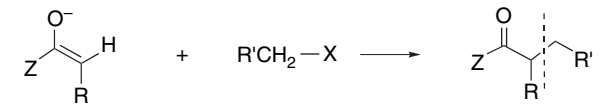
1

Alkylation of Enolates and Other Carbon Nucleophiles

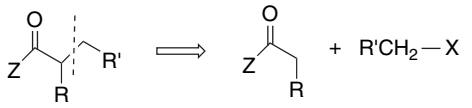
Introduction

Carbon-carbon bond formation is the basis for the construction of the molecular framework of organic molecules by synthesis. One of the fundamental processes for carbon-carbon bond formation is a reaction between a nucleophilic and an electrophilic carbon. The focus in this chapter is on *enolates*, *imine anions*, and *enamines*, which are carbon nucleophiles, and their reactions with *alkylating agents.* Mechanistically, these are usually S_N2 reactions in which the carbon nucleophile displaces a halide or other leaving group with inversion of configuration at the alkylating group. Efficient carbon-carbon bond formation requires that the S_N2 alkylation be the dominant reaction. The crucial factors that must be considered include: (1) the conditions for generation of the carbon nucleophile; (2) the effect of the reaction conditions on the structure and reactivity of the nucleophile; and (3) the regio- and stereoselectivity of the alkylation reaction. The reaction can be applied to various carbonyl compounds, including ketones, esters, and amides.

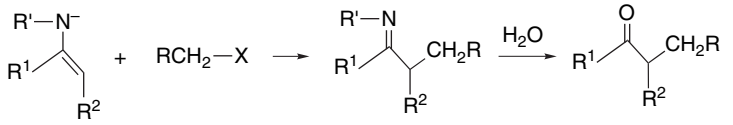


Z = R, RO, R_2N enolate alkylation

These reactions introduce a new substituent α to the carbonyl group and constitute an important method for this transformation. In the retrosynthetic sense, the disconnection is between the α-carbon and a potential alkylating agent.



There are similar reactions involving nitrogen analogs called *imine anions*. The alkylated imines can be hydrolyzed to the corresponding ketone, and this reaction is discussed in Section 1.3.



Either enolate or imine anions can be used to introduce alkyl α-substituents to a carbonyl group. Because the reaction involves a nucleophilic substitution, primary groups are the best alkylating agents, with methyl, allyl, and benzyl compounds being particularly reactive. Secondary groups are less reactive and are likely to give lower yields because of competing elimination. Tertiary and aryl groups cannot be introduced by an S_N2 mechanism.

1.1. Generation and Properties of Enolates and Other Stabilized Carbanions

1.1.1. Generation of Enolates by Deprotonation

The fundamental aspects of the structure and stability of carbanions were discussed in Chapter 6 of Part A. In the present chapter we relate the properties and reactivity of carbanions stabilized by carbonyl and other EWG substituents to their application as nucleophiles in synthesis. As discussed in Section 6.3 of Part A, there is a fundamental relationship between the stabilizing functional group and the acidity of the C−H groups, as illustrated by the pK data summarized in Table 6.7 in Part A. These pK data provide a basis for assessing the stability and reactivity of carbanions. The acidity of the reactant determines which bases can be used for generation of the anion. Another crucial factor is the distinction between *kinetic or thermodynamic control of enolate formation by deprotonation* (Part A, Section 6.3), which determines the enolate composition. Fundamental mechanisms of S_N2 alkylation reactions of carbanions are discussed in Section 6.5 of Part A. A review of this material may prove helpful.

A primary consideration in the generation of an enolate or other stabilized carbanion by deprotonation is the choice of base. In general, reactions can be carried out under conditions in which the enolate is *in equilibrium* with its conjugate acid or under which the reactant is *completely converted* to its conjugate base. The key determinant is the amount and strength of the base. For complete conversion, the base must be derived from a substantially weaker acid than the reactant. Stated another way, the reagent must be a stronger base than the anion of the reactant. Most current procedures for alkylation of enolates and other carbanions involve complete conversion to the anion. Such procedures are generally more amenable to both regiochemical and stereochemical control than those in which there is only a small equilibrium concentration of the enolate. The solvent and other coordinating or chelating additives also have strong effects on the structure and reactivity of carbanions formed by

deprotonation. The nature of the solvent determines the degree of ion pairing and aggregation, which in turn affect reactivity.

Table 1.1 gives approximate pK data for various functional groups and some of the commonly used bases. The strongest acids appear at the top of the table and the strongest bases at the bottom. The values listed as pK_{ROH} are referenced to water and are appropriate for hydroxylic solvents. Also included in the table are pK values determined in dimethyl sulfoxide (pK_{DMSO}). The range of acidities that can be measured directly in DMSO is greater than that in protic media, thereby allowing direct comparisons between weakly acidic compounds to be made more confidently. The pK values in DMSO are normally larger than in water because water stabilizes anions more effectively, by hydrogen bonding, than does DMSO. Stated another way, many anions are more strongly basic in DMSO than in water. This relationship is particularly apparent for the oxy anion bases, such as acetate, hydroxide, and the alkoxides, which are much more basic in DMSO than in protic solvents. At the present time, the pK_{DMSO} scale includes the widest variety of structural types of synthetic interest.[1] The pK values collected in Table 1.1 provide an ordering of some important

Table 1.1. Approximate pK Values from Some Compounds with Carbanion Stabilizing Groups and Some Common Bases[a]

Compound	pK_{ROH}	pK_{DMSO}	Base	pK_{ROH}	pK_{DMSO}
$O_2NCH_2NO_2$	3.6		$CH_3CO_2^-$	4.2	11.6
$CH_3COCH_2NO_2$	5.1				
$CH_3CH_2NO_2$	8.6	16.7	HCO_3^-	6.5	
$CH_3COCH_2COCH_3$	9				
$PhCOCH_2COCH_3$	9.6		PhO^-	9.9	16.4
CH_3NO_2	10.2	17.2			
$CH_3COCH_2CO_2C_2H_5$	10.7	14.2	CO_3^{2-}	10.2	
$NCCH_2CN$	11.2	11.0	$(C_2H_5)_3N$	10.7	
$PhCH_2NO_2$		12.3	$(CH_3CH_2)_2NH$	11	
$CH_2(SO_2CH_3)_2$	12.2	14.4			
$CH_2(CO_2C_2H_5)_2$	12.7	16.4			
Cyclopentadiene	15		CH_3O^-	15.5	29.0
$PhSCH_2COCH_3$		18.7	HO^-	15.7	31.4
$CH_3CH_2CH(CO_2C_2H_5)_2$	15		$C_2H_5O^-$	15.9	29.8
$PhSCH_2CN$		20.8	$(CH_3)_2CHO^-$		30.3
$(PhCH_2)_2SO_2$		23.9	$(CH_3)_3CO^-$	19	32.2
$PhCOCH_3$	15.8	24.7			
$PhCH_2COCH_3$	19.9				
CH_3COCH_3	20	26.5			
$CH_3CH_2COCH_2CH_3$		27.1			
Fluorene	20.5	22.6			
$PhSO_2CH_3$		29.0			
$PhCH_2SOCH_3$	29.0		$[(CH_3)_3Si]_2N^-$	30[b]	
CH_3CN	25	31.3			
Ph_2CH_2		32.2			
Ph_3CH	33	30.6	NH_2^-	35	41
			$CH_3SOCH_2^-$	35	35.1
			$(CH_3CH_2)_2N^-$	36	
$PhCH_3$		43			
CH_4		56			

a. From F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).
b. In THF; R. R. Fraser and T. S. Mansour, *J. Org. Chem.*, **49**, 3442 (1984).

1. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).

substituents with respect to their ability to stabilize carbanions. The order indicated is $NO_2 > COR > CN \sim CO_2R > SO_2R > SOR > Ph \sim SR > H > R$. Familiarity with the relative acidity and approximate pK values is important for an understanding of the reactions discussed in this chapter.

There is something of an historical division in synthetic procedures involving carbanions as nucleophiles in alkylation reactions.[2] As can be seen from Table 1.1, β-diketones, β-ketoesters, malonates, and other compounds with two stabilizing groups have pK values slightly below ethanol and the other common alcohols. As a result, these compounds can be converted completely to enolates by sodium or potassium alkoxides. These compounds were the usual reactants in carbanion alkylation reactions until about 1960. Often, the second EWG is extraneous to the overall purpose of the synthesis and its removal requires an extra step. After 1960, procedures using aprotic solvents, especially THF, and amide bases, such as lithium di-isopropylamide (LDA) were developed. The dialkylamines have a pK around 35. These conditions permit the conversion of monofunctional compounds with p$K > 20$, especially ketones, esters, and amides, completely to their enolates. Other bases that are commonly used are the anions of hexaalkyldisilylamines, especially hexamethyldisilazane.[3] The lithium, sodium, and potassium salts are abbreviated LiHMDS, NaHMDS, and KHMDS. The disilylamines have a pK around 30.[4] The basicity of both dialkylamides and hexaalkyldisilylamides tends to increase with branching in the alkyl groups. The more branched amides also exhibit greater steric discrimination. An example is lithium tetramethylpiperidide, LiTMP, which is sometimes used as a base for deprotonation.[5] Other strong bases, such as amide anion ($^-NH_2$), the conjugate base of DMSO (sometimes referred to as the "dimsyl" anion),[6] and triphenylmethyl anion, are capable of effecting essentially complete conversion of a ketone to its enolate. Sodium hydride and potassium hydride can also be used to prepare enolates from ketones, although the reactivity of the metal hydrides is somewhat dependent on the means of preparation and purification of the hydride.[7]

By comparing the approximate pK values of the bases with those of the carbon acid of interest, it is possible to estimate the position of the acid-base equilibrium for a given reactant-base combination. For a carbon acid C−H and a base B−H,

$$K_{a_{(C-H)}} = \frac{[C^-][H^+]}{[C-H]} \text{ and } K_{a_{(B-H)}} = \frac{[B^-][H^+]}{[B-H]}$$

at equilibrium

$$\frac{K_{a_{(C-H)}}[C-H]}{[C^-]} = \frac{K_{a_{(B-H)}}[B-H]}{[B^-]}$$

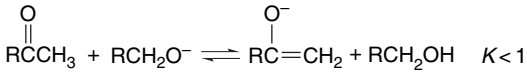
for the reaction

$$C-H + B^- \rightleftharpoons B-H + C^-$$

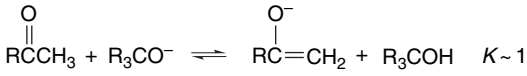
2. D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1988).
3. E. H. Amonoco-Neizer, R. A. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965); C. R. Kruger and E. G. Rochow, *J. Organomet. Chem.*, **1**, 476 (1964).
4. R. R. Fraser and T. S. Mansour, *J. Org. Chem.*, **49**, 3442 (1984).
5. M. W. Rathke and R. Kow, *J. Am. Chem. Soc.*, **94**, 6854 (1972); R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 581, 582 (1973).
6. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).
7. C. A. Brown, *J. Org. Chem.*, **39**, 1324 (1974); R. Pi, T. Friedl, P. v. R. Schleyer, P. Klusener, and L. Brandsma, *J. Org. Chem.*, **52**, 4299 (1987); T. L. Macdonald, K. J. Natalie, Jr., G. Prasad, and J. S. Sawyer, *J. Org. Chem.*, **51**, 1124 (1986).

$$K = \frac{[\mathrm{B{-}H}][\mathrm{C}^-]}{[\mathrm{C{-}H}][\mathrm{B}^-]} = \frac{K_{a_{(\mathrm{C-H})}}}{K_{a_{(\mathrm{B-H})}}}$$

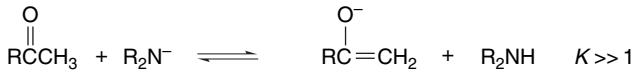
If we consider the case of a simple alkyl ketone in a protic solvent, for example, we see that hydroxide ion or primary alkoxide ions will convert only a fraction of a ketone to its anion.



The slightly more basic tertiary alkoxides are comparable to the enolates in basicity, and a more favorable equilibrium will be established with such bases.



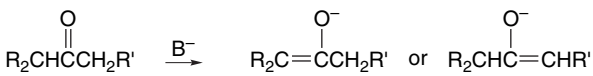
Note also that dialkyl ketones such as acetone and 3-pentanone are slightly *more acidic* than the simple alcohols in DMSO. Use of alkoxide bases in DMSO favors enolate formation. For the amide bases, $K_{a(\mathrm{B-H})} << K_{a(\mathrm{C-H})}$, and complete formation of the enolate occurs.



It is important to keep the position of the equilibria in mind as we consider reactions of carbanions. The base and solvent used determine the extent of deprotonation. Another important physical characteristic that has to be kept in mind is the degree of aggregation of the carbanion. Both the solvent and the cation influence the state of aggregation. This topic is discussed further in Section 1.1.3.

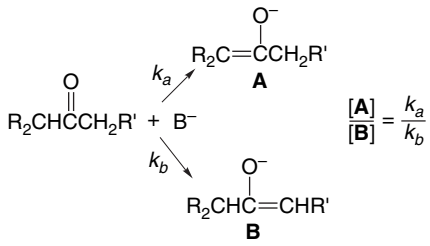
1.1.2. Regioselectivity and Stereoselectivity in Enolate Formation from Ketones and Esters

Deprotonation of the corresponding carbonyl compound is a fundamental method for the generation of enolates, and we discuss it here for ketones and esters. An unsymmetrical dialkyl ketone can form two *regioisomeric* enolates on deprotonation.



Full exploitation of the synthetic potential of enolates requires control over the regioselectivity of their formation. Although it may not be possible to direct deprotonation so as to form one enolate to the exclusion of the other, experimental conditions can often be chosen to favor one of the regioisomers. The composition of an enolate mixture can be governed by kinetic or thermodynamic factors. The enolate ratio is governed

by *kinetic control* when the product composition is determined by the *relative rates of the competing proton abstraction reactions*.



Kinetic control of isomeric enolate composition

By adjusting the conditions of enolate formation, it is possible to establish either kinetic or thermodynamic control. *Conditions for kinetic control of enolate formation are those in which deprotonation is rapid, quantitative, and irreversible.*[8] This requirement is met experimentally by using a very strong base such as LDA or LiHMDS in an aprotic solvent in the absence of excess ketone. Lithium is a better counterion than sodium or potassium for regioselective generation of the kinetic enolate, as it maintains a tighter coordination at oxygen and reduces the rate of proton exchange. Use of an aprotic solvent is essential because protic solvents permit enolate equilibration by reversible protonation-deprotonation, which gives rise to the thermodynamically controlled enolate composition. Excess ketone also catalyzes the equilibration by proton exchange.

Scheme 1.1 shows data for the regioselectivity of enolate formation for several ketones under various reaction conditions. A consistent relationship is found in these and related data. *Conditions of kinetic control usually favor formation of the less-substituted enolate*, especially for methyl ketones. The main reason for this result is that removal of a less hindered hydrogen is faster, for steric reasons, than removal of a more hindered hydrogen. Steric factors in ketone deprotonation are accentuated by using bulky bases. The most widely used bases are LDA, LiHMDS, and NaHMDS. Still more hindered disilylamides such as hexaethyldisilylamide[9] and *bis*-(dimethylphenylsilyl)amide[10] may be useful for specific cases.

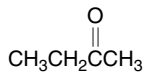
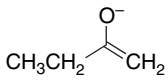
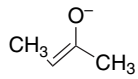
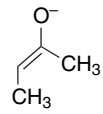
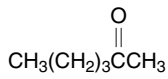
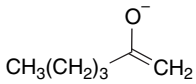
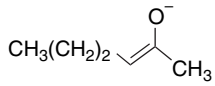
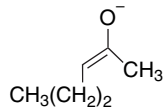
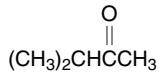
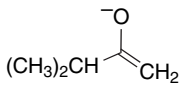
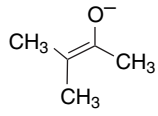
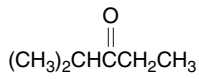
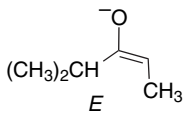
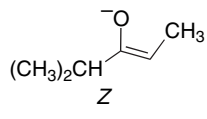
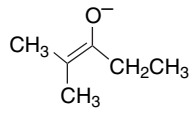
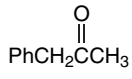
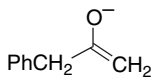
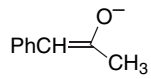
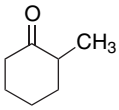
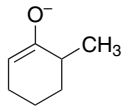
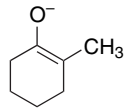
The equilibrium ratios of enolates for several ketone-enolate systems are also shown in Scheme 1.1. Equilibrium among the various enolates of a ketone can be established by the presence of an excess of ketone, which permits reversible proton transfer. Equilibration is also favored by the presence of dissociating additives such as HMPA. The composition of the equilibrium enolate mixture is usually more closely balanced than for kinetically controlled conditions. In general, the more highly substituted enolate is the preferred isomer, but if the alkyl groups are sufficiently branched as to interfere with solvation, there can be exceptions. This factor, along with CH_3/CH_3 steric repulsion, presumably accounts for the stability of the less-substituted enolate from 3-methyl-2-butanone (Entry 3).

[8] For reviews, see J. d'Angelo, *Tetrahedron*, **32**, 2979 (1976); C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992).

[9] S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).

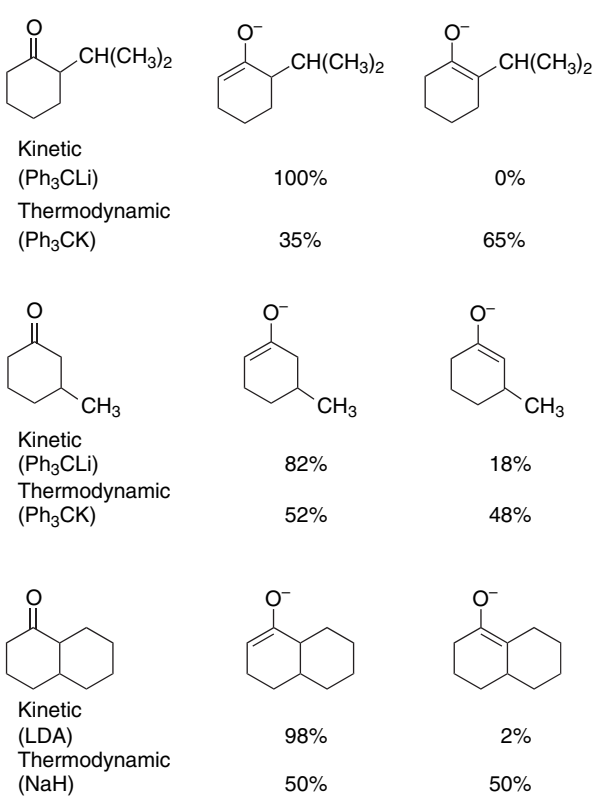
[10] S. R. Angle, J. M. Fevig, S. D. Knight, R. W. Marquis, Jr., and L. E. Overman, *J. Am. Chem. Soc.*, **115**, 3966 (1993).

Scheme 1.1. Composition of Enolate Mixtures Formed under Kinetic and Thermodynamic Control[a]

1				
	Kinetic, (LDA 0° C)	71%	13%	16%
2				
	Kinetic			
	(LDA –78°C)	100%	0%	0%
	Thermodynamic			
	(KH, 20°C)	42%	46%	12%
3				
	Kinetic			
	(KHMDS, –78°C)	99%	1%	
	Thermodynamic			
	(KH)	88%	12%	
4[b]		 *E*	 *Z*	
	Kinetic			
	LDA	40%	60%	0%
	LTMP	32%	68%	0%
	LHMDS	2%	98%	0%
	$LiNHC_6H_2Cl_3$	2%	98%	0%
5			 *E,Z*- combined	
	Kinetic			
	(LDA 0°C)	14%	86%	
	Thermodynamic			
	(NaH)	2%	98%	
6				
	Kinetic			
	(LDA, 0°C)	99%	1%	
	Thermodynamic			
	(NaH)	26%	74%	

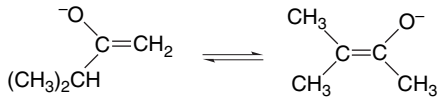
(Continued)

Scheme 1.1. ***(Continued)***



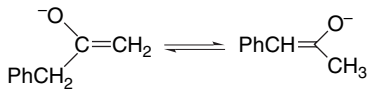
a. Selected from a more complete compilation by D. Caine, in *Carbon-Carbon Bond Formation*, R. L. Augustine, ed., Marcel Dekker, New York, 1979.

b. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980); L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.* **68**, 641 (2003).



88% 12%

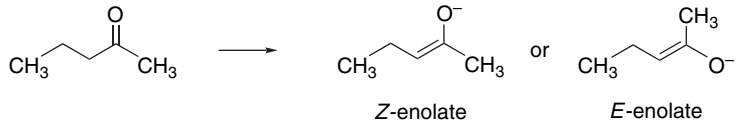
The acidifying effect of an adjacent phenyl group outweighs steric effects in the case of 1-phenyl-2-propanone, and as a result the conjugated enolate is favored by both kinetic and thermodynamic conditions (Entry 5).



For cyclic ketones conformational factors also come into play in determining enolate composition. 2-Substituted cyclohexanones are kinetically deprotonated at the C(6) methylene group, whereas the more-substituted C(2) enolate is slightly favored

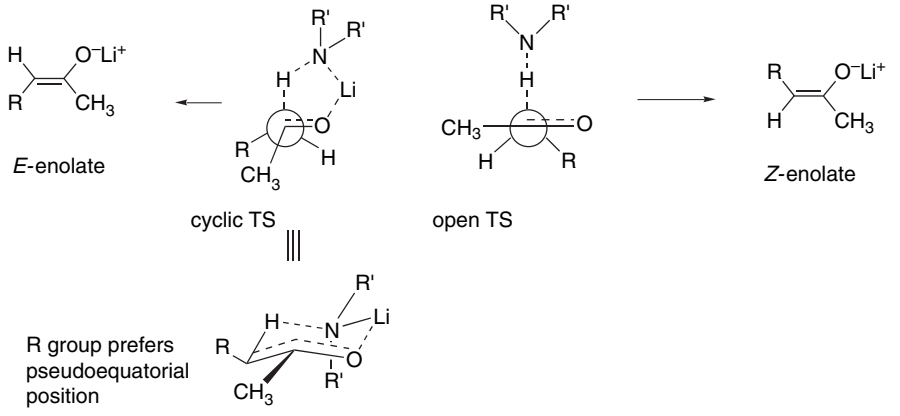
at equilibrium (Entries 6 and 7). A 3-methyl group has a significant effect on the regiochemistry of kinetic deprotonation but very little effect on the thermodynamic stability of the isomeric enolates (Entry 8).

Many enolates can exist as both *E*- and *Z*-isomers.[11] The synthetic importance of LDA and HMDS deprotonation has led to studies of enolate stereochemistry under various conditions. In particular, the stereochemistry of some enolate reactions depends on whether the *E*- or *Z*-isomer is involved. Deprotonation of 2-pentanone was examined with LDA in THF, with and without HMPA. C(1) deprotonation is favored under both conditions, but the *Z*:*E* ratio for C(3) deprotonation is sensitive to the presence of HMPA.[12] More *Z*-enolate is formed when HMPA is present.



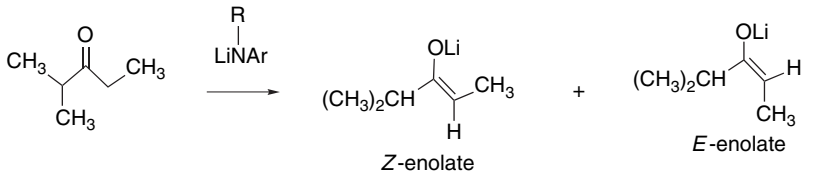
Ratio C(1):C(3) deprotonation		Ratio *Z*:*E* for C(3) deprotonation
0° C, THF alone	7.9	0.20
−60° C, THF alone	7.1	0.15
0° C, THF-HMPA	8.0	1.0
−60° C, THF-HMPA	5.6	3.1

These and other related enolate ratios are interpreted in terms of a tight, reactant-like cyclic TS in THF and a looser TS in the presence of HMPA. The cyclic TS favors the *E*-enolate, whereas the open TS favors the *Z*-enolate. The effect of the HMPA is to solvate the Li^+ ion, reducing the importance of Li^+ coordination with the carbonyl oxygen.[13]



11. The enolate oxygen is always taken as a high-priority substituent in assigning the *E*- or *Z*-configuration.
12. L. Xie and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **113**, 3123 (1991).
13. 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 (1972); R. E. Ireland, P. Wipf, and J. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

In contrast to LDA, LiHMDS favors the *Z*-enolate.[14] Certain other bases show a preference for formation of the *Z*-enolate. For example, lithium 2,4,6-trichloroanilide, lithium diphenylamide, and lithium trimethylsilylanilide show nearly complete *Z*-selectivity with 2-methyl-3-pentanone.[15]

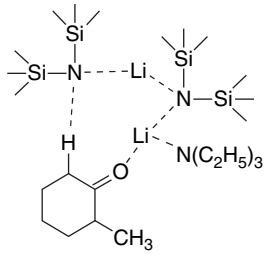


$LiNH(C_6H_2Cl_3)$	98%	2%
$LiNPh_2$	100%	0%
$LiN(Ph)Si(CH_3)_3$	95%	5%

The *Z*-selectivity seems to be associated primarily with reduced basicity of the amide anion. It is postulated that the shift to *Z*-stereoselectivity is the result of a looser TS, in which the steric effects of the chair TS are reduced.

