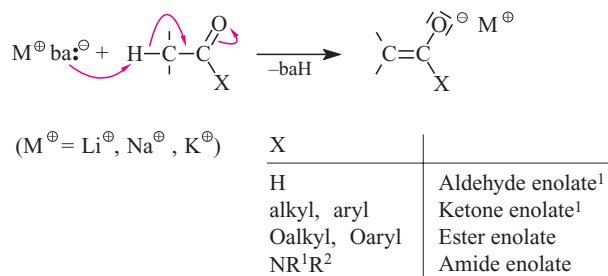


Aldehydes, ketones, carboxylic esters, carboxylic amides, imines and *N,N*-disubstituted hydrazones react as electrophiles at their sp^2 -hybridized carbon atoms. These compounds also become nucleophiles, if they contain an H atom in the α -position relative to their C=O or C=N bonds. This is because they can undergo tautomerization to the corresponding enol as seen in Chapter 12. They are also C,H-acidic at this position, i.e., the H atom in the α -position can be removed with a base (Figure 13.1). The deprotonation forms the conjugate bases of these substrates, which are called **enolates**. The conjugate bases of imines and hydrazones are called **aza enolates**. The reactions discussed in this chapter all proceed via enolates.



¹Also called simply enolate.

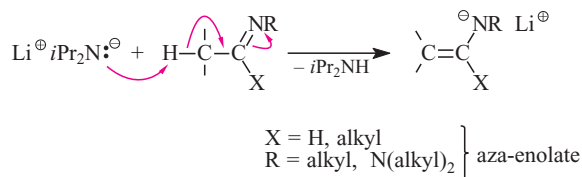


Fig. 13.1. Formation of enolates from different C,H acids.

13.1 Basic Considerations

13.1.1 Notation and Structure of Enolates

In valence bond theory, every enolate can be described by two resonance forms. The negative formal charge is located at a C atom in one of these resonance forms and at an O or an N atom in the other resonance form. In the following, we refer to these resonance forms as the *carbanion* and the *enolate* resonance forms, respectively. Only the enolate resonance form is shown in Figure 13.1, because this resonance form has the higher weight according to reso-

nance theory. The enolate resonance form places negative charge on the more electronegative heteroatom (O or N). These heteroatoms stabilize the negative charge better than the less electronegative C atom in the carbanion resonance form.

In Figure 13.1, the enolate structures are shown with the charge on the heteroatom and with the heteroatom in association with a metal ion. The metal ion stems from the reagent used in the enolate formation. In the majority of the reactions in Chapter 13, the enolate is generated by deprotonation of C,H acids. The commonly employed bases contain the metal ions Li^+ , Na^+ , or K^+ . Therefore, in Chapter 13, we will consider the chemistry of lithium, sodium, and potassium enolates.

It is known that the chemistry of enolates depends on the nature of the metal. Moreover, the metals are an integral part of the structures of enolates. Lithium enolates are most frequently employed, and in the solid state the lithium cations definitely are associated with the heteroatoms rather than with the carbanionic C atoms. Presumably the same is true in solution. The bonding between the heteroatom and the lithium may be regarded as ionic or polar covalent. However, the heteroatom is not the only bonding partner of the lithium cation irrespective of the nature of the bond between lithium and the heteroatom:

- Assuming ionic Li^+O^- or Li^+NR^- interactions, it may be appropriate to draw a parallel between the structures of enolates and ionic crystals of the Li^+O^- or Li^+NR^- types. In the latter structures, every lithium atom is coordinated by six neighboring anions.
- From the viewpoint of polar, yet covalent $\text{Li}-\text{O}$ and $\text{Li}-\text{N}$ bonds, lithium would be unable to reach a valence electron octet in the absence of bonding partners besides the heteroatom. The lithium thus has to surround itself by other donors in much the same way as has been seen in the case of the organolithium compounds (cf. Section 10.1).

Be this as it may, lithium attempts to bind to several bonding partners; the structural consequences for the enolates of a ketone, an ester, and an amide are shown in Figure 13.2: In contrast to the usual notation, these enolates are not monomers at all! The heteroatom that carries the negative charge in the enolate resonance form is an excellent bonding partner such that several of these heteroatoms are connected to every lithium atom. Lithium enolates often result in “tetramers” if they are crystallized in the absence of other lithium salts and in the absence of other suitable neutral donors. The lithium enolate of *tert*-butyl methyl ketone, for example, crystallizes from THF in the form shown in Figure 13.3.

“Tetramers” like the one in Figure 13.3 contain cube skeleta in which the corners are occupied in an alternating fashion by lithium and enolate oxygen atoms. Every lithium atom is surrounded by three enolate oxygen atoms, and vice versa. Every lithium atom binds a molecule of THF as its fourth ligand. It is for this reason that the term “tetramer” was used in quotation marks; the overall structure is a THF complex of the tetramer.

Figure 13.2 shows structures that contain two lithium enolates each. But again, these structures are not *pure* dimers. Both lithium atoms employ two of their coordination sites to bind to an N atom of the bidentate ligand TMEDA (see Figure 13.2 for name and structure).

“Oligomeric” enolates along with the associated neutral ligands also are called **aggregates**. Lithium enolates are likely to exist as aggregates not only in the solid state but also in solution. The neutral ligands in these aggregates can be TMEDA, DMPU (structure in Figure 2.17), HMPA (structure in Figure 2.17), THF and/or $\text{HN}(\text{iPr})_2$. Lithium enolates may occur in such **homoaggregates**, but they also may be part of so-called **mixed aggregates**.

