6

Concerted Cycloadditions, Unimolecular Rearrangements, and Thermal Eliminations

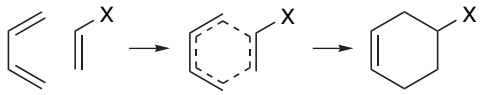
Introduction

Most of the reactions described in the preceding chapters involve polar or polarizable reactants and proceed through polar intermediates and/or transition structures. One reactant can be identified as nucleophilic and the other as electrophilic. Carbanion alkylations, nucleophilic additions to carbonyl groups, and electrophilic additions to alkenes are examples of such reactions. The reactions to be examined in this chapter, on the other hand, occur via a reorganization of electrons through transition structures that may not be much more polar than the reactants. These reactions proceed through cyclic transition structures. The activation energy can be provided by thermal or photochemical excitation of the reactant(s) and often no other reagents are involved. Most of the transformations fall into the category of *concerted pericyclic reactions*, in which there are no intermediates and the transition structures are stabilized by favorable orbital interactions, as discussed in Chapter 10 of Part A. These reactions can be classified into three broad types: cycloadditions, unimolecular rearrangements, and eliminations. We also discuss some reactions that effect closely related transformations, but which on mechanistic scrutiny are found to proceed through discrete intermediates.

6.1. Diels-Alder Reactions

6.1.1. The Diels-Alder Reaction: General Features

Cycloaddition reactions result in the formation of a new ring from two reactants. A concerted mechanism requires that a single transition state, and therefore no intermediate, lie on the reaction path between reactants and adduct. The most important example of cycloaddition is the *Diels-Alder (D-A) reaction*. The cycloaddition of alkenes and dienes is a very useful method for forming substituted cyclohexenes.[1]



A clear understanding of concerted cycloaddition reactions developed as a result of the formulation of the mechanisms within the framework of molecular orbital theory. Consideration of the MOs of reactants and products reveals that in many cases a smooth transformation of the orbitals of the reactants to those of products is possible. In other cases, reactions that might appear feasible if no consideration is given to the symmetry and spatial orientation of the orbitals are found to require high-energy TSs when the orbitals are considered in detail. (Review Section 10.1 of Part A for a discussion of the orbital symmetry analysis of cycloaddition reactions.) The relationships between reactants and TS orbitals permit description of potential cycloaddition reactions as "allowed" or "forbidden" and indicate whether specific reactions are likely to be energetically favorable. The same orbital symmetry relationships that are informative as to the feasibility of a reaction are often predictive of the regiochemistry and stereochemistry. This predictability is an important feature for synthetic purposes. Another attractive aspect of the D-A reaction is the fact that *two new carbon-carbon bonds* are formed in a single reaction.

In the terminology of orbital symmetry classification, the Diels-Alder reaction is a $[4\pi_s + 2\pi_s]$ cycloaddition, an allowed process. There have been a large number of computational studies of the D-A reaction, and as it is a fundamental example of a concerted reaction, it has frequently been the subject of advanced calculations.[2] These studies support a concerted mechanism, which is also supported by good agreement between experimental and calculated (B3LYP/6-31G*) kinetic isotope effects.[3] The TS for a concerted reaction requires that the diene adopt the *s-cis* conformation. The diene and substituted alkene (called the *dienophile*) approach each other in approximately parallel planes. The symmetry properties of the π orbitals permit stabilizing interactions between C(1) and C(4) of the diene and the dienophile. Usually, the strongest bonding

1. L. W. Butz and A. W. Rytina, *Org. React.*, **5**, 136 (1949); M. C. Kloetzel, *Org. React.*, **4**, 1 (1948); A. Wasserman, *Diels-Alder Reactions*, Elsevier, New York (1965); F. Fringuelli and A. Tatacchi, *Diels-Alder Reactions: Selected Practical Methods*, Wiley, New York, 2001.
2. P. D. Karadakov, D. L. Cooper, and J. Gerratt, *J. Am. Chem. Soc.*, **120**, 3975 (1998); H. Lischka, E. Ventura, and M. Dallows, *Chem. Phys. Phys. Chem.*, **5**, 1365 (2004); E. Kraka, A. Wu, and D. Cremer, *J. Phys. Chem. A*, **107**, 9008 (2003); S. Berski, J. Andres, B. Silvi, and L. R. Domingo, *J. Phys. Chem. A*, **107**, 6014 (2003); H. I. Sobe, Y. Takano, Y. Kitagawa, T. Kawakami, S. Yamanaka, K. Yamagushi, and K. N. Houk, *J. Phys. Chem. A*, **107**, 682 (2003).
3. E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996); D. R. Singleton, S. R. Merrigan, B. R. Beno, and K. N. Houk, *Tetrahedron Lett.*, **40**, 5817 (1999).

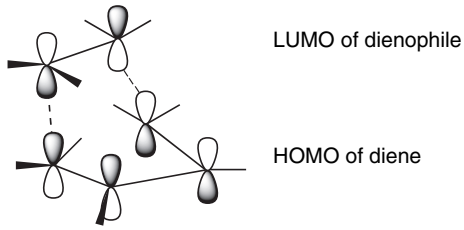
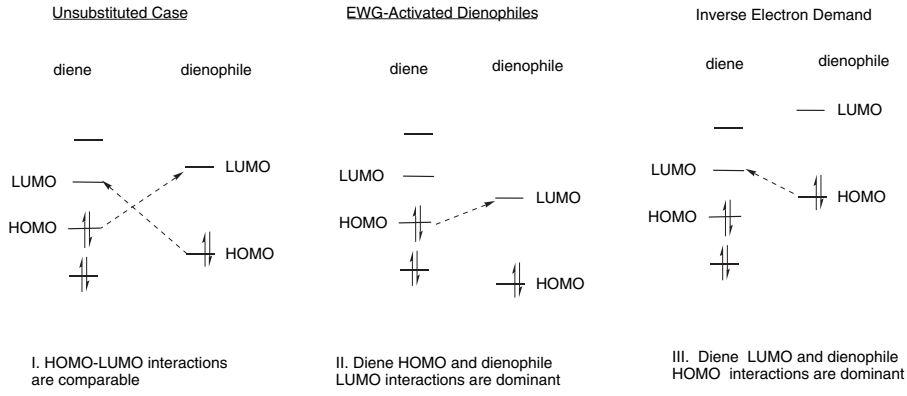


Fig. 6.1. Interaction between LUMO of dienophile and HOMO of diene in the Diels-Alder reaction.

interaction is between the HOMO of the diene and the LUMO of the dienophile. The interaction between the frontier orbitals is depicted in Figure 6.1.

6.1.2. Substituent Effects on the Diels-Alder Reaction

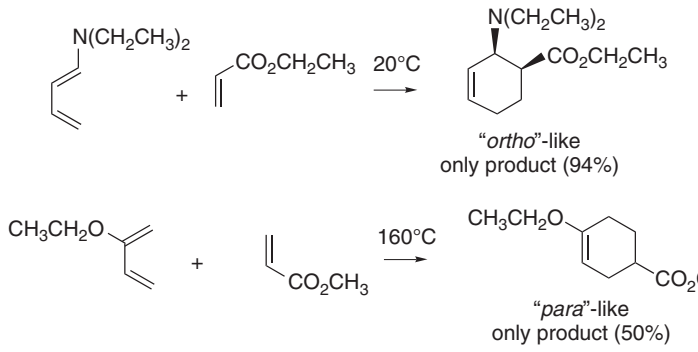
There is a strong electronic substituent effect on the D-A reaction. The most reactive dienophiles for simple dienes are those having electron-attracting groups. Thus, quinones, maleic anhydride, and nitroalkenes are among the most reactive dienophiles. α,β-Unsaturated aldehydes, esters, ketones, and nitriles are also effective dienophiles. It is significant that if an electron-poor diene is utilized, the preference is reversed and electron-rich alkenes, such as vinyl ethers, are the best dienophiles. Such reactions are called *inverse electron demand Diels-Alder reactions*, and the relationships involved are readily understood in terms of frontier orbital theory. Electron-rich dienes have high-energy HOMOs and interact strongly with the LUMOs of electron-poor dienophiles. When the substituent pattern is reversed and the diene is electron-poor, the strongest interaction is between the dienophile HOMO and the diene LUMO.



Frontier orbital theory can also explain the regioselectivity observed when both the diene and alkene are unsymmetrically substituted.[4] Generally, there is a preference

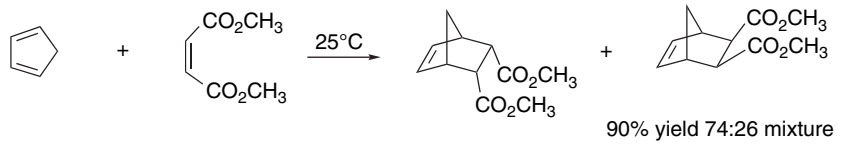
[4] K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975); I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley-Interscience, New York, 1976; O. Eisenstein, J. M. LeFour, N. T. Anh, and R. F. Hudson, *Tetrahedron*, **33**, 523 (1977).

for the "*ortho*" product when the diene has a donor (ERG) substituent at C(1) and for "*para*" product when the diene has an ERG at C(2), as in the examples shown.[5]



When the dienophile bears an EWG substituent and the diene an ERG, the strongest interaction is between the HOMO of the diene and the LUMO of the dienophile. The reactants are oriented so that the carbons having the highest coefficients of these two frontier orbitals can begin the bonding process, and this leads to the observed regiochemical preference as summarized in Figure 6.2.

Diels-Alder reactions are *stereospecific* with respect to the *E*- and *Z*-relationships in both the dienophile and the diene. For example, addition of dimethyl fumarate and dimethyl maleate with cyclopentadiene is completely stereospecific with respect to the *cis* or *trans* orientation of the ester substituents.



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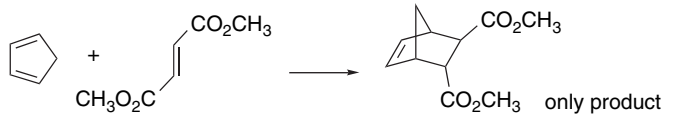
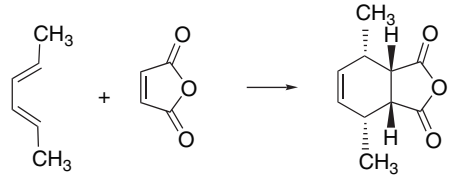


Ref. 7

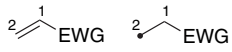
Similarly, *E*,*E*-2,4-hexadiene gives a product that is stereospecific with respect to the diene methyl groups.



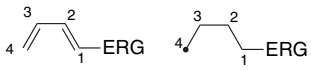
Ref. 8

5. J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967).
6. W. Kirmse, U. Mrotzeck, and R. Siegfried, *Chem. Ber.*, **124**, 238 (1991).
7. C. Girard and R. Bloch, *Tetrahedron Lett.*, **23**, 3683 (1982).
8. G. Berube and P. Deslongchamps, *Bull. Soc. Chim. Fr.*, 103 (1987).

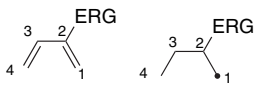
a) Coefficient at C(2) is higher than at C(1) in the LUMO of a dienophile bearing and electron-withdrawing substituent.



(b) Coefficient at C(4) is higher than at C(1) in HOMO of a diene bearing an electron-releasing substituent at C(1).



(c) Coefficient at C(1) is higher than at C(4) in HOMO of a diene bearing an electron-releasing substituent at C(1).



(d) The regioselectivity of the Diels-Alder reaction corresponds to matching the carbon atoms having the largest coefficients of the frontier orbitals.

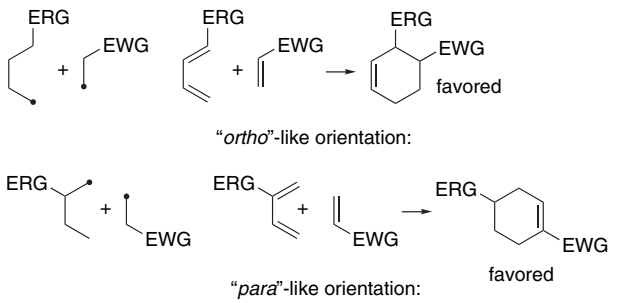
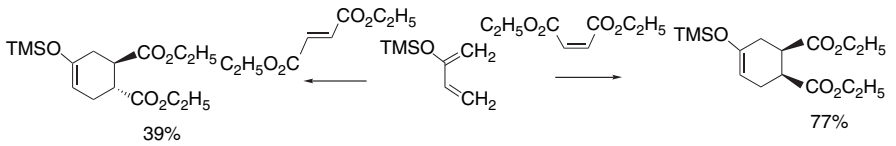


Fig. 6.2. HOMO-LUMO interactions rationalize regioselectivity of Diels-Alder reactions.

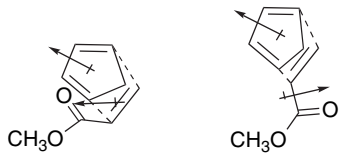
Stereospecificity also is exhibited for dienes having stronger electron-releasing groups, such as trimethylsiloxy.



Ref. 9

9. M. E. Jung and C. A. McCombs, *Org. Synth.*, **58**, 163 (1978); M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976).

For an unsymmetrical dienophile there are two possible stereochemical orientations with respect to the diene, *endo* and *exo*, as illustrated in Figure 6.3. In the *endo* TS the reference substituent on the dienophile is oriented toward the π orbitals of the diene. In the *exo* TS the substituent is oriented away from the π system. For many substituted butadiene derivatives, the TSs lead to two different stereoisomeric products. The *endo* mode of addition is usually preferred when an electron-attracting substituent such as a carbonyl group is present on the dienophile. The empirical statement that describes this preference is called the *Alder rule*. Frequently a mixture of both stereoisomers is formed and sometimes the *exo* product predominates, but the Alder rule is a useful initial guide to prediction of the stereochemistry of a D-A reaction. The *endo* product is often the more sterically congested. The preference for the *endo* TS is strongest for relatively rigid dienophiles such as maleic anhydride and benzoquinone. For methyl acrylate, methyl methacrylate, and methyl crotonate the selectivity ratios are not high.[10] The preference for the *endo* TS increases somewhat with increasing solvent polarity.[11] This has been attributed to a higher polarity of the *endo* TS, resulting from alignment of the dipoles.



endo TS *exo* TS

The preference for the *endo* TS is considered to be the result of interaction between the dienophile substituent and the π electrons of the diene. These are called *secondary orbital interactions*. Dipolar attractions and van der Waals attractions may also be involved.[12] Some *exo-endo* ratios for thermal D-A reactions of cyclopentadiene are

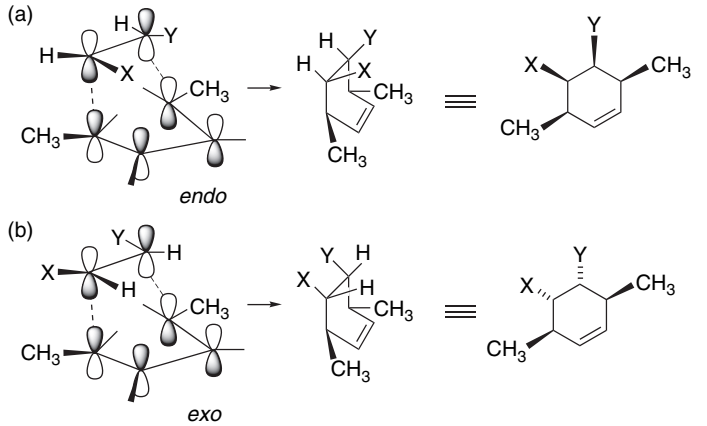


Fig. 6.3. *Endo* (a) and *exo* (b) stereochemistry in Diels-Alder reactions.

10. K. N. Houk and L. J. Lusku, *J. Am. Chem. Soc.*, **93**, 4606 (1971).
11. J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962).
12. Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Funeo, *J. Am. Chem. Soc.*, **94**, 3633 (1972); K. L. Williamson and Y.-F. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).

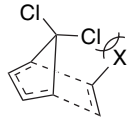
Table 6.1. *Endo*:*Exo* Stereoselectivity toward Cyclopentadiene

Dienophile	*Endo*:*exo* ratio
$CH_2{=}CHCH{=}O$[a]	80:20
$CH_2{=}CHCOCH_3$[a]	82:18
$CH_2{=}CHCO_2CH_3$[b]	73:27
$CH_2{=}C(CH_3)CO_2CH_3$[b]	30:70
$CH_3CH{=}CHCO_2CH_3$[b]	52:48
$CH_2{=}CHSO_2CH_3$[c]	75:25
$CH_2{=}CHPO(OCH_3)_2$[d]	55:45
$CH_2{=}CHCN$[e]	58:42
$CH_2{=}C(CH_3)CN$[e]	12:88
$CH_3CH{=}CHCN$[e]	34:66

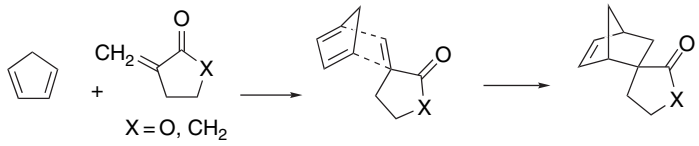
a. O. F. Guner, R. M Ottenbrite and D. D. Shillady, *J. Org. Chem.*, **53**, 5348 (1988).
b. K. N. Houk and L. J. Lusku, *J. Am. Chem. Soc*., **93**, 4606 (1971).
c. J. C. Philips and M. Oku, *J. Org. Chem.*, **37**, 4479 (1972).
d. H. J. Callot and C. Berezra, *J. Chem. Soc., Chem. Commun.*, 485 (1970).
e. A. I. Konovalov and G. I. Kamasheva, *Russ. J. Org Chem* (*Engl. Trans.*), **8**, 1879 (1972)

given in Table 6.1. Most of the data pertain to dienophiles with carbonyl substituents. Note that tetrahedral noncarbonyl EWGs such as sulfonyl and phosphonyl also exhibit a small preference for the *endo* TS. The cyano group shows little *endo*:*exo* preference. Both α- and β-methyl groups result in more *exo* product, as seen for the methyl-substituted esters and nitriles. As we will see shortly, the use of Lewis acid catalysts usually increases the preference for the *endo* TS.

Steric effects play a dominant role with more highly substituted dienes. Hexachlorocyclopentadiene, for example, shows a higher *endo* preference than cyclopentadiene because the 5-chlorine causes steric interference with *exo* substituents.[13]

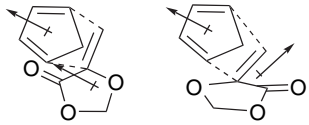


Cyclic α-methylene ketones and lactones, in which the *syn* conformation is enforced, give predominantly *exo* adducts.[14]



13. K. L. Williamson, Y.-F. L. Hsu, R. Lacko, and C. H. Youn, *J. Am. Chem. Soc.*, **91**, 6129 (1969).
14. F. Fotiadu, F. Michel, and G. Buono, *Tetrahedron Lett.*, **31**, 4863 (1990); J. Mattay, J. Mertes, and G. Maas, *Chem. Ber.*, **122**, 327 (1989).

It has been suggested that this is due to a more favorable alignment of dipoles in the *exo* TS.[15]



endo TS *exo* TS

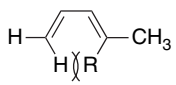
Computational studies predict a preference for the *endo* TS.[16] There have been several computational efforts to dissect the various factors that contribute to the differences between the *exo* and *endo* TS.[17] These generally are in agreement with the experimental preference for the *endo* TS, but there is no consensus on the dominant factors in this preference.[18]

Diels-Alder cycloadditions are sensitive to steric effects of two major types in the diene. Bulky substituents on the termini of the diene hinder approach of the two components to each other and decrease the rate of reaction. This effect can be seen in the relative reactivity of 1-substituted butadienes toward maleic anhydride.[19]

R	k_{rel} (25°C)
–H	1
$-CH_3$	4.2
$-C(CH_3)_3$	< 0.05

Substitution of hydrogen by methyl results in a slight rate *increase* as a result of the electron-releasing effect of the methyl group. A *t*-butyl substituent produces a large rate *decrease* because the steric effect is dominant.

Another type of steric effect results from interactions between diene substituents. Adoption of the *s-cis* conformation of the diene in the TS brings the *cis*-oriented 1- and 4-substituents on a diene close together. *E*-1,3-Pentadiene is 10^3 times more reactive than 4-methyl-1,3-pentadiene toward the very reactive dienophile tetracyanoethylene. This is because the unfavorable interaction between the additional methyl substituent and the C(1) hydrogen in the *s-cis* conformation raises the energy of the TS.[20]

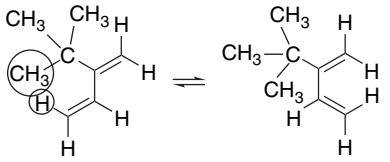


R	k_{rel}
–H	1
$-CH_3$	10^{-3}

Relatively small substituents at C(2) and C(3) of the diene exert little steric influence on the rate of D-A addition. 2,3-Dimethylbutadiene reacts with maleic anhydride about ten times faster than butadiene owing to the electronic effect of the methyl

15. W. R. Roush and B. B. Brown, *J. Org. Chem.*, **57**, 3380 (1992).
16. (a) R. J. Loncharich, T. R. Schwartz, and K. N. Houk, *J. Am. Chem. Soc.*, **109**, 14 (1987); (b) R. J. Loncharich, T. R. Schwartz, and K. N. Houk, *J. Org. Chem.*, **54**, 1129 (1989); (c) D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990); (d) J. I. Garcia, V. Martinez-Merino, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **120**, 2415 (1998).
17. W. L. Jorgensen, D. Lim, and J. F. Blake, *J. Am. Chem. Soc.*, **115**, 2936 (1993); A. Arrieta, F. P. Cossio, and B. Lecea, *J. Org. Chem.*, **66**, 6178 (2001); J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Eur. J. Org. Chem.*, 85, (2004).
18. J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Acc. Chem. Res.*, **33**, 658 (2000).
19. D. Craig, J. J. Shipman, and R. B. Fowler, *J. Am. Chem. Soc.*, **83**, 2885 (1961).
20. C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963).

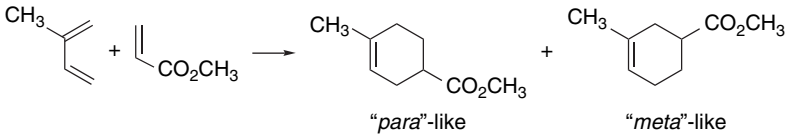
groups. 2-*t*-Butyl-1,3-butadiene is 27 times more reactive than butadiene. The *t*-butyl substituent favors the *s-cis* conformation because of steric repulsions in the *s-trans* conformation.



The presence of a *t*-butyl substituent on *both* C(2) and C(3), however, prevents attainment of the *s-cis* conformation, and D-A reactions of 2,3-di-(*t*-butyl)-1,3-butadiene have not been observed.[21]

6.1.3. Lewis Acid Catalysis of the Diels-Alder Reaction

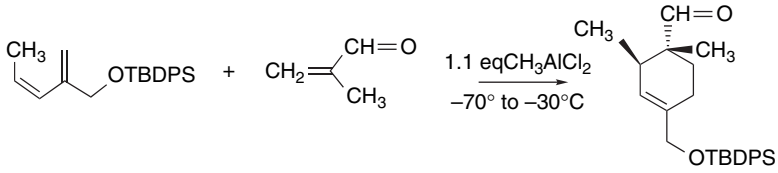
Lewis acids such as zinc chloride, boron trifluoride, tin tetrachloride, aluminum chloride, methylaluminum dichloride, and diethylaluminum chloride catalyze Diels-Alder reactions.[22] The catalytic effect is the result of coordination of the Lewis acid with the dienophile. The complexed dienophile is more electrophilic and more reactive toward electron-rich dienes. The mechanism of the addition is believed to be concerted and enhanced regio- and stereoselectivity is often observed.[23]



	Product ratio	
Uncatalyzed reaction: 120°C, 6 h	70%	30%
Aluminum chloride catalyzed: 20°C, 3 h	95%	5%

Ref. 24

Among the catalysts currently in use, CH_3AlCl_2 was the most effective when employed with *Z*-dienes, which often exhibit low reactivity.



Ref. 22g

21. H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **58**, 643 (1939).
22. (a) P. Yates and P. Eaton, *J. Am. Chem. Soc.*, **82**, 4436 (1960); (b) T. Inukai and M. Kasai, *J. Org. Chem.*, **30**, 3567 (1965); (c) T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 2032 (1966); (d) T. Inukai and T. Kojima, *J. Org. Chem.*, **32**, 869, 872 (1967); (e) F. Fringuelli, F. Pizzo, A. Taticchi, and E. Wenkert, *J. Org. Chem.*, **48**, 2802 (1983); (f) F. K. Brown, K. N. Houk, D. J. Burnell, and Z. Valenta, *J. Org. Chem.*, **52**, 3050 (1987); (g) W. R. Roush and D. A. Barda, *J. Am. Chem. Soc.*, **119**, 7402 (1997).
23. K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4094 (1973).
24. T. Inukai and Kojima, *J. Org. Chem.*, **31**, 1121 (1966).

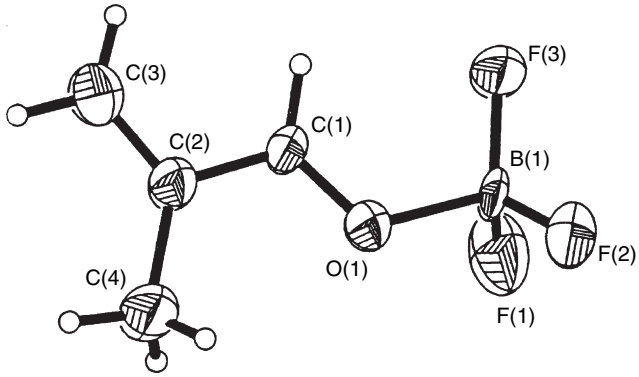


Fig. 6.4. Structure of the BF_3–2-methylpropenal complex. Reproduced from *Tetrahedron Lett.*, **33**, 6945 (1992), by permission of Elsevier.

The stereoselectivity of any particular reaction depends on the details of the structure of the TS. The structures of several enone–Lewis acid complexes have been determined by X-ray crystallography.[25] The site of complexation is the carbonyl oxygen, which maintains a trigonal geometry, but with somewhat expanded angles (130°–140°). The Lewis acid is normally *anti* to the larger carbonyl substituent. Boron trifluoride complexes are tetrahedral, but Sn(IV) and Ti(IV) complexes can be tetrahedral, bipyramidal or octahedral. The structure of the 2-methylpropenal–BF_3 complex in Figure 6.4 is illustrative.[26] Chelation can favor a particular structure. For example, *O*-acryloyl lactates adopt a chelated hexacoordinate structure with $TiCl_4$, as shown in Figure 6.5.[27]

Computational studies have explored the differences between thermal and Lewis acid–catalyzed D-A reactions. Ab initio calculations (HF/6-31G*) have been used to compare the energy of four possible TSs for the D-A reaction of the BF_3 complex of propenal with 1,3-butadiene.[16d] The TSs are designated *endo* and *exo* and *s-cis* and *s-trans*. The latter designations refer to the dienophile conformation. The results are summarized in Figure 6.6. In the thermal reaction, the *endo-cis* and *exo-cis* TSs are nearly equal in total and activation energies. In the BF_3-catalyzed reaction, the

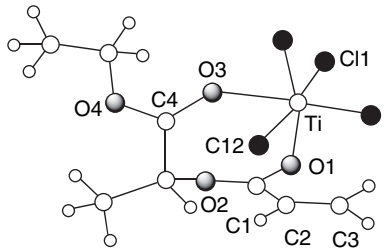
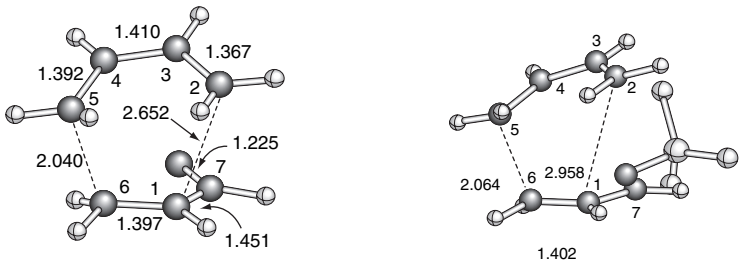


Fig. 6.5. Structure of the $TiCl_4$ complex of *O*-acryloyl ethyl lactate. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **24**, 112 (1985), by permission of Wiley-VCH.

25. S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.*, **29**, 256 (1990).
26. E. J. Corey, T.-P. Loh, S. Sarshar, and M. Azimioara, *Tetrahedron Lett.*, **33**, 6945 (1992).
27. T. Poll, J. O. Metter, and G. Helmchen, *Angew. Chem. Int. Ed. Engl.*, **24**, 112 (1985).



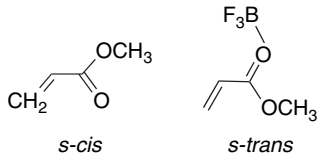
Relative Energies and Activation Energies

Thermal	$\Delta\Delta E_{298}$	ΔG^*_{298}	BF_3-catalyzed	$\Delta\Delta E_{298}$	ΔG^*_{298}
Endo-cis	0.00	32.7	*Endo-cis*	0.00	23.2
Endo-trans	1.24	33.9	*Endo-trans*	2.25	25.7
Exo-cis	0.06	32.7	*Exo-cis*	1.72	24.3
Exo-trans	1.93	34.5	*Exo-trans*	5.61	28.3

Fig. 6.6. Relative energies of four possible transition structures for Diels-Alder reaction of 1,3-butadiene and propenal, with and without BF_3 catalyst. Geometric parameters of the most stable transition structures (*endo-cis*) are shown. Adapted from *J. Am. Chem. Soc.*, **120**, 2415 (1998), by permission of the American Chemical Society.

endo-cis TS is favored by 1.7 kcal/mol. The calculated ΔG^* is reduced by nearly 10 kcal/mol for the catalyzed reaction, relative to the thermal reaction. The catalyzed reaction shows significantly greater asynchronicity than the thermal reaction. In the BF_3-catalyzed reaction, the forming bond distances are 2.06 and 2.96 Å, whereas in the thermal reaction they are 2.04 and 2.65 Å. (See Topic 10.1 of Part A for discussion of asynchronicity.)

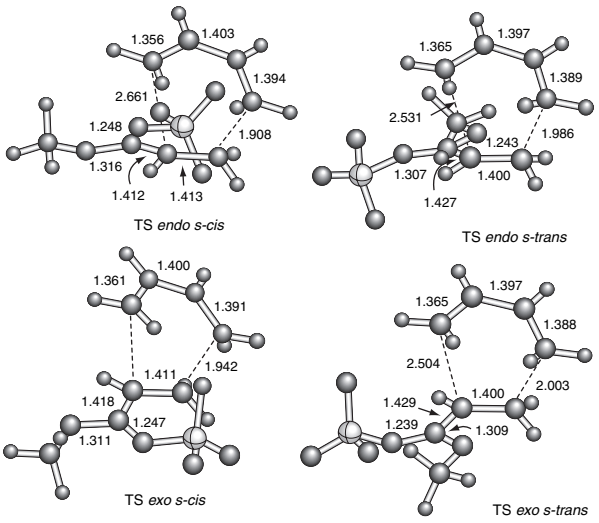
A similar study was done with methyl acrylate as the dienophile.[28] The uncatalyzed and catalyzed TSs are shown in Figure 6.7. As with propenal, the catalyzed reaction is quite asynchronous with C(2)−C(3) bonding running ahead of C(1)−C(6) bonding. In this system, there is a shift from favoring the *exo-s-cis* TS in the thermal reaction to the *endo-s-trans* TS in the catalyzed reaction. A large component in this difference is the relative stability of the free and complexed dienophile. The free dienophile favors the *s-cis* conformation, whereas the BF_3 complex favors the *s-trans* conformation.



Visual models, additional information and exercises on the Diels-Alder Reaction can be found in the Digital Resource available at: Springer.com/carey-sundberg.

In terms of both the effect of substituents and Lewis acid catalysis, the rates of D-A reactions *increase as the donor-acceptor character of the reactive*

[28] J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Tetrahedron*, **53**, 6057 (1997).

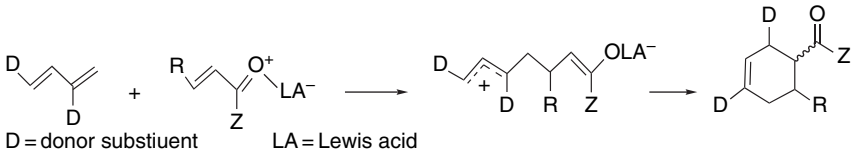


Relative Energies

Thermal	$\Delta\Delta E_{298}$	BF_3-catalyzed	$\Delta\Delta E_{298}$
Endo-cis	0.38	*Endo-cis*	2.23
Endo-trans	1.65	*Endo-trans*	0.00
Exo-cis	0.00	*Exo-cis*	0.82
Exo-trans	1.44	*Exo-trans*	0.83

Fig. 6.7. Transition structures for the reaction between 1,3-butadiene and the methyl acrylate–BF_3 complex calculated at the ab initio HF/6-31G* level. Relative energies are in kcal/mol. Adapted from *Tetrahedron*, **53**, 6057 (1997), by permission of Elsevier.

complex increases. That is, the better the donor substituents in the diene and the stronger the acceptor substituents in the dienophile, the faster the reaction. Similarly, the more electrophilic the Lewis acid, the faster the reaction. In extreme cases, cycloaddition may become stepwise.



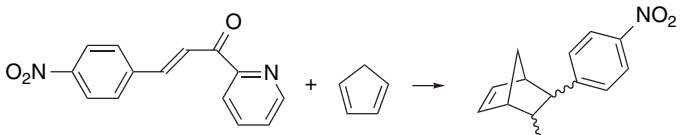
Such a stepwise reaction would not be expected to change the regiochemistry of cycloaddition, but it could lead to loss of stereospecificity if the zwitterionic intermediate has a long enough lifetime. In most reactions where only carbon-carbon bonds are being formed, the D-A reaction remains stereospecific.

In one study, the mechanisms of the reaction of methyl cinnamate and cyclopentadiene with BF_3, $AlCl_3$, and catecholborane bromide as catalysts were compared.[29] According to these computations (B3LYP/6-31G*), the uncatalyzed and BF_3- and $AlCl_3$-catalyzed reactions proceed by asynchronous concerted mechanisms, but a

[29] C. N. Alves, F. F. Camilo, J. Gruber, and A. B. F. da Silva, *Chem. Phys.*, **306**, 35 (2004).

stepwise mechanism is found with catecholborane bromide. Experimentally, this is the only catalyst that is effective for this reaction.[30]

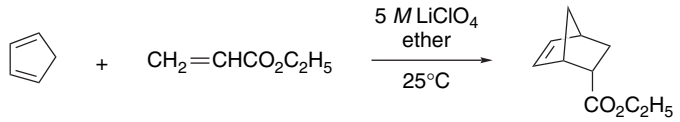
Metal cations can catalyze reactions of certain dienophiles. For example, Cu^{2+} strongly catalyzes addition reactions of 2-pyridyl styryl ketones, presumably through a chelate involving the carbonyl oxygen and pyridine nitrogen.[31]



Rate ($M^{-1}s^{-1}$)	Relative rate	Solvent
1.3×10^{-5}	1	Acetonitrile
3.8×10^{-5}	2.9	Ethanol
4.0×10^{-3}	310	Water
3.25	250,000	Water + 0.01 *M* $Cu(NO_3)_2$

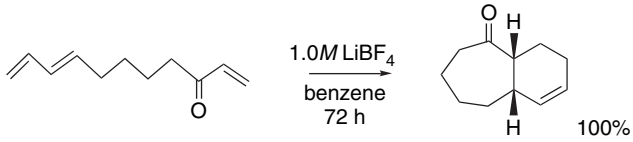
This reaction has been studied computationally with Zn^{2+} as the metal cation.[32] The calculations indicate that a stepwise reaction occurs, beginning with electrophilic attack of the complexed dienophile on the diene.

Some D-A reactions are catalyzed by high concentrations of $LiClO_4$ in ether,[33] a catalysis that involves Lewis acid complexation of Li^+ with the dienophile.[34]



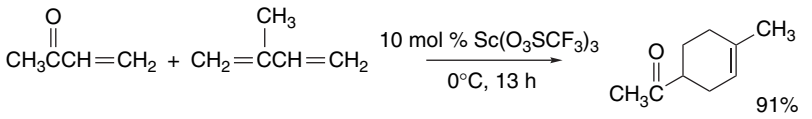
The $LiClO_4$-diethyl ether system shows a considerable dependency on concentration, with the maximal effect around 5 *M*, which may be due to the detailed structure of $LiClO_4$ in ether. The optimum reactivity may be associated with a monosolvate. Dilute solutions have more of the dietherate, whereas in more concentrated solution $LiClO_4$ may form less reactive aggregates.[35] $LiN(SO_2SCF_3)_2$ has been recommended as an alternative to avoid the use of a perchlorate salt.[36]

Lithium *tetrakis*-(3,5-ditrifluoromethyl)borate, which provides an unsolvated lithium cation in noncoordinating solvents, exhibits a several thousandfold catalysis of the reaction of cyclopentadiene and methyl vinyl ketone.[37] Lithium tetrafluoroborate is also an effective catalyst and in some instances has worked when $LiClO_4$ has failed, such as in the intramolecular reaction shown below.[38]

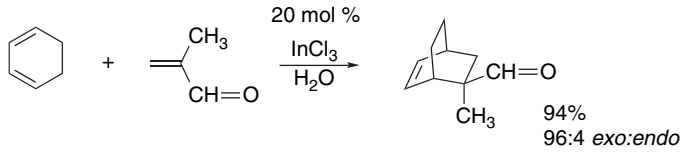


30. F. Camilo and J. Gruber, *Quim. Nova*, **22**, 382 (1999).
31. S. Otto and J. B. F. N. Engberts, *Tetrahedron Lett.*, **36**, 2645 (1995).
32. L. R. Domingo, J. Andres, and C. N. Alves, *Eur. J. Org. Chem.*, **15**, 2557 (2002).
33. P. A. Grieco, J. J. Nunes, and M. D. Gaul, *J. Am. Chem. Soc.*, **112**, 4595 (1990).
34. M. A. Forman and W. P. Dailey, *J. Am. Chem. Soc.*, **113**, 2761 (1991).
35. A. Kumar and S. S. Pawar, *J. Org. Chem.*, **66**, 7646 (2001).
36. S. T. Handy, P. A. Grieco, C. Mineur, and L. Ghosez, *Synlett*, 565 (1995).
37. K. Fujiki, S.-Y. Ikeda, H. Kobayashi, M. Hiroshi, A. Nagira, J. Nie, T. Sonoda, and Y. Yagupolskii, *Chem. Lett.*, 62 (2000).
38. D. A. Smith and K. N. Houk, *Tetrahedron Lett.*, **32**, 1549 (1991).

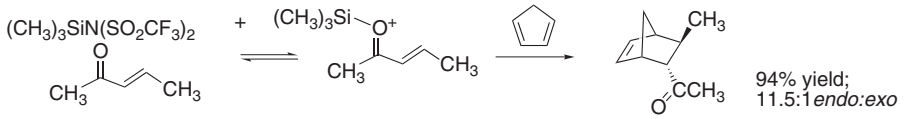
Scandium triflate has been found to catalyze D-A reactions.[39] For example, with 10 mol % $Sc(O_3SCF_3)_3$ present, isoprene and methyl vinyl ketone react to give the expected adduct in 91% yield after 13 h at 0° C.



Among the unique features of $Sc(O_3SCF_3)_3$ is its ability to function as a catalyst in hydroxylic solvents. Other dienophiles, including *N*-acryloyloxazolidinones, also are subject to catalysis by $Sc(O_3SCF_3)_3$. Indium trichloride is another Lewis acid that can act as a catalyst in aqueous solution.[40]



Reversible O-silylation also enhances the electrophilicity of carbonyl dienophiles. For example, 10 mol % *N*-trimethylsilyl triflimide catalyzes the reaction of pent-3-en-2-one with cyclopentadiene. A hindered base, such as 2,6-*bis*-*t*-butyl-4-methylpyridine improves the yield in cases in which the catalyst causes the occurrence of reactant degradation.



Ref. 41

The solvent also has an important effect on the rate of D-A reactions. The traditional solvents were nonpolar organic solvents such as aromatic hydrocarbons. However, water and other highly polar solvents, such as ethylene glycol and formamide, accelerate a number of D-A reactions.[42] The accelerating effect of water is attributed to "enforced hydrophobic interactions." That is, the strong hydrogen-bonding network in water tends to exclude nonpolar solutes and force them together, resulting in higher effective concentrations and relative stabilization of the developing TS.[43] More specific hydrogen bonding with the TS also contributes to the rate acceleration.[44]

39. S. Kobayashi, I. Hachiya, M. Araki, and H. Ishitami, *Tetrahedron Lett.*, **34**, 3755 (1993); S. Kobayashi, H. Ishitani, M. Araki, and I. Hachiya, *Tetrahedron Lett.*, **35**, 6325, (1994); S. Kobayahsi, *Eur. J. Org. Chem.*, 15 (1999).
40. T.-P. Loh, J. Pei, and M. Lin, *Chem. Commun.*, 2315 (1995); 505 (1996).
41. B. Mathieu and L. Ghosez, *Tetrahedron*, **58**, 8219 (2002).
42. D. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980); R. Breslow and T. Guo, *J. Am. Chem. Soc.*, **110**, 5613 (1988); T. Dunams, W. Hoekstra, M. Pentaleri, and D. Liotta, *Tetrahedron Lett.*, **29**, 3745 (1988).
43. R. Breslow and C. J. Rizzo, *J. Am. Chem. Soc.*, **113**, 4340 (1991).
44. W. Blokzijl, M. J. Blandamer, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991); W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **114**, 5440 (1992); S. Otto, W. Blokzijl, and J. B. F. N. Engberts, *J. Org. Chem.*, **59**, 5372 (1994); A. Meijer, S. Otto, and J. B. F. N. Engberts, *J. Org. Chem.*, **65**, 8989 (1998).

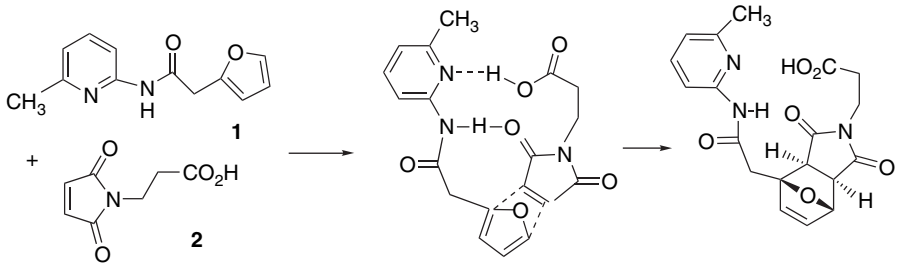


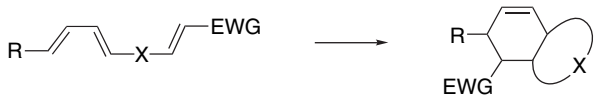
Fig. 6.8. Proposed hydrogen bonding in TS for addition of **1** and **2**. Reproduced from *Tetrahedron Lett.*, **45**, 4777 (2004), by permission of Elsevier.

Hydrogen-bonding interactions can be designed into reaction systems. For example, the reactants **1** and **2** were found to react much more rapidly than the corresponding ester and to give exclusively the *exo* product.[45] Molecular mechanics and spectroscopic studies indicate that the hydrogen-bonding pattern shown in Figure 6.8 is responsible.

To summarize the key points, D-A reactions are usually concerted processes. The regio- and stereoselectivity can be predicted by applying FMO analysis. The reaction between electron donor dienes and electron acceptor dienophiles is facilitated by Lewis acids, polar solvents, and favorable hydrogen-bonding interactions. The D-A reaction is quite sensitive to steric factors, which can retard the reaction and also influence the stereoselectivity with respect to *exo* or *endo* approach.

6.1.4. The Scope and Synthetic Applications of the Diels-Alder Reaction

Schemes 10.1 and 10.4 of Part A, respectively, give the structure of a number of typical dienophiles and show representative D-A reactions involving relatively simple reactants. The D-A reaction is frequently used in synthesis and can either be utilized early in a process to construct basic ring structures or to bring together two subunits in a convergent synthesis. The intramolecular version, which will be discussed in section 6.1.7, can be used to construct two new rings.

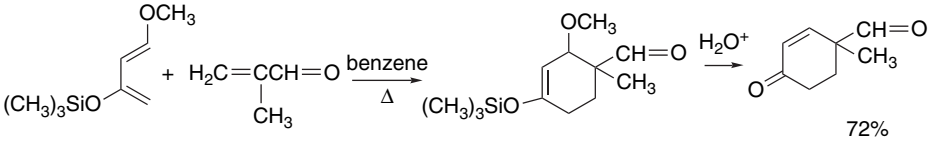


The virtues of the D-A reaction include its ability to create a cyclohexene ring by formation of *two new bonds with predictable regiochemistry.* The reaction can also create as many as four contiguous stereogenic centers. The stereoselectivity is also often predictable on the basis of the *supra-supra* stereospecificity and considerations of the preference for the *endo* or *exo* TS.

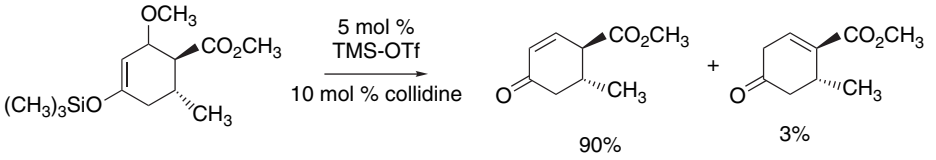
6.1.4.1. Examples of Dienes and Dienophiles. The synthetic value of D-A reactions can be enhanced in various ways. In addition to hydrocarbon dienes, substituted dienes can be used to introduce functional groups into the products. One example that illustrates the versatility of such reagents is 1-methoxy-3-trimethylsiloxy-1,3-butadiene

[45.] R. J. Pearson, E. Kassianidis, and D. Philip, *Tetrahedron Lett.*, **45**, 4777 (2004).

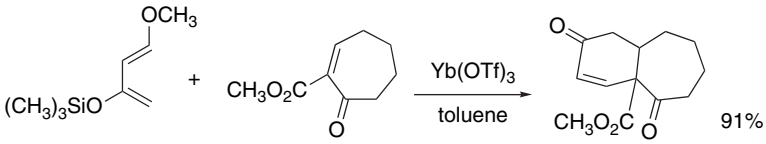
(*Danishefsky's diene*).[46] The two donor substituents provide strong regiochemical control. The D-A adducts are trimethylsilyl enol ethers that can be readily hydrolyzed to ketones. The β-methoxy group is often eliminated during hydrolysis, resulting in formation of cyclohexenones.



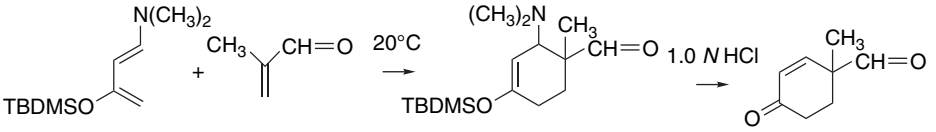
A milder protocol for the conversion to enones involves use of a catalytic amount of TMSOTf and a pyridine base.[47]



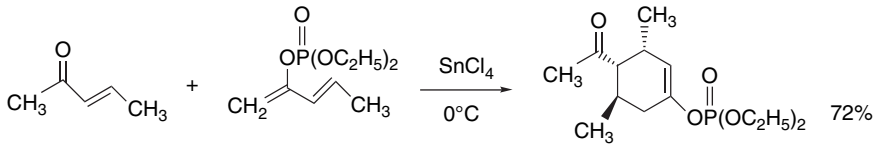
The desilylation is also promoted by various Lewis acids, $Yb(OTf)_3$ being among the most effective. This catalyst can be used in a one-pot sequence in which it promotes both the cycloaddition and subsequent elimination.[48]



An analogous silyoxydienamine shows a similar reactivity pattern.[49]

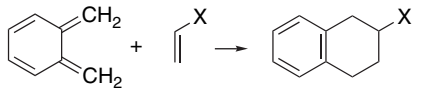


2-(Diethoxyphosphoryloxy)-1,3-butadiene and 2-(diethoxyphosphoryloxy)-1,3-pentadiene are good dienes and are compatible with Lewis acid catalysts.[50] They exhibit the regioselectivity expected for a donor substituent and show a preference for *endo* addition with enones.



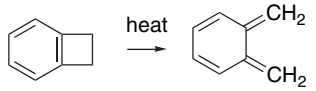
46. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).
47. P. E. Vorndam, *J. Org. Chem.*, **55**, 3693 (1990).
48. T. Inokuchi, M. Okano, T. Miyamoto, H. B. Madon, and M. Takagi, *Synlett*, 1549 (2000); T. Inokuchi, M. Okano, and T. Miyamoto, *J. Org. Chem.*, **66**, 8059 (2001).
49. S. A. Kozmin and V. H. Rawal, *J. Org. Chem.*, **62**, 5252 (1997).
50. H.-J. Liu, W. M. Feng, J. B. Kim, and E. N. C. Browne, *Can. J. Chem.*, **72**, 2163 (1994).

Unstable dienes can be generated in situ in the presence of a dienophile. Among the most useful examples are the *ortho*-quinodimethanes. These compounds are exceedingly reactive as dienes because the cycloaddition reestablishes a benzenoid ring and results in aromatic stabilization.[51]

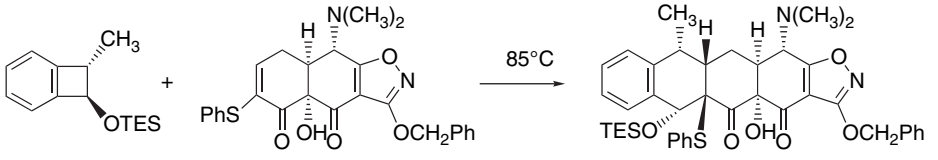


quinodimethane

There are several general routes to quinodimethanes. One is pyrolysis of benzocyclobutenes.[52]



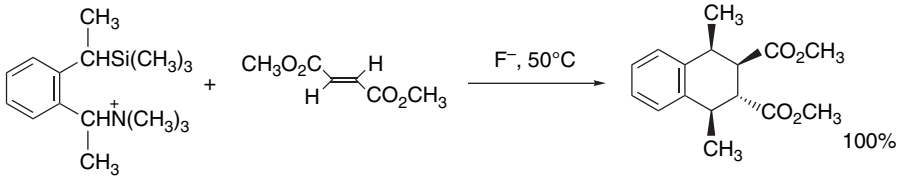
This reaction can be applied to substituted benzocyclobutenes. For example, the reaction has been used to form an array of five linear rings containing most of the functionality for the antibiotic tetracycline.



64%

Ref. 53

1,4-Eliminations from α,α′-*ortho*-disubstituted benzenes can be carried out with various potential leaving groups. Benzylic silyl substituents can serve as the carbanion precursors.

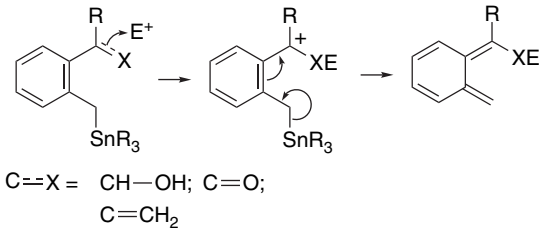


100%

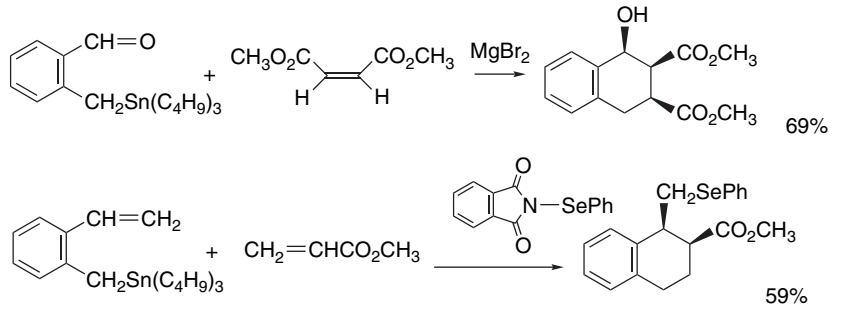
Ref. 54

51. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); T. Kametani and K. Fukumoto, *Heterocycles*, **3**, 29 (1975); J. J. McCullogh, *Acc. Chem. Res.*, **13**, 270 (1980); W. Oppolzer, *Synthesis*, 793 (1978); J. L. Charlton and M. M. Alauddin, *Tetrahedron*, **43**, 2873 (1987); H. N. C. Wong, K.-L. Lau, and K. F. Tam, *Top. Curr. Chem.*, **133**, 85 (1986); P. Y. Michellys, H. Pellissier, and M. Santelli, *Org. Prep. Proced. Int.*, **28**, 545 (1996).
52. M. P. Cava and M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York, 1967, Chap. 6; I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970); R. P. Thummel, *Acc. Chem. Res.*, **13**, 70 (1980).
53. M. G. Charest, D. R. Siegel, and A. G. Myers, *J. Am. Chem. Soc.*, **127**, 8292 (2005).
54. Y. Ito, M. Nakatsuka, and T. Saegusa, *J. Am. Chem. Soc.*, **104**, 7609 (1982).

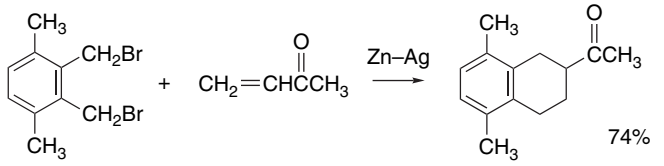
Several procedures have been developed for obtaining quinodimethane intermediates from *o*-substituted benzylstannanes. The reactions occur by generating an electrophilic center at the adjacent benzylic position, which triggers a 1,4-elimination.



Specific examples include treatment of *o*-stannyl benzyl alcohols with TFA,[55] reactions of ketones and aldehydes with Lewis acids,[56] and electrophilic selenation of styrenes.[57]



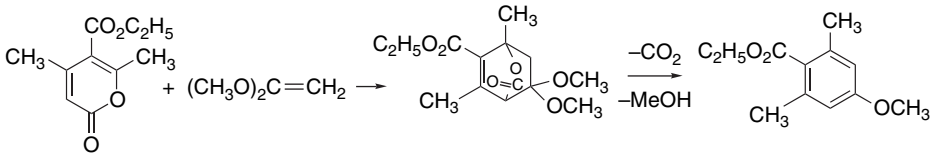
o-bis-(Bromomethyl)benzenes can be converted to quinodimethanes with reductants such as zinc, nickel, chromous ion, and tri-*n*-butylstannide.[58]



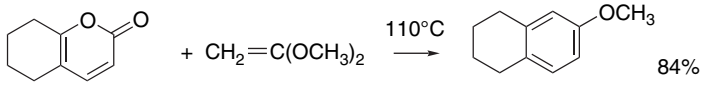
Quinodimethanes have been especially useful in intramolecular D-A reactions, as is illustrated in Section 6.1.7.

Pyrones are useful dienes, although they are not particularly reactive. The adducts have the potential for elimination of carbon dioxide, resulting in the formation of an aromatic ring. Pyrones react best with electron-rich dienophiles. Vinyl ethers are frequently used as dienophiles with pyrones. The regiochemical preference places the dienophile donor *ortho* to the pyrone carbonyl.

55. H. Sans, H. Ohtsuka, and T. Migita, *J. Am. Chem. Soc.*, **110**, 2014 (1988).
56. S. H. Woo, *Tetrahedron Lett.*, **35**, 3975 (1994).
57. S. H. Woo, *Tetrahedron Lett.*, **34**, 7587 (1993).
58. G. M. Rubottom and J. E. Wey, *Synth. Commun.*, **14**, 507 (1984); S. Inaba, R. M. Wehmeyer, M. W. Forkner, and R. D. Rieke, *J. Org. Chem.*, **53**, 339 (1988); D. Stephan, A. Gorques, and A. LeCoq, *Tetrahedron Lett.*, **25**, 5649 (1984); H. Sato, N. Isono, K. Okamura, T. Date, and M. Mori, *Tetrahedron Lett.*, **35**, 2035 (1994).

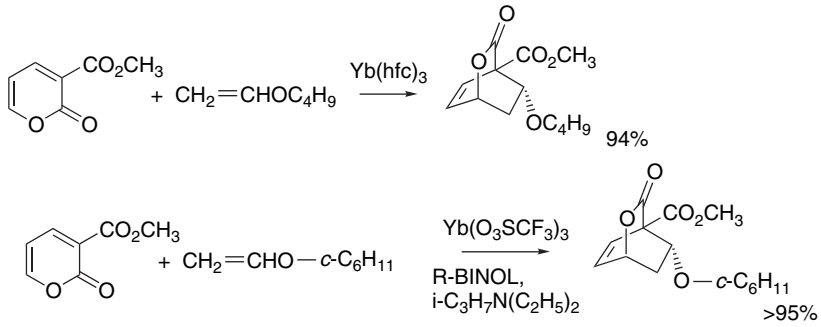


Ref. 59



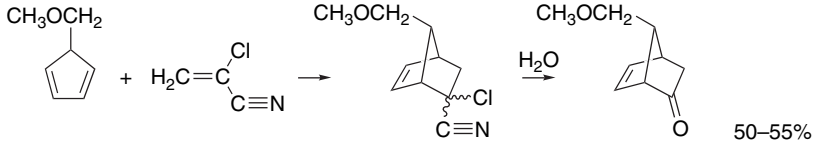
Ref. 60

These reactions can be catalyzed by Lewis acids such as *bis*-alkoxytitanium dichlorides[61] and lanthanide salts.[62]



Another type of special diene, the polyaza benzene heterocyclics, such as triazines and tetrazines, is discussed in Section 6.6.2.

