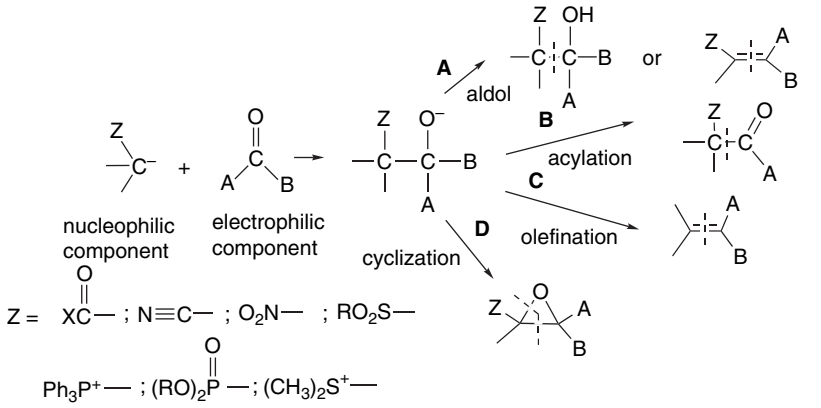
2

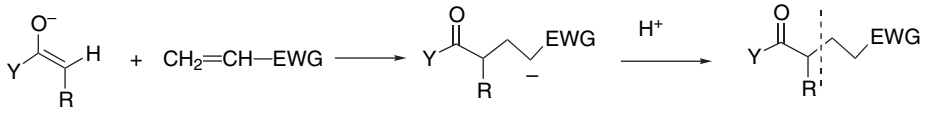
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Introduction

The reactions described in this chapter include some of the most useful methods for carbon-carbon bond formation: *the aldol reaction*, the *Robinson annulation*, the *Claisen condensation* and other *carbon acylation* methods, and the *Wittig reaction* and other *olefination methods*. All of these reactions begin with the addition of a stabilized carbon nucleophile to a carbonyl group. The product that is isolated depends on the nature of the stabilizing substituent (Z) on the carbon nucleophile, the substituents (A and B) at the carbonyl group, and the ways in which A, B, and Z interact to complete the reaction pathway from the addition intermediate to the product. Four fundamental processes are outlined below. Aldol addition and condensation lead to β-hydroxyalkyl or α-alkylidene derivatives of the carbon nucleophile (Pathway **A**). The acylation reactions follow Pathway **B**, in which a group leaves from the carbonyl electrophile. In the Wittig and related olefination reactions, the oxygen in the adduct reacts with the group Z to give an elimination product (Pathway **C**). Finally, if the enolate has an α-substituent that is a leaving group, cyclization can occur, as in Pathway **D**. This is observed, for example, with enolates of α-haloesters. The fundamental mechanistic concepts underlying these reactions were introduced in Chapter 7 of Part A. Here we emphasize the scope, stereochemistry, and synthetic utility of these reactions.

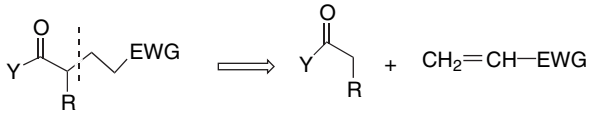


A second important reaction type considered in this chapter is *conjugate addition*, which involves addition of nucleophiles to electrophilic double or triple bonds. A crucial requirement for this reaction is an electron-withdrawing group (EWG) that can stabilize the negative charge on the intermediate. We focus on reactions between enolates and α,β-unsaturated carbonyl compounds and other electrophilic alkenes such as nitroalkenes.



enolate conjugate addition

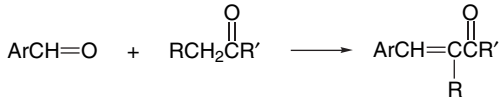
The retrosynthetic dissection is at a bond that is α to a carbonyl and β to an anion-stabilizing group.



2.1. Aldol Addition and Condensation Reactions

2.1.1. The General Mechanism

The general mechanistic features of the aldol addition and condensation reactions of aldehydes and ketones were discussed in Section 7.7 of Part A, where these general mechanisms can be reviewed. That mechanistic discussion pertains to reactions occurring in *hydroxylic solvents* and under *thermodynamic control*. These conditions are useful for the preparation of aldehyde dimers (aldols) and certain α,β-unsaturated aldehydes and ketones. For example, the mixed condensation of aromatic aldehydes with aliphatic aldehydes and ketones is often done under these conditions. The conjugation in the β-aryl enones provides a driving force for the elimination step.



The aldol reaction is also important in the synthesis of more complex molecules and in these cases control of both regiochemistry and stereochemistry is required. In most cases, this is accomplished under conditions of *kinetic control*. In the sections that follow, we discuss how variations of the basic mechanism and selection of specific reagents and reaction conditions can be used to control product structure and stereochemistry.

The addition reaction of enolates and enols with carbonyl compounds is of broad scope and of great synthetic importance. Essentially all of the stabilized carbanions mentioned in Section 1.1 are capable of adding to carbonyl groups, in what is known as the *generalized aldol reaction*. Enolates of aldehydes, ketones, esters, and amides, the carbanions of nitriles and nitro compounds, as well as phosphorus- and sulfur-stabilized carbanions and ylides undergo this reaction. In the next section we emphasize the fundamental regiochemical and stereochemical aspects of the reactions of ketones and aldehydes.

2.1.2. Control of Regio- and Stereoselectivity of Aldol Reactions of Aldehydes and Ketones

The synthetic utility of the aldol reaction depends on both the versatility of the reactants and the control of the regio- and stereochemistry. The term *directed aldol addition* is applied to reactions that are designed to achieve specific regio- and stereochemical outcomes.[1] Control of product structure requires that one reactant act exclusively as the *nucleophile* and the other exclusively as the *electrophile*. This requirement can be met by pre-forming the nucleophilic enolate by deprotonation, as described in Section 1.1. The enolate that is to serve as the nucleophile is generated stoichiometrically, usually with lithium as the counterion in an aprotic solvent at low temperature. Under these conditions, the kinetic enolate does not equilibrate with the other regio- or stereoisomeric enolates that can be formed from the ketone. The enolate gives a specific adduct, provided that the addition step is fast relative to proton exchange between the nucleophilic and electrophilic reactants. The reaction is under *kinetic control*, at both the stage of formation of the enolate and the addition step.

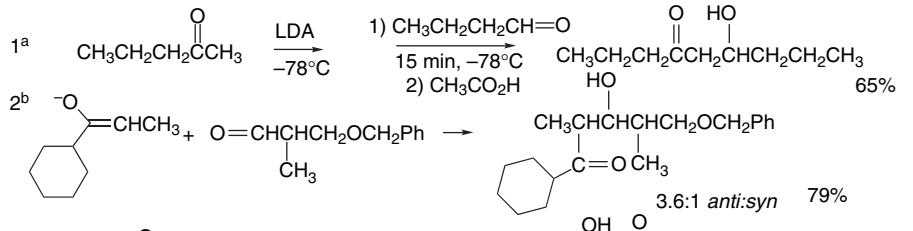
Under other reaction conditions, the product can result from *thermodynamic control*. Aldol reactions can be effected for many compounds using less than a stoichiometric amount of base. In these circumstances, the aldol reaction is reversible and the product ratio is determined by the relative stability of the various possible products. Thermodynamic conditions also permit equilibration among the enolates of the nucleophile. The conditions that lead to equilibration include higher reaction temperatures, protic or polar dissociating solvents, and the use of weakly coordinating cations. Thermodynamic conditions can be used to enrich the composition in the *most stable* of the isomeric products.

Reaction conditions that involve other enolate derivatives as nucleophiles have been developed, including boron enolates and enolates with titanium, tin, or zirconium as the metal. These systems are discussed in detail in the sections that follow, and in Section 2.1.2.5, we discuss reactions that involve *covalent enolate equivalents*, particularly silyl enol ethers. Scheme 2.1 illustrates some of the procedures that have been developed. A variety of carbon nucleophiles are represented in Scheme 2.1, including lithium and boron enolates, as well as titanium and tin derivatives, but in

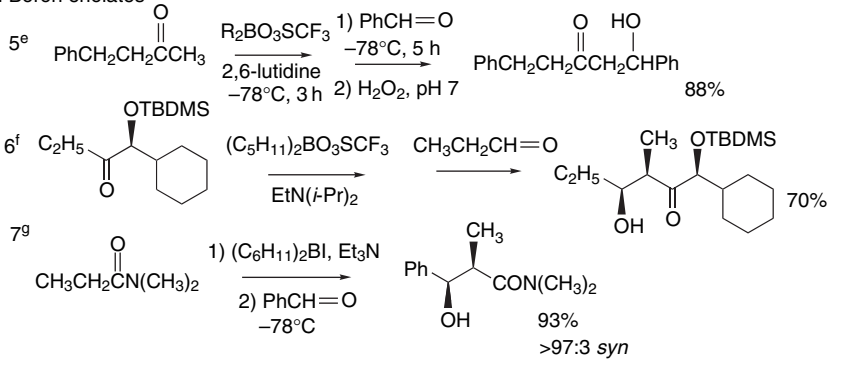
[1] T. Mukaiyama, *Org. React.*, **28**, 203 (1982).

Scheme 2.1. Examples of Directed Aldol Reactions

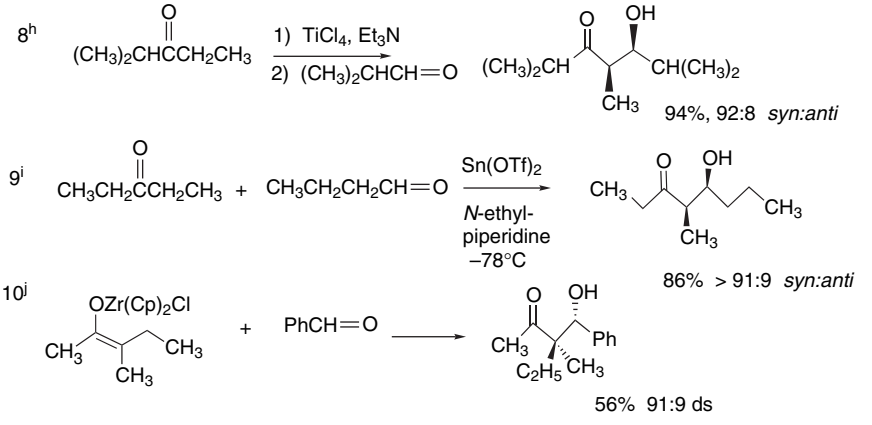
A. Lithium enolates



B. Boron enolates

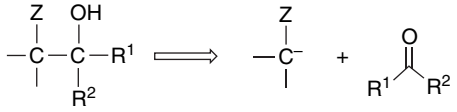


C. Titanium, tin and zirconium enolates



a. G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, **39**, 3459 (1974).
b. S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).
c. R. Bal, C. T. Buse, K. Smith, and C. Heathcock, *Org. Synth.*, **63**, 89 (1984).
d. P. J. Jerris and A. B. Smith, III, *J. Org. Chem.*, **46**, 577 (1981).
e. T. Inoue, T. Uchimaru, and T. Mukaiyama, *Chem. Lett.*, 153 (1977).
f. S. Masamune, W. Choy, F. A. J. Kerdesky, and B. Imperiali, *J. Am. Chem. Soc.*, **103**, 1566 (1981).
g. K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 7346 (1994).
h. D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).
i. T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Hagu, *Tetrahedron*, **40**, 1381 (1984).
j. S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56**, 2098 (1991).

each case the electrophile is an aldehyde. Pay particular attention to the retrosynthetic relationship between the products and the reactants, which corresponds in each case to Path **A** (p. 64). We see that the aldol addition reaction provides β-hydroxy carbonyl compounds or, more generally, adducts with a hydroxy group β to the stabilizing group Z of the carbon nucleophile.



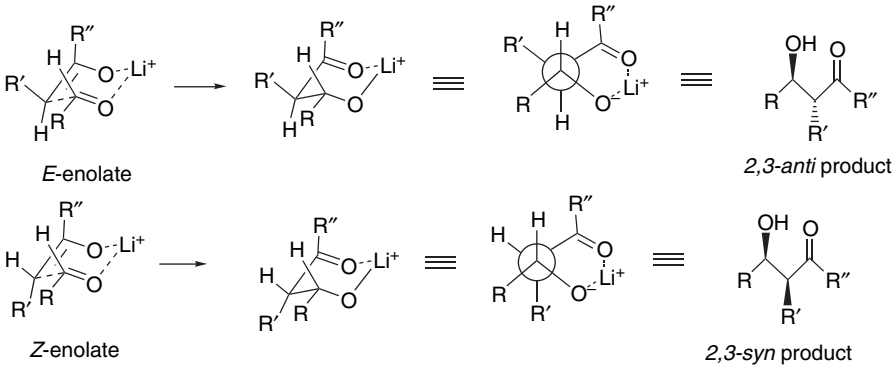
Note also the stereochemistry. In some cases, two new stereogenic centers are formed. The hydroxy group and any C(2) substituent on the enolate can be in a *syn* or *anti* relationship. For many aldol addition reactions, the stereochemical outcome of the reaction can be predicted and analyzed on the basis of the detailed mechanism of the reaction. Entry 1 is a mixed ketone-aldehyde aldol addition carried out by kinetic formation of the less-substituted ketone enolate. Entries 2 to 4 are similar reactions but with more highly substituted reactants. Entries 5 and 6 involve boron enolates, which are discussed in Section 2.1.2.2. Entry 7 shows the formation of a boron enolate of an amide; reactions of this type are considered in Section 2.1.3. Entries 8 to 10 show titanium, tin, and zirconium enolates and are discussed in Section 2.1.2.3.

2.1.2.1. Aldol Reactions of Lithium Enolates. Entries 1 to 4 in Scheme 2.1 represent cases in which the nucleophilic component is a lithium enolate formed by kinetically controlled deprotonation, as discussed in Section 1.1. Lithium enolates are usually highly reactive toward aldehydes and addition occurs rapidly when the aldehyde is added, even at low temperature. The low temperature ensures kinetic control and enhances selectivity. When the addition step is complete, the reaction is stopped by neutralization and the product is isolated.

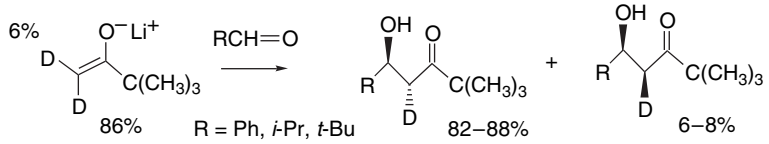
The fundamental mechanistic concept for diastereoselectivity of aldol reactions of lithium enolates is based on a cyclic TS in which both the carbonyl and enolate oxygen are coordinated to the lithium cation.[2] The Lewis acid character of the lithium ion promotes reaction by increasing the carbonyl group electrophilicity and by bringing the reactants together in the TS. Other metal cations and electrophilic atoms can play the role of the Lewis acid, as we will see when we discuss reactions of boron and other metal enolates. The fundamental concept is that the aldol addition normally occurs through a chairlike TS. It is assumed that the structure of the TS is sufficiently similar to a chair cyclohexane that the conformational concepts developed for cyclohexane rings can be applied. In the structures that follow, the reacting aldehyde is shown with R rather than H in the equatorial-like position, which avoids a 1,3-diaxial interaction with the enolate C(1) substituent. A consequence of this mechanism is that the reaction

[2.] (a) H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957); (b) P. Fellman and J. E. Dubois, *Tetrahedron*, **34**, 1349 (1978); (c) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

is *stereospecific with respect to the E- or Z-configuration of the enolate*. The *E*-enolate gives the *anti* aldol product, whereas the *Z*-enolate gives the *syn*-aldol.[3]

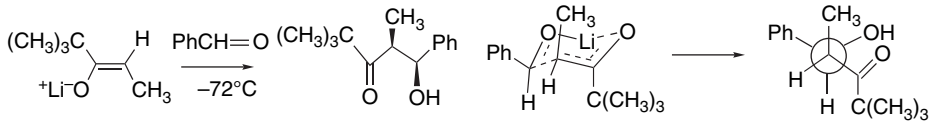


The preference for chairlike TSs has been confirmed by using deuterium-labeled enolates prepared from the corresponding silyl enol ethers. The ratio of the location of the deuterium corresponds closely to the ratio of the stereoisomeric enolates for several aldehydes.[4]



Provided that the reaction occurs through a chairlike TS, the $E \rightarrow anti/Z \rightarrow syn$ relationship will hold. There are three cases that can lead to departure from this relationship. These include a nonchair TS, that can involve either an open TS or a nonchair cyclic TS. Internal chelation of the aldehyde or enolate can also cause a change in TS structure.

The first element of stereocontrol in aldol addition reactions of ketone enolates is the enolate structure. Most enolates can exist as two stereoisomers. In Section 1.1.2, we discussed the factors that influence enolate composition. The enolate formed from 2,2-dimethyl-3-pentanone under kinetically controlled conditions is the *Z*-isomer.[5] When it reacts with benzaldehyde only the *syn* aldol is formed.[4] The product stereochemistry is correctly predicted if the TS has a conformation with the phenyl substituent in an equatorial position.

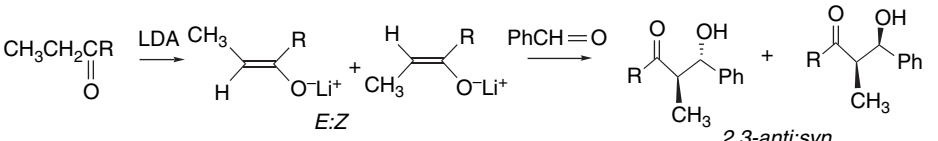


[3] For consistency in designating the relative configuration the carbonyl group is numbered (1). The newly formed bond is labeled 2,3- and successive carbons are numbered accordingly. The carbons derived from the enolate are numbered 2′,3′, etc., starting with the α′-carbon.

[4] C. M. Liu, W. J. Smith, III, D. J. Gustin, and W. R. Roush, *J. Am. Chem. Soc.*, **127**, 5770 (2005).

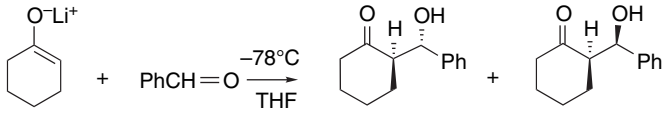
[5] To avoid potential uncertainties in the application of the Cahn-Ingold-Prelog priority rules, by convention the enolate oxygen is assigned the higher priority.

A similar preference for formation of the *syn* aldol is found for other *Z*-enolates derived from ketones in which one of the carbonyl substituents is bulky. Ketone enolates with less bulky substituents show a decreasing stereoselectivity in the order *t*-butyl > *i*-propyl > ethyl.[2c] This trend parallels a decreasing preference for stereoselective formation of the *Z*-enolate.



R =	E:Z	2,3-anti:syn
C_2H_5	70:30	36:64
$CH(CH_3)_2$	40:60	18:82
$C(CH_3)_3$	2:98	2:98

The enolates derived from cyclic ketones are necessarily *E*-isomers. The enolate of cyclohexanone reacts with benzaldehyde to give both possible stereoisomeric products. The stereoselectivity is about 5:1 in favor of the *anti* isomer under optimum conditions.[6]



anti 84% *syn* 16%

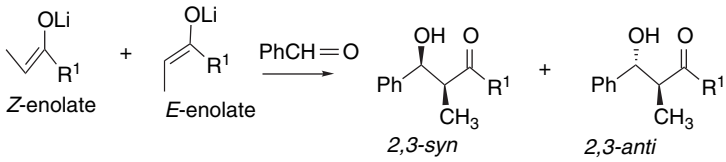
From these and many related examples the following generalizations can be made about kinetic stereoselection in aldol additions of lithium enolates. (1) The chair TS model provides a basis for analyzing the stereoselectivity observed in aldol reactions of ketone enolates having one bulky substituent. The preference is *Z*-enolate → *syn* aldol; *E*-enolate → *anti* aldol. (2) When the enolate has no bulky substituent, stereoselectivity is low. (3) *Z*-Enolates are more stereoselective than *E*-enolates. Table 2.1 gives some illustrative data.

The requirement that an enolate have at least one bulky substituent restricts the types of compounds that give highly stereoselective aldol additions via the lithium enolate method. Furthermore, only the enolate formed by kinetic deprotonation is directly available. Whereas ketones with one tertiary alkyl substituent give mainly the *Z*-enolate, less highly substituted ketones usually give mixtures of *E*- and *Z*-enolates.[7] (Review the data in Scheme 1.1.) Therefore efforts aimed at increasing the stereoselectivity of aldol additions have been directed at two facets of the problem: (1) better control of enolate stereochemistry, and (2) enhancement of the degree of stereoselectivity in the addition step, which is discussed in Section 2.1.2.2.

The *E*:*Z* ratio can be modified by the precise conditions for formation of the enolate. For example, the *E*:*Z* ratio for 3-pentanone and 2-methyl-3-pentanone can be increased by use of a 1:1 lithium tetramethylpiperidide(LiTMP)-LiBr mixture for

6. M. Majewski and D. M. Gleave, *Tetrahedron Lett.*, **30**, 5681 (1989).
7. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976); W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 247 (1977); Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, *J. Am. Chem. Soc.*, **102**, 3959 (1980).

Table 2.1. Diastereoselectivity of Addition of Lithium Enolates to Benzaldehyde



R^1	*Z*:*E* ratio	*syn*:*anti* ratio
H	100:0	50:50
H	0:100	65:35
C_2H_5	30:70	64:36
C_2H_5	66:34	77:23
$(CH_3)_2CH$	>98:2	90:10
$(CH_3)_2CH$	0:100	45:55
$(CH_3)_3C$	>98:2	>98:2
1-Adamantyl	>98:2	>98:2
C_6H_5	>98:2	88:12
Mesityl	8:92	8:92
Mesityl	87:13	88:12

a. From C. H. Heathcock, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 2.

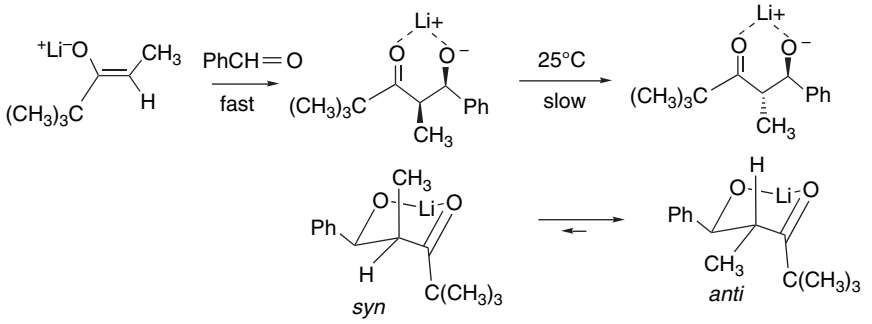
kinetic enolization.[8] The precise mechanism of this effect is still a matter of investigation, but it is probably due to an aggregate species containing bromide acting as the base (see Section 1.1.1).[9]

	E:*Z* Stereoselectivity		
	LDA	LiTMP	LiTMP + LiBr
$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3$	3.3:1	5:1	50:1
$(CH_3)_2CH\overset{\overset{O}{\|}}{C}CH_2CH_3$	1.7:1	2:1	21:1
$(CH_3)_3C\overset{\overset{O}{\|}}{C}CH_2CH_3$	1: >50	1: >20	1:>20

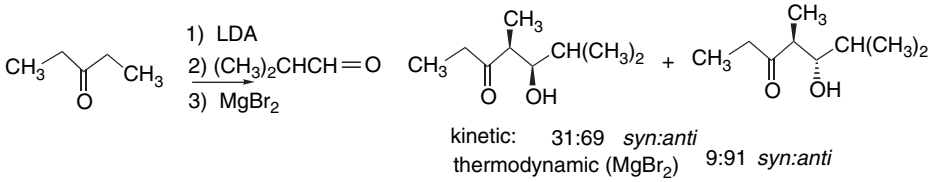
Other changes in deprotonation conditions can influence enolate composition. Relatively weakly basic lithium anilides, specifically lithium 2,4,6-trichloroanilide and lithium diphenylamide, give high *Z*:*E* ratios.[10] Lithio 1,1,3,3-tetramethyl-1,3-diphenyldisilylamide is also reported to favor the *Z*-enolate.[11] On the other hand, lithium *N*-trimethylsilyl-*iso*-propylamide and lithium *N*-trimethylsilyl-*tert*-butylamide give selectivity for the *E*-enolate[12] (see Scheme 1.1).

8. P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991).
9. F. S. Mair, W. Clegg, and P. A. O'Neil, *J. Am. Chem. Soc.*, **115**, 3388 (1993).
10. L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).
11. S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).
12. L. Xie, K. M. Isenberger, G. Held, and L. M. Dahl, *J. Org. Chem.*, **62**, 7516 (1997).

When aldol addition is carried out under thermodynamic conditions, the product stereoselectivity is usually not as high as under kinetic conditions. All the regio- and stereoisomeric enolates can participate as nucleophiles. The adducts can return to reactants, so the difference in *stability* of the stereoisomeric *anti* and *syn* products determines the product composition. In the case of lithium enolates, the adducts can be equilibrated by keeping the reaction mixture at room temperature. This has been done, for example, with the product from the reaction of the enolate of 2,2-dimethyl-3-pentanone and benzaldehyde. The greater stability of the *anti* isomer is attributed to the pseudoequatorial position of the methyl group in the chairlike product chelate. With larger substituent groups, the thermodynamic preference for the *anti* isomer is still greater.[13]



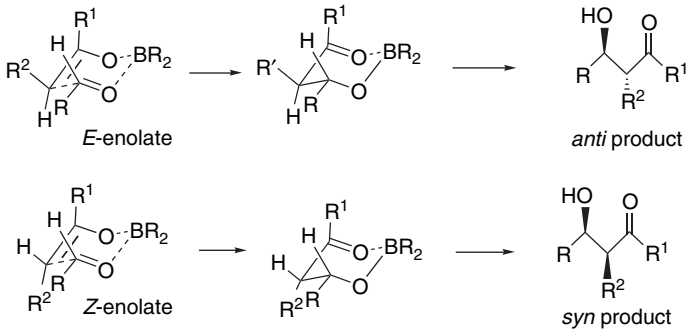
For synthetic efficiency, it is useful to add $MgBr_2$, which accelerates the equilibration.



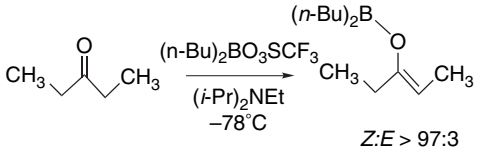
Ref. 14

2.1.2.2. Aldol Reactions of Boron Enolates. The matter of increasing stereoselectivity in the addition step can be addressed by using other reactants. One important version of the aldol reaction involves the use of boron enolates.[15] A cyclic TS similar to that for lithium enolates is involved, and the same relationship exists between enolate configuration and product stereochemistry. In general, the stereoselectivity is higher than for lithium enolates. The O–B bond distances are shorter than for lithium enolates, and this leads to a more compact structure for the TS and magnifies the steric interactions that control stereoselectivity.

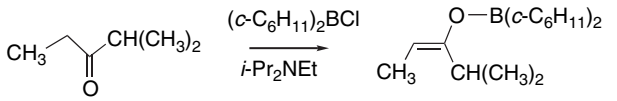
13. C. H. Heathcock and J. Lampe, *J. Org. Chem.*, **48**, 4330 (1983).
14. K. A. Swiss, W.-B. Choi, D. C. Liotta, A. F. Abdel-Magid, and C. A. Maryanoff, *J. Org. Chem.*, **56**, 5978 (1991).
15. C. J. Cowden and I. A. Paterson, *Org. React.*, **51**, 1 (1997); E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *Adv. Carbanion Chem.*, **2**, 111 (1996).



Boron enolates can be prepared by reaction of the ketone with a dialkylboron trifluoromethanesulfonate (triflate) and a tertiary amine.[16] Use of boron triflates and a bulky amine favors the *Z*-enolate. The resulting aldol products are predominantly the *syn* stereoisomers.

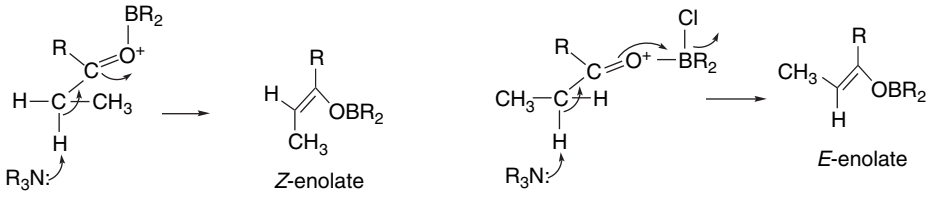


The *E*-boron enolates of some ketones can be preferentially obtained by using dialkylboron chlorides.[17]

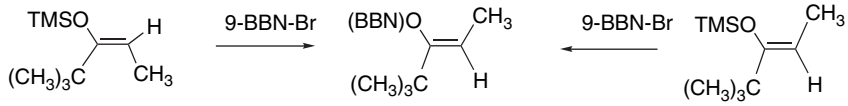


The contrasting stereoselectivity of the boron triflates and chlorides has been discussed in terms of reactant conformation and the stereoelectronic requirement for alignment of the hydrogen being removed with the carbonyl group π orbital.[18] With the triflate reagents, the boron is *anti* to the enolizable group. With the bulkier dicyclohexylboron chloride, the boron favors a conformation *cis* to the enolizable group. A computational study of the reaction also indicates that the size of the boron ligand and the resulting conformational changes are the dominant factors in determining stereoselectivity.[19] There may also be a distinction between the two types of borylation reagents in the extent of dissociation of the leaving group. The triflate is probably an ion pair, whereas with the less reactive chloride, the deprotonation may be a concerted (E2-like) process.[18b] The two proposed TSs are shown below.

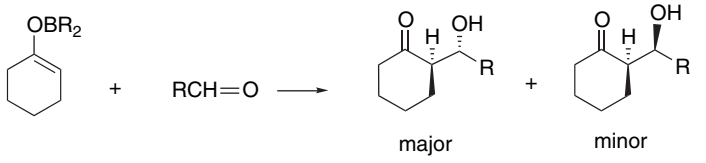
16. D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979); D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).
17. H. C. Brown, R. K. Dhar, R. K. Bakshi, P. K. Pandiarajan, and B. Singaram, *J. Am. Chem. Soc.*, **111**, 3441 (1989); H. C. Brown, R. K. Dhar, K. Ganesan, and B. Singaram, *J. Org. Chem.*, **57**, 499 (1992); H. C. Brown, R. K. Dhar, K. Ganesan, and B. Singaram, *J. Org. Chem.*, **57**, 2716 (1992); H. C. Brown, K. Ganesan, and R. K. Dhar, *J. Org. Chem.*, **58**, 147 (1993); K. Ganesan and H. C. Brown, *J. Org. Chem.*, **58**, 7162 (1993).
18. (a) J. M. Goodman and I. Paterson, *Tetrahedron Lett.*, **33**, 7223 (1992); (b) E. J. Corey and S. S. Kim, *J. Am. Chem. Soc.*, **112**, 4976 (1990).
19. J. Murga, E. Falomir, M. Carda, and J. A. Marco, *Tetrahedron*, **57**, 6239 (2001).



Z-Boron enolates can also be obtained from silyl enol ethers by reaction with the bromoborane derived from 9-BBN (9-borabicyclo[3.3.1]nonane). This method is necessary for ketones such as 2,2-dimethyl-3-pentanone, which give *E*-boron enolates by other methods. The *Z*-stereoisomer is formed from either the *Z*- or *E*-silyl enol ether.[20]



The *E*-boron enolate from cyclohexanone shows a preference for the *anti* aldol product. The ratio depends on the boron alkyl groups and is modest (2:1) with di-*n*-butylboron but greater than 20:1 for cyclopentyl-*n*-hexylboron.[16]

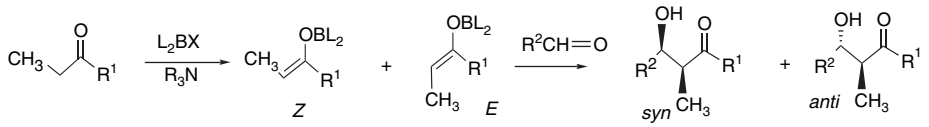


The general trend is that boron enolates *parallel* lithium enolates in their stereoselectivity but show *enhanced stereoselectivity*. There also are some advantages in terms of access to both stereoisomeric enol derivatives. Another important characteristic of boron enolates is that they are not subject to internal chelation. The tetracoordinate dialkylboron in the cyclic TS is not able to accept additional ligands, so there is no tendency to form a chelated TS when the aldehyde or enolate carries a donor substituent. Table 2.2 gives some typical data for boron enolates and shows the strong correspondence between enolate configuration and product stereochemistry.

2.1.2.3. Aldol Reactions of Titanium, Tin, and Zirconium Enolates. Metals such as Ti, Sn, and Zr give enolates that are intermediate in character between the ionic Li^+ enolates and covalent boron enolates. The Ti, Sn, or Zr enolates can accommodate additional ligands. Tetra-, penta-, and hexacoordinate structures are possible. This permits the formation of chelated TSs when there are nearby donor groups in the enolate or electrophile. If the number of anionic ligands exceeds the oxidation state of the metal, the complex has a formal negative charge on the metal and is called an "ate" complex. Such structures enhance the nucleophilicity of enolate ligands. Depending on the nature of the metal ligands, either a cyclic or an acyclic TS can be involved. As we will see in Section 2.1.3.5, the variability in the degree and nature of coordination provides an additional factor in analysis and control of stereoselectivity.

[20] J. L. Duffy, T. P. Yoon, and D. A. Evans, *Tetrahedron Lett.*, **36**, 9245 (1993).

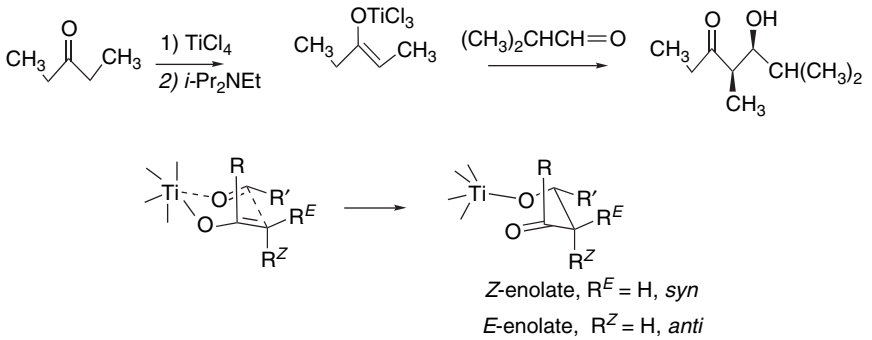
Table 2.2. Diastereoselectivity of Boron Enolates toward Aldehydes[a]



R^1	L	X	R^2	*Z* : *E*	*syn*:*anti*
C_2H_5[b]	*n*-C_4H_9	OTf	Ph	>97:3	>97:3
C_2H_5[b]	*n*-C_4H_9	OTf	Ph	69:31	72:28
C_2H_5[b]	*n*-C_4H_9	OTf	*n*-C_3H_7	>97:3	>97:3
C_2H_5[b]	*n*-C_4H_9	OTf	*t*-C_4H_9	>97:3	>97:3
C_2H_5[b]	*n*-C_4H_9	OTf	CH_2=$CHCH_3$	>97:3	92:8
C_2H_5[b]	*n*-C_4H_9	OTf	*E*-C_4H_7	>97:3	93:7
i-C_3H_7[b]	*n*-C_4H_9	OTf	Ph	45:55	44:56
i-C_4H_9[b]	*n*-C_4H_9	OTf	Ph	>99:1	>97:3
t-C_4H_9[b]	*n*-C_4H_9	OTf	Ph	>99:1	>97:3
n-C_5H_{11}[c]	*n*-C_4H_9	OTf	Ph	95:5	94:6
n-C_9H_{19}[c]	*n*-C_4H_9	OTf	Ph	91:9	91:9
c-C_6H_{11}[c]	*n*-C_4H_9	OTf	Ph	95:5	94:6
$PhCH_2$[c]	*n*-C_4H_9	OTf	Ph	98:2	>99:1
Ph[b]	*n*-C_4H_9	OTf	Ph	96:4	95:5
C_2H_5[d]	*c*-C_6H_{11}	Cl	Ph		21:79
i-C_3H_7[d]	*c*-C_6H_{11}	Cl	Ph		<3:97
c-C_6H_{11}[d]	*c*-C_6H_{11}	Cl	Ph		<1:99
t-C_4H_9[d]	*c*-C_6H_{11}	Cl	Ph		<3:97

a. From a more complete compilation, see C. H. Heathcock, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 3.
b. D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).
c. I. Kuwajima, M. Kato, and A. Mori, *Tetrahedron Lett.*, **21**, 4291 (1980).
d. H. C. Brown, R. K. Dhar, R. K. Bakshi, P. K. Pandiarajan, and P. Singaram, *J. Am. Chem. Soc.*, **111**, 3441 (1989); H. C. Brown, K. Ganesan, and R. K. Dhar, *J. Org. Chem.*, **58**, 147 (1993).

Titanium enolates can be prepared from lithium enolates by reaction with a trialkoxytitanium(IV) chloride, such as *tris*-(isopropoxy)titanium chloride.[21] Titanium enolates are usually prepared directly from ketones by reaction with $TiCl_4$ and a tertiary amine.[22] Under these conditions, the *Z*-enolate is formed and the aldol adducts have *syn* stereochemistry. The addition step proceeds through a cyclic TS assembled around titanium.

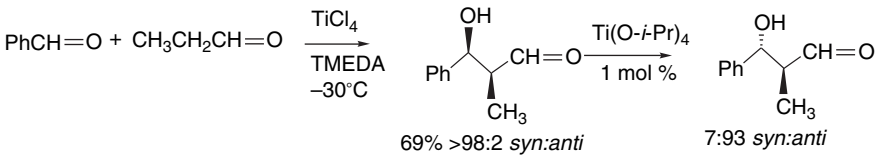


Entry 8 in Scheme 2.1 is an example of this method. Titanium enolates are frequently employed in the synthesis of complex molecules and with other carbonyl derivatives,

21. C. Siegel and E. R. Thornton, *J. Am. Chem. Soc.*, **111**, 5722 (1989).
22. D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).

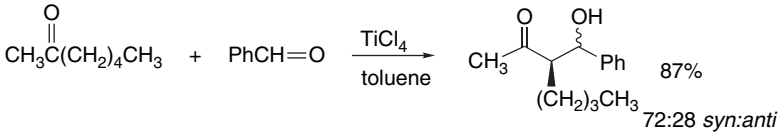
such as the *N*-acyloxazolidinones that serve as chiral auxiliaries (see Section 2.1.3.4).

Mixed aldehyde-aldehyde additions have been carried out using $TiCl_4$ and TMEDA. The reaction gives *syn* adducts, presumably through a cyclic TS. Treatment of the *syn* adducts with 1 mol % $Ti(O\text{-}i\text{-}Pr)_4$ leads to equilibration to the more stable *anti* isomer.[23]

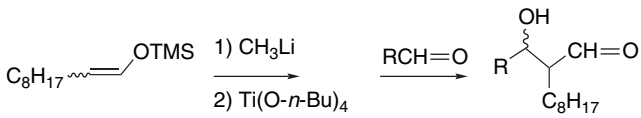


The equilibration in this case is believed to involve oxidation-reduction at the alcohol center, rather than reversal of the addition. (See Section 5.3.2 for a discussion of $Ti(O\text{-}i\text{-}Pr)_4$ as an oxidation-reduction catalyst.)

Ketone-aldehyde additions have been effected using $TiCl_4$ in toluene.[24] These reactions exhibit the same stereoselectivity trends as other titanium-mediated additions. With unsymmetrical ketones, this procedure gives the product from the more-substituted enolate.[25]



Titanium enolates can also be used under conditions in which the titanium exists as an "ate" species. Crossed aldehyde-aldehyde additions have been accomplished starting with trimethylsilyl enol ethers, which are converted to lithium enolates and then to "ate" species by addition of $Ti(O\text{-}n\text{-}Bu)_4$.[26] These conditions show only modest stereoselectivity.

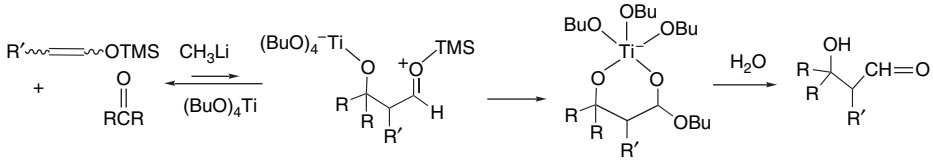


Silyl enol ether	R	*syn*:*anti*
Z	C_2H_5	28:72
Z	$(CH_3)_2CH$	20:80
Z	$(CH_3)_3C$	10:90
Z	Ph	54:46
E	$(CH_3)_2CH$	47:53
E	$(CH_3)_3C$	28:72

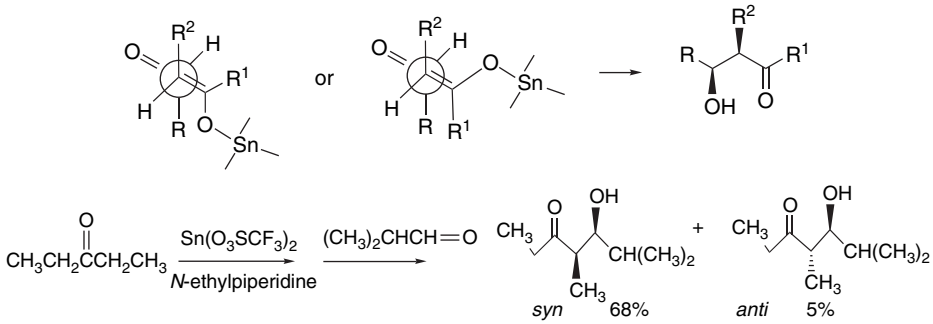
Titanium "ate" species have also been used to add aldehyde enolates to ketones. This reaction is inherently difficult because of the greater reactivity of aldehyde

[23] R. Mahrwald, B. Costisella, and B. Gundogan, *Synthesis*, 262 (1998).
[24] R. Mahrwald, *Chem. Ber.*, **128**, 919 (1995).
[25] R. Mahrwald and B. Gundogan, *J. Am. Chem. Soc.*, **120**, 413 (1998).
[26] K. Yachi, H. Shinokubo, and K. Oshima, *J. Am. Chem. Soc.*, **121**, 9465 (1999).

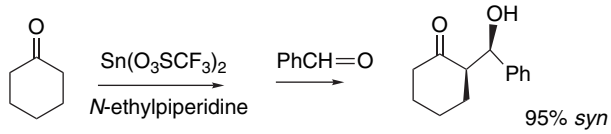
carbonyls over ketone carbonyls. The reaction works best with ketones having EWG substituents such as alkynones and α-haloketones. The reaction is thought to proceed through a cyclic intermediate that is stable until hydrolysis. This cyclic intermediate may be necessary to drive the normally unfavorable equilibrium of the addition step.



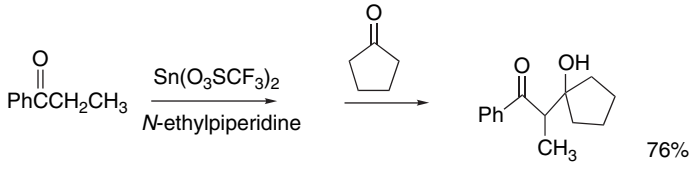
Tin enolates are also used in aldol reactions.[27] Both the Sn(II) and Sn(IV) oxidation states are reactive. Tin(II) enolates can be generated from ketones and $Sn(II)(O_3SCF_3)_2$ in the presence of tertiary amines.[28] The subsequent aldol addition is *syn* selective and independent of enolate configuration.[29] This preference arises from avoidance of *gauche* interaction of the aldehyde group and the enolate β-substituent. The *syn* stereoselectivity indicates that reaction occurs through an open TS.



Even cyclohexanone gives the *syn* product.



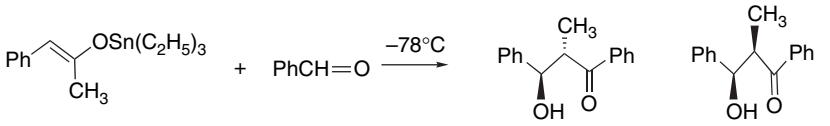
Entry 9 of Scheme 2.1 is an example of application of these conditions. Tin(II) enolates prepared in this way also show good reactivity toward ketones as the electrophilic component.



Ref. 30

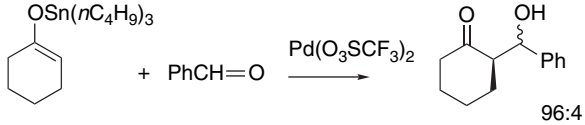
27. T. Mukaiyama and S. Kobayashi, *Org. React.*, **46**, 1 (1994).
28. T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, *Tetrahedron*, **40**, 1381 (1984); I. Shibata and A. Babu, *Org. Prep. Proc. Int.*, **26**, 85 (1994).
29. T. Mukaiyama, R. W. Stevens, and N. Iwasawa, *Chem. Lett.*, 353 (1982).
30. R. W. Stevens, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, 1459 (1982).

Trialkylstannyl enolates can be prepared from enol acetates by reaction with trialkyltin alkoxides and are sufficiently reactive to add to aldehydes. Uncatalyzed addition of trialkylstannyl enolates to benzaldehyde shows *anti* stereoselectivity.[31]



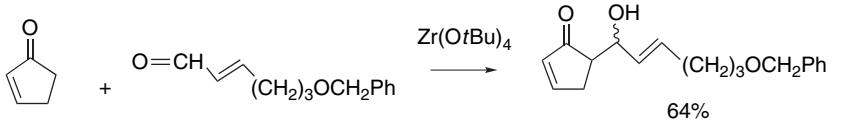
9:1 *anti:syn*

Isolated tri-*n*-butylstannyl enolates react with benzaldehyde under the influence of metal salts including $Pd(O_3SCF_3)_2$, $Zn(O_3SCF_3)_2$, and $Cu(O_3SCF_3)_2$.[32] The tri-*n*-butylstannyl enol derivative of cyclohexanone gives mainly *anti* product. The *anti*:*syn* ratio depends on the catalyst, with $Pd(O_3SCF_3)_2$ giving the highest ratio.



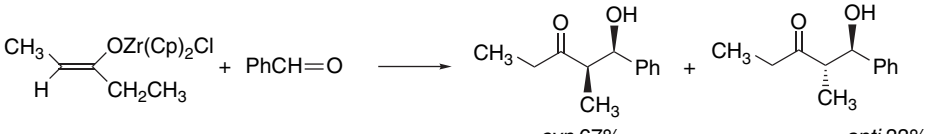
96:4 *anti:syn*

Zirconium *tetra-t*-butoxide is a mildly basic reagent that has occasionally been used to effect aldol addition.[33]



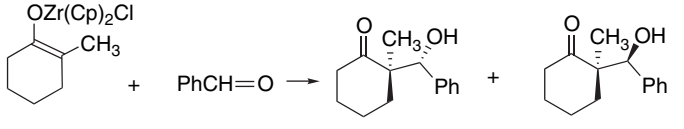
64%

Zirconium enolates can also prepared by reaction of lithium enolates with $(Cp)_2ZrCl_2$, and they act as nucleophiles in aldol addition reactions.[34]



syn 67% *anti* 33%

Ref. 34d

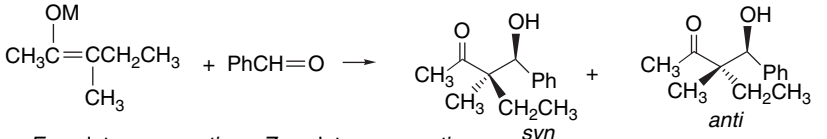


anti 83% *syn* 17%

Ref. 34d

[31] S. S. Labadie and J. K. Stille, *Tetrahedron*, **40**, 2329 (1984).
[32] A. Yanagisawa, K. Kimura, Y. Nakatsuka, and M. Yamamoto, *Synlett*, 958 (1998).
[33] H. Sasai, Y. Kirio, and M. Shibasaki, *J. Org. Chem.*, **55**, 5306 (1990).
[34] (a) D. A. Evans and L. R. McGee, *Tetrahedron Lett.*, **21**, 3975 (1980); (b) Y. Yamamoto and K. Maruyama, *Tetrahedron Lett.*, **21**, 4607 (1980); (c) M. Braun and H. Sacha, *Angew. Chem. Int. Ed. Engl.*, **30**, 1318 (1991); (d) S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56,** 2098 (1991).

A comparison of the *anti*:*syn* diastereoselectivity of the lithium, dibutylboron, and $(Cp)_2Zr$ enolates of 3-methyl-2-hexanone with benzaldehyde has been reported.[34d] The order of stereoselectivity is $Bu_2B > (Cp)_2Zr > Li$. These results suggest that the reactions of the zirconium enolates proceed through a cyclic TS.



E-enolate	*syn*:*anti*	*Z*-enolate	*syn*:*anti*
Li	17:83	Li	45:55
Bu_2B	3:97	Bu_2B	94:6
$(Cp)_2ZrCl$	9:91	$(Cp)_2ZrCl$	86:14

2.1.2.4. Summary of the Relationship between Diastereoselectivity and the Transition Structure. In this section we considered *simple diastereoselection* in aldol reactions of ketone enolates. Numerous observations on the reactions of enolates of ketones and related compounds are consistent with the general concept of a chairlike TS.[35] These reactions show a consistent $E \rightarrow anti : Z \rightarrow syn$ relationship. Noncyclic TSs have more variable diastereoselectivity. The prediction or interpretation of the specific ratio of *syn* and *anti* product from any given reaction requires assessment of several variables: (1) What is the stereochemical composition of the enolate? (2) Does the Lewis acid promote tight coordination with both the carbonyl and enolate oxygen atoms and thereby favor a cyclic TS? (3) Does the TS have a chairlike conformation? (4) Are there additional Lewis base coordination sites in either reactant that can lead to reaction through a chelated TS? Another factor comes into play if either the aldehyde or the enolate, or both, are chiral. In that case, facial selectivity becomes an issue and this is considered in Section 2.1.5.

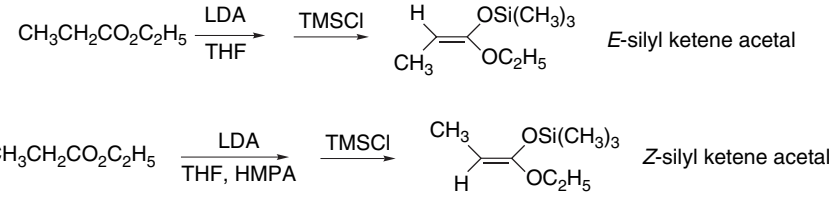
2.1.3. Aldol Addition Reactions of Enolates of Esters and Other Carbonyl Derivatives

The enolates of other carbonyl compounds can be used in mixed aldol reactions. Extensive use has been made of the enolates of esters, thiol esters, amides, and imides, including several that serve as chiral auxiliaries. The methods for formation of these enolates are similar to those for ketones. Lithium, boron, titanium, and tin derivatives have all been widely used. The silyl ethers of ester enolates, which are called *silyl ketene acetals*, show reactivity that is analogous to silyl enol ethers and are covalent equivalents of ester enolates. The silyl thioketene acetal derivatives of thiol esters are also useful. The reactions of these enolate equivalents are discussed in Section 2.1.4.

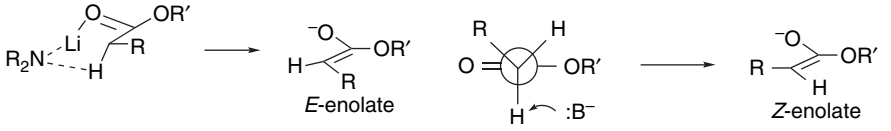
Because of their usefulness in aldol additions and other synthetic methods (see especially Section 6.4.2.3), there has been a good deal of interest in the factors that

[35] C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992); C. H. Heathcock, in *Asymmetric Syntheses*, Vol. 3, J. D. Morrison, ed., 1984, Chap. 2, Academic Press; C. H. Heathcock, in *Comprehensive Carbanion Chemistry*, Part B, E. Buncel and T. Durst, ed., Elsevier, Amsterdam, 1984, Chap. 4; D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, **13**, 1 (1982); A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968); R. Mahrwald, ed., *Modern Aldol Reactions*, Wiley-VCH (2004).

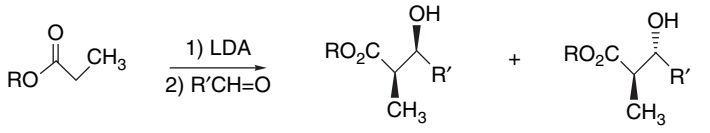
control the stereoselectivity of enolate formation from esters. For simple esters such as ethyl propanoate, the *E*-enolate is preferred under kinetic conditions using a strong base such as LDA in THF solution. Inclusion of a strong cation-solvating cosolvent, such as HMPA or DMPU, favors the *Z*-enolate.[36] These enolates can be trapped and analyzed as the corresponding silyl ketene acetals. The relationships are similar to those discussed for formation of ketone enolates in Section 1.1.2.



These observations are explained in terms of a chairlike TS for the LDA/THF conditions and a more open TS in the presence of an aprotic dipolar solvent.



Despite the ability to control ester enolate geometry, the aldol addition reactions of unhindered ester enolate are not very stereoselective.[37]



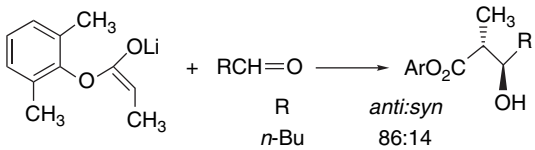
R	R′	*syn:anti*
CH_3	$(CH_3)_2CH$	45:55
CH_3	Ph	45:55
$(CH_3)_3C$	Ph	49:51

This stereoselectivity can be improved by use of a very bulky group. 2,6-Dimethylphenyl esters give *E*-enolates and *anti* aldol adducts.[38]

[36] R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976); R. E. Ireland, P. Wipf, and J. D. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

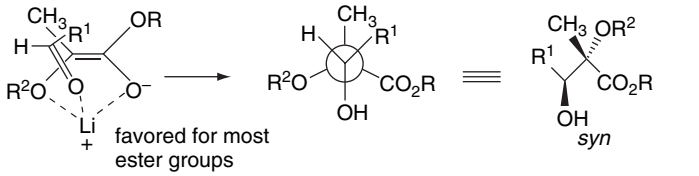
[37] A. I. Meyers and P. J. Reider, *J. Am. Chem. Soc.*, **101**, 2501 (1979); C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

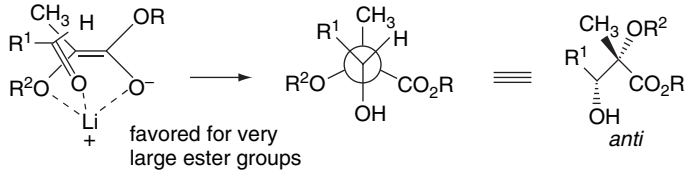
[38] M. C. Pirrung and C. H. Heathcock, *J. Org. Chem.*, **45**, 1728 (1980).



R	*anti:syn*
n-Bu	86:14
i-Pr	>98:2
t-Bu	>98:2
Ph	88:12

The lithium enolates of α-alkoxy esters exhibit high stereoselectivity, which is consistent with involvement of a chelated enolate.[37a,39] The chelated ester enolate is approached by the aldehyde in such a manner that the aldehyde R group avoids being between the α-alkoxy and methyl groups in the ester enolate. A *syn* product is favored for most ester groups, but this shifts to *anti* with extremely bulky groups.

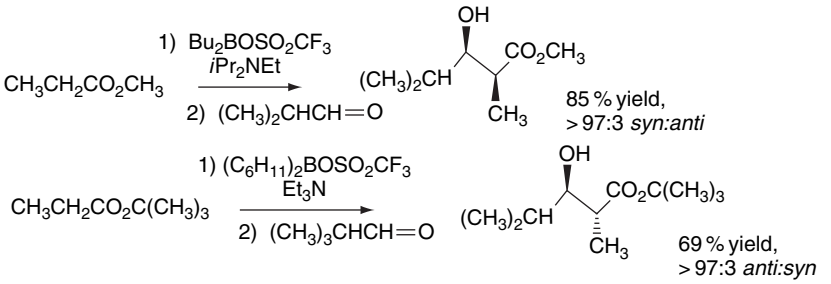




RO	*syn:anti*
Methyl	70:30
2,6-Dimethylphenyl	83:17
2,6-Di-(*i*-propyl)phenyl	33:67
2,6-Di-(*t*-butyl)-4-methylphenyl	< 3:97

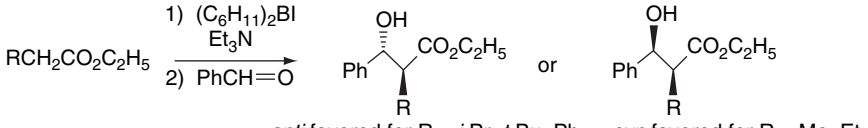
Boron enolates can be obtained from esters[40,41] and amides[42] by methods that are similar to those used for ketones. Various combinations of borylating reagents and amines have been used and the *E*:*Z* ratios are dependent on the reagents and conditions. In most cases esters give *Z*-enolates, which lead to *syn* adducts, but there are exceptions. Use of branched-chain alcohols increases the amount of *anti* enolate, and with *t*-butyl esters the product ratio is higher than 97:3.

39. C. H. Heathcock, M. C. Pirrung, S. D. Young, J. P. Hagen, E. T. Jarvi, U. Badertscher, H.-P. Marki, and S. H. Montgomery, *J. Am. Chem. Soc.*, **106**, 8161 (1984).
40. K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 2336 (1994).
41. A. Abiko, J.-F. Liu, and S. Masamune, *J. Org. Chem.*, **61**, 2590 (1996); T. Inoue, J.-F. Liu, D. C. Buske, and A. Abiko, *J. Org. Chem.*, **67**, 5250 (2002).
42. K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 7346 (1994).



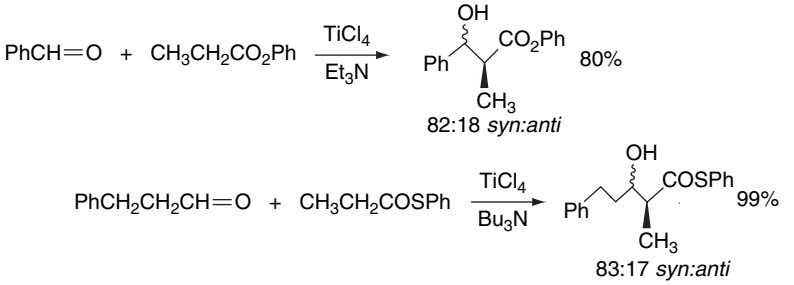
Ref. 41

Branched-chain esters also give mainly *anti* adducts when the enolates are formed using dicyclohexyliodoborane.

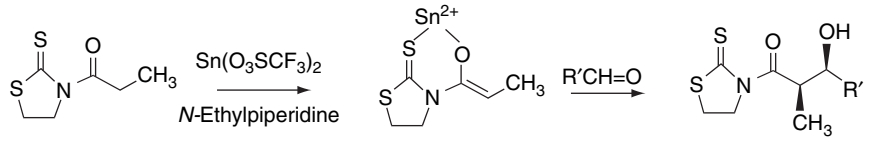


Ref. 40

Phenyl and phenylthio esters have proven to be advantageous in $TiCl_4$-mediated additions, perhaps because they are slightly more acidic than the alkyl analogs. The reactions show *syn* diastereoselectivity, indicating that *Z*-enolates are formed.[43]



Among the most useful carbonyl derivatives are *N*-acyloxazolidinones, and as we shall see in Section 2.3.4, they provide facial selectivity in aldol addition reactions. 1,3-Thiazoline-2-thiones constitute another useful type of chiral auxiliary, and they can be used in conjunction with $Bu_2BO_3SCF_3$,[44] $Sn(O_3SCF_3)_2$,[45] or $TiCl_4$[46] for generation of enolates. The stereoselectivity of the reactions is consistent with formation of a *Z*-enolate and reaction through a cyclic TS.

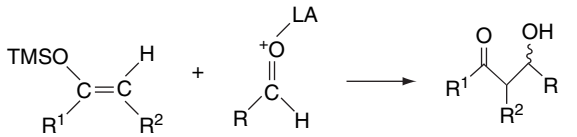


Ref. 47

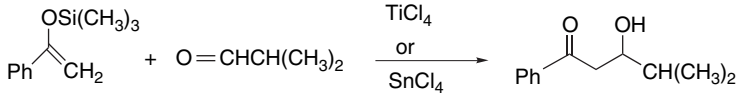
43. Y. Tanabe, N. Matsumoto, S. Funakoshi, and N. Manta, *Synlett*, 1959 (2001).
44. C.-N. Hsiao, L. Liu, and M. J. Miller, *J. Org. Chem.*, **52**, 2201 (1987).
45. Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto, and E. Fujita, *J. Org. Chem.*, **51**, 2391 (1986); Y. Nagao, Y. Nagase, T. Kumagai, H. Matsunaga, T. Abe, O. Shimada, T. Hayashi, and Y. Inoue, *J. Org. Chem.*, **57**, 4243 (1992).
46. D. A. Evans, S. J. Miller, M. D. Ennis, and P. L. Ornstein, *J. Org. Chem.*, **57**, 1067 (1992).
47. T. Mukaiyama and N. Isawa, *Chem. Lett.*, 1903 (1982); N. Isawa, H. Huang, and T. Mukaiyama, *Chem. Lett.*, 1045 (1985).

2.1.4. The Mukaiyama Aldol Reaction

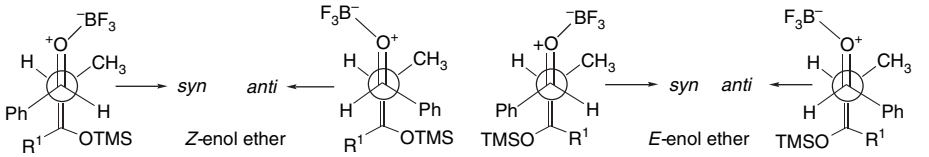
The *Mukaiyama aldol reaction* refers to Lewis acid–catalyzed aldol addition reactions of silyl enol ethers, silyl ketene acetals, and similar *enolate equivalents*.[48] Silyl enol ethers are not sufficiently nucleophilic to react directly with aldehydes or ketones. However, Lewis acids cause reaction to occur by coordination at the carbonyl oxygen, activating the carbonyl group to nucleophilic attack.



Lewis acids such as $TiCl_4$ and $SnCl_4$ induce addition of both silyl enol ethers and ketene silyl acetals to aldehydes.[49]



If there is no other interaction, the reaction proceeds through an acyclic TS and steric factors determine the amount of *syn* versus *anti* addition. This is the case with BF_3, where the tetracoordinate boron-aldehyde adduct does not offer any free coordination sites for formation of a cyclic TS. Stereoselectivity increases with the steric bulk of the silyl enol ether substituent R^1.[50]



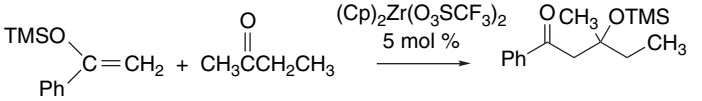
	Z-silyl enol ether	*E*-silyl enol ether
R^1	*syn:anti*	*syn:anti*
Et	60:40	57:43
i-Pr	56:44	35:65
t-Bu	<5 : 95	–
Ph	47:53	30:70

Quite a number of other Lewis acids can catalyze the Mukaiyama aldol reaction, including $Bu_2Sn(O_3SCF_3)_2$,[51] Bu_3SnClO_4,[52] $Sn(O_3SCF_3)_2$,[53] $Zn(O_3SCF_3)_2$,[54] and

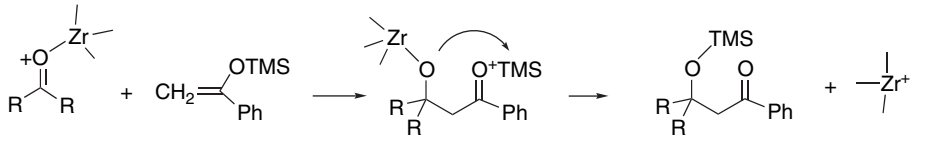
48. R. Mahrwald, *Chem. Rev.*, **99**, 1095 (1999).
49. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
50. C. H. Heathcock, K. T. Hug, and L. A. Flippin, *Tetrahedron Lett.*, **25**, 5973 (1984).
51. T. Sato, J. Otera, and H. Nozaki, *J. Am. Chem. Soc.*, **112**, 901 (1990).
52. J. Otera and J. Chen, *Synlett*, 321 (1996).
53. T. Oriyama, K. Iwanami, Y. Miyauchi, and G. Koga, *Bull. Chem. Soc. Jpn.*, **63**, 3716 (1990).
54. M. Chini, P. Crotti, C. Gardelli, F. Minutolo, and M. Pineschi, *Gazz. Chim. Ital.*, **123**, 673 (1993).

