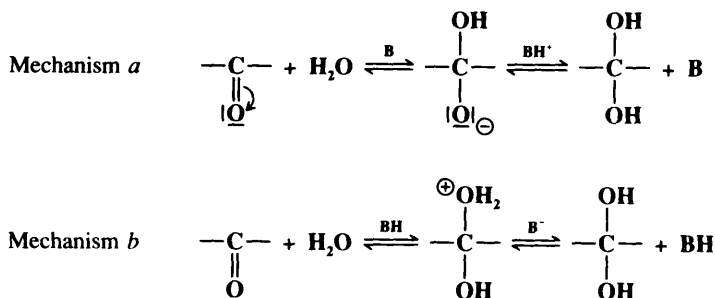
chloral hydrate



hydrate of cyclopropanone

polyfluorinated aldehydes and ketones<sup>16</sup> and α-keto aldehydes also form stable hydrates, as do cyclopropanones.<sup>17</sup> In the last case<sup>18</sup> formation of the hydrate relieves some of the I strain (p. 276) of the parent ketone.

The reaction is subject to both general-acid and general-base catalysis; the following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively:<sup>19</sup>



<sup>11</sup>For reviews, see Bell *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973, pp. 183-187; *Adv. Phys. Org. Chem.* **1966**, *4*, 1-29; Le Hénaff *Bull. Soc. Chim. Fr.* **1968**, 4687-4700.

<sup>12</sup>Bell; Clunie *Trans. Faraday Soc.* **1952**, *48*, 439. See also Bell; McDougall *Trans. Faraday Soc.* **1960**, *56*, 1281.

<sup>13</sup>Cohn; Urey *J. Am. Chem. Soc.* **1938**, *60*, 679.

<sup>14</sup>For a review of chloral, see Luknitskii *Chem. Rev.* **1975**, *75*, 259-289.

<sup>15</sup>For a discussion, see Schulman; Bonner; Schulman; Laskovics *J. Am. Chem. Soc.* **1976**, *98*, 3793.

<sup>16</sup>For a review of addition to fluorinated ketones, see Gambaryan; Rokhlin; Zeifman; Ching-Yun; Knunyants *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 947-956 [*Angew. Chem.* **78**, 1008-1017].

<sup>17</sup>For other examples, see Krois; Langer; Lehner *Tetrahedron* **1980**, *36*, 1345; Krois; Lehner *Monatsh. Chem.* **1982**, *113*, 1019.

<sup>18</sup>Turro; Hammond *J. Am. Chem. Soc.* **1967**, *89*, 1028; Schaafsma; Steinberg; de Boer *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 651. For a review of cyclopropanone chemistry, see Wasserman; Clark; Turley *Top. Curr. Chem.* **1974**, *47*, 73-156.

<sup>19</sup>Bell; Rand; Wynne-Jones *Trans. Faraday Soc.* **1956**, *52*, 1093; Pocker *Proc. Chem. Soc.* **1960**, 17; Funderburk; Aldwin; Jencks *J. Am. Chem. Soc.* **1978**, *100*, 5444; Sørensen; Jencks *J. Am. Chem. Soc.* **1987**, *109*, 4675. For a comprehensive treatment, see Lowry; Richardson *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987, pp. 662-680.

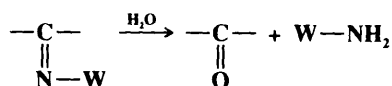
In mechanism *a*, as the  $\text{H}_2\text{O}$  attacks, the base pulls off a proton, and the net result is addition of  $\text{OH}^-$ . This can happen because the base is already hydrogen-bonded to the  $\text{H}_2\text{O}$  molecule before the attack. In mechanism *b*, because HB is already hydrogen-bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way B and HB accelerate the reaction even beyond the extent that they form  $\text{OH}^-$  or  $\text{H}_3\text{O}^+$  by reaction with water. Reactions in which the catalyst donates a proton to the electrophilic reagent (in this case the aldehyde or ketone) in one direction and removes it in the other are called class e reactions. Reactions in which the catalyst does the same to the nucleophilic reagent are called class n reactions.<sup>20</sup> Thus the acid-catalyzed process here is a class e reaction, while the base catalyzed process is a class n reaction.

For the reaction between ketones and  $\text{H}_2\text{O}_2$ , see 7-49.

There are no OS references, but see OS 66, 142, for the reverse reaction.

## 6-2 Hydrolysis of the Carbon-Nitrogen Double Bond

### Oxo-de-alkylimino-bisubstitution, etc.



Compounds containing carbon-nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones. For imines ( $\text{W} = \text{R}$  or  $\text{H}$ ) the hydrolysis is easy and can be carried out with water. When  $\text{W} = \text{H}$ , the imine is seldom stable enough for isolation, and hydrolysis usually occurs in situ, without isolation. The hydrolysis of Schiff bases ( $\text{W} = \text{Ar}$ ) is more difficult and requires acid or basic catalysis. Oximes ( $\text{W} = \text{OH}$ ), arylhydrazones ( $\text{W} = \text{NHAr}$ ), and, most easily, semicarbazones ( $\text{W} = \text{NHCONH}_2$ ) can also be hydrolyzed. Often a reactive aldehyde, e.g., formaldehyde, is added to combine with the liberated amine.

A number of other reagents<sup>21</sup> have been used to cleave  $\text{C}=\text{N}$  bonds, especially those not easily hydrolyzable with acidic or basic catalysts or which contain other functional groups that are attacked under these conditions. In particular, oximes have been converted to the corresponding aldehyde or ketone by treatment with, among other reagents, thallium(III) nitrate,<sup>22</sup> aqueous  $\text{TiCl}_3$  and acetic acid,<sup>23</sup> aqueous  $\text{NaHSO}_3$ ,<sup>24</sup> benzeneseleninic anhydride ( $\text{PhSeO})_2\text{O}$ ,<sup>25</sup>  $\text{N}_2\text{O}_4$ ,<sup>26</sup>  $\text{Me}_3\text{SiCl-NaNO}_2$ ,<sup>27</sup>  $\text{LiAlH}_4\text{-HMPA}$ ,<sup>28</sup> Amberlyst 15 and acetone,<sup>29</sup> pyridinium dichromate-*t*-BuOOH,<sup>30</sup> alkaline  $\text{H}_2\text{O}_2$ ,<sup>31</sup> and by treatment of the O-acetate of the oxime with chromium(II) acetate.<sup>32</sup> Tosylhydrazones can be hydrolyzed to the corresponding ketones with  $\text{NaOCl}$ ,<sup>33</sup> aqueous acetone and  $\text{BF}_3\text{-etherate}$ ,<sup>34</sup>  $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ ,<sup>35</sup> so-

<sup>20</sup>Jencks *Acc. Chem. Res.* **1976**, 9, 425-432.

<sup>21</sup>For a list of many of these reagents, with references, see Ranu; Sarkar *J. Org. Chem.* **1988**, 53, 878.

<sup>22</sup>McKillop; Hunt; Naylor; Taylor *J. Am. Chem. Soc.* **1971**, 93, 4918.

<sup>23</sup>Timms; Wildsmith *Tetrahedron Lett.* **1971**, 195. See also McMurry; Silvestri *J. Org. Chem.* **1975**, 40, 1502; Balicki; Kaczmarek; Malinowski *Liebigs Ann. Chem.* **1989**, 1139.

<sup>24</sup>Pinc; Chemerda; Kozłowski *J. Org. Chem.* **1966**, 31, 3446.

<sup>25</sup>Barton; Lester; Ley *J. Chem. Soc., Perkin Trans. 1* **1980**, 1212.

<sup>26</sup>Shim; Kim; Kim *Tetrahedron Lett.* **1987**, 28, 645.

<sup>27</sup>Lee; Kwak; Hwang *Tetrahedron Lett.* **1990**, 31, 6677.

<sup>28</sup>Wang; Sukenik *J. Org. Chem.* **1985**, 50, 5448.

<sup>29</sup>Ballini; Pettrini *J. Chem. Soc., Perkin Trans. 1* **1988**, 2563.

<sup>30</sup>Chidambaram; Satyanarayana; Chandrasekaran *Synth. Commun.* **1989**, 19, 1727.

<sup>31</sup>Ho *Synth. Commun.* **1980**, 10, 465.

<sup>32</sup>Corey; Richman *J. Am. Chem. Soc.* **1970**, 92, 5276.

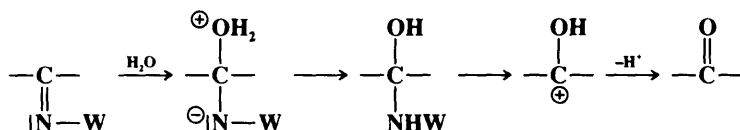
<sup>33</sup>Ho; Wong *J. Org. Chem.* **1974**, 39, 3453.

<sup>34</sup>Sacks; Fuchs *Synthesis* **1976**, 456.

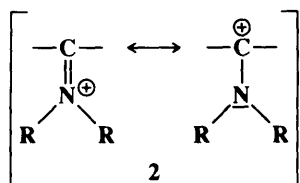
<sup>35</sup>Attanasi; Gasperoni *Gazz. Chim. Ital.* **1978**, 108, 137.

dium peroxide,<sup>36</sup> as well as with other reagents.<sup>37</sup> Among other reagents that have been used to cleave C=N bonds are nitrous acid (as well as nitrosonium salts such as  $\text{NO}^+ \text{BF}_4^-$ )<sup>38</sup> and ozone<sup>39</sup> (see 9-9).

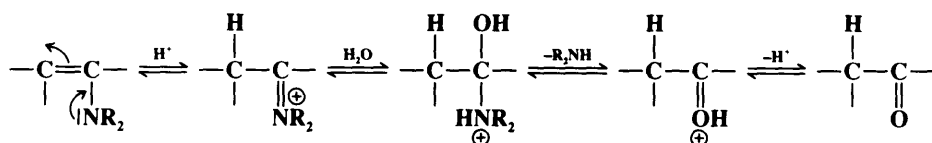
The hydrolysis of carbon-nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:



It is thus an example of reaction type A (p. 882). The sequence shown is generalized.<sup>40</sup> In specific cases there are variations in the sequence of the steps, depending on acid or basic catalysis or other conditions.<sup>41</sup> Which step is rate-determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.<sup>42</sup> Iminium ions (2)<sup>43</sup> would



be expected to undergo hydrolysis quite readily, since there is a contributing form with a positive charge on the carbon. Indeed, they react with water at room temperature.<sup>44</sup> Acid-catalyzed hydrolysis of enamines (the last step of the Stork reaction, 2-19) involves conversion to iminium ions:<sup>45</sup>



The mechanism of enamine hydrolysis is thus similar to that of vinyl ether hydrolysis (0-6).

OS I, 217, 298, 318, 381; II, 49, 223, 234, 284, 310, 333, 395, 519, 522; III, 20, 172, 626, 818; IV, 120; V, 139, 277, 736, 758; VI, 1, 358, 640, 751, 901, 932; VII, 8; 65, 108, 183; 67, 33.

<sup>36</sup>Ho; Olah *Synthesis* **1976**, 611.

<sup>37</sup>For references, see Jiricny; Orere; Reese *Synthesis* **1970**, 919.

<sup>38</sup>Doyle; Wierenga; Zaleta *J. Org. Chem.* **1972**, 37, 1597; Doyle; Zaleta; DeBoer; Wierenga *J. Org. Chem.* **1973**, 38, 1663; Olah; Ho *Synthesis* **1976**, 610.

<sup>39</sup>For example, see Erickson; Andrusis; Collins; Lungle; Mercer *J. Org. Chem.* **1969**, 34, 2961.

<sup>40</sup>For reviews of the mechanism, see Bruylants; Feytmants-de Medicis, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*; Wiley: New York, 1970, pp. 465-504; Salomaa, in Patai, Ref. 2, pt. 1, pp. 199-205.

<sup>41</sup>For example, see Reeves *J. Am. Chem. Soc.* **1962**, 82, 3332; Sayer; Conlon *J. Am. Chem. Soc.* **1980**, 102, 3592.

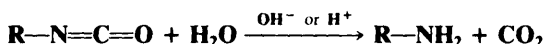
<sup>42</sup>Cordes; Jencks *J. Am. Chem. Soc.* **1963**, 85, 2843.

<sup>43</sup>For a review of iminium ions, see Böhme; Haake *Adv. Org. Chem.* **1976**, 9, pt. 1, 107-223.

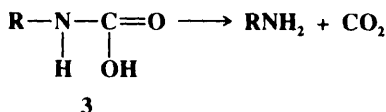
<sup>44</sup>Hauser; Lednicer *J. Org. Chem.* **1959**, 24, 46. For a study of the mechanism, see Gopalakrishnan; Hogg *J. Org. Chem.* **1989**, 54, 768.

<sup>45</sup>Stamhuis; Maas *J. Org. Chem.* **1965**, 30, 2156; Maas; Janssen; Stamhuis; Wynberg *J. Org. Chem.* **1967**, 32, 1111; Sollenberger; Martin *J. Am. Chem. Soc.* **1970**, 92, 4261. For a review of enamine hydrolysis, see Stamhuis; Cook, in Cook *Enamines*, 2nd ed.; Marcel Dekker: New York, 1988, pp. 165-180.

## 6-3 Hydrolysis of Isocyanates and Isothiocyanates

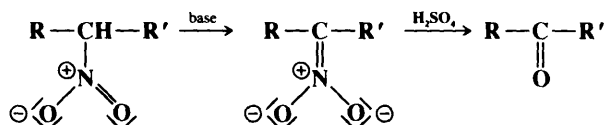
**Oxo-de-alkylimino-bisubstitution**

A common method for the preparation of primary amines involves the hydrolysis of isocyanates or isothiocyanates.<sup>46</sup> The latter react more slowly and more vigorous conditions are required. The reaction is catalyzed by acids or bases. In this case simple addition of water to the carbon-nitrogen double bond would give an N-substituted carbamic acid (**3**). Such compounds are unstable and break down to carbon dioxide (or COS in the case of isothiocyanates) and the amine:

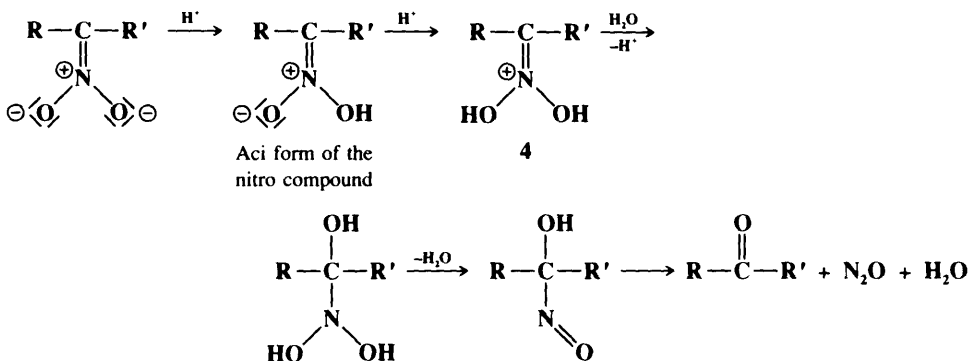


OS II, 24; IV, 819; V, 273; VI, 910.

## 6-4 Hydrolysis of Aliphatic Nitro Compounds

**Oxo-de-hydro,nitro-bisubstitution**

Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.<sup>47</sup> Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like **6-2**, this reaction involves hydrolysis of a C=N double bond. A possible mechanism is<sup>48</sup>



Intermediates of type **4** have been isolated in some cases.<sup>49</sup>

<sup>46</sup>For a study of the mechanism, see Castro; Moodie; Sansom *J. Chem. Soc., Perkin Trans. 2* **1985**, 737. For a review of the mechanisms of reactions of isocyanates with various nucleophiles, see Satchell; Satchell *Chem. Soc. Rev.* **1975**, 4, 231-250.

<sup>47</sup>For reviews, see Pinnick *Org. React.* **1990**, 38, 655-792; Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1988, pp. 220-231, 416-419.

<sup>48</sup>Hawthorne *J. Am. Chem. Soc.* **1957**, 79, 2510. A similar mechanism, but with some slight differences, was suggested earlier by van Tamelen; Thiede *J. Am. Chem. Soc.* **1952**, 74, 2615. See also Sun; Folliard *Tetrahedron* **1971**, 27, 323.

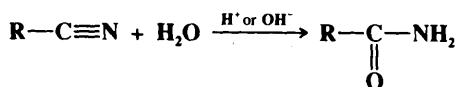
<sup>49</sup>Feuer; Spinicelli *J. Org. Chem.* **1977**, 42, 2091.

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods. Among these are treatment of the nitro compound with aqueous  $\text{TiCl}_3$ ,<sup>50</sup> cetyltrimethylammonium permanganate,<sup>51</sup> tin complexes and  $\text{NaHSO}_3$ ,<sup>52</sup> activated dry silica gel,<sup>53</sup> or 30%  $\text{H}_2\text{O}_2$ - $\text{K}_2\text{CO}_3$ ,<sup>54</sup> and treatment of the conjugate base<sup>55</sup> of the nitro compound with  $\text{KMnO}_4$ ,<sup>56</sup> *t*-BuOOH and a catalyst,<sup>57</sup> ceric ammonium nitrate (CAN),<sup>58</sup>  $\text{MoO}_5$ -pyridine-HMPA,<sup>59</sup> or ozone.<sup>60</sup>

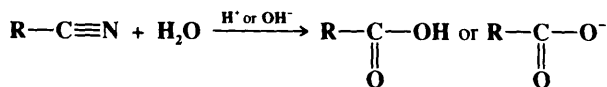
When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for preparing them.<sup>61</sup> Both the Nef reaction and the hydroxamic acid process involve the aci form; the difference in products arises from higher acidity, e.g., a difference in sulfuric acid concentration from 2 *M* to 15.5 *M* changes the product from the aldehyde to the hydroxamic acid.<sup>62</sup> The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated aci form of the nitro compound is further protonated.

OS VI, 648; VII, 414. See also OS IV, 573.

## 6-5 Hydrolysis of Nitriles



### *NN*-Dihydro-C-oxo-biaddition



### Hydroxy,oxo-de-nitrilo-tersubstitution

Nitriles can be hydrolyzed to give either amides or carboxylic acids.<sup>63</sup> The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is the more common product. When the acid is desired,<sup>64</sup> the reagent of choice is

<sup>50</sup>McMurry; Melton *J. Org. Chem.* **1973**, 38, 4367; McMurry *Acc. Chem. Res.* **1974**, 7, 281-286, pp. 282-284. See also Kirchhoff *Tetrahedron Lett.* **1976**, 2533.

<sup>51</sup>Vankar; Rathore; Chandrasekaran *Synth. Commun.* **1987**, 17, 195.

<sup>52</sup>Urfi; Vilarrasa *Tetrahedron Lett.* **1990**, 31, 7499.

<sup>53</sup>Keinan; Mazur *J. Am. Chem. Soc.* **1977**, 99, 3861.

<sup>54</sup>Olah; Arvanaghi; Vankar; Prakash *Synthesis* **1980**, 662.

<sup>55</sup>For other methods, see Barton; Motherwell; Zard *Tetrahedron Lett.* **1983**, 24, 5227; Yano; Ohshima; Sutoh *J. Chem. Soc., Chem. Commun.* **1984**, 695.

<sup>56</sup>Shechter; Williams *J. Org. Chem.* **1962**, 27, 3699; Freeman; Yeramyam *J. Org. Chem.* **1970**, 35, 2061; Freeman; Lin *J. Org. Chem.* **1971**, 36, 1335; Kornblum; Erickson; Kelly; Henggeler *J. Org. Chem.* **1982**, 47, 4534; Steliou; Poupart *J. Org. Chem.* **1985**, 50, 4971.

<sup>57</sup>Bartlett; Green; Webb *Tetrahedron Lett.* **1977**, 331.

<sup>58</sup>Olah; Gupta *Synthesis* **1980**, 44.

<sup>59</sup>Galobardes; Pinnick *Tetrahedron Lett.* **1981**, 22, 5235.

<sup>60</sup>McMurry; Melton; Padgett *J. Org. Chem.* **1974**, 39, 259. See Williams; Unger; Moore *J. Org. Chem.* **1978**, 43, 1271, for the use of singlet oxygen instead of ozone.

<sup>61</sup>Hydroxamic acids can also be prepared from primary nitro compounds with  $\text{SeO}_2$  and  $\text{Et}_3\text{N}$ : Sosnovsky; Krogh *Synthesis* **1980**, 654.

<sup>62</sup>Kornblum; Brown *J. Am. Chem. Soc.* **1965**, 87, 1742. See also Cundall; Locke *J. Chem. Soc. B* **1968**, 98; Edward; Tremaine *Can J. Chem.* **1971**, 49, 3483, 3489, 3493.

<sup>63</sup>For reviews, see Zil'berman *Russ. Chem. Rev.* **1984**, 53, 900-912; Compagnon; Miocque *Ann. Chim. (Paris)* **1970**, [14] 5, 11-22, 23-37.

<sup>64</sup>For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, p. 993.

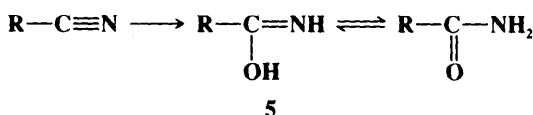
aqueous NaOH containing about 6 to 12%  $\text{H}_2\text{O}_2$ , though acid-catalyzed hydrolysis is also frequently carried out. However, there are a number of procedures for stopping at the amide stage,<sup>65</sup> among them the use of concentrated  $\text{H}_2\text{SO}_4$ ; formic acid and HCl or HBr;<sup>66</sup> acetic acid and  $\text{BF}_3$ ;  $\text{H}_2\text{O}_2$  and  $\text{OH}^-$ ;<sup>67</sup> 30%  $\text{H}_2\text{O}_2$  in  $\text{Me}_2\text{SO}$ ,<sup>68</sup> sodium percarbonate,<sup>69</sup> and dry HCl followed by  $\text{H}_2\text{O}$ . The same result can also be obtained by use of water and certain metal ions or complexes;<sup>70</sup>  $\text{MnO}_2$  in methylene chloride<sup>71</sup> or on silica gel;<sup>72</sup> sodium perborate in aqueous MeOH;<sup>73</sup>  $\text{Hg}(\text{OAc})_2$  in HOAc;<sup>74</sup> 2-mercaptoethanol in a phosphate buffer;<sup>75</sup>  $\text{KF}\cdot\text{Al}_2\text{O}_3$ ;<sup>76</sup> or  $\text{TiCl}_4$  and water.<sup>77</sup> Nitriles can be hydrolyzed to the carboxylic acids without disturbing carboxylic ester functions also present, by the use of tetrachloro- or tetrafluorophthalic acid.<sup>78</sup>

The hydrolysis of nitriles to carboxylic acids is one of the best methods for the preparation of these compounds. Nearly all nitriles give the reaction, with either acidic or basic catalysts. The sequences



are very common. The last two sequences are often carried out without isolation of the cyanide intermediates. Hydrolysis of cyanohydrins  $\text{RCH}(\text{OH})\text{CN}$  is usually carried out under acidic conditions, because basic solutions cause competing reversion of the cyanohydrin to the aldehyde and  $\text{CN}^-$ . However, cyanohydrins have been hydrolyzed under basic conditions with borax or alkaline borates.<sup>79</sup>

The first addition product is **5**, which tautomerizes to the amide.



Thiocyanates can be converted to thiocarbamates, in a similar reaction:<sup>80</sup>  $\text{R}-\text{S}-\text{C}\equiv\text{N} + \text{H}_2\text{O} \xrightarrow{\text{H}^+} \text{R}-\text{S}-\text{CO}-\text{NH}_2$ . Hydrolysis of cyanamides gives amines, produced by the breakdown of the unstable carbamic acid intermediates:  $\text{R}_2\text{NCN} \rightarrow [\text{R}_2\text{NCOOH}] \rightarrow \text{R}_2\text{NH}$ .

OS **I**, 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II**, 29, 44, 292, 376, 512, 586 (see, however, **V**, 1054), 588; **III**; 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV**, 58, 93, 496, 506, 664, 760, 790; **V**, 239; **VI**, 932. Also see OS **III**, 609; **IV**, 359, 502; **66**, 142.

<sup>65</sup>For a discussion, see Beckwith, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 119-125. For a list of reagents, with references, see Ref. 64, p. 994.

<sup>66</sup>Becke; Fleig; Pässler *Liebigs Ann. Chem.* **1971**, 749, 198.

<sup>67</sup>For an example with phase transfer catalysis, see Cacchi; Misiti; La Torre *Synthesis* **1980**, 243.

<sup>68</sup>Katritzky; Pilarski; Urogdi *Synthesis* **1989**, 949.

<sup>69</sup>Kabalka; Deshpande; Wadgaonkar; Chatla *Synth. Commun.* **1990**, 20, 1445.

<sup>70</sup>For example, see Watanabe *Bull. Chem. Soc. Jpn.* **1959**, 32, 1280, **1964**, 37, 1325; Bennett; Yoshida *J. Am. Chem. Soc.* **1973**, 95, 3030; Paraskewas *Synthesis* **1974**, 574; McKenzie; Robson *J. Chem. Soc., Chem. Commun.* **1988**, 112.

<sup>71</sup>Cook; Forbes; Kahn *Chem. Commun.* **1966**, 121.

<sup>72</sup>Liu; Shih; Huang; Hu *Synthesis* **1988**, 715.

<sup>73</sup>McKillop; Kemp *Tetrahedron* **1989**, 45, 3299; Reed; Gupton; Solarz *Synth. Commun.* **1990**, 20, 563.

<sup>74</sup>Plummer; Menendez; Songster *J. Org. Chem.* **1989**, 54, 718.

<sup>75</sup>Lee; Goo; Lee; Lee *Tetrahedron Lett.* **1989**, 30, 7439.

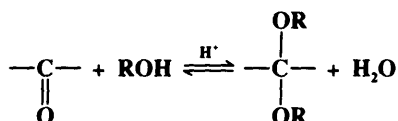
<sup>76</sup>Rao *Synth. Commun.* **1982**, 12, 177.

<sup>77</sup>Mukaiyama; Kamio; Kobayashi; Takei *Chem. Lett.* **1973**, 357.

<sup>78</sup>Rounds; Eaton; Urbanowicz; Gribble *Tetrahedron Lett.* **1988**, 29, 6557.

<sup>79</sup>Jammot; Pascal; Commeyras *Tetrahedron Lett.* **1989**, 30, 563.

<sup>80</sup>Zil'berman; Lazaris *J. Gen. Chem. USSR* **1963**, 33, 1012.