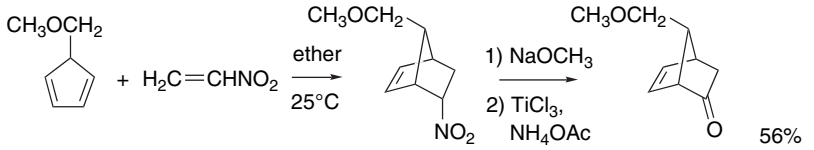
The synthetic utility of the D-A reaction can be expanded by the use of dienophiles that contain *masked functionality* and are the *synthetic equivalents* of unreactive or inaccessible compounds. (See Section 13.1.2 for a more complete discussion of the concept of synthetic equivalents.) For example, α-chloroacrylonitrile shows satisfactory reactivity as a dienophile. The α-chloronitrile functionality in the adduct can be hydrolyzed to a carbonyl group. Thus, α-chloroacrylonitrile can function as the equivalent of ketene, $CH_2{=}C{=}O$,[63] which is not a suitable dienophile because it has a tendency to react with dienes by [2 + 2] cycloaddition, rather than the desired [4 + 2] fashion.



Ref. 64

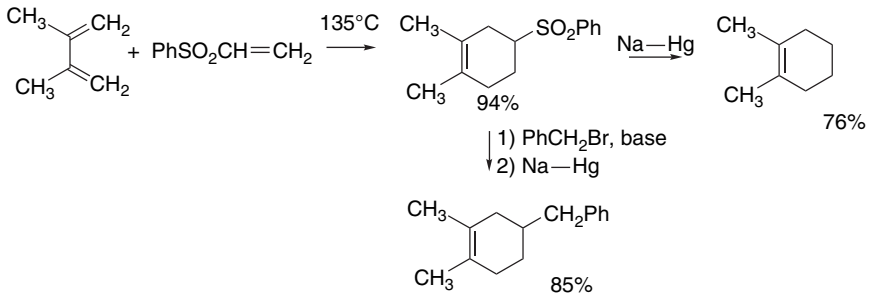
59. M. E. Jung and J. A. Hagenah, *J. Org. Chem.*, **52**, 1889 (1987).
60. D. L. Boger and M. D. Mullican, *Org. Synth.*, **65**, 98 (1987).
61. G. H. Posner, J.-C. Carry, J. K. Lee, D. S. Bull, and H. Dai, *Tetrahedron Lett.*, **35**, 1321 (1994); G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor, and S. Petr, Jr., *J. Org. Chem.*, **61**, 671 (1996).
62. G. H. Posner, J.-C. Carry, T. E. N. Anjeh, and A. N. French, *J. Org. Chem.*, **57**, 7012 (1992).
63. V. K. Aggarwal, A. Ali, and M. P. Coogan, *Tetrahedron*, **55**, 293 (1999).
64. E. J. Corey, N. M. Weinshenker, T. K. Schaff, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

Nitroalkenes are good dienophiles and the variety of transformations available for nitro groups makes them versatile intermediates.[65] Nitro groups can be converted to carbonyl groups by reductive hydrolysis, so nitroethylene can be used as a ketene equivalent.[66]

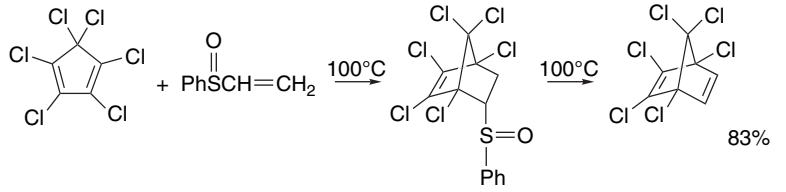


Ref. 67

Vinyl sulfones are reactive as dienophiles. The sulfonyl group can be removed reductively with sodium amalgam (see Section 5.6.2). In this two-step reaction sequence, the vinyl sulfone functions as an ethylene equivalent. The sulfonyl group also permits alkylation of the adduct, via the carbanion. This three-step sequence permits the vinyl sulfone to serve as the synthetic equivalent of a terminal alkene.[68]



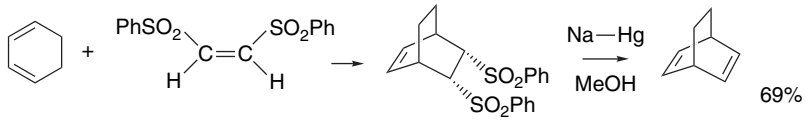
Phenyl vinyl sulfoxide can serve as an acetylene equivalent. Its D-A adducts can undergo thermal elimination of benzenesulfenic acid.



Ref. 69

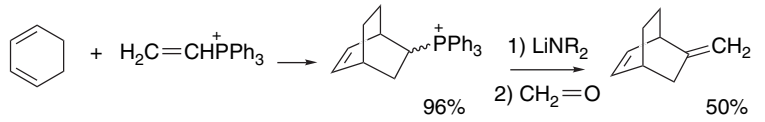
65. D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, and R. Iyengar, *J. Org. Chem.*, **45**, 1185 (1980).
66. For a review of ketene equivalents, see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Synthesis*, 289 (1977).
67. S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *J. Am. Chem. Soc.*, **96**, 5261 (1974).
68. R. V. C. Carr and L. A. Paquette, *J. Am. Chem. Soc.*, **102**, 853 (1980); R. V. C. Carr, R. V. Williams, and L. A. Paquette, *J. Org. Chem.*, **48**, 4976 (1983); W. A. Kinney, G. O. Crouse, and L. A. Paquette, *J. Org. Chem.*, **48**, 4986 (1983).
69. L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.*, **100**, 1597 (1978).

Cis- and *trans-bis*-benzenesulfonylethene are also acetylene equivalents. The two sulfonyl groups undergo reductive elimination on reaction with sodium amalgam.

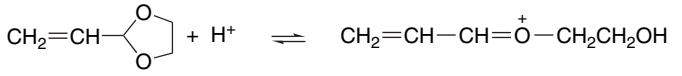


Ref. 70

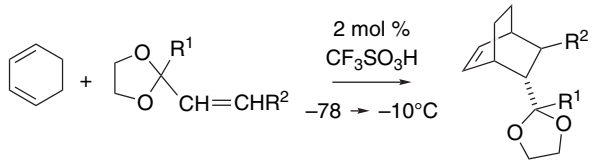
Vinylphosphonium salts are reactive as dienophiles as a result of the EWG character of the phosphonium substituent. The D-A adducts can be deprotonated to give ylides that undergo the Wittig reaction to introduce an exocyclic double bond. This sequence of reactions corresponds to a D-A reaction employing allene as the dienophile.[71]



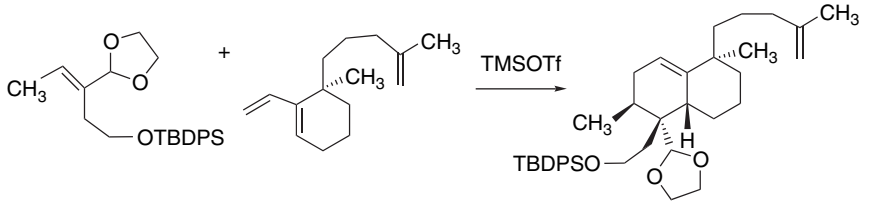
The use of 2-vinyldioxolane, the ethylene glycol acetal of acrolein, as a dienophile illustrates application of the masked functionality concept in a different way. The acetal itself would not be expected to be a reactive dienophile, but in the presence of a catalytic amount of acid the acetal is in equilibrium with the electrophilic oxonium ion.



Diels-Alder addition occurs through this cationic intermediate at room temperature.[72] Similar reactions occur with substituted alkenyldioxolanes.

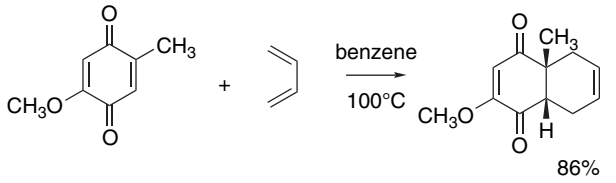


This reaction has been used to construct the carbon skeleton found in dysidiolide, a cell cycle inhibitor isolated from a marine sponge.[73] In this case, the reactive oxonium ion intermediate was generated by O-silylation.



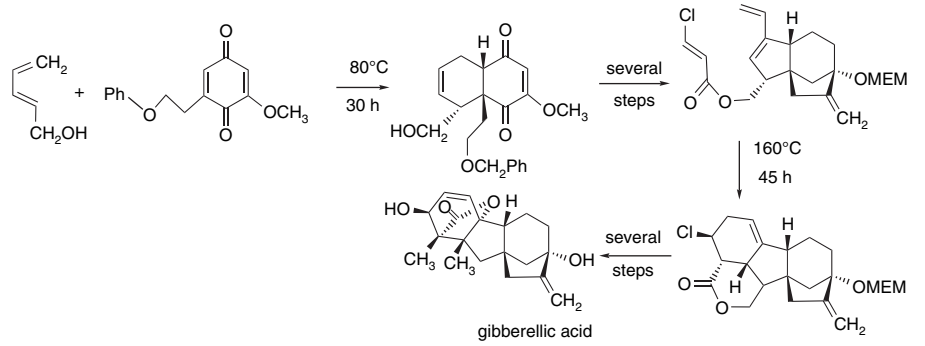
70. O. DeLucchi, V. Lucchini, L. Pasquato, and G. Modena, *J. Org. Chem.*, **49**, 596 (1984).
71. R. Bonjouklian and R. A. Ruden, *J. Org. Chem.*, **42**, 4095 (1977).
72. P. G. Gassman, D. A. Singleton, J. J. Wilwerding, and S. P. Chavan, *J. Am. Chem. Soc.*, **109**, 2182 (1987).
73. S. R. Magnuson, L. Sepp-Lorenzino, N. Rosen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **120**, 1615 (1998).

6.1.4.2. Synthetic Applications of the Diels-Alder Reaction. Diels-Alder reactions have long played an important role in synthetic organic chemistry.[74] The reaction of a substituted benzoquinone and 1,3-butadiene, for example, was the first step in one of the early syntheses of steroids. The angular methyl group was introduced by the methyl group on the quinone and the other functional groups were used for further elaboration.



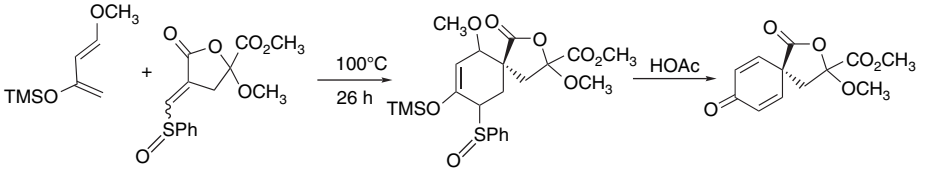
Ref. 75

In a synthesis of gibberellic acid, a diene and quinone, both with oxygen-substituted side chains, gave the initial intermediate. Later in the synthesis, an intramolecular D-A reaction was used to construct the A-ring.



Ref. 76

Functionality can be built into either the diene or dienophile for purposes of subsequent transformations. For example, in the synthesis of prephenic acid, the diene has the capacity to generate an enone. The dienophile contains a sulfoxide substituent that is subsequently used to introduce a second double bond by elimination.



Ref. 77

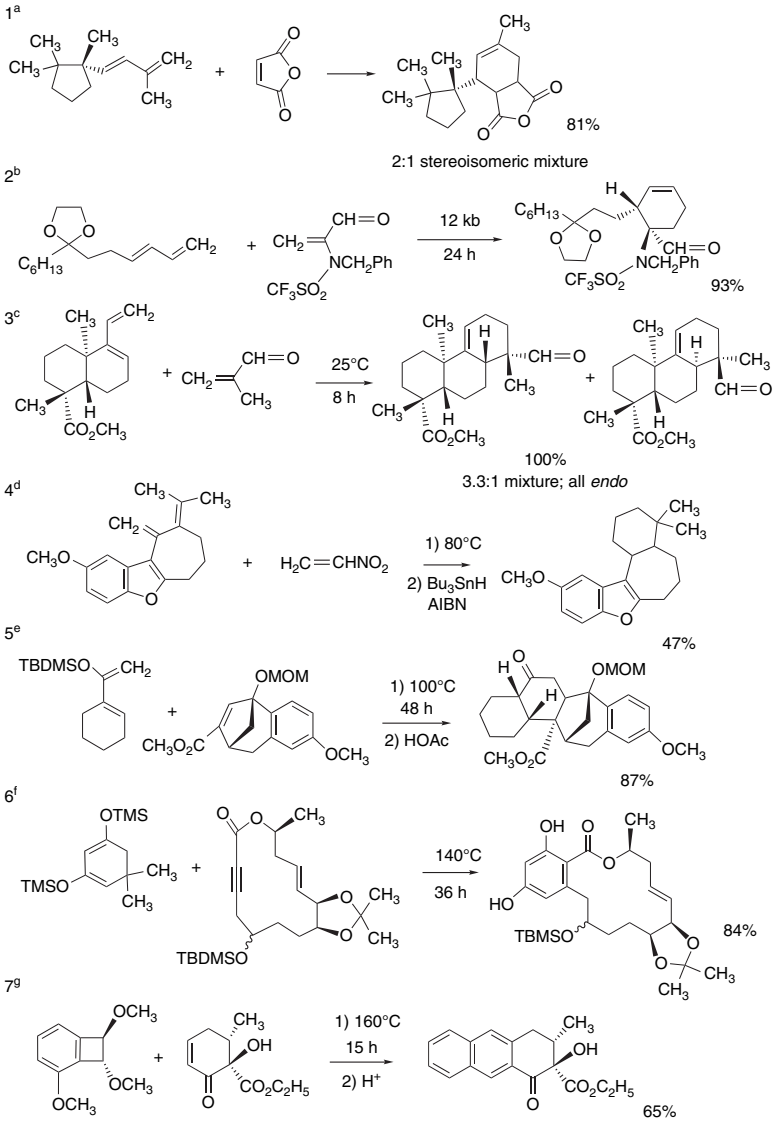
74. K. C. Nicolaou, S. A. Snyder, T. Montagnon, and G. Vassilikogiannakis, *Angew. Chem. Int. Ed. Engl.*, **41**, 1668 (2002).

75. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

76. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978); E. J. Corey, R. L. Danheiser, S. Chandrakeskaran, G. E. Keck, B. Gopalan, S. D. Larsen, P. Siret, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8034 (1978).

77. S. J. Danishefsky, M. Hirama, N. Fitsch, and J. Clardy, *J. Am. Chem. Soc.*, **101**, 7013 (1979).

Scheme 6.1. Examples of Thermal Diels-Alder Reactions

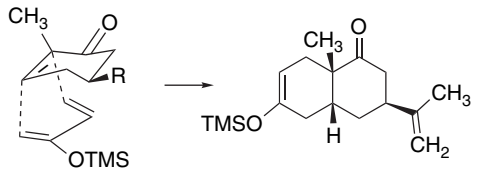


a. A. Nayek and S. Ghosh, *Tetrahedron Lett.*, **43**, 1313 (2002).
b. J.-H. Maeng and R. L. Funk, *Org. Lett.*, **4**, 331 (2002).
c. T. Ling, B. A. Kramer, M. A. Palladino, and E. A. Theodorakis, *Org. Lett.*, **2**, 2073 (2000).
d. M. Inoue, M. W. Carson, A. J. Frontier, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **123**, 1878 (2001).
e. P. D. O'Connor, L. N. Mander, and M. W. McLachlan, *Org. Lett.*, **6**, 703 (2004).
f. X. Geng and S. J. Danishefsky, *Org. Lett.*, **6**, 413 (2004).
g. K. Yamamoto, M. F. Hentemann, J. G. Allen, and S. J. Danishefsky, *Chem. Eur. J.*, **9**, 3242 (2003).

Scheme 6.1 gives some additional examples of application of thermal D-A reactions in syntheses. The reaction in Entry 1 was eventually used to construct an aromatic ring by decarboxylation and aromatization. The reaction did not exhibit much facial selectivity, but this was irrelevant for the particular application. Entry

2 illustrates the use of high pressure to accelerate reaction. This reaction gives only an *endo* product, since both the electronic effect of the formyl group and the steric effect of the sulfonamido group favor this orientation. The reaction in Entry 3 involves a typical diene and dienophiles. The reaction is completely regiospecific in the direction expected [donor alkyl groups at C(1) and C(3) of the diene unit] and is also completely *endo* selective. The facial selectivity with respect to the diene, however, is only 3.3:1. Entry 4 is an example of the use of nitroethene as an ethene equivalent. The nitro group was removed by reduction with Bu_3SnH. The reaction in Entry 5 involves a diene unit activated by a 2-siloxy substituent. On exposure to acid, this provides the product as a ketone. The reaction is evidently completely regio- and stereoselective. Entry 6 involves a doubly activated diene. The aromatic ring is formed by extrusion of isobutylene from a bicyclic intermediate. Entry 7 involves the ring opening of a benzocyclobutene to a quinodimethane. In this case, aromatization occurs as the result of the loss of two methoxy groups.

Owing to their advantages in terms of the lower temperature required and the higher regio- and stereoselectivity, Lewis acid–catalyzed D-A reactions are often preferable to the corresponding thermal version. Scheme 6.2 gives some examples of D-A reactions catalyzed by Lewis acids. Entries 1 and 2 are cases with substituent groups on the reacting bonds. Systems of this type are often relatively unreactive in thermal D-A reactions. The reaction in Entry 2 is an inverse electron demand case, and the catalyst activates the *diene* rather than the dienophile. Entry 3 involves a relatively highly substituted diene. The reaction was used to create a structure corresponding to the A-ring of the antitumor substance taxol. Entries 4, 5, and 6 involve dienes that have donor substituents that impart regioselectivity. The products of each of the reactions result from *endo* addition. The reaction in Entry 4 involves a cyclohexenone dienophile. 5-Substituted cyclohexenones have a strong preference for *anti* approach relative to the substituent.[78] The isopropenyl substituent establishes a conformational preference and the diene approaches from the *anti* direction.

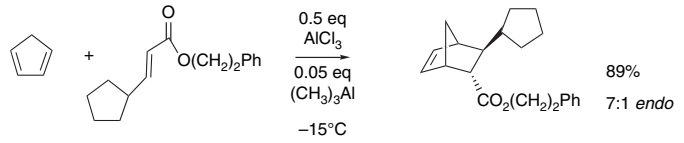


Entries 5 and 6 exhibit the "ortho" regioselectivity expected for a 1-ERG on the diene. These dienes also present the possibility for competing Lewis acid coordination sites in the diene that would be expected to be *deactivating.* In Entry 6, the phenyl substituent on the oxazolidinone ring establishes a facial preference. The dienophiles in Entries 7 and 8 have both ERG and EWG substituents (sometimes called capto-dative dienophiles). The regiochemistry is consistent with the acceptor substituent having the dominant influence.[79] Entry 9 illustrates the excellent regio- and stereoselectivity often seen for Lewis acid–catalyzed reactions. Only a single product was found.

78. F. Fringuelli, L. Minuti, F. Pizzo, and A. Taticchi, *Acta Chem. Scand.*, **47**, 255 (1993).
79. R. Herrera, H. A. Jiminez-Vazquez, A. Modelli, D. Jones, B. C. Soderberg, and J. Tamariz, *Eur. J. Org. Chem.*, 4657 (2001).

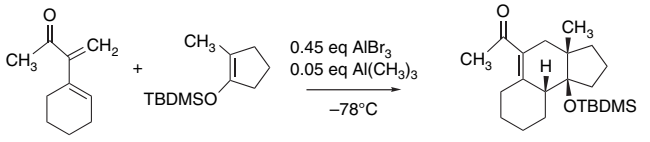
Scheme 6.2. Diels-Alder Reactions Catalyzed by Lewis-Acids

1[a]



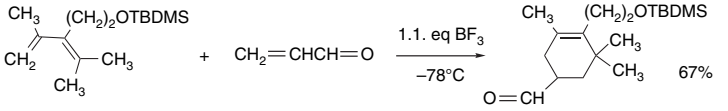
89%
7:1 *endo*

2[b]



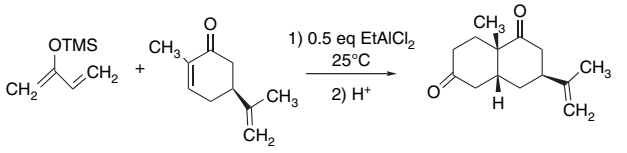
77%
10:1 *endo*

3[c]



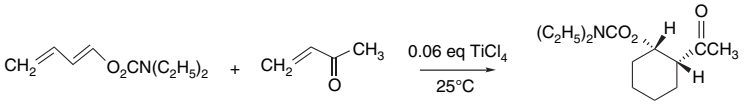
67%

4[d]



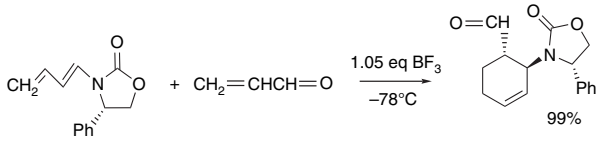
73%
95:5 *dr*

5[e]



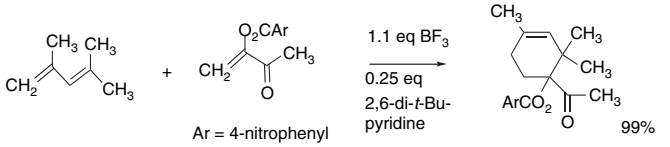
88%

6[f]



99%

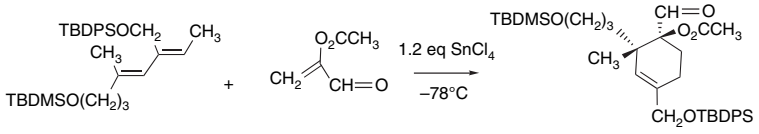
7[g]



Ar = 4-nitrophenyl

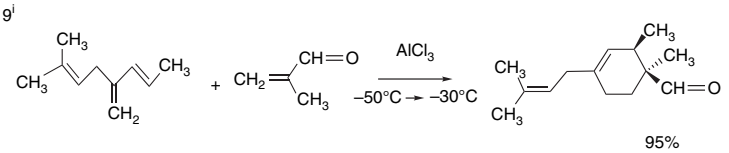
99%

8[h]



90%
96:4 *endo:exo*

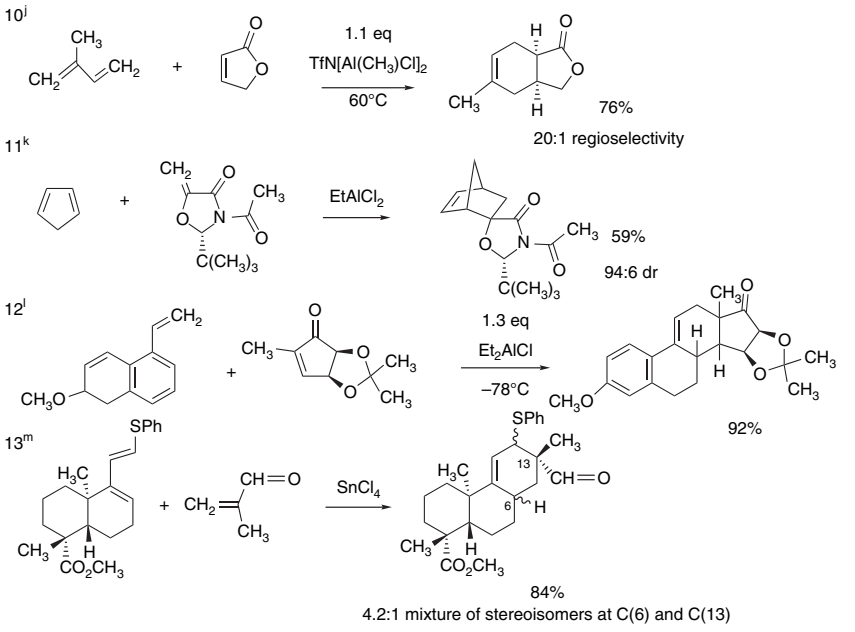
9[i]



95%

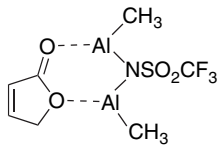
(*Continued*)

Scheme 6.2. (*Continued*)

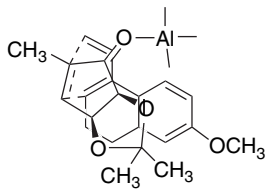


a. R. D. Hubbard and B. L. Miller, *J. Org. Chem.*, **63**, 4143 (1998).
b. M. E. Jung and P. Davidov, *Angew. Chem. Int. Ed. Engl.*, **41**, 4125 (2002).
c. M. W. Tjepkema, P. D. Wilson, H. Audrain, and A. G. Fallis, *Can. J. Chem.*, **75**, 1215 (1997).
d. A. A. Haaksma, B. J. M. Jansen, and A. de Groot, *Tetrahedron*, **48**, 3121 (1992).
e. P. F. De Cusati and R. A. Olofson, *Tetrahedron Lett.*, **31**, 1409 (1990).
f. D. A. Vosburg, S. Weiler, and E. J. Sorensen, *Chirality*, **15**, 156 (2003).
g. J. D. Dudones and P. Sampson, *J. Org. Chem.*, **62**, 7508 (1997).
h. W. R. Roush and D. A. Barda, *J. Am. Chem. Soc.*, **119**, 7402 (1997).
i. G. Frater, U. Mueller, and F. Schroeder, *Tetrahedron: Asymmetry*, **15**, 3967 (2004).
j. A. Saito, H. Yanai, and T. Taguchi, *Tetrahedron Lett.*, **45**, 9439 (2004).
k. W. R. Roush, A. P. Essenfeld, J. S. Warmus, and B. B. Brown, *Tetrahedron Lett.*, **30**, 7305 (1989).
l. K. Tanaka, H. Nakashima, T. Taniguchi, and K. Ogasawara, *Org. Lett.*, **2**, 1915 (2000).
m. T. Ling, B. A. Kramer, M. A. Palladino, and E. A. Theodorakis, *Org. Lett.*, **2**, 2073 (2000).

Entries 10 and 11 involve lactones and lactams, respectively. The catalyst used in Entry 10 is thought to be capable of interaction with both the carbonyl and ether oxygens.



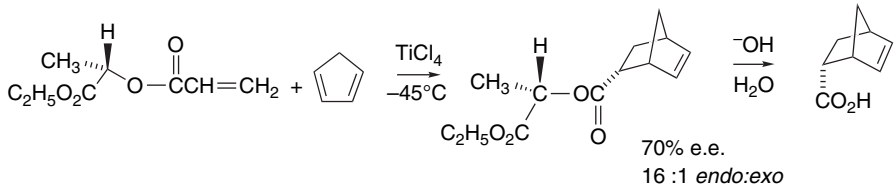
In Entry 11 the dienophile is an α-methylene lactam. As noted for this class of dienophiles, the stereoselectivity results from preferred *exo* addition (see p. 471). The reaction in Entry 12 was used in an enantiospecific synthesis of estrone. The dienophile was used in enantiomerically pure form and the dioxolane ring imparts a high facial selectivity to the dienophile. The reaction occurs through an *endo* TS.



The reaction in Entry 13 is completely regioselective and both stereoisomers are formed through an *endo* TS. The two stereoisomers result from competing facial approaches to the diene.

6.1.5. Diastereoselective Diels-Alder Reactions Using Chiral Auxiliaries

The highly ordered cyclic TS of the D-A reaction permits design of diastereo- or enantioselective reactions. (See Section 2.4 of Part A to review the principles of diastereoselectivity and enantioselectivity.) One way to achieve this is to install a chiral auxiliary.[80] The cycloaddition proceeds to give two diastereomeric products that can be separated and purified. Because of the lower temperature required and the greater stereoselectivity observed in Lewis acid–catalyzed reactions, the best diastereoselectivity is observed in catalyzed reactions. Several chiral auxiliaries that are capable of high levels of diastereoselectivity have been developed. Chiral esters and amides of acrylic acid are particularly useful because the auxiliary can be recovered by hydrolysis of the purified adduct to give the enantiomerically pure carboxylic acid. Early examples involved acryloyl esters of chiral alcohols, including lactates and mandelates. Esters of the lactone of 2,4-dihydroxy-3,3-dimethylbutanoic acid (pantolactone) have also proven useful.

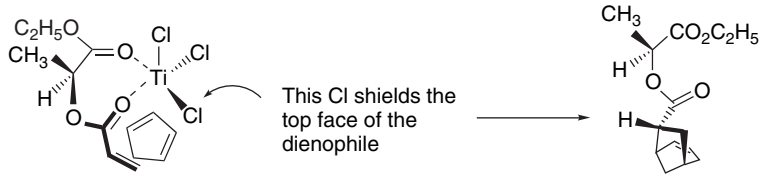


Ref. 81

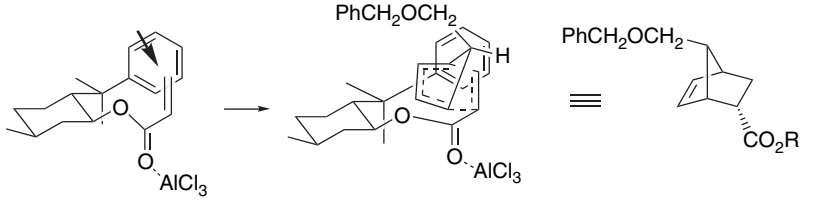
Prediction and analysis of diastereoselectivity are based on steric, stereoelectronic, and complexing interactions in the TS.[82] In the case of the lactic acid auxiliary, a chelated structure promotes facial selectivity. In the $TiCl_4$ complex of *O*-acryloyl ethyl lactate,

80. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **23**, 876 (1984); M. J. Tascher, in *Organic Synthesis: Theory and Applications*, Vol. 1, T. Hudlicky, ed., JAI Press, Greenwich, CT, 1989, pp. 1–101; H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992); K. Narasaka, *Synthesis*, 16 (1991).
81. T. Poll, G. Helmchen, and B. Bauer, *Tetrahedron Lett.*, **25**, 2191 (1984).
82. For example, see T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, *Tetrahedron Lett.*, **26**, 3095 (1985).

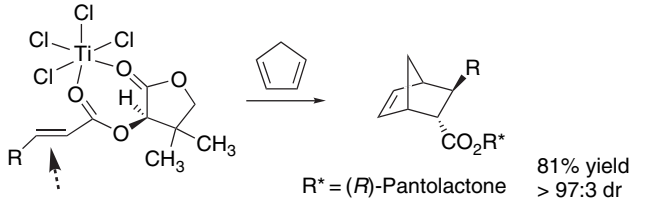
one of the chlorines attached to titanium shields one face of the double bond (see also Figure 6.5).



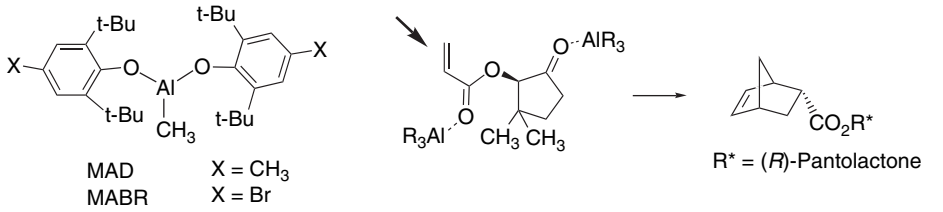
An 8-phenylmenthol ester was employed as the chiral auxiliary to achieve enantioselectivity in the synthesis of prostaglandin precursors.[83] The crucial features of the TS are the *anti* disposition of the Lewis acid relative to the alcohol moiety and a π stacking with the phenyl ring that provides both stabilization and steric shielding of the α-face.



The cyclic α-hydroxylactone, pantolactone, has been used extensively as a chiral auxiliary in D-A reactions.[84] Reactions involving $TiCl_4$ and $SnCl_4$ occur through chelated TSs.[85]



Several other Lewis acids including BF_3, Et_2AlCl, and $EtAlCl_2$ gave somewhat reduced levels of diastereoselectivity, but still favored the chelation-controlled product.[86] However, use of two equivalents of a highly hindered monodentate Lewis acid of the MAD type favored the other diastereoisomer. These reactions are thought to proceed through an open 2:1 complex exhibiting the opposite facial selectivity.



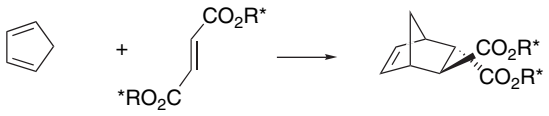
83. E. J. Corey, T. K. Schaaf, W. Huber, H. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.*, **92**, 397 (1970).

84. P. Campos and D. Munoz-Torreno, *Curr. Org. Chem.*, **8**, 1339 (2004).

85. T. Poll, A. F. Abdel Hady, R. Karge, G. Linz, J. Weetman, and G. Helmchen, *Tetrahedron Lett.*, **30**, 5595 (1989).

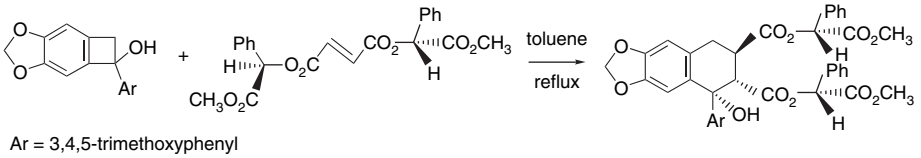
86. R. Maruoka, M. Oishi, and H. Yamamoto, *Synlett*, 683 (1993).

For the diester of fumaric acid, $EtAlCl_2$ was the most effective catalyst and the reaction proceeded with more than 90% diastereoselectivity.[87]

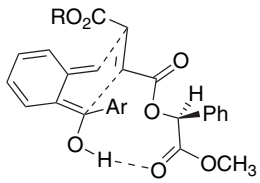


R* = (R)-Pantolactone

Mandelate and lactate esters have been found to generate diastereoselectivity in reactions of hydroxy-substituted quinodimethanes generated by thermolysis of benzocyclobutenols.[88] The reactions are thought to proceed by an *exo* TS with a crucial hydrogen bond between the hydroxy group and a dienophile carbonyl. The phenyl (or methyl in the case of lactate) group promotes facial selectivity.

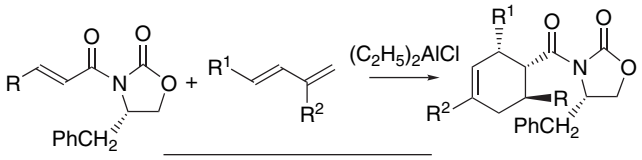


Ar = 3,4,5-trimethoxyphenyl



Several aspects of this reaction are intriguing. Despite the relatively high temperature (105° C), the nine-membered ring seems to have a strong influence on the stereoselectivity. The tendency for planarity at the ester bond may also contribute to the stability of the TS.

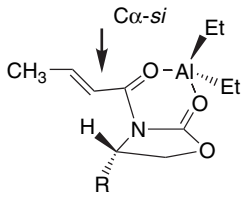
α, β-Unsaturated derivatives of chiral oxazolidinones have proven to be especially useful chiral auxiliaries for D-A additions. Reaction occurs at low temperatures in the presence of Lewis acids. The most effective catalyst for this system is $(C_2H_5)_2AlCl$.[89]



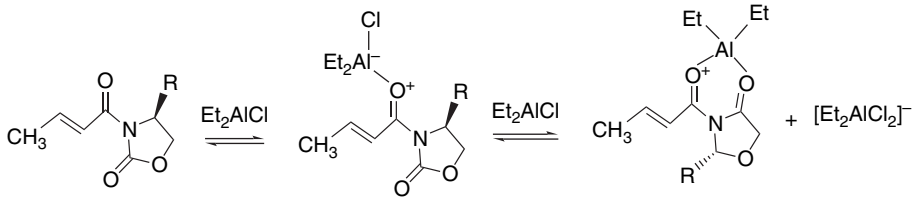
R	R^1	R^2	Yield	dr
H	H	CH_3	85%	95:5
H	CH_3	H	84%	>100:1
CH_3	H	CH_3	83%	94:6
CH_3	CH_3	H	77%	95:5

87. G. Helmchen, A. F. A. Hady, H. Hartmann, R. Karge, A. Krotz, K. Sartor, and M. Urmann, *Pure Appl. Chem.*, **61**, 409 (1989).
88. D. E. Bogucki and J. L. Charlton, *J. Org. Chem.*, **60**, 588 (1995); J. L. Charlton and S. Maddaford, *Can. J. Chem.*, **71**, 827 (1993).
89. D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).

The highest level of enantioselectivity is obtained using 1.5–2.0 equivalents of $(C_2H_5)_2AlCl$. Under these conditions the reactions are thought to proceed through a chelated TS having the vinyl substituent in the *s-cis*-conformation. For oxazolidinones having *S*-configuration at C(4) of the ring, this structure exposes the *si* face at the α-carbon of the dienophile.

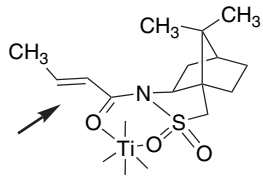


This complex is formed with more than 1.0 equivalents of $(C_2H_5)_2AlCl$ with concomitant formation of $[Et_2AlCl_2]^-$. The open and chelated structures have been characterized by NMR.[90] The chelated structure is substantially *more reactive* than the open complex, which accounts for the increase in enantioselectivity with more than 1.0 equivalents of catalyst.



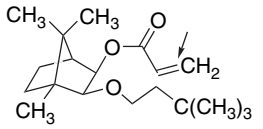
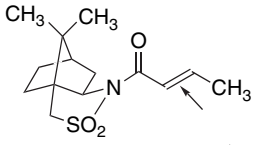
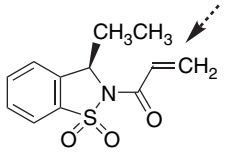
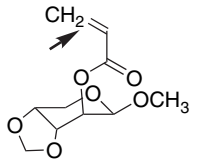
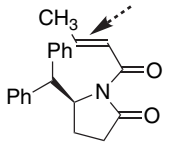
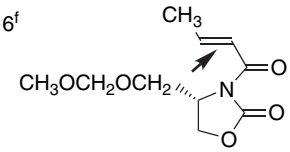
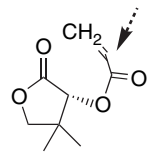
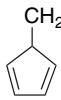
Chelation alone, however, is not sufficient to induce high enantioselectivity since other Lewis acids capable of chelation, such as $SnCl_4$ and $TiCl_4$, give lower enantioselectivity.

Scheme 6.3 gives some other examples of use of chiral auxiliaries in D-A reactions.[91] Entries 1 and 2 show two chiral auxiliaries developed from terpene precursors. The acrylate shown in Entry 1 gave excellent enantioselectivity with cyclopentadiene and 1,3-butadiene, but introduction of a methyl substituent on the dienophile (crotonyl derivative) resulted in a very slow reaction owing to steric problems. The sulfonamide auxiliary shown in Entry 2 has been exploited in other contexts (see, e.g., p. 123). The acyl derivatives give very good facial selectivity and are thought to react through a chelated TS. The carbocyclic ring establishes facial selectivity.



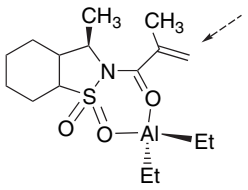
90. S. Castellino and W. J. Dwight, *J. Am. Chem. Soc.*, **115**, 2986 (1993).
91. For additional examples, see W. Oppolzer, *Tetrahedron*, **43**, 1969, 4057 (1987).

Scheme 6.3. Diels-Alder Reactions with Chiral Auxiliaries

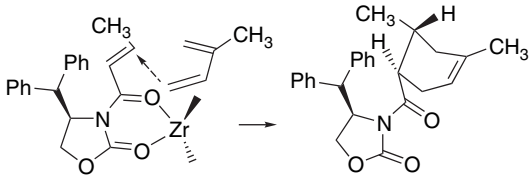
Entry	Dienophile	Diene	Catalyst, temperature	Yield (%)	dr
1[a]			$TiCl_2(i\text{-}OPr)_2$, –20°C 1.5 equiv	90	>99:1
2[b]			$TiCl_4$, –78°C 0.5 equiv	88	99:1
3[c]			$(C_2H_5)_2AlCl$, –40°C	94	98:2
4[d]			$SnCl_4$, –78°C 2 equiv	93	96:4
5[e]			$ZrCl_4$, –78°C	86	>99:1
6[f]			$(C_2H_5)_2AlCl$, 78°C 1.1 equiv	62	97:3
7[g]			$TiCl_4$, –55° to –20°C	79	96:2

a. W. Oppolzer, C. Chapuis, D. Dupuis, and M. Guo, *Helv. Chim. Acta*, **68**, 2100 (1985).
b. W. Oppolzer, C. Chapuis, and G. Bernardinelli, *Helv. Chim. Acta*, **67**, 1397 (1984); M. Vanderwalle, J. Van der Eycken, W. Oppolzer, and C. Vullioud, *Tetrahedron*, **42**, 4035 (1986).
c. W. Oppolzer, B. M. Seletsky, and G. Bernardinelli, *Tetrahedron Lett.*, **35**, 3509 (1994).
d. R. Nougier, J.-L. Gras, B. Giraud, and A. Virgilli, *Tetrahedron Lett.*, **32**, 5529 (1991).
e. M. P. Sibi, P. K. Deshpande, and J. Ji, *Tetrahedron Lett.*, **36**, 8965 (1995).
f. M. Ikota, *Chem. Pharm. Bull.*, **37**, 2219 (1989).
g. K. Miyaji, Y. Ohara, Y. Takahashi, T. Tsuruda, and K. Arai, *Tetrahedron Lett.*, **32**, 4557 (1991).

Entry 3 involves another sultam auxiliary. The chirality of the product is consistent with approach of the diene from the *re* face of a conformation in which the carbonyl oxygen is *syn* to the sulfonyl group.

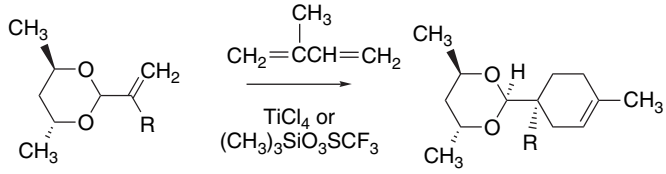


Entry 4 shows a carbohydrate-derived auxiliary with $SnCl_4$ as the Lewis acid. This dienophile also gives good enantioselectivity using $TiCl_4$ as the Lewis acid. Entry 5 is a proline-derived oxazolidinone auxiliary used in conjunction with $ZrCl_4$. The observed diastereoselectivity is consistent with a chelated TS having an *s-cis* conformation at the carbonyl group.



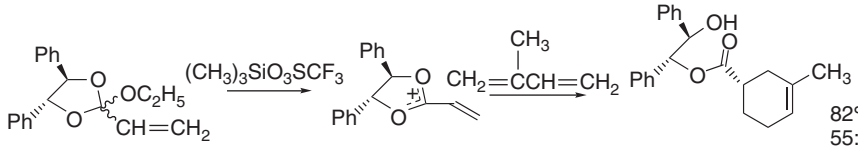
Entry 6 uses a chiral auxiliary derived from pyroglutamic acid. Entry 7 is an example of the use of pantolactone as a chiral auxiliary to form a prostaglandin precursor.

The alkenyl oxonium ion dienophiles generated from dioxolanes can be made diastereoselective by use of chiral diols. For example, acetals derived from *anti*-pentane-2,4-diol react under the influence of $TiCl_4/Ti(i\text{-}OPr)_4$ with stereoselectivity ranging from 3:1 to 15:1.



Ref. 92

Dioxolanes derived from *syn*-1,2-diphenylethane-1,2-diol react with dienes such as cyclopentadiene and isoprene, but in most cases the diastereoselectivity is low.

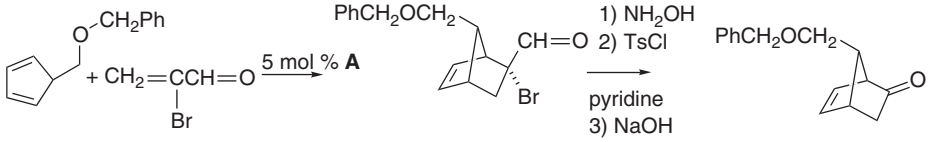


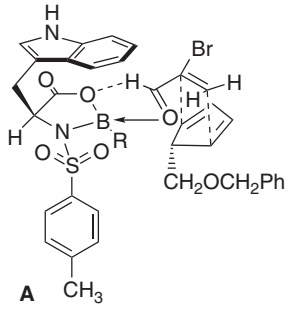
Ref. 93

92. T. Sammakia and M. A. Berliner, *J. Org. Chem.*, **59**, 6890 (1994).
93. A. Haudrechy, W. Picoul, and Y. Langlois, *Tetrahedron: Asymmetry*, **8**, 129 (1997).

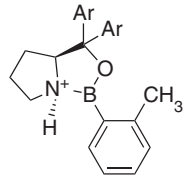
6.1.6. Enantioselective Catalysts for Diels-Alder Reactions

Enantioselectivity can also be achieved with chiral catalysts. The chiral oxazaborolidinones introduced in Section 2.1.5.6 as enantioselective aldol addition catalysts have been found to be useful in D-A reactions. The tryptophan-derived catalyst **A** can achieve 99% enantioselectivity in the cycloaddition between 5-benzyloxymethyl-1,3-cyclopentadiene and 2-bromopropenal. The indole ring provides π stacking and steric shielding. There is also believed to be a *formyl hydrogen bond* to the ring oxygen. A significant feature of this reaction is that the product is *exo* with respect to the formyl group. The adduct can be converted to an important intermediate for the synthesis of prostaglandins.[94]

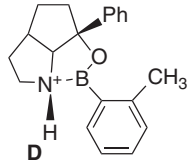




The oxazaborolidines **B** and **C** derived from proline are also effective catalysts. The protonated forms of these catalysts, generated using triflic acid or triflimide, are very active catalysts,[95] and the triflimide version is more stable above 0° C. Another protonated catalyst **D** is derived from 2-cyclopentenylacetic acid.

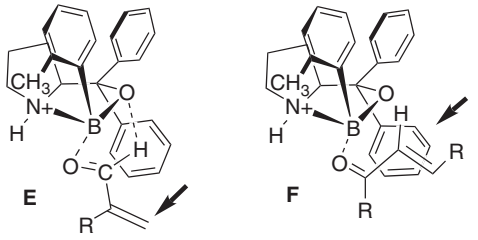


Ar=phenyl (**B**) or
3,5-dimethylphenyl (**C**)

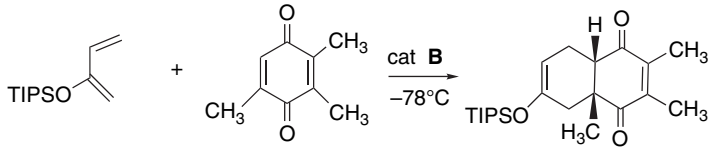


94. E. J. Corey and T. P. Loh, *J. Am. Chem. Soc.*, **113**, 8966 (1991).
95. E. J. Corey, T. Shibata, and T. W. Lee, *J. Am. Chem. Soc.*, **124**, 3808 (2002); D. H. Ryu and E. J. Corey, *J. Am. Chem. Soc.*, **125**, 6388 (2003); E. J. Corey, *Angew. Chem. Int. Ed.*, **41**, 1650 (2002).

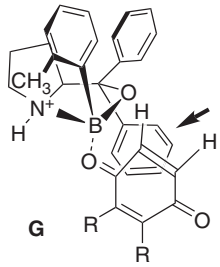
α, β-Unsaturated aldehydes react via TS **E**, whereas α,β-unsaturated ketones and esters react via TS **F**.



With trisubstituted benzoquinones and use of the cationic oxazaborolidinium catalyst **B**, 2-[*tris*-(isopropyl)silyloxy]-1,3-butadiene reacts at the monosubstituted quinone double bond. The reactions exhibit high regioselectivity and more than 95% e.e. With 2-mono- and 2,3-disubstituted quinones, reaction occurs at the unsubstituted double bond. The regiochemistry is directed by coordination to the catalyst at the more basic carbonyl oxygen.

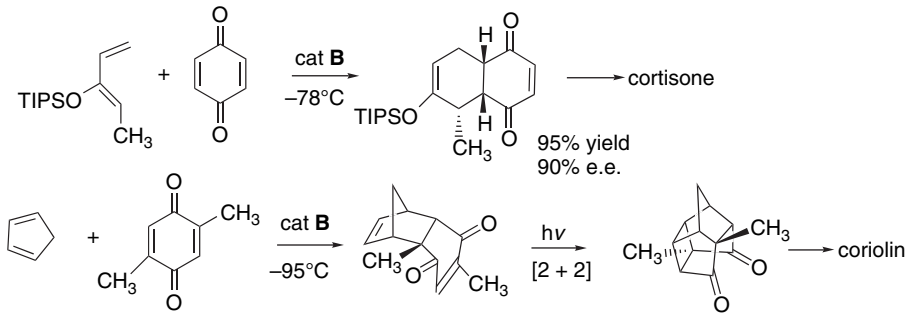


The enantioselectivity is consistent with a TS in which the less-substituted double bond of the quinone is oriented toward the catalyst, as in TS **G**.

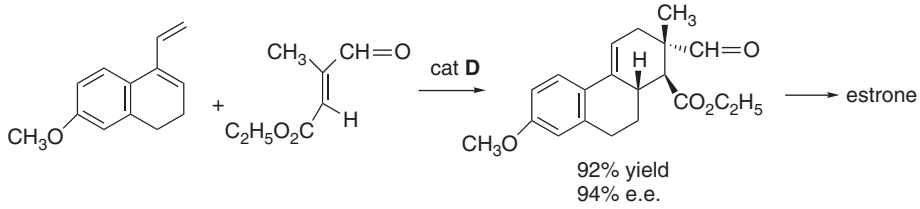


These catalysts have been applied to D-A reactions that are parts of several important synthetic routes, thereby making them enantioselective.[96] For example, key intermediates in the synthesis of cortisone and coriolin were prepared in enantiomerically pure form using catalyst **B**.

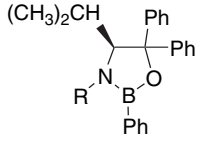
[96] Q.-Y. Hu, G. Zhou, and E. J. Corey, *J. Am. Chem. Soc.*, **126**, 13708 (2004).



Similarly, an enantioselective synthesis of estrone is based on catalyst **D**.[97]



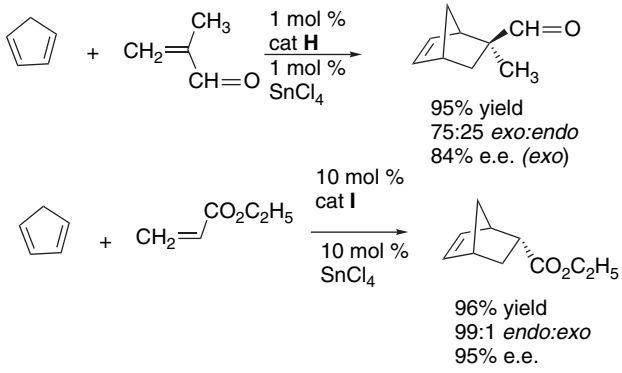
A valine-derived oxazaborolidine derivative has been found to be subject to activation by Lewis acids, with $SnCl_4$ being particularly effective.[98] This catalyst combination also has reduced sensitivity to water and other Lewis bases.



H R = *n*-octyl

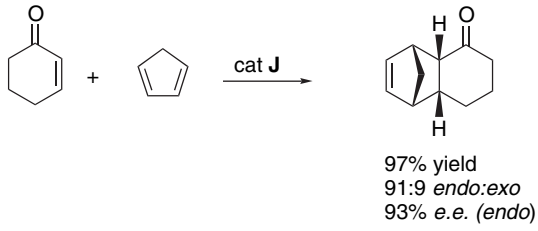
I R = 1-naphthylmethyl

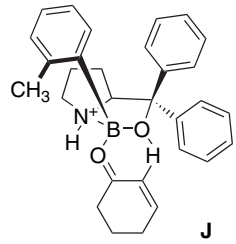
Catalyst **H** and the corresponding *N*-(1-naphthylmethyl) derivative **I** give high e.e. and good *endo* stereoselectivity for several typical dienophiles with cyclopentadiene.



97. Q.-Y. Hu, P. D. Rege, and E. J. Corey, *J. Am. Chem. Soc.*, **126**, 5984 (2004).
98. K. Futatsugi and H. Yamamoto, *Angew. Chem. Int. Ed. Engl.*, **44**, 1484 (2005).

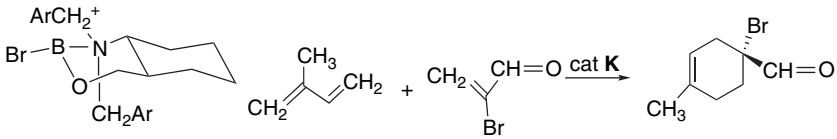
Cationic oxazaborolidines derived from α,α-diphenylpyrrolidine-2-methanol have been examined and shown to considerably extend the range of dienophiles that are responsive to the catalysts.[99] The best proton source for activation of these catalysts is triflimide, $(CF_3SO_2)_2NH$.[100] For example, cyclohexenone and cyclopentadiene react with 93% enantioselectivity using catalyst **J**.





J

Another cyclic boron catalyst **K**, derived from *trans*-2-aminocyclohexanemethanol, can be prepared with a quaternary nitrogen that enhances activity.[101] This particular catalyst is not very stable, but it is highly active.



Ar=3,5-dimethylphenyl

99% yield
96% e.e.

K

Another useful group of catalysts for D-A reactions is made up of Cu^{2+} chelates of *bis*-oxazolines.[102] The copper salts are the most effective of the first transition metal series because they offer both strong Lewis acid activation and fast ligand exchange. The anion is also important and must be noncoordinating. The triflates can be used, but the hexafluoroantimonates are even more active.[103] These catalysts have been applied to dienophiles with two donor sites, in particular *N*-acyloxazolidinones. The chelated structures provide strong facial differentiation, as shown in Figure 6.9.[104] Installing chirality into the oxazolidinone results in matched and mismatched combinations. In addition to the *t*-butyl derivative, the 4-isopropyl-5,5-phenyl derivatives have also been explored.[105] The *bis*-oxazolines derived from *cis*-2-aminoindanol have also proven to be effective catalysts.[106] Various solid-supported forms of these BOX catalysts have been developed.[107]

99. E. J. Corey, T. Shibata, and T. W. Lee, *J. Am. Chem. Soc.*, **124**, 3808 (2002); D. H. Ryu, T. W. Lee, and E. J. Corey, *J. Am. Chem. Soc.*, **124**, 9992 (2002).
100. D. H. Ryu and E. J. Corey, *J. Am. Chem. Soc.*, **125**, 6388 (2003).
101. Y. Hayashi, J. J. Rohde, and E. J. Corey, *J. Am. Chem. Soc.*, **118**, 5502 (1996).
102. J. J. Johnson and D. A. Evans, *Acc. Chem. Res.*, **33**, 325 (2000).
103. D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, and K. R. Campos, *J. Am. Chem. Soc.*, **121**, 7582 (1999).
104. D. A. Evans, S. J. Miller, T. Lectka, and P. von Matt, *J. Am. Chem. Soc.*, **121**, 7559 (1999).
105. T. Hintermann and D. Seebach, *Helv. Chim. Acta*, **81**, 2093 (1998).
106. A. K. Ghosh, S. Fidanze, and C. H. Senanayake, *Synthesis*, 937 (1998); C. H. Senanayake, *Aldrichimica Acta*, **31**, 3 (1998).
107. D. Rechavi and M. Lemaine, *Chem. Rev.*, **102**, 3467 (2002).

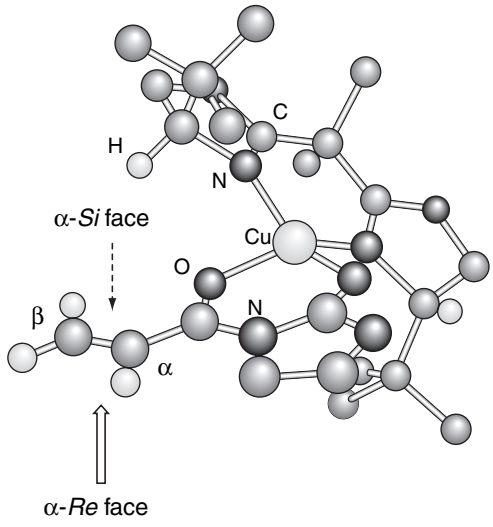
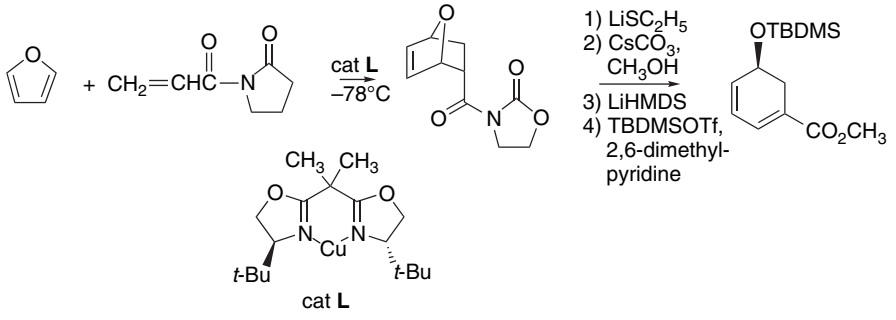


Fig. 6.9. Model of Cu(*S*,*S*-*t*-BuBOX) catalyst with *N*-acryloyloxazolidinone showing facial stereodifferentiation. Reproduced from *J. Am. Chem. Soc.*, **121**, 7559 (1999), by permission of the American Chemical Society.