$LiClO_4$.[55] Cerium, samarium, and other lanthanide halides promote addition of silyl ketene acetals to aldehydes.[56] Triaryl perchlorate salts are also very active catalysts.[57] In general terms, there are at least three possible mechanisms for catalysis. One is through Lewis acid activation of the electrophilic carbonyl component, similar to that discussed for BF_3, $TiCl_4$, and $SnCl_4$. Another is by exchange with the enolate equivalent to generate a more nucleophilic species. A third is activation of a catalytic cycle that generates trimethylsilyl cation as the active catalysts.

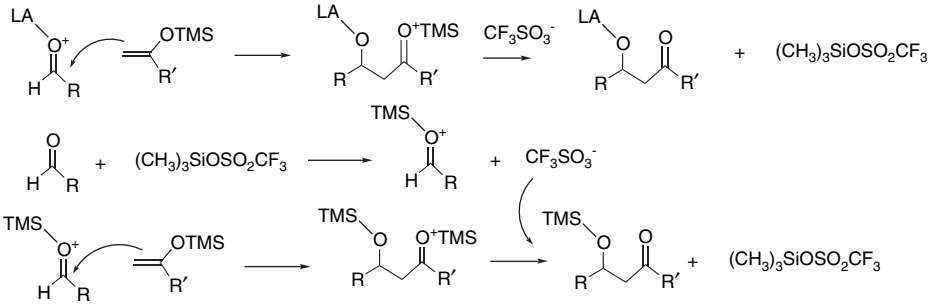
Aldol additions of silyl enol ethers and silyl ketene acetals can be catalyzed by $(Cp)_2Zr^{2+}$ species including $[(Cp)_2ZrO\text{-}t\text{-}Bu]^+$ and $(Cp)_2Zr(O_3SCF_3)_2$.[58]



The catalytic cycle involves transfer of the silyl group to the adduct.

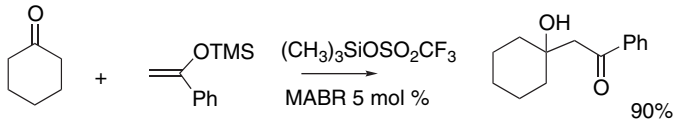


Trialkylsilyl cations may play a key role in other Lewis acid–catalyzed reactions.[59] For example, trimethylsilyl triflate can be formed by intermolecular transfer of the silyl group. When this occurs, the trimethylsilyl triflate can initiate a catalytic cycle that does not directly involve the Lewis acid.



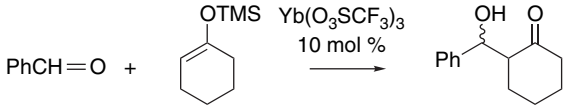
55. M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, **34**, 1119 (1993).
56. P. Van de Weghe and J. Colin, *Tetrahedron Lett.*, **34**, 3881 (1993); A. E. Vougioukas and H. B. Kagan, *Tetrahedron Lett.*, **28**, 5513 (1987).
57. T. Mukaiyama, S. Kobayashi, and M. Murakami, *Chem. Lett.*, 447 (1985); T. Mukaiyama, S. Kobayashi, and M. Murakami, *Chem. Lett.*, 1759 (1984); S. E. Denmark and C.-T. Chen, *Tetrahedron Lett.*, **35**, 4327 (1994).
58. (a) T. K. Hollis, N. P. Robinson, and B. Bosnich, *Tetrahedron Lett.*, **33**, 6423 (1992); (b) Y. Hong, D. J. Norris, and S. Collins, *J. Org. Chem.*, **58**, 3591 (1993).
59. E. M. Carreira and R. A. Singer, *Tetrahedron Lett.*, **35**, 4323 (1994); T. K. Hollis and B. Bosnich, *J. Am. Chem. Soc.*, **117**, 4570 (1995).

Hindered *bis*-phenoxyaluminum derivatives are powerful cocatalysts for reactions mediated by TMS triflate and are believed to act by promoting formation of trimethylsilyl cations by sequestering the triflate anion.[60]



MABR = *bis*-(4-bromo-2,6-di-*tert*-butylphenoxy)methylaluminum

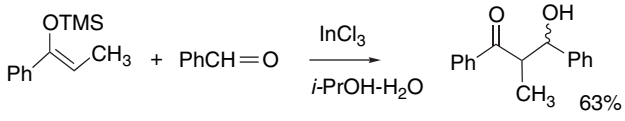
The lanthanide salts are unique among Lewis acids in that they can be effective as catalysts in aqueous solution.[61] Silyl enol ethers react with formaldehyde and benzaldehyde in water-THF mixtures using lanthanide triflates such as $Yb(O_3SCF_3)_3$. The catalysis reflects the strong affinity of lanthanides for carbonyl oxygen, even in aqueous solution.



91% yield, 73:27 *syn*:*anti*

Ref. 62

Certain other metal ions also exhibit catalysis in aqueous solution. Two important criteria are rate of ligand exchange and the acidity of the metal hydrate. Metal hydrates that are too acidic lead to hydrolysis of the silyl enol ether, whereas slow exchange limits the ability of catalysis to compete with other processes. Indium(III) chloride is a borderline catalysts by these criteria, but nevertheless is effective. The optimum solvent is 95:5 isopropanol-water. Under these conditions, the reaction is *syn* selective, suggesting a cyclic TS.[63]

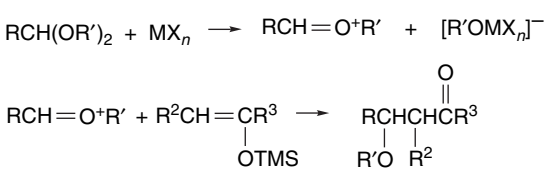


96:4 *syn*:*anti*

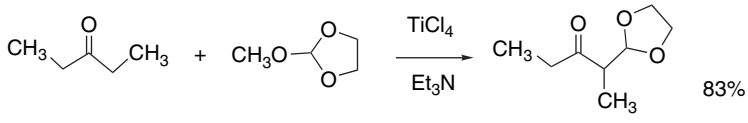
In addition to aldehydes, acetals can serve as electrophiles in Mukaiyama aldol reactions.[64] Effective catalysts include $TiCl_4$,[65] $SnCl_4$,[66] $(CH_3)_3SiO_3SCF_3$,[67] and

60. M. Oishi, S. Aratake, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 8271 (1998).
61. S. Kobayashi and K. Manabe, *Acc. Chem. Res.*, **35**, 209 (2002).
62. S. Kobayashi and I. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994).
63. O. Munoz-Muniz, M. Quintanar-Audelo, and E. Juaristi, *J. Org. Chem.*, **68**, 1622 (2003).
64. Y. Yamamoto, H. Yatagai, Y. Naruta, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 7107 (1980); T. Mukaiyama and M. Murakami, *Synthesis*, 1043 (1987).
65. T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974).
66. R. C. Cambie, D. S. Larsen, C. E. F. Rickard, P. S. Rutledge, and P. D. Woodgate, *Austr. J. Chem.*, **39**, 487 (1986).
67. S. Murata, M. Suzuki, and R. Noyori, *Tetrahedron*, **44**, 4259 (1988).

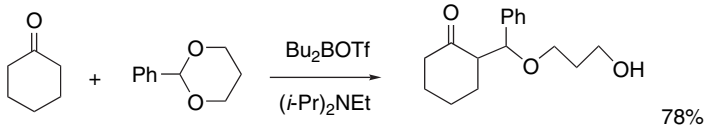
$Bu_2Sn(O_3SCF_3)_2$.[68] The Lewis acids promote ionization of the acetal to an oxonium ion that acts as the electrophile. The products are β-alkoxy ketones.



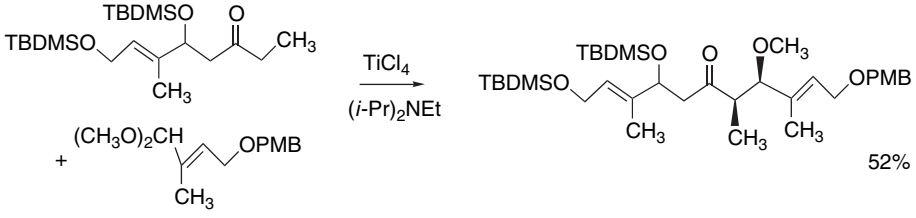
In some cases, the enolate can be formed directly in the presence of the acetal with the Lewis acid also activating the acetal.[69]



Dibutylboron triflate promotes both enol borinate formation and addition.[70]



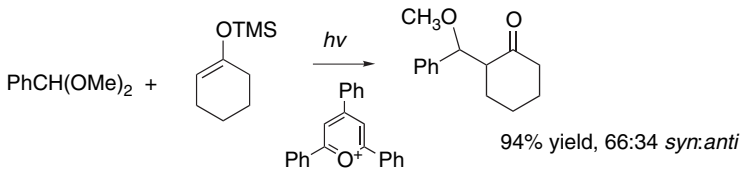
Reactions with acetals can serve to introduce β-alkoxy groups into complex molecules, as in the following reaction.[71]



It has been proposed that there may be a single electron transfer mechanism for the Mukaiyama reaction under certain conditions.[72] For example, photolysis of benzaldehyde dimethylacetal and 1-trimethylsilyloxycyclohexene in the presence of a

68. T. Sato, J. Otera, and H. Nozaki, *J. Am. Chem. Soc.*, **112**, 901 (1990).
69. D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, and M. T. Bilodeau, *J. Am. Chem. Soc.*, **112**, 8215 (1990).
70. L.-S. Li, S. Das, and S. C. Sinha, *Org. Lett.*, **6**, 127 (2004).
71. G. E. Keck, C. A. Wager, T. T. Wager, K. A. Savin, J. A. Covel, M. D. McLaws, D. Krishnamurthy, and V. J. Cee, *Angew. Chem. Int. Ed. Engl.*, **40**, 231 (2001).
72. T. Miura and Y. Masaki, *J. Chem. Soc., Perkin Trans. 1*, 1659 (1994); T. Miura and Y. Masaki, *J. Chem. Soc., Perkin Trans. 1*, 2155 (1995); J. Otera, Y. Fujita, N. Sakuta, M. Fujita, and S. Fukuzumi, *J. Org. Chem.*, **61**, 2951 (1996).

typical photoelectron acceptor, triphenylpyrylium cation, gives an excellent yield of the addition product.



Ref. 73

These reactions may operate by providing a source of trimethylsilyl cations, which serve as the active catalyst by a cycle similar to that for Lewis acids.

The Mukaiyama aldol reaction can provide access to a variety of β-hydroxy carbonyl compounds and use of acetals as reactants can provide β-alkoxy derivatives. The issues of stereoselectivity are the same as those in the aldol addition reaction, but the tendency toward acyclic rather than cyclic TSs reduces the influence of the *E*- or *Z*-configuration of the enolate equivalent on the stereoselectivity.

Scheme 2.2 illustrates several examples of the Mukaiyama aldol reaction. Entries 1 to 3 are cases of addition reactions with silyl enol ethers as the nucleophile and $TiCl_4$ as the Lewis acid. Entry 2 demonstrates steric approach control with respect to the silyl enol ether, but in this case the relative configuration of the hydroxy group was not assigned. Entry 4 shows a fully substituted silyl enol ether. The favored product places the larger C(2) substituent *syn* to the hydroxy group. Entry 5 uses a silyl ketene thioacetal. This reaction proceeds through an open TS and favors the *anti* product.

Entries 6 to 9 involve reactions conducted under catalytic conditions. Entry 6 uses an yttrium catalyst that is active in aqueous solution. Entries 7 and 8 are examples of the use of $(Cp)_2Ti(O_3SCF_3)_2$ as a Lewis acid. Entry 9 illustrates the TMS triflate-MABR catalytic combination.

Entries 10 to 14 show reactions involving acetals. Interestingly, Entry 10 shows much-reduced stereoselectivity compared to the corresponding reaction of the aldehyde (The BF_3-catalyzed reaction of the aldehyde is reported to be 24:1 in favor of the *anti* product; ref. 80, p. 91). There are no stereochemical issues in Entries 11 or 12. Entry 13, involving two cyclic reactants, gave a 2:1 mixture of stereoisomers. Entry 14 is a step in a synthesis directed toward the taxane group of diterpenes. Four stereoisomeric products were produced, including the *Z*:*E* isomers at the new enone double bond.

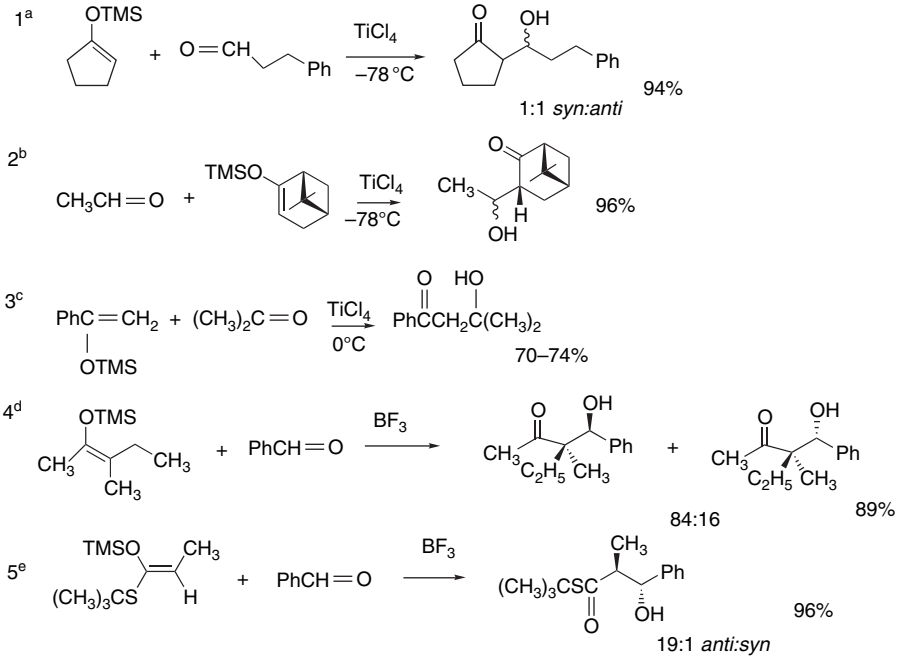
2.1.5. Control of Facial Selectivity in Aldol and Mukaiyama Aldol Reactions

In the discussion of the stereochemistry of aldol and Mukaiyama reactions, the most important factors in determining the *syn* or *anti* diastereoselectivity were identified as the nature of the TS (cyclic, open, or chelated) and the configuration (*E* or *Z*) of the enolate. If either the aldehyde or enolate is chiral, an additional factor enters the picture. The aldehyde or enolate then has two nonidentical faces and the stereochemical outcome will depend on *facial selectivity*. In principle, this applies to any stereocenter in the molecule, but the strongest and most studied effects are those of α- and β-substituents. If the aldehyde is chiral, particularly when the stereogenic center is adjacent to the carbonyl group, the competition between the two diastereotopic faces of the carbonyl group determines the stereochemical outcome of the reaction.

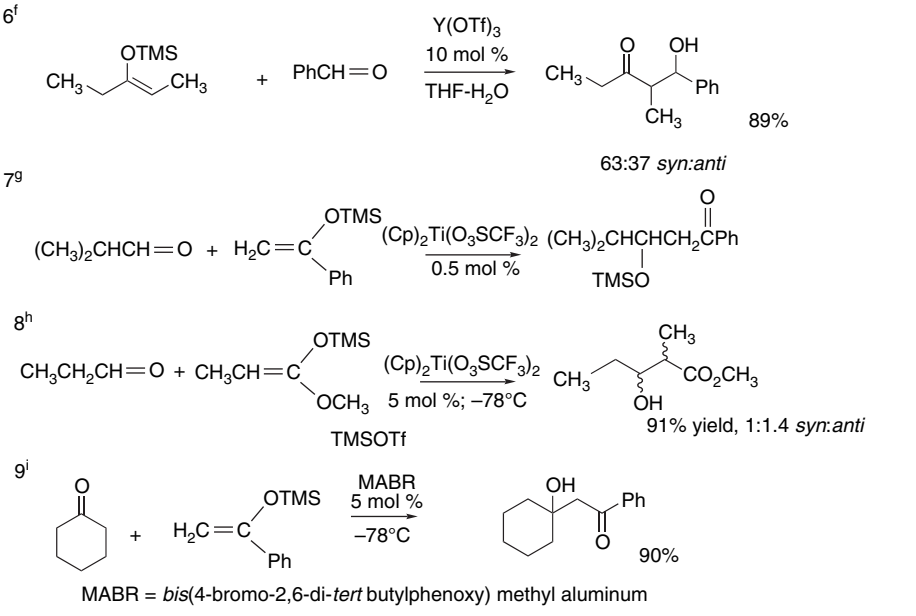
[73.] M. Kamata, S. Nagai, M. Kato, and E. Hasegawa, *Tetrahedron Lett.*, **37**, 7779 (1996).

Scheme 2.2. The Mukaiyama Aldol Reaction

A. Reactions of silyl end ethers with aldehydes and ketones



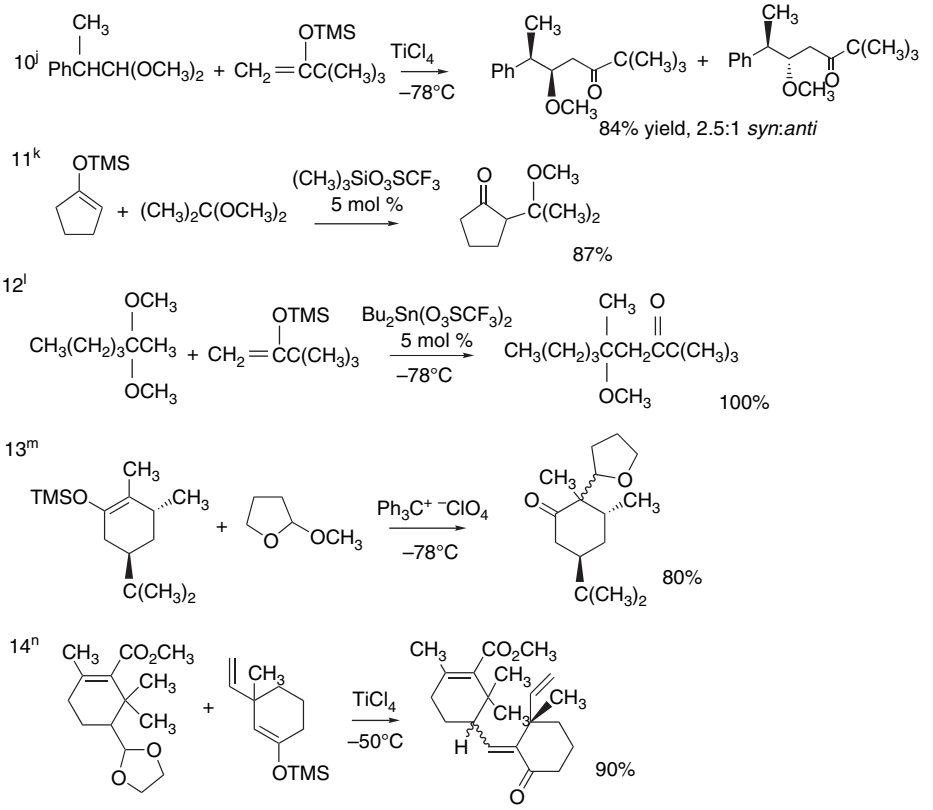
B. Catalytic Mukaiyama Reactions



(*Continued*)

Scheme 2.2. (*Continued*)

C. Reactions with acetals



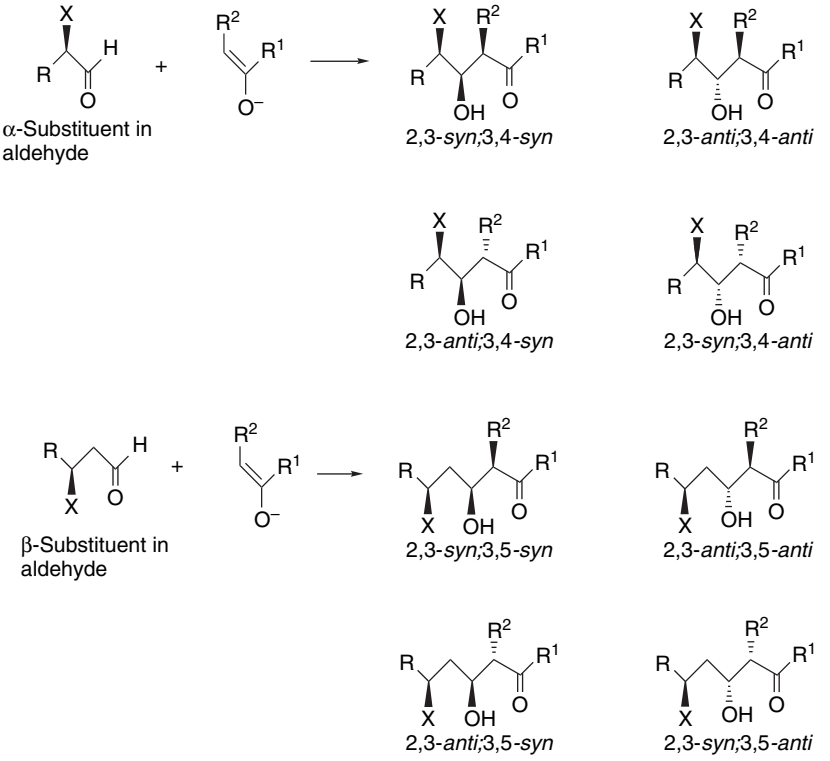
a. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
b. T. Yanami, M. Miyashita, and A. Yoshikoshi, *J. Org. Chem.*, **45**, 607 (1980).
c. T. Mukaiyama and K. Narasaka, *Org. Synth.*, **65**, 6 (1987).
d. S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56**, 2098 (1991)
e. C. Gennari, A. Bernardi, S. Cardani, and C. Scolastico, *Tetrahedron Lett.*, **26**, 797 (1985).
f. S. Kobayashi and I. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994).
g. T. K. Hollis, N. Robinson, and B. Bosnich, *Tetrahedron Lett.*, **33**, 6423 (1992).
h. Y. Hong, D. J. Norris, and S. Collins, *J. Org. Chem.*, **58**, 3591 (1993).
i. M. Oishi, S. Aratake, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 8271 (1998).
j. I. Mori, K. Ishihara, L. A. Flippin, K. Nozaki, H. Yamamoto, P. A. Bartlett, and C. H. Heathcock, *J. Org. Chem.*, **55**, 6107 (1990).
k. S. Murata, M. Suzuki, and R. Noyori, *Tetrahedron*, **44**, 4259 (1998).
l. T. Satay, J. Otera, and H. N. Zaki, *J. Am. Chem. Soc.*, **112**, 901 (1990).
m. T. M. Meulemans, G. A. Stork, B. J. M. Jansen, and A. de Groot, *Tetrahedron Lett.*, **39**, 6565 (1998).
n. A. S. Kende, S. Johnson, P. Sanfilippo, J. C. Hodges, and L. N. Jungheim, *J. Am. Chem. Soc.*, **108**, 3513 (1986).

Similarly, there will be a degree of selectivity between the two faces of the enolate if it contains a stereocenter.

The stereogenic centers may be integral parts of the reactants, but chiral auxiliaries can also be used to impart facial diastereoselectivity and permit eventual isolation of enantiomerically enriched product. Alternatively, use of chiral Lewis acids as catalysts can also achieve facial selectivity. Although the general principles of control of the stereochemistry of aldol addition reactions have been well developed for simple molecules, the application of the principles to more complex molecules and the

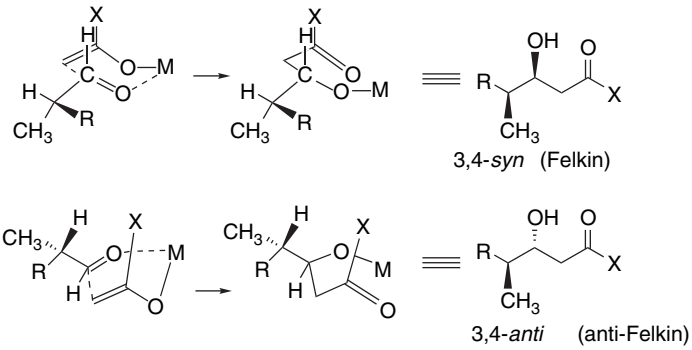
selection of the optimum enolate system requires analyses of the individual cases.[74] Often, one of the available reactant systems proves to be superior.[75] Sometimes a remote structural feature strongly influences the stereoselectivity.[76] The issues that have to be addressed in specific cases include the structure of the reactants, including its configuration and potential sites for chelation; the organization of the TS (cyclic, open, or chelated); and the steric, electronic, and polar factors affecting the facial selectivity.

2.1.5.1. Stereochemical Control by the Aldehyde. A chiral center in an aldehyde can influence the direction of approach by an enolate or other nucleophile. This facial selectivity is in addition to the simple *syn*, *anti* diastereoselectivity so that if either the aldehyde or enolate contains a stereocenter, four stereoisomers are possible. There are four possible chairlike TSs, of which two lead to *syn* product from the *Z*-enolate and two to *anti* product from the *E*-enolate. The two members of each pair differ in the facial approach to the aldehyde and give products of opposite configuration at *both of the newly formed stereocenters*. If the substituted aldehyde is racemic, the enantiomeric products will be formed, making a total of eight stereoisomers possible.

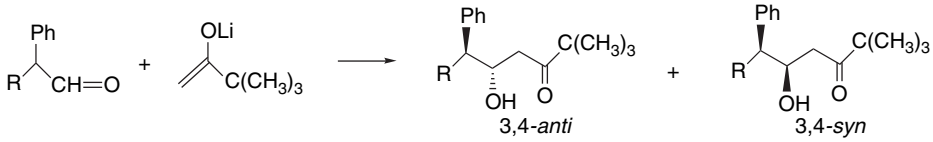


74. (a) W. R. Roush, *J. Org. Chem.*, **56**, 4151 (1991); (b) C. Gennari, S. Vieth, A. Comotti, A. Vulpetti, J. M. Goodman, and I. Paterson, *Tetrahedron*, **48**, 4439 (1992); (c) D. A. Evans, M. J. Dart, J. L. Duffy, and M. G. Yang, *J. Am. Chem. Soc.*, **118**, 4322 (1996); (d) A. S. Franklin and I. Paterson, *Contemp. Org. Synth.*, **1**, 317 (1994).
75. E. J. Corey, G. A. Reichard, and R. Kania, *Tetrahedron Lett.*, **34**, 6977 (1993).
76. A. Balog, C. Harris, K. Savin, X.-G. Zhang, T. C. Chou, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **37**, 2675 (1998).

If the substituents are nonpolar, such as an alkyl or aryl group, the control is exerted mainly by steric effects. In particular, for α-substituted aldehydes, the Felkin TS model can be taken as the starting point for analysis, in combination with the cyclic TS. (See Section 2.4.1.3, Part A to review the Felkin model.) The analysis and prediction of the direction of the preferred reaction depends on the same principles as for simple diastereoselectivity and are done by consideration of the attractive and repulsive interactions in the presumed TS. In the Felkin model for nucleophilic addition to carbonyl centers the larger α-substituent is aligned *anti* to the approaching enolate and yields the 3,4-*syn* product. If reaction occurs by an alternative approach, the stereochemistry is reversed, and this is called an anti-Felkin approach.



A study of the lithium enolate of pinacolone with several α-phenyl aldehydes gave results generally consistent with the Felkin model. Steric, rather than electronic, effects determine the conformational equilibria.[77] If the alkyl group is branched, it occupies the "large" position. Thus, the *t*-butyl group occupies the "large" position, not the phenyl.

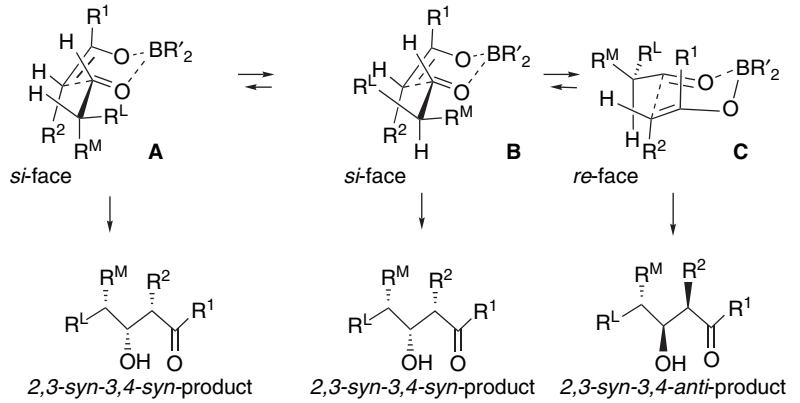


R	3,4-*anti:syn* ratio
CH_3	3.64:1
C_2H_5	6.05:1
$(CH_3)_2CH$	2.25:1
$(CH_3)_3C$	1:1.7

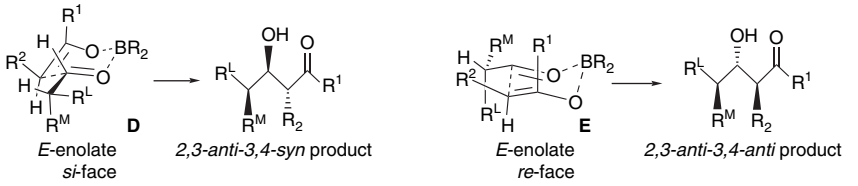
The situation encounters another factor with enolates having a C(2) substituent. The case of steric control has been examined carefully. The stereoselectivity depends on the orientation of the stereocenter relative to the remainder of the TS. The Felkin TS is **A**. TS **B** represents a non-Felkin conformer, but with the same facial approach as **A**. The preferred TS for the *Z*-enolate is believed to be structure **C**. This TS is preferred to **A** because of the interaction between the R^M group and the R^2 group of the enolate

[77] E. P. Lodge and C. H. Heathcock, *J. Am. Chem. Soc.*, **109**, 3353 (1987).

in **A**.[78] This *double-gauche* interaction is analogous to the 1,3-diaxial relationship in chair cyclohexane. TS **C** results in the anti-Felkin approach. The relative energy of TS **B** and TS **C** depends on the size of R^L, with larger R groups favoring TS **C** because of an increased R^2/R^L interaction.

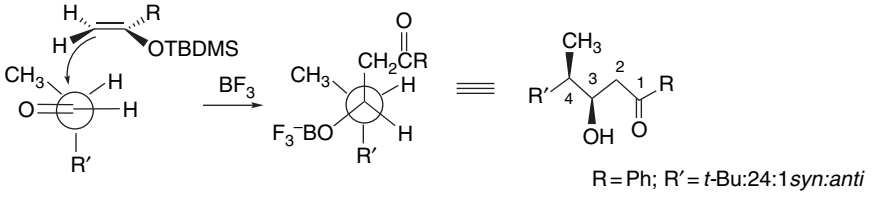


For *E*-enolates the Felkin TS is preferred, the enolate approaches opposite the largest aldehyde substituent, and the preferred product is 2,3-*anti*-3,4-*syn*. TS **D** is preferred for *E*-enolates because of the *gauche* interaction between R^2 and R^L in TS **E**.



The qualitative application of these models depends on evaluating the magnitude of the steric interactions among the various groups. In this regard, phenyl and vinyl groups seem to be smaller than alkyl groups, perhaps because of their ability to rotate into conformations in which the π dimension minimizes steric repulsions. These concepts have been quantitatively explored using force field models. For nonpolar substituents, steric interactions are the controlling factor in the stereoselectivity, but there is considerable flexibility for adjustment of the TS geometry in response to the specific interactions.[79]

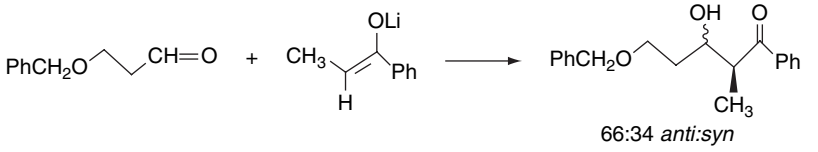
Mukaiyama reactions of α-methyl aldehydes proceed through an open TS and show a preference for the 3,4-*syn* stereoisomer, which is consistent with a Felkin TS.[80]



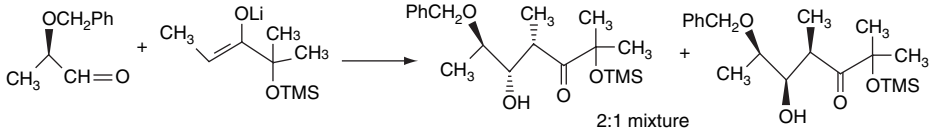
78. W. R. Roush, *J. Org. Chem.*, **56**, 4151 (1991).
79. C. Gennari, S. Vieth, A. Comotti, A. Vulpetti, J. M. Goodman, and I. Paterson, *Tetrahedron*, **48**, 4439 (1992).
80. C. H. Heathcock and L. A. Flippin, *J. Am. Chem. Soc.*, **105**, 1667 (1983); D. A. Evans and J. R. Gage, *Tetrahedron Lett.*, **31**, 6129 (1990).

The stereoselectivity of aldol addition is also affected by chelation.[81] α- and β-Alkoxy aldehydes can react through chelated structures with Li^+ and other Lewis acids that can accommodate two donor groups.

The potential for coordination depends on the oxy substituents.[82] Alkoxy substituents are usually chelated, whereas highly hindered silyloxy groups usually do not chelate. Trimethylsiloxy groups are intermediate in chelating ability. The extent of chelation also depends on the Lewis acid. Studies with α-alkoxy and β-alkoxy aldehydes with lithium enolates found only modest diastereoselectivity.[83]

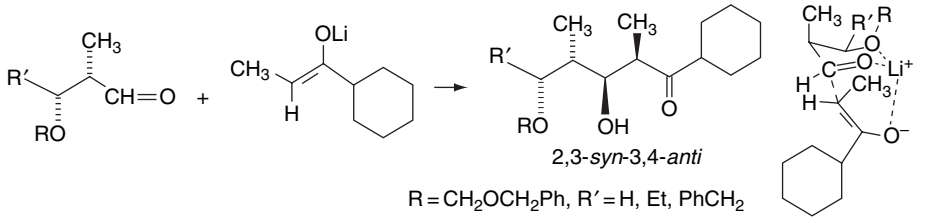


Ref. 84



Ref. 83b

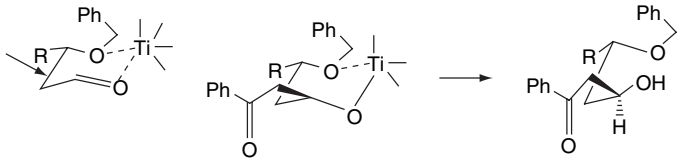
Several α-methyl-β-alkoxyaldehydes show a preference for 2,3-*syn*-3,4-*anti* products on reaction with *Z*-enolates. A chelated TS can account for the observed stereochemistry.[85] The chelated aldehyde is most easily approached from the face opposite the methyl and R′ substituents.



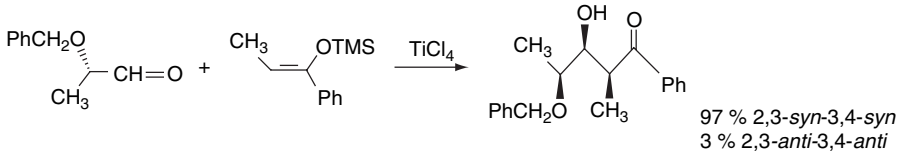
Dialkylboron enolates cannot accommodate an additional aldehyde ligand group and chelated TSs are not expected. When BF_3 is used as the Lewis acid, chelation is

81. M. T. Reetz, *Angew. Chem. Int. Ed. Engl.*, **23**, 556 (1984); R. Mahrwald, *Chem. Rev.*, **99**, 105 (1999).
82. X. Chen, E. R. Hortelano, E. L. Eliel, and S. V. Frye, *J. Am. Chem. Soc.*, **114**, 1778 (1992).
83. (a) C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. Van Derveer, *J. Org. Chem.*, **45**, 3846 (1980); (b) C. H. Heathcok, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, *J. Org. Chem.*, **46**, 2290 (1981).
84. M. T. Reetz, K. Kesseler, and A. Jung, Tetrahedron, **40**, 4327 (1984).
85. S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).

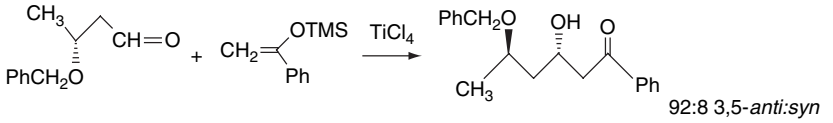
also precluded in Mukaiyama reactions. Chelation control does occur in the Mukaiyama reaction using other Lewis acids. Both α- and β-alkoxy aldehydes give chelation-controlled products with $SnCl_4$ and $TiCl_4$, but not with BF_3.[86] If there is an additional substituent on the aldehyde, the chelate establishes a facial preference for the approach of the nucleophile.[87]



In each instance, the silyl enol ether approaches *anti* to the methyl substituent on the chelate. This results in a 3,4-*syn* relationship between the hydroxy and alkoxy groups for α-alkoxy aldehydes and a 3,5-*anti* relationship for β-alkoxy aldehydes with the main chain in the extended conformation.



Ref. 88



Ref. 84

A crystal structure is available for the $SnCl_4$ complex of 2-benzyloxy-3-pentanone.[89] The steric shielding by the methyl group with respect to the C=O is evident in this structure (Figure 2.1). NMR studies indicate that the reaction involves

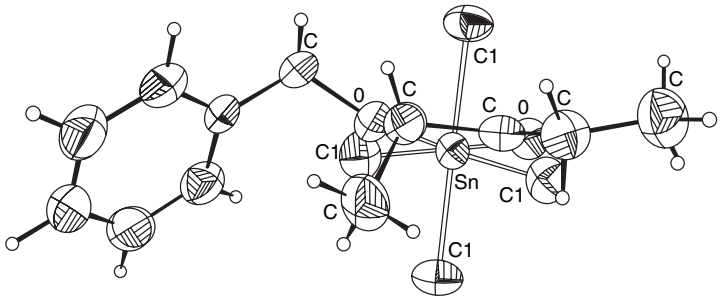
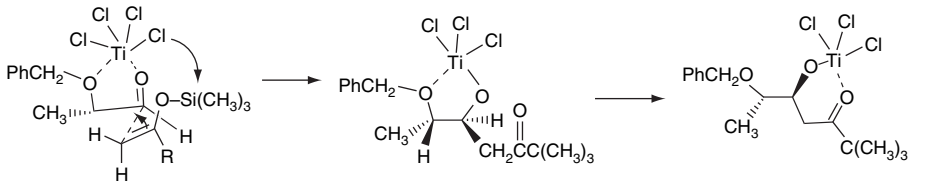


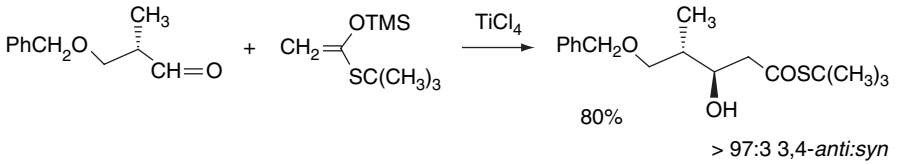
Fig. 2.1. Structure of the $SnCl_4$ complex of 2-benzyloxy-3-pentanone. Reproduced from *Acc. Chem. Res.*, **26**, 462 (1993) by permission of the American Chemical Society.

86. C. H. Heathcock, S. K. Davidsen, K. T. Hug, and L. A. Flippin, *J. Org. Chem.*, **51**, 3027 (1986).
87. M. T. Reetz and A. Jung, *J. Am. Chem. Soc.*, **105**, 4833 (1983); C. H. Heathcock, S. Kiyooka, and T. A. Blumenkopf, *J. Org. Chem.*, **51**, 4214 (1984).
88. M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, and P. Steinbach, *Angew. Chem. Int. Ed. Engl.*, **22**, 989 (1983).
89. M. T. Reetz, K. Harms, and W. Reif, *Tetrahedron Lett.*, **29**, 5881 (1988).

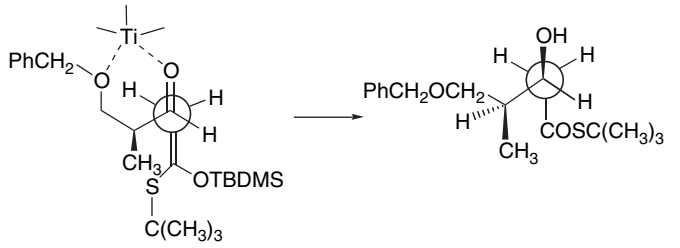
formation of trimethylsilyl chloride from the chelated intermediate. This step is followed by conversion to the more stable aldol chelate.[90]



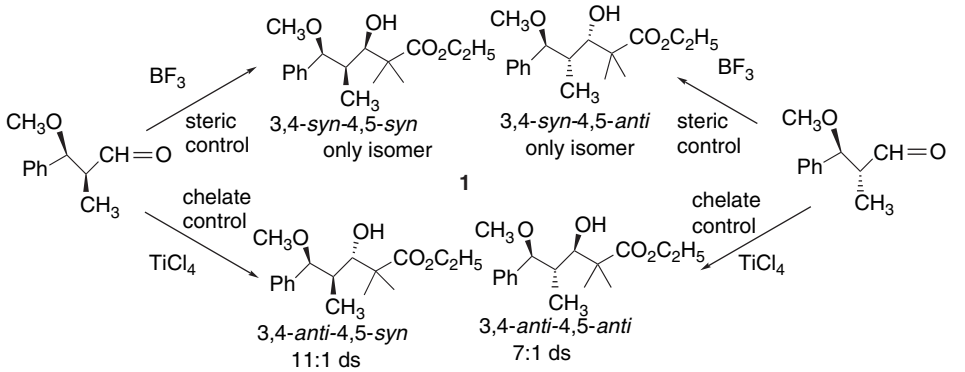
With α- and β-benzyloxyaldehydes, the *t*-butylthio ketene acetals also gave chelation-controlled addition.[91]



This reaction occurs through a TS in which the aldehyde is chelated, but the silyl thioketene acetal is not coordinated to the Ti (open TS).



The choice of Lewis acid can determine if a chelated or open TS is involved. For example, all four possible stereoisomers of **1** were obtained by variation of the Lewis acid and the stereochemistry in the reactant.[92] The BF_3-catalyzed reactions occur through an open TS, whereas the $TiCl_4$ reactions are chelation controlled.

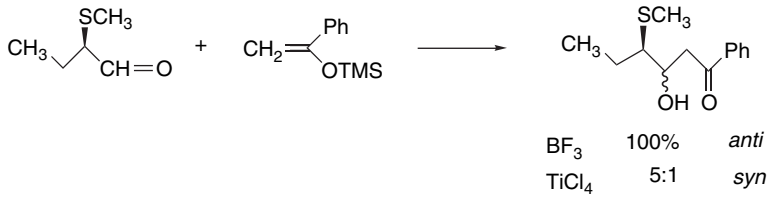


[90] M. T. Reetz, B. Raguse, C. F. Marth, H. M. Hügel, T. Bach, and D. N. A. Fox, *Tetrahedron*, **48**, 5731 (1992); M. T. Reetz, *Acc. Chem. Res.*, **26**, 462 (1993).

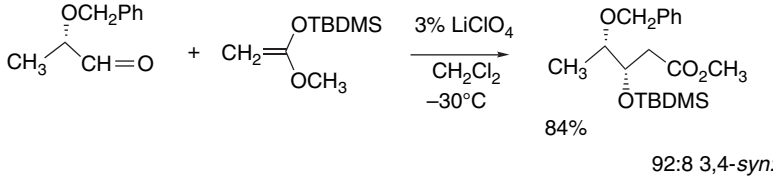
[91] C. Gennari and P. G. Cozzi, *Tetrahedron*, **44**, 5965 (1988).

[92] S. Kiyooka, M. Shiinoki, K. Nakata, and F. Goto, *Tetrahedron Lett.*, **43**, 5377 (2002).

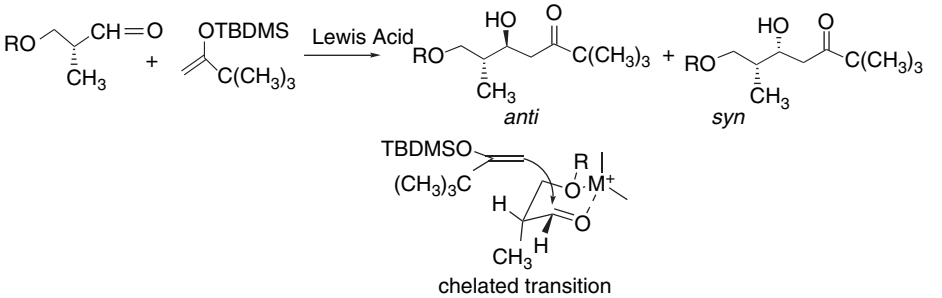
In the reaction of α-methylthiobutanal, where the methylthio group has the potential for chelation, BF_3 gave 100% of *anti* product, whereas $TiCl_4$ gave a 5:1 *syn*:*anti* ratio.[93]



Chelation-controlled product is formed from reaction of α-benzyloxypropanal and the TBDMS silyl ketene acetal derived from ethyl acetate using 3% $LiClO_4$ as catalyst.[94]



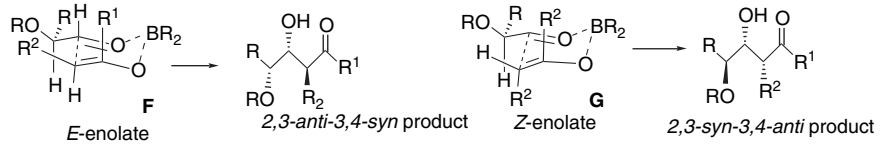
Recently, $(CH_3)_2AlCl$ and CH_3AlCl_2 have been shown to have excellent chelation capacity. These catalysts effect chelation control with both 3-benzyloxy- and 3-(*t*-butyldimethylsilyoxy)-2-methylpropanal, whereas BF_3 leads to mainly *syn* product.[95] The reaction is believed to occur through a cationic complex, with the chloride ion associated with a second aluminum as $[(CH_3)_2AlCl_2]^-$. Interestingly, although $TiCl_4$ induced chelation control with the benzyloxy group, it did not do so with the TBDMS group.



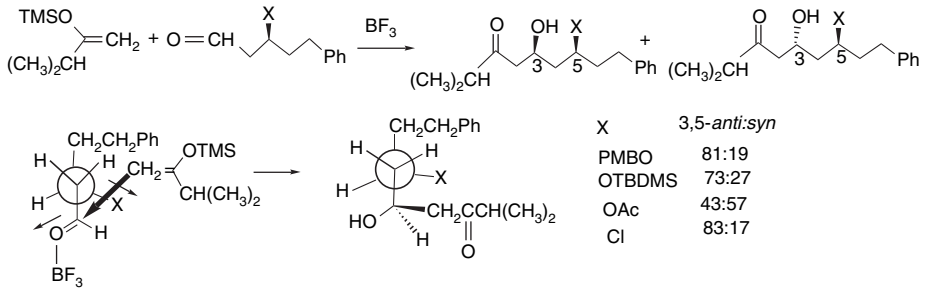
Lewis acid	R = CH_2Ph	R = OTBDMS
	anti:*syn*	*anti*:*syn*
BF_3	26:74	9:91
$SnCl_4$	50:50	7:93
$TiCl_4$	97:3	7:93
$(CH_3)_2AlCl$	90:10	97:3
CH_3AlCl_2	78:22	77:23

93. R. Annuziata, M. Cinquini, F. Cozzi, P. G. Cozzi, and E. Consolandi, *J. Org. Chem.*, **57**, 456 (1992).
94. M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, **34**, 1119 (1993).
95. D. A. Evans, B. D. Allison, and M. G. Yang, *Tetrahedron Lett.*, **40**, 4457 (1999); D. A. Evans, B. D. Allison, M. G. Yang, and C. E. Masse, *J. Am. Chem. Soc.*, **123**, 10840 (2001).

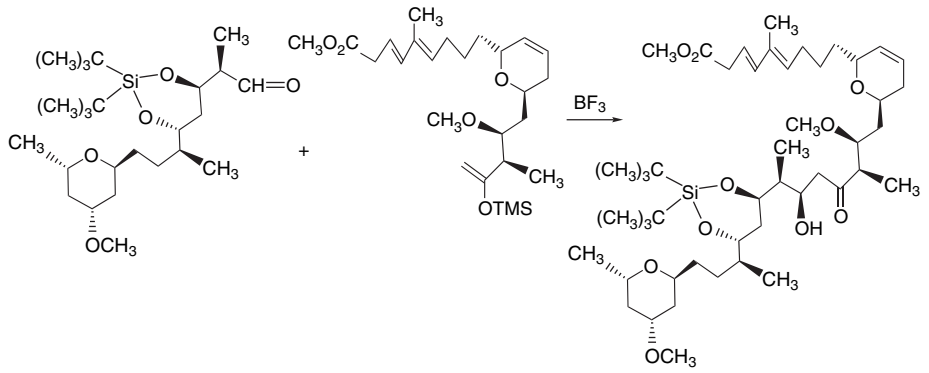
Heteroatom substituents also introduce polar effects. In the case of α-alkoxy aldehydes the preferred TS appears to be **F** and **G** for the *E*- and *Z*-enolates, respectively. These differ from the normal Felkin TS for nucleophilic addition. The reactant conformation is believed to be determined by minimization of dipolar repulsion between the alkoxy substituent and the carbonyl group.[96] This model predicts higher 3,4-*anti* ratios for *Z*-enolates, and this is observed.



Dipole-dipole interactions may also be important in determining the stereoselectivity of Mukaiyama aldol reactions proceeding through an open TS. A BF_3-catalyzed reaction was found to be 3,5-*anti* selective for several β-substituted 5-phenylpentanals. This result can be rationalized by a TS that avoids an unfavorable alignment of the C=O and C–X dipoles.[97]



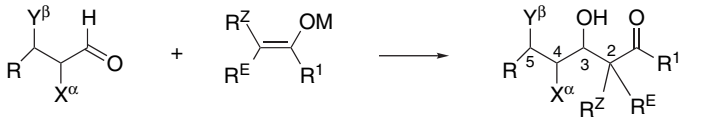
The same stereoselectivity was observed with a more complex pair of reactants in which the β-substituent is a cyclic siloxy oxygen.[98]



Thus we see that steric effects, chelation, and the polar effects of α- and β-substituents can influence the facial selectivity in aldol additions to aldehydes. These relationships provide a starting point for prediction and analysis of stereoselectivity

96. D. A. Evans, S. J. Siska, and V. J. Cee, *Angew. Chem. Int. Ed. Engl.*, **42**, 1761 (2003).
97. D. A. Evans, M. J. Dart, J. L. Duffy, and M. G. Yang, *J. Am. Chem. Soc.*, **118**, 4322 (1996).
98. I. Paterson, R. A. Ward, J. D. Smith, J. G. Cumming, and K.-S. Yeung, *Tetrahedron*, **51**, 9437 (1995).

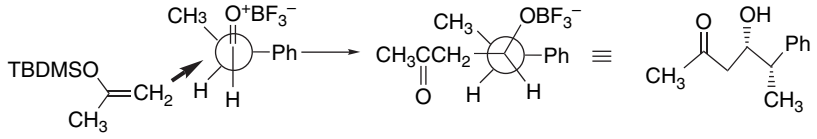
Table 2.3. Summary of Stereoselectivity for Aldol Addition Reactions



Aldehyde Steric (Felkin) Control	Aldehyde Chelate TS	Aldehyde Polar Substituent Control
Cyclic TS		
3,4-*syn* for X^{α} = medium *E*-enolate 2,3-anti, 3,4-*syn* *Z*-enolate 2,3-syn, 3,4-anti	X^{α} = alkoxy 3,4-*syn* Y^{β} = alkoxy 3,5-*anti*	X^{α} = alkoxy *E*-enolate 2,3-*anti,* 3,4-weak *Z*-enolate 2,3-*syn,*3,4-anti Y^{β} = alkoxy 3,5-*anti*
Open TS		
3,4-*syn* for X^{α} = medium		

based on structural effects in the reactant aldehyde. These general principles have been applied to the synthesis of a number of more complex molecules. Table 2.3 summarizes the relationships discussed in this section.

Scheme 2.3 shows reactions of several substituted aldehydes of varying complexity that illustrate aldehyde facial diastereoselectivity in the aldol and Mukaiyama reactions. The stereoselectivity of the new bond formation depends on the effect that reactant substituents have on the detailed structure of the TS. The 3,4-*syn* stereoselectivity of Entry 1 derives from a Felkin-type acyclic TS.



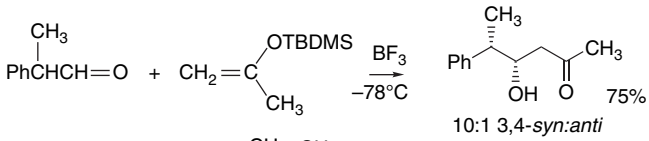
Entry 2 shows an *E*-enolate of a hindered ester reacting with an aldehyde having both an α-methyl and β-methoxy group. The reaction shows a 13:1 preference for the Felkin approach product (3,4-*syn*) and is controlled by the steric effect of the α-methyl substituent. Another example of steric control with an ester enolate is found in a step in the synthesis of (+)-discodermolide.[99] The *E*-enolate of a hindered aryl ester was generated using LiTMP and LiBr. Reaction through a Felkin TS resulted in *syn* diastereoselectivity for the hydroxy and ester groups at the new bond.

[99.] I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, and N. Sereinig, *J. Am. Chem. Soc.*, **123**, 9535 (2001).

Scheme 2.3. Examples of Aldol and Mukaiyama Reactions with Stereoselectivity Based on Aldehyde Structure

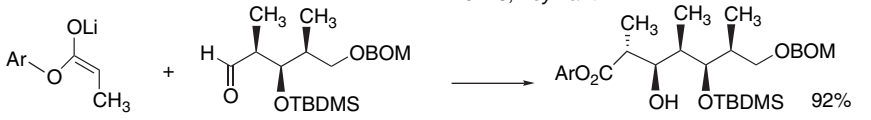
A. Steric Contol

1[a]



10:1 3,4-*syn*:*anti*

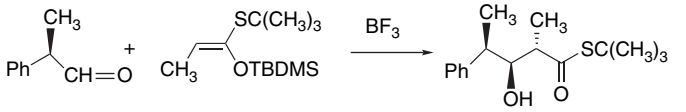
2[b]



13:1 2,3-*anti:syn*-*3,4-syn*

Ar = 2,6-dimethylphenyl BOM = benzyloxymethyl

3[c]



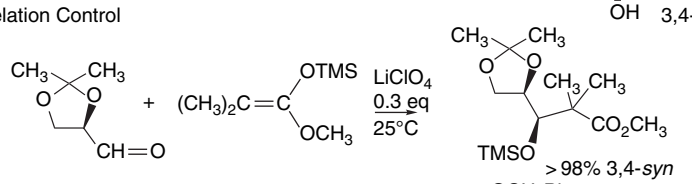
13:1 2,3-*anti:syn*-3,4-*syn*

4[d]

3,4-*syn*

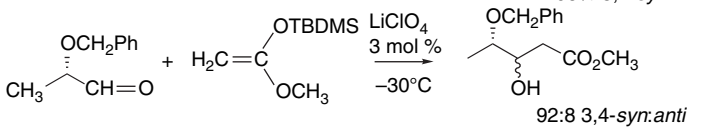
B. Chelation Control

5[e]



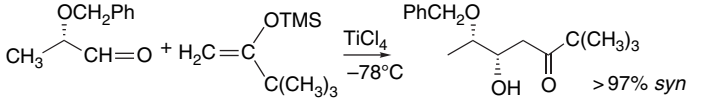
>98% 3,4-*syn*

6[f]



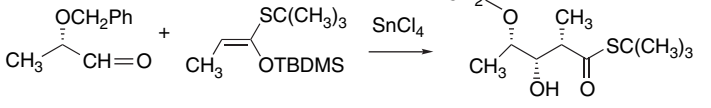
92:8 3,4-*syn*:*anti*

7[g]



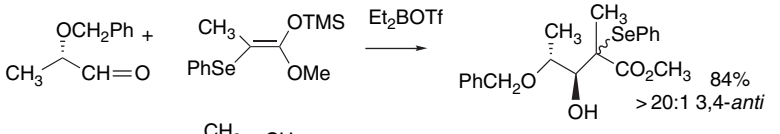
>97% *syn*

8[c]



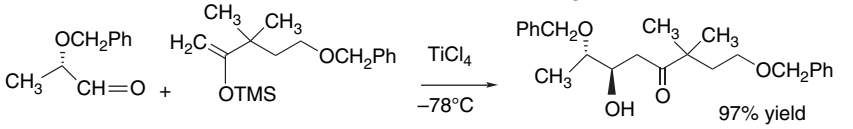
9[d]

2,3-*syn*-3,4-*syn*



>20:1 3,4-*anti*

10[h]

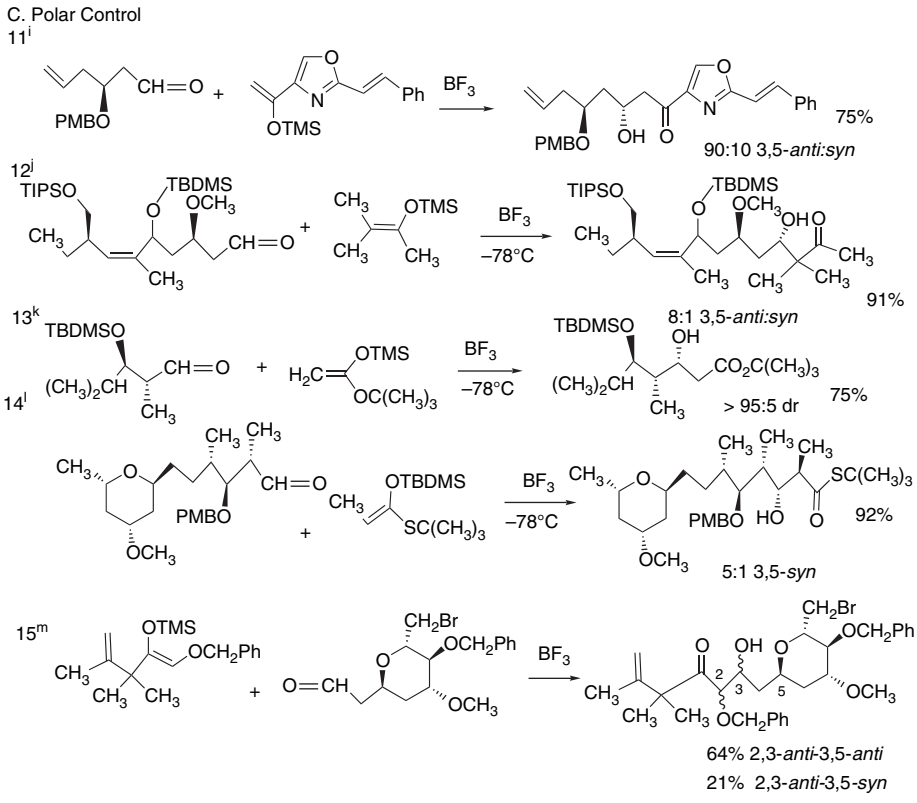


97% yield

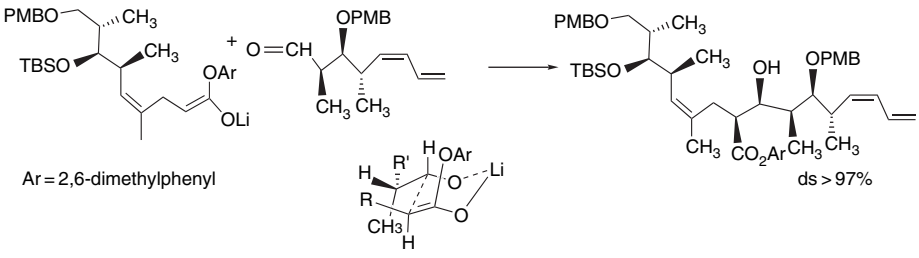
99:1 3,4-*syn*

(*Continued*)

Scheme 2.3. (***Continued***)

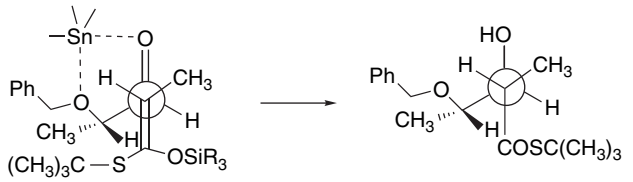


a. C. H. Heathcock and L. A. Flippin, *J. Am. Chem. Soc.*, **105**, 1667 (1983).
b. I. Paterson, *Tetrahedron Lett.*, **24**, 1311 (1983).
c. C. Gennari, M. G. Beretta, A. Bernardi, G. Moro, C. Scolastico, and R. Todeschini, *Tetrahedron*, **42**, 893 (1986).
d. Y. Guindon, M. Prevost, P. Mochirian, and B. Guerin, *Org. Lett.*, **4**, 1019 (2002).
e. J. Ipaktschi and A. Heydari, *Chem. Ber.*, **126**, 1905 (1993).
f. M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, **34**, 1119 (1993).
g. M. T. Reetz, B. Raguse, C. F. Marth, H. M. Hügel, T. Bach, and D. N. A. Fox, *Tetrahedron*, **48**, 5731 (1992).
h. C. Q. Wei, X. R. Jiang, and Y. Ding, *Tetrahedron*, **54**, 12623 (1998).
i. F. Yokokawa, T. Asano, and T. Shioiri, *Tetrahedron*, **57**, 6311 (2001).
j. R. E. Taylor and M. Jin, *Org. Lett.*, **5**, 4959 (2003).
k. L. C. Dias, L. J. Steil and V. de A. Vasconcelos, *Tetrahedron: Asymmetry*, **15**, 147 (2004).
l. G. E. Keck and G. D. Lundquist, *J. Org. Chem.*, **64**, 4482 (1999).
m. D. W. Engers, M. J. Bassindale, and B. L. Pagenkopf, *Org. Lett.*, **6**, 663 (2004).

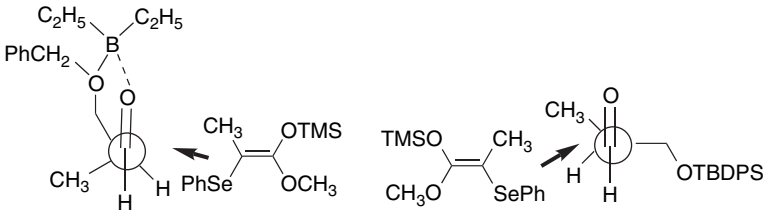


Entries 3 and 8 show additions of a silyl thioketene acetal to α-substituted aldehydes. Entry 3 is under steric control and gives an 13:1 2,3-*anti*-*syn* ratio. The reaction proceeds through an open TS with respect to the nucleophile and both the

E- and *Z*-silyl thioketene acetals give the 2,3-*anti* product. The 3,4-*syn* ratio is 50:1, and is consistent with the Felkin model. When this nucleophile reacts with 2-benzyloxypropanal (Entry 8), a chelation product results. The facial selectivity with respect to the methyl group is now reversed. Both isomers of the silyl thioketene acetal give mainly the 2,3-*syn*-3,4-*syn* product. The ratio is higher than 30:1 for the *Z*-enolate but only 3:1 for the *E*-enolate.



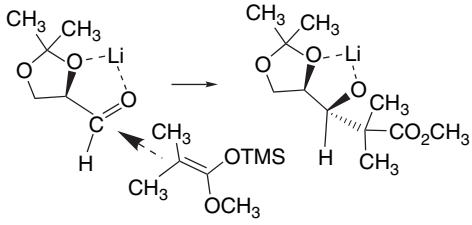
Entries 4 and 9 are closely related structures that illustrate the ability to control stereochemistry by choice of the Lewis acid. In Entry 4, the Lewis acid is BF_3 and the β-oxygen is protected as a *t*-butyldiphenylsilyl derivative. This leads to reaction through an open TS, and the reaction is under steric control, resulting in the 3,4-*syn* product. In Entry 9, the enolate is formed using di-*n*-butylboron triflate (1.2 equiv.), which permits the aldehyde to form a chelate. The chelated aldehyde then reacts via an open TS with respect to the silyl ketene acetal, and the 3,4-*anti* isomer dominates by more than 20:1.