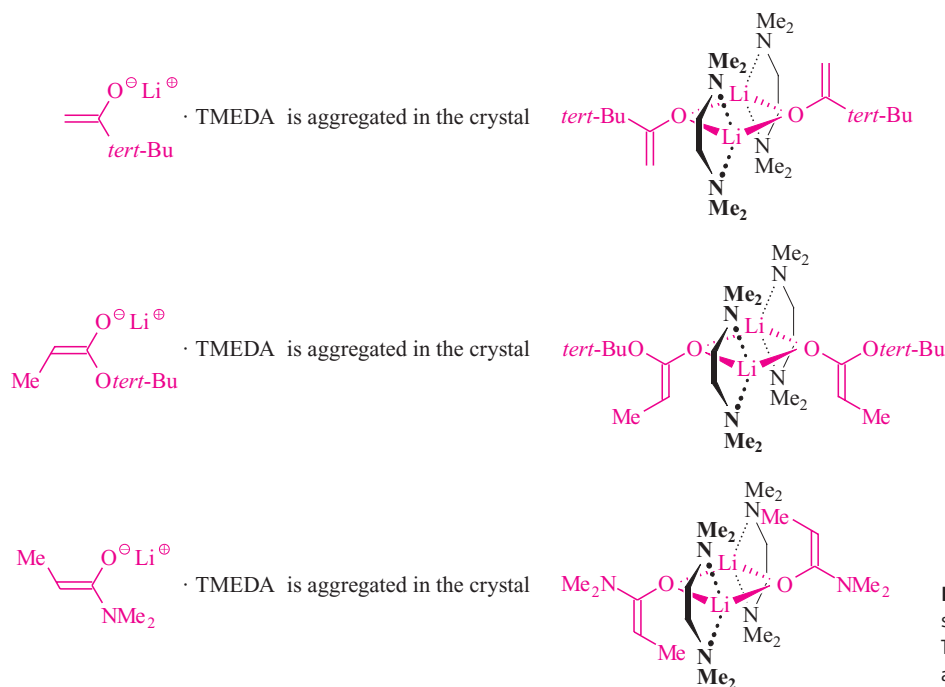


Fig. 13.2. X-ray single crystal structures of lithium enolates. TMEDA, tetramethylethylenediamine.

The latter are aggregates that also contain other lithium compounds (e. g., LiHal, LiOR or LDA).

It is not known whether lithium enolates exist in solution as homoaggregates or as mixed aggregates, nor is it known whether lithium enolates react as aggregates or via other species that might be present in low concentration. But it is certain that the reactivity of lithium enolates is affected by the presence or absence of molecules that are capable of forming aggregates. However, all these insights about aggregation do not preclude focusing on the enolate monomers in discussions of the elemental aspects of enolate reactivity. Hence, in Chapter 13, all reactions are formulated in a simplified and unified format considering monomeric enolates. There also are enolates of metals other than Li, Na, or K, but these are not considered in this book. In addition, there are some metal-free enolates, the ammonium enolates, which can be generated in equilibrium reactions between amines and so-called active-methylene

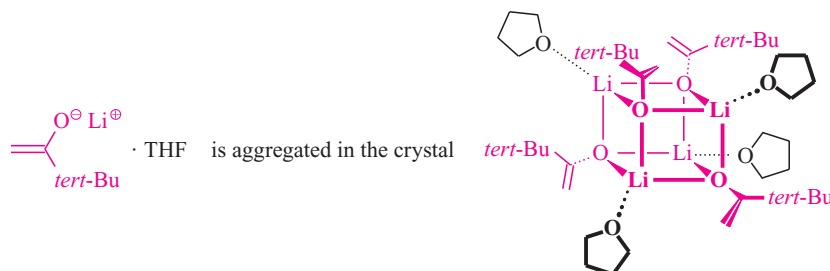
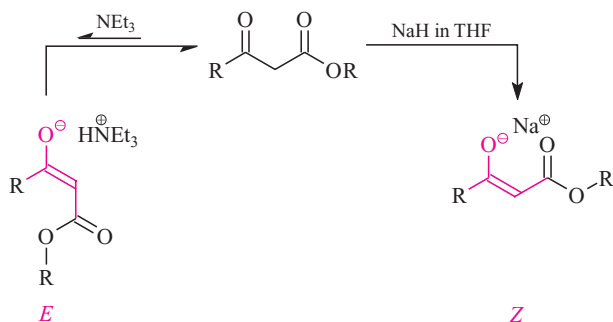


Fig. 13.3. X-ray crystal structure of $\text{H}_2\text{C=C(O}^-\text{Li}^+\text{)(tert-Bu) THF}$.

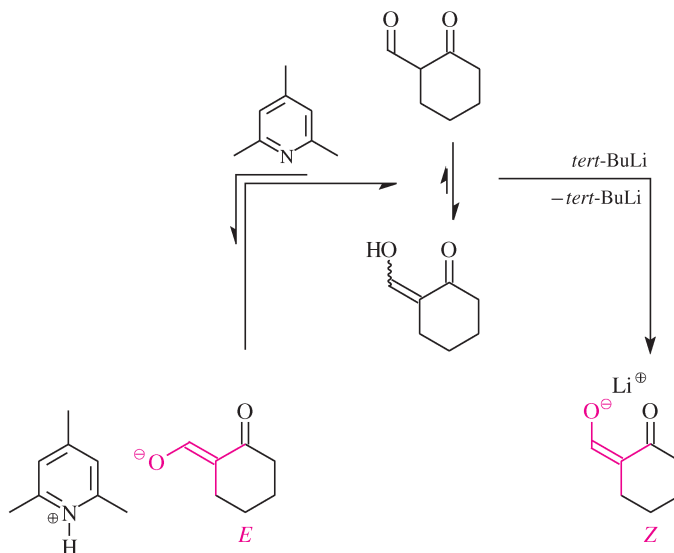
Fig. 13.4. Stereoselective deprotonation of a β -ketoester to trialkylammonium or sodium enolates. The *E*- and *Z*-enolates are formed when NEt_3 and NaH , respectively, are employed.



compounds. These are compounds that contain two geminal acceptor substituents with strong $-\text{M}$ effects.

Starting from β -ketoesters (Figure 13.4, see Figure 13.25 for a synthetic application), or β -ketoaldehydes (Figure 13.5), ammonium enolates are formed with a stereostructure (*E*-enolates) that differs from that of the corresponding alkaline earth metal enolates (*Z*-enolates). In the latter, the lithium atom forms a bridge between the two negatively charged O atoms such that a six-membered chelate results. In contrast, the ammonium ion cannot play such a role in the ammonium enolate, and the more stable *E*-enolate is formed as the result of product development or thermodynamic control. The negatively charged O atoms are at a greater distance from each other in the *E*-enolate than in the *Z*-enolate. The greater distance between the O atoms in the *E*-enolate reduces charge-charge and dipole-dipole repulsions.

Fig. 13.5. Stereoselective deprotonation of a β -ketoaldehyde and its enol tautomer to substituted pyridinium or lithium enolates, respectively. Similar to the deprotonation of Figure 13.4, the *E*-enolate is formed when the amine is used and the *Z*-enolate is formed when the metal-containing base is employed.