Ref. 108

The related PyBOX ligands incorporate a pyridine ring that provides an additional coordination site and are tridentate. The Sc^{3+} and lanthanide ions with the PyBOX ligand can accommodate seven to nine donors. In these complexes, the enantioselectivity is influenced by the number and identity of the coordinating species.[109] Figure 6.10 shows examples of a monohydrated Sc^{3+} triflate[110] having seven contacts and a tetrahydrated lanthanide cation with a total of nine contacts, including two triflate anions.[111]

The basis of the enantioselectivity of the BOX catalysts has been probed using B3LYP/6-31G* calculations.[112] It has been proposed that in the case of the *t*-butyl

108. D. A. Evans and D. M. Barnes, *Tetrahedron Lett.*, **38**, 57 (1997).
109. G. Desimoni, G. Faita, M. Guala, and C. Pratelli, *J. Org. Chem.*, **68**, 7862 (2003).
110. D. A. Evans, Z. K. Sweeney, T. Rovis, and J. S. Tedrow, *J. Am. Chem. Soc.*, **123**, 12095 (2001).
111. G. Desimoni, G. Faita, S. Filippone, M. Mella, M. G. Zampori, and M. Zema, *Tetrahedron*, **57**, 10203 (2001).
112. J. DeChancie, O. Acevedo, and J. D. Evanseck, *J. Am. Chem. Soc.*, **126**, 6043 (2004).

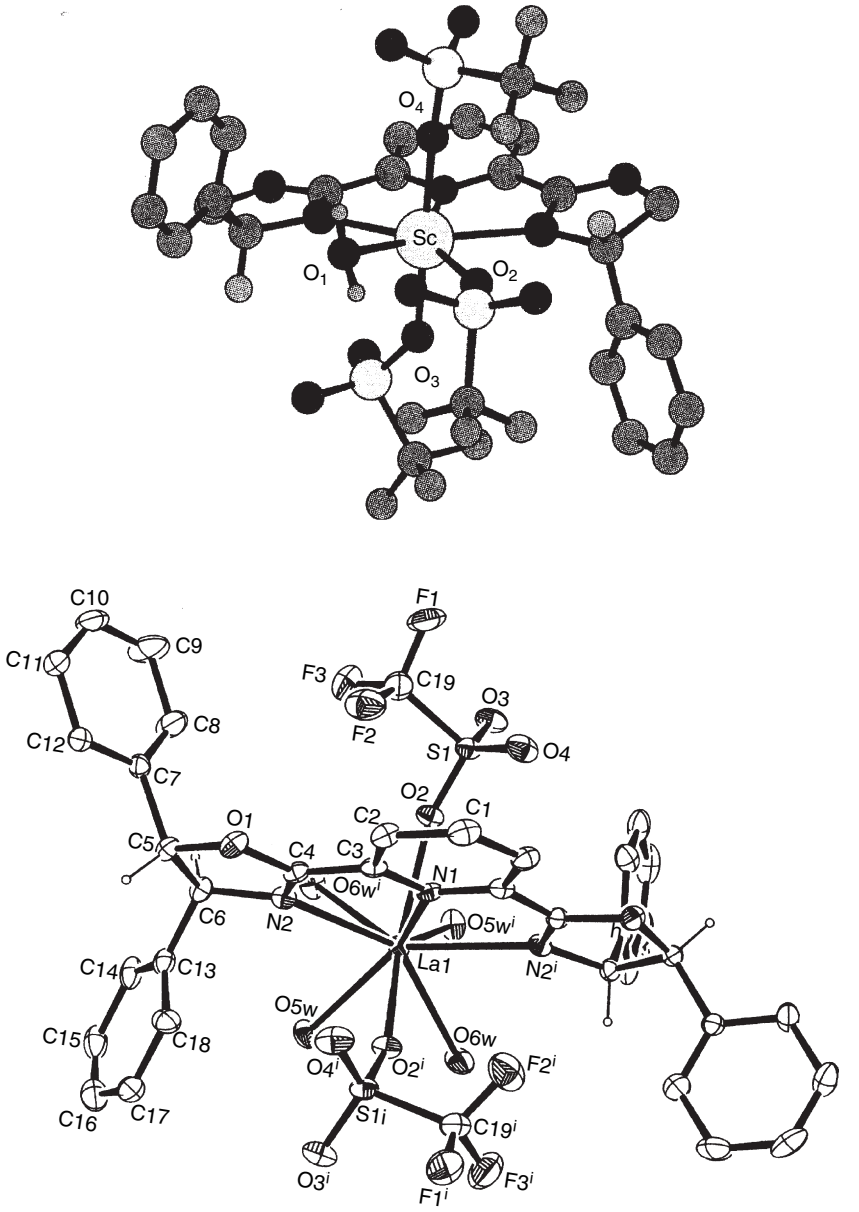
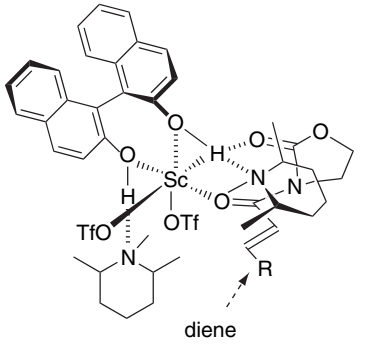


Fig. 6.10. (top) Scandium[*S*,*S*-phenylPyBOX(H_2O)($CF_3SO_3^-$)$_3$. Reproduced from *J. Am. Chem. Soc.*, **123**, 12095 (2001), by permission of the American Chemical Society. (bottom) Lanthanum[*R*,*R*-phenylPyBOX(H_2O)$_4$($CF_3SO_3^-$)$_2$ cation. Reproduced from *Tetrahedron*, **57**, 10203 (2001), by permission of Elsevier.

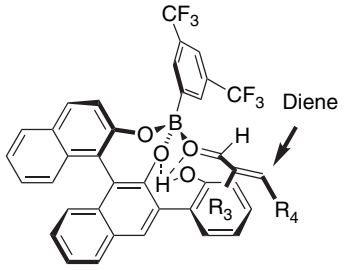
derivatives, catalyst activity and enantioselectivity are governed by the degree to which solvent or anions can approach the copper ion. The most active catalysts are those in which nucleophilic coordination is restricted by a *t*-butyl group.

Several catalysts for enantioselective D-A reactions are based on BINOL. For example, additions of *N*-acryloyloxazolidinones can be made enantioselective using

$Sc(O_3SCF_3)_3$ in the presence of a BINOL ligand.[113] Optimized conditions involved use of 5–20 mol % of the catalyst along with a hindered amine such as *cis*-1,2,6-trimethylpiperidine. A hexacoordinate TS in which the amine is hydrogen bonded to the BINOL has been proposed.



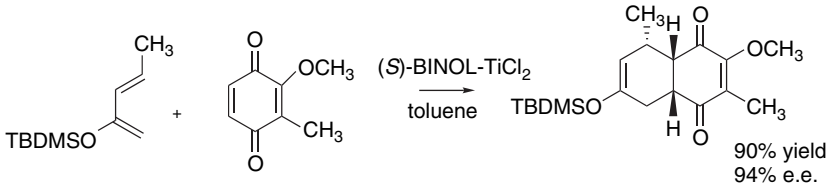
Enantioselective D-A reactions of acrolein are also catalyzed by 3-(2-hydroxyphenyl) derivatives of BINOL in the presence of an aromatic boronic acid. The optimum boronic acid is 3,5-di-(trifluoromethyl)benzeneboronic acid, with which more than 95% e.e. can be achieved. The TS is believed to involve Lewis acid complexation of the boronic acid at the carbonyl oxygen and hydrogen bonding with the hydroxy substituent. In this TS π-π interactions between the dienophile and the hydroxybiphenyl substituent can also help to align the dienophile.[114]



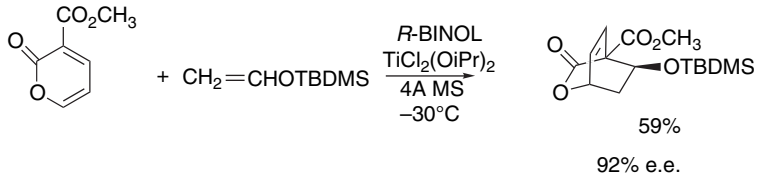
Dienophile	Yield (%)	*exo*:*endo*	e.e. (%)
$CH_2{=}CHCH{=}O$	84	3:97	95
$CH_2{=}C(Br)CH{=}O$	99	90:10	>99
E-$CH_3CH{=}CHCH{=}O$	94	10:90	95
E-$PhCH{=}CHCH{=}O$	94	26:74	80

BINOL has also been used in conjunction with Ti(IV). (*S*)-BINOL-$TiCl_2$ provided an enantiomerically enriched starting material in the synthesis of (–)colombiasin A.[115]

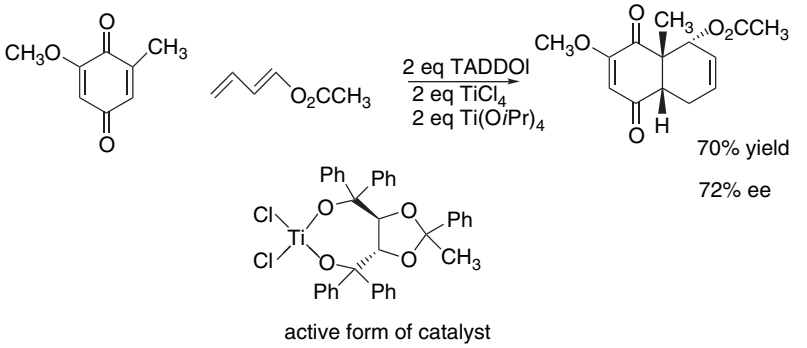
113. S. Kobayashi, M. Araki, and I. Hachiya, *J. Org. Chem.*, **59**, 3758 (1994).
114. K. Ishihara, H. Kurihara, M. Matsumoto, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 6920 (1995).
115. K. C. Nicolaou, G. Vassilikogiannakis, W. Magerlein, and R. Kranich, *Angew. Chem. Int. Ed. Engl.*, **40**, 2482 (2001); K. C. Nicolaou, G. Vassilikogiannakis, W. Magerlein, and R. Kranich, *Chem. Eur. J.*, **7**, 5359 (2001).



BINOL in conjunction with $TiCl_2(O\text{-}i\text{-}Pr)_2$ gives good enantioselectivity in a D-A reaction with a pyrone as the diene.[116] This is a case of an inverse electron demand reaction and the catalysts would be complexed to the diene.



The α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) chiral ligands have also been the basis of enantioselective catalysis of the D-A reaction. In a study using 2-methoxy-6-methylquinone as the dienophile, evidence was found that the chloride-ligated form of the catalysts was more active than the dimeric oxy-bridged form.[117]



A computational study [B3LYP/3-21G(*d*)] examined a related aspect of the mechanism of TADDOL-$TiCl_2$ catalysis of reactions with *N*-acryloyloxazolidinone.[118] The TS model does not address the steric shielding provided by the ligand substituents but rather the role of the coordination geometry at Ti. The results of this study suggest that the reaction may proceed through a *nonminimum energy complex*. Three different TSs corresponding to different coordination geometries of the ligands were characterized, as shown in Figure 6.11. Although complex MA is lowest in energy, MB has the lowest LUMO. This structure places the exocyclic carbonyl *trans* to a chloride. The authors suggest that it may therefore be the *most reactive* complex. This issue

116. G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor, and S. Peter, Jr., *J. Org. Chem.*, **61**, 671 (1996).
117. S. M. Moharrram, G. Hirai, K. Koyama, H. Oguri,and M. Hirama, *Tetrahedron Lett.*, **41**, 6669 (2000).
118. J. I. Garcia, V. Martinez-Merino, and J. A. Mayoral, *J. Org. Chem.*, **63**, 2321 (1998).

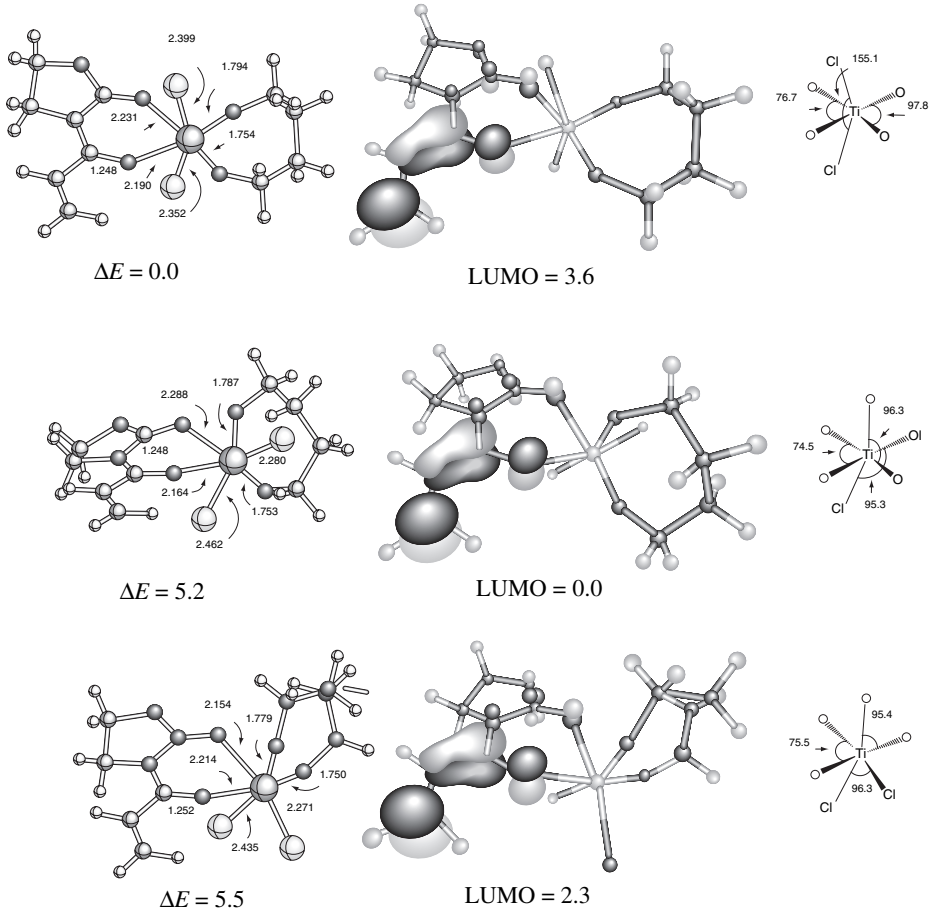


Fig. 6.11. Representation of transition structure and the LUMO orbitals for three stereoisomeric complexes of *N*-acryloyloxazolidinone with a TADDOL model, $Ti[O(CH_2)_4O]Cl_2$. The LUMO energies (B3LYP/6-3111+G(*d*)) in kcal/mol. Reproduced from *J. Org. Chem.*, **63**, 2321 (1998), by permission of the American Chemical Society.

has not been resolved, but there is some experimental evidence that the reaction may proceed through a minor complex.[119]

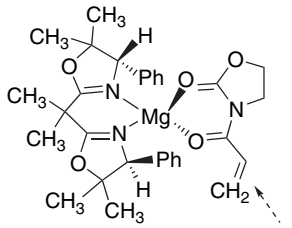
Visual models and additional information on Asymmetric Diels-Alder Reactions can be found in the Digital Resource available at: Springer.com/carey-sundberg.

These examples serve to illustrate several general points about use of chiral catalysts for D-A reactions. A cationic metal center is present in nearly all of the catalysts developed to date and has several functions. It is the anchor for the chiral ligands and also serves as a Lewis acid with respect to the dienophile. The chiral ligands establish the facial selectivity of the complexed dienophile. There are several indications of the importance of the anions to catalytic activity. Anions, in general,

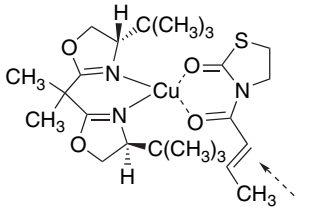
119. D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner, and F. N. M. Kuhnle, *J. Org. Chem.*, **60**, 1788 (1995); D. Seebach, R. E. Marti, and T. Hinterman, *Helv. Chim. Acta*, **79**, 710 (1996); C. Haase, C. R. Sarko, and M. Di Mare, *J. Org. Chem.*, **60**, 1777 (1995).

can compete for the ligand binding sites on the metal so that catalytic activity is improved with weakly coordinating anions. Finally, there are some indications in the TADDOL-type catalysts that the anions may exert electronic effects and serve to distinguish between reactivity of dienophiles in *cis* or *trans* positions in the octahedral coordination complex.

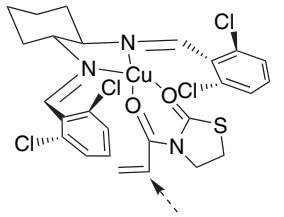
Several examples of catalytic enantioselective D-A reactions are given in Scheme 6.4. Entries 1 to 6 involve *N*-acyloxazolidinones and *N*-acylthiazolidinones as dienophiles. Note that there are no stereogenic centers in the reactants, so racemic mixtures would result from reaction in the absence of a chiral catalyst. The metal ions used in these reactions can accommodate two additional ligands in addition to those present in the catalyst. The reactions are believed to involve a chelated TS similar to those involved when chiral oxazolidinone are used (see p. 509). The catalyst in Entry 1 has a BOX-type ligand. The phenyl substituents and the tetrahedral coordination geometry at magnesium give rise to a well-defined geometry. Note that the catalyst has c_2 symmetry. The phenyl substituents cause differential facial shielding.



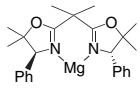
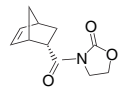
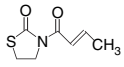
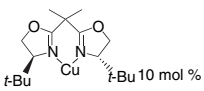
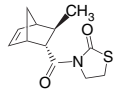
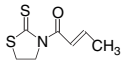
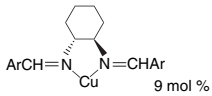
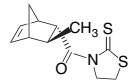
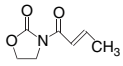
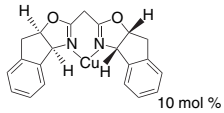
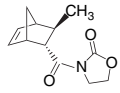
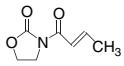
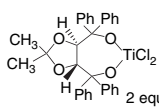
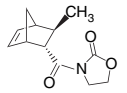
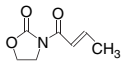
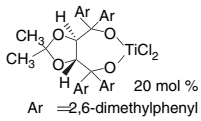
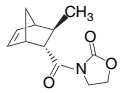
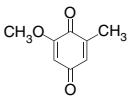
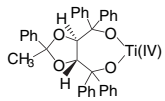
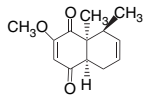
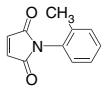
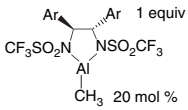
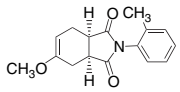
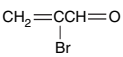
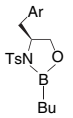
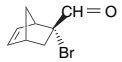
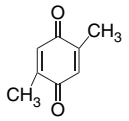
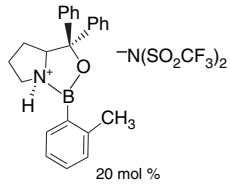
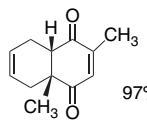
The enantioselectivity of this catalyst, which is prepared as the iodide salt, is somewhat dependent on the anion that is present. If $AgSbF_6$ is used as a cocatalyst, the iodide is removed by precipitation and the e.e. increases from 81 to 91%. These results indicate that the absence of a coordinating anion improved enantioselectivity. Entry 2 shows the extensively investigated *t*-BuBOX ligand with an *N*-acryloylthiazolidinone dienophile. With Cu^{2+} as the metal, the coordination geometry is square planar. The complex exposes the *re* face of the dienophile.



Entry 3 involves a catalyst derived from (*R*,*R*)-*trans*-cyclohexane-1,2-diamine. The square planar Cu^{2+} complex exposes the *re* face of the dienophile. As with the BOX catalysts, this catalyst has c_2 symmetry.

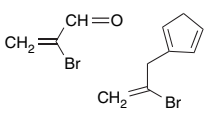
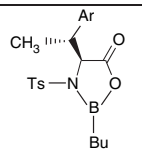
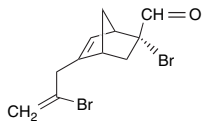
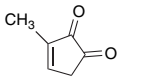
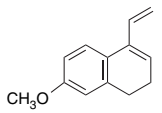
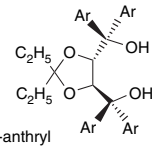
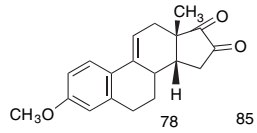
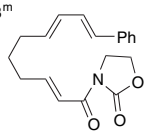
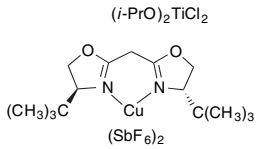
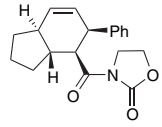
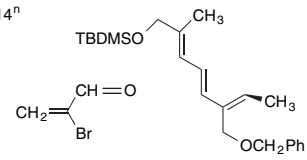
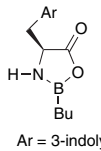
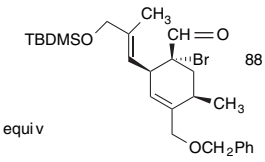
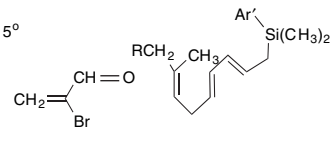
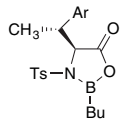
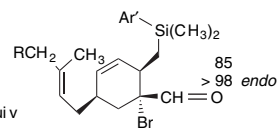


Scheme 6.4. Catalytic Enantioselective Diels-Alder Reactions

Entry	Dienophile	Diene	Catalyst	Amount	Product	Yield (%)	e.e.
1[a]				10 mol %		82	95
2[b]				10 mol %		79	94
3[c]				9 mol % Ar = 2,6-dichlorophenyl		86	91
4[d]				10 mol %		88	84
5[e]				2 equiv		93	92
6[f]				20 mol % Ar = 2,6-dimethylphenyl		92	93
7[g]						94	80
8[h]				1 equiv 20 mol % Ar = 3,5-dimethylphenyl		98	93
9[i]				5 mol % Ar = 3-indolyl		>99.5	
10[j]				20 mol %		97%	91%

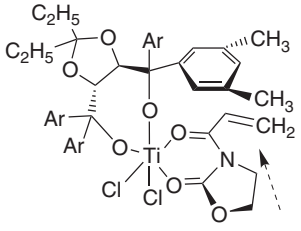
(*Continued*)

Scheme 6.4. (*Continued*)

Entry	Dienophile	Diene	Catalyst	Amount	Product	Yield (%)	e.e.
11[k]			 Ar = 3-indolyl	10 mol %		81 > 99:1 *exo*	99
12[l]	 + 		 Ar = 9-anthryl	+ 20 mol %		78	85
13[m]			 $(SbF_6)_2$	5 mol %		86 > 95:5 *endo*	92
14[n]			 Ar = 3-indolyl	1 equiv		88	72
15[o]	 R = *E,E*-Farnesyl		 Ar = 3-indolyl	0.5 equiv		85 > 98 *endo*	97

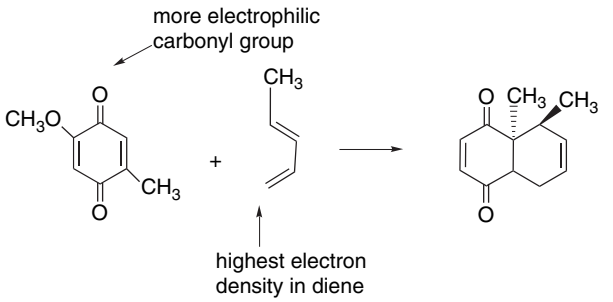
a. E. J. Corey and K. Ishihara, *Tetrahedron Lett.*, **33**, 6807 (1992).
b. D. A. Evans, S. J. Miller, and T. Lectka, *J. Am. Chem. Soc.*, **115**, 6460 (1993).
c. D. A. Evans, T. Lectka, and S. J. Miller, *Tetrahedron Lett.*, **34**, 7027 (1993).
d. A. K. Ghosh, H. Cho, and J. Cappiello, *Tetrahedron: Asymmetry*, **9**, 3687 (1998).
e. K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989).
f. E. J. Corey and Y. Matsumura, *Tetrahedron Lett.*, **32**, 6289 (1991).
g. T. A. Engler, M. A. Letavic, K. O. Lynch, Jr., and F. Takusagawa, *J. Org. Chem.*, **59**, 1179 (1994).
h. E. J. Corey, S. Sarshar, and D.-H. Lee, *J. Am. Chem. Soc.*, **116**, 12089 (1994).
i. E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara, and M. C. Noe, *J. Am. Chem. Soc.*, **114**, 8290 (1992).
j. D. H. Ryu and E. J. Corey, *J. Am. Chem. Soc.*, **125**, 6388 (2003).
k. E. J. Corey, A. Guzman-Perez, and T.-P. Loh, *J. Am. Chem. Soc.*, **116**, 3611 (1994).
l. G. Quinkert, A. Del Grosso, A. Doering, and W. Doering, R. I. Schenkel, M. Bauch, G. T. Dambacher, J. W. Bats, G. Zimmerman, and G. Durrer, *Helv. Chim. Acta*, **78**, 1345 (1995).
m. D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaugnessy and K. R. Campos, *J. Am. Chem. Soc.*, **121**, 7582 (1999).
n. J. A. Marshall and S. Xie, *J. Org. Chem.*, **57**, 2987 (1992).
o. T. W. Lee and E. J. Corey, *J. Am. Chem. Soc.*, **123**, 1872 (2001).

Entry 4 is a BOX-type catalyst derived from *cis*-1-aminoindan-2-ol. This is a somewhat more rigid ligand than the monocyclic BOX ligands. The chiral ligands in Entries 5 to 7 are TADDOLS (see p. 512) derived from tartaric acid. In Entry 5 the catalyst is prepared from $TiCl_2(O\text{-}i\text{-}Pr)_2$ and 4A molecular sieves. About 0.10 equivalent of the catalyst is used. In Entry 6, the catalyst was prepared using $Ti(O\text{-}i\text{-}Pr)_4$ and $SiCl_4$. In this catalyst, the aryl groups are carry 3,5-dimethyl groups. The 3,5-di-CF_3 and 3,5-di-Cl derivatives, which were also studied, gave high *exo*:*endo* ratios, but much reduced enantioselectivity. This is thought to be due to the reduced π donor character of the rings with EWG substituents. As mentioned on p. 513, the presence of chlorides at the Ti center is also probably an important factor in the reactivity of the catalyst.



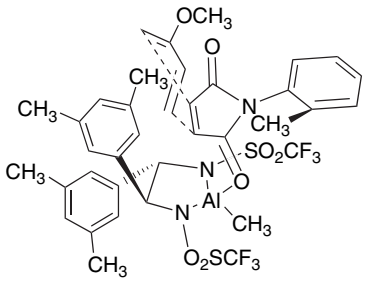
Ar = 3,5-dimethylphenyl

Entry 7 features a quinone dienophile. The reaction exhibits the expected selectivity for the more electrophilic quinone double bond (see p. 506). The reaction is also regioselective with respect to the diene, with the methyl group acting as a donor substituent. The enantioselectivity is 80%.



In this case, the catalyst was formed by premixing $Ti(O\text{-}i\text{-}Pr)_4$ and $TiCl_4$ and adding the TADDOL ligand. These conditions also gave good regioselectivity with isoprene, although the e.e. was not as high.

Entry 8 uses a *bis*-trifluoromethanesulfonamido chelate of methylaluminum as the catalyst. As in Entry 6, the use of a 3,5-dimethylphenyl group in place of phenyl improved enantioselectivity. The *ortho*-methylphenyl substituent on the maleimide dienophile restricts the potential coordination sites at the metal center. NMR characterization of the reactant-catalyst complex suggests that reaction occurs through the TS shown below.



Entry 9 uses the oxaborazolidine catalysts discussed on p. 505 with 2-bromopropenal as the dienophile. The aldehyde adopts the *exo* position in each case, which is consistent with the proposed TS model. Entry 10 illustrates the use of a cationic oxaborazolidine catalyst. The chirality is derived from *trans*-1,2-diaminocyclohexane. Entry 12 shows the use of a TADDOL catalyst in the construction of the steroid skeleton. Entry 13 is an intramolecular D-A reaction catalyzed by a Cu-*bis*-oxazoline. Entries 14 and 15 show the use of the oxazaborolidinone catalyst with more complex dienes.

6.1.7. Intramolecular Diels-Alder Reactions

Intramolecular Diels-Alder (IMDA) reactions are very useful in the synthesis of polycyclic compounds.[120] The stereoselectivity of a number of IMDA reactions has been analyzed and conformational factors in the TS often play the dominant role in determining product structure.[121] It has also been noted in certain systems that the stereoselectivity is influenced by the activating substituent on the dienophile double bond, both for thermal and Lewis acid–catalyzed reactions.[122] The general trends in regioselectivity are in agreement with frontier orbital concepts, with conformational effects being the main factors in determining stereoselectivity. Since the conformational interactions depend on the substituent pattern in the specific case, no general rules for stereoselectivity can be put forward. Molecular modeling can frequently identify the controlling structural features.[123]

It is possible to introduce substituents that can influence the conformational equilibria to favor a particular product. In the reactions shown below, the addition of the trimethylsilyl substituent leads to a single stereoisomer in 85% yield, whereas in the unsubstituted system two stereoisomers are formed in ratios from 4:1 to 8:1.[124]

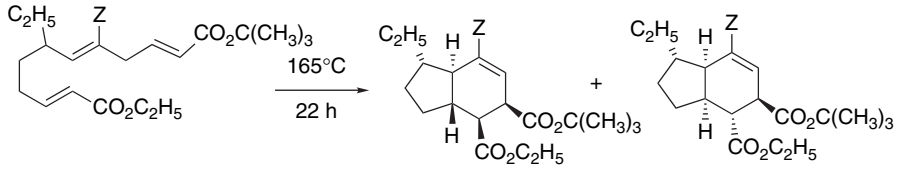
120. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); G. Brieger and J. N. Bennett, *Chem. Rev.*, **80**, 63 (1980); E. Ciganek, *Org. React.*, **32**, 1 (1984); D. F. Taber, *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer-Verlag, Berlin, 1984.

121. W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.*, **45**, 4264 (1980); R. K. Boeckman, Jr., and S. K. Ko, *J. Am. Chem. Soc.*, **102**, 7146 (1980); W. R. Roush and S. E. Hall, *J. Am. Chem. Soc.*, **103**, 5200 (1981); K. A. Parker and T. Iqbal, *J. Org. Chem.*, **52**, 4369 (1987).

122. J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984); W. R. Roush, A. P. Essenfeld, and J. S. Warmus, *Tetrahedron Lett.*, **28**, 2447 (1987); T.-C. Wu and K. N. Houk, *Tetrahedron Lett.*, **26**, 2293 (1985).

123. K. J. Shea, L. D. Burke, and W. P. England, *J. Am. Chem. Soc.*, **110**, 860 (1988); L. Raimondi, F. K. Brown, J. Gonzalez, and K. N. Houk, *J. Am. Chem. Soc.*, **114**, 4796 (1992); D. P. Dolata and L. M. Harwood, *J. Am. Chem. Soc.*, **114**, 10738 (1992); F. K. Brown, U. C. Singh, P. A. Kollman, L. Raimondi, K. N. Houk, and C. W. Bock, *J. Org. Chem.*, **57**, 4862 (1992); J. D. Winkler, H. S. Kim, S. Kim, K. Ando, and K. N. Houk, *J. Org. Chem.*, **62**, 2957 (1997).

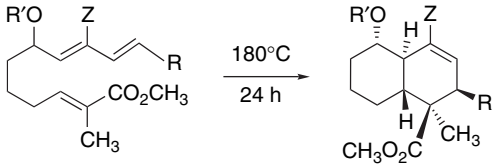
124. R. K. Boeckman, Jr., and T. E. Barta, *J. Org. Chem.*, **50**, 3421 (1985).



Z = H major product
Z = Si(CH3)3 only product

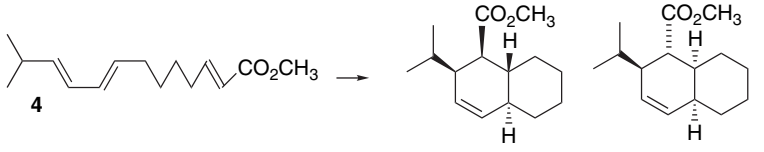
Z = H minor product

Similarly, the 2,8,10-triene **3a** gives a mixture of four isomers, but introduction of a TMS group as in **3b** gives a single stereoisomer in 89% yield. The reason for the improved stereoselectivity is that the steric effect introduced by the TMS substituent favors a single conformer.



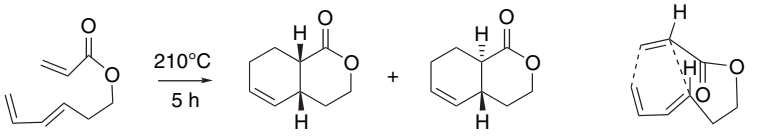
3a R = CH_3; R′ TBDMS; Z = H
3b R = $CH_2CH_2OCH_2Ph$; R′ = MOM; Z = $Si(CH_3)_3$

Lewis acid catalysis usually substantially improves the stereoselectivity of IMDA reactions, just as it does in intermolecular cases. For example, the thermal cyclization of **4** at 160° C gives a 50:50 mixture of two stereoisomers, but the use of $(C_2H_5)_2AlCl$ as a catalyst permits the reaction to proceed at room temperature and *endo* addition is favored by 7:1.[125]



	endo	*exo*
thermal (160°C)	50%	50%
Et_2AlCl (23°C)	88%	12%

There has been quite thorough study of 3,5-hexadienyl acrylates, where the ester functions both as part of the link and an activating substituent. The reaction tends to be quite slow, even though at first glance it would appear to encounter little strain. The *cis* ring juncture is favored by 9:1.



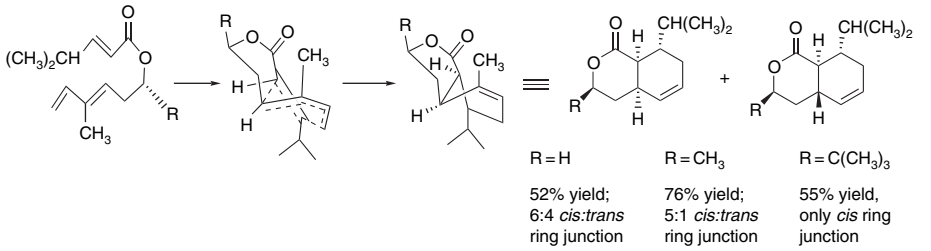
42% yield 9:1 *cis:trans* ratio

preferred transition structure

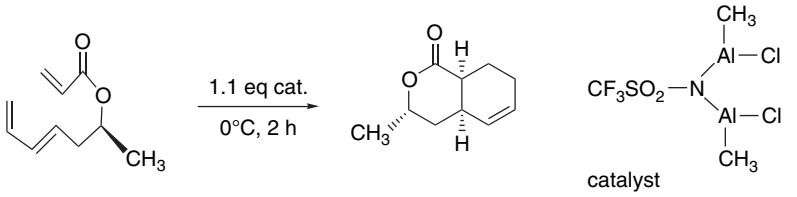
Ref. 126

125. W. R. Roush and H. R. Gillis, *J. Org. Chem.*, **47**, 4825 (1982).
126. S. F. Martin, S. A.Williamson, R. P. Gist, and K. M. Smith, *J. Org. Chem.*, **48**, 5170 (1983).

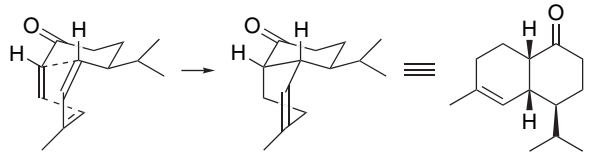
One factor that is believed to contribute to the sluggishness of the reaction is that a chairlike arrangement of the linking group causes a twist in the ester group from the preferred planarity. The TS also requires that the ester alkyl group be in an *anti* relationship to the carbonyl group, rather than the preferred *syn* conformation. Several substituted systems have been studied and they react primarily through a boatlike *endo* TS.[127] The size of the α-substituent R controls the degree of preference for the TS.



This system has been studied computationally at the B3LYP/6-31 + G* level.[128] In agreement with the experimental results, the *endo* boat TS was found to be the most stable. The *endo* chair and *exo* boat were about 1.3 kcal/mol higher in energy, and the *exo* chair still higher. This study confirmed that the boatlike TS allows the ester group to stay closer to planarity. Eclipsing interactions also contribute to the higher energy of the chairlike TS. In accordance with the idea that a bidentate Lewis acid might both effect Lewis acid catalysis and promote a planar geometry at the ester group, it was found that the reaction could be effectively catalyzed by a bidentate Lewis acid.[129] Use of one equivalent of the catalyst gave 95% yield after 2 h at 0° C. The catalyst is believed to be coordinated with both the carbonyl and the ester oxygens.



Some examples of IMDA reactions are given in Scheme 6.5. In Entry 1 the dienophilic portion bears a carbonyl substituent and cycloaddition occurs easily. Two stereoisomeric products are formed, but both have the *cis* ring fusion, which is the stereochemistry expected for an *endo* TS, with the major diastereomer being formed from the TS with an equatorial isopropyl group.

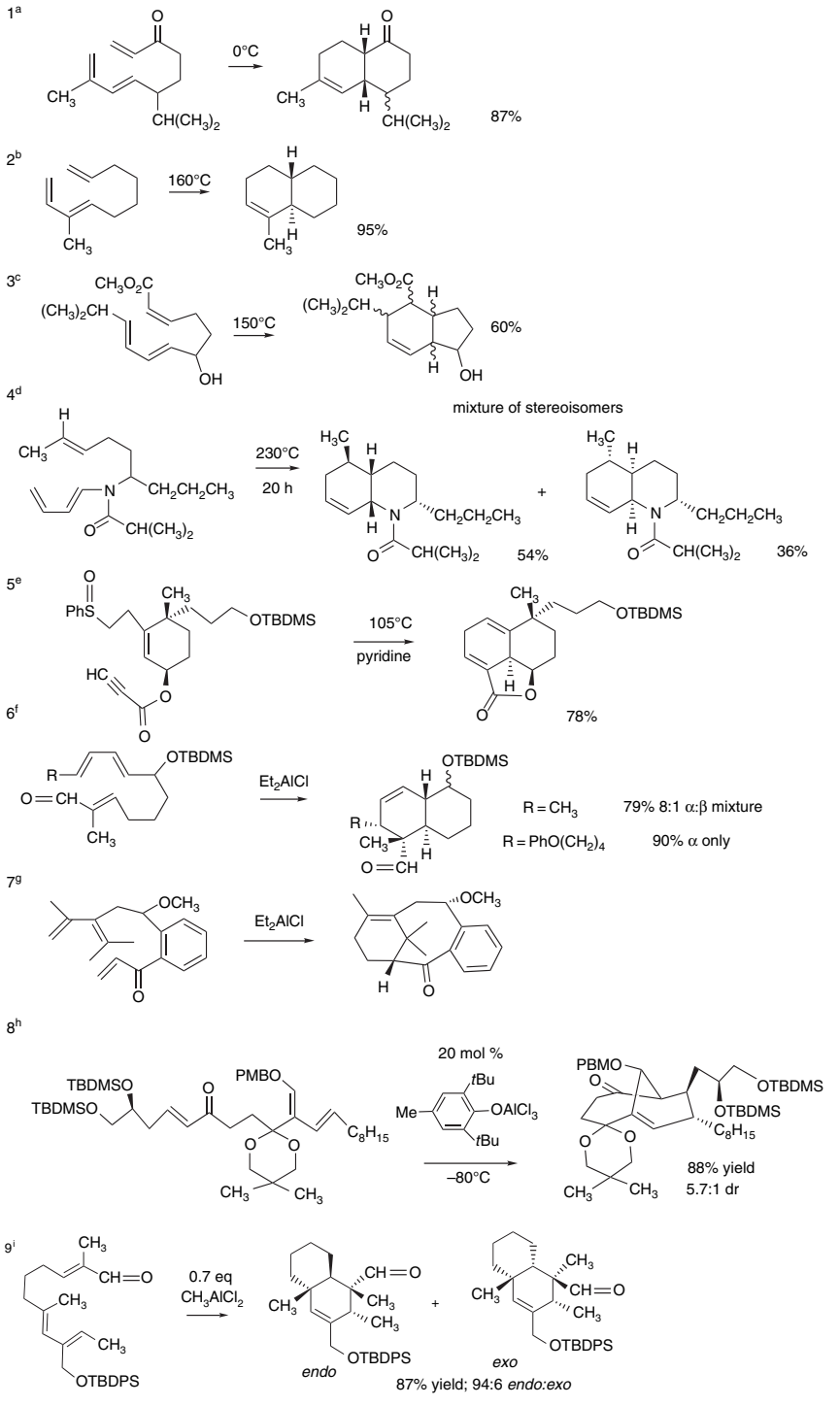


[127] M. E. Jung, A. Huang, and T. W. Johnson, *Org. Lett.*, **2**, 1835 (2000); P. Kim, M. H. Nantz, M. J. Kurth, and M. M. Olmstead, *Org. Lett.*, **2**, 1831 (2000).

[128] D. J. Tantillo, K. N. Houk, and M. E. Jung, *J. Org. Chem.*, **66**, 1938 (2001).

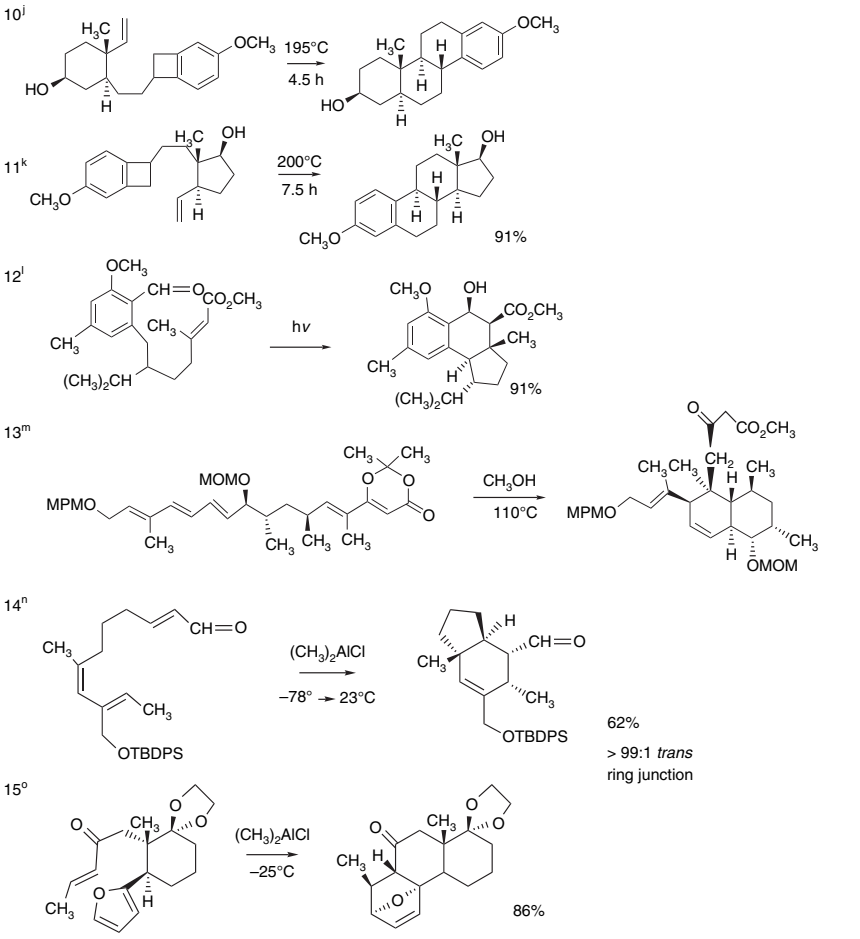
[129] A. Saito, H. Ito, and T. Taguchi, *Org. Lett.*, **4**, 4619 (2002).

Scheme 6.5. Intramolecular Diels-Alder Reactions



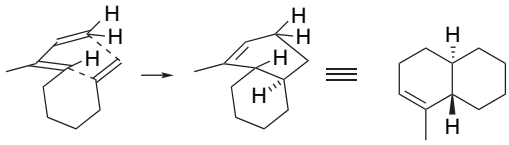
(*Continued*)

Scheme 6.5. (*continued*)



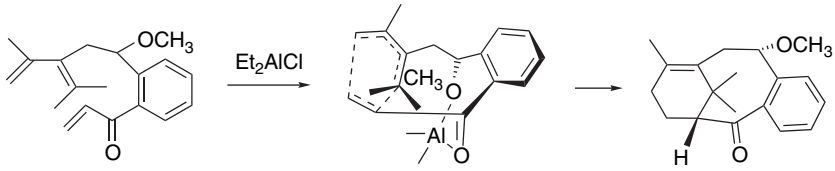
a. D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc.*, **101**, 3992 (1979).
b. S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.*, **100**, 6289 (1978).
c. W. R. Roush, *J. Am. Chem. Soc.*, **102**, 1390 (1980).
d. W. Oppolzer and E. Flaskamp, *Helv. Chim. Acta*, **60**, 204 (1977); W. Oppolzer, E. Flaskamp, and L. W. Bieber, *Helv. Chim. Acta*, **84**, 141 (2001).
e. H. Miyaoka, Y. Kajiwara, and Y. Yamada, *Tetrahedron Lett.*, **41**, 911 (2000).
f. J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984).
g. D. V. Smil, A. Laurent, N. S. Spassova, and A. G. Fallis, *Tetrahedron Lett.*, **44**, 5129 (2003).
h. K. C. Nicolaou, J. Jung, W. H. Yoon, K. C. Fong, H.-S. Choi, Y. He, Y.-L. Zhong, and P. S. Baran, *J. Am. Chem. Soc.*, **124**, 2183 (2002).
i. N. A. Yakelis and W. R. Roush, *Org. Lett.*, **3**, 957 (2001).
j. T. Kametani, K. Suzuki, and H. Nemoto, *J. Org. Chem.*, **45**, 2204 (1980); *J. Am. Chem. Soc.*, **103**, 2890 (1981).
k. P. A. Grieco, T. Takigawa, and W. J. Schillinger, *J. Org. Chem.*, **45**, 2247 (1980).
l. K. C. Nicolaou, D. Gray, and J. Tae, *Angew. Chem. Int. Ed. Engl.*, **40**, 3679 (2001); K. C. Nicolaou, D. L. F. Gray, and J. Tae, *J. Am. Chem. Soc.*, **126**, 613 (2004).
m. R. K. Boeckman, Jr., T. E. Barta, and S. G. Nelson, *Tetrahedron Lett.*, **32**, 4091 (1991).
n. N. A. Yakelis and W. R. Roush, *Org. Lett.*, **3**, 957 (2001).
o. S. Claeys, D. Van Haver, P. J. De Clerc, M. Milanesio, and D. Viterbo, *Eur. J. Org. Chem.*, 1051 (2002).

In Entry 2 a similar triene that lacks the activating carbonyl group undergoes reaction but a much higher temperature is required. In this case the ring junction is *trans*, which corresponds to an *exo* TS and may reflect the absence of secondary orbital interaction between the diene and dienophile.

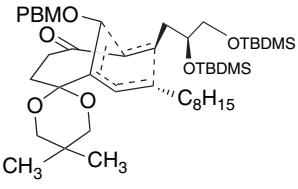


In Entry 3 the dienophilic double bond bears an EWG substituent, but a higher temperature is required than for Entry 1 because the connecting chain contains one less methylene group, which leads to a more strained TS. A mixture of stereoisomers is formed, reflecting a conflict between the Alder rule, which favors *endo* addition, and conformational factors, which favor the *exo* TS. The reaction in Entry 4 was carried out as a key step in the synthesis of the frog neurotoxin, pumiliotoxin C. The isolated double bond has no activating substituents and the reaction requires forcing conditions. Nevertheless, the yield is excellent and both products are formed with a *cis* ring juncture, but there is minimal facial selectivity. In Entry 5, the diene system is generated in situ by thermal elimination of the sulfoxide group and then reacts with the acetylenic dienophile.

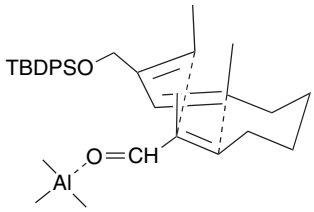
Entry 6 shows a stereoselective formation of a highly substituted *trans*-decalin system. The reaction in Entry 7 establishes a taxanelike structure. The stereochemistry is consistent with a TS in which both the carbonyl oxygen and the methoxy group are coordinated to aluminum.



The reaction in Entry 8 was used in the synthesis of members of the phomoidrides. The cyclohexene ring that is constructed creates a bicyclo[4.3.1]skeleton containing seven- and nine-membered rings.

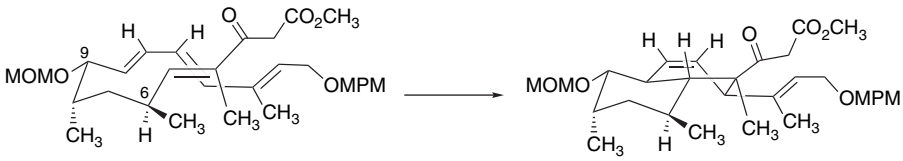


Entry 9 is a Lewis acid–catalyzed example, and the major stereoisomer is formed through a TS having an *endo* orientation of the complexed formyl group. Interestingly, the thermal version of this reaction favors the *exo* stereoisomer.

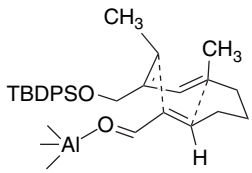


Entries 10 and 11 are examples of reactions involving thermal generation of quinodimethanes. In Entry 12 a quinodimethane is generated by photoenolization and used in conjunction with an IMDA reaction to create the carbon skeleton found in the hamigerans, which are marine natural products having antiviral activity.

In Entry 13, the dioxinone ring undergoes thermal decomposition to an acyl ketene that is trapped by the solvent methanol. The resulting β-keto-γ,δ-enoate ester then undergoes stereoselective cyclization. The stereoselectivity is controlled by the preference for pseudoequatorial conformations of the C(6) and C(9) substituents.



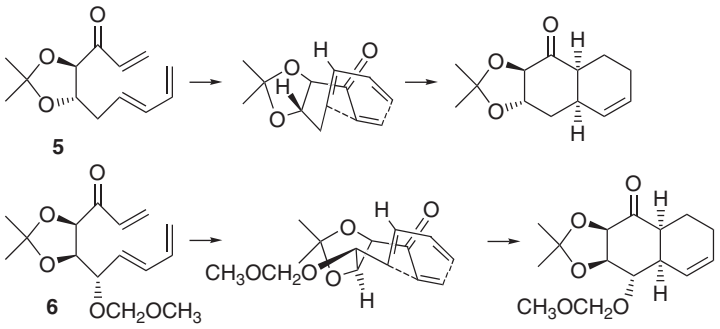
Entry 14 forms a *trans* ring juncture with greater than 99:1 selectivity. In contrast, the thermal reaction in this case shows a 2:1 preference for the *cis* ring juncture. Evidently the Lewis acid changes the structure of the TS sufficiently that the steric effects that control the thermal reaction are diminished.



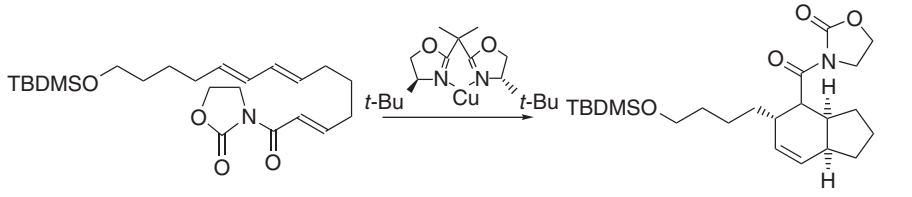
Entry 15 creates a portion of the steroid skeleton and also illustrates the use of a furan ring as a diene.

As in intermolecular reactions, enantioselectivity can be achieved in IMDA additions by use of chiral components. For example, the dioxolane ring in **5** and **6** results in TS structures that lead to enantioselective reactions.[130] The chirality in the dioxolane ring is reflected in the respective TSs, both of which have an *endo* orientation of the carbonyl group.

[130.] T. Wong, P. D. Wilson, S. Woo, and A. G. Fallis, *Tetrahedron Lett.*, **40**, 7045 (1997).



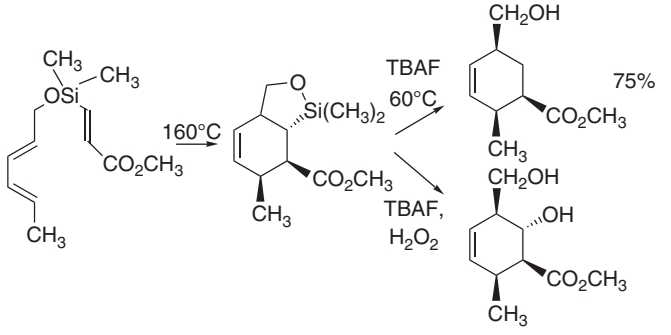
Chiral catalysts (see Section 6.1.6) can also achieve enantioselectivity in IMDA reactions.



96% e.e.

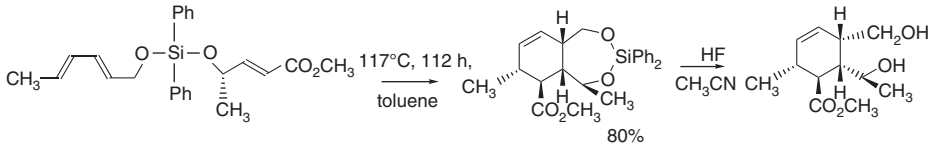
Ref. 131

The kinetic advantages of IMDA additions can be exploited by installing temporary links (tethers) between the diene and dienophile components.[132] After the addition reaction, the tether can be broken. Siloxy derivatives have been used in this way, since silicon-oxygen bonds can be readily cleaved by solvolysis or by fluoride ion.[133] The silyl group can also be used to introduce a hydroxy function by oxidation.



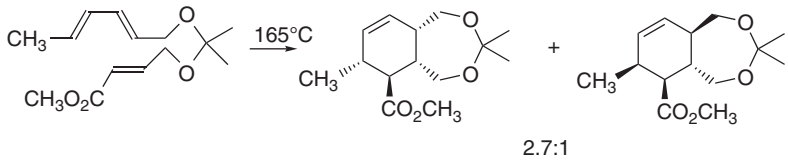
Ref. 133a

131. D. A. Evans and J. S. Johnson, *J. Org. Chem.*, **62**, 786 (1997).
132. L. Fensterbank, M. Malacria, and S. McN. Sieburth, *Synthesis*, 813 (1997); M. Bols and T. Skrydstrup, *Chem. Rev.*, **95**, 1253 (1995).
133. (a) G. Stork, T. Y. Chan, and G. A. Breault, *J. Am. Chem. Soc.*, **114**, 7578 (1992); (b) S. McN. Sieburth and L. Fensterbank, *J. Org. Chem.*, **57**, 5279 (1992); (c) J. W. Gillard, R. Fortin, E. L. Grimm, M. Maillard, M. Tjepkema, M. A. Bernstein, and R. Glaser, *Tetrahedron Lett.*, **32**, 1145 (1991); (d) D. Craig and J. C. Reader, *Tetrahedron Lett.*, **33**, 4073 (1992).



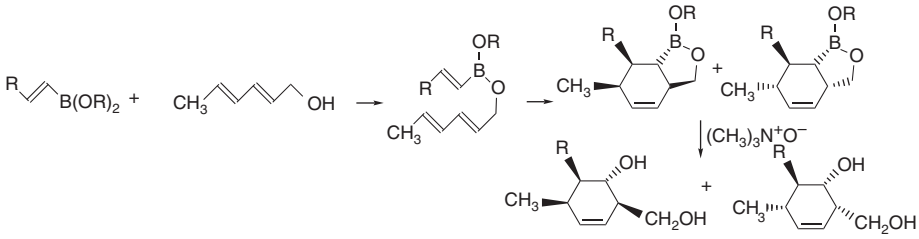
Ref. 133d

Acetals have also been used as removable tethers.



Ref. 134

The activating capacity of boronate groups can be combined with the ability for facile transesterification at boron to permit intramolecular reactions between vinylboronates and 2,4-dienols.



Ref. 135

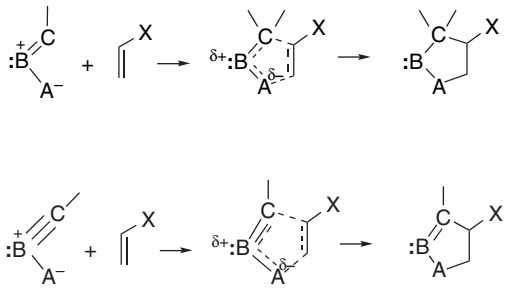
6.2. 1,3-Dipolar Cycloaddition Reactions

In Chapter 10 of Part A, the mechanistic classification of *1,3-dipolar cycloadditions* as concerted cycloadditions was developed. Dipolar cycloaddition reactions are useful both for syntheses of heterocyclic compounds and for carbon-carbon bond formation. Table 6.2 lists some of the types of molecules that are capable of dipolar cycloaddition. These molecules, which are called *1,3-dipoles*, have π electron systems that are isoelectronic with allyl or propargyl anions, consisting of two filled and one empty orbital. Each molecule has at least one charge-separated resonance structure with opposite charges in a 1,3-relationship, and it is this structural feature that leads to the name 1,3-dipolar cycloadditions for this class of reactions.[136]

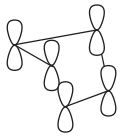
134. P. J. Ainsworth, D. Craig, A. J. P. White, and D. J. Williams, *Tetrahedron*, **52**, 8937 (1996).
135. R. A. Batey, A. N. Thadani, and A. J. Lough, *J. Am. Chem. Soc.*, **121**, 450 (1999).
136. For comprehensive reviews of 1,3-dipolar cycloaddition reactions, see R. Huisgen, R. Grashey and J. Sauer in *The Chemistry of Alkenes*, S. Patai, ed., Interscience London, 1965, pp. 806–878; G. Bianchi, C. DeMicheli, and R. Gandolfi, in *The Chemistry of Double Bonded Functional Groups*, Part I, Supplement *A*, S. Patai, ed., Wiley-Interscience, New York, 1977, pp. 369–532; A. Padwa, ed., *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, 1984.