Strong effects owing to the presence of lithium halides have been noted. With 3-pentanone, the *E*:*Z* ratio can be improved from 10:1 to 60:1 by addition of one equivalent of LiBr in deprotonation by LiTMP.[16] (Note a similar effect for 2-methyl-3-pentanone in Table 1.2) NMR studies show that the addition of the halides leads to formation of mixed 1:1 aggregates, but precisely how this leads to the change in stereoselectivity has not been unraveled. A crystal structure has been determined for a 2:1:4:1 complex of the enolate of methyl *t*-butyl ketone, with an HMDS anion, four lithium cations, and one bromide.[17] This structure, reproduced in Figure 1.1, shows that the lithium ions are clustered around the single bromide, with the enolate oxygens bridging between two lithium ions. The amide base also bridges between lithium ions.

Very significant acceleration in the rate of deprotonation of 2-methylcyclohexanone was observed when triethylamine was included in enolate-forming reactions in toluene. The rate enhancement is attributed to a TS containing LiHMDS dimer and triethylamine. Steric effects in the amine are crucial in selective stabilization of the TS and the extent of acceleration that is observed.[18]



14. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).
15. L. Xie, K. M. Isenberger, G. Held, and L. M. Dahl, *J. Org. Chem.*, **62**, 7516 (1997); L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).
16. P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991); P. L. Hall, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, and D. B. Collum, **113**, 9575 (1991).
17. K. W. Henderson, A. E. Dorigo, P. G. W. Williard, and P. R. Bernstein, *Angew. Chem. Int. Ed. Engl.*, **35**, 1322 (1996).
18. P. Zhao and D. B. Collum, *J. Am. Chem. Soc.*, **125**, 4008, 14411 (2003).

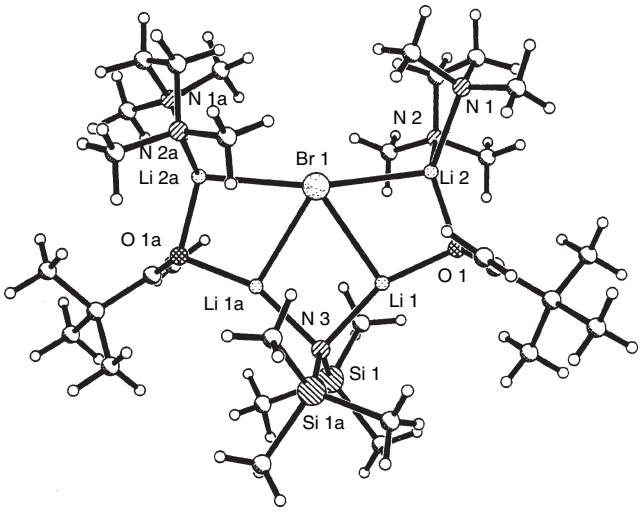
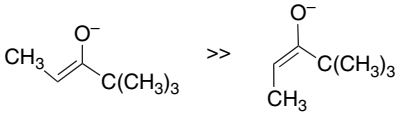


Fig. 1.1. Crystal structure of lithium enolate of methyl *t*-butyl ketone in a structure containing four Li^+, two enolates, and one HMDA anions, one bromide ion, and two TMEDA ligands. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **35**, 1322 (1996), by permission of Wiley-VCH.

These effects of LiBr and triethylamine indicate that there is still much to be learned about deprotonation and that there is potential for further improvement in regio- and stereoselectivity.

Some data on the stereoselectivity of enolate formation from both esters and ketones is given in Table 1.2. The switch from *E* to *Z* in the presence of HMPA is particularly prominent for ester enolates. There are several important factors in determining regio- and stereoselectivity in enolate formation, including the strength of the base, the identity of the cation, and the nature of the solvent and additives. In favorable cases such as 2-methyl-3-pentanone and ethyl propanoate, good selectivity is possible for both stereoisomers. In other cases, such as 2,2-dimethyl-3-pentanone, the inherent stability difference between the enolates favors a single enolate, regardless of conditions.



Chelation affects the stereochemistry of enolate formation. For example, the formation of the enolates from α-siloxyesters is *Z* for LiHMDS, but *E* for LiTMP.[19]

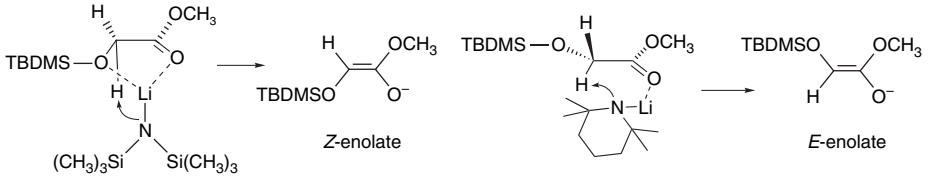
[19] K. Hattori and H. Yamamoto, *J. Org. Chem.*, **58**, 5301 (1993); K. Hattori and H. Yamamoto, *Tetrahedron*, **50**, 3099 (1994).

Table 1.2. Stereoselectivity of Enolate Formation[a]

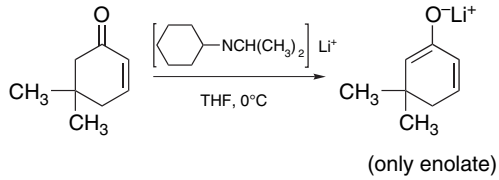
Reactant	Base	THF (hexane) (*Z*:*E*)	THF (23% HMPA) (*Z*:*E*)
Ketones			
$CH_3CH_2COCH_2CH_3$[b,c]	LDA	30:70	92:8
$CH_3CH_2COCH_2CH_3$[b]	LiTMP	20:80	
$CH_3CH_2COCH_2CH_3$[b]	LiHMDS	34:66	
$CH_3CH_2COCH(CH_3)_2$[b]	LDA	56:44	
$CH_3CH_2COCH(CH_3)_2$[b]	LiHMDS	> 98:2	
$CH_3CH_2COCH(CH_3)_2$[d]	$LiNPh_2$	100:0	
$CH_3CH_2COCH(CH_3)_2$[e]	LiTMP.LiBr	4:96	
$CH_3CH_2COC(CH_3)_3$[b]	LDA	< 2:98	
CH_3CH_2COPh[b]	LDA	> 97:3	
Esters			
$CH_3CH_2CO_2CH_2CH_3$[f]	LDA	6:94	88:15
$CH_3CO_2C(CH_3)_3$[g]	LDA	5:95	77:23
$CH_3(CH_2)_3CO_2CH_3$[g]	LDA	9:91	84:16
$PhCH_2CO_2CH_3$[h]	LDA	19:81	91:9
Amides			
$CH_3CH_2CON(C_2H_5)_2$[i]	LDA[i]	> 97:3	
$CH_3CH_2CON(CH_2)_4$[i]	LDA	> 97:3	

a. From a more extensive compilation given by C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992).
b. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).
c. Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, *J. Am. Chem. Soc.*, **102**, 3959 (1980).
d. L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).
e. P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991).
f. R. E. Ireland, P. Wipf, and J. D. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).
g. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
h. F. Tanaka and K. Fuji, *Tetrahedron Lett.*, **33**, 7885 (1992).
i. J. M. Takacs, Ph. D. Thesis, California Institute of Technology, 1981.

It has been suggested that this stereoselectivity might arise from a chelated TS in the case of the less basic LiHMDS.



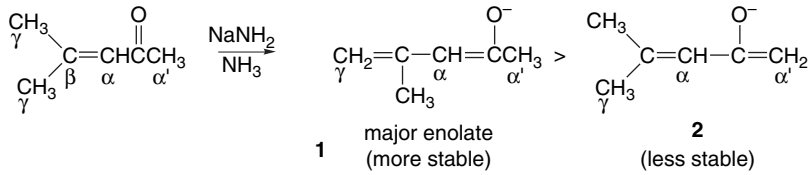
Kinetically controlled deprotonation of α,β-unsaturated ketones usually occurs preferentially at the α′-carbon adjacent to the carbonyl group. The polar effect of the carbonyl group is probably responsible for the faster deprotonation at this position.



Ref. 20

20. R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973).

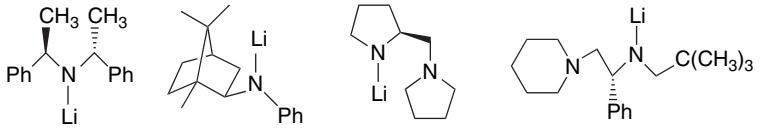
Under conditions of thermodynamic control, however, it is the enolate corresponding to deprotonation of the γ-carbon that is present in the greater amount.



Ref. 21

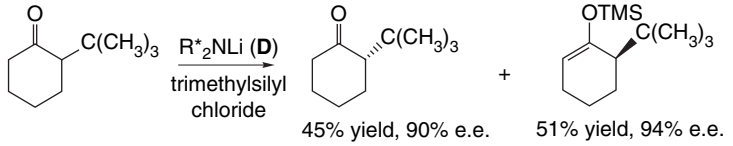
These isomeric enolates differ in that **1** is fully conjugated, whereas the π system in **2** is cross-conjugated. In isomer **2**, the delocalization of the negative charge is restricted to the oxygen and the α′-carbon, whereas in the conjugated system of **1** the negative charge is delocalized on oxygen and both the α- and γ-carbon.

It is also possible to achieve *enantioselective enolate formation* by using chiral bases. Enantioselective deprotonation requires discrimination between two enantiotopic hydrogens, such as in *cis*-2,6-dimethylcyclohexanone or 4-(*t*-butyl)cyclohexanone. Among the bases that have been studied are chiral lithium amides such as **A** to **D**.[22]



A[23] **B**[24] **C**[25] **D**[26]

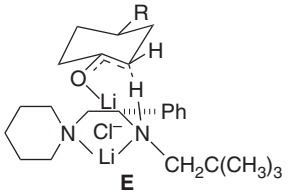
Enantioselective enolate formation can also be achieved by *kinetic resolution* through preferential reaction of one of the enantiomers of a racemic chiral ketone such as 2-(*t*-butyl)cyclohexanone (see Section 2.1.8 of Part A to review the principles of kinetic resolution).



Ref. 25a

21. G. Buchi and H. Wuest, *J. Am. Chem. Soc.*, **96**, 7573 (1974).
22. P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1439 (1998); H. J. Geis, *Methods of Organic Chemistry*, Vol. E21a, Houben-Weyl, G. Thieme Stuttgart, 1996, p. 589.
23. P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, **2**, 1 (1991); N. S. Simpkin, *Pure Appl. Chem.*, **68**, 691 (1996); B. J. Bunn and N. S. Simpkins, *J. Org. Chem.*, **58**, 533 (1993).
24. C. M. Cain, R. P. C. Cousins, G. Coumbarides, and N. S. Simpkins, *Tetrahedron*, **46**, 523 (1990).
25. (a) D. Sato, H. Kawasaki, T. Shimada, Y. Arata, K. Okamura, T. Date, and K. Koga, *J. Am. Chem. Soc.*, **114**, 761 (1992); (b) T. Yamashita, D. Sato, T. Kiyoto, A. Kumar, and K. Koga, *Tetrahedron Lett.*, **37**, 8195 (1996); (c) H. Chatani, M. Nakajima, H. Kawasaki, and K. Koga, *Heterocycles*, **46**, 53 (1997); (d) R. Shirai, D. Sato, K. Aoki, M. Tanaka, H. Kawasaki, and K. Koga, *Tetrahedron*, **53**, 5963 (1997).
26. M. Asami, *Bull. Chem. Soc. Jpn.*, **63**, 721 (1996).

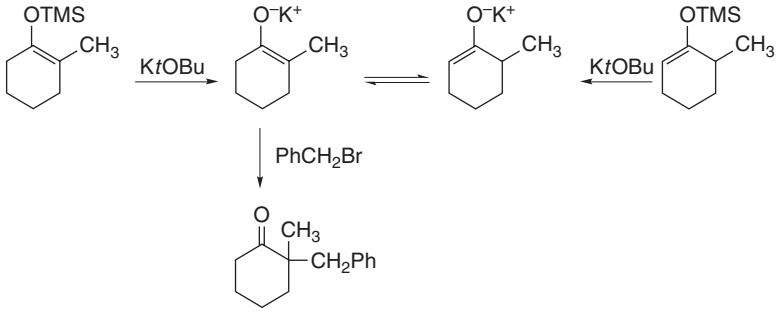
Such enantioselective deprotonations depend upon kinetic selection between prochiral or enantiomeric hydrogens and the chiral base, resulting from differences in diastereomeric TSs.[27] For example, transition structure **E** has been proposed for deprotonation of 4-substituted cyclohexanones by base **D**.[28] This structure includes a chloride generated from trimethylsilyl chloride.



E

1.1.3. Other Means of Generating Enolates

Reactions other than deprotonation can be used to generate specific enolates under conditions in which lithium enolates do not equilibrate with regio- and stereoisomers. Several methods are shown in Scheme 1.2. Cleavage of trimethylsilyl enol ethers or enol acetates by methyllithium (Entries 1 and 3), depends on the availability of these materials in high purity. Alkoxides can also be used to cleave silyl enol ethers and enol acetates.[29] When KO-*t*-Bu is used for the cleavage, subsequent alkylation occurs at the more-substituted position, regardless of which regioisomeric silyl enol ether is used.[30] Evidently under these conditions, the potassium enolates equilibrate and the more highly substituted enolate is more reactive.

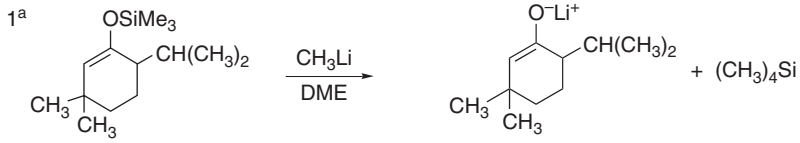


Trimethylsilyl enol ethers can also be cleaved by tetraalkylammonium fluoride (Entry 2) The driving force for this reaction is the formation of the very strong Si−F bond, which has a bond energy of 142 kcal/mol.[31] These conditions, too, lead to enolate equilibration.

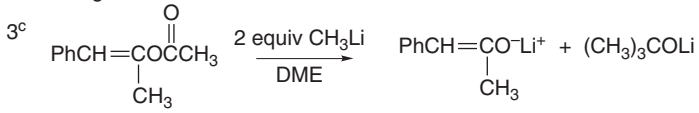
27. A. Corruble, J.-Y. Valnot, J. Maddaluno, Y. Prigent, D. Davoust, and P. Duhamel, *J. Am. Chem. Soc.*, **119**, 10042 (1997); D. Sato, H. Kawasaki, and K. Koga, *Chem. Pharm. Bull.*, **45**, 1399 (1997); K. Sugasawa, M. Shindo, H. Noguchi, and K. Koga, *Tetrahedron Lett.*, **37**, 7377 (1996).
28. M. Toriyama, K. Sugasawa, M. Shindo, N. Tokutake, and K. Koga, *Tetrahedron Lett.*, **38**, 567 (1997).
29. D. Cahard and P. Duhamel, *Eur. J. Org. Chem.*, 1023 (2001).
30. P. Duhamel, D. Cahard, Y. Quesnel, and J.-M. Poirier, *J. Org. Chem.*, **61**, 2232 (1996); Y. Quesnel, L. Bidois-Sery, J.-M. Poirier, and L. Duhamel, *Synlett*, 413 (1998).
31. For reviews of the chemistry of O-silyl enol ethers, see J. K. Rasmussen, *Synthesis*, 91 (1977); P. Brownbridge, *Synthesis*, 1, 85 (1983); I. Kuwajima and E. Nakamura, *Acc. Chem. Res.*, **18**, 181 (l985).

Scheme 1.2. Other Means of Generating Specific Enolates

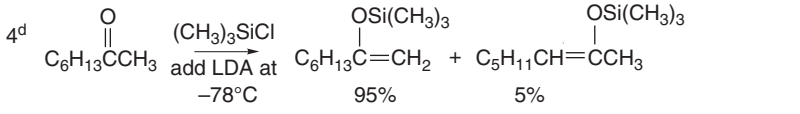
A. Cleavage of trimethylsilyl ethers



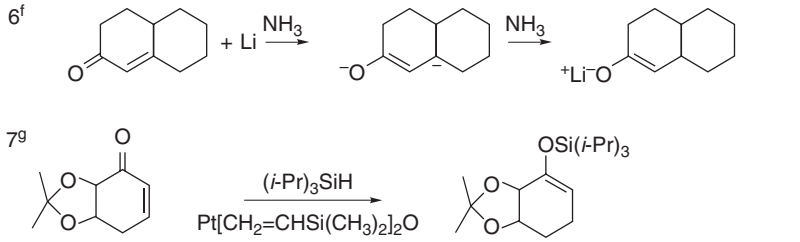
B. Cleavage of enol acetates



C. Regioselective silylation of ketones by in situ enolate trapping



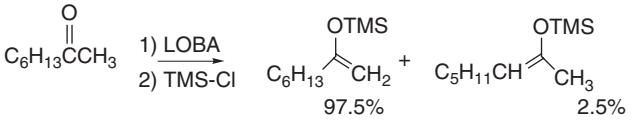
D. Reduction of α,β-unsaturated ketones



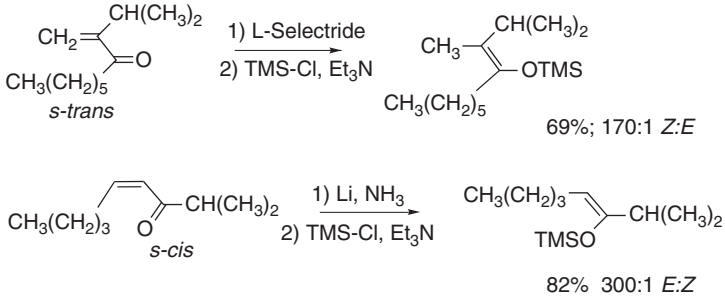
a. G. Stork and P. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4464 (1968); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
b. I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3258 (1975).
c. G. Stork and S. R. Dowd, *Org. Synth.*, **55**, 46 (1976); see also H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).
d. E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, **25**, 495 (1984).
e. E. Emde, A. Goetz, K. Hofmann, and G. Simchen, *Justus Liebigs Ann. Chem.*, 1643 (1981).
f. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).
g. C. R. Johnson and R. K. Raheja, *J. Org. Chem.*, **59**, 2287 (1994).

The composition of the trimethylsilyl enol ethers prepared from an enolate mixture reflects the enolate composition. If the enolate formation can be done with high regioselection, the corresponding trimethylsilyl enol ether can be obtained in high purity. If not, the silyl enol ether mixture must be separated. Trimethylsilyl enol ethers can be prepared directly from ketones. One procedure involves reaction with trimethylsilyl

chloride and a tertiary amine.[32] This procedure gives the regioisomers in a ratio favoring the thermodynamically more stable enol ether. Use of *t*-butyldimethylsilyl chloride with potassium hydride as the base also seems to favor the thermodynamic product.[33] Trimethylsilyl trifluoromethanesulfonate (TMS-OTf), which is more reactive, gives primarily the less-substituted trimethylsilyl enol ether.[34] Higher ratios of the less-substituted enol ether are obtained by treating a mixture of ketone and trimethylsilyl chloride with LDA at −78° C.[35] Under these conditions the kinetically preferred enolate is immediately trapped by reaction with trimethylsilyl chloride. Even greater preferences for the less-substituted silyl enol ether can be obtained by using the more hindered lithium amide from *t*-octyl-*t*-butylamine (LOBA).

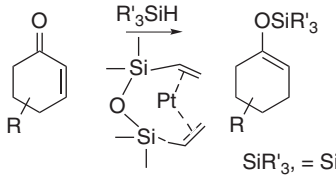


Lithium-ammonia reduction of α, β-unsaturated ketones (Entry 6) provides a very useful method for generating specific enolates.[36] The starting enones are often readily available and the position of the double bond in the enone determines the structure of the resulting enolate. For acyclic enones, the TMS-Cl trapping of enolates generated by conjugate reduction gives a silyl enol ether having a composition that reflects the conformation of the enone.[37] (See Section 2.2.1 of Part A to review enone conformation.)



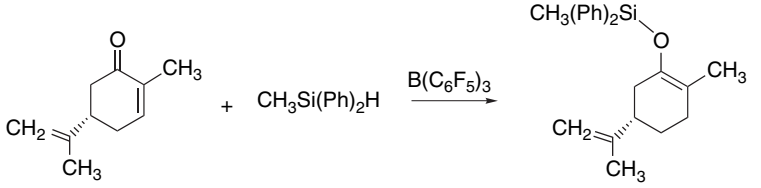
Trimethylsilyl enol ethers can also be prepared by 1,4-reduction of enones using silanes as reductants. Several effective catalysts have been found,[38] of which the most versatile appears to be a Pt complex of divinyltetramethyldisiloxane.[39] This catalyst gives good yields of substituted silyl enol ethers (e.g., Scheme 1.2, Entry 7).

32. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); R. D. Miller and D. R. McKean, *Synthesis*, 730 (1979).
33. J. Orban, J. V. Turner, and B. Twitchin, *Tetrahedron Lett.*, **25**, 5099 (1984).
34. H. Emde, A. Goetz, K. Hofmann, and G. Simchen, *Liebigs Ann. Chem.*, 1643 (1981); see also E. J. Corey, H. Cho, C. Ruecker, and D. Hua, *Tetrahedron Lett.*, 3455 (1981).
35. E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, **25**, 495 (1984).
36. For a review of α, β-enone reduction, see D. Caine, *Org. React.*, **23**, 1 (1976).
37. A. R. Chamberlin and S. H. Reich, *J. Am. Chem. Soc.*, **107**, 1440 (1985).
38. I. Ojima and T. Kogure, *Organometallics*, **1**, 1390 (1982); T. H. Chan and G. Z. Zheng, *Tetrahedron Lett.*, **34**, 3095 (1993); D. E. Cane and M. Tandon, *Tetrahedron Lett.*, **35**, 5351 (1994).
39. C. R. Johnson and R. K Raheja, *J. Org. Chem.*, **59**, 2287 (1994).



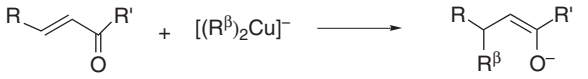
SiR'_3, = $Si(Et)_3$, $Si(i\text{-}Pr)_3$, $Si(Ph)_3$, $Si(Me)_2C(Me)_3$

Excellent yields of silyl enol have also been obtained from enones using $B(C_6F_5)_3$ as a catalyst.[40] *t*-Butyldimethylsilyl, triethylsilyl, and other silyl enol ethers can also be made under these conditions.



These and other reductive methods for generating enolates from enones are discussed more fully in Chapter 5.

Another very important method for specific enolate generation is the conjugate addition of organometallic reagents to enones. This reaction, which not only generates a specific enolate, but also adds a carbon substituent, is discussed in Section 8.1.2.3.



1.1.4. Solvent Effects on Enolate Structure and Reactivity

The rate of alkylation of enolate ions is strongly dependent on the solvent in which the reaction is carried out.[41] The relative rates of reaction of the sodium enolate of diethyl *n*-butylmalonate with *n*-butyl bromide are shown in Table 1.3. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) are particularly effective in enhancing the reactivity of enolate ions. Both of these are *polar aprotic solvents*. Other

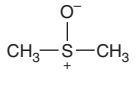
Table 1.3. Relative Alkylation Rates of Sodium Diethyl *n*-Butylmalonate in Various Solvents[a]

Solvent	Dielectric constant ϵ	Relative rate
Benzene	2.3	1
Tetrahydrofuran	7.3	14
Dimethoxyethane	6.8	80
N,*N*-Dimethylformamide	37	970
Dimethyl sulfoxide	47	1420

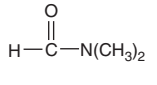
a. From H. E. Zaugg, *J. Am. Chem. Soc.*, **83**, 837 (1961).

40. J. M. Blackwell, D. J. Morrison, and W. E. Piers, *Tetrahedron*, **58**, 8247 (2002).
41. For reviews, see (a) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); (b) L. M. Jackmamn and B. C. Lange, *Tetrahedron*, **33**, 2737 (1977).