13.1.2 Preparation of Enolates by Deprotonation

Suitable Bases

According to Figure 13.1, carbon-bound H atoms are acidic if they are bound to carbon atoms that are in the α -position with respect to an electron acceptor that can stabilize a negative charge via resonance ($-M$ effect). Carbon-bound H atoms are even more acidic if they are located in the α -position of *two* such electron acceptors, which is the case in the so-called active-methylene compounds. Enolates derived from active-methylene compounds require three resonance forms for their description, and resonance forms **A** and **B** (Figure 13.6) are the more important ones. Compounds that contain an H atom in the α -position with respect to three electron acceptors are even more acidic than active-methylene compounds. However, such compounds do not play a significant role in organic chemistry.

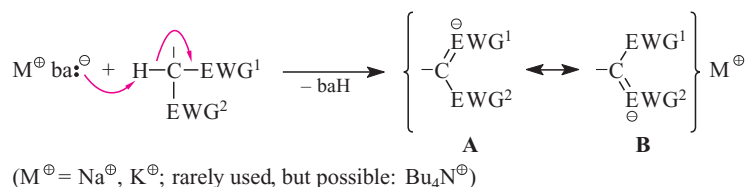


Fig. 13.6. Enolate formation of active-methylene compounds.

Table 13.1 lists the $\text{p}K_{\text{a}}$ values of C,H-acidic compounds with a variety of electron acceptors. It shows that multiple substitution by a given acceptor enhances the acidity of the α -H atom more than monosubstitution. Table 13.1 also shows that the nitro group is the most activating substituent. One nitro group causes the same acidity of an α -H atom as do two carbonyl or two ester groups.

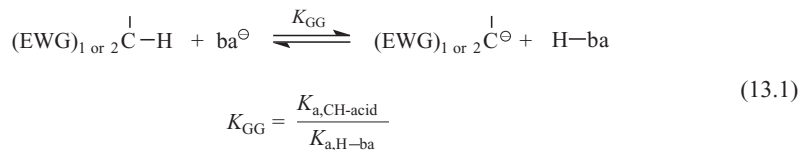
The acidifying effect of the remaining acceptor substituents of Table 13.1 decreases in the order $-\text{C}(=\text{O})-\text{H} > -\text{C}(=\text{O})-\text{alkyl} > -\text{C}(=\text{O})-\text{O-alkyl}$, and the amide group $-\text{C}(=\text{O})-\text{NR}_2$ is even less effective. This ordering essentially reflects substituent effects on the

Tab. 13.1 Effects of Substituents on C,H Acidity*

$\text{p}K_{\text{a}}$ of ... for EWG =	$\text{H}-\underset{ }{\overset{ }{\text{C}}}-\text{EWG}$	$\text{H}-\underset{\text{EWG}}{\overset{ }{\text{C}}}-\text{EWG}$
$-\text{NO}_2$	10.2	3.6
$\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{H} \end{array}$	16	5
$\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{Me} \end{array}$	19.2	9.0
$\begin{array}{c} \text{O} \\ \\ -\text{C}-\text{OMe} \end{array}$	24.5	13.3

stability of the C=O double bond in the respective C,H-acidic compound. The resonance stabilization of these C=O double bonds drastically increases in the order $R-C(=O)-H < R-C(=O)-alkyl < R-C(=O)-O-alkyl < R-C(=O)-NR_2$ (cf. Table 6.1; see Section 9.1.1 for a comparison between the C=O double bonds in aldehydes and ketones). This resonance stabilization is lost completely once the α -H atom has been removed by way of deprotonation and the respective enolate has formed.

The equilibrium constant K_{eq} of the respective deprotonation equilibrium shows whether a base can deprotonate a C,H-acidic compound quantitatively, in part, or not at all:



$$= 10^{pK_{a,H-ba} - pK_{a,CH-acid}} \quad (13.2)$$

Equation 13.1 shows that these equilibrium constants in turn depend on the acidity constants of the two weak acids involved, that is, the acidity constant $K_{a,C,H \text{ acid}}$ of the C,H acid and the acidity constant $K_{a,H-base}$ of the conjugate acid (H-base) of the base ($ba^{\ominus}$) employed. Equation 13.2 makes the same statement in terms of the corresponding pK_a values. From this equation it follows:

**Rules of Thumb
Regarding the Position of
the Equilibria of C,H-
Acidic Compounds**

1. A C,H acid is deprotonated quantitatively (or nearly so) by an equimolar amount of base if the pK_a value of the conjugate acid of the base employed is higher than the pK_a value of the C,H acid.
2. A C,H acid is deprotonated by an equimolar amount of base only to the extent of 10%, 1%, or 0.1%, and so on, if the pK_a value of the conjugate acid of the base employed is 1, 2, 3, ... units lower than the pK_a value of the C,H acid.
3. In cases of incomplete C,H acid deprotonation, an excess of base can be employed to increase the enolate fraction. According to the principle of Le Chatelier, the base excess increases the enolate fraction by a factor that equals the square root of the number of mole equivalents of the base employed.

**Side Note 13.1.
Conformational Depen-
dence of the C,H Acidity
of Carboxylic Acid Esters**

“For every rule, there is an exception!” or so they say. Sometimes this is also true in chemistry. It appears, for example, that the pK_a values of carboxylic acid esters vary more widely than is allowed or acknowledged by Table 13.1. This does not justify, though, the abandonment of the above mentioned “rules of thumb” for estimating the position of the deprotonation equilibrium of C,H-acidic compounds. As it were, *one* structural effect on the C,H acidity of carboxylic acid esters has so far been totally ignored, namely the effect of the conformation that the substructure $C-O-C=O$ adopts in relation to the highlighted bond (printed in boldface), i.e., which dihedral angle occurs between the C–O and the C=O bond.