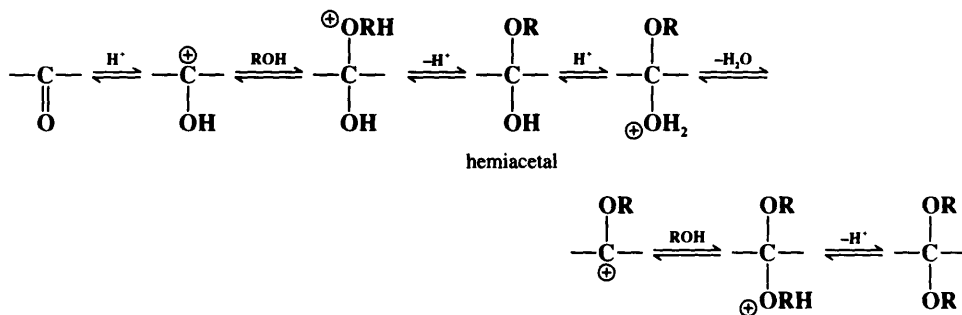
**B. Attack by OR (Addition of ROH)****6-6 The Addition of Alcohols to Aldehydes and Ketones**  
**Dialkoxo-de-oxo-bisubstitution**

Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.<sup>81</sup> This reaction is reversible, and acetals and ketals can be hydrolyzed by treatment with acid (0-6). With small unbranched aldehydes the equilibrium lies to the right. If it is desired to prepare ketals, or acetals of larger molecules, the equilibrium must be shifted, usually by removal of water. This can be done by azeotropic distillation, ordinary distillation, or the use of a drying agent such as  $\text{Al}_2\text{O}_3$  or a molecular sieve.<sup>82</sup> The reaction in neither direction is catalyzed by bases, so most acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This makes this reaction a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope. Most aldehydes are easily converted to acetals.<sup>83</sup> With ketones the process is more difficult, presumably for steric reasons, and the reaction often fails, though many ketals, especially from cyclic ketones, have been made in this manner.<sup>84</sup> Many functional groups may be present without being affected. 1,2-Glycols and 1,3-glycols form cyclic acetals and ketals, e.g.,



and these are often used to protect aldehydes and ketones.

The mechanism, which involves initial formation of a *hemiacetal*,<sup>85</sup> is the reverse of that given for acetal hydrolysis (0-6):



<sup>81</sup>For reviews, see Meskens *Synthesis* **1981**, 501-522; Schmitz; Eichhorn, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 309-351.

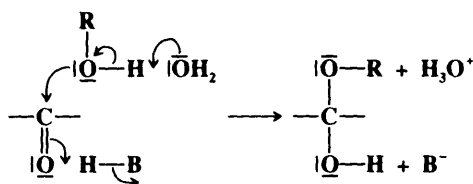
<sup>82</sup>For many examples of each of these methods, see Meskens, Ref. 81, pp. 502-505.

<sup>83</sup>For other methods, see Caputo; Ferreri; Palumbo *Synthesis* **1987**, 386; Ott; Tombo; Schmid; Venanzi; Wang; Ward *Tetrahedron Lett.* **1989**, 30, 6151; *New J. Chem.* **1990**, 14, 495; Liao; Huang; Zhu *J. Chem. Soc., Chem. Commun.* **1990**, 493; Chan; Brook; Chaly *Synthesis* **1983**, 203.

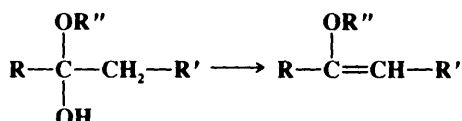
<sup>84</sup>High pressure has been used to improve the results with ketones: Dauben; Gerdes; Look *J. Org. Chem.* **1986**, 51, 4964. For other methods, see Otera; Mizutani; Nozaki *Organometallics* **1989**, 8, 2063; Thurkauf; Jacobson; Rice *Synthesis* **1988**, 233.

<sup>85</sup>For a review of hemiacetals, see Hurd *J. Chem. Educ.* **1966**, 43, 527-531.

In a study of the acid-catalyzed formation of the hemiacetal, Grunwald has shown<sup>86</sup> that the data best fit a mechanism in which the three steps shown here are actually all concerted; that is, the reaction is simultaneously catalyzed by acid and base, with water acting as the base:<sup>87</sup>



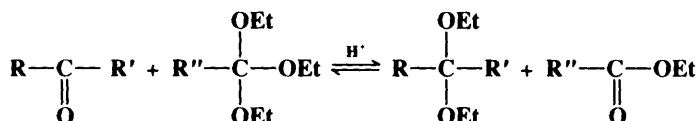
If the original aldehyde or ketone has an  $\alpha$  hydrogen, it is possible for water to split out in that way and enol ethers can be prepared in this manner:



Similarly, treatment with an anhydride and a catalyst can give an enol ester.<sup>88</sup>

Hemiacetals themselves are no more stable than the corresponding hydrates (6-1). As with hydrates, hemiacetals of cyclopropanones<sup>89</sup> and of polychloro and polyfluoro aldehydes and ketones may be quite stable.

When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, it is possible to get a transacetalation (see 0-17). In another type of transacetalation, aldehydes or ketones can be converted to acetals or ketals by treatment with another acetal or ketal or with an ortho ester,<sup>90</sup> in the presence of an acid catalyst (shown for an ortho ester):



This method is especially useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. In another method, the substrate is treated with an alkoxysilane  $\text{ROSiMe}_3$  in the presence of trimethylsilyl trifluoromethanesulfonate.<sup>91</sup>

<sup>86</sup>Grunwald *J. Am. Chem. Soc.* **1985**, *107*, 4715.

<sup>87</sup>Grunwald also studied the mechanism of the base-catalyzed formation of the hemiacetal, and found it to be the same as that of base-catalyzed hydration (6-1, mechanism a): Grunwald *J. Am. Chem. Soc.* **1985**, *107*, 4710. See also Sørensen; Pedersen; Pedersen; Kanagasabapathy; McClelland *J. Am. Chem. Soc.* **1988**, *110*, 5118; Leussing *J. Org. Chem.* **1990**, *55*, 666.

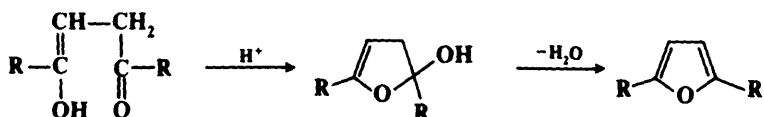
<sup>88</sup>For a list of catalysts, with references, see Ref. 64, p. 743.

<sup>89</sup>For a review, see Salaun *Chem. Rev.* **1983**, *83*, 619-632.

<sup>90</sup>For a review with respect to ortho esters, see DeWolfe *Carboxylic Ortho Ester Derivatives*; Academic Press: New York, 1970, pp. 154-164.

<sup>91</sup>Tsunoda; Suzuki; Noyori *Tetrahedron Lett.* **1980**, *21*, 1357; Kato; Iwasawa; Mukaiyama *Chem. Lett.* **1985**, 743. See also Torii; Takagishi; Inokuchi; Okumoto *Bull. Chem. Soc. Jpn.* **1987**, *60*, 775.

1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form that adds:

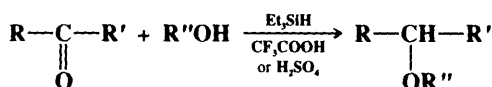


Similarly, 1,5-diketones give pyrans. Formic acid reacts with alcohols to give orthoformates.

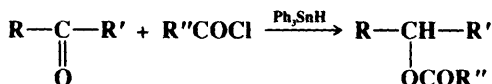
OS **I**, 1, 298, 364, 381; **II**, 137; **III**, 123, 387, 502, 536, 644, 731, 800; **IV**, 21, 479, 679; **V**, 5, 292, 303, 450, 539; **VI**, 567, 666, 954; **VII**, 59, 149, 168, 177, 241, 271, 297; **67**, 202. Also see OS **IV**, 558, 588; **V**, 25; **67**, 193.

## 6-7 Reductive Alkylation of Alcohols

### C-Hydro-O-alkyl-addition



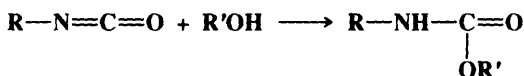
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid<sup>92</sup> or by hydrogenation in alcoholic acid in the presence of platinum oxide.<sup>93</sup> The process can formally be regarded as addition of ROH to give a hemiacetal  $\text{RR}'\text{C}(\text{OH})\text{OR}''$ , followed by reduction of the OH. In this respect it is similar to **6-15**. In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.<sup>94</sup>



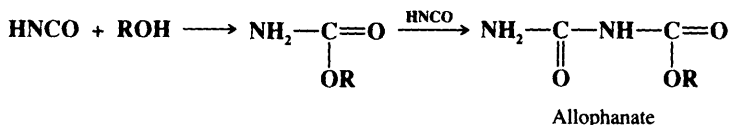
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone  $\rightarrow$  dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.<sup>95</sup>

## 6-8 The Addition of Alcohols to Isocyanates

### N-Hydro-C-alkoxy-addition



Carbamates (substituted urethans) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. Isocyanic acid HNCO gives unsubstituted carbamates. Addition of a second mole of HNCO gives *allophanates*.



<sup>92</sup>Doyle; DeBruyn; Kooistra *J. Am. Chem. Soc.* **1972**, 94, 3659.

<sup>93</sup>Verzele; Acke; Anteunis *J. Chem. Soc.* **1963**, 5598. For still another method, see Loim; Parnes; Vasil'eva; Kursanov *J. Org. Chem. USSR* **1972**, 8, 902.

<sup>94</sup>Kaplan *J. Am. Chem. Soc.* **1966**, 88, 4970.

<sup>95</sup>Sassaman; Kotian; Prakash; Olah *J. Org. Chem.* **1987**, 52, 4314. See also Kikugawa *Chem. Lett.* **1979**, 415.

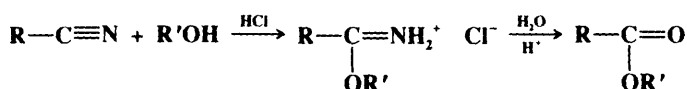
Polyurethans are made by combining compounds with two NCO groups with compounds containing two OH groups. Isothiocyanates similarly give thiocarbamates<sup>96</sup> RNHCSOR', though they react slower than the corresponding isocyanates.

The details of the mechanism are poorly understood,<sup>97</sup> though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.<sup>98</sup> The addition of ROH to isocyanates can also be catalyzed by metallic compounds,<sup>99</sup> by light,<sup>100</sup> or, for tertiary ROH, by lithium alkoxides<sup>101</sup> or *n*-butyllithium.<sup>102</sup>

OS I, 140; V, 162; VI, 95, 226, 788, 795.

## 6-9 Alcoholysis of Nitriles

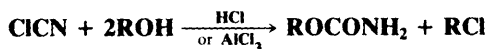
### Alkoxy,oxo-de-nitrilo-tersubstitution



The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.<sup>103</sup> The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aqueous HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.<sup>104</sup>

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present.

Cyanogen chloride reacts with alcohols in the presence of an acid catalyst such as dry HCl or AlCl<sub>3</sub> to give carbamates:<sup>105</sup>



ROH can also be added to nitriles in another manner (6-55).

OS I, 5, 270; II, 284, 310; IV, 645; VI, 507; 67, 193.

<sup>96</sup>For a review of thiocarbamates, see Walter; Bode *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 281-293 [*Angew. Chem.* 79, 285-297].

<sup>97</sup>For reviews, see Satchell; Satchell, Ref. 46; Entelis; Nesterov *Russ. Chem. Rev.* **1966**, 35, 917-930.

<sup>98</sup>See for example, Robertson; Stutchbury *J. Chem. Soc.* **1964**, 4000; Lammiman; Satchell *J. Chem. Soc., Perkin Trans. 2* **1972**, 2300, **1974**, 877; Donohoe; Satchell; Satchell *J. Chem. Soc., Perkin Trans. 2* **1990**, 1671. See also Sivakamasundari; Ganesan *J. Org. Chem.* **1984**, 49, 720.

<sup>99</sup>For example, see Davies; Puddephatt *J. Chem. Soc. C* **1967**, 2663, **1968**, 1479; Hazzard; Lammiman; Poon; Satchell; Satchell *J. Chem. Soc., Perkin Trans. 2* **1985**, 1029; Duggan; Imagire *Synthesis* **1989**, 131.

<sup>100</sup>McManus; Bruner; Coble; Ortiz *J. Org. Chem.* **1977**, 42, 1428.

<sup>101</sup>Bailey; Griffith *J. Org. Chem.* **1978**, 43, 2690.

<sup>102</sup>Nikoforov; Jirovetz; Buchbauer *Liebigs Ann. Chem.* **1989**, 489.

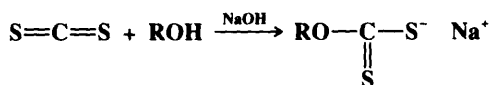
<sup>103</sup>For a review, see Compagnon; Miocque *Ann. Chim. (Paris)* [14] **5**, 23-27, pp. 24-26. For a review of imino esters, see Neilson, in Patai *The Chemistry of Amidines and Imidates*; Wiley: New York, 1975, pp. 385-489.

<sup>104</sup>Schaefer; Peters *J. Org. Chem.* **1961**, 26, 412.

<sup>105</sup>Bodrikov; Danova *J. Org. Chem. USSR* **1968**, 4, 1611, **1969**, 5, 1558; Fuks; Hartemink *Bull. Soc. Chim. Belg.* **1973**, 82, 23.

### 6-10 The Formation of Xanthates

#### S-Metallo-C-alkoxy-addition



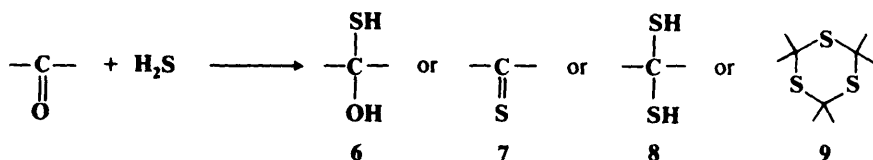
The addition of alcohols to carbon disulfide in the presence of a base produces xanthates.<sup>106</sup> The base is often  $\text{OH}^-$ , but in some cases better results can be obtained by using methylsulfinyl carbanion  $\text{MeSOCH}_2^-$ .<sup>107</sup> If an alkyl halide  $\text{RX}$  is present, the xanthate ester  $\text{ROCSSR}'$  can be produced directly. In a similar manner, alkoxide ions add to  $\text{CO}_2$  to give carbonate ester salts  $\text{ROCOO}^-$ .

OS V, 439; VI, 207, 418; VII, 139.

### C. Sulfur Nucleophiles

### 6-11 The Addition of $\text{H}_2\text{S}$ and Thiols to Carbonyl Compounds

#### O-Hydro-C-mercapto-addition<sup>108</sup>



The addition of  $\text{H}_2\text{S}$  to an aldehyde or ketone can result in a variety of products. The most usual product is the trithiane **9**.<sup>109</sup>  $\alpha$ -Hydroxy thiols (**6**) can be prepared from polychloro and polyfluoro aldehydes and ketones.<sup>110</sup> Apparently **6** are stable only when prepared from these compounds, and not even for all of them. Thioketones<sup>2</sup> (**7**) can be prepared from certain ketones, such as diaryl ketones, by treatment with  $\text{H}_2\text{S}$  and an acid catalyst, usually  $\text{HCl}$ . They are often unstable and tend to trimerize (to **9**) or to react with air. Thioaldehydes<sup>111</sup> are even less stable and simple ones<sup>112</sup> apparently have never been isolated, though *t*-BuCHS has been prepared in solution, where it exists for several hours at  $20^\circ\text{C}$ .<sup>113</sup> A high-yield synthesis of thioketones involves treatment of acyclic<sup>114</sup> ketones with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide **10** (known as Lawesson's

<sup>106</sup>For a review of the formation and reactions of xanthates, see Dunn; Rudolf *Carbon Disulphide in Organic Chemistry*; Ellis Horwood: Chichester, 1989, pp. 316-367.

<sup>107</sup>Meurling; Sjöberg; Sjöberg *Acta Chem. Scand.* **1972**, 26, 279.

<sup>108</sup>This name applies to formation of **6**. Names for formation of **7**, **8**, and **9**, are, respectively, **thioxo-de-oxo-bisubstitution**, **dimercapto-de-oxo-bisubstitution**, and **carbonyl-trithiane transformation**.

<sup>109</sup>Campaigne; Edwards *J. Org. Chem.* **1962**, 27, 3760.

<sup>110</sup>Harris *J. Org. Chem.* **1960**, 25, 2259.

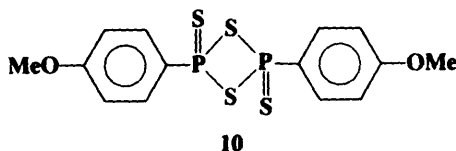
<sup>111</sup>For a review of thioaldehydes, see Usov; Timokhina; Voronkov *Russ. Chem. Rev.* **1990**, 59, 378-395.

<sup>112</sup>For the preparation and reactions of certain substituted thioaldehydes, see Hofstra; Kamphuis; Bos *Tetrahedron Lett.* **1984**, 25, 873; Okazaki; Ishii; Inamoto *J. Am. Chem. Soc.* **1987**, 109, 279; Adelaere; Guemas; Quiniou *Bull. Soc. Chim. Fr.* **1987**, 517; Muraoka; Yamamoto; Enomoto; Takeshima *J. Chem. Soc., Perkin Trans. 1* **1989**, 1241, and references cited in these papers.

<sup>113</sup>Vedejs; Perry *J. Am. Chem. Soc.* **1983**, 105, 1683. See also Baldwin; Lopez *J. Chem. Soc., Chem. Commun.* **1982**, 1029.

<sup>114</sup>Cyclopentanone and cyclohexanone gave different products: Scheibye; Shabana; Lawesson; Rømming *Tetrahedron* **1982**, 38, 993.

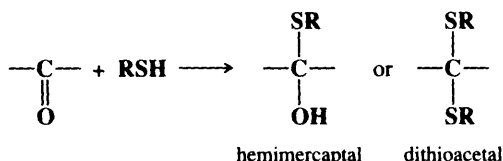
reagent<sup>115</sup>).<sup>116</sup> **10** also converts the C=O groups of amides and carboxylic esters<sup>117</sup> to C=S groups.<sup>118</sup> In similar reactions, bis(tricyclohexyltin)sulfide (R<sub>3</sub>Sn)<sub>2</sub>S [R = cyclohexyl] and



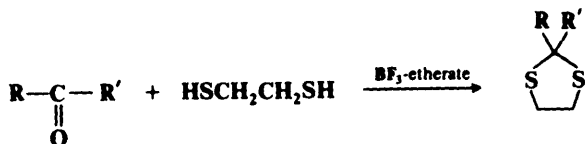
BCl<sub>3</sub> convert C=O groups of ketones, lactones, and lactams to C=S groups<sup>119</sup> and H<sub>2</sub>S-Me<sub>3</sub>SiCl-i-Pr<sub>2</sub>NLi converts carboxylic esters to thiono esters.<sup>120</sup> Carboxylic acids RCOOH can be converted directly to dithiocarboxylic esters RCSSR',<sup>120a</sup> in moderate yield, with P<sub>4</sub>S<sub>10</sub> and a primary alcohol R'OH.<sup>121</sup> Thioketones can also be prepared by treatment of ketones with P<sub>4</sub>S<sub>10</sub>,<sup>122</sup> and from oximes or various types of hydrazone (overall conversion C=N— → C=S).<sup>123</sup>

*gem*-Dithiols (**8**) are much more stable than the corresponding hydrates or α-hydroxy thiols.<sup>124</sup> They have been prepared by the treatment of ketones with H<sub>2</sub>S under pressure<sup>125</sup> and under mild conditions with HCl as a catalyst.<sup>126</sup>

Thiols add to aldehydes and ketones to give hemimercaptals and dithioacetals. Hemimercaptals are ordinarily unstable,<sup>127</sup> though they are more stable than the corresponding



hemiacetals and can be isolated in certain cases.<sup>128</sup> Dithioacetals, like acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one<sup>129</sup> (see 0-97). A common method for the protection of ketones involves treatment



<sup>115</sup>For reviews of this and related reagents, see Cava; Levinson *Tetrahedron* **1985**, *41*, 5061-5087; Cherkasov; Kuttyrev; Pudovik *Tetrahedron* **1985**, *41*, 2567-2624. For the preparation of **10**, see Thomsen; Clausen; Scheibye; Lawesson *Org. Synth.* **VII**, 372.

<sup>116</sup>Pedersen; Scheibye; Nilsson; Lawesson *Bull. Soc. Chim. Belg.* **1978**, *87*, 223. For a study of the mechanism, see Rauchfuss; Zank *Tetrahedron Lett.* **1986**, *27*, 3445.

<sup>117</sup>For a review of thiono esters RC(=S)OR', see Jones; Bradshaw *Chem. Rev.* **1984**, *84*, 17-30.

<sup>118</sup>Scheibye; Pedersen; Lawesson *Bull. Soc. Chim. Belg.* **1978**, *87*, 229; Ghattas; El-Khrisy; Lawesson *Sulfur Lett.* **1982**, *1*, 69; Yde; Yousif; Pedersen; Thomsen; Lawesson *Tetrahedron* **1984**, *40*, 2047; Thomsen et al., *Ref.* 115.

<sup>119</sup>Steliou; Mrani *J. Am. Chem. Soc.* **1982**, *104*, 3104.

<sup>120</sup>Corey; Wright *Tetrahedron Lett.* **1984**, *25*, 2639.

<sup>120a</sup>For a review of dithiocarboxylic esters, see Kato; Ishida *Sulfur Rep.* **1988**, *8*, 155-323.

<sup>121</sup>Davy; Metzner *Chem. Ind. (London)* **1985**, 824.

<sup>122</sup>See, for example, Scheeren; Ooms; Nivard *Synthesis* **1973**, 149.

<sup>123</sup>See for example, Kimura; Niwa; Motoki *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2751; de Mayo; Petrašiūnas; Weedon *Tetrahedron Lett.* **1978**, 4621; Okazaki; Inoue; Inamoto *Tetrahedron Lett.* **1979**, 3673.

<sup>124</sup>For a review of the preparation of *gem*-dithiols, see Mayer; Hiller; Nitzschke; Jentzsch *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 370-373 [*Angew. Chem.* **75**, 1011-1014].

<sup>125</sup>Cairns; Evans; Larchar; McKusick *J. Am. Chem. Soc.* **1952**, *74*, 3982.

<sup>126</sup>*Ref.* 109; Demuyck; Vialle *Bull. Soc. Chim. Fr.* **1967**, 1213.

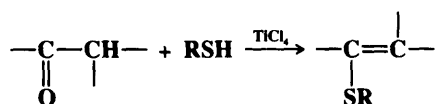
<sup>127</sup>See, for example, Fournier; Lamaty; Nata; Roque *Tetrahedron* **1975**, *31*, 809.

<sup>128</sup>For example, see Field; Sweetman *J. Org. Chem.* **1969**, *34*, 1799.

<sup>129</sup>Truce; Roberts *J. Org. Chem.* **1963**, *28*, 961.

with ethanedithiol to give a cyclic dithioketal.<sup>130</sup> After subsequent reactions involving the R or R' group, the protecting group can then be removed by 0-6. Alternatively, the dithioketal can be desulfurized with Raney nickel (4-36), giving the overall conversion  $C=O \rightarrow CH_2$ . Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of  $TiCl_4$ ,<sup>131</sup>  $SiCl_4$ ,<sup>132</sup> or polyphosphoric acid trimethylsilyl ester,<sup>133</sup> with a disulfide  $RSSR$  (R = alkyl or aryl),<sup>134</sup> or with methylthiotrimethylsilane  $MeSSiMe_3$ .<sup>135</sup>

If an aldehyde or ketone possesses an  $\alpha$  hydrogen, it can be converted to the corresponding enol thioether by treatment with a thiol in the presence of  $TiCl_4$ .<sup>136</sup>

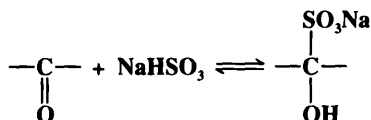


Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine-borane,  $RCOR' + R''SH \xrightarrow{BH_3} RR'CHSR''$ ,<sup>137</sup> in a reductive alkylation reaction, analogous to 6-7.

OS II, 610; IV, 927; VI, 109; VII, 124, 372. Also see OS III, 332; IV, 967; V, 780; VI, 556; 65, 215.

## 6-12 Formation of Bisulfite Addition Products

### O-Hydro-C-sulfonato-addition



Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings),  $\alpha$ -keto esters, and isocyanates, upon treatment with sodium bisulfite. Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base<sup>138</sup>)<sup>139</sup> and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.<sup>140</sup>

OS I, 241, 336; III, 438; IV, 903; V, 437.

<sup>130</sup>For a review, see Olsen; Currie, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 521-532.

<sup>131</sup>Kumar; Dev *Tetrahedron Lett.* **1983**, 24, 1289.

<sup>132</sup>Ku; Oh *Synth. Commun.* **1989**, 433.

<sup>133</sup>Kakimoto; Seri; Imai *Synthesis* **1987**, 164.

<sup>134</sup>Tazaki; Takagi *Chem. Lett.* **1979**, 767.

<sup>135</sup>Evans; Grimm; Truesdale *J. Am. Chem. Soc.* **1975**, 97, 3229.

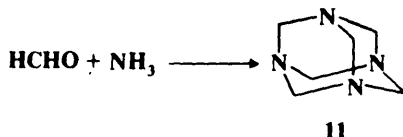
<sup>136</sup>Mukaiyama; Saigo *Chem. Lett.* **1973**, 479.

<sup>137</sup>Kikugawa *Chem. Lett.* **1981**, 1157.

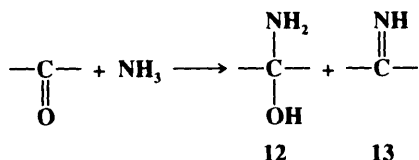
<sup>138</sup>For cleavage with ion-exchange resins, see Khusid; Chizhova *J. Org. Chem. USSR* **1985**, 21, 37.

<sup>139</sup>For a discussion of the mechanism, see Young; Jencks *J. Am. Chem. Soc.* **1978**, 100, 1228.

<sup>140</sup>The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara; Wakabayashi; Taya *Chem. Lett.* **1981**, 1657.

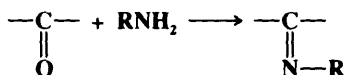
**D. Attack by  $\text{NH}_2$ ,  $\text{NHR}$ , or  $\text{NR}_2$  (Addition of  $\text{NH}_3$ ,  $\text{RNH}_2$ ,  $\text{R}_2\text{NH}$ )****6-13 The Addition of Ammonia to Aldehydes and Ketones****Formaldehyde-hexamethylenetetramine transformation**

The addition of ammonia<sup>141</sup> to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals*<sup>142</sup> (also called “aldehyde ammonias”) (**12**) and/or imines (**13**):



However, these compounds are generally unstable. Most imines with a hydrogen on the nitrogen spontaneously polymerize.<sup>143</sup> Stable hemiaminals can be prepared from polychlorinated and polyfluorinated aldehydes and ketones, and diaryl ketones do give stable imines  $\text{Ar}_2\text{C}=\text{NH}$ .<sup>144</sup> Aside from these, when stable compounds *are* prepared in this reaction, they are the result of combinations and condensations of one or more molecules of **12** and/or **13** with each other or with additional molecules of ammonia or carbonyl compound. The most important example of such a product is hexamethylenetetramine<sup>145</sup> (**11**), prepared from ammonia and formaldehyde.<sup>146</sup> Aromatic aldehydes give hydrobenzamides  $\text{ArCH}(\text{N}=\text{CHAr})_2$  derived from three molecules of aldehyde and two of ammonia.<sup>147</sup>

OS II, 214, 219; IV, 451; VI, 664, 976. Also see OS III, 471; V, 897.