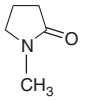
compounds that are used as cosolvents in reactions between enolates and alkyl halides include *N*-methylpyrrolidone (NMP), hexamethylphosphoric triamide (HMPA) and *N*,*N*′-dimethylpropyleneurea (DMPU).[42] Polar aprotic solvents, as the name indicates, are materials that have high dielectric constants but lack hydroxy or other hydrogen-bonding groups. Polar aprotic solvents possess excellent metal cation coordination ability, so they can solvate and dissociate enolates and other carbanions from ion pairs and clusters.



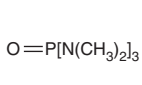
dimethyl sulfoxide (DMSO) ε = 47



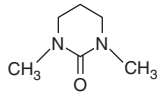
N,*N*-dimethylformamide (DMF) ε = 37



N-methylpyrrolidone (NMP) ε = 32

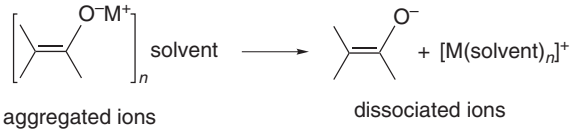


hexamethylphosphoric triamide (HMPA) ε = 30

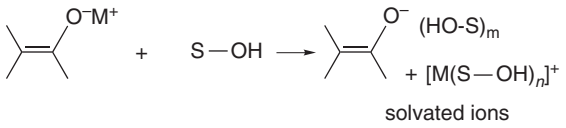


N,*N*′-dimethylpropyleneurea (DMPU)

The reactivity of alkali metal (Li^+, Na^+, K^+) enolates is very sensitive to the state of aggregation, which is, in turn, influenced by the reaction medium. The highest level of reactivity, which can be approached but not achieved in solution, is that of the "bare" unsolvated enolate anion. For an enolate-metal ion pair in solution, the maximum reactivity is expected when the cation is strongly solvated and the enolate is very weakly solvated. Polar aprotic solvents are good cation solvators and poor anion solvators. Each one has a negatively polarized oxygen available for coordination to the metal cation. Coordination to the enolate anion is less effective because the positively polarized atoms of these molecules are not nearly as exposed as the oxygen. Thus, these solvents provide a medium in which enolate-metal ion aggregates are dissociated to give a less encumbered, more reactive enolate.



Polar protic solvents such as water and alcohols also possess a pronounced ability to separate ion aggregates, but are less favorable as solvents in enolate alkylation reactions because they can coordinate to both the metal cation and the enolate anion. Solvation of the enolate anion occurs through hydrogen bonding. The solvated enolate is relatively less reactive because the hydrogen bonding must be disrupted during alkylation. Enolates generated in polar protic solvents such as water, alcohols, or ammonia are therefore less reactive than the same enolate in a polar aprotic solvent such as DMSO. Of course, hydroxylic solvents also impose limits on the basicity of enolates that are stable.



[42] T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, **65**, 385 (1982).

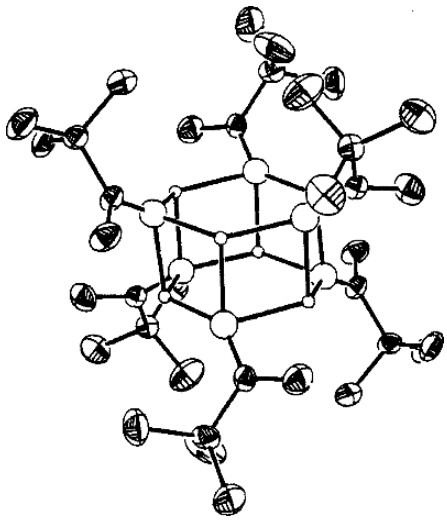


Fig. 1.2. Unsolvated hexameric aggregate of lithium enolate of methyl *t*-butyl ketone; the open circles represent oxygen and the small circles are lithium. Reproduced from *J. Am. Chem. Soc.*, **108**, 462 (1986), by permission of the American Chemical Society.

Tetrahydrofuran (THF) and dimethoxyethane (DME) are slightly polar solvents that are moderately good cation solvators. Coordination to the metal cation involves the oxygen unshared electron pairs. These solvents, because of their lower dielectric constants, are less effective at separating ion pairs and higher aggregates than are the polar aprotic solvents. The structures of the lithium and potassium enolates of methyl *t*-butyl ketone have been determined by X-ray crystallography. The structures are shown in Figures 1.2 and 1.3.[43] Whereas these represent the solid state structures,

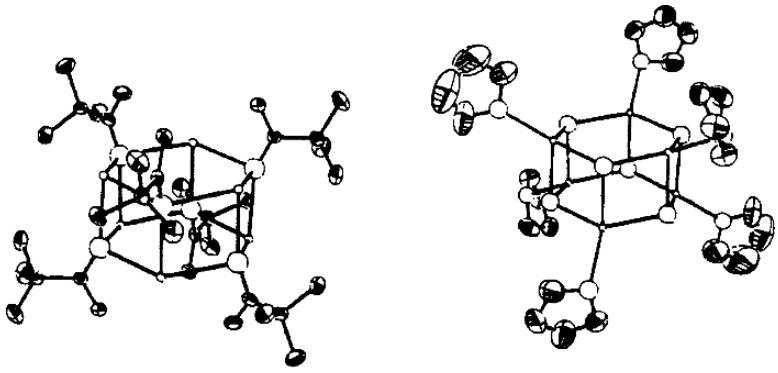


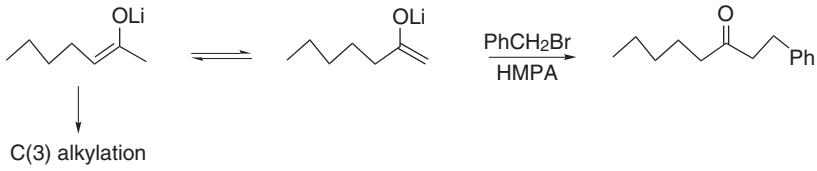
Fig. 1.3. Potassium enolate of methyl *t*-butyl ketone; open circles are oxygen and small circles are potassium. (a) left panel shows only the enolate structures; (b) right panel shows only the solvating THF molecules. The actual structure is the superposition of both panels. Reproduced from *J. Am. Chem. Soc.*, **108**, 462 (1986), by permission of the American Chemical Society.

[43.] P. G. Williard and G. B. Carpenter, *J. Am. Chem. Soc.*, **108,** 462 (1986).

the hexameric clusters are a good indication of the nature of the enolates in relatively weakly coordinating solvents. In both structures, series of alternating metal cations and enolate oxygens are assembled in two offset hexagons. The cluster is considerably tighter with Li^+ than with K^+. The M−O bonds are about 1.9 Å for Li^+ and 2.6 Å for K^+. The enolate C−O bond is longer (1.34 Å) for Li^+ than for K^+ (1.31 Å), whereas the C=C bond is shorter for Li^+ (1.33 Å) than for K^+ (1.35 Å). Thus, the Li^+ enolate has somewhat more of oxy-anion character and is expected to be a "harder" than the potassium enolate.

Despite the somewhat reduced reactivity of aggregated enolates, THF and DME are the most commonly used solvents for synthetic reactions involving enolate alkylation. They are the most suitable solvents for *kinetic enolate generation* and also have advantages in terms of product workup and purification over the polar aprotic solvents. Enolate reactivity in these solvents can often be enhanced by adding a reagent that can bind alkali metal cations more strongly. Popular choices are HMPA, DMPU, tetramethylethylenediamine (TMEDA), and the crown ethers. TMEDA chelates metal ions through the electron pairs on nitrogen. The crown ethers encapsulate the metal ions through coordination with the ether oxygens. The 18-crown-6 structure is of such a size as to allow sodium or potassium ions to fit in the cavity. The smaller 12-crown-4 binds Li^+ preferentially. The cation complexing agents lower the degree of aggregation of the enolate and metal cations, which results in enhanced reactivity.

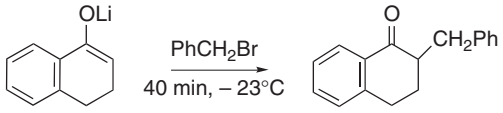
The effect of HMPA on the reactivity of cyclopentanone enolate has been examined.[44] This enolate is primarily a dimer, even in the presence of excess HMPA, but the reactivity increases by a factor of 7500 for a tenfold excess of HMPA at −50° C. The kinetics of the reaction with CH_3I are consistent with the dimer being the active nucleophile. It should be kept in mind that the reactivity of regio- and stereoisomeric enolates may be different and the alkylation product ratio may not reflect the enolate composition. This issue was studied with 2-heptanone.[45] Although kinetic deprotonation in THF favors the 1-enolate, a nearly equal mixture of C(1) and C(3) alkylation was observed. The inclusion of HMPA improved the C(1) selectivity to 11:1 and also markedly accelerated the rate of the reaction. These results are presumably due to increased reactivity and less competition from enolate isomerization in the presence of HMPA.



The effect of chelating polyamines on the rate and yield of benzylation of the lithium enolate of 1-tetralone was compared with HMPA and DMPU. The triamine

44. M. Suzuki, H. Koyama, and R. Noyori, *Bull. Chem. Soc. Jpn.*, **77**, 259 (2004); M. Suzuki, H. Koyama, and R. Noyori, *Tetrahedron*, **60**, 1571 (2004).
45. C. L. Liotta and T. C. Caruso, *Tetrahedron Lett.*, **26**, 1599 (1985).

and tetramine were even more effective than HMPA in promoting reaction.[46] These results, too, are presumably due to disaggregation of the enolate by the polyamines.



Additive (3eq)	Yield (%)
none	6
HMPA	34
DMPU	3
$Me_2NCH_2CH_2NMe_2$	6
$(Me_2NCH_2CH_2)_2NMe$	50
$(Me_2NCH_2CH_2NCH_2)_2$ (Me)	72
$Me_2N(CH_2CH_2N)_3CH_2CH_2NMe_2$ (Me)	33

The reactivity of enolates is also affected by the metal counterion. For the most commonly used ions the order of reactivity is $Mg^{2+} < Li^+ < Na^+ < K^+$. The factors that are responsible for this order are closely related to those described for solvents. The smaller, harder Mg^{2+} and Li^+ cations are more tightly associated with the enolate than are the Na^+ and K^+ ions. The tighter coordination decreases the reactivity of the enolate and gives rise to more highly associated species.

1.2. Alkylation of Enolates[47]

1.2.1. Alkylation of Highly Stabilized Enolates

Relatively acidic compounds such as malonate esters and β-ketoesters were the first class of compounds for which reliable conditions for carbanion alkylation were developed. The alkylation of these relatively acidic compounds can be carried out in alcohols as solvents using metal alkoxides as bases. The presence of two electron-withdrawing substituents facilitates formation of the resulting enolate. Alkylation occurs by an S_N2 process, so the alkylating agent must be reactive toward nucleophilic displacement. Primary halides and sulfonates, especially allylic and benzylic ones, are the most reactive alkylating agents. Secondary systems react more slowly and often give only moderate yields because of competing elimination. Tertiary halides give only elimination products. Methylene groups can be dialkylated if sufficient base and alkylating agent are used. Dialkylation can be an undesirable side reaction if the monoalkyl derivative is the desired product. Sequential dialkylation using two different alkyl groups is possible. Use of dihaloalkanes as alkylating reagents leads to ring formation. The relative rates of cyclization for ω-haloalkyl malonate esters

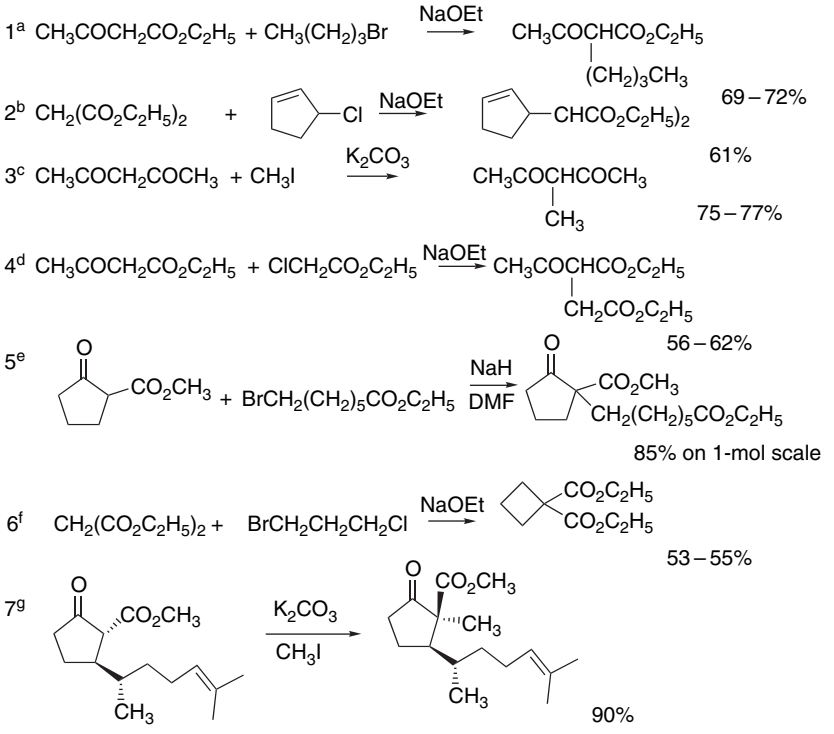
46. M. Goto, K. Akimoto, K. Aoki, M. Shindo, and K. Koga, *Chem. Pharm. Bull.*, **48**, 1529 (2000).
47. For general reviews of enolate alkylation, see D. Caine, in *Carbon-Carbon Bond Formation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1979, Chap. 2; C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992).

are 650,000:1:6500:5 for formation of three-, four-, five-, and six-membered rings, respectively.[48] (See Section 4.3 of Part A to review the effect of ring size on S_N2 reactions.)

Some examples of alkylation reactions involving relatively acidic carbon acids are shown in Scheme 1.3. Entries 1 to 4 are typical examples using sodium ethoxide as the base. Entry 5 is similar, but employs sodium hydride as the base. The synthesis of diethyl cyclobutanedicarboxylate in Entry 6 illustrates ring formation by *intramolecular alkylation reactions*. Additional examples of intramolecular alkylation are considered in Section 1.2.5. Note also the stereoselectivity in Entry 7, where the existing branched substituent leads to a *trans* orientation of the methyl group.

The 2-substituted β-ketoesters (Entries 1, 4, 5, and 7) and malonic ester (Entries 2 and 6) prepared by the methods illustrated in Scheme 1.3 are useful for the synthesis

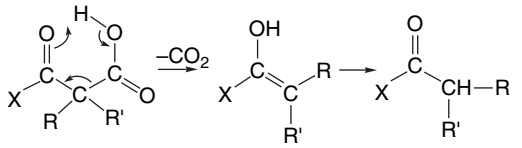
Scheme 1.3. Alkylation of Enolates Stabilized by Two Functional Groups



a. C. S. Marvel and F. D. Hager, *Org. Synth.*, **I**, 248 (1941).
b. R. B. Moffett, *Org. Synth.*, **IV**, 291 (1963).
c. A. W. Johnson, E. Markham, and R. Price, *Org. Synth.*, **42**, 75 (1962).
d. H. Adkins, N. Isbell, and B. Wojcik, *Org. Synth.*, **II**, 262 (1943).
e. K. F. Bernardy, J. F. Poletto, J. Nocera, P. Miranda, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.*, **45**, 4702 (1980).
f. R. P. Mariella and R. Raube, *Org. Synth.*, **IV**, 288 (1963).
g. D. F. Taber and S. C. Malcom, *J. Org. Chem.*, **66**, 944 (2001).

48. A. C. Knipe and C. J. Stirling, *J. Chem. Soc. B*, 67 (1968); For a discussion of factors that affect intramolecular alkylation of enolates, see J. Janjatovic and Z. Majerski, *J. Org. Chem.*, **45**, 4892 (1980).

of ketones and carboxylic acids. Both β-keto acids and malonic acids undergo facile decarboxylation.

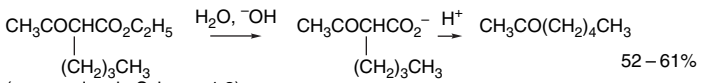


β-keto acid: X = alkyl or aryl = ketone
substituted malonic acid: X = OH = substituted acetic acid

Examples of this approach to the synthesis of ketones and carboxylic acids are presented in Scheme 1.4. In these procedures, an ester group is removed by hydrolysis and decarboxylation after the alkylation step. The malonate and acetoacetate carbanions are the *synthetic equivalents* of the simpler carbanions that lack the additional ester substituent. In the preparation of 2-heptanone (Entry 1), for example, ethyl acetoacetate functions

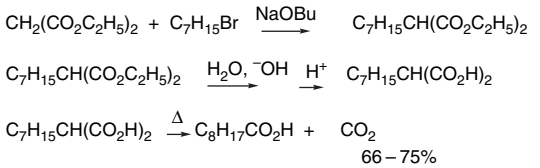
Scheme 1.4. Synthesis by Decarboxylation of Malonates and other β-Dicarbonyl Compounds

1[a]

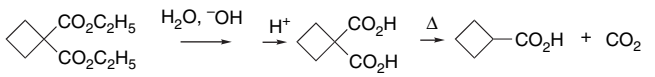


(prepared as in Scheme 1.3)

2[b]

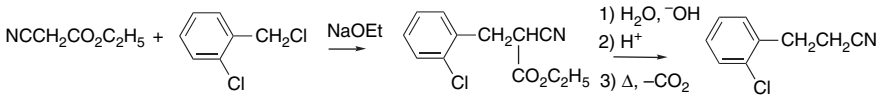


3[c]

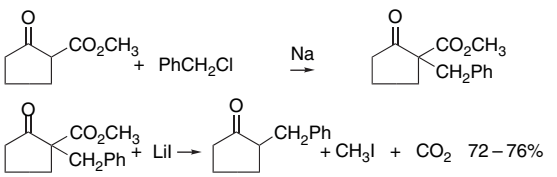


(prepared as in Scheme 1.3)

4[d]



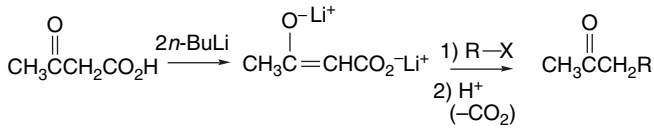
5[e]



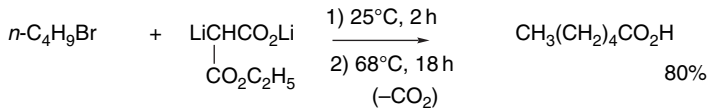
a. J. R. Johnson and F. D. Hager, *Org. Synth.*, **I**, 351 (1941).
b. E. E. Reid and J. R. Ruhoff, *Org. Synth.*, **II**, 474 (1943).
c. G. B. Heisig and F. H. Stodola, *Org. Synth.*, **III**, 213 (1955).
d. J. A. Skorcz and F. E. Kaminski, *Org. Synth.*, **48**, 53 (1968).
e. F. Elsinger, *Org. Synth.*, **V**, 76 (1973).

as the synthetic equivalent of acetone. Entries 2 and 3 show synthesis of carboxylic acids via the malonate ester route. Entry 4 is an example of a nitrile synthesis, starting with ethyl cyanoacetate as the carbon nucleophile. The cyano group also facilitates decarboxylation. Entry 5 illustrates an alternative decarboxylation procedure in which lithium iodide is used to cleave the β-ketoester by nucleophilic demethylation.

It is also possible to use the dilithium derivative of acetoacetic acid as the synthetic equivalent of acetone enolate.[49] In this case, the hydrolysis step is unnecessary and decarboxylation can be done directly on the alkylation product.



Similarly, the dilithium dianion of monoethyl malonate is easily alkylated and the product decarboxylates after acidification.[50]



1.2.2. Alkylation of Ketone Enolates

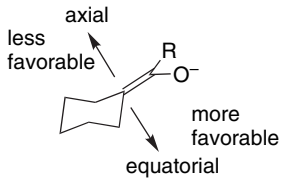
The preparation of ketones and ester from β-dicarbonyl enolates has largely been supplanted by procedures based on selective enolate formation. These procedures permit direct alkylation of ketone and ester enolates and avoid the hydrolysis and decarboxylation of keto ester intermediates. The development of conditions for stoichiometric formation of both kinetically and thermodynamically controlled enolates has permitted the extensive use of enolate alkylation reactions in multistep synthesis of complex molecules. One aspect of the alkylation reaction that is crucial in many cases is the stereoselectivity. The alkylation has a stereoelectronic preference for approach of the electrophile perpendicular to the plane of the enolate, because the π electrons are involved in bond formation. A major factor in determining the stereoselectivity of ketone enolate alkylations is the difference in steric hindrance on the two faces of the enolate. The electrophile approaches from the less hindered of the two faces and the degree of stereoselectivity depends on the steric differentiation. Numerous examples of such effects have been observed.[51] In ketone and ester enolates that are exocyclic to a conformationally biased cyclohexane ring there is a small preference for

[49] R. A. Kjonaas and D. D. Patel, *Tetrahedron Lett.*, **25**, 5467 (1984).

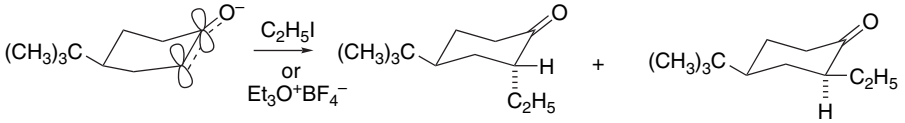
[50] J. E. McMurry and J. H. Musser, *J. Org. Chem.*, **40**, 2556 (1975).

[51] For reviews, see D. A. Evans, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 1; D. Caine, in *Carbon-Carbon Bond Formation*, R. L. Augustine, ed., Marcel Dekker, New York, 1979, Chap. 2.

the electrophile to approach from the equatorial direction.[52] If the axial face is further hindered by addition of a substituent, the selectivity is increased.

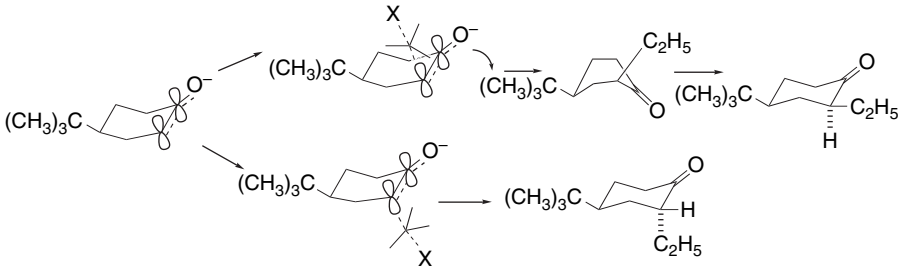


For simple, conformationally biased cyclohexanone enolates such as that from 4-*t*-butylcyclohexanone, there is little steric differentiation. The alkylation product is a nearly 1:1 mixture of the *cis* and *trans* isomers.

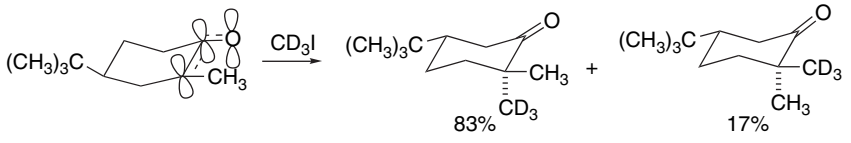


Ref. 53

The *cis* product must be formed through a TS with a twistlike conformation to adhere to the requirements of stereoelectronic control. The fact that this pathway is not disfavored is consistent with other evidence that the TS in enolate alkylations occurs *early* and reflects primarily the structural features of the reactant, not the product. A late TS would disfavor the formation of the *cis* isomer because of the strain associated with the nonchair conformation of the product.

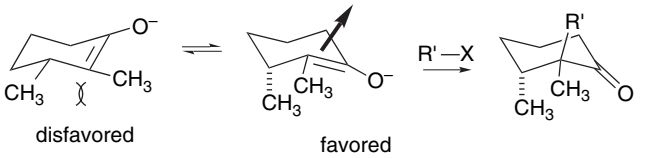


The introduction of an alkyl substituent at the α-carbon in the enolate enhances stereoselectivity somewhat. This is attributed to a steric effect in the enolate. To minimize steric interaction with the solvated oxygen, the alkyl group is distorted somewhat from coplanarity, which biases the enolate toward attack from the axial direction. The alternate approach from the upper face increases the steric interaction by forcing the alkyl group to become eclipsed with the enolate oxygen.[54]

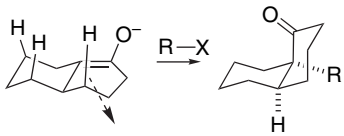


52. A. P. Krapcho and E. A. Dundulis, *J. Org. Chem.*, **45**, 3236 (1980); H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).
53. H. O. House, B. A. Terfertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).
54. H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 1000 (1973).