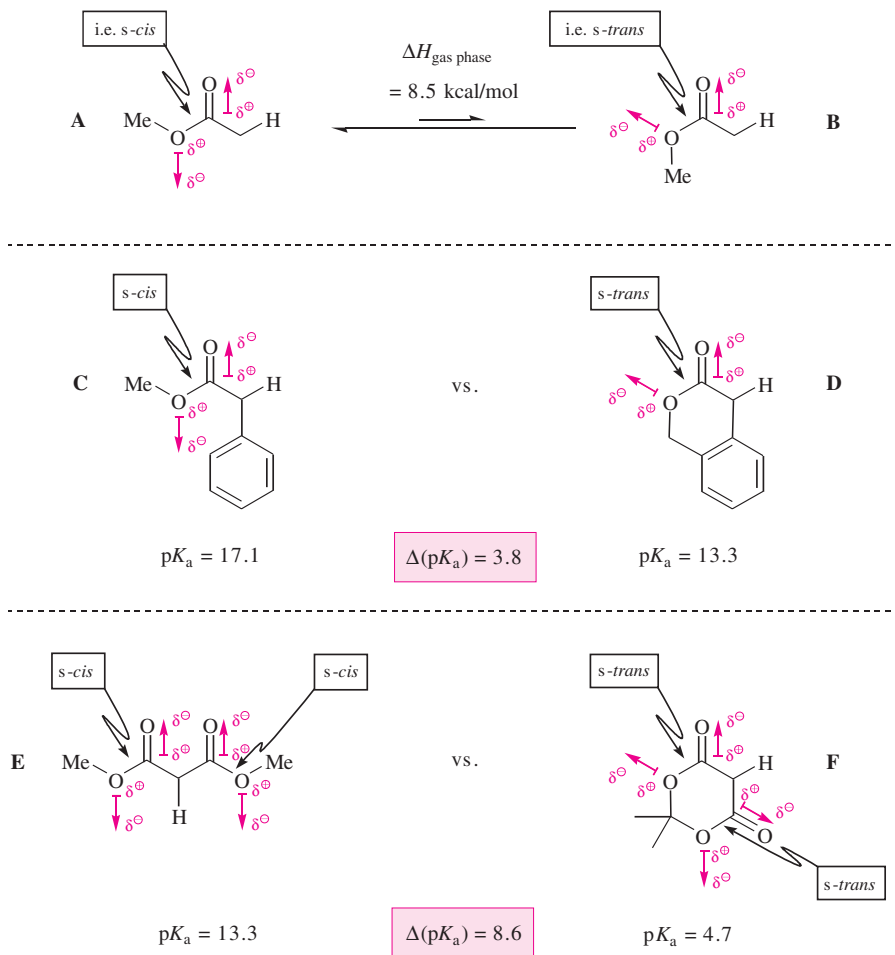


Fig. 13.7. Conformational dependence of the enthalpy of carboxylic acid esters and the conformational dependence of the C,H acidity of carboxylic acid esters based on it.

Using the pK_a values of the ester pairs in Figure 13.7, this conformational effect on the C,H acidity may be conceived as follows: if the dihedral angle between the C–O and the C=O bond in the C–O–C=O substructure of carboxylic acid esters is 0° —that is, if this substructure displays the so-called *s-cis-conformation*—the pK_a value of this ester is predicted by Table 13.1 in the correct range. If in the same substructure C–O–C=O of a carboxylic acid ester the dihedral angle between the C–O and the C=O bond measures 180° —i.e., if this ester displays the so-called *s-trans-conformation*—its pK_a value is underestimated in Table 13.1 by several orders of magnitude. This is why phenylacetic ester (Formula **C** in Figure 13.7; dihedral angle $\text{C-O/C=O} = 0^\circ$) is by 4 pK units less acidic than its lactone analog **D** (dihedral angle $\text{C-O/C=O} = 180^\circ$). The doubling of this conformational effect in comparison to malonic acid dimethyl ester (Formula **E** in Figure 13.7; both dihedral angles $\text{C-O/C=O} = 0^\circ$) and Meldrum's acid (**F**; both dihedral angles $\text{C-O/C=O} = 180^\circ$) explains why the former is less acidic than the latter by almost 9 pK units.

The reason for this conformational effect has to do with the pronounced endothermic character of the transformation of *s-cis*- into *s-trans*-methyl acetate ($\Delta H_R = +8.5$ kcal/mol; Figure 13.7). This is due to the partial dipole moments that occur in each of the conformers involved because of the polarized C=O double bond or the asymmetric distribution of the nonbonding electrons on the other oxygen atom. In the *s-cis*-conformer of methyl acetate and all other *s-cis*-carboxylic acid esters these partial moments are antiparallel, i.e., they nearly eliminate each other. However, in the *s-trans*-conformer of methyl acetate and all other *s-trans*-carboxylic acid esters these partial dipole moments are aligned. Hence, repulsion occurs between them, destabilizing the *s-trans*-ester conformer by 8–9 kcal/mol. In the enolate resulting from the deprotonation of a carboxylic acid ester, there are no similar large polar effects—irrespective of the configuration of the enolate double bond. This means that only an *s-trans*-, but not an *s-cis*-configured carboxylic acid ester will lose dipole/dipole repulsion when it reacts as a C,H acid and is converted into the enolate. This is what renders *s-trans*-configured esters more acidic than *s-cis*-configured esters.

With the pK_a values of the conjugate acids of the most commonly used organic bases (Table 13.3) and the pK_a values of the C,H acids compiled in Table 13.1, the foregoing statements lead to the following deductions (see also Table 13.2):

Tab. 13.2 Survey of the Deprotonation Ability of C,H-Acidic Compounds. The ease of deprotonation of C,H-acidic compounds depends on (a) the type and number of the electron-withdrawing groups in the substrate and (b) on the base employed

		$\begin{array}{c} \text{O} \\ \parallel \\ \text{H}-\text{C}-\text{C}-\text{H/R/OR} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{H}-\text{C}-\text{N}^+-\text{O}^- \text{ or} \\ \\ \text{H} \end{array}$ $\text{H}-\text{C}-\left(\text{C}=\text{O}-\text{H/R/OR}\right)_2$
	pK_a	18–25	4–13
+ NEt ₃ ($\rightleftharpoons$ HNEt ₃ ⁺ , with a $pK_a = 10.7$)		little deprotonation	partial deprotonation
+ OH [−] ($\rightleftharpoons$ H ₂ O, with a $pK_a = 15.5$) or + OEt [−] ($\rightleftharpoons$ EtOH, with a $pK_a = 15.7$) or + <i>Otert</i> -Bu [−] ($\rightleftharpoons$ <i>tert</i> -BuOH, with a $pK_a = 19$)		partial deprotonation	quantitative deprotonation
+ LDA ($\rightleftharpoons$ HN <i>i</i> Pr ₂ , with a $pK_a \approx 36$)		quantitative deprotonation	hardly ever employed as this would be overkill

Tab. 13.3 Basicity of Typical Reagents Employed in the Generation of Enolates via Deprotonation

Reagent	p <i>K</i> _a -value of the conjugate acid
Li [⊕] NR ₂ [⊖]	35 to 40
K [⊕] <i>Otert</i> -Bu [⊖]	19
Na [⊕] OEt [⊖]	15.7
Na [⊕] OH [⊖]	15.5
NEt ₃	10.7

- All aldehydes, ketones, and carboxylic esters can be deprotonated quantitatively to enolates with lithium amides. The same substrates and alkoxides give only small amounts of enolate in equilibrium reactions, but even these small amounts of enolate may be large enough to allow for enolate reactions.
- For the quantitative deprotonation of nitroalkanes and active-methylene compounds, there is no need to employ the “heavy artillery” of lithium amides. Rather, it suffices to employ alkaline earth metal alkoxides or alkaline earth metal hydroxides. In addition, equilibrium reactions between these C,H acids and amines form enough enolate to initiate enolate reactions.