Table 6.2. 1,3-Dipolar Compounds

$:\overset{+}{N}=\ddot{N}-\bar{C}R_2$	$:N\equiv\overset{+}{N}-\bar{C}R_2$	Diazoalkane
$:\overset{+}{N}=\ddot{N}-\bar{N}R$	$:N\equiv\overset{+}{N}-\bar{N}R$	Azide
$RC^{+}=N-\bar{C}R_2$	$RC\equiv\overset{+}{N}-\bar{C}R_2$	Nitrile ylide
$RC^{+}=N-\bar{N}R$	$RC\equiv\overset{+}{N}-\bar{N}R$	Nitrile imine
$RC^{+}=N-\bar{O}:$	$RC\equiv\overset{+}{N}-\bar{O}:$	Nitrile oxide
$R_2C^{+}-N-\bar{C}R_2$	$R_2C=\overset{+}{N}(R)-\bar{C}R_2$	Azomethine ylide
$R_2C^{+}-N(R)-\bar{O}:$	$R_2C=\overset{+}{N}(R)-\bar{O}:$	Nitrone
$R_2C^{+}-O-O:^{-}$	$R_2C=O^{+}-O:^{-}$	Carbonyl oxide



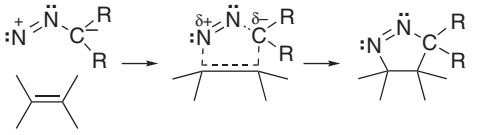
The other reactant in a dipolar cycloaddition, usually an alkene or alkyne, is referred to as the *dipolarophile*. Other multiply bonded functional groups such as imine, azo, and nitroso can also act as dipolarophiles. The 1,3-dipolar cycloadditions involve four π electrons from the 1,3-dipole and two from the dipolarophile. As in the D-A reaction, the reactants approach one another in parallel planes to permit interaction between the π and π^* orbitals.



Mechanistic studies have shown that the TSs for 1,3-dipolar cycloadditions (1,3-DCA) are not very polar, the rate of reaction is not strongly sensitive to solvent polarity, and in most cases the reaction is a concerted $[2\pi_s + 4\pi_s]$ cycloaddition.[137] The destruction of charge separation that is implied is more apparent than real because

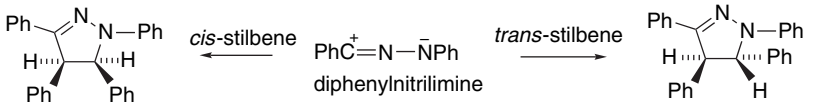
[137] P. K. Kadaba, *Tetrahedron*, **25**, 3053 (1969); R. Huisgen, G. Szeimes, and L. Mobius, *Chem. Ber.*, **100**, 2494 (1967); P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).

most 1,3-dipolar compounds are not highly polar. The polarity implied by any single structure is balanced by other contributing structures.

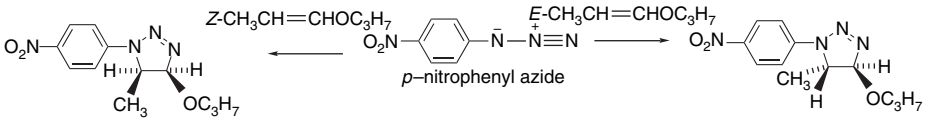


6.2.1. Regioselectivity and Stereochemistry

Two issues are essential for predicting the structure of 1,3-DCA products: (1) What is the regiochemistry? and (2) What is the stereochemistry? Many specific examples demonstrate that 1,3-dipolar cycloaddition is a stereospecific *syn* addition with respect to the dipolarophile, as expected for a concerted process.

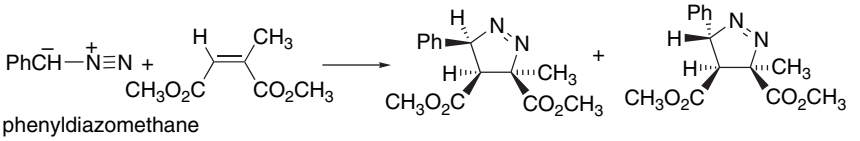


Ref. 138



Ref. 139

With some 1,3-dipoles, two possible stereoisomers can be formed by *syn* addition. These result from two differing orientations of the reacting molecules that are analogous to the *endo* and *exo* TS in D-A reactions. Phenyldiazomethane, for example, can add to unsymmetrical dipolarophiles to give two diastereomers.



Ref. 140

Each 1,3-dipole exhibits a characteristic regioselectivity toward different types of dipolarophiles. The dipolarophiles can be grouped, as were dienophiles, depending upon whether they have ERG or EWG substituents. The regioselectivity can be

138. R. Huisgen, M. Seidel, G. Wallibillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1965).
139. R. Huisgen and G. Szeimies, *Chem. Ber.*, **98**, 1153 (1965).
140. R. Huisgen and P. Eberhard, *Tetrahedron Lett.*, 4343 (1971).

interpreted in terms of frontier orbital theory. Depending on the relative orbital energies in the 1,3-dipole and dipolarophile, the strongest interaction may be between the HOMO of the dipole and the LUMO of the dipolarophile or vice versa. Usually for dipolarophiles with EWGs the dipole-HOMO/dipolarophile-LUMO interaction is dominant. The reverse is true for dipolarophiles with ERG substituents. In some circumstances the magnitudes of the two interactions may be comparable.[141] When HOMO-LUMO interactions control regioselectivity, the reaction is said to be under *electronic control*. If steric effects are dominant, the reaction is under *steric control*.

The prediction of regiochemistry requires estimation or calculation of the energies of the orbitals that are involved, which permits identification of the frontier orbitals. The energies and orbital coefficients for the most common dipoles and dipolarophiles have been summarized.[141] Figure 10.15 of Part A gives the orbital coefficients of some representative 1,3-dipoles. Regioselectivity is determined by the preference for the orientation that results in bond formation between the atoms having the largest coefficients in the two frontier orbitals. This analysis is illustrated in Figure 6.12.

Apart from the role of substituents in determining regioselectivity, several other structural features affect the reactivity of dipolarophiles. Strain increases reactivity; norbornene, for example, is consistently more reactive than cyclohexene in 1,3-DCA reactions. Conjugated functional groups usually increase reactivity. This increased reactivity has most often been demonstrated with electron-attracting substituents, but for some 1,3-dipoles, enol ethers, enamines, and other alkenes with donor substituents are also quite reactive. Some reactivity data for a series of alkenes with several 1,3-dipoles are given in Table 10.6 of Part A. Additional discussion of these reactivity trends can be found in Section 10.3.1 of Part A.

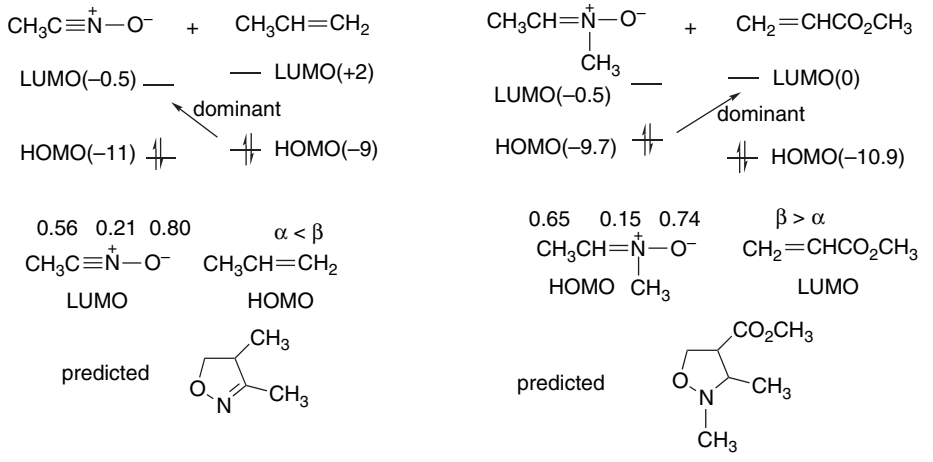
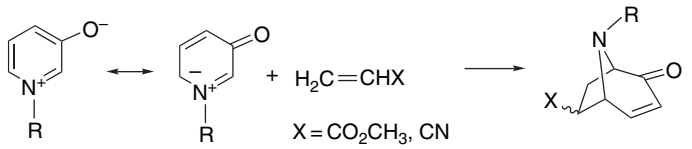


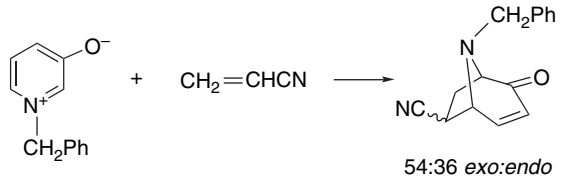
Fig. 6.12. Prediction of regioselectivity of 1,3-dipolar cycloaddition on the basis of FMO theory. The energies of the HOMO and LUMO of the reactants (in eV) are indicated in parentheses.

[141] K. N. Houk, J. Sims, B. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New York, 1977; K. N. Houk, in *Pericyclic Reactions*, Vol. II, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, pp. 181–271.

1,3-Dipoles can be embedded in heterocyclic structures, just as diene units are present in pyrones and other ring structures (see p. 491). N-Substituted pyridinium-3-ols can be deprotonated to give 3-oxidopyridinium betaines that have 1,3-dipolar character.[142]

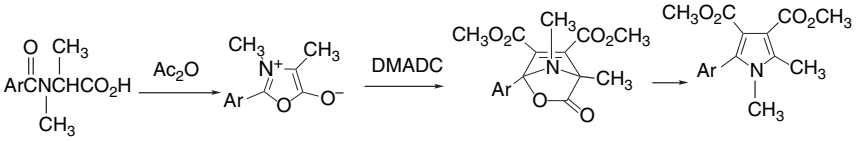


A reaction of this type was used to prepare an intermediate in the synthesis of a natural compound with antiglaucoma activity.[143]

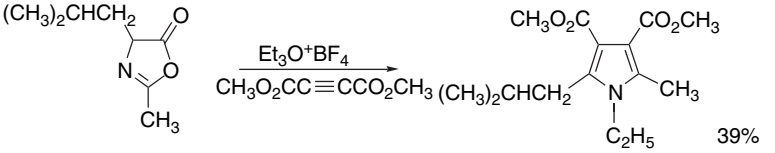


54:36 *exo:endo*

Oxazolium oxides, which can be generated by cyclization of α-amido acids, give pyrroles on reaction with acetylenic dipolarophiles.[144] These reactions proceed by formation of oxazolium oxide intermediates. The bicyclic adduct can then undergo a concerted (retro 4 + 2) decarboxylation.

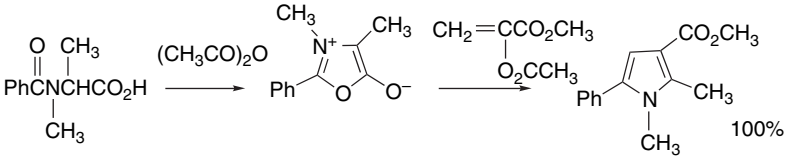


Oxazolium oxides can also be made by *N*-alkylation of oxazolinones.[145]



39%

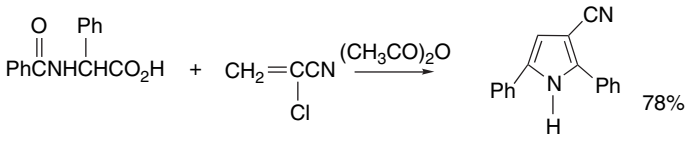
Pyrroles are also formed from dipolarophiles such as α-acetoxy esters and α-chloroacrylonitrile that have potential leaving groups.



100%

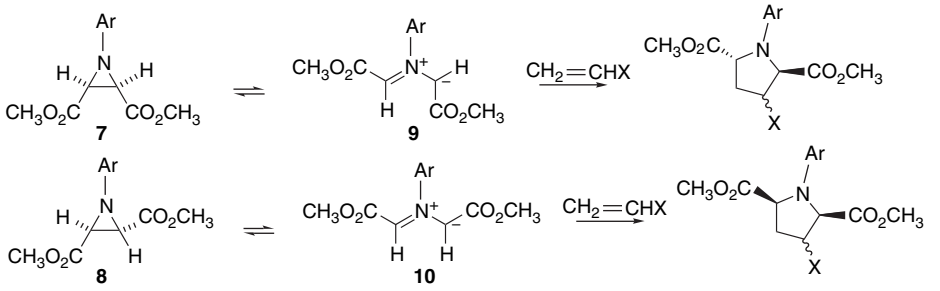
Ref. 146

142. N. Dennis, A. R. Katritzky, and Y. Takeuchi, *Angew. Chem. Int. Ed. Engl.*, **15**, 1 (1976).
143. M. E. Jung, Z. Longmei, P. Tangsheng, Z. Huiyan, L. Yan, and S. Jingyu, *J. Org. Chem.*, **57**, 3528 (1992).
144. H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).
145. F. M. Hershenson and M. R. Pavia, *Synthesis*, 999 (1988).
146. G. Grassi, F. Foti, F. Risitano, and D. Zona, *Tetrahedron Lett.*, **46**, 1061 (2005).



Ref. 147

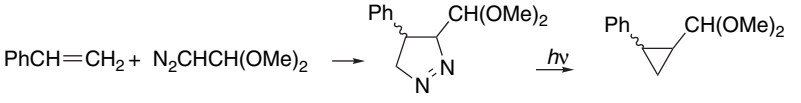
Another interesting variation of the 1,3-dipolar cycloaddition involves generation of 1,3-dipoles from three-membered rings. As an example, aziridines **7** and **8** give adducts derived from apparent formation of 1,3-dipoles **9** and **10**, respectively.[148]



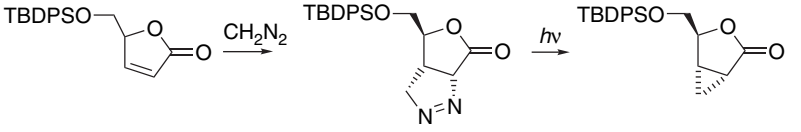
The evidence for the involvement of 1,3-dipoles as discrete intermediates includes the observation that the reaction rates are independent of dipolarophile concentration. This fact indicates that the ring opening is the rate-determining step in the reaction. Ring opening is most facile for aziridines that have an electron-attracting substituent to stabilize the carbanion center in the dipole.

6.2.2. Synthetic Applications of Dipolar Cycloadditions

1,3-DCA reactions are an important means of synthesis of a wide variety of heterocyclic molecules, some of which are useful intermediates in multistage syntheses. Pyrazolines, which are formed from alkenes and diazo compounds, for example, can be pyrolyzed or photolyzed to give cyclopropanes.



Ref. 149

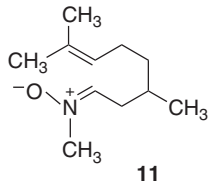


Ref. 150

147. I. A. Benages and S. M. Albonico, *J. Org. Chem.*, **43**, 4273 (1978).
148. R. Huisgen and H. Mader, *J. Am. Chem. Soc.*, **93**, 1777 (1971).
149. P. Carrie, *Heterocycles*, **14**, 1529 (1980).
150. M. Martin-Villa, N. Hanafi, J. M. Jiminez, A. Alvarez-Larena, J. F. Piniella, V. Branchadell, A. Oliva, and R. M. Ortuno, *J. Org. Chem.*, **63**, 3581 (1998).

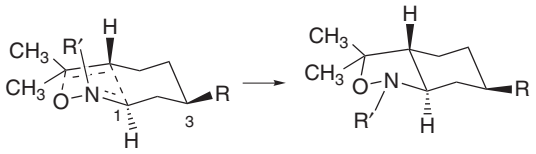
Scheme 6.6 gives some examples of 1,3-DCA reactions. Entry 1 is an addition of an aryl azide to norbornene. The EWG nitro group is rate enhancing and the reaction occurs with a rate constant of $6.3 \times 10^{-3}\, M^{-1}\, s^{-1}$ at 25° C. Owing to steric approach control, the product is the *exo* stereoisomer. Entry 2 involves an acetylenic dipolarophile and gives an aromatic triazole as the product. Entry 3 is an addition of diazomethane to the dioxolane derivative of acrolein. The reaction is carried out in a closed vessel at room temperature. Entry 4 involves a nitrone as the 1,3-dipole. Nitrone cycloadditions are particularly useful in synthesis because a new carbon-carbon bond is formed and the adducts can be reduced to β-amino alcohols. Nitrile oxides, which are formed by dehydration of nitroalkanes or by oxidation of oximes with hypochlorite,[151] are also useful 1,3-dipoles. They are highly reactive, must be generated in situ,[152] and react with both alkenes and alkynes. The product in Entry 5 is an example in an isoxazole that was eventually converted to a prostaglandin derivative.

Intramolecular 1,3-dipolar cycloadditions have proven to be especially useful in synthesis.[153] The products of nitrone-alkene cycloadditions are isoxazolines and the oxygen-nitrogen bond can be cleaved by reduction, leaving both an amino and hydroxy function in place. A number of imaginative syntheses have employed this strategy. Entry 6 shows the formation of a new six-membered carbocyclic ring. The nitrone **11** is generated by condensation of the aldehyde group with *N*-methylhydroxylamine and then goes on to product by intramolecular cycloaddition.



11

These reactions are highly stereoselective, provided a substituent is present at C(3). The stereochemistry is consistent with a chairlike TS having the 3-subsituent in an equatorial position.



[151] G. A. Lee, *Synthesis*, 508 (1982).

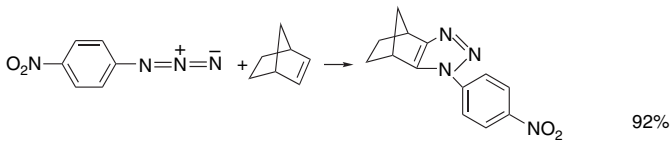
[152] K. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH Publishers, New York, 1988.

[153] For reviews of nitrone cycloadditions, see D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975); J. J. Tufariello, *Acc. Chem. Res.*, **12**, 396 (1979); P. N. Confalone and E. M. Huie, *Org. React.*, **36**, 1 (1988); K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, **98**, 863 (1998).

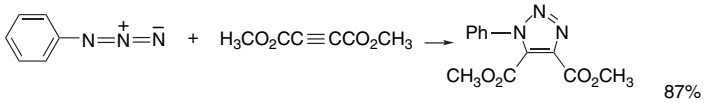
Scheme 6.6. Typical 1,3-Dipolar Cycloaddition Reactions

A. Intermolecular cycloaddition

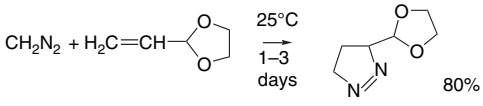
1[a]



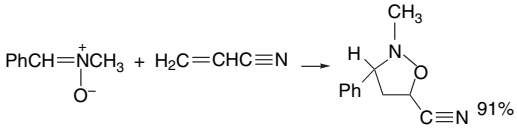
2[b]



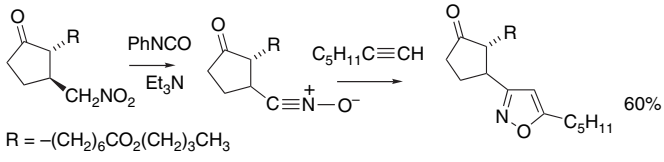
3[c]



4[d]

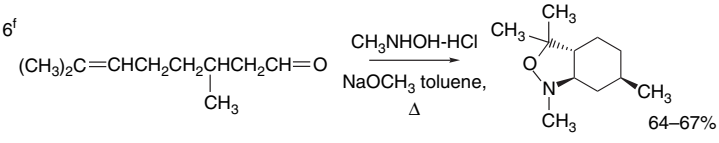


5[e]

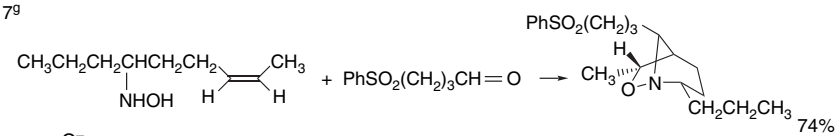


B. Intramolecular cycloaddition

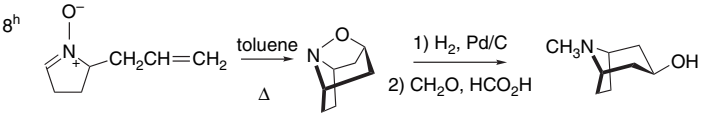
6[f]



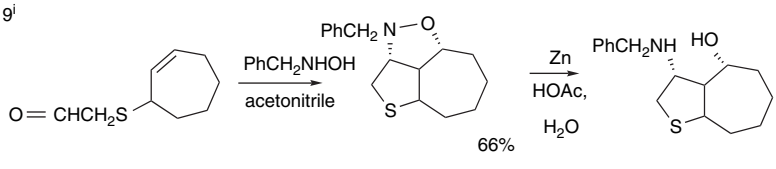
7[g]



8[h]

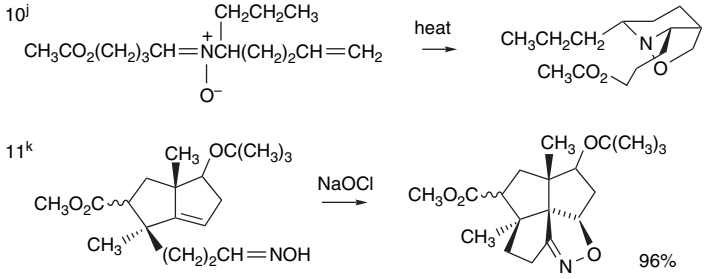


9[i]



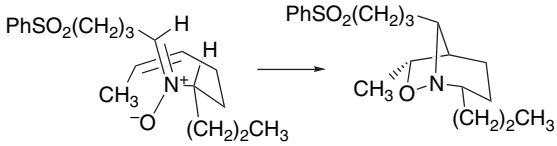
(*Continued*)

Scheme 6.6. (*Continued*)

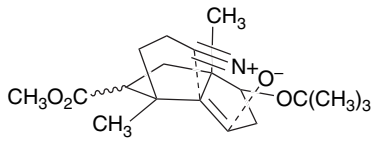


a. P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).
b. R. Huisgen, R. Knorr, L. Mobius, and G. Szeimies, *Chem. Ber.*, **98**, 4014 (1965).
c. J. M. Stewart, C. Carlisle, K. Kem, and G. Lee, *J. Org. Chem.*, **35**, 2040 (1970).
d. R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).
e. A. Barco, S. Benetti, G. P. Pollini, P. G. Baraldi, M. Guarneri, D. Simoni, and C. Gandolfi, *J. Org. Chem.*, **46**, 4518 (1981).
f. N. A. LeBel and D. Hwang, *Org. Synth.*, **58**, 106 (1978); N. A. LeBel, M. E. Post, and J. J. Whang, *J. Am. Chem. Soc.*, **86**, 3759 (1964).
g. N. A. LeBel and N. Balasubramanian, *J. Am. Chem. Soc.*, **111**, 3363 (1989).
h. J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, and S. A. Ali, *J. Am. Chem. Soc.*, **101**, 2435 (1979).
i. P. N. Confalone, G. Pizzolato, D. I. Confalone, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **102**, 1954 (1980).
j. A. L. Smith, S. F. Williams, A. B. Holmes, L. R. Hughes, Z. Lidert, and C. Swithenbank, *J. Am. Chem. Soc.*, **110**, 8696 (1988).
k. M. Ihara, Y. Tokunaga, N. Taniguchi, K. Fukumoto, and C. Kabuto, *J. Org. Chem.*, **56**, 5281 (1991).

Entry 7 is another intramolecular nitrone cycloaddition, but in this case the hydroxylamine function is present in the alkene.

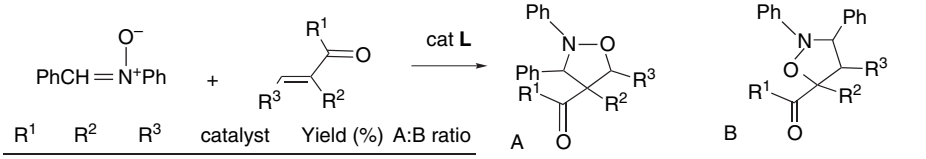


The product of the reaction in Entry 8 was used in the synthesis of the alkaloid pseudotropine. The proper stereochemical orientation of the hydroxy group is determined by the structure of the oxazoline ring formed in the cycloaddition. Entry 9 portrays the early stages of synthesis of the biologically important molecule biotin. The reaction in Entry 10 was used to establish the carbocyclic skeleton and stereochemistry of a group of toxic indolizidine alkaloids found in dart poisons from frogs. Entry 11 involves generation of a nitrile oxide. Three other stereoisomers are possible. The observed isomer corresponds to approach from the less hindered convex face of the molecule.



6.2.3. Catalysis of 1,3-Dipolar Cycloaddition Reactions

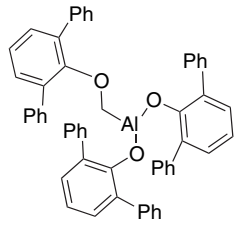
The role of Lewis acid catalysts in 1,3-DCA reactions is similar to that in D-A reactions. The catalysis results from a lowering of the LUMO energy of the dipolarophile, which is analogous to the Lewis acid catalysis of D-A reactions. The more organized TS, incorporating the metal ion and associated ligands, then enforces a preferred orientation of the reagents. In contrast to the D-A reaction involving hydrocarbon dienes, 1,3-DCA reactions may encounter competing complexation at the 1,3-dipole. Lewis acid interaction with the 1,3-dipole is likely to be detrimental if the dipole is the more nucleophilic component of the reaction. For example, with nitrones and enones, formation of a Lewis acid adduct with the nitrone in competition with the enone is detrimental. One approach to the need for selectivity is to use highly substituted catalysts that are selective for the less-substituted reactant. Bulky aryloxyaluminum compounds are excellent catalysts for nitrone cycloaddition and also enhance regioselectivity. The reaction of diphenylnitrone with enones is usually subject to steric regiochemical control. With the catalyst **L** high *electronic regiochemical control* is achieved and reactivity is greatly enhanced. The catalyst does not, however, strongly affect the *exo*:*endo* selectivity, which is 23:77 for propenal.



R^1	R^2	R^3	catalyst	Yield (%)	A:B ratio
H	H	H	no	5	20:80
			yes	100	>99:1
CH_3	H	H	no	7	8:92
			yes	82	100:0
H	CH_3	H	no	5	0:100
			yes	100	91:9
H	H	CH_3	no	2	100:0
			yes	100	100:0

electronically-controlled product

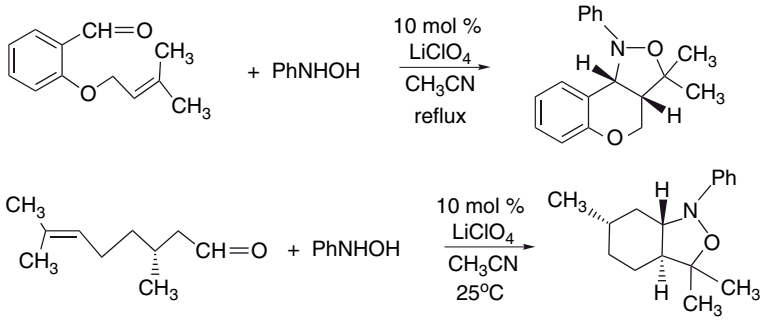
sterically-controlled product



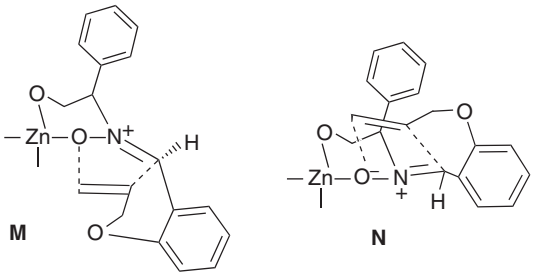
catalyst **L**

Lithium perchlorate and lithium triflate in acetonitrile catalyze intramolecular cycloaddition reactions of nitrones of allyloxybenzaldehydes and unsaturated aldehydes.[154]

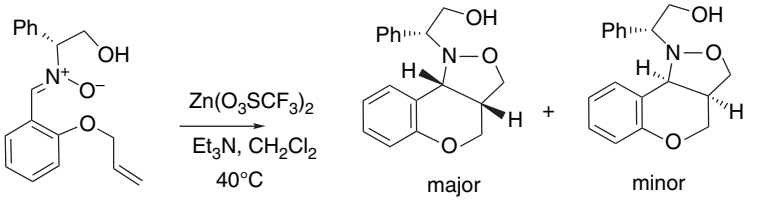
154. J. S. Yadav, B. V. S. Reddy, D. Narsimhaswamy, K. Narsimulu, and A. C. Kumar, *Tetrahedron Lett.*, **44**, 3697 (2003).



A series of similar reactions was examined in the course of synthesis of substituted chromanes.[155] The reactions are thought to proceed through TS **M** in preference to **N** because of steric interactions with the phenyl ring on the chiral hydroxylamine.



The best Lewis acid found was $Zn(OTf)_2$, which improved stereoselectivity from 6:1 to 22:1.



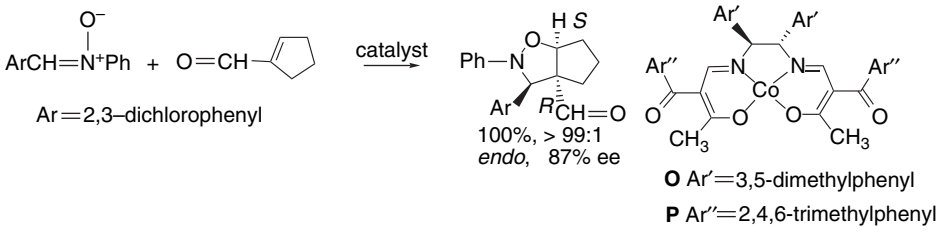
Interestingly, the reactions were modestly *slower* in the presence of the Lewis acid. It is suggested that the catalyst inverts the HOMO-LUMO relationships, making the complexed nitrone the electrophilic reactant. In agreement with this interpretation, the reaction is favored by EWGs on the aromatic ring.

As with D-A reactions, it is possible to achieve enantioselective cycloaddition in the presence of chiral catalysts.[156] Many of the catalysts are similar to those used in enantioselective D-A reactions. The catalysis usually results from a lowering of the LUMO energy of the dipolarophile, which is analogous to the Lewis acid catalysis of D-A reactions. The more organized TS, incorporating a metal ion and associated

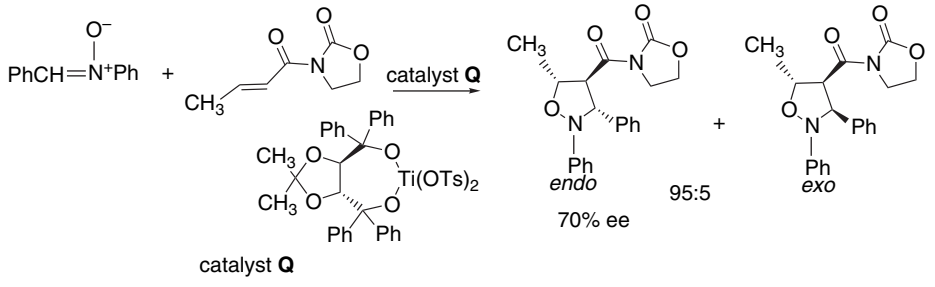
155. Q. Zhao, F. Han, and D. L. Romero, *J. Org. Chem.*, **67**, 3317 (2002).

156. K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, **98**, 863 (1998); M. Frederickson, *Tetrahedron*, **53**, 503 (1997).

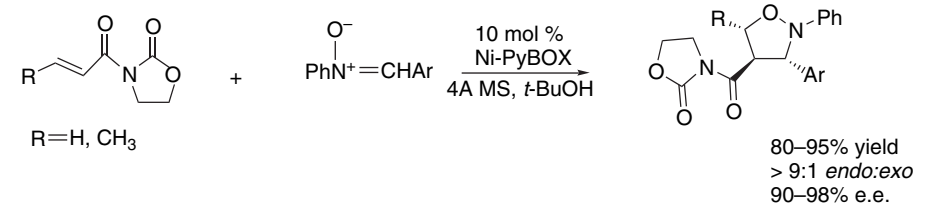
ligands, then enforces a preferred orientation of the reagents. For example, the bulky aryl groups in the catalysts **O** and **P** favor one direction of approach of the nitrone reactant.[157]



The Ti(IV) TADDOL catalyst **Q** leads to moderate enantioselectivity in nitrone-alkene cycloaddition.[158]



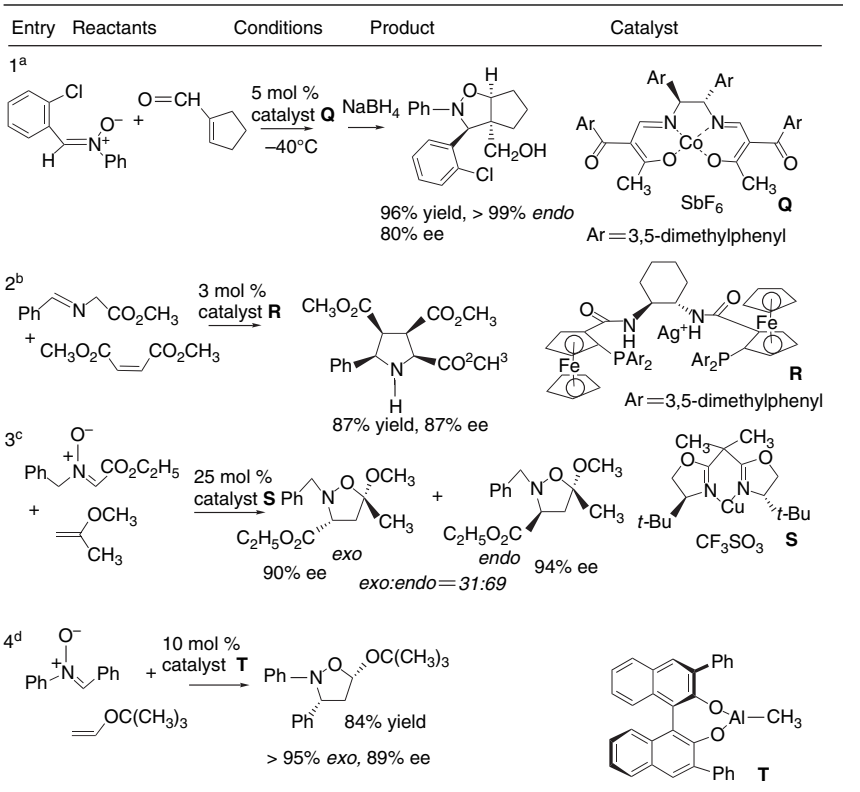
Favorable results have also been achieved using PyBOX type catalysts. Acryloyl and crotonoyloxazolidinones gave 80–95% yields, 90–98% e.e., and more than 9:1 *endo*-diastereoselectivity in reactions with *N*-phenylbenzylidene nitrones.[159]



Other effective enantioselective catalysts include $Yb(OTf)_3$ with BINOL,[160] Mg^{2+}-*bis*-oxazolines,[161] and oxazaborolidinones.[162]

157. T. Mita, N. Ohtsuki, T. Ikeno, and T. Yamada, *Org. Lett.*, **4**, 2457 (2002).
158. K. V. Gothelf and K. A. Jorgensen, *Acta Chem. Scand.*, **50**, 652 (1996); K. B. Jensen, K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **62**, 2471 (1997); K. B. Jensen, K. V. Gothelf, and K. A. Jorgensen, *Helv. Chim. Acta*, **80**, 2039 (1997).
159. S. Iwasa, H. Maeda, K. Nishiyama, S. Tsushima, Y. Tsukamoto, and H. Nishiyama, *Tetrahedron*, **58**, 8281 (2002).
160. M. Kawamura and S. Kobayashi, *Tetrahedron Lett.*, **40**, 3213 (1999).
161. G. Desimoni, G. Faita, A. Mortoni, and P. Righetti, *Tetrahedron Lett.*, **40**, 2001 (1999); K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **63**, 5483 (1998).
162. J. P. G. Seerden, M. M. M. Boeren, and H. W. Scheeren, *Tetrahedron*, **53**, 11843 (1997).

Scheme 6.7. Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reactions



a. T.Mitra, N. Ohtsuki, T.Ikeno, and T. Yamada. *Org. Lett.*, **4**, 2457 (2002).
b. J. M. Longmire, B. Wang, and X. M. Zhang, *J. Am. Chem. Soc.*, **124**, 13400 (2002).
c. K. B. Jensen, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **64**, 2353 (1999).
d. K. B. Simonsen, B. Bayon, R. G. Hazell, D. V. Gothelf, and K. A. Jorgensen, *J. Am. Chem. Soc.*, **121**, 3845 (1999).

Scheme 6.7 shows some other examples of enantioselective catalysts. Entry 1 illustrates the use of a Co(III) complex, with the chirality derived from the diamine ligand. Entry 2 is a silver-catalyzed cycloaddition involving generation of an azomethine ylide. The ferrocenylphosphine groups provide a chiral environment by coordination of the catalytic Ag^+ ion. Entries 3 and 4 show typical Lewis acid catalysts in reactions in which nitrones are the electrophilic component.

6.3. [2 + 2] Cycloadditions and Related Reactions Leading to Cyclobutanes

As discussed in Section 10.4 of Part A, concerted suprafacial $[2\pi + 2\pi]$ cycloadditions are forbidden by orbital symmetry rules. Two types of $[2 + 2]$ cycloadditions are of synthetic value: addition reactions of ketenes and photochemical additions. The latter group includes reactions of alkenes, dienes, enones, and carbonyl compounds, and these additions are discussed in the sections that follow.

[2+2] Cycloadditions of ketenes and alkenes have synthetic utility for the preparation of cyclobutanones.[163] The stereoselectivity of ketene-alkene cycloaddition can be analyzed in terms of the Woodward-Hoffmann rules.[164] To be an allowed process, the $[2\pi + 2\pi]$ cycloaddition must be suprafacial in one component and antarafacial in the other. An alternative description of the TS is a $2\pi_s + (2\pi_s + 2\pi_s)$ addition.[165] Figure 6.13 illustrates these combinations. Note that both representations predict formation of the *cis*-substituted cyclobutanone.

Ketenes are especially reactive in [2+2] cycloadditions and an important reason is that they offer a low degree of steric interaction in the TS. Another reason is the electrophilic character of the ketene LUMO. As discussed in Section 10.4 of Part A, there is a large net charge transfer from the alkene to the ketene, with bond formation at the ketene *sp* carbon running ahead of that at the sp^2 carbon. The stereoselectivity of ketene cycloadditions is the result of steric effects in the TS. Minimization of interaction between the substituents R and R′ leads to a cyclobutanone in which these substituents are *cis*, which is the stereochemistry usually observed in these reactions.

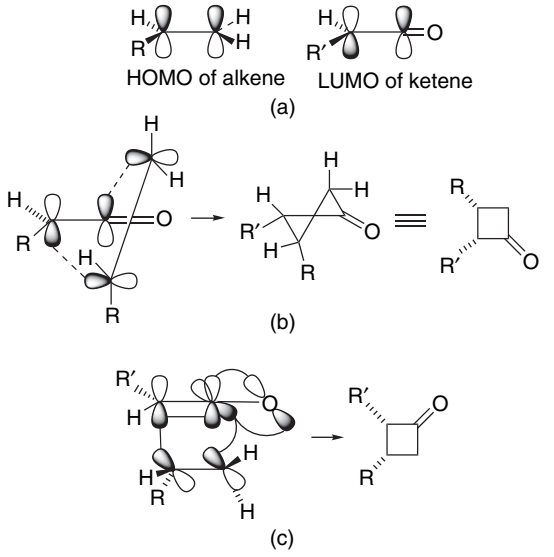
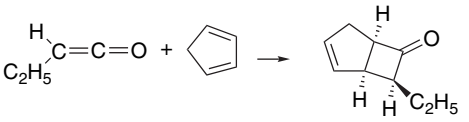


Fig. 6.13. HOMO-LUMO interactions in the [2+2] cycloadditions of an alkene and a ketene: (a) frontier orbitals of the alkene and ketene; (b) $[2\pi_s + 2\pi_a]$ representation of suprafacial addition to the alkene and antarafacial addition to the ketene; (c) $[2\pi_s + (2\pi_s + 2\pi_s)]$ alignment of orbitals.

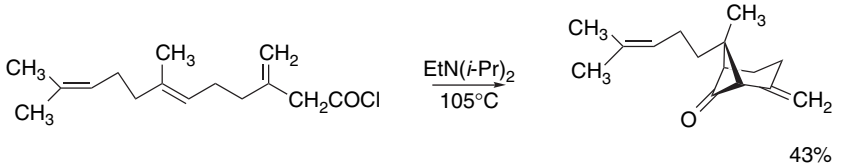
163. For reviews, see W. T. Brady, in *The Chemistry of Ketenes, Allenes, and Related Compounds*, S. Patai, ed., Wiley-Interscience, New York, 1980, Chap. 8; W. T. Brady, *Tetrahedron*, **37**, 2949 (1981); J. Hyatt and R. W. Reynolds, *Org. React.*, **45**, 159 (1994); T. T. Tidwell, *Ketenes*, Wiley, New York, 1995.
164. R. B. Woodward and R. Hoffman, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).
165. D. J. Pasto, *J. Am. Chem. Soc.*, **101** 37 (1979); E. Valenti, M. A. Pericas, and A. Moyano, *J. Org. Chem.*, **55**, 3582 (1990).



Ref. 166

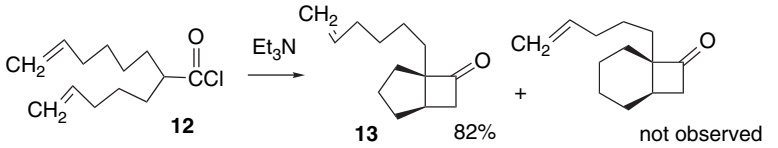
The best yields are obtained when the ketene has an electronegative substituent, such as halogen. Simple ketenes are not very stable and must usually be generated in situ. The most common method for generating ketenes for synthesis is by dehydrohalogenation of acyl chlorides. This is usually done with an amine such as triethylamine.[167] Other activated carboxylic acid derivatives, such as acyloxypyridinium ions, have also been used as ketene precursors.[168] Ketene itself and certain alkyl derivatives can be generated by pyrolysis of carboxylic anhydrides.[169]

Intramolecular ketene cycloadditions are possible if the ketene and alkene functionalities can achieve an appropriate orientation.[170]

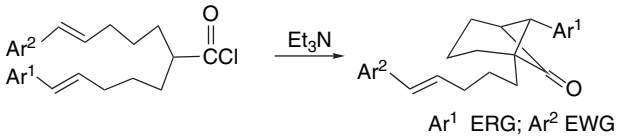


Ref. 171

Some trends in relative reactivity for intramolecular ketene cycloadditions have been examined by internal competitions.[172] For example, **12** gives exclusively **13**, pointing to a preference for five-membered rings over six-membered ones.

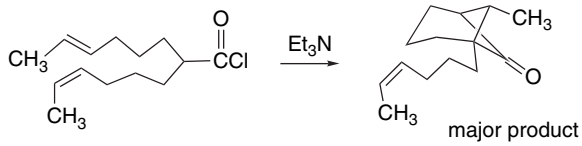


When two different aryl substituents are compared, the double bond with an ERG substituent is more reactive, as would be expected if the alkene acts primarily as an electron donor.

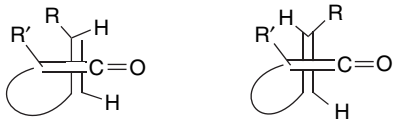


166. M. Rey, S. M. Roberts, A. S. Dreiding, A. Roussel, H. Vanlierde, S. Toppert, and L. Ghosez, *Helv. Chim. Acta*, **65**, 703 (1982).
167. K. Shishido, T. Azuma, and M. Shibuya, *Tetrahedron Lett.*, **31**, 219 (1990).
168. R. L. Funk, P. M. Novak, and M. M. Abelman, *Tetrahedron Lett.*, **29**, 1493 (1988).
169. G. J. Fisher, A. F. MacLean, and A. W. Schnizer, *J. Org. Chem.*, **18**, 1055 (1953).
170. B. B. Snider, *Chem. Rev.*, **88**, 793 (1988).
171. E. J. Corey and M. C. Desai, *Tetrahedron Lett.*, **26**, 3535 (1985).
172. G. Belanger, F. Levesque, J. Paquet, and G. Barbe, *J. Org. Chem.*, **70**, 291 (2005).

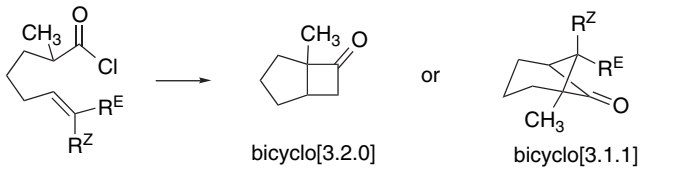
Comparison of *E*- and *Z*-double bonds indicates that the former are about 30 times more reactive.[173]



This relative reactivity results from larger steric interactions in the TS for the *Z*-double bond.

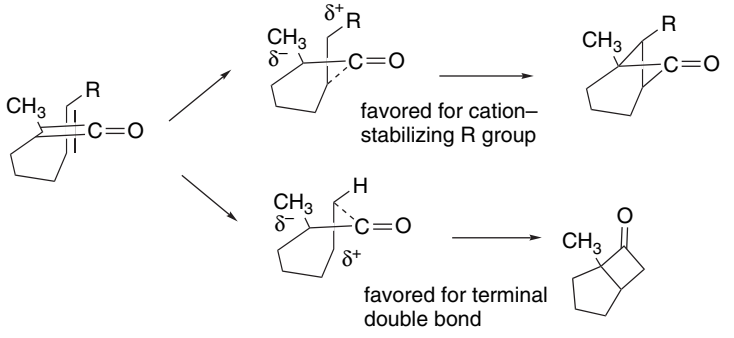


The competition between formation of bicyclo[3.2.0] and bicyclo[3.1.1] products is determined by substitution on the alkene.



R^E	R^Z		
H	H	45% (only product)	23% (only product)
CH_3	H		
CH_3	CH_3		45% (only product)

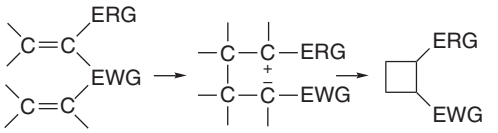
Initial bond formation occurs between the ketene carbonyl and the more nucleophilic end of the alkene double bond. This is related to the charge separation in the TS and results in the second bond being formed between the terminal ketene carbon and the carbon that is best able to support positive character.[174]



173. B. B. Snider, A. J. Allentoff, and M. B. Walner, *Tetrahedron*, **46**, 8031 (1990).
174. B. B. Snider, R. A. H. F. Hui, and Y. S. Kulkarni, *J. Am. Chem. Soc.*, **107**, 2194 (1985).

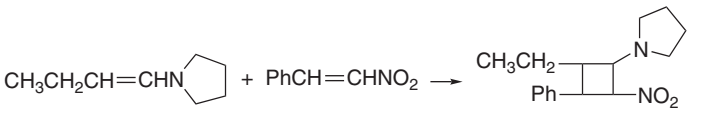
Scheme 6.8 gives some examples of ketene-alkene cycloadditions. In Entry 1, dimethylketene was generated by pyrolysis of the dimer, 2,2,4,4-tetramethylcyclobutane-1,3-dione and passed into a solution of the alkene maintained at 70° C. Entries 2 and 3 involve generation of chloromethylketene by dehydrohalogenation of α-chloropropanoyl chloride. Entry 4 involves formation of dichloroketene. Entry 5 is an intramolecular addition, with the ketene being generated from a 2-pyridyl ester. Entries 6, 7, and 8 are other examples of intramolecular ketene additions.

Cyclobutanes can also be formed by nonconcerted processes involving zwitterionic intermediates. The combination of an electron-rich alkene (enamine, enol ether) and an electrophilic one (nitro- or polycyanoalkene) is required for such processes.



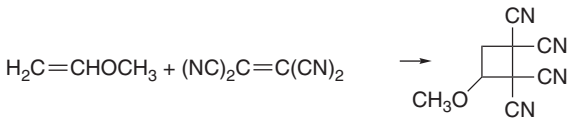
ERG = electron releasing group (–OR, $–NR_2$)
EWG = electron withdrawing group ($–NO_2$, –C≡N)

Two examples of this reaction type are shown below.



100%

Ref. 175

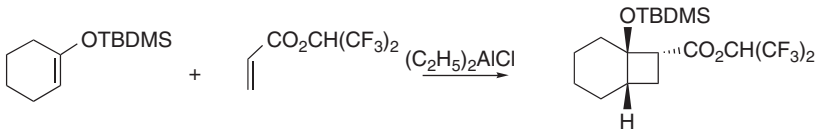


90%

Ref. 176

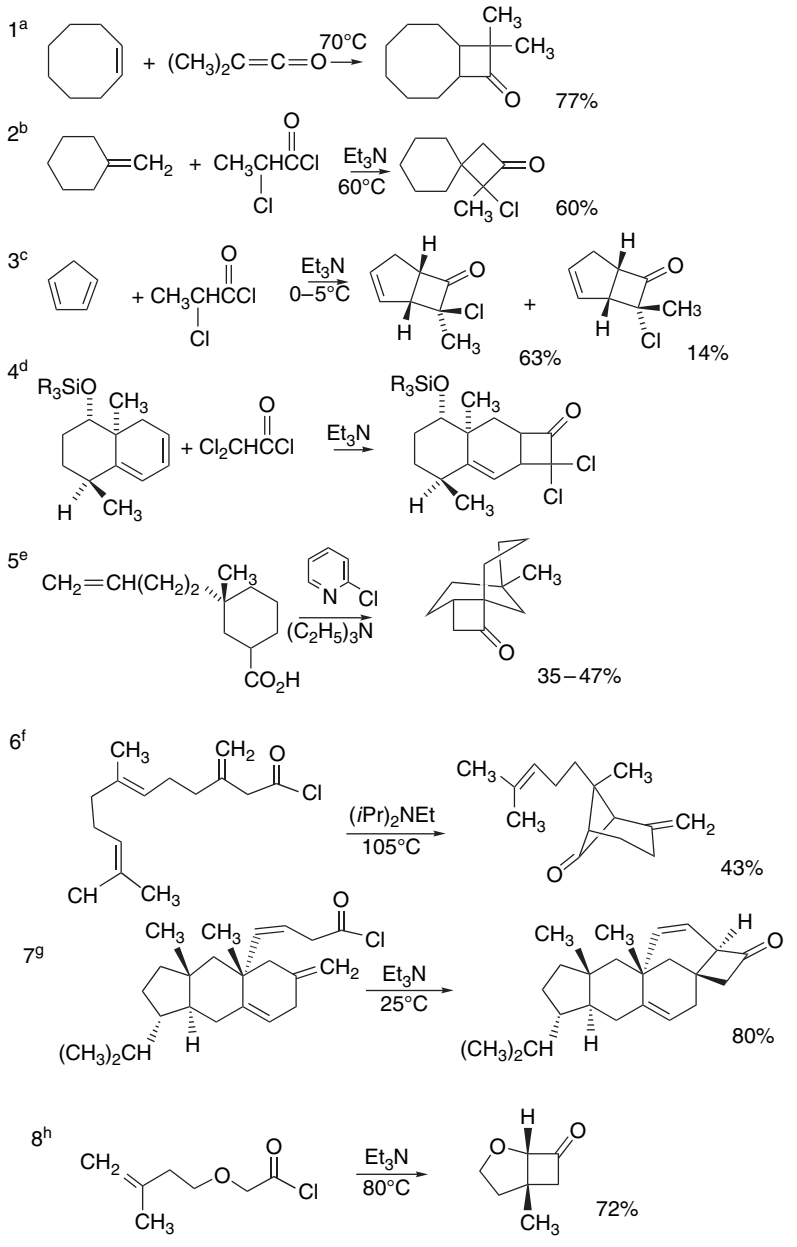
The stereochemistry of these reactions depends on the lifetime of the dipolar intermediate, which, in turn, is influenced by the polarity of the solvent. In the reactions of enol ethers with tetracyanoethylene, the stereochemistry of the enol ether is retained in nonpolar solvents. In polar solvents, cycloaddition is nonstereospecific, as a result of a longer lifetime for the zwitterionic intermediate.[177]

Lewis acid catalysis has been used to promote stepwise [2 + 2] cycloaddition of silyl enol ethers and unsaturated esters.[178] The best catalyst is $(C_2H_5)_2AlCl$ and polyfluoroalkyl esters give the highest stereoselectivity. The reactions give the more stable *trans* products.



175. M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).
176. J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962).
177. R. Huisgen, *Acc. Chem. Res.*, **10**, 117, 199 (1977).
178. K. Takasu, M. Ueno, K. Inanaga, and M. Ihara, *J. Org. Chem.*, **69**, 517 (2004).

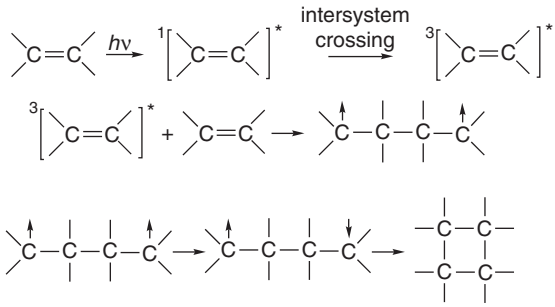
Scheme 6.8. [2 + 2] Cycloadditions of Ketenes



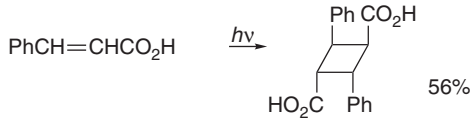
a. A. P. Krapcho and J. H. Lesser, *J. Org. Chem.*, **31**, 2030 (1966).
b. W. T. Brady and A. D. Patel, *J. Org. Chem.*, **38**, 4106 (1973).
c. W. T. Brady and R. Roe, *J. Am. Chem. Soc.*, **93**, 1662 (1971).
d. P. A. Grieco, T. Oguri, and S. Gilman, *J. Am. Chem. Soc.*, **102**, 5886 (1980).
e. R. L. Funk, P. M. Novak, and M. M. Abraham, *Tetrahedron Lett.*, **29**, 1493 (1988).
f. E. J. Corey and M. C. Desai, *Tetrahedron Lett.*, **26**, 3535 (1985).
g. E. J. Corey, M. C. Desai, and T. A. Engler, *J. Am. Chem. Soc.*, **107**, 4339 (1985).
h. B. B. Snider, R. A. H. F. Hui, and Y. S. Kulkarni, *J. Am. Chem. Soc.*, **107**, 2194 (1985).

6.3.2. Photochemical Cycloaddition Reactions

6.3.2.1. Photocycloaddition of Alkenes and Dienes. Photochemical cycloadditions provide a method that is often complementary to thermal cycloadditions with regard to the types of compounds that can be prepared. The theoretical basis for this complementary relationship between thermal and photochemical modes of reaction lies in orbital symmetry relationships, as discussed in Chapter 10 of Part A. The reaction types permitted by photochemical excitation that are particularly useful for synthesis are [2+2] additions between two carbon-carbon double bonds and [2+2] additions of alkenes and carbonyl groups to form oxetanes. Photochemical cycloadditions are often not concerted processes because in many cases the reactive excited state is a triplet. The initial adduct is a triplet 1,4-diradical that must undergo spin inversion before product formation is complete. Stereospecificity is lost if the intermediate 1,4-diradical undergoes bond rotation faster than ring closure.

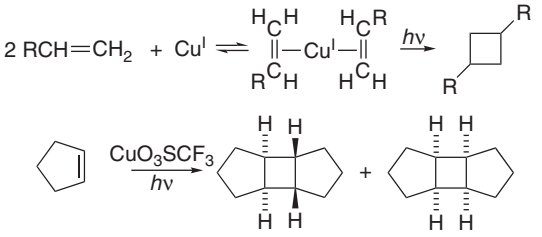


Intermolecular photocycloadditions of alkenes can be carried out by photosensitization with mercury or directly with short-wavelength light.[179] Relatively little preparative use has been made of this reaction for simple alkenes. Dienes can be photosensitized using benzophenone, butane-2,3-dione, and acetophenone.[180] The photodimerization of derivatives of cinnamic acid was among the earliest photochemical reactions to be studied.[181] Good yields of dimers are obtained when irradiation is carried out in the crystalline state. In solution, *cis-trans* isomerization is the dominant reaction.

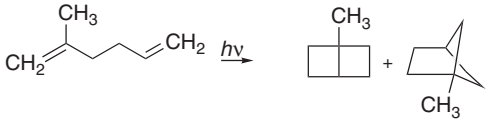


The presence of Cu(I) salts promotes intermolecular photocycloaddition of simple alkenes. Copper(I) triflate is especially effective.[182] It is believed that the photoreactive species is a 2:1 alkene:Cu(I) complex in which the two alkene molecules are brought together prior to photoexcitation.[183]

179. H. Yamazaki and R. J. Cvetanovic, *J. Am. Chem. Soc.*, **91**, 520 (1969).
180. G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.*, **28**, 3297 (1963).
181. A. Mustafa, *Chem. Rev.*, **51**, 1 (1962).
182. R. G. Salomon, *Tetrahedron*, **39**, 485 (1983); R. G. Salomon and S. Ghosh, *Org. Synth.*, **62**, 125 (1984).
183. R. G. Salomon, K. Folking, W. E. Streib, and J. K. Kochi, *J. Am. Chem. Soc.*, **96**, 1145 (1974).

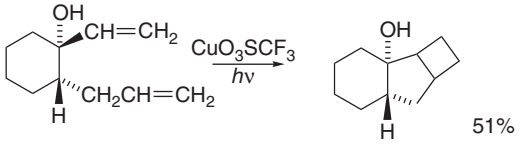


Intramolecular [2 + 2] photocycloadditions of alkenes is an important method of formation of compounds containing four-membered rings.[184] Direct irradiation of simple nonconjugated dienes leads to cyclobutanes.[185] Strain makes the reaction unfavorable for 1,4-dienes but when the alkene units are separated by at least two carbon atoms cycloaddition becomes possible.



Ref. 186

Copper(I) triflate can facilitate these intramolecular additions, as is the case for intermolecular reactions.