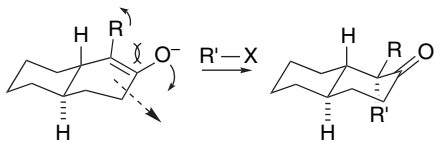
When an additional methyl substituent is placed at C(3), there is a strong preference for alkylation *anti* to the 3-methyl group. This is attributed to the conformation of the enolate, which places the C(3) methyl in a pseudoaxial orientation because of allylic strain (see Part A, Section 2.2.1). The axial C(3) methyl then shields the lower face of the enolate.[55]



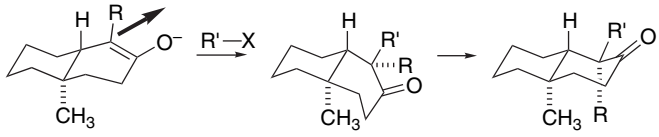
The enolates of 1- and 2-decalone derivatives provide further insight into the factors governing stereoselectivity in enolate alkylations. The 1(9)-enolate of 1-decalone shows a preference for alkylation to give the *cis* ring juncture, and this is believed to be due primarily a steric effect. The upper face of the enolate presents three hydrogens in a 1,3-diaxial relationship to the approaching electrophile. The corresponding hydrogens on the lower face are equatorial.[56]



The 2(1)-enolate of *trans*-2-decalone is preferentially alkylated by an axial approach of the electrophile.

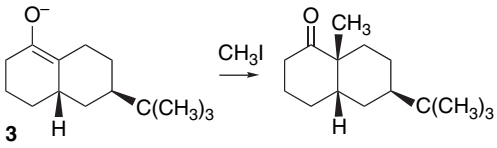


The stereoselectivity is enhanced if there is an alkyl substituent at C(1). The factors operating in this case are similar to those described for 4-*t*-butylcyclohexanone. The *trans*-decalone framework is conformationally rigid. Axial attack from the lower face leads directly to the chair conformation of the product. The 1-alkyl group enhances this stereoselectivity because a steric interaction with the solvated enolate oxygen distorts the enolate to favor the axial attack.[57] The placement of an axial methyl group at C(10) in a 2(1)-decalone enolate introduces a 1,3-diaxial interaction with the approaching electrophile. The preferred alkylation product results from approach on the opposite side of the enolate.

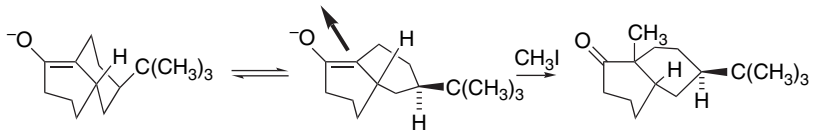


55. R. K. Boeckman, Jr., *J. Org. Chem.*, **38**, 4450 (1973).
56. H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).
57. R. S. Mathews, S. S. Grigenti, and E. A. Folkers, *J. Chem. Soc., Chem. Commun.*, 708 (1970); P. Lansbury and G. E. DuBois, *Tetrahedron Lett.*, 3305 (1972).

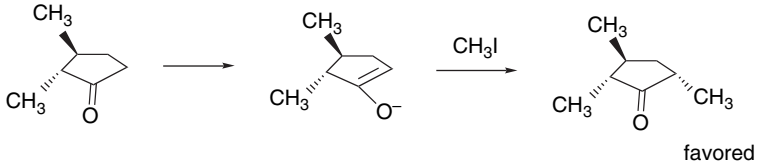
The prediction and interpretation of alkylation stereochemistry requires consideration of conformational effects in the enolate. The decalone enolate **3** was found to have a strong preference for alkylation to give the *cis* ring junction, with alkylation occurring *cis* to the *t*-butyl substituent.[58]



According to molecular mechanics (MM) calculations, the minimum energy conformation of the enolate is a twist-boat (because the chair leads to an axial orientation of the *t*-butyl group). The enolate is convex in shape with the second ring shielding the bottom face of the enolate, so alkylation occurs from the top.



Houk and co-workers examined the role of torsional effects in the stereoselectivity of enolate alkylation in five-membered rings, and their interpretation can explain the preference for C(5) alkylation *syn* to the 2-methyl group in *trans*-2,3-dimethylcyclopentanone.[59]



The *syn* TS is favored by about 1 kcal/mol, owing to reduced eclipsing, as illustrated in Figure 1.4. An experimental study using the kinetic enolate of 3-(*t*-butyl)-2-methylcyclopentanone in an alkylation reaction with benzyl iodide gave an 85:15 preference for the predicted *cis*-2,5-dimethyl derivative.

In acyclic systems, the enolate conformation comes into play. β,β-Disubstituted enolates prefer a conformation with the hydrogen eclipsed with the enolate double bond. In unfunctionalized enolates, alkylation usually takes place *anti* to the larger substituent, but with very modest stereoselectivity.

58. H. O. House, W. V. Phillips, and D. Van Derveer, *J. Org. Chem.*, **44,** 2400 (1979).
59. K. Ando, N. S. Green, Y. Li, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 5334 (1999).

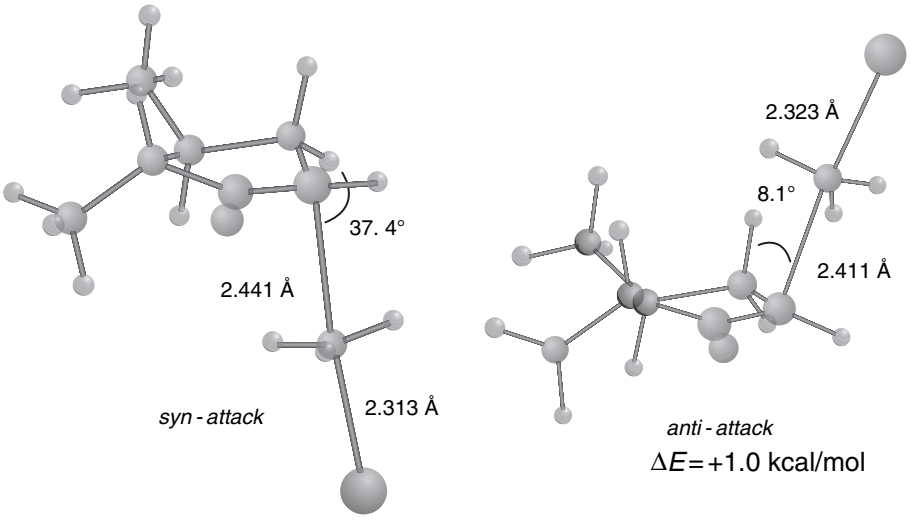
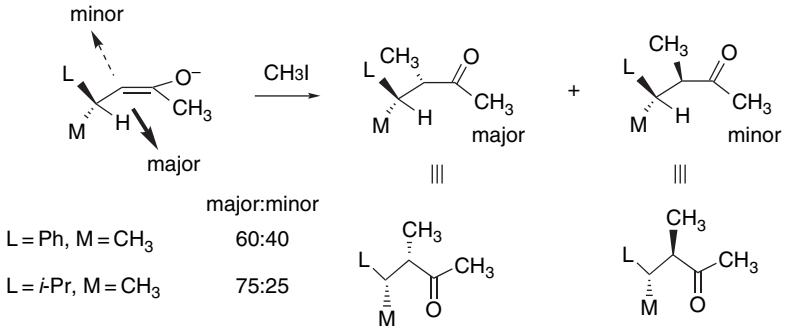


Fig. 1.4. Transition structures for *syn* and *anti* attack on the kinetic enolate of *trans*-2,3-dimethylcyclopentanone showing the staggered versus eclipsed nature of the newly forming bond. Reproduced from *J. Am. Chem. Soc.*, **121**, 5334 (1999), by permission of the American Chemical Society.

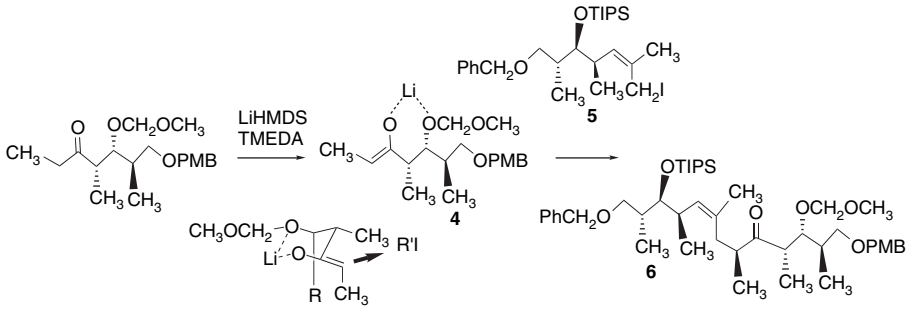


Ref. 60

These examples illustrate the issues that must be considered in analyzing the stereoselectivity of enolate alkylation. *The major factors are the conformation of the enolate, the stereoelectronic requirement for an approximately perpendicular trajectory, the steric preference for the least hindered path of approach, and minimization of torsional strain.* In cyclic systems the ring geometry and positioning of substituents are often the dominant factors. For acyclic enolates, the conformation and the degree of steric discrimination govern the stereoselectivity.

For enolates with additional functional groups, chelation may influence stereoselectivity. Chelation-controlled alkylation has been examined in the context of the synthesis of a polyol lactone (-)-discodermolide. The lithium enolate **4** reacts with the allylic iodide **5** in a hexane:THF solvent mixture to give a 6:1 ratio favoring the desired stereoisomer. Use of the sodium enolate gives the opposite stereoselectivity, presumably because of the loss of chelation.[61] The solvent seems to be quite important in promoting chelation control.

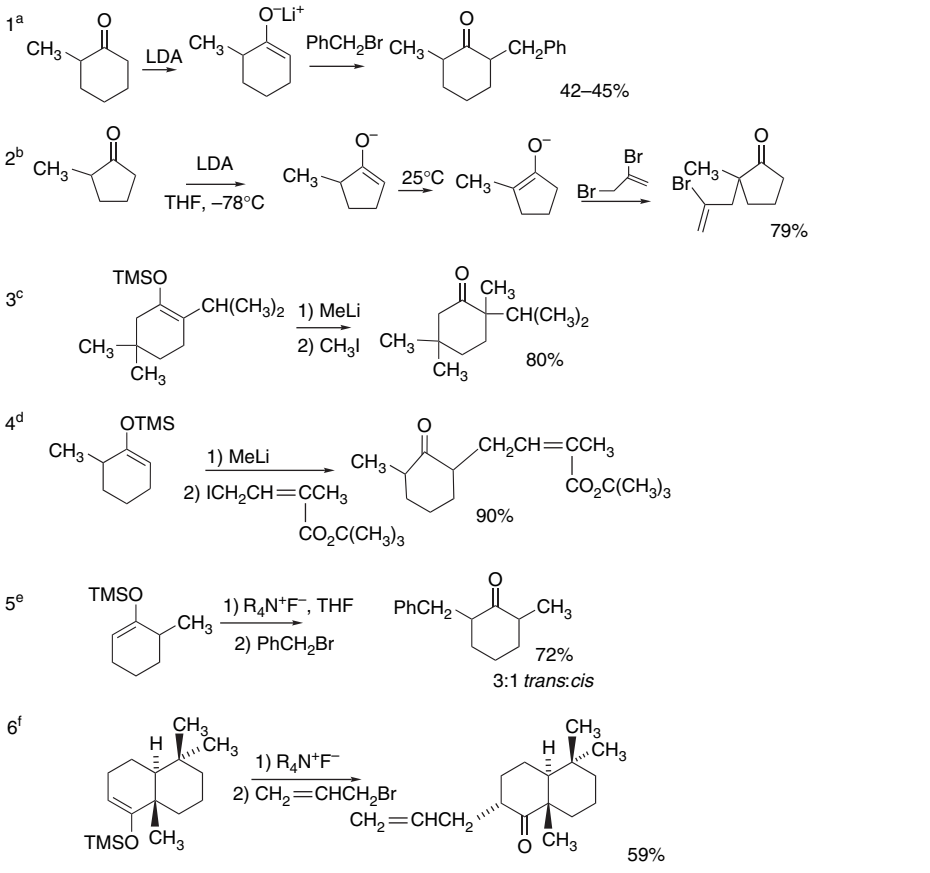
[60.] I. Fleming and J. J. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 3257 (1992).
[61.] S. S. Harried, G. Yang, M. A. Strawn, and D. C. Myles, *J. Org. Chem.*, **62**, 6098 (1997).



Previous studies with related enolates having different protecting groups also gave products with the opposite C(16)–R configuration.[62]

Scheme 1.5 gives some examples of alkylation of ketone enolates. Entries 1 and 2 involve formation of the enolates by deprotonation with LDA. In Entry 2, equilibration

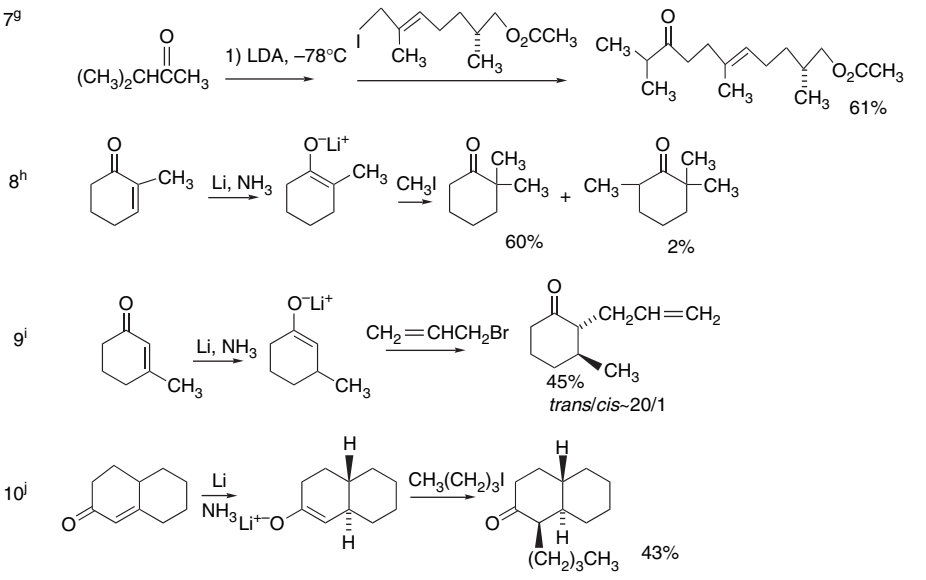
Scheme 1.5. Alkylation of Ketone Enolates



(Continued)

62. D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **118**, 11054 (1996); D. L. Clark and C. H. Heathcock, *J. Org. Chem.*, **58**, 5878 (1993).

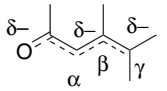
Scheme 1.5. ***(Continued)***



a. M. Gall and H. O. House, *Org. Synth.*, **52**, 39 (1972).
b. S. C. Welch and S. Chayabunjonglerd, *J. Am. Chem. Soc.*, **101**, 6768 (1979).
c. G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4464 (1968).
d. P. L. Stotter and K. A. Hill, *J. Am. Chem. Soc.*, **96**, 6524 (1974).
e. I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **104**, 1025 (1982).
f. A. B. Smith, III, and R. Mewshaw, *J. Org. Chem.*, **49**, 3685 (1984).
g. Y. L. Li, C. Huang, W. Li, and Y. Li, *Synth. Commun.*, **27**, 4341 (1997).
h. H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967).
i. D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.*, **56**, 52 (1977).
j. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsujii, *J. Am. Chem. Soc.*, **87**, 275 (1965).

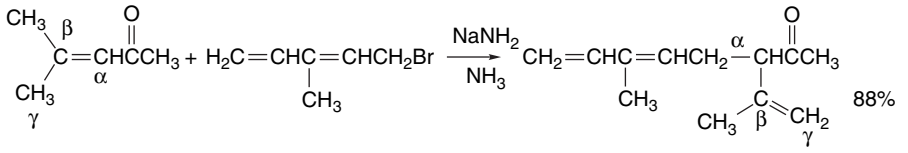
to the more-substituted enolate precedes alkylation. Entries 3 and 4 show regiospecific generation of enolates by reaction of silyl enol ethers with methyllithium. Alkylation can also be carried out using silyl enol ethers by generating the enolate by fluoride ion.[63] Anhydrous tetraalkylammonium fluoride salts in anhydrous are normally the fluoride ion source.[64] Entries 5 and 6 illustrate this method. Entry 7 shows the kinetic deprotonation of 3-methylbutanone, followed by alkylation with a functionalized allylic iodide. Entries 8, 9, and 10 are examples of alkylation of enolates generated by reduction of enones. Entry 10 illustrates the preference for axial alkylation of the 2-(1)-decalone enolate.

In enolates formed by proton abstraction from α,β-unsaturated ketones, there are three potential sites for attack by electrophiles: the oxygen, the α-carbon, and the γ-carbon. The kinetically preferred site for both protonation and alkylation is the α-carbon.[65]

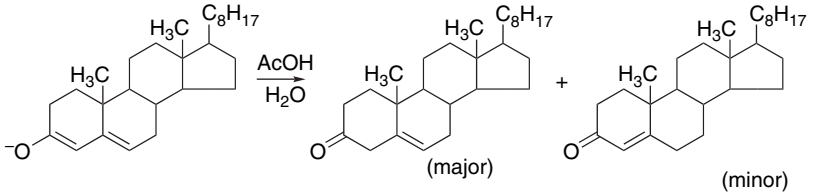


63. I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **104**, 1025 (1982).
64. A. B. Smith, III, and R. Mewshaw, *J. Org. Chem.*, **49**, 3685 (1984).
65. R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973); J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5662 (1974).

The selectivity for electrophilic attack at the α-carbon presumably reflects a greater negative charge, as compared with the γ-carbon.



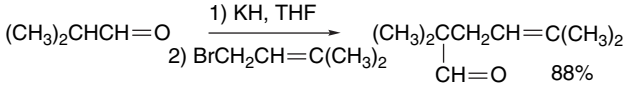
Protonation of the enolate provides a method for converting α,β-unsaturated ketones and esters to the less stable β,γ-unsaturated isomers.



Ref. 66

1.2.3. Alkylation of Aldehydes, Esters, Carboxylic Acids, Amides, and Nitriles

Among the compounds capable of forming enolates, the alkylation of ketones has been most widely studied and applied synthetically. Similar reactions of esters, amides, and nitriles have also been developed. Alkylation of aldehyde enolates is not very common. One reason is that aldehydes are rapidly converted to aldol addition products by base. (See Chapter 2 for a discussion of this reaction.) Only when the enolate can be rapidly and quantitatively formed is aldol formation avoided. Success has been reported using potassium amide in liquid ammonia[67] and potassium hydride in tetrahydrofuran.[68] Alkylation via enamines or enamine anions provides a more general method for alkylation of aldehydes. These reactions are discussed in Section 1.3.

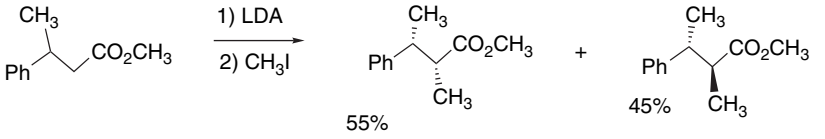


Ref. 68

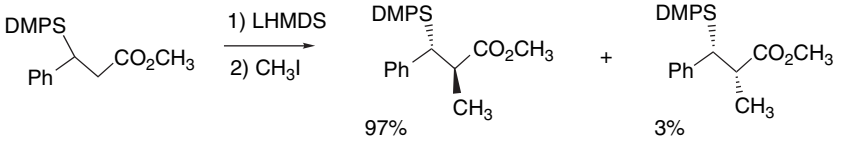
Ester enolates are somewhat less stable than ketone enolates because of the potential for elimination of alkoxide. The sodium and potassium enolates are rather unstable, but Rathke and co-workers found that the lithium enolates can be generated at −78° C.[69] Alkylations of simple esters require a strong base because relatively weak bases such as alkoxides promote condensation reactions (see Section 2.3.1). The successful formation of ester enolates typically involves an amide base, usually LDA or LiHDMS, at low temperature.[70] The resulting enolates can be successfully alkylated with alkyl bromides or iodides. HMPA is sometimes added to accelerate the alkylation reaction.

66. H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, 669 (1962); S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963).
67. S. A. G. De Graaf, P. E. R. Oosterhof, and A. van der Gen, *Tetrahedron Lett.*, 1653 (1974).
68. P. Groenewegen, H. Kallenberg, and A. van der Gen, *Tetrahedron Lett.*, 491 (1978).
69. M. W. Rathke, *J. Am. Chem. Soc.*, **92**, 3222 (1970); M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973).
70. (a) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93,** 2318 (1971); (b) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973); (c) J. L. Herrmann and R. H. Schlessinger, *J. Chem. Soc., Chem. Commun.*, 711 (1973).

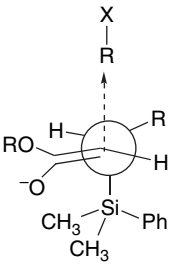
In acyclic systems, the stereochemistry of alkylation depends on steric factors. Stereoselectivity is low for small substituents.[71]



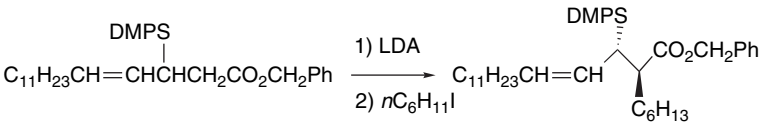
When a larger substituent is present, the reaction becomes much more selective. For example, a β-dimethylphenylsilyl substituent leads to more than 95:5 *anti* alkylation in ester enolates.[72]



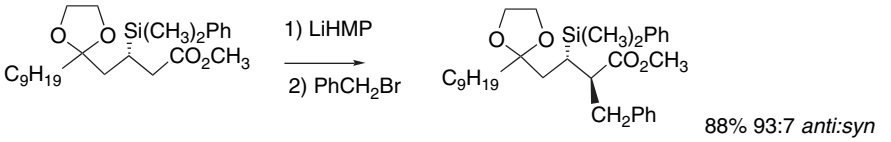
This stereoselectivity is the result of the conformation of the enolate and steric shielding by the silyl substituent.



This directive effect has been employed in stereoselective synthesis.



Ref. 72



Ref. 73

A careful study of the alkylation of several enolates of dialkyl malate esters has been reported.[74] These esters form dianions resulting from deprotonation of the hydroxy

[71] R. A. N. C. Crump, I. Fleming, J. H. M. Hill, D. Parker, N. L. Reddy, and D. Waterson, *J. Chem. Soc., Perkin Trans. 1*, 3277 (1992).
[72] I. Fleming and N. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 2679 (1998).
[73] R. Verma and S.K. Ghosh, *J. Chem. Soc., Perkin Trans. 2*, 265(1999).
[74] M. Sefkow, A. Koch, and E. Kleinpeter, *Helv. Chim. Acta*, **85**, 4216 (2002).

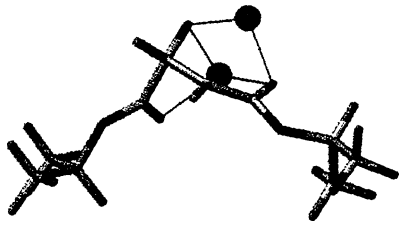
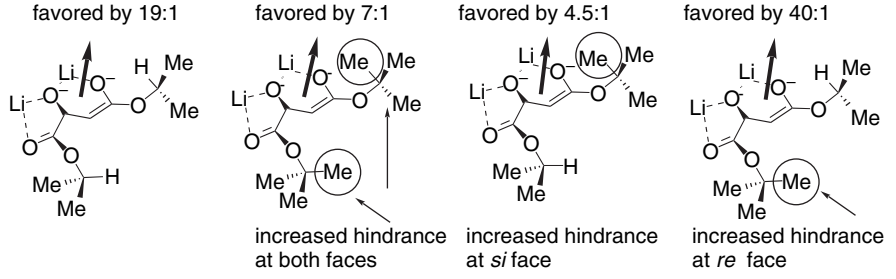
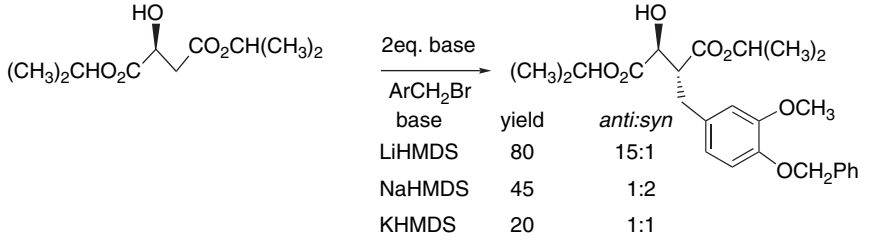


Fig. 1.5. Minimum energy structure of dilithium derivative of di-*iso*-propyl malate. Reproduced from *Helv. Chim. Acta*, **85**, 4216 (2002), by permission of Wiley-VCH.

group as well as the C(3). HF/6-31G* computations indicate that tricoordinate structures are formed, such as that shown for the di-*iso*-propyl ester in Figure 1.5. Curiously, the highest diastereoselectivity (19:1) is seen with the di-*iso*-propyl ester. For the dimethyl, diethyl, and di-*t*-butyl esters, the ratios are about 8:1. The diastereoselectivity is even higher (40:1) with the mixed *t*-butyl-*iso*-propyl ester. This result can be understood by considering the differences in the *si* and *re* faces of the enolates. In the di-*t*-butyl ester, both faces are hindered and selectivity is low. The di-*iso*-propyl ester has more hindrance to the *re* face, and this is accentuated in the mixed ester.