The foregoing classification is of fundamental significance for the understanding of enolate chemistry. For every pair of C,H acid and base, one needs to know whether the combination effects quantitative or partial enolate formation. If deprotonation is only partial, then the unreacted substrate may represent an electrophile that can react with the enolate nucleophile. In such a case, it depends on the specific circumstances whether an enolate reacts with any remaining substrate or whether it reacts only with an added *different* electrophile. The occurrence of a reaction between enolate and unreacted substrate is avoided if the C,H acid is deprotonated completely with a stoichiometric amount of a sufficiently strong base.

There is only one exception to the last statement in that aldehydes cannot be converted quantitatively into aldehyde enolates. Any attempt to achieve a quantitative deprotonation of an aldehyde—with a lithium amide, for example—necessarily leads to a situation in which some aldehyde enolate is formed while some aldehyde substrate is still present, and these species cannot coexist even at temperatures as low as that of dry ice. The aldehyde is such an excellent electrophile that it reacts much faster with the enolate than it is deprotonated by the base.

Table 13.4 allows for a comparison of the basicities of the strongest lithium-containing bases. The basicities are measured by the heats of deprotonation liberated upon mixing the reference acid isopropanol with these bases. These heats of deprotonation reveal that organolithium compounds are even stronger bases than lithium amides. Their basicities decrease from *tert*-BuLi via *sec*-BuLi and *n*-BuLi to PhLi.

Considering these heats of deprotonation, one wonders whether organolithium compounds should not be at least as suitable as lithium amides for effecting the deprotonation of carbonyl and carboxyl compounds. However, this is usually not the case, since organolithium com-

Tab. 13.4 Thermochemistry of Selected Acid/Base Reactions: Deprotonation Enthalpies (kcal/mol) for Deprotonations of *i*PrOH with Various Organolithium Compounds and Lithium Amides

<i>tert</i> -BuLi	−56.2	LTMP	−30.4
<i>sek</i> -BuLi	−52.8	LDA	−28.6
<i>n</i> -BuLi	−50.0	LiHMDS	−12.1
PhLi	−42.3		

pounds react almost always as nucleophiles rather than as bases. Organolithium compounds thus would add to the carbonyl carbon (Section 10.5) or engage in a substitution reaction at the carboxyl carbon (Section 6.5).

Obviously, only **nonnucleophilic bases** can be employed for the formation of enolates from carbonyl and carboxyl compounds. A base is nonnucleophilic if it is very bulky. The only non-nucleophilic organolithium compounds that *deprotonate* carbonyl and carboxyl compounds are mesityllithium (2,4,6-trimethylphenyllithium) and trityllithium (triphenylmethylolithium). However, these bases do not have any significance for the generation of enolates because of the difficulties associated with their preparation and with the separation of their conjugate acid hydrocarbons.

Alkaline earth metal amides have a unique place in enolate chemistry in light of the preceding discussion. Yet, amides without steric demand—from NaNH_2 to LiNEt_2 —also are usually not suitable for the formation of enolates, since their nucleophilicities exceed their basicities. On the other hand, the amides LTMP, LDA, and LiHMDS (structures in Figure 4.18) are so bulky that they can never act as nucleophiles and always deprotonate C,H acids to the respective enolates.

Table 13.4 also shows that the deprotonation of isopropanol with LiHMDS is less than half as exothermic as the deprotonations with LDA or LTMP. Hence, LiHMDS is a much weaker base than the other two amides. This is due to the ability of the SiMe_3 groups of LiHMDS to stabilize the negative charge in the α -position at the N atom. The mechanism of this stabilization might be the same as in the case of the isoelectronic triphenylphosphonium center in *P* ylides (Figure 11.1), that is, a combination of an inductive effect and anomeric effect. Because of its relatively low basicity, LiHMDS is employed for the preparation of enolates primarily when it is important to achieve high chemoselectivity.

Side Note 13.2.
Neutral, but Superbasic:
Schwesinger Bases!

Schwesinger's " P_5 base" is as basic as the strongest amide bases and also non-nucleophilic. Figure 13.8 suggests that the index "5" represents the five phosphorus atoms of this base and that there might be analogous " P_2 ", " P_3 " and " P_4 bases." And indeed, there are. They are all collected under the generic term "Schwesinger bases." But regarding basicity, the " P_5 base" is entitled to leadership: at 34–35, the $\text{p}K_{\text{a}}$ value of its conjugate acid is quite similar to the $\text{p}K_{\text{a}}$ value of diisopropylamine, the conjugate acid of LDA! This is due to the extraordinarily good stabilization of the positive charge in the conjugate acid of the " P_5 base": there are 12 *all*-octet resonance forms that contribute to this stabilization (Figure 13.8). The " P_5 base" provides access to metal-free enolates and thus to a chemistry which, in particular cases, differs markedly from the chemistry of metal enolates.