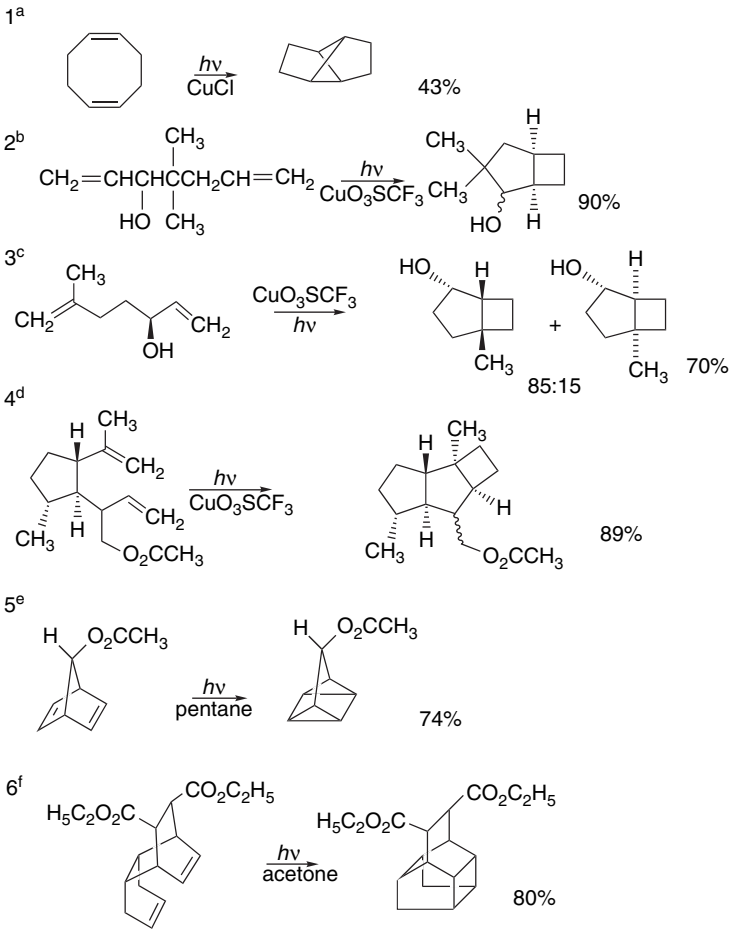
Ref. 187

The most widely exploited photochemical cycloadditions involve irradiation of dienes in which the two double bonds are fairly close and result in formation of polycyclic cage compounds. Some examples of alkene photocyclizations are given in Scheme 6.9. Entry 1 is a transannular cyclization. The preference for the observed product over tricyclo[4.2.0.$0^{2,5}$]octane does not seem to have been analyzed in detail. Entries 2, 3, and 4 involve photolysis in the presence of CuO_3SCF_3. Entries 5 and 6 are cases in which the double bonds are in close proximity and can cyclize to caged structures.

6.3.2.2. Photocycloaddition Reactions of Enones. Cyclic α,β-unsaturated ketones are another class of molecules that undergo photochemical cycloadditions.[188] The reactive

184. P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971).
185. R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 4141 (1962); *J. Am. Chem. Soc.*, **90**, 4498 (1968).
186. J. Meinwald and G. W. Smith, *J. Am. Chem. Soc.*, **89**, 4923 (1967); R. Srinivasan and K. H. Carlough, *J. Am. Chem. Soc.*, **89**, 4932 (1967).
187. K. Avasthi and R. G. Salomon, *J. Org. Chem.*, **51**, 2556 (1986).
188. A. C. Weedon, in *Synthetic Organic Photochemistry*, W. M. Horspool, ed., Plenum Press, New York, 1984, Chap. 2; D. I. Schuster, G. Lem, and N. A. Kaprinidis, *Chem. Rev.*, **93**, 3 (1993); M. T. Crimmins and T. L. Reinhold, *Org. React.*, **44**, 297 (1993); D. I. Schuster, in *CRC Handbook of Organic Photochemistry and Photobiology*, W. Horspool and F. Lanci, eds., CRC Press, Boca Raton, FL, 2002, pp. 72-1–72-24.

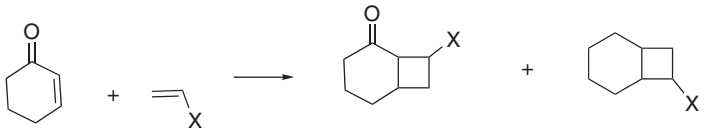
Scheme 6.9. Intramolecular [2 + 2] Photocycloadditions of Dienes



a. P. Srinivasan, *J. Am. Chem. Soc.*, **86**, 3318 (1964); *Org. Photochem. Synth.*, **1**, 101 (1971).
b. R. G. Salomon and S. Ghosh, *Org. Synth.*, **62**, 125 (1984).
c. K. Lange and J. Mattay, *J. Org. Chem.*, **60**, 7256 (1995).
d. T. Bach and A. Spiegel, *Synlett*, 1305 (2002).
e. P. G. Gassman and D. S. Patton, *J. Am. Chem. Soc.*, **90**, 7276 (1968).
f. B. M. Jacobson, *J. Am. Chem. Soc.*, **95**, 2579 (1973).

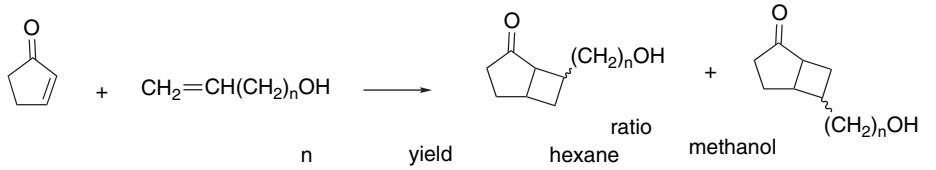
excited state is a π-π^* triplet of the enone. The reaction is most successful with cyclopentenones and cyclohexenones. The excited states of acyclic enones and larger ring compounds are rapidly deactivated by *cis-trans* isomerization and do not readily add to alkenes. Photoexcited enones can also add to alkynes.[189] Unsymmetrical alkenes can undergo two regioisomeric modes of addition. It is generally observed that alkenes with donor groups are oriented such that the substituted carbon becomes bound to the β-carbon, whereas with acceptor substituents the other orientation is preferred.[190]

189. R. L. Cargill, T. Y. King, A. B. Sears, and M. R. Willcott, *J. Org. Chem.*, **36**, 1423 (1971); W. C. Agosta and W. W. Lowrance, *J. Org. Chem.*, **35**, 3851 (1970).
190. E. J. Corey, J. D. Bass, R. Le Mahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1984); T. Suishu, T. Shimo, and K. Somekawa, *Tetrahedron*, **53**, 3545 (1997).



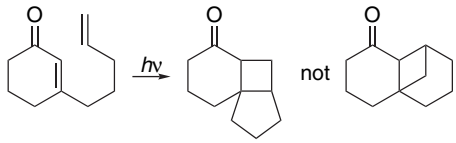
The photoadditions proceed through 1,4-diradical intermediates. Trapping experiments with hydrogen atom donors indicate that the initial bond formation can take place at either the α- or β-carbon of the enone. The excited enone has its highest nucleophilic character at the β-carbon. The initial bond formation occurs at the β-carbon for electron-poor alkenes but at the α-carbon for electron-rich alkenes.[191] Selectivity is low for alkenes without strong donor or acceptor substituents.[192] The final product ratio also reflects the rate and efficiency of ring closure relative to fragmentation of the biradical.[193]

Other structural factors can influence regioselectivity. Comparison of 2-propenol, 3-butenol, and 4-pentenol in various solvents suggests that hydrogen bonding can orient the reactants.[194] The reversal of regioselectivity between hexane and methanol suggests that the hydrogen bonding effects are swamped in the hydroxylic solvent methanol.

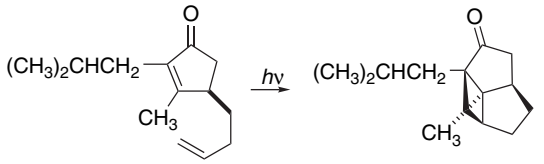


n	yield	ratio hexane	ratio methanol
1	84	71:26	33:67
2	86	65:35	34:66
3	79	60:40	32:68

Intramolecular enone-alkene cycloadditions are also possible. In the case of β-(5-pentenyl) substituents, there is a general preference for *exo*-type cyclization to form a five-membered ring.[195] This is consistent with the general pattern for radical cyclizations and implies initial bonding at the β-carbon of the enone.

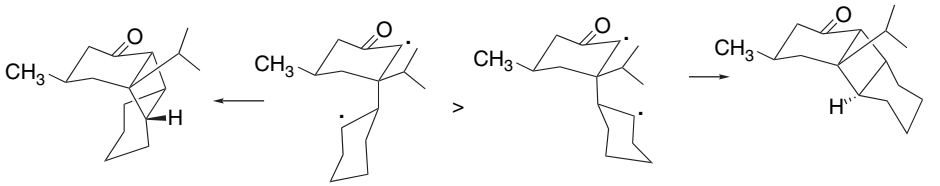


191. J. L. Broecker, J. E. Eksterowicz, A. J. Belk, and K. N. Houk, *J. Am. Chem. Soc.*, **117**, 1847 (1995).
192. J. D. White and D. N. Gupta, *J. Am. Chem. Soc.*, **88**, 5364 (1966); P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968).
193. D. I. Schuster, G. E. Heibel, P. B. Brown, N. J. Turro, and C. V. Kumar, *J. Am. Chem. Soc.*, **110**, 8261 (1988); N. A. Kaprinidis, G. Lem, S. H. Courtney, and D. I. Schuster, *J. Am. Chem. Soc.*, **115**, 3324 (1993); D. Andrew, D. J. Hastings, and A. C. Weedon, *J. Am. Chem. Soc.*, **116**, 10870 (1994).
194. L. K. Syudnes, K. I. Hansen, D. L. Oldroyd, A. C. Weedon, and E. Jorgensen, *Acta Chem. Scand.*, **47**, 916 (1993).
195. (a) W. C. Agosta and S. Wolff, *J. Org. Chem.*, **45**, 3139 (1980); (b) M. C. Pirrung, *J. Am. Chem. Soc.*, **103**, 82 (1981); (c) P. J. Connolly and C. H. Heathcock, *J. Org. Chem.*, **50**, 4135 (1985).

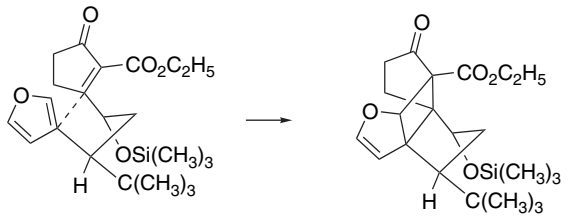


Ref. 195c

Scheme 6.10 gives some examples of enone cycloaddition reactions. The reaction in Entry 1 was done by direct irradiation ($\lambda > 290$ nm) in benzene. No regiochemical issues arise and the cyano group does not change the course of the reaction. The reaction in Entry 2 was used to construct [4.2.2]propellane, and was done at low temperature. The reaction in Entry 3 presumably occurs by initial bonding at the β-carbon. The preference for the *syn* orientation of the cyclohexane ring appears to be due to a steric interaction with the isopropyl group. The closure of the cyclobutane ring shows little stereoselectivity, resulting in a 2:1 mixture of stereoisomers.



The stereochemistry of the adduct formed in Entry 4 is evidently *cis* at the cyclopentane ring but it is not clear if the cyclobutane ring is *syn* or *anti.* The reaction in Entry 6 gave a mixture of stereoisomers that was subjected to reductive elimination of the vicinal dichloride. The reaction in Entry 7 exhibited complete facial stereoselectivity based on the convex shape of the ring and the presence of the methyl group on the concave face. Entries 8 to 13 are intramolecular additions that generate polycyclic rings. The reaction in Entry 8 was used in the synthesis of longifolene, a tricyclic terpene. Entry 9 gave a single stereoisomer that was used in the synthesis of a sesquiterpene, isocomene. Entry 10 was part of a synthetic route to [5.5.5.4]fenestrane. The fenestranes are tetracyclic compounds that share a central carbon. The reaction in Entry 11 was used in the synthesis of a nitrogenous terpene, incarvilline. In Entry 12, a furan ring is involved in the photocyclization. The stereochemistry seems to be determined by the reactant conformation. Other conformations of the reactant have more destabilizing steric interactions.



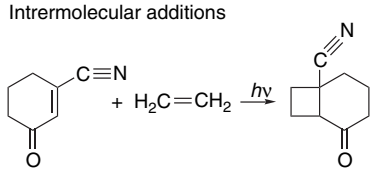
6.3.2.3. Photocycloaddition Reactions of Carbonyl Compounds and Alkenes. Photocycloaddition of ketones and aldehydes with alkenes can result in formation of four-membered cyclic ethers (oxetanes), a process often referred to as the *Paterno-Buchi reaction*.[196]

[196] D. R. Arnold, *Adv. Photochem.*, **6**, 301 (1968); H. A. J. Carless, in *Synthetic Organic Photochemistry*, W. M. Horspool, ed., Plenum Press, New York, 1984, Chap. 8; T. Bach, *Synthesis*, 683 (1998).

Scheme 6.10. Photocycloadditions of Enones with Alkenes and Alkynes

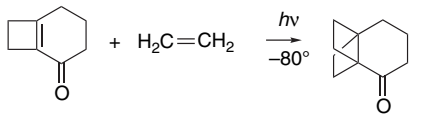
A. Intrermolecular additions

1[a]



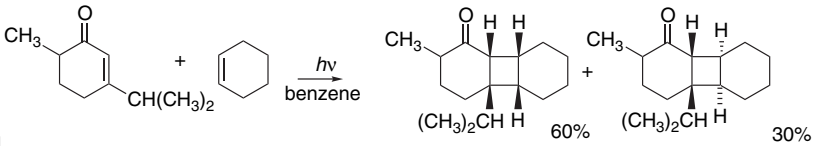
62%

2[b]



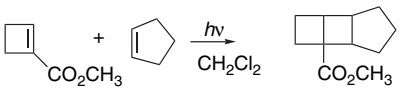
50%

3[c]



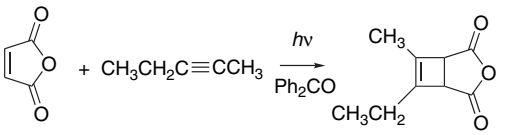
30%

4[d]



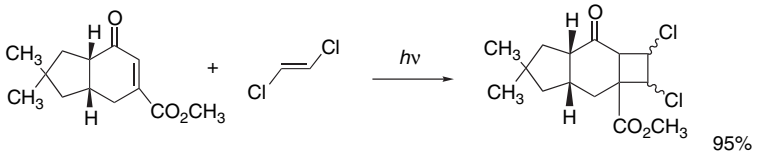
67%

5[e]



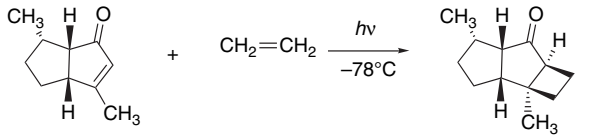
79%

6[f]



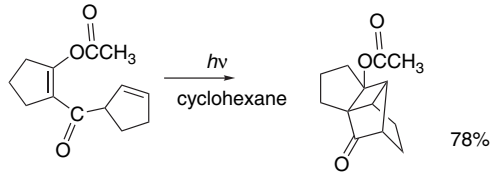
95%

7[g]



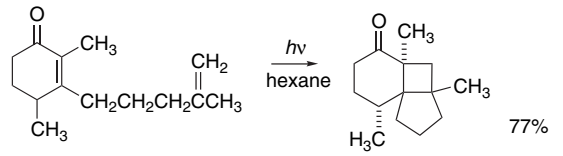
B. Intramolecular Additions

8[h]



78%

9[i]

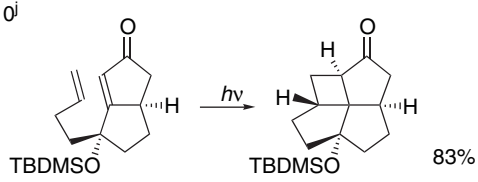


77%

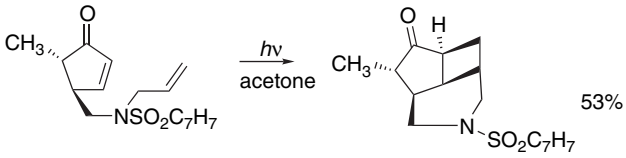
(*Continued*)

Scheme 6.10. (*Continued*)

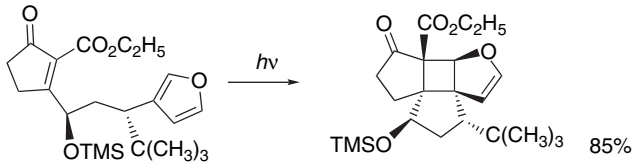
10[j]



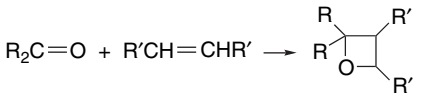
11[k]



12[l]

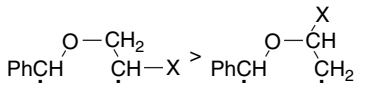


a. W. C. Agosta and W. W. Lowrance, Jr., *J. Org. Chem.*, **35**, 3851 (1970).
b. P. E. Eaton and K. Nyi, *J. Am. Chem. Soc.*, **93**, 2786 (1971).
c. P. Singh, *J. Org. Chem.*, **36**, 3334 (1971).
d. P. A. Wender and J. C. Lechleiter, *J. Am. Chem. Soc.*, **99**, 267 (1977).
e. R. M. Scarborough, Jr., B. H. Toder, and A. B. Smith, III, *J. Am. Chem. Soc.*, **102**, 3904 (1980).
f. G. Mehta and K. Sreenivas, *Tetrahedron Lett.*, **43**, 703 (2002).
g. E. Piers and A. Orellana, *Synthesis*, 2138 (2001).
h. W. Oppolzer and T. Godel, *J. Am. Chem. Soc.*, **100**, 2583 (1978).
i. M. C. Pirrung, *J. Am. Chem. Soc.*, **103**, 82 (1981).
j. M. Thommen and R. Keese, *Synlett*, 231 (1997).
k. M. Ichikawa, S. Aoyagi, and C. Kibayashi, *Tetrahedron Lett.*, **46**, 2327 (2005).
l. M. T. Crimmins, J. M. Pace, P. G. Naternet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, and A. S. Wagman, *J. Am. Chem. Soc.*, **122**, 8453 (2000).

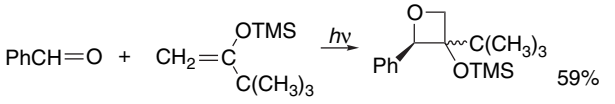


The reaction is stereospecific for at least some aliphatic ketones but not for aromatic carbonyls.[197] This result suggests that the reactive excited state is a singlet for aliphatics and a triplets for aromatics. With aromatic ketones, the regioselectivity of addition can usually be predicted on the basis of formation of the more stable of the two possible diradical intermediates obtained by bond formation between oxygen and the alkene.[198]

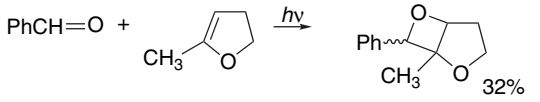
197. N. C. Yang and W. Eisenhardt, *J. Am. Chem. Soc.*, **93**, 1277 (1971); D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964); N. J. Turro and P. A. Wriede, *J. Am. Chem. Soc.*, **90**, 6863 (1968); J. A. Barltrop and H. A. J. Carless, *J. Am. Chem. Soc.*, **94**, 8761 (1972).
198. A. Griesbach, S. Buhr, M. Fiegel, J. Lex, and H. Schmickler, *J. Org. Chem.*, **63**, 3847 (1998).



Stereochemistry can be interpreted in terms of conformation effects in the 1,4-biradical intermediates.[199] Vinyl enol ethers and enamides add to aromatic ketones to give 3-substituted oxetanes, usually with the *cis* isomer preferred.[200]

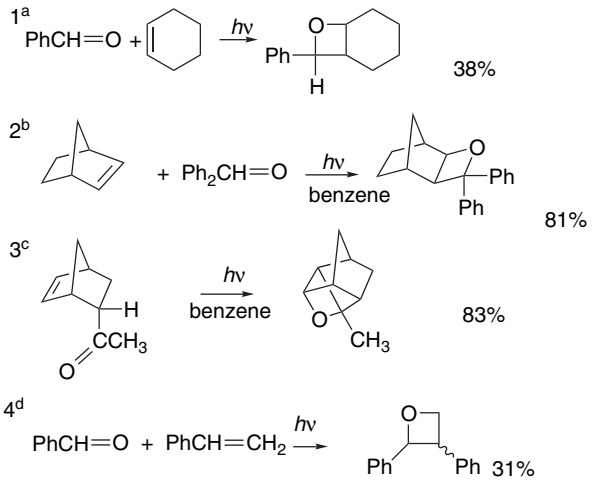


Ref. 200a



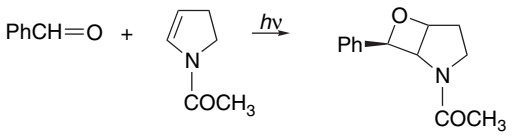
Ref. 199

Scheme 6.11. Photocycloaddition Reactions of Carbonyl Compounds and Alkenes



a. J. S. Bradshaw, *J. Org. Chem.*, **31**, 237 (1966).
b. D. R. Arnold, A. H. Glick, and V. Y. Abraitys, *Org. Photochem. Synth.*, **1**, 51 (1971).
c. R. R. Sauers, W. Schinksi, and B. Sickles, *Org. Photochem. Synth.*, **1**, 76 (1971).
d. H. A. J. Carless, A. K. Maitra, and H. S. Trivedi *J. Chem. Soc., Chem. Commun.*, 984 (1979).

199. A. G. Griesbach and S. Stadtmuller, *J. Am. Chem. Soc.*, **113**, 6923 (1991).
200. (a) T. Bach, *Tetrahedron Lett.*, **32**, 7037 (1991); (b) A. G. Griesbeck and S. Stadtmuller, *J. Am. Chem. Soc.*, **113**, 6923 (1991); (c) T. Bach, *Liebigs Ann. Chem.*, 1627 (1997); T. Bach, *Synthesis*, 683 (1998).



Ref. 200c

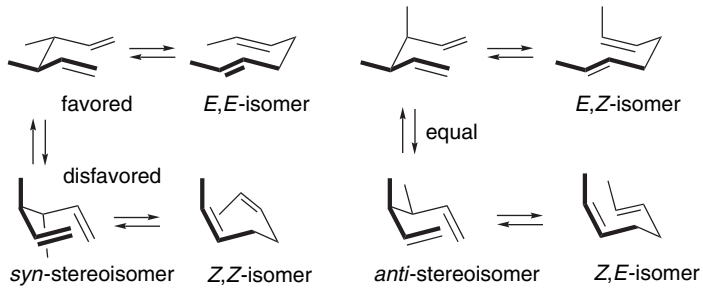
Some other examples of Paterno-Buchi reactions are given in Scheme 6.11.

6.4. [3,3]-Sigmatropic Rearrangements

The mechanistic basis of sigmatropic rearrangements was introduced in Chapter 10 of Part A. The sigmatropic process that is most widely applied in synthesis is the [3,3]-sigmatropic rearrangement. The principles of orbital symmetry establish that concerted [3,3]-sigmatropic rearrangements are allowed processes. Stereochemical predictions and analyses are based on the cyclic transition structure for a concerted reaction mechanism. Some of the various [3,3]-sigmatropic rearrangements that are used in synthesis are presented in outline form in Scheme 6.12.[201] We discuss these reactions in succeeding sections.

6.4.1. Cope Rearrangements

The Cope rearrangement is the conversion of a 1,5-hexadiene derivative to an isomeric 1,5-hexadiene by the [3,3]-sigmatropic mechanism. For unstrained compounds, the reaction occurs in the range of 150°–250° C. The reaction is both stereospecific and stereoselective. It is stereospecific in that a *Z*- or *E*-configurational relationship at either double bond is maintained in the TS and governs the relative configuration at the newly formed single bond in the product.[202] However, the relationship depends on the conformation of the TS. When a chair TS is favored the *E*,*E*- and *Z*,*Z*-dienes lead to *anti*-3,4-diastereomers, whereas the *E*,*Z*- and *Z*,*E*-isomers give the 3,4-*syn* product. TS conformation also determines the stereochemistry of the new double bond. If both *E*- and *Z*-stereoisomers are possible for the product, the product ratio reflects product (and TS) stability. The *E*-arrangement is normally favored for the newly formed double bonds. The stereochemical aspects of the Cope rearrangements for simple acyclic reactants are consistent with a chairlike TS in which the larger substituent at C(3) [or C(4)] adopts an equatorial-like conformation.

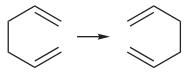


201. For reviews of synthetic application of [3,3]sigmatropic rearrangements, see G. B. Bennett, *Synthesis*, 589 (1977); F. E. Ziegler, *Acc. Chem. Res.*, **10**, 227 (1977).

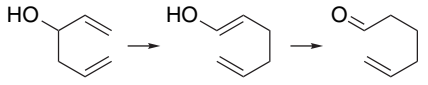
202. W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

Scheme 6.12. [3,3]-Sigmatropic Rearrangements

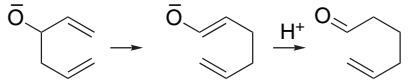
1[a] Cope rearrangement



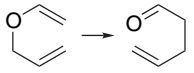
2[b] Oxy-Cope rearrangement



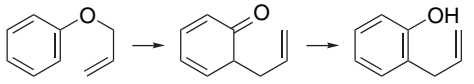
3[c] Anionic oxy-Cope rearrangement



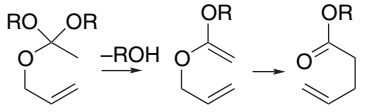
4[d] Claisen rearrangement of allyl vinyl ethers



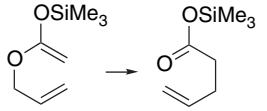
5[d] Claisen rearrangement of allyl phenyl ethers



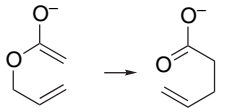
6[e] Ortho ester Claisen rearrangement



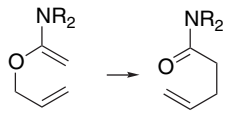
7[f] Ireland-Claisen rearrangement of *O*-allyl-*O′*-trimethylsilyl ketene acetals



8[g] Ester enolate Claisen rearrangement



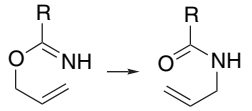
9[h] Claisen rearrangement of *O*-allyl-*N,N*-dialkyl ketene aminals



(*Continued*)

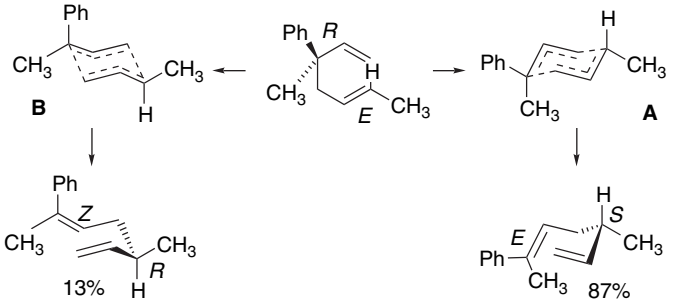
Scheme 6.12. (*Continued*)

10[i] Aza-Claisen rearrangement of *O*-allyl imidates



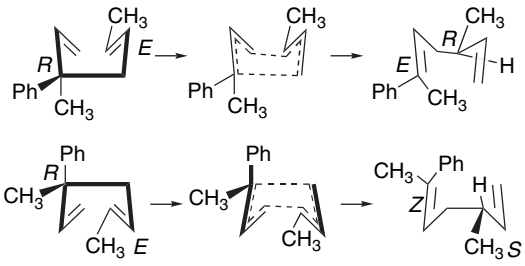
a. S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
b. J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.*, **86**, 5019 (1964).
c. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).
d. D. S. Tarbell, *Org. React.*, **2**, 1 (1944).
e. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).
f. R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5898 (1972).
g. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
h. D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
i. L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).

Owing to the concerted mechanism, chirality at C(3) [or C(4)] leads to enantiospecific formation of new stereogenic centers formed at C(1) [or C(6)].[203] These relationships are illustrated in the example below. Both the configuration of the new stereocenter and the new double bond are those expected on the basis of a chairlike TS. Since there are two stereogenic centers, the double bond and the asymmetric carbon, there are four possible stereoisomers of the product. Only two are formed. The *E*-double bond isomer has the *S*-configuration at C(4) and the *Z*-isomer has the *R*-configuration. These are the products expected for a chair TS. The stereochemistry of the new double bond is determined by the relative stability of the two chair TSs. TS **B** is less favorable than **A** because of the axial placement of the larger phenyl substituent.



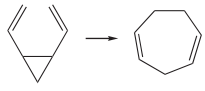
The products corresponding to boatlike TSs are usually not observed for acyclic dienes. However, this TS is allowed and if steric factors make a boat TS preferable to a chair, reaction can proceed through a boat. Thermochemical[204] and computational[205] studies indicate that the boat TS is intrinsically 6–10 kcal/mol higher in energy. Reactions that proceed through a boat TS have the reverse stereochemical relationships between the configuration at the stereogenic center and the double bond.

203. R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967); R. K. Hill, in *Asymmetric Synthesis*, Vol. 4, J. D. Morrison, ed., Academic Press, New York, 1984, pp. 503–572.
204. M. Goldstein and M. S. Benzon, *J. Am. Chem. Soc.*, **94**, 7147 (1972).
205. O. Wiest, K. A. Black, and K. N. Houk, *J. Am. Chem. Soc.*, **116**, 10336 (1995).

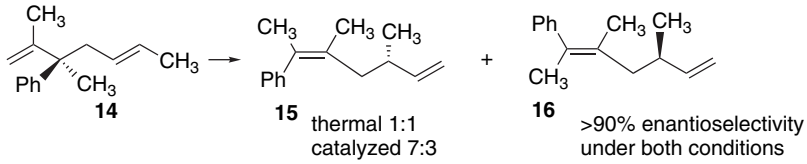


Cope rearrangements are reversible reactions and, as there is no change in the number or types of bonds as a result of the reaction, to a first approximation the total bond energy is unchanged. The position of the final equilibrium is governed by the relative stability of the starting material and product. In the example cited above, the equilibrium is favorable because the product is stabilized by conjugation of the alkene with the phenyl ring.

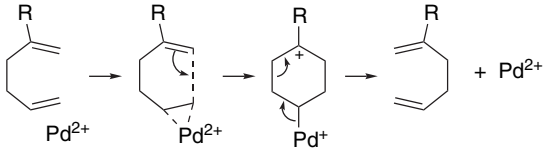
When ring strain is relieved, Cope rearrangements can occur at much lower temperatures and with complete conversion to ring-opened products. A striking example is the conversion of *cis*-divinylcyclopropane to 1,4-cycloheptadiene, a reaction that occurs readily below −40° C.[206]



Several transition metal ions and complexes, especially Pd(II) salts, have been found to catalyze Cope rearrangements.[207] The catalyst that has been adopted for synthetic purposes is $PdCl_2(CH_3CN)_2$, and with it the rearrangement of **14** to **15** and **16** occurs at room temperature, as contrasted to 240° C in its absence.[208] The catalyzed reaction shows enhanced stereoselectivity and is consistent with a chairlike TS.



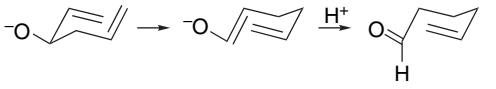
The mechanism for catalysis is formulated as a stepwise process in which the electrophilic character of Pd(II) facilitates the bond formation.[209]



When there is a hydroxy substituent at C(3) of the diene system, the Cope rearrangement product is an enol that is subsequently converted to the corresponding

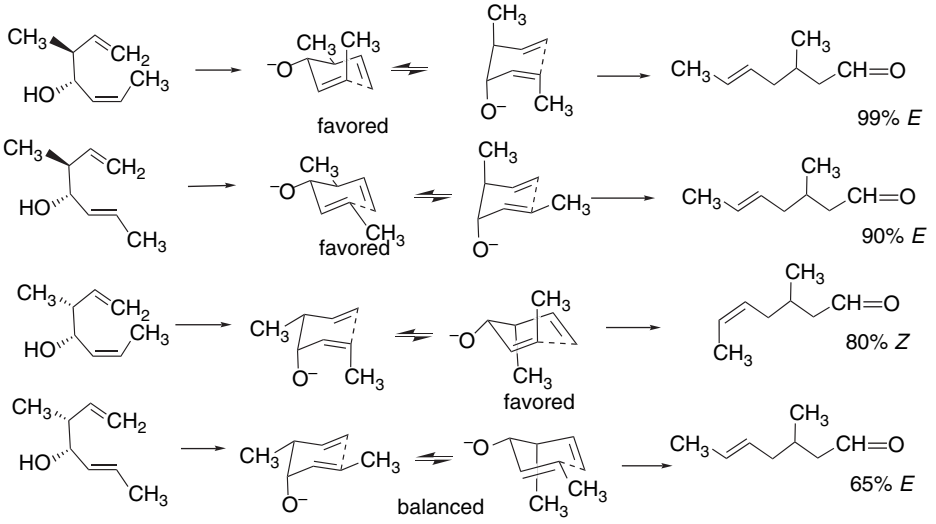
206. W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).
207. R. P. Lutz, *Chem. Rev.*, **84**, 205 (1984).
208. L. E. Overman and F. M. Knoll, *J. Am. Chem. Soc.*, **102**, 865 (1980).
209. L. E. Overman and A. F. Renaldo, *J. Am. Chem. Soc.*, **112**, 3945 (1990).

carbonyl compound. This is called the *oxy-Cope rearrangement*.[210] The formation of the carbonyl compound provides a net driving force for the reaction.[211]



An important improvement in the oxy-Cope reaction was made when it was found that the reaction is strongly catalyzed by base.[212] When the C(3) hydroxy group is converted to its alkoxide, the reaction is accelerated by a factor of 10^{10}–10^{17}. These base-catalyzed reactions are called *anionic oxy-Cope rearrangements*, and their rates depend on the degree of cation coordination at the oxy anion. The reactivity trend is $K^+ > Na^+ > Li^+$. Catalytic amounts of tetra-*n*-butylammonium salts lead to accelerated rates in some cases. This presumably results from the dissociation of less reactive ion pair species promoted by the tetra-*n*-butylammonium ion.[213]

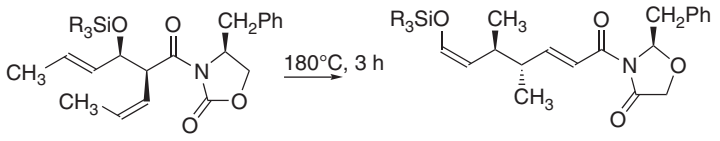
The stereochemistry of acyclic anionic oxy-Cope rearrangements is consistent with a chair TS having a conformation that favors equatorial placement of both alkyl and oxy substituents and minimizes the number of 1,3-diaxial interactions.[214] For the reactions shown below, the double-bond configuration is correctly predicted on the basis of the most stable TS available in the first three reactions. In the fourth reaction, the TSs are of comparable energy and a 2:1 mixture of *E*- and *Z*-isomers is formed.



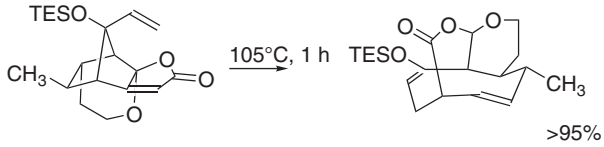
Silyl ethers of vinyl allyl alcohols can also be used in oxy-Cope rearrangements.[215] Known as the *siloxy-Cope rearrangement*, this methodology has been used in

210. S. R. Wilson, *Org. React.*, **43**, 93 (1993); L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, **29**, 609 (1990); L. A. Paquette, *Tetrahedron*, **53**, 13971 (1997).
211. A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Am. Chem. Soc.*, **89**, 3462 (1967).
212. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975); D. A. Evans, D. J. Balillargeon, and J. V. Nelson, *J. Am. Chem. Soc.*, **100**, 2242 (1978).
213. M. George, T.-F. Tam, and B. Fraser-Reid, *J. Org. Chem.*, **50**, 5747 (1985).
214. K. Tomooka, S.-Y. Wei, and T. Nakai, *Chem. Lett.*, 43 (1991).
215. R. W. Thies, M. T. Wills, A. W. Chin, L. E. Schick, and E. S. Walton, *J. Am. Chem. Soc.*, **95**, 5281 (1973).

connection with *syn*-selective aldol additions in stereoselective synthesis.[216] The use of the silyloxy group prevents reversal of the aldol addition, which would otherwise occur under anionic conditions. The reactions proceed at convenient rates at 140°–180° C.

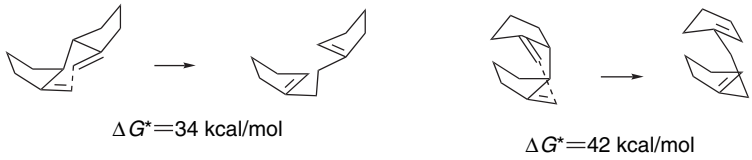


Ref. 217



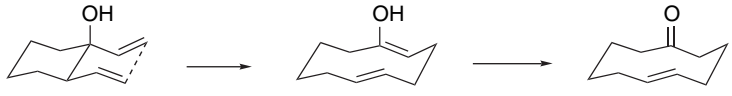
Ref. 218

Scheme 6.13 gives some examples of Cope and oxy-Cope rearrangements. Entry 1 shows a reaction that was done to compare the energy of chair and boat TSs. The chiral diastereomer shown can react through a chair TS and has a ΔG^* about 8 kcal/mol lower than the *meso* isomer, which must react through a boat TS. The equilibrium is biased toward product by the fact that the double bonds in the product are more highly substituted, and therefore more stable, than those in the reactant.



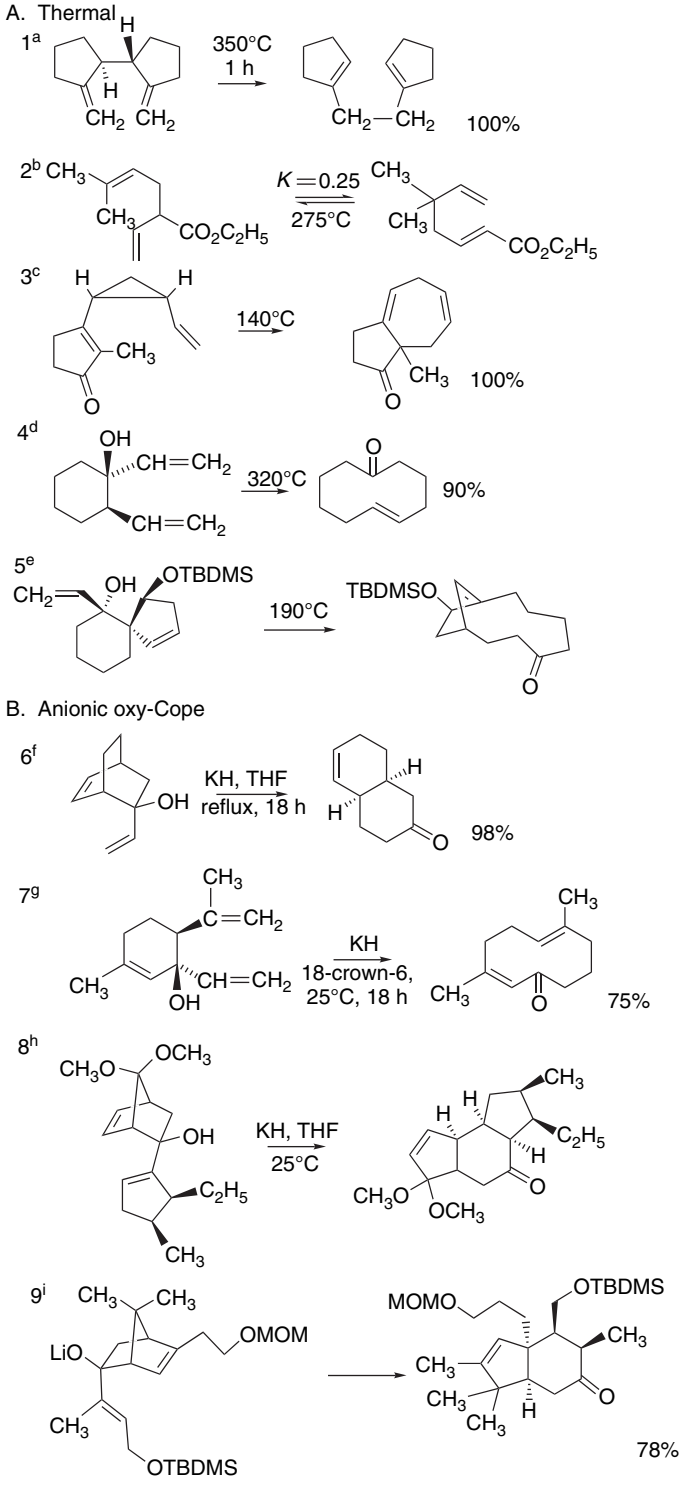
Entry 2 illustrates the reversibility of the Cope rearrangement. In this case, the equilibrium is closely balanced with the reactant benefiting from a more-substituted double bond, whereas the product is stabilized by conjugation. The reaction in Entry 3 involves a *cis*-divinylcyclopropane and proceeds at much lower temperature than the previous examples. The reaction was used in the preparation of an intermediate for the synthesis of pseudoguiane-type natural products.

Entries 4 and 5 illustrate the use of the oxy-Cope rearrangement in formation of medium-size rings. The *trans*-double bond in the product for Entry 4 arises from a chair TS.



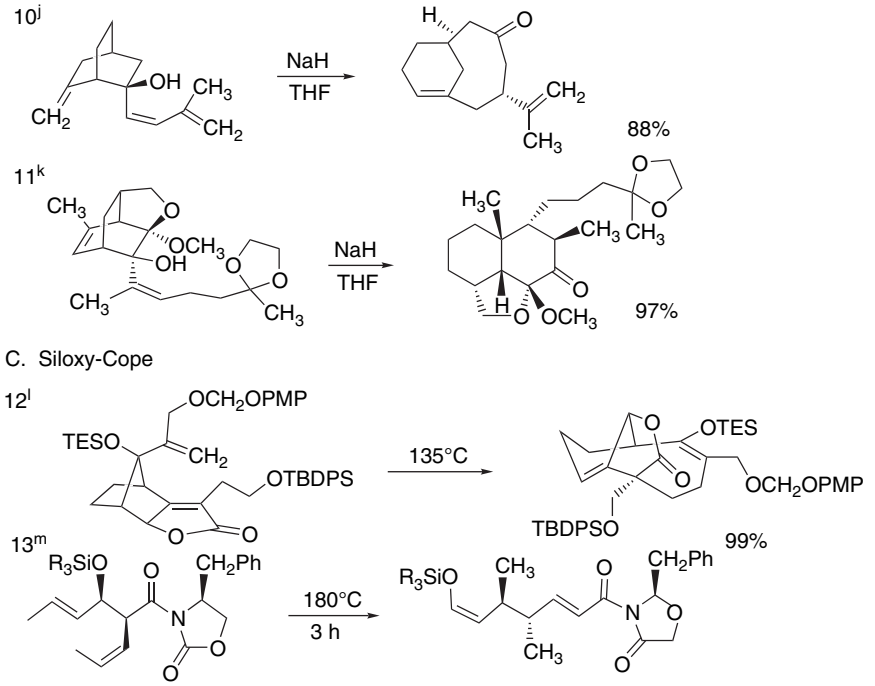
[216] C. Schneider and M. Rehfeuter, *Synlett*, 212 (1996); C. Schneider and M. Rehfeuter, *Tetrahedron*, **53**, 133 (1997); W. C. Black, A. Giroux, and G. Greidanus, *Tetrahedron Lett.*, **37**, 4471 (1996).
[217] C. Schneider, *Eur. J. Org. Chem.*, 1661 (1998).
[218] M. M. Bio and J. L. Leighton, *J. Am. Chem. Soc.*, **121**, 890 (1999).

Scheme 6.13. Cope and Oxy-Cope Rearrangements of 1,5-Dienes



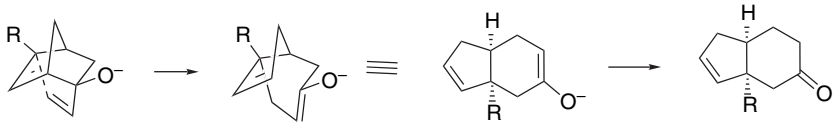
(*Continued*)

Scheme 6.13. (*Continued*)



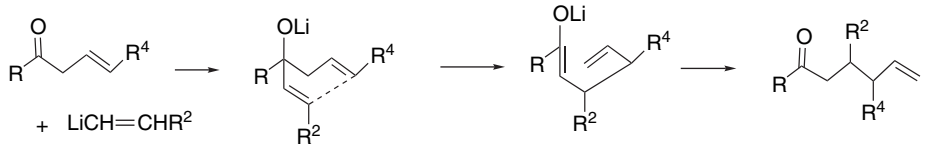
a. K. J. Shea and R. B. Phillips, *J. Am. Chem. Soc.*, **102**, 3156 (1980).
b. F. E. Ziegler and J. J. Piwinski, *J. Am. Chem. Soc.*, **101**, 1612 (1979).
c. P. A. Wender, M. A. Eissenstat, and M. P. Filosa, *J. Am. Chem. Soc.*, **101**, 2196 (1979).
d. E. N. Marvell and W. Whalley, *Tetrahedron Lett.*, 509 (1970).
e. G. Ladouceur and L.A. Paquette, *Synthesis*, 185 (1992)
f. D. A. Evans, A. M. Golob, N. S. Mandel, and G. S. Mandel, *J. Am. Chem. Soc.*, **100**, 8170 (1978).
g. W. C. Still, *J. Am. Chem. Soc.*, **99**, 4186 (1977).
h. L. A. Paquette, K. S. Learn, J. L. Romine, and H.-S. Lin, *J. Am. Chem. Soc.*, **110**, 879 (1988); L. A. Paquette, J. L. Romine, H.-S. Lin, and J. Wright, *J. Am. Chem. Soc.*, **112**, 9284 (1990).
i. L. A. Paquette and F.-T. Hong, *J. Org. Chem.*, **68**, 6905 (2003).
j. L. Gentric, I. Hanna, A. Huboux, and R. Zaghdoudi, *Org. Lett.*, **5**, 3631 (2003).
k. D. S. Hsu and C-C. Liao, *Org. Lett.*, **5**, 3631 (2003).
l. D. L. J. Clive, S. Sun, V. Gagliardini, and M. K. Sano, *Tetrahedron Lett.*, **41**, 6259 (2000).
m. C. Schneider, *Eur. J. Org. Chem.*, 1661 (1998).

The reaction in Entry 5 is a case in which the thermal conditions were preferable to the basic conditions because of the base sensitivity of the product. Entries 6 to 10 show anionic oxy-Cope reactions. Entries 6 and 7 are early examples of the application of the reaction in synthesis. Entries 8 and 9 involve rearrangements of bicyclo[2.2.1]hept-2-en-2-ol derivatives to give *cis*-fused bicyclo[4.3.0]non-7-en-3-ones.

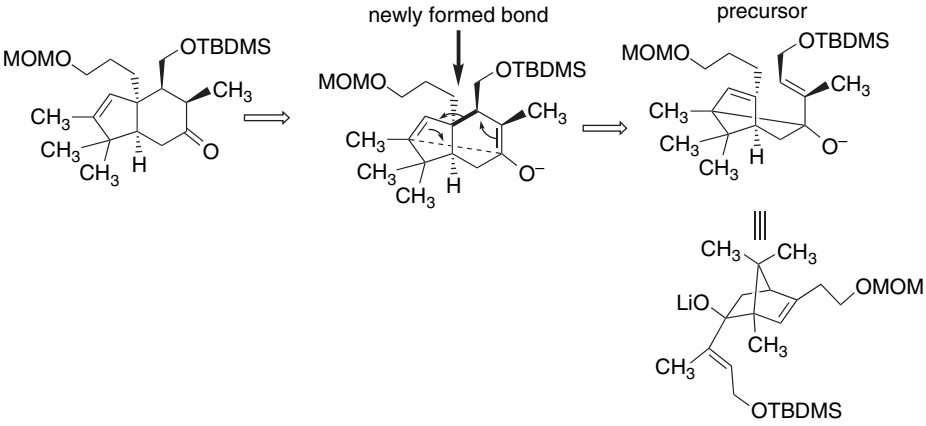


The rearrangement in Entry 9 occurs spontaneously on warming of the reaction mixture from addition of an organolithium reagent to form the vinyl carbinol unit. This is a very general means of constructing reactants for oxy-Cope rearrangements that leads

to carbon-carbon bond formation between C(2) of the vinyllithium reagent and C(4) of the β,γ-enone.

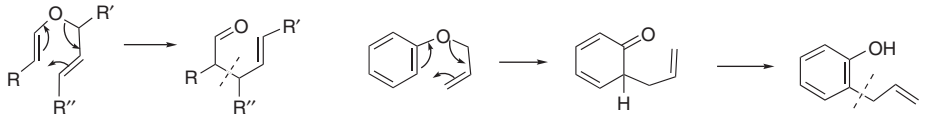


The reaction in Entry 10 demonstrated that a vinyl substituent in conjugation with the vinyl carbinol accelerates rearrangement. The reaction was considerably more facile than the corresponding reaction with a saturated isopropyl group. The reaction in Entry 11 was used in the synthesis of terpene derivatives. Entries 12 and 13 are examples of the siloxy-Cope version of the reaction. These entries illustrate the utility of the oxy-Cope reaction in the synthesis of ring systems. Some of these transformations may be difficult to recognize, at least at first glance. The retrosynthetic transformation can be recognized by identifying the δ,ϵ-enone and locating the bond that is formed in the rearrangement. For example, the retrosynthetic formulation of the reaction in Entry 9 identifies the precursor.



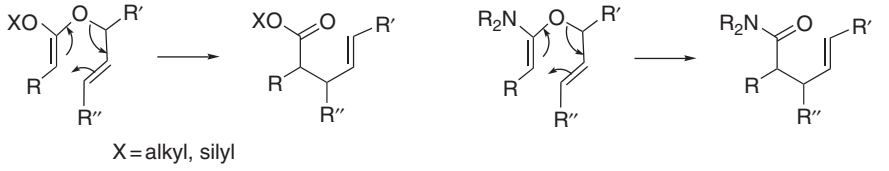
6.4.2. Claisen and Modified Claisen Rearrangements

The basic pattern of the Claisen rearrangement is the conversion of a vinyl allyl ether to a γ,δ-enone. The reaction is also observed for allyl phenyl ethers, in which case the products are *o*-allylphenols.

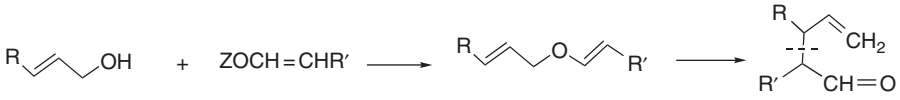


There are several synthetically important adaptations of the reaction. It can be applied to orthoesters (Section 6.4.2.2) or silyl ketene acetals (Section 6.4.2.3), in which case the products are γ,δ-unsaturated acids or esters. An analogous reaction using amide

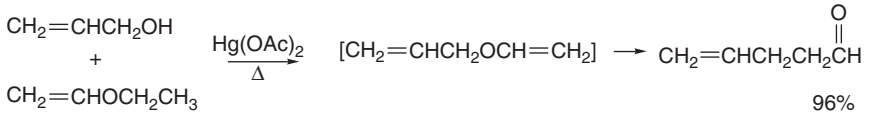
acetals gives γ,δ-unsaturated amides (Section 6.4.2.4). In all cases, the reactions occur with 1,3-transposition of the allylic group.



6.4.2.1. Claisen Rearrangements of Allyl Vinyl Ethers. The [3,3]-sigmatropic rearrangement of allyl vinyl ethers leads to γ,δ-enones and is known as the *Claisen rearrangement*.[219] The reaction is mechanistically analogous to the Cope rearrangement and occurs at temperatures above 150° C. As the product is a carbonyl compound, the equilibrium is usually favorable. The reaction introduces an α-acyl alkyl group at the γ-carbon of the allylic alcohol, with 1,3-transposition of the allylic double bond.

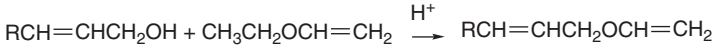


The reactants can be made from allylic alcohols by mercuric ion-catalyzed exchange with ethyl vinyl ether.[220] The allyl vinyl ether need not be isolated and is often prepared under conditions that lead to its rearrangement. The simplest of all Claisen rearrangements, the conversion of allyl vinyl ether to 4-pentenal, typifies this process.



Ref. 221

Acid-catalyzed exchange can also be used to prepare the vinyl ethers.

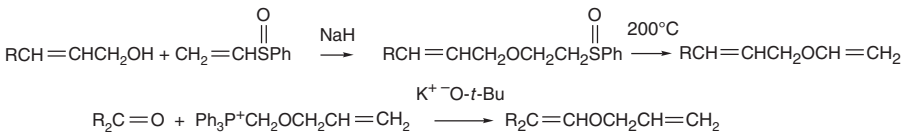


Ref. 222

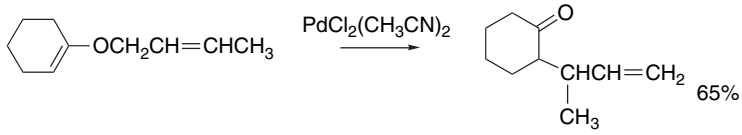
Vinyl ethers can also be generated by thermal elimination reactions. For example, base-catalyzed conjugate addition of allyl alcohols to phenyl vinyl sulfone generates 2-(phenylsulfinyl)ethyl ethers that can undergo elimination at 200° C.[223] The sigmatropic

219. F. E. Ziegler, *Chem. Rev.*, **88**, 1423 (1988); A. M. M. Castro, *Chem. Rev.*, **104**, 2939 (2004).
220. W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957); D. B. Tulshian, R. Tsang, and B. Fraser-Reid, *J. Org. Chem.*, **49**, 2347 (1984).
221. S. E. Wilson, *Tetrahedron Lett.*, 4651 (1975).
222. G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967); R. Marbet and G. Saucy, *Helv. Chim. Acta*, **50**, 2095 (1967).
223. T. Mandai, S. Matsumoto, M. Kohama, M. Kawada, J. Tsuji, S. Saito, and T. Moriwake, *J. Org. Chem.*, **55**, 5671 (1990); T. Mandai, M. Ueda, S. Hagesawa, M. Kawada, J. Tsuji, and S. Saito, *Tetrahedron Lett.*, **31**, 4041 (1990).

rearrangement proceeds under these conditions. Allyl vinyl ethers can also be prepared by Wittig reactions using ylides generated from allyloxymethylphosphonium salts.[224]

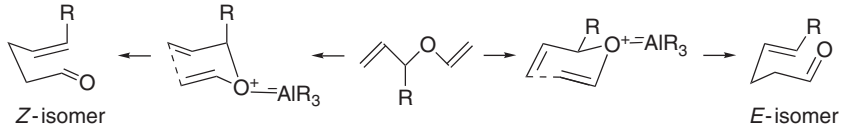


As with the Cope rearrangement, $PdCl_2$ can catalyze the Claisen rearrangement.

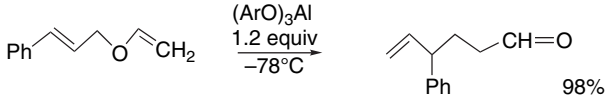


Ref. 225

However, it can also catalyze competing reactions and works best for relatively highly substituted systems.[226] Catalysis of Claisen rearrangements has been achieved using highly hindered *bis*-(phenoxy)methylaluminum as Lewis acids.[227] These reagents also have the ability to control the E:Z ratio of the products. Very bulky catalysts tend to favor the *Z*-isomer by forcing the α-substituent of the allyl group into an axial conformation.



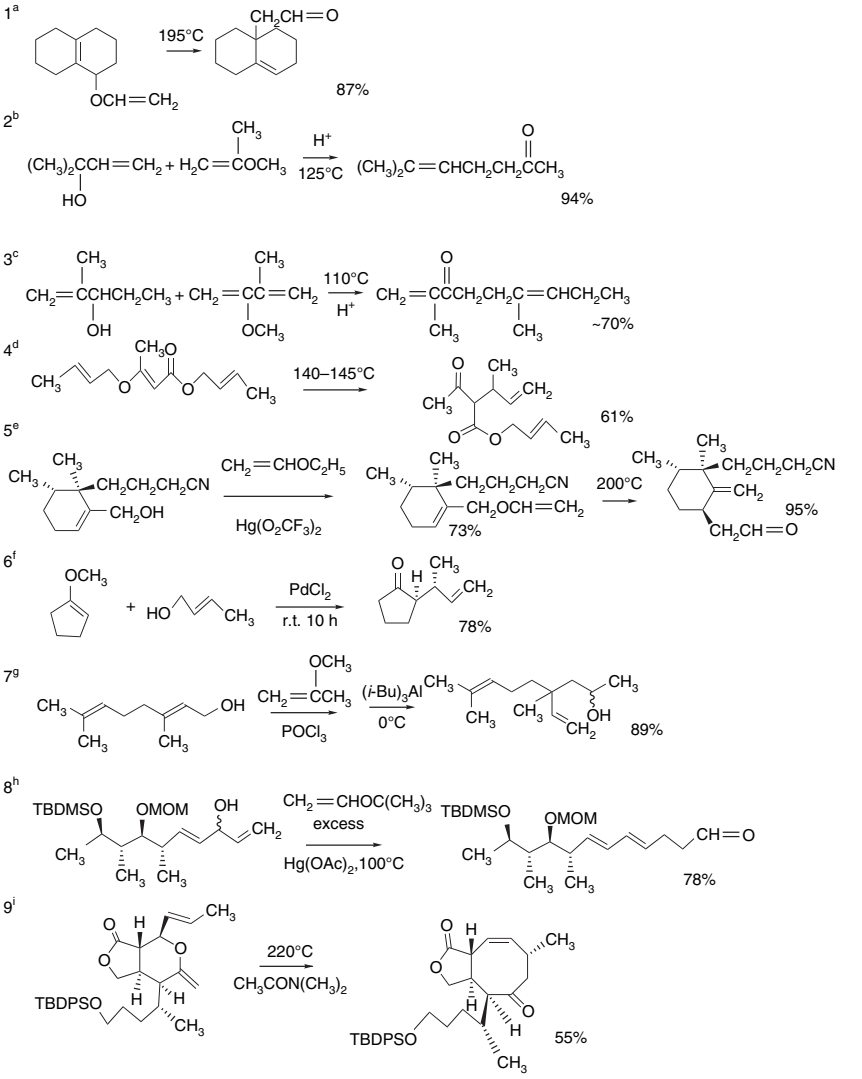
tris-Aryloxyaluminum compounds are also effective catalysts for the Claisen rearrangement.[228] When used in a 1.2 molar ratio, the rearrangement occurs at −78° C.