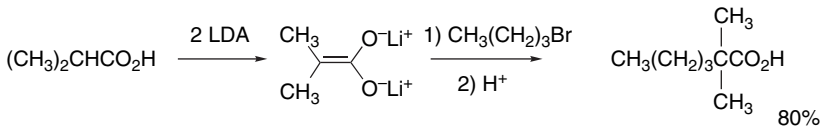
Alkylations of this type also proved to be sensitive to the cation. Good stereoselectivity (15:1) was observed for the lithium enolate, but the sodium and potassium enolates were much less selective.[75] This probably reflects the weaker coordination of the latter metals.



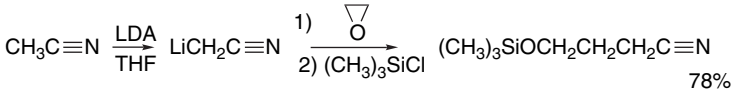
Carboxylic acids can be directly alkylated by conversion to dianions with two equivalents of LDA. The dianions are alkylated at the α-carbon, as would be expected, because the enolate carbon is more strongly nucleophilic than the carboxylate anion.[76]

[75.] M. Sefkow, *J. Org. Chem.*, **66**, 2343 (2001).

[76.] P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972); P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); P. L. Creger, *Org. Synth.*, **50**, 58 (1970).

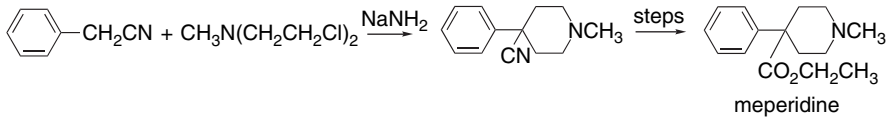


Nitriles can also be converted to anions and alkylated. Acetonitrile ($pK_{DMSO} = 31.3$) can be deprotonated, provided a strong nonnucleophilic base such as LDA is used.



Ref. 77

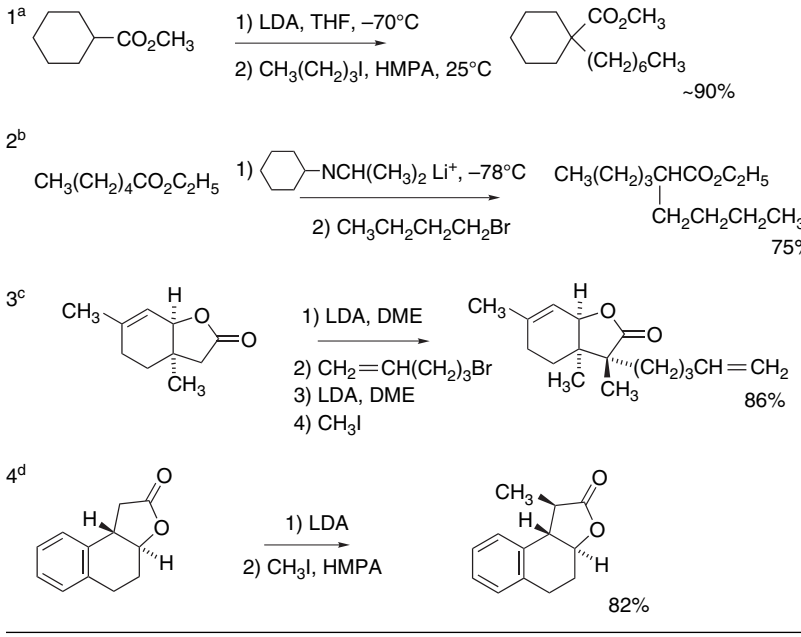
Phenylacetonitrile ($pK_{DMSO} = 21.9$) is considerably more acidic than acetonitrile. Dialkylation has been used in the synthesis of meperidine, an analgesic substance.[78]



We will see in Section 1.2.6 that the enolates of *imides* are very useful in synthesis. Particularly important are the enolates of chiral *N*-acyloxazolidinones.

Scheme 1.6 gives some examples of alkylation of esters, amides, and nitriles. Entries 1 and 2 are representative ester alkylations involving low-temperature

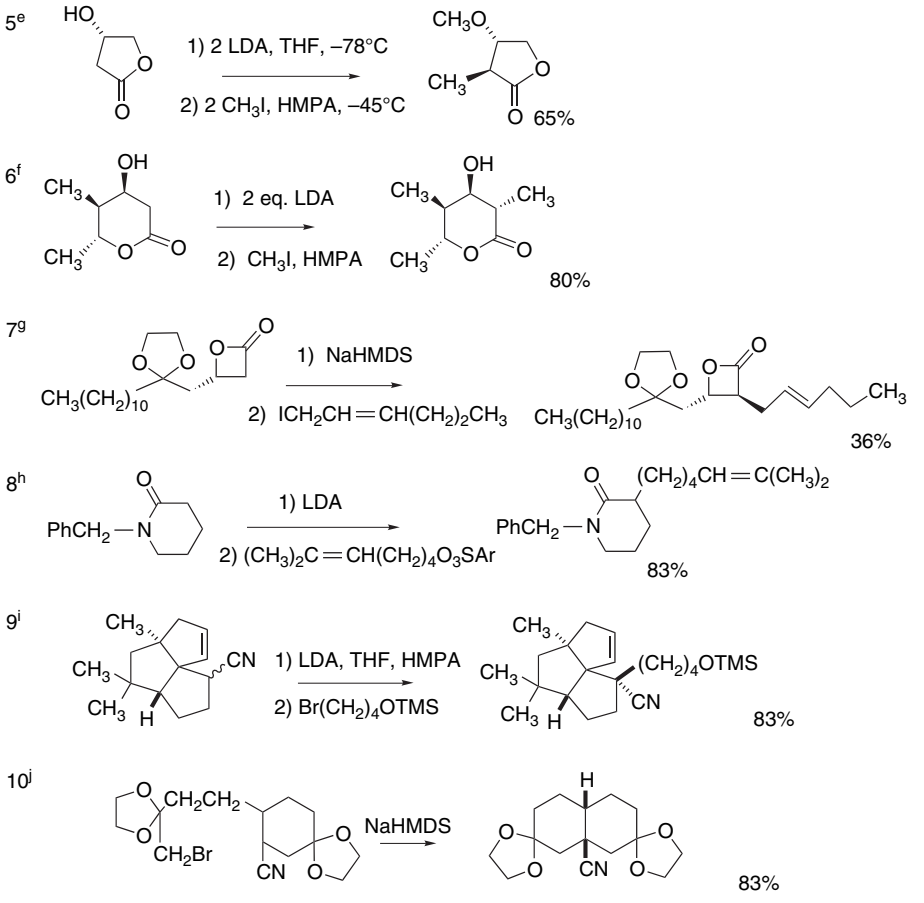
Scheme 1.6. Alkylation of Esters, Amides, and Nitriles



(Continued)

77. S. Murata and I. Matsuda, *Synthesis*, 221 (1978).
78. O. Eisleb, *Ber.*, **74,** 1433 (1941); cited in H. Kagi and K. Miescher, *Helv. Chim. Acta*, **32,** 2489 (1949).

Scheme 1.6. ***(Continued)***

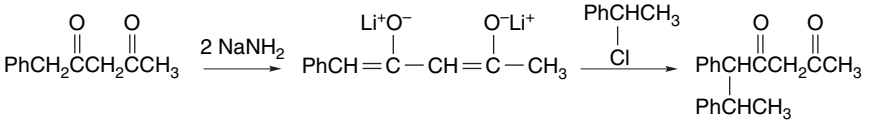


a. T. R. Williams and L. M. Sirvio, *J. Org. Chem.*, **45**, 5082 (1980).
b. M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2320 (1971).
c. S. C. Welch, A. S. C. Prakasa Rao, G. G. Gibbs, and R. Y. Wong, *J. Org. Chem.*, **45**, 4077 (1980).
d. W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **45**, 4111 (1980).
e. H.-M. Shieh and G. D. Prestwich, *J. Org. Chem.*, **46**, 4319 (1981).
f. J. Tholander and E. M. Carriera, *Helv. Chim. Acta*, **84**, 613 (2001).
g. P. J. Parsons and J. K. Cowell, *Synlett*, 107 (2000).
h. D. Kim, H. S. Kim, and J. Y. Yoo, *Tetrahedron Lett.*, **32**, 1577 (1991).
i. L. A. Paquette, M. E. Okazaki, and J.-C. Caille, *J. Org. Chem.*, **53**, 477 (1988).
j. G. Stork, J. O. Gardner, R. K. Boeckman, Jr., and K. A. Parker, *J. Am. Chem. Soc.*, **95**, 2014 (1973).

deprotonation by hindered lithium amides. Entries 3 to 7 are lactone alkylations. Entry 3 involves two successive alkylation steps, with the second group being added from the more open face of the enolate. Entry 4 also illustrates stereoselectivity based on a steric effect. Entry 5 shows alkylation at both the enolate and a hydroxy group. Entry 6 is a step in the synthesis of the C(33)–C(37) fragment of the antibiotic amphotericin B. Note that in this case although the hydroxy group is deprotonated it is not methylated under the reaction conditions being used. Entry 7 is a challenging alkylation of a sensitive β-lactone. Although the corresponding saturated halide was not reactive enough, the allylic iodide gave a workable yield. Entry 8 is an alkylation of a lactam. Entries 9 and 10 are nitrile alkylations, the latter being intramolecular.

1.2.4. Generation and Alkylation of Dianions

In the presence of a very strong base, such as an alkyllithium, sodium or potassium hydride, sodium or potassium amide, or LDA, 1,3-dicarbonyl compounds can be converted to their *dianions* by two sequential deprotonations.[79] For example, reaction of benzoylacetone with sodium amide leads first to the enolate generated by deprotonation at the more acidic methylene group between the two carbonyl groups. A second equivalent of base deprotonates the benzyl methylene group to give a dienediolate.



Ref. 80

Alkylation of dianions occurs at the *more basic carbon*. This technique permits alkylation of 1,3-dicarbonyl compounds to be carried out cleanly at the less acidic position. Since, as discussed earlier, alkylation of the monoanion occurs at the carbon between the two carbonyl groups, the site of monoalkylation can be controlled by choice of the amount and nature of the base. A few examples of the formation and alkylation of dianions are collected in Scheme 1.7. In each case, alkylation occurs at the less stabilized anionic carbon. In Entry 3, the α-formyl substituent, which is removed after the alkylation, serves to direct the alkylation to the methyl-substituted carbon. Entry 6 is a step in the synthesis of artemisinin, an antimalarial component of a Chinese herbal medicine. The sulfoxide serves as an anion-stabilizing group and the dianion is alkylated at the less acidic α-position. Note that this reaction is also stereoselective for the *trans* isomer. The phenylsulfinyl group is removed reductively by aluminum. (See Section 5.6.2 for a discussion of this reaction.)

1.2.5. Intramolecular Alkylation of Enolates

There are many examples of formation of three- through seven-membered rings by intramolecular enolate alkylation. The reactions depend on attainment of a TS having an approximately linear arrangement of the nucleophilic carbon, the electrophilic carbon, and the leaving group. Since the HOMO of the enolate (ψ_2) is involved, the approach must be approximately perpendicular to the enolate.[81] In intramolecular alkylation, these stereoelectronic restrictions on the direction of approach of the electrophile to the enolate become important. Baldwin has summarized the general principles that govern the energetics of intramolecular ring-closure reactions.[82] Analysis of the stereochemistry of intramolecular enolate alkylation requires consideration of both the direction of approach and enolate conformation. The intramolecular alkylation reaction of **7** gives exclusively **8**, having the *cis* ring juncture.[83] The alkylation probably occurs through a TS like **F**. The TS geometry permits the π electrons of the enolate to achieve an approximately colinear alignment with the sulfonate leaving group. The TS **G** for

[79] For reviews, see (a) T. M. Harris and C. M. Harris, *Org. React.*, **17**, 155 (1969); E. M. Kaiser, J. D. Petty, and P. L. A. Knutson, *Synthesis*, 509 (1977); C. M. Thompson and D. L. C. Green, *Tetrahedron*, **47**, 4223 (1991); C. M. Thompson, *Dianion Chemistry in Organic Synthesis*, CRC Press, Boca Raton, FL, 1994.

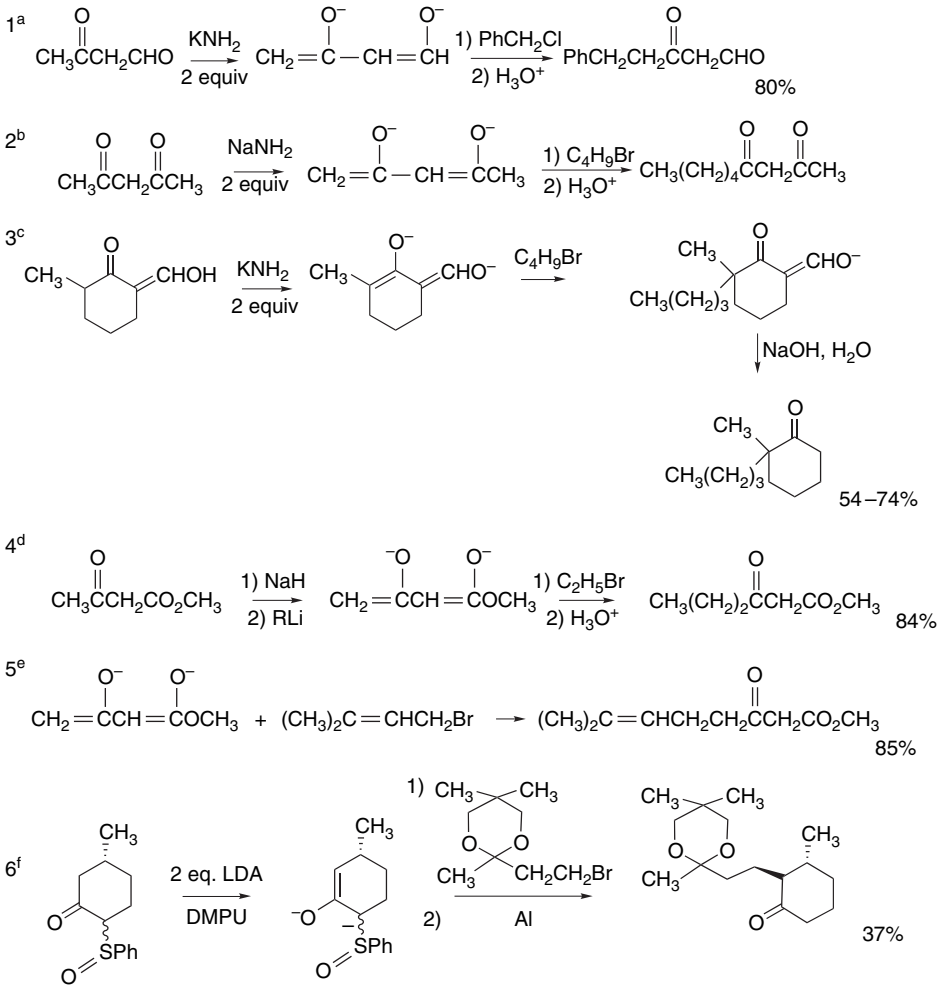
[80] D. M. von Schriltz, K. G. Hampton, and C. R. Hauser, *J. Org. Chem.*, **34**, 2509 (1969).

[81] J. E. Baldwin and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 233 (1977).

[82] J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

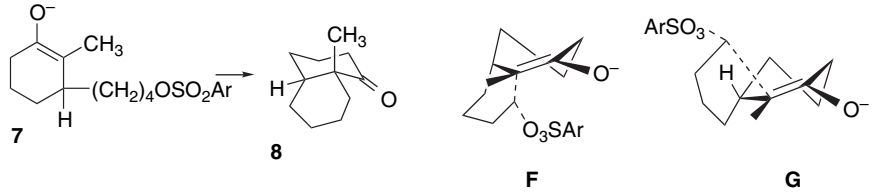
[83] J. M. Conia and F. Rouessac, *Tetrahedron*, **16**, 45 (1961).

Scheme 1.7. Generation and Alkylation of Dianions

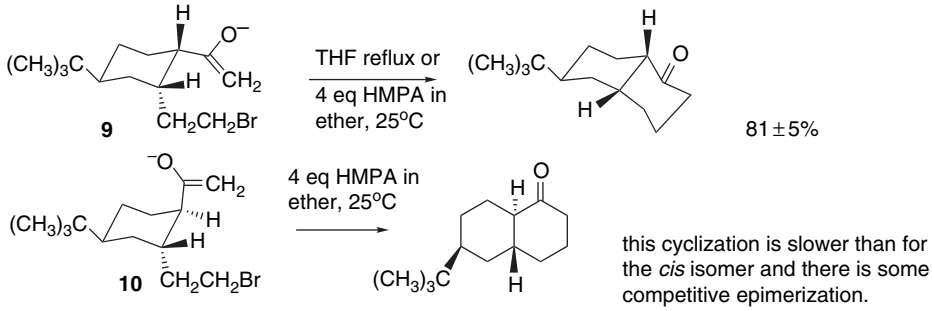


a. T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3273 (1963); S. Boatman, T. M. Harris, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 82 (1965); K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **28**, 1946 (1963).
b. K. G. Hampton, T. M. Harris, and C. R. Hauser, *Org. Synth.*, **47**, 92 (1967).
c. S. Boatman, T. M. Harris, and C. R. Hauser, *Org. Synth.*, **48**, 40 (1968).
d. S. N Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**,1082 (1974).
e. F. W. Sum and L. Weiler, *J. Am. Chem. Soc.*, **101**, 4401 (1979).
f. M. A. Avery, W. K. M. Chong, and C. Jennings-White, *J. Am. Chem. Soc.*, **114**, 974 (1992).

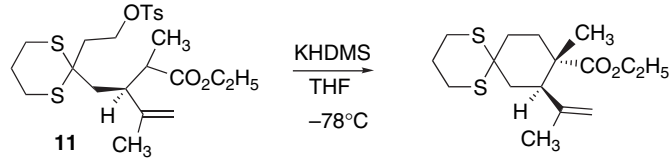
formation of the *trans* ring junction would be more strained because of the necessity to span the distance to the opposite face of the enolate π system.



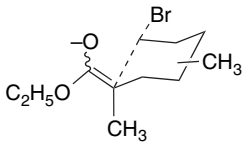
Geometric factors in the TS are also responsible for differences in the case of cyclization of enolates **9** and **10**.[84]



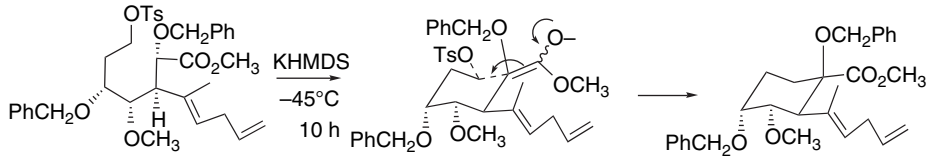
A number of examples of good stereoselectivity based on substituent control of reactant conformation have been identified. For example, **11** gives more than 96% stereoselectivity for the isomer in which the methyl and 2-propenyl groups are *cis*.[85]



Similar *cis* stereoselectivity was observed in formation of four- and five-membered rings.[86] The origin of this stereoselectivity was probed systematically by a study in which a methyl substituent was placed at the C(3), C(4), C(5), and C(6) positions of ethyl 7-bromoheptanoate. Good (> 93%) stereoselectivity was noted for all but the C(5) derivative.[87] These results are consistent with a chairlike TS with the enolate in an equatorial-like position. In each case the additional methyl group can occupy an equatorial position. The reduced selectivity of the 5-methyl isomer may be due to the fact that the methyl group is farther from the reaction site than in the other cases.



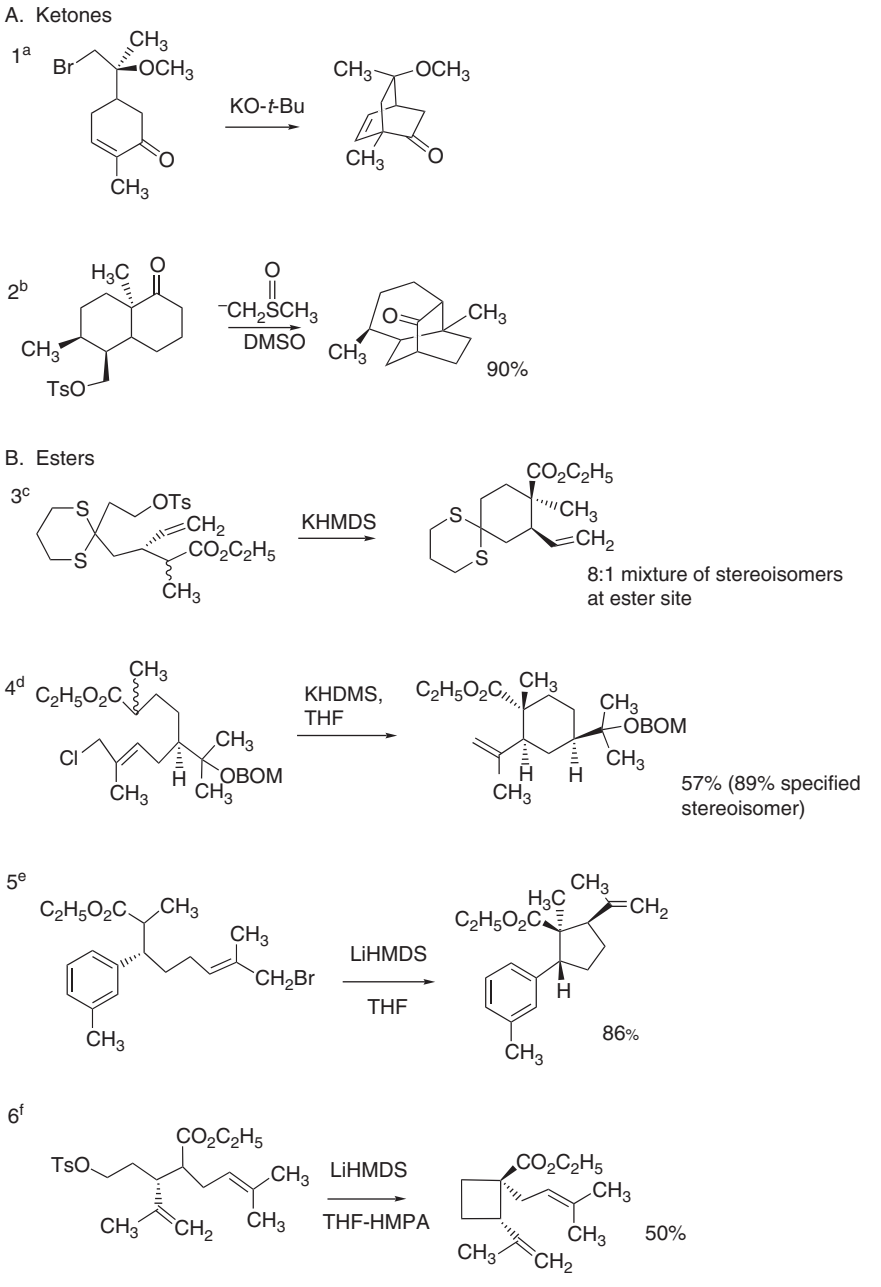
An intramolecular alkylation following this stereochemical pattern was used in the synthesis of (-)-fumagillol, with the alkadienyl substituent exerting the dominant conformational effect.[88]



84. H. O. House and W. V. Phillips, *J. Org. Chem.*, **43**, 3851 (1978).
85. D. Kim and H. S. Kim, *J. Org. Chem.*, **52**, 4633 (1987).
86. D. Kim, Y. M. Jang, I. O. Kim, and S. W. Park, *J. Chem. Soc., Chem. Commun.*, 760 (1988).
87. T. Tokoroyama and H. Kusaka, *Can. J. Chem.*, **74**, 2487 (1996).
88. D. Kim, S. K. Ahn, H. Bae, W. J. Choi, and H. S. Kim, *Tetrahedron Lett.*, **38**, 4437 (1997).