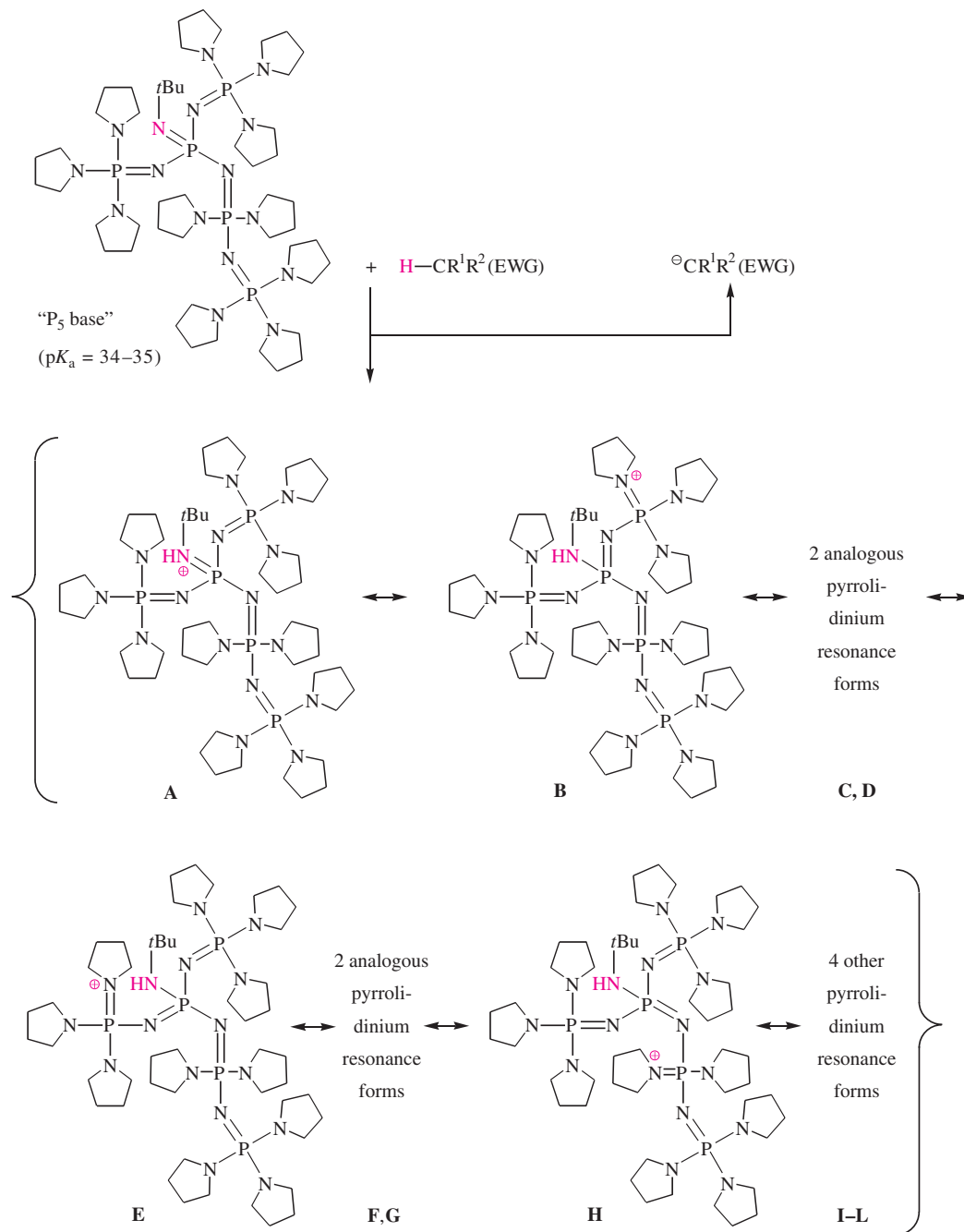
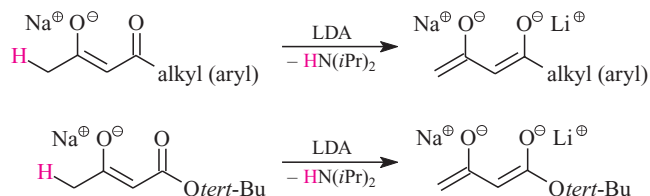


Fig. 13.8. The strongest Schwesinger base: metal-free, but as strong as alkali metal amides!

Fig. 13.9. Formation of bisenolates.



The basicity of LDA is so high that it is even possible to generate bisenolates from β -diketones and β -ketoesters (Figure 13.9). Even carboxylates can be deprotonated at the α -carbon if the strongest organic bases are employed (Figure 13.10). However, the twofold deprotonation of phenylacetic acid by ethylmagnesium bromide is not commonly used. This reaction is mentioned in Figure 13.10 only because the resulting enolate **A** acts as the nucleophile in the Ivanov reaction in Figure 13.45. The double deprotonation of malonic acid monoethyl ester actually requires only magnesium ethoxide, which may conveniently be generated *in situ*. Of course, this is due to the fact that the resulting **B** is not a true carboxylate enolate, but a carboxylate-substituted ester enolate. An example of the synthetic use of this enolate is given in Figure 13.65 (middle).

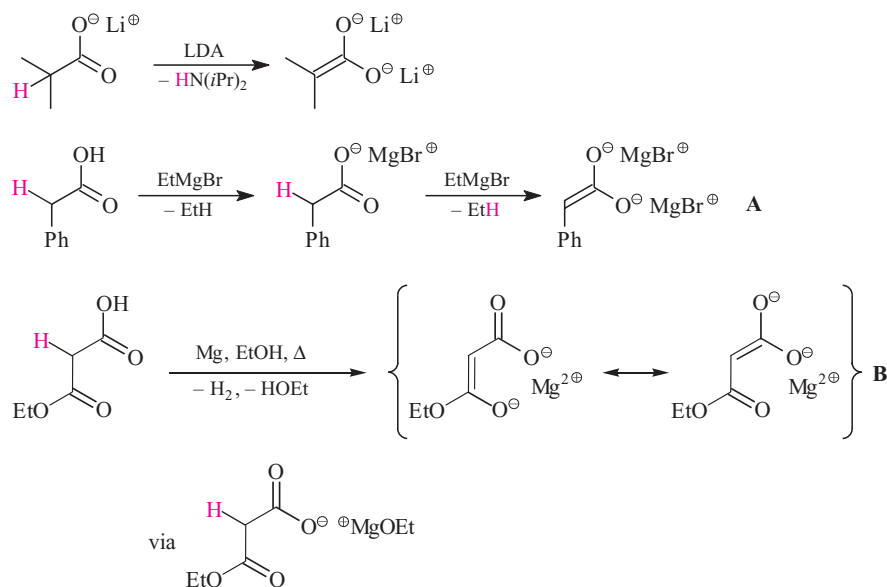


Fig. 13.10. Formation of carboxylate enolates ("carboxylic acid dianions") by reaction of carboxylic acid salts with strong bases.