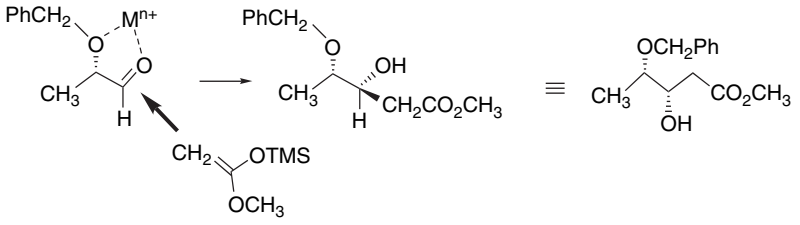
TS for chelate control

TS for steric control

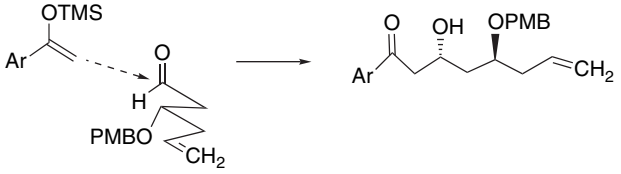
Entry 5 is an example of $LiClO_4$ catalysis and results in very high stereoselectivity, consistent with a chelated structure for the aldehyde.



Entries 6 and 7 are examples of reactions of α-benzyloxypropanal. In both cases, the product stereochemistry is consistent with a chelated TS.

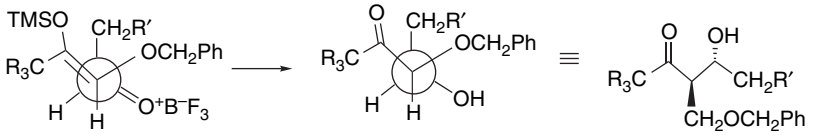


Entry 10 is an example of the application of chelate-controlled stereoselectivity using $TiCl_4$. Entry 11 also involves stereodirection by a β-(*p*-methoxybenzyloxy) substituent. In this case, the BF_3-catalyzed reaction should proceed through an open TS and the β-polar effect described on p. 96 prevails, resulting in the *anti*-3,5-isomer.

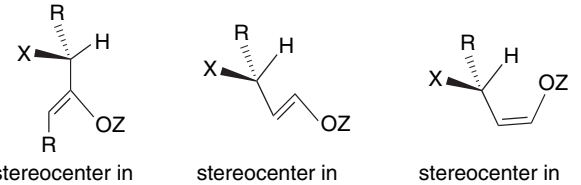


The β-methoxy group in Entry 12 has a similar effect. The aldehydes in Entries 13 and 14 have α-methyl-β-oxy substitution and the reactions in these cases are with a silyl ketene acetal and silyl thioketene acetal, respectively, resulting in a 3,4-*syn* relationship between the newly formed hydroxy and α-methyl substituents.

Entry 15 involves a benzyloxy group at C(2) and is consistent with control by a β-oxy substituent, which in this instance is part of a ring. The *anti* relationship between the C(2) and the C(3) groups results from steric control by the branched substituent in the silyl enol ether. The stereogenic center in the ring has only a modest effect.



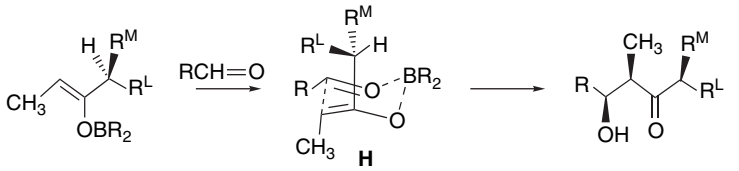
2.1.5.2. Stereochemical Control by the Enolate or Enolate Equivalent. The facial selectivity of aldol addition reactions can also be controlled by stereogenic centers in the nucleophile. A stereocenter can be located at any of the adjacent positions on an enolate or enolate equivalent. The configuration of the substituent can influence the direction of approach of the aldehyde.



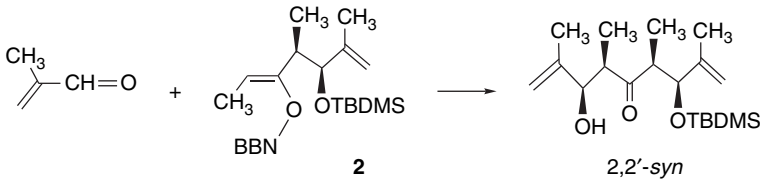
stereocenter in the 1-substituent | stereocenter in the *E*-substituent | stereocenter in the *Z*-substituent

When there is a nonchelating stereocenter at the 1-position of the enolate, the two new stereocenters usually adopt a 2,2′-*syn* relationship to the M substituent. This

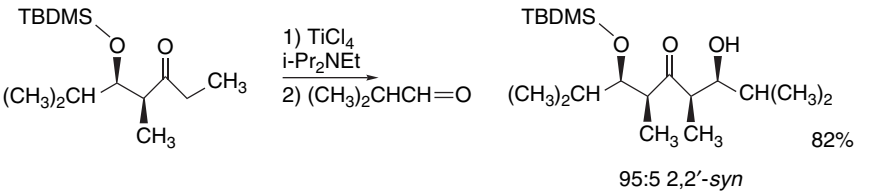
result is consistent with a cyclic TS having a conformation of the chiral group with the hydrogen pointed toward the boron and the approach to the aldehyde from the smaller of the other two substituents as in TS **H**.[100]



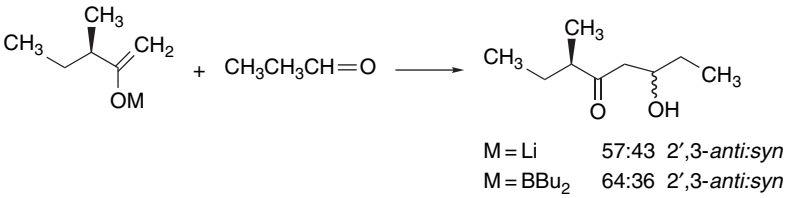
This stereoselectivity, for example, was noted with enolate **2**.[101]



The same effects are operative with titanium enolates.[100a]



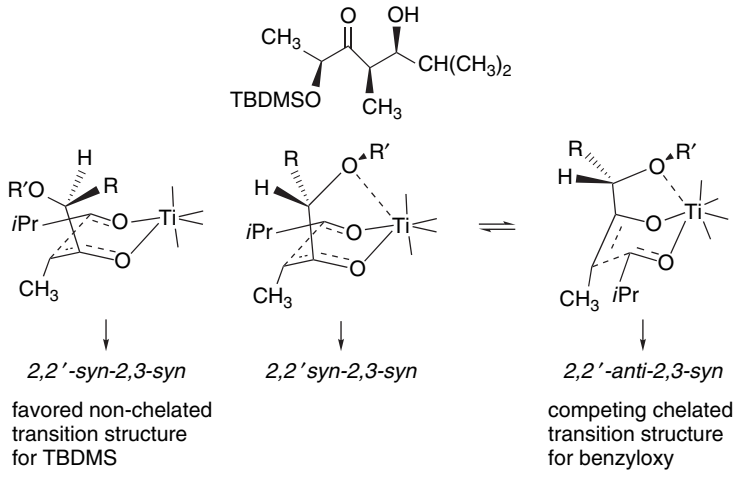
Little steric differentiation is observed with either the lithium or boron enolates of 2-methyl-2-pentanone.[102]



α-Oxygenated enolates show a strong dependency on the nature of the oxygenated substituent. TBDMS derivatives are highly selective for 2, 2′-*syn*-2,3-*syn* product, but benzyloxy substituents are much less selective. This is attributed to involvement of two competing chelated TSs in the case of benzyloxy, but of a nonchelated TS for the siloxy substituent.[103] The contrast between the oxy substituents is consistent with the tendency for alkoxy groups to be better donors toward Ti(IV) than siloxy groups.

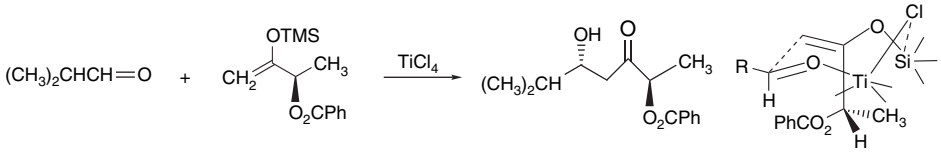
100. (a) D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991); (b) A. Bernardi, A. M. Capelli, A. Comotti, C. Gennari, M. Gardner, J. M. Goodman, and I. Paterson, *Tetrahedron*, **47**, 3471 (1991).
101. I. Paterson and A. N. Hulme, *J. Org. Chem.*, **60**, 3288 (1995).
102. D. Seebach, V. Ehrig, and M. Teschner, *Liebigs Ann. Chem.*, 1357 (1976); D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).
103. S. Figueras, R. Martin, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **38**, 1637 (1997).

Oxy substituent	R	2, 2′-*syn*-2,3-*syn*:2,2′-*anti*-2,3-*syn*
TBDMS	CH_3	30:1
TBDMS	$PhCH_2$	35:1
TBDMS	$(CH_3)_2CH$	> 95:1
$PhCH_2$	CH_3	5:1
$PhCH_2$	$PhCH_2$	4:1
$PhCH_2$	$(CH_3)_2CH$	1:1



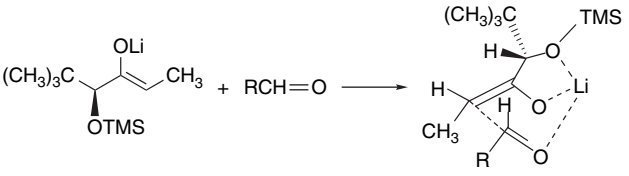
The stereoselectivity of this reaction also depends on the titanium reagent used to prepare the enolate.[104] When the substituent is benzyloxy, the 2, 2′-*anti*-2,3-*syn* product is preferred when (*i*-PrO)$TiCl_3$ is used as the reagent, as would be expected for a chelated TS. However, when $TiCl_4$ is used, the 2, 2′-*syn*-2,3-*syn* product is formed. A detailed explanation for this observation has not been established, but it is expected that the benzyloxy derivative would still react through a chelated TS. The reversal on use of $TiCl_4$ indicates that the identity of the titanium ligands is also an important factor.

High facial selectivity attributable to chelation was observed with the TMS silyl ethers of 3-acyloxy-2-butanone.[105]



Several enolates of 4,4-dimethyl-3-(trimethylsiloxy)-2-pentanone have been investigated.[106] The lithium enolate reacts through a chelated TS with high 2,2′-*anti* stereoselectivity, based on the steric differentiation by the *t*-butyl group.

[104] J. G. Solsona, P. Romea, F. Urpi, and J. Villarrasa, *Org. Lett.*, **5**, 519 (2003).
[105] B. M. Trost and H. Urabe, *J. Org. Chem.*, **55**, 3982 (1990).
[106] C. H. Heathcock and S. Arseniyadis, *Tetrahedron Lett.*, **26**, 6009 (1985) and Erratum *Tetrahedron Lett.*, **27**, 770 (1986); N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, and C. H. Heathcock, *J. Org. Chem.*, **56**, 2499 (1991).

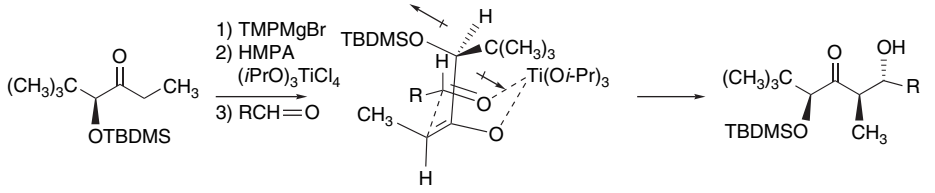


major

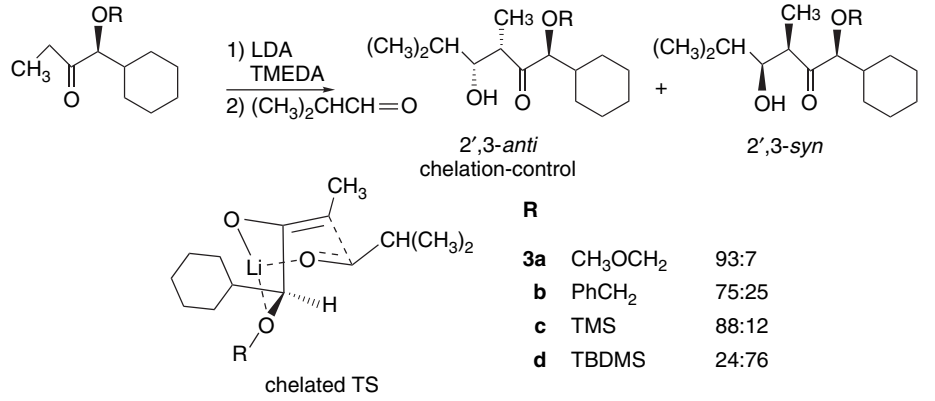
R	*2,2′-anti:syn*
i-Pr	> 95:5
t-Bu	> 95:5
Ph	> 95:5
$PhCH_2OCH_2$	> 95:5

The corresponding di-*n*-butylboron enolate gives the 2,2′-*syn* adduct. The nonchelating boron is thought to react through a TS in which the conformation of the substituent is controlled by a dipolar effect.

The *E*-titanium enolate was prepared by deprotonation with TMP-MgBr, followed by reaction with $(i\text{-PrO})_3TiCl$ in the presence of HMPA. The TS for addition is also dominated by a polar effect and gives and 2,2′-*anti* product.



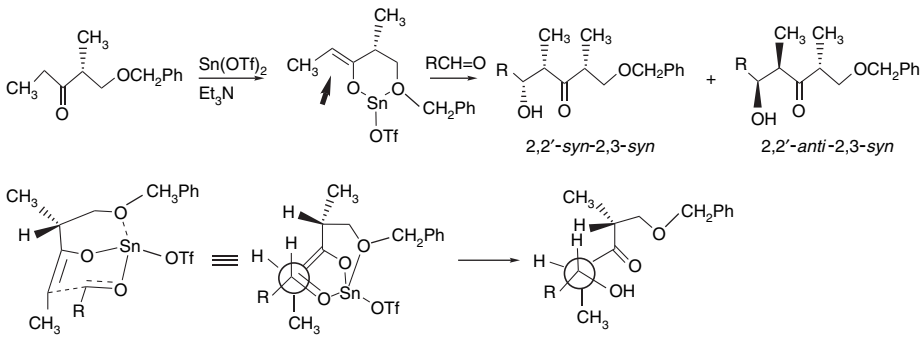
An indication of the relative effectiveness of oxygen substituent in promoting chelation of lithium enolates is found in the enolates **3a–d**. The order of preference for the chelation-controlled product is CH_3OCH_2O > TMSO > $PhCH_2O$ > TBDMSO, with the nonchelation product favored for TBDMSO.[107]



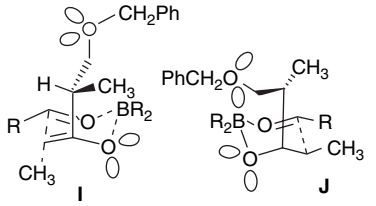
	R	
3a	CH_3OCH_2	93:7
b	$PhCH_2$	75:25
c	TMS	88:12
d	TBDMS	24:76

[107] C. Siegel and E. R. Thornton, *Tetrahedron Lett.*, **27**, 457 (1986); A Choudhury and E. R. Thornton, *Tetrahedron Lett.*, **34**, 2221 (1993).

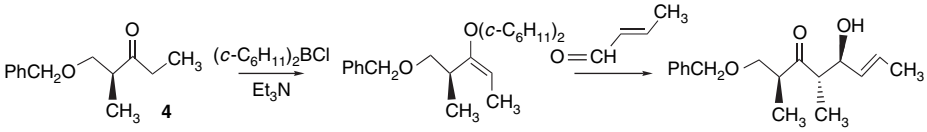
Tin(II) enolates having 3′-benzyloxy substituents are subject to chelation control. The enolate from 2-(benzyloxymethyl)-3-pentanone gave mainly 2,2′-*syn*-2,3-*syn* product, a result that is consistent with a chelated TS.[108]



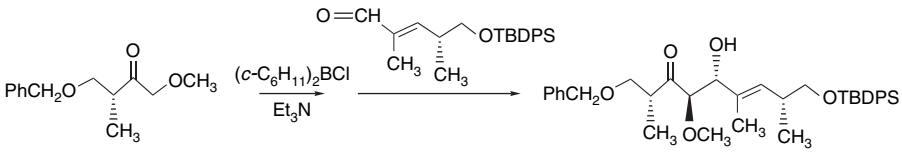
Polar effects appear to be important for 3′-alkoxy substituents in enolates. 3-Benzyloxy groups enhance the facial selectivity of *E*-boron enolates, and this is attributed to a TS **I** in which the benzyloxy group faces toward the approaching aldehyde. This structure is thought to be preferable to an alternate conformation **J**, which may be destabilized by electron pair repulsions between the benzyloxy oxygen and the enolate oxygen.[109]



This effect is seen in the case of ketone **4**, where the stereoselectivity of the benzyloxy derivative is much higher than the compound lacking the benzyloxy group.[110]

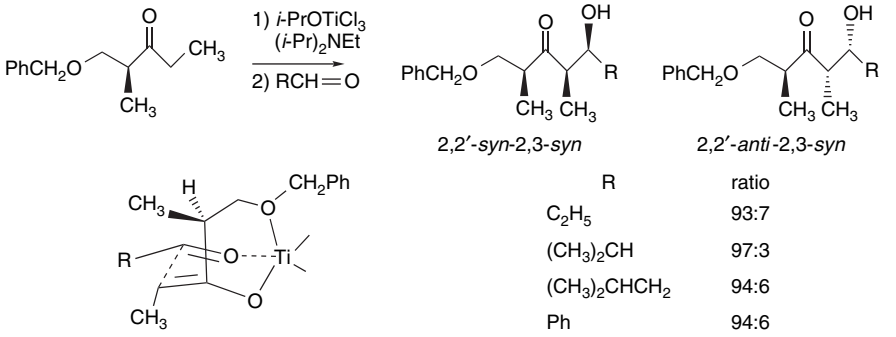


The same β-alkoxy effect appears to be operative in a 2'-methoxy substituted system.[111]



[108] I. Paterson and R. D. Tillyer, *Tetrahedron Lett.*, **33**, 4233 (1992).
[109] A. Bernardi, C. Gennari, J. M. Goodman, and I. Paterson, *Tetrahedron: Asymmetry*, **6**, 2613 (1995).
[110] I. Paterson, J. M. Goodman, and M. Isaka, *Tetrahedron Lett.*, **30**, 7121 (1989).
[111] I. Paterson and R. D. Tillyer, *J. Org. Chem.*, **58**, 4182 (1993).

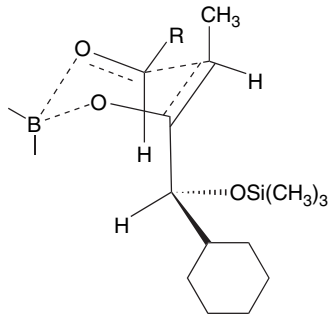
A 3′-benzyloxy ketone gives preferential 2,2′-*syn* stereochemistry through a chelated TS for several titanium enolates. The best results were obtained using isopropoxytitanium trichloride.[112] The corresponding *E*-boron enolate gives the 2,2'-*anti*-2,3-*anti* isomer as the main product through a nonchelated TS.[110]



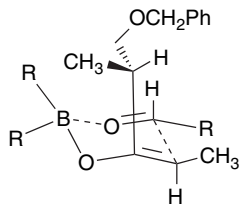
R	ratio
C_2H_5	93:7
$(CH_3)_2CH$	97:3
$(CH_3)_2CHCH_2$	94:6
Ph	94:6

In summary, the same factors that operate in the electrophile, namely steric, chelation, and polar effects, govern facial selectivity for enolates. The choice of the Lewis acid can determine if the enolate reacts via a chelate. The final outcome depends upon the relative importance of these factors within the particular TS.

Scheme 2.4 provides some specific examples of facial selectivity of enolates. Entry 1 is a case of steric control with Felkin-like TS with approach *anti* to the cyclohexyl group.

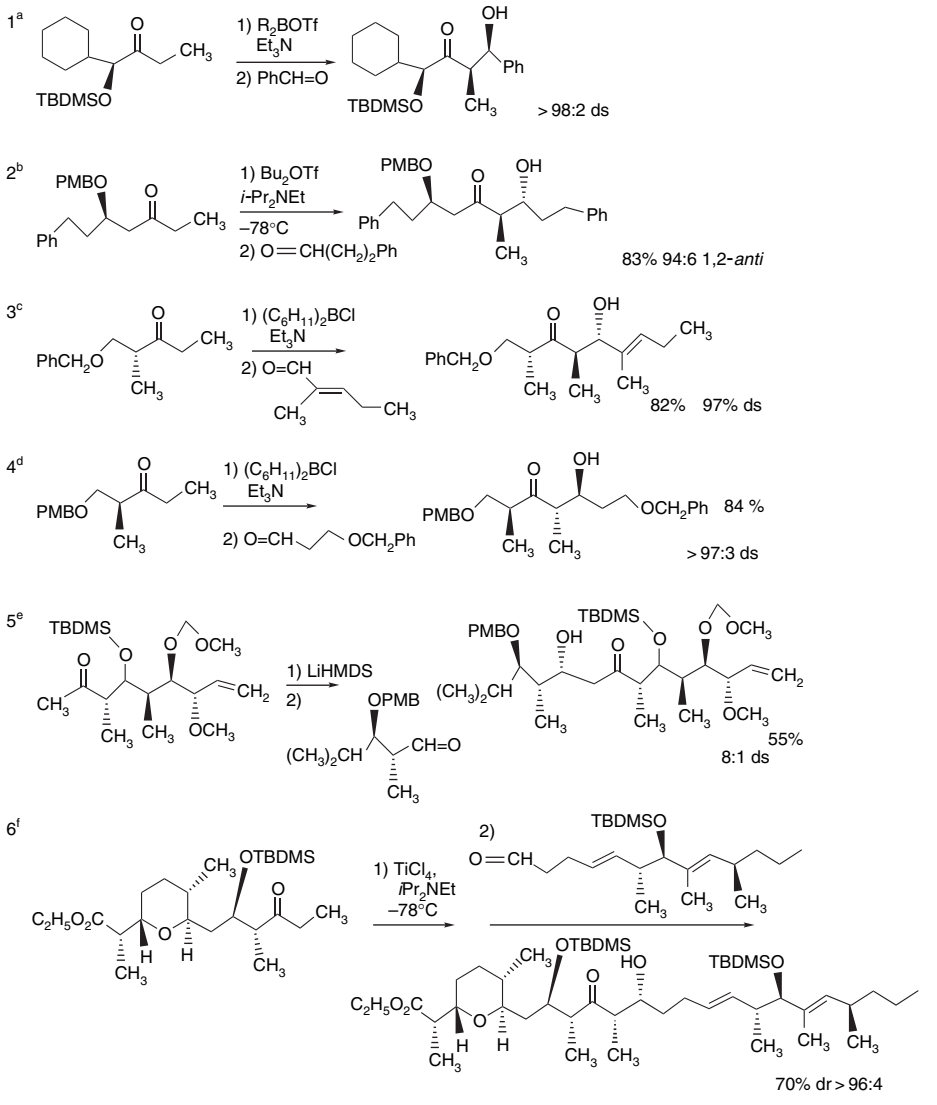


Entry 2 is an example of the polar β-oxy directing effect. Entries 3 and 4 involve formation of *E*-enolates using dicyclohexylboron chloride. The stereoselectivity is consistent with a cyclic TS in which a polar effect orients the benzyloxy group away from the enolate oxygen.



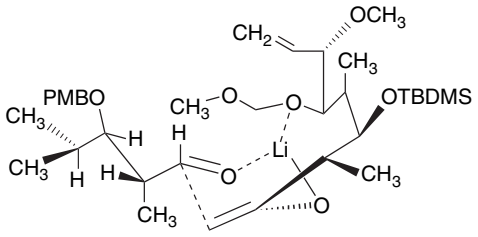
112. J. G. Solsona, J. Nebot, P. Romea, and F. Urpi, *J. Org. Chem.*, **70**, 6533 (2005).

Scheme 2.4. Examples of Facial Selectivity in Aldol and Mukaiyama Reactions Based on Enolate Structure

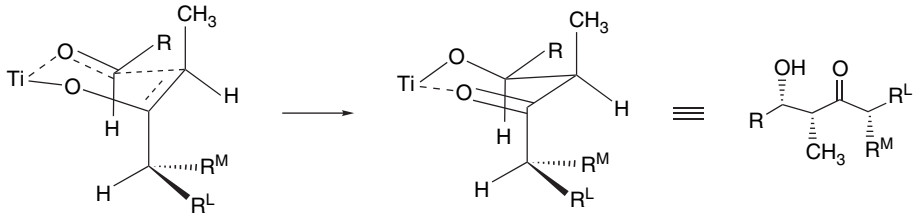


a. D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).
b. D. A. Evans, P. J. Coleman, and B. Cote, *J. Org. Chem.*, **62**, 788 (1997).
c. I. Paterson and M. V. Perkins, *Tetrahedron*, **52**, 1811 (1996).
d. I. Paterson and I. Lyothier, *J. Org. Chem.*, **70**, 5454 (2005).
e. W. R. Roush, T. D. Bannister, M. D. Wendt, J. A. Jablonsowki, and K. A. Scheidt, *J. Org. Chem.*, **67**, 4275 (2002).
f. M. Defosseux, N. Blanchard, C. Meyer, and J. Cossy, *J. Org. Chem.*, **69**, 4626 (2004).

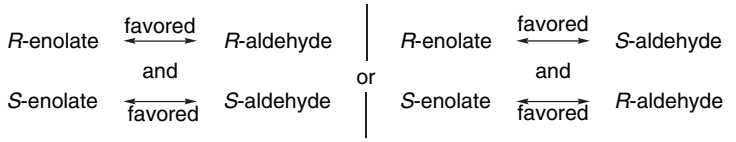
Entry 5, where the same stereochemical issues are involved was used in the synthesis of (+)-discodermolide. (See Section 13.5.6 for a more detailed discussion of this synthesis.) There is a suggestion that this entry involves a chelated lithium enolate and there are two stereogenic centers in the aldehyde. In the next section, we discuss how the presence of stereogenic centers in both reactants affects stereoselectivity.



Entry 6 involves a titanium enolate of an ethyl ketone. The aldehyde has no nearby stereocenters. Systems with this substitution pattern have been shown to lead to a 2,2′-*syn* relationship between the methyl groups flanking the ketone, and in this case, the β-siloxy substituent has little effect on the stereoselectivity. The configuration (*Z*) and conformation of the enolate determines the 2,3-*syn* stereochemistry.[113]

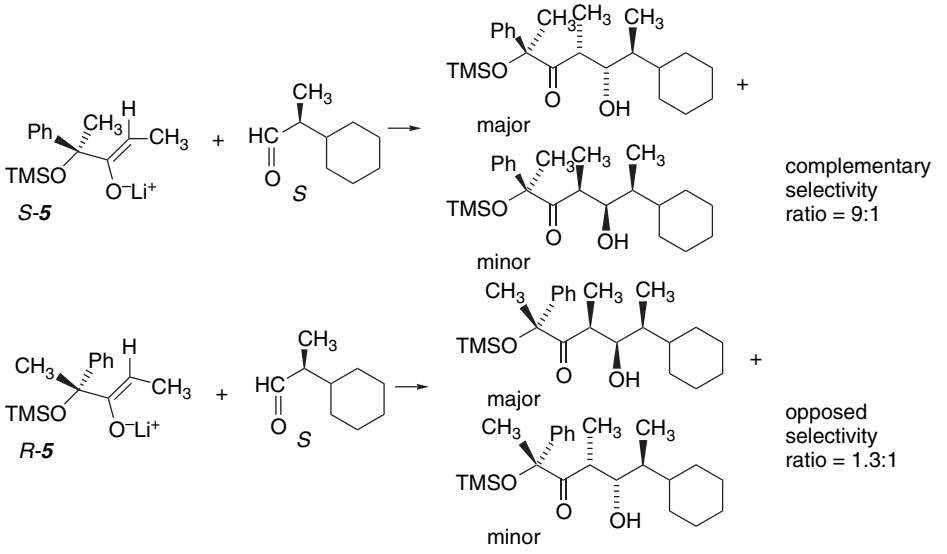


2.1.5.3. Complementary/Competitive Control: Double Stereodifferentiation. If both the aldehyde and the enolate in an aldol addition are chiral, mutual combinations of stereoselectivity come into play. The chirality in the aldehyde and enolate each impose a bias toward one absolute configuration. The structure of the chairlike TS imposes a bias toward the relative configuration (*syn* or *anti*) of the newly formed stereocenters as described in Section 2.1.2. One combination of configurations, e.g., (*R*)-aldehyde/(*S*)-enolate, provides complementary, reinforcing stereoselection, whereas the alternative combination results in opposing preferences and leads to diminished overall stereoselectivity. The combined interaction of stereocenters in both the aldehyde and the enolate component is called *double stereodifferentiation*.[114] The reinforcing combination is called *matched* and the opposing combination is called *mismatched.*



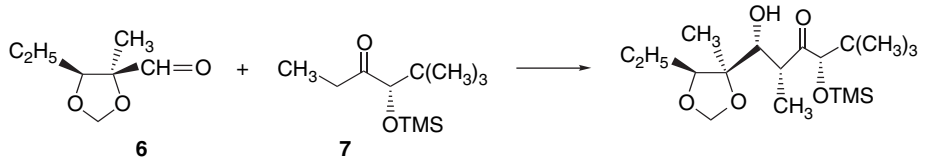
[113.] D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).
[114.] S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem. Int. Ed. Engl.*, **24**, 1 (1985).

For example the aldol addition of (*S*)-2-cyclohexylpropanal is more stereoselective with the enolate (*S*)-**5** than with the enantiomer (*R*)-**5**. The stereoselectivity of these cases derives from relative steric interactions in the matched and mismatched cases.



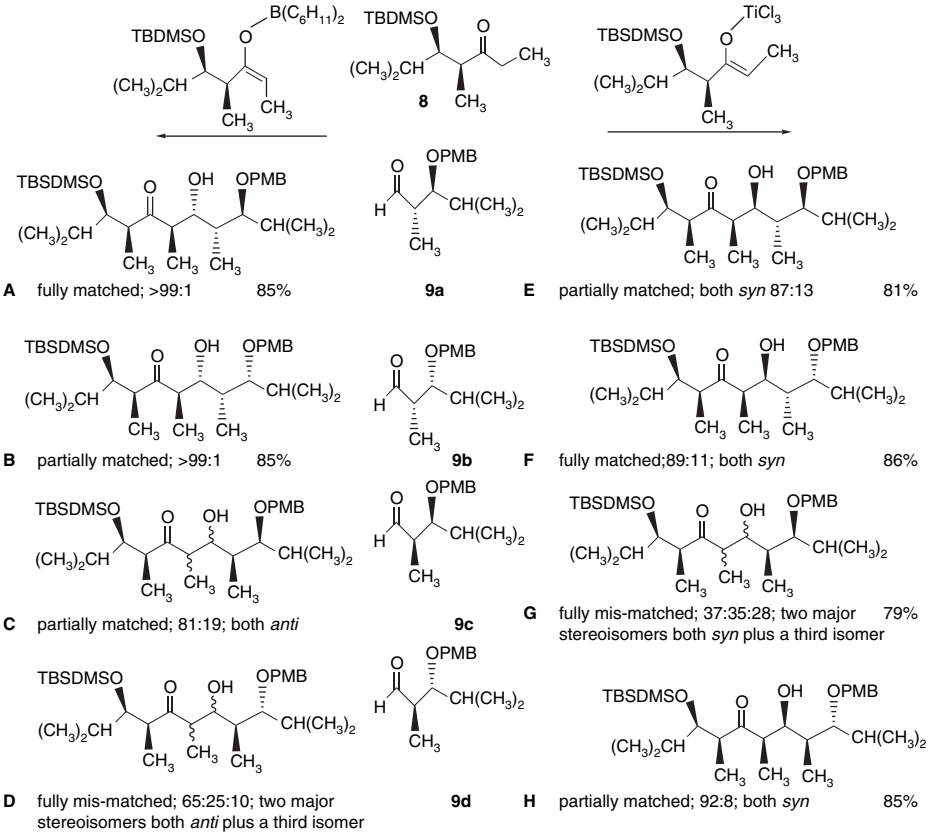
Ref. 115

Chelation can also be involved in double stereodifferentiation. The lithium enolate of the ketone **7** reacts selectively with the chiral aldehyde **6** to give a single stereoisomer.[116] The enolate is thought to be chelated, blocking one face and leading to the observed product.



There can be more than two stereocenters, in which case there are additional combinations. For example with three stereocenters, there will be one fully matched set, one fully mismatched set, and two partially matched sets. In the latter two, one of the factors may dominate the others. For example, the ketone **8** and the four stereoisomers of the aldehyde **9** have been examined.[117] Both the *E*-boron and the *Z*-titanium enolates were studied. The results are shown below.

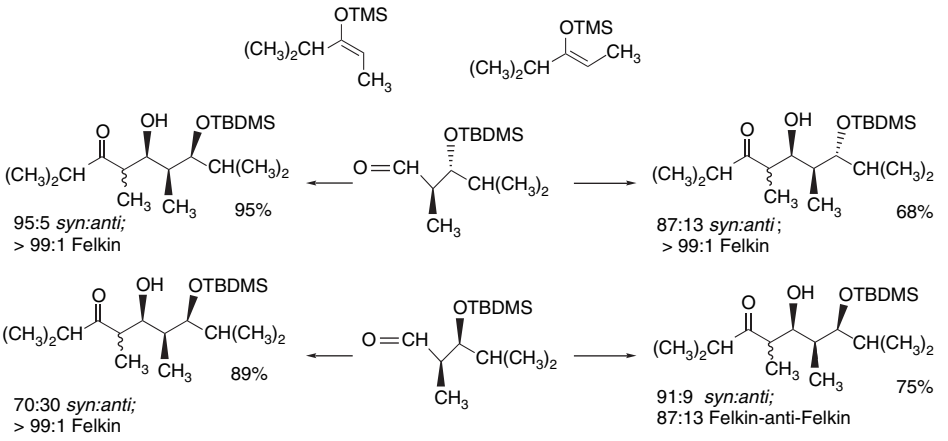
115. S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980).
116. C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, *J. Am. Chem. Soc.*, **101**, 7077 (1979).
117. D. A. Evans, M. J. Dart, J. L. Duffy, and D. L. Rieger, *J. Am. Chem. Soc.*, **117**, 9073 (1995).



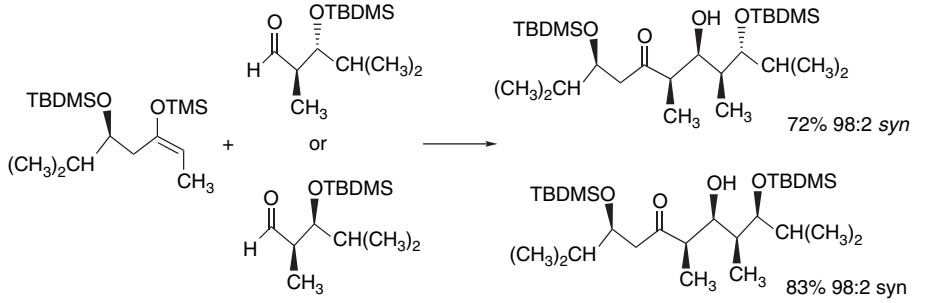
The results for the boron enolates show that when the aldehyde and enolate centers are matched the diastereoselectivity is high (Cases **A** and **B**). In Case **C**, the enolate is matched with respect to the β-alkoxy group but mismatched with the α-methyl group. The result is an 81:19 dominance of the anti-Felkin product. For the titanium enolates, Cases **E** and **F** correspond to a matched relationship with the α-stereocenter. Case **G** is fully mismatched and shows little selectivity. In Case **H**, the matched relationship between the enolate and the β-alkoxy group overrides the α-methyl effect and a 2,3-*syn* (Felkin) product is formed. The corresponding selectivity ratios have also been determined for the lithium enolates.[118] Comparison with the boron enolates shows that although the stereoselectivity of the fully matched system is higher with the boron enolate, in the mismatched cases for the lithium enolate, the aldehyde bias overrides the enolate bias and gives modest selectivity for the alternative *anti* isomer.

In general, BF_3-catalyzed Mukaiyama reactions lack a cyclic organization because of the maximum coordination of four for boron. In these circumstances, the reactions show a preference for the Felkin type of approach and exhibit a preference for *syn* stereoselectivity that is independent of silyl enol ether structure.[119]

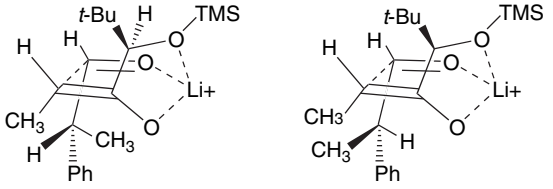
118. D. A. Evans, M. G. Yang, M. J. Dart, and J. L. Duffy, *Tetrahedron Lett.*, **37**, 1957 (1996).
119. D. A. Evans, M. G. Yang, M. J. Dart, J. L. Duffy, and A. S. Kim, *J. Am. Chem. Soc.*, **117**, 9598 (1995).



When there is also a stereogenic center in the silyl enol ether, it can enhance or detract from the underlying stereochemical preferences. The two reactions shown below possess reinforcing structures with regard to the aldehyde α-methyl and the enolate TBDMSO groups and lead to high stereoselectivity. The stereochemistry of the β-TBDMSO group in the aldehyde has little effect on the stereoselectivity.



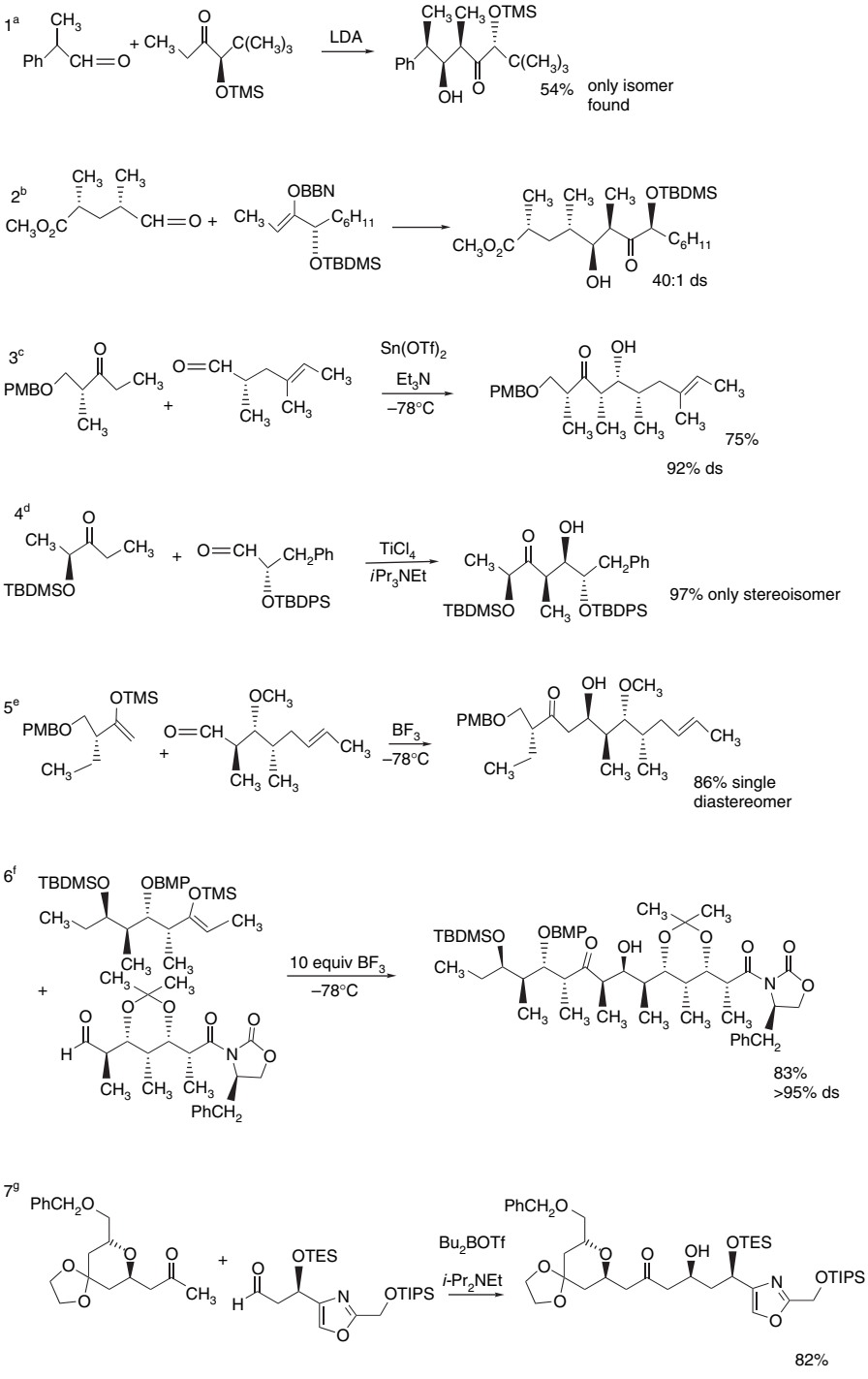
Scheme 2.5 gives some additional examples of double stereodifferentiation. Entry 1 combines the steric (Felkin) facial selectivity of the aldehyde with the facial selectivity of the enolate, which is derived from chelation. In reaction with the racemic aldehyde, the (*R*)-enantiomer is preferred.



Entry 2 involves the use of a sterically biased enol boronate with an α-substituted aldehyde. The reaction, which gives 40:1 facial selectivity, was used in the synthesis of 6-deoxyerythronolide B and was one of the early demonstrations of the power of double diastereoselection in synthesis. In Entry 3, the *syn* selectivity is the result of a chelated TS, in which the β-*p*-methoxybenzyl substituent interacts with the tin ion.[120]

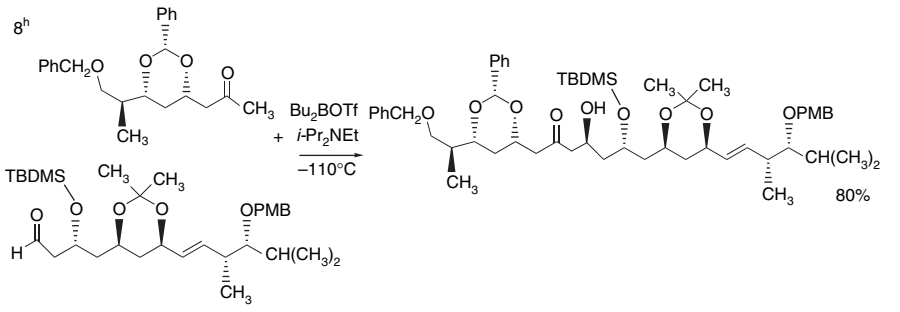
[120] I. Paterson and R. D. Tillyer, *Tetrahedron Lett.*, **33**, 4233 (1992).

Scheme 2.5. Examples of Double Stereodifferentiation in Aldol and Mukaiyama Reactions



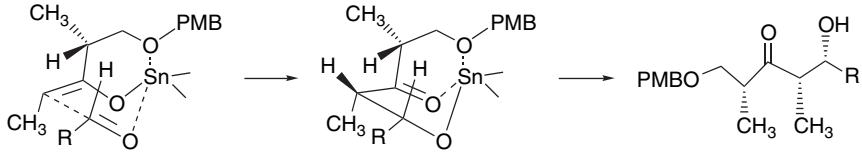
(*Continued*)

Scheme 2.5. (***Continued***)

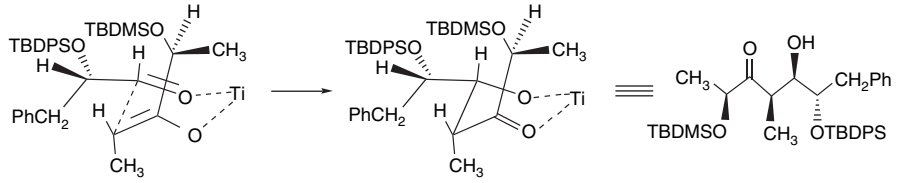


a. C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, *J. Org. Chem.*, **46**, 2290 (1981).
b. S. Masamune, M. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, *J. Am. Chem. Soc.*, **103**, 1568 (1981).
c. I. R. Correa, Jr., and R. A. Pilli, *Angew. Chem. Int. Ed. Engl.*, **42**, 3017 (2003).
d. C. Esteve, M. Ferrero, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **40**, 5083 (1999).
e. G. E. Keck, C. E. Knutson, and S. A. Wiles, *Org. Lett.*, **3**, 707 (2001).
f. D. A. Evans, A. S. Kim, R. Metternich, and V. J. Novack, *J. Am. Chem. Soc.*, **120**, 5921 (1998).
g. D. A. Evans, D. M. Fitch, T. E. Smith, and V. J. Cee, *J. Am. Chem. Soc.*, **122**, 10033 (2000).
h. D. A. Evans, B. Cote, P. J. Coleman, and B. T. Connell, *J. Am. Chem. Soc.*, **125**, 10893 (2003).

The aldehyde α-methyl substituent determines the facial selectivity with respect to the aldehyde.



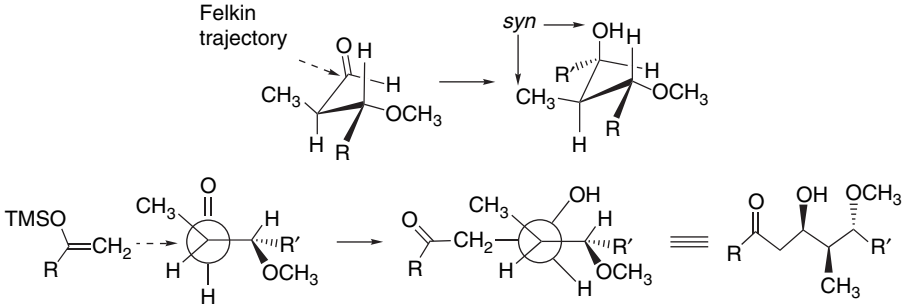
Entry 4 has siloxy substituents in both the (titanium) enolate and the aldehyde. The TBDPSO group in the aldehyde is in the "large" Felkin position, that is, perpendicular to the carbonyl group.[121] The TBDMS group in the enolate is nonchelated but exerts a steric effect that governs facial selectivity.[122] In this particular case, the two effects are matched and a single stereoisomer is observed.



Entry 5 is a case in which the α- and β-substituents reinforce the stereoselectivity, as shown below. The largest substituent is perpendicular to the carbonyl, as in the Felkin model. When this conformation is incorporated into the TS, with the α-methyl

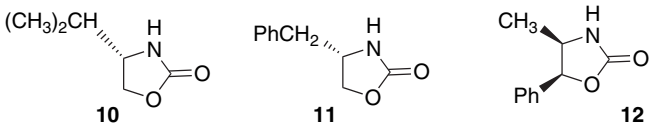
121. C. Esteve, M. Ferrero, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **40**, 5079 (1999).
122. S. Figueras, R. Martin, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **38**, 1637 (1997).

group in the "medium position," the predicted approach leads to the observed 3,4-*syn* stereochemistry.



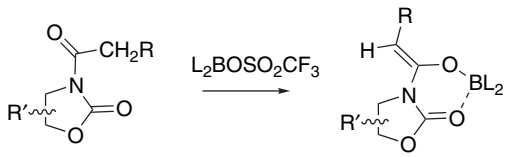
Entry 6 is an example of the methodology incorporated into a synthesis of 6-deoxyerythronolide.[123] Entries 7 and 8 illustrates the operation of the β-alkoxy group in cyclic structures. The reaction in Entry 7 was used in the synthesis of phorboxazole B.

2.1.5.4. Stereochemical Control Through Chiral Auxiliaries. Another approach to control of stereochemistry is installation of a *chiral auxiliary*, which can achieve a high degree of facial selectivity.[124] A very useful method for enantioselective aldol reactions is based on the oxazolidinones **10**, **11**, and **12**. These compounds are available in enantiomerically pure form and can be used to obtain either enantiomer of the desired product.



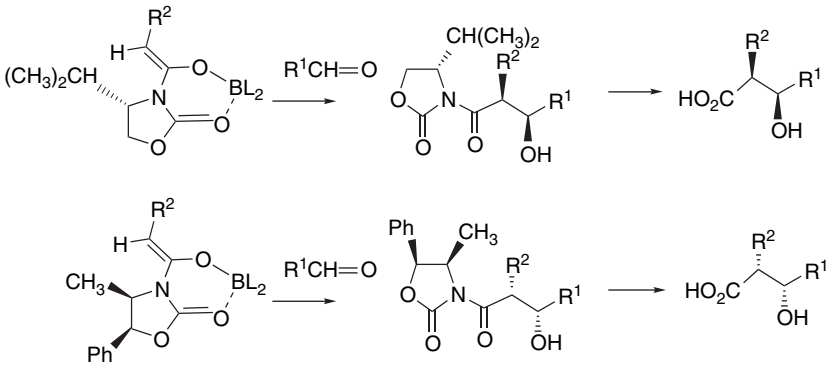
10 **11** **12**

These oxazolidinones can be acylated and converted to the lithium, boron, tin, or titanium enolates by the same methods applicable to ketones and esters. For example, when they are converted to boron enolates using di-*n*-butylboron triflate and triethylamine, the enolates are the *Z*-stereoisomers.[125]

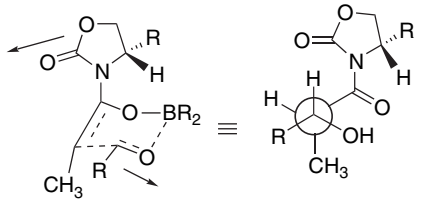


The substituents direct the approach of the aldehyde. The acyl oxazolidinones can be solvolyzed in water or alcohols to give the enantiomeric β-hydroxy acid or ester. Alternatively, they can be reduced to aldehydes or alcohols.

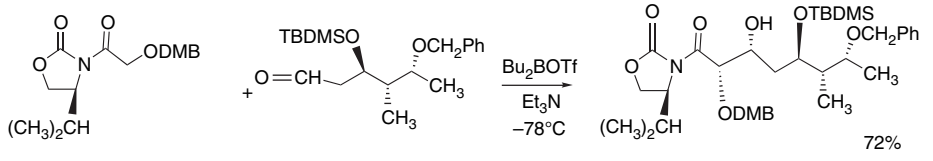
123. D. A. Evans, A. S. Kim, R. Metternich, and V. J. Novack, *J. Am. Chem. Soc.*, **120**, 5921 (1998).
124. M. Braun and H. Sacha, *J. Prakt. Chem.*, **335**, 653 (1993); S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998); E. Carreira, in *Catalytic Asymmetric Synthesis*, 2nd Edition, I. Ojima, ed., Wiley-VCH, 2000, pp. 513–541; F. Velazquez and H. F. Olivo, *Curr. Org. Chem.*, **6**, 303 (2002).
125. D. A. Evans, J. Bartoli, and T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981).



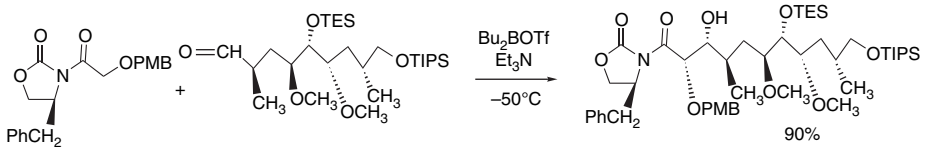
The reacting aldehyde displaces the oxazolidinone oxygen at the tetravalent boron in the reactive TS. The conformation of the addition TS for boron enolates is believed to have the oxazolidinone ring oriented with opposed dipoles of the ring and the aldehyde carbonyl groups.



The chiral auxiliary methodology using boron enolates has been successfully applied to many complex structures (see also Scheme 2.6).



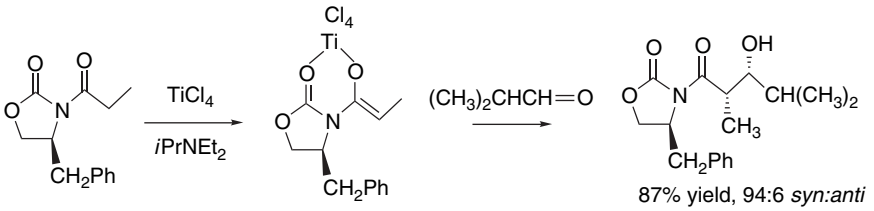
Ref. 126.



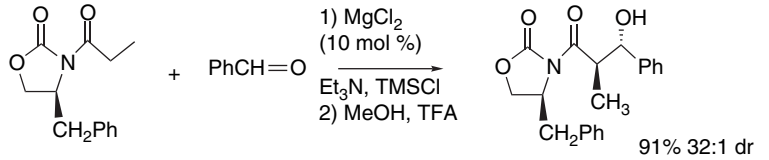
Ref. 127.

126. W. R. Roush, T. G. Marron, and L. A. Pfeifer, *J. Org. Chem.*, **62**, 474 (1997).
127. T. K. Jones, R. A. Reamer, R. Desmond, and S. G. Mills, *J. Am. Chem. Soc.*, **112**, 2998 (1990).

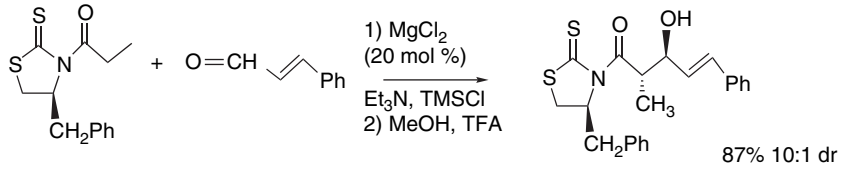
Titanium enolates also can be prepared from *N*-acyloxazolidinones. These *Z*-enolates, which are chelated with the oxazolidinone carbonyl oxygen,[128] show *syn* stereoselectivity, and the oxazolidinone substituent exerts facial selectivity.



The *N*-acyloxazolidinones give *anti* products when addition is effected by a catalytic amount of $MgCl_2$ in the presence of a tertiary amine and trimethylsilyl chloride. Under these conditions the adduct is formed as the trimethylsilyl ether.[129]



Under similar conditions, the corresponding thiazolidinethione derivatives give *anti* product of the *opposite absolute configuration*, at least for cinnamaldehyde.

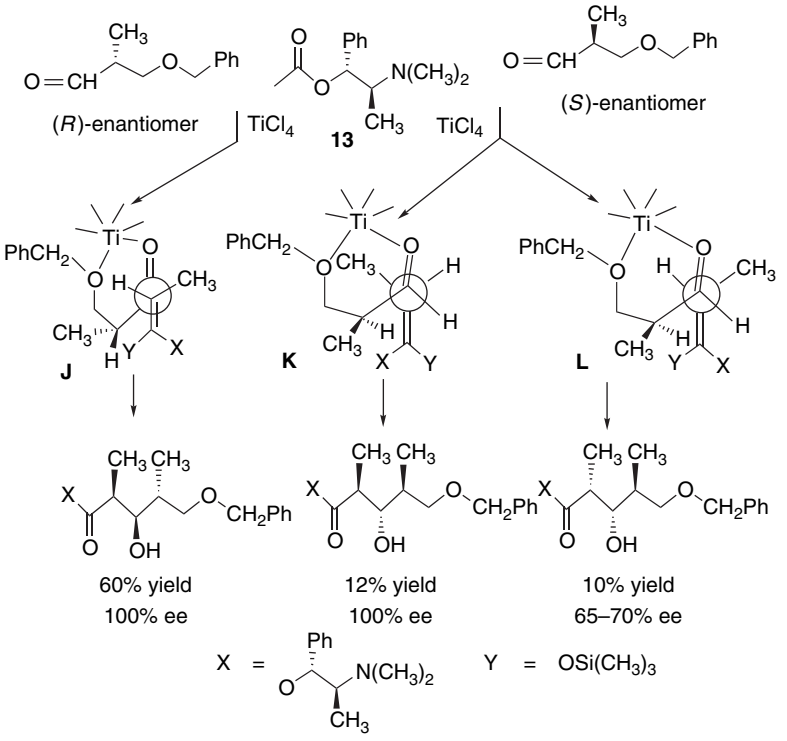


The mechanistic basis for the stereoselectivity of these conditions remains to be determined. The choice of reactant and conditions can be used to exert a substantial degree of control of the stereoselectivity.

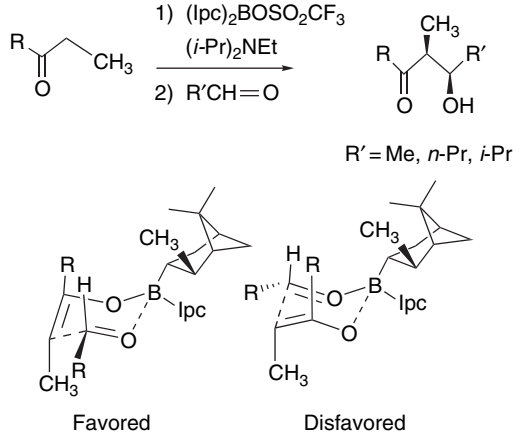
Recently several other molecules have been developed as chiral auxiliaries. These include derivatives of ephedrine and pseudoephedrine. The *N*-methylephedrine [(1*R*,2*S*)-2-dimethyamino-1-phenyl-1-propanol] chiral auxiliary **13** has been examined with both the (*S*)- and (*R*)-enantiomers of 2-benzyloxy-2-methylpropanal.[130] The two enantiomers reacted quite differently. The (*R*)-enantiomer gave a 60% yield of a pure enantiomer with a *syn* configuration at the new bond. The (*S*)-enantiomer gave a combined 22% yield of two diastereomeric products in a 1.3:1 ratio. The aldehyde is known from NMR studies to form a chelated complex with $TiCl_4$,[131] and presumably reacts through a chelated TS. The TS **J** from the (*R*)-enantiomer has the methyl groups from both the chiral auxiliary and the silyl enol ether in favorable environments (matched pair). The products from the (*S*)-enantiomer arise from TS **K** and

128. D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).
129. D. A. Evans, J. S. Tedrow, J. T. Shaw, and C. W. Downey, *J. Am. Chem. Soc.*, **124**, 392 (2002).
130. G. Gennari, L. Colombo, G. Bertolini, and G. Schimperna, *J. Org. Chem.*, **52**, 2754 (1987).
131. G. E. Keck and S. Castellino, *J. Am. Chem. Soc.*, **108**, 3847 (1986).

TS **L**, each of which has one of the methyl groups in an unfavorable environment. (mismatched pairs).

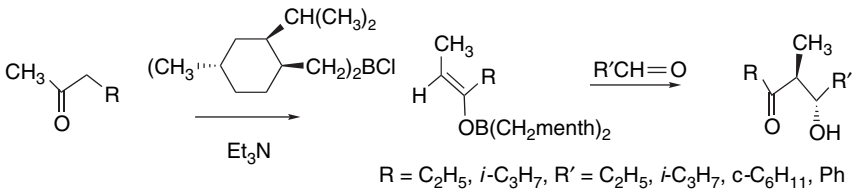


Enantioselectivity can also be induced by use of chiral boron enolates. Both the (+) and (−) enantiomers of diisopinocampheylboron triflate have been used to generate *syn* addition through a cyclic TS.[132] The enantioselectivity was greater than 80% for most cases that were examined. *Z*-Boron enolates are formed under these conditions and the products are 2,3-*syn*.



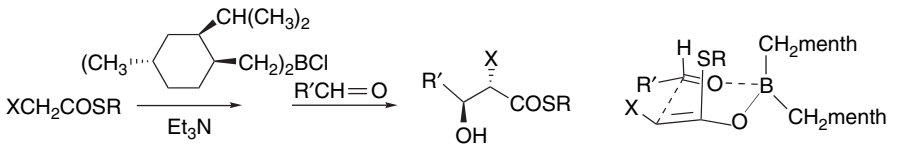
[132.] I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, and R. D. Norcross, *Tetrahedron*, **46**, 4663 (1990).

Another promising boron enolate is derived from (−)-menthone.[133] It yields *E*-boron enolates that give good enantioselectivity in the formation of *anti* products.[134]



R = C_2H_5, *i*-C_3H_7, R′ = C_2H_5, *i*-C_3H_7, c-C_6H_{11}, Ph

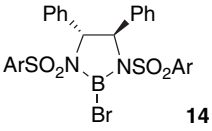
The boron enolates of α-substituted thiol esters also give excellent facial selectivity.[135]



X = Cl, Br, OCH_2Ph

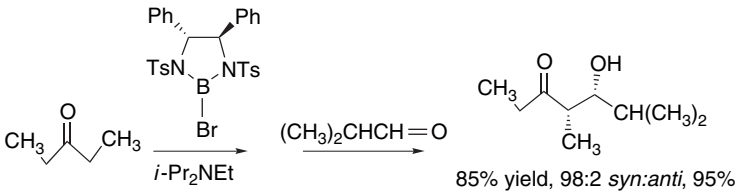
The facial selectivity in these chiral boron enolates has its origin in the steric effects of the boron substituents.

Several chiral heterocyclic borylating agents have been found useful for enantioselective aldol additions. The diazaborolidine **14** is an example.[136]



14

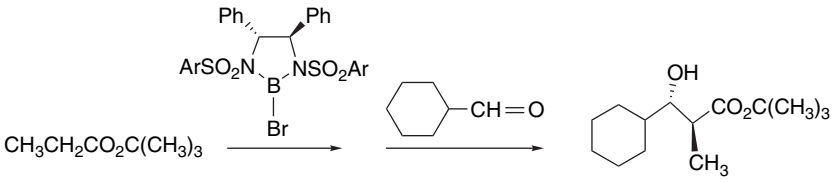
Ar = 3,5-di(trifluoromethyl)phenyl

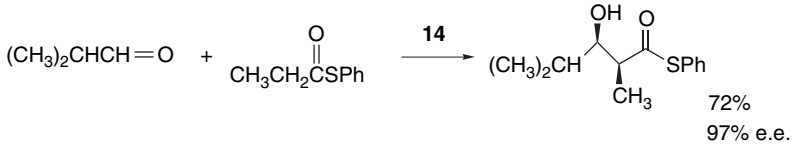


85% yield, 98:2 *syn:anti*, 95% e.e.

Derivatives with various substituted sulfonamides have been developed and used to form enolates from esters and thioesters.[137] An additional feature of this chiral auxiliary is the ability to select for *syn* or *anti* products, depending upon choice of reagents and reaction conditions. The reactions proceed through an acyclic TS, and diastereoselectivity is determined by whether the *E*- or *Z*-enolate is formed.[138] *t*-Butyl esters give *E*-enolates and *anti* adducts, whereas phenylthiol esters give *syn* adducts.[136]

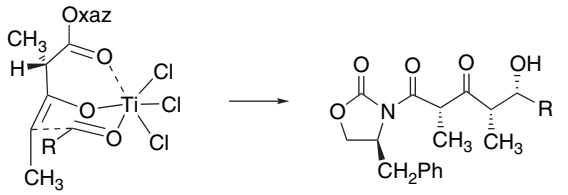
133. C. Gennari, *Pure Appl. Chem.*, **69**, 507 (1997).
134. G. Gennari, C. T. Hewkin, F. Molinari, A. Bernardi, A. Comotti, J. M. Goodman, and I. Paterson, *J. Org. Chem.*, **57**, 5173 (1992).
135. C. Gennari, A. Vulpetti, and G. Pain, *Tetrahedron*, **53**, 5909 (1997).
136. E. J. Corey, R. Imwinkelried, S. Pikul, and Y. B. Xiang, *J. Am. Chem. Soc.*, **111**, 5493 (1989).
137. E. J. Corey and S. S. Kim, *J. Am. Chem. Soc.*, **112**, 4976 (1990).
138. E. J. Corey and D. H. Lee, *Tetrahedron Lett.*, **34**, 1737 (1993).





Scheme 2.6 shows some examples of the use of chiral auxiliaries in the aldol and Mukaiyama reactions. The reaction in Entry 1 involves an achiral aldehyde and the chiral auxiliary is the only influence on the reaction diastereoselectivity, which is very high. The *Z*-boron enolate results in *syn* diastereoselectivity. Entry 2 has both an α-methyl and a β-benzyloxy substituent in the aldehyde reactant. The 2,3-*syn* relationship arises from the *Z*-configuration of the enolate, and the 3,4-*anti* stereochemistry is determined by the stereocenters in the aldehyde. The product was isolated as an ester after methanolysis. Entry 3, which is very similar to Entry 2, was done on a 60-kg scale in a process development investigation for the potential antitumor agent (+)-discodermolide (see page 1244).

Entries 4 and 5 are cases in which the oxazolidinone substituent is a β-ketoacyl group. The α-hydrogen (between the carbonyls) does not react as rapidly as the γ-hydrogen, evidently owing to steric restrictions to optimal alignment. The all-*syn* stereochemistry is consistent with a TS in which the exocyclic carbonyl is chelated to titanium.

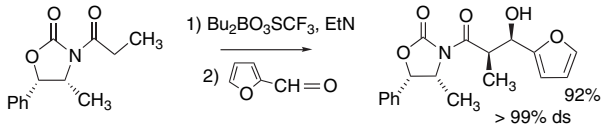


In Entry 5, the aldehyde is also chiral and double stereodifferentiation comes into play. Entry 6 illustrates the use of an oxazolidinone auxiliary with another highly substituted aldehyde. Entry 7 employs conditions that were found effective for α-alkoxyacyl oxazolidinones. Entries 8 and 9 are examples of the application of the thiazolidine-2-thione auxiliary and provide the 2,3-*syn* isomers with diastereofacial control by the chiral auxiliary.