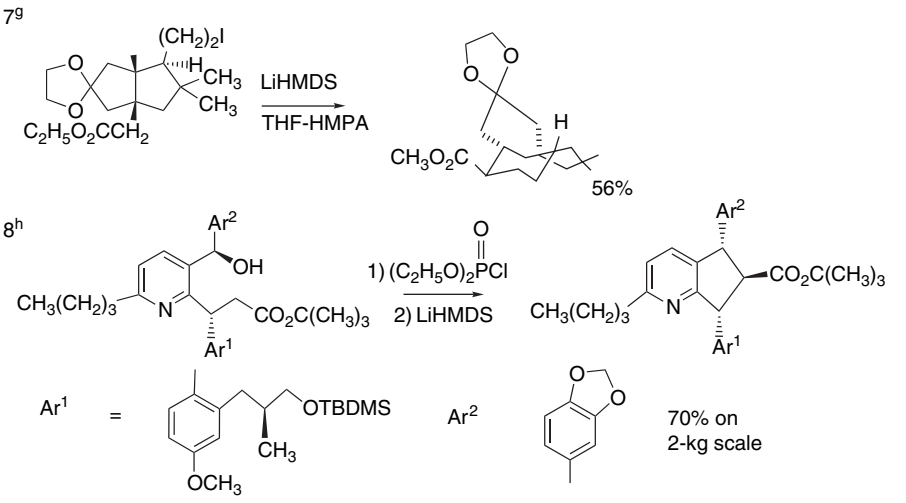
Scheme 1.8 shows some intramolecular enolate alkylations. The reactions in Section A involve alkylation of ketone enolates. Entry 1 is a case of α-alkylation of a conjugated dienolate. In this case, the α-alkylation is also favored by ring strain effects because γ-alkylation would lead to a four-membered ring. The intramolecular alkylation in Entry 2 was used in the synthesis of the terpene seychellene.

Scheme 1.8. Intramolecular Enolate Alkylation



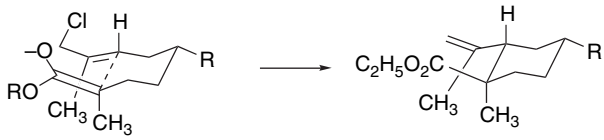
(Continued)

Scheme 1.8. ***(Continued)***



a. A. Srikrishna, G. V. R. Sharma, S. Danieldoss, and P. Hemamalini, *J. Chem. Soc., Perkin Trans. 1*, 1305 (1996).
b. E. Piers, W. de Waal, and R. W. Britton, *J. Am. Chem. Soc.*, **93**, 5113 (1971).
c. D. Kim, S. Kim, J.-J. Lee, and H. S. Kim, *Tetrahedron Lett.*, **31**, 4027 (1990).
d. D. Kim, J. I. Lim, K. J. Shin, and H. S. Kim, *Tetrahedron Lett*., **34**, 6557 (1993).
e. J. Lee and J. Hong, *J. Org. Chem.*, **69**, 6433 (2004).
f. F.-D. Boyer and P.-H. Ducrot, *Eur. J. Org. Chem.*, 1201 (1999).
g. S. Danishefsky, K. Vaughan, R. C. Gadwood, and K. Tsuzuki, *J. Am. Chem. Soc.*, **102**, 4262 (1980).
h. Z. J. Song, M. Zhao, R. Desmond, P. Devine, D. M. Tschaen, R. Tillyer, L.Frey, R. Heid, F. Xu;, B. Foster, J. Li, R. Reamer, R. Volante, E. J. Grabowski, U. H. Dolling, P. J. Reider, S. Okada, Y. Kato and E. Mano, *J. Org. Chem.*, **64**, 9658 (1999).

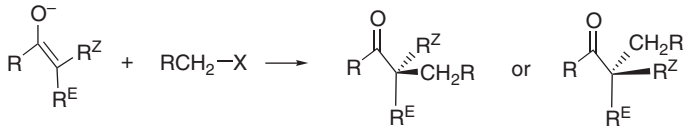
Entries 3 to 6 are examples of ester enolate alkylations. These reactions show stereoselectivity consistent with cyclic TSs in which the hydrogen is eclipsed with the enolate and the larger substituent is pseudoequatorial. Entries 4 and 5 involve S_N2' substitutions of allylic halides. The formation of the six- and five-membered rings, respectively, is the result of ring size preferences with $5 > 7$ and $6 > 8$. In Entry 4, reaction occurs through a chairlike TS with the tertiary C(5) substituent controlling the conformation. The cyclic TS results in a *trans* relationship between the ester and vinylic substituents.



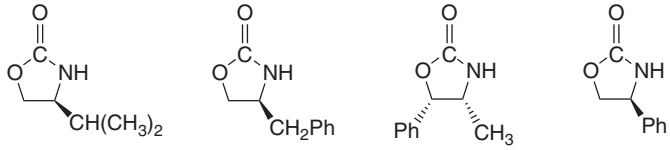
Entry 6 results in the formation of a four-membered ring and shows good stereoselectivity. Entry 7 is a step in the synthesis of a tetracyclic lactone, quadrone, that is isolated from a microorganism. Entry 8 is a step in a multikilo synthesis of an endothelin receptor antagonist called cyclopentapyridine I. The phosphate group was chosen as a leaving group because sulfonates were too reactive at the diaryl carbinol site. The reaction was shown to go with inversion of configuration.

1.2.6. Control of Enantioselectivity in Alkylation Reactions

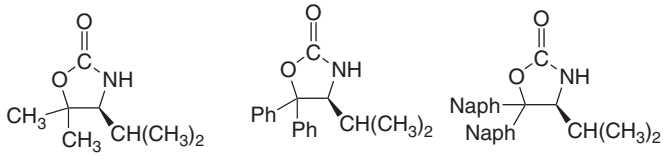
The alkylation of an enolate creates a new stereogenic center when the α-substituents are nonidentical. In enantioselective synthesis, it is necessary to control the direction of approach and thus the configuration of the new stereocenter.



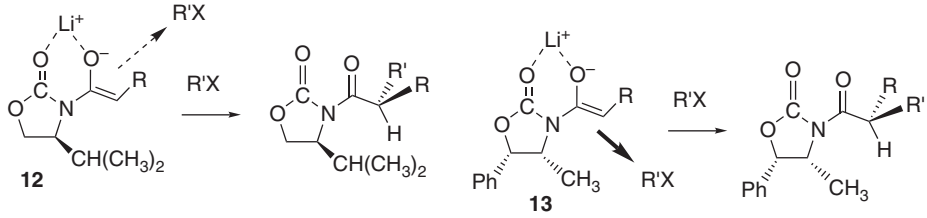
Enantioselective enolate alkylation can be done using chiral auxiliaries. (See Section 2.6 of Part A to review the role of chiral auxiliaries in control of reaction stereochemistry.) The most frequently used are the *N*-acyloxazolidinones.[89] The 4-isopropyl and 4-benzyl derivatives, which can be obtained from valine and phenylalanine, respectively, and the *cis*-4-methyl-5-phenyl derivatives are readily available. Another useful auxiliary is the 4-phenyl derivative.[90]



Several other oxazolidinones have been developed for use as chiral auxiliaries. The 4-isopropyl-5,5-dimethyl derivative gives excellent enantioselectivity.[91] 5,5-Diaryl derivatives are also quite promising.[92]



The reactants are usually *N*-acyl derivatives. The lithium enolates form chelate structures with *Z*-stereochemistry at the double bond. The ring substituents then govern the preferred direction of approach.

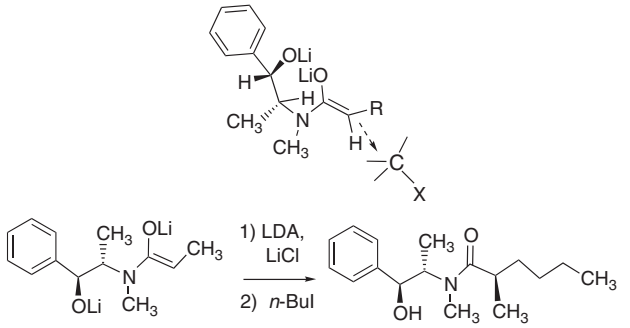


12 **13**

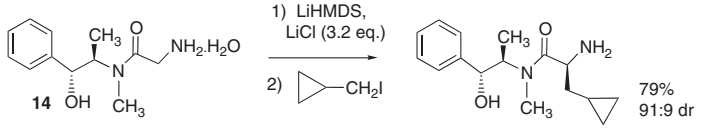
89. D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982); D. J. Ager, I. Prakash, and D. R. Schaad, *Chem. Rev.*, **96**, 835 (1996); D. J. Ager, I. Prakash, and D. R. Schaad, *Aldrichimica Acta*, **30**, 3 (1997).
90. E. Nicolas, K. C. Russell, and V. J. Hruby, *J. Org. Chem.*, **58**, 766 (1993).
91. S. D. Bull, S. G. Davies, S. Jones, and H. J. Sanganee, *J. Chem. Soc., Perkin Trans. 1*, 387 (1999); S. G. Davies and H. J. Sangaee, *Tetrahedron: Asymmetry*, **6**, 671 (1995); S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee, and A. D. Smith, *Org. Biomed. Chem.*, **1**, 2886 (2003).
92. T. Hintermann and D. Seebach, *Helv. Chim. Acta*, **81**, 2093 (1998); C. L. Gibson, K. Gillon, and S. Cook, *Tetrahedron Lett.*, **39**, 6733 (1998).

In **12** the upper face is shielded by the isopropyl group, whereas in **13** the lower face is shielded by the methyl and phenyl groups. As a result, alkylation of the two derivatives gives products of the opposite configuration. The initial alkylation product ratios are typically 95:5 in favor of the major isomer. Since these products are diastereomeric mixtures, they can be separated and purified. Subsequent hydrolysis or alcoholysis provides acids or esters in enantiomerically enriched form. Alternatively, the acyl imides can be reduced to alcohols or aldehydes. The final products can often be obtained in greater than 99% enantiomeric purity.

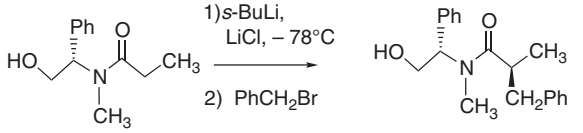
A number of other types of chiral auxiliaries have been employed in enolate alkylation. Excellent results are obtained using amides of pseudoephedrine. Alkylation occurs *anti* to the α-oxybenzyl group.[93] The reactions involve the *Z*-enolate and there is likely bridging between the two lithium cations, perhaps by di-(isopropyl)amine.[94]



Both enantiomers of the auxiliary are available, so either enantiomeric product can be obtained. This methodology has been applied to a number of enantioselective syntheses.[95] For example, the glycine derivative **14** can be used to prepare α-amino acid analogs.[96]



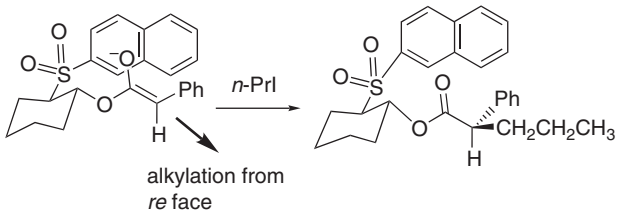
Enolates of phenylglycinol amides also exhibit good diastereoselectivity.[97] A chelating interaction with the deprotonated hydroxy group is probably involved here as well.



The *trans*-2-naphthyl cyclohexyl sulfone **15** can be prepared readily in either enantiomeric form. The corresponding ester enolates can be alkylated in good yield and diastereoselectivity.[98] In this case, the steric shielding is provided by the naphthyl

93. A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, and J. L. Gleason, *J. Am. Chem. Soc.*, **119**, 6496 (1997); A. G. Myers, M. Siu, and F. Ren, *J. Am. Chem. Soc.*, **124**, 4230 (2002).
94. J. L. Vicario, D. Badia, E. Dominguez, and L. Carrillo, *J. Org. Chem.*, **64**, 4610 (1999).
95. S. Karlsson and E. Hedenstrom, *Acta Chem. Scand.*, **53**, 620 (1999).
96. A. G. Myers, P. S. Schnider, S. Kwon, and D. W. Kung, *J. Org. Chem.*, **64**, 3322 (1999).
97. V. Jullian, J.-C. Quirion, and H.-P. Husson, *Synthesis*, 1091 (1997).
98. G. Sarakinos and E. J. Corey, *Org. Lett.*, **1**, 1741 (1999).

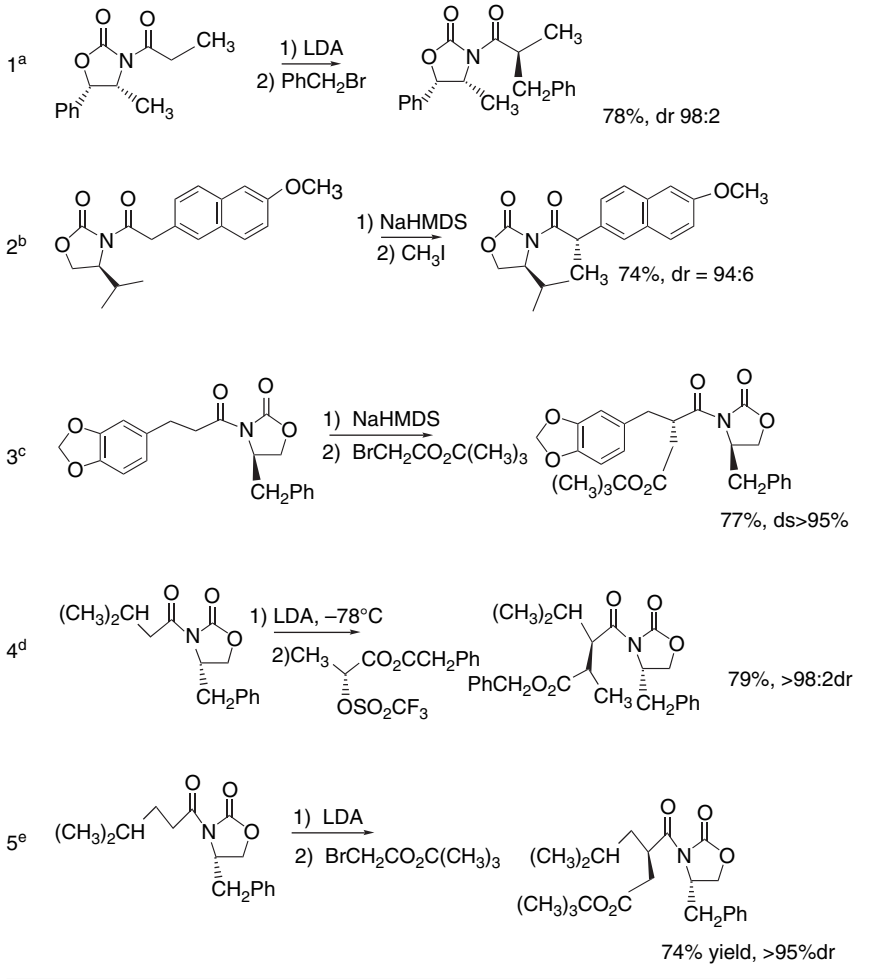
group and there is probably also a $\pi - \pi$ interaction between the naphthalene ring and the enolate.



As with the acyl oxazolidinone auxiliaries, each of these systems permits hydrolytic removal and recovery of the chiral auxiliary.

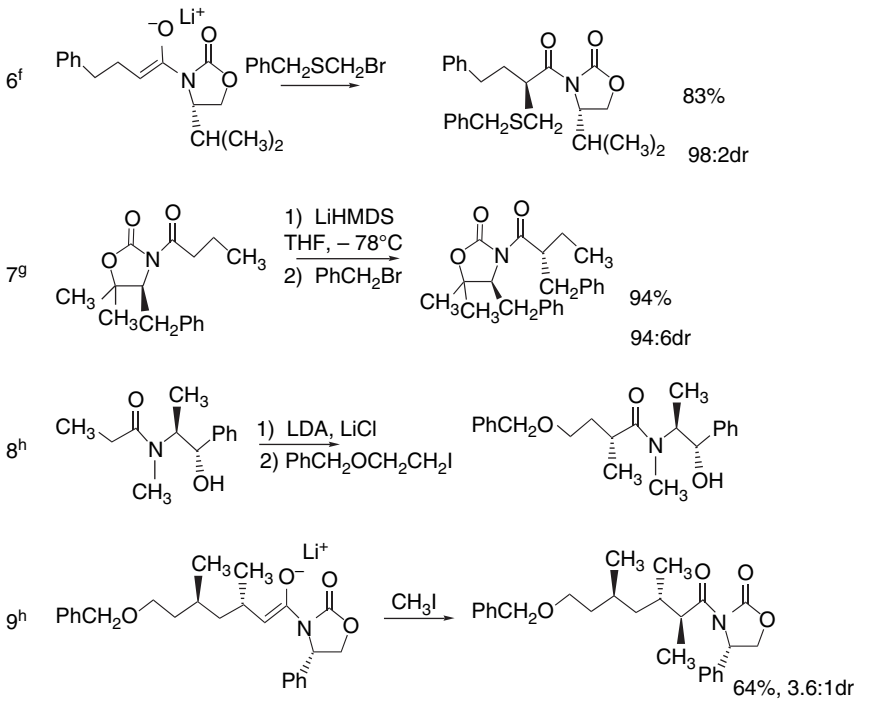
Scheme 1.9 gives some examples of diastereoselective enolate alkylations. Entries 1 to 6 show the use of various *N*-acyloxazolidinones and demonstrate the

Scheme 1.9. Diastereoselective Enolate Alkylation Using Chiral Auxiliaries



(Continued)

Scheme 1.9. ***(Continued)***



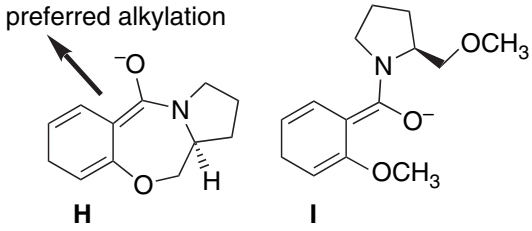
a. D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982).
b. A. Fadel, *Synlett*, 48 (1992).
c. J. L. Charlton and G-L. Chee, *Can. J. Chem.*, **75,** 1076 (1997).
d. C. P. Decicco, D. J. Nelson, B. L. Corbett, and J. C. Dreabit, *J. Org. Chem.*, **60**, 4782 (1995).
e. R. P. Beckett, M. J. Crimmin, M. H. Davis, and Z. Spavold, *Synlett*, 137 (1993).
f. D. A. Evans, D. J. Mathre, and W. L. Scott, *J. Org. Chem.*, **50**, 1830 (1985).
g. S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee, and A. D. Smith, *Organic and Biomolec. Chem.*, **1**, 2886 (2003).
h. J. D. White, C.-S. Lee and Q. Xu, *Chem. Commun.* 2012 (2003).

stereochemical control by the auxiliary ring substituent. Entry 2 demonstrated the feasibility of enantioselective synthesis of α-aryl acetic acids such as the structure found in naproxen. Entries 3 to 6 include ester groups in the alkylating agent. In the case of Entry 4, it was shown that inversion occurs in the alkylating reagent. Entry 7 is an example of the use of one of the more highly substituted oxazolidinone derivatives. Entries 8 and 9 are from the synthesis of a neurotoxin isolated from a saltwater bacterium. The pseudoephedrine auxiliary shown in Entry 8 was used early in the synthesis and the 4-phenyloxazolidinone auxiliary was used later, as shown in Entry 9.

The facial selectivity of a number of more specialized enolates has also been explored, sometimes with surprising results. Schultz and co-workers compared the cyclic enolate **H** with **I**.[99] Enolate **H** presents a fairly straightforward picture. Groups such as methyl, allyl, and benzyl all give selective β-alkylation, and this is attributed to steric factors. Enolate **I** can give either α- or β-alkylation, depending on the conditions. The presence of NH_3 or use of LDA favors α-alkylation, whereas the use

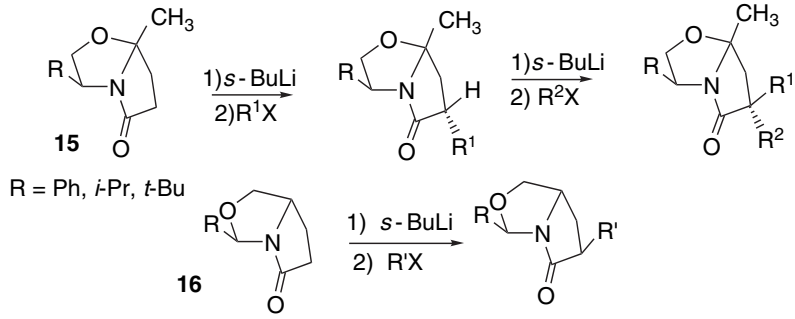
[99.] A. G. Schultz, M. Macielag, P. Sudararaman, A. G. Taveras, and M. Welch, *J. Am. Chem. Soc.*, **110**, 7828 (1988).

of *n*-butyllithium as the base favors β-alkylation. Other changes in conditions also affect the stereoselectivity. This is believed to be due to alternative aggregated forms of the enolate.

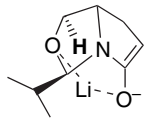


H **I**

The compact bicyclic lactams **15** and **16** are examples of chiral systems that show high facial selectivity. Interestingly, **15** is alkylated from the convex face. When two successive alkylations are done, both groups are added from the *endo* face, so the configuration of the newly formed quaternary center can be controlled. The closely related **16** shows *exo* stereoselectivity. [100]



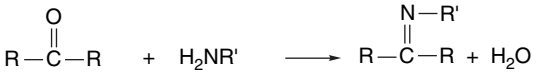
Crystal structure determination and computational studies indicate substantial pyramidalization of both enolates with the higher HOMO density being on the *endo* face for both **15** and **16**. However, the TS energy [MP3/6-31G+(*d*)] correlates with experiment, favoring the *endo* TS for **15** (by 1.3 kcal/mol) and *exo* for **16** (by 0.9 kcal/mol). A B3LYP/6-31G(*d*) computational study has also addressed the stereoselectivity of **16**.[101] As with the ab intitio calculation, the Li^+ is found in the *endo* position with an association with the heterocyclic oxygen. The *exo* TS is favored but the energy difference is very sensitive to the solvent model. The differences between the two systems seems to be due to the *endo* C(4) hydrogen that is present in **16** but not in **15**.



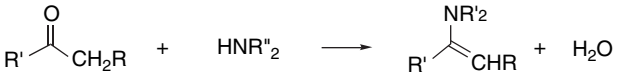
100. A. I. Meyers, M. A. Seefeld, B. A. Lefker, J. F. Blake, and P. G. Williard, *J. Am. Chem. Soc.*, **120**, 7429 (1998).
101. Y. Ikuta and S. Tomoda, *Org. Lett.*, **6**, 189 (2004).

1.3. The Nitrogen Analogs of Enols and Enolates: Enamines and Imine Anions

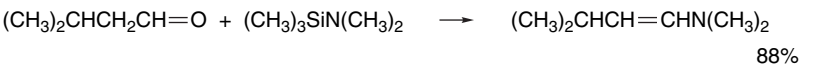
The nitrogen analogs of ketones and aldehydes are called imines, azomethines, or Schiff bases, but *imine* is the preferred name and we use it here. These compounds can be prepared by condensation of primary amines with ketones or aldehydes.[102] The equilibrium constants are unfavorable, so the reaction is usually driven forward by removal of water.



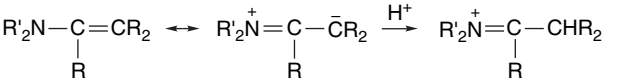
When secondary amines are heated with ketones or aldehydes in the presence of an acidic catalyst, a related reaction occurs, and the product is a substituted vinylamine or *enamine*.



There are other methods for preparing enamines from ketones that utilize strong chemical dehydrating reagents. For example, mixing carbonyl compounds and secondary amines followed by addition of titanium tetrachloride rapidly gives enamines. This method is especially applicable to hindered amines.[103] Triethoxysilane can also be used.[104] Another procedure involves converting the secondary amine to its *N*-trimethylsilyl derivative. Owing to the higher affinity of silicon for oxygen than nitrogen, enamine formation is favored and takes place under mild conditions.[105]



The β-carbon atom of an enamine is a nucleophilic site because of conjugation with the nitrogen atom. Protonation of enamines takes place at the β-carbon, giving an iminium ion.



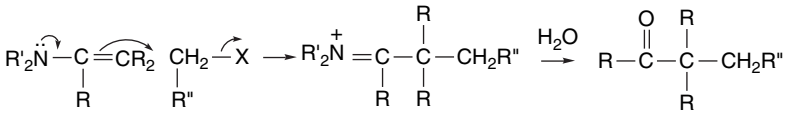
[102] For general reviews of imines and enamines, see P. Y. Sollenberger and R. B. Martin, in *Chemistry of the Amino Group*, S. Patai, ed., Interscience, New York, 1968, Chap. 7; G. Pitacco and E. Valentin, in *Chemistry of Amino, Nitroso and Nitro Groups and Their Derivatives*, Part 1, S. Patai, ed., Interscience, New York, 1982, Chap. 15; P. W. Hickmott, *Tetrahedron*, **38**, 3363 (1982); A. G. Cook, ed., *Enamines, Synthesis, Structure and Reactions*, Marcel Dekker, New York, 1988.