Some representative Claisen rearrangements are shown in Scheme 6.14. Entry 1 illustrates the application of the Claisen rearrangement in the introduction of a substituent at the junction of two six-membered rings. Introduction of a substituent at this type of position is frequently necessary in the synthesis of steroids and terpenes. In Entry 2, formation and rearrangement of a 2-propenyl ether leads to formation of a methyl ketone. Entry 3 illustrates the use of 3-methoxyisoprene to form the allylic ether. The rearrangement of this type of ether leads to introduction of isoprene structural units into the reaction product. Entry 4 involves an allylic ether prepared by O-alkylation of a β-keto enolate. Entry 5 was used in the course of synthesis of a diterpene lactone. Entry 6 is a case in which $PdCl_2$ catalyzes both the formation and rearrangement of the reactant.

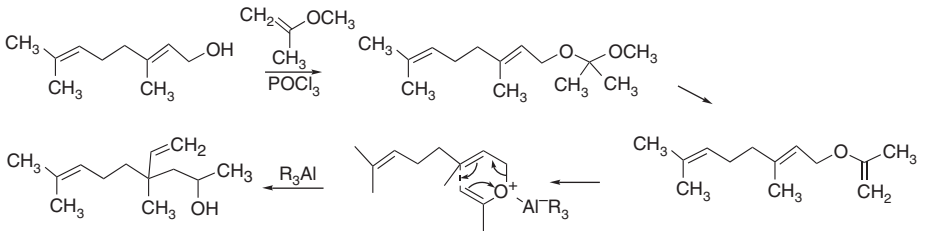
224. M. G. Kulkarni, D. S. Pendharkar, and R. M. Rasne, *Tetrahedron Lett.*, **38**, 1459 (1997).
225. J. L. van der Baan and F. Bickelhaupt, *Tetrahedron Lett.*, **27**, 6267 (1986).
226. M. Hiersemann and L. Abraham, *Eur. J. Org. Chem.*, 1461 (2002).
227. K. Nonoshita, H. Banno, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **112**, 316 (1990).
228. S. Saito, K. Shimada, and H. Yamamoto, *Synlett*, 720 (1996).

Scheme 6.14. Claisen Rearrangements of Allyl Vinyl Ethers and Related Compounds



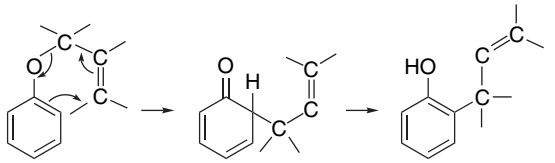
a. A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961).
b. G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967).
c. D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, **95**, 553 (1973).
d. J. W. Ralls, R. E. Lundin, and G. F. Bailey, *J. Org. Chem.*, **28**, 3521 (1963).
e. L. A. Paquette, T.-Z. Wang, S. Nang and C. M. G. Philippo, *Tetrahedron Lett.*, **34**, 3523 (1993).
f. K. Mitami, K. Takahashi, and T. Nakai, *Tetrahedron Lett.*, **28**, 5879 (1987).
g. S. D. Rychnovsky and J. L. Lee, *J. Org. Chem.*, **60**, 4318 (1995).
h. T. Berkenbusch and R. Brueckner, *Chem. Eur. J.*, **10**, 1545 (2004).
i. T.-Z. Wang, E. Pinard, and L. A. Paquette, *J. Am. Chem. Soc.*, **118**, 1309 (1996).

Entry 7 illustrates reaction conditions that were applicable to formation and rearrangement of an isopropenyl allylic ether. The tri-isopropylaluminum is thought to both catalyze the sigmatropic rearrangement and reduce the product ketone.

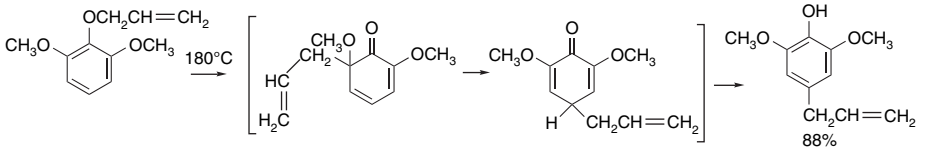


The reaction in Entry 8 was conducted in excess refluxing vinyl *t*-butyl ether, using 1.1 equivalent of $Hg(OAc)_2$ to catalyze the exchange reaction. In Entry 9 a thermal reaction leads to formation of an eight-membered ring.

Aryl allyl ethers can also undergo [3,3]-sigmatropic rearrangement. In fact, Claisen rearrangements of allyl phenyl ethers to *ortho*-allyl phenols were the first [3,3]-sigmatropic rearrangements to be thoroughly studied.[229] The reaction proceeds through a cyclohexadienone that enolizes to the stable phenol.

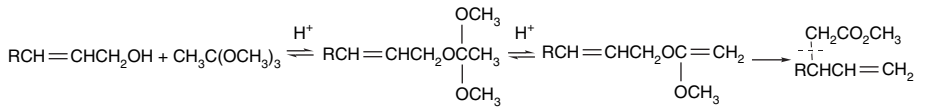


If both *ortho*-positions are substituted, the allyl group undergoes a second migration, giving the *para*-substituted phenol:



Ref. 230

6.4.2.2. Orthoester Claisen Rearrangements. There are several variations of the Claisen rearrangement that make it a powerful tool for the synthesis of γ,δ-unsaturated carboxylic acids. The *orthoester modification of the Claisen rearrangement* allows carboalkoxymethyl groups to be introduced at the γ-position of allylic alcohols.[231] A mixed orthoester is formed as an intermediate and undergoes sequential elimination and sigmatropic rearrangement.



[229] S. J. Rhoads, in *Molecular Rearrangements*, Vol. 1, P. de Mayo, ed., Interscience, New York, 1963, pp. 655–684.

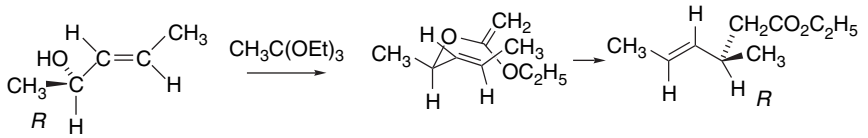
[230] I. A. Pearl, *J. Am. Chem. Soc.*, **70**, 1746 (1948).

[231] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).

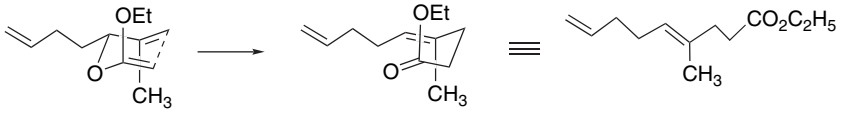
Both the exchange and elimination are catalyzed by the addition of a small amount of a weak acid, such as propanoic acid. These reactions are usually conducted at the reflux temperature of the orthoester, which is about 110° C for the trimethyl ester and 140° C for the triethyl ester. Microwave heating has been used and is reported to greatly accelerate orthoester-Claisen rearrangements.[232]

The mechanism and stereochemistry of the orthoester Claisen rearrangement is analogous to the Cope rearrangement. The reaction is stereospecific with respect to the double bond present in the initial allylic alcohol. In acyclic molecules, the stereochemistry of the product can usually be predicted on the basis of a chairlike TS.[233] When steric effects or ring geometry preclude a chairlike structure, the reaction can proceed through a boatlike TS.[234]

High levels of enantiospecificity have been observed in the rearrangement of chiral reactants. This method can be used to establish the configuration of the newly formed carbon-carbon bond on the basis of the configuration of the C−O bond in the starting allylic alcohol. Treatment of (2*R*, 3*E*)-3-penten-2-ol with ethyl orthoacetate gives the ethyl ester of (3*R*, 4*E*)-3-methyl-4-hexenoic acid in 90% enantiomeric purity.[235] The configuration of the new stereocenter is that predicted by a chairlike TS with the methyl group occupying a pseudoequatorial position.



Scheme 6.15 gives some representative examples of the orthoester Claisen rearrangement. Entry 1 is an example of the standard conditions for the orthoester Claisen rearrangement using triethyl orthoacetate as the reactant. The allylic alcohol is heated in an excess of the orthoester (5.75 equivalents) with 5 mol % of propanoic acid. Ethanol is distilled from the reaction mixture. The *E*-double bond arises from the chair TS.

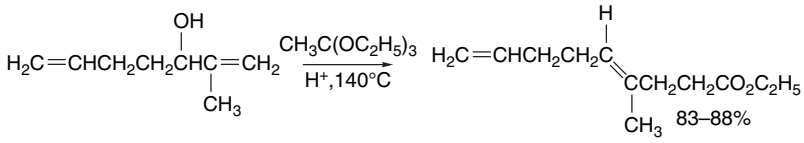


The reaction in Entry 2, involving trimethyl orthoacetate, was effected in the course of synthesis of an insect juvenile hormone. The reaction is highly stereoselective (> 98%) for the *E*-isomer at the new double bond. The reactions in Entries 3 and 4 were used to introduce ester substituents on the nitrogen-containing rings. Note that in Entry 4 an orthobutanoate ester is used, demonstrating that longer-chain orthoesters

232. A. Srikrishna, S. Nagaraju, and P. Kondaiah, *Tetrahedron*, **51**, 1809 (1995).
233. G. W. Daub, J. P. Edwards, C. R. Okada, J. W. Allen, C. T. Makey, M. S. Wells, A. S. Goldstien, M. J. Dibley, C. J. Wang, D. P. Ostercamp, S. Chung, P. S. Lunningham, and M. A. Berliner, *J. Org. Chem.*, **62**, 1976 (1997).
234. R. J. Cave, B. Lythgoe, D. A. Metcalf, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1218 (1977); G. Buchi and J. E. Powell, Jr., *J. Am. Chem. Soc.*, **92**, 3126 (1970); J. J. Gajewski and J. L. Jiminez, *J. Am. Chem. Soc.*, **108**, 468 (1986).
235. R. K. Hill, R. Soman, and S. Sawada, *J. Org. Chem.*, **37**, 3737 (1972); **38**, 4218 (1973).

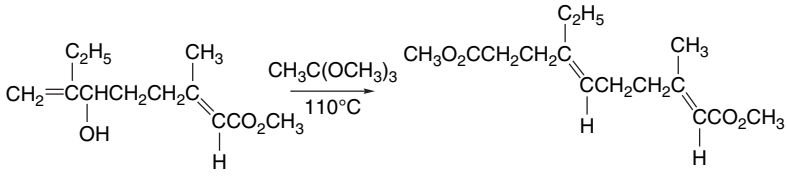
Scheme 6.15. Orthoester-Claisen Rearrangements

1[a]



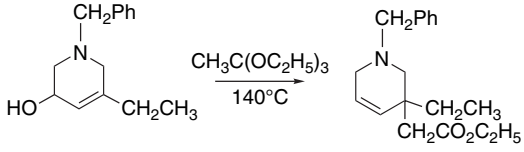
83–88%

2[b]



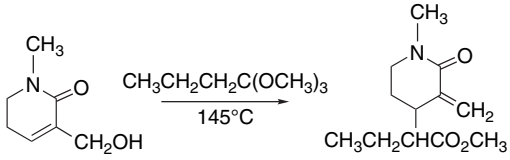
85%

3[c]



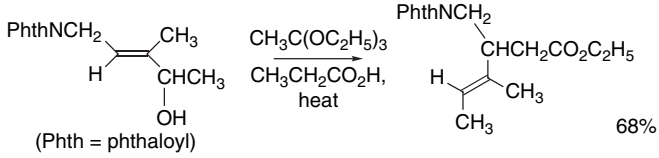
74%

4[d]



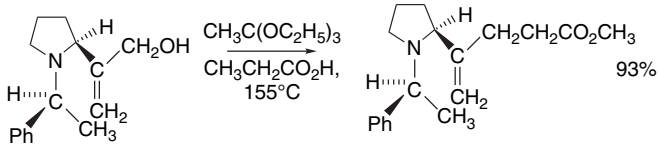
96%

5[e]



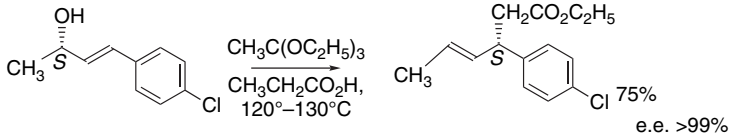
68%

6[f]



93%

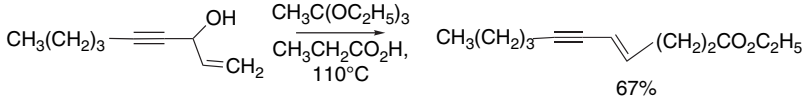
7[g]



75%

e.e. >99%

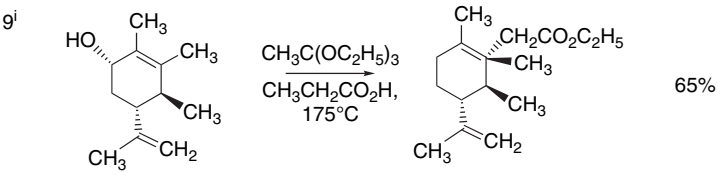
8[h]



67%

(*Continued*)

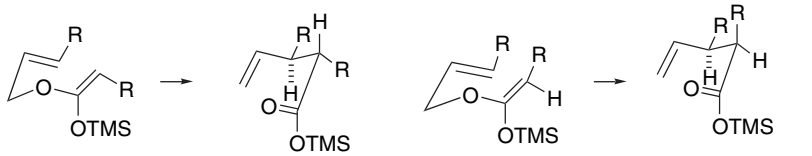
Scheme 6.15. (*Continued*)



a. R. I. Trust and R. E. Ireland, *Org. Synth.*, **53**, 116 (1973).
b. C. A. Hendrick, R. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.*, **94**, 5374 (1972).
c. F. E. Ziegler and G. B. Bennett, *J. Am. Chem. Soc.*, **95**, 7458 (1973).
d. J. J. Plattner, R. D. Glass, and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 8614 (1972).
e. L. Serfass and P. J. Casara, *Bioorg. Med. Chem. Lett.*, **8**, 2599 (1998).
f. D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy, and T. Gallagher, *J. Am. Chem. Soc.*, **113**, 2652 (1991).
g. E. Brenna, N. Caraccia, C. Fuganti, and P. Graselli, *Tetrahedron: Asymmetry*, **8**, 3801 (1997).
h. L. C. Passaro and F. X. Webster, *Synthesis*, 1187 (2003).
i. A. Srikrishna and D. Vijaykumar, *J. Chem. Soc., Perkin Trans. 1*, 2583 (2000).

are suitable for the reaction and permit the synthesis of α, α-disubstituted esters. The reaction in Entry 5 was used in the synthesis of protected analogs of γ-amino acids. The reaction gave the expected *E*-double bond. The reaction in Entry 6 was used in an enantiospecific synthesis of a pumiliotoxin alkaloid. Entry 7 presents a case of chirality transfer. The *S*-allylic alcohol generates the *S*-configuration at the new C−C bond with an e.e. of more than 99%. The reaction in Entry 8 was used in the synthesis of an insect pheromone, and the triple bond was eventually reduced to a *Z*-double bond. The reaction in Entry 9 was part of enantiospecific synthesis of more complex terpenoids from *R*-carvone. Note that in this case, the cyclic TS results in introduction of the ester substituent *syn* to the hydroxy group on the ring, which is a general result for cyclic reactants.

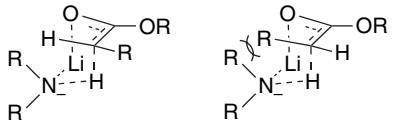
6.4.2.3. Rearrangements of Silyl Ketene Acetals and Ester Enolates. Esters of allylic alcohols can be rearranged to γ, δ-unsaturated carboxylic acids via the *O*-trimethylsilyl ethers of the ester enolate.[236] These intermediates are called *silyl ketene acetals*. This version of the reaction, known as the *Ireland-Claisen rearrangement*,[237] takes place under much milder conditions than the orthoester method. The reaction occurs at room temperature or slightly above. The stereochemistry of the silyl ketene acetal Claisen rearrangement is controlled not only by the configuration of the double bond in the allylic alcohol but also by the stereochemistry of the silyl ketene acetal. The chair TS predicts that the relative configuration at the newly formed C−C bond will be determined by the *E*- or *Z*-stereochemistry of the silyl ketene acetal.



Z-silyl ketene acetal *syn* isomer *E*-silyl ketene acetal *anti* isomer

236. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
237. For reviews, see S. Pereira and M. Srebnik, *Aldrichimica Acta*, **26**, 17 (1993); Y. Chai, S. Hong, H. A. Lindsay, C. McFarland, and M. C. McIntosh, *Tetrahedron*, **58**, 2905 (2002).

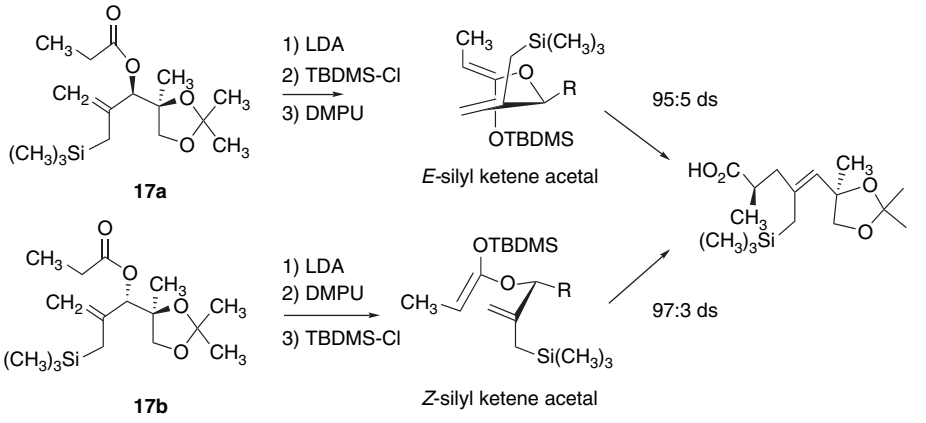
The stereochemistry of the silyl ketene acetal can be controlled by the conditions of preparation. The base that is usually used for enolate formation is lithium diisopropylamide (LDA). If the enolate is prepared in pure THF, the *E*-enolate is generated and this stereochemistry is maintained in the silyl derivative. The preferential formation of the *E*-enolate can be explained in terms of a cyclic TS in which the proton is abstracted from the stereoelectronically preferred orientation perpendicular to the carbonyl plane. The carboxy substituent is oriented away from the alkyl groups on the amide base.



transition structure for *E*-enolate

transition structure for *Z*-enolate

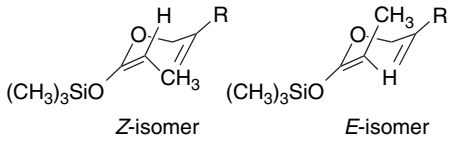
If HMPA is included in the solvent, the *Z*-enolate predominates.[236,238] DMPU also favors the *Z*-enolate. The switch to the *Z*-enolate with HMPA or DMPU is attributed to a looser, perhaps acyclic TS being favored as the result of strong solvation of the lithium ion. The steric factors favoring the *E*-TS are therefore diminished.[239] These general principles of solvent control of enolate stereochemistry are applicable to other systems.[240] For example, by changing the conditions for silyl ketene acetal formation, the diastereomeric compounds **17a** and **17b** can be converted to the same product with high diastereoselectivity.[241]



A number of steric effects on the rate of rearrangement have been observed and can be accommodated by the chairlike TS model.[242] The *E*-silyl ketene acetals rearrange

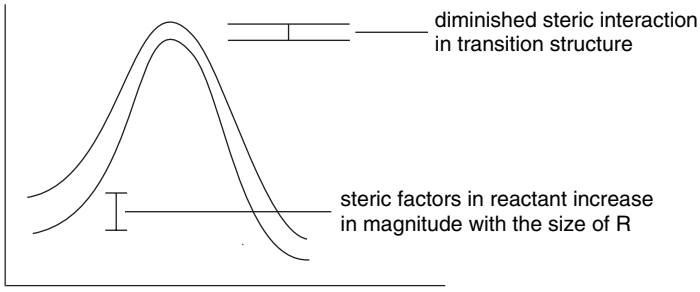
238. R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); R. E. Ireland, P. Wipf, and J. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).
239. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lamp, *J. Org. Chem.*, **45**, 1066 (1980).
240. J. Corset, F. Froment, M.-F. Lautie, N. Ratovelomanana, J. Seyden-Penne, T. Strzalko, and M. C. Roux-Schmitt, *J. Am. Chem. Soc.*, **115**, 1684 (1993).
241. S. D. Hiscock, P. B. Hitchcock, and P. J. Parsons, *Tetrahedron*, **54**, 11567 (1998).
242. C. S. Wilcox and R. E. Babston, *J. Am. Chem. Soc.*, **108**, 6636 (1986).

somewhat more slowly than the corresponding *Z*-isomer. This is interpreted as resulting from the pseudoaxial placement of the methyl group in the *E*-transition structure.

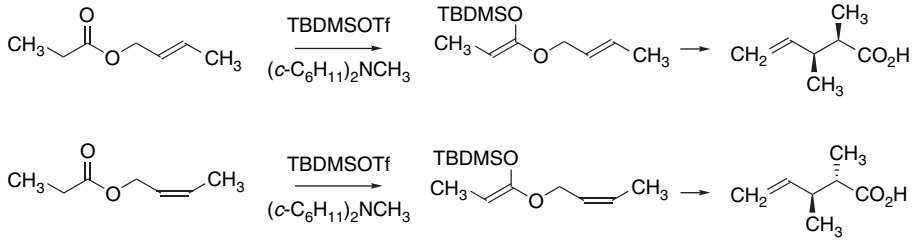


Z-isomer *E*-isomer

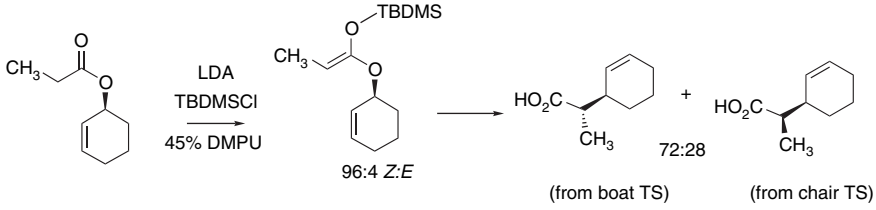
The size of the substituent R also influences the rate, with the rate increasing somewhat for both isomers as R becomes larger. It is believed that steric interactions with R are relieved as the C−O bond stretches. The rate acceleration reflects the higher ground state energy resulting from these steric interactions.



The silyl ketene acetal rearrangement can also be carried out by reaction of the ester with a silyl triflate and tertiary amine, without formation of the ester enolate. Optimum results are obtained with bulky silyl triflates and amines, e.g., *t*-butyldimethylsilyl triflate and *N*-methyl-*N*, *N*-dicyclohexylamine. Under these conditions the reaction is stereoselective for the *Z*-silyl ketene acetal and the stereochemistry of the allylic double bond determines the *syn* or *anti* configuration of the product.[243]



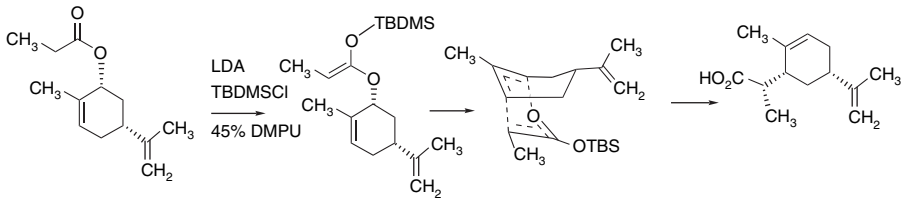
The stereochemistry of Ireland-Claisen rearrangements of cyclic compounds is sometimes indicative of reaction through a boat TS. For example, the major product from 2-cyclohexenyl propanoate is formed through a boat TS.[244]



243. M. Kobayashi, K. Matsumoto, E. Nakai, and T. Nakai, *Tetrahedron Lett.*, **37**, 3005 (1996).

244. (a) R. E. Ireland and P. Maienfisch, *J. Org. Chem.*, **53**, 640 (1988); (b) R. E. Ireland, P. Wipf, and J.D. Armstrong, *J. Org. Chem.*, **56**, 650 (1991); (c) R. E. Ireland, P. Wipf, and J.-N. Xiang, *J. Org. Chem.*, **56**, 3572 (1991).

The reason for the trend toward boat TSs in cyclic systems is the introduction of additional steric factors. For example, addition of methyl and isopropenyl substituents leads to a TS in which the cyclohexene ring adopts a boat conformation, whereas the TS is chairlike.



Heteroatoms, particularly oxygen, introduce electronic factors that favor boat TSs.

Computational modeling (B3LYP/6-31G*) of rearrangement of cyclohexenol identified the four potential TS geometries shown in Figure 6.14.[245] Using the *O*-methyl enol ether as a model, a 2-cyclohexenyl ester prefers a *syn*-boat TS, in agreement with the experimental results. As in the experimental work, the placement of additional substituents alters the relative energies of these TSs.

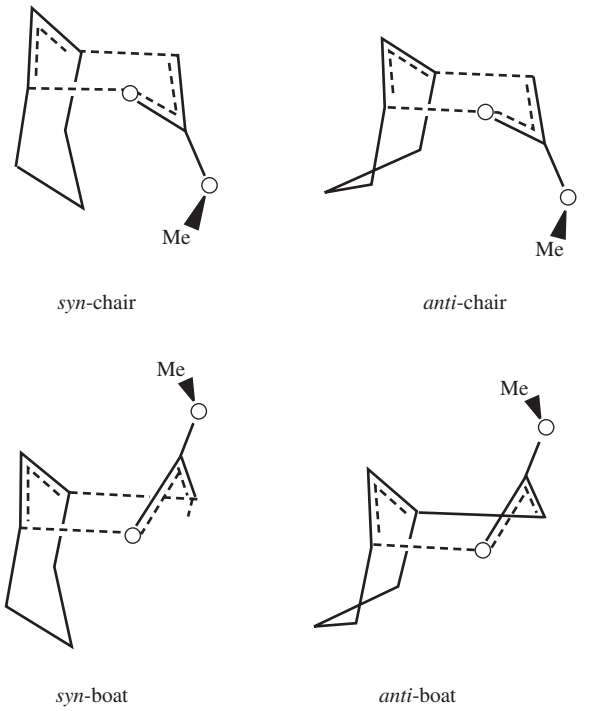
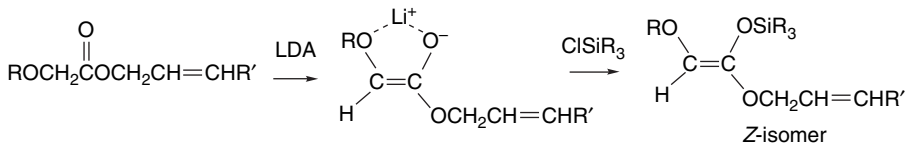


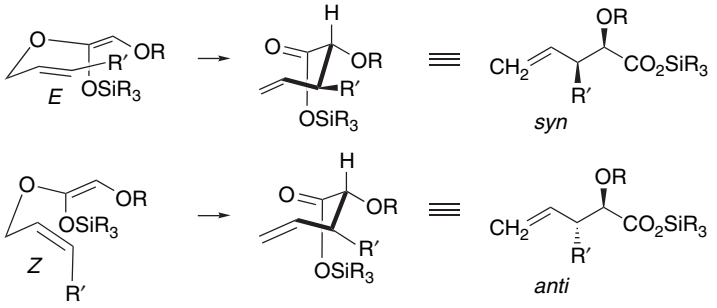
Fig. 6.14. Possible transition structures for [3,3]-sigmatropic rearrangement of 2-cyclohexenyl ester enol ethers. Adapted from *J. Org. Chem.*, **68**, 572 (2003), by permission of the American Chemical Society.

245. M. M. Khaledy, M. Y. S. Kalani, K. S. Khuong, K. N. Houk, V. Aviyente, R. Neier, N. Soldermann, and J. Velker, *J. Org. Chem.*, **68**, 572 (2003).

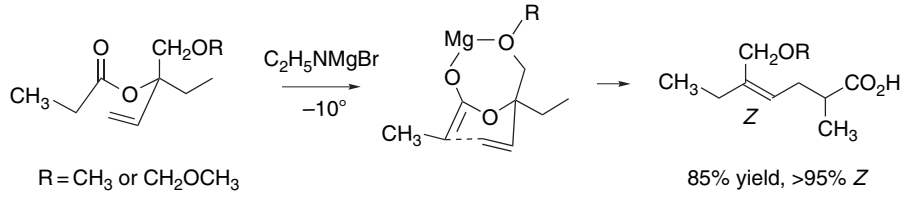
The stereoselectivity of silyl ketene acetal Claisen rearrangements can also be controlled by specific intramolecular interactions.[246] The enolates of α-alkoxy esters adopt the *Z*-configuration because of chelation by the alkoxy substituent.



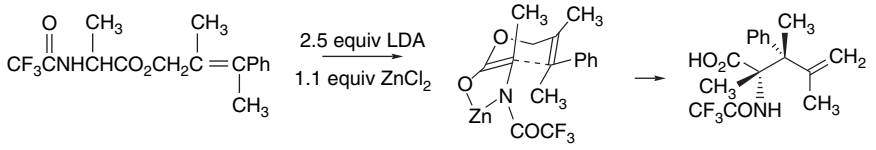
The configuration at the newly formed C−C bond is then controlled by the stereochemistry of the double bond in the allylic alcohol. The *E*-isomer gives a *syn* orientation, whereas the *Z*-isomer gives rise to *anti* stereochemistry.[247]



Similar chelation effects are present in α-alkoxymethyl derivatives. Magnesium enolates give predominantly the *Z*-enolate as a result of this chelation. The corresponding trimethylsilyl ketene acetals give *E*,*Z* mixtures.[248]

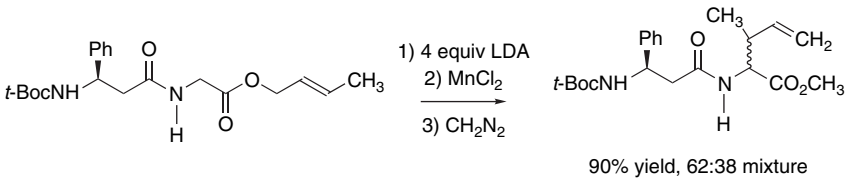


Enolates of allyl esters of α-amino acids are also subject to chelation-controlled Claisen rearrangement.[249]



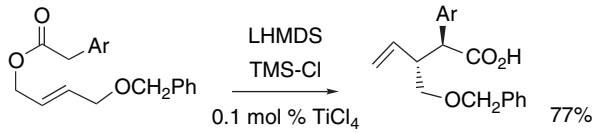
246. H. Frauenrath, in *Stereoselective Synthesis*, G. Helmchen, R. W. Hoffmann, J. Mulzer, and E. Schaumann, eds., Georg Thieme Verlag, Stuttgart, 1996.
247. T. J. Gould, M. Balestra, M. D. Wittman, J. A. Gary, L. T. Rossano, and J. Kallmerten, *J. Org. Chem.*, **52**, 3889 (1987); S. D. Burke, W. F. Fobare, and G. J. Pacofsky, *J. Org. Chem.*, **48**, 5221 (1983); P. A. Bartlett, D. J. Tanzella, and J. F. Barstow, *J. Org. Chem.*, **47**, 3941 (1982).
248. M. E. Krafft, O. A. Dasse, S. Jarrett, and A. Fierve, *J. Org. Chem.*, **60**, 5093 (1995).
249. U. Kazmaier, *Liebigs Ann. Chem.*, 285 (1997); U. Kazmeier, *J. Org. Chem.*, **61**, 3694 (1996); U. Kazmaier and S. Maier, *Tetrahedron*, **52**, 941 (1996).

Various salts can achieve chelation but $ZnCl_2$ and $MgCl_2$ are suitable for most cases. The rearrangement is a useful reaction for preparing amino acid analogs and has also been applied to synthesis of modified dipeptides.[250]



90% yield, 62:38 mixture

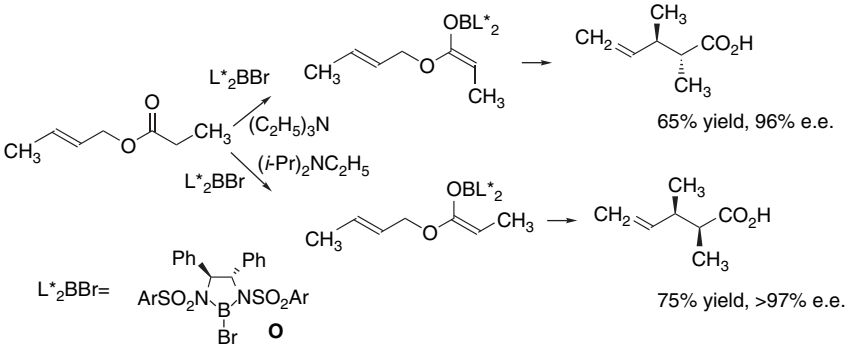
Lewis acid catalysis of Ireland-Claisen rearrangements by $TiCl_4$ has been observed.[251] This methodology was employed in the synthesis of a novel type of anti-inflammatory drug candidate.[252]



Ar = 4-methoxyphenyl

13:1 *anti:syn*

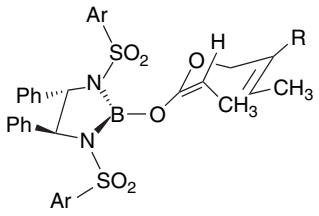
The possibility of using chiral auxiliaries or chiral catalysts to achieve enantioselective Claisen rearrangements has been explored.[253] One approach is to use chiral boron enolates. For example, enolates prepared with the chiral diazaborolidine bromide **O** lead to rearranged products of more than 95% enantiomeric excess.[254]



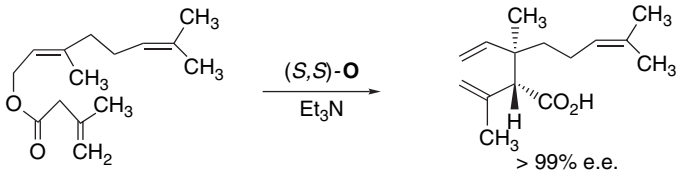
Ar = 3,5-bis(trifluoromethyl)phenyl

The enantioselectivity is consistent with a chairlike TS in which the stereocenters control the rotational preference for the sulfonyl groups that provide stereodifferentiation at the boron center.

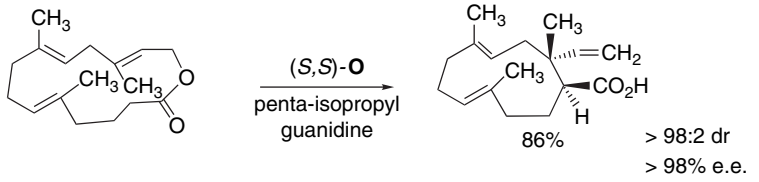
250. U. Kazmaier and S. Maier, *J. Chem. Soc., Chem. Commun.*, 2535 (1998).
251. G. Koch, P. Janser, G. Kottirsch, and E. Romero-Giron, *Tetrahedron Lett.*, **43**, 4837 (2002).
252. G. Koch, G. Kottirsch, B. Wiefeld, and E. Kuesters, *Org. Proc. Res. Dev.*, **6**, 652 (2002).
253. D. Enders, M. Knopp, and R. Schiffers, *Tetrahedron: Asymmetry*, **7**, 1847 (1996).
254. E. J. Corey and D.-H. Lee, *J. Am. Chem. Soc.*, **113**, 4026 (1991).



This methodology has been applied to both acyclic esters and macrocyclic lactones.



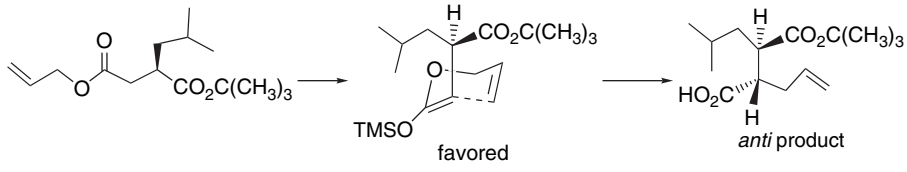
Ref. 255



Ref. 256

Scheme 6.16 gives some examples of Ireland-Claisen rearrangements of silyl ketene acetals and related intermediates. Entry 1 is an example from an early investigation of this version of the rearrangement. Entry 2 involves direct rearrangement of the enolate without silylation. The reaction in Entry 3 was used for stereoselective synthesis of the γ, δ-unsaturated acid, which was used in the synthesis of a butterfly pheromone. The TBDMS derivative gave a somewhat higher yield than the TMS derivative in this case. The reaction in Entry 4 was used in the conversion of carbohydrate-derived starting materials to structures found in ionophore antibiotics. The reaction conditions, which involved use of *premixed* LDA and TMS-Cl, were designed to avoid a competing β-elimination of the enolate by rapid silylation of the enolate.

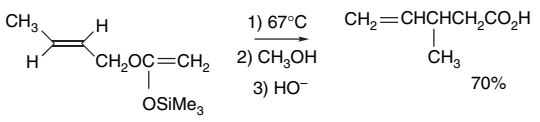
In Entry 5, the chirality at an alkylated succinate ester is maintained and a 9:1 dr favoring the *anti* product is achieved, based on a preferred orientation relative to the branched substituent.



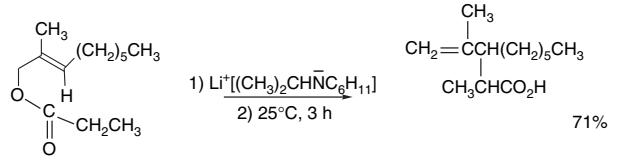
255. E. J. Corey, B. E. Roberts, and B. R. Dixon, *J. Am. Chem. Soc.*, **117**, 193 (1995).
256. E. J. Corey and R. S. Kania, *J. Am. Chem. Soc.*, **118**, 1229 (1996).

Scheme 6.16. Rearrangement of Silyl Ketene Acetals and Ester Enolates

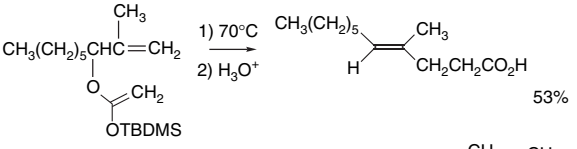
1[a]



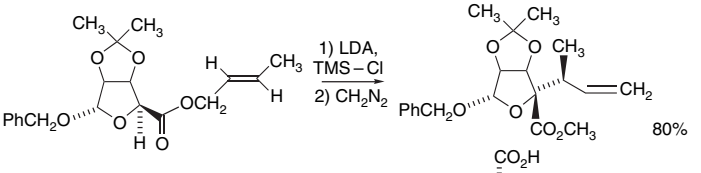
2[a]



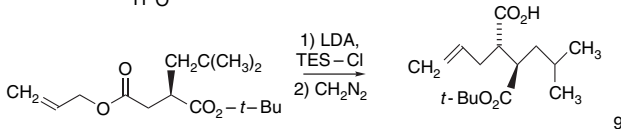
3[b]



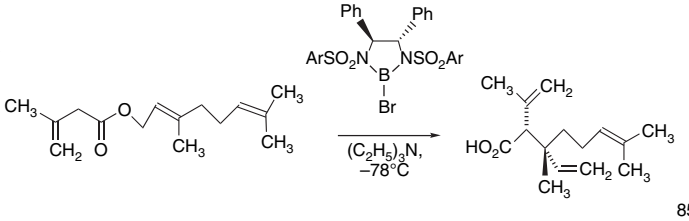
4[c]



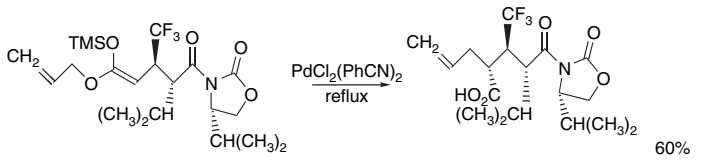
5[d]



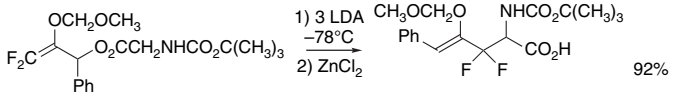
6[e]



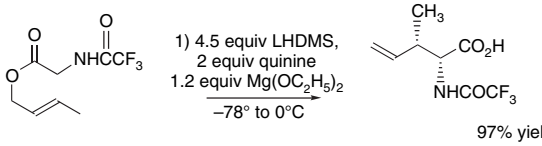
7[f]



8[g]

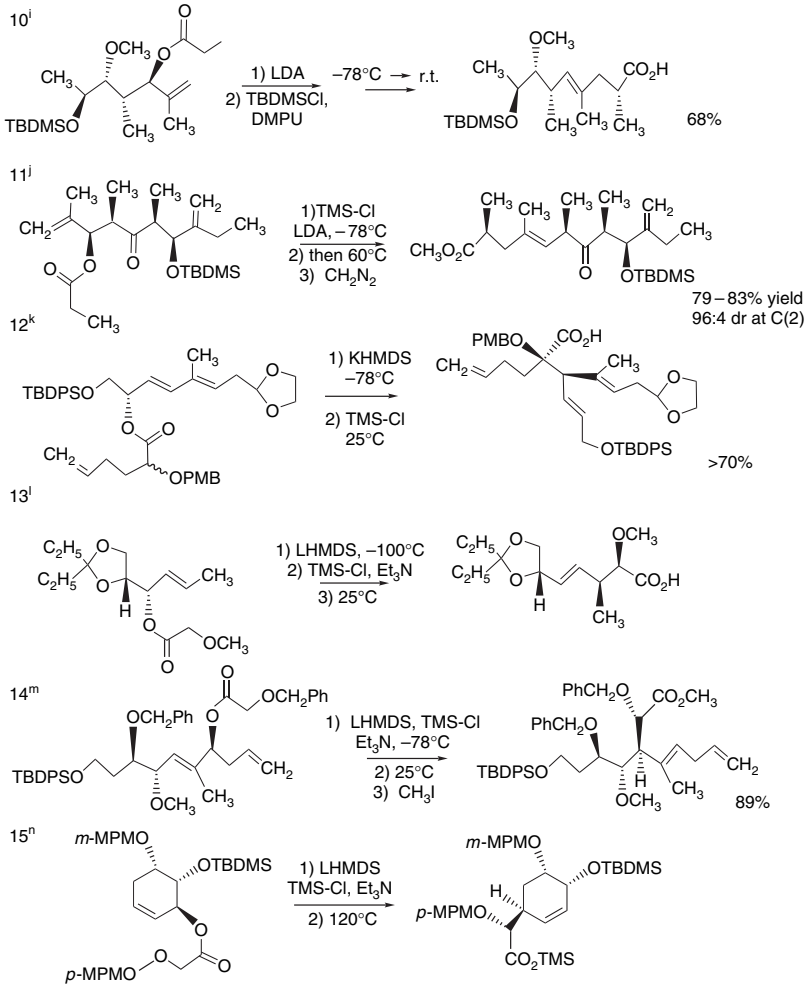


9[h]



(*Continued*)

Scheme 6.16. (*Continued*)

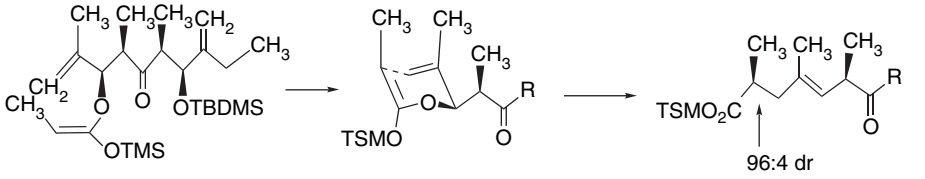


a. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
b. J. A. Katzenellenbogen and K. J. Cristy, *J. Org. Chem.*, **39**, 3315 (1974).
c. R. E. Ireland and D. W. Norbeck, *J. Am. Chem. Soc.*, **107**, 3279 (1985).
d. L. M. Pratt, S. A. Bowler, S. F. Courney, C. Hidden, C. N. Lewis, F. M. Martin, and R. S. Todd, *Synlett*, 531 (1998).
e. E. J. Corey, B. E. Roberts, and B. R. Dixon, *J. Am. Chem. Soc.*, **117**, 193 (1995).
f. T. Yamazaki, N. Shinohara, T. Katzume, and S. Sato, *J. Org. Chem.*, **60**, 8140 (1995).
g. J. M. Percy, M.E. Prime, and M J. Broadhurst, *J. Org. Chem.*, **63**, 8049 (1998).
h. A. Kazmaier and A. Krebs, *Tetrahedron Lett.*, **40**, 479 (1999).
i. P. R. Blakemore, P. J. Kocienski, A. Morley, and K. Muir, *J. Chem. Soc., Perkin Trans. 1*, 955 (1999).
j. I. Paterson and A. N. Hulme, *J. Org. Chem.*, **60**, 3288 (1995).
k. O. Bedell, A. Haudrecky, and Y. Langlois, *Eur. J. Org. Chem.*, 3813 (2004).
l. S. D. Burke, J. Hong, J. R. Lennox, and A. P. Mongin, *J. Org. Chem.*, **63**, 6952 (1998).
m. D. Kim, S. K. Ahn, H. Bae, W. J. Choi, and H. S. Kim, *Tetrahedron Lett.*, **38**, 4437 (1997).
n. S. D. Burke, J. J. Letourneau, and M. Matulenko, *Tetrahedron Lett.*, **40**, 9 (1999).

Entry 6 is an example of application of the chiral diazaborolidine enolate method (see p. 572). Entry 7 involves generation of the silyl ketene acetal by silylation after conjugate addition of the enolate of 3-methylbutanoyloxazolidinone to allyl 3,3,3-trifluoroprop-2-enoate. A palladium catalyst improved the yield in the rearrangement

step. Entry 8 involves another fluorinated reactant. The reaction is an adaptation of the rearrangement of α-amido ester enolates, as discussed on p. 572, and involves a chelated enolate. Entry 9 is another example of this type of reaction. Use of quinine or quinidine with the chelating metal leads to enantioselectivity.

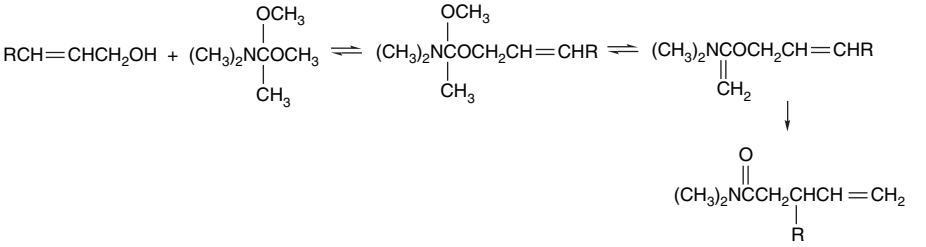
Entries 10 to 15 involve use of the Ireland-Claisen rearrangement in multistep syntheses. An interesting feature of Entry 11 is the presence of an unprotected ketone. The reaction was done by adding LDA to the ester, which was premixed with TMS-Cl and Et_3N. The reaction generates the *E*-silyl ketene acetal, which rearranges through a chair TS.



Entries 12 to 15 are examples of α-alkoxy (protected glycolate) esters. These reactions proceed through chelated TSs. (See the discussion on p. 571.) The TS for Entries 13 and 14 are shown below.

Entry 15 also demonstrates the suprafacial specificity with a cyclic allylic alcohol.

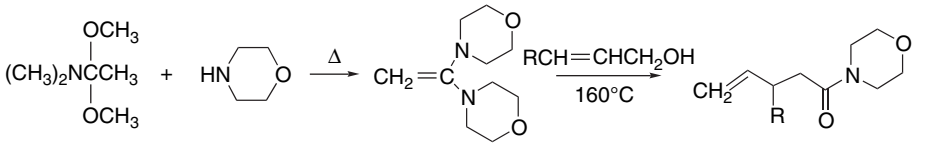
6.4.2.4. Claisen Rerrangements of Ketene Aminals and Imidates. A reaction that is related to the orthoester Claisen rearrangement utilizes an amide acetal, such as dimethylacetamide dimethyl acetal, in the exchange reaction with allylic alcohols.[257] The products are γ, δ-unsaturated amides. The stereochemistry of the reaction is analogous to the other variants of the Claisen rearrangement.[258]



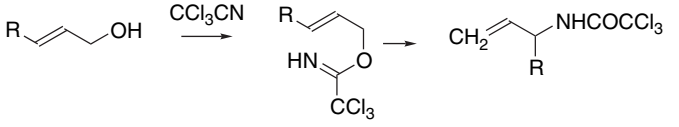
257. A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964); D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).

258. W. Sucrow, M. Slopianka, and P. P. Calderia, *Chem. Ber.*, **108**, 1101 (1975).

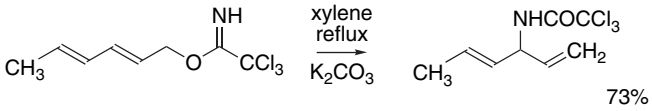
The rearrangement can be applied to other secondary amines by prior equilibration, which is driven forward by removal of the more volatile dimethylamine.[259]



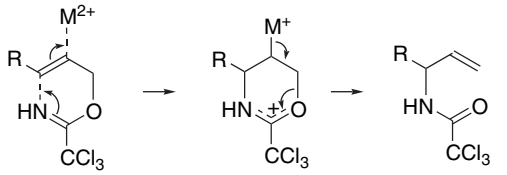
O-Allyl imidate esters undergo [3,3]-sigmatropic rearrangements to *N*-allyl amides. Trichloromethyl imidates can be made easily from allylic alcohols by reaction with trichloroacetonitrile. The rearrangement then provides trichloroacetamides of *N*-allylamines.[260]



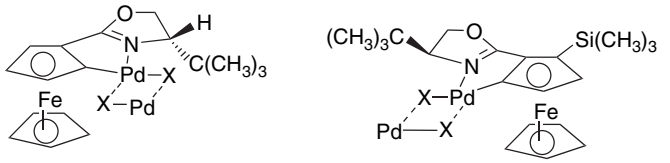
Yields in the reaction are sometimes improved by inclusion of K_2CO_3 in the reaction mixture.[261]



Trifluoromethyl imidates show similar reactivity.[262] Imidate rearrangements are catalyzed by palladium salts.[263] The mechanism is presumably similar to that for the Cope rearrangement (see p. 555).

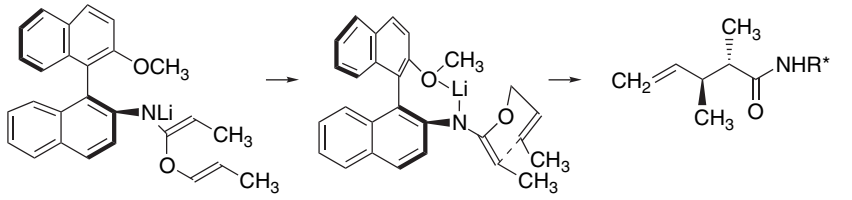


Chiral Pd catalysts can achieve enantioselectivity. The best catalysts developed to date are dimeric ferrocenyl derivatives.[264]

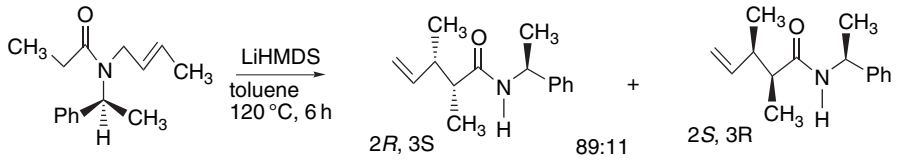


259. S. N. Gradl, J. J. Kennedy-Smith, J. Kim, and D. Trauner, *Synlett*, 411 (2002).
260. L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976); L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).
261. T. Nishikawa, M. Asai, N. Ohyabu, and M. Isobe, *J. Org. Chem.*, **63**, 188 (1998).
262. A. Chen, J. Savage, E. D. Thomas, and P. D. Wilson, *Tetrahedron Lett.*, **34**, 6769 (1993).
263. L. E. Overman, *Angew. Chem. Int. Ed. Engl.*, **23**, 579 (1984); T. G. Schenck and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2058 (1985); P. Metz, C. Mues, and A. Schoop, *Tetrahedron*, **48**, 1071 (1992).
264. Y. Donde and L. E. Overman, *J. Am. Chem. Soc.*, **121**, 2933 (1999).

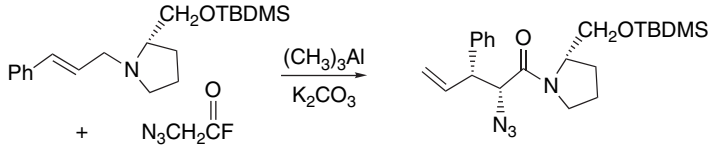
Imidate esters can also be generated by reaction of imidoyl chlorides and allylic alcohols. The lithium anions of these imidates, prepared using lithium diethylamide, rearrange at around 0° C. When a chiral amine is used, this reaction can give rise to enantioselective formation of γ, δ-unsaturated amides. Good results were obtained with a chiral binaphthylamine.[265] The methoxy substituent is believed to play a role as a Li^+ ligand in the reactive enolate.



Enolates of *N*-allyl amides undergo [3,3]-sigmatropic rearrangement. This reaction is analogous to the ester enolate Claisen rearrangement, but the conditions required are more vigorous.[266] An attractive feature of this reaction is that it permits introduction of a chiral group at nitrogen, which then has the potential to effect enantioselective formation of a new C−C bond. For example, α-arylethyl substituents induced enantioselectivity ranging from 3:1 to 11:1.

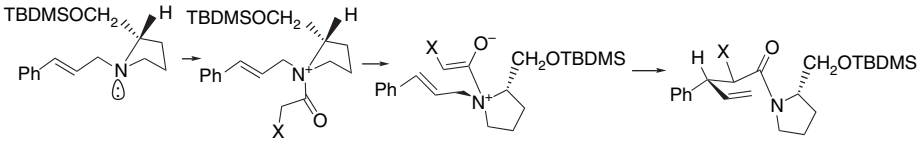


Analogous rearrangement occurs under much milder conditions when the reactant is a zwitterion generated by deprotonation of an acylammonium ion. Substituted pyrrolidines were used as the chiral auxiliary, with the highest enantioselectivity being achieved with a 2-TBDMS derivative.[267]



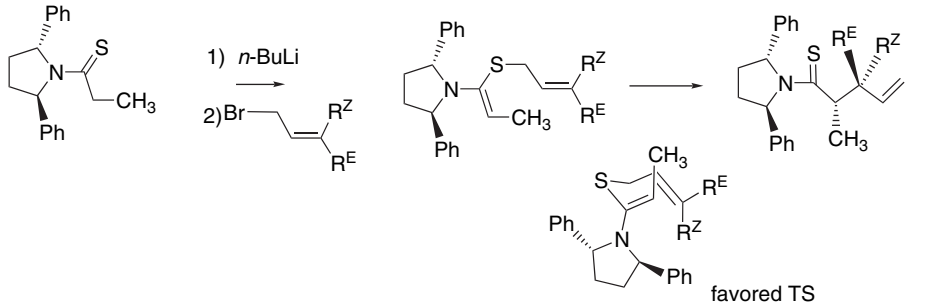
91% yield, > 95% de

The preferred TS is a chair with the enolate oriented *syn* to the bulky pyrrolidine substituent. It was suggested that the *syn* acylation occurs through an envelope conformation of the pyrrolidine ring with the nitrogen electron pair oriented axially.

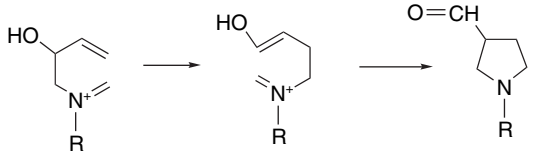


265. P. Metz and B. Hungerhoff, *J. Org. Chem.*, **62**, 4442 (1997).
266. T. Tsunoda, M. Sakai, O. Sasaki, Y. Sato, Y. Hondo, and S. Ito, *Tetrahedron Lett.*, **33**, 1651 (1992).
267. S. Laabs, W. Munch, J.-W. Bats, and U. Nubbemeyer, *Tetrahedron*, **58**, 1317 (2002).

Another promising variant involves thioamides, which provide *Z*-thioenolates on deprotonation.[268] Use of *trans*-2,4-diphenylpyrrolidine as the chiral auxiliary leads to good enantioselectivity.[269] Allyl groups with *E*-configuration give mainly *anti* products with somewhat reduced diastereoselectivity. These results indicate that a steric interaction between the pyrrolidine substituent and the *Z*-allyl group is a controlling factor in diastereoselectivity.