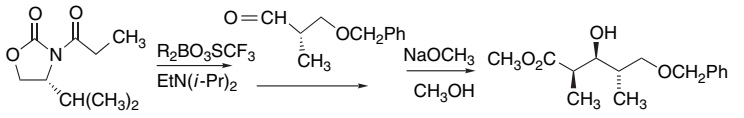
2.1.5.5. Stereochemical Control Through Reaction Conditions. In the early 1990s it was found that the stereochemistry of reactions of boron enolates of *N*-acyloxazolidinones can be altered by using a Lewis acid complex of the aldehyde or an excess of the Lewis acid. These reactions are considered to take place through an open TS, with the stereoselectivity dependent on the steric demands of the Lewis acid. With various aldehydes, $TiCl_4$ gave a *syn* isomer, whereas the reaction was

Scheme 2.6. Control of Stereochemistry of Aldol and Mukaiyama Aldol Reactions Using Chiral Auxiliaries

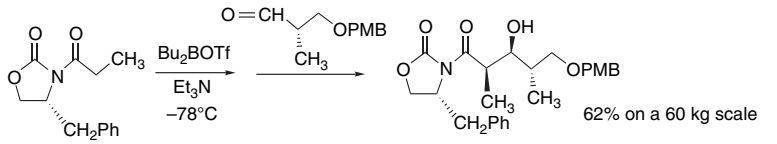
1[a]



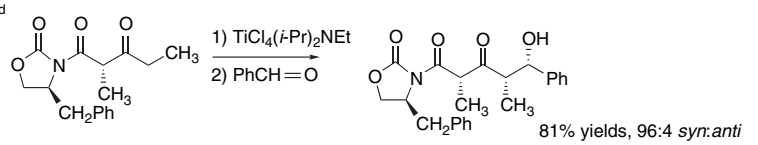
2[b]



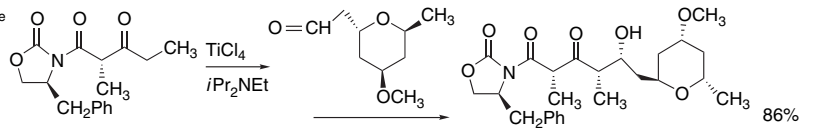
3[c]



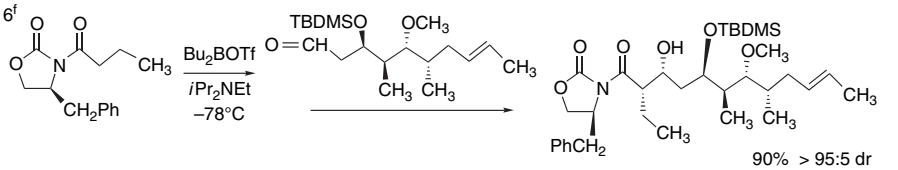
4[d]



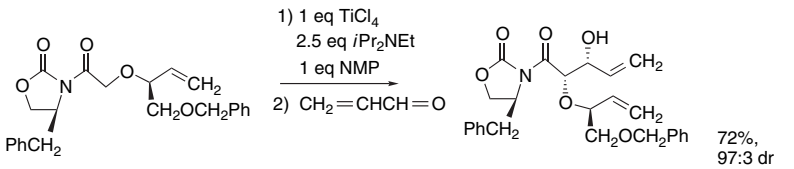
5[e]



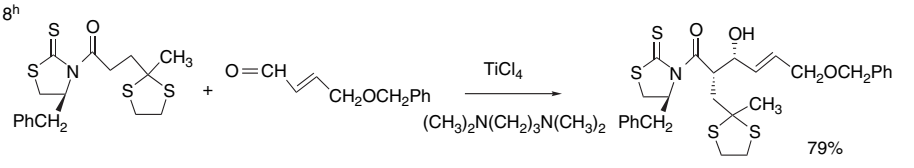
6[f]



7[g]

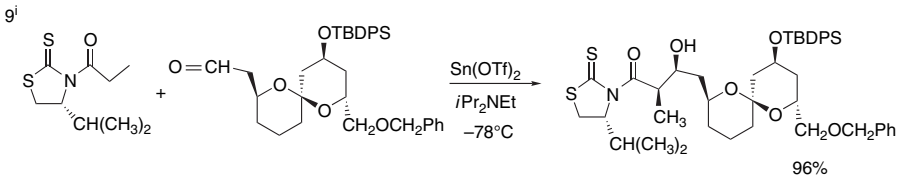


8[h]



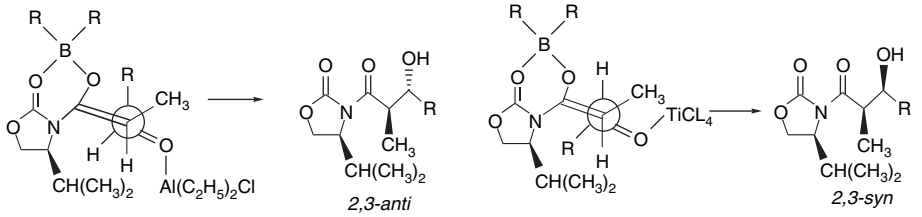
(*Continued*)

Scheme 2.6. (***Continued***)



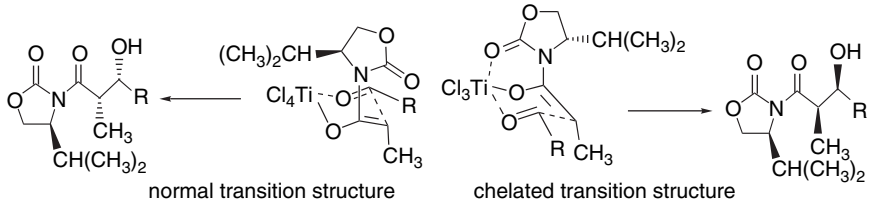
a. S. F. Martin and D. E. Guinn, *J. Org. Chem.*, **52**, 5588 (1987).
b. D. Seebach, H.-F. Chow, R. F. W. Jackson, K. Lawson, M. A. Sutter, S. Thaisrivongs, and J. Zimmerman, *J. Am. Chem. Soc.*, **107**, 5292 (1985).
c. S. J. Mickel, G. H. Sedelmeier, D. Niererer, R. Daeffler, A. Osmani, K. Schreiner, M. Seeger-Weibel, B. Berod, K. Schaer, R. Gamboni, S. Chen, W. Chen, C. T. Jagoe, F. Kinder, M. Low, K. Prasad, O. Repic, W. C. Shieh, R. M. Wang, L. Wakole, D. Xu, and S. Xue, *Org. Proc. Res. Dev.*, **8**, 92 (2004).
d. D. A. Evans, J. S. Clark, R. Metternich, V. J. Novack, and G. S. Sheppard, *J. Am. Chem. Soc.*, **112**, 866 (1990).
e. G. E. Keck and G. D. Lundquist, *J. Org. Chem.*, **64**, 4482 (1999).
f. L. C. Dias, L. G. de Oliveira, and M. A. De Sousa, *Org. Lett.*, **5**, 265 (2003).
g. M. T. Crimmins and J. She, *Synlett*, 1371 (2004).
h. J. Wu, X. Shen, Y.-Q. Yang, Q. Hu, and J.-H. Huang, *J. Org. Chem.*, **69**, 3857 (2004).
i. D. Zuev and L. A. Paquette, *Org. Lett.*, **2**, 679 (2000).

anti selective using $(C_2H_5)_2AlCl$.[139] The *anti* selectivity is proposed to arise as a result of the greater size requirement for the complexed aldehyde with $(C_2H_5)_2AlCl$. These reactions both give a different stereoisomer than the reaction done *without the additional Lewis acid*. The chiral auxiliary is the source of facial selectivity.



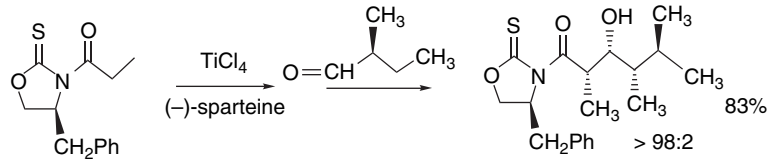
R = C_2H_5, $(CH_3)_3CH$, $(CH_3)_2CHCH_2$, $(CH_3)_3C$, Ph

With titanium enolates it was found that use of excess (3 equiv.) of the titanium reagent reversed facial selectivity of oxazolidinone enolates.[140] This was attributed to generation of a chelated TS in the presence of the excess Lewis acid. The chelation rotates the oxazolidinone ring and reverses the facial preference, while retaining the *Z*-configuration *syn* diastereoselectivity.

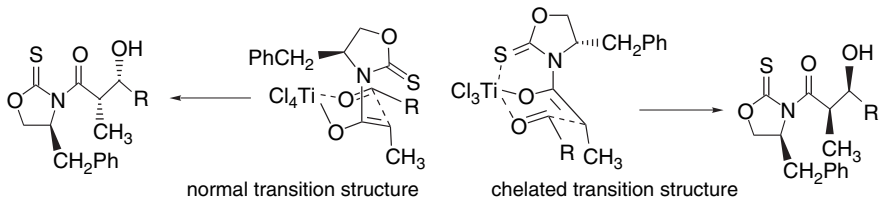


139. M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, **56**, 5747 (1991).
140. M. Nerz-Stormes and E. R. Thornton, *Tetrahedron Lett.*, **27**, 897 (1986); M. Nerz-Stormes and E. R. Thornton, *J. Org. Chem.*, **56**, 2489 (1991).

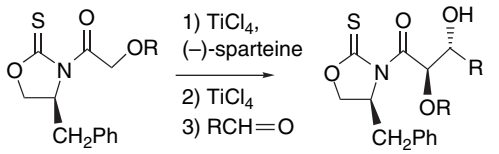
Crimmins and co-workers have developed *N*-acyloxazolidinethiones as chiral auxiliaries. These reagents show excellent 2,3-*syn* diastereoselectivity and enantioselectivity in additions to aldehydes. The titanium enolates are prepared using $TiCl_4$, with (−)-sparteine being a particularly effective base.[141]



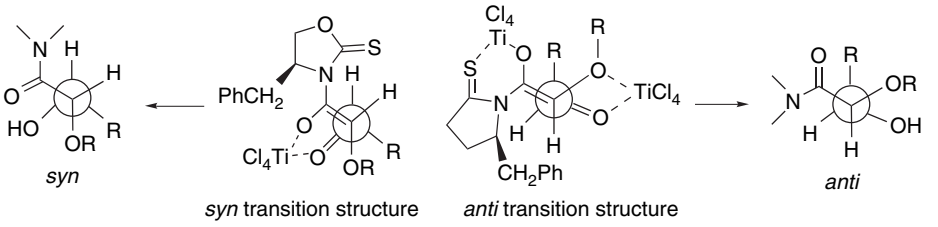
The facial selectivity of these compounds is also dependent on the amount of $TiCl_4$ that is used. With two equivalents, the facial selectivity is reversed. This reversal is also achieved by adding $AgSbF_6$. It was suggested that the excess reagent or the silver salt removes a Cl^- from the titanium coordination sphere and promotes chelation with the thione sulfur.[142] This changes the facial selectivity of the enolate by causing a reorientation of the oxazolidinethione ring. The greater affinity of titanium for sulfur over oxygen makes the oxazolidinethiones particularly effective in these circumstances. The increased tendency for chelation has been observed with other chiral auxiliaries having thione groups.[143]



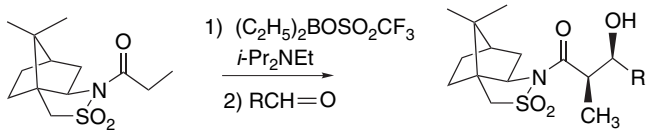
A related effect is noted with α-alkoxyacyl derivatives. These compounds give mainly the *anti* adducts when a second equivalent of $TiCl_4$ is added prior to the aldehyde.[144] The *anti* addition is believe to occur through a TS in which the alkoxy oxygen is chelated. In the absence of excess $TiCl_4$, a nonchelated cyclic TS accounts for the observed *syn* selectivity.



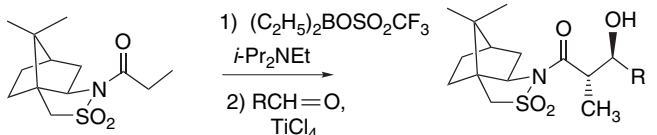
141. M. T. Crimmins and B. W. King, *J. Am. Chem. Soc.*, **120**, 9084 (1998); M. T. Crimmins, B. W. King, E. A. Tabet, and C. Chaudhary, *J. Org. Chem.*, **66**, 894 (2001); M. T. Crimmins and J. She, *Synlett*, 1371 (2004).
142. M. T. Crimmins, B. W. King, and E. A. Tabet, *J. Am. Chem. Soc.*, **119**, 7883 (1997).
143. T. H. Yan, C. W. Tan, H. C. Lee, H. C. Lo, and T. Y. Huang, *J. Am. Chem. Soc.*, **115**, 2613 (1993).
144. M. T. Crimmins and P. J. McDougall, *Org. Lett.*, **5**, 591 (2003).



Camphor-derived sulfonamide can also permit control of enantioselectivity by use of additional Lewis acid. These chiral auxiliaries can be used under conditions in which either cyclic or noncyclic TSs are involved. This frequently allows control of the *syn* or *anti* stereoselectivity.[143] The boron enolates give *syn* products, but inclusion of $SnCl_4$ or $TiCl_4$ gave excellent selectivity for *anti* products and high enantioselectivity for a range of aldehydes.[145]

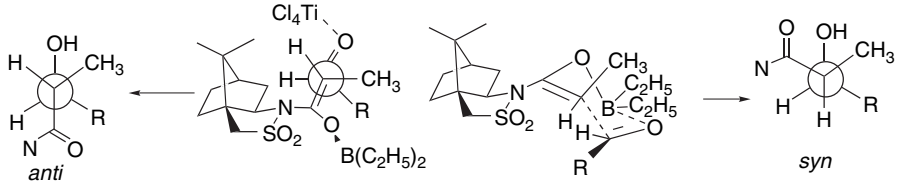


Ref. 146



Ref. 147

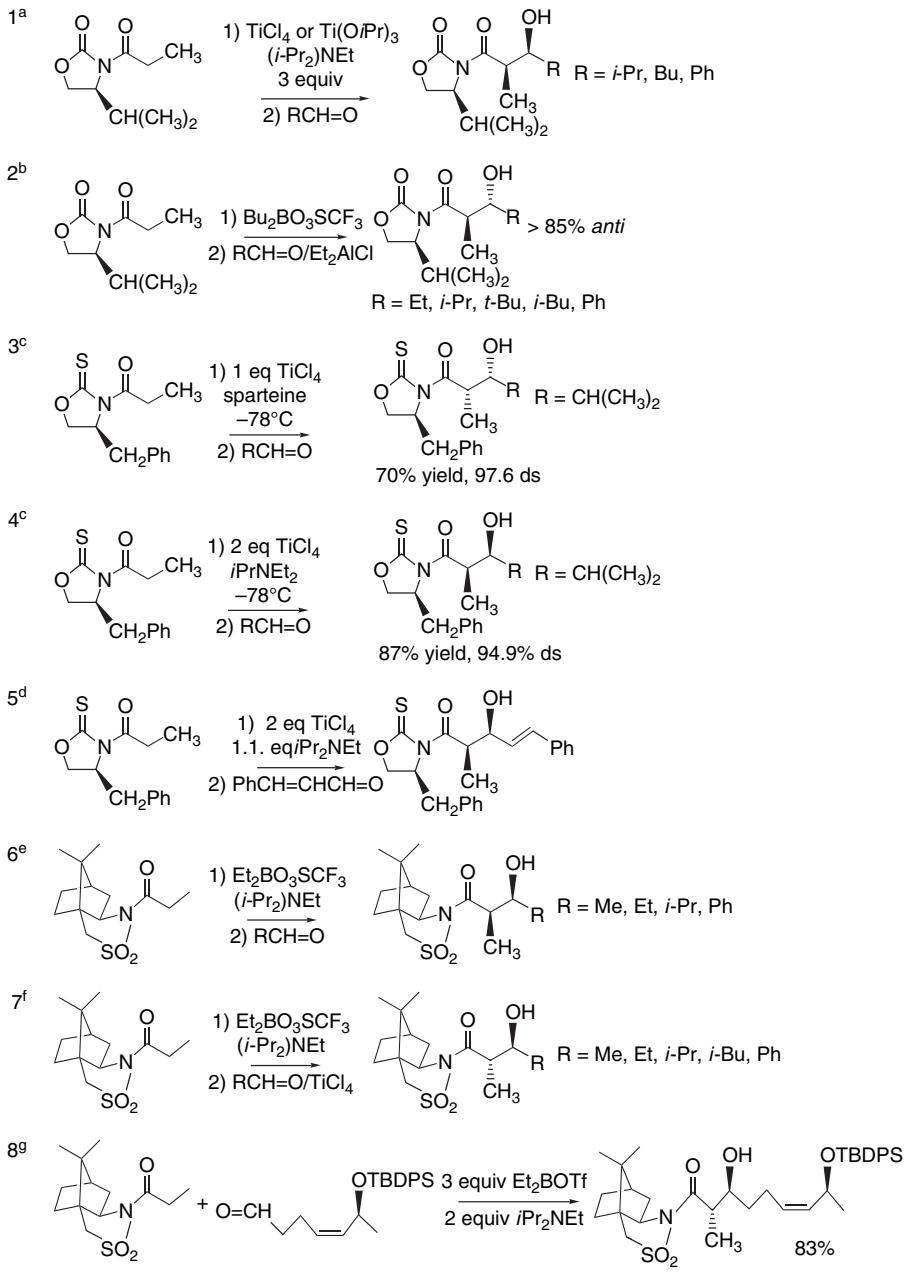
In the case of boron enolates of the camphor sulfonamides, the $TiCl_4$-mediated reaction is believed to proceed through an open TS, whereas in its absence, the reaction proceeds through a cyclic TS.



Scheme 2.7 gives some examples of the control of stereoselectivity by use of additional Lewis acid and related methods. Entry 1 shows the effect of the use of excess $TiCl_4$. Entry 2 demonstrates the ability of $(C_2H_5)_2AlCl$ to shift the boron enolate toward formation of the 2,3-*anti* diastereomer. Entries 3 and 4 compare the use of one versus two equivalents of $TiCl_4$ with an oxazoldine-2-thione auxiliary. There is a nearly complete shift of facial selectivity. Entry 5 shows a subsequent application of this methodology. Entries 6 and 7 show the effect of complexation of the aldehyde

145. Y.-C. Wang, A.-W. Hung, C.-S. Chang, and T.-H. Yan, *J. Org. Chem.*, **61**, 2038 (1996).
146. W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990).
147. W. Oppolzer and P. Lienhard, *Tetrahedron Lett.*, **34**, 4321 (1993).

Scheme 2.7. Examples of Control of Stereoselectivity by Use of Additional Lewis Acid

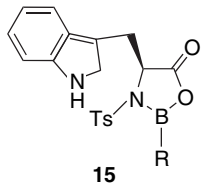


a. M. Nerz-Stormes and E. R. Thornton, *J. Org. Chem.*, **56**, 2489 (1991).
b. M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, **56**, 5747 (1991).
c. M. T. Crimmins, B. W. King, and E. A. Tabet, *J. Am. Chem. Soc.*, **119**, 7883 (1997).
d. T. K. Chakraborty, S. Jayaprakash, and P. Laxman, *Tetrahedron*, **57**, 9461 (2001).
e. W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990).
f. W. Oppolzer and P. Lienhard, *Tetrahedron Lett.*, **34**, 4321 (1993).
g. B. Fraser and P. Perlmutter, *J. Chem. Soc., Perkin Trans. 1*, 2896 (2002).

with $TiCl_4$ using the camphor sultam auxiliary. Entry 8 is an example of the use of excess diethylboron triflate to obtain the *anti* stereoisomer in a step in the synthesis of epothilone.

These examples and those in Scheme 2.6 illustrate the key variables that determine the stereochemical outcome of aldol addition reactions using chiral auxiliaries. The first element that has to be taken into account is the configuration of the ring system that is used to establish steric differentiation. Then the nature of the TS, whether it is acyclic, cyclic, or chelated must be considered. Generally for boron enolates, reaction proceeds through a cyclic but nonchelated TS. With boron enolates, excess Lewis acid can favor an acyclic TS by coordination with the carbonyl electrophile. Titanium enolates appear to be somewhat variable but can be shifted to chelated TSs by use of excess reagent and by auxiliaries such as oxazolidine-2-thiones that enhance the tendency to chelation. Ultimately, all of the factors play a role in determining which TS is favored.

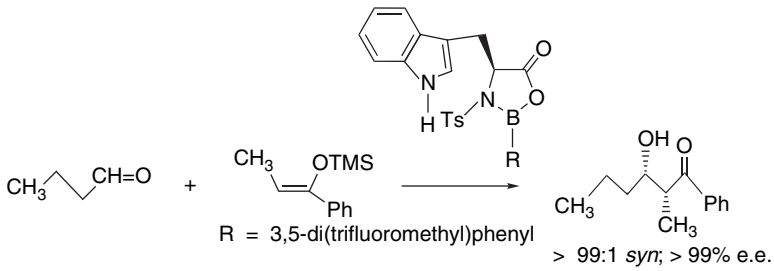
2.1.5.6. Enantioselective Catalysis of the Aldol Addition Reaction. There are also several catalysts that can effect enantioselective aldol addition. The reactions generally involve enolate equivalents, such as silyl enol ethers, that are unreactive toward the carbonyl component alone, but can react when activated by a Lewis acid. The tryptophan-based oxazaborolidinone **15** has proven to be a useful catalyst.[148]



15

This catalyst induces preferential *re* facial attack on simple aldehydes, as indicated in Figure 2.2. The enantioselectivity appears to involve the shielding of the *si* face by the indole ring through a π-stacking interaction.

The *B*-3,5-*bis*-(trifluoromethyl)phenyl derivative was found to be a very effective catalyst.[149]



148. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992); E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara, and M. C. Noe, *J. Am. Chem. Soc.*, **114**, 8290 (1992); S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998).

149. K. Ishihara, S. Kondo, and H. Yamamoto, *J. Org. Chem.*, **65**, 9125 (2000).

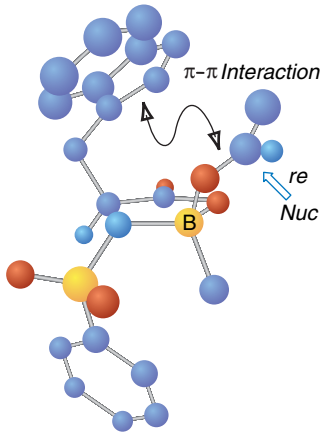
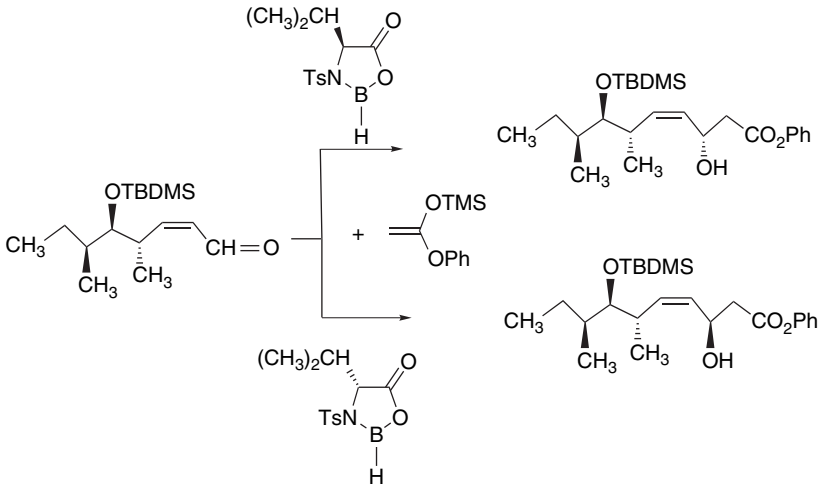


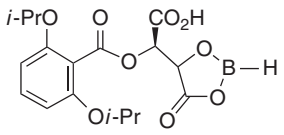
Fig. 2.2. Origin of facial selectivity in indolylmethyloxazaborolidinone structure. Reproduced from *Tetrahedron: Asymmetry*, **9**, 357 (1998), by permission of Elsevier. (See also color insert.)

An oxazaborolidinone derived from valine is also an effective catalyst. In one case, the two enantiomeric catalysts were completely enantioselective for the newly formed center.[150]

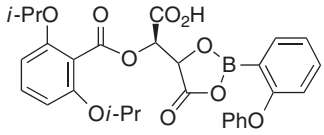


Another group of catalysts consist of cyclic borinates derived from tartaric acid. These compounds give good reactivity and enantioselectivity in Mukaiyama aldol reactions. Several structural variations such as **16** and **17** have been explored.[151]

150. S. Kiyooka, K. A. Shahid, F. Goto, M. Okazaki, and Y. Shuto, *J. Org. Chem.*, **68**, 7967 (2003).
151. K. Ishihara, T. Maruyama, M. Mouri, Q. Gao, K. Furuta, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **66**, 3483 (1993).

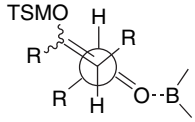


16

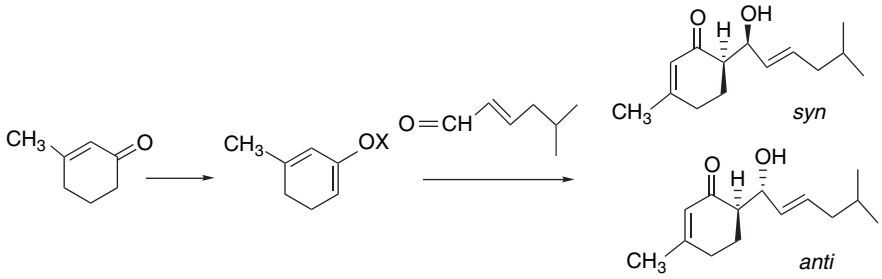


17

These catalysts are believed to function through an acyclic TS. In addition to the normal steric effects of the open TS, the facial selectivity is probably influenced by π stacking with the aryl ring and possibly hydrogen bonding by the formyl hydrogen.[152]



An interesting example of the use of this type of catalysis is a case in which the addition reaction of 3-methylcyclohex-2-enone to 5-methyl-2-hexenal was explored over a range of conditions. The reaction was investigated using both the lithium enolate and the trimethylsilyl enol ether. The yield and stereoselectivity are given for several sets of conditions.[153] Whereas the lithium enolate and achiral Lewis acids $TiCl_4$ and BF_3 gave moderate *anti* diastereoselectivity, the catalyst **17** induces good *syn* selectivity, as well as high enantioselectivity.

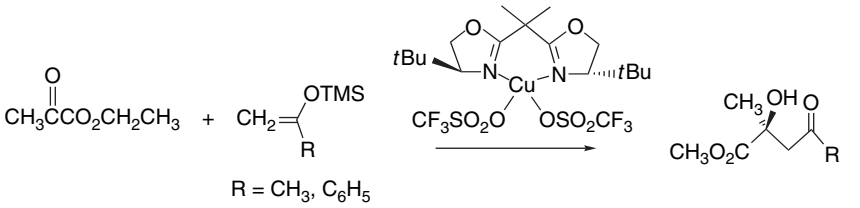


X	Conditions	Yield	*syn*	*anti*	e.e.
Li	(kinetic)	63	18	82	–
Li	(thermo)	66	55	45	–
TMS	$TiCl_4$	53	15	85	–
TMS	BF_3	68	25	75	–
TMS	Cat **16**	51	42	58	24(*R*)
TMS	Cat **17**	94	91	9	99(*R*)

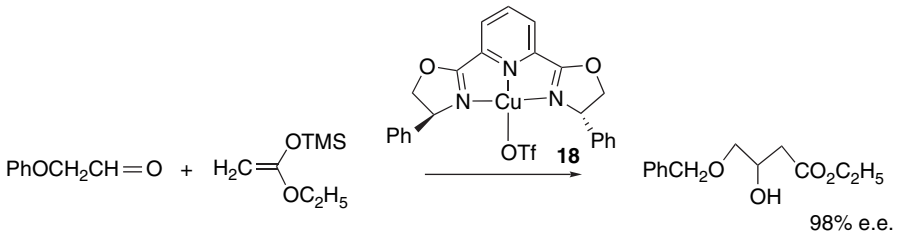
The lesson from this case is that reactions that are quite unselective under simple Lewis acid catalysis can become very selective with chiral catalysts. Moreover, as this particular case also shows, they can be very dependent on the specific structure of the catalyst.

152. K. Furuta, T. Maruyama, and H. Yamamoto, *J. Am. Chem. Soc.*, **113**, 1041 (1991); K. Ishihara, Q. Gao, and H. Yamamoto, *J. Am. Chem. Soc.*, **115**, 10412 (1993).
153. K. Takao, T. Tsujita, M. Hara, and K. Tadano, *J. Org. Chem.*, **67**, 6690 (2002).

Another effective group of catalysts is composed of copper *bis*-oxazolines.[154] The chirality is derived from the 4-substituents on the ring.

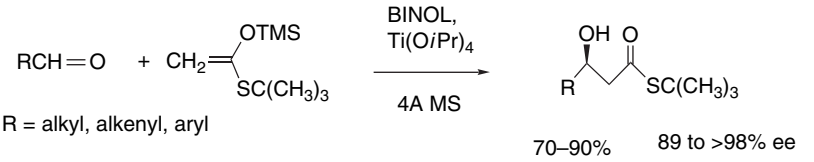


This and similar catalysts are effective with silyl ketene acetals and silyl thioketene acetals.[155] One of the examples is the tridentate pyridine-BOX-type catalyst **18**. The reactivity of this catalyst has been explored using α- and β-oxy substituted aldehydes.[154] α-Benzyloxyacetaldehyde was highly enantioselective and the α-trimethylsilyoxy derivative was weakly so (56% e.e.). Nonchelating aldehydes such as benzaldehyde and 3-phenylpropanal gave racemic product. 3-Benzyloxypropanal also gave racemic product, indicating that the β-oxy aldehydes do not chelate with this catalyst.



The Cu-BOX catalysts function as Lewis acids at the carbonyl oxygen. The chiral ligands promote facial selectivity, as shown in Figure 2.3.

Several catalysts based on Ti(IV) and BINOL have shown excellent enantioselectivity in Mukaiyama aldol reactions.[156] A catalyst prepared from a 1:1 mixture of BINOL and Ti(O-*i*-Pr)$_4$ gives good results with silyl thioketene acetals in ether, but is very solvent sensitive.[157]



The structure of the active catalyst and the mechanism of catalysis have not been completely defined. Several solid state complexes of BINOL and Ti(O-*i*-Pr)$_4$ have been characterized by X-ray crystallography.[158] Figure 2.4 shows the structures of complexes having the composition (BINOLate)Ti$_2$(O-*i*-Pr)$_6$ and (BINOLate)Ti$_3$(O-*i*-Pr)$_{10}$.

154. D. A. Evans, J. A. Murry, and M. C. Kozlowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996).
155. D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, **119**, 10859 (1997); D. A. Evans, M. C. Kozlowski, C. S. Burgey, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997).
156. S. Matsukawa and K. Mikami, *Tetrahedron: Asymmetry*, **6**, 2571 (1995); H. Matsunaga, Y. Yamada, T. Ide, T. Ishizuka, and T. Kunieda, *Tetrahedron: Asymmetry*, **10**, 3095 (1999).
157. G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.*, **117**, 2363 (1995).
158. T. J. Davis, J. Balsells, P. J. Carroll, and P. J. Walsh, *Org. Lett.*, **3**, 699 (2001).

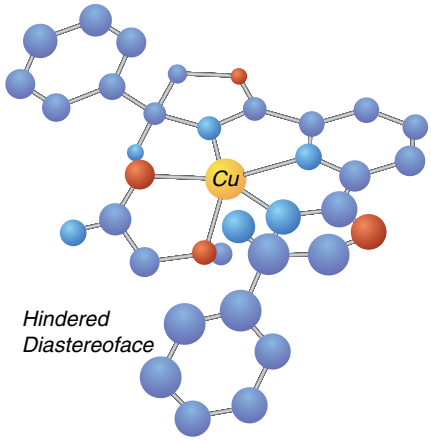
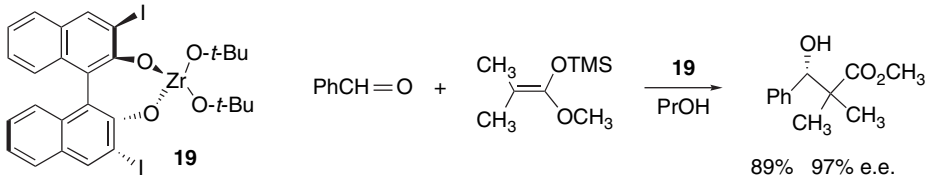


Fig. 2.3. Origin of facial selectivity of *bis*-oxazoline catalyst. Reproduced from *Tetrahedron: Asymmetry*, **9**, 357 (1998), by permission of Elsevier. (See also color insert.)

Halogenated BINOL derivatives of $Zr(O\text{-}t\text{-}Bu)_4$ such as **19** also give good yields and enantioselectivity.[159]



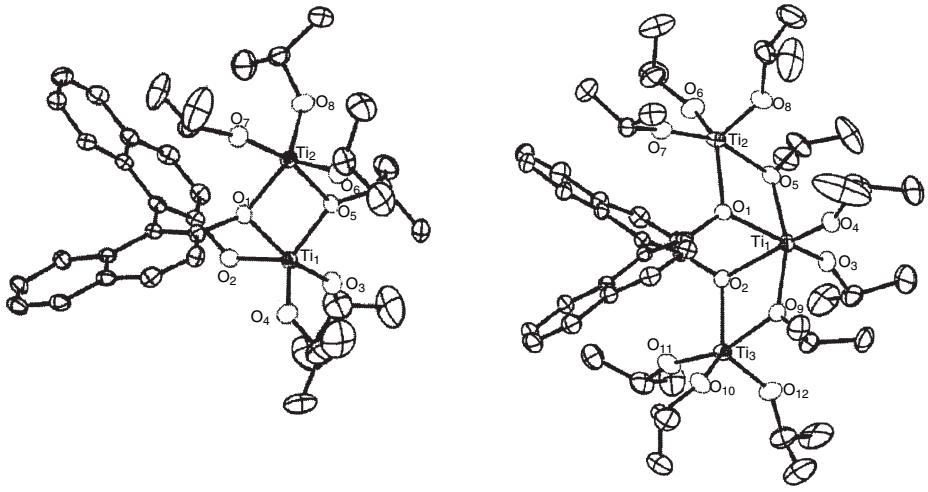
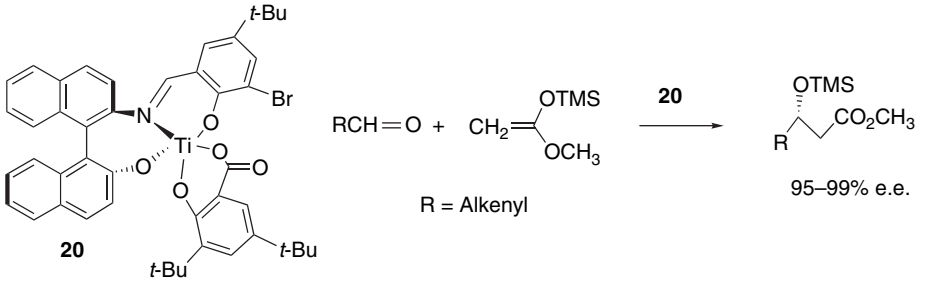


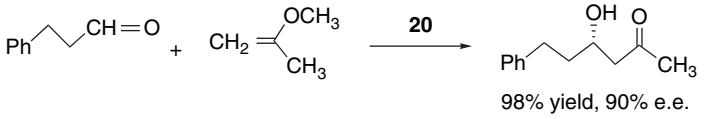
Fig. 2.4. Left: dinuclear complex of composition $(BINOLate)Ti_2(O\text{-}i\text{-}Pr)_6$. Right: trinuclear complex of composition $(BINOLate)Ti_3(O\text{-}i\text{-}Pr)_{10}$. Reproduced from *Org. Lett.*, **3**, 699 (2001), by permission of the American Chemical Society.

159. S. Kobayashi, H. Ishitani, Y. Yamashita, M. Ueno, and H. Shimizu, *Tetrahedron*, **57**, 861 (2001).

A titanium catalyst **20** that incorporates binaphthyl chirality along with imine and phenolic (salen) donors is highly active in addition of silyl ketene acetals to aldehydes.[160]

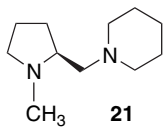


This catalyst is also active toward the simple enol ether 2-methoxypropene.[161]



Entry 6 in Scheme 2.9 is an example of the use of this catalyst in a multistep synthesis.

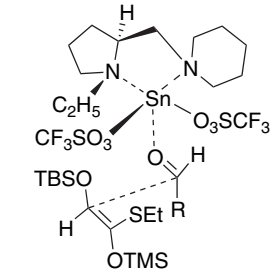
The enantioselectivity of Sn(II) enolate reactions can be controlled by chiral diamine additives. These reagents are particularly effective for silyl thioketene acetals.[162] Several diamines derived from proline have been explored and 1-methyl-2-(1-piperidinomethyl)pyrrolidine **21** is an example. Even higher enantioselectivity can be achieved by attachment of bicyclic amines to the pyrrolidinomethyl group.[163]



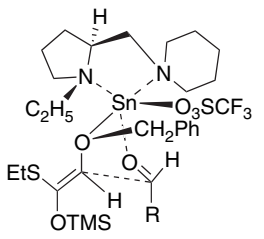
21

These reactions have been applied to α-benzyloxy and α-(*t*-butyldimethylsiloxy)-thioacetate esters.[164] The benzyloxy derivatives are *anti* selective, whereas the siloxy derivatives are *syn* selective. These differences are attributed to a chelated structure in the case of the benzyloxy derivative and an open TS for the siloxy system.

160. E. M. Carreira, R. A. Singer, and W. Lee, *J. Am. Chem. Soc.*, **116**, 8837 (1994).
161. E. M. Carreira, W. Lee, and R. A. Singer, *J. Am. Chem. Soc.*, **117**, 3649 (1995).
162. S. Kobayashi, H. Uchiro, Y. Fujishita, I. Shiina, and T. Mukaiyama, *J. Am. Chem. Soc.*, **113**, 4247 (1991); S. Kobayashi, H. Uchiro, I. Shiina, and T. Mukaiyama, *Tetrahedron*, **49**, 1761 (1993).
163. S. Kobayashi, M. Horibe, and M. Matsumura, *Synlett*, 675 (1995); S. Kobayashi and M. Horibe, *Chem. Eur. J.*, **3**, 1472 (1997).
164. T. Mukaiyama, I. Shiina, H. Uchiro, and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, **67**, 1708 (1994).

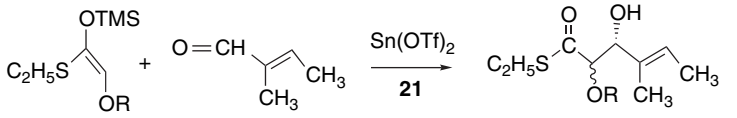


open TS leading to *syn* product



chelated TS leading to *anti* product

White and Deerberg explored this reaction system in connection with the synthesis of a portion of the structure of rapamycin.[165] Better yields were observed from benzyloxy than for a methoxy substituent, and there was a slight enhancement of stereoselectivity with the addition of ERG substituents to the benzyloxy group.



R	*syn:anti*	e.e.
CH_3O	70:30	87
$PhCH_2O$	85:15	93
PMB	90:10	96
2,4-DMB	95:5	92

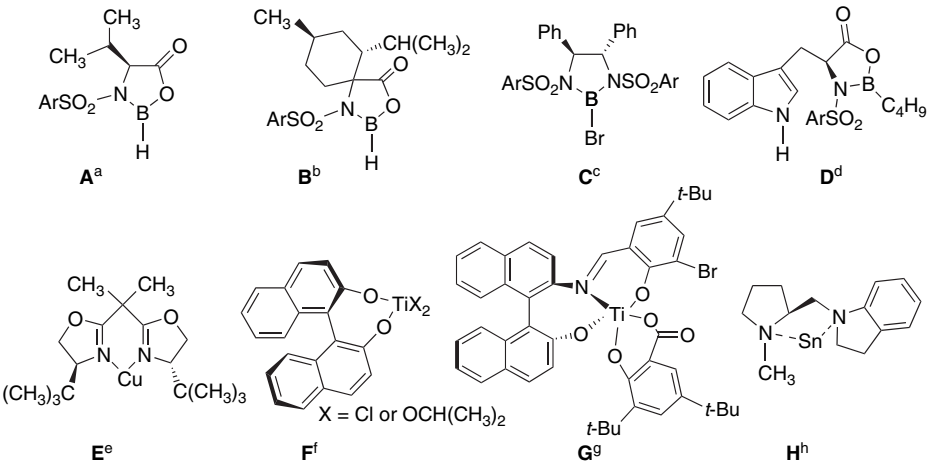
Scheme 2.8 gives some examples of chiral Lewis acids that have been used to catalyze aldol and Mukaiyama reactions.

Scheme 2.9 gives some examples of use of enantioselective catalysts. Entries 1 to 4 are cases of the use of the oxazaborolidinone-type of catalyst with silyl enol ethers and silyl ketene acetals. Entries 5 and 6 are examples of the use of BINOL-titanium catalysts, and Entry 7 illustrates the use of $Sn(OTf)_2$ in conjunction with a chiral amine ligand. The enantioselectivity in each of these cases is determined entirely by the catalyst because there are no stereocenters adjacent to the reaction sites in the reactants.

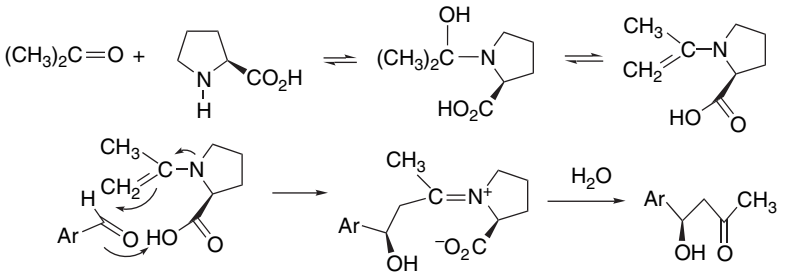
A different type of catalysis is observed using proline as a catalyst.[166] Proline promotes addition of acetone to aromatic aldehydes with 65–77% enantioselectivity. It has been suggested that the carboxylic acid functions as an intramolecular proton donor and promotes reaction through an enamine intermediate.

165. J. D. White and J. Deerberg, *Chem. Commun.*, 1919 (1997).
166. B. List, R. A. Lerner, and C. F. Barbas, III, *J. Am. Chem. Soc.*, **122**, 2395 (2000); B. List, L. Hoang, and H. J. Martin, *Proc. Natl. Acad. Sci., USA*, **101**, 5839 (2004).

Scheme 2.8. Chiral Catalysts for the Mukaiyama Aldol Reactions

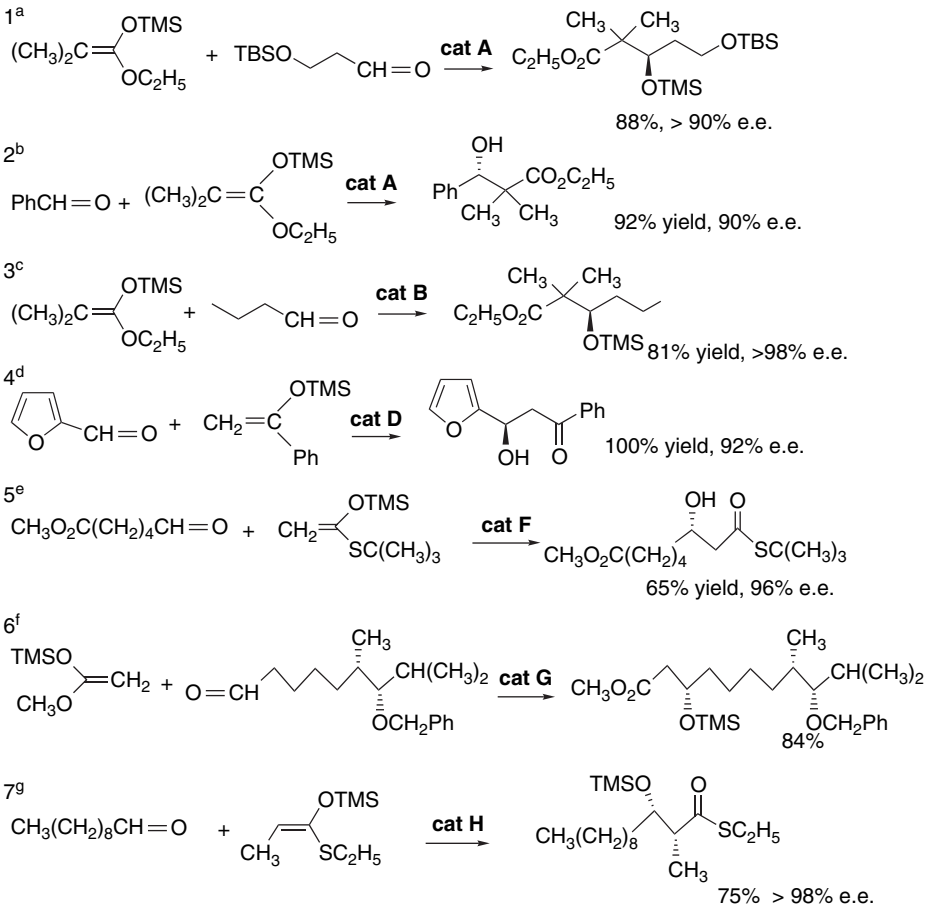


a. S. Kiyooka, Y. Kaneko, M. Komura, H. Matsuo, and M. Nakano, *J. Org. Chem.*, **56**, 2276 (1991).
b. E. R. Parmee, O. Tempkin, S. Masamune, and A. Abiko, *J. Am. Chem. Soc.*, **113**, 9365 (1991).
c. E. J. Corey, R. Imwinkelried, S. Pakul, and Y. B. Xiang, *J. Am. Chem. Soc.*, **111**, 5493 (1989).
d. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992); E. J. Corey, D. Barnes-Seeman, and T. W. Lee, *Tetrahedron Lett.*, **38**, 1699 (1997).
e. D. A. Evans, J. A. Murry, and M. C. Koslowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996); D. A. Evans, M. C. Koslowski, C. S. Burgey, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997); D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, **119**, 10859 (1997).
f. K. Mitami and S. Matsukawa, *J. Am. Chem. Soc.*, **115**, 7039 (1993); K. Mitami and S. Matsukawa, *J. Am. Chem. Soc.*, **116**, 4077 (1994); G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.*, **117**, 2363 (1995); G. E. Keck, X.-Y. Li, and D. Krishnamurthy, *J. Org. Chem.*, **60**, 5998 (1995).
g. E. M. Carreira, R. A. Singer, and W. Lee, *J. Am. Chem. Soc.*, **116**, 8837 (1994).
h. S. Kobayashi and M. Horibe, *Chem. Eur. J.*, **3**, 1472 (1997).



A DFT study found a corresponding TS to be the lowest energy.[167] This study also points to the importance of the solvent, DMSO, in stabilizing the charge buildup that occurs. A further computational study analyzed the stereoselectivity of the proline-catalyzed aldol addition reactions of cyclohexanone with acetaldehyde, isobutyraldehyde, and benzaldehyde on the basis of a similar TS.[168] Another study, which explored the role of proline in intramolecular aldol reactions, is discussed in the next section.[169]

167. K. N. Rankin, J. W. Gauld, and R. J. Boyd, *J. Phys. Chem. A*, **106**, 5155 (2002).
168. S. Bahmanyar, K. N. Houk, H. J. Martin, and B. List, *J. Am. Chem. Soc.*, **125**, 2475 (2003).
169. S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, **123**, 12911 (2001).



a. J. Mulzer, A. J. Mantoulidis, and E. Ohler, *Tetrahedron Lett.*, **39**, 8633 (1998).
b. S. Kiyooka, Y. Kaneko, and K. Kume, *Tetrahedron Lett.*, **33**, 4927 (1992).
c. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992).
d. E. R. Parmee, O. Tempkin, S. Masamune, and A. Abiko, *J. Am. Chem. Soc.*, **113**, 9365 (1991).
e. R. Zimmer, A. Peritz, R. Czerwonka, L. Schefzig, and H.-U. Reissig, *Eur. J. Org. Chem.*, 3419 (2002).
f. S. D. Rychnovsky, U. R. Khire, and G. Yang, *J. Am. Chem. Soc.*, **119**, 2058 (1997).
g. S. Kobayashi, H. Uchiro, I. Shiina, and T. Mukaiyama, *Tetrahedron*, **49**, 1761 (1993).

Visual models, additional information and exercises on Proline-Catalyzed Aldol Reactions can be found in the Digital Resource available at: Springer.com/carey-sundberg.

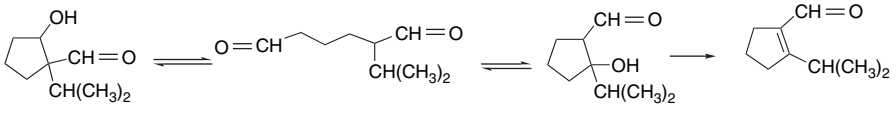
2.1.5.7. Summary of Facial Stereoselectivity in Aldol and Mukaiyama Reactions. The examples provided in this section show that there are several approaches to controlling the facial selectivity of aldol additions and related reactions. The *E*- or *Z*-configuration of the enolate and the open, cyclic, or chelated nature of the TS are the departure points for prediction and analysis of stereoselectivity. The Lewis acid catalyst and the donor strength of potentially chelating ligands affect the structure of the TS. Whereas dialkyl boron enolates and BF_3 complexes are tetracoordinate, titanium and tin can be

hexacoordinate. If the reactants are chiral, facial selectivity must be taken into account. Examples of steric, chelation, and polar effects on TS structure have been described. Chiral auxiliaries can influence facial selectivity not only by their inherent steric effects, but also on the basis of the conformation of their Lewis acid complexes. This can be controlled by the choice of the enolate metal and reaction conditions. Dialkylboron enolates react through a cyclic TS that cannot accommodate additional coordination. Titanium and tin enolates of oxazolidinones are chelated under normal conditions, but the use of excess Lewis acid can modify the TS structure and reverse facial selectivity. Chiral catalysts require that additional stereochemical features be taken into account, and the issue becomes the fit of the reactants within the chiral environment. Although most catalysts rely primarily on steric factors for facial selectivity, hydrogen bonding and π stacking can also come into play.

2.1.6. Intramolecular Aldol Reactions and the Robinson Annulation

The aldol reaction can be applied to dicarbonyl compounds in which the two groups are favorably disposed for intramolecular reaction. Kinetic studies on cyclization of 5-oxohexanal, 2,5-hexanedione, and 2,6-heptanedione indicate that formation of five-membered rings is thermodynamically somewhat more favorable than formation of six-membered rings, but that the latter is several thousand times faster.[170] A catalytic amount of acid or base is frequently satisfactory for formation of five- and six-membered rings, but with more complex structures, the techniques required for directed aldol condensations are used.

Scheme 2.10 illustrates intramolecular aldol condensations. Entries 1 and 2 are cases of formation of five-membered rings, with aldehyde groups serving as the electrophilic center. The regioselectivity in Entry 1 is due to the potential for dehydration of only one of the cyclic aldol adducts.



dehydration not available

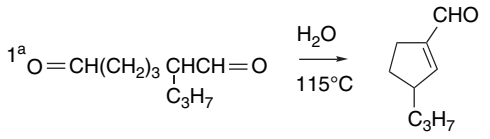
In Entry 2, the more reactive aldehyde group serves as the electrophilic component in preference to the ketone. Entries 3 to 6 are examples of construction of new rings in preexisting cyclic systems. The structure and stereochemistry of the products of these reactions are dictated by ring geometry and the proximity of reactive groups. Entry 5 is interesting in that it results in the formation of a bridgehead double bond. Entries 7 to 9 are intramolecular Mukaiyama reactions, using acetals as the precursor of the electrophilic center. Entry 9, which is a key step in the synthesis of jatrophones, involves formation of an eleven-membered ring. From a retrosynthetic perspective, bonds between a carbinol (or equivalent) carbon and a carbon that is α to a carbonyl carbon are candidates for formation by intramolecular aldol additions.

A particularly important example of the intramolecular aldol reaction is the *Robinson annulation*, a procedure that constructs a new six-membered ring from a ketone.[171] The reaction sequence starts with conjugate addition of the enolate to methyl

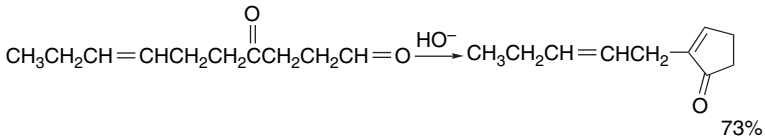
[170.] J. P. Guthrie and J. Guo, *J. Am. Chem. Soc.*, **118**, 11472 (1996).

Scheme 2.10. Intramolecular Aldol and Mukaiyama Aldol Reactions

1[a]

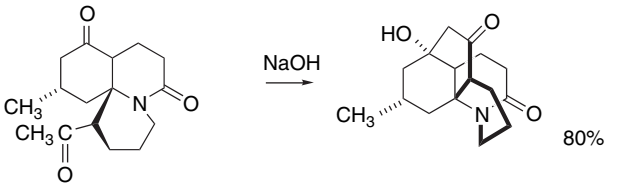


2[b]



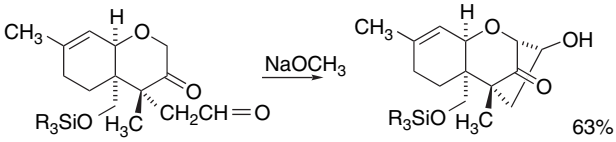
73%

3[c]



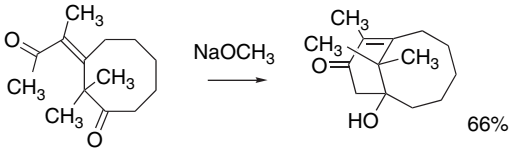
80%

4[d]



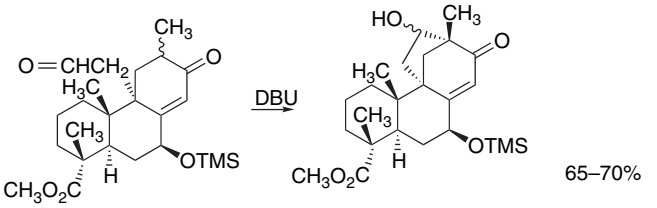
63%

5[e]



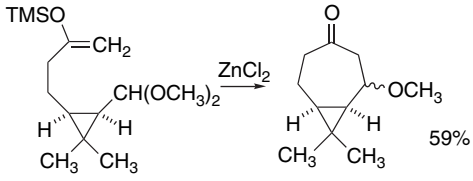
66%

6[f]



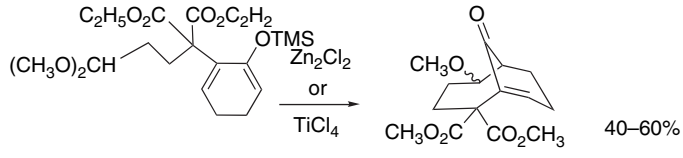
65–70%

7[g]



59%

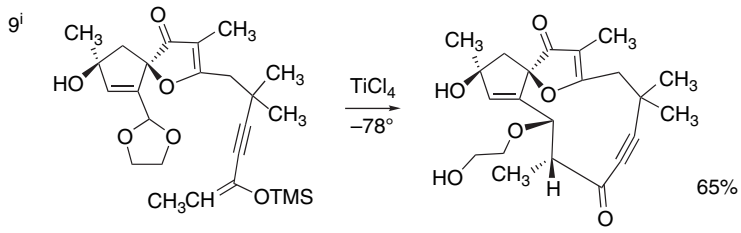
8[h]



40–60%

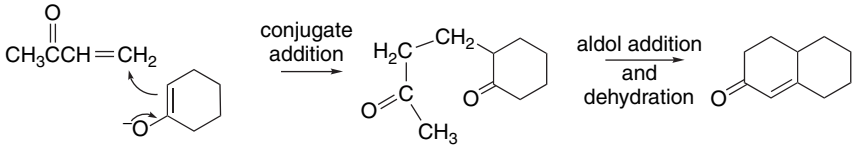
(*Continued*)

Scheme 2.10. (*Continued*)



a. J. English and G. W. Barber, *J. Am. Chem. Soc.*, **71**, 3310 (1949).
b. A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).
c. K. Wiesner, V. Musil, and K. J. Wiesner, *Tetrahedron Lett.*, 5643 (1968).
d. G. A. Kraus, B. Roth, K. Frazier, and M. Shimagaki, *J. Am. Chem. Soc.*, **104**, 1114 (1982).
e. K. Yamada, H. Iwadare, and T. Mukaiyama, *Chem. Pharm. Bull.*, **45**, 1898 (1997).
f. J. K. Tagat, M. S. Puar, and S. W. McCombie, *Tetrahedron Lett.*, **37**, 8463 (1996).
g. M. D. Taylor, G. Minaskanian, K. N. Winzenberg, P. Santone, and A. B. Smith, III, *J. Org. Chem.*, **47**, 3960 (1962).
h. A. Armstrong, T. J. Critchley, M. E. Gourdel-Martin, R. D. Kelsey, and A. A. Mortlock, *J. Chem. Soc., Perkin Trans. 1*, 1344 (2002).
i. A. B. Smith, III, A. T. Lupo, Jr., M. Ohba, and K. Chen, *J. Am. Chem. Soc.*, **111**, 6648 (1989).

vinyl ketone or a similar enone. This is followed by cyclization by an intramolecular aldol addition. Dehydration usually occurs to give a cyclohexenone derivative.



Other α,β-unsaturated enones can be used, but the reaction is somewhat sensitive to substitution at the β-carbon and adjustment of the reaction conditions is necessary.[172]

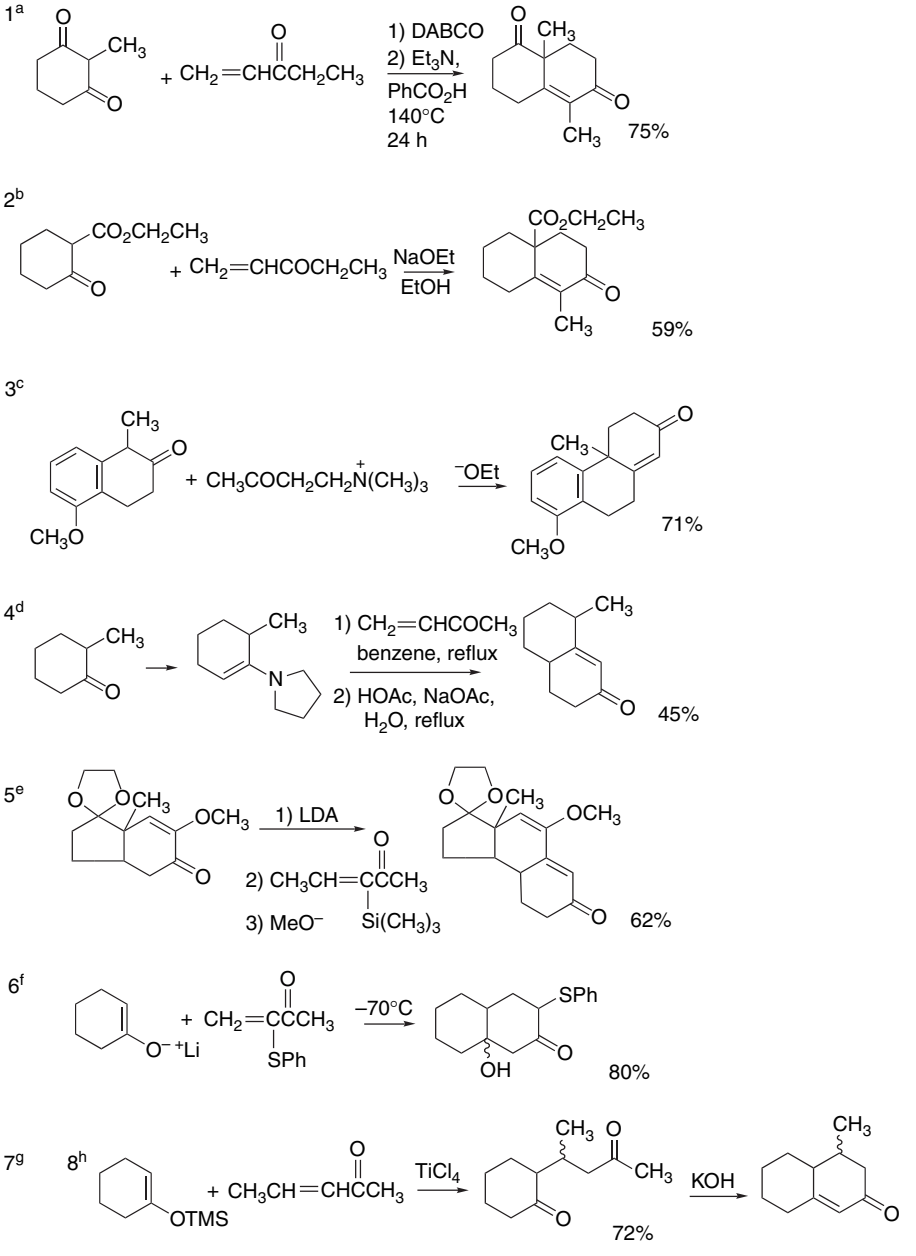
Scheme 2.11 shows some examples of Robinson annulation reactions. Entries 1 and 2 show annulation reactions of relatively acidic dicarbonyl compounds. Entry 3 is an example of use of 4-(trimethylammonio)-2-butanone as a precursor of methyl vinyl ketone. This compound generates methyl vinyl ketone in situ by β-elimination. The original conditions developed for the Robinson annulation reaction are such that the ketone enolate composition is under thermodynamic control. This usually results in the formation of product from the more stable enolate, as in Entry 3. The C(1) enolate is preferred because of the conjugation with the aromatic ring. For monosubstituted cyclohexanones, the cyclization usually occurs at the more-substituted position in hydroxylic solvents. The alternative regiochemistry can be achieved by using an enamine. Entry 4 is an example. As discussed in Section 1.9, the less-substituted enamine is favored, so addition occurs at the less-substituted position.

Conditions for kinetic control of enolate formation can be applied to the Robinson annulation to control the regiochemistry of the reaction. Entries 5 and 6 of Scheme 2.11 are cases in which the reaction is carried out on a preformed enolate. Kinetic

[171] E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1950); J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949); R. Gawley, *Synthesis*, 777 (1976); M. E. Jung, *Tetrahedron*, **32**, 3 (1976); B. P. Mundy, *J. Chem. Ed.*, **50**, 110 (1973).

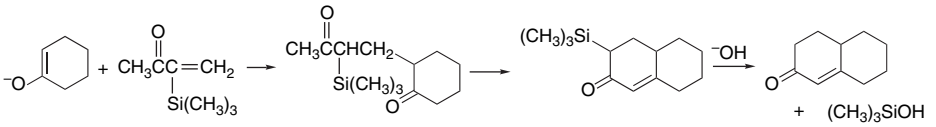
[172] C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.*, **93**, 1539 (1971).

Scheme 2.11. The Robinson Annulation Reaction



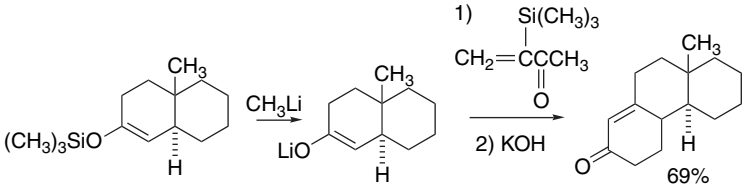
a. F. E. Ziegler, K.-J. Hwang, J. F. Kadow, S. I. Klein, U. K. Pati, and T.-F. Wang, *J. Org. Chem.*, **51**, 4573 (1986).
b. D. L. Snitman, R. J. Himmelsbach, and D. S. Watt, *J. Org. Chem.*, **43**, 4578 (1978).
c. J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).
d. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
e. G. Stork, J. D. Winkler, and C. S. Shiner, *J. Am. Chem. Soc.*, **104**, 3767 (1982).
f. K. Takaki, M. Okada, M. Yamada, and K. Negoro, *J. Org. Chem.*, **47**, 1200 (1982).
g. J. W. Huffman, S. M. Potnis, and A. V. Smith, *J. Org. Chem.*, **50**, 4266 (1985).

control is facilitated by use of somewhat more activated enones, such as methyl 1-(trimethylsilyl)vinyl ketone.