[103] W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967); R. Carlson, R. Phan-Tan-Luu, D. Mathieu, F. S. Ahounde, A. Babadjamian, and J. Metzger, *Acta Chem. Scand.*, **B32,** 335 (1978); R. Carlson, A. Nilsson, and M. Stromqvist, *Acta Chem. Scand.*, **B37**, 7 (1983); R. Carlson and A. Nilsson, *Acta Chem. Scand.*, **B38**, 49 (1984); S. Schubert, P. Renaud, P.-A. Carrupt, and K. Schenk, *Helv. Chim. Acta*, **76**, 2473 (1993).

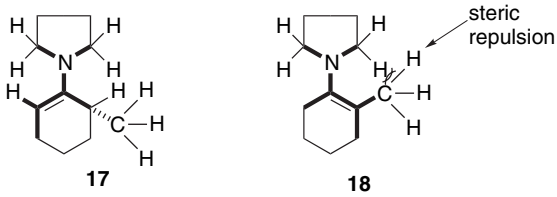
[104] B. E. Love and J. Ren, *J. Org. Chem.*, **58**, 5556 (1993).

[105] R. Comi, R. W. Franck, M. Reitano, and S. M. Weinreb, *Tetrahedron Lett.*, 3107 (1973).

The nucleophilicity of the β-carbon atoms permits enamines to be used synthetically for alkylation reactions.

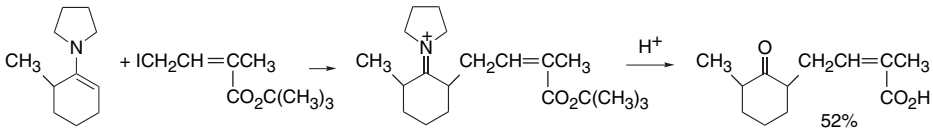


The enamines derived from cyclohexanones are of particular interest. The pyrrolidine enamine is most frequently used for synthetic applications. The enamine mixture formed from pyrrolidine and 2-methylcyclohexanone is predominantly isomer **17**.[106] A steric effect is responsible for this preference. Conjugation between the nitrogen atom and the π orbitals of the double bond favors coplanarity of the bonds that are darkened in the structures. In isomer **17** the methyl group adopts a quasi-axial conformation to avoid steric interaction with the amine substituents.[107] A serious nonbonded repulsion ($A^{1,3}$ strain) in **18** destabilizes this isomer.



17 **18**

Owing to the predominance of the less-substituted enamine, alkylations occur primarily at the less-substituted α-carbon. Synthetic advantage can be taken of this selectivity to prepare 2,6-disubstituted cyclohexanones. The iminium ions resulting from C-alkylation are hydrolyzed in the workup procedure.



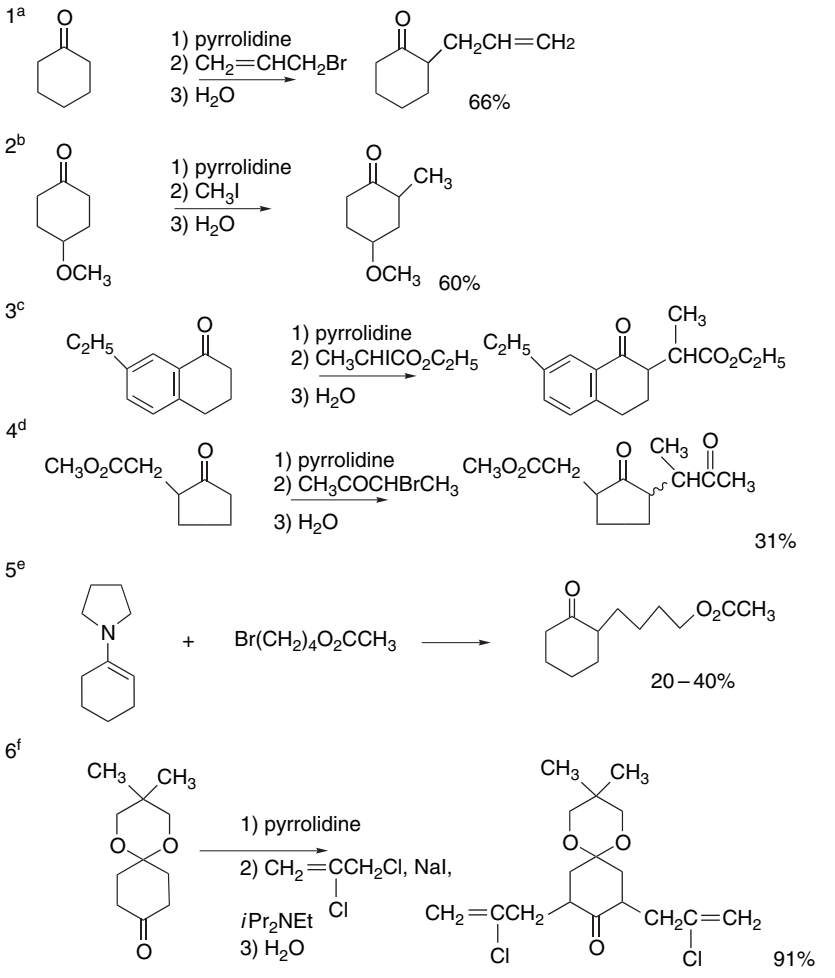
Ref. 108

Alkylation of enamines requires relatively reactive alkylating agents for good results. Methyl iodide, allyl and benzyl halides, α-halo esters, α-halo ethers, and α-halo ketones are the most successful alkylating agents. The use of enamines for selective alkylation has largely been supplanted by the methods for kinetic enolate formation described in Section 1.2.

Some enamine alkylation reactions are shown in Scheme 1.10. Entries 1 and 2 are typical alkylations using reactive halides. In Entries 3 and 4, the halides are secondary with α-carbonyl substituents. Entry 5 involves an unactivated primary bromide and the yield is modest. The reaction in Entry 6 involves introduction of two groups. This

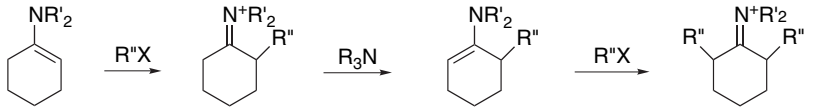
106. W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967).
107. F. Johnson, L. G. Duquette, A. Whitehead, and L. C. Dorman, *Tetrahedron*, **30**, 3241 (1974); K. Muller, F. Previdoli, and H. Desilvestro, *Helv. Chim. Acta*, **64**, 2497 (1981); J. E. Anderson, D. Casarini, and L. Lunazzi, *Tetrahedron Lett.*, **25**, 3141 (1988).
108. P. L. Stotter and K. A. Hill, *J. Am. Chem. Soc.*, **96**, 6524 (1974).

Scheme 1.10. Alkylation of Enamines



a. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
b. G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).
c. D. M. Locke and S. W. Pelletier, *J. Am. Chem. Soc.*, **80**, 2588 (1958).
d. K. Sisido, S. Kurozumi, and K. Utimoto, *J. Org. Chem.*, **34**, 2661 (1969).
e. I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, **33**, 2013 (1968).
f. J. A. Marshall and D. A. Flynn, *J. Org. Chem.*, **44**, 1391 (1979).

was done by carrying out the reaction in the presence of an amine, which deprotonates the iminium ion and permits the second alkylation to occur.



Imines can be deprotonated at the α-carbon by strong bases to give the nitrogen analogs of enolates. Originally, Grignard reagents were used for deprotonation but lithium amides are now usually employed. These anions, referred to as *imine anions*

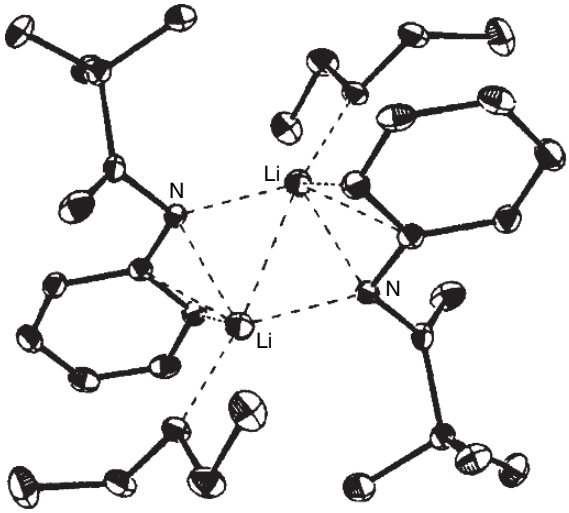
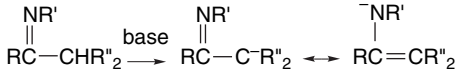


Fig. 1.6. Crystal structure of dimer of lithium salt of *N*-phenylimine of methyl *t*-butyl ketone. Two molecules of diethyl ether are present. Reproduced from *J. Am. Chem. Soc.*, **108**, 2462 (1986), by permission of the American Chemical Society.

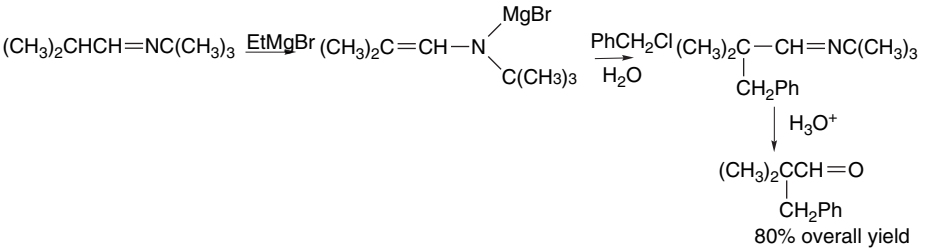
or *metalloenamines*,[109] are isoelectronic and structurally analogous to both enolates and allyl anions; they can also be called *azaallyl anions*.



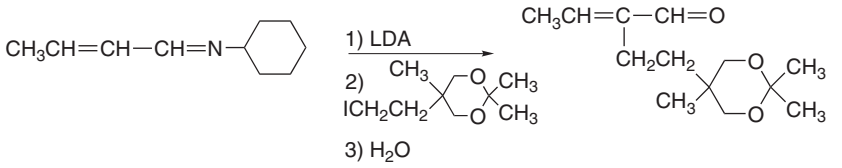
Spectroscopic investigations of the lithium derivatives of cyclohexanone *N*-phenylimine indicate that it exists as a dimer in toluene and that as a better donor solvent, THF, is added, equilibrium with a monomeric structure is established. The monomer is favored at high THF concentrations.[110] A crystal structure determination was done on the lithiated *N*-phenylimine of methyl *t*-butyl ketone, and it was found to be a dimeric structure with the lithium cation positioned above the nitrogen and closer to the phenyl ring than to the β-carbon of the imine anion.[111] The structure, which indicates substantial ionic character, is shown in Figure 1.6.

Just as enamines are more nucleophilic than enol ethers, imine anions are more nucleophilic than enolates and react efficiently with alkyl halides. One application of imine anions is for the alkylation of aldehydes.

109. For a general review of imine anions, see J. K. Whitesell and M. A. Whitesell, *Synthesis*, 517 (1983).
110. N. Kallman and D. B. Collum, *J. Am. Chem. Soc.*, **109**, 7466 (1987).
111. H. Dietrich, W. Mahdi, and R. Knorr, *J. Am. Chem. Soc.*, **108**, 2462 (1986); P. Knorr, H. Dietrich, and W. Mahdi, *Chem. Ber.*, **124**, 2057 (1991).

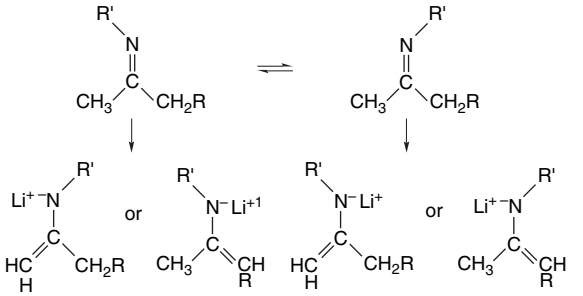


Ref. 112

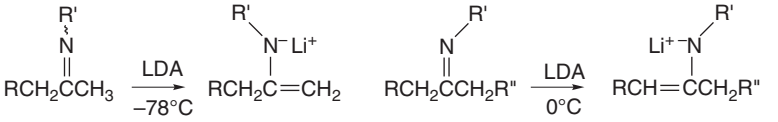


Ref. 113

Ketone imine anions can also be alkylated. The prediction of the regioselectivity of lithioenamine formation is somewhat more complex than for the case of kinetic ketone enolate formation. One of the complicating factors is that there are two imine stereoisomers, each of which can give rise to two regioisomeric imine anions. The isomers in which the nitrogen substituent R' is *syn* to the double bond are the more stable.[114]



For methyl ketimines good regiochemical control in favor of methyl deprotonation, regardless of imine stereochemistry, is observed using LDA at −78° C. With larger *N*-substituents, deprotonation at 25° C occurs *anti* to the nitrogen substituent.[115]



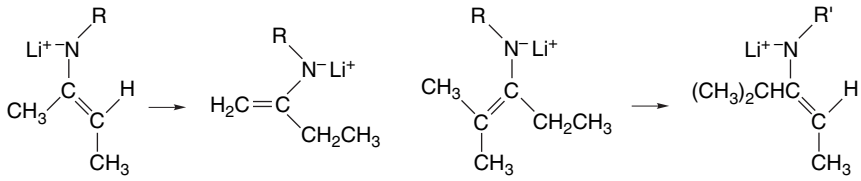
[112] G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

[113] T. Kametani, Y. Suzuki, H. Furuyama, and T. Honda, *J. Org. Chem.*, **48**, 31 (1983).

[114] K. N. Houk, R. W. Stozier, N. G. Rondan, R. R. Frazier, and N. Chauqui-Ottermans, *J. Am. Chem. Soc.*, **102**, 1426 (1980).

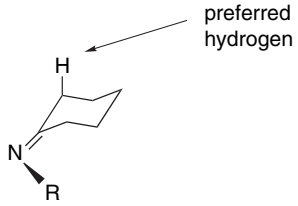
[115] J. K. Smith, M. Newcomb, D. E. Bergbreiter, D. R. Williams, and A. I. Meyer, *Tetrahedron Lett.*, **24**, 3559 (1983); J. K. Smith, D. E. Bergbreiter, and M. Newcomb, *J. Am. Chem. Soc.*, **105**, 4396 (1983); A. Hosomi, Y. Araki, and H. Sakurai, *J. Am. Chem. Soc.*, **104,** 2081 (1982).

The thermodynamic composition is established by allowing the lithiated ketimines to come to room temperature. The most stable structures are those shown below, and each case represents the less-substituted isomer.



The complete interpretation of regiochemistry and stereochemistry of imine deprotonation also requires consideration of the state of aggregation and solvation of the base.[116]

A thorough study of the factors affecting the rates of formation of lithiated imines from cyclohexanone imines has been carried out.[117] Lithiation occurs preferentially *anti* to the *N*-substituent and with a preference for abstraction of an axial hydrogen.



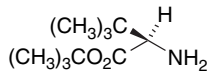
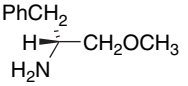
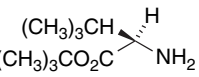
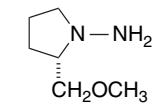
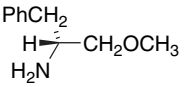
If the amine carries a chelating substituent, as for 2-methoxyethylamine, the rate of deprotonation is accelerated. For any specific imine, ring substituents also influence the imine conformation and rate of deprotonation. These relationships reflect steric, stereoelectronic, and chelation influences, and sorting out each contribution can be challenging.

One of the potentially most useful aspects of the imine anions is that they can be prepared from enantiomerically pure amines. When imines derived from chiral amines are alkylated, the new carbon-carbon bond is formed with a bias for one of the two possible stereochemical configurations. Hydrolysis of the imine then leads to enantiomerically enriched ketone. Table 1.4 lists some examples that have been reported.[118]

The interpretation and prediction of the relationship between the configuration of the newly formed chiral center and the configuration of the amine is usually based on steric differentiation of the two faces of the imine anion. Most imine anions that show high stereoselectivity incorporate a substituent that can engage the metal cation in a

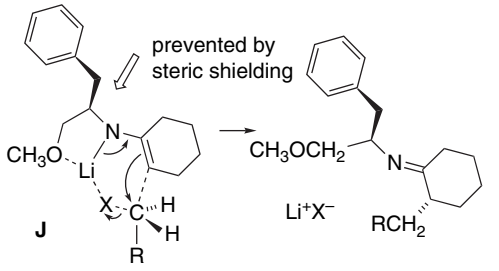
116. M. P. Bernstein and D. B. Collum, *J. Am. Chem. Soc.*, **115**, 8008 (1993).
117. S. Liao and D. B. Collum, *J. Am. Chem. Soc.*, **125**, 15114 (2003).
118. For a review, see D. E. Bergbreiter and M. Newcomb, in *Asymmetric Synthesis*, Vol. 2, J. D. Morrison, ed., Academic Press, New York, 1983, Chap. 9.

Table 1.4. Enantioselective Alkylation of Ketimines

	Amine	Ketone	Alkyl group	Yield%	e.e.
1[a]		Cyclohexanone	$CH_2=CHCH_2Br$	75	84
2[b]		Cyclohexanone	$CH_2=CHCH_2Br$	80	>99
3[c]		2-Carbomethoxy-cyclohexanone	CH_3I	57	>99
4[d]		3-pentanone	$CH_3CH_2CH_2I$	57	97
5[e]		5-Nonanone	$CH_2=CHCH_2Br$	80	94

a. S. Hashimoto and K. Koga, *Tetrahedron Lett.*, 573 (1978).
b. A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, **103**, 3081 (1981).
c. K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, *J. Am. Chem. Soc.*, **106**, 1718 (1984).
d. D. Enders, H. Kipphardt, and P. Fey, *Org. Synth.*, **65**, 183 (1987).
e. A. I. Meyers, D. R. Williams, S. White, and G. W. Erickson, *J. Am. Chem. Soc.*, **103**, 3088 (1981).

compact TS by chelation. In the case of Entry 2 in Table 1.4, for example, the TS **J** rationalizes the observed enantioselectivity.

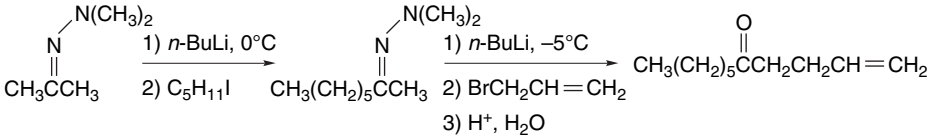


The important features of this transition structure are: (1) the chelation of the methoxy group with the lithium ion, which establishes a rigid structure; (2) the interaction of the lithium ion with the bromide leaving group, and (3) the steric effect of the benzyl group, which makes the underside the preferred direction of approach for the alkylating agent.

Hydrazones can also be deprotonated to give lithium salts that are reactive toward alkylation at the β-carbon. Hydrazones are more stable than alkylimines and therefore have some advantages in synthesis.[119] The *N*,*N*-dimethylhydrazones of methyl ketones are kinetically deprotonated at the methyl group. This regioselectivity is independent

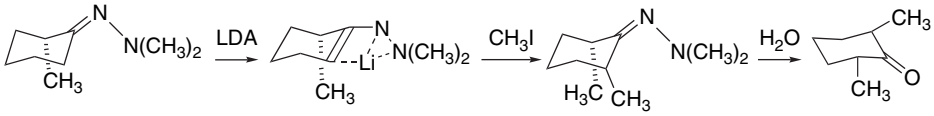
[119] D. Enders, in *Asymmetric Synthesis*, J. D. Morrison, ed., Academic Press, Orlando, FL, 1984.

of the stereochemistry of the hydrazone.[120] Two successive alkylations of the *N*,*N*-dimethylhydrazone of acetone provides unsymmetrical ketones.

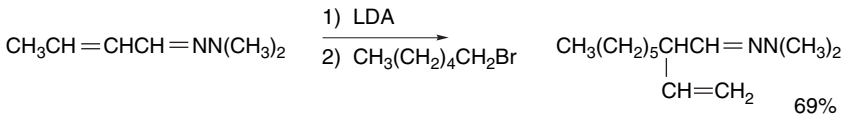


Ref. 121

The anion of cyclohexanone *N*,*N*-dimethylhydrazone shows a strong preference for axial alkylation.[122] 2-Methylcyclohexanone *N*,*N*-dimethylhydrazone is alkylated by methyl iodide to give *cis*-2,6-dimethylcyclohexanone. The 2-methyl group in the hydrazone occupies a pseudoaxial orientation. Alkylation apparently occurs *anti* to the lithium cation, which is on the face opposite the 2-methyl substituent.



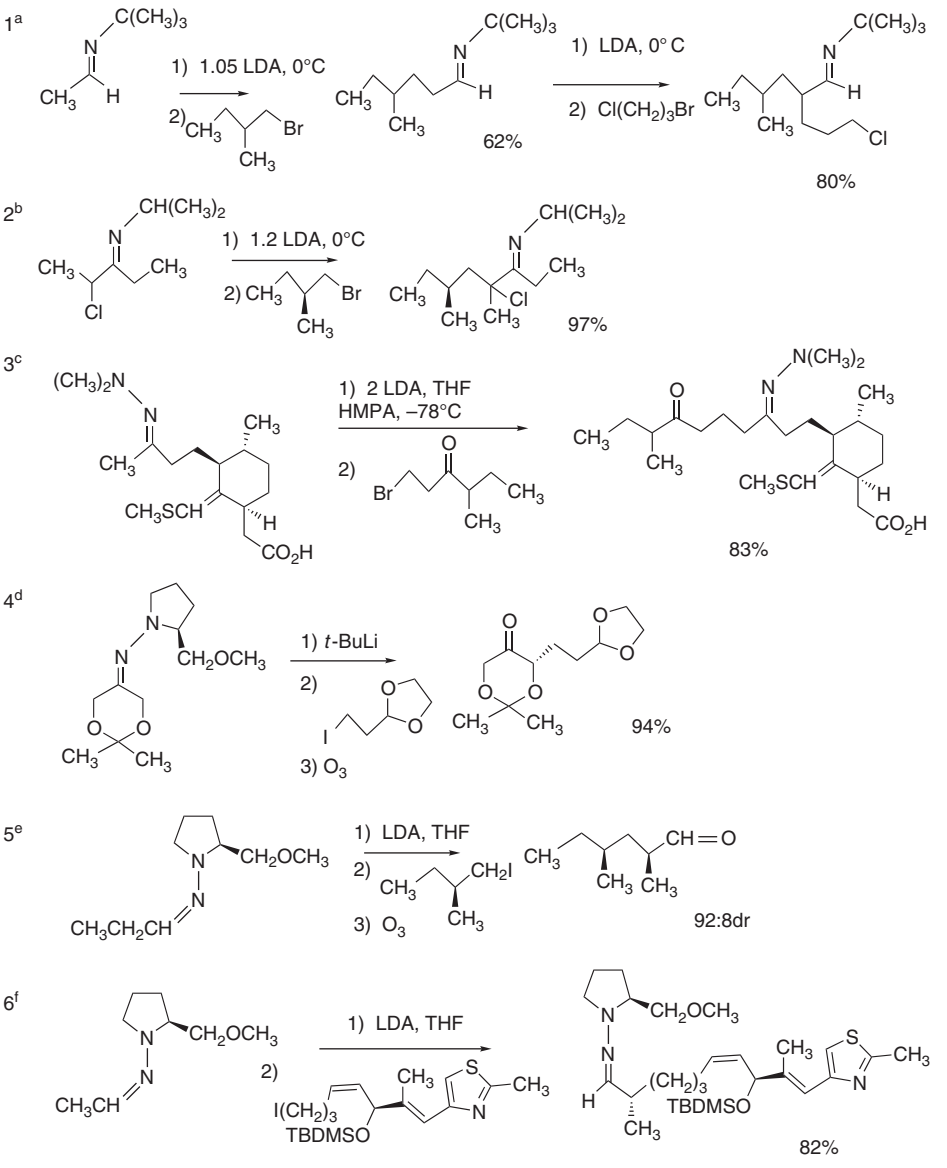
The *N*,*N*-dimethylhydrazones of α,β-unsaturated aldehydes give α-alkylation, similarly to the enolates of enones.[123]



Chiral hydrazones have also been developed for enantioselective alkylation of ketones. The hydrazones are converted to the lithium salt, alkylated, and then hydrolyzed to give alkylated ketone in good chemical yield and with high diastereoselective[124] (see Table 1.4, Entry 4). Several procedures have been developed for conversion of the hydrazones back to ketones.[125] Mild conditions are necessary to maintain the configuration at the enolizable position adjacent to the carbonyl group. The most frequently used hydrazones are those derived from *N*-amino-2-methoxymethypyrrolidine, known as SAMP. The (*R*)-enantiomer is called RAMP. The crystal structure of the lithium anion of the SAMP hydrazone from 2-acetylnaphthalene has been determined[126] (Figure 1.7). The lithium cation is chelated by the exocyclic nitrogen and the methoxy group.