Regiocontrol in the Formation of Lithium Enolates

Only one enolate can be generated from aldehydes or their aza analogs, from symmetric ketones or their aza analogs, or from carboxylic esters or carboxylic amides. For the moment we are ignoring the possibility that two stereoisomers, *E*- and *Z*-enolates, may occur for each of these enolates. On the other hand, constitutionally isomeric (regioisomeric) enolates may be derived from unsymmetrical ketones and from their aza analogs if they contain acidic H atoms

at the C_α and $C_{\alpha'}$ centers. From certain unsymmetrical ketones or their aza analogs one or sometimes even both of these enolates can be generated regioselectively (see also Figure 13.35).

For example, 2-phenylcyclohexanone can be deprotonated regioselectively with LDA (Figure 13.11). This reaction is most successful at -78°C in THF because the reaction is irreversible under these conditions as long as a small excess of LDA is employed. Hence, the reaction is kinetically controlled and proceeds via the most stable transition state. The standard transition state of *all* enolate formations from C,H acids with LDA is thought to be cyclic, six-membered, and preferentially in the chair conformation (**A** and **B** in Figure 13.11). To be as

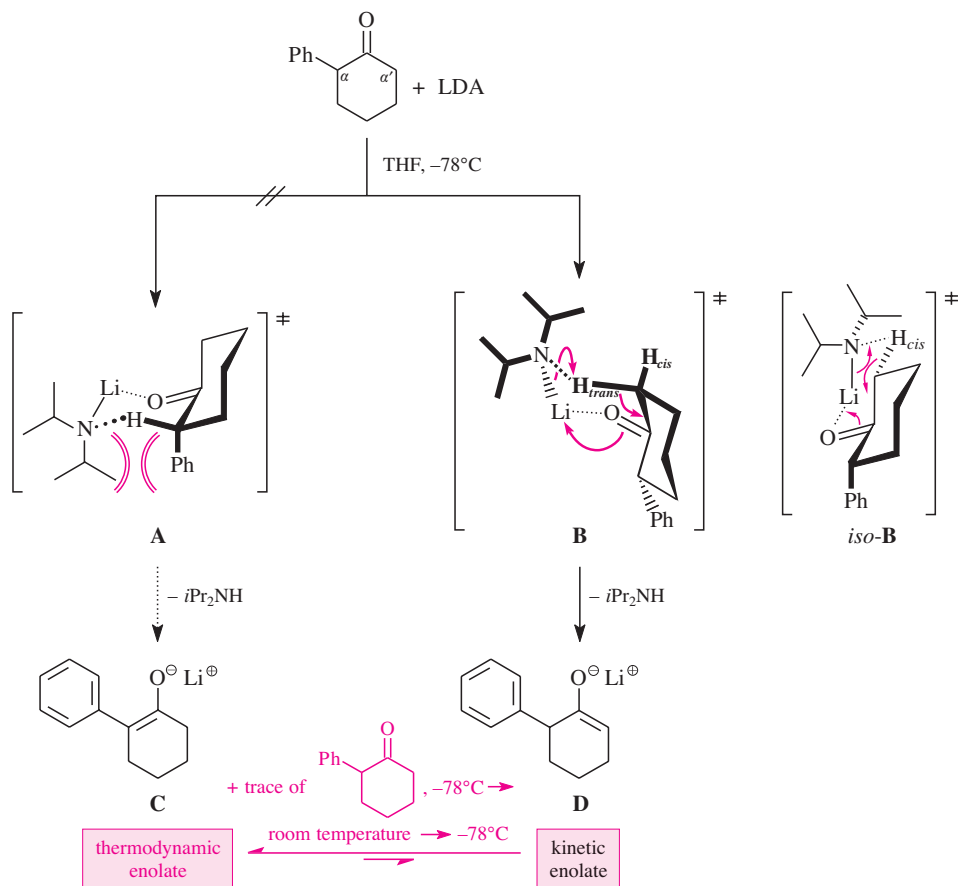


Fig. 13.11. Regioselective generation of ketone enolates, I: the effects of different substituents in the α - and α' -positions. Enolate **D** is formed in THF at -78°C with LDA irrespective of whether a substoichiometric amount or an excess of LDA is used. However, if one employs slightly less than the stoichiometric amount of LDA (so that a trace of the neutral ketone is present), then, upon warming, the initially formed enolate **D** isomerizes quantitatively to enolate **C** with its more highly substituted $\text{C}=\text{C}$ double bond. It should be noted that LDA removes an axially oriented α -H from the cyclohexanone; this is because only then does the resulting lone pair of electrons receive optimum stabilization by the adjacent $\text{C}=\text{O}$ bond. With the kinetically preferred deprotonation leading to the enolate **D** the axial α -H is transferred to the base (via transition state **B**), but not the equatorial α -H (via transition state *iso-B*.)

stable as possible, this transition state should not feature any steric hindrance that can be avoided. In particular, the transition state should not contain any substituent in the six-membered ring that is parallel with the pseudo-axially oriented amide *N*-isopropyl group. Such a substituent would suffer from 1,3-diaxial repulsion because of its interaction with the isopropyl group. It follows that transition state **A** of Figure 13.11 is less stable than transition state **B**. The enolate formation thus proceeds selectively via transition state **B** and results in the **kinetic enolate D**.

The C=C double bond of **D** is not conjugated to the phenyl ring. It is therefore less stable than the regioisomeric enolate **C**, which benefits from such a conjugation. In this context, **C** is called the **thermodynamic enolate**. Because **C** is more stable than **D**, **C** can be generated from the kinetic enolate **D** as soon as the opportunity for isomerization is provided. The opportunity for isomerization arises if a weak acid is present that allows for the protonation of the enolate to the ketone. This can be accomplished by allowing the presence of a trace of unreacted substrate ketone, which happens if one treats the substrate ketone with a slightly less than stoichiometric amount of LDA. Under these conditions, at temperatures above $-78\text{ }^{\circ}\text{C}$, the remaining substrate ketone reacts with the kinetic enolate **D** to yield the thermodynamic enolate **C** and newly formed substrate ketone. This occurs fast enough to effect a quantitative isomerization of **D** into **C**.