Ref. 173

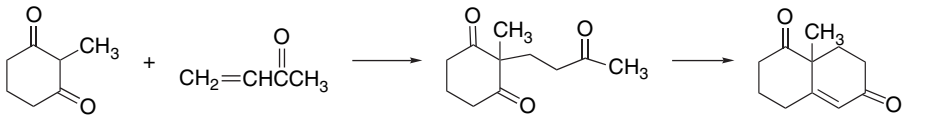
The role of the trimethylsilyl group is to stabilize the enolate formed in the conjugate addition. The silyl group is then removed during the dehydration step. Methyl 1-trimethylsilylvinyl ketone can be used under aprotic conditions that are compatible with regiospecific methods for enolate generation. The direction of annulation of unsymmetrical ketones can therefore be controlled by the method of enolate formation.



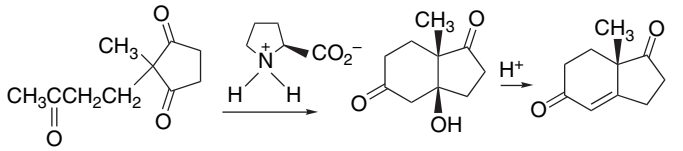
Ref. 174

Methyl 1-phenylthiovinyl ketones can also be used as enones in kinetically controlled Robinson annulation reactions, as illustrated by Entry 6. Entry 7 shows a annulation using silyl enol ether as the enolate equivalent. These reactions are called *Mukaiyama-Michael reactions* (see Section 2.6.3).

The Robinson annulation is a valuable method for preparing bicyclic and tricyclic structures that can serve as starting materials for the preparation of steroids and terpenes.[175] Reaction with 2-methylcyclohexan-1,3-dione gives a compound called the *Wieland-Miescher ketone*.



A similar reaction occurs with 2-methylcyclopentane-1,3-dione,[176] and can be done enantioselectively by using the amino acid L-proline to form an enamine intermediate. The (*S*)-enantiomer of the product is obtained in high enantiomeric excess.[177]



[173] G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973); G. Stork and J. Singh, *J. Am. Chem. Soc.*, **96**, 6181 (1974).

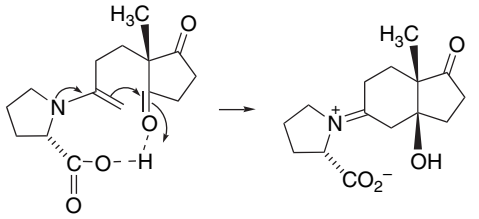
[174] R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **96**, 6179 (1974).

[175] N. Cohen, *Acc. Chem. Res.*, **9**, 412 (1976).

[176] Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **39**, 1615 (1974); U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem. Int. Ed. Engl.*, **10**, 496 (1971); Z. G. Hajos and D. R. Parrish, *Org. Synth.*, **63**, 26 (1985).

[177] J. Gutzwiller, P. Buchshacher, and A. Furst, *Synthesis*, 167 (1977); P. Buchshacher and A. Furst, *Org. Synth.*, **63**, 37 (1984); T. Bui and C. F. Barbas, III, *Tetrahedron Lett.*, **41**, 6951 (2000).

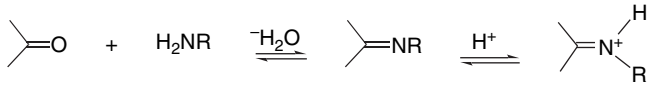
The detailed mechanism of this enantioselective transformation remains under investigation.[178] It is known that the acidic carboxylic group is crucial, and the cyclization is believed to occur via the enamine derived from the catalyst and the exocyclic ketone. A computational study suggested that the proton transfer occurs through a TS very similar to that described for the proline-catalyzed aldol reaction (see page 132).[179]



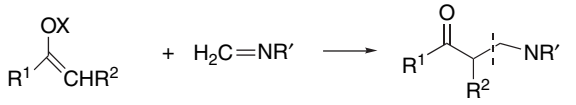
Visual models, additional information and exercises on Proline-Catalyzed Aldol Reactions can be found in the Digital Resource available at: Springer.com/carey-sundberg.

2.2. Addition Reactions of Imines and Iminium Ions

Imines and iminium ions are nitrogen analogs of carbonyl compounds and they undergo nucleophilic additions like those involved in aldol reactions. The reactivity order is C=NR < C=O < $[C{=}NR_2]^+$ < $[C{=}OH]^+$. Because iminium ions are more reactive than imines, the reactions are frequently run under mildly acidic conditions. Under some circumstances, the iminium ion can be the reactive species, even though it is a minor constituent in equilibrium with the amine, carbonyl compound, and unprotonated imine.



Addition of enols, enolates, or enolate equivalents to imines or iminium ions provides an important route to β-amino ketones.

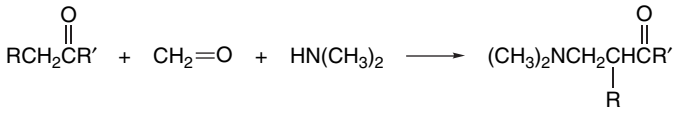


178. P. Buchschacher, J.-M. Cassal, A. Furst, and W. Meier, *Helv. Chim. Acta*, **60**, 2747 (1977); K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, and C. Kratky, *Helv. Chim. Acta*, **61**, 3108 (1978); C. Agami, F. Meynier, C. Puchot, J. Guilhem, and C. Pascard, *Tetrahedron*, **40**, 1031 (1984); C. Agami, J. Levisalles, and C. Puchot, *J. Chem. Soc., Chem. Commun.*, 441 (1985); C. Agami, *Bull. Soc. Chim. Fr.*, 499 (1988).

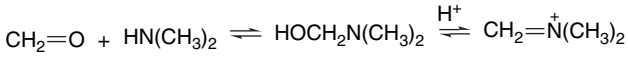
179. S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, **123**, 12911 (2001).

2.2.1. The Mannich Reaction

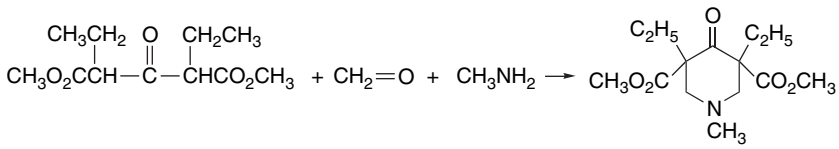
The *Mannich reaction* is the condensation of an enolizable carbonyl compound with an iminium ion.[180] It is usually done using formaldehyde and introduces an α-dialkylaminomethyl substituent.



The electrophile is often generated in situ from the amine and formaldehyde.



The reaction is normally limited to secondary amines, because dialkylation can occur with primary amines. The dialkylation reaction can be used to advantage in ring closures.



Ref. 181

Scheme 2.12 shows some representative Mannich reactions. Entries 1 and 2 show the preparation of typical "Mannich bases" from a ketone, formaldehyde, and a dialkylamine following the classical procedure. Alternatively, formaldehyde equivalents may be used, such as *bis*-(dimethylamino)methane in Entry 3. On treatment with trifluoroacetic acid, this aminal generates the iminium trifluoroacetate as a reactive electrophile. *N*,*N*-(Dimethyl)methylene ammonium iodide is commercially available and is known as *Eschenmoser's salt*.[182] This compound is sufficiently electrophilic to react directly with silyl enol ethers in neutral solution.[183] The reagent can be added to a solution of an enolate or enolate precursor, which permits the reaction to be carried out under nonacidic conditions. Entries 4 and 5 illustrate the preparation of Mannich bases using Eschenmoser's salt in reactions with preformed enolates.

The dialkylaminomethyl ketones formed in the Mannich reaction are useful synthetic intermediates.[184] Thermal elimination of the amines or the derived quaternary salts provides α-methylene carbonyl compounds.

180. F. F. Blicke, *Org. React.*, **1**, 303 (1942); J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 99 (1953); M. Tramontini and L. Angiolini, *Tetrahedron*, **46**, 1791 (1990); M. Tramontini and L. Angiolini, *Mannich Bases: Chemistry and Uses*, CRC Press, Boca Raton, FL, 1994; M. Ahrend, B. Westerman, and N. Risch, *Angew. Chem. Int. Ed. Engl.*, **37**, 1045 (1998).

181. C. Mannich and P. Schumann, *Chem. Ber.*, **69**, 2299 (1936).

182. J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.*, **10**, 330 (1971).

183. S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).

184. G. A. Gevorgyan, A. G. Agababyan, and O. L. Mndzhoyan, *Russ. Chem. Rev.* (Engl. Transl.), **54**, 495 (1985).

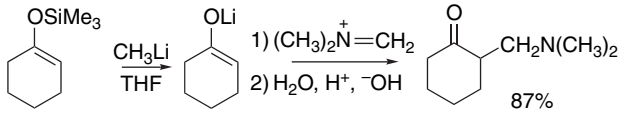
Scheme 2.12. Synthesis and Utilization of Mannich Bases

A. Aminomethylation Using the Mannich Reaction

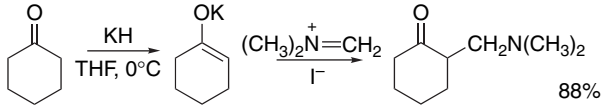
1[a] $PhCOCH_3 + CH_2O + (CH_3)_2\overset{+}{N}H_2Cl^- \longrightarrow PhCOCH_2CH_2\overset{H}{\overset{+}{N}}(CH_3)_2Cl^-$ 70%

2[b] $CH_3COCH_3 + CH_2O + (CH_3CH_2)_2\overset{+}{N}H_2Cl^- \longrightarrow CH_3COCH_2CH_2\overset{H}{\overset{+}{N}}(C_2H_5)_2Cl^-$ 66–75%

3[c] $(CH_3)_2CHCOCH_3 + [(CH_3)_2N]_2CH_2 \xrightarrow{CF_3CO_2H} (CH_3)_2CHCOCH_2CH_2N(CH_3)_2$

4[d] 

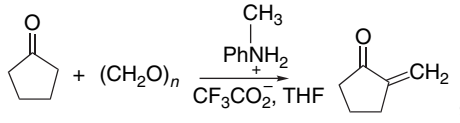
87%

5[e] 

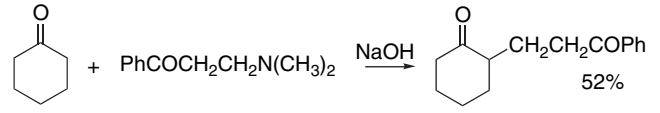
88%

B. Reactions Involving Secondary Transformations of Aminomethylation Products.

6[f] $CH_3CH_2CH_2CH{=}O + CH_2O + (\overset{+}{C}H_3)_2NH_2Cl^- \xrightarrow[2)\ \text{distill}]{1)\ 60°C,\ 6\ h} CH_2{=}C(CH_2CH_3)CH{=}O$ 73%

7[g] 

90%

8[h] 

52%

9[i] $PhCOCH_2CH_2N(CH_3)_2 + KCN \longrightarrow PhCOCH_2CH_2CN$ 67%

a. C. E. Maxwell, *Org. Synth.*, **III**, 305 (1955).
b. A. L. Wilds, R. M. Novak, and K. E. McCaleb, *Org. Synth*., **IV**, 281 (1963).
c. M. Gaudry, Y. Jasor, and T. B. Khac, *Org. Synth.*, **59**, 153 (1979).
d. S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).
e. J. L. Roberts, P. S. Borromeo, and C. D. Poulter, *Tetrahedron Lett.*, 1621 (1977).
f. C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Am. Chem. Soc.*, **70**, 1694 (1948).
g. J. L. Gras, *Tetrahedron Lett.*, 2111, 2955 (1978).
h. A. C. Cope and E. C. Hermann, *J. Am. Chem. Soc.*, **72**, 3405 (1950).
i. E. B. Knott, *J. Chem. Soc.*, 1190 (1947).

$$(CH_3)_2CHCH(CH_2N(CH_3)_2)CH{=}O \xrightarrow{\text{heat}} (CH_3)_2CHC(CH_2){=}CH{=}O$$

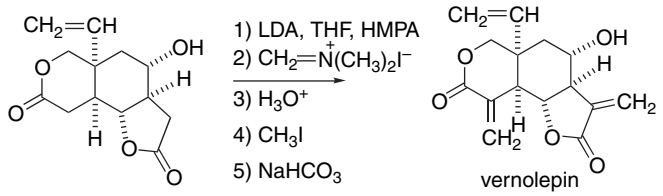
Ref. 185

These α,β-unsaturated ketones and aldehydes are used as reactants in conjugate additions (Section 2.6), Robinson annulations (Section 2.1.4), and in a number of other reactions that we will encounter later. Entries 8 and 9 in Scheme 2.12 illustrate

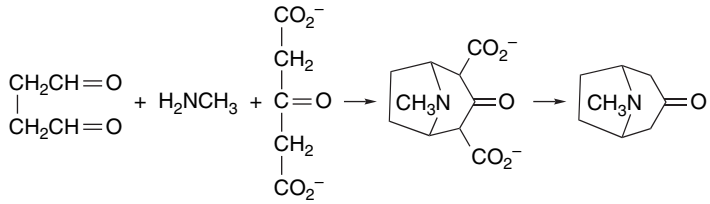
185. C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Am. Chem. Soc.*, **70**, 1694 (1948).

conjugate addition reactions carried out by in situ generation of α,β-unsaturated carbonyl compounds from Mannich bases.

α-Methylenelactones are present in a number of natural products.[186] The reaction of ester enolates with *N*,*N*-(dimethyl)methyleneammonium trifluoroacetate,[187] or Eschenmoser's salt,[188] has been used for introduction of the α-methylene group in the synthesis of vernolepin, a compound with antileukemic activity.[189,190]



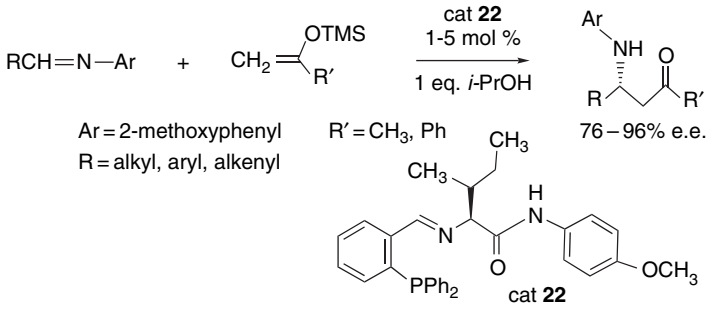
Mannich reactions, or a mechanistic analog, are important in the biosynthesis of many nitrogen-containing natural products. As a result, the Mannich reaction has played an important role in the synthesis of such compounds, especially in syntheses patterned after the biosynthesis, i.e., *biomimetic synthesis*. The earliest example of the use of the Mannich reaction in this way was Sir Robert Robinson's successful synthesis of tropinone, a derivative of the alkaloid tropine, in 1917.



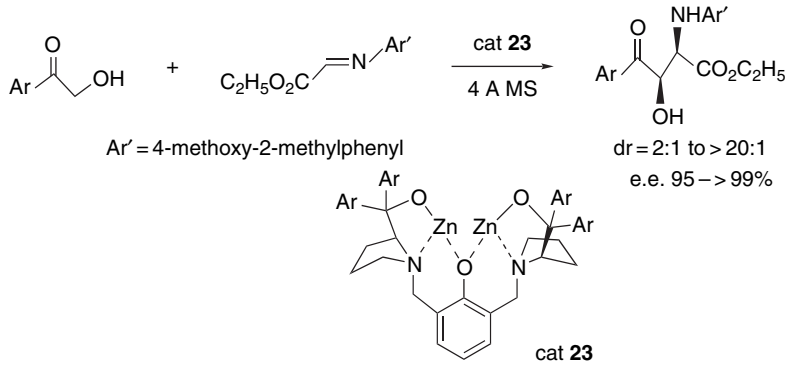
Ref. 191

As with aldol and Mukaiyama addition reactions, the Mannich reaction is subject to enantioselective catalysis.[192] A catalyst consisting of Ag^+ and the chiral imino aryl phosphine **22** achieves high levels of enantioselectivity with a range of *N*-(2-methoxyphenyl)imines.[193] The 2-methoxyphenyl group is evidently involved in an interaction with the catalyst and enhances enantioselectivity relative to other *N*-aryl substituents. The isopropanol serves as a proton source and as the ultimate acceptor of the trimethylsilyl group.

186. S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
187. N. L. Holy and Y. F. Wang, *J. Am. Chem. Soc.*, **99**, 499 (1977).
188. J. L. Roberts, P. S. Borromes, and C. D. Poulter, *Tetrahedron Lett.*, 1621 (1977).
189. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc.*, **99**, 6066 (1977).
190. For reviews of methods for the synthesis of α-methylene lactones, see R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synth. Comm.*, **5**, 245 (1975); J. C. Sarma and R. P. Sharma, *Heterocycles*, **24**, 441 (1986); N. Petragnani, H. M. C. Ferraz, and G. V. J. Silva, *Synthesis*, 157 (1986).
191. R. Robinson, *J. Chem. Soc.*, 762 (1917).
192. A. Cordova, *Acc. Chem. Res.*, **37**, 102 (2004).
193. N. S. Josephsohn, M. L. Snapper, and A. H. Hoveyda, *J. Am. Chem. Soc.*, **126**, 3734 (2004).

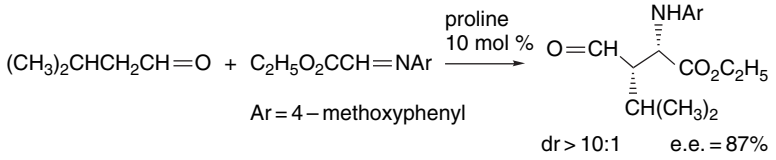


A zinc catalyst **23** was found effective for aryl hydroxymethyl ketones in reactions with glyoxylic imines. In this case, the 4-methoxy-2-methylphenylimines gave the best results.[194] Interestingly, the 2-methoxyphenyl ketone gave substantially enhanced 2,3-diastereoselectivity (20:1) compared to about 10:1 for most other aryl groups, suggesting that the *o*-methoxy group may introduce an additional interaction with the catalyst. All the compounds gave e.e. > 95%.



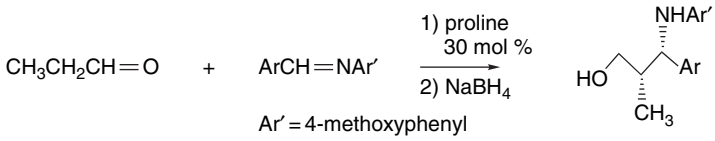
Other types of catalysts that are active in Mannich reactions include the Cu-*bis*-oxazolines.[195] Most of the cases examined to date are for relatively reactive imines, such as those derived from glyoxylate or pyruvate esters.

As already discussed for aldol and Robinson annulation reactions, proline is also a catalyst for enantioselective Mannich reactions. Proline effectively catalyzes the reactions of aldehydes such as 3-methylbutanal and hexanal with *N*-arylimines of ethyl glyoxalate.[196] These reactions show 2,3-*syn* selectivity, although the products with small alkyl groups tend to isomerize to the *anti* isomer.

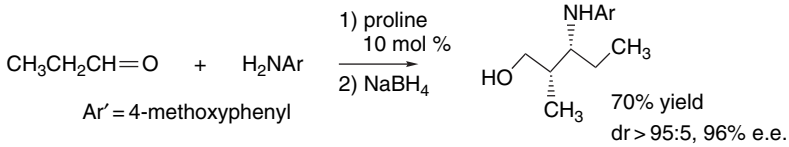


194. B. M. Trost and L. M. Terrell, *J. Am. Chem. Soc.*, **125**, 338 (2003).
195. K. Juhl and K. A. Jorgensen, *J. Am. Chem. Soc.*, **124**, 2420 (2002); M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, and K. A. Jorgensen, *Chem. Eur. J.*, **9**, 2359 (2003).
196. W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, and C. F. Barbas, III, *J. Org. Chem.*, **68**, 9624 (2003).

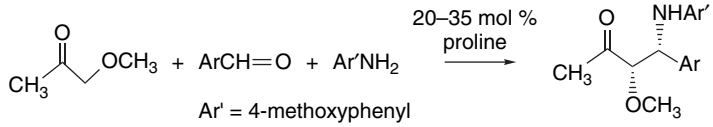
With aromatic aldehydes, d.r. ranged up to more than 10:1 for propanal.



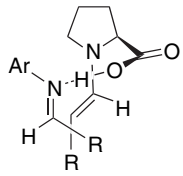
The proline-catalyzed reaction has been extend to the reaction of propanal, butanal, and pentanal with a number of aromatic aldehydes and proceeds with high *syn* selectivity.[197] The reaction can also be carried out under conditions in which the imine is formed in situ. Under these conditions, the conjugative stabilization of the aryl imines leads to the preference for the aryl imine to act as the electrophile. A good yield of the expected β-aminoalcohol was obtained with propanal serving as both the nucleophilic and the electrophilic component. The product was isolated as a γ-amino alcohol after reduction with $NaBH_4$.



Ketones such as acetone, hydroxyacetone, and methoxyacetone can be condensed with both aromatic and aliphatic aldehydes.[198]

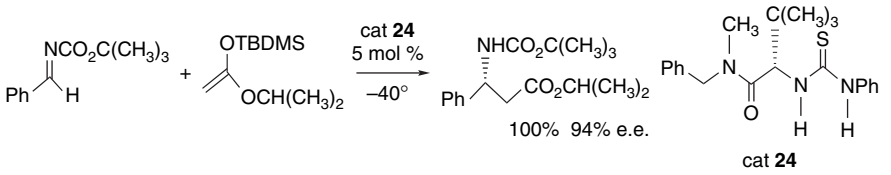


The TS proposed for these proline-catalyzed reactions is very similar to that for the proline-catalyzed aldol addition (see p. 132). In the case of imines, however, the aldehyde substituent is directed *toward* the enamine double bond because of the dominant steric effect of the *N*-aryl substituent. This leads to formation of *syn* isomers, whereas the aldol reaction leads to *anti* isomers. This is the TS found to be the most stable by B3LYP/6-31G* computations.[199] The proton transfer is essentially complete at the TS. As with the aldol addition TS, the enamine is oriented *anti* to the proline carboxy group in the most stable TS.



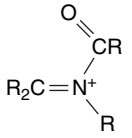
197. Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, and K. Sakai, *Angew. Chem. Int. Ed. Engl.*, **42**, 3677 (2003).
198. B. List, P. Pojarliev, W. T. Biller, and H. J. Martin, *J. Am. Chem. Soc.*, **124**, 827 (2002).
199. S. Bahmanyar and K. N. Houk, *Org. Lett.*, **5**, 1249 (2003).

Structure **24**, which is a simplification of an earlier catalyst,[200] gives excellent results with *N*-*t*-butoxycarbonylimines.[201] Catalysts of this type are thought to function through hydrogen-bonding interactions.

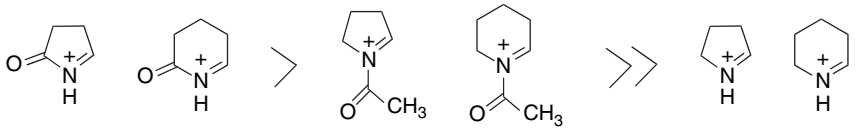


2.2.2. Additions to *N*-Acyl Iminium Ions

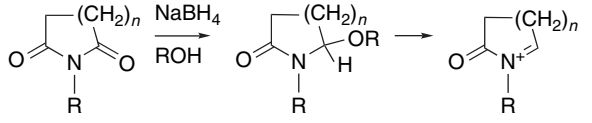
Even more reactive C=N bonds are present in *N-acyliminium ions*.[202]



Gas phase reactivity toward allyltrimethylsilane was used to compare the reactivity of several cyclic *N*-acyliminium ions and related iminium ions.[203] Compounds with endocyclic acyl groups were found to be more reactive than compounds with exocyclic acyl substituents. Five-membered ring compounds are somewhat more reactive than six-membered ones. The higher reactivity of the endocyclic acyl derivatives is believed to be due to geometric constraints that maximize the polar effect of the carbonyl group.



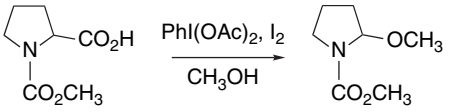
N-Acyliminium ions are usually prepared in situ in the presence of a potential nucleophile. There are several ways of generating acyliminium ions. Cyclic examples can be generated by partial reduction of imides.[204]



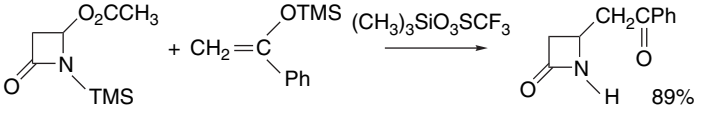
Various oxidations of amides or carbamates can also generate acyliminium ions. An electrochemical oxidation forms α-alkoxy amides and lactams, which then generate

200. P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.*, **124**, 10012 (2002).
201. A. G. Wenzel, M. P. Lalonde, and E. N. Jacobsen, *Synlett*, 1919 (2003).
202. H. Hiemstra and W. N. Speckamp, in *Comprehensive Organic Synthesis*, Vol. 2, B. Trost and I. Fleming, eds., 1991, pp. 1047–1082; W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, **56**, 3817 (2000); B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, and C. A. Maryanoff, *Chem. Rev.*, **104**, 1431 (2004).
203. M. G. M. D'Oca, L. A. B. Moraes, R. A. Pilli, and M. N. Eberlin, *J. Org. Chem.*, **66**, 3854 (2001).
204. J. C. Hubert, J. B. P. A. Wijnberg, and W. Speckamp, *Tetrahedron*, **31**, 1437 (1975); H. Hiemstra, W. J. Klaver, and W. N. Speckamp, *J. Org. Chem.*, **49**, 1149 (1984); P. A. Pilli, L. C. Dias, and A. O. Maldaner, *J. Org. Chem.*, **60**, 717 (1995).

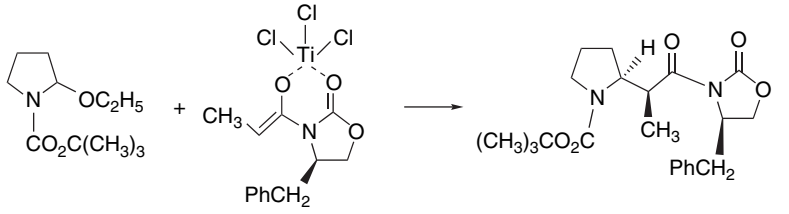
acyliminium ions.[205] *N*-Acyliminium ions can also be obtained by oxidative decarboxylation of *N*-acyl-α-amino acids such as *N*-acyl proline derivatives.[206]



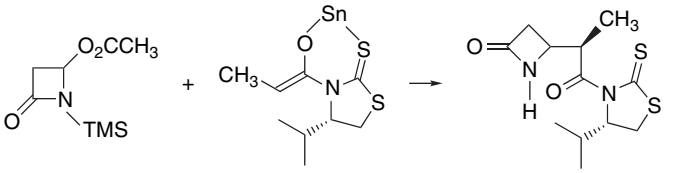
Acyliminium ions are sufficiently electrophilic to react with enolate equivalents such as silyl enol ethers[207] and isopropenyl acetate.[208]



Acyliminium ions can be used in enantioselective additions with enolates having chiral auxiliaries, such as *N*-acyloxazolidinones or *N*-acylthiazolidinethiones.



Ref. 209



Ref. 210

205. T. Shono, H. Hamaguchi, and Y. Matsumura, *J. Am. Chem. Soc.*, **97**, 4264 (1975); T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa, and T. Aoki, *J. Am. Chem. Soc.*, **104**, 6697 (1982); T. Shono, *Tetrahedron*, **40**, 811 (1984).

206. A. Boto, R. Hernandez, and E. Suarez, *J. Org. Chem.*, **65**, 4930 (2000).

207. R. P. Attrill, A. G. M. Barrett, P. Quayle, J. van der Westhuizen, and M. J. Betts, *J. Org. Chem.*, **49,** 1679 (1984); K. T. Wanner, A. Kartner, and E. Wadenstorfer, *Heterocycles*, **27**, 2549 (1988); M. A. Ciufolini, C. W. Hermann, K. H. Whitmire, and N. E. Byrne, *J. Am. Chem. Soc.*, **111**, 3473 (1989); D. S. Brown, M. J. Earle, R. A. Fairhurst, H. Heaney, G. Papageorgiou, R. F. Wilkins, and S. C. Eyley, *Synlett*, 619 (1990).

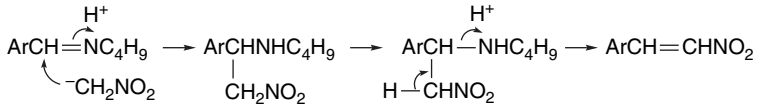
208. T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, **103**, 1172 (1981).

209. R. A. Pilli and D. Russowsky, *J. Org. Chem.*, **61**, 3187 (1996); R. A. Pilli, C. de F. Alves, M. A. Boeckelmann, Y. P. Mascarenhas, J. G. Nery, and I. Vencato, *Tetrahedron Lett.*, **40**, 2891 (1999).

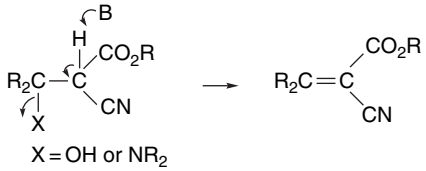
210. Y. Nagao, T. Kumagi, S. Tamai, T. Abe, Y. Kuramoto, T. Taga, S. Aoyagi, Y. Nagase, M. Ochiai, Y. Inoue, and E. Fujita, *J. Am. Chem. Soc.*, **108**, 4673 (1986); T. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J. Org. Chem.*, **55**, 1148 (1990).

2.2.3. Amine-Catalyzed Condensation Reactions

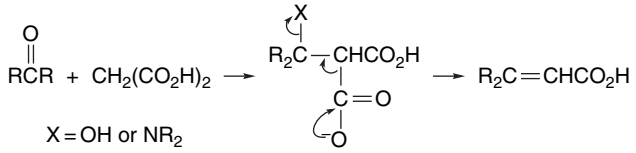
Iminium ions are intermediates in a group of reactions that form α,β-unsaturated compounds having structures corresponding to those formed by mixed aldol addition followed by dehydration. These reactions are catalyzed by amines or buffer systems containing an amine and an acid and are referred to as *Knoevenagel condensations*.[211] The reactive electrophile is probably the protonated form of the imine, since it is a more reactive electrophile than the corresponding carbonyl compound.[212]



The carbon nucleophiles in amine-catalyzed reaction conditions are usually rather acidic compounds containing two EWG substituents. Malonate esters, cyanoacetate esters, and cyanoacetamide are examples of compounds that undergo condensation reactions under Knoevenagel conditions.[213] Nitroalkanes are also effective as nucleophilic reactants. The single nitro group activates the α-hydrogens enough to permit deprotonation under the weakly basic conditions. A relatively acidic proton in the nucleophile is important for two reasons. First, it permits weak bases, such as amines, to provide a sufficient concentration of the enolate for reaction. An acidic proton also facilitates the elimination step that drives the reaction to completion. Usually the product that is isolated is the α,β-unsaturated derivative of the original adduct.



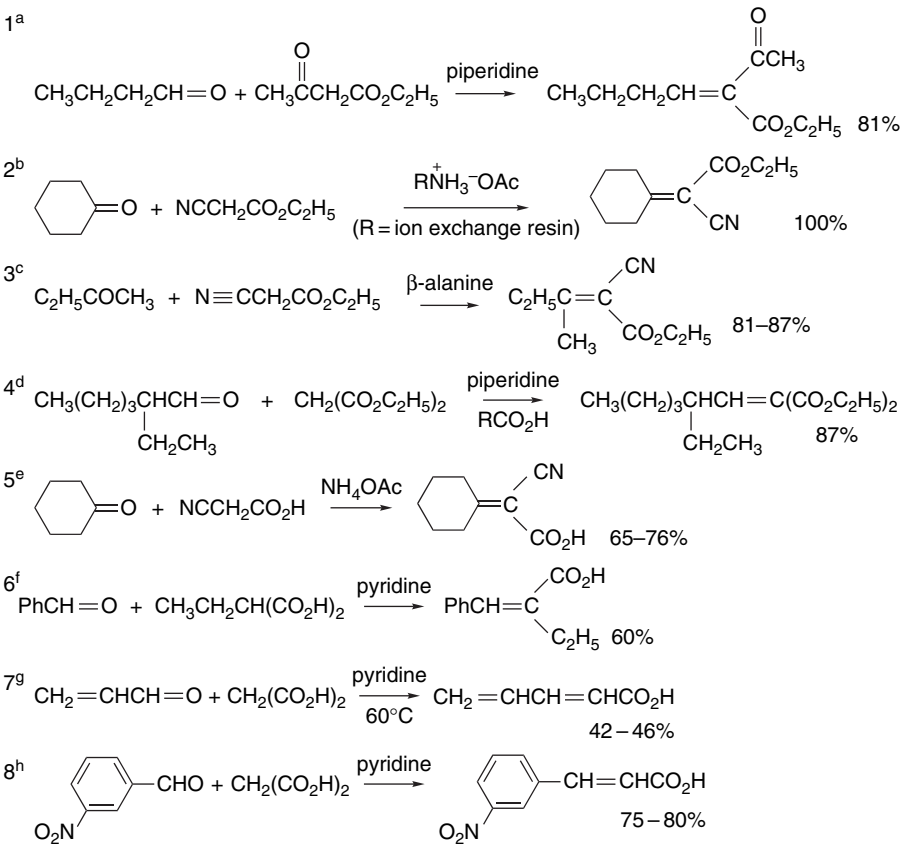
Malonic acid or cyanoacetic acid can also be used as the nucleophile. With malonic acid or cyanoacetic acid as reactants, the products usually undergo decarboxylation. This may occur as a concerted fragmentation of the adduct.[214]



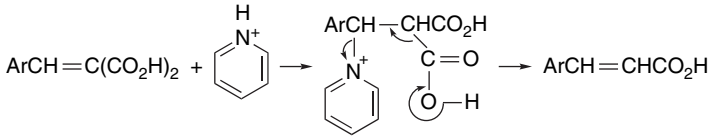
Decarboxylative condensations of this type are sometimes carried out in pyridine, which cannot form an imine intermediate, but has been shown to catalyze the decarboxylation of arylidene malonic acids.[215] The decarboxylation occurs by concerted decomposition of the adduct of pyridine to the α,β-unsaturated diacid.

211. G. Jones, *Org. React.*, **15**, 204 (1967); R. L. Reeves, in *The Chemistry of the Carbonyl Group*, S. Patai, ed., Interscience, New York, 1966, pp. 593–599.
212. T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953).
213. A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
214. E. J. Corey, *J. Am. Chem. Soc.*, **74**, 5897 (1952).
215. E. J. Corey and G. Fraenkel, *J. Am. Chem. Soc.*, **75**, 1168 (1953).

Scheme 2.13. Amine-Catalyzed Condensation Reactions of the Knoevenagel Type



a. A. C. Cope and C. M. Hofmann, *J. Am. Chem. Soc.*, **63**, 3456 (1941).
b. R. W. Hein, M. J. Astle, and J. R. Shelton, *J. Org. Chem.*, **26**, 4874 (1961).
c. F. S Prout, R. J. Harman, E. P.-Y. Huang, C. J. Korpics, and G. R. Tichelaar, *Org. Synth.*, **IV**, 93 (1963).
d. E. F. Pratt and E. Werbie, *J. Am. Chem. Soc.*, **72**, 4638 (1950).
e. A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, *Org. Synth.*, **IV**, 234 (1963).
f. W. J. Gensler and E. Berman, *J. Am. Chem. Soc.*, **80**, 4949 (1958).
g. P. J. Jessup, C. B. Petty, J. Roos, and L. E. Overman, *Org. Synth.*, **59**, 1 (1979).
h. R. H. Wiley and N. R. Smith, *Org. Synth.*, **IV**, 731 (1963).

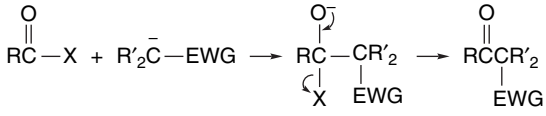


Scheme 2.13 gives some examples of Knoevenagel condensation reactions.

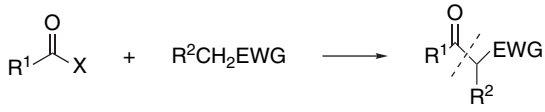
2.3. Acylation of Carbon Nucleophiles

The reactions that are discussed in this section involve addition of carbon nucleophiles to carbonyl centers having a potential leaving group. The tetrahedral intermediate formed in the addition step reacts by expulsion of the leaving group. The overall

transformation results in the *acylation* of the carbon nucleophile. This transformation corresponds to the general reaction Path **B**, as specified at the beginning of this chapter (p. 64).

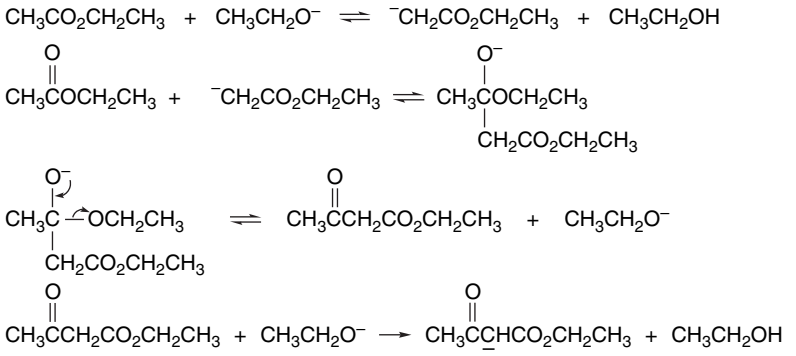


The reaction pattern can be used for the synthesis of 1,3-dicarbonyl compounds and other systems in which an acyl group is β to an anion-stabilizing group.



2.3.1. Claisen and Dieckmann Condensation Reactions

An important group of acylation reactions involves esters, in which case the leaving group is alkoxy or aryloxy. The self-condensation of esters is known as the *Claisen condensation*.[216] Ethyl acetoacetate, for example, is prepared by Claisen condensation of ethyl acetate. All of the steps in the mechanism are reversible, and a full equivalent of base is needed to bring the reaction to completion. Ethyl acetoacetate is more acidic than any of the other species present and is converted to its conjugate base in the final step. The β-ketoester product is obtained after neutralization.



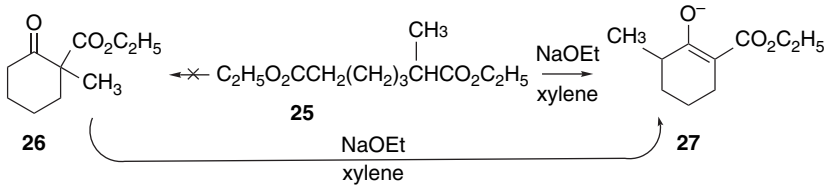
As a practical matter, the alkoxide used as the base must be the same as the alcohol portion of the ester to prevent product mixtures resulting from ester interchange. Sodium hydride with a small amount of alcohol is frequently used as the base for ester condensation. The reactive base is the sodium alkoxide formed by reaction of sodium hydride with the alcohol released in the condensation.

As the final proton transfer cannot occur when α-substituted esters are used, such compounds do not condense under the normal reaction conditions, but this limitation

[216] C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, **1**, 266 (1942).

can be overcome by use of a very strong base that converts the reactant ester completely to its enolate. Entry 2 of Scheme 2.14 illustrates the use of triphenylmethylsodium for this purpose. The sodium alkoxide is also the active catalyst in procedures that use sodium metal, such as in Entry 3 in Scheme 2.14. The alkoxide is formed by reaction of the alcohol that is formed as the reaction proceeds.

The intramolecular version of ester condensation is called the *Dieckmann condensation*.[217] It is an important method for the formation of five- and six-membered rings and has occasionally been used for formation of larger rings. As ester condensation is reversible, product structure is governed by thermodynamic control, and in situations where more than one product can be formed, the product is derived from the most stable enolate. An example of this effect is the cyclization of the diester **25**.[218] Only **27** is formed, because **26** cannot be converted to a stable enolate. If **26**, synthesized by another method, is subjected to the conditions of the cyclization, it is isomerized to **27** by the reversible condensation mechanism.



Entries 3 to 8 in Scheme 2.14 are examples of Dieckmann condensations. Entry 6 is a Dieckmann reaction carried out under conventional conditions, followed by decarboxylation. The product is a starting material for the synthesis of a number of sarpagine-type indole alkaloids and can be carried out on a 100-g scale. The combination of a Lewis acid, such as $MgCl_2$, with an amine can also promote Dieckmann cyclization.[219] Entry 7, which shows an application of these conditions, is a step in the synthesis of a potential drug. These conditions were chosen to avoid the use of $TiCl_4$ in a scale-up synthesis and can be done on a 60-kg scale. The 14-membered ring formation in Entry 8 was carried out under high dilution by slowly adding the reactant to the solution of the NaHMDS base. The product is a mixture of both possible regioisomers (both the 5- and 7-carbomethoxy derivatives are formed) but a single product is obtained after decarboxylation.

Mixed condensations of esters are subject to the same general restrictions as outlined for mixed aldol reactions (Section 2.1.2). One reactant must act preferentially as the acceptor and another as the nucleophile for good yields to be obtained. Combinations that work best involve one ester that cannot form an enolate but is relatively reactive as an electrophile. Esters of aromatic acids, formic acid, and oxalic acid are especially useful. Some examples of mixed ester condensations are shown in Section C of Scheme 2.14. Entries 9 and 10 show diethyl oxalate as the acceptor, and aromatic esters function as acceptors in Entries 11 and 12.

2.3.2. Acylation of Enolates and Other Carbon Nucleophiles

Acylation of carbon nucleophiles can also be carried out with more reactive acylating agents such as acid anhydrides and acyl chlorides. These reactions must

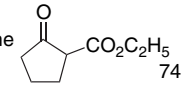
217. J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 1 (1967).
218. N. S. Vul'fson and V. I. Zaretskii, *J. Gen. Chem. USSR*, **29**, 2704 (1959).
219. S. Tamai, H. Ushitogochi, S. Sano, and Y. Nagao, *Chem. Lett.*, 295 (1995).

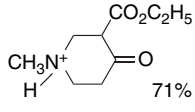
A. Intermolecular ester condensations

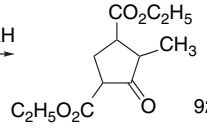
1[a] $CH_3(CH_2)_3CO_2C_2H_5 \xrightarrow{NaOEt} CH_3(CH_2)_3COCHCO_2C_2H_5$ (CH$_2$CH$_2$CH$_3$) 77%

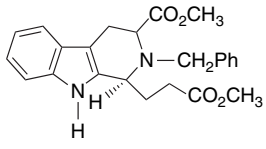
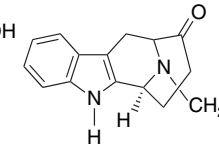
2[b] $CH_3CH_2CHCO_2C_2H_5$ (CH$_3$) $\xrightarrow{Ph_3C^-\ Na^+}$ $CH_3CH_2CHC(=O)-CCO_2C_2H_5$ (CH$_2$CH$_3$; CH$_3$; CH$_3$) 63%

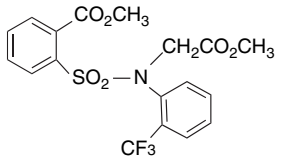
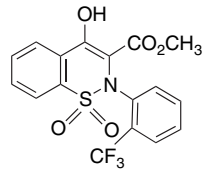
B. Cyclization of diesters

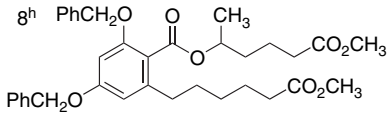
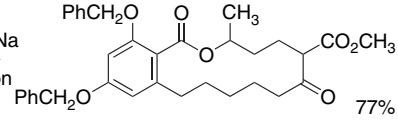
3[c] $C_2H_5O_2C(CH_2)_4CO_2C_2H_5 \xrightarrow{Na,\ toluene}$  74–81%

4[d] $CH_3-N(CH_2CH_2CO_2C_2H_5)_2 \xrightarrow[benzene]{NaOEt} \xrightarrow{HCl}$  71%

5[e] $C_2H_5O_2CCH_2CH_2CH(CO_2C_2H_5)CHCH_3$ (CH$_3$) $\xrightarrow{NaH}$  92%

6[f]  $\xrightarrow[2)\ HCl,\ H_2O,\ CH_3CO_2H]{1)\ NaH,\ CH_3OH,\ toluene}$  85%

7[g]  $\xrightarrow[DBU]{MgCl_2}$  90%

8[h]  $\xrightarrow[dilute\ solution]{[(CH_3)_3Si]_2NNa}$  77%

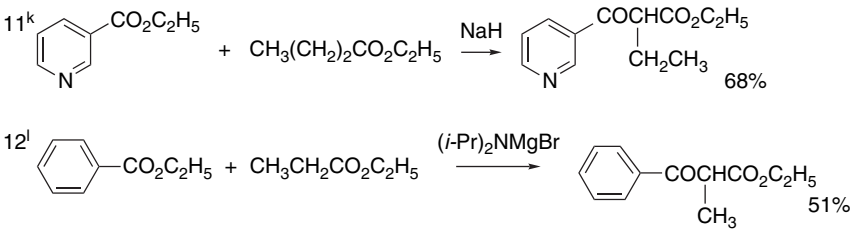
C. Mixed ester condensations

9[i] $(CH_2CO_2C_2H_5)_2 + (CO_2C_2H_5)_2 \xrightarrow{NaOEt}$ $CH(COCO_2C_2H_5)(CO_2C_2H_5)(CH_2CO_2C_2H_5)$ 86–91%

10[j] $C_{17}H_{35}CO_2C_2H_5 + (CO_2C_2H_5)_2 \xrightarrow{NaOEt}$ $C_{16}H_{33}CH(COCO_2C_2H_5)CO_2C_2H_5$ 68–71%

(*Continued*)

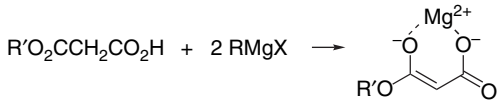
Scheme 2.14. (***Continued***)



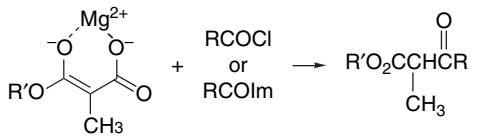
a. R. R. Briese and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1697 (1933).
b. B. E. Hudson, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **63**, 3156 (1941).
c. P. S. Pinkney, *Org. Synth.*, **II**, 116 (1943).
d. E. A. Prill and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933).
e. M. S. Newman and J. L. McPherson, *J. Org. Chem.*, **19**, 1717 (1954).
f. J. Yu, T. Wang, X. Liu, J. Deschamps, J. Flippen-Anderson, X. Liao, and J. M. Cook, *J. Org. Chem.*, **68**, 7565 (2003); P. Yu, T. Wang, J. Li, and J. M. Cook, *J. Org. Chem.*, **65**, 3173 (2000).
g. T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Karrick, J. L. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanninga, G. S. Risedorph, R. E. Seamans, R. Skeean, D. D. Winkle, and T. M. Zennie, *Org. Proc. Res. Develop.* **8**, 201 (2004).
h. R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38**, 390 (1973).
i. E. M. Bottorff and L. L. Moore, *Org. Synth.*, **44**, 67 (1964).
j. F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).
k. D. E. Floyd and S. E. Miller, *Org. Synth.*, **IV**, 141 (1963).
l. E. E. Royals and D. G. Turpin, *J. Am. Chem. Soc.*, **76**, 5452 (1954).

be done in nonnucleophilic solvents to avoid solvolysis of the acylating agent. The use of these reactive acylating agents can be complicated by competing O-acylation. Magnesium enolates play a prominent role in these C-acylation reactions. The magnesium enolate of diethyl malonate, for example, can be prepared by reaction with magnesium metal in ethanol. It is soluble in ether and undergoes C-acylation by acid anhydrides and acyl chlorides. The preparation of diethyl benzoylmalonate (Entry 1, Scheme 2.15) is an example of the use of an acid anhydride. Entries 2 to 5 illustrate the use of acyl chlorides. Entry 3 is carried out in basic aqueous solution and results in deacylation of the initial product.

Monoalkyl esters of malonic acid react with Grignard reagents to give a chelated enolate of the malonate monoanion.



These carbon nucleophiles react with acyl chlorides[220] or acyl imidazolides.[221] The initial products decarboxylate readily so the isolated products are β-ketoesters.

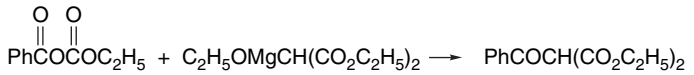


220. R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959).
221. J. Maibaum and D. H. Rich, *J. Org. Chem.*, **53**, 869 (1988); W. H. Moos, R. D. Gless, and H. Rapoport, *J. Org. Chem.*, **46**, 5064 (1981); D. W. Brooks, L. D.-L. Lu, and S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **18**, 72 (1979).

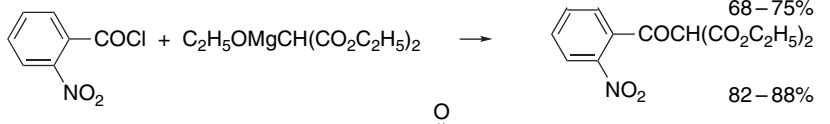
Scheme 2.15. Acylation of Ester Enolates with Acyl Halides, Anhydrides, and Imidazolides

A. Acylation with acyl halides and mixed anhydrides

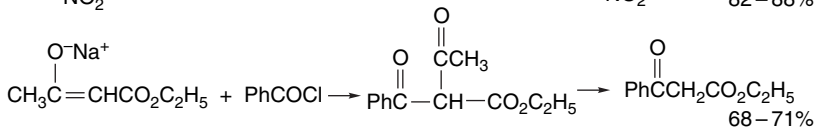
1[a]



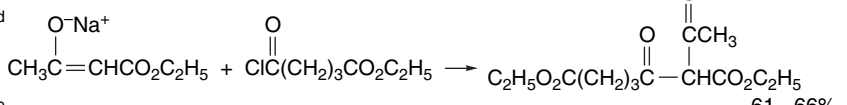
2[b]



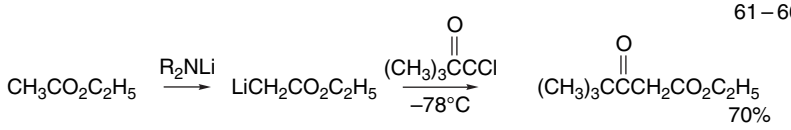
3[c]



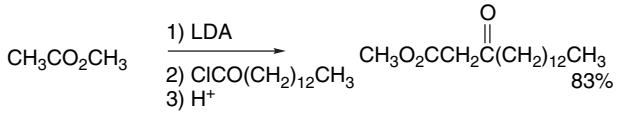
4[d]



5[e]

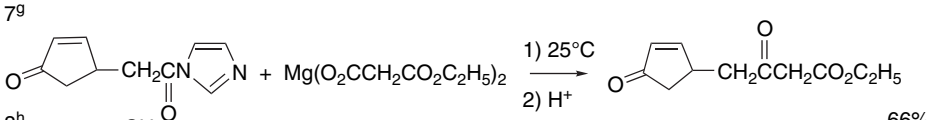


6[f]

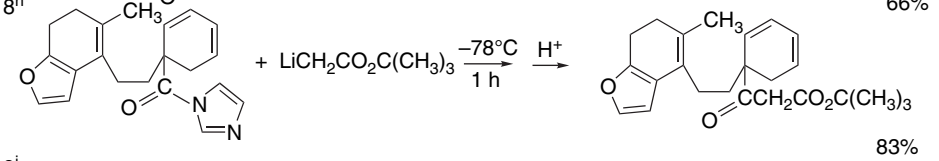


B. Acylation with imidazolides

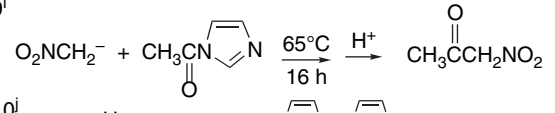
7[g]



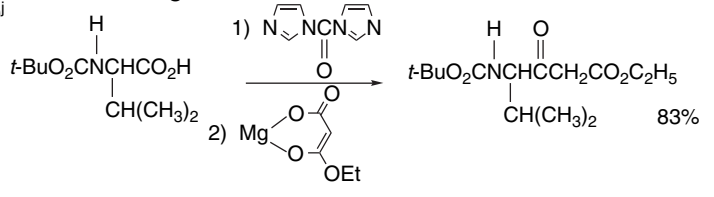
8[h]



9[i]

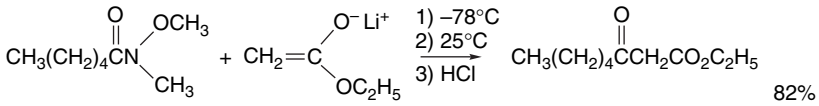


10[j]



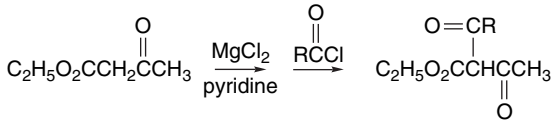
a. J. A. Price and D. S. Tarbell, *Org. Synth.*, **IV**, 285 (1963).
b. G. A. Reynolds and C. R. Hauser, *Org. Synth.*, **IV**, 708 (1963).
c. J. M. Straley and A. C. Adams, *Org. Synth.*, **IV**, 415 (1963).
d. M. Guha and D. Nasipuri, *Org. Synth.*, **V**, 384 (1973).
e. M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971).
f. D. F. Taber, P. B. Deker, H. M. Fales, T. H. Jones, and H. A. Lloyd, *J. Org. Chem.*, **53**, 2968 (1988).
g. A. Barco, S. Bennetti, G. P. Pollini, P. G. Baraldi, and C. Gandolfi, *J. Org. Chem.*, **45**, 4776 (1980).
h. E. J. Corey, G. Wess, Y. B. Xiang, and A. K. Singh, *J. Am. Chem. Soc.*, **109**, 4717 (1987).
i. M. E. Jung, D. D. Grove, and S. I. Khan, *J. Org. Chem.*, **52**, 4570 (1987).
j. J. Maibaum and D. H. Rich, *J. Org. Chem.*, **53**, 869 (1988).

Acyl imidazolides are more reactive than esters but not as reactive as acyl halides. Entry 7 is an example of formation of a β-ketoesters by reaction of magnesium enolate monoalkyl malonate ester by an imidazolide. Acyl imidazolides also are used for acylation of ester enolates and nitromethane anion, as illustrated by Entries 8, 9, and 10. *N*-Methoxy-*N*-methylamides are also useful for acylation of ester enolates.

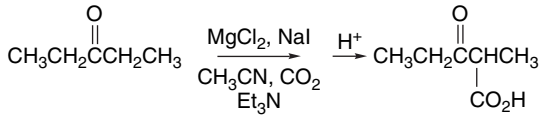


Ref. 222

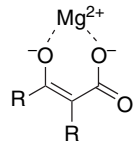
Both diethyl malonate and ethyl acetoacetate can be acylated by acyl chlorides using magnesium chloride and pyridine or triethylamine.[223]



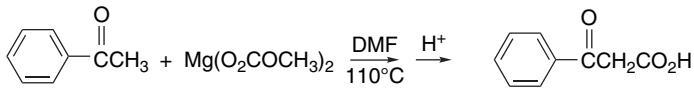
Rather similar conditions can be used to convert ketones to β-keto acids by carboxylation.[224]



These reactions presumably involve formation of a magnesium chelate of the keto acid. The β-ketoacid is liberated when the reaction mixture is acidified during workup.

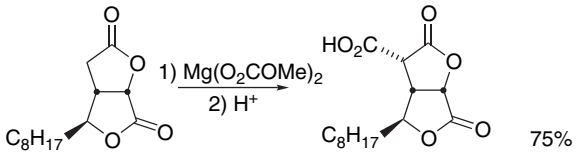


Carboxylation of ketones and esters can also be achieved by using the magnesium salt of monomethyl carbonate.



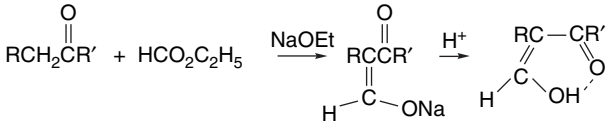
Ref. 225

222. J. A. Turner and W. S. Jacks, *J. Org. Chem.*, **54**, 4229 (1989).
223. M. W. Rathke and P. J. Cowan, *J. Org. Chem.*, **50**, 2622 (1985).
224. R. E. Tirpak, R. S. Olsen, and M. W. Rathke, *J. Org. Chem.*, **50**, 4877 (1985).
225. M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959).

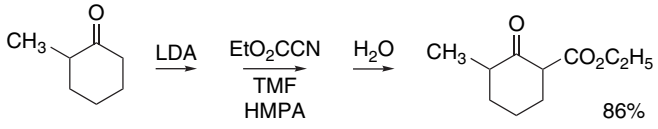


Ref. 226

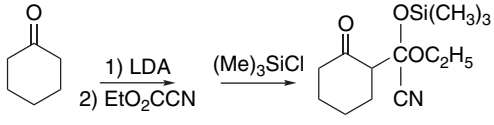
The enolates of ketones can be acylated by esters and other acylating agents. The products of these reactions are β-dicarbonyl compounds, which are rather acidic and can be alkylated by the procedures described in Section 1.2. Reaction of ketone enolates with formate esters gives a β-ketoaldehyde. As these compounds exist in the enol form, they are referred to as *hydroxymethylene derivatives*. Entries 1 and 2 in Scheme 2.16 are examples. Product formation is under thermodynamic control so the structure of the product can be predicted on the basis of the stability of the various possible product anions.



Ketones are converted to β-ketoesters by acylation with diethyl carbonate or diethyl oxalate, as illustrated by Entries 4 and 5 in Scheme 2.16. Alkyl cyanoformate can be used as the acylating reagent under conditions where a ketone enolate has been formed under kinetic control.[227]

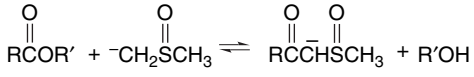


When this type of reaction is quenched with trimethylsilyl chloride, rather than by neutralization, a trimethylsilyl ether of the adduct is isolated. This result shows that the tetrahedral adduct is stable until the reaction mixture is hydrolyzed.



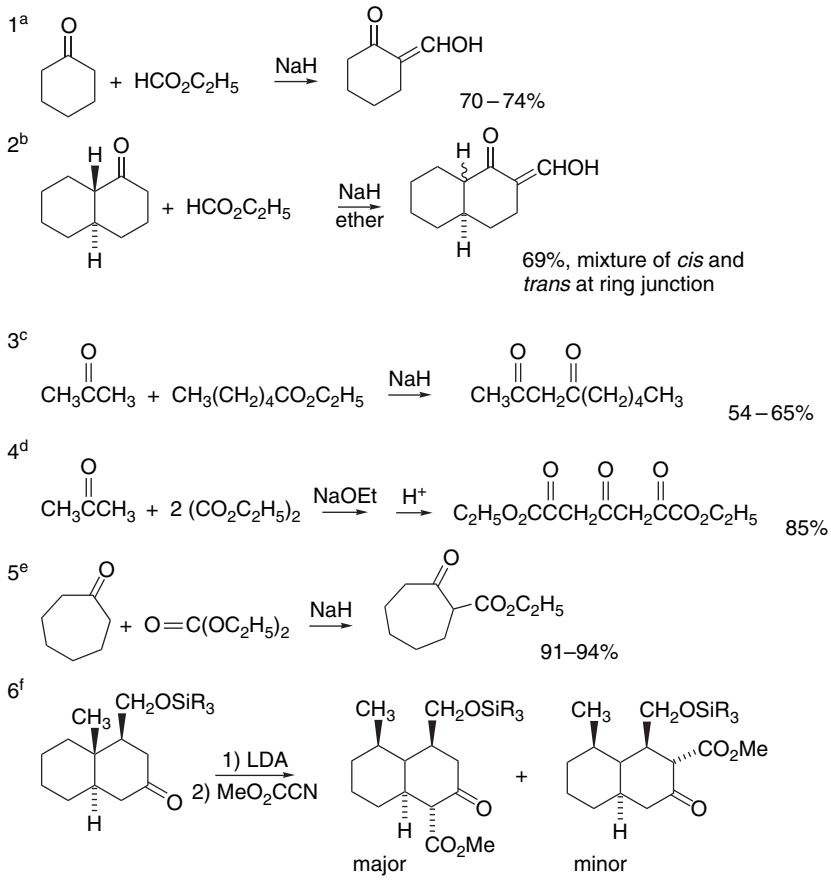
Ref. 228

β-Keto sulfoxides can be prepared by acylation of dimethyl sulfoxide anion with esters.[229]



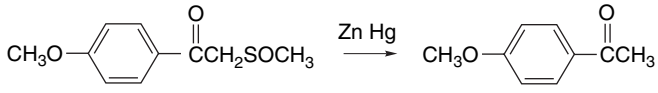
[226.] W. L. Parker and F. Johnson, *J. Org. Chem.*, **38**, 2489 (1973).
[227.] L. N. Mander and S. P. Sethi, *Tetrahedron Lett.*, **24**, 5425 (1983).
[228.] F. E. Ziegler and T.-F. Wang, *Tetrahedron Lett.*, **26**, 2291 (1985).
[229.] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965); H. D. Becker, G. J. Mikol, and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3410 (1963).

Scheme 2.16. Acylation of Ketones by Esters



a. C. Ainsworth, *Org. Synth.*, **IV**, 536 (1963).
b. P. H. Lewis, S. Middleton, M. J. Rosser, and L. E. Stock, *Aust. J. Chem.*, **32**, 1123 (1979).
c. N. Green and F. B. La Forge, *J. Am. Chem. Soc.*, **70**, 2287 (1948); F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).
d. E. R. Riegel and F. Zwilgmeyer, *Org. Synth.*, **II**, 126 (1943).
e. A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Synth.*, **47**, 20 (1967).
f. F. E. Ziegler, S. I. Klein, U. K. Pati, and T.-F. Wang, *J. Am. Chem. Soc.*, **107**, 2730 (1985).

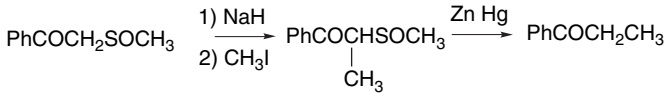
Mechanistically, this reaction is similar to ketone acylation. The β-keto sulfoxides have several synthetic applications. The sulfoxide substituent can be removed reductively, which leads to methyl ketones.



Ref. 230

The β-keto sulfoxides can be alkylated via their anions. Inclusion of an alkylation step prior to the reduction provides a route to ketones with longer chains.

230. G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966).

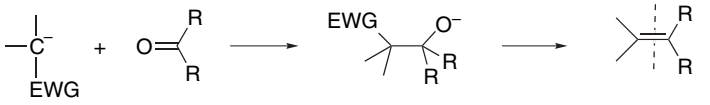


Ref. 231

These reactions accomplish the same overall synthetic transformation as the acylation of ester enolates, but use desulfurization rather than decarboxylation to remove the anion-stabilizing group. Dimethyl sulfone can be subjected to similar reaction sequences.[232]

2.4. Olefination Reactions of Stabilized Carbon Nucleophiles

This section deals with reactions that correspond to Pathway **C,** defined earlier (p. 64), that lead to formation of alkenes. The reactions discussed include those of phosphorus-stabilized nucleophiles (Wittig and related reactions), α-silyl (Peterson reaction) and α-sulfonyl carbanions (Julia olefination) with aldehydes and ketones. These important rections can be used to convert a carbonyl group to an alkene by reaction with a carbon nucleophile. In each case, the addition step is followed by an elimination.



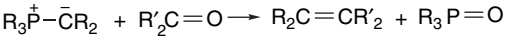
A crucial issue for these reactions is the stereoselectivity for formation of *E*- or *Z*-alkene. This is determined by the mechanisms of the reactions and, as we will see, can be controlled in some cases by the choice of particular reagents and reaction conditions.

2.4.1. The Wittig and Related Reactions of Phosphorus-Stabilized Carbon Nucleophiles

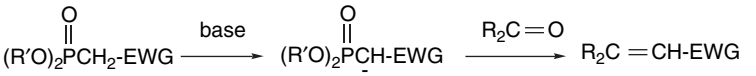
The *Wittig reaction* involves *phosphonium ylides* as the nucleophilic carbon species.[233] An ylide is a molecule that has a contributing resonance structure with opposite charges on adjacent atoms, each of which has an octet of electrons. Although this definition includes other classes of compounds, the discussion here is limited to ylides having the negative charge on the carbon. Phosphonium ylides are stable, but quite reactive, compounds. They can be represented by two limiting resonance structures, which are referred to as the ylide and ylene forms.