**6-14 The Addition of Amines to Aldehydes and Ketones****Alkylimino-de-oxo-bisubstitution**

Primary, secondary, and tertiary amines can add to aldehydes<sup>148</sup> and ketones to give different kinds of products. Primary amines give imines.<sup>149</sup> In contrast to imines in which the nitrogen

<sup>141</sup>For a review of this reagent in organic synthesis, see Jeyaraman, in *Pizey Synthetic Reagents*, vol. 5; Wiley: New York, 1983, pp. 9-83.

<sup>142</sup>These compounds have been detected by <sup>13</sup>C nmr: Chudek; Foster; Young *J. Chem. Soc., Perkin Trans. 2* **1985**, 1285.

<sup>143</sup>Methanimine  $\text{CH}_2=\text{NH}$  is stable in solution for several hours at  $-95^\circ\text{C}$ , but rapidly decomposes at  $-80^\circ\text{C}$ : Brailon; Lasne; Ripoll; Denis *Nouv. J. Chim.* **1982**, 6, 121. See also Bock; Dammel *Chem. Ber.* **1987**, 120, 1961.

<sup>144</sup>Verardo; Giumanini; Strazzolini; Poiana *Synth. Commun.* **1988**, 18, 1501.

<sup>145</sup>For a review of this compound, see Blažević; Kolbah; Belin; Šunjić; Kajfež *Synthesis* **1979**, 161-176.

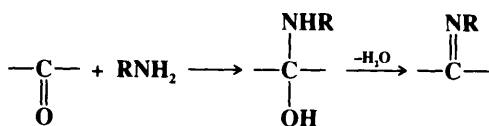
<sup>146</sup>For a discussion of the mechanism, see Nielsen; Moore; Ogan; Atkins *J. Org. Chem.* **1979**, 44, 1678.

<sup>147</sup>Ogata; Kawasaki; Okumura *J. Org. Chem.* **1964**, 29, 1985; Crowell; McLeod *J. Org. Chem.* **1967**, 32, 4030.

<sup>148</sup>For a review of the reactions between amines and formaldehyde, see Farrar *Rec. Chem. Prog.* **1968**, 29, 85-101.

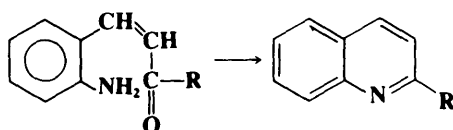
<sup>149</sup>For reviews of reactions of carbonyl compounds leading to the formation of  $\text{C}=\text{N}$  bonds, see Dayagi; Degani, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*; Ref. 40, pp. 64-83; Reeves, in Patai, Ref. 2, pp. 600-614.

is attached to a hydrogen (**6-13**), these imines are stable enough for isolation. However, in some cases, especially with simple R groups, they rapidly decompose or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases*, and this reaction is the best way to prepare them. The reaction is straightforward and proceeds in high yields. The initial N-substituted hemiaminals<sup>150</sup> lose water to give the stable Schiff bases:



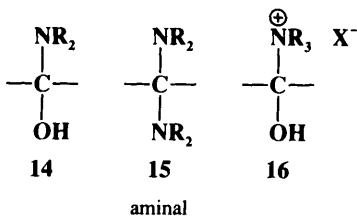
In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.<sup>151</sup> In addition, the equilibrium must often be shifted, usually by removal of the water, either azeotropically by distillation, or with a drying agent such as  $\text{TiCl}_4$ ,<sup>152</sup> or with a molecular sieve.<sup>153</sup>

The reaction is often used to effect ring closure.<sup>154</sup> The *Friedländer quinoline synthesis*<sup>155</sup> is an example:



Pyrylium ions react with ammonia or primary amines to give pyridinium ions<sup>156</sup> (see p. 354).

When secondary amines are added to aldehydes or ketones, the initially formed N,N-disubstituted hemiaminals (**14**) cannot lose water in the same way, and it is possible to isolate them.<sup>157</sup> However, they are generally unstable, and under the reaction conditions



usually react further. If no  $\alpha$  hydrogen is present, **14** is converted to the more stable *aminal* (**15**).<sup>158</sup> However, if an  $\alpha$  hydrogen is present, water (from **14**) or  $\text{RNH}_2$  (from **15**) can be lost in that direction to give an enamine:<sup>159</sup>

<sup>150</sup>Some of these have been observed spectrally; see Forlani; Marianucci; Todesco *J. Chem. Res. (S)* **1984**, 126.

<sup>151</sup>For improved methods, see Morimoto; Sekiya *Chem. Lett.* **1985**, 1371; Eisch; Sanchez *J. Org. Chem.* **1986**, 51, 1848.

<sup>152</sup>Weingarten; Chupp; White *J. Org. Chem.* **1967**, 32, 3246.

<sup>153</sup>Bonnett; Emerson *J. Chem. Soc.* **1965**, 4508; Roelofsen; van Bekkum *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 605.

<sup>154</sup>For a review of such ring closures, see Katritzky; Ostercamp; Yousaf *Tetrahedron* **1987**, 43, 5171-5186.

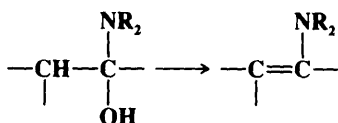
<sup>155</sup>For a review, see Cheng; Yan *Org. React.* **1982**, 28, 37-201.

<sup>156</sup>For a review, see Zvezdina; Zhadonva; Dorofeenko *Russ. Chem. Rev.* **1982**, 51, 469-484.

<sup>157</sup>For example, see Duhamel; Cantacuzène *Bull. Soc. Chim. Fr.* **1962**, 1843.

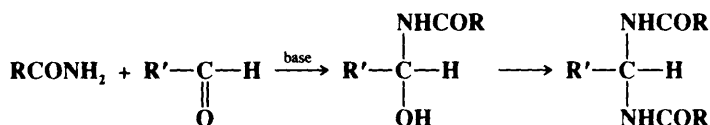
<sup>158</sup>For a review of aminals, see Duhamel, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 849-907.

<sup>159</sup>For reviews of the preparation of enamines, see Haynes; Cook, in Cook, Ref. 45, pp. 103-163; Pitacco; Valentin, in Patai, Ref. 158, pt. 1, pp. 623-714.



This is the most common method<sup>160</sup> for the preparation of enamines and usually takes place when an aldehyde or ketone containing an  $\alpha$  hydrogen is treated with a secondary amine. The water is usually removed azeotropically or with a drying agent,<sup>161</sup> but molecular sieves can also be used.<sup>162</sup> Secondary amine perchlorates react with aldehydes and ketones to give iminium salts (**2**, p. 885).<sup>163</sup> Tertiary amines can only give salts (**16**).

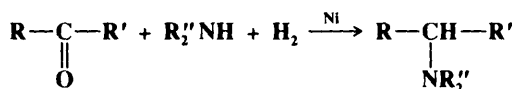
Amides can add to aldehydes in the presence of bases (so the nucleophile is actually  $\text{RCONH}^-$ ) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides:<sup>164</sup>



If the  $\text{R}'$  group contains an  $\alpha$  hydrogen, water may split out.

OS **I**, 80, 355, 381; **II**, 31, 49, 65, 202, 231, 422; **III**, 95, 328, 329, 332, 358, 374, 513, 753, 827; **IV**, 210, 605, 638, 824; **V**, 191, 277, 533, 567, 627, 703, 716, 736, 758, 808, 941, 1070; **VI**, 5, 448, 474, 496, 520, 526, 592, 601, 818, 901, 1014; **VII**, 8, 135, 144, 473; **65**, 108, 119, 146, 183; **66**, 133, 142, 203; **68**, 206. Also see OS **IV**, 283, 464; **VII**, 197; **66**, 52; **69**, 55, 158.

### 6-15 Reductive Alkylation of Ammonia or Amines Hydro,dialkylamino-de-oxo-bisubstitution



When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen and a hydrogenation catalyst (heterogeneous or homogeneous), *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.<sup>165</sup> The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably does correspond to the actual sequence of steps:<sup>166</sup>

<sup>160</sup>For another method, see Katritzky; Long; Lue; Jozwiak *Tetrahedron* **1990**, 46, 8153.

<sup>161</sup>For example,  $\text{TiCl}_4$ : White; Weingarten *J. Org. Chem.* **1967**, 32, 213; Kuo; Daly *J. Org. Chem.* **1970**, 35, 1861; Nilsson; Carlson *Acta Chem. Scand. Sect. B* **1984**, 38, 523.

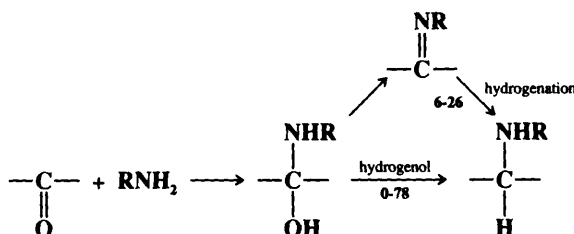
<sup>162</sup>Brannock; Bell; Burpitt; Kelly *J. Org. Chem.* **1964**, 29, 801; Taguchi; Westheimer *J. Org. Chem.* **1971**, 36, 1570; Roelofsens; van Bekkum. Ref. 153; Carlson; Nilsson; Strömqvist *Acta Chem. Scand., Ser. B* **1983**, 37, 7.

<sup>163</sup>Leonard; Paukstelis *J. Org. Chem.* **1964**, 28, 3021.

<sup>164</sup>For reviews, see Challis; Challis, in Zabicky, Ref. 65, pp. 754-759; Zaugg; Martin *Org. React.* **1965**, 14, 52-269, pp. 91-95, 104-112. For a discussion, see Gilbert *Synthesis* **1972**, 30.

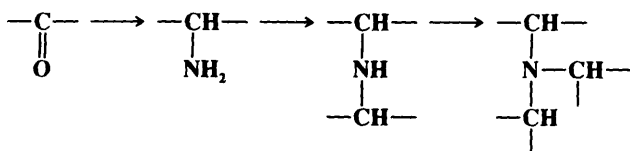
<sup>165</sup>For reviews, see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985, pp. 82-93; Klyuev; Khidekel *Russ. Chem. Rev.* **1980**, 49, 14-27; Rylander, *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967, pp. 291-303.

<sup>166</sup>See, for example, Le Bris; Lefebvre; Coussement *Bull. Soc. Chim. Fr.* **1964**, 1366, 1374, 1584, 1594.



For ammonia and primary amines there are two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. Other reducing agents<sup>167</sup> can be used instead of hydrogen and a catalyst, among them zinc and HCl, sodium cyanoborohydride  $\text{NaBH}_3\text{CN}$ ,<sup>168</sup> sodium triacetoxyborohydride,<sup>169</sup> sodium borohydride,<sup>170</sup> iron pentacarbonyl and alcoholic KOH,<sup>171</sup>  $\text{BH}_3$ -pyridine,<sup>172</sup> and formic acid. When the last is used, the process is called the *Wallach reaction*. In the particular case where primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is called the *Eschweiler-Clarke procedure*. It is possible to use ammonium (or amine) salts of formic acid,<sup>173</sup> or formamides, as a substitute for the Wallach conditions. This method is called the *Leuckart reaction*,<sup>174</sup> and in this case the products obtained are often the N-formyl derivatives of the amines instead of the free amines. Primary and secondary amines can be N-ethylated (e.g.,  $\text{ArNHR} \rightarrow \text{ArNREt}$ ) by treatment with  $\text{NaBH}_4$  in acetic acid.<sup>175</sup>

When the reagent is ammonia, it is possible for the initial product to react again and for this product to react again, so that secondary and tertiary amines are usually obtained as side products:



Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have

<sup>167</sup>For a list of many of these, with references, see Ref. 64, pp. 421-423.

<sup>168</sup>Borch; Bernstein; Durst *J. Am. Chem. Soc.* **1971**, 93, 2897; Mattson; Pham; Leuck; Cowen *J. Org. Chem.* **1990**, 55, 2552. See also Barney; Huber; McCarthy *Tetrahedron Lett.* **1990**, 31, 5547. For reviews of  $\text{NaBH}_3\text{CN}$ , see Hutchins; Natale *Org. Prep. Proced. Int.* **1979**, 11, 201-246; Lane *Synthesis* **1975**, 135-146.

<sup>169</sup>Abdel-Magid; Maryanoff; Carson *Tetrahedron Lett.* **1990**, 31, 5595.

<sup>170</sup>Schellenberg *J. Org. Chem.* **1963**, 28, 3259; Gribble; Nutaitis *Synthesis* **1987**, 709.

<sup>171</sup>Watanabe; Yamashita; Mitsudo; Tanaka; Takegami *Tetrahedron Lett.* **1974**, 1879; Watanabe; Mitsudo; Yamashita; Shim; Takegami *Chem. Lett.* **1974**, 1265.

<sup>172</sup>Pelter; Rosser; Mills *J. Chem. Soc., Perkin Trans. 1* **1984**, 717.

<sup>173</sup>For a review of ammonium formate in organic synthesis, see Ram; Ehrenkauf *Synthesis* **1988**, 91-95.

<sup>174</sup>For a review, see Moore, *Org. React.* **1949**, 5, 301-330; for discussions of the mechanism, see Lukasiwicz *Tetrahedron* **1963**, 19, 1789; Ito; Oba; Sekiya *Bull. Chem. Soc. Jpn.* **1976**, 49, 2485; Awachie; Agwada *Tetrahedron* **1990**, 46, 1899.

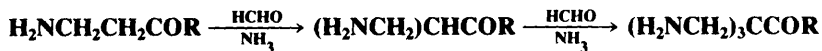
<sup>175</sup>Gribble; Lord; Skotnicki; Dietz; Eaton; Johnson *J. Am. Chem. Soc.* **1974**, 96, 7812; Gribble; Jasinski; Pellicone; Panetta *Synthesis* **1978**, 766. See also Marchini; Liso; Reho; Liberatore; Moracci *J. Org. Chem.* **1975**, 40, 3453. For a review, see Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985**, 17, 317-384, pp. 336-350.



The Mannich base can react further in three ways. If it is a primary or secondary amine, it may condense with one or two additional molecules of aldehyde and active compound, e.g.,



If the active hydrogen compound has two or three active hydrogens, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine, e.g.,

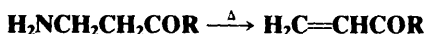


Another further reaction consists of condensation of the Mannich base with excess formaldehyde:

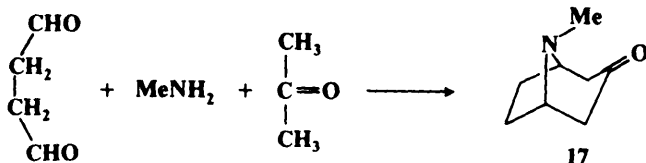


Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are side products.

When the Mannich base contains an amino group  $\beta$  to a carbonyl (and it usually does), ammonia is easily eliminated. This is a route to  $\alpha,\beta$ -unsaturated aldehydes, ketones, esters, etc.:

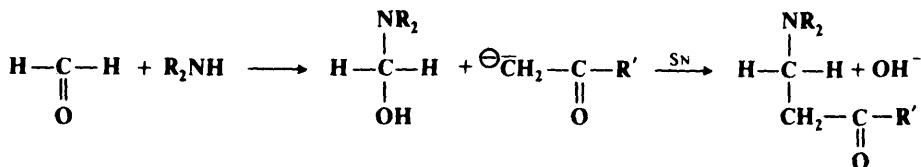


The Mannich reaction is an important biosynthetic route to natural products, mainly alkaloids, and some of these routes have been duplicated in the laboratory. A classic example is the synthesis of tropinone (**17**) by Robinson in 1917. Robinson synthesized tropinone by a Mannich reaction involving succindialdehyde, methylamine, and acetone:<sup>183</sup>



Studies of the reaction kinetics have led to the following proposals for the mechanism of the Mannich reaction.<sup>184</sup>

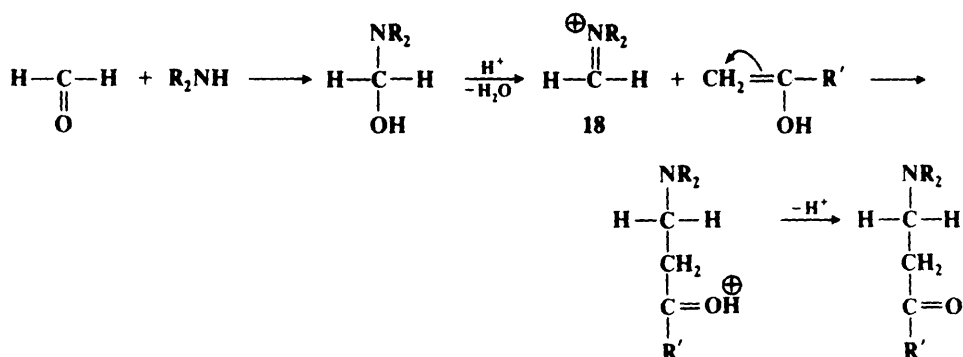
The base-catalyzed reaction



<sup>183</sup>Robinson *J. Chem. Soc.* **1917**, 111, 762.

<sup>184</sup>Cummings; Shelton *J. Org. Chem.* **1960**, 25, 419.

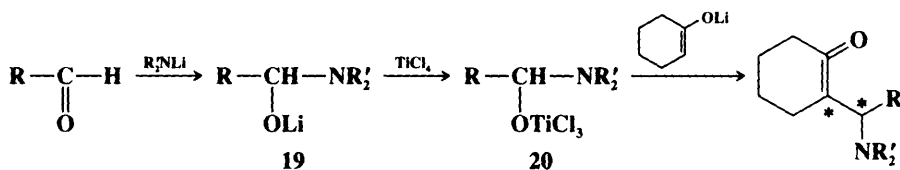
The acid-catalyzed reaction



According to this mechanism, it is the free amine, not the salt that reacts, even in acid solution; and the active-hydrogen compound (in the acid-catalyzed process) reacts as the enol when that is possible. This latter step is similar to what happens in 2-4. There is kinetic evidence for the intermediacy of the iminium ion (18).<sup>185</sup>

When it is desired to use an unsymmetrical ketone as the active-hydrogen component, it is possible to get two products. Regioselectivity has been obtained by treatment of the ketone with preformed iminium ions:<sup>186</sup> the use of  $\text{Me}_2\text{N}=\text{CH}_2 \text{ CF}_3\text{COO}^-$  in  $\text{CF}_3\text{COOH}$  gives substitution at the more highly substituted position, while with  $\text{iso-Pr}_2\text{N}=\text{CH}_2 \text{ ClO}_4^-$  the reaction takes place at the less highly substituted position.<sup>187</sup> The preformed iminium compound dimethyl(methylene)ammonium iodide  $\text{CH}_2=\text{NMe}_2^+ \text{ I}^-$ , called *Eschenmoser's salt*,<sup>188</sup> has also been used in Mannich reactions.<sup>189</sup>

Another type of preformed reagent (20) has been used to carry out diastereoselective Mannich reactions. The lithium salts 19 are treated with  $\text{TiCl}_4$  to give 20, which is then treated with the enolate of a ketone.<sup>190</sup>



Also see 6-50 and 1-25.

OS III, 305; IV, 281, 515, 816; VI, 474, 981, 987; VII, 34. See also OS 68, 188.

<sup>185</sup>Benkovic; Benkovic; Comfort *J. Am. Chem. Soc.* **1969**, 91, 1860.

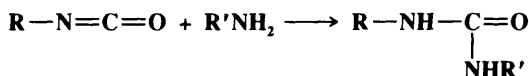
<sup>186</sup>For earlier use of preformed iminium ions in the Mannich reaction, see Ahond; Cavé; Kan-Fan; Husson; de Rostolan; Potier *J. Am. Chem. Soc.* **1968**, 90, 5622; Ahond; Cavé; Kan-Fan; Potier *Bull. Soc. Chim. Fr.* **1970**, 2707; Ref. 188.

<sup>187</sup>Jasor; Luche; Gaudry; Marquet *J. Chem. Soc., Chem. Commun.* **1974**, 253; Gaudry; Jasor; Khac *Org. Synth.* VI, 474.

<sup>188</sup>Schreiber; Maag; Hashimoto; Eschenmoser *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 330 [*Angew. Chem.* 83, 355].

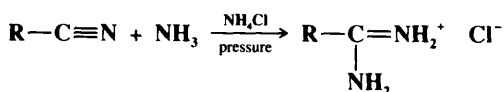
<sup>189</sup>See Holy; Fowler; Burnett; Lorenz *Tetrahedron* **1979**, 35 613; Bryson; Bonitz; Reichel; Dardis *J. Org. Chem.* **1980**, 45, 524, and references cited in these papers.

<sup>190</sup>Seebach; Betschart; Schweizer *Helv. Chim. Acta* **1984**, 67, 1593; Seebach; Schiess; Schweizer *Chimia* **1985**, 39, 272. See also Heaney; Papageorgiou; Wilkins *J. Chem. Soc., Chem. Commun.* **1988**, 1161; Katritzky; Harris *Tetrahedron* **1990**, 46, 987.

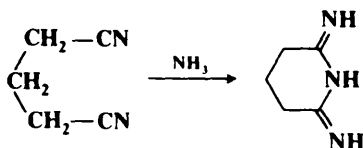
**6-17 The Addition of Amines to Isocyanates*****N*-Hydro-*C*-alkylamino-addition**

Ammonia and primary and secondary amines can be added to isocyanates<sup>191</sup> to give substituted ureas.<sup>192</sup> Isothiocyanates give thioureas. This is an excellent method for the preparation of ureas and thioureas, and these compounds are often used as derivatives for primary and secondary amines. Isocyanic acid HNCO also gives the reaction; usually its salts, e.g., NaNCO, are used. Wöhler's famous synthesis of urea involved the addition of ammonia to a salt of this acid.<sup>193</sup>

OS II, 79; III, 76, 617, 735; IV, 49, 180, 213, 515, 700; V, 555, 801, 802, 967; VI, 936, 951; 65, 173.

**6-18 The Addition of Ammonia or Amines to Nitriles*****N*-Hydro-*C*-amino-addition**

Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.<sup>194</sup> Many amidines have been made in this way. Dinitriles of suitable chain length can give imidines:<sup>195</sup>



Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; e.g.,  $\text{Cl}_3\text{CCN}$  gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.<sup>196</sup> However, ordinary nitriles can be converted to amidines by treatment with an alkylchloroaluminum amide  $\text{MeAl}(\text{Cl})\text{NR}_2$  ( $\text{R} = \text{H}$  or  $\text{Me}$ ).<sup>197</sup> The addition of ammonia to cyanamide  $\text{NH}_2\text{CN}$  gives guanidine  $(\text{NH}_2)_2\text{C}=\text{NH}$ .

If water is present, and a ruthenium complex catalyst is used, the addition of a

<sup>191</sup>For a review of the mechanism, see Satchell; Satchell, Ref. 46.

<sup>192</sup>For a review of substituted ureas, see Vishnyakova; Golubeva; Glebova *Russ. Chem. Rev.* **1985**, 54, 249-261.

<sup>193</sup>For a history of the investigation of the mechanism of the Wöhler synthesis, see Shorter, *Chem. Soc. Rev.* **1978**, 7, 1-14. See also Williams; Jencks *J. Chem. Soc., Perkin Trans. 2* **1974**, 1753, 1760; Hall; Watts *Aust. J. Chem.* **1977**, 30, 781, 903.

<sup>194</sup>For reviews of amidines, see Granik *Russ. Chem. Rev.* **1983**, 52, 377-393; Gautier; Miocque; Farnoux, in Patai, Ref. 103, pp. 283-348.

<sup>195</sup>Elvidge; Linstead; Salaman *J. Chem. Soc.* **1959**, 208.

<sup>196</sup>Grivas; Taurins *Can. J. Chem.* **1961**, 39, 761.

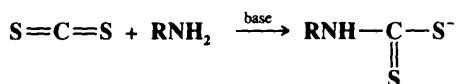
<sup>197</sup>Garigipati *Tetrahedron Lett.* **1990**, 31, 1969.

primary or secondary amine to a nitrile gives an amide:  $\text{RCN} + \text{R}'\text{NHR}'' + \text{H}_2\text{O} \rightarrow \text{RCONR}'\text{R}'' + \text{NH}_3$  ( $\text{R}''$  may be H).<sup>198</sup>

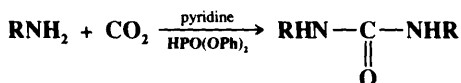
OS I, 302 [but also see OS V, 589]; IV, 245, 247, 515, 566, 769. See also OS V, 39.

### 6-19 The Addition of Amines to Carbon Disulfide and Carbon Dioxide

#### S-Metallo-C-alkylamino-addition



Salts of dithiocarbamic acid can be prepared by the addition of primary or secondary amines to carbon disulfide.<sup>199</sup> This reaction is similar to 6-10.  $\text{H}_2\text{S}$  can be eliminated from the product, directly or indirectly, to give isothiocyanates  $\text{RNCS}$ . Isothiocyanates can be obtained directly by the reaction of primary amines and  $\text{CS}_2$  in pyridine in the presence of dicyclohexylcarbodiimide.<sup>200</sup> In the presence of diphenyl phosphite and pyridine, primary amines add to  $\text{CO}_2$  and to  $\text{CS}_2$  to give, respectively, symmetrically substituted ureas and thioureas:<sup>201</sup>

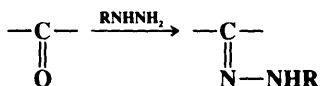


OS I, 447; III, 360, 394, 599, 763; V, 223.

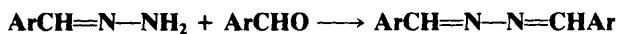
### E. Other Nitrogen Nucleophiles

### 6-20 The Addition of Hydrazine Derivatives to Carbonyl Compounds

#### Hydrazono-de-oxo-bisubstitution



The product of condensation of a hydrazine and an aldehyde or ketone is called a *hydrazone*. Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones, either no useful product can be isolated, or the remaining  $\text{NH}_2$  group condenses with a second mole of carbonyl compound to give an *azine*. This type of product is especially important for aromatic aldehydes:



An azine

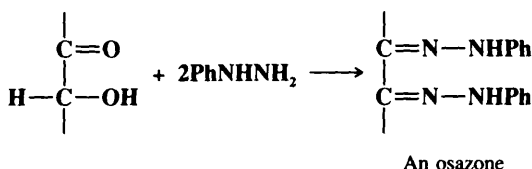
<sup>198</sup>Murahashi; Naota; Saito *J. Am. Chem. Soc.* **1986**, *108*, 7846.

<sup>199</sup>For reviews, see Ref. 106, pp. 226-315; Katritzky; Faïd-Allah; Marson *Heterocycles* **1987**, *26*, 1657-1670; Yokoyama; Imamoto *Synthesis* **1984**, 797-824, pp. 804-812. For a review of the addition of heterocyclic amines to  $\text{CO}_2$  to give, e.g., salts of pyrrole-1-carboxylic acids, see Katritzky; Marson; Faïd-Allah *Heterocycles* **1987**, *26*, 1333-1344.