120. D. E. Bergbreiter and M. Newcomb, *Tetrahedron Lett.*, 4145 (1979); M. E. Jung, T. J. Shaw, R. R. Fraser, J. Banville, and K. Taymaz, *Tetrahedron Lett.*, 4149 (1979).
121. M. Yamashita, K. Matsumiya, M. Tanabe, and R. Suetmitsu, *Bull. Chem. Soc. Jpn.*, **58**, 407 (1985).
122. D. B. Collum, D. Kahne, S. A. Gut, R. T. DePue, F. Mohamadi, R. A. Wanat, J. Clardy, and G. Van Duyne, *J. Am. Chem. Soc.*, **106**, 4865 (1984); R. A. Wanat and D. B. Collum, *J. Am. Chem. Soc.*, **107**, 2078 (1985).
123. M. Yamashita, K. Matsumiya, and K. Nakano, *Bull. Chem. Soc. Jpn.*, **60**, 1759 (1993).
124. D. Enders, H. Eichenauer, U. Baus, H. Schubert, and K. A. M. Kremer, *Tetrahedron*, **40,** 1345 (1984); D. Enders, H. Kipphardt, and P. Fey, *Org. Synth.*, **65**, 183 (1987); D. Enders and M. Klatt, *Synthesis*, 1403 (1996).
125. D. Enders, L. Wortmann, and R. Peters, *Acc. Chem. Res.*, **33**, 157 (2000).
126. D. Enders, G. Bachstadtler, K. A. M. Kremer, M. Marsch, K. Hans, and G. Boche, *Angew. Chem. Int. Ed. Engl.*, **27**, 1522 (1988).

Scheme 1.11. Alkylation of Imine and Hydrazone Anions



a. C. Stevens and N. De Kimpe, *J. Org. Chem.*, **58**, 132 (1993).
b. N. De Kimpe and W. Aelterman, *Tetrahedron*, **52**, 12815 (1996).
c. M. A. Avery, S. Mehrotra, J. D. Bonk, J. A. Vroman, D. K. Goins, and R. Miller, *J. Med. Chem.*, **39**, 2900 (1996).
d. M. Majewski and P. Nowak, *Tetrahedron Asymmetry*, **9**, 2611 (1998).
e. K. C. Nicolaou, E. W. Yue, S. LaGreca, A. Nadin, Z. Yang, J. E. Leresche, T. Tsuri, Y. Naniwa, and F. De Riccardis, *Chem. Eur. J.*, **1**, 467 (1995).
f. K. C. Nicolaou, F. Sarabia, S. Ninkovic, M. Ray, V. Finlay, and C. N. C. Body, *Angew. Chem. Int. Ed. Engl.*, **37**, 81 (1998).

Scheme 1.11 provides some examples of alkylation of imine and hydrazone anions. Entries 1 and 2 involve alkylation of anions derived from *N*-alkylimines. In Entry 1, two successive alkyl groups are added. In Entry 2, complete regioselectivity

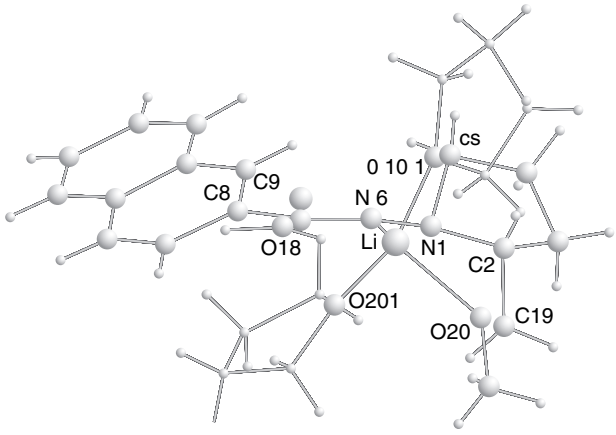


Fig. 1.7. Crystal structure of lithium salt of SAMP hydrazone of 2-acetylnaphthalene. Two molecules of THF are present. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **27**, 1522 (1988), by permission of Wiley-VCH.

for the chloro-substituted group is observed. This reaction was used in the synthesis of an ant alarm pheromone called (*S*)-manicone. Entry 3 is an alkylation of a methyl group in an *N*,*N*-dimethylhydrazone. This reaction was used to synthesize analogs of the antimalarial substance arteminsinin. Entries 4 to 6 take advantage of the SAMP group to achieve enantioselective alkylations in the synthesis of natural products. Note that in Entries 4 and 5 the hydrazone was cleaved by ozonolysis. The reaction in Entry 6 was done in the course of synthesis of epothilone analogs. (See Section 13.2.5. for several epothilone syntheses.) In this case, the hydrazone was first converted to a nitrile by reaction with magnesium monoperoxyphthalate and then reduced to the aldehyde using DiBAlH.[127]

General References

D. E. Bergbreiter and M. Newcomb, in *Asymmetric Synthesis*, J. D. Morrison, ed., Academic Press, New York, 1983, Chap. 9.

D. Caine, in *Carbon-Carbon Bond Formation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1979, Chap. 2.

A. G. Cook, ed., *Enamines: Synthesis, Structure and Reactions*, 2d Edition, Marcel Dekker, New York, 1988

C. H. Heathcock, *Modern Synthetic Methods,* **6**, 1 (1992).

V. Snieckus, ed., *Advances in Carbanion Chemistry*, Vol. 1, JAI Press, Greenwich, CT, 1992.

J. C. Stowell, *Carbanions in Organic Synthesis*, Wiley-Interscience, New York, 1979.

127. D. Enders, D. Backhaus, and J. Runsink, *Tetrahedron*, **52**, 1503 (1996).

Problems

(*References for these problems will be found on page 1271.*)

1.1. Arrange each series of compounds in order of decreasing acidity.

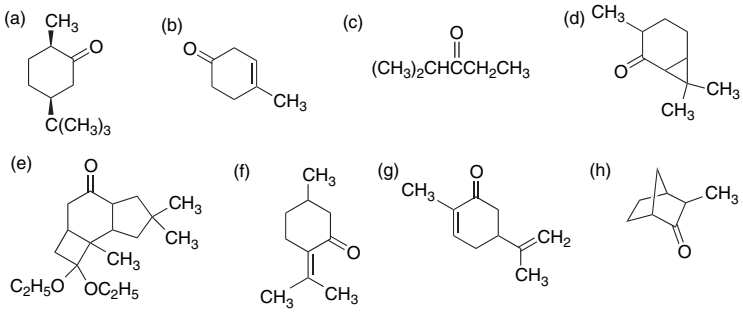
(a) $CH_3CH_2NO_2$, $(CH_3)_2CHCPh$, CH_3CH_2CN, $CH_2(CN)_2$

(b) $[(CH_3)_2CH]_2NH$, $(CH_3)_2CHOH$, $(CH_3)_2CH_2$, $(CH_3)_2CHPh$

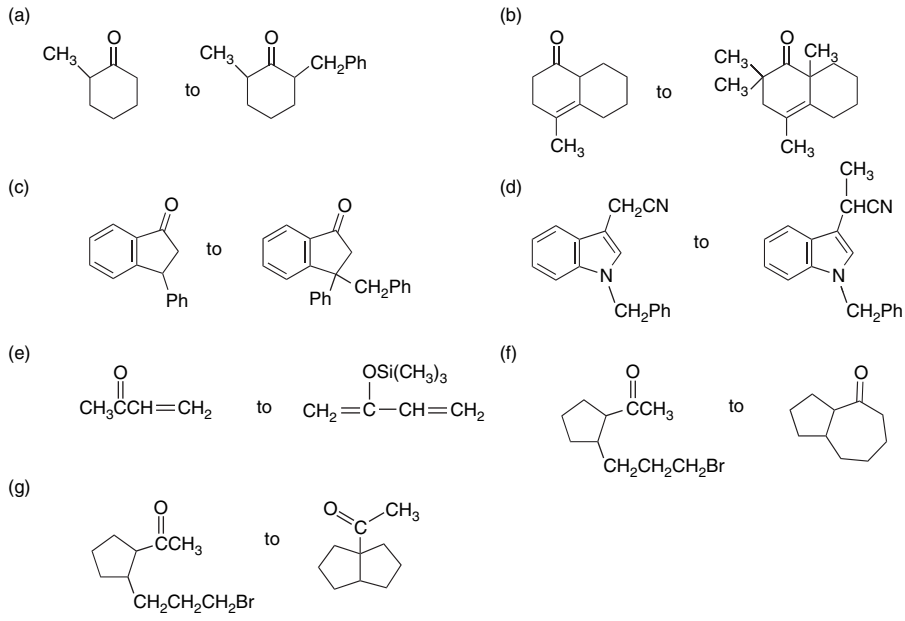
(c) $CH_3CCH_2CO_2CH_3$, $CH_3CCH_2CCH_3$, CH_3OCCH_2Ph, CH_3COCH_2Ph

(d) $PhCCH_2Ph$, $(CH_3)_3CCCH_3$, $(CH_3)_3CCCH(CH_3)_2$, $PhCCH_2CH_2CH_3$

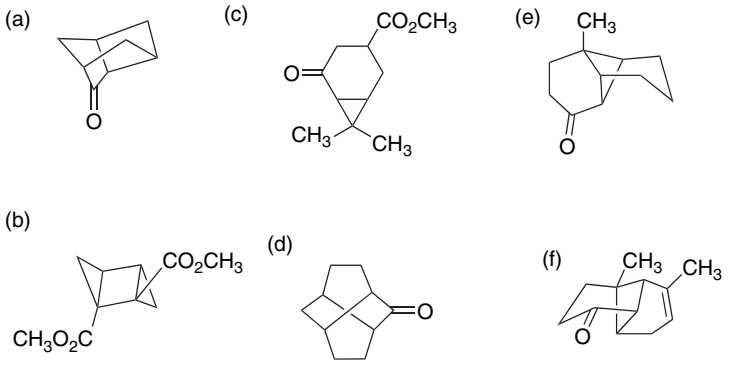
1.2. Write the structures of all possible enolates for each ketone. Indicate which you expect to be favored in a kinetically controlled deprotonation. Indicate which you would expect to be the most stable enolate.



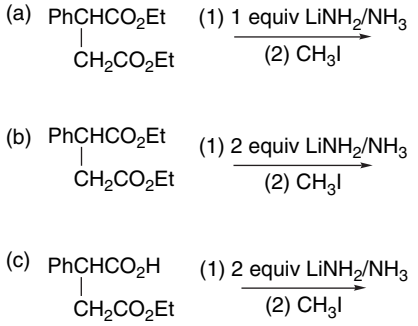
1.3. Suggest reagents and reaction conditions that would be suitable for effecting each of the following conversions.



1.4. Intramolecular alkylation of enolates can be used to synthesize bi- and tricyclic compounds. Identify all the bonds in the following compounds that could be formed by intramolecular enolate alkylation. Select the one that you think is most likely to succeed and suggest reasonable reactants and reaction conditions for cyclization.

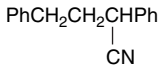


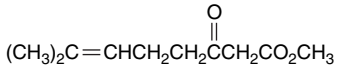
1.5. Predict the major product of each of the following reactions:

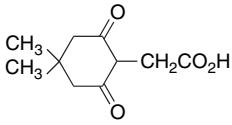


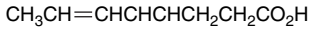
1.6. Treatment of 2,3,3-triphenylpropanonitrile with one equivalent of KNH_2 in liquid ammonia, followed by addition of benzyl chloride, gives 2-benzyl-2,3,3-triphenylpropanonitrile in 97% yield. Use of two equivalents of KNH_2 gives an 80% yield of 2,3,3,4-tetraphenylbutanonitrile under the same reaction conditions. Explain.

1.7. Suggest readily available starting materials and reaction conditions suitable for obtaining each of the following compounds by a procedure involving alkylation of a carbon nucleophile.

(a) 

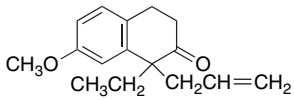
(b) 

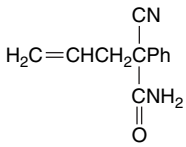
(c) 

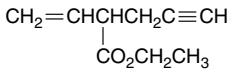
(d) 

(e) 2,2,3-triphenylpropanonitrile

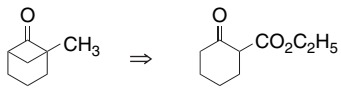
(f) 2,6-diallylcyclohexanone

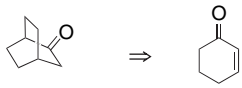
(g) 

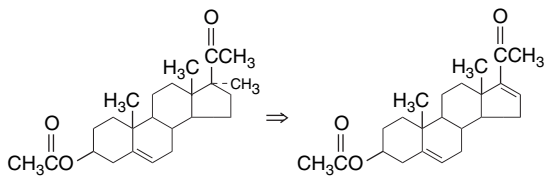
(h) 

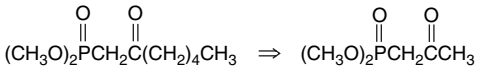
(i) 

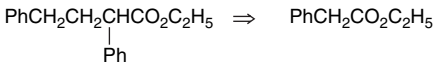
1.8. Perform a retrosynthetic dissection of each of the following compounds to the suggested starting material using reactions that involve alkylation of an enolate or an enolate equivalent. Then suggest a sequence of reactions that you think would succeed in converting the suggested starting material to the desired product.

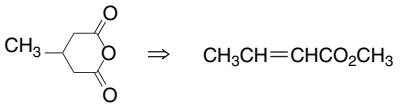
(a) 

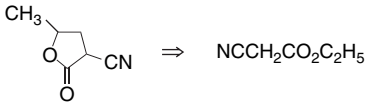
(b) 

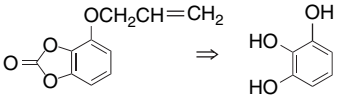
(c) 

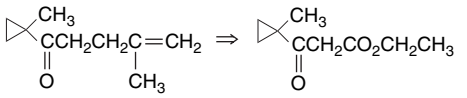
(d) 

(e) 

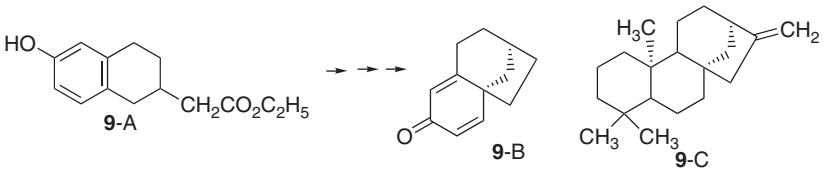
(f) 

(g) 

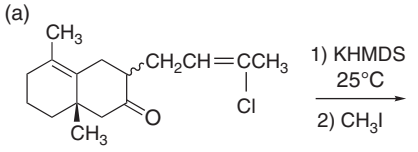
(h) 

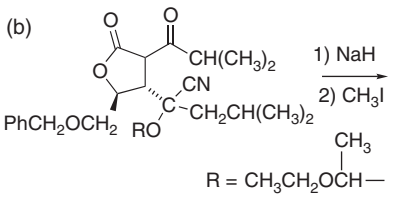
(i) 

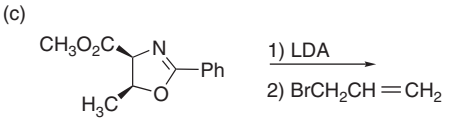
1.9. The carbon skeleton in structure **9-B** is found in certain natural substances, such as **9-C**. Outline a strategy to synthesize **9-B** from **9-A.**

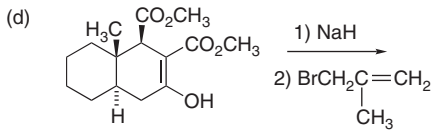


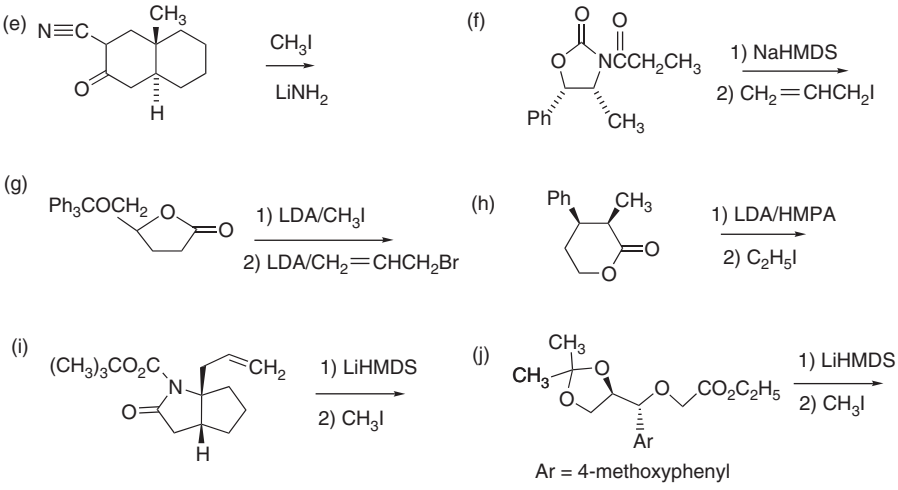
1.10. Analyze the factors that you expect to control the stereochemistry of the following reactions:

(a) 

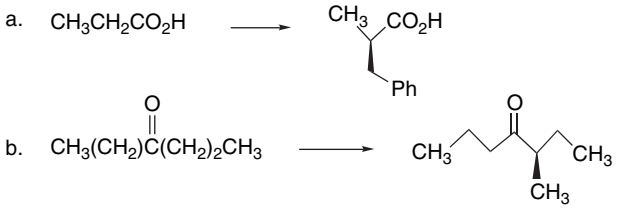
(b) 

(c) 

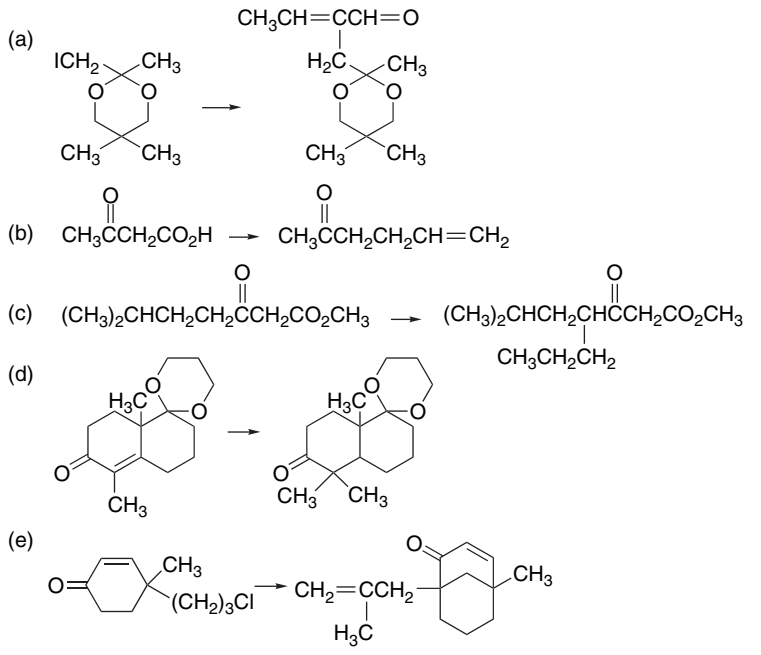
(d) 



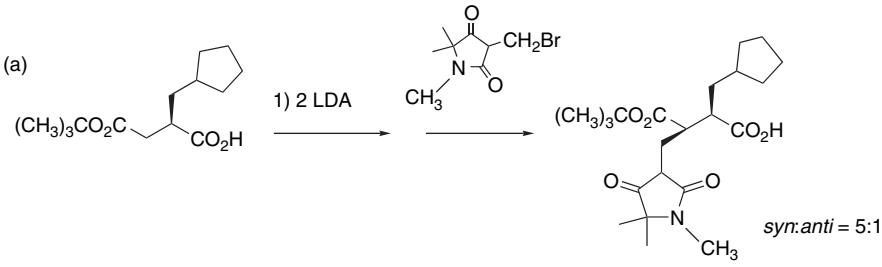
1.11. Suggest methodology for carrying out the following transformations in a way that high enantioselectivity could be achieved.

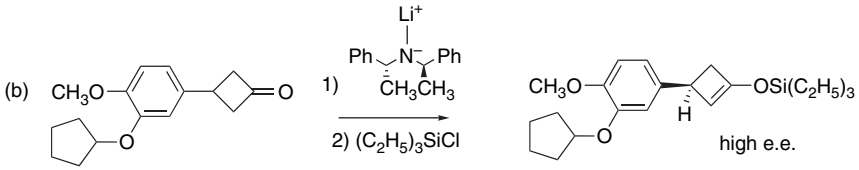


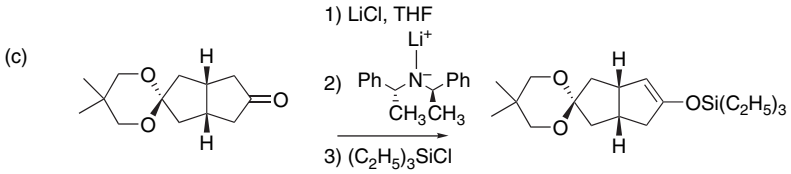
1.12. Indicate reagents and approximate reaction conditions that could be used to effect the following transformations. More than one step may be required.

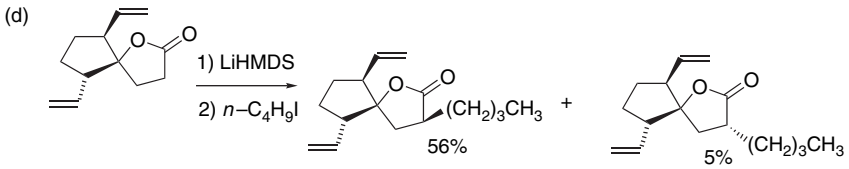


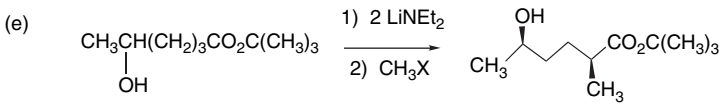
1.13. The observed stereoselectivity of each of the following reactions is somewhat enigmatic. Discuss factors that could contribute to stereoselectivity in these reactions.





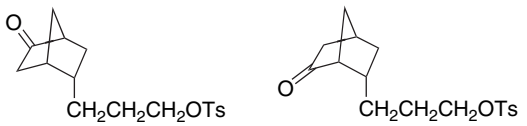






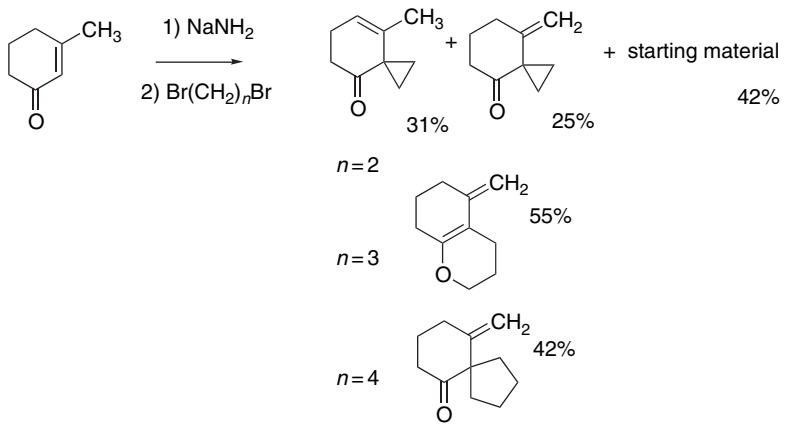
CH_3X	HMPA	*syn*	*anti*
CH_3I	no	56	44
CH_3I	yes	87	13
$(CH_3O)_2SO_2$	yes	90	10

1.14. One of the compounds shown below undergoes intramolecular cyclization to give a tricyclic ketone on being treated with NaHMDS, but the other does not cyclize. Indicate which compound will cyclize more readily and offer and explanation.



1.15. The alkylation of the enolate of 3-methyl-2-cyclohexenone with several different dibromides led to the products shown below. Discuss the course

of each reaction and offer an explanation for the dependence of the product structure on the chain length of the dihalide.



1.16. Treatment of ethyl 2-azidobutanoate with a catalytic amount of lithium ethoxide in THF leads to evolution of nitrogen. Quenching the resulting solution with 3 *N* HCl gives ethyl 2-oxobutanoate in 86% yield. Suggest a mechanism for this process.