The 2-azonia analog of the Cope rearrangement is estimated to be accelerated by 10^6, relative to the unsubstituted system.[270] The product of the rearrangement is an isomeric iminium ion, which is a mild electrophile. In synthetic applications, the reaction is often designed to generate this electrophilic site in a position that can lead to a cyclization by reaction with a nucleophilic site. For example, the presence of a 4-hydroxy substituent generates an enol that can react with the iminiun ion intermediate to form a five-membered ring.[271]



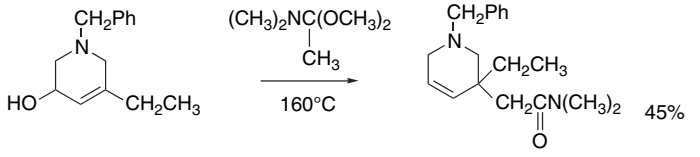
Scheme 6.17 gives some examples of the orthoamide and imidate versions of the Claisen rearrangement. Entry 1 applied the reaction in the synthesis of a portion of the alkaloid tabersonine. The reaction in Entry 2 was used in an enantiospecific synthesis of pravastatin, one of a family of drugs used to lower cholesterol levels. The product from the reaction in Entry 3 was used in a synthesis of a portion of the antibiotic rampamycin. Entries 4 and 5 were used in the synthesis of polycyclic natural products. Note that the reaction in Entry 4 also leads to isomerization of the double bond into conjugation with the ester group. Entries 1 to 5 all involve cyclic reactants, and the concerted TS ensures that the substituent is introduced *syn* to the original hydroxy substituent.

Entry 6 is analogous to a silyl ketene acetal rearrangement. The reactant in this case is an imide. Entry 7 is an example of $PdCl_2$-catalyzed imidate rearrangement. Entry 8 is an example of an azonia-Cope rearrangement, with the monocylic intermediate then undergoing an intramolecular Mannich condensation. (See Section 2.2.1 for a discussion of the Mannich reaction). Entry 9 shows a thioimidate rearrangement.

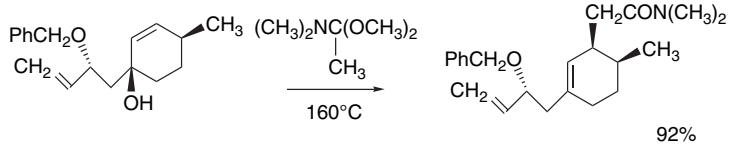
268. Y. Tamaru, Y. Furukawa, M. Mizutani, O. Kitao, and Z. Yoshida, *J. Org. Chem.*, **48**, 3631 (1983).
269. S. He, S. A. Kozmin, and V. H. Rawal, *J. Am. Chem. Soc.*, **122**, 190 (2000).
270. L. A. Overman, *Acc. Chem. Res.*, **25**, 353 (1992).
271. L. E. Overman and M. Kakimoto, *J. Am. Chem. Soc.*, **101**, 1310 (1979); L. E. Overman, M. Kakimoto, M. Okazaki, and G. P. Meier , *J. Am. Chem. Soc.*, **105**, 6622 (1983).

Scheme 6.17. Rearrangements of Orthoamides and Imidates

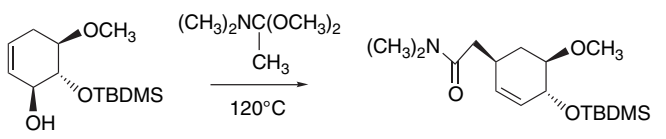
1[a]



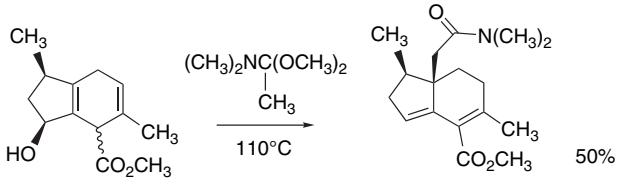
2[b]



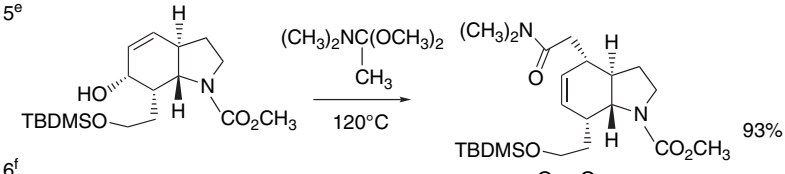
3[c]



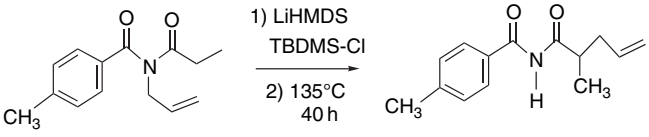
4[d]



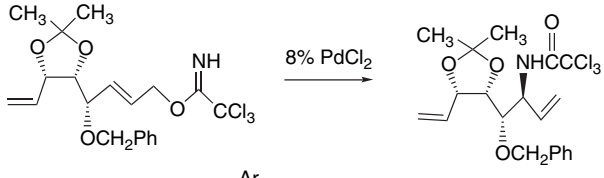
5[e]



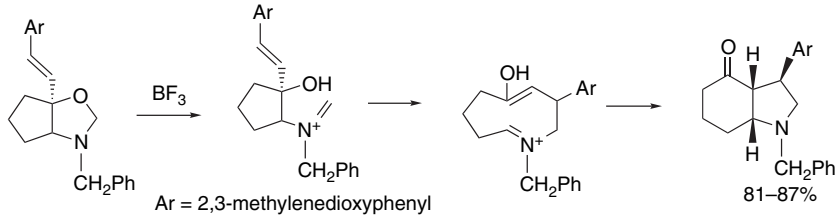
6[f]



7[g]



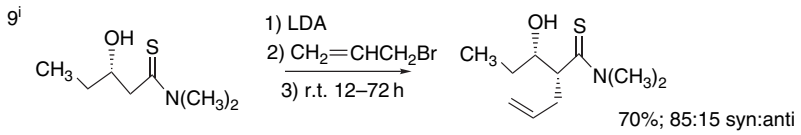
8[h]



Ar = 2,3-methylenedioxyphenyl

(*Continued*)

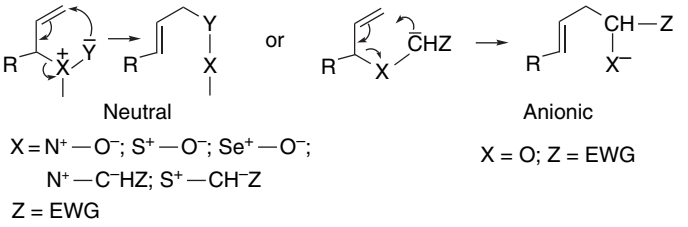
Scheme 6.17. (*Continued*)



a. F. E. Ziegler and G. B. Bennett, *J. Am. Chem. Soc.*, **95**, 7458 (1973).
b. A. R. Daniewski, P. M. Wovkulich, and M. R. Uskokovic, *J. Org. Chem.* , **57**, 7133 (1992).
c. K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty, and N. Minowa, *J. Chem. Soc., Chem. Commun.*, 619 (1993).
d. T.-P. Loh and Q.-Y. Hu, *Org. Lett.*, **3**, 279 (2001).
e. C.-Y. Chen and D. J. Hart, *J. Org. Chem.*, **58**, 3840 (1993).
f. K. Neuschutz, J.-M. Simone, T. Thyrann, and R. Neier, *Helv. Chim. Acta*, **83**, 2712 (2000).
g. H. Ovaa, J. D. C. Codee, B. Lastdrager, H. Overkleeft, G. A.van der Marel, and J. H. van Boom, *Tetrahedron Lett.*, **40**, 5063 (1999).
h. L. E. Overman and J. Shim, *J. Org. Chem.*, **58**, 4662 (1993).
i. P. Beslin and B. Lelong, *Tetrahedron*, **53**, 17253 (1997).

6.5. [2,3]-Sigmatropic Rearrangements

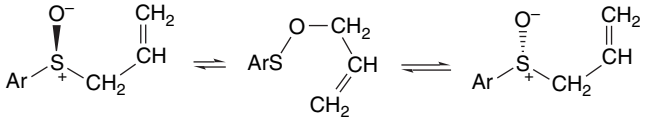
The [2,3]-sigmatropic class of rearrangements is represented by two generic charge types, neutral and anionic.



The rearrangements of allylic sulfoxides, selenoxides, and amine oxides are an example of the first type. Allylic sulfonium ylides and ammonium ylides also undergo [2,3]-sigmatropic rearrangements. Rearrangements of carbanions of allylic ethers are the major example of the anionic type. These reactions are considered in the following sections.

6.5.1. Rearrangement of Allylic Sulfoxides, Selenoxides, and Amine Oxides

The rearrangement of allylic sulfoxides to allylic sulfenates was first studied in connection with the mechanism of racemization of allyl aryl sulfoxides.[272] Although the allyl sulfoxide structure is strongly favored at equilibrium, rearrangement through the achiral allyl sulfenate provides a low-energy pathway for racemization.

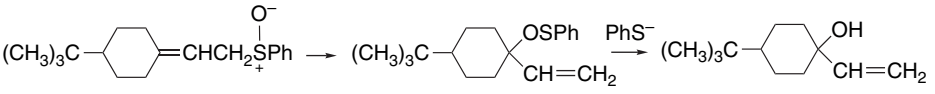


[272] R. Tang and K. Mislow, *J. Am. Chem. Soc.*, **92**, 2100 (1970).

The reactions occur preferentially though an *endo* TS in which the sulfur substituent is oriented toward the allylic group.[273] Computational studies (MP2/6-31G*) found the *endo* TS to be favored over the *exo* by 1.5–2.2. kcal/mol.[274]

endo TS *exo* TS

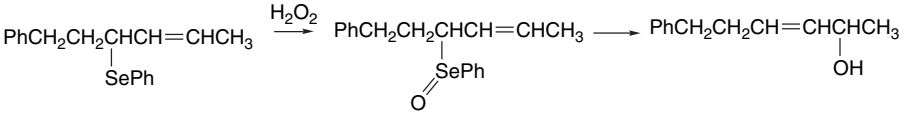
The allyl sulfoxide–allyl sulfenate rearrangement can be used to prepare allylic alcohols.[275] The reaction is carried out in the presence of a reagent, such as phenylthiolate or trimethyl phosphite, that reacts with the sulfenate to cleave the S−O bond.

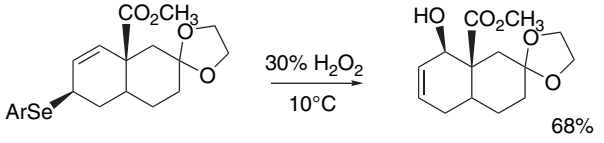


95%

Ref. 276

An analogous reaction occurs when allylic selenoxides are generated in situ by oxidation of allylic selenyl ethers.[277]

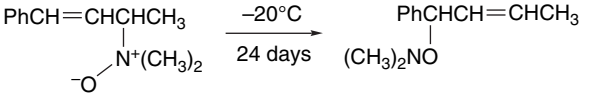




68%

Ref. 278

N-Allylamine oxides represent the general pattern for [2,3]-sigmatropic rearrangement where X = N and Y = $O^{-\cdot}$ The rearrangement provides *O*-allyl hydroxylamine derivatives.

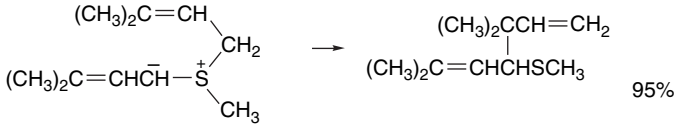


Ref. 279

273. P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968).
274. D. K. Jones-Hertzog and W. L. Jorgensen, *J. Am. Chem. Soc.*, **117**, 9077 (1995).
275. D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
276. D. A. Evans, G. C. Andrews, and C. L. Sims, *J. Am. Chem. Soc.*, **93**, 4956 (1971).
277. H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975); D. L. J. Clive, G. Chittatu, N. J. Curtis, and S. M. Menchen, *Chem. Commun.*, 770 (1978).
278. P. A. Zoretic, R. J. Chambers, G. D. Marbury, and A. A. Riebiro, *J. Org. Chem.*, **50**, 2981 (1985).
279. Y. Yamamoto, J. Oda, and Y. Inouye, *J. Org. Chem.*, **41**, 303 (1976).

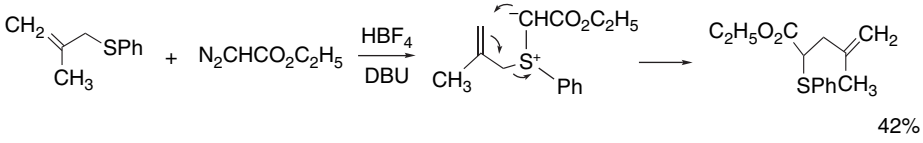
6.5.2. Rearrangement of Allylic Sulfonium and Ammonium Ylides

Allylic sulfonium ylides readily undergo [2,3]-sigmatropic rearrangement.[280] The ylides are usually formed by deprotonation of the *S*-allyl sulfonium salts.

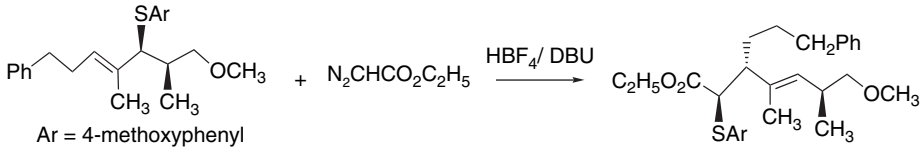


The reaction proceeds best when the ylide has a carbanion-stabilizing substituent. This reaction results in carbon-carbon bond formation and has found synthetic application in ring-expansion sequences for generation of medium-sized rings.

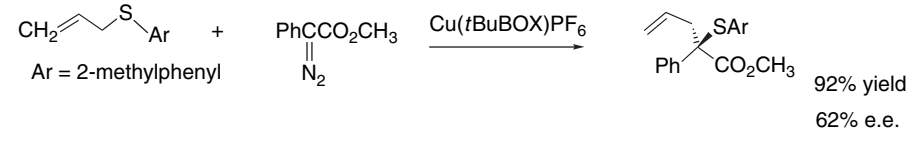
Sulfonium ylides can also be generated by *in situ* alkylation with diazo compounds. The alkylation can be carried out by reaction of a diazo compound with HBF_4 and DBU.[281] The reagents are added alternately in small portions and the reaction presumably proceeds by trapping of the carbocation generated by dediazonization and deprotonation.



Reactions of this type lead to preferential formation of the *anti* stereochemistry at the new C—C bond.

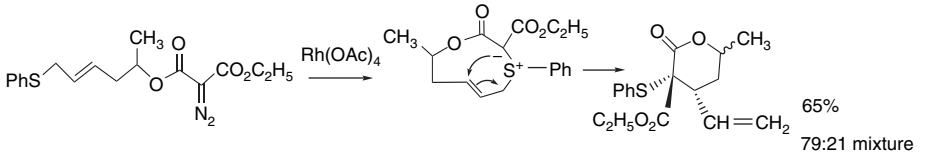


Sulfonium ylides can also be generated from diazo compounds under carbenoid conditions by using metal catalysts. (See Section 10.2.3.2 for discussion of this means of carbene generation.) The reaction results in transposition of the ester fragment and the sulfide group to the γ-carbon of the allylic group. This reaction has been investigated using chiral catalysts such as Cu(*t*-BuBOX)PF_6. Modest enantioselectivity has been achieved using ethyl diazoacetate[282] and methyl phenyldiazoacetate[283] as the carbene precursors.

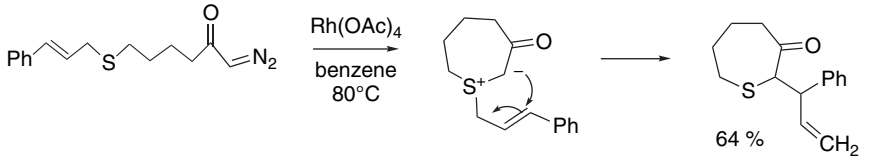


280. J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 537 (1968).
281. M. J. Kurth, S. H. Tahir, and M. M. Olmstead, *J. Org. Chem.*, **55**, 2286 (1990); R. C. Hartley, S. Warren, and I. C. Richards, *J. Chem. Soc., Perkin Trans. 1*, 507 (1994).
282. D. W. McMillen, N. Varga, B. A. Reed, and C. King, *J. Org. Chem.*, **65**, 2532 (2000).
283. X. Zhang, Z. Qu, Z. Ma, W. Shi, X. Jin, and J. Wang, *J. Org. Chem.*, **67**, 5621 (2002).

Rhodium catalysis have been used for formation of ylides by intramolecular reactions.

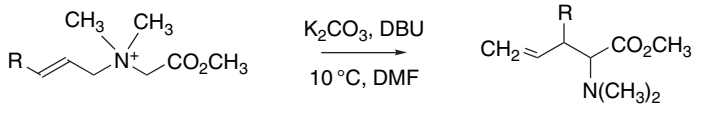


Ref. 284.

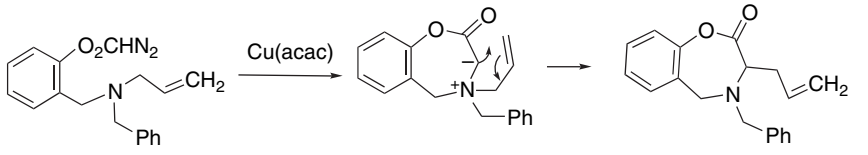


Ref. 285.

Ammonium ylides can also be generated when one of the nitrogen substituents has an anion stabilizing group on the α-carbon. For example, quaternary salts of *N*-allyl α-aminoesters readily rearrange to γ,δ-unsaturated α-aminoesters.[286]



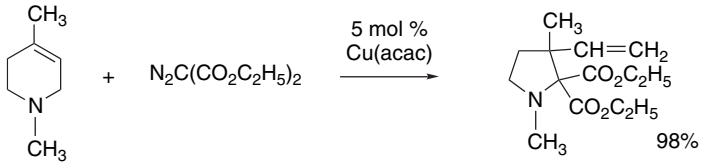
Ammonium ylides can also be generated by the carbenoid route.



Ref. 287.

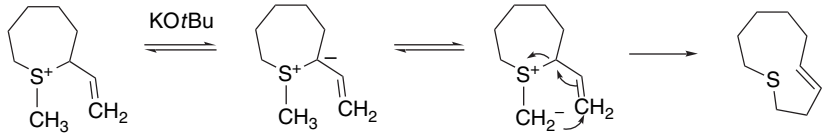
Copper-catalyzed reactions are particularly effective with α-diazo-β-dicarbonyl compounds such as diethyl diazomalonate.

284. F. Kido, S. C. Sinha, T. Abiko, M. Watanabe, and A. Yoshikoshi, *Tetrahedron*, **46**, 4887 (1990).
285. C. J. Moody and R. J. Taylor, *Tetrahedron*, **46**, 6501 (1990).
286. I. Coldham, M. L. Middleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2951 (1997); I. Coldham, M. L. Midleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2817 (1998).
287. J. S. Clark and M. L. Middleton, *Org. Lett.*, **4**, 765 (2002).

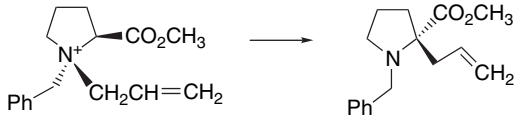


Ref. 288

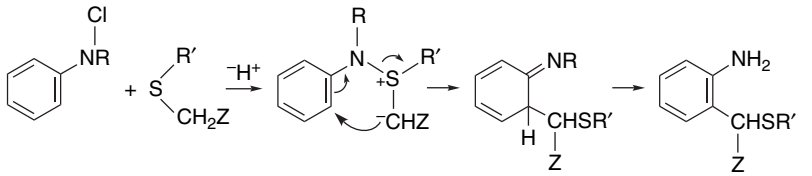
Scheme 6.18 illustrates typical reaction conditions for [2,3]-sigmatropic rearrangements of sulfonium and ammonium ylides. The reactant sulfonium salt used in Entry 1 is generated by alkylation of ethyl methylthioacetate and rearrangement occurs in the presence of potassium carbonate. Entries 2 and 3 show ring-expansion reactions. The reactant in Entry 2 has no activating group and the reaction presumably proceeds through a small equilibrium concentration of the methylide.



Entries 5 to 8 involve ammonium ylides. These reactions effect an N to C transfer of the substituent with 1,3-allylic transposition. In the case of Entry 7, the anionic stabilization is provided by a vinylogous ester group. The reaction in Entry 8 begins with N-allylation, which takes place *syn* to the ester group because of the *trans* orientation of the ester and benzyl groups, and the chirality is thereby induced at the nitrogen atom. The [2,3]-rearrangement then transfers chirality to C(2) of the pyrrolidine ring.



A useful method for *ortho*-alkylation of aromatic amines is based on [2,3]-sigmatropic rearrangement of *S*-anilinosulfonium ylides. These ylides are generated from anilinosulfonium ions, which can be prepared from *N*-chloroanilines and sulfides.[289]



This method is the basis for synthesis of nitrogen-containing heterocyclic compounds when Z is a carbonyl-containing substituent.[290]

288. E. Roberts, J. P. Sancon, J. B. Sweeney, and J. A. Workman, *Org. Lett.*, **5**, 4775 (2003).

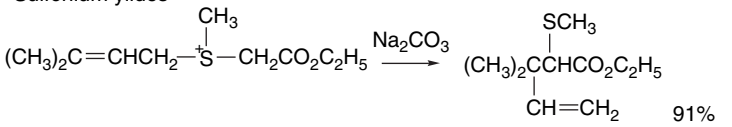
289. P. G. Gassman and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974); P. G. Gassman and H. R. Drewes, *J. Am. Chem. Soc.*, **100**, 7600 (1978).

290. P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **96**, 5495 (1974); P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974); P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974).

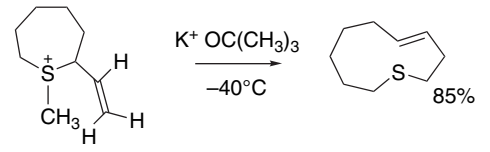
Scheme 6.18. Carbon-Carbon Bond Formation via [2,3]-Sigmatropic Rearrangements of Sulfonium and Ammonium Ylides

A. Sulfonium ylides

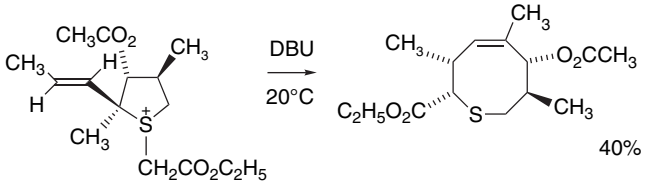
1[a]



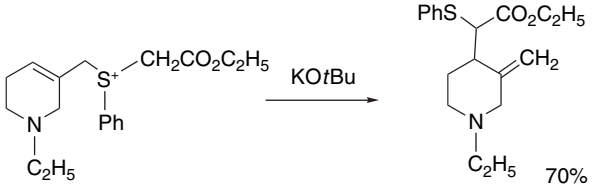
2[b]



3[c]

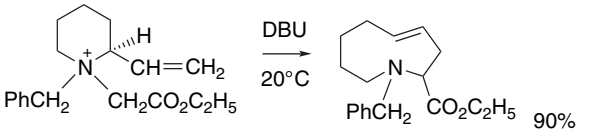


4[d]

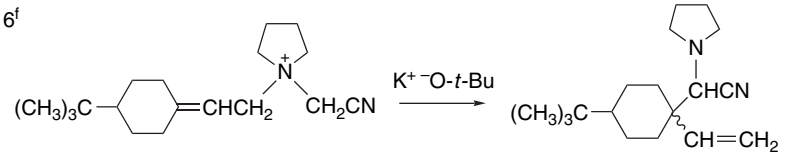


B. Ammonium ylides

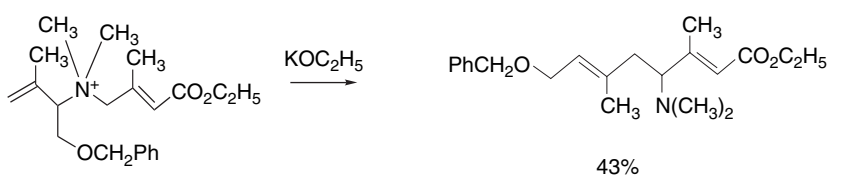
5[e]



6[f]



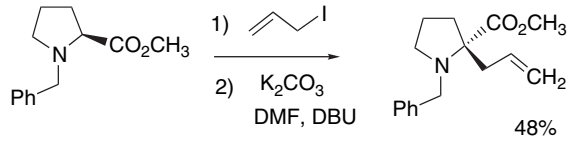
7[g]



(*Continued*)

Scheme 6.18. (*Continued*)

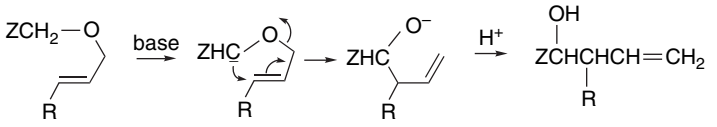
8[h]



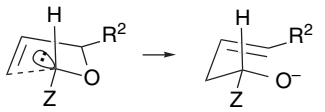
a. K. Ogura, S. Furukawa, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **102**, 2125 (1980).
b. V. Cere, C. Paolucci, S. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.*, **43**, 4826 (1978).
c. E. Vedejs and M. J. Mullins, *J. Org. Chem.*, **44**, 2947 (1979).
d. R. C. Hartley, S. Warren, and I. C. Richards, *J. Chem. Soc., Perkin Trans. 2*, 507 (1994).
e. E. Vedejs, M. J. Arco, D. W. Powell, J. M. Renga, and S. P. Singer, *J. Org. Chem.*, **43**, 4831 (1978).
f. L. N. Mander and J. V. Turnerk, *Aust. J. Chem.*, **33**, 1559 (1980).
g. K. Honda, I. Yoshii, and S. Inoue, *Chem. Lett.*, 671 (1996).
h. A. P. A. Arbore, D. J. Cane-Honeysett, I. Coldham, and M. L. Middleton, *Synlett*, 236 (2000).

6.5.3. Anionic Wittig and Aza-Wittig Rearrangements

The [2,3]-sigmatropic rearrangement pattern is also observed with anionic species. The most important case for synthetic purposes is the *Wittig rearrangement*, in which a strong base converts allylic ethers to α-allylalkoxides.[291] Since the deprotonation at the α′-carbon must compete with deprotonation of the α-carbon in the allyl group, most examples involve a conjugated or EWG substituent Z.[292]



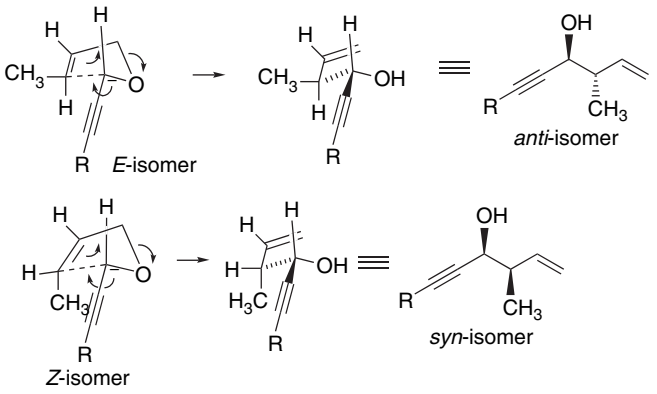
The stereochemistry of the Wittig rearrangement can be predicted in terms of a cyclic five-membered TS in which the α-substituent prefers an equatorial orientation.[293]



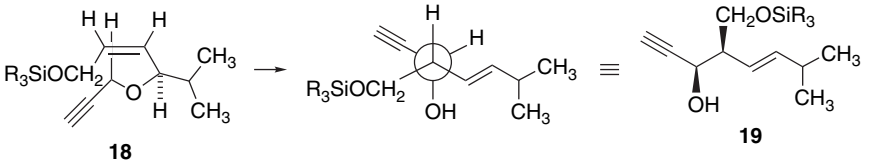
A consistent feature of the stereoselectivity is a preference for *E*-configuration at the newly formed double bond. The reaction can also show stereoselectivity at the newly formed single bond. This stereoselectivity has been carefully studied for the case in

291. J. Kallmarten, in *Stereoselective Synthesis: Houben Weyl Methods in Organic Chemistry*, Vol E21d, R. W. Hoffmann, J. Mulzer, and E. Schaumann, eds., G. Thieme Verlag, Stuttgart, 1996, pp. 3810 ff.
292. For a review of [2,3]-sigmatropic rearrangement of allyl ethers, see T. Nakai and K. Mikami, *Chem. Rev.*, **86**, 885 (1986).
293. R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **18**, 563 (1979); K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, **48**, 279 (1983); K. Mikami, K. Azuma, and T. Nakai, *Tetrahedron*, **40**, 2303 (1984); Y.-D. Wu, K. N. Houk, and J. A. Marshall, *J. Org. Chem.*, **55**, 1421 (1990).

which the substituent Z is an alkynyl group. The *E*-isomer leads to *anti* product and the *Z*-isomer to the *syn* product.



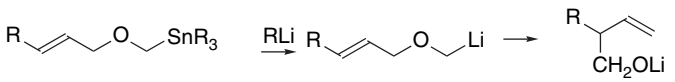
The preferred TS minimizes interaction between the Z and allylic substituents. This stereoselectivity is illustrated in the rearrangement of **18** to **19**.



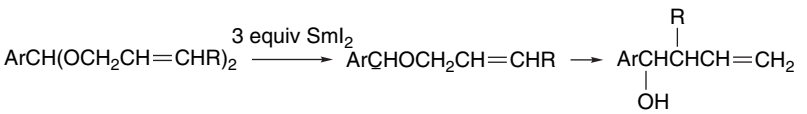
18 **19**

Ref. 294

There are other means of generating the anions of allyl ethers. One of the most useful for synthetic purposes involves a lithium-tin exchange on stannylmethyl ethers (see Section 7.1.2.4).[295]



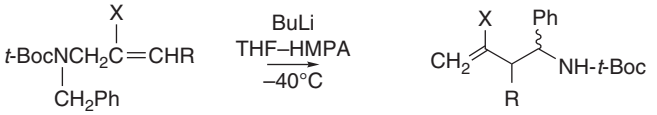
Another means involves reduction of allylic acetals of aromatic aldehydes by SmI_2.[296]



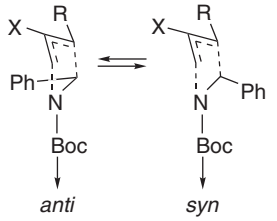
[2,3]-Sigmatropic rearrangements of anions of *N*-allyl amines have also been observed and are known as *aza-Wittig rearrangements*.[297] The reaction requires anion stabilizing substituents and is favored by *N*-benzyl and by silyl or sulfenyl substituents

294. M. M. Midland and J. Gabriel, *J. Org. Chem.*, **50**, 1143 (1985).
295. W. C. Still and A. Mitra, *J. Am. Chem. Soc.*, **100**, 1927 (1978).
296. H. Hioki, K. Kono, S. Tani, and M. Kunishima, *Tetrahedron Lett.*, **39**, 5229 (1998).
297. C. Vogel, *Synlett*, 497 (1997).

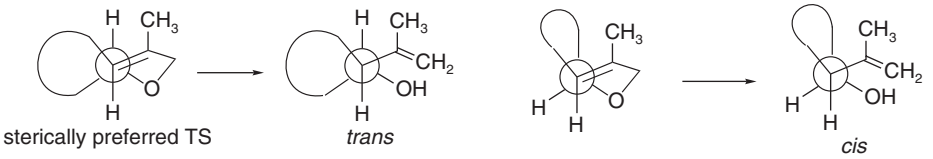
on the allyl group.[298] The trimethylsilyl substituents can also influence the stereoselectivity of the reaction. The steric interactions between the benzyl group and allyl substituent govern the stereoselectivity and it is markedly improved in the trimethylsilyl derivatives.[299]



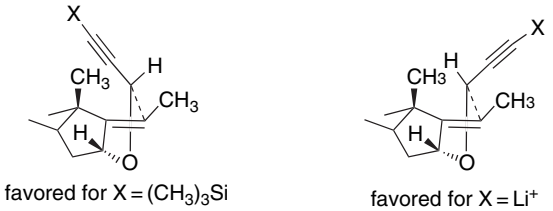
R	X	*anti*:*syn*
CH_3	H	3:2
C_2H_5	H	1:1
$(CH_3)_2CH$	H	4:3
CH_3	$Si(CH_3)_3$	<1:20
C_2H_5	$Si(CH_3)_3$	1:18
$(CH_3)_2CH$	$Si(CH_3)_3$	1:11



Some examples of synthetic application of the anionic Wittig rearrangement are given in Scheme 6.19. The reaction in Entry 1 provided a 93:7 ratio favoring the *syn* isomer, as expected for the preferred *endo* TS. Entry 2 is an example that employs the lithium-stannane exchange to generate the anion. The reaction in Entry 3 accomplishes a ring contraction. Under normal conditions, it is selective for the *trans* stereoisomer, as would be expected from steric factors in the TS. In the presence of HMPA, the *cis* isomer dominates, but the reason for the change is not known.

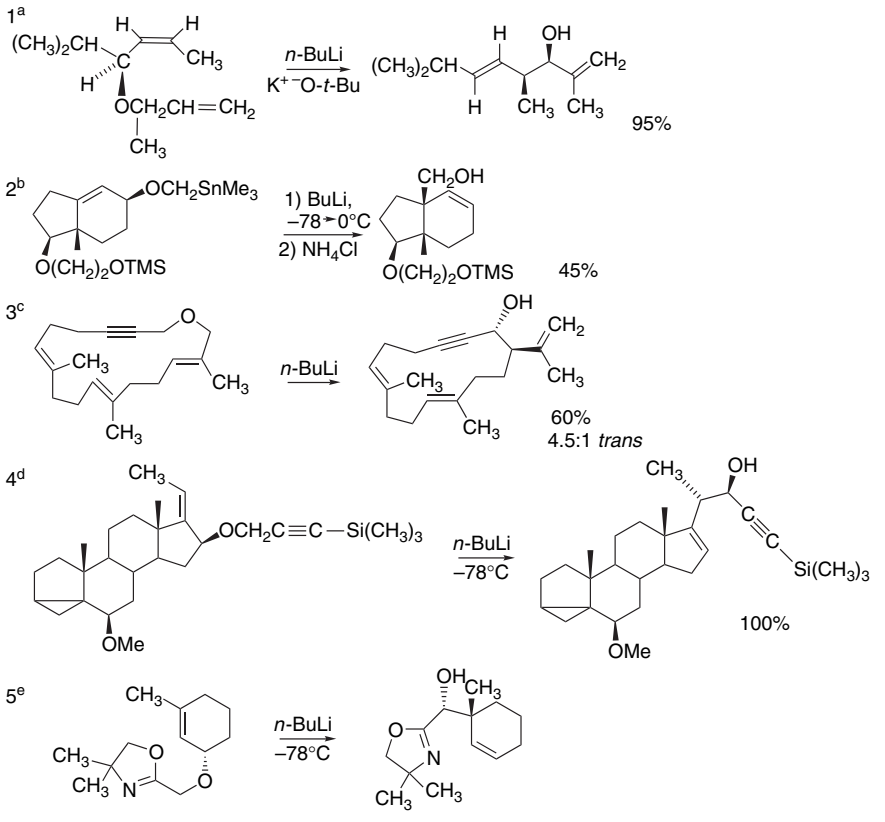


In Entry 4 the silyl group appears to introduce a controlling steric factor, leading to the observed stereoisomer. The unsubstituted terminal alkyne, which reacts through the dianion, gives the alternate isomer.



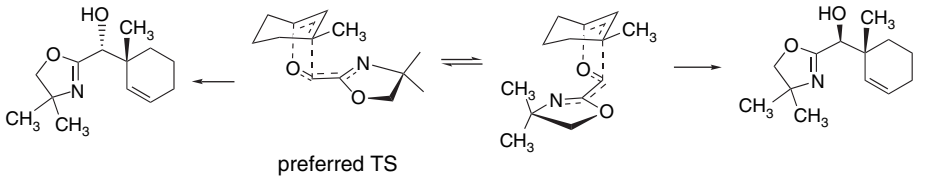
[298] J. C. Anderson, S. C. Smith, and M. E. Swarbrick, *J. Chem. Soc., Perkin Trans. 1*, 1517 (1997).
[299] J. C. Anderson, D. C. Siddons, S. C. Smith, and M. E. Swarbrick, *J. Org. Chem.*, **61**, 4820 (1996).

Scheme 6.19. [2,3]-Anionic Wittig Rearrangements



a. D. J.-S. Tsai and M. M. Midland, *J. Am. Chem. Soc.*, **107**, 3915 (1985).
b. T. Sugimura and L. A. Paquette, *J. Am. Chem. Soc.*, **109**, 3017 (1987).
c. J. A. Marshall, T. M. Jenson, and D. S. De Hoff, *J. Org. Chem.*, **51**, 4316 (1986).
d. K. Mikami, K. Kawamoto, and T. Nakai, *Tetrahedron Lett.*, **26**, 5799 (1985).
e. M. H. Kress, B. F. Kaller, and Y. Kishi, *Tetrahedron Lett.*, **34**, 8047 (1993).

The stereoselectivity of the reaction in Entry 5 is also determined by steric factors. Note also that in this case the oxazoline ring serves to stabilize the anion.



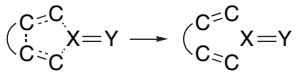
6.6. Unimolecular Thermal Elimination Reactions

This section describes reactions in which elimination to form a double bond or a new ring occurs as a result of thermal activation. There are several such thermal elimination reactions that are used syntheses, some of which are concerted processes. The

activation energy requirements and stereochemistry of concerted elimination processes can be analyzed in terms of orbital symmetry considerations. Cheletropic eliminations are discussed in Section 6.6.1 and elimination of nitrogen from azo compounds in Section 6.6.2. We consider an important group of unimolecular β-elimination reactions in Section 6.6.3.

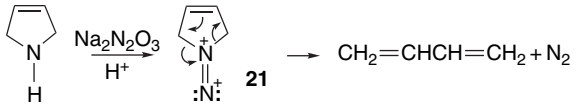
6.6.1. Cheletropic Elimination

Cheletropic processes are defined as reactions in which two bonds are broken at a single atom. Concerted cheletropic reactions are subject to orbital symmetry analysis in the same way as cycloadditions and sigmatropic processes. In the elimination processes of interest here, the atom X is normally bound to other atoms in such a way that elimination gives rise to a stable molecule. In particular, elimination of SO_2, N_2, or CO from five-membered 3,4-unsaturated rings can be a facile process.

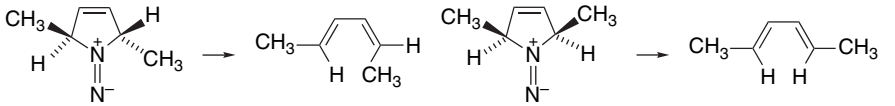


X=Y= C=O, N=N, SO_2

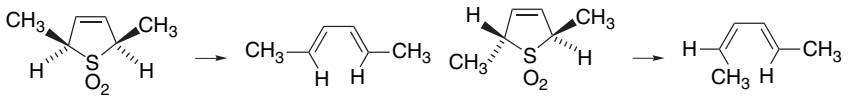
A good example of a concerted cheletropic elimination is the reaction of 3-pyrroline with *N*-nitrohydroxylamine, which gives rise the the diazene **21**, which then undergoes elimination of nitrogen.



Use of substituted systems has shown that the reaction is stereospecific.[300] The groups on C(2) and C(5) of the pyrroline ring rotate in the disrotatory mode on going to product. This stereochemistry is consistent with conservation of orbital symmetry.



The most synthetically useful cheletropic elimination involves 2,5-dihydrothiophene-1,1-dioxides (sulfolene dioxides). At moderate temperatures they fragment to give dienes and sulfur dioxide.[301] The reaction is stereospecific. For example, the dimethyl derivatives **22** and **23** give the *E*,*E*- and *Z*,*E*-isomers of 2,4-hexadiene, respectively, at temperatures of 100°–150° C.[302] This stereospecificity corresponds to disrotatory elimination.



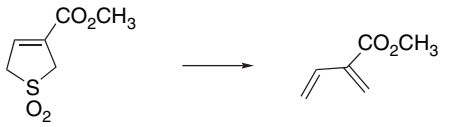
22 **23**

[300] D. M. Lemal and S. D. McGregor, *J. Am. Chem. Soc.*, **88**, 1335 (1966).

[301] W. L. Mock, in *Pericyclic Reactions*, Vol. II, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, Chap. 3.

[302] W. L. Mock, *J. Am. Chem. Soc.*, **88**, 2857 (1966); S. D. McGregor and D. M. Lemal, *J. Am. Chem. Soc.*, **88**, 2858 (1966).

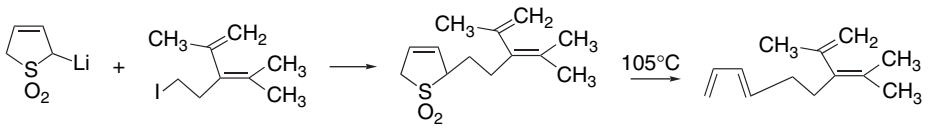
Elimination of sulfur dioxide has proven to be a useful method for generating dienes that can undergo subsequent D-A addition.



Ref. 303

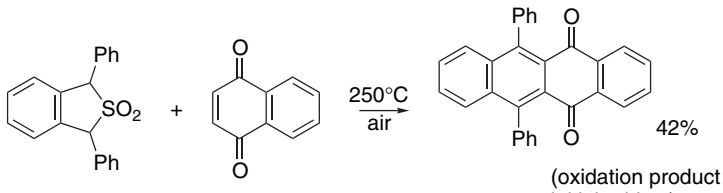
Ref. 304

Sulfolene dioxide is subject to α-lithiation and alkylation, and this reaction has been used to introduce the ring into more complex molecules.

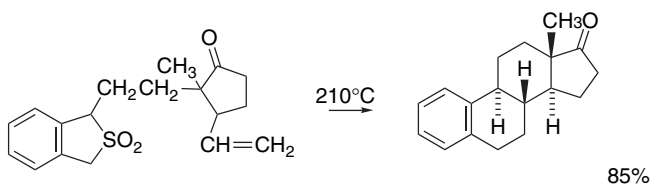


Ref. 305

Sulfolene dioxide thermolysis has also been applied to formation of *o*-quinodimethanes.



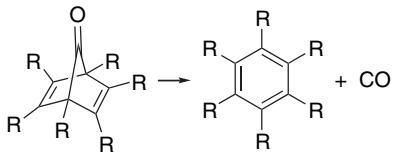
Ref. 306



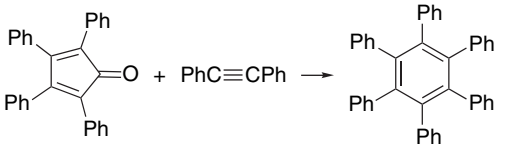
Ref. 307

303. J. M. McIntosh and R. A. Sieler, *J. Org. Chem.*, **43**, 4431 (1978).
304. A. M. Gomez, J. C. Lopez, and B. Fraser-Reid, *Synthesis*, 943 (1993).
305. J. D. Winkler, H. S. Kim, S. Kim, K. Ando, and K. N. Houk, *J. Org. Chem.*, **62**, 2957 (1997).
306. M. P. Cava, M. J. Mitchell, and A. A. Deana, *J. Org. Chem.*, **25**, 1481 (1960).
307. K. C. Nicolaou, W. E. Barnette, and P. Ma, *J. Org. Chem.*, **45**, 1463 (1980).

The elimination of carbon monoxide can occur by a concerted process in some cyclic ketones. The elimination of carbon monoxide from bicyclo[2.2.1]heptadien-7-ones is very facile. In fact, generation of bicyclo[2.2.1]heptadien-7-ones is usually accompanied by spontaneous decarbonylation.

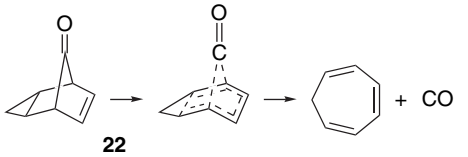


The ring system can be generated by D-A addition of a substituted cyclopentadienone and an alkyne. A reaction sequence involving addition followed by CO elimination can be used for the synthesis of highly substituted benzene rings.[308]



Ref. 309

The synthetic utility of cyclopentadienones is limited, however, because they are quite unstable. Exceptionally facile elimination of CO also takes place from **22**, in which homoaromaticity can facilitate elimination.

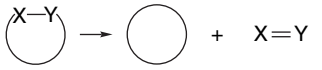


22

Ref. 310

6.6.2. Decomposition of Cyclic Azo Compounds

Another significant group of elimination reactions involves processes in which a small molecule is eliminated from a ring system and the two reactive sites that remain re-form a ring.



The most common example is decomposition of azo compounds, where −X−Y− is −N=N−.[311] The elimination of nitrogen from cyclic azo compounds can be carried

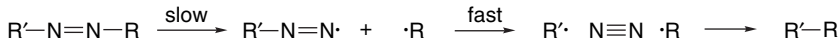
[308.] M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.*, **65**, 261 (1965).
[309.] L. F. Fieser, *Org. Synth.*, **V**, 604 (1973).
[310.] B. A. Halton, M. A. Battiste, R. Rehberg, C. L. Deyrup, and M. E. Brennan, *J. Am. Chem. Soc.*, **89**, 5964 (1967).
[311.] P. S. Engel, *Chem. Rev.*, **80**, 99 (1980).

out either photochemically or thermally. Although the reaction usually does not proceed by a concerted mechanism, there are some special cases in which concerted elimination is possible. We consider these cases first and then move on to the more general case. An interesting illustration of the importance of orbital symmetry effects is the contrasting stability of azo compounds **23** and **24**. Compound **23** decomposes to norbornene and nitrogen only above 100° C. In contrast **24** eliminates nitrogen immediately on preparation, even at −78° C.[312]

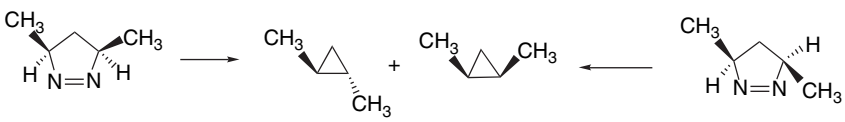
23 **24**

The reason for this difference is that if **23** were to undergo a concerted elimination it would have to follow the forbidden (high-energy) $[2\pi_s + 2\pi_s]$ pathway. For **24**, the elimination can take place by the allowed $[2\pi_s + 4\pi_s]$ pathway. Thus, these reactions are the reverse, respectively, of the $[2\pi_s + 2\pi_s]$ and $[2\pi_s + 4\pi_s]$ cycloadditions, and only the latter is an allowed concerted process. The temperature at which **23** decomposes is fairly typical for strained azo compounds and it presumably proceeds by a nonconcerted diradical mechanism. Since a C−N bond must be broken without concomitant compensation by carbon-carbon bond formation, the activation energy is higher than for a concerted process.

Although the concerted mechanism described in the preceding paragraph is available only to those azo compounds with appropriate orbital arrangements, the nonconcerted mechanism occurs at low enough temperatures to be synthetically useful. The elimination can also be carried out photochemically. These reactions presumably occur by stepwise elimination of nitrogen, and the ease of decomposition depends on the stability of the radical R·.



The stereochemistry of the nonconcerted reaction has been a topic of considerable study. Frequently, there is partial stereorandomization, indicating a short-lived diradical intermediate. The details vary from case to case, and both preferential inversion and retention of relative stereochemistry have been observed.

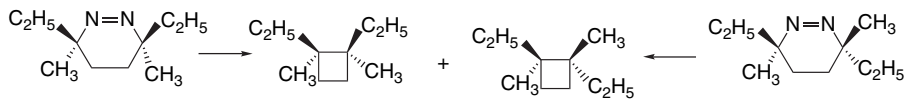


66:33 from *cis*
25:72 from *trans*

predominant inversion

Ref. 313

312. N. Rieber, J. Alberts, J. A. Lipsky, and D. M. Lemal, *J. Am. Chem. Soc.*, **91**, 5668 (1969).
313. R. J. Crawford and A. Mishra, *J. Am. Chem. Soc.*, **88**, 3963 (1966).



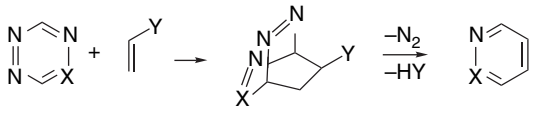
43:2.5 from *cis*
3.5:42 from *trans*

predominant retention

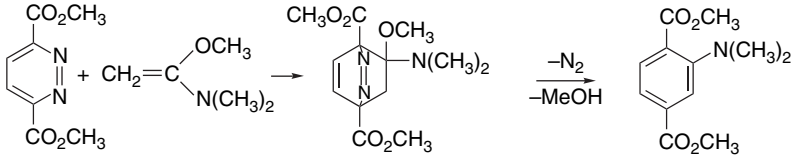
Ref. 314

These results can be interpreted in terms of competition between recombination of the diradical intermediate and conformational equilibration, which would destroy the stereochemical relationships present in the azo compound. The main synthetic application of azo compound decomposition is in the synthesis of cyclopropanes and other strained-ring systems. Some of the required azo compounds can be made by 1,3-dipolar cycloadditions of diazo compounds (see Section 6.2).

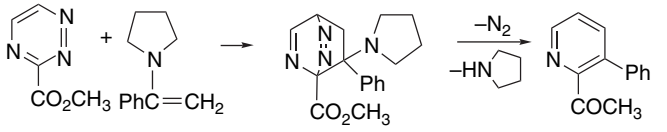
Elimination of nitrogen from D-A adducts of certain heteroaromatic rings has been useful in syntheses of substituted aromatic compounds.[315] Pyrazines, triazines, and tetrazines react with electron-rich dienophiles in inverse electron demand cycloadditions. The adducts then aromatize with loss of nitrogen and a dienophile substituent.[316]



Pyridazine-3,6-dicarboxylate esters react with electron-rich alkenes to give adducts that undergo subsequent elimination to give terephthalate derivatives.[317]

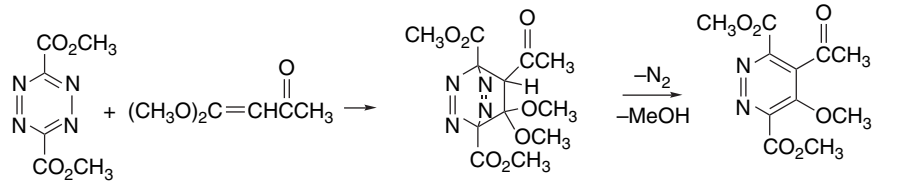


Similar reactions have been developed for 1,2,4-triazines and 1,2,4,5-tetrazines.



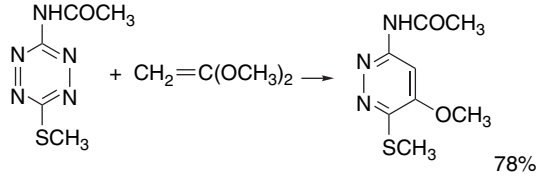
Ref. 318

314. P. D. Bartlett and N. A. Porter, *J. Am. Chem. Soc.*, **90**, 5317 (1968).
315. D. L. Boger, *Chem. Rev.*, **86**, 781 (1986).
316. D. L. Boger, *J. Heterocycl. Chem.*, **33**, 1519 (1996).
317. H. Neunhoeffer and G. Werner, *Liebigs Ann. Chem.*, 437, 1955 (1973).
318. D. L. Boger and J. S. Panek, *J. Am. Chem. Soc.*, **107**, 5745 (1985).

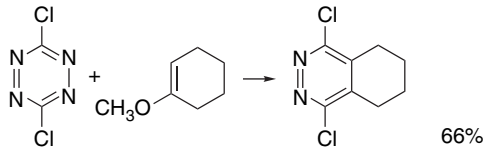


Ref. 319

The heterocycles frequently carry substituents such as chloro, methylthio, or alkoxycarbonyl.

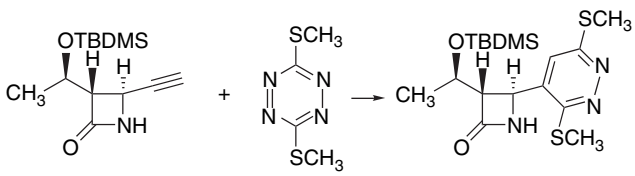


Ref. 320



Ref. 321

Acetylenic dienophiles lead directly to aromatic adducts on loss of nitrogen.



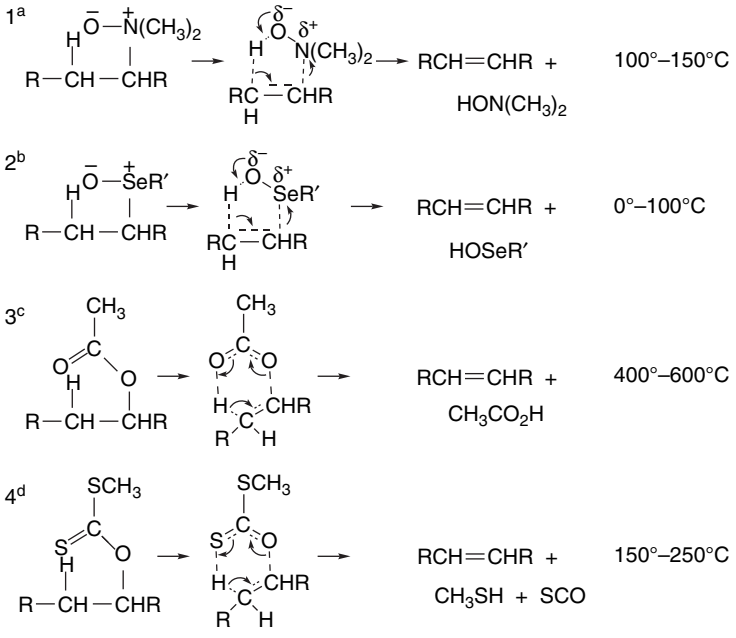
Ref. 322

6.6.3. β-Eliminations Involving Cyclic Transition Structures

Another important family of elimination reactions has as its common mechanistic feature cyclic TSs in which an intramolecular hydrogen transfer accompanies elimination to form a new carbon-carbon double bond. Scheme 6.20 depicts examples of these reaction types. These are thermally activated unimolecular reactions that normally do not involve acidic or basic catalysts. There is, however, a wide variation in the temperature at which elimination proceeds at a convenient rate. The cyclic TS dictates that elimination occurs with *syn* stereochemistry. At least in a formal sense, all the reactions can proceed by a concerted mechanism. The reactions, as a group, are often referred to as *thermal syn eliminations*.

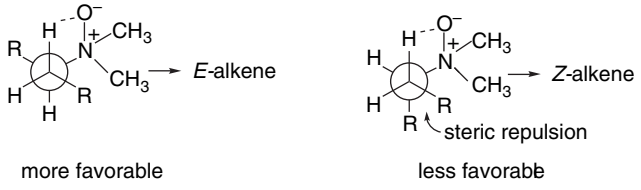
319. D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc.*, **109**, 2717 (1987).
320. D. L. Boger, R. P. Schaum, and R. M. Garbaccio, *J. Org. Chem.*, **63**, 6329 (1998).
321. T. J. Sparey and T. Harrison, *Tetrahedron Lett.*, **39**, 5893 (1998).
322. S. M. Sakya, T. W. Strohmeyer, S. A. Lang, and Y.-I. Lin, *Tetrahedron Lett.*, **38**, 5913 (1997).

Scheme 6.20. Thermal Eliminations via Cyclic Transition Structures



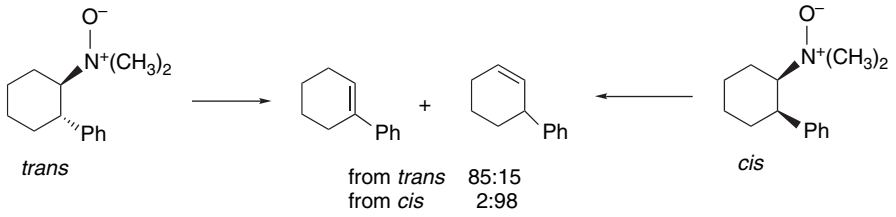
a. A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).
b. D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978).
c. C. H. De Puy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).
d. H. R. Nace, *Org. React.*, **12**, 57 (1962).

Amine oxide pyrolysis occurs at temperatures of 100°–150° C. The reaction can proceed at room temperature in DMSO.[323] If more than one type of β-hydrogen can attain the eclipsed conformation of the cyclic TS, a mixture of alkenes is formed. The product ratio parallels the relative stability of the competing TSs. Usually more of the *E*-alkene is formed because of the larger steric interactions present in the TS leading to the *Z*-alkene, but the selectivity is generally not high.



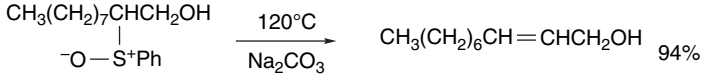
In cyclic systems, conformational effects and the requirement for a cyclic TS determine the product composition. This effect can be seen in the product ratios from pyrolysis of *N*,*N*-dimethyl-2-phenylcyclohexylamine-*N*-oxide.

323. D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).



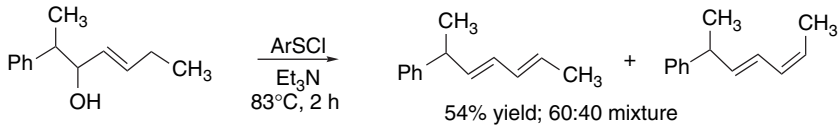
In the *trans* isomer, elimination to give a double bond conjugated with an aromatic ring is especially favorable. This presumably reflects both the increased acidity of the proton α to the phenyl ring and the stabilizing effect of the developing conjugation in the TS. In the *cis* isomer there is no *syn* hydrogen at the phenyl-substituted carbon and the nonconjugated regioisomer is formed. Amine oxides can be readily prepared from amines by oxidation with hydrogen peroxide or a peroxycarboxylic acid. Some typical examples of amine oxide elimination are given in Section A of Scheme 6.21.

Sulfoxides also undergo thermal elimination reactions. The elimination tends to give β, γ-unsaturation from β-hydroxysulfoxides and can be used to prepare allylic alcohols.