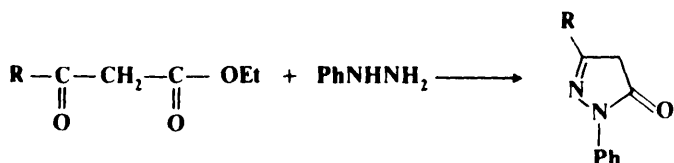
<sup>200</sup>Jochims *Chem. Ber.* **1968**, *101*, 1746. For other methods, see Sakai; Fujinami; Aizawa *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2981; Gittos; Davies; Iddon; Suschitzky *J. Chem. Soc., Perkin Trans. I* **1976**, 141; Shibamura; Shiono; Mukaiyama *Chem. Lett.* **1977**, 573; Molina; Alajarin; Arques *Synthesis* **1982**, 596.

<sup>201</sup>Yamazaki; Higashi; Iguchi *Tetrahedron Lett.* **1974**, 1191. For other methods for the conversion of amines and  $\text{CO}_2$  to ureas, see Ogura; Takeda; Tokue; Kobayashi *Synthesis* **1978**, 394; Fournier; Bruneau; Dixneuf; Lécolier *J. Org. Chem.* **1991**, *56*, 4456.

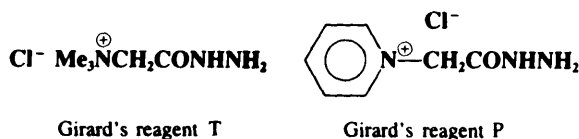
However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.<sup>202</sup> Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl,<sup>203</sup> are used much more often and give the corresponding hydrazones with most aldehydes and ketones.<sup>204</sup> Since these are usually solids, they make excellent derivatives and are commonly employed for this purpose.  $\alpha$ -Hydroxy aldehydes and ketones and  $\alpha$ -dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon–nitrogen double bonds:



Osazones are particularly important in carbohydrate chemistry. In contrast to this behavior,  $\beta$ -diketones and  $\beta$ -keto esters give *pyrazoles* and *pyrazolones*, respectively (illustrated for  $\beta$ -keto esters):

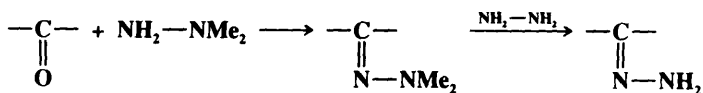


Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide  $\text{NH}_2\text{NHCONH}_2$ , in which case the hydrazone is called a semicarbazone, and *Girard's reagents T and P*, in which case the hydrazone is water-soluble because of the ionic



group. Girard's reagents are often used for purification of carbonyl compounds.<sup>205</sup>

Simple N-unsubstituted hydrazones can be obtained by an exchange reaction. The N,N-dimethylhydrazone is prepared first and then treated with hydrazine:<sup>206</sup>



No azines are formed under these conditions.

<sup>202</sup>For example, see Day; Whiting *Org. Synth.* VI, 10.

<sup>203</sup>For an improved procedure for the preparation of 2,4-dinitrophenylhydrazones, see Behforouz; Bolan; Flynt *J. Org. Chem.* **1985**, 50, 1186.

<sup>204</sup>For a review of arylhydrazones, see Buckingham *Q. Rev., Chem. Soc.* **1969**, 23, 37-56.

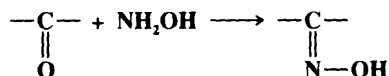
<sup>205</sup>For a study of the mechanism with Girard's reagent T, see Stachissini; do Amaral *J. Org. Chem.* **1991**, 56, 1419.

<sup>206</sup>Newkome; Fishel *J. Org. Chem.* **1966**, 31, 677.

OS II, 395; III, 96, 351; IV, 351, 377, 536, 884; V, 27, 258, 747, 929; VI, 10, 12, 62, 242, 293, 679, 791; VII, 77, 438. Also see OS III, 708; VI, 161; 66, 142.

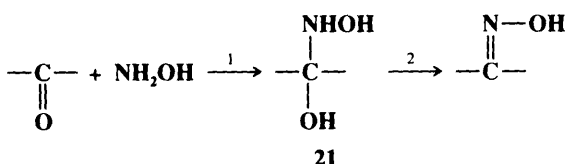
## 6-21 The Formation of Oximes

### Hydroxyimino-de-oxo-bisubstitution



In a reaction very much like 6-20, oximes can be prepared by the addition of hydroxylamine to aldehydes or ketones. Derivatives of hydroxylamine, e.g.,  $\text{H}_2\text{NOSO}_3\text{H}$  and  $\text{HON}(\text{SO}_3\text{Na})_2$ , have also been used. For hindered ketones, such as hexamethylacetone, high pressures, e.g., 10,000 atm, may be necessary.<sup>207</sup>

It has been shown<sup>208</sup> that the rate of formation of oximes is at a maximum at a pH which depends on the substrate but is usually about 4, and that the rate decreases as the pH is either raised or lowered from this point. We have previously seen (p. 332) that bell-shaped curves like this are often caused by changes in the rate-determining step. In this case, at low pH values step 2 is rapid (because it is acid-catalyzed), and step 1 is slow (and rate-



determining), because under these acidic conditions most of the  $\text{NH}_2\text{OH}$  molecules have been converted to the conjugate  $\text{NH}_3\text{OH}^+$  ions, which cannot attack the substrate. As the pH is slowly increased, the fraction of free  $\text{NH}_2\text{OH}$  molecules increases and consequently so does the reaction rate, until the maximum rate is reached at about  $\text{pH} = 4$ . As the rising pH has been causing an increase in the rate of step 1, it has also been causing a *decrease* in the rate of the acid-catalyzed step 2, although this latter process has not affected the overall rate since step 2 was still faster than step 1. However, when the pH goes above about 4, step 2 becomes rate-determining, and although the rate of step 1 is still increasing (as it will until essentially all the  $\text{NH}_2\text{OH}$  is unprotonated), it is now step 2 that determines the rate, and this step is slowed by the decrease in acid concentration. Thus the overall rate decreases as the pH rises beyond about 4. It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.<sup>209</sup> There is evidence that when the nucleophile is 2-methylthiosemicarbazide, there is a second change in the rate-determining step: above pH about 10 *basic* catalysis of step 2 has increased the rate of this step to the point where step 1 is again rate-determining.<sup>210</sup> Still a third change in the rate-determining step has been found at about  $\text{pH} = 1$ , showing

<sup>207</sup>Jones; Tristram; Benning *J. Am. Chem. Soc.* **1959**, *81*, 2151.

<sup>208</sup>Jencks *J. Am. Chem. Soc.* **1959**, *81*, 475, *Prog. Phys. Org. Chem.* **1964**, *2*, 63-128.

<sup>209</sup>For reviews of the mechanism of such reactions, see Cockerill; Harrison, in Patai *The Chemistry of Functional Groups: Supplement A*, pt. 1; Wiley: New York, 1977, pp. 288-299; Sollenberger; Martin, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 367-392. For isotope effect studies, see Rossi; Stachissini; do Amaral *J. Org. Chem.* **1990**, *55*, 1300.

<sup>210</sup>Sayer; Jencks *J. Am. Chem. Soc.* **1972**, *94*, 3262.

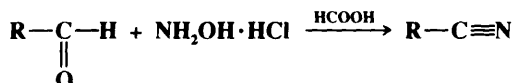
that at least in some cases step 1 actually consists of two steps: formation of a zwitterion, e.g.,  $\text{HONH}_2^+-\text{C}(\text{O})-\text{O}^-$  in the case shown above, and conversion of this to **21**.<sup>211</sup> The intermediate **21** has been detected by nmr in the reaction between  $\text{NH}_2\text{OH}$  and acetaldehyde.<sup>212</sup>

In another type of process, oximes can be obtained by passing a mixture of ketone vapor,  $\text{NH}_3$ , and  $\text{O}_2$  over a silica-gel catalyst.<sup>213</sup> Ketones can also be converted to oximes by treatment with other oximes, in a transoximation reaction.<sup>214</sup>

OS **I**, 318, 327; **II**, 70, 204, 313, 622; **III**, 690, **IV**, 229; **V**, 139, 1031; **VII**, 149. See also OS **VI**, 670.

## 6-22 The Conversion of Aldehydes to Nitriles

### Nitrilo-de-hydro,oxo-tersubstitution



Aldehydes can be converted to nitriles in one step by treatment with hydroxylamine hydrochloride and either formic acid,<sup>215</sup> concentrated  $\text{HCl}$ ,<sup>216</sup>  $\text{SeO}_2$ ,<sup>217</sup>  $\text{MeNO}_2$ -polyphosphoric acid,<sup>218</sup> or pyridine-toluene.<sup>219</sup> The reaction is a combination of **6-21** and **7-37**. Direct nitrile formation has also been accomplished with certain derivatives of  $\text{NH}_2\text{OH}$ , notably,  $\text{N,O}$ -bistrifluoroacetylhydroxylamine  $\text{F}_3\text{CCONHOCOCF}_3$ <sup>220</sup> and  $\text{NH}_2\text{OSO}_2\text{OH}$ .<sup>221</sup> Another method involves treatment with hydrazoic acid, though the Schmidt reaction (**8-17**) may compete.<sup>222</sup> Aromatic aldehydes have been converted to nitriles in good yield with  $\text{NH}_4\text{H}_2\text{PO}_4$  and nitropropane in acetic acid,<sup>223</sup> with trimethylsilyl azide,<sup>224</sup> with  $\text{S,S}$ -dimethylsulfurdiimide,<sup>225</sup> with  $\text{NH}_4\text{Cl}-\text{O}_2-\text{Cu}$  in pyridine,<sup>226</sup> with hydroxylamine hydrochloride,  $\text{MgSO}_4$ , and  $\text{TsOH}$ ,<sup>227</sup> and with ammonia and iodine or lead tetraacetate.<sup>228</sup>

<sup>211</sup>Rosenberg; Silver; Sayer; Jencks *J. Am. Chem. Soc.* **1974**, *96*, 7986; Sayer; Pinsky; Schonbrunn; Washtien *J. Am. Chem. Soc.* **1974**, *96*, 7998; Sayer; Edman *J. Am. Chem. Soc.* **1979**, *101*, 3010.

<sup>212</sup>Cocivera; Fyfe; Effio; Vaish; Chen *J. Am. Chem. Soc.* **1976**, *98*, 1573; Cocivera; Effio *J. Am. Chem. Soc.* **1976**, *98*, 7371.

<sup>213</sup>Armor *J. Am. Chem. Soc.* **1980**, *102*, 1453.

<sup>214</sup>For example, see Block; Newman *Org. Synth.* **V**, 1031.

<sup>215</sup>Olah; Keumi *Synthesis* **1979**, 112.

<sup>216</sup>Findlay; Tang *Can. J. Chem.* **1967**, *45*, 1014.

<sup>217</sup>Sosnovsky; Krogh; Umhoefer *Synthesis* **1979**, 722.

<sup>218</sup>Ganboa; Palomo *Synth. Commun.* **1983**, *13*, 999.

<sup>219</sup>Saednya *Synthesis* **1982**, 190.

<sup>220</sup>Pomeroy; Craig *J. Am. Chem. Soc.* **1959**, *81*, 6340.

<sup>221</sup>Streith; Fizet; Fritz *Helv. Chim. Acta* **1976**, *59*, 2786.

<sup>222</sup>For additional methods, see Glass; Hoy *Tetrahedron Lett.* **1976**, 1781; Ikeda; Machii; Okahara *Synthesis* **1978**, 301; Nakagawa; Mineo; Kawamura; Horikawa; Tokumoto; Mori *Synth. Commun.* **1979**, *9*, 529; Furukawa; Fukumura; Akasaka; Yoshimura; Oae *Tetrahedron Lett.* **1980**, *21*, 761; Gelas-Mialhe; Vessière *Synthesis* **1980**, 1005; Arques; Molina; Soler *Synthesis* **1980**, 702; Sato; Itoh; Itoh; Nishina; Goto; Saito *Chem. Lett.* **1984**, 1913; Reddy; Reddy *Synth. Commun.* **1988**, *18*, 2179; Neunhoeffer; Diehl; Karafiat *Liebigs Ann. Chem.* **1989**, 105; Said; Skarzewski; Mlochowski *Synthesis* **1989**, 223.

<sup>223</sup>Blatter; Lukaszewski; de Stevens, *J. Am. Chem. Soc.* **1961**, *83*, 2203. See also Dauzonne; Demerseman; Royer *Synthesis* **1981**, 739; Karmarkar; Kelkar; Wadia *Synthesis* **1985**, 510.

<sup>224</sup>Nishiyama; Oba; Watanabe *Tetrahedron* **1987**, *43*, 693.

<sup>225</sup>Georg; Pfeifer; Haake *Tetrahedron Lett.* **1985**, *26*, 2739.

<sup>226</sup>Capdevielle; Lavigne; Maumy *Synthesis* **1989**, 451. See also Yamazaki; Yamazaki *Chem. Lett.* **1990**, 571.

<sup>227</sup>Ganboa; Palomo *Synth. Commun.* **1983**, *13*, 219.

<sup>228</sup>Misono; Osa; Koda *Bull. Chem. Soc. Jpn.* **1966**, *39*, 854, **1967**, *40*, 2875; Parameswaran; Friedman *Chem. Ind. (London)* **1965**, 988.

On treatment with two equivalents of dimethylaluminum amide  $\text{Me}_2\text{AlNH}_2$ , carboxylic esters can be converted to nitriles:  $\text{RCOOR}' \rightarrow \text{RCN}$ .<sup>229</sup> This is very likely a combination of 0-55 and 7-39.

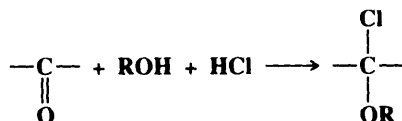
See also 9-5.

OS V, 656.

## F. Halogen Nucleophiles

### 6-23 The Formation of $\alpha$ -Halo Ethers

#### Alkoxy, halo-de-oxo-bisubstitution



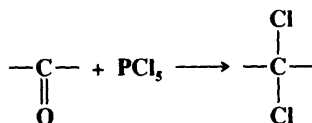
$\alpha$ -Halo ethers can be prepared by treatment of aldehydes and ketones with an alcohol and HX. The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. Aromatic aldehydes and ketones react poorly.<sup>230</sup>

The addition of HX to an aldehyde or ketone gives  $\alpha$ -halo alcohols, which are usually unstable, though exceptions are known, especially with perfluoro and perchloro species.<sup>231</sup> Unstable  $\alpha$ -halo alcohols may be quite stable in the dimeric form  $2\text{XCR}_2\text{OH} \rightarrow \text{XCR}_2\text{OCR}_2\text{X}$ .

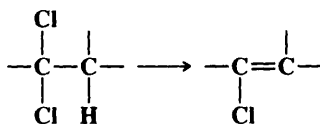
OS I, 377; IV, 101 (see, however, OS V, 218), 748; VI, 101.

### 6-24 The Formation of *gem*-Dihalides from Aldehydes and Ketones

#### Dihalo-de-oxo-bisubstitution



Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides<sup>232</sup> by treatment with  $\text{PCl}_5$ . The reaction fails for perhalo ketones.<sup>233</sup> If the aldehyde or ketone has an  $\alpha$  hydrogen, elimination of HCl may follow and a vinylic chloride is a frequent side product:<sup>234</sup>



<sup>229</sup>Wood; Khatri; Weinreb *Tetrahedron Lett.* **1979**, 4907.

<sup>230</sup>Klages; Mühlbauer *Chem. Ber.* **1959**, 92, 1818.

<sup>231</sup>For example, see Andreades; England *J. Am. Chem. Soc.* **1961**, 83, 4670; Clark; Emsley; Hibbert *J. Chem. Soc., Perkin Trans. 2* **1968**, 1107.

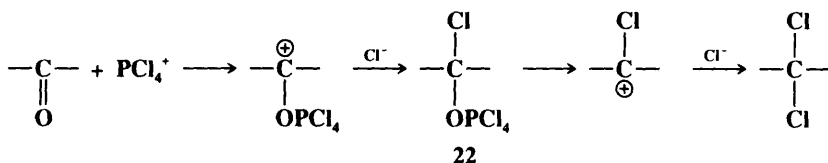
<sup>232</sup>For a list of reagents that convert aldehydes and ketones to *gem*-dihalides or vinylic halides, with references, see Ref. 64, pp. 372-375.

<sup>233</sup>Farah; Gilbert *J. Org. Chem.* **1965**, 30, 1241.

<sup>234</sup>See, for example, Nikolenko; Popov *J. Gen. Chem. USSR* **1962**, 32, 29.

or even the main product.<sup>235</sup>  $\text{PBr}_5$  does not give good yields of *gem*-dibromides,<sup>236</sup> but these can be obtained from aldehydes, by the use of  $\text{Br}_2$  and triphenyl phosphite.<sup>237</sup>

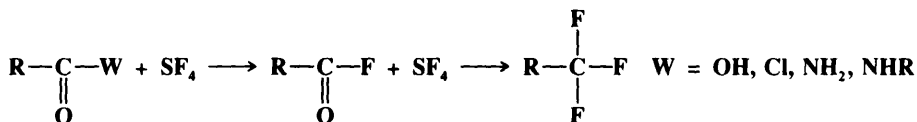
The mechanism of *gem*-dichloride formation involves initial attack of  $\text{PCl}_4^+$  (which is present in solid  $\text{PCl}_5$ ) at the oxygen, followed by addition of  $\text{Cl}^-$  to the carbon:<sup>238</sup>



This chloride ion may come from  $\text{PCl}_6^-$  (which is also present in solid  $\text{PCl}_5$ ). There follows a two-step  $\text{S}_{\text{N}}1$  process. Alternatively, 22 can be converted to the product without going through the chlorocarocation, by an  $\text{S}_{\text{N}}i$  process.

This reaction has sometimes been performed on carboxylic esters, though these compounds very seldom undergo any addition to the  $\text{C}=\text{O}$  bond. An example is the conversion of  $\text{F}_3\text{CCOOPh}$  to  $\text{F}_3\text{CCCl}_2\text{OPh}$ .<sup>239</sup> However, formates commonly give the reaction.

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride  $\text{SF}_4$ ,<sup>240</sup> including quinones, which give 1,1,4,4-tetrafluorocyclohexadiene derivatives. With ketones, yields can be raised and the reaction temperature lowered, by the addition of anhydrous  $\text{HF}$ .<sup>241</sup> Carboxylic acids, acyl chlorides, and amides react with  $\text{SF}_4$  to give 1,1,1-trifluorides. In these cases the first product is the acyl fluoride, which then undergoes the *gem*-difluorination reaction:



The acyl fluoride can be isolated. Carboxylic esters also give trifluorides, though more vigorous conditions are required, but in this case the carbonyl group of the ester is attacked first, and  $\text{RCF}_2\text{OR}'$  can be isolated from  $\text{RCOOR}'$ <sup>242</sup> and then converted to the trifluoride. Anhydrides can react in either manner, and both types of intermediate are isolable under the right conditions.  $\text{SF}_4$  even converts carbon dioxide to  $\text{CF}_4$ . A disadvantage of reactions with  $\text{SF}_4$  is that they require a pressure vessel lined with stainless steel. Selenium tetrafluoride  $\text{SeF}_4$  gives similar reactions, but atmospheric pressure and ordinary glassware can be used.<sup>243</sup> Another reagent that is often used to convert aldehydes and ketones to *gem*-difluorides is the commercially available diethylaminosulfur trifluoride (DAST)  $\text{Et}_2\text{NSF}_3$ .<sup>244</sup> Among other

<sup>235</sup>See, for example, Newman; Fraenkel; Kirn *J. Org. Chem.* **1963**, 28, 1851.

<sup>236</sup>For an indirect method of converting ketones to *gem*-dibromides, see Napolitano; Fiaschi; Mastroiilli *Synthesis* **1986**, 122.

<sup>237</sup>Hoffmann; Bovicelli *Synthesis* **1990**, 657. See also Lansinger; Ronald *Synth. Commun.* **1979**, 9, 341.

<sup>238</sup>Newman; Wood *J. Am. Chem. Soc.* **1959**, 81, 4300; Newman *J. Org. Chem.* **1969**, 34, 741.

<sup>239</sup>Kirsanov; Molosnova *J. Gen. Chem. USSR* **1958**, 28, 31; Clark; Simons *J. Org. Chem.* **1961**, 26, 5197.

<sup>240</sup>For reviews, see Wang *Org. React.* **1985**, 34, 319-400; Boswell; Ripka; Scribner; Tullock *Org. React.* **1974**, 21, 1-124.

<sup>241</sup>Muratov; Mohamed; Kunshenko; Burmakov; Alekseeva; Yagupol'skii *J. Org. Chem. USSR* **1985**, 21, 1292.

<sup>242</sup>For methods of converting  $\text{RCOOR}'$  to  $\text{RCF}_2\text{OR}'$ , see Boguslavskaya; Panteleeva; Chuvatkin *J. Org. Chem. USSR* **1982**, 18, 198; Bunnelle; McKinnis; Narayanan *J. Org. Chem.* **1990**, 55, 768.

<sup>243</sup>Olah; Nojima; Kerekes *J. Am. Chem. Soc.* **1974**, 96, 925.

<sup>244</sup>Markovskij; Pashinnik; Kirsanov *Synthesis* **1973**, 787; Middleton *J. Org. Chem.* **1975**, 40, 574. For a review of DAST and related reagents, see Hudlický *Org. React.* **1988**, 35, 513-637.

reagents<sup>245</sup> used have been phenylsulfur trifluoride  $\text{PhSF}_3$ ,<sup>246</sup> and molybdenum hexafluoride  $\text{MoF}_6$ .<sup>247</sup>

The mechanism with  $\text{SF}_4$  is probably similar in general nature, if not in specific detail, to that with  $\text{PCl}_5$ .

Aromatic aldehydes, ketones, and carboxylic acids and esters can be halogenated and reduced in one operation (e.g.,  $\text{ArCHO} \rightarrow \text{ArCH}_2\text{Br}$ ), by treatment with  $\text{LiAlH}_4$  followed by  $\text{HBr}$ .<sup>248</sup>

OS II, 549; V, 365, 396, 1082; VI, 505, 845; 66, 173. Also see OS I, 506.

## G. Attack by Hydrogen

### 6-25 Reduction of Aldehydes and Ketones to Alcohols C,O-Dihydro-addition



Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents,<sup>249</sup> of which lithium aluminum hydride and other metallic hydrides are the most commonly used.<sup>250</sup> These reagents have two main advantages over many other reducing agents: they do not reduce carbon-carbon double (or triple) bonds, and they generally contain a lot of hydrogen in a small amount of reagent—with  $\text{LiAlH}_4$ , all four hydrogens are usable for reduction. The reaction is broad and general.  $\text{LiAlH}_4$  easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes, containing double or triple bonds and/or nonreducible groups such as  $\text{NR}_3$ ,  $\text{OH}$ ,  $\text{OR}$ ,  $\text{F}$ , etc. If the molecule contains a group reducible by  $\text{LiAlH}_4$  (e.g.,  $\text{NO}_2$ ,  $\text{CN}$ ,  $\text{COOR}$ ), then it is also reduced.  $\text{LiAlH}_4$  reacts readily with water and alcohols, so these compounds must be excluded. Common solvents are ether and THF.  $\text{NaBH}_4$  has a similar scope but is more selective and so may be used with  $\text{NO}_2$ ,  $\text{Cl}$ ,  $\text{COOR}$ ,  $\text{CN}$ , etc. in the molecule. Another advantage of  $\text{NaBH}_4$  is that it can be used in water or alcoholic solvents and so reduces compounds such as sugars that are not soluble in ethers.<sup>251</sup> The scope of these reagents with ketones is similar to that with aldehydes.  $\text{LiAlH}_4$  reduces even sterically hindered ketones.

The double bonds that are generally not affected by metallic hydrides may be isolated or conjugated, but double bonds that are conjugated with the  $\text{C}=\text{O}$  group may or may not be reduced, depending on the substrate, reagent, and reaction conditions.<sup>252</sup> Some reagents that reduce only the  $\text{C}=\text{O}$  bonds of  $\alpha,\beta$ -unsaturated aldehydes and ketones are

<sup>245</sup>For some indirect methods, see Sondej; Katzenellenbogen *J. Org. Chem.* **1986**, *51*, 3508; Prakesh; Reddy; Li; Olah *Synlett* **1990**, 594; Rozen; Zamir *J. Org. Chem.* **1991**, *56*, 4695.

<sup>246</sup>Sheppard *J. Am. Chem. Soc.* **1962**, *84*, 3058.

<sup>247</sup>Mathey; Bensoam *Tetrahedron* **1971**, *27*, 3965, **1975**, *31*, 391.

<sup>248</sup>Bilger; Royer; Demerseman *Synthesis* **1988**, 902.

<sup>249</sup>For a review, see Hudlický *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984, pp. 96-129. For a list of reagents, with references, see Ref. 64, pp. 527-547.

<sup>250</sup>For books on metal hydrides, see Seyden-Penne *Reductions by the Alumino- and Borohydrides*; VCH: New York, 1991; Hajos *Complex Hydrides*; Elsevier: New York, 1979. For reviews, see House, Ref. 180, pp. 49-71; Wheeler, in Patai, Ref. 2, pp. 507-566.

<sup>251</sup> $\text{NaBH}_4$  reduces solid ketones in the absence of any solvent (by mixing the powders); Toda; Kiyoshige; Yagi *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 320 [*Angew. Chem.* **101**, 329].

<sup>252</sup>For a review of the reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds, see Keinan; Greenspoon, in Patai; Rappaport *The Chemistry of Enones*, pt. 2; Wiley: New York, 1989, pp. 923-1022.

$\text{AlH}_3$ ,<sup>253</sup>  $\text{NaBH}_4$ , or  $\text{LiAlH}_4$  in the presence of lanthanide salts (e.g.,  $\text{LaCl}_3$ ,  $\text{CeBr}_3$ ),<sup>254</sup>  $\text{NaBH}_3(\text{OAc})$ ,<sup>255</sup>  $\text{Et}_3\text{SiH}$ ,<sup>256</sup> lithium *n*-butylborohydride,<sup>257</sup> and diisobutylaluminum hydride (DIBALH).<sup>258</sup> Also, both  $\text{LiAlH}_4$ <sup>259</sup> and  $\text{NaBH}_4$ <sup>260</sup> predominantly reduce only the  $\text{C}=\text{O}$  bonds of  $\text{C}=\text{C}-\text{C}=\text{O}$  systems in most cases, though substantial amounts of fully saturated alcohols have been found in some cases<sup>259</sup> (p. 774). For some reagents that reduce only the  $\text{C}=\text{C}$  bonds of conjugated aldehydes and ketones, see 5-9.