231. P. G. Gassman and G. D. Richmond, *J. Org. Chem.*, **31,** 2355 (1966).
232. H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 61 (1968).
233. For general reviews of the Wittig reaction, see A. Maercker, *Org. React.*, **14**, 270 (1965); I. Gosney and A. G. Rowley, in *Organophosphorus Reagents in Organic Synthesis*, J. I. G. Cadogan, ed., Academic Press, London, 1979, pp. 17–153; B. A. Maryanoff and A. B. Reitz, *Chem. Rev.*, **89**, 863 (1989); A. W. Johnson, *Ylides and Imines of Phosphorus*, John Wiley, New York, 1993; N. J. Lawrence, in *Preparation of Alkenes*, Oxford University Press, Oxford, 1996, pp. 19–58; K. C. Nicolaou, M. W. Harter, J. L. Gunzer, and A. Nadin, *Liebigs Ann. Chem.*, 1283 (1997).

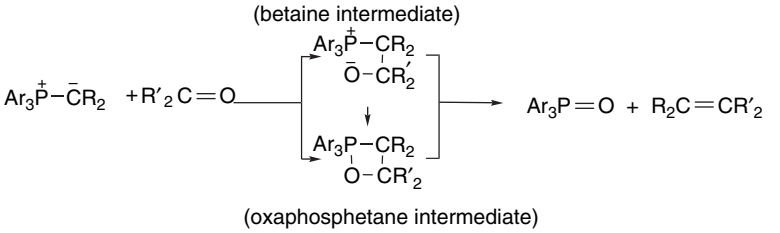
NMR spectroscopic studies (^{1}H, ^{13}C, and ^{31}P) are consistent with the dipolar ylide structure and suggest only a minor contribution from the ylene structure.[234] Theoretical calculations support this view.[235] The phosphonium ylides react with carbonyl compounds to give olefins and the phosphine oxide.



There are related reactions involving phosphonate esters or phosphines oxides. These reactions differ from the Wittig reaction in that they involve *carbanions* formed by deprotonation. In the case of the phosphonate esters, a second EWG substituent is usually present.



2.4.1.1. Olefination Reactions Involving Phosphonium Ylides. The synthetic potential of phosphonium ylides was developed initially by G. Wittig and his associates at the University of Heidelberg. The reaction of a phosphonium ylide with an aldehyde or ketone introduces a carbon-carbon double bond in place of the carbonyl bond. The mechanism originally proposed involves an addition of the nucleophilic ylide carbon to the carbonyl group to form a dipolar intermediate (a *betaine*), followed by elimination of a phosphine oxide. The elimination is presumed to occur after formation of a four-membered *oxaphosphetane* intermediate. An alternative mechanism proposes direct formation of the oxaphosphetane by a cycloaddition reaction.[236] There have been several computational studies that find the oxaphosphetane structure to be an intermediate.[237] Oxaphosphetane intermediates have been observed by NMR studies at low temperature.[238] Betaine intermediates have been observed only under special conditions that retard the cyclization and elimination steps.[239]



234. H. Schmidbaur, W. Bucher, and D. Schentzow, *Chem. Ber.*, **106**, 1251 (1973).

235. A. Streitwieser, Jr., A. Rajca, R. S. McDowell, and R. Glaser, *J. Am. Chem. Soc.*, **109**, 4184 (1987); S. M. Bachrach, *J. Org. Chem.*, **57**, 4367 (1992); D. G. Gilheany, *Chem. Rev.*, **94**, 1339 (1994).

236. E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.*, **95**, 5778 (1973); E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **112**, 3905 (1990).

237. R. Holler and H. Lischka, *J. Am. Chem. Soc.*, **102**, 4632 (1980); F. Volatron and O. Eisenstein, *J. Am. Chem. Soc.*, **106**, 6117 (1984); F. Mari, P. M. Lahti, and W. E. McEwen, *J. Am. Chem. Soc.*, **114**, 813 (1992); A. A. Restrepocossio, C. A. Gonzalez, and F. Mari, *J. Phys. Chem. A*, **102**, 6993 (1998); H. Yamataka and S. Nagase, *J. Am. Chem. Soc.*, **120**, 7530 (1998).

238. E. Vedejs, G. P. Meier, and K. A. J. Snoble, *J. Am. Chem. Soc.*, **103**, 2823 (1981); B. E. Maryanoff, A. B. Reitz, M. S. Mutter, R. R. Inners, H. R. Almond, Jr., R. R. Whittle, and R. A. Olofson, *J. Am. Chem. Soc.*, **108**, 7684 (1986).

239. R. A. Neumann and S. Berger, *Eur. J. Org. Chem.*, 1085 (1998).

Phosphonium ylides are usually prepared by deprotonation of phosphonium salts. The phosphonium salts that are used most often are alkyltriphenylphosphonium halides, which can be prepared by the reaction of triphenylphosphine and an alkyl halide. The alkyl halide must be reactive toward S_N2 displacement.

$$Ph_3P + RCH_2X \longrightarrow Ph_3\overset{+}{P}-CH_2R\ X^-$$

X = I, Br, or Cl

$$Ph_3\overset{+}{P}\overset{-}{C}H_2R \xrightarrow{\text{base}} Ph_3P{=}CHR$$

Alkyltriphenylphosphonium halides are only weakly acidic, and a strong base must be used for deprotonation. Possibilities include organolithium reagents, the anion of dimethyl sulfoxide, and amide ion or substituted amide anions, such as LDA or NaHMDS. The ylides are not normally isolated, so the reaction is carried out either with the carbonyl compound present or with it added immediately after ylide formation. Ylides with nonpolar substituents, e.g., R = H, alkyl, aryl, are quite reactive toward both ketones and aldehydes. Ylides having an α-EWG substituent, such as alkoxycarbonyl or acyl, are less reactive and are called *stabilized ylides.*

The stereoselectivity of the Wittig reaction is believed to be the result of steric effects that develop as the ylide and carbonyl compound approach one another. The three phenyl substituents on phosphorus impose large steric demands that govern the formation of the diastereomeric adducts.[240] Reactions of unstabilized phosphoranes are believed to proceed through an early TS, and steric factors usually make these reactions selective for the *cis*-alkene.[241] Ultimately, however, the precise stereoselectivity is dependent on a number of variables, including reactant structure, the base used for ylide formation, the presence of other ions, solvent, and temperature.[242]

Scheme 2.17 gives some examples of Wittig reactions. Entries 1 to 5 are typical examples of using ylides without any functional group stabilization. The stereoselectivity depends strongly on both the structure of the ylide and the reaction conditions. Use of sodium amide or NaHMDS as bases gives higher selectivity for *Z*-alkenes than do ylides prepared with alkyllithium reagents as base (see Entries 3 to 6). Benzylidenetriphenylphosphorane (Entry 6) gives a mixture of both *cis*- and *trans*-stilbene on reaction with benzaldehyde. The diminished stereoselectivity is attributed to complexes involving the lithium halide salt that are present when alkyllithium reagents are used as bases.

β-Ketophosphonium salts are considerably more acidic than alkylphosphonium salts and can be converted to ylides by relatively weak bases. The resulting ylides, which are stabilized by the carbonyl group, are substantially less reactive than unfunctionalized ylides. More vigorous conditions are required to bring about reactions with ketones. Stabilized ylides such as (carboethoxymethylidene)triphenylphosphorane (Entries 8 and 9) react with aldehydes to give exclusively *trans* double bonds.

240. M. Schlosser, *Top. Stereochem.*, **5**, 1 (1970); M. Schlosser and B. Schaub, *J. Am. Chem. Soc.*, **104**, 5821 (1982); H. J. Bestmann and O. Vostrowsky, *Top. Curr. Chem.*, **109**, 85 (1983); E. Vedejs, T. Fleck, and S. Hara, *J. Org. Chem.*, **52**, 4637 (1987).

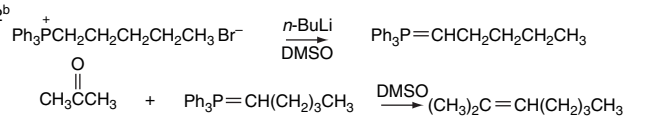
241. E. Vedejs, C. F. Marth, and P. Ruggeri, *J. Am. Chem. Soc.*, **110**, 3940 (1988); E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **110**, 3948 (1988); E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **112**, 3905 (1990).

242. A. B. Reitz, S. O. Nortey, A. D. Jordan, Jr., M. S. Mutter, and B. E. Maryanoff, *J. Org. Chem.*, **51**, 3302 (1986); B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, **89**, 863 (1989); E. Vedejs and M. J. Peterson, *Adv. Carbanion Chem.*, **2**, 1 (1996); E. Vedejs and M. J. Peterson, *Top. Stereochem.*, **21**, 1 (1994).

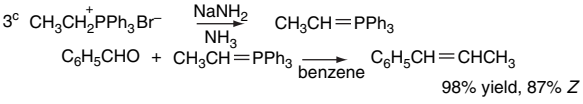
Scheme 2.17. The Wittig Reaction

1[a]

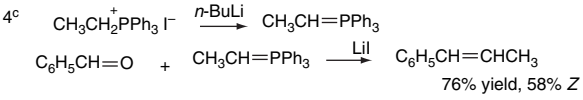
2[b]



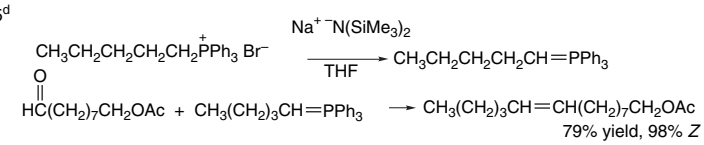
3[c]



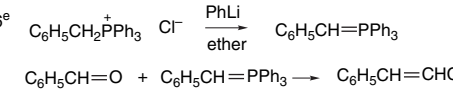
4[c]



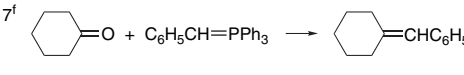
5[d]



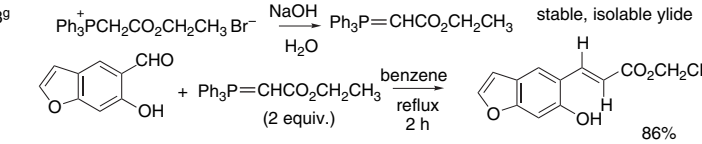
6[e]



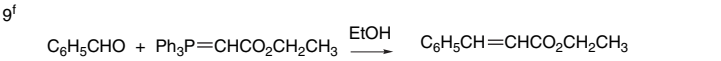
7[f]



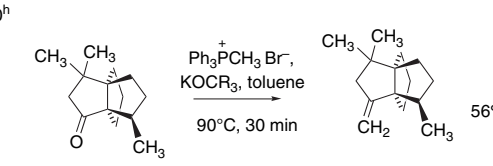
8[g]



9[f]

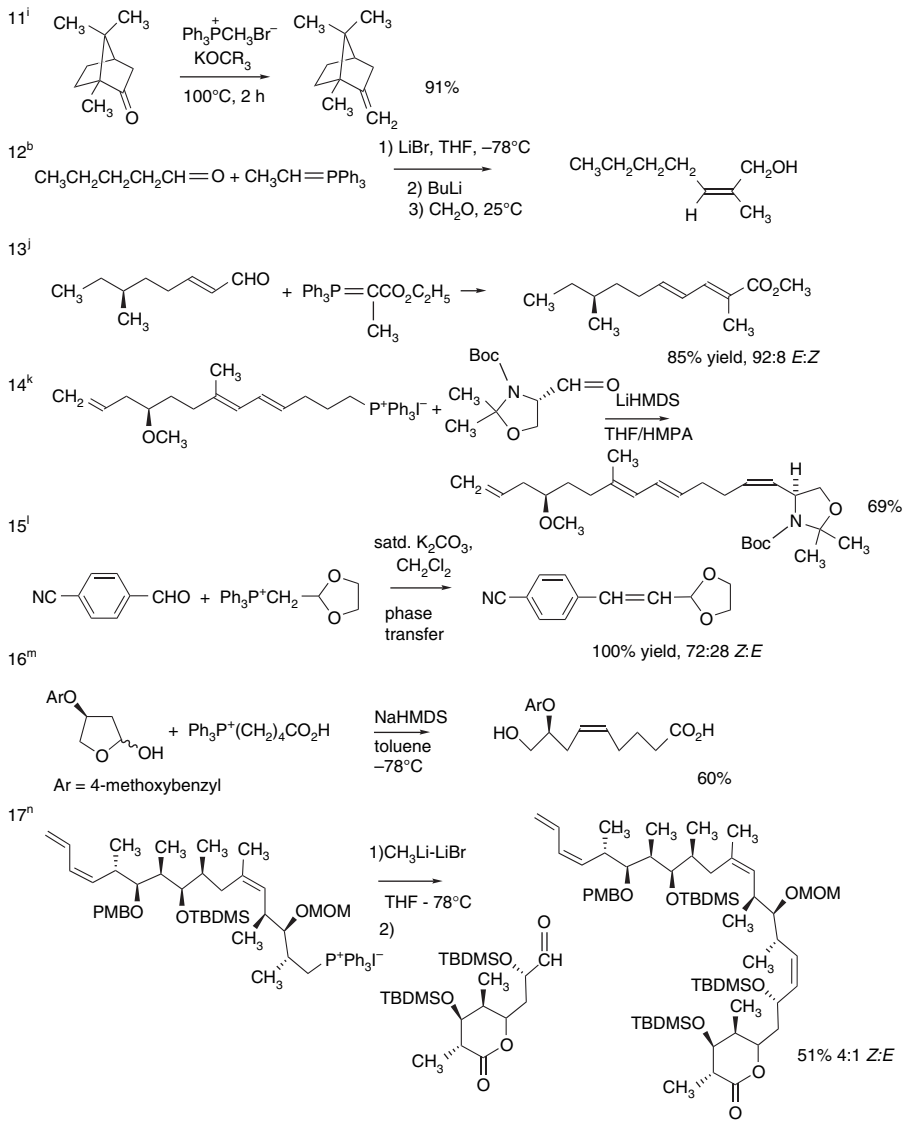


10[h]



(*Continued*)

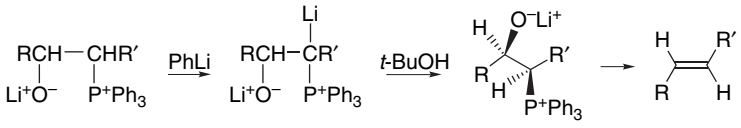
Scheme 2.17. (*Continued*)



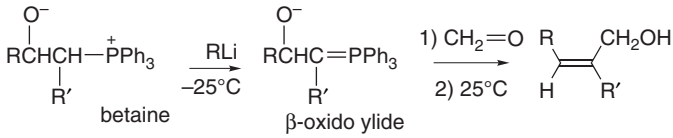
a. R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
b. U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971).
c. M. Schlosser and K. F. Christmann, *Liebigs Ann. Chem.*, **708**, 1 (1967).
d. H. J. Bestmann, K. H. Koschatzky, and O. Vostrowsky, *Chem. Ber.*, **112**, 1923 (1979).
e. G. Wittig and U. Schollkopf, *Chem. Ber.*, **87**, 1318 (1954).
f. G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).
g. Y. Y. Liu, E. Thom, and A. A. Liebman, *J. Heterocycl. Chem.*, **16**, 799 (1979).
h. A. B. Smith, III, and P. J. Jerris, *J. Org. Chem.*, **47**, 1845 (1982).
i. L. Fitjer and U. Quabeck, *Synth. Commun.*, **15**, 855 (1985).
j. J. D. White, T. S. Kim, and M. Nambu, *J. Am. Chem. Soc.*, **119**, 103 (1997).
k. N. Daubresse, C. Francesch, and G. Rolando, *Tetrahedron*, **54**, 10761 (1998).
l. A. G. M. Barrett, M. Pena, and J. A. Willardsen, *J. Org. Chem.*, **61**, 1082 (1996).
m. D. Critcher, S. Connoll, and M. Wills, *J. Org. Chem.*, **62**, 6638 (1997).
n. A. B. Smith, III, B. S. Freeze, I. Brouard, and T. Hirose, *Org. Lett.*, **5**, 4405 (2003).

When a hindered ketone is to be converted to a methylene derivative, the best results are obtained if potassium *t*-alkoxide is used as the base in a hydrocarbon solvent. Under these conditions the reaction can be carried out at elevated temperatures.[243] Entries 10 and 11 illustrate this procedure.

The reaction of nonstabilized ylides with aldehydes can be induced to yield *E*-alkenes with high stereoselectivity by a procedure known as the *Schlosser modification* of the Wittig reaction.[244] In this procedure, the ylide is generated as a lithium halide complex and allowed to react with an aldehyde at low temperature, presumably forming a mixture of diastereomeric betaine-lithium halide complexes. At the temperature at which the addition is carried out, there is no fragmentation to an alkene and triphenylphosphine oxide. This complex is then treated with an equivalent of strong base such as phenyllithium to form a β-*oxido ylide*. Addition of one equivalent of *t*-butyl alcohol protonates the β-oxido ylide stereoselectivity to give the *syn*-betaine as a lithium halide complex. Warming the solution causes the *syn*-betaine-lithium halide complex to give *trans*-alkene by a *syn* elimination.



An extension of this method can be used to prepare allylic alcohols. Instead of being protonated, the β-oxido ylide is allowed to react with formaldehyde. The β-oxido ylide and formaldehyde react to give, on warming, an allylic alcohol. Entry 12 is an example of this reaction. The reaction is valuable for the stereoselective synthesis of *Z*-allylic alcohols from aldehydes.[245]



The Wittig reaction can be applied to various functionalized ylides.[246] Methoxymethylene and phenoxymethylene ylides lead to vinyl ethers, which can be hydrolyzed to aldehydes.[247]

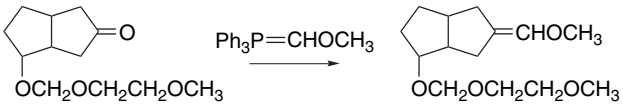
243. J. M. Conia and J. C. Limasset, *Bull. Soc. Chim. France*, 1936 (1967); J. Provin, F. Leyendecker, and J. M. Conia, *Tetrahedron Lett.*, 4053 (1975); S. R. Schow and T. C. Morris, *J. Org. Chem.*, **44**, 3760 (1979).

244. M. Schlosser and K.-F. Christmann, *Liebigs Ann. Chem.*, **708**, 1 (1967); M. Schlosser, K.-F. Christmann, and A. Piskala, *Chem. Ber.*, **103**, 2814 (1970).

245. E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 226 (1970); E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Am. Chem. Soc.*, **92**, 6635 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6636 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6637 (1970); E. J. Corey, J. I. Shulman, and H. Yamamoto, *Tetrahedron Lett.*, 447 (1970).

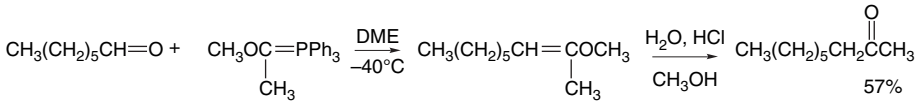
246. S. Warren, *Chem. Ind. (London)*, 824 (1980).

247. S. G. Levine, *J. Am. Chem. Soc.*, **80**, 6150 (1958); G. Wittig, W. Boll, and K. H. Kruck, *Chem. Ber.*, **95**, 2514 (1962).



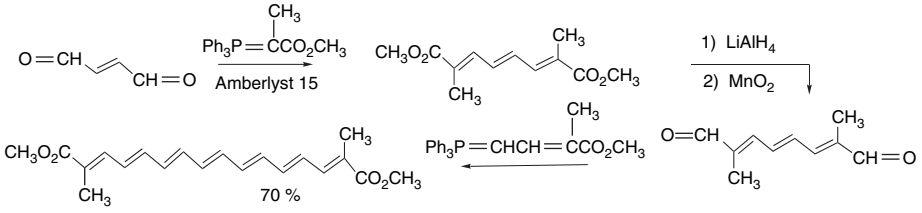
Ref. 248

2-(1,3-Dioxolanyl)methyl ylides can be used for the introduction of α, β-unsaturated aldehydes (see Entry 15, Scheme 2.17). Methyl ketones can be prepared by a reaction using the α-methoxyethylidene phosphorane.

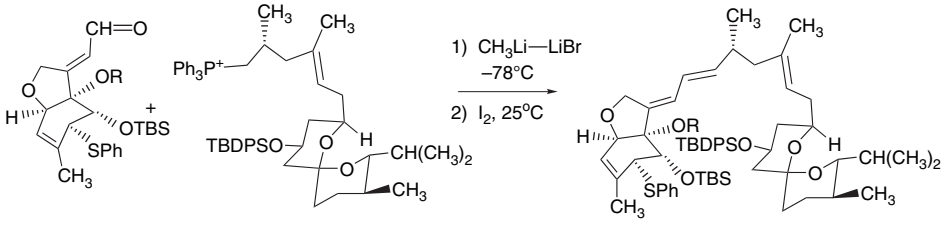


Ref. 249

There have been many applications of the Wittig reaction in multistep syntheses. The reaction can be used to prepare extended conjugated systems, such as crocetin dimethyl ester, which has seven conjugated double bonds. In this case, two cycles of Wittig reactions using stabilized ylides provided the seven double bonds. Note the use of a conjugated stabilized ylide in the second step.[250]

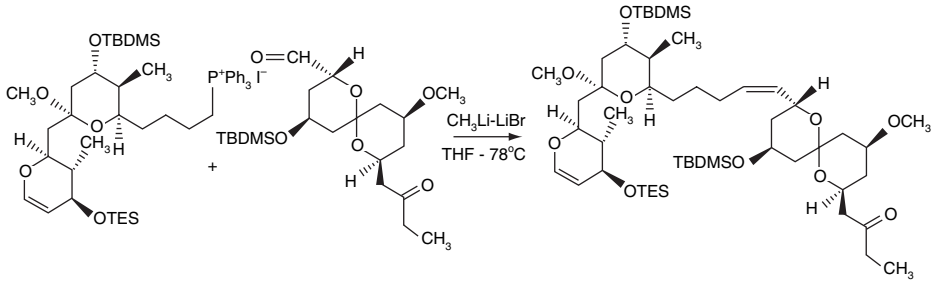


In several cases of syntheses of highly functionalized molecules, use of CH_3Li-LiBr for ylide formation has been found to be advantageous. For example, in the synthesis of milbemycin D, Crimmins and co-workers obtained an 84% yield with 10:1 *Z*:*E* selectivity.[251] In this case, the more stable *E*-isomer was required and it was obtained by I_2-catalyzed isomerization.



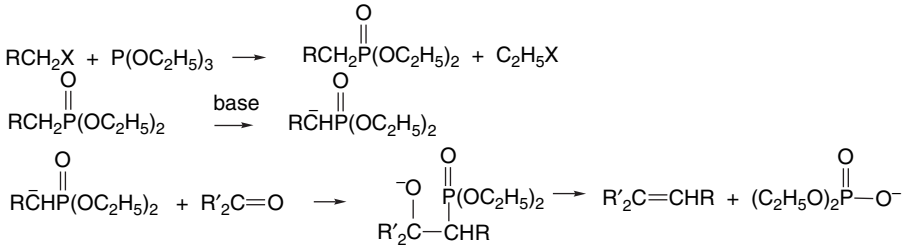
[248.] M. Yamazaki, M. Shibasaki, and S. Ikegami, *J. Org. Chem.*, **48**, 4402 (1983).
[249.] D. R. Coulsen, *Tetrahedron Lett.*, 3323 (1964).
[250.] D. Frederico, P. M. Donate, M. G. Constantino, E. S. Bronze, and M. I. Sairre, *J. Org. Chem.*, **68**, 9126 (2003).
[251.] M. T. Crimmins, R. S. Al-awar, I. M. Vallin, W. G. Hollis, Jr., R. O'Mahony, J. G. Lever, and D. M. Bankaitis-Davis, *J. Am. Chem. Soc.*, **118**, 7513 (1996).

This methodology was also used in the connecting of two major fragments in the synthesis of spongistatins.[252]

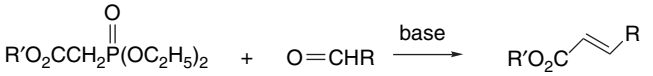


These conditions were also employed for a late stage of the synthesis of (+)-discodermolide (see Entry 17, Scheme 2.17).

2.4.1.2. Olefination Reactions Involving Phosphonate Anions. An important complement to the Wittig reaction involves the reaction of phosphonate carbanions with carbonyl compounds.[253] The alkylphosphonic acid esters are made by the reaction of an alkyl halide, preferably primary, with a phosphite ester. Phosphonate carbanions are generated by treating alkylphosphonate esters with a base such as sodium hydride, *n*-butyllithium, or sodium ethoxide. Alumina coated with KF or KOH has also found use as the base.[254]



Reactions with phosphonoacetate esters are used frequently to prepare α,β-unsaturated esters. This reaction is known as the *Wadsworth-Emmons reaction* and usually leads to the *E*-isomer.



The conditions can be modified to favor the *Z*-isomer. Use of KHMDS with 18-crown-6 favors the *Z*-product.[255] This method was used, for example, to control the

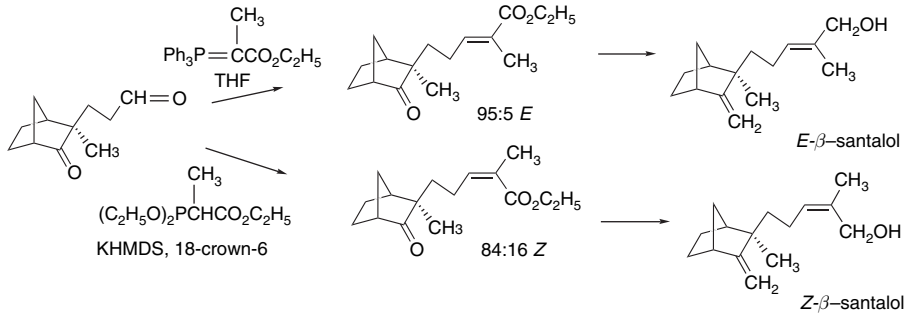
252. M. T. Crimmins, J. D. Katz, D. G. Washburn, S. P. Allwein, and L. F. McAtee, *J. Am. Chem. Soc.*, **124**, 5661 (2002); see also C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes, and G. R. Ott, *J. Am. Chem. Soc.*, **125**, 12844 (2003).

253. For reviews of reactions of phosphonate carbanions with carbonyl compounds, see J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974); W. S. Wadsworth, Jr., *Org. React.*, **25**, 73 (1977); H. Gross and I. Keitels, *Z. Chem.*, **22**, 117 (1982).

254. F. Texier-Boullet, D. Villemin, M. Ricard, H. Moison, and A. Foucaud, *Tetrahedron*, **41**, 1259 (1985); M. Mikolajczyk and R. Zurawinski, *J. Org. Chem.*, **63**, 8894 (1998).

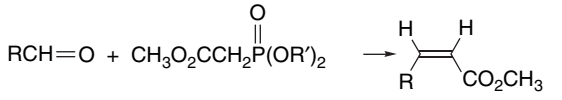
255. W. C. Still and C. Gennari, *Tetrahedron Lett.*, **24**, 4405 (1983).

stereochemistry in the synthesis of the *Z*- and *E*-isomers of β-santalol, a fragrance that is a component of sandalwood oil.



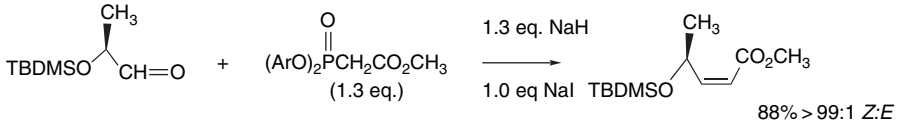
Ref. 256

Several modified phosphonoacetate esters show selectivity for the *Z*-enoate product. Trifluoroethyl,[256] phenyl,[257] 2-methylphenyl,[258] and 2,6-difluorophenyl[259] esters give good *Z*-stereoselectivity with aldehydes. The trifluoroethyl esters also give *Z*-selectivity with ketones.[260]

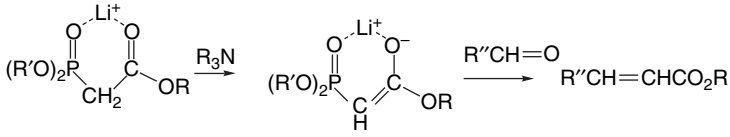


R′ = CH_2CF_3, phenyl, 2-methylphenyl, 2,6-difluorophenyl

Several other methodologies have been developed for control of the stereoselectivity of Wadsworth-Emmons reactions. For example, K_2CO_3 in chlorobenzene with a catalytic amount of 18-crown-6 is reported to give excellent *Z*-selectivity.[261] Another group found that use of excess Na^+, added as NaI, improved *Z*-selectivity for 2-methylphenyl esters.

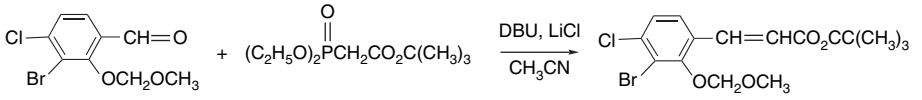


An alternative procedure for effecting the condensation of phosphonoacetates is to carry out the reaction in the presence of lithium chloride and an amine such as diisopropylethylamine. The lithium chelate of the substituted phosphonate is sufficiently acidic to be deprotonated by the amine.[262]



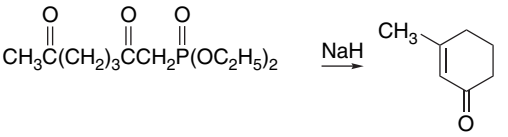
256. A. Krotz and G. Helmchen, *Liebigs Ann. Chem.*, 601 (1994).
257. K. Ando, *Tetrahedron Lett.*, **36**, 4105 (1995); K. Ando, *J. Org. Chem.*, **63**, 8411 (1998).
258. K. Ando, *J. Org. Chem.*, **62**, 1934 (1997); K. Ando, T. Oishi, M. Hirama, H. Ohno, and T. Ibuka, *J. Org. Chem.*, **65**, 4745 (2000).
259. K. Kokin, J. Motoyoshiya, S. Hayashi, and H. Aoyama, *Synth. Commun.*, **27**, 2387 (1997).
260. S. Sano, K. Yokoyama, M. Shiro, and Y. Nagao, *Chem. Pharm. Bull.*, **50**, 706 (2002).
261. F. P. Touchard, *Tetrahedron Lett.*, **45**, 5519 (2004).
262. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai, *Tetrahedron Lett.*, **25**, 2183 (1984).

This version of the Wadsworth-Emmons reaction has been used in the scaled-up syntheses of drugs and drug-candidate molecules. For example, it is used to prepare a cinnamate ester that is a starting material for pilot plant synthesis of a potential integrin antagonist.[263]



Entries 10 and 11 of Scheme 2.18 also illustrate this procedure.

Scheme 2.18 gives some representative olefination reactions of phosphonate anions. Entry 1 represents a typical preparative procedure. Entry 2 involves formation of a 2,4-dienoate ester using an α,β-unsaturated aldehyde. Diethyl benzylphosphonate can be used in the Wadsworth-Emmons reaction, as illustrated by Entry 3. Entries 4 to 6 show other anion-stabilizing groups. Intramolecular reactions can be used to prepare cycloalkenes.[264]



Ref. 265

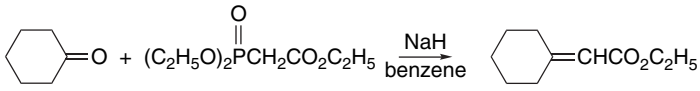
Intramolecular condensation of phosphonate carbanions with carbonyl groups carried out under conditions of high dilution have been utilized in macrocycle syntheses. Entries 7 and 8 show macrocyclizations involving the Wadsworth-Emmons reaction. Entries 9 to 11 illustrate the construction of new double bonds in the course of a multistage synthesis. The LiCl/amine conditions are used in Entries 9 and 10.

The stereoselectivity of the reactions of stabilized phosphonate anions is usually considered to be the result of reversible adduct formation, followed by rate/product-controlling elimination that favors the *E*-isomer. This matter has been investigated by computation. The Wadsworth-Emmons reaction between lithio methyl dimethylphosphonoacetate and acetaldehyde has been modeled at the HF/6-31G* level. Energies were also calculated at the B3LYP/6-31G* level.[266] The energy profile for the intermediates and TSs are shown in Figure 2.5. In agreement with the prevailing experimental interpretation, the highest barrier is for formation of the oxaphosphetane and the addition step is reversible. The stereochemistry, then, is determined by the relative ease of formation of the stereoisomeric oxaphosphetanes. The oxaphosphetane species is of marginal stability and proceeds rapidly to product. At the B3LYP/6-31 + G* level, $TS2_{trans}$ is 2.2 kcal/mol more stable than $TS2_{cis}$. The path to the *cis* product encounters two additional small barriers associated with slightly stable stereoisomeric

263. J. D. Clark, G. A. Weisenburger, D. K. Anderson, P.-J. Colson, A. D. Edney, D. J. Gallagher, H. P. Kleine, C. M. Knable, M. K. Lantz, C. M. V. Moore, J. B. Murphy, T. E. Rogers, P. G. Ruminski, A. S. Shah, N. Storer, and B. E. Wise, *Org. Process Res. Devel.*, **8**, 51 (2004).
264. K. B. Becker, *Tetrahedron*, **36**, 1717 (1980).
265. P. A. Grieco and C. S. Pogonowski, *Synthesis*, 425 (1973).
266. K. Ando, *J. Org. Chem.*, **64**, 6815 (1999).

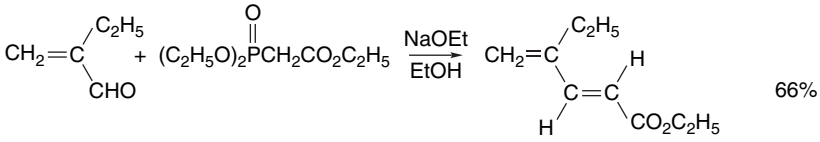
Scheme 2.18. Carbonyl Olefination Using Phosphonate Carbanions

1[a]



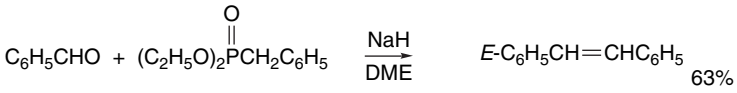
67–77%

2[b]



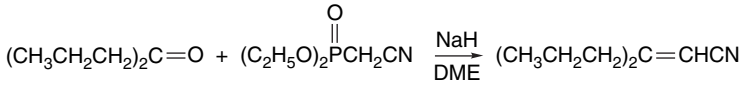
66%

3[c]



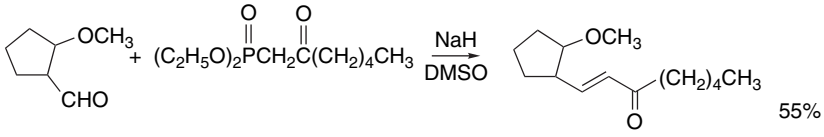
63%

4[d]



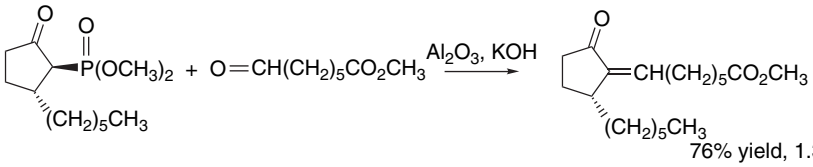
74%

5[e]



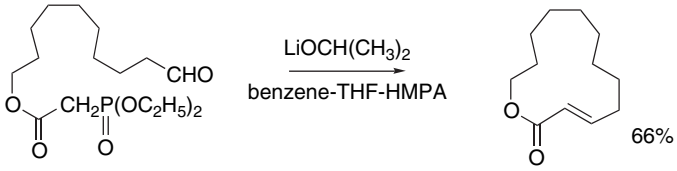
55%

6[f]



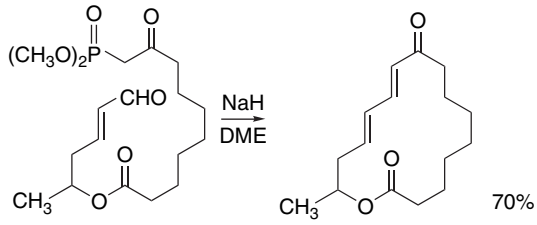
76% yield, 1.3:1 *E*:*Z*

7[g]



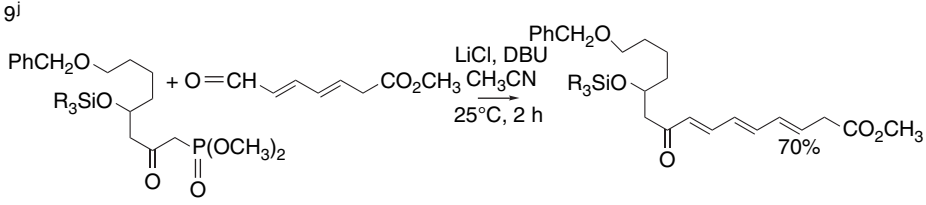
66%

8[h]



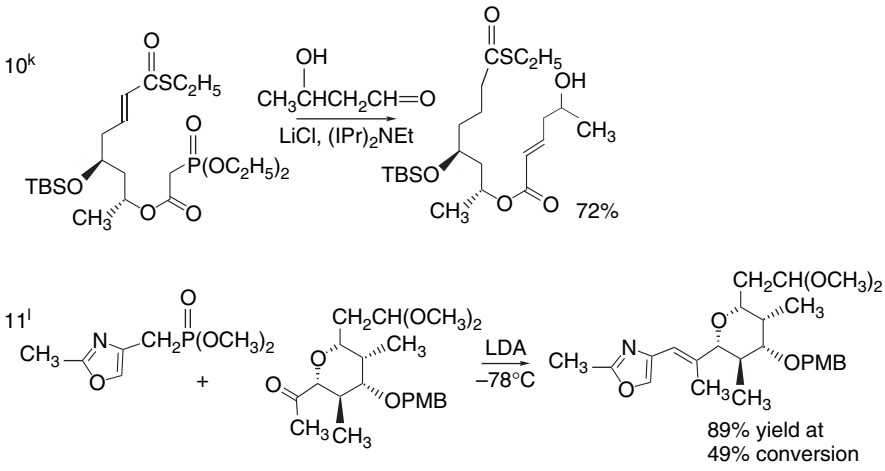
70%

9[j]



(*Continued*)

Scheme 2.18. (*Continued*)



a. W. S. Wadsworth, Jr., and W. D. Emmons, *Org. Synth.*, **45**, 44 (1965).
b. R. J. Sundberg, P. A. Bukowick, and F. O. Holcombe, *J. Org. Chem.*, **32**, 2938 (1967).
c. W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
d. J. A. Marshall, C. P. Hagan, and G. A. Flynn, *J. Org. Chem.*, **40**, 1162 (1975).
e. N. Finch, J. J. Fitt, and I. H. S. Hsu, *J. Org. Chem.*, **40**, 206 (1975).
f. M Mikolajczyk and R. Zurawski, *J. Org. Chem.*, **63**, 8894 (1998).
g. G. M. Stork and E. Nakamura, *J. Org. Chem.*, **44**, 4010 (1979).
h. K. C. Nicolaou, S. P. Seitz, M. R. Pavia, and N. A. Petasis, *J. Org. Chem.*, **44**, 4010 (1979).
i. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai, *Tetrahedron Lett.*, **25**, 2183 (1984).
j. G. E. Keck and J. A. Murry, *J. Org. Chem.*, **56**, 6606 (1991).
k. G. Pattenden, M. A. Gonzalez, P. B. Little, D. S. Millan, A. T. Plowright, J. A. Tornos, and T. Ye, *Org. Biomolec. Chem.*, **1**, 4173 (2003).

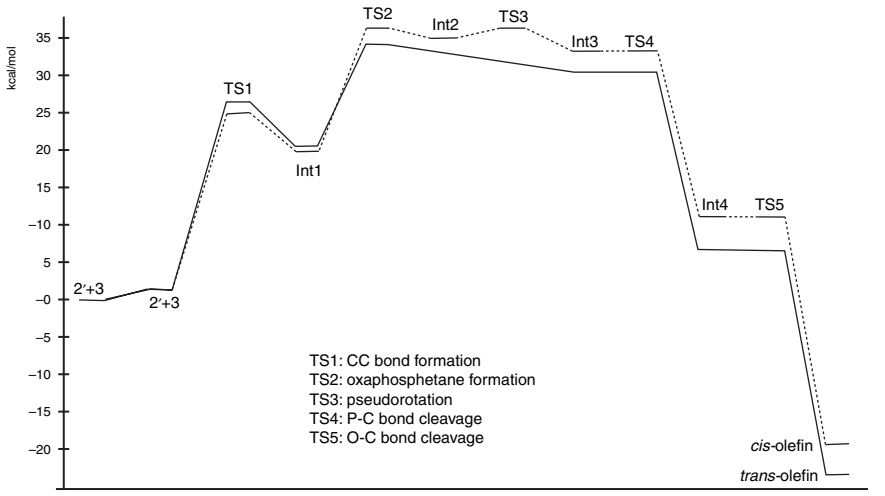
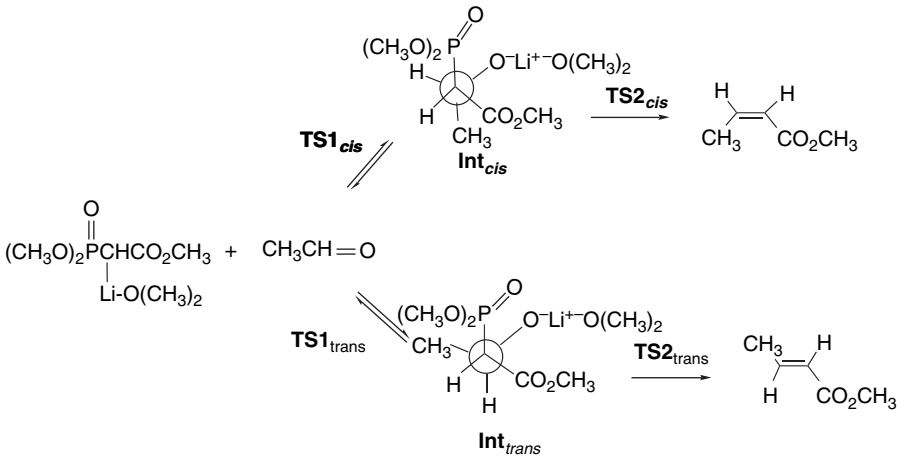


Fig. 2.5. Comparison of energy profile (ΔG) for pathways to *E*- and *Z*-product from the reaction of lithio methyl dimethylphosphonoacetate and acetaldehyde. One molecule of dimethyl ether is coordinated to the lithium ion. Reproduced from *J. Org. Chem.*, **64**, 6815 (1999), by permission of the American Chemical Society.

oxaphosphetane intermediates. The oxaphosphatane is not a stable intermediate on the path to *trans* product.



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

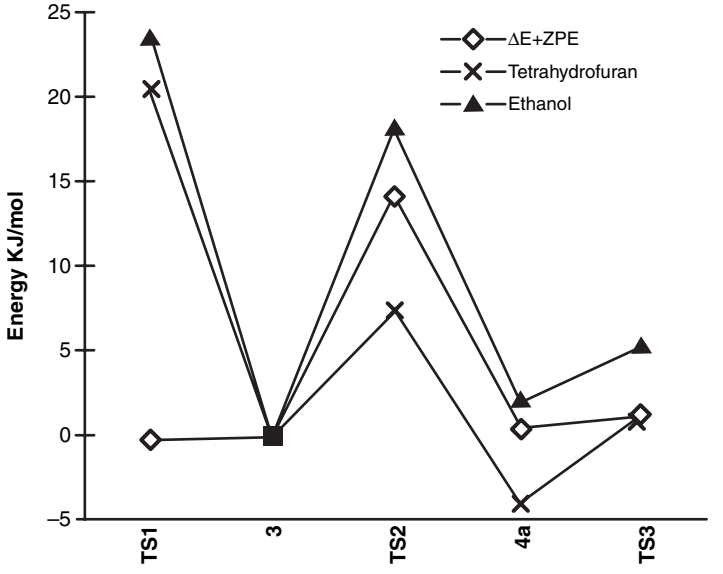
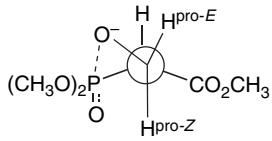
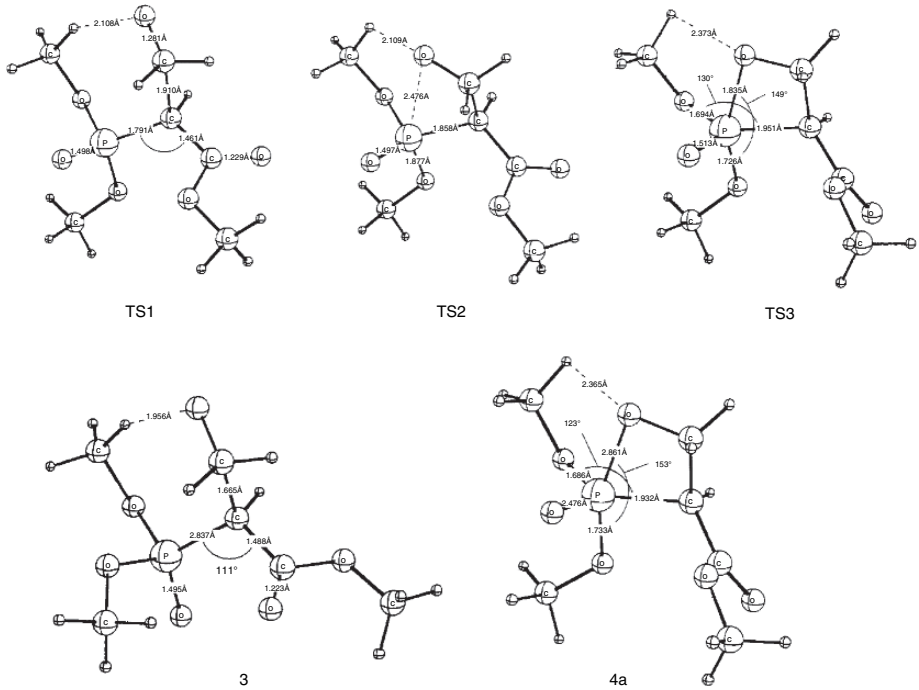


Fig. 2.6. Free-energy profile (B3LYP/6-31 + G* with ZPE correction) for intermediates and transition structures for Wadsworth-Emmons reactions between the lithium enolate of trimethyl phosphonoacetate anion and formaldehyde in the gas phase and in tetrahydrofuran or ethanol. Adapted from *J. Org. Chem.*, **63**, 1280 (1998), by permission of the American Chemical Society.

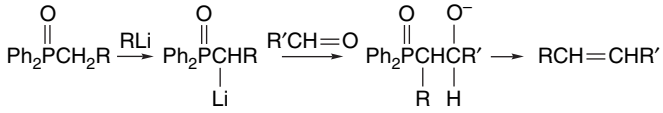
Another computational study included a solvation model.[267] Solvation strongly stabilized the oxyanion adduct, suggesting that its formation may be rate and product determining under certain circumstances. When this is true, analysis of stereoselectivity must focus on the addition TS. Figure 2.6 shows the computed energy profile for the TSs and intermediates. TS1 is the structure leading to the oxyanion intermediate. According to the energy profile, its formation is irreversible in solution and therefore determines the product stereochemistry. The structure shows a rather small (30°–35°) dihedral angle and suggests that steric compression would arise with a *Z*-substituent.



Structure **3** is the intermediate oxyanion adduct. TS2 is the structure leading to cyclization of the oxyanion to the oxaphosphetane. Structure **4a** is the oxaphosphetane, and the computation shows only a small barrier for its conversion to product.

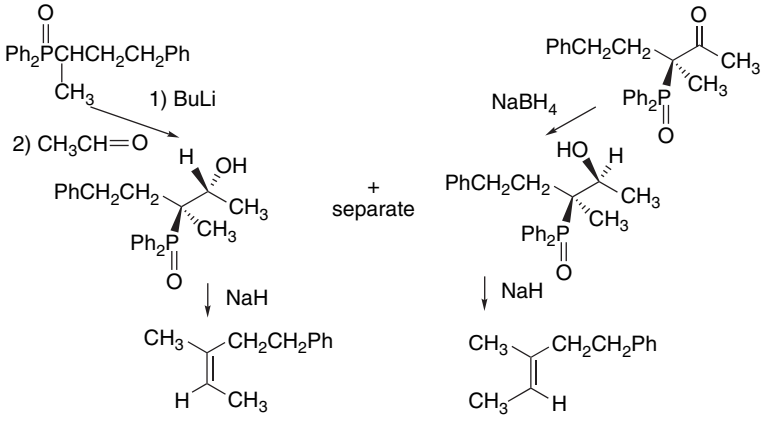


Carbanions derived from phosphine oxides also add to carbonyl compounds. The adducts are stable but undergo elimination to form alkene on heating with a base such as sodium hydride. This reaction is known as the *Horner-Wittig* reaction.[268]



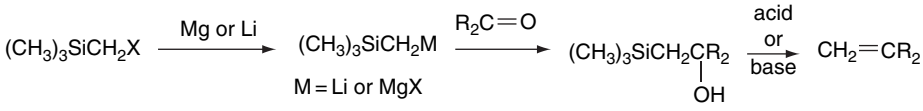
267. P. Brandt, P.-O. Norrby, I. Martin, and T. Rein, *J. Org. Chem.*, **63**, 1280 (1998).
268. For a review, see J. Clayden and S. Warren, *Angew. Chem. Int. Ed. Engl.*, **35**, 241 (1996).

The unique feature of the Horner-Wittig reaction is that the addition intermediate can be isolated and purified, which provides a means for control of the reaction's stereochemistry. It is possible to separate the two diastereomeric adducts in order to prepare the pure alkenes. The elimination process is *syn*, so the stereochemistry of the alkene that is formed depends on the stereochemistry of the adduct. Usually the *anti* adduct is the major product, so it is the *Z*-alkene that is favored. The *syn* adduct is most easily obtained by reduction of β-ketophosphine oxides.[269]

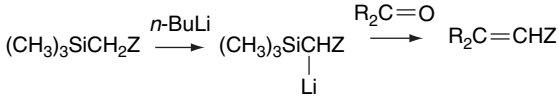


2.4.2. Reactions of α-Trimethylsilylcarbanions with Carbonyl Compounds

Trialkylsilyl groups have a modest stabilizing effect on adjacent carbanions (see Part A, Section 3.4.2). Reaction of the carbanions with carbonyl compounds gives β-hydroxyalkylsilanes. β-Hydroxyalkylsilanes are converted to alkenes by either acid or base.[270] These eliminations provide the basis for a synthesis of alkenes. The reaction is sometimes called the *Peterson reaction*.[271] For example, the Grignard reagent derived from chloromethyltrimethylsilane adds to an aldehyde or ketone and the intermediate can be converted to a terminal alkene by acid or base.[272]



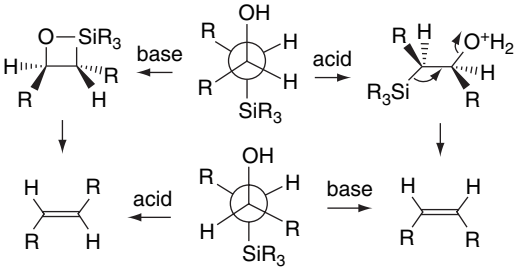
Alternatively, organolithium reagents of the type $(CH_3)_3SiCH(Li)Z$, where Z is a carbanion-stabilizing substituent, can be prepared by deprotonation of $(CH_3)_3SiCH_2Z$ with *n*-butyllithium.



269. A. D. Buss and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2307 (1985).
270. P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464 (1975).
271. For reviews, see D. J. Ager, *Org. React.*, **38**, 1 (1990); D. J. Ager, *Synthesis*, 384 (1984); A. G. M. Barrett, J. M. Hill, E. M. Wallace, and J. A. Flygare, *Synlett*, 764 (1991).
272. D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).

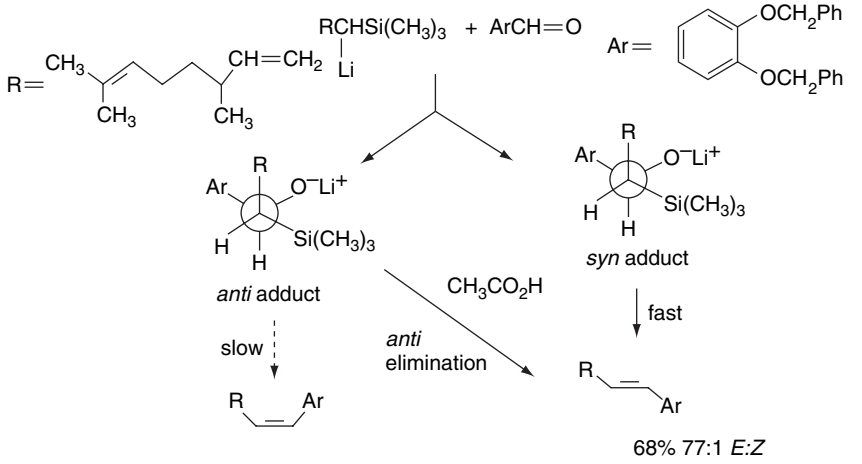
These reagents usually react with aldehydes and ketones to give substituted alkenes directly. No separate elimination step is necessary because fragmentation of the intermediate occurs spontaneously under the reaction conditions.

In general, the elimination reactions are *anti* under acidic conditions and *syn* under basic conditions. This stereoselectivity is the result of a cyclic mechanism under basic conditions, whereas under acidic conditions an acyclic β-elimination occurs.



The *anti* elimination can also be achieved by converting the β-silyl alcohols to trifluoroacetate esters.[273] The stereoselectivity of the Peterson olefination depends on the generation of pure *syn* or *anti* β-silylalcohols, so several strategies have been developed for their stereoselective preparation.[274]

There can be significant differences in the rates of elimination of the stereoisomeric β-hydroxysilanes. Van Vranken and co-workers took advantage of such a situation to achieve a highly stereoselective synthesis of a styryl terpene. (The lithiated reactant is prepared by reductive lithiation; see p. 625). The *syn* adduct decomposes rapidly at −78° C but because of steric effects, the *anti* isomer remains unreacted. Acidification then promotes *anti* elimination to the desired *E*-isomer.[275]

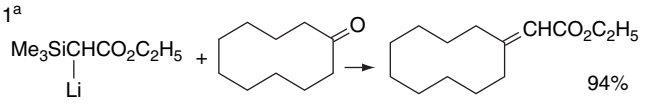


Scheme 2.19 provides some examples of the Peterson olefination. The Peterson olefination has not been used as widely in synthesis as the Wittig and Wadsworth-Emmons reactions, but it has been used advantageously in the preparation of relatively

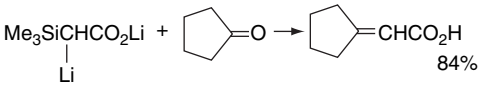
273. M. F. Connil, B. Jousseaume, N. Noiret, and A. Saux, *J. Org. Chem.*, **59**, 1925 (1994).
274. A. G. M. Barrett and J. A. Flygare, *J. Org. Chem.*, **56**, 638 (1991); L. Duhamel, J.Gralak, and A. Bouyanzer, *J. Chem. Soc., Chem. Commun.*, 1763 (1993).
275. J. B. Perales, N. F. Makino, and D. L. Van Vranken, *J. Org. Chem.*, **67**, 6711 (2002).

Scheme 2.19. Carbonyl Olefination Using Trimethylsilyl-Substituted Organolithium Reagents

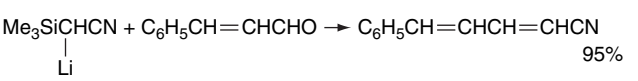
1[a]



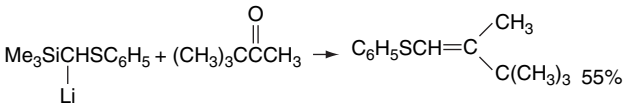
2[b]



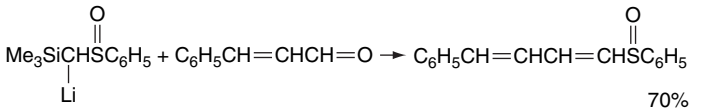
3[c]



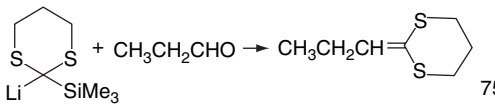
4[d]



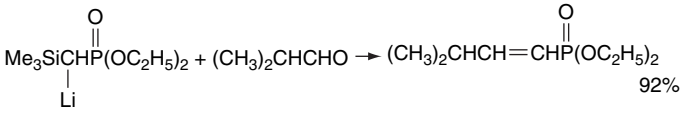
5[e]



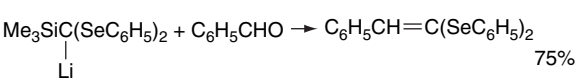
6[f]



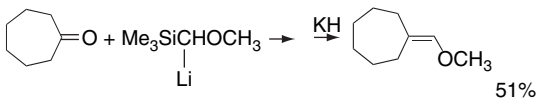
7[d]



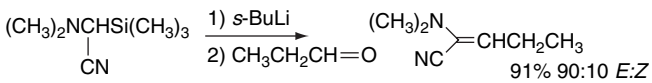
8[g]



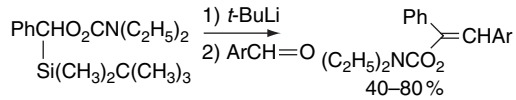
9[h]



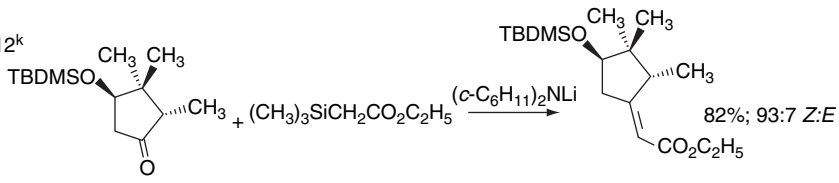
10[i]



11[j]



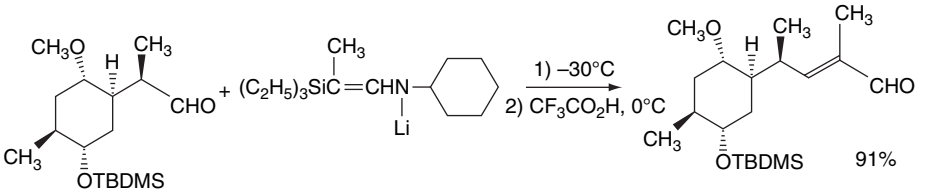
12[k]



(*Continued*)

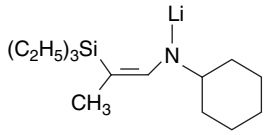
Scheme 2.19. (*Continued*)

13[l]



a. K. Shimoji, H. Taguchi, H. Yamamoto, K. Oshima, and H. Hozaki, *J. Am. Chem. Soc.*, **96**, 1620 (1974).
b. P. A. Grieco, C. L. J. Wang, and S. D. Burke, *J. Chem. Soc. Chem. Commun.*, 537 (1975).
c. I. Matsuda, S. Murata, and Y. Ishii, *J. Chem. Soc., Perkin Trans. 1*, 26 (1979).
d. F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 939 (1972).
e. F. A. Carey and O. Hernandez, *J. Org. Chem.*, **38**, 2670 (1973).
f. D. Seebach, M. Kolb, and B.-T. Grobel, *Chem. Ber.*, **106**, 2277 (1973).
g. B. T. Grobel and D. Seebach, *Chem. Ber.*, **110**, 852 (1977).
h. P. Magnus and G. Roy, *Organometallics*, **1**, 553 (1982).
i. W. Adam and C. M. Ortega-Schulte, *Synlett*, 414 (2003).
j. L. F. van Staden, B. Bartels-Rahm, J. S. Field, and N. D. Emslie, *Tetrahedron*, **54,** 3255 (1998).
k. J.-M. Galano, G. Audran, and H. Monti, *Tetrahedron Lett.*, **42**, 6125 (2001).
l. S. F. Martin, J. A. Dodge, L. E. Burgess, and M. Hartmann, *J. Org. Chem.*, **57**, 1070 (1992).

unstable olefins. Entries 1 to 8 show the use of lithio silanes having a range of anion-stabilizing groups. The anions are prepared using alkyllithium reagents or lithium amides. Entries 9 to 11 illustrate the utility of the reaction to prepare relatively unstable substituted alkenes. The silyl anions are typically more reactive than stabilized Wittig ylides, and in the case of Entry 12 good results were obtained while the triphenylphosphonium ylide was unreactive. Entry 13 shows the use of Peterson olefination for chain extension with an α-methyl-α, β-unsaturated aldehyde. The preferred reagent for this transformation is a lithio β-trialkylsilylenamine.[276]

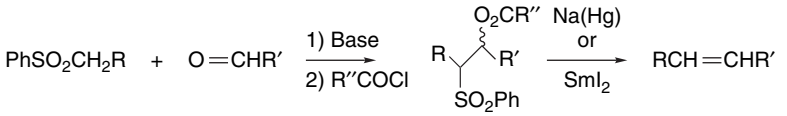


2.4.3. The Julia Olefination Reaction

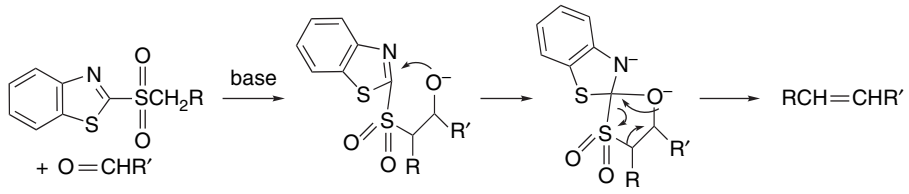
The *Julia olefination* involves the addition of a sulfonyl-stabilized carbanion to a carbonyl compound, followed by elimination to form an alkene.[277] In the initial versions of the reaction, the elimination was done under *reductive conditions*. More recently, a modified version that avoids this step was developed. The former version is sometimes referred to as the *Julia-Lythgoe olefination*, whereas the latter is called the *Julia-Kocienski olefination.* In the reductive variant, the adduct is usually acylated and then treated with a reducing agent, such as sodium amalgam or samarium diiodide.[278]

276. R. Desmond, S. G. Mills, R. P. Volante, and I. Shinkai, *Tetrahedron Lett.*, **29**, 3895 (1988).
277. P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2563 (2002).
278. A. S. Kende and J. Mendoza, *Tetrahedron Lett.*, **31**, 7105 (1990); G. E. Keck, K. A. Savin, and M. A. Weglarz, *J. Org. Chem.*, **60**, 3194 (1995); K. Fukumoto, M. Ihara, S. Suzuki, T. Taniguchi, and Y. Yokunaga, *Synlett*, 895 (1994); I. E. Marko, F. Murphy, and S. Dolan, *Tetrahedron Lett.*, **37**, 2089 (1996); I. E. Marko, F. Murphy, L. Kumps, A. Ates, R. Touillaux, D. Craig, S. Carballares, and S. Dolan, *Tetrahedron*, **57**, 2609 (2001).

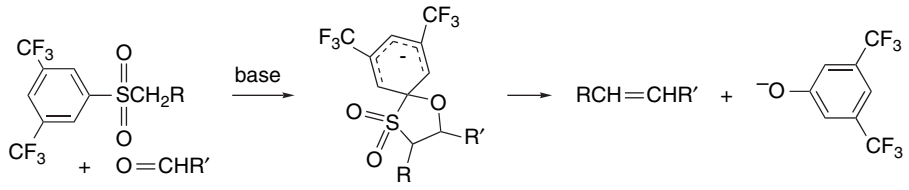
The mechanistic details of reductive elimination reactions of this type are considered in Section 5.8.