Ref. 324

Sulfoxide elimination in conjunction with [2,3]-sigmatropic rearrangement has been used to convert allylic alcohols to dienes.



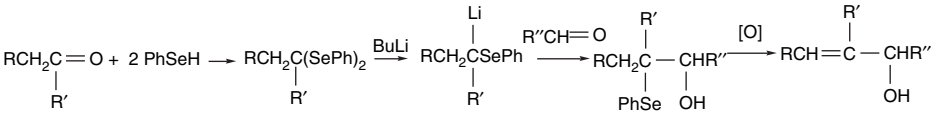
Ref. 325

EWG substituents promote the removal of hydrogen, and sulfoxide eliminations are particularly favorable for β-keto and similar sulfoxides.

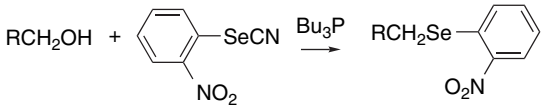
Selenoxides are even more reactive than sulfoxides toward β-elimination. In fact, many selenoxides react spontaneously when generated at room temperature. Synthetic procedures based on selenoxide eliminations usually involve synthesis of the corresponding selenide followed by oxidation and in situ elimination. We have already discussed examples of these procedures in Section 4.3.2, where the conversion of ketones and esters to their α, β-unsaturated derivatives is considered. Selenides can

[324.] J. Nokami, K. Ueta, and R. Okawara, *Tetrahedron Lett.*, 4903 (1978).
[325.] H. J. Reich and S. Wollowitz, *J. Am. Chem. Soc.*, **104**, 7051 (1982).

also be prepared by electrophilic addition of selenenyl halides and related compounds to alkenes (see Section 4.1.6). Selenide anions are powerful nucleophiles and can displace halides or tosylates and open epoxides.[326] Selenide substituents stabilize an adjacent carbanion, so α-selenenyl carbanions can be prepared. One procedure involves conversion of a ketone to a *bis*-selenoketal, which can then be cleaved by *n*-butyllithium.[327] The carbanions in turn add to ketones to give β-hydroxyselenides.[328] Elimination gives an allylic alcohol.



Alcohols can be converted to *o*-nitrophenylselenides by reaction with *o*-nitrophenyl selenocyanate and tri(*n*-butyl)phosphine.[329]



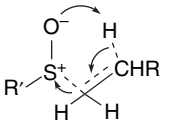
The selenides prepared by any of these methods can be converted to selenoxides by such oxidants as hydrogen peroxide, sodium metaperiodate, peroxycarboxylic acids, *t*-butyl hydroperoxide, or ozone.

Like amine oxide elimination, selenoxide eliminations normally favor formation of the *E*-isomer in acyclic structures. In cyclic systems the stereochemical requirements of the cyclic TS govern the product composition. Section B of Scheme 6.21 gives some examples of selenoxide eliminations.

Amine oxide and sulfoxide elimination TS structures have been compared by computations at the MP2/6-31G(*d*) level.[330] The calculated E_a values are 26 and 33 kcal/mol, respectively. Kinetic isotope effects have also been calculated[331] and are in good agreement with experimental values. The experimental E_a values for sulfoxide eliminations are typically near 30 kcal/mol.[332] For aryl sulfoxides, the E_a is somewhat lower, around 25–28 kcal/mol. Several sulfoxide elimination reactions have been examined computationally.[333] MP2/6-311+G(3*df*,2*p*) calculations gave generally good agreement with experimental values for ΔH, $\Delta H^{\ddagger}$, and kinetic isotope effects.

326. D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978).
327. W. Dumont, P. Bayet, and A. Krief, *Angew. Chem. Int. Ed. Engl.*, **13**, 804 (1974).
328. D. Van Ende, W. Dumont, and A. Krief, *Angew. Chem. Int. Ed. Engl.*, **14**, 700 (1975); W. Dumont and A. Krief, *Angew. Chem. Int. Ed. Engl.*, **14**, 350 (1975).
329. P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **41**, 1485 (1976); A. Krief and A.-M. Laval, *Bull. Soc. Chim. Fr.*, **134**, 869 (1997).
330. B. S. Jursic, *Theochem*, **389**, 257 (1997).
331. R. D. Bach, C. Gonzalez, J. L. Andres, and H. B. Schlegel, *J. Org. Chem*, **60**, 4653 (1995).
332. D. W. Emerson, A. P. Craig, and I. W. Potts, Jr., *J. Org. Chem.*, **32**, 102, 3725 (1967); C. Walling and L. Bollyky, *J. Org. Chem.*, **29**, 2699 (1964).
333. J. W. Cubbage, Y. Guo, R. D. McCulla, and W. S. Jenks, *J. Org. Chem.*, **66**, 8722 (2001).

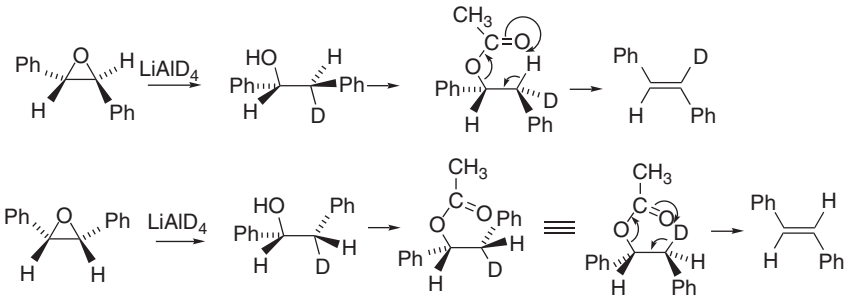
The minimum-energy TSs are planar and the O−H and C−H bond orders were usually less than 0.4 and less than 0.5, respectively, and the S−C bond order was less than 0.5. The C−C bond order was around 1.3. The reaction can be described as a concerted intramolecular proton transfer, with the sulfoxide oxygen acting as a base and the sulfur as a leaving group.



The TS for selenoxide elimination has also been examined computationally.[334] The C−H bond cleavage runs ahead of the C−Se cleavage.

A third category of *syn* eliminations involves pyrolytic decomposition of esters with elimination of a carboxylic acid. The pyrolysis of acetate esters normally requires temperatures above 400° C and is usually a vapor phase reaction. In the laboratory this is done by using a glass tube in the heating zone of a small furnace. The vapors of the reactant are swept through the hot chamber by an inert gas and into a cold trap. Similar reactions occur with esters derived from long-chain acids. If the boiling point of the ester is above the decomposition temperature, the reaction can be carried out in the liquid phase, with distillation of the pyrolysis product.

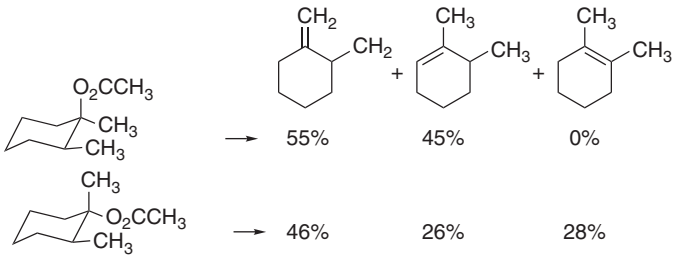
Ester pyrolysis has been shown to be a *syn* elimination in the case of formation of stilbene by the use of deuterium labels.[335]



Although recognizing the existence of the concerted cyclic mechanism, it has been proposed that most preparative pyrolyses proceed as surface-catalyzed reactions.[336]

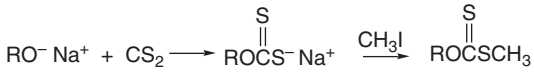
Mixtures of alkenes are formed when more than one type of β-hydrogen is present. In acyclic compounds the product composition often approaches that expected on a statistical basis from the number of each type of hydrogen. The *E*-alkene usually predominates over the *Z*-alkene for a given isomeric pair. In cyclic structures, elimination is in the direction that the cyclic mechanism can operate most favorably.

334. N. Kondo, H. Fueno, H. Fujimoto, M. Makino, H. Nakaoka, I. Aoki, and S. Uemura, *J. Org. Chem.*, **59**, 5254 (1994).
335. D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.*, **75**, 6011 (1953).
336. D. H. Wertz and N. L. Allinger, *J. Org. Chem.*, **42**, 698 (1977).

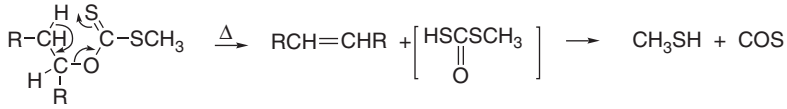


Ref. 336

Alcohols can be dehydrated via xanthate esters at temperatures that are much lower than those required for acetate pyrolysis. The preparation of xanthate esters involves reaction of the alkoxide with carbon disulfide. The resulting salt is alkylated with methyl iodide.



The elimination is often effected simply by distillation.



Product mixtures are observed when more than one type of β-hydrogen can participate in the reaction. As with the other *syn* thermal eliminations, there are no intermediates that are prone to skeletal rearrangement.

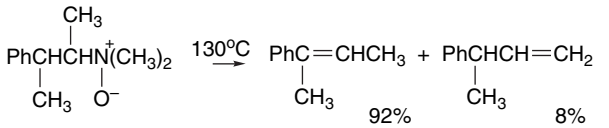
Scheme 6.21 gives some examples of thermal elimination reactions. Entries 1 to 3 show amine-oxide decompositions. The reaction in Entry 1 shows a preference for the conjugated product. This reaction was also conducted in dry DMSO, where it was found to proceed at 25° C.[338] Entry 2 illustrates the use of the reaction to prepare methylenecyclohexane. The method is particularly useful in this case because there is no tendency for competing elimination or rearrangement to the more stable 1-methylcyclohexene. Entries 4 and 5 are sulfoxide eliminations. Entry 4 is favored by the conjugation of the phenyl group and occurs under very mild conditions. The conditions for elimination in Entry 5 are more typical. Entries 6 to 9 are selenoxide eliminations. In Entries 6 and 7, the selenide group is introduced by nucleophilic substitution. In Entry 8, electrophilic selenolactonization was used to synthesize the reactant. Although the yield of the product, oxete, in Entry 9 is quite low, this was one of the first preparations of this compound. Entries 10 to 12 are high-temperature acetate pyrolyses. Entries 13 to 17 are xanthate pyrolyses. In Entry 15, the use of DMSO as the solvent for the preparation of the dialcoholate was found to be advantageous.

336. D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *J. Am. Chem. Soc.*, **81**, 643 (1959).
338. D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).

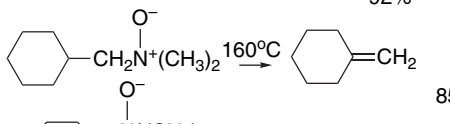
Scheme 6.21. Thermal Eliminations Via Cyclic Transition Structures

A. Amine oxide pyrolyses

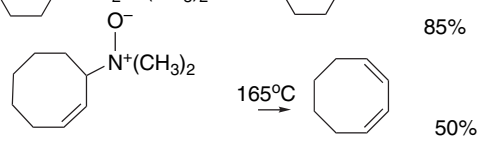
1[a]



2[b]

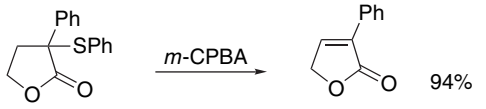


3[c]

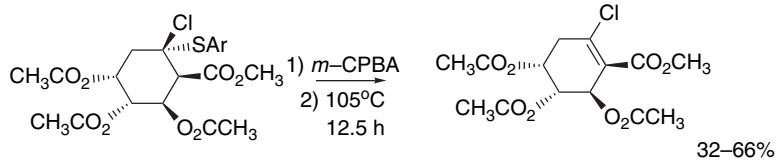


B. Sulfoxide elimination

4[d]



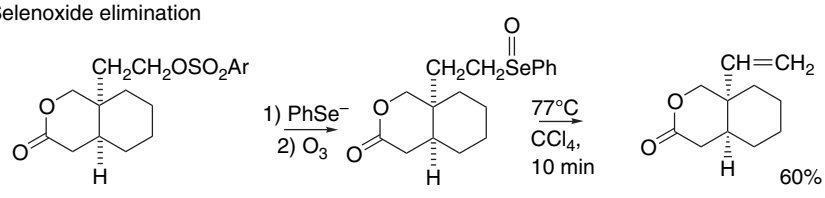
5[e]



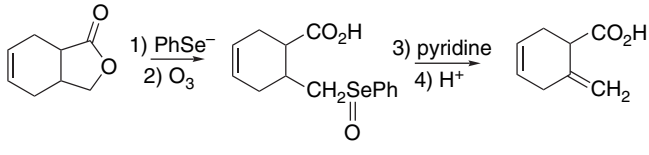
Ar = 4-methoxyphenyl

C. Selenoxide elimination

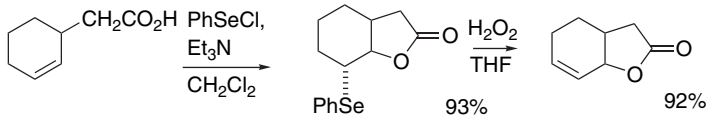
6[f]



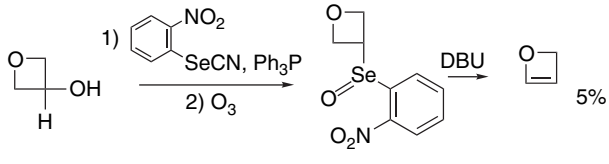
7[g]



8[h]



9[i]

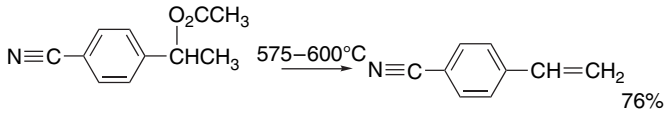


(*Continued*)

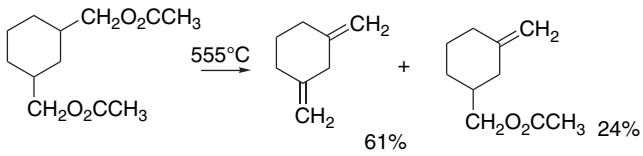
Scheme 6.21. (*Continued*)

D. Acetate pyrolyses

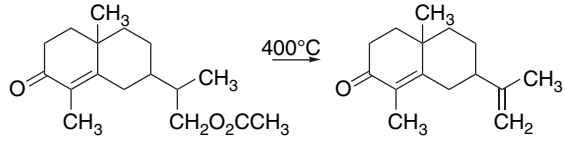
10[j]



11[k]

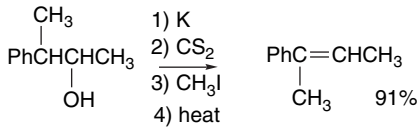


12[l]

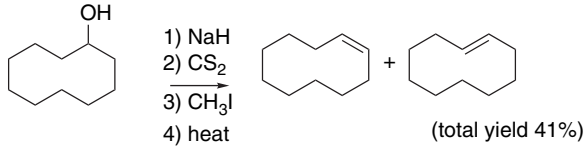


E. Xanthate ester pyrolyses

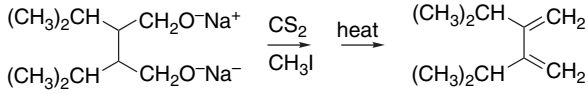
13[m]



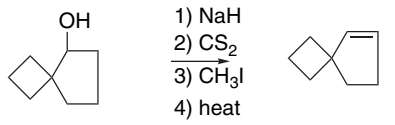
14[n]



15[o]



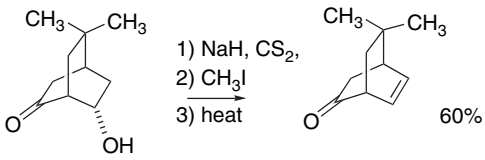
16[p]



(*Continued*)

Scheme 6.21. (*Continued*)

17[q]

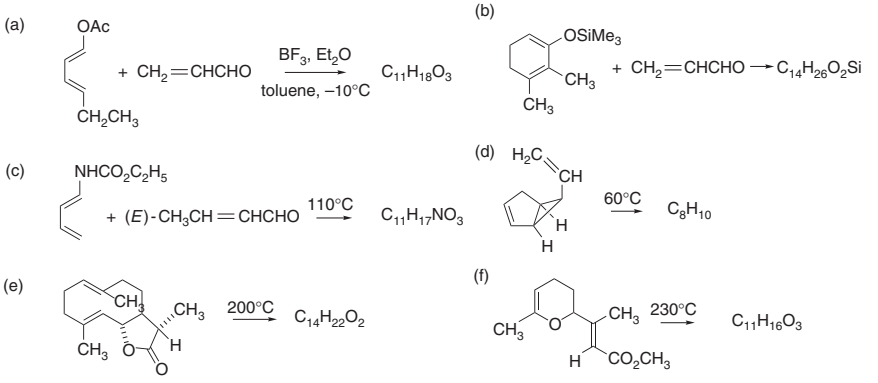


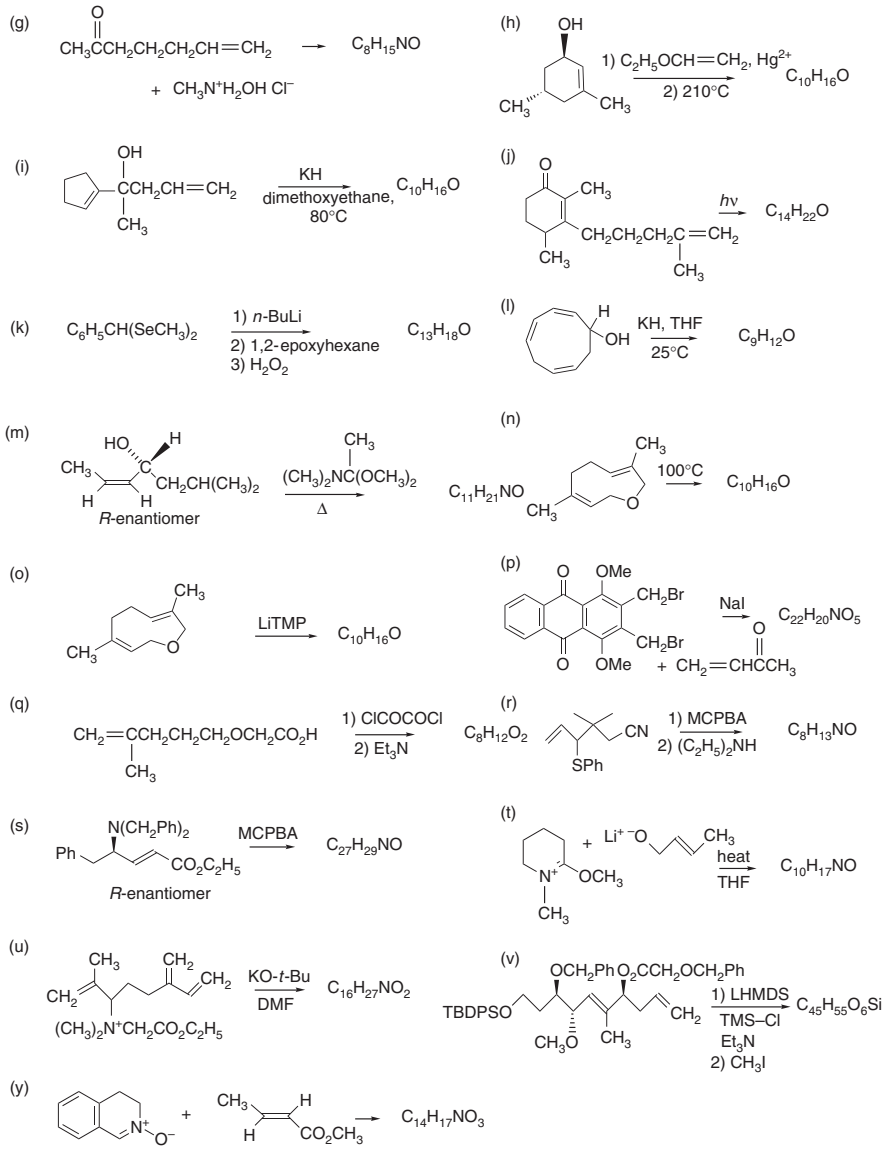
a. D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **76**, 5740 (1954).
b. A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959); A. C. Cope and E. Ciganek, *Org. Synth.*, **IV**, 612 (1963).
c. A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.*, **78**, 2812 (1956).
d. J.-X. Gu and H. L. Holland, *Synth. Commun.*, **28**, 3305 (1998).
e. R. H. Rich, B. M. Lawrence, and P. A. Bartlett, *J. Org. Chem.*, **59**, 693 (1994).
f. R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **41**, 1396 (1976).
g. D. Liotta and H. Santiesteban, *Tetrahedron Lett.*, 4369 (1977); R. M. Scarborough, Jr., and A. B. Smith, III, *Tetrahedron Lett.*, 4361 (1977).
h. K. C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.*, **99**, 3185 (1977).
i. L. E. Friedrich and P. Y. S. Lam, *J. Org. Chem.*, **46**, 306 (1981).
j. C. G. Overberger and R. E. Allen, *J. Am. Chem. Soc.*, **68**, 722 (1946).
k. W. J. Bailey and J. Economy, *J. Org. Chem.*, **23**, 1002 (1958).
l. E. Piers and K. F. Cheng, *Can. J. Chem.*, **46**, 377 (1968).
m. D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949).
n. A. T. Blomquist and A. Goldstein, *J. Am. Chem. Soc.*, **77**, 1001 (1955).
o. A. de Groot, B. Evenhuis, and H. Wynberg, *J. Org. Chem.*, **33**, 2214 (1968).
p. C. F. Wilcox, Jr., and C. G. Whitney, *J. Org. Chem.*, **32**, 2933 (1967).
q. L. A. Paquette and H.-C. Tsai, *J. Org. Chem.*, **61**, 142 (1996).

Problems

(*References for these problems will be found on page 1280.*)

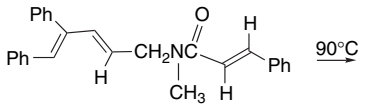
6.1. Predict the products of the following reactions on the basis of the reaction mechanism and anticipated transition structure. Be sure to consider all elements of stereochemistry. Unless otherwise specified, the reactants and reagents are racemic.



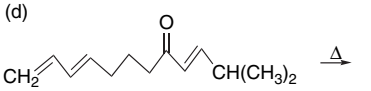


6.2. Intramolecular cycloaddition reactions occur under the conditions specified for each of the following reactions. Show the structures of the products of each reaction, including all aspects of stereochemistry and indicate the structure of the product-determining TS and any key intermediates.

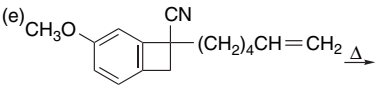
(c)



(d)

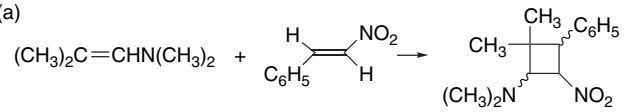


(e)

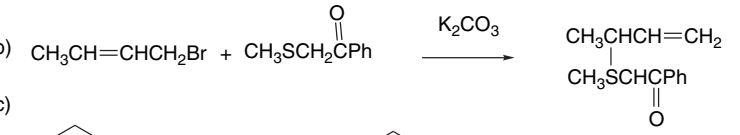


6.3. Indicate the mechanistic type to which each of these reactions belongs and write out a mechanism showing any intermediates.

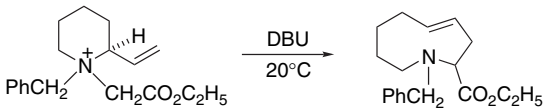
(a)



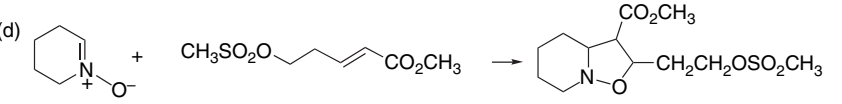
(b)



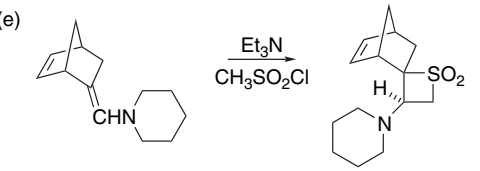
(c)



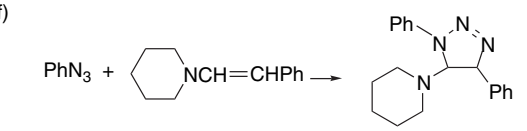
(d)



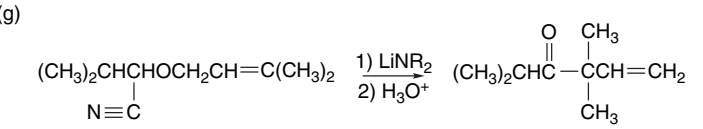
(e)



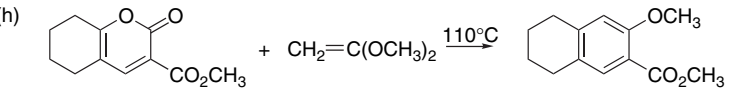
(f)



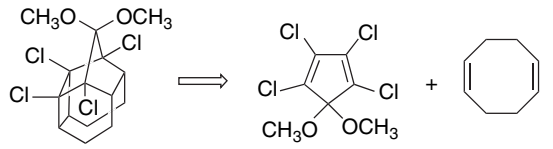
(g)

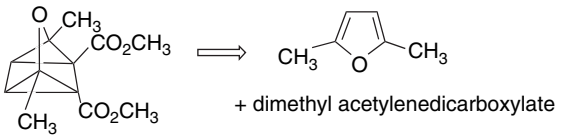


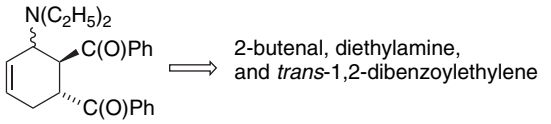
(h)

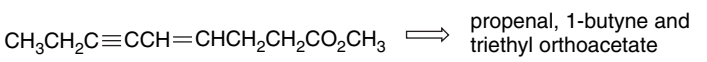


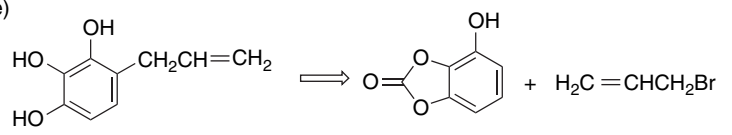
6.4. Apply retrosynthetic analysis to the following transformation and show how each of the target molecules could be prepared from the starting materials given. No more than three separate steps are needed in any of the syntheses.

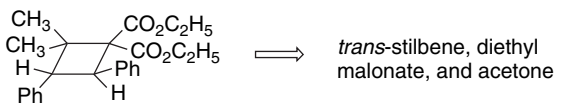
(a) 

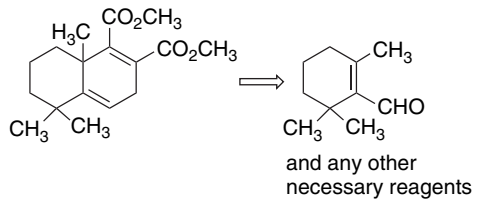
(b) 

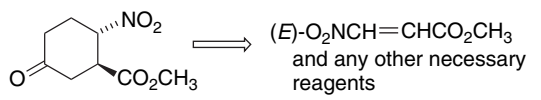
(c) 

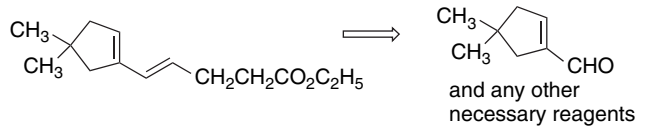
(d) 

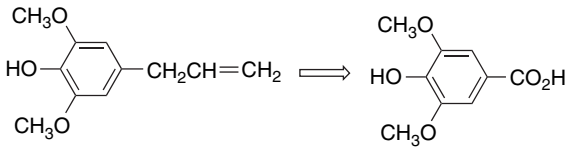
(e) 

(f) 

(g) 

(h) 

(i) 

(j) 

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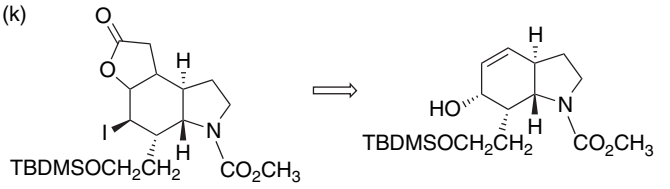

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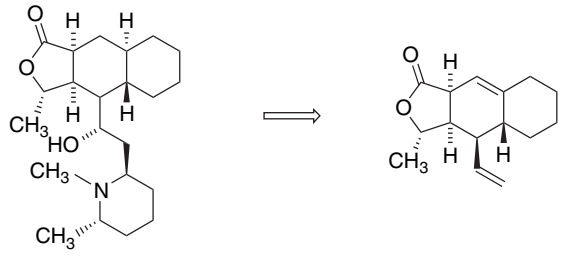
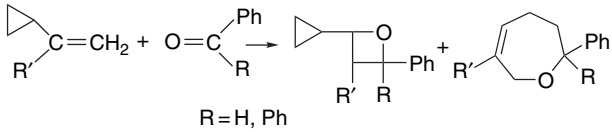


6.5. Suggest mechanisms by which the following transformations occur.

a. The addition reaction of tetracyanoethylene and ethyl vinyl ether in acetone gives 94% of a [2 + 2] adduct and 6% of an adduct having the composition tetracyanoethylene + ethyl vinyl ether + acetone. If the [2 + 2] adduct is kept in contact with acetone for several days, it is completely converted to the minor product. What is a likely structure for the minor product? How is it formed in the original reaction and on standing in acetone?

b. When vinylcylopropane is irradiated with benzophenone or benzaldehyde both oxetane and oxepene products are obtained. How are the oxepenes formed?



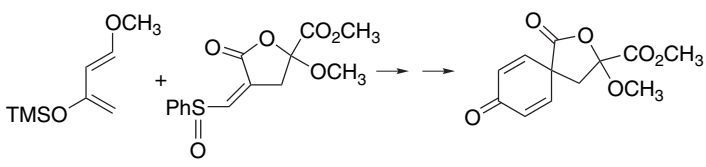
R = H, Ph

c. A convenient preparation of 2-allylcyclohexanone involves simply heating the diallyl acetal of cyclohexanone in toluene containing a trace of *p*-toluenesulfonic acid and collecting a distillate of toluene and allyl alcohol.

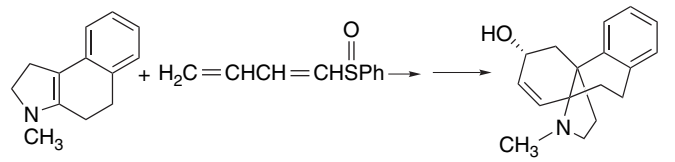
d. A solution of 2-butenal, 2-acetoxypropene, and dimethyl acetylenedicarboxylate refluxed in the presence of a small amount of an acid catalyst gives an 80% yield of dimethyl phthalate.

6.6. The following syntheses were carried by short tandem reaction sequences starting with the Diels-Alder reaction shown. Show the reagents and approximate reaction conditions required to complete the transformation.

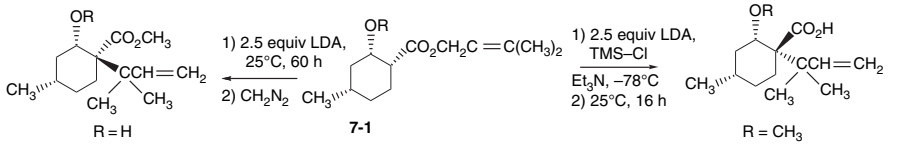
(a)



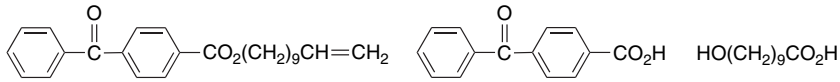
(b)



6.7. The ester **7-1** gives alternative stereoisomers when subjected to Claisen rearrangement as the lithium enolate or as the silyl ketene acetal. Analyze the respective transition structures and develop a rationale to explain these results.



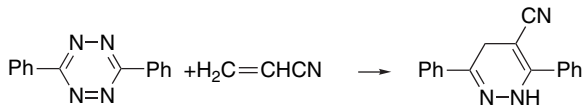
6.8. Photolysis of **8-1** gives an isomeric compound **8-2** in 83% yield. Alkaline hydrolysis of **8-2** affords a hydroxy carboxylic acid, **8-3**, $C_{25}H_{32}O_4$. Treatment of **8-2** with silica gel in hexane yields **8-4**, $C_{24}H_{28}O_2$. **8-4** is converted by $NaIO_4$-$KMnO_4$ to a mixture of **8-5** and **8-6**. What are the structures of **8-2**, **8-3**, and **8-4**?



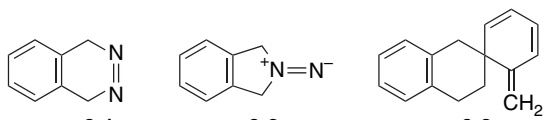
8-1 **8-5** **8-6**

6.9. Suggest mechanisms for the following reactions that involve loss of N_2.

a. 1,2,4,5-Tetrazines react with alkenes to give dihydropyridazines, as in the example below.

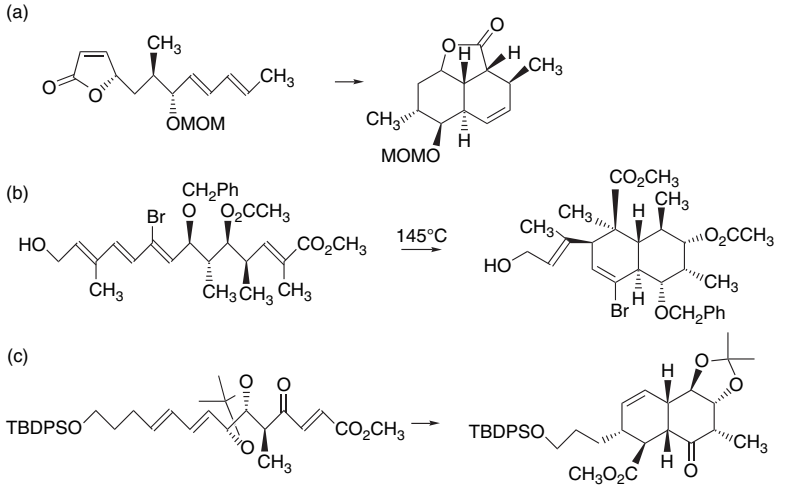


b. Compounds **9-1** and **9-2** are both unstable toward loss of nitrogen at room temperature and both give **9-3** as the product.

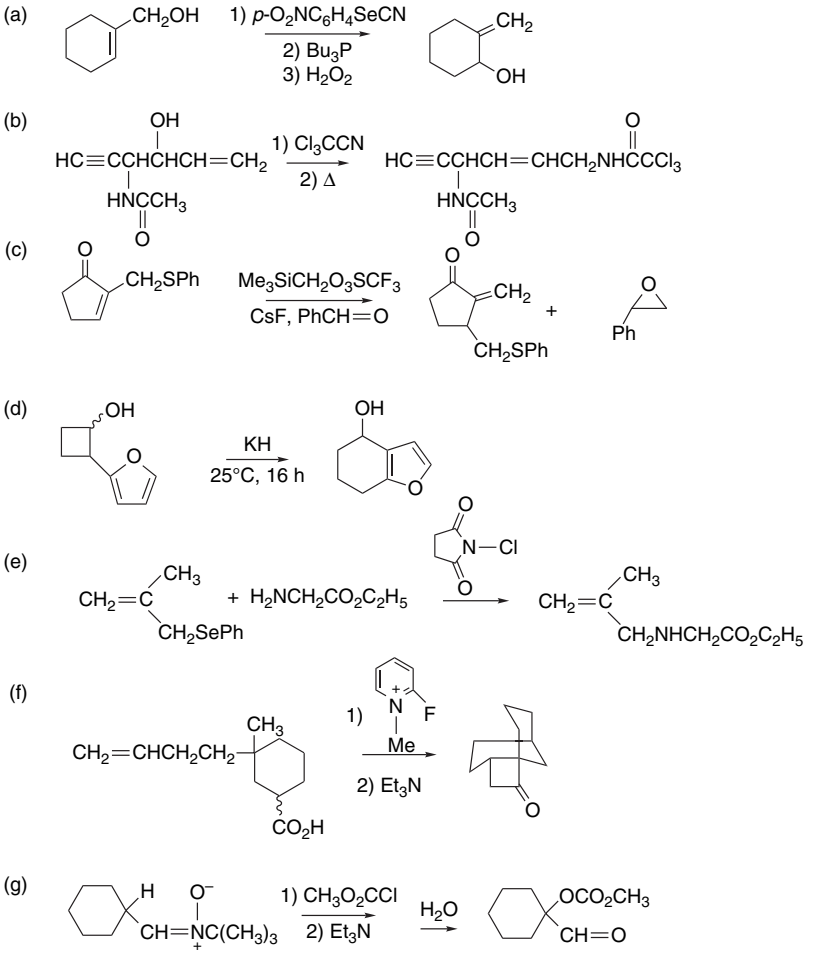


9-1 **9-2** **9-3**

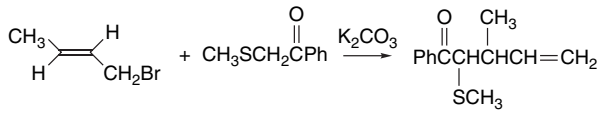
6.10. For each of the following reactions propose a transition structure that would account for the observed stereoselectivity. Identify important conformational and other features of the proposed transition structure.



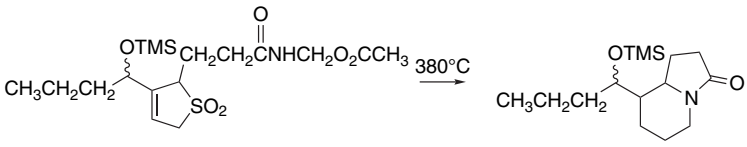
6.11. Provide an outline of the mechanisms of the following transformations.



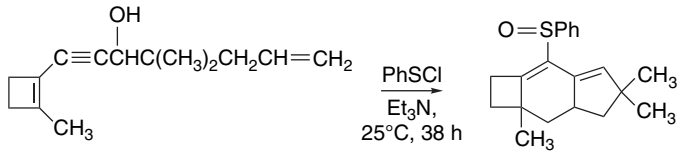
(h)



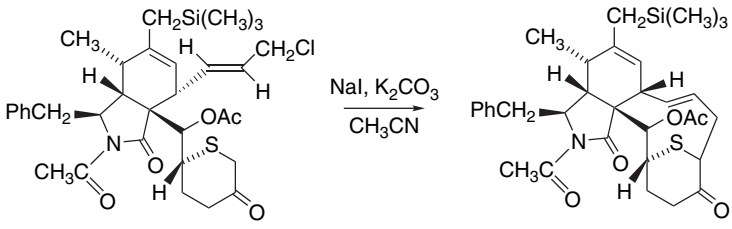
(i)



(j)



(k)



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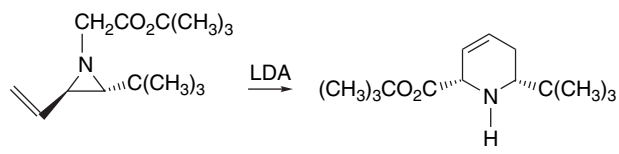
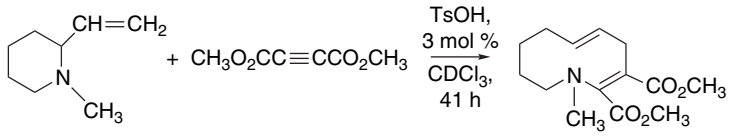
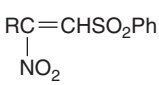


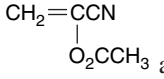
(m)



6.12. In each part, the molecule shown was employed as a synthetic equivalent in a cycloaddition reaction. Show a sequence of reactions by which the adduct can be converted to the desired product.

(a)  as an alkyne equivalent in reaction with 1,3-pentadiene.

(b) $PhSO_2CH{=}CHSi(CH_3)_3$ as an acetylene equivalent in reaction with anthracene.

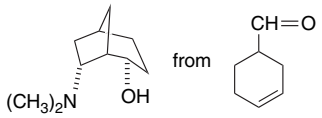
(c)  as a ketene equivalent in reaction with 5-(isopropylidene)-1,3-cyclopentadiene (dimethylfulvene).

(d) $CH_2{=}CHNO_2$ as a ketene equivalent in reaction with 5-methoxymethyl-1,3-cyclopentadiene.

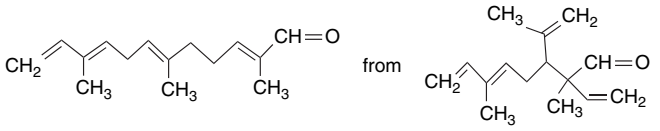
6.13. Suggest reaction sequences for accomplishing each of the following synthetic transformations.

(a) Squalene from succinaldehyde, 2-bromopropene, and 3-methoxy-2-methyl-1,3-butadiene.

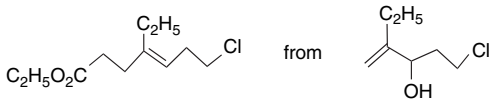
(b)



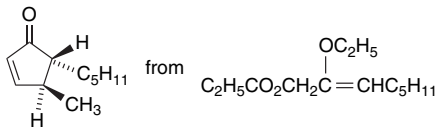
(c)



(d)



(e)



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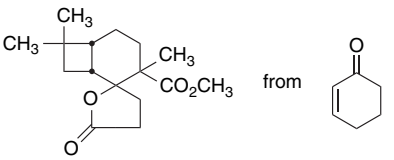
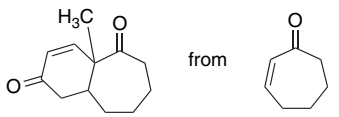
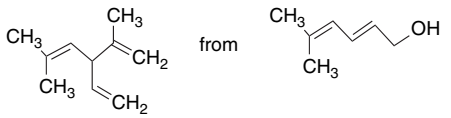


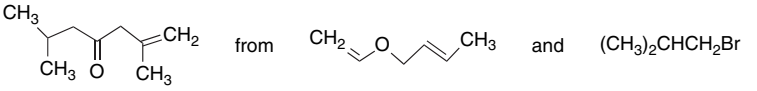
(g)



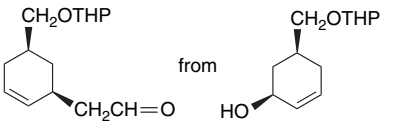
(h)

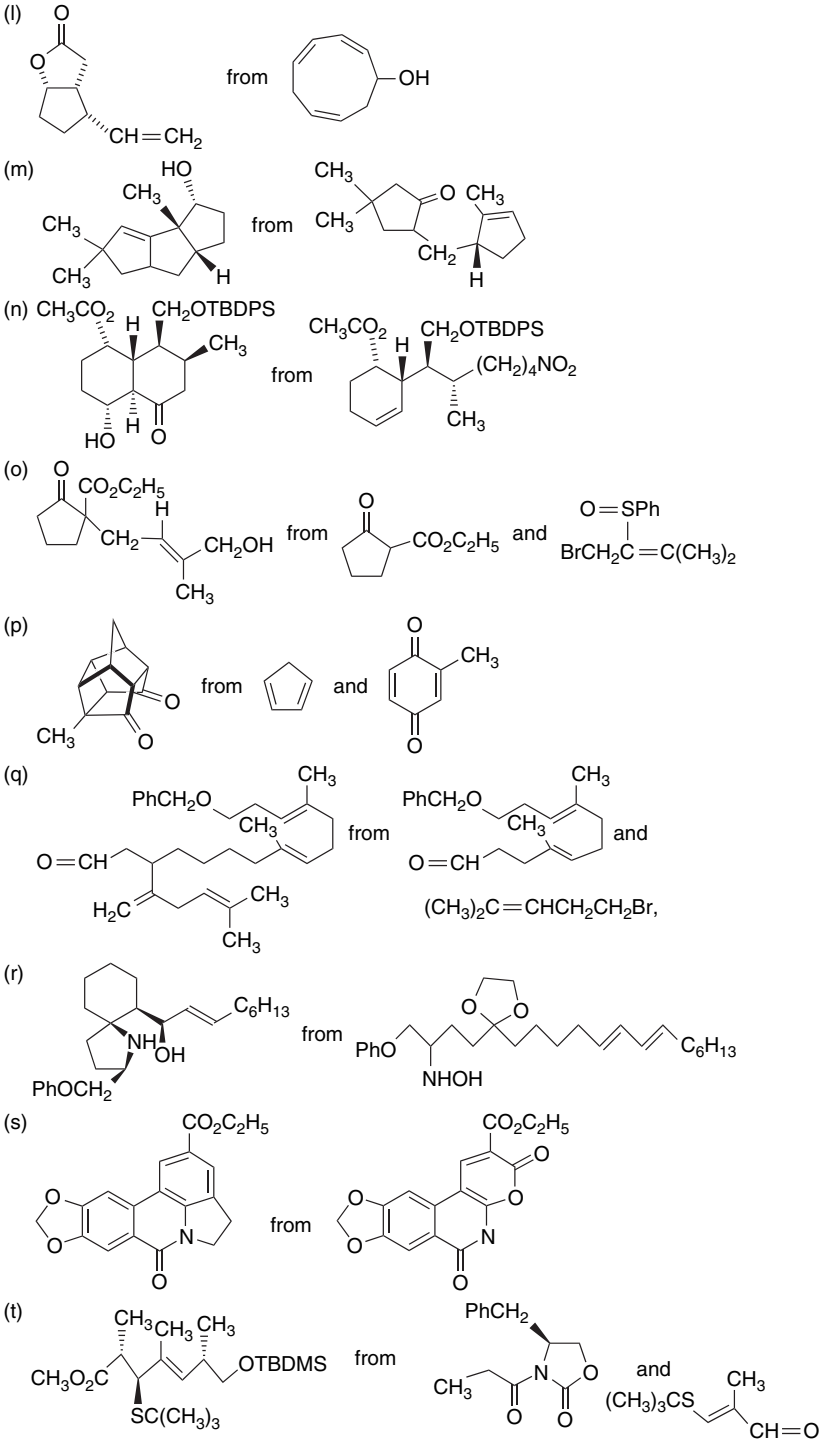


(i)

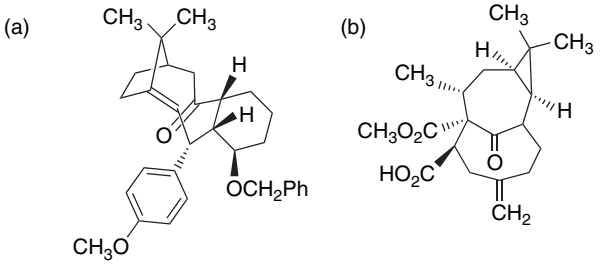


(j)

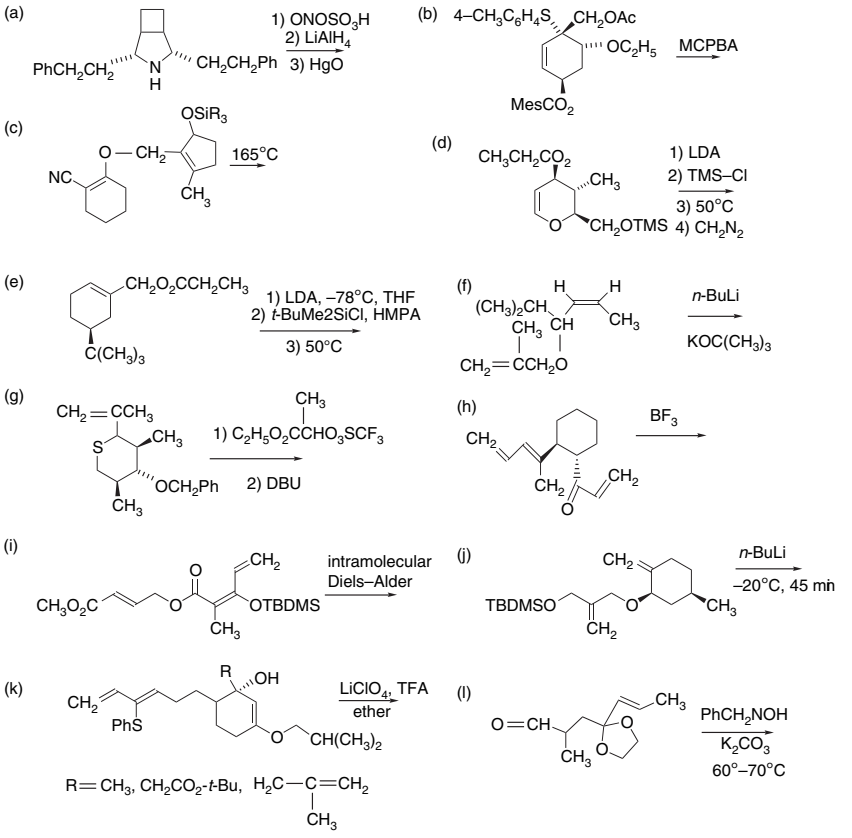




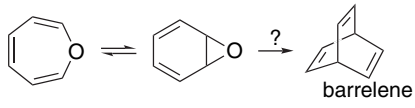
6.14. By retrosynthetic analysis, identify a precursor that could provide the desired product by a single pericyclic reaction. Indicate appropriate reaction conditions for the transformation you identify.



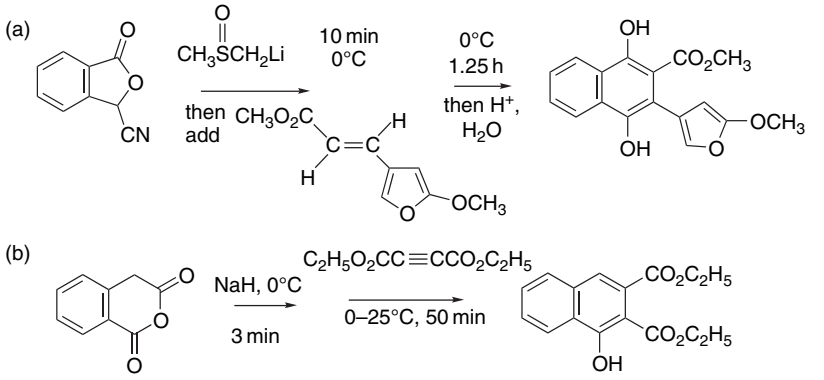
6.15. Predict the structure of the major product, including stereochemistry, of the following reactions. Draw the transition structures and identify the features that control the stereochemistry of the reaction.



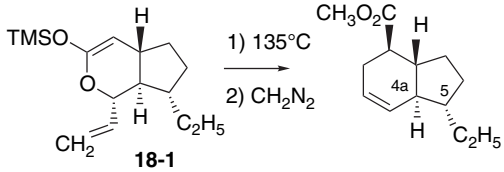
6.16. Oxepin is in equilibrium with benzene oxide by a [3,3]-sigmatropic shift. Advantage has been taken of this equilibrium to develop a short synthesis of barrelene. Outline a way that this could be done.



6.17. The following transformations involve generation of anionic intermediates that then undergo cycloaddition reactions. Identify the anion intermediate and outline the mechanism for each transformation.

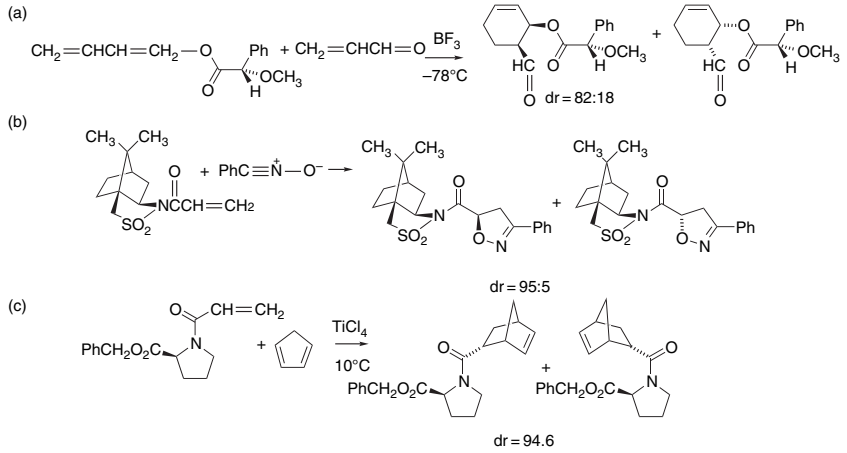


6.18. When the lactone silyl ketene acetal **18-1** is heated to 135° C a mixture of four stereoisomers is obtained. Although the major one is the expected [3,3]-sigmatropic rearrangement product, lesser amounts of other possible C(4a) and C(5) epimers are also formed. When the reaction mixture is heated to 100° C, partial conversion to the same mixture of stereoisomers is observed, but most of the product at this temperature is an acyclic triene ester. Suggest a structure for the triene ester and show how it can be formed. Discuss the significance of the observation of the triene ester for the lack of complete stereospecificity in the rearrangement.

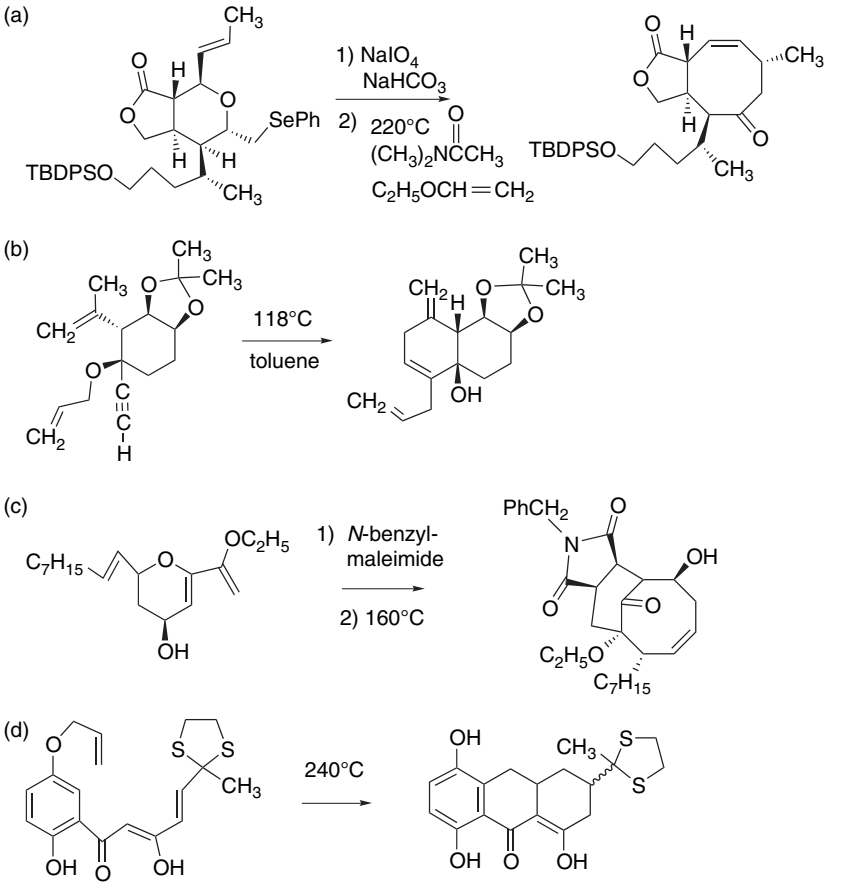


18-1

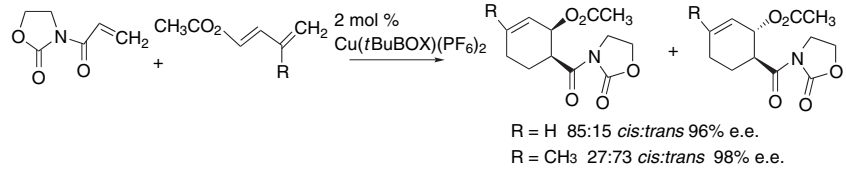
6.19. The following cycloaddition reactions involve chiral auxiliaries and proceed with a good degree of diastereoselectivity. Provide a rationalization of the formation of the preferred product on the basis of a TS.



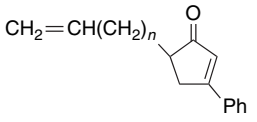
6.20. The following transformations involve two or more pericyclic reactions occurring in tandem during the process. Suggest a plausible sequence of reactions that can lead to the observed product.



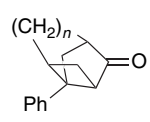
6.21. The Diels-Alder reaction of *N*-acryloyloxazolidinone catalyzed by Cu(*t*-Bu)BOX shows a reversal of stereoselectivity between 1-acetoxybutadiene and 1-acetoxy-3-methylbutadiene. The former gives a 85:15 *endo*:*exo* ratio, whereas the latter is 27:73 *endo*:*exo*. Explain this reversal in terms of the transition structure model given on p. 509.

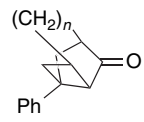


6.22. The alkenyl cyclopentenone **22a-c** have been subjected to photolysis with the results shown below. Analyze these results in terms of the mechanistic interpretation give on p. 547.



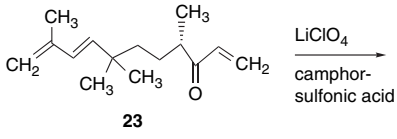
22



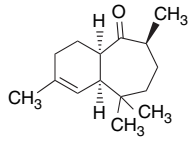


	n	parallel	crossed
22a	1	only product	not found
22b	2	minor product	major product
22c	3	only product	not found

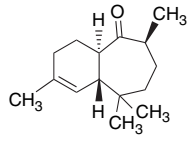
6.23. The intramolecular Diels-Alder reaction of **23-1** carried out under $LiClO_4$ catalysis is rather nonselective. Use a molecular mechanics program to assess the energies of the competing TSs and products. Are the results in agreement with the experimental outcome?



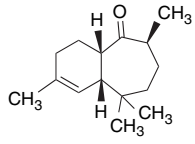
23



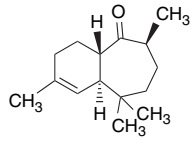
36.5%



15.4%



18.6%



29.5%