When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be *chemoselective*. A number of reagents have been found to reduce aldehydes much faster than ketones. Among these<sup>261</sup> are  $\text{NaBH}_4$  in isopropyl alcohol,<sup>262</sup> sodium triacetoxyborohydride,<sup>263</sup> lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride  $\text{Li}(\text{Et}_3\text{CO})_3\text{AlH}$ ,<sup>264</sup> zinc borohydride in  $\text{THF}$ ,<sup>264a</sup> and tributyltin hydride.<sup>265</sup> On the other hand, ketones can be chemoselectively reduced in the presence of aldehydes with  $\text{NaBH}_4$  in aqueous  $\text{EtOH}$  at  $-15^\circ\text{C}$  in the presence of cerium trichloride  $\text{CeCl}_3$ .<sup>266</sup> The reagent lithium *N*-dihydropyridylaluminum hydride reduces diaryl ketones much better than dialkyl or alkyl aryl ketones.<sup>267</sup> Most other hydrides reduce diaryl ketones more slowly than other types of ketones. Saturated ketones can be reduced in the presence of  $\alpha,\beta$ -unsaturated ketones with  $\text{NaBH}_4$ -50%  $\text{MeOH}-\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ <sup>268</sup> and with zinc borohydride.<sup>269</sup> In general,  $\text{NaBH}_4$  reduces carbonyl compounds in this order: aldehydes  $>$   $\alpha,\beta$ -unsaturated aldehydes  $>$  ketones  $>$   $\alpha,\beta$ -unsaturated ketones, and a carbonyl group of one type can be selectively reduced in the presence of a carbonyl group of a less reactive type.<sup>270</sup> Potassium triphenylborohydride  $\text{KPh}_3\text{BH}$  shows 99.4:0.6 selectivity between cyclohexanone and 4-heptanone, and 97:3 selectivity between cyclohexanone and cyclopentanone.<sup>271</sup> A number of reagents will preferentially reduce the less sterically hindered of two carbonyl compounds, but by the use of DIBALH in the presence of the Lewis acid methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide), it was possible selectively to reduce the *more hindered* of a mixture of two ketones.<sup>272</sup> It is obvious that reagents can often be found to reduce one kind of carbonyl

<sup>253</sup>Jorgenson *Tetrahedron Lett.* **1962**, 559; Dilling; Plepys *J. Org. Chem.* **1970**, 35, 2971.

<sup>254</sup>Gemal; Luche *J. Am. Chem. Soc.* **1981**, 103, 5454; Fukuzawa; Fujinami; Yamauchi; Sakai *J. Chem. Soc., Perkin Trans. I* **1986**, 1929. See also Chênevert; Ampleman *Chem. Lett.* **1985**, 1489; Varma; Kabalka *Synth. Commun.* **1985**, 15, 985.

<sup>255</sup>Nutaitis; Bernardo *J. Org. Chem.* **1989**, 54, 5629.

<sup>256</sup>Ojima; Kogure *Organometallics* **1982**, 1, 1390.

<sup>257</sup>Kim; Moon; Ahn *J. Org. Chem.* **1982**, 47, 3311.

<sup>258</sup>Wilson; Seidner; Masamune *Chem. Commun.* **1970**, 213.

<sup>259</sup>Johnson; Rickborn *J. Org. Chem.* **1970**, 35, 1041.

<sup>260</sup>Chaikin; Brown *J. Am. Chem. Soc.* **1949**, 71, 122.

<sup>261</sup>For some others (not all of them metal hydrides) see Hutchins; Kandasamy *J. Am. Chem. Soc.* **1973**, 95, 6131; Risbood; Ruthven *J. Org. Chem.* **1979**, 44, 3969; Babler; Invergo *Tetrahedron Lett.* **1981**, 22, 621; Fleet; Harding *Tetrahedron Lett.* **1981**, 22, 675; Yamaguchi; Kabuto; Yasuhara *Chem. Lett.* **1981**, 461; Kim; Kang; Yang *Tetrahedron Lett.* **1984**, 25, 2985; Kamitori; Hojo; Masuda; Yamamoto *Chem. Lett.* **1985**, 253; Borbaruah; Barua; Sharma *Tetrahedron Lett.* **1987**, 28, 5741.

<sup>262</sup>Brown; Wheeler; Ichikawa *Tetrahedron* **1957**, 1, 214; Adams *Synth. Commun.* **1984**, 14, 1349.

<sup>263</sup>Gribble; Ferguson *J. Chem. Soc., Chem. Commun.* **1975**, 535. See also Nutaitis; Gribble *Tetrahedron Lett.* **1983**, 24, 4287.

<sup>264</sup>Krishnamurthy *J. Org. Chem.* **1981**, 46, 4628.

<sup>264a</sup>Ranu; Chakraborty *Tetrahedron Lett.* **1990**, 31, 7663.

<sup>265</sup>Fung; Mayo; Schauble; Weedon *J. Org. Chem.* **1978**, 43, 3977; Shibata; Yoshida; Baba; Matsuda *Chem. Lett.* **1989**, 619; Adams; Schemenaur *Synth. Commun.* **1990**, 20, 2359. For a review, see Kuivila *Synthesis* **1970**, 499-509.

<sup>266</sup>Luche; Gemal *J. Am. Chem. Soc.* **1979**, 101, 5848. See also Gemal; Luche *Tetrahedron Lett.* **1981**, 22, 4077. For other methods, see Paradisi; Zecchini; Ortar *Tetrahedron Lett.* **1980**, 21, 5085; Bordoloi; Sarmah *Chem. Ind. (London)* **1987**, 459.

<sup>267</sup>Lansbury; Peterson *J. Am. Chem. Soc.* **1962**, 84, 1756.

<sup>268</sup>Ward; Rhee; Zoghaib *Tetrahedron Lett.* **1988**, 29, 517.

<sup>269</sup>Sarkar; Das; Ranu *J. Org. Chem.* **1990**, 55, 5799.

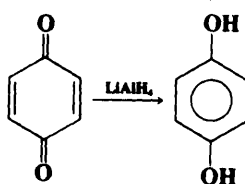
<sup>270</sup>Ward, Rhee *Can. J. Chem.* **1989**, 67, 1206.

<sup>271</sup>Yoon; Kim; Kang *J. Org. Chem.* **1986**, 51, 226.

<sup>272</sup>Maruoka; Araki; Yamamoto *J. Am. Chem. Soc.* **1988**, 110, 2650.

function in the presence of another.<sup>273</sup> For a discussion of selectivity in reduction reactions, see p. 1206.

Quinones are reduced to hydroquinones by  $\text{LiAlH}_4$ ,  $\text{SnCl}_2\text{-HCl}$ , or sodium hydrosulfite  $\text{Na}_2\text{S}_2\text{O}_4$ , as well as by other reducing agents.



The reagent lithium tri-*sec*-butylborohydride  $\text{LiBH}(\text{sec-Bu})_3$  reduces cyclic and bicyclic ketones in a highly stereoselective manner, giving the less stable isomer.<sup>274</sup> For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity greater than 99%. The more usual reagents, e.g.,  $\text{LiAlH}_4$ ,  $\text{NaBH}_4$ , reduce relatively unhindered cyclic ketones either with little or no stereoselectivity<sup>275</sup> or give predominant formation of the more stable isomer (axial attack).<sup>276</sup> The less stable alcohol is also predominantly formed when cyclohexanones are reduced with (among other reagents)  $\text{AlH}_3$  in ether at  $-70^\circ\text{C}$ <sup>277</sup> and with triethyl phosphite and iridium tetrachloride in aqueous isopropyl alcohol.<sup>278</sup> Cyclohexanones that have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the less stable alcohol, even with  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ .

Among other reagents that reduce aldehydes and ketones to alcohols<sup>279</sup> are the following:

**1. Hydrogen and a catalyst.**<sup>280</sup> The most common catalysts are platinum and ruthenium, but homogeneous catalysts have also been used.<sup>281</sup> Before the discovery of the metal hydrides this was one of the most common ways of effecting this reduction, but it suffers from the fact that  $\text{C}=\text{C}$ ,  $\text{C}\equiv\text{C}$ ,  $\text{C}=\text{N}$  and  $\text{C}\equiv\text{N}$  bonds are more susceptible to attack than  $\text{C}=\text{O}$  bonds.<sup>282</sup> For aromatic aldehydes and ketones, reduction to the hydrocarbon (**9-37**) is a side reaction, stemming from hydrogenolysis of the alcohol initially produced (**0-78**).

<sup>273</sup>For lists of some of these chemoselective reagents, with references, see Ref. 64, pp. 535-537, and references given in Ref. 270.

<sup>274</sup>Brown; Krishnamurthy *J. Am. Chem. Soc.* **1972**, *94*, 7159; Krishnamurthy; Brown *J. Am. Chem. Soc.* **1976**, *98*, 3383.

<sup>275</sup>For reviews of the stereochemistry and mechanism, see Caro; Boyer; Lamaty; Jaouen *Bull. Soc. Chim. Fr.* **1983**, II-281-II-303; Boone; Ashby *Top. Stereochem.* **1979**, *11*, 53-95; Wigfield *Tetrahedron* **1979**, *35*, 449-462. For a review of stereoselective synthesis of amino alcohols by this method, see Tramontini *Synthesis* **1982**, 605-644.

<sup>276</sup>For a discussion of why this isomer is predominantly formed, see Mukherjee; Wu; Fronczek; Houk *J. Am. Chem. Soc.* **1988**, *110*, 3328.

<sup>277</sup>Ayres; Sawdaye *J. Chem. Soc. B* **1967**, 581; Ayres; Kirk; Sawdaye *J. Chem. Soc. B* **1970**, 505.

<sup>278</sup>Henbest; Mitchell *J. Chem. Soc. C* **1970**, 785; Eliel; Doyle; Hutchins; Gilbert *Org. Synth.* VI, 215. See also Henbest; Zurqiyah *J. Chem. Soc., Perkin Trans. I* **1974**, 604.

<sup>279</sup>This can also be done electrochemically. For a review, see Feoktistov; Lund, in Baizer; *Lund Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 315-358, pp. 315-326. See also Coche; Moutet *J. Am. Chem. Soc.* **1987**, *109*, 6887.

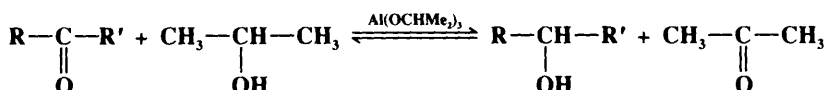
<sup>280</sup>For reviews, see Parker, in Hartley *The Chemistry of the Metal-Carbon Bond*, vol. 4; Wiley: New York, 1987, pp. 979-1047; Tanaka, in Červený *Catalytic Hydrogenation*; Elsevier: New York, 1986, pp. 79-104; Rylander *Hydrogenation Methods*, Ref. 165, pp. 66-77; Rylander *Catalytic Hydrogenation over Platinum Metals*, Ref. 165, pp. 238-290.

<sup>281</sup>For a review, see Heck *Organotransition Metal Chemistry*; Academic Press: New York, 1974, pp. 65-70.

<sup>282</sup>For catalysts that allow hydrogenation of only the  $\text{C}=\text{O}$  bond of  $\alpha,\beta$ -unsaturated aldehydes, see Galvagno; Poltarzewski; Donato; Neri; Pietropaolo *J. Chem. Soc., Chem. Commun.* **1986**, 1729; Farnetti; Pesce; Kašpar; Spogliarich; Graziani *J. Chem. Soc., Chem. Commun.* **1986**, 746; Narasimhan; Deshpande; Ramnarayan *J. Chem. Soc., Chem. Commun.* **1988**, 99.

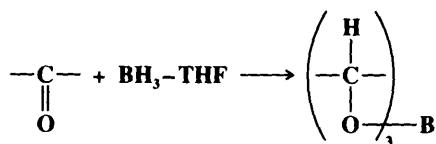
2. *Sodium in ethanol*.<sup>283</sup> This is called the *Bouveault-Blanc procedure* and was more popular for the reduction of carboxylic esters (9-42) than of aldehydes or ketones before the discovery of  $\text{LiAlH}_4$ .

3. *Isopropyl alcohol and aluminum isopropoxide*. This is called the *Meerwein-Ponndorf-Verley reduction*. It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (see 9-3):



The equilibrium is shifted by removal of the acetone by distillation. The reaction takes place under very mild conditions and is highly specific for aldehydes and ketones, so that  $\text{C}=\text{C}$  bonds (including those conjugated with the  $\text{C}=\text{O}$  bonds) and many other functional groups can be present without themselves being reduced.<sup>284</sup> This includes acetals, so that one of two carbonyl groups in a molecule can be specifically reduced if the other is first converted to an acetal.  $\beta$ -Keto esters,  $\beta$ -diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction.

4. Borane  $\text{BH}_3$  and substituted boranes reduce aldehydes and ketones in a manner similar to their addition to  $\text{C}=\text{C}$  bonds (5-12).<sup>285</sup> That is, the boron adds to the oxygen and the hydrogen to the carbon:<sup>286</sup>



The borate is then hydrolyzed to the alcohol. 9-BBN<sup>287</sup> (p. 785) and  $\text{BH}_3\text{-Me}_2\text{S}$ <sup>288</sup> reduce only the  $\text{C}=\text{O}$  group of conjugated aldehydes and ketones.

5. *Diimide* ( $\text{N}_2\text{H}_2$ , see p. 779) reduces aromatic aldehydes<sup>289</sup> and ketones, but aliphatic carbonyl compounds react very poorly.<sup>290</sup>

6. A single carbonyl group of an  $\alpha$ -diketone can be reduced (to give an  $\alpha$ -hydroxy ketone) by heating with zinc powder in aqueous DMF.<sup>291</sup> This has also been accomplished with aqueous  $\text{VCl}_2$ <sup>292</sup> and with  $\text{Zn-ZnCl}_2\text{-EtOH}$ .<sup>293</sup>

7. In the *Cannizzaro reaction* (9-69) aldehydes without an  $\alpha$  hydrogen are reduced to alcohols.

<sup>283</sup>For a discussion, see House, Ref. 180, pp. 152-160.

<sup>284</sup>Diisobornyloxyaluminum isopropoxide gives higher yields under milder conditions than aluminum isopropoxide: Hutton, *Synth. Commun.* **1979**, 9, 483. For other substitutes for aluminum isopropoxide, see Namy; Souppe; Collin; Kagan *J. Org. Chem.* **1984**, 49, 2045; Okano; Matsuoka; Konishi; Kiji *Chem. Lett.* **1987**, 181.

<sup>285</sup>For a review, see Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 324-335.

<sup>286</sup>Brown; Subba Rao *J. Am. Chem. Soc.* **1960**, 82, 681; Brown; Korytnyk *J. Am. Chem. Soc.* **1960**, *J. Am. Chem. Soc.* **1960**, 82, 3866.

<sup>287</sup>Krishnamurthy; Brown *J. Org. Chem.* **1975**, 40, 1864; Lane *Aldrichimica Acta* **1976**, 9, 31.

<sup>288</sup>Mincione *J. Org. Chem.* **1978**, 43, 1829.

<sup>289</sup>Curry; Uff; Ward *J. Chem. Soc. C* **1967**, 1120.

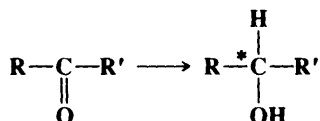
<sup>290</sup>van Tamelen; Davis; Deem *Chem. Commun.* **1965**, 71.

<sup>291</sup>Kreiser *Liebigs Ann. Chem.* **1971**, 745, 164.

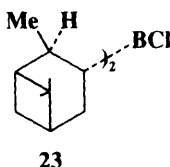
<sup>292</sup>Ho; Olah *Synthesis* **1976**, 815.

<sup>293</sup>Toda; Tanaka; Tange *J. Chem. Soc., Perkin Trans. 1* **1989**, 1555.

Unsymmetrical ketones are prochiral (p. 135); that is, reduction creates a new chiral center:



Much effort has been put into finding optically active reducing agents that will produce one enantiomer of the alcohol enantioselectively, and considerable success has been achieved,<sup>294</sup> both with biologically-derived reducing agents<sup>295</sup> such as baker's yeast,<sup>296</sup> and with synthetic reagents. Each reagent is more effective for certain types of ketones than for others.<sup>297</sup> H.C. Brown and co-workers reduced various types of ketone with a number of reducing agents,<sup>298</sup> and reported in 1987 that of the reagents available at that time, the highest enantiomeric excesses (ee) for acyclic ketones were obtained with (*R,R*)- or (*S,S*)-2,5-dimethylborolane (47 and 48 on p. 787).<sup>299</sup> For cyclic ketones the best reagents were diisopinocampheylchloroborane (23),<sup>300</sup> (*S*)-2-amino-1,1-diphenylbutan-1-ol-BH<sub>3</sub>,<sup>301</sup> and K-Glucoride, a boron derivative of a carbohydrate.<sup>302</sup> These workers also determined the relative effectiveness of



various reagents for reduction of 8 other types of ketone, including heterocyclic, aralkyl,  $\beta$ -keto esters, etc.<sup>298</sup> In most cases, ee values of greater than 90% can be obtained with the proper reagent.<sup>303</sup>

Asymmetric reduction with very high ee values has also been achieved with achiral reducing agents and optically active catalysts. The two most important examples are (1) homogeneous catalytic hydrogenation with the catalyst 2,2'-bis(diphenylphosphino)-1,1'-

<sup>294</sup>For reviews, see Midland *Chem. Rev.* **1989**, 89, 1553-1561; N6grádi *Stereoselective Synthesis*; VCH: New York, 1986, pp. 105-130; in Morrison *Asymmetric Synthesis*; Academic Press: New York, 1983, the articles by Midland, vol. 2, pp. 45-69, and Grandbois; Howard; Morrison, vol. 2, pp. 71-90; Haubenstock *Top. Stereochem.* **1983**, 14, 231-300.

<sup>295</sup>For a review, see Sih; Chen *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 570-578 [*Angew. Chem.* 96, 556-565].

<sup>296</sup>See, for example, Fujisawa; Hayashi; Kishioka *Chem. Lett.* **1987**, 129; Nakamura; Kawai; Ohno *Tetrahedron Lett.* **1990**, 31, 267; Spiliotis; Papahatjis; Ragoussis *Tetrahedron Lett.* **1990**, 31, 1615.

<sup>297</sup>For a list of many of these reducing agents, with references, see Ref. 64, pp. 540-547.

<sup>298</sup>Brown; Park; Cho; Ramachandran *J. Org. Chem.* **1987**, 52, 5406.

<sup>299</sup>First used in this way by Imai; Tamura; Yamamuro; Sato; Wollmann; Kennedy; Masamune *J. Am. Chem. Soc.* **1986**, 108, 7402; Masamune; Kennedy; Petersen; Houk; Wu *J. Am. Chem. Soc.* **1986**, 108, 7404.

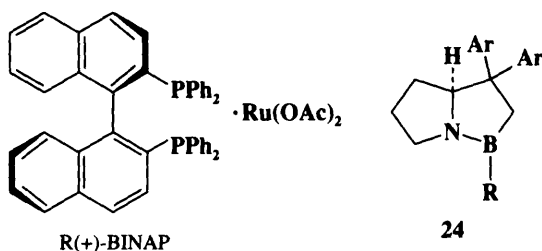
<sup>300</sup>Chandrasekharan; Ramachandran; Brown *J. Org. Chem.* **1985**, 50, 5446; Brown; Chandrasekharan; Ramachandran *J. Org. Chem.* **1986**, 51, 3394; *J. Am. Chem. Soc.* **1988**, 110, 1539; Srebnik; Ramachandran; Brown *J. Org. Chem.* **1988**, 53, 2916. See also Brown; Srebnik; Ramachandran *J. Org. Chem.* **1989**, 54, 1577.

<sup>301</sup>For the preparation and use of this and related reagents, see Itsuno; Nakano; Miyazaki; Masuda; Ito; Hirao; Nakahama *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039, and other papers in this series.

<sup>302</sup>Brown; Park; Cho *J. Org. Chem.* **1986**, 51, 1934, 3278; Brown; Cho; Park *J. Org. Chem.* **1986**, 51, 3396, **1988**, 53, 1231.

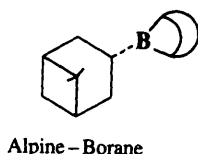
<sup>303</sup>For some recent examples, see Youn; Lee; Pak *Tetrahedron Lett.* **1988**, 29, 4453; Meyers; Brown *Tetrahedron Lett.* **1988**, 29, 5617; Brown; Ramachandran; Weissman; Swaminathan *J. Org. Chem.* **1990**, 55, 6328; Rama Rao; Gurjar; Sharma; Kaiwar *Tetrahedron Lett.* **1990**, 31, 2341; Midland; Kazubski; Woodling *J. Org. Chem.* **1991**, 56, 1068.

binaphthyl-ruthenium acetate [BINAP-Ru(OAc)<sub>2</sub>],<sup>304</sup> which reduces  $\beta$ -keto esters in >98% ee,<sup>305</sup> and (2) reduction with BH<sub>3</sub>-THF or catecholborane, using an oxazaborolidine



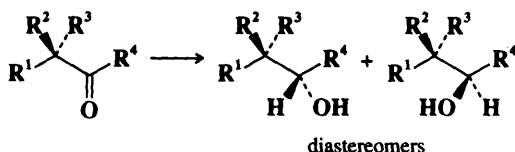
**24** (R = H, Me, or *n*-Bu; Ar = Ph or  $\beta$ -naphthyl) as a catalyst.<sup>306</sup> This method gives high ee values with various types of ketone, especially  $\alpha,\beta$ -unsaturated ketones.

Enantioselective reduction is not possible for aldehydes, since the products are primary alcohols in which the reduced carbon is not chiral, but deuterated aldehydes RCDO give a chiral product, and these have been reduced enantioselectively with B-(3-pinanyl)-9-bora-bicyclo[3.3.1]nonane (Alpine-Borane) with almost complete optical purity.<sup>307</sup>



In the above cases an optically active reducing agent or catalyst interacts with a prochiral substrate. Asymmetric reduction of ketones has also been achieved with an achiral reducing agent, if the ketone is complexed to an optically active transition metal Lewis acid.<sup>308</sup>

There are other stereochemical aspects to the reduction of aldehydes and ketones. If there is a chiral center  $\alpha$  to the carbonyl group,<sup>309</sup> even an achiral reducing agent can give



<sup>304</sup>For reviews of BINAP, see Noyori *Science* **1990**, 248, 1194-1199; Noyori; Takaya *Acc. Chem. Res.* **1990**, 23, 345-350. For the synthesis of BINAP, see Takaya; Akutagawa; Noyori *Org. Synth.* 67, 20.

<sup>305</sup>Noyori; Ohkuma; Kitamura; Takaya; Sayo; Kumobayashi; Akutagawa *J. Am. Chem. Soc.* **1987**, 109, 5856; Taber; Silverberg *Tetrahedron Lett.* **1991**, 32, 4227. See also Kitamura; Ohkuma; Inoue; Sayo; Kumobayashi; Akutagawa; Ohta; Takaya; Noyori; *J. Am. Chem. Soc.* **1988**, 110, 629.

<sup>306</sup>Corey; Bakshi; Shibata *J. Am. Chem. Soc.* **1987**, 109, 5551; Corey; Bakshi; Shibata; Chen; Singh *J. Am. Chem. Soc.* **1987**, 109, 7924; Corey; Link; *Tetrahedron Lett.* **1989**, 30, 6275; Corey; Bakshi *Tetrahedron Lett.* **1990**, 31, 611.

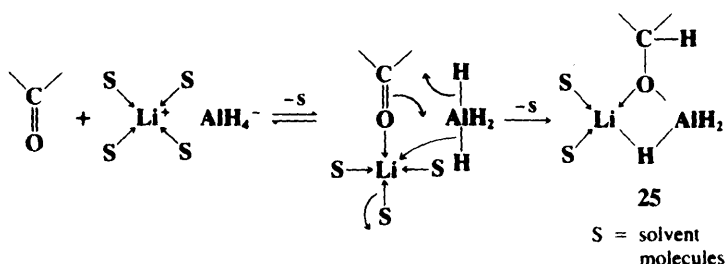
<sup>307</sup>Midland; Greer; Tramontano; Zderic *J. Am. Chem. Soc.* **1979**, 101, 2352. See also Noyori; Tomino; Tanimoto *J. Am. Chem. Soc.* **1979**, 101, 3129; Brown; Jadhav; Mandal *Tetrahedron* **1981**, 37, 3547-3587; Midland; Zderic *J. Am. Chem. Soc.* **1982**, 104, 525.

<sup>308</sup>Dalton; Gladysz *J. Organomet. Chem.* **1989**, 370, C17.

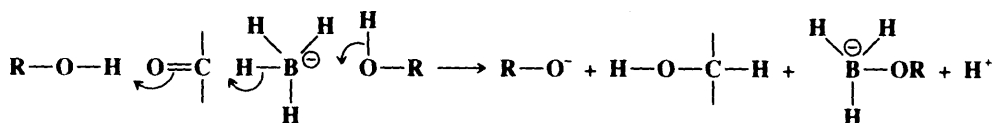
<sup>309</sup>In theory, the chiral center can be anywhere in the molecule, but in practice, reasonable diastereoselectivity is most often achieved when it is in the  $\alpha$  position. For examples of high diastereoselectivity when the chiral center is further away, especially in reduction of  $\beta$ -hydroxy ketones, see Narasaka; Pai *Tetrahedron* **1984**, 40, 2233; Hassine; Gorsane; Pecher; Martin *Bull. Soc. Chim. Belg.* **1985**, 94, 597; Bloch; Gilbert; Girard *Tetrahedron Lett.* **1988**, 53, 1021; Evans; Chapman; Carreira *J. Am. Chem. Soc.* **1988**, 110, 3560.

more of one diastereomer than of the other. Such diastereoselective reductions have been carried out with considerable success.<sup>310</sup> In most such cases Cram's rule (p. 117) is followed, but exceptions are known.<sup>311</sup>

With most reagents there is an initial attack on the carbon of the carbonyl group by  $\text{H}^-$  or some carrier of it, though with  $\text{BH}_3$ <sup>312</sup> the initial attack is on the oxygen. Detailed mechanisms are not known in most cases.<sup>275</sup> With  $\text{AlH}_4^-$  (or  $\text{BH}_4^-$ ) compounds, the attacking species is the  $\text{AlH}_4^-$  (or  $\text{BH}_4^-$ ) ion, which, in effect, transfers  $\text{H}^-$  to the carbon. The following mechanism has been proposed for  $\text{LiAlH}_4$ :<sup>313</sup>



Evidence that the cation plays an essential role, at least in some cases, is that when the  $\text{Li}^+$  was effectively removed from  $\text{LiAlH}_4$  (by the addition of a crown ether), the reaction did not take place.<sup>314</sup> The complex **25** must now be hydrolyzed to the alcohol. For  $\text{NaBH}_4$  the  $\text{Na}^+$  does not seem to participate in the transition state, but kinetic evidence shows that an OR group from the solvent does participate and remains attached to the boron:<sup>315</sup>



Free  $\text{H}^-$  cannot be the attacking entity in most reductions with boron or aluminum hydrides because the reactions are frequently sensitive to the size of the  $\text{MH}_4^-$  [or  $\text{MR}_m\text{H}_n^-$  or  $\text{M}(\text{OR})_m\text{H}_n^-$ , etc.].