In the modified procedure one of several heteroaromatic sulfones is used. The crucial role of the heterocyclic ring is to provide a nonreductive mechanism for the elimination step, which occurs by an addition-elimination mechanism that results in fragmentation to the alkene. The original example used a benzothiazole ring,[279] but more recently tetrazoles have been developed for this purpose.[280]



Other aryl sulfones that can accommodate the nucleophilic addition step also react in the same way. For example, excellent results have been obtained using 3,5-*bis*-(trifluoromethyl)phenyl sulfones.[281]

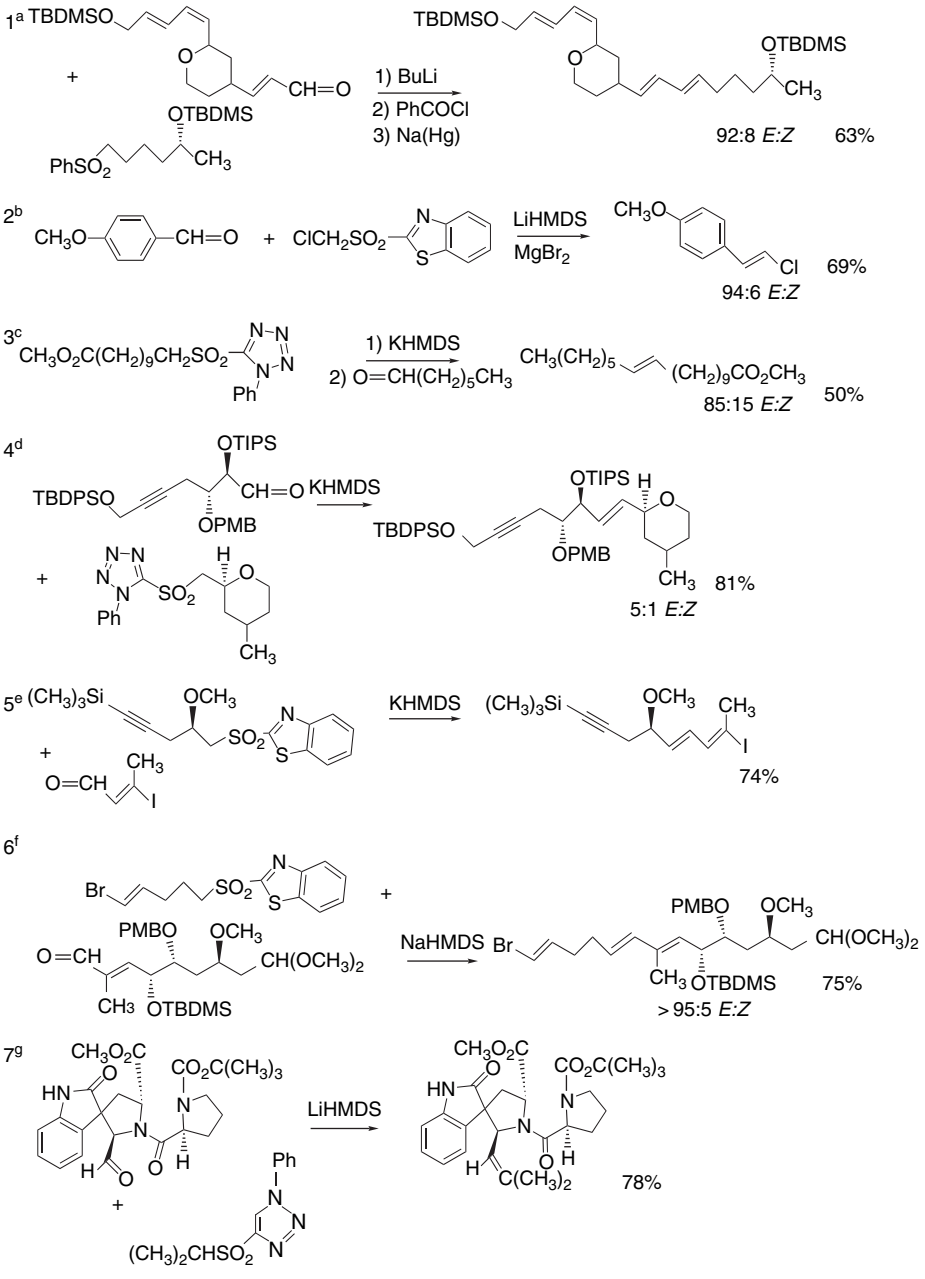


As is the case with the Wittig and Peterson olefinations, there is more than one point at which the stereoselectivity of the reaction can be determined, depending on the details of the mechanism. Adduct formation can be product determining or reversible. Furthermore, in the reductive mechanism, there is the potential for stereorandomization if radical intermediates are involved. As a result, there is a degree of variability in the stereoselectivity. Fortunately, the modified version using tetrazolyl sulfones usually gives a predominance of the *E*-isomer.

Scheme 2.20 gives some examples of the application of the Julia olefination in synthesis. Entry 1 demonstrates the reductive elimination conditions. This reaction gave a good *E*:*Z* ratio under the conditions shown. Entry 2 is an example of the use of the modified reaction that gave a good *E*:*Z* ratio in the synthesis of vinyl chlorides. Entry 3 uses the tetrazole version of the reaction in the synthesis of a long-chain ester. Entries 4 to 7 illustrate the use of modified conditions for the synthesis of polyfunctional molecules.

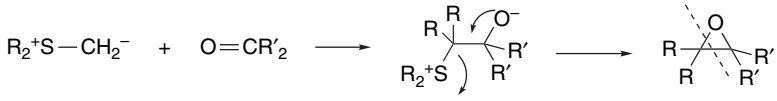
279. J. B. Baudin, G. Hareau, S. A. Julia, and O. Ruel, *Tetrahedron Lett.*, **32**, 1175 (1991).
280. P. R. Blakemore, W. J. Cole, P. J. Kocienski, and A. Morley, *Synlett*, 26 (1998); P. J. Kocienski, A. Bell, and P. R. Blakemore, *Synlett*, 365 (2000).
281. D.A. Alonso, M. Fuensanta, C. Najera, and M. Varea, *J. Org. Chem.*, **70**, 6404 (2005).

Scheme 2.20. Julia Olefination Reactions

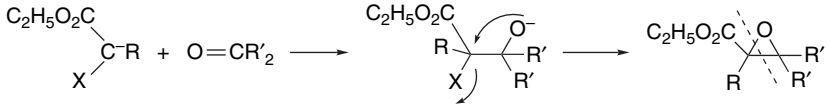


a. J. P. Marino, M. S. McClure, D. P. Holub, J. V. Comasseto, and F. C. Tucci, *J. Am. Chem. Soc.*, **124**, 1664 (2002).
b. M.-E. Lebrun, P. Le Marquand, and C. Berthelette, *J. Org. Chem.*, **71**, 2009 (2006).
c. P. E. Duffy, S. M. Quinn, H. M. Roche, and P. Evans, *Tetrahedron*, **62**, 4838 (2006).
d. A. Sivaramakrishnan, G. T. Nadolski, I. A. McAlexander, and B. S. Davidson, *Tetrahedron Lett.*, **43**, 2132 (2002).
e. G. Pattenden, A. T. Plowright, J. A. Tornos, and T. Ye, *Tetrahedron Lett.*, **39**, 6099 (1998).
f. D. A. Evans, V. J. Cee, T. E. Smith, D. M. Fitch, and P. S. Cho, *Angew. Chem. Int. Ed. Engl.*, **39**, 2533 (2000).
g. C. Marti and E. M. Carreira, *J. Am. Chem. Soc.*, **127**, 11505 (2005).

The reactions in this section correspond to the general Pathway **D** discussed earlier (p. 64), in which the carbon nucleophile contains a potential leaving group. This group can be the same or a different group from the anion-stabilizing group. One group of reagents that reacts according to this pattern are the sulfonium ylides, which react with carbonyl compounds to give epoxides.

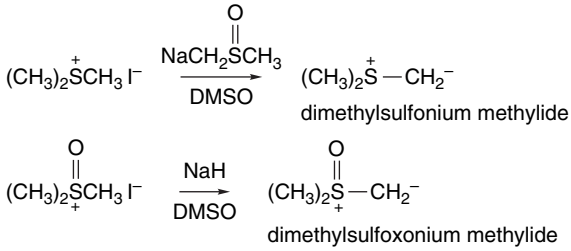


There are related reactions in which the sulfur is at the sulfoxide or sulfilimine oxidation level. Another example of the addition-cyclization route involves α-haloesters, which react to form epoxides by displacement of the halide ion.

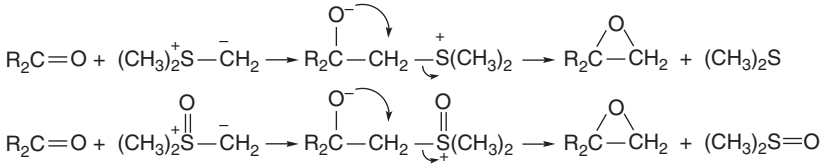


2.5.1. Sulfur Ylides and Related Nucleophiles

Sulfur ylides have several applications as reagents in synthesis.[282] Dimethylsulfonium methylide and dimethylsulfoxonium methylide are particularly useful.[283] These sulfur ylides are prepared by deprotonation of the corresponding sulfonium salts, both of which are commercially available.



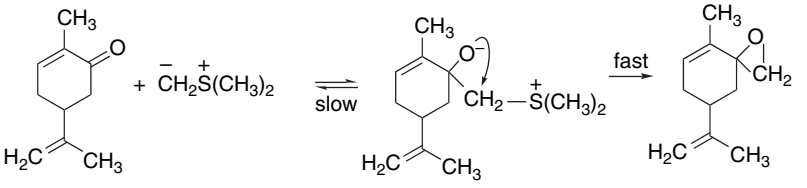
Whereas phosphonium ylides normally react with carbonyl compounds to give alkenes, dimethylsulfonium methylide and dimethylsulfoxonium methylide yield epoxides. Instead of a four-center elimination, the adducts from the sulfur ylides undergo intramolecular displacement of the sulfur substituent by oxygen. In this reaction, the sulfur substituent serves both to promote anion formation and as the leaving group.



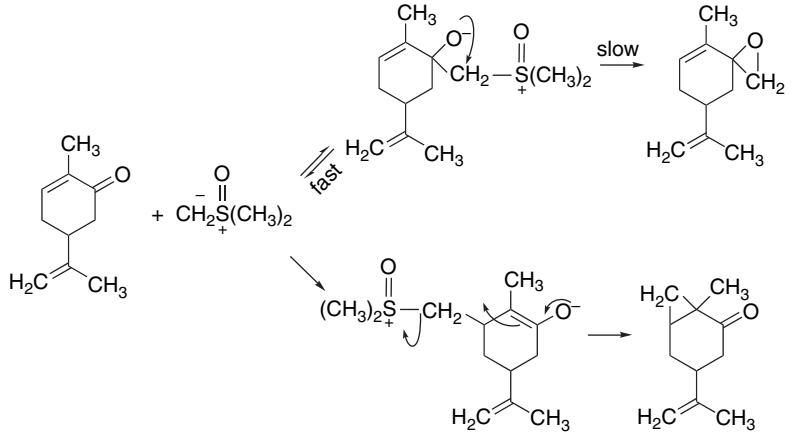
[282] B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Academic Press, New York, 1975; E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York, 1978.

[283] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

Dimethylsulfonium methylide is both more reactive and less stable than dimethylsulfoxonium methylide, so it is generated and used at a lower temperature. A sharp distinction between the two ylides emerges in their reactions with α,β-unsaturated carbonyl compounds. Dimethylsulfonium methylide yields epoxides, whereas dimethylsulfoxonium methylide reacts by conjugate addition and gives cyclopropanes (compare Entries 5 and 6 in Scheme 2.21). It appears that the reason for the difference lies in the relative rates of the two reactions available to the betaine intermediate: (a) reversal to starting materials, or (b) intramolecular nucleophilic displacement.[284] Presumably both reagents react most rapidly at the carbonyl group. In the case of dimethylsulfonium methylide the intramolecular displacement step is faster than the reverse of the addition, and epoxide formation takes place.

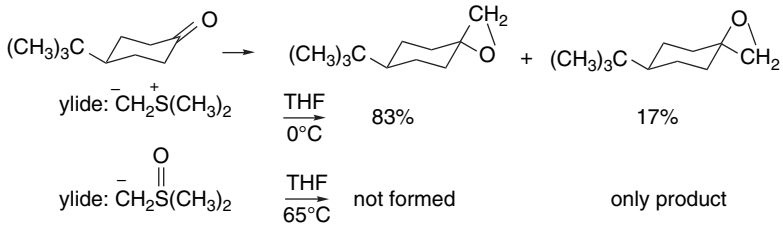


With the more stable dimethylsulfoxonium methylide, the reversal is relatively more rapid and product formation takes place only after conjugate addition.



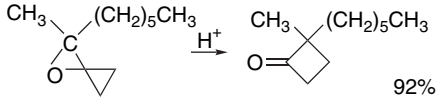
Another difference between dimethylsulfonium methylide and dimethylsulfoxonium methylide concerns the stereoselectivity in formation of epoxides from cyclohexanones. Dimethylsulfonium methylide usually adds from the axial direction whereas dimethylsulfoxonium methylide favors the equatorial direction. This result may also be due to reversibility of addition in the case of the sulfoxonium methylide.[92] The product from the sulfonium ylide is the result the kinetic preference for axial addition by small nucleophiles (see Part A, Section 2.4.1.2). In the case of reversible addition of the sulfoxonium ylide, product structure is determined by the rate of displacement and this may be faster for the more stable epoxide.

284. C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *J. Am. Chem. Soc.*, **95**, 7424 (1973).

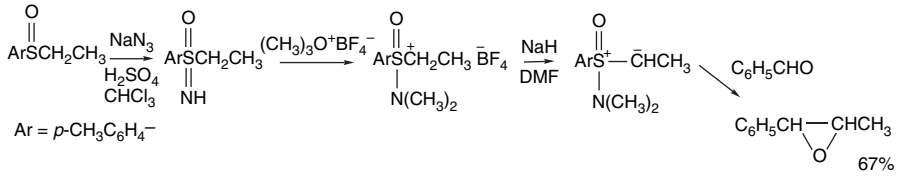


Examples of the use of dimethylsulfonium methylide and dimethylsulfoxonium methylide are listed in Scheme 2.21. Entries 1 to 5 are conversions of carbonyl compounds to epoxides. Entry 6 is an example of cyclopropanation with dimethyl sulfoxonium methylide. Entry 7 compares the stereochemistry of addition of dimethylsulfonium methylide to dimethylsulfoxonium methylide for nornborn-5-en-2-one. The product in Entry 8 was used in a synthesis of α-tocopherol (vitamin E).

Sulfur ylides can also transfer substituted methylene units, such as isopropylidene (Entries 10 and 11) or cyclopropylidene (Entries 12 and 13). The oxaspiropentanes formed by reaction of aldehydes and ketones with diphenylsulfonium cyclopropylide are useful intermediates in a number of transformations such as acid-catalyzed rearrangement to cyclobutanones.[285]



Aside from the methylide and cyclopropylide reagents, the sulfonium ylides are not very stable. A related group of reagents derived from sulfoximines offers greater versatility in alkylidene transfer reactions.[286] The preparation and use of this class of ylides is illustrated below.



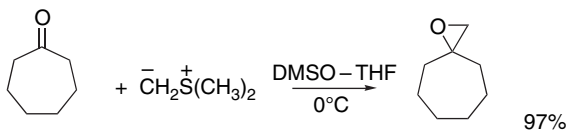
A similar pattern of reactivity has been demonstrated for the anions formed by deprotonation of *S*-alkyl-*N*-*p*-toluenesulfoximines (see Entry 14 in Scheme 2.21).[287]

The sulfoximine group provides anion-stabilizing capacity in a chiral environment and a number of synthetic applications have been developed based on these properties.[288]

285. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5321 (1973).
286. C. R. Johnson, *Acc. Chem. Res.*, **6**, 341 (1973); C. R.Johnson, *Aldrichimica Acta*, **18**, 3 (1985).
287. C. R. Johnson, R. A. Kirchoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.*, **95**, 4287 (1973).
288. M. Reggelin and C. Zur, *Synthesis*, 1 (2000).

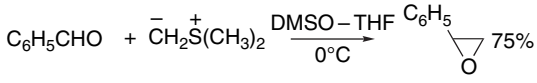
Scheme 2.21. Reactions of Sulfur Ylides

1[a]



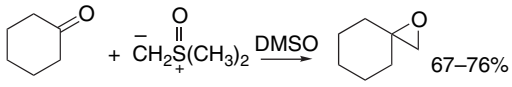
97%

2[a]



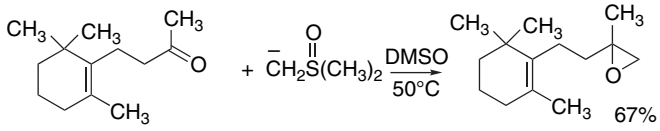
75%

3[b]



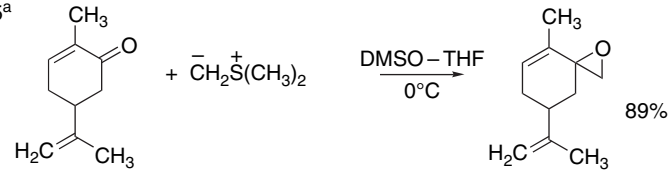
67–76%

4[c]



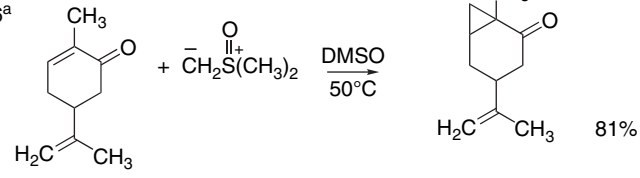
67%

5[a]



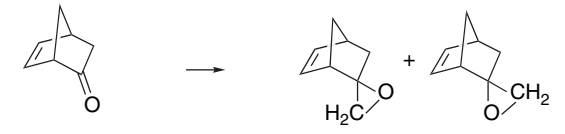
89%

6[a]



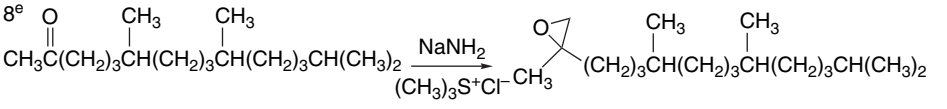
81%

7[d]



ylide: $\bar{C}H_2\overset{+}{S}(CH_3)_2$	DMSO–THF, 0°C	6%	94%
ylide: $\bar{C}H_2\overset{O}{\overset{\|}{S}}{}^{+}(CH_3)_2$	DMSO, 60°C	65%	27%

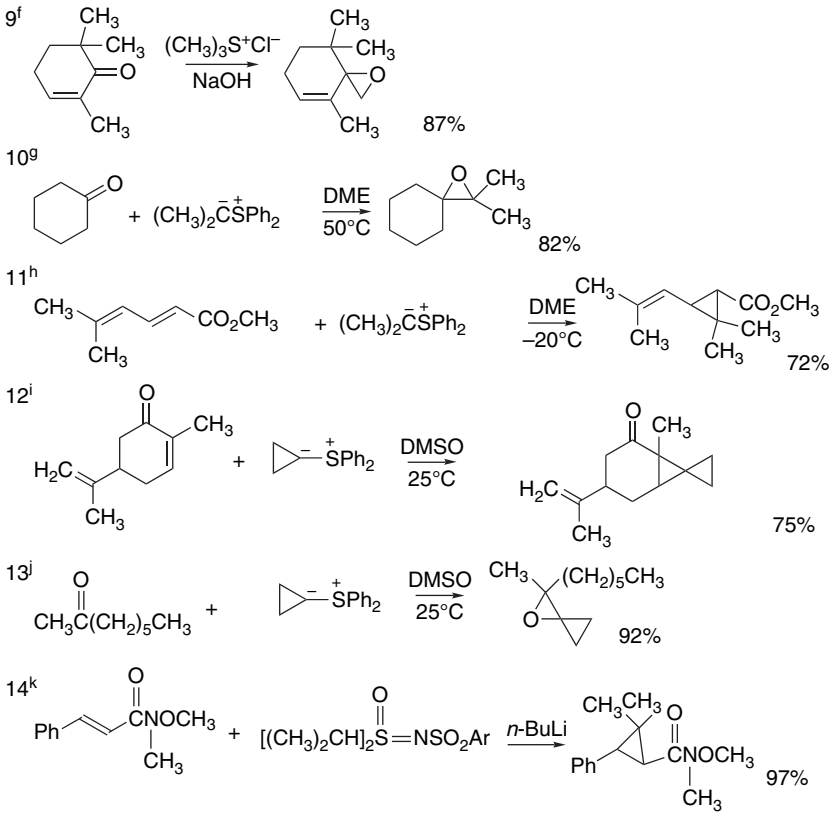
8[e]



92%

(*Continued*)

Scheme 2.21. (*Continued*)



a. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
b. E. J. Corey and M. Chaykovsky, *Org. Synth.*, **49**, 78 (1969).
c. M. G. Fracheboud, O. Shimomura, R. K. Hill, and F. H. Johnson, *Tetrahedron Lett.*, 3951 (1969).
d. R. S. Bly, C. M. DuBose, Jr., and G. B. Konizer, *J. Org. Chem.*, **33**, 2188 (1968).
e. G. L. Olson, H.-C. Cheung, K. Morgan, and G. Saucy, *J. Org. Chem.*, **45**, 803 (1980).
f. M. Rosenberger, W. Jackson, and G. Saucy, *Helv. Chim. Acta*, **63**, 1665 (1980).
g. E. J. Corey, M. Jautelat, and W. Oppolzer, *Tetrahedron Lett.*, 2325 (1967).
h. E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, **89**, 3112 (1967).
i. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5307 (1973).
j. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5311 (1973).
k. K. E. Rodriques, *Tetrahedron Lett.*, **32**, 1275 (1991).

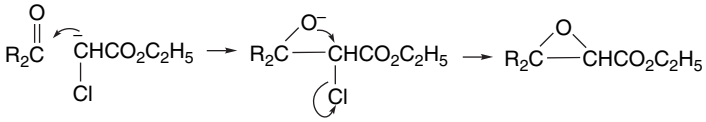
Dimethylsulfonium methylide reacts with reactive alkylating reagents such as allylic and benzylic bromides to give terminal alkenes. A similar reaction occurs with primary alkyl bromides in the presence of LiI. The reaction probably involves alkylation of the ylide, followed by elimination.[289]

$$RCH_2{-}X + CH_2{=}S^+(CH_3)_2 \longrightarrow RCH_2CH_2S^+(CH_3)_2 \longrightarrow RCH{=}CH_2$$

289. L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. LeGall, D.-S. Shin, and J. R. Falck, *Tetrahedron Lett.*, **35**, 5453 (1994).

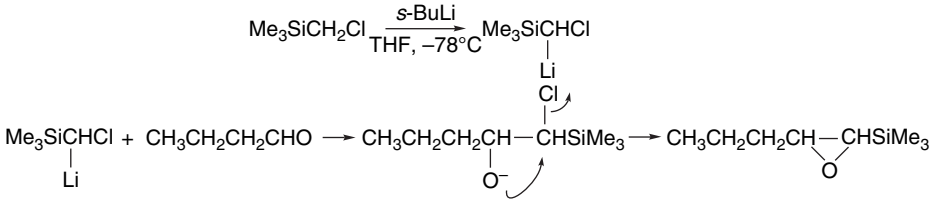
2.5.2. Nucleophilic Addition-Cyclization of α-Haloesters

The pattern of nucleophilic addition at a carbonyl group followed by intramolecular nucleophilic displacement of a leaving group present in the nucleophile can also be recognized in a much older synthetic technique, the *Darzens reaction*.[290] The first step in this reaction is addition of the enolate of the α-haloester to the carbonyl compound. The alkoxide oxygen formed in the addition then effects nucleophilic attack, displacing the halide and forming an α, β-epoxy ester (also called a glycidic ester).

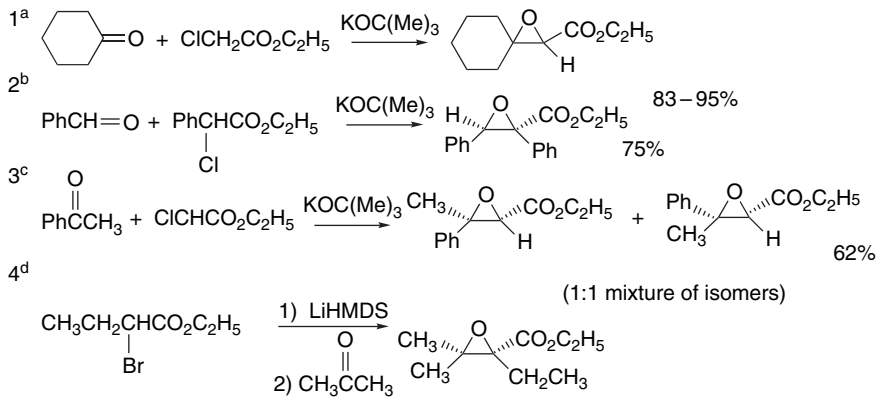


Scheme 2.22 shows some examples of the Darzens reaction.

Trimethylsilylepoxides can be prepared by an addition-cyclization process. Reaction of chloromethyltrimethylsilane with *sec*-butyllithium at very low temperature gives an α-chloro lithium reagent that leads to an epoxide on reaction with an aldehyde or ketone.[291]



Scheme 2.22. Darzens Condensation Reaction

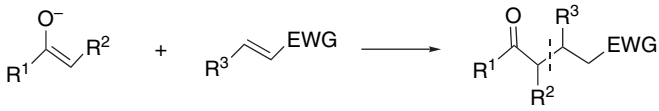


a. R. H. Hunt, L. J. Chinn, and W. S. Johnson, *Org. Synth.*, **IV**, 459 (1963).
b. H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, **82**, 5459 (1960).
c. F. W. Bachelor and R. K. Bansal, *J. Org. Chem.*, **34**, 3600 (1969).
d. R. F. Borch, *Tetrahedron Lett.*, 3761 (1972).

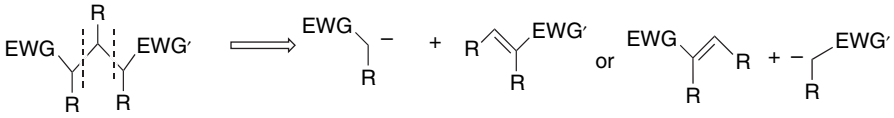
290. M. S. Newman and B. J. Magerlein, *Org. React.*, **5**, 413 (1951).
291. C. Burford, F. Cooke, E. Ehlinger, and P. D. Magnus, *J. Am. Chem. Soc.*, **99**, 4536 (1977).

2.6. Conjugate Addition by Carbon Nucleophiles

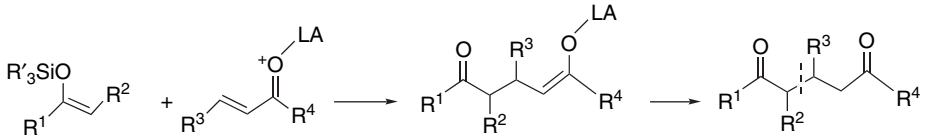
The previous sections dealt with reactions in which the new carbon-carbon bond is formed by addition of the nucleophile to a carbonyl group. Another important method for alkylation of carbon nucleophiles involves addition to an electrophilic multiple bond. The electrophilic reaction partner is typically an α,β-unsaturated ketone, aldehyde, or ester, but other electron-withdrawing substituents such as nitro, cyano, or sulfonyl also activate carbon-carbon double and triple bonds to nucleophilic attack. The reaction is called *conjugate addition* or the *Michael reaction.*



More generally, many combinations of EWG substituents can serve as the anion-stabilizing and alkene-activating groups. Conjugate addition has the potential to form a bond α to one group and β to the other to form a α,γ-disubstituted system.



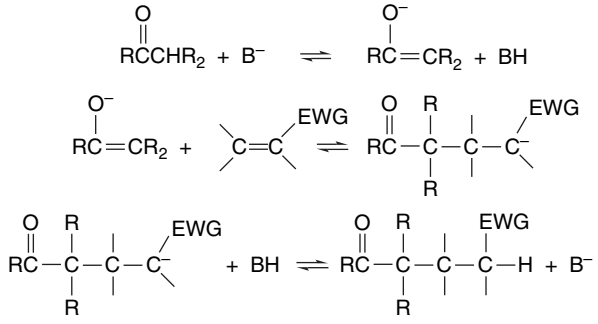
The scope of the conjugate addition reaction can be further expanded by use of Lewis acids in conjunction with enolate equivalents, especially silyl enol ethers and silyl ketene acetals. The adduct is stabilized by a new bond to the Lewis acid and products are formed from the adduct.



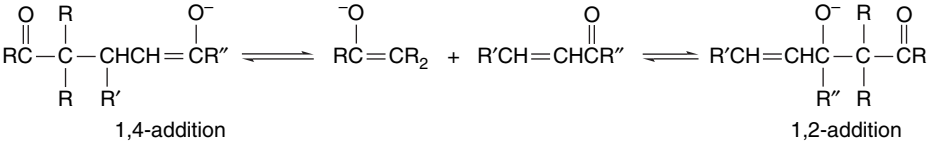
Other kinds of nucleophiles such as amines, alkoxides, and sulfide anions also react with electrophilic alkenes, but we focus on the carbon-carbon bond forming reactions.

2.6.1. Conjugate Addition of Enolates

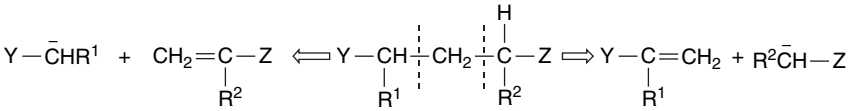
Conjugate addition of enolates under some circumstances can be carried out with a catalytic amount of base. All the steps are reversible.



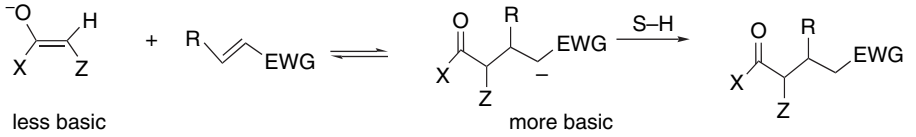
When the EWG is a carbonyl group, there can be competition with 1,2-addition, which is especially likely for aldehydes but can also occur with ketones. With successively less reactive carbonyl groups, 1,4-addition becomes more favorable. Highly reactive, hard nucleophiles tend to favor 1,2-addition and the reaction is irreversible if the nucleophile is a poor leaving group. For example with organometallic reagents, 1,2-addition is usually observed and it is irreversible because there is no tendency to expel an alkyl anion. Section 2.6.5 considers some exceptions in which organometallic reagents are added in the 1,4-manner. With less basic nucleophiles, the 1,2-addition is more easily reversible and the 1,4-addition product is usually more stable.



Retrosynthetically, there are inherently two possible approaches to the products of conjugate addition as represented below, where Y and Z represent two different anion-stabilizing groups.



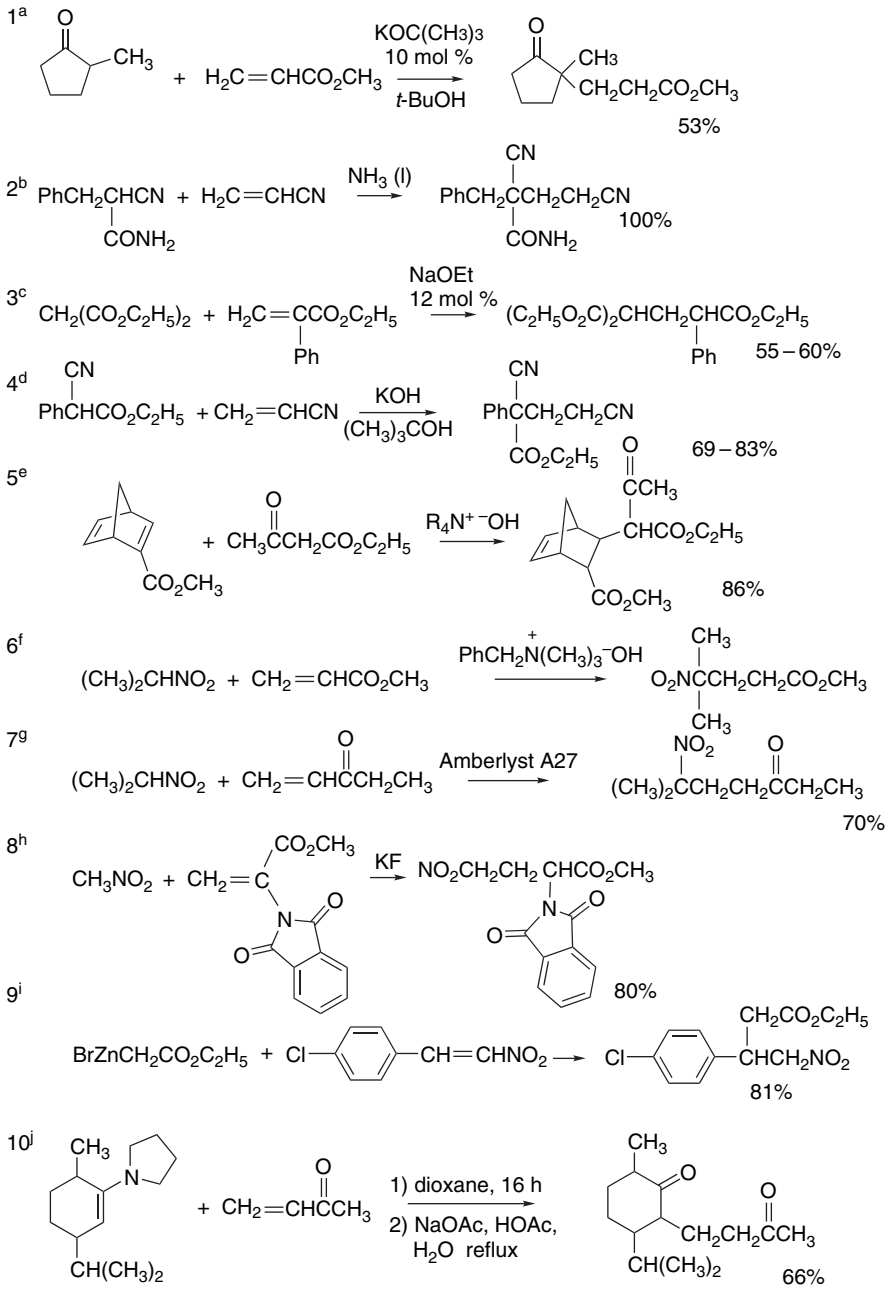
When a catalytic amount of base is used, the most effective nucleophiles are enolates derived from relatively acidic compounds such as β-ketoesters or malonate esters. The adduct anions are more basic than the nucleophile and are protonated under the reaction conditions.



Scheme 2.23 provides some examples of conjugate addition reactions. Entry 1 illustrates the tendency for reaction to proceed through the more stable enolate. Entries 2 to 5 are typical examples of addition of doubly stabilized enolates to electrophilic alkenes. Entries 6 to 8 are cases of addition of nitroalkanes. Nitroalkanes are comparable in acidity to β-ketoesters (see Table 1.1) and are often excellent nucleophiles for conjugate addition. Note that in Entry 8 fluoride ion is used as the base. Entry 9 is a case of adding a zinc enolate (Reformatsky reagent) to a nitroalkene. Entry 10 shows an enamine as the carbon nucleophile. All of these reactions were done under equilibrating conditions.

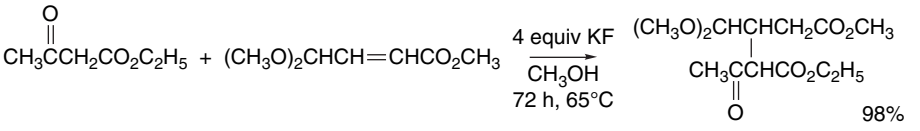
The fluoride ion is an effective catalyst for conjugate additions involving relatively acidic carbon nucleophiles.[292] The reactions can be done in the presence of excess

[292.] J. H. Clark, *Chem. Rev.*, **80**, 429 (1980).

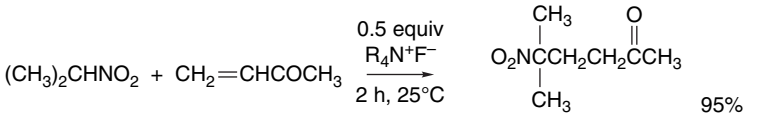


a. H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).
b. S. Wakamatsu, *J. Org. Chem.*, **27**, 1285 (1962).
c. E. M. Kaiser, C. L. Mao, C. F. Hauser, and C. R. Hauser, *J. Org. Chem.*, **35**, 410 (1970).
d. E. C. Horning and A. F. Finelli, *Org. Synth.*, **IV**, 776 (1963).
e. K. Alder, H. Wirtz, and H. Koppelberg, *Liebigs Ann. Chem.*, **601**, 138 (1956).
f. R. B. Moffett, *Org. Synth.*, **IV**, 652 (1963).
g. R. Ballini, P. Marziali, and A. Mozziacafreddo, *J. Org. Chem.*, **61**, 3209 (1996).
h. M. J. Crossley, Y. M. Fung, J. J. Potter, and A. W. Stamford, *J. Chem. Soc., Perkin Trans. 2*, 1113 (1998).
i. R. Menicagli and S. Samaritani, *Tetrahedron*, **52**, 1425 (1996).
j. K. D. Croft, E. L. Ghisalberti, P. R. Jefferies, and A. D. Stuart, *Aust. J. Chem.*, **32**, 2079 (1979).

fluoride, where the formation of the [F–H–F$^-$] ion occurs, or by use of a tetralkylammonium fluoride in an aprotic solvent.



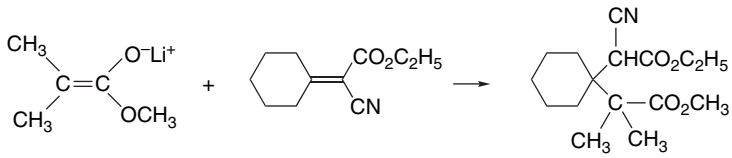
Ref. 293



Ref. 294

As in the case of aldol addition, the scope of conjugate addition reactions can be extended by the use of techniques for regio- and stereospecific preparation of enolates and enolate equivalents. If the reaction is carried out with a stoichiometrically formed enolate in the absence of a proton source, the initial product is the enolate of the adduct. The replacement of a π bond by a σ bond ensures a favorable ΔH.

Among Michael acceptors that have been shown to react with ketone and ester enolates under kinetic conditions are methyl α-trimethylsilylvinyl ketone,[295] methyl α-methylthioacrylate,[296] methyl methylthiovinyl sulfoxide,[297] and ethyl α-cyanoacrylate.[298] Each of these acceptors benefits from a second anion-stabilizing substituent. The latter class of acceptors has been found to be capable of generating contiguous quaternary carbon centers.

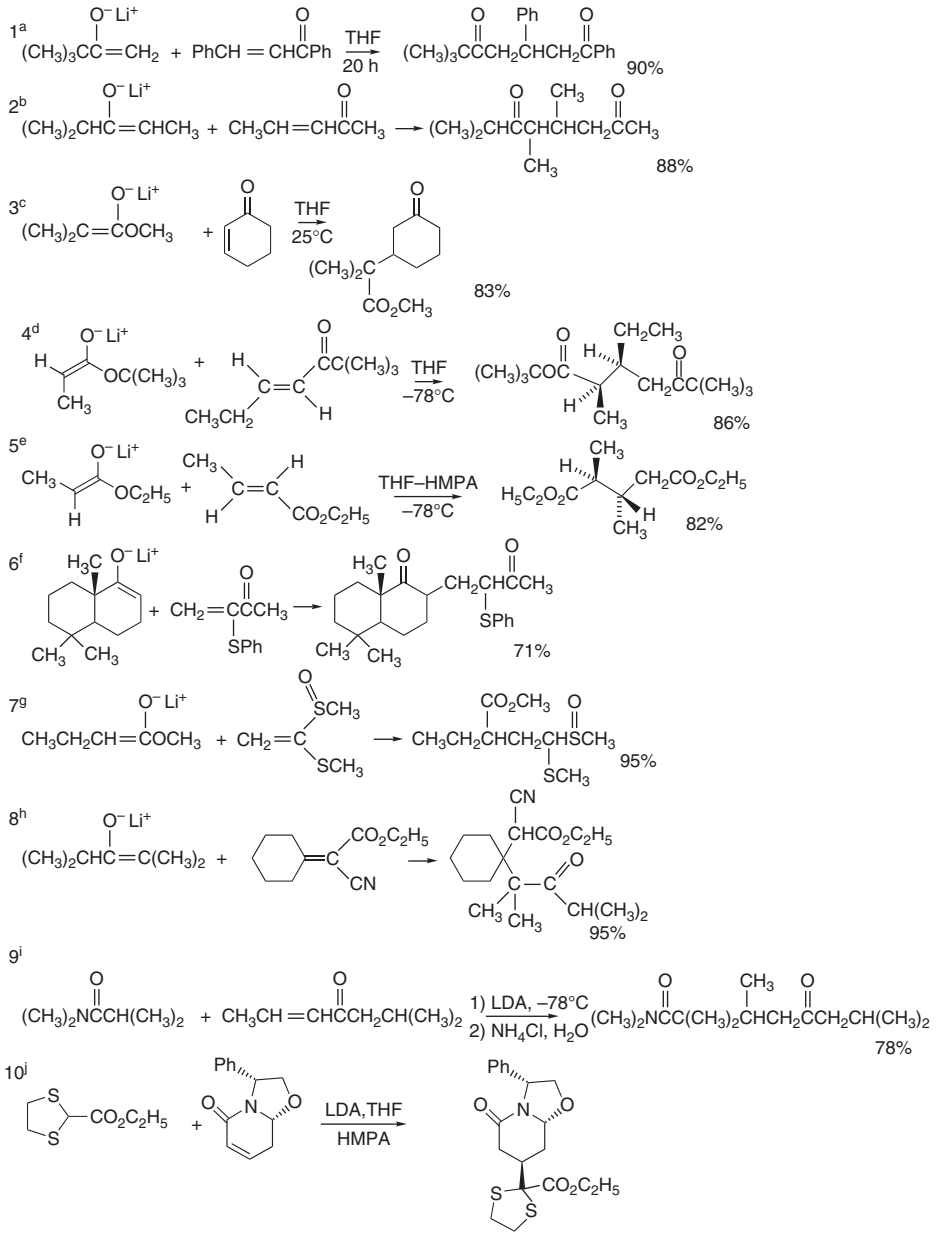


Ref. 298

Several examples of conjugate addition of carbanions carried out under aprotic conditions are given in Scheme 2.24. The reactions are typically quenched by addition of a proton source to neutralize the enolate. It is also possible to trap the adduct by silylation or, as we will see in Section 2.6.2, to carry out a tandem alkylation. Lithium enolates preformed by reaction with LDA in THF react with enones to give 1,4-diketones (Entries 1 and 2). Entries 3 and 4 involve addition of ester enolates to enones. The reaction in Entry 3 gives the 1,2-addition product at -78°C but isomerizes to the 1,4-product at 25° C. Esters of 1,5-dicarboxylic acids are obtained by addition of ester enolates to α,β-unsaturated esters (Entry 5). Entries 6 to 8 show cases of

293. S. Tori, H. Tanaka, and Y. Kobayashi, *J. Org. Chem.*, **42**, 3473 (1977).
294. J. H. Clark, J. M. Miller, and K.-H. So, *J. Chem. Soc., Perkin Trans. I*, 941 (1978).
295. G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973).
296. R. J. Cregge, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 2603 (1973).
297. J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepple, and R. H. Schlessinger, *Tetrahedron Lett.*, 4711 (1973).
298. R. A. Holton, A. D. Williams, and R. M. Kennedy, *J. Org. Chem.*, **51**, 5480 (1986).

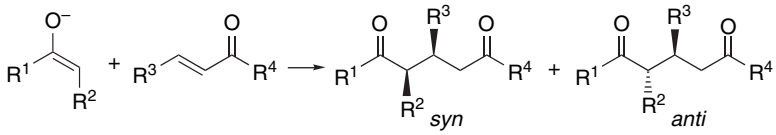
Scheme 2.24. Conjugate Addition under Aprotic Conditions



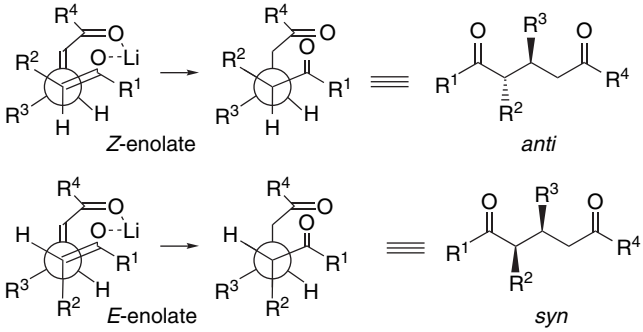
a. J. Bertrand, L. Gorrichon, and P. Maroni, *Tetrahedron*, **40**, 4127 (1984).
b. D. A. Oare and C. H. Heathcock, *Tetrahedron Lett.*, **27**, 6169 (1986).
c. A. G. Schultz and Y. K. Yee, *J. Org. Chem.*, **41**, 4044 (1976).
d. C. H. Heathcock and D. A. Oare, *J. Org. Chem.*, **50**, 3022 (1985).
e. M. Yamaguchi, M. Tsukamoto, S. Tanaka, and I. Hirao, *Tetrahedron Lett.*, **25**, 5661 (1984).
f. K. Takaki, M. Ohsugi, M. Okada, M. Yasumura, and K. Negoro, *J. Chem. Soc., Perkin Trans. 1*, 741 (1984).
g. J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Lett.*, 4711 (1973).
h. R. A. Holton, A. D. Williams, and R. M. Kennedy, *J. Org. Chem.*, **51**, 5480 (1986).
i. D. A. Oare, M. A. Henderson, M. A. Sanner, and C. H. Heathcock, *J. Org. Chem.*, **55**, 132 (1990).
j. M. Amat, M. Perez, N. Llor, and J. Bosch, *Org. Lett.*, **4**, 2787 (2002).

enolate addition to acceptors with two anion-stabilizing groups. Entry 8 is noteworthy in that it creates two contiguous quaternary carbons. Entry 9 shows an addition of an amide anion. Entry 10 is a case of an enolate stabilized by both the dithiane ring and ester substituent. The acceptor, an α,β-unsaturated lactam, is relatively unreactive but the addition is driven forward by formation of a new σ bond. The chiral moiety incorporated into the five-membered ring promotes enantioselective formation of the new stereocenter.

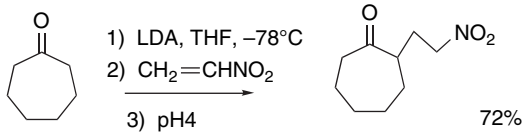
There have been several studies of the stereochemistry of conjugate addition reactions. If there are substituents on both the nucleophilic enolate and the acceptor, either *syn* or *anti* adducts can be formed.



The reaction shows a dependence on the *E*- or *Z*-stereochemistry of the enolate. *Z*-enolates favor *anti* adducts and *E*-enolates favor *syn* adducts. These tendencies can be understood in terms of an eight-membered chelated TS.[299] The enone in this TS is in an *s-cis* conformation. The stereochemistry is influenced by the *s-cis/s-trans* equilibria. Bulky R^4 groups favor the *s-cis* conformer and enhance the stereoselectivity of the reaction. A computational study on the reaction also suggested an eight-membered TS.[300]



The carbonyl functional groups are the most common both as activating EWG substituents in the acceptor and as the anion-stabilizing group in the enolate, but several other EWGs also undergo conjugate addition reactions. Nitroalkenes are excellent acceptors. The nitro group is a strong EWG and there is usually no competition from nucleophilic attack on the nitro group.



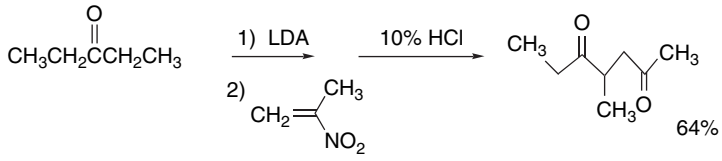
Ref. 301

[299] D. Oare and C. H. Heathcock, *J. Org. Chem.*, **55**, 157 (1990); D. A. Oare and C. H. Heathcock, *Top. Stereochem.*, **19**, 227 (1989); A. Bernardi, *Gazz. Chim. Ital.*, **125**, 539 (1995).

[300] A. Bernardi, A. M. Capelli, A. Cassinari, A. Comotti, C. Gennari, and C. Scolastico, *J. Org. Chem.*, **57**, 7029 (1992).

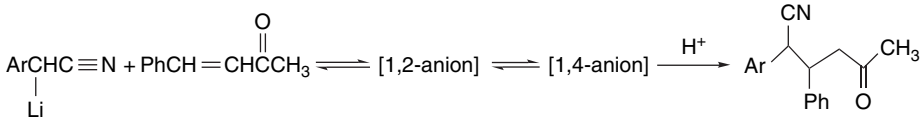
[301] R. J. Flintoft, J. C. Buzby, and J. A. Tucker, *Tetrahedron Lett.*, **40**, 4485 (1999).

The nitro group can be converted to a ketone by hydrolysis of the nitronate anion, permitting the synthesis of 1,4-dicarbonyl compounds.

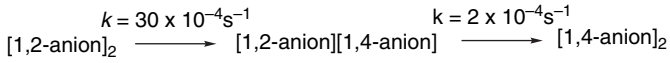


Ref. 302

Anions derived from nitriles can act as nucleophiles in conjugate addition reactions. A range of substituted phenylacetonitriles undergoes conjugate addition to 4-phenylbut-3-en-2-one.



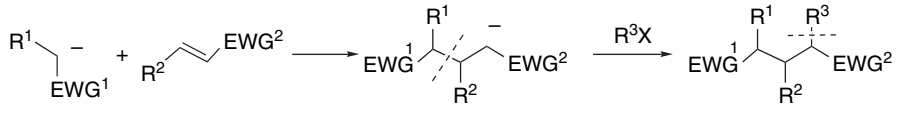
The reaction occurs via the 1,2-adduct, which isomerizes to the 1,4-adduct,[303] and there is an energy difference of about 5 kcal/mol in favor of the 1,4-adduct. With the parent compound in THF, the isomerization reaction has been followed kinetically and appears to occur in two phases. The first part of the reaction occurs with a half-life of a few minutes, and the second with a half-life of about an hour. A possible explanation is the involvement of dimeric species, with the homodimer being more reactive than the heterodimer.



A very important extension of the conjugate addition reaction is discussed in Chapter 8. Organocopper reagents have a strong preference for conjugate addition. Organocopper nucleophiles do not require anion-stabilizing substituents, and they allow conjugate addition of alkyl, alkenyl, and aryl groups to electrophilic alkenes.

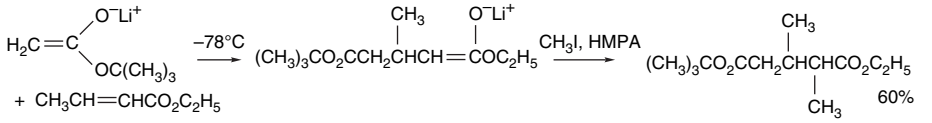
2.6.2. Conjugate Addition with Tandem Alkylation

When conjugate addition is carried out under aprotic conditions with stoichiometric formation of the enolate, the adduct is present as an enolate until the reaction mixture is quenched with a proton source. It is therefore possible to effect a second reaction of the enolate by addition of an alkyl halide or sulfonate to the solution of the adduct enolate, which results in an alkylation. This reaction sequence permits the formation of two new C−C bonds.

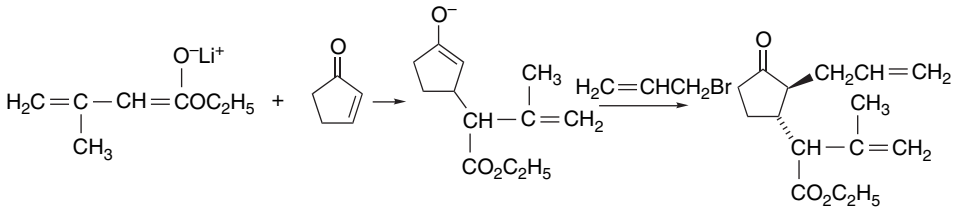


[302] M. Miyashita, B. Z. Awen, and A. Yoshikoshi, *Synthesis*, 563 (1990).
[303] H. J. Reich, M. M. Biddle, and R. J. Edmonston, *J. Org. Chem.*, **70**, 3375 (2005).

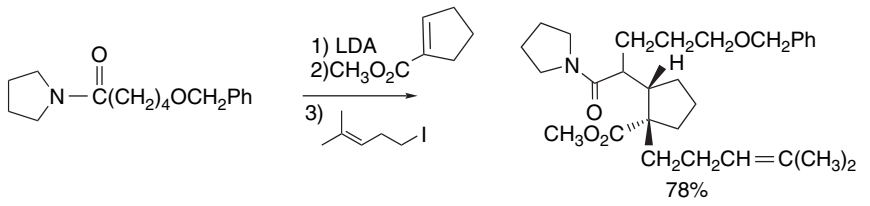
Several examples of tandem conjugate addition-alkylation follow.



Ref. 304



Ref. 305

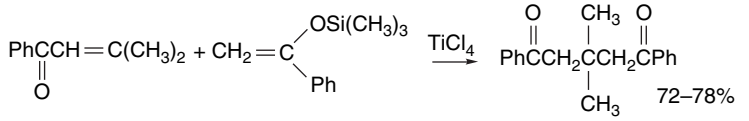


Ref. 306

Tandem conjugate addition-alkylation has proven to be an efficient means of introducing groups at both α- and β-positions at enones.[307] As with simple conjugate addition, organocopper reagents are particularly important in this application, and they are discussed further in Section 8.1.2.3.

2.6.3. Conjugate Addition by Enolate Equivalents

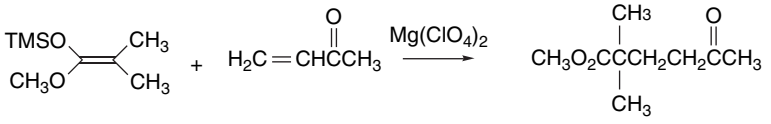
Conditions for effecting conjugate addition of neutral enolate equivalents such as silyl enol ethers in the presence of Lewis acids have been developed and are called *Mukaiyama-Michael reactions*. Trimethylsilyl enol ethers can be caused to react with electrophilic alkenes by use of $TiCl_4$. These reactions proceed rapidly even at $-78°$ C.[308]



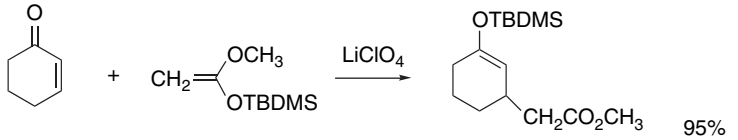
Ref. 309

304. M. Yamaguchi, M. Tsukamoto, and I. Hirao, *Tetrahedron Lett.*, **26**, 1723 (1985).
305. W. Oppolzer, R. P. Heloud, G. Bernardinelli, and K. Baettig, *Tetrahedron Lett.*, **24**, 4975 (1983).
306. C. H. Heathcock, M. M. Hansen, R. B. Ruggeri, and J. C. Kath, *J. Org. Chem.*, **57**, 2544 (1992).
307. For additional examples, see M. C. Chapdelaine and M. Hulce, *Org. React.*, **38**, 225 (1990); E. V. Gorobets, M. S. Miftakhov, and F. A. Valeev, *Russ. Chem. Rev.*, **69**, 1001 (2000).
308. K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 779 (1976).
309. K. Narasaka, *Org. Synth.*, **65**, 12 (1987).

Silyl ketene acetals also undergo conjugate addition. For example, $Mg(ClO_4)_2$ and $LiClO_4$ catalyze addition of silyl ketene acetals to enones.

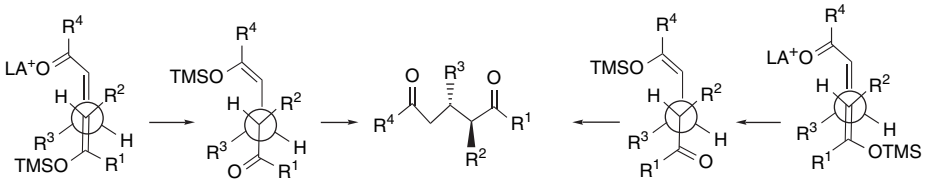


Ref. 310

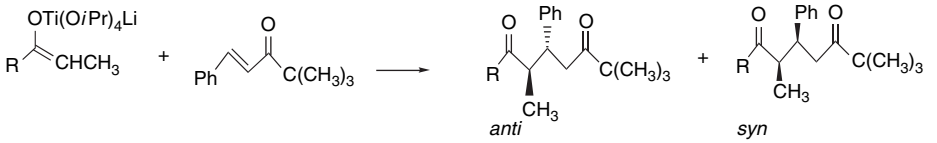


Ref. 311

Initial stereochemical studies suggested that the Mukaiyama-Michael reaction proceeds through an open TS, since there was a tendency to favor *anti* diastereoselectivity, regardless of the silyl enol ether configuration.[312]



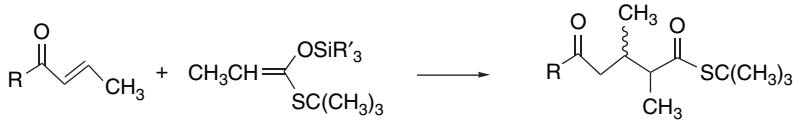
The stereoselectivity can be enhanced by addition of $Ti(O\text{-}i\text{-}Pr)_4$. The active nucleophile under these conditions is expected to be an "ate" complex in which a much larger $Ti(O\text{-}i\text{-}Pr)_4$ group replaces Li^+ as the Lewis acid.[313] Under these conditions, the *syn*:*anti* ratio is dependent on the stereochemistry of the enolate.



R	Configuration	*anti*:*syn*	Yield(%)
Et	*Z*	95:5	69
Ph	*Z*	> 92:8	85
i-Pr	*Z*	> 97:3	65
i-Pr	*E*	17:83	91

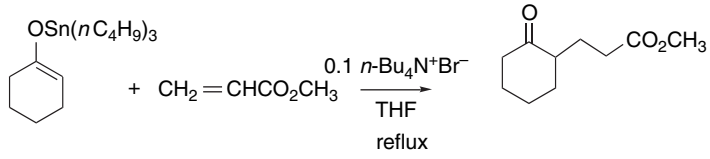
Silyl acetals of thiol esters have also been studied. With $TiCl_4$ as the Lewis acid, there is correspondence between the configuration of the silyl thioketene acetal and the adduct stereochemistry.[314] *E*-Isomers show high *anti* selectivity, whereas *Z*-isomers are less selective.

310. S. Fukuzumi, T. Okamoto, K. Yasui, T. Suenobu, S. Itoh, and J. Otera, *Chem. Lett.*, 667 (1997).
311. P. A. Grieco, R. J. Cooke, K. J. Henry, and J. M. Vander Roest, *Tetrahedron Lett.*, **32**, 4665 (1991).
312. C. H. Heathcock, M. H. Norman, and D. E. Uehling, *J. Am. Chem. Soc.*, **107**, 2797 (1985).
313. A. Bernardi, P. Dotti, G. Poli, and C. Scolastico, *Tetrahedron*, **48**, 5597 (1992); A. Bernardi, M. Cavicchioi, and C. Scolastico, *Tetrahedron*, **49**, 10913 (1993).
314. Y. Fujita, J. Otera, and S. Fukuzumi, *Tetrahedron*, **52**, 9419 (1996).

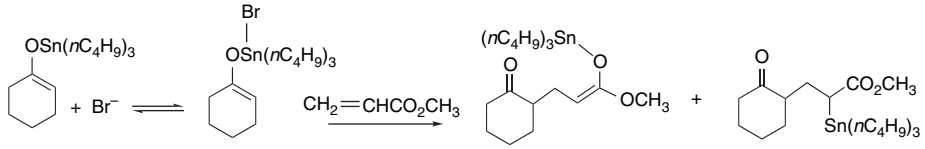


R	SiR'_3	configuration	*syn:anti*
t-Bu	TBDMS	*E*	5:95
t-Bu	TBDMS	*Z*	91:9
Ph	TBDMS	*E*	7:93
Ph	TBDMS	Z	54:46
CH_3	TBDMS	*E*	8:92
CH_3	TBDMS	*Z*	40:60

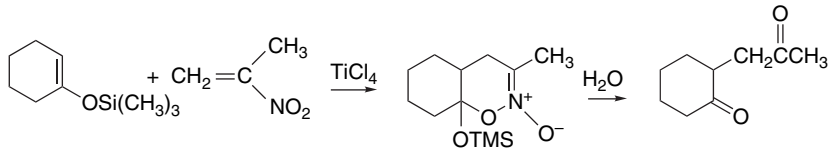
Stannyl enolates give good addition yields in the presence of a catalytic amount of n-$(C_4H_9)_4N^+Br^-$.[315] The bromide ion plays an active role in this reaction by forming a more reactive species via coordination at the tin atom.



It is believed that this reaction involves the formation of the α-stannyl ester. Metals such as lithium that form ionic enolates would be more likely to reverse the addition step.

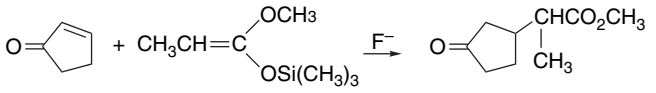


Nitroalkenes are also reactive Michael acceptors under Lewis acid–catalyzed conditions. Titanium tetrachloride or stannic tetrachloride can induce addition of silyl enol ethers. The initial adduct is trapped in a cyclic form by trimethylsilylation.[316] Hydrolysis of this intermediate regenerates the carbonyl group and also converts the *aci*-nitro group to a carbonyl.[317]



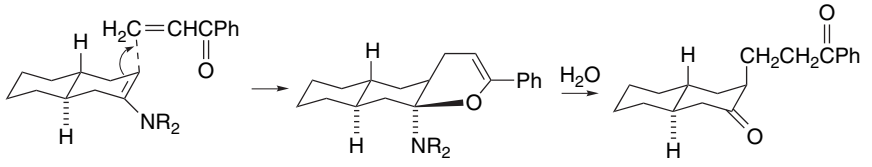
315. M. Yasuda, N. Ohigashi, I. Shibata, and A. Baba, *J. Org. Chem.*, **64**, 2180 (1999).
316. A. F. Mateos and J. A. de la Fuento Blanco, *J. Org. Chem.*, **55**, 1349 (1990).
317. M. Miyashita, T. Yanami, T. Kumazawa, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **106**, 2149 (1984).

Fluoride ion can also induce reaction of silyl ketene acetals with electrophilic alkenes. The fluoride source in these reactions is *tris*-(dimethylamino)sulfonium difluorotrimethylsilicate (TASF).



Ref. 318

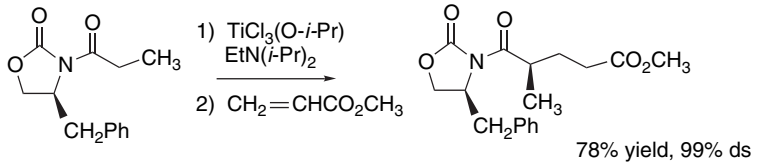
Enamines also react with electrophilic alkenes to give conjugate addition products. The addition reactions of enamines of cyclohexanones show a strong preference for attack from the axial direction.[319] This is anticipated on stereoelectronic grounds because the π orbital of the enamine is the site of nucleophilicity.



Scheme 2.25 shows some examples of additions of enolate equivalents. A range of Lewis acid catalysts has been used in addition to $TiCl_4$ and $SnCl_4$. Entry 1 shows uses of a lanthanide catalyst. Entry 2 employs $LiClO_4$ as the catalyst. The reaction in Entry 3 includes a chiral auxiliary that controls the stereoselectivity; the chiral auxiliary is released by a cyclization using *N*-methylhydroxylamine. Entries 4 and 5 use the triphenylmethyl cation as a catalyst and Entries 6 and 7 use trimethylsilyl triflate and an enantioselective catalyst, respectively.