There has been much controversy about whether the initial complex in the  $\text{LiAlH}_4$  reduction (**25**, which can be written as  $\text{H}-\text{C}-\text{OAlH}_3^-$ , **26**) can reduce another carbonyl to give  $(\text{H}-\text{C}-\text{O})_2\text{AlH}_2^-$ , and so on. It has been shown<sup>316</sup> that this is probably not the

<sup>310</sup>For reviews, see Nógrádi, Ref. 294, pp. 131-148; Oishi; Nakata *Acc. Chem. Res.* **1984**, *17*, 338-344.

<sup>311</sup>One study showed that the Cram's rule product predominates with metal hydride reducing agents, but the other product with Bouveault-Blanc and dissolving metal reductions: Yamamoto; Matsuoka; Nemoto *J. Am. Chem. Soc.* **1988**, *110*, 4475.

<sup>312</sup>For a discussion of the mechanism with boranes, see Brown, Wang, Chandrasekharan *J. Am. Chem. Soc.* **1983**, *105*, 2340.

<sup>313</sup>Ashby; Boone *J. Am. Chem. Soc.* **1976**, *98*, 5524.

<sup>314</sup>Pierre; Handel *Tetrahedron Lett.* **1974**, 2317. See also Loupy, Seyden-Penne; Tchoubar *Tetrahedron Lett.* **1976**, 1677; Ref. 313.

<sup>315</sup>Wigfield; Gowland *J. Org. Chem.* **1977**, *42*, 1108, *Tetrahedron Lett.* **1976**, 3373. See however Adams; Gold; Reuben *J. Chem. Soc., Chem. Commun.* **1977**, 182, *J. Chem. Soc., Perkin Trans 2* **1977**, 1466, 1472; Kayser; Eliev; Eisenstein *Tetrahedron Lett.* **1983**, *24*, 1015.

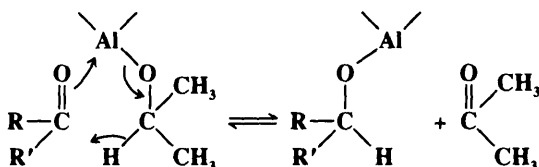
<sup>316</sup>Haubenstock; Eliel *J. Am. Chem. Soc.* **1962**, *84*, 2363; Malmvik; Obenius; Henriksson *J. Chem. Soc., Perkin Trans. 2* **1986**, 1899, 1905.

case but that, more likely, **26** disproportionates to  $(\text{H}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}})_4\text{Al}^-$  and  $\text{AlH}_4^-$ , which is the

only attacking species. Disproportionation has also been reported in the  $\text{NaBH}_4$  reaction.<sup>317</sup>

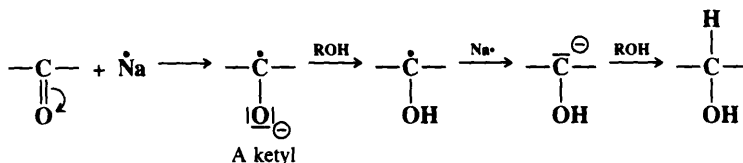
**26** is essentially  $\text{LiAlH}_4$  with one of the hydrogens replaced by an alkoxy group, i.e.,  $\text{LiAlH}_3\text{OR}$ . The fact that **26** and other alkoxy derivatives of  $\text{LiAlH}_4$  are less reactive than  $\text{LiAlH}_4$  itself has led to the use of such compounds as reducing agents that are less reactive and more selective than  $\text{LiAlH}_4$ .<sup>318</sup> We have already met some of these, e.g.,  $\text{LiAlH}(\text{O}-t\text{-Bu})_3$  (reactions **0-83** to **0-85**; see also Table 19.5). As an example of chemoselectivity in this reaction it may be mentioned that  $\text{LiAlH}(\text{O}-t\text{-Bu})_3$  has been used to reduce only the keto group in a molecule containing both keto and carboxylic ester groups.<sup>319</sup> However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause  $\text{LiAlH}_4$  to be the active species, even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.<sup>320</sup>

The Meerwein-Ponndorf-Verley reaction usually<sup>321</sup> involves a cyclic transition state:<sup>322</sup>



but in some cases 2 moles of aluminum alkoxide are involved—one attacking the carbon and the other the oxygen, a conclusion that stems from the finding that in these cases the reaction was 1.5 order in alkoxide.<sup>323</sup> Although, for simplicity, we have shown the alkoxide as a monomer, it actually exists as trimers and tetramers, and it is these that react.<sup>324</sup>

For the reaction with sodium in ethanol the following mechanism<sup>325</sup> has been suggested:<sup>326</sup>



The ketyl intermediate can be isolated.<sup>327</sup>

<sup>317</sup>Malmvik; Obenius; Henriksson *J. Org. Chem.* **1988**, 53, 221.

<sup>318</sup>For reviews of reductions with alkoxyaluminum hydrides, see Málek *Org. React.* **1988**, 36, 249-590, **1985**, 34, 1-317; Málek; Černý *Synthesis* **1972**, 217-234.

<sup>319</sup>Levine; Eudy *J. Org. Chem.* **1970**, 35, 549; Heusler; Wieland; Meystre *Org. Synth.* V, 692.

<sup>320</sup>Brown; Krishnamurthy; Kim *J. Chem. Soc., Chem. Commun.* **1973**, 391.

<sup>321</sup>It has been that shown in some cases reduction with metal alkoxides, including aluminum isopropoxide, involves free-radical intermediates (SET mechanism): Screttas; Cazianis *Tetrahedron* **1978**, 34, 933; Ashby; Goel; Argyropoulos *Tetrahedron Lett.* **1982**, 23, 2273; Nasipuri; Gupta; Banerjee *Tetrahedron Lett.* **1984**, 25, 5551; Ashby; Argyropoulos *Tetrahedron Lett.* **1986**, 27, 465; *J. Org. Chem.* **1986**, 51, 3593; Yamataka; Hanafusa *Chem. Lett.* **1987**, 643.

<sup>322</sup>See, for example, Shiner; Whittaker *J. Am. Chem. Soc.* **1963**, 85, 2337; Warnhoff; Reynolds-Warnhoff; Wong *J. Am. Chem. Soc.* **1980**, 102, 5956.

<sup>323</sup>Moulton; Van Atta; Ruch *J. Org. Chem.* **1961**, 26, 290.

<sup>324</sup>Williams; Krieger; Day *J. Am. Chem. Soc.* **1953**, 75, 2404; Shiner; Whittaker *J. Am. Chem. Soc.*, **1969**, 91, 394.

<sup>325</sup>For reviews of the mechanisms of these reactions, see Pradhan *Tetrahedron* **1986**, 42, 6351-6388; Huffman *Acc. Chem. Res.* **1983**, 16, 399-405. For discussions of the mechanism in the absence of protic solvents, see Huffman; Liao; Wallace *Tetrahedron Lett.* **1987**, 28, 3315; Rautenstrauch *Tetrahedron* **1988**, 44, 1613; Song; Dewald *J. Chem. Soc., Perkin Trans. 2* **1989**, 269. For a review of the stereochemistry of these reactions in liquid  $\text{NH}_3$ , see Rassat *Pure Appl. Chem.* **1977**, 49, 1049-1058.

<sup>326</sup>House, Ref. 180, p. 151. See, however Giordano; Perdoncin; Castaldi *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 499 [*Angew. Chem.* 97, 510].

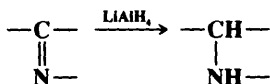
<sup>327</sup>For example, see Rautenstrauch; Geoffroy *J. Am. Chem. Soc.* **1976**, 98, 5035, **1977**, 99, 6280.

The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction 5-9, though not much is known about it.<sup>328</sup>

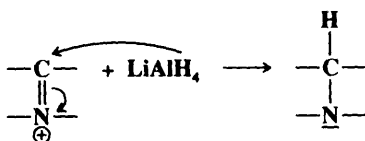
For other reduction reactions of aldehydes and ketones, see 9-37, 9-62, and 9-69.

OS I, 90, 304, 554; II, 317, 545, 598; III, 286; IV, 15, 25, 216, 660; V, 175, 294, 595, 692; VI, 215, 769, 887; VII, 129, 215, 241, 402, 417; 65, 203, 215; 68, 56; 69, 44.

## 6-26 Reduction of the Carbon-Nitrogen Double Bond C,N-Dihydro-addition



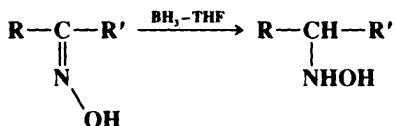
Imines, Schiff bases, hydrazones, and other C=N compounds can be reduced with LiAlH<sub>4</sub>, NaBH<sub>4</sub>, Na-EtOH, hydrogen and a catalyst, as well as with other reducing agents.<sup>329</sup> Iminium salts are also reduced by LiAlH<sub>4</sub>, though here there is no "addition" to the nitrogen:<sup>330</sup>



Reduction of imines has been carried out enantioselectively.<sup>331</sup>

Isocyanates have been catalytically hydrogenated to N-substituted formamides: RNC=O → R-NH-CHO.<sup>332</sup>

Oximes are generally reduced to amines (9-51), but simple addition of H<sub>2</sub> to give hydroxylamines can be accomplished with borane<sup>333</sup> or sodium cyanoborohydride.<sup>168</sup>



OS III, 328, 827; VI, 905; 66, 185; 69, 154. Also see OS IV, 283.

## 6-27 The Reduction of Nitriles to Amines CC,NN-Tetrahydro-biaddition



<sup>328</sup>For a review of the mechanism of gas-phase hydrogenation, see Pavlenko *Russ. Chem. Rev.* **1989**, 58, 453-469.

<sup>329</sup>For a review, see Harada, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*, Ref. 40, pp. 276-293. For a review with respect to catalytic hydrogenation, see Rylander, *Catalytic Hydrogenation over Platinum Metals*, Ref. 165, pp. 123-138.

<sup>330</sup>For a review of nucleophilic addition to iminium salts, see Paukstelis; Cook, in Cook, Ref. 45, pp. 275-356.

<sup>331</sup>See Cho; Chun *J. Chem. Soc., Perkin Trans. I* **1990**, 3200; Chan; Osborn *J. Am. Chem. Soc.* **1990**, 112, 9400, and references cited in these papers.

<sup>332</sup>Howell *Synth. Commun.* **1983**, 13, 635.

<sup>333</sup>Feuer; Vincent *J. Am. Chem. Soc.* **1962**, 84, 3771; Feuer; Vincent; Bartlett *J. Org. Chem.* **1965**, 30, 2877; Ioffe; Tartakovskii; Medvedeva; Novikov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 1446; Kawase; Kikugawa, *J. Chem. Soc., Perkin Trans. I* **1979**, 643.

Nitriles can be reduced to primary amines with many reducing agents,<sup>334</sup> including  $\text{LiAlH}_4$ ,  $\text{BH}_3\text{-Me}_2\text{S}$ ,<sup>335</sup>  $\text{NaOEt}$ , and hydrogen and a catalyst.<sup>336</sup>  $\text{NaBH}_4$  does not generally reduce nitriles but does so in alcoholic solvents when a  $\text{CoCl}_2$  catalyst is added<sup>337</sup> or in the presence of Raney nickel.<sup>338</sup> The reaction is of wide scope and has been applied to many nitriles. When catalytic hydrogenation is used, secondary amines  $(\text{RCH}_2)_2\text{NH}$  are often side products.<sup>339</sup> These can be avoided by adding a compound such as acetic anhydride, which removes the primary amine as soon as it is formed,<sup>340</sup> or by the use of excess ammonia to drive the equilibria backward.<sup>341</sup>

It is not possible to stop with the addition of only 1 mole of hydrogen, i.e., to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (6-28).

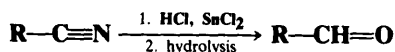
N-Alkylnitrilium ions are reduced to secondary amines by  $\text{NaBH}_4$ .<sup>342</sup>



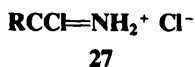
Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see 6-9), this is a method for the conversion of nitriles to secondary amines.

OS III, 229, 358, 720; VI, 223.

## 6-28 The Reduction of Nitriles to Aldehydes Hydro,oxy-de-nitrilo-tersubstitution



There are two principal methods for the reduction of nitriles to aldehydes.<sup>343</sup> In one of these, known as the *Stephen reduction*, the nitrile is treated with  $\text{HCl}$  to form



This is reduced with anhydrous  $\text{SnCl}_2$  to  $\text{RCH}=\text{NH}$ , which precipitates as a complex with  $\text{SnCl}_4$  and is then hydrolyzed (6-2) to the aldehyde. The Stephen reduction is most successful when  $\text{R}$  is aromatic, but it can be done for aliphatic  $\text{R}$  up to about six carbons.<sup>344</sup> It is also possible to prepare 27 in a different way, by treating  $\text{ArCONHPh}$  with  $\text{PCl}_5$ . The 27 obtained in this way can then be converted to the aldehyde. This is known as the *Sonn-Müller method*.

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 mole of hydrogen and hydrolysis, in situ, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with  $\text{LiAlH}_4$ ,

<sup>334</sup>For a review, see Rabinovitz, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 307-340. For a list of reagents, with references, see Ref. 64, pp. 437-438.

<sup>335</sup>See Brown; Choi; Narasimhan *Synthesis* 1981, 605.

<sup>336</sup>For reviews of catalytic hydrogenation of nitriles, see Volf; Pašek, in Červený, Ref. 280, pp. 105-144; Rylander, Ref. 329, pp. 203-226; Freidlin; Sladkova *Russ. Chem. Rev.* 1964, 33, 319-330.

<sup>337</sup>Sato; Suzuki *Tetrahedron Lett.* 1969, 4555. For a discussion of the mechanism, see Heinzman; Ganem *J. Am. Chem. Soc.* 1982, 104, 6801.

<sup>338</sup>Egli *Helv. Chim. Acta* 1970, 53, 47.

<sup>339</sup>For a method of making secondary amines the main products, see Galán; de Mendoza; Prados; Rojo; Echavarren *J. Org. Chem.* 1991, 56, 452.

<sup>340</sup>For example, see Carothers; Jones *J. Am. Chem. Soc.* 1925, 47, 3051; Gould; Johnson; Ferris *J. Org. Chem.* 1960, 25, 1658.

<sup>341</sup>For example, see Freifelder *J. Am. Chem. Soc.* 1960, 82, 2386.

<sup>342</sup>Borch *Chem. Commun.* 1968, 442.

<sup>343</sup>For a review, see Rabinovitz, Ref. 334. For a list of reagents, with references, see Ref. 64, pp. 624-625.

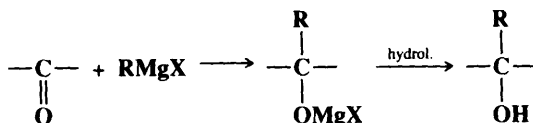
<sup>344</sup>Zil'berman; Pyryalova *J. Gen. Chem. USSR* 1963, 33, 3348.

$\text{LiAlH}(\text{OEt})_3$ ,<sup>345</sup> DIBALH,<sup>346</sup> and  $\text{NaAlH}_4$ .<sup>347</sup> The metal hydride method is useful for aliphatic and aromatic nitriles. Reduction to the aldehyde has also been accomplished by treatment of the nitrile with sodium hypophosphate and Raney nickel in aqueous acetic acid-pyridine or formic acid,<sup>348</sup> and with zinc and a Cob(I)alamin catalyst in aqueous acetic acid.<sup>349</sup>

OS III, 626, 818; VI, 631.

## H. Carbon Attack by Organometallic Compounds<sup>350</sup>

### 6-29 The Addition of Organometallic Compounds to Aldehydes and Ketones O-Hydro-C-alkyl-addition



The addition of Grignard reagents to aldehydes and ketones is known as the *Grignard reaction*.<sup>351</sup> Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols; and ketones give tertiary alcohols. The reaction is of very broad scope, and hundreds of alcohols have been prepared in this manner. R may be alkyl or aryl. In many cases the hydrolysis step is carried out with dilute HCl or  $\text{H}_2\text{SO}_4$ , but this cannot be done for tertiary alcohols in which at least one R group is alkyl because such alcohols are easily dehydrated under acidic conditions (7-1). In such cases (and often for other alcohols as well) an aqueous solution of ammonium chloride is used instead of a strong acid. Other organometallic compounds can also be used,<sup>352</sup> but in general only of active metals; e.g., alkylmercurys do not react. In practice, the only organometallic compounds used to any extent, besides Grignard reagents, are alkyl- and aryllithiums,<sup>353</sup> and alkylzinc reagents<sup>354</sup> where enantioselective addition is desired (see below). For the addition of acetylenic groups, sodium may be the metal used:  $\text{RC}\equiv\text{CNa}$  (6-41); while vinylic alanes (prepared as in 5-13) are the reagents of choice for the addition of vinylic groups.<sup>355</sup> Many methods have been reported

<sup>345</sup>Brown; Shoaf *J. Am. Chem. Soc.* **1964**, 86, 1079. For a review of reductions with this and related reagents, see Málek *Org. React.* **1988**, 36, 249-590, pp. 287-289, 438-448.

<sup>346</sup>Miller; Biss; Schwartzman *J. Org. Chem.* **1959**, 24, 627; Marshall; Andersen; Schlicher *J. Org. Chem.* **1970**, 35, 858.

<sup>347</sup>Zakharkin; Maslin; Gavrilenko *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 1415.

<sup>348</sup>Backeberg; Staskun *J. Chem. Soc.* **1962**, 3951; van Es; Staskun *J. Chem. Soc.* **1965**, 5775, *Org. Synth.* VI, 631. For a related method, see Khai; Arcelli *J. Org. Chem.* **1989**, 54, 949.

<sup>349</sup>Fischli *Helv. Chim. Acta* **1978**, 61, 2560.

<sup>350</sup>Discussions of most of the reactions in this section are found in Hartley; Patai *The Chemistry of the Metal-Carbon Bond*, vols. 2, 3 and 4; Wiley: New York, 1985-1987.

<sup>351</sup>For reviews of the addition of organometallic compounds to carbonyl groups, see Eicher, in Patai, Ref. 2, pp. 621-693; Kharasch; Reinmuth *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, 1954, pp. 138-528. For a review of reagents that extend carbon chains by 3 carbons, with some functionality at the new terminus, see Stowell *Chem. Rev.* **1984**, 84, 409-435.

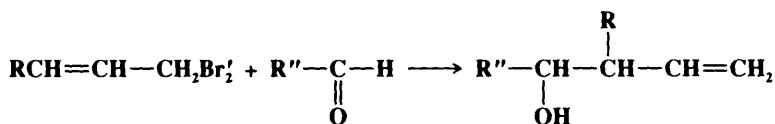
<sup>352</sup>For a list of reagents, with references, see Ref. 64, pp. 559-567.

<sup>353</sup>For a discussion, see Wakefield *Organolithium Methods*; Academic Press: New York, 1988, pp. 67-75.

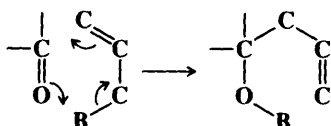
<sup>354</sup>For a review with respect to organozinc compounds, see Furukawa; Kawabata *Adv. Organomet. Chem.* **1974**, 12, 103-112. For a review with respect to organocadmium compounds, see Jones; Desio *Chem. Rev.* **1978**, 78, 491-516.

<sup>355</sup>Newman *Tetrahedron Lett.* **1971**, 4571. Vinylic groups can also be added with 9-vinylic-9-BBN compounds; Jacob; Brown *J. Org. Chem.* **1977**, 42, 579.

for the addition of allylic groups.<sup>356</sup> Among these are the use of allyltrialkyltin compounds (in the presence of  $\text{BF}_3$ -etherate),<sup>357</sup> allyltrialkylsilanes (in the presence of a Lewis acid),<sup>358</sup> as well as other allylic metal compounds.<sup>359</sup> Although organoboranes do not generally add to aldehydes and ketones,<sup>360</sup> allylic boranes are exceptions.<sup>361</sup> When they add, an allylic rearrangement always takes place, e.g.,



indicating a cyclic mechanism:



Allylic rearrangements sometimes take place with the other reagents as well.

Certain functional groups ( $\text{COOEt}$ ,  $\text{CONMe}_2$ ,  $\text{CN}$ ) can be present in the R group when organotin reagents  $\text{RSnEt}_3$  are added to aldehydes.<sup>362</sup> A trifluoromethyl group can be added with  $\text{Me}_3\text{SiCF}_3$ , with  $\text{Bu}_4\text{NF}$  as a catalyst, in THF.<sup>363</sup>

The reaction with alkyl- and aryllithium reagents has also been carried out without preliminary formation of  $\text{RLi}$ : a mixture of  $\text{RX}$  and the carbonyl compound was added to a suspension of lithium pieces in THF.<sup>364</sup> Yields were generally satisfactory. The magnesium analog of this process is called the *Barbier reaction*.<sup>365</sup> Lithium dimethylcopper  $\text{Me}_2\text{CuLi}$

<sup>356</sup>For a list of reagents and references, see Ref. 64, pp. 567-572.

<sup>357</sup>Naruta; Ushida; Maruyama *Chem. Lett.* **1979**, 919. For a review, see Yamamoto *Aldrichimica Acta* **1987**, 20, 45-49.

<sup>358</sup>For reviews, see Fleming; Dunoguès; Smithers *Org. React.* **1989**, 37, 57-575, pp. 113-125, 290-328; Parnes; Boleslava *Synthesis* **1984**, 991-1008, pp. 997-1000. For studies of the mechanism, see Denmark; Wilson; Willson *J. Am. Chem. Soc.* **1988**, 110, 984; Denmark; Weber; Wilson; Willson *Tetrahedron* **1989**, 45, 1053; Keck; Andrus; Castellino *J. Am. Chem. Soc.* **1989**, 111, 8136.

<sup>359</sup>See, for example, Furuta; Ikeda; Meguriya; Ikeda; Yamamoto *Bull. Chem. Soc. Jpn.* **1984**, 57, 2781; Pétrier; Luche *J. Org. Chem.* **1985**, 50, 910; Tanaka; Yamashita; Hamatani; Ikemoto; Torii *Chem. Lett.* **1986**, 1611; *Synth. Commun.* **1987**, 17, 789; Guo; Doubleday; Cohen *J. Am. Chem. Soc.* **1987**, 109, 4710; Hosomi *Acc. Chem. Res.* **1988**, 21, 200-206; Araki; Butsugan *Chem. Lett.* **1988**, 457; Minato; Tsuji *Chem. Lett.* **1988**, 2049; Coxon; van Eyk; Steel *Tetrahedron* **1989**, 45, 1029; Knochel; Rao *J. Am. Chem. Soc.* **1990**, 112, 6146; Wada; Ohki; Akiba *Bull. Chem. Soc. Jpn.* **1990**, 63, 1738; Marton; Tagliavini; Zordan; Wardell *J. Organomet. Chem.* **1990**, 390, 127; Wang; Shi; Xu; Huang *J. Chem. Soc., Perkin Trans. 1* **1990**, 424; Shono; Ishifune; Kashimura *Chem. Lett.* **1990**, 449.

<sup>360</sup>For another exception, involving a vinylic borane, see Satoh; Tayano; Hara; Suzuki *Tetrahedron Lett.* **1989**, 30, 5153.

<sup>361</sup>For reviews, see Hoffmann; Niel; Schlapbach *Pure Appl. Chem.* **1990**, 62, 1993-1998; Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 310-318. For a review of allylic boranes, see Bubnov *Pure Appl. Chem.* **1987**, 21, 895-906.

<sup>362</sup>Kashin; Tulchinsky; Beletskaya *J. Organomet. Chem.* **1985**, 292, 205.

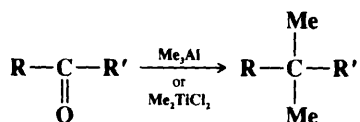
<sup>363</sup>Prakash; Krishnamurti; Olah *J. Am. Chem. Soc.* **1989**, 111, 393.

<sup>364</sup>Pearce; Richards; Scilly *J. Chem. Soc., Perkin Trans. 1* **1972**, 1655; de Souza-Barboza; Pétrier; Luche; *J. Org. Chem.* **1988**, 53, 1212.

<sup>365</sup>For a review, with Mg, Li, and other metals, see Blomberg; Hartog *Synthesis* **1977**, 18-30. For a discussion of the mechanism, see Molle; Bauer *J. Am. Chem. Soc.* **1982**, 104, 3481. For a list of Barbier-type reactions, with references, see Ref. 64, pp. 553-555.

reacts with aldehydes<sup>366</sup> and with certain ketones<sup>367</sup> to give the expected alcohols. The similar reagents  $\text{RCu(CN)ZnI}$  also react with aldehydes, in the presence of  $\text{BF}_3$ -etherate, to give secondary alcohols. Carboxylic ester, nitrile, and imide groups in the R are not affected by the reaction conditions.<sup>368</sup>

Trimethylaluminum<sup>369</sup> and dimethyltitanium dichloride<sup>370</sup> exhaustively methylate ketones to give *gem*-dimethyl compounds<sup>371</sup> (see also 0-90):



The titanium reagent also dimethylates aromatic aldehydes.<sup>372</sup>

$\alpha,\beta$ -Unsaturated aldehydes or ketones can give 1,4-addition as well as normal 1,2 addition (see 5-18). In general, alkylolithiums give less 1,4 addition than the corresponding Grignard reagents.<sup>373</sup> Quinones add Grignard reagents on one or both sides or give 1,4 addition. In a compound containing both an aldehyde and a ketone function it is possible to add  $\text{RMgX}$  chemoselectively to the aldehyde function without significantly disturbing the ketonic group<sup>374</sup> (see also p. 927). On the other hand, chemoselective addition to a ketonic group can be carried out if the aldehyde is protected with a titanium tetrakis(dialkylamide).<sup>375</sup>

As with the reduction of aldehydes and ketones (6-25), the addition of organometallic compounds to these substrates can be carried out enantioselectively and diastereoselectively.<sup>376</sup> Chiral secondary alcohols have been obtained with high ee values by addition to aromatic aldehydes of Grignard and organolithium compounds in the presence of optically active amino alcohols as ligands.<sup>377</sup> High ee values have also been obtained with other organometallics,<sup>378</sup> including organotitanium compounds (methyl, aryl, allylic) in which an optically active ligand is coordinated to the titanium,<sup>379</sup> allylic boron compounds, and organozinc compounds.

<sup>366</sup>Barreiro; Luche; Zweig; Crabbé *Tetrahedron Lett.* **1975**, 2353; Zweig; Luche; Barreiro; Crabbé *Tetrahedron Lett.* **1975**, 2355.

<sup>367</sup>House; Prabhu; Wilkins; Lee *J. Org. Chem.* **1976**, *41*, 3067; Matsuzawa; Isaka; Nakamura; Kuwajima *Tetrahedron Lett.* **1989**, *30*, 1975.

<sup>368</sup>Yeh; Knochel; Santa *Tetrahedron Lett.* **1988**, *29*, 3887.

<sup>369</sup>Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 1655. See also Jeffery; Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 2569. For discussions of the mechanism of this reaction, see Ashby; Goel *J. Organomet. Chem.* **1981**, *221*, C15; Ashby; Smith *J. Organomet. Chem.* **1982**, *225*, 71. For a review of organoaluminum compounds in organic synthesis, see Maruoka; Yamamoto *Tetrahedron* **1988**, *44*, 5001-5032.

<sup>370</sup>Reetz; Westermann; Kyung *Chem. Ber.* **1985**, *118*, 1050.