2.6.4. Control of Facial Selectivity in Conjugate Addition Reactions

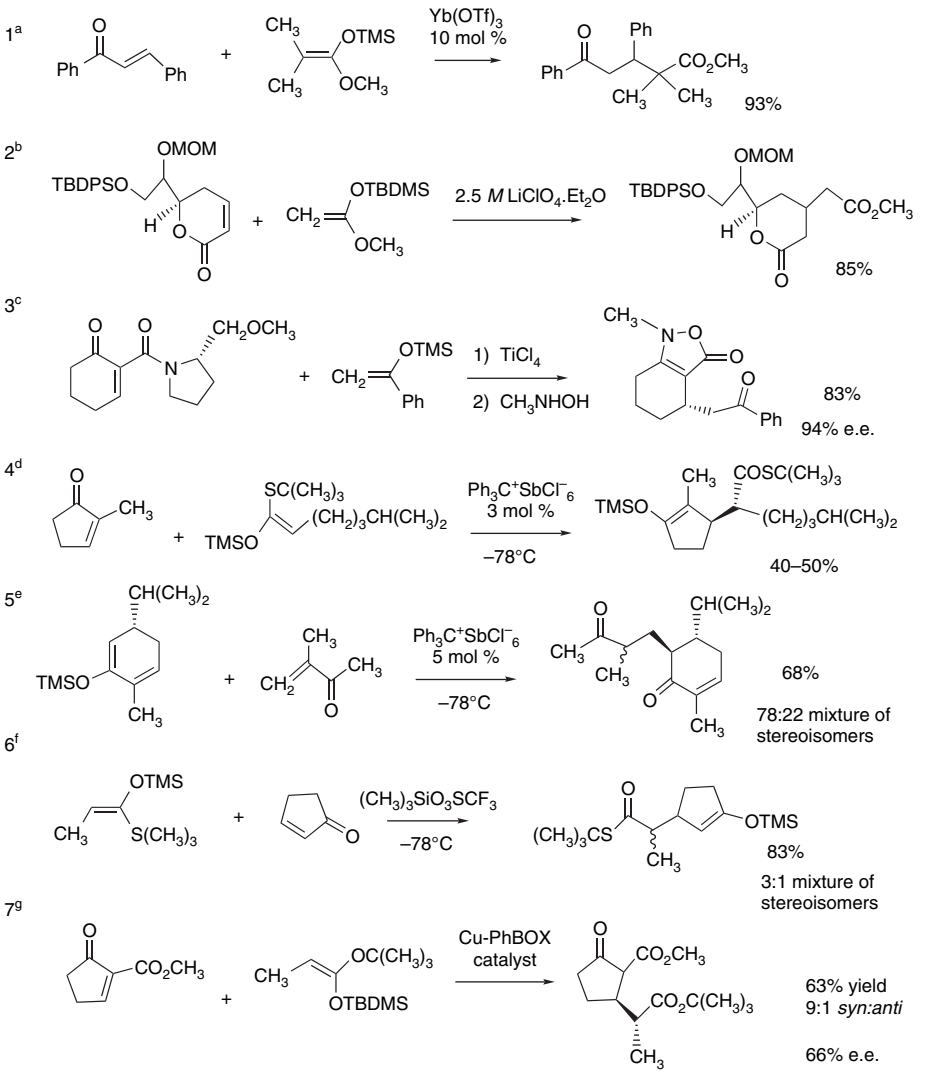
As is the case for aldol addition, chiral auxiliaries and catalysts can be used to control stereoselectivity in conjugate addition reactions. Oxazolidinone chiral auxiliaries have been used in both the nucleophilic and electrophilic components under Lewis acid–catalyzed conditions. *N*-Acyloxazolidinones can be converted to nucleophilic titanium enolates with $TiCl_3$(O-*i*-Pr).[320]



78% yield, 99% ds

318. T. V. Rajan Babu, *J. Org. Chem.*, **49**, 2083 (1984).
319. E. Valentin, G. Pitacco, F. P. Colonna, and A. Risalti, *Tetrahedron*, **30**, 2741 (1974); M. Forchiassin, A. Risalti, C. Russo, M. Calligaris, and G. Pitacco, *J. Chem. Soc.*, 660 (1974).
320. D. A. Evans, M. T. Bilodeau, T. C. Somers, J. Clardy, D. Cherry, and Y. Kato, *J. Org. Chem.*, **56**, 5750 (1991).

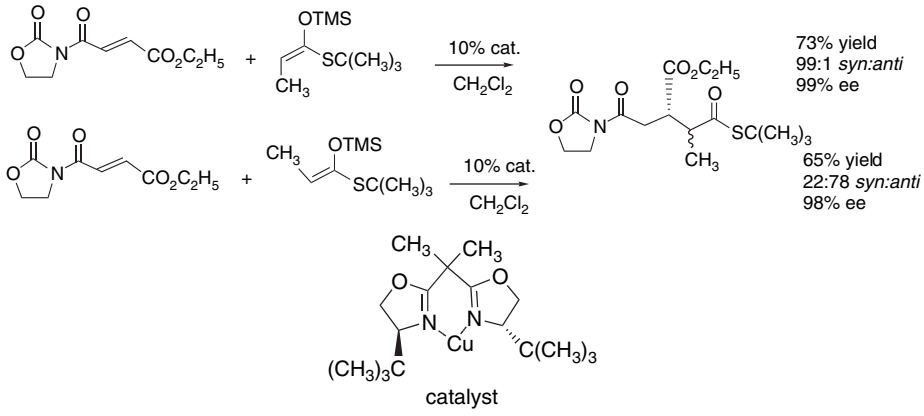
Scheme 2.25. Conjugate Addition of Enolate Equivalents



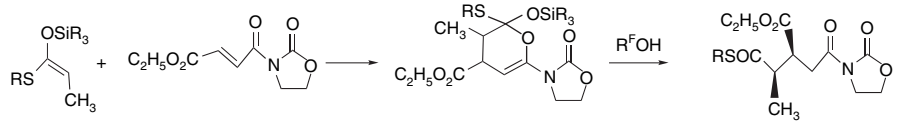
a. S. Kobayahi, I. Hachiya, T. Takahori, M. Araki, and H. Ishitani, *Tetrahedron Lett.*, **33**, 6815 (1992).
b. P. A. Grieco, R. J. Cooke, K. J. Henry, and J. M. Vander Roest, *Tetrahedron Lett.*, **32**, 4665 (1991).
c. A. G. Schultz and H. Lee, *Tetrahedron Lett.*, **33**, 4397 (1992).
d. P. Grzywacz, S. Marczak, and J. Wicha, *J. Org. Chem.* **62**, 5293 (1997).
e. A. V. Baranovsky, B. J. M. Jansen, T. M Meulemans, and A. de Groot, *Tetrahedron*, **54**, 5623 (1998).
f. K. Michalak and J. Wicha, *Polish J. Chem.*, **78**, 205 (2004).
g. A. Bernardi, G. Colombo and C. Scolastico, *Tetrahedron Lett.*, **37**, 8921 (1996).

Unsaturated acyl derivatives of oxazolidinones can be used as acceptors, and these reactions are enantioselective in the presence of chiral *bis*-oxazoline catalysts.[321] Silyl ketene acetals of thiol esters are good reactants and the stereochemistry depends on the ketene acetal configuration. The *Z*-isomer gives higher diastereoselectivity than the *E*-isomer.

321. D. A. Evans, K. A. Scheidt, J. N. Johnston, and M. C. Willis, *J. Am. Chem. Soc.*, **123**, 4480 (2001).

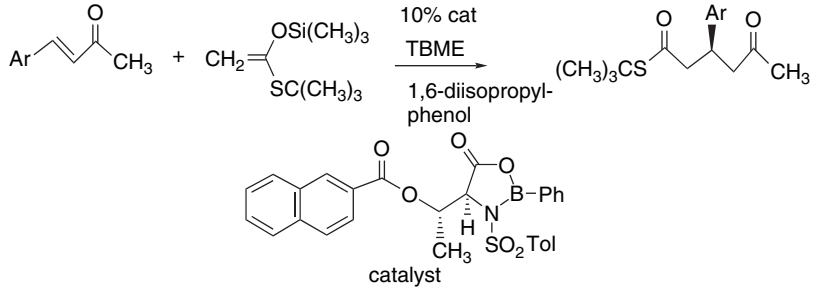


The above examples contain an ester group that acts as a second activating group. The reactions are also accelerated by including one equivalent of $(CF_3)_2CHOH$. This alcohol functions by promoting solvolysis of a dihydropyran intermediate that otherwise inhibits the catalyst.



Alkylidenemalonate esters are also good acceptors in reactions with silyl ketene acetals of thiol esters under very similar conditions.[322]

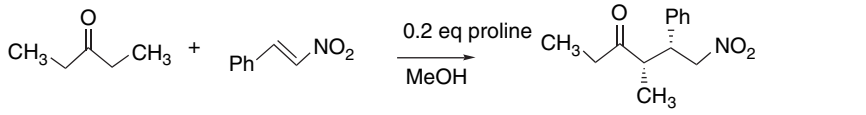
A number of other chiral catalysts can promote enantioselective conjugate additions of silyl enol ethers, silyl ketene acetals, and related compounds. For example, an oxazaborolidinone derived from allothreonine achieves high enantioselectivity in additions of silyl thioketene acetals.[323] The optimal conditions for this reaction also include a hindered phenol and an ether additive.

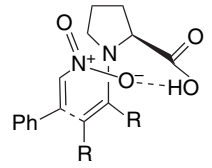


Enantioselectivity has been observed for acyclic ketones, using proline as a catalyst. Under optimum conditions, ds > 80% and e.e. > 70% were observed.[324] These

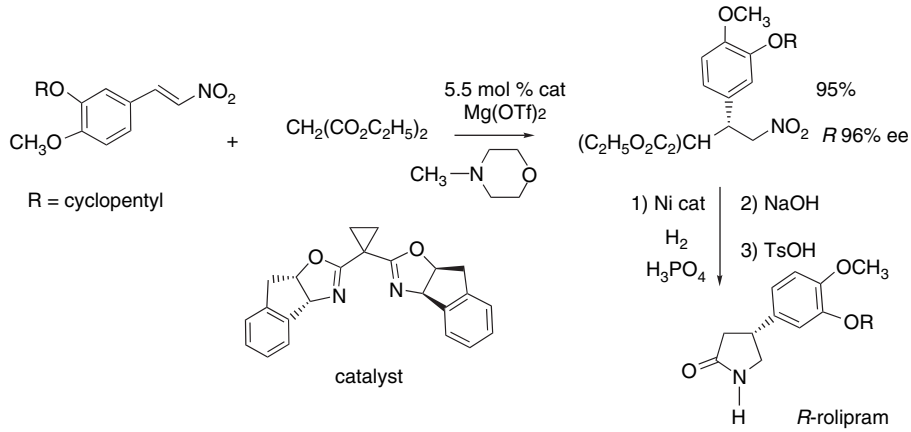
322. D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, and J. S. Tedrow, *J. Am. Chem. Soc.*, **122**, 9134 (2000).
323. X. Wang, S. Adachi, H. Iwai, H. Takatsuki, K. Fujita, M. Kubo, A. Oku, and T. Harada, *J. Org. Chem.*, **68**, 10046 (2003).
324. D. Enders and A. Seki, *Synlett*, 26 (2002).

reactions presumably involve the proline-derived enamine. (See Section 2.1.5.6 for a discussion of enantioselective reactions of proline enamines.)

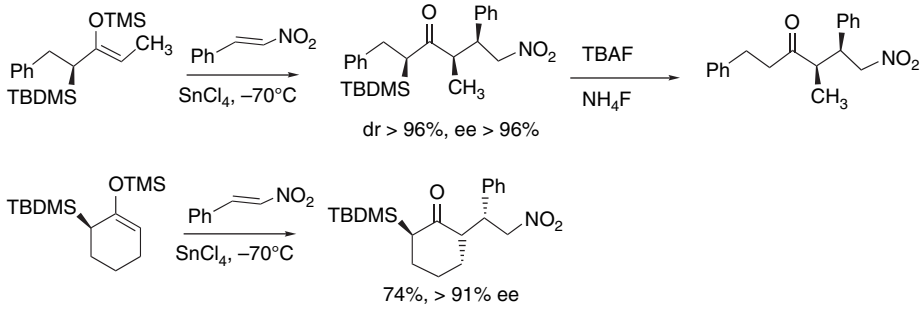




Enantioselective additions of β-dicarbonyl compounds to β-nitrostyrenes have been achieved using *bis*-oxazolidine catalysts. This method was used in an enantioselective synthesis of the antidepressant drug rolipram.[325]



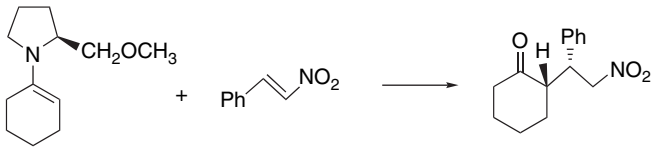
Enantioselectivity can also be based on structural features present in the reactants. A silyl substituent has been used to control stereochemistry in both cyclic and acyclic systems. The silyl substituent can then be removed by TBAF.[326] As with enolate alkylation (see p. 32), the steric effect of the silyl substituent directs the approach of the acceptor to the opposite face.



325. D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, and J. Zhang, *J. Am. Chem. Soc.*, **124**, 13097 (2002).

326. D. Enders and T. Otten, *Synlett*, 747 (1999).

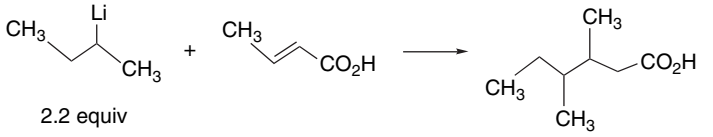
High stereoselectivity is also observed in the addition of an enamine using 2-methoxymethylpyrrolidine as the amine.[327]



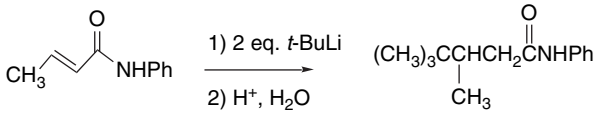
2.6.5. Conjugate Addition of Organometallic Reagents

There are relatively few examples of organolithium compounds acting as nucleophiles in conjugate addition. Usually, organolithium compounds react at the carbonyl group, to give 1,2-addition products. Here, we consider a few cases of organometallic reagents that give conjugate addition products. There are a very large number of copper-mediated conjugate additions, and we discuss these reactions in Section 8.1.2.3.

Alkyl and aryllithium compounds have been found to undergo 1,4-addition with the salts of α, β-unsaturated acids.[328] This result reflects the much reduced reactivity of the carboxylate carbonyl group as an electrophile.

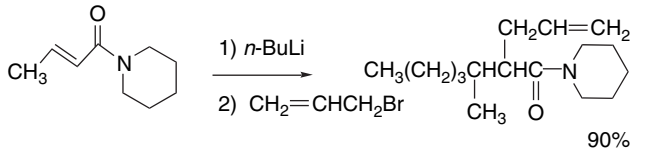


α,β-Unsaturated amides have been found to be good reactants toward organometallic reagents. These reactions involve the deprotonated amide ion, which is less susceptible to 1,2-addition than ketones and esters.



Ref. 329

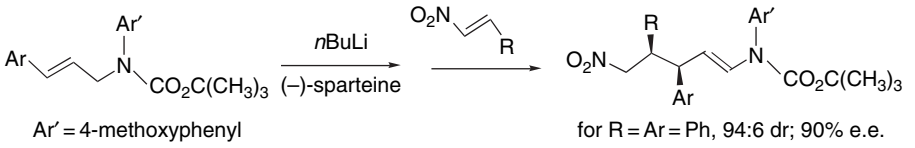
Similar reactions have also been observed with tertiary amides and the adducts can be alkylated by tandem S_N2 reactions.



Ref. 330

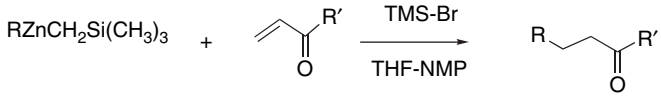
327. S. J. Blarer, W. B. Schweizer, and D. Seebach, *Helv. Chim. Acta*, **65**, 1637 (1982); S. J. Blarer and D. Seebach, *Chem. Ber.*, **116**, 2250 (1983).
328. B. Plunian, M. Vaultier, and J. Mortier, *Chem. Commun.*, 81 (1998).
329. J. E. Baldwin and W. A. Dupont, *Tetrahedron Lett.*, **21**, 1881 (1980).
330. G. B. Mpango, K. K. Mahalanabis, S. Mahdavi-Damghani, and V. Snieckus, *Tetrahedron Lett.*, **21**, 4823 (1980).

Lithiated *N*-allylcarbamates add to nitroalkenes. In the presence of (–)-sparteine, this reaction is both diastereoselective (*anti*) and enantioselective.[331]

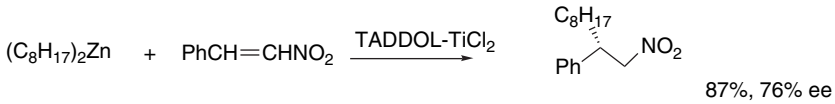


The enantioselectivity is due to the retention of the chiral sparteine in the lithiated reagent. The adducts have been used to synthesize a number of pyrrolidine and piperidine derivatives.

Several mixed organozinc reagents having a trimethylsilylmethyl group as the nonreacting substituent add to enones under the influence of TMS-Br.[332] The types of groups that can be added include alkyl, aryl, heteroaryl, and certain functionalized alkyl groups, including 5-pivaloyloxypentyl and 3-ethoxycarbonylpropyl.

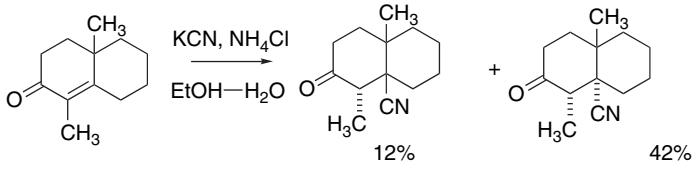


α,β-Unsaturated aldehydes and esters, as well as nitroalkenes, can also function as acceptors under these conditions. Dialkylzinc reagents add to β-nitrostyrene in the presence of TADDOL-$TiCl_2$.[333]



2.6.6. Conjugate Addition of Cyanide Ion

Cyanide ion acts as a carbon nucleophile in the conjugate addition reaction. The p*K* of HCN is 9.3, so addition in hydroxylic solvents is feasible. An alcoholic solution of potassium or sodium cyanide is suitable for simple compounds.

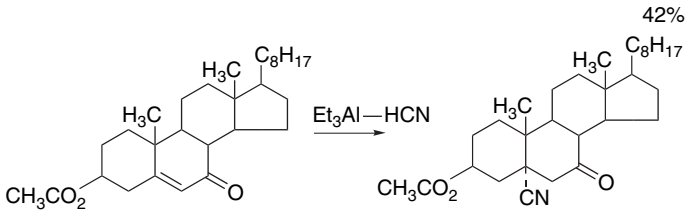


Ref. 334

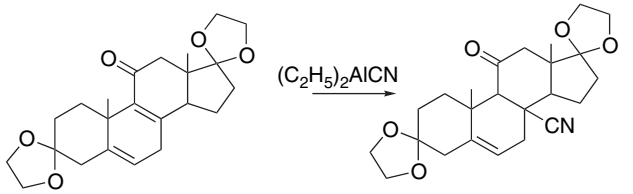
Cyanide addition has also been done under Lewis acid catalysis. Triethylaluminum-hydrogen cyanide and diethylaluminum cyanide are useful reagents for conjugate

331. T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtis, and P. Beak, *J. Am. Chem. Soc.*, **124**, 11689 (2002).
332. P. Jones, C. K. Reddy, and P. Knochel, *Tetrahedron*, **54**, 1471 (1998).
333. H. Schaefer and D. Seebach, *Tetrahedron*, **51**, 2305 (1995).
334. O. R. Rodig and N. J. Johnston, *J. Org. Chem.*, **34**, 1942 (1969).

addition of cyanide. The latter is the more reactive of the two reagents. These reactions presumably involve the coordination of the aluminum reagent at the carbonyl oxygen.

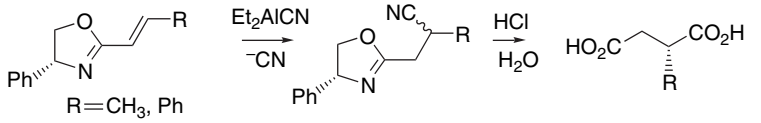


Ref. 335



Ref. 336

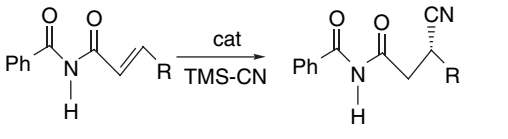
Diethylaluminum cyanide mediates conjugate addition of cyanide to α,β-unsaturated oxazolines. With a chiral oxazoline, 30–50% diastereomeric excess can be achieved. Hydrolysis gives partially resolved α-substituted succinic acids. The rather low enantioselectivity presumably reflects the small size of the cyanide ion.

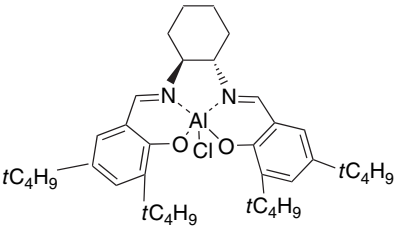


$R = CH_3$, d.e. = 50–56%; e.e. = 45–50%
R = Ph, d.e. = 45–52%; e.e. = 57%

Ref. 337

A chiral aluminum-salen catalyst gives good enantioselectivity in the addition of cyanide (from TMS-CN) to unsaturated acyl imides.[338]





catalyst

335. W. Nagata and M. Yoshioka, *Org. Synth.*, **52**, 100 (1972).
336. W. Nagata, M. Yoshioka, and S. Hirai, *J. Am. Chem. Soc.*, **94**, 4635 (1972).
337. M. Dahuron and N. Langlois, *Synlett*, 51 (1996).
338. G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, **125**, 4442 (2003).

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Problems

(*References for these problems will be found on page 1272.*)

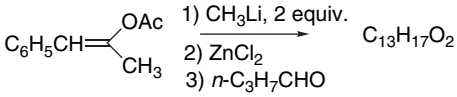
2.1 Predict the product formed in each of the following reactions:

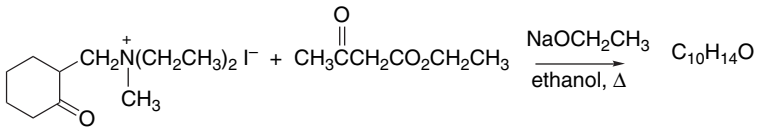
(a) γ-butyrolactone + ethyl oxalate $\xrightarrow[2)\ H^+]{1)\ NaOCH_2CH_3}$ $C_8H_{10}O_5$

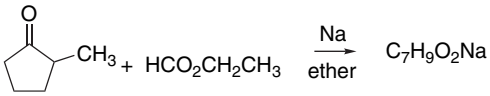
(b) 4-bromobenzaldehyde + ethyl cyanoacetate $\xrightarrow[\text{piperidine}]{\text{ethanol}}$ $C_{12}H_{10}BrNO_2$

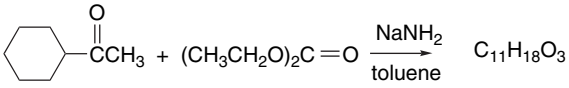
(c) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$ $\xrightarrow[2)\ CH_3CH_2CHO,\ 15\ min\\ 3)H_2O]{1)\ LiN(i\text{-}Pr)_2,\ -78°C}$ $C_8H_{16}O_2$

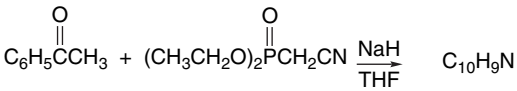
(d)  + $PhCH_2\overset{O}{\overset{\|}{C}}CH_3$ $\xrightarrow{NaOH,\ H_2O}$ $C_{13}H_{10}O_2$

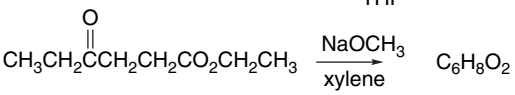
(e) 

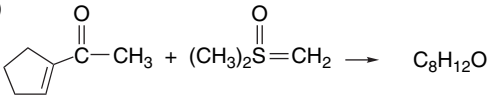
(f) 

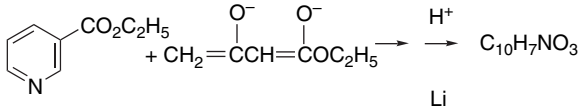
(g) 

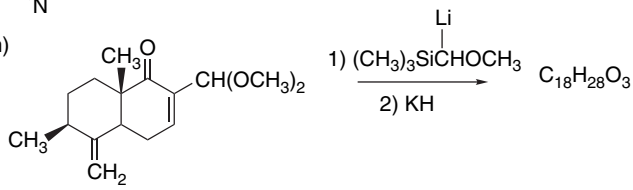
(h) 

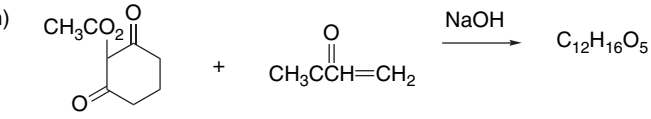
(i) 

(j) 

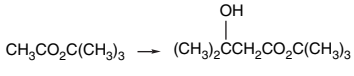
(k) 

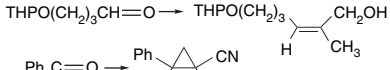
(l) 

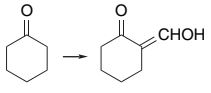
(m) 

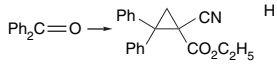
(n) 

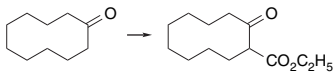
2.2. Indicate reaction conditions or a series of reactions that could effect each of the following synthetic conversions:

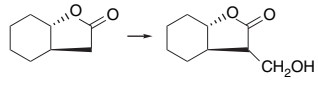
(a) 

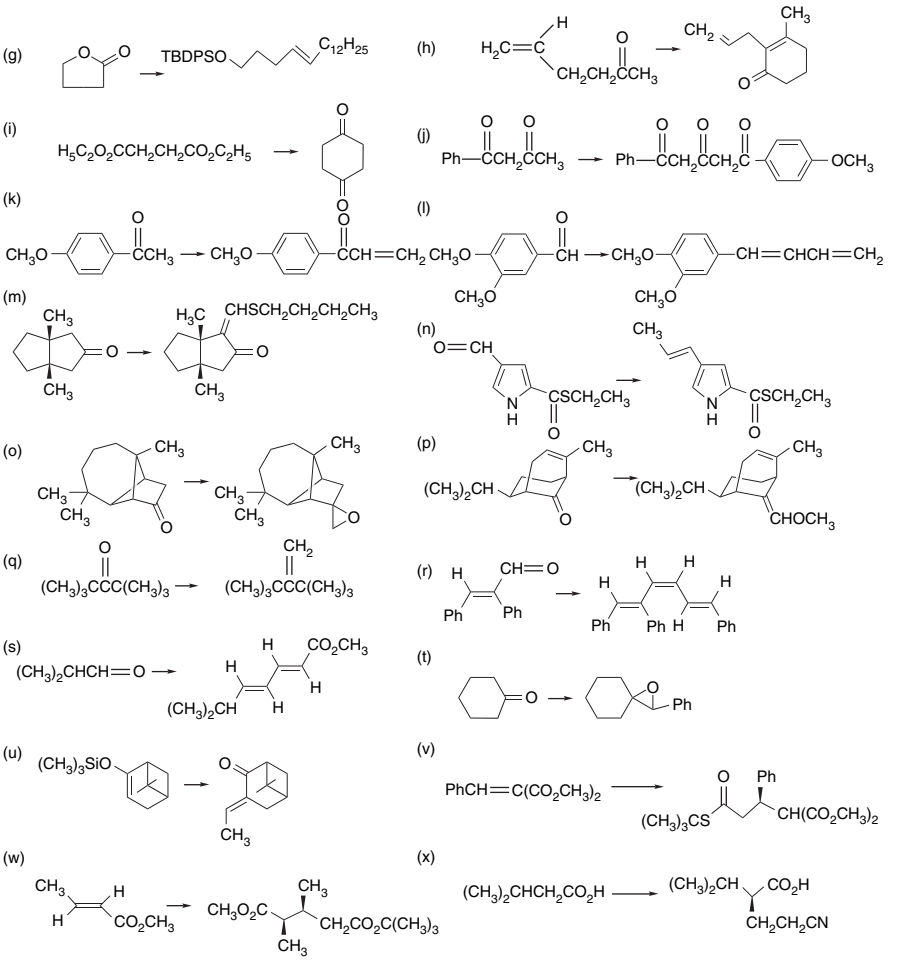
(b) 

(c) 

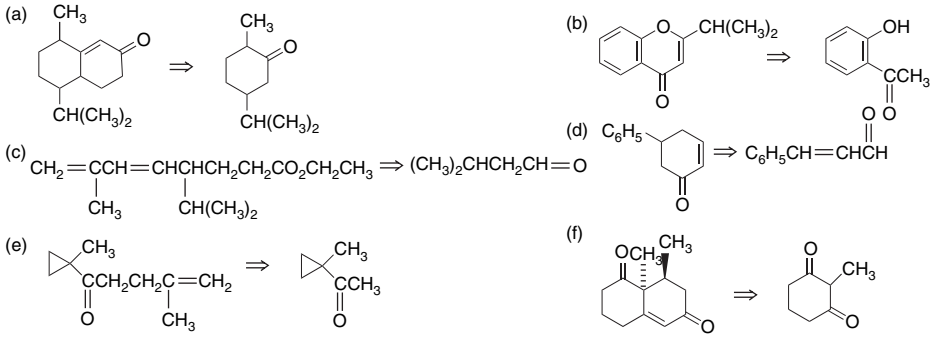
(d) 

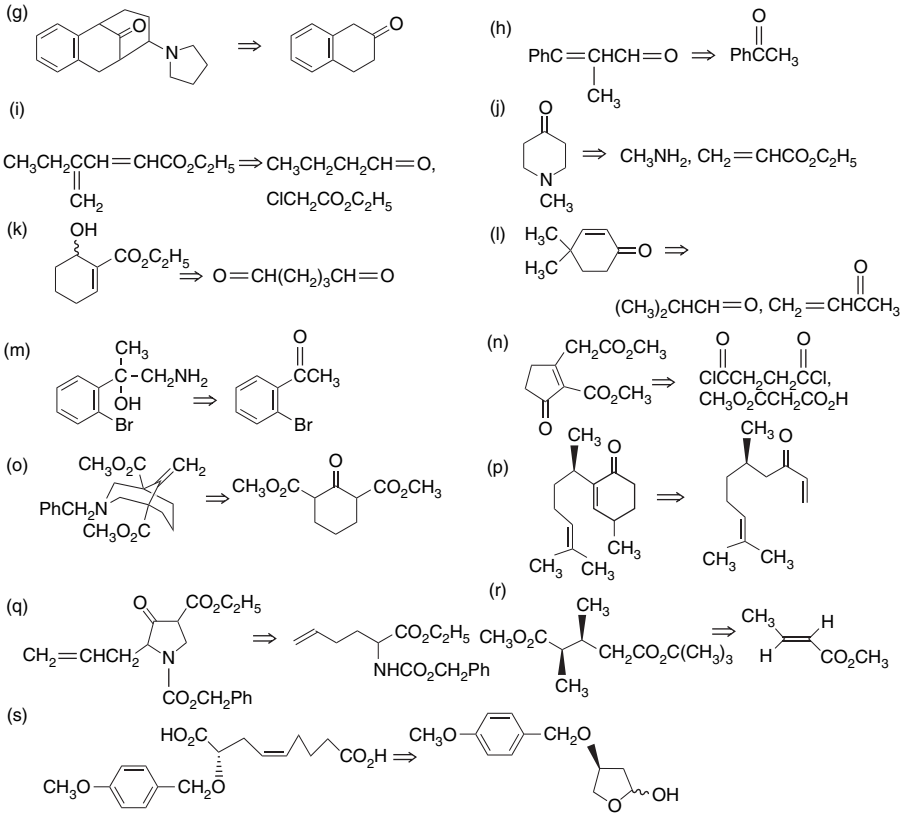
(e) 

(f) 

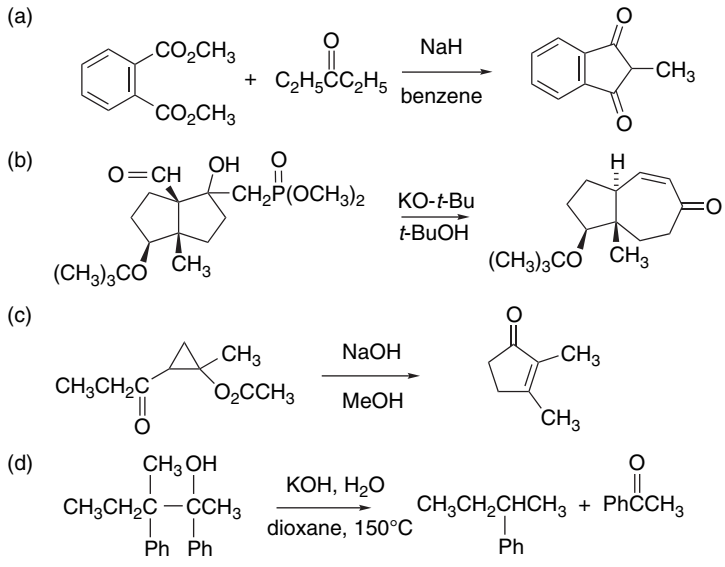


2.3. Step-by-step retrosynthetic analysis of each of the target molecules reveals that they can be efficiently prepared in a few steps from the starting material shown on the right. Do a retrosynthetic analysis and suggest reagents and reaction conditions for carrying out the desired synthesis.





2.4. Offer a mechanism for each of the following reactions:



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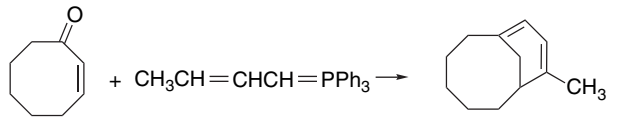

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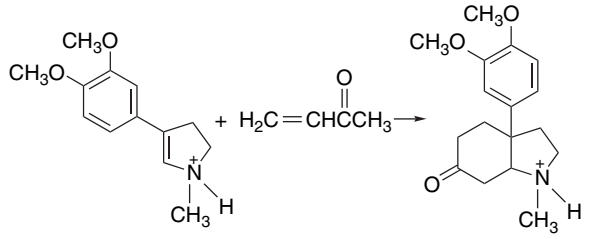

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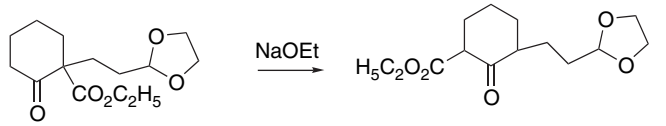

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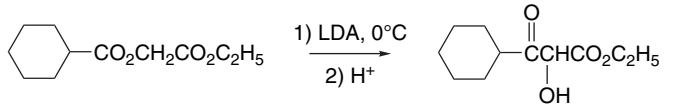

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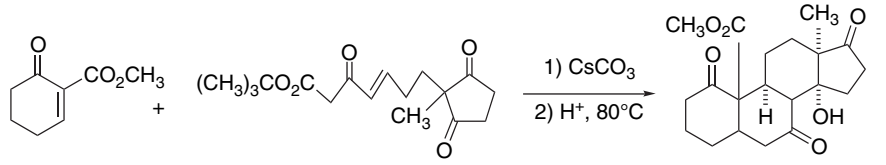

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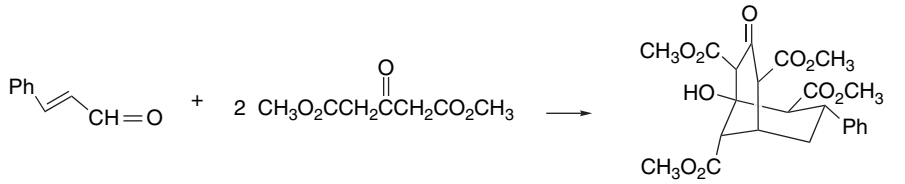
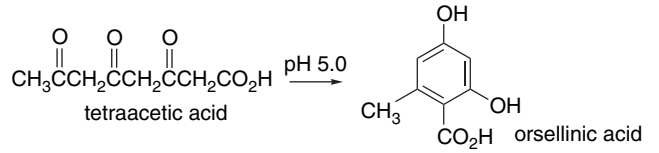


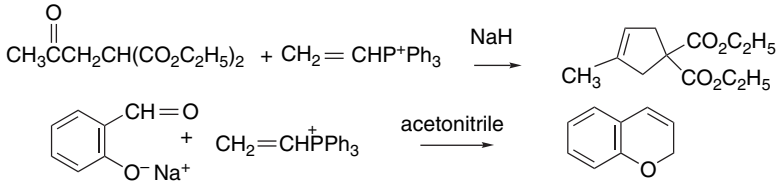
2.5. Tetraacetic acid (or a biological equivalent) is suggested as an intermediate in the biosynthesis of phenolic natural products. In the laboratory, it can be readily converted to orsellinic acid. Suggest a mechanism for this reaction under the conditions specified.



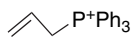
2.6. a. A stereospecific method for deoxygenating epoxides to alkenes involves reaction of the epoxide with the diphenylphosphide ion, followed by methyl iodide. The method results in overall inversion of alkene stereochemistry. Thus, *cis*-cyclooctene epoxide gives *trans*-cyclooctene. Propose a mechanism for this reaction and discuss its relationship to the Wittig reaction.

b. Reaction of the epoxide of *E*-4-octene (*trans*-2,3-dipropyloxirane) with potassium trimethylsilanide gives *Z*-4-octene as the only alkene product in 93% yield. Suggest a reasonable mechanism for this reaction.

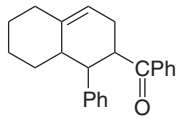
2.7. a. A fairly general method for ring closure has been developed that involves vinyltriphenylphosphonium haldides as reactants. Indicate the mechanism of this reaction, as applied to the two examples shown below. Suggest two other types of rings that could be synthesized using vinyltriphenylphosphonium salts.



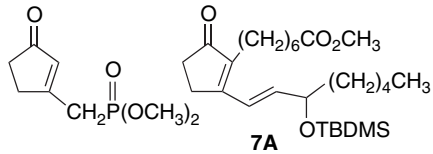
b. Allylphosphonium salts were used as a synthon in the synthesis of cyclohexadienes. Suggest an appropriate co-reactant and other reagents that would be expected to lead to cyclohexadienes.



c. The product shown below is formed by the reaction of vinyltriphenylphosphonium bromide, the lithium enolate of cyclohexanone, and 1,3-diphenyl-2-propen-1-one. Formulate a mechanism.



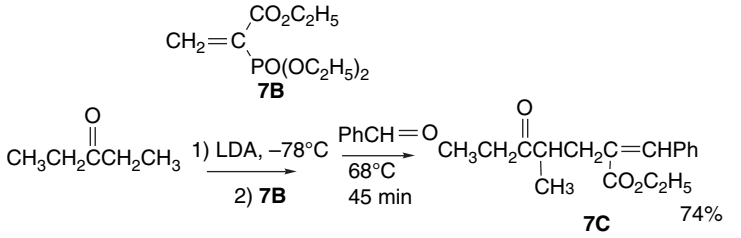
d. The dimethoxy phosphonylmethylcylcopentenone shown below has been used as a starting material for the synthesis of prostaglandin analogs such as **7A**. The reaction involves formation of the anion, reaction with an alkyl halide, and a Wadsworth-Emmons reaction. What reactivity of the anion makes this approach feasible?



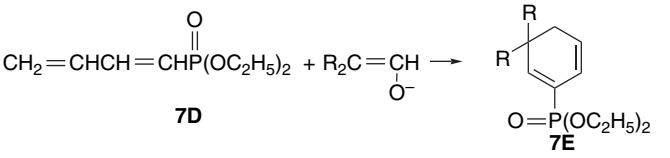
7A

e. The reagent **7B** has found use in the expeditious construction of more complex molecules from simple starting materials. For example, the enolate of 3-pentanone when treated first with **7B** and then with benzaldehyde gives **7C**

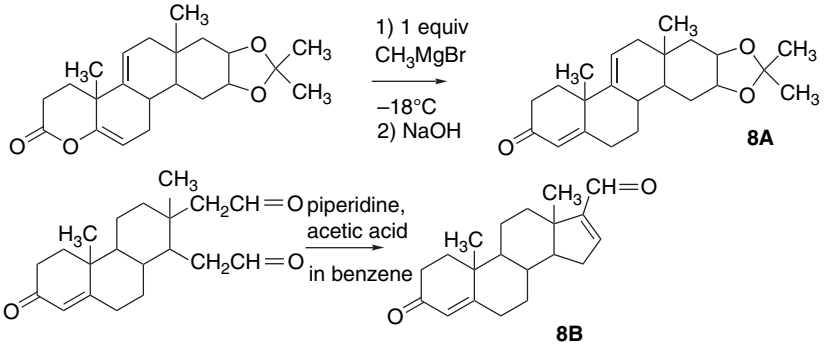
as a 2:1 mixture of stereoisomers. Explain the mechanism by which this reaction occurs.



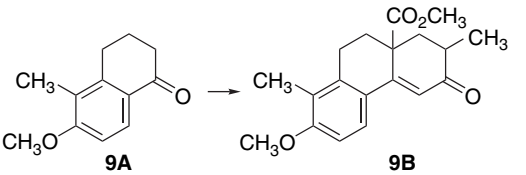
f. The reagent **7D** converts enolates of aldehydes into cyclohexadienyl phosphonates **7E**. Write a mechanism for this reaction. What alternative products might have been observed?



2.8. Compounds **8A** and **8B** were key intermediates in an early total synthesis of cholesterol. Rationalize their formation by the routes shown.

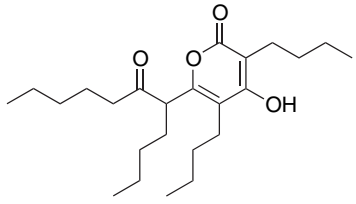


2.9. The first few steps in a synthesis of the alkaloid conessine produce **9B**, starting from **9A**. Suggest a sequence of reactions for effecting this conversion.

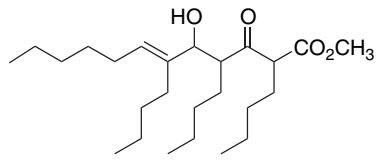


2.10. A substance known as elastase is involved in various inflammatory diseases such as arthritis, pulmonary emphysema, and pancreatitis. Elastase activity can be inhibited by a compound known as elasnin, obtained from a microorganism.

A synthesis of elasnin has been reported that utilizes compound **10A** as a key intermediate. Suggest a synthesis of **10A** from methyl hexanoate and hexanal.

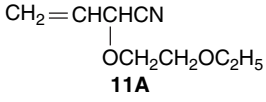


Elasnin

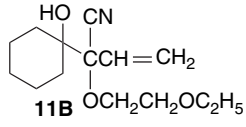


10A

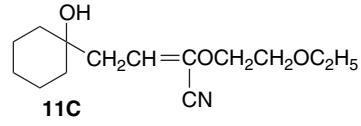
2.11. Treatment of compound **11A** with LDA followed by cyclohexanone can give either **11B** or **11C.** Compound **11B** is formed when the aldehyde is added at −78° C, whereas **11C** is formed if the aldehyde is added at 0° C. Treatment of **11B** with LDA at 0° C gives **11C**. Explain these results.



11A

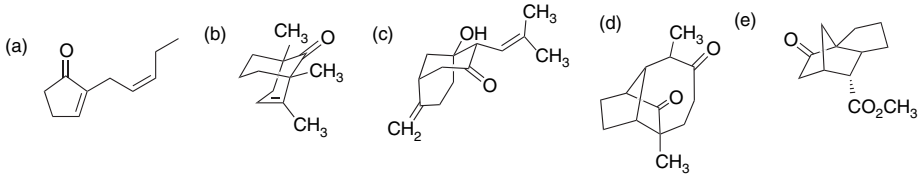


11B

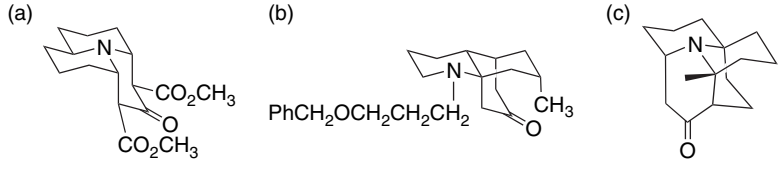


11C

2.12. Dissect the following molecules into potential precursors by locating all bonds that could be made by intramolecular aldol or conjugate addition reactions. Suggest possible starting materials and conditions for performing the desired reactions.



2.13. Mannich condensations permit one-step reactions to form the following substances from substantially less complex starting materials. Identify a potential starting material that would give rise to the product shown in a single step under Mannich reaction conditions.



2.14. Indicate whether or not the aldol reactions shown below would be expected to exhibit high stereoselectivity. Show the stereochemistry of the expected product(s).

(a) $Ph_3CCCH_2CH_3$ (O) — 1) BuLi, –50°C (enolate formation); 2) PhCH=O

(b) $CH_3CH_2CCHOTBDMS$ (O; (*R*); cyclohexyl) — 1) $(i\text{-Pr})_2NC_2H_5$; 2) $Bu_2BOSO_2CF_3$, –78°C; $CH_3CH_2CH{=}O$

(c) $CH_3CH_2CCH_2CH_3$ (O) — 1) LDA, THF, –70°C; 2) $C_6H_5CH{=}O$

(d) $OSi(CH_3)_3$ (cyclohexenyl) — KF; $C_6H_5CH{=}O$

(e) $PhCCH_2CH_3$ (O) — 1) $Bu_2BOSO_2CF_3$, $(i\text{-Pr})_2NC_2H_5$; 2) PhCH=O

(f) $CH_3CH_2C(CH_3)(COTMS)CH_3$ (O) — –78°C; 1) LDA, –70°C; 2) $(CH_3)_2CHCH{=}O$

(g) $CH_3CH_2CH{=}O$ — 1) Et_3N (2 equiv), $TiCl_4$ (2 equiv); 2) PhCH=O, –78°C

(h) CH_3, O, C_6H_{13}, TBDMSO — $TiCl_4$; *i*PrNEt2, –78°; $O{=}CH$, CH_3, (*S*), OTBDPS

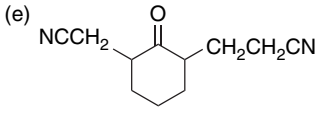
2.15. Suggest transition structures that would account for the observed stereoselectivity of the following reactions.

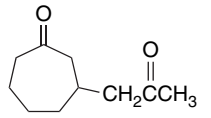
(a) R_3Si, O, O, O, CH_3, CH_3 — 1) $(c\text{-}C_6H_{11})_2BCl$, $C_2H_5N(CH_3)_2$; 2) PhCH=O; R_3Si, O, OH, Ph, O, O, CH_3, CH_3; $R_3Si = (C_2H_5)_2C(CH_3)Si(CH_3)_2$

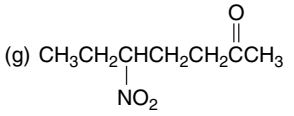
(b) $CH_3CHCH_2CH{=}O$ ($PhCH_2O$) + $CH_2{=}CPh$ (OTMS) — $TiCl_4$ → CH_3, Ph, $PhCH_2O$, OH, O (major); CH_3, Ph, $PhCH_2O$, OH, O (minor)

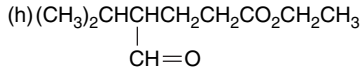
2.16. Suggest starting materials and reaction conditions suitable for obtaining each of the following compounds by a procedure involving conjugate addition.

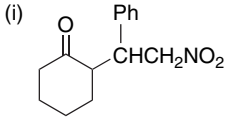
(a) 4,4-dimethyl-5-nitropentan-2-one
(b) diethyl 2,3-diphenylglutarate
(c) ethyl 2-benzoyl-4-(2-pyridyl)butanoate
(d) 2-phenyl-3-oxocyclohexaneacetic acid

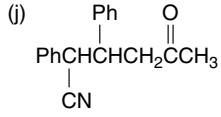


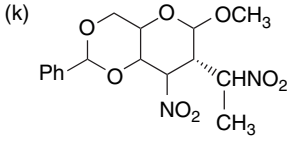


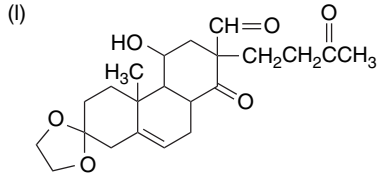




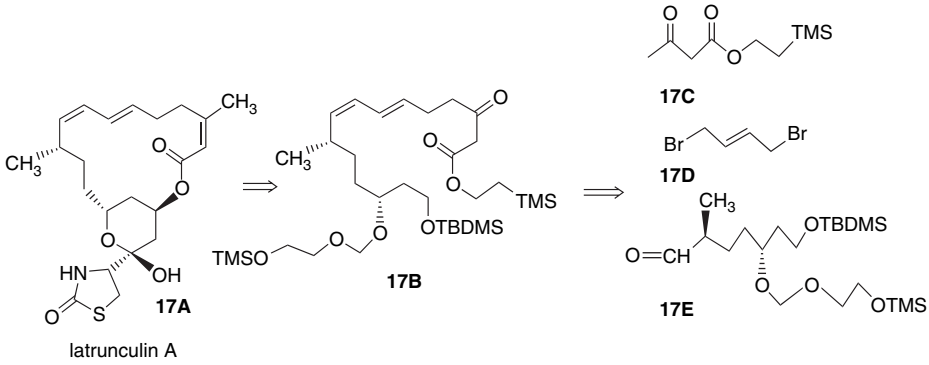




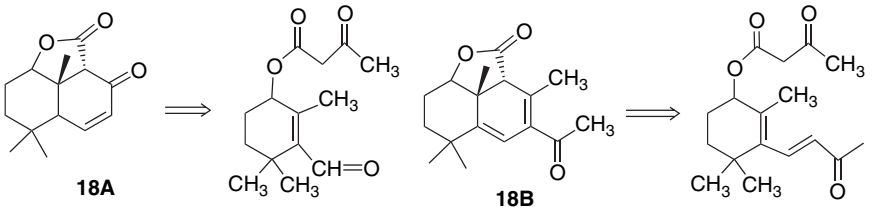




2.17. In the synthesis of a macrolide **17A**, known as latrunculin A, the intermediate **17B** was assembled from components **17C**, **17D**, and **17E** in a "one-pot" tandem process. By a retrosynthetic analysis, show how the synthesis could occur and identify a sequence of reactions and corresponding reagents.

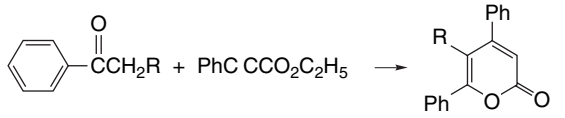


2.18. The tricyclic substance **18A** and **18B** are both potential synthetic intermediates for synthesis of the biologically active diterpene forskolin. These intermediates can be prepared from the monocyclic precursors shown. Indicate the nature of the reactions involved in these transformations.



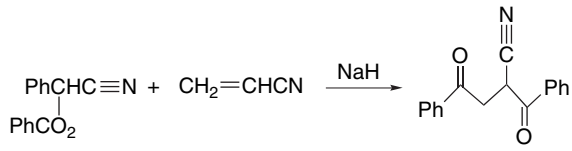
2.19. Account for the course of the following reactions:

a. Substituted acetophenones react with ethyl phenylpropynoate under basic conditions to give pyrones. Formulate a mechanism for this reaction.

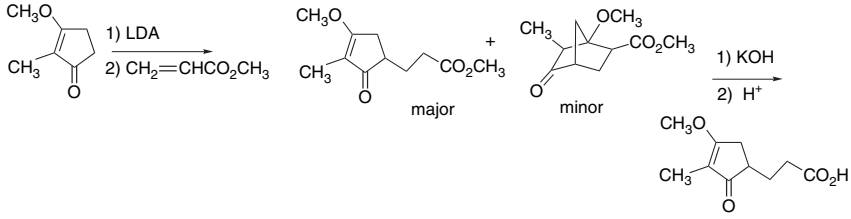


b. The reaction of simple ketones such as 2-butanone or 1-phenyl-2-propanone with α,β-unsaturated ketones gives cyclohexanone on heating with methanol containing potassium methoxide. Indicate how the cyclohexanones could be formed. Can more than one isomeric cyclohexanone be formed? Can you suggest a means for distinguishing between possible cyclohexanones?

c. α-Benzolyloxyphenylacetonitrile reacts with acrylonitrile in the presence of NaH to give 2-cyano-1,4-diphenylbutane-2,4-dione.

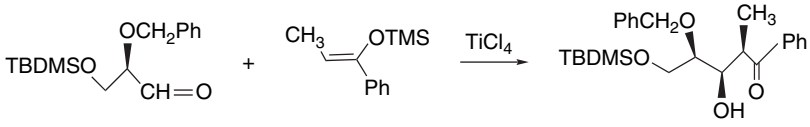


d. Reaction of the lithium anion of 3-methoxy-2-methylcyclopentanone with methyl acrylate gives the two products shown as an 82:18 mixture. Alkaline hydrolysis of the mixture gives a single pure product. How is the minor product formed and how is it converted to the hydrolysis product?

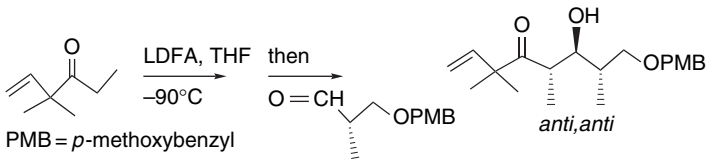


2.20. Explain the stereochemical outcome of the following reactions.

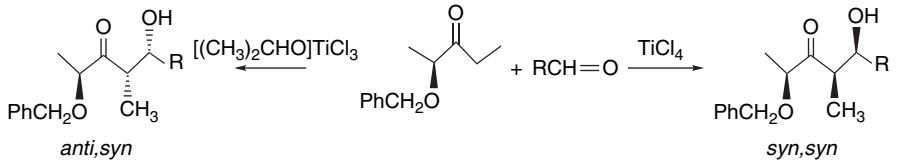
a.



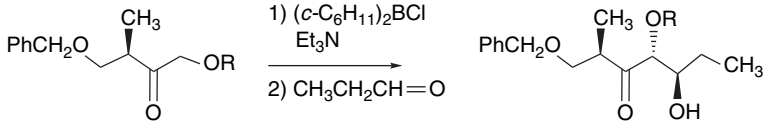
b.



c. The facial selectivity of 2-benzyloxy-3-pentanone toward typical alkyl, alkenyl, and aryl aldehydes is reversed by a change of catalyst from $TiCl_4$ to $[(CH_3)_2CHO]TiCl_3$.

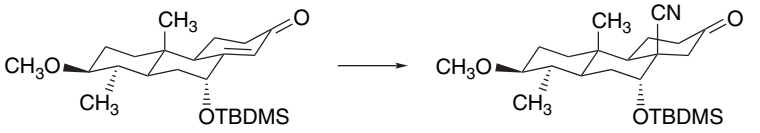


d. The boron enolates generated from ketones **20A** and **20B** give more than 95% selectivity for the *anti*,*anti* diastereomer.

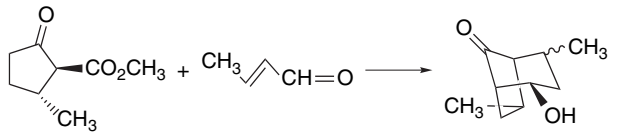


20A R = CH_3
20B R = CH_2Ph

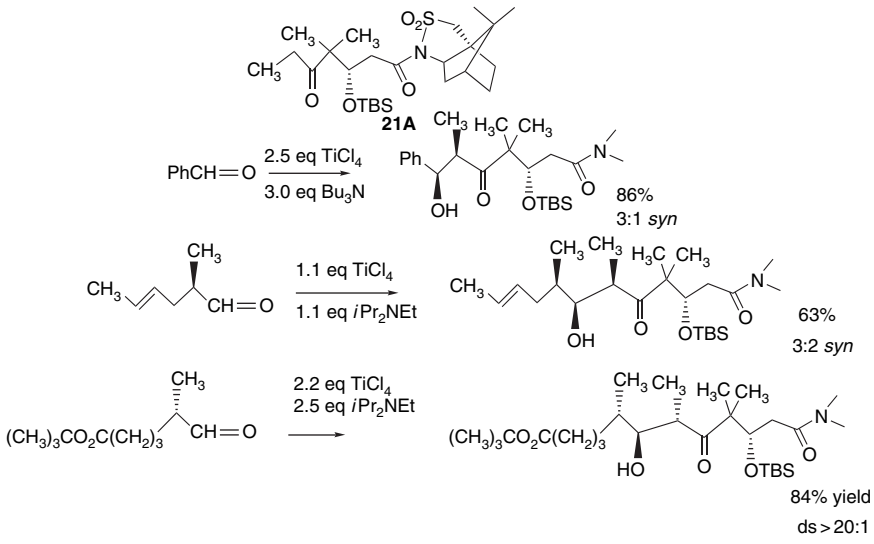
e.



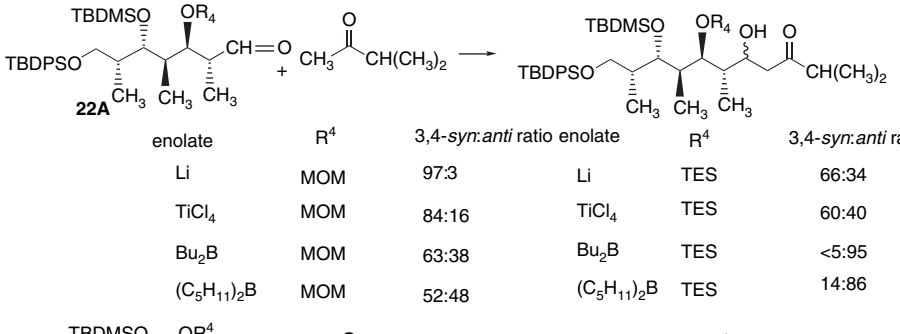
f.



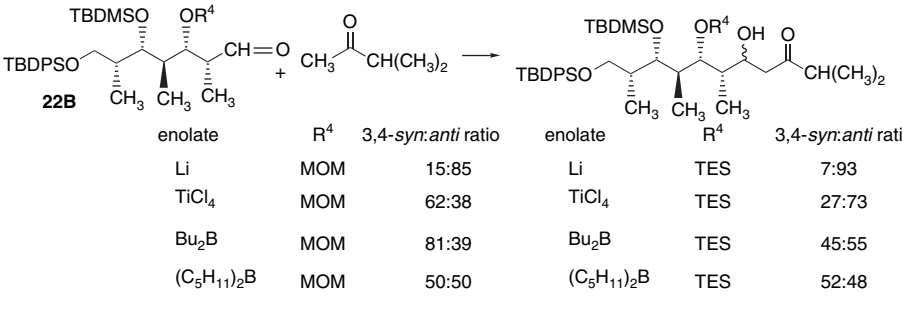
2.21. The camphor sultam derivative **21A** was used in a synthesis of epothilone. The stereoselectivity of the aldol addition was examined with several different aldehydes. Discuss the factors that lead to the variable stereoselectivity in the three cases shown.



2.22. The facial selectivity of the aldehydes **22A** and **22B** is dependent on both the configuration at the β-center and the nature of the enolate as indicated by the data below. Consider possible transition structures for these reactions and offer a rationale for the observed facial selectivity.



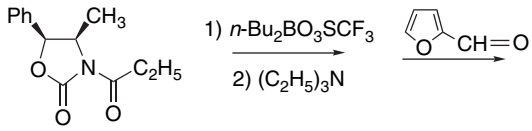
enolate	R^4	3,4-*syn*:*anti* ratio	enolate	R^4	3,4-*syn*:*anti* ratio
Li	MOM	97:3	Li	TES	66:34
$TiCl_4$	MOM	84:16	$TiCl_4$	TES	60:40
Bu_2B	MOM	63:38	Bu_2B	TES	<5:95
$(C_5H_{11})_2B$	MOM	52:48	$(C_5H_{11})_2B$	TES	14:86



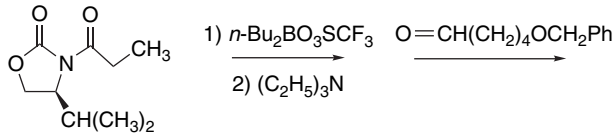
enolate	R^4	3,4-*syn*:*anti* ratio	enolate	R^4	3,4-*syn*:*anti* ratio
Li	MOM	15:85	Li	TES	7:93
$TiCl_4$	MOM	62:38	$TiCl_4$	TES	27:73
Bu_2B	MOM	81:39	Bu_2B	TES	45:55
$(C_5H_{11})_2B$	MOM	50:50	$(C_5H_{11})_2B$	TES	52:48

2.23. Predict the stereochemical outcome of the following aldol addition reactions involving chiral auxiliaries.

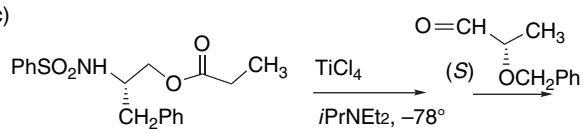
(a)



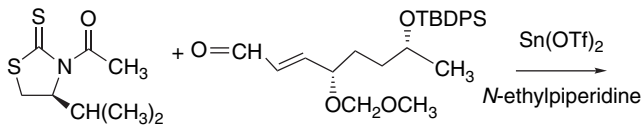
(b)



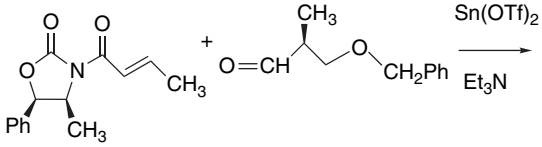
(c)



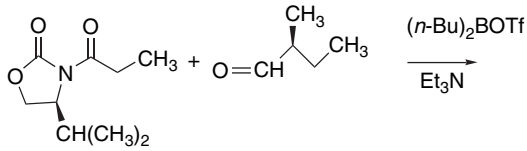
(d)



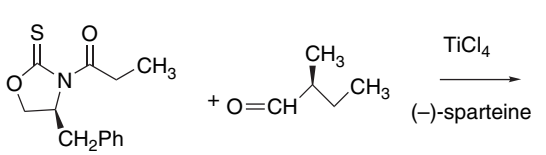
(e)



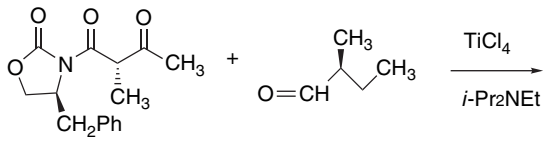
(f)



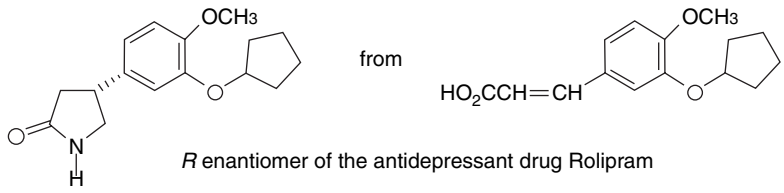
(g)



(h)



2.24. Suggest an enantioselective synthetic route to the antidepression drug rolipram from the suggested reactant.



R enantiomer of the antidepressant drug Rolipram

2.25. Figure 2.P25 shows the calculated [B3LYP/6-31G(d,p)] reaction energy profile for the aldol addition of benzaldehyde and cyclohexanone catalyzed by alanine. The best TSs leading to (*S*,*R*); (*R*,*S*); (*S*,*S*); and (*R*,*R*) products are given. What factors favor the observed (*R*,*S*) product?

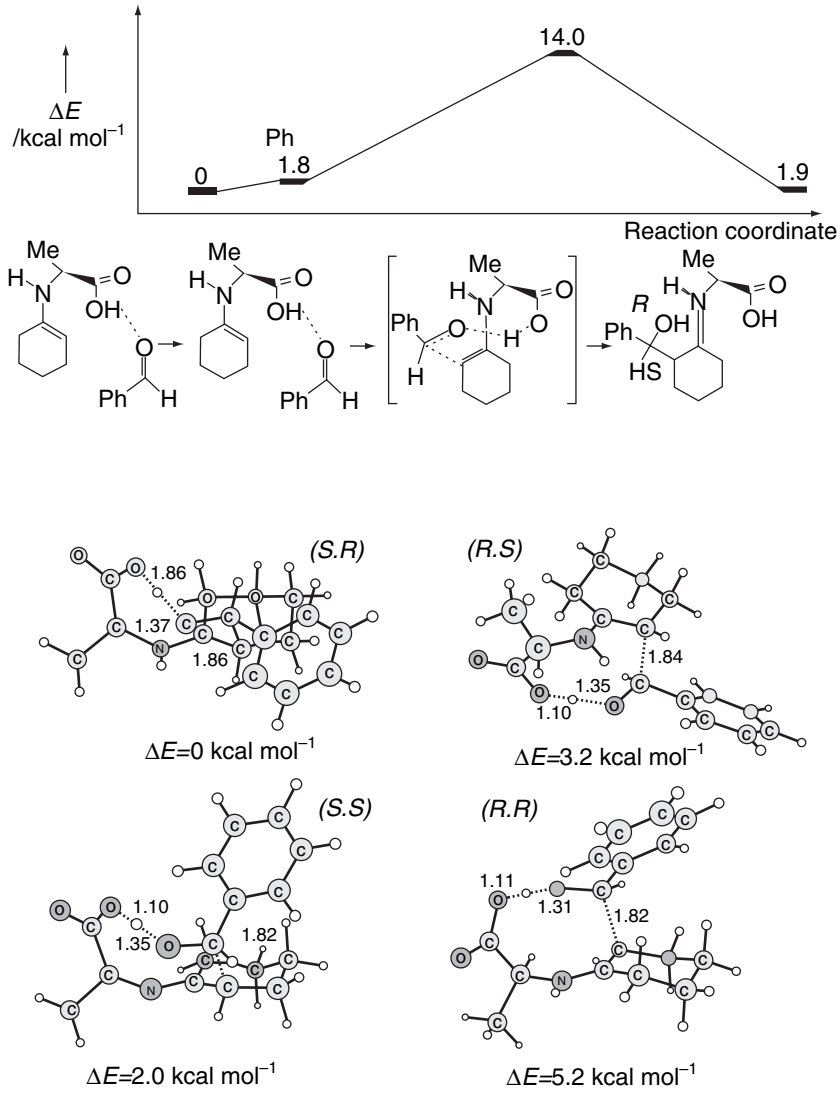


Fig. 2.P25. Top: Reaction energy profile for alanine-catalyzed aldol reaction of benzaldehyde and cyclohexanone. Bottom: Diastereomeric transition structures. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **44**, 7028 (2005), by permission of Wiley-VCH