<sup>371</sup>For the *gem*-dialylation of anhydrides, with an indium reagent, see Araki; Katsumura; Ito; Butsugan *Tetrahedron Lett.* **1989**, *30*, 1581.

<sup>372</sup>Reetz; Kyung *Chem. Ber.* **1987**, *120*, 123.

<sup>373</sup>An example was given on p. 799.

<sup>374</sup>Vaskan; Kovalev *J. Org. Chem. USSR* **1973**, *9*, 501.

<sup>375</sup>Reetz; Wenderoth; Peter *J. Chem. Soc., Chem. Commun.* **1983**, 406. For another method, see Maruoka; Araki; Yamamoto *Tetrahedron Lett.* **1988**, *29*, 3101.

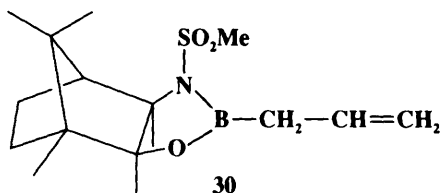
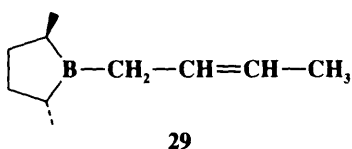
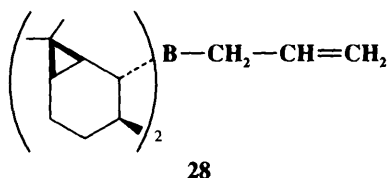
<sup>376</sup>For reviews, see Solladié, in Morrison, Ref. 294, vol. 2, pp. 157-199, pp. 158-183; Nógrádi, Ref. 294, pp. 160-193; Noyori; Kitamura *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69 [*Angew. Chem.* *103*, 34-55].

<sup>377</sup>Mukaiyama; Soai; Sato; Shimizu; Suzuki *J. Am. Chem. Soc.* **1979**, *101*, 1455; Mazaleyra; Cram *J. Am. Chem. Soc.* **1981**, *103*, 4585; Eleveld; Hogeveen *Tetrahedron Lett.* **1984**, *25*, 5187.

<sup>378</sup>For examples involving other organometallic compounds, see Abenham; Boireau; Deberly *J. Org. Chem.* **1985**, *50*, 4045; Minowa; Mukaiyama *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697; Takai; Kataoka; Utimoto *J. Org. Chem.* **1990**, *55*, 1707.

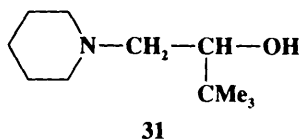
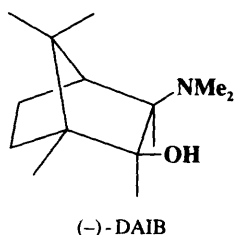
<sup>379</sup>Reetz; Kükenhöfner; Weinig *Tetrahedron Lett.* **1986**, *27*, 5711; Wang; Fan; Feng; Quian *Synthesis* **1989**, 291; Riediker; Duthaler *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 494 [*Angew. Chem.* *101*, 488]; Riediker; Hafner; Piantini; Rihs; Togni *Angew. Chem. Int. Ed. Engl.* **1989**, *30*, 499 [*Angew. Chem.* *101*, 493].

A number of optically active allylic boron compounds have been used, including<sup>380</sup> B-allylbis(2-isocaranyl)borane (**28**),<sup>381</sup> *E*- and *Z*-crotyl-(*R,R*)-2,5-dimethylborolanes (**29**),<sup>382</sup>



and the borneol derivative **30**,<sup>383</sup> all of which allylate aldehydes with ee values of 90% or more. Where the substrate possesses an aryl group or a triple bond, enantioselectivity is enhanced by using a a metal carbonyl complex of the substrate.<sup>384</sup>

As for the organozinc reagents, very high ee values (90-98%) were obtained from  $R_2Zn$  reagents ( $R$  = alkyl) and aromatic<sup>385</sup> aldehydes by the use of a small amount (2 mole percent) of the catalyst<sup>386</sup> (-)-3-*exo*-(dimethylamino)isoborneol (DAIB).<sup>387</sup> High ee values



were also achieved with diviny zinc and both aromatic and aliphatic aldehydes, with other optically active amino alcohols as catalysts.<sup>388</sup> When benzaldehyde was treated with  $Et_2Zn$

<sup>380</sup>For some others, see Hoffmann *Pure Appl. Chem.* **1988**, 60, 123; Corey; Yu; Kim *J. Am. Chem. Soc.* **1989**, 111, 5495; Roush; Ando; Powers, Palkowitz; Halterman *J. Am. Chem. Soc.* **1990**, 112, 6339; Brown; Randad *Tetrahedron Lett.* **1990**, 31, 455; Stürmer; Hoffmann *Synlett* **1990**, 759.

<sup>381</sup>Brown; Randad *Tetrahedron* **1990**, 46, 4457; Racherla; Brown *J. Org. Chem.* **1991**, 56, 401, and references cited in these papers.

<sup>382</sup>Garcia; Kim; Masamune *J. Org. Chem.* **1987**, 52, 4831.

<sup>383</sup>Reetz; Zierke *Chem. Ind. (London)* **1988**, 663.

<sup>384</sup>Roush; Park *J. Org. Chem.* **1990**, 55, 1143.

<sup>385</sup>For catalysts that are also successful for aliphatic aldehydes, see Takahashi; Kawakita; Yoshioka; Kobayashi; Ohno *Tetrahedron Lett.* **1989**, 30, 7095; Tanaka; Ushio; Suzuki *J. Chem. Soc., Chem. Commun.* **1989**, 1700; Soai; Yokoyama; Hayasaka *J. Org. Chem.* **1991**, 56, 4264.

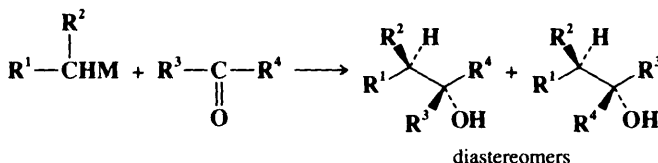
<sup>386</sup>For some other optically active catalysts used with  $R_2Zn$  and  $ArCHO$ , see Smaardijk; Wynberg *J. Org. Chem.* **1987**, 52, 135; Joshi; Srebnik; Brown *Tetrahedron Lett.* **1989**, 30, 5551; Soai; Watanabe; Yamamoto *J. Org. Chem.* **1990**, 55, 4832; Soai; Hori; Kawahara *Tetrahedron: Asymmetry* **1990**, 1, 769; Chelucci; Falorni; Giacomelli *Tetrahedron: Asymmetry* **1990**, 1, 843; Chaloner; Langadianou *Tetrahedron Lett.* **1990**, 31, 5185; Corey; Yuen; Hannon; Wierda *J. Org. Chem.* **1990**, 55, 784.

<sup>387</sup>Kitamura; Okada; Suga; Noyori *J. Am. Chem. Soc.* **1989**, 111, 4028; Noyori; Suga; Kawai; Okada; Kitamura; Oguni; Hayashi; Kaneko; Matsuda *J. Organomet. Chem.* **1990**, 382, 19.

<sup>388</sup>Oppolzer; Radinov *Tetrahedron Lett.* **1988**, 29, 5645; Watanabe; Araki; Butsugan; Uemura *J. Org. Chem.* **1991**, 56, 2218; Soai; Watanabe *Tetrahedron: Asymmetry* **1991**, 2, 97; Asami; Inoue *Chem. Lett.* **1991**, 685.

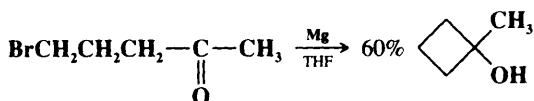
in the presence of the optically active catalyst 1-piperidino-3,3-dimethyl-2-butanol (**31**), a surprising result was obtained. Although the catalyst had only 10.7% excess of one enantiomer, the product PhCH(OH)Me had an ee of 82%.<sup>389</sup> When the catalyst ee was increased to 20.5%, the product ee rose to 88%. The question is, how could a catalyst produce a product with an ee much higher than itself? One possible explanation<sup>390</sup> is that *R* and *S* molecules of the catalyst form a complex with each other, and that only the uncomplexed molecules are actually involved in the reaction. Since initially the number of *R* and *S* molecules was not the same, the *R*:*S* ratio of the uncomplexed molecules must be considerably higher (or lower) than that of the initial mixture.

Diastereoselective addition<sup>391</sup> has been carried out with achiral reagents and chiral substrates,<sup>392</sup> similar to the reduction shown on p. 915,<sup>393</sup> but because the attacking atom in this case is carbon, not hydrogen, it is also possible to get diastereoselective addition with an achiral substrate and an optically active reagent.<sup>394</sup> Use of suitable reactants creates, in the most general case, two new chiral centers, so the product can exist as two pairs of enantiomers:



Even if the organometallic compound is racemic, it still may be possible to get a diastereoselective reaction; that is, one pair of enantiomers is formed in greater amount than the other.<sup>395</sup>

In some cases the Grignard reaction can be performed intramolecularly.<sup>396</sup> For example, treatment of 5-bromo-2-pentanone with magnesium and a small amount of mercuric chloride in THF produced 1-methyl-1-cyclobutanol in 60% yield.<sup>397</sup> Other four- and five-membered



<sup>389</sup>Oguni; Matsuda; Kaneko *J. Am. Chem. Soc.* **1988**, *110*, 7877.

<sup>390</sup>See Wynberg *Chimia* **1989**, *43*, 150.

<sup>391</sup>For a review, see Yamamoto; Maruyama *Heterocycles* **1982**, *18*, 357-386.

<sup>392</sup>For a review of cases in which the substrate bears a group that can influence the diastereoselectivity by chelating with the metal, see Reetz *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556-569 [*Angew. Chem.* **96**, 542-555]. See also Keck; Castellino *J. Am. Chem. Soc.* **1986**, *108*, 3847.

<sup>393</sup>See, for example, Eliel; Morris-Natschke *J. Am. Chem. Soc.* **1984**, *106*, 2937; Reetz; Steinbach; Westermann; Peter; Wenderoth *Chem. Ber.* **1985**, *118*, 1441; Yamamoto; Matsuoka *J. Chem. Soc., Chem. Commun.* **1987**, 923; Boireau; Deberly; Abenham *Tetrahedron Lett.* **1988**, *29*, 2175; Page; Westwood; Slawin; Williams *J. Chem. Soc., Perkin Trans. 1* **1989**, 1158; Soai; Niwa; Hatanaka *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2129. For examples in which both reactants were chiral, see Roush; Halterman *J. Am. Chem. Soc.* **1986**, *108*, 294; Hoffmann; Dresely; Hildebrandt *Chem. Ber.* **1988**, *121*, 2225; Paquette; Learn; Romine; Lin *J. Am. Chem. Soc.* **1988**, *110*, 879; Brown; Bhat; Randad *J. Org. Chem.* **1989**, *54*, 1570.

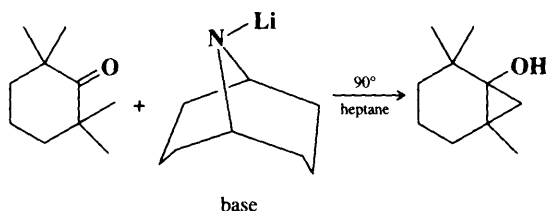
<sup>394</sup>For a review of such reactions with crotylmetallic reagents, see Hoffmann *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555-566 [*Angew. Chem.* **94**, 569-580]. For a discussion of the mechanism, see Denmark; Weber *J. Am. Chem. Soc.* **1984**, *106*, 7970. For some examples, see Hoffmann; Landmann *Chem. Ber.* **1986**, *119*, 2013; Zweifel; Shoup *J. Am. Chem. Soc.* **1988**, *110*, 5578; Gung; Smith; Wolf *Tetrahedron Lett.* **1991**, *32*, 13.

<sup>395</sup>For examples, see Coxon; van Eyk; Steel *Tetrahedron Lett.* **1985**, *26*, 6121; Mukaiyama; Ohshima; Miyoshi *Chem. Lett.* **1987**, 1121; Masuyama; Takahara; Kurusu *Tetrahedron Lett.* **1989**, *30*, 3437.

<sup>396</sup>For a list of reagents, with references, see Ref. 64, p. 557.

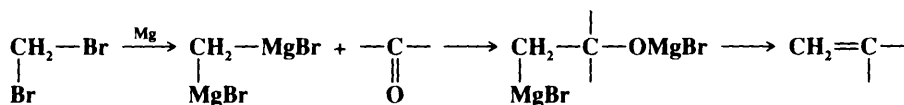
<sup>397</sup>Leroux *Bull. Soc. Chim. Fr.* **1968**, 359.

ring compounds were also prepared by this procedure. Similar closing of five- and six-membered rings was achieved by treatment of a  $\delta$ - or  $\epsilon$ -halocarbonyl compound, not with a metal, but with a dianion derived from nickel tetraphenylporphine.<sup>398</sup> An interesting organometallic ring closure is

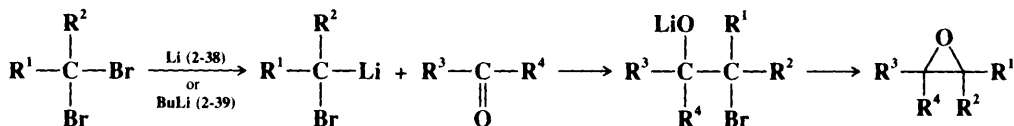


In this case, because the ketone has no  $\alpha$  hydrogen, the base removed a  $\beta$  hydrogen (from a  $\text{CH}_3$  group), and the intramolecular addition to the  $\text{C}=\text{O}$  followed.<sup>399</sup>

The *gem*-disubstituted magnesium compounds formed from  $\text{CH}_2\text{Br}_2$  or  $\text{CH}_2\text{I}_2$  (2-38) react with aldehydes or ketones to give olefins in moderate-to-good yields.<sup>400</sup> The reaction could



not be extended to other *gem*-dihalides. Similar reactions with *gem*-dimetallic compounds prepared with metals other than magnesium have also produced olefins.<sup>401</sup> The  $\alpha,\alpha$ -dimetallic derivatives of phenyl sulfones  $\text{PhSO}_2\text{CM}_2\text{R}$  ( $\text{M} = \text{Li}$  or  $\text{Mg}$ ) react with aldehydes or ketones  $\text{R}'\text{COR}''$  to give good yields of the  $\alpha,\beta$ -unsaturated sulfones  $\text{PhSO}_2\text{CR}=\text{CR}'\text{R}''$ ,<sup>402</sup> which can be reduced with aluminum amalgam (see 0-94) or with  $\text{LiAlH}_4\text{--CuCl}_2$  to give the olefins  $\text{CHR}=\text{CR}'\text{R}''$ .<sup>403</sup> Olefins can also be obtained from organolithium compounds  $\text{R}^1\text{R}^2\text{CHLi}$ , by treating them with ketones  $\text{R}^3\text{COR}^4$ , followed by  $\text{SOCl}_2$ , a procedure which gives  $\text{R}^1\text{R}^2\text{C}=\text{CR}^3\text{R}^4$ .<sup>404</sup> These reactions are closely related to the Wittig reaction (6-47) and, like it, provide a means of achieving the conversion  $\text{R}_2\text{C}=\text{O} \rightarrow \text{R}_2\text{C}=\text{CR}'\text{R}''$ . On the other hand, *gem*-dihalides treated with a carbonyl compound and  $\text{Li}$  or  $\text{BuLi}$  give epoxides<sup>405</sup> (see also 6-61).



<sup>398</sup>Corey; Kuwajima *J. Am. Chem. Soc.* **1970**, 92, 395. For another method, see Molander; Etter; Zinke *J. Am. Chem. Soc.* **1987**, 109, 453; Molander; McKie *J. Org. Chem.* **1991**, 56, 4112.

<sup>399</sup>Shiner; Berks; Fisher *J. Am. Chem. Soc.* **1988**, 110, 957.

<sup>400</sup>Bertini; Grasselli; Zubiani; Cainelli *Tetrahedron* **1970**, 26, 1281.

<sup>401</sup>For example, see Zweifel; Steele *Tetrahedron Lett.* **1966**, 6021; Cainelli; Bertini; Grasselli; Zubiani *Tetrahedron Lett.* **1967**, 1581; Takai; Hotta; Oshima; Nozaki *Bull. Chem. Soc. Jpn.* **1980**, 53, 1698; Knochel; Normant *Tetrahedron Lett.* **1986**, 27, 1039; Barluenga; Fernández-Simón; Concellón; Yus *J. Chem. Soc., Chem. Commun.* **1986**, 1665; Okazoe; Takai; Ukimoto *J. Am. Chem. Soc.* **1987**, 109, 951; Piotrowski; Malpass; Boleslawski; Eisch *J. Org. Chem.* **1988**, 53, 2829; Tour; Bedworth; Wu *Tetrahedron Lett.* **1989**, 30, 3927; Lombardo *Org. Synth.* **65**, 81.

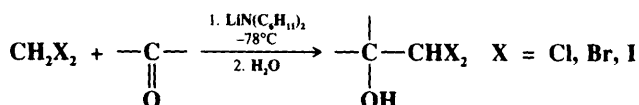
<sup>402</sup>Pascali; Tangari; Umani-Ronchi *J. Chem. Soc., Perkin Trans. 1* **1973**, 1166.

<sup>403</sup>Pascali; Umani-Ronchi *J. Chem. Soc., Chem. Commun.* **1973**, 351.

<sup>404</sup>Olah; Wu; Farooq *J. Org. Chem.* **1989**, 54, 1375.

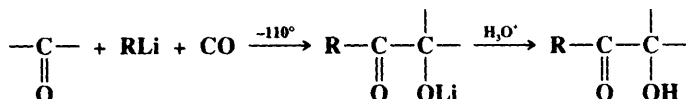
<sup>405</sup>Cainelli; Umani-Ronchi; Bertini; Grasselli; Zubiani *Tetrahedron* **1971**, 27, 6109; Cainelli; Tangari; Umani-Ronchi *Tetrahedron* **1972**, 28, 3009.

In other uses of *gem*-dihalo compounds, aldehydes and ketones add the  $\text{CH}_2\text{I}$  group ( $\text{R}_2\text{CO} \rightarrow \text{R}_2\text{C}(\text{OH})\text{CH}_2\text{I}$ ) when treated with  $\text{CH}_2\text{I}_2$  in the presence of  $\text{SmI}_2$ <sup>406</sup> and the  $\text{CHX}_2$  group when treated with methylene halides and lithium dicyclohexylamide at low temperatures.<sup>407</sup>



A hydroxymethyl group can be added to an aldehyde or ketone with the masked reagent  $\text{Me}_2(\text{i-PrO})\text{SiCH}_2\text{MgCl}$ , which with  $\text{R}_2\text{CO}$  gives  $\text{R}_2\text{C}(\text{OH})\text{CH}_2\text{Si}(\text{O-i-Pr})\text{Me}_2$ , which, with  $\text{H}_2\text{O}_2$ , give 1,2-diols  $\text{R}_2\text{C}(\text{OH})\text{CH}_2\text{OH}$ .<sup>408</sup>

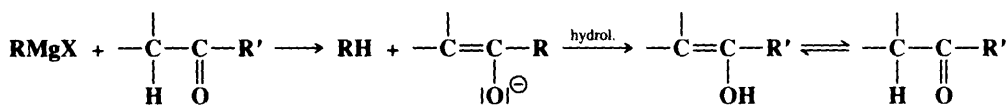
It is possible to add an acyl group to a ketone to give (after hydrolysis) an  $\alpha$ -hydroxy ketone.<sup>409</sup> This can be done by adding  $\text{RLi}$  and  $\text{CO}$  to the ketone at  $-110^\circ\text{C}$ .<sup>410</sup>



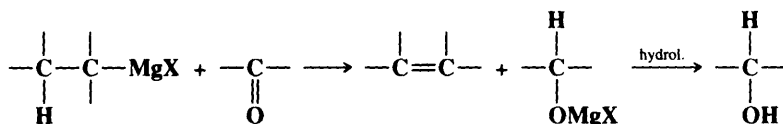
When the same reaction is carried out with carboxylic esters  $\text{R}'\text{COOR}''$ ,  $\alpha$ -diketones  $\text{RCOCOR}'$  are obtained.<sup>410</sup> Another way to add  $\text{RCO}$  to aldehydes and ketones is to treat the substrate with  $\text{ArCOLi}$ , generated by treating  $\text{ArCOTeBu}$  with  $\text{BuLi}$ .<sup>411</sup>

Although most aldehydes and ketones react very nicely with most Grignard reagents, there are several types of side reaction that occur mostly with hindered ketones and with bulky Grignard reagents. The two most important of these are *enolization* and *reduction*. The former requires that the aldehyde or ketone have an  $\alpha$  hydrogen, and the latter requires that the Grignard reagent have a  $\beta$  hydrogen:

#### Enolization



#### Reduction



Enolization is an acid-base reaction (2-24) in which a proton is transferred from the  $\alpha$  carbon to the Grignard reagent. The carbonyl compound is converted to its enolate ion form, which, on hydrolysis, gives the original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those that have a relatively high percentage of enol form, e.g.,  $\beta$ -keto esters, etc. In reduction, the carbonyl compound is reduced to an alcohol (6-25)

<sup>406</sup>Imamoto; Takeyama; Koto *Tetrahedron Lett.* **1986**, 27, 3243.

<sup>407</sup>Taguchi; Yamamoto; Nozaki *J. Am. Chem. Soc.* **1974**, 96, 3010 *Bull. Chem. Soc. Jpn.* **1977**, 50, 1588.

<sup>408</sup>Tamao; Ishida *Tetrahedron Lett.* **1984**, 25, 4245. For another method, see Imamoto; Takeyama; Yokoyama *Tetrahedron Lett.* **1984**, 25, 3225.

<sup>409</sup>For a review, see Seyferth; Weinstein; Wang; Hui; Archer *Isr. J. Chem.* **1984**, 24, 167-175.

<sup>410</sup>Seyferth; Weinstein; Wang *J. Org. Chem.* **1983**, 48, 1144; Seyferth; Weinstein; Wang; Hui; *Tetrahedron Lett.* **1983**, 24, 4907.

<sup>411</sup>Hiirio; Morita; Inoue; Kambe; Ogawa; Ryu; Sonoda *J. Am. Chem. Soc.* **1990**, 112, 455.

by the Grignard reagent, which itself undergoes elimination to give an olefin. Two other side reactions are condensation (between enolate ion and excess ketone) and Wurtz-type coupling (0-92). Such highly hindered tertiary alcohols as triisopropylcarbinol, tri-*t*-butylcarbinol, and diisopropylneopentylcarbinol cannot be prepared (or can be prepared only in extremely low yields) by the addition of Grignard reagents to ketones, because reduction and/or enolization become prominent.<sup>412</sup> However, these carbinols can be prepared by the use of alkyllithiums at  $-80^{\circ}\text{C}$ ,<sup>413</sup> under which conditions enolization and reduction are much less important.<sup>414</sup> Other methods of increasing the degree of addition at the expense of reduction consist of complexing the Grignard reagent with  $\text{LiClO}_4$  or  $\text{Bu}_4\text{N}^+ \text{Br}^-$ ,<sup>415</sup> or using benzene or toluene instead of ether as solvent.<sup>416</sup> Both reduction and enolization can be avoided by adding  $\text{CeCl}_3$  to the Grignard reagent.<sup>417</sup>

Another way to avoid complications is to add  $(\text{RO})_3\text{TiCl}$ ,  $\text{TiCl}_4$ ,<sup>418</sup>  $(\text{RO})_3\text{ZrCl}$ , or  $(\text{R}_2\text{N})_3\text{TiX}$  to the Grignard or lithium reagent. This produces organotitanium or organozirconium compounds that are much more selective than Grignard or organolithium reagents.<sup>419</sup> An important advantage of these reagents is that they do not react with  $\text{NO}_2$  or  $\text{CN}$  functions that may be present in the substrate, as Grignard and organolithium reagents do. Furthermore, organotitanium reagents can be made to add chemoselectively to aldehydes in presence of ketones.<sup>420</sup> Organomanganese compounds are also chemoselective in this way.<sup>421</sup>

There has been much controversy regarding the mechanism of addition of Grignard reagents to aldehydes and ketones.<sup>422</sup> The reaction is difficult to study because of the variable nature of the species present in the Grignard solution (p. 183) and because the presence of small amounts of impurities in the magnesium seems to have a great effect on the kinetics of the reaction, making reproducible experiments difficult.<sup>423</sup> There seem to be two basic mechanisms, depending on the reactants and the reaction conditions. In one of these, the R group is transferred to the carbonyl carbon with its electron pair. A detailed mechanism of this type has been proposed by Ashby and co-workers,<sup>424</sup> based on the discovery that this reaction proceeds by two paths—one first order in  $\text{MeMgBr}$  and the other first order in  $\text{Me}_2\text{Mg}$ .<sup>425</sup> According to this proposal, both  $\text{MeMgBr}$  and  $\text{Me}_2\text{Mg}$  add to the carbonyl

<sup>412</sup>Whitmore; George *J. Am. Chem. Soc.* **1942**, *64*, 1239.

<sup>413</sup>Bartlett; Lefferts *J. Am. Chem. Soc.* **1955**, *77*, 2804; Zook; March; Smith *J. Am. Chem. Soc.* **1959**, *81*, 1617; Bartlett; Tidwell *J. Am. Chem. Soc.* **1968**, *90*, 4421. See also Lomas *Nouv. J. Chim.* **1984**, *8*, 365; Molle; Briand; Bauer; Dubois *Tetrahedron* **1984**, *40*, 5113.

<sup>414</sup>Buhler *J. Org. Chem.* **1973**, *38*, 904.

<sup>415</sup>Chastrette; Amouroux *Chem. Commun.* **1970**, 470, *Bull. Soc. Chim. Fr.* **1970**, 4348. See also Richey; De-Stephano *J. Org. Chem.* **1990**, *55*, 3281.

<sup>416</sup>Canonne; Foscolos; Caron; Lemay *Tetrahedron* **1982**, *38*, 3563.

<sup>417</sup>Imamoto; Takiyama; Nakamura; Hatajima; Kamiya *J. Am. Chem. Soc.* **1989**, *111*, 4392.

<sup>418</sup>See Reetz; Kyung; Hüllmann *Tetrahedron* **1986**, *42*, 2931.

<sup>419</sup>For a monograph, see Reetz *Organotitanium Reagents in Organic Synthesis*; Springer: New York, 1986. For reviews, see Weidmann; Seebach *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31-45 [*Angew. Chem.* **95**, 12-26]; Reetz *Top. Curr. Chem.* **1982**, *106*, 1-54.

<sup>420</sup>Reetz, Ref. 419 (monograph), pp. 75-86. See also Reetz; Maus *Tetrahedron* **1987**, *43*, 101.

<sup>421</sup>Cahiez; Figadere *Tetrahedron Lett.* **1986**, *27*, 4445. For other organometallic reagents with high selectivity towards aldehyde functions, see Kauffmann; Hamsen; Beirich *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 144 [*Angew. Chem.* **94**, 145]; Takai; Kimura; Kuroda; Hiyama; Nozaki *Tetrahedron Lett.* **1983**, *24*, 5281; Soai; Watanabe; Koyano *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2124.

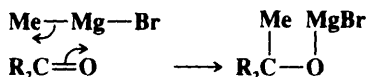
<sup>422</sup>For reviews, see Holm *Acta Chem. Scand., Ser. B* **1983**, *37*, 567-584; Ashby *Pure Appl. Chem.* **1980**, *52*, 545-569, *Bull. Soc. Chim. Fr.* **1972**, 2133-2142, *Q. Rev. Chem. Soc.* **1967**, *21*, 259-285; Ashby; Laemmle; Neumann *Acc. Chem. Res.* **1974**, *7*, 272-280; Blomberg *Bull. Soc. Chim. Fr.* **1972**, 2143-2149. For a review of the stereochemistry of the reaction, see Ashby; Laemmle, Ref. 5. For a review of the effects of the medium and the cation, see Solv'yanov; Beletskaya *Russ. Chem. Rev.* **1987**, *56*, 465-476.

<sup>423</sup>See, for example, Ashby; Walker; Neumann *Chem. Commun.* **1970**, 330; Ashby; Neumann; Walker; Laemmle; Chao *J. Am. Chem. Soc.* **1973**, *95*, 3330.

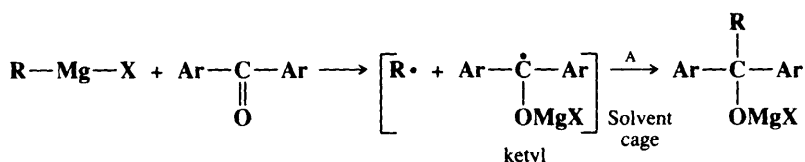
<sup>424</sup>Ashby; Laemmle; Neumann *J. Am. Chem. Soc.* **1972**, *94*, 5421.

<sup>425</sup>Ashby; Laemmle; Neumann *J. Am. Chem. Soc.* **1971**, *93*, 4601; Laemmle; Ashby; Neumann *J. Am. Chem. Soc.* **1971**, *93*, 5120.

carbon, though the exact nature of the step by which  $\text{MeMgBr}$  or  $\text{Me}_2\text{Mg}$  reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:<sup>426</sup>



The other type of mechanism is a single electron transfer (SET) process<sup>427</sup> with a ketyl intermediate:<sup>428</sup>



This mechanism, which has been mostly studied with diaryl ketones, is more likely for aromatic and other conjugated aldehydes and ketones than it is for strictly aliphatic ones. Among the evidence<sup>429</sup> for the SET mechanism are esr spectra<sup>430</sup> and the obtention of  $\text{Ar}_2\text{C} \text{---} \text{CAr}_2$  side products (from dimerization of the ketyl).<sup>431</sup> In the case of addition of



$\text{RMgX}$  to benzil  $\text{PhCOCOPh}$ , esr spectra of two different ketyl radicals were observed, both reported to be quite stable at room temperature.<sup>432</sup> Carbon isotope effect studies with  $\text{Ph}^{14}\text{COPh}$  showed that the rate-determining step with most Grignard reagents is the carbon-carbon bond-forming step (marked A), though with allylmagnesium bromide it is the initial electron transfer step.<sup>433</sup>

Mechanisms for the addition of organolithium reagents have been investigated much less.<sup>434</sup> Addition of a cryptand that binds  $\text{Li}^+$  inhibited the normal addition reaction, showing that the lithium is necessary for the reaction to take place.<sup>435</sup>

There is general agreement that the mechanism leading to reduction<sup>436</sup> is usually as follows:

<sup>426</sup>Tuulmets *Org. React. (USSR)* **1967**, 4, 5; House; Oliver *J. Org. Chem.* **1968**, 33, 929; Ashby; Yu; Roling; *J. Org. Chem.* **1972**, 37, 1918. See also Billet; Smith *J. Am. Chem. Soc.* **1968**, 90, 4108; Lasperas; Perez-Rubalcaba; Quiroga-Feijoo *Tetrahedron* **1980**, 36, 3403.

<sup>427</sup>For a review, see Dagonneau *Bull. Soc. Chim. Fr.* **1982**, II-269-II-280.

<sup>428</sup>There is kinetic evidence that the solvent cage shown may not be necessary; Walling *J. Am. Chem. Soc.* **1986**, 110, 6846.

<sup>429</sup>For other evidence, see Savin; Kitaev *J. Org. Chem. USSR* **1975**, 11, 2622; Ōkubo *Bull. Chem. Soc. Jpn.* **1977**, 50, 2379; Ashby; Bowers *J. Am. Chem. Soc.* **1981**, 103, 2242; Holm *Acta Chem. Scand., Ser. B* **1982**, 36, 266. **1988**, 42, 685; Liotta; Saindane; Waykole *J. Am. Chem. Soc.* **1983**, 105, 2922; Zhang; Wenderoth; Su; Ashby *J. Organomet. Chem.* **1985**, 292, 29; Yamataka; Miyano; Hanafusa *J. Org. Chem.* **1991**, 56, 2573.

<sup>430</sup>Fauvarque; Rouget, C. R. *Acad. Sci., Ser. C* **1968**, 267, 1355; Maruyama; Katagiri *Chem. Lett.* **1987**, 731, 735, *J. Phys. Org. Chem.* **1988**, 1, 21.

<sup>431</sup>Blomberg; Mosher *J. Organomet. Chem.* **1968**, 13, 519; Holm; Crossland *Acta Chem. Scand.* **1971**, 25, 59.

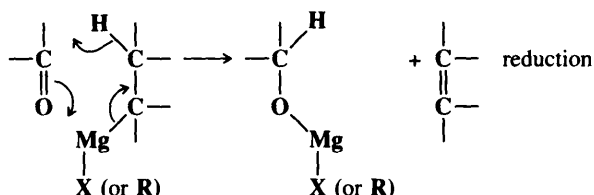
<sup>432</sup>Maruyama; Katagiri *J. Am. Chem. Soc.* **1986**, 108, 6263, *J. Phys. Org. Chem.* **1989**, 2, 205. See also Holm *Acta Chem. Scand., Ser. B* **1987**, 41, 278; Maruyama; Katagiri *J. Phys. Org. Chem.* **1991**, 4, 158.

<sup>433</sup>Yamataka; Matsuyama; Hanafusa *J. Am. Chem. Soc.* **1989**, 111, 4912.

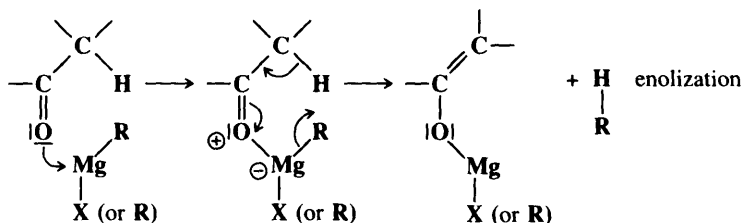
<sup>434</sup>See, for example, Al-Aseer; Smith *J. Org. Chem.* **1984**, 49, 2608; Yamataka; Kawafuji; Nagareda; Miyano; Hanafusa *J. Org. Chem.* **1989**, 54, 4706.

<sup>435</sup>Perraud; Handel; Pierre *Bull. Soc. Chim. Fr.* **1980**, II-283.

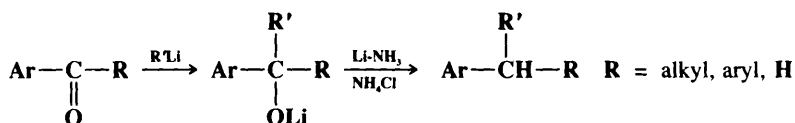
<sup>436</sup>For discussions of the mechanism of reduction, see Singer; Salinger; Mosher *J. Org. Chem.* **1967**, 32, 3821; Denise; Fauvarque; Ducom *Tetrahedron Lett.* **1970**, 335; Cabaret; Welvert *J. Organomet. Chem.* **1974**, 80, 199; Holm *J. Organomet. Chem.* **1971**, 29, C45, *Acta Chem. Scand.* **1973**, 27, 1552; Morrison; Tomaszewski; Mosher; Dale; Miller; Elsenbaumer *J. Am. Chem. Soc.* **1977**, 99, 3167; Okuhara *J. Am. Chem. Soc.* **1980**, 102, 244.



There is evidence that the mechanism leading to enolization is also cyclic, but involves prior coordination with magnesium:<sup>437</sup>



Aromatic aldehydes and ketones can be alkylated and reduced in one reaction vessel by treatment with an alkyl- or aryllithium, followed by lithium and ammonia and then by ammonium chloride.<sup>438</sup>

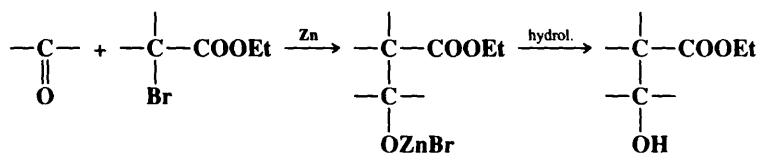


A similar reaction has been carried out with N,N-disubstituted amides:  $\text{RCONR}'_2 \rightarrow \text{RR}'\text{CHNR}'_2$ .<sup>439</sup> When the reagent is  $\text{MeNbCl}_4$ , ketones  $\text{R}_2\text{CO}$  are converted to  $\text{R}_2\text{C}(\text{Cl})\text{Me}$ .<sup>440</sup>

OS I, 188; **II**, 406, 606; **III**, 200, 696, 729, 757; **IV**, 771, 792; **V**, 46, 452, 608, 1058; **VI**, 478, 537, 542, 606, 737, 991, 1033; **VII**, 177, 271, 447; **65**, 81; **67**, 180, 210; **69**, 96, 106, 114, 120, 220.

## 6-30 The Reformatsky Reaction

### O-Hydro-C- $\alpha$ -ethoxycarbonylalkyl-addition



<sup>437</sup>Pinkus; Servoss *J. Chem. Soc., Perkin Trans. 2* **1979**, 1600; Pinkus; Sabesan *J. Chem. Soc., Perkin Trans. 2*, **1981**, 273.

<sup>438</sup>Hall; Lipsky *J. Org. Chem.* **1973**, 38, 1735; Lipsky; Hall *Org. Synth. VI*, 537; McEnroe; Sha; Hall *J. Org. Chem.* **1976**, 41, 3465.

<sup>439</sup>Hwang; Chu; Fowler *J. Org. Chem.* **1985**, 50, 3885.

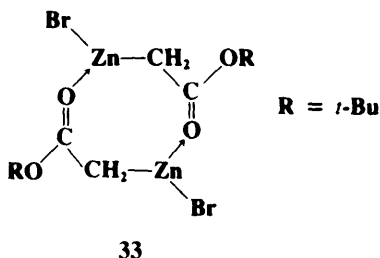
<sup>440</sup>Kauffmann; Abel; Neiteler; Schreer *Tetrahedron Lett.* **1990**, 503.

The *Reformatsky reaction* is very similar to **6-29**.<sup>441</sup> An aldehyde or ketone is treated with zinc and a halide; the halide is usually an  $\alpha$ -halo ester or a vinyllog of an  $\alpha$ -halo ester (e.g.,  $\text{RCHBrCH}=\text{CHCOOEt}$ ), though  $\alpha$ -halo nitriles,<sup>442</sup>  $\alpha$ -halo ketones,<sup>443</sup>  $\alpha$ -halo N,N-disubstituted amides, and the zinc salts of  $\alpha$ -halo carboxylic acids<sup>444</sup> have also been used. With the last reagent the product is a  $\beta$ -hydroxy acid. Especially high reactivity can be achieved with activated zinc,<sup>445</sup> with zinc/silver-graphite,<sup>446</sup> and with zinc and ultrasound.<sup>447</sup> The reaction has also been carried out with other metals instead of zinc (e.g., In,<sup>448</sup> Mn<sup>449</sup>) and with certain other compounds, including  $\text{Sml}_2$ ,<sup>450</sup>  $\text{Bu}_2\text{Te}$ ,<sup>451</sup> and  $\text{Bu}_3\text{Sb}$ .<sup>452</sup> The aldehyde or ketone can be aliphatic, aromatic, or heterocyclic or contain various functional groups. Solvents used are generally ethers, including  $\text{Et}_2\text{O}$ , THF, and 1,4-dioxane.

Formally, the reaction can be regarded as if it were analogous to the Grignard reaction

(**6-29**), with  $\text{EtOOC}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{ZnBr}$  (**32**) as an intermediate analogous to  $\text{RMgX}$ . There is an

intermediate derived from zinc and the ester, the structure of which has been shown to be **33**, by x-ray crystallography of the solid intermediate prepared from  $t\text{-BuOCOCH}_2\text{Br}$  and



Zn. As can be seen, it has some of the characteristics of **32**.

Usually, after hydrolysis, the alcohol is the product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an olefin. By the use of  $\text{Bu}_3\text{P}$  along with Zn, the olefin can be made the main product,<sup>454</sup> making this an alternative to the Wittig reaction (**6-47**). Since Grignard reagents cannot be formed from  $\alpha$ -halo esters, the method is quite useful, though there are competing reactions and yields are sometimes low. A similar reaction (called the *Blaise reaction*) has been carried out on nitriles.<sup>455</sup>

<sup>441</sup>For reviews, see Fürstner *Synthesis* **1989**, 571-590; Rathke *Org. React.* **1975**, 22, 423-460; Gaudemar *Organomet. Chem. Rev., Sect. A* **1972**, 8, 183-233.

<sup>442</sup>Vinograd; Vul'fson *J. Gen. Chem. USSR* **1959**, 29, 248, 1118, 2656, 2659; Palomo; Aizpurua; López; Aurrekoetxea *Tetrahedron Lett.* **1990**, 31, 2205; Zheng; Yu; Shen *Synth. Commun.* **1990**, 20, 3277.

<sup>443</sup>For examples (with  $\text{R}_3\text{Sb}$  and  $\text{CrCl}_2$ , respectively, instead of Zn), see Huang; Chen; Shen *J. Chem. Soc., Perkin Trans. I* **1988**, 2855; Dubois; Axiotis; Bertounesque *Tetrahedron Lett.* **1985**, 26, 4371.

<sup>444</sup>Bellassoued; Gaudemar *J. Organomet. Chem.* **1975**, 102, 1.

<sup>445</sup>Rieke; Uhm *Synthesis* **1975**, 452; Bouhllel; Rathke *Synth. Commun.* **1991**, 21, 133.

<sup>446</sup>Csuk; Fürstner; Weidmann *J. Chem. Soc., Chem. Commun.* **1986**, 775. See also Bortolussi; Seyden-Penne *Synth. Commun.* **1989**, 19, 2355.

<sup>447</sup>Han; Boudjouk *J. Org. Chem.* **1982**, 47, 5030.

<sup>448</sup>Chao; Rieke *J. Org. Chem.* **1975**, 40, 2253; Araki; Ito; Butsugan *Synth. Commun.* **1988**, 18, 453.

<sup>449</sup>Cahiez; Chavant *Tetrahedron Lett.* **1985**, 30, 7373.

<sup>450</sup>Kagan; Namy; Girard *Tetrahedron Suppl.* **1981**, 37, 175; Tabuchi; Kawamura; Inanaga; Yamaguchi *Tetrahedron Lett.* **1986**, 27, 3889; Molander; Etter *J. Am. Chem. Soc.* **1987**, 109, 6556.

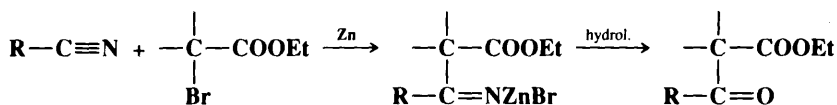
<sup>451</sup>Huang; Xie; Wu *Tetrahedron Lett.* **1987**, 28, 801.

<sup>452</sup>Chen; Huang; Shen; Liao *Heteroat. Chem.* **1990**, 1, 49.

<sup>453</sup>Dekker; Budzelaar; Boersma; van der Kerk; Spek *Organometallics* **1984**, 3, 1403.

<sup>454</sup>Shen; Xin; Zhao *Tetrahedron Lett.* **1988**, 29, 6119. For another method, see Huang; Shi; Li; Wen *J. Chem. Soc., Perkin Trans. I* **1989**, 2397.

<sup>455</sup>See Cason; Rinehart; Thornton *J. Org. Chem.* **1953**, 18, 1594; Bellassoued; Gaudemar *J. Organomet. Chem.* **1974**, 81, 139; Hannick; Kishi *J. Org. Chem.* **1983**, 48, 3833.

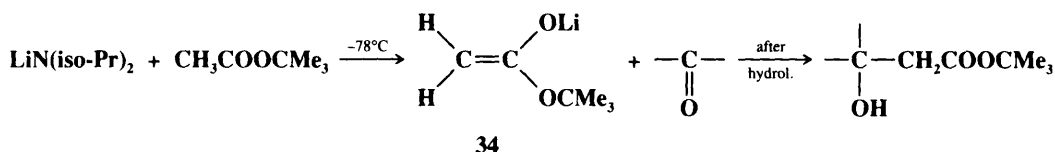


Carboxylic esters have also been used as substrates, but then, as might be expected (p. 881), the result is substitution and not addition:



The product in this case is the same as with the corresponding nitrile, though the pathways are different.

Addition of *t*-butyl acetate to lithium diisopropylamide (LDA) in hexane at  $-78^\circ\text{C}$  gives the lithium salt of *t*-butyl acetate<sup>456</sup> (**2-22**) as a stable solid. The nmr and ir spectra of this

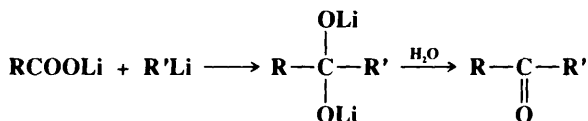


salt in benzene show it to have the enolate structure **34**. Reaction of **34** with a ketone provides a simple rapid alternative to the Reformatsky reaction as a means of preparing  $\beta$ -hydroxy *t*-butyl esters. A similar reaction involves treatment of a ketone with a silyl ketene acetal  $\text{R}_2\text{C}=\text{C}(\text{OSiMe}_3)\text{OR}'$  in the presence of  $\text{TiCl}_4$ <sup>457</sup> (see also the reaction between silyl enol ethers and aldehydes and ketones, in **6-39**).

OS **III**, 408; **IV**, 120, 444.

### 6-31 The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds

#### Alkyl-de-oxido-substitution



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkylolithium reagent, followed by hydrolysis.<sup>458</sup>  $\text{R}'$  may be aryl or primary, secondary, or tertiary alkyl. MeLi and PhLi have been employed most often. R may be

<sup>456</sup>Rathke; Sullivan *J. Am. Chem. Soc.* **1973**, 95, 3050.

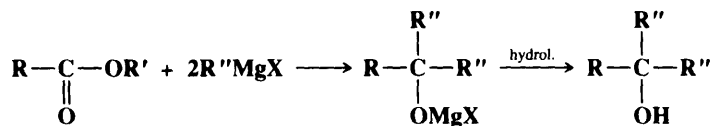
<sup>457</sup>See for example, Saigo; Osaki; Mukaiyama *Chem. Lett.* **1975**, 989; Palazzi; Colombo; Gennari *Tetrahedron Lett.* **1986**, 27, 1735; Oppolzer; Marco-Contelles *Helv. Chim. Acta* **1986**, 69, 1699; Hara; Mukaiyama *Chem. Lett.* **1989**, 1909. For a list of references, see Ref. 64, pp. 885-887. For methods of preparing silyl ketene acetals, see Revis; Hilty *Tetrahedron Lett.* **1987**, 28, 4809, and references cited therein.

<sup>458</sup>For a review, see Jorgenson *Org. React.* **1970**, 18, 1-97. For an improved procedure, see Rubottom; Kim *J. Org. Chem.* **1983**, 48, 1550.

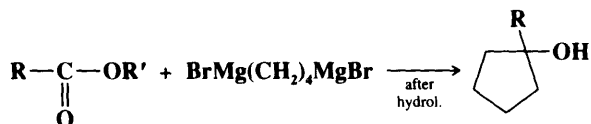
alkyl or aryl, though lithium acetate generally gives low yields. Tertiary alcohols are side products.

OS V, 775.

**6-32** The Addition of Grignard Reagents to Acid Derivatives  
**Dialkyl,hydroxy-de-alkoxy,oxo-ter**substitution

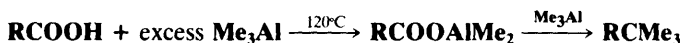


When carboxylic esters are treated with Grignard reagents, there is usually concomitant addition to the carbonyl (6-29) and substitution of R'' for OR' (0-104), so that tertiary alcohols are formed in which two R groups are the same. Formates give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same:  $(\text{EtO})_2\text{C}=\text{O} + \text{RMgX} \rightarrow \text{R}_3\text{COMgX}$ . Acyl halides and anhydrides behave similarly, though these substrates are employed less often.<sup>459</sup> There are many side reactions possible, especially when the acid derivative or the Grignard reagent is branched: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (0-104), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanol.<sup>460</sup>

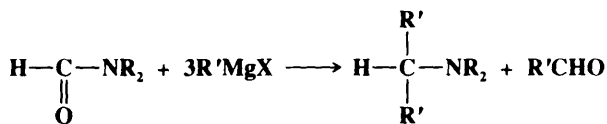


1,5-Dimagnesium compounds give cyclohexanols, but in lower yields.<sup>460</sup>

Trimethylaluminum, which exhaustively methylates ketones (6-29), also exhaustively methylates carboxylic acids to give *t*-butyl compounds<sup>461</sup> (see also 0-90):



Disubstituted formamides can give addition of 2 moles of Grignard reagent. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.<sup>462</sup> The use



of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. It has proven possible to add two different R groups by sequential addition

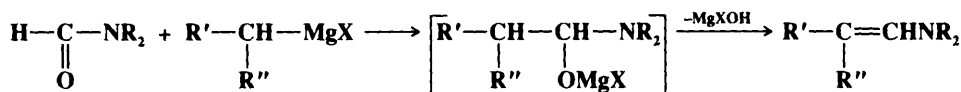
<sup>459</sup>For a review of these reactions, see Kharasch; Reinmuth, Ref. 351, pp. 549-766, 846-869.

<sup>460</sup>Canonne; Bernatchez *J. Org. Chem.* **1986**, 51, 2147, **1987**, 52, 4025.

<sup>461</sup>Meisters; Mole *Aust. J. Chem.* **1974**, 27, 1665.

<sup>462</sup>For a review, see Ref. 176, pp. 59-63.

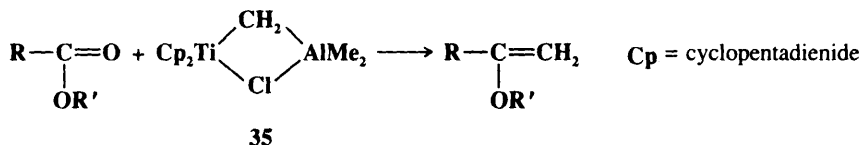
of two Grignard reagents.<sup>463</sup> Alternatively, if R' contains an  $\alpha$  hydrogen, the product may be an enamine, and enamines have been synthesized in good yields by this method.<sup>464</sup>



OS I, 226; II, 179, 602; III, 237, 831, 839; IV, 601; VI, 240, 278; 65, 42; 67, 125.

### 6-33 Conversion of Carboxylic Esters to Enol Ethers

#### Methylene-de-oxo-bisubstitution



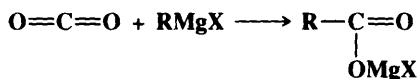
Carboxylic esters and lactones can be converted in good yields to the corresponding enol ethers by treatment with the titanium cyclopentadienide complex **35** (Tebbe's reagent) in toluene-THF containing a small amount of pyridine.<sup>465</sup> **35** is prepared from dicyclopentadienyltitaniumdichloride and trimethylaluminum.<sup>466</sup> Dimethyltitanocene has been used instead of **35**.<sup>467</sup> There are several methods for the conversion  $\text{C}=\text{O}$  to  $\text{C}=\text{CH}_2$  when the substrate is an aldehyde or ketone (see 6-29, 6-30, 6-39 to 6-44, 6-47), but very few ways to make the same conversion for a carboxylic ester. (Tebbe's reagent also gives good results with ketones.<sup>468</sup>) The enol ether can be hydrolyzed to a ketone (0-6), so this is also an indirect method for making the conversion  $\text{RCOOR}' \rightarrow \text{RCOCH}_3$  (see also 0-105).

Carboxylic esters undergo the conversion  $\text{C}=\text{O} \rightarrow \text{C}=\text{CHR}$  ( $\text{R}$  = primary or secondary alkyl) when treated with  $\text{RCHBr}_2$ ,  $\text{Zn}$ , and  $\text{TiCl}_4$  in the presence of  $\text{N,N,N',N'}$ -tetramethylethylenediamine.<sup>469</sup> Metal carbene complexes<sup>470</sup>  $\text{R}_2\text{C}=\text{ML}_n$  ( $\text{L}$  = ligand), where  $\text{M}$  is a transition metal such as  $\text{Zr}$ ,  $\text{W}$ , or  $\text{Ta}$ , have also been used to convert the  $\text{C}=\text{O}$  of carboxylic esters and lactones to  $\text{CR}_2$ .<sup>471</sup> It is likely that the complex  $\text{Cp}_2\text{Ti}=\text{CH}_2$  is an intermediate in the reaction with Tebbe's reagent.

OS 69, 72.

### 6-34 The Addition of Organometallic Compounds to $\text{CO}_2$

#### C-Alkyl-O-halomagnesio-addition



<sup>463</sup>Comins; Dernel Tetrahedron Lett. 1981, 22, 1085.

<sup>464</sup>Hansson; Wickberg J. Org. Chem. 1973, 38, 3074.

<sup>465</sup>Tebbe; Parshall; Reddy J. Am. Chem. Soc. 1978, 100, 3611; Pine; Pettit; Geib; Cruz; Gallego; Tijerina; Pine J. Org. Chem. 1985, 50, 1212. See also Clawson; Buchwald; Grubbs Tetrahedron Lett. 1984, 25, 5733; Clift; Schwartz J. Am. Chem. Soc. 1984, 106, 8300.

<sup>466</sup>For a method of generating this reagent in situ, see Cannizzo; Grubbs J. Org. Chem. 1985, 50, 2386.

<sup>467</sup>Petasis; Bzowej J. Am. Chem. Soc. 1990, 112, 6392.

<sup>468</sup>Pine; Shen; Hoang Synthesis 1991, 165.

<sup>469</sup>Okazoe; Takai; Oshima; Utimoto J. Org. Chem. 1987, 52, 4410. This procedure is also successful for silyl esters, to give silyl enol ethers: Takai; Kataoka; Okazoe; Utimoto Tetrahedron Lett. 1988, 29, 1065.

<sup>470</sup>For a review of the synthesis of such complexes, see Agüero; Osborn New J. Chem. 1988, 12, 111-118.

<sup>471</sup>See, for example, Schrock J. Am. Chem. Soc. 1976, 98, 5399; Agüero; Kress; Osborn J. Chem. Soc., Chem. Commun. 1986, 531; Hartner; Schwartz; Clift J. Am. Chem. Soc. 1990, 112, 640.