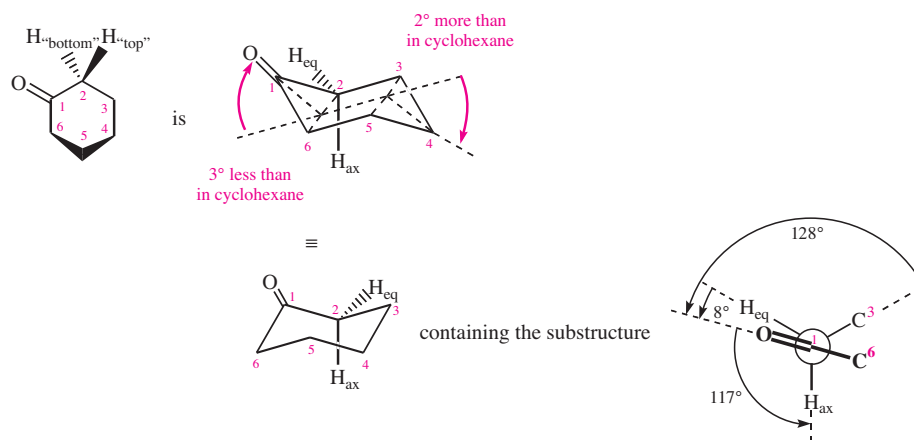
We thus reach the following interesting result. Depending on the reaction conditions, both the kinetic and the thermodynamic enolates of 2-phenylcyclohexanone can be generated with perfect regiocontrol. The same is true for many ketones that carry a different number of *alkyl* groups at the C_{α} and $\text{C}_{\alpha'}$ centers, but not always to the same extent. 2-Methylcyclohexanone, for example, reacts with LDA at $-78\text{ }^{\circ}\text{C}$ to yield a 99:1 mixture of kinetic and thermodynamic enolates. Under equilibrium conditions, however, a ratio of only 80:20 of the thermodynamic and the kinetic enolate, respectively, is obtained. A much more noticeable stabilization is provided by the same methyl group in the corresponding magnesium enolate. Thus, the thermodynamic enolate is produced “exclusively” if under equilibrium conditions 2-methylcyclohexanone is deprotonated with $(i\text{Pr}_2\text{N})\text{MgBr}$ (Figure 13.23).

Side Note 13.3.
Cyclohexanone Conformations and C,H Acidity

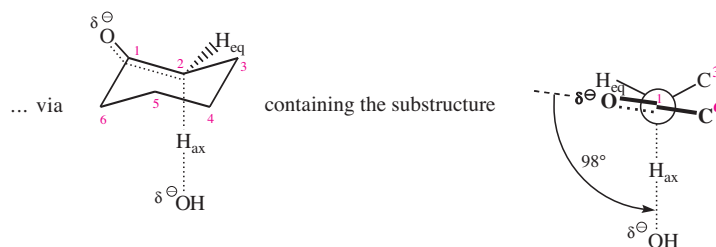
One structural aspect of the preferred transition state **B** (Figure 13.11) of the deprotonation of 2-phenylcyclohexanone has so far been ignored because it did not have any relation with the topic “Regiocontrol in the Formation of Lithium Enolates” discussed in that section. Yet, it shall be explicitly addressed because familiarity with this aspect will in the following subsection “Stereocontrol in the Formation of Lithium Enolates” allow us to understand why the deprotonation of carboxylic acid esters with LDA in THF containing DMPU or HMPT will lead to a “*Z*”-enolate (see Figure 13.17). Also, in the transition state **B** of Figure 13.11 the cyclohexanone depicted is deprotonated *diastereoselectively*: The LDA selectively abstracts the H atom that is in *trans*-position to the phenyl substituent and thus pseudo-axially oriented. This is due to the bonding situation in the resulting enolate **D** and, in particular, to the fact that in this transition state rehybridization from sp^3 to sp^2 begins with the carbon atom that will become the enolate carbon.

At the beginning of the reaction, an sp^3 AO originating from this carbon atom is bound to the hydrogen atom H_{trans} . At the end of the reaction, the $2p_z$ AO, which originates with the C atom under scrutiny via deprotonation, must overlap with the π^* MO of the adjacent C=O

double bond, since it is only because of this “ $C-H/\pi^*_{C=O}$ overlap” that the enolate **D** can be formed. In the transition state **B** of the formation of **D**, the latter overlap is needed and requires the $sp^3 \rightarrow 2p_z$ AO to be as perpendicular as possible to the double bond plane of the adjacent carbonyl group. The dihedral angle between the $C_{\text{enolate}}-H_{\text{trans}}$ bond and the $C=O$ double bond in the phenylcyclohexanone of Figure 13.11 is about 117° , since the corresponding dihedral angle between the $C_{\text{enolate}}-H_{\text{pseudo-axial}}$ bond and the $C=O$ double bond in the cyclohexanone itself exactly measures these 117° (Figure 13.12). In contrast, the dihedral angle between the $C_{\text{enolate}}-H_{\text{cis}}$ and the $C=O$ double bond in the phenylcyclohexanone of Figure 13.11 must be around 8° , since the corresponding dihedral angle between the $C_{\text{enolate}}-H_{\text{pseudo-equatorial}}$ bond and



It can be deprotonated during the gas phase of $OH^\ominus$, either ...



... or – with an extra activation energy of 2.8 kcal/mol through – ...

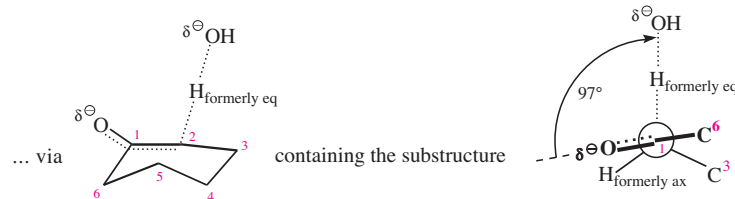


Fig. 13.12. Which H atom in the α -position to the carbonyl group of cyclohexanone(s) will be more rapidly removed by a base: the equatorial or the axial one? Answer: the H atom which is bound to the $C-H$ bond whose σ_{C-H} orbital in the transition state of the deprotonation is *parallel* to the $2p_z$ orbitals of the $\pi^*_{C=O}$ orbital of the adjacent carbonyl group, and hence overlaps with it most effectively (explanation: see text).

the C=O double bond of cyclohexanone again measures precisely 8° (Figure 13.12). The dihedral angle of 117° sufficiently approaches the optimal dihedral angle of 90° , and 8° is sufficiently remote so that the LDA reacts with the $\text{C}_{\text{enolate}}\text{--H}_{\text{trans}}$ bond of 2-phenylcyclohexanone while leaving its $\text{C}_{\text{enolate}}\text{--H}_{\text{cis}}$ bond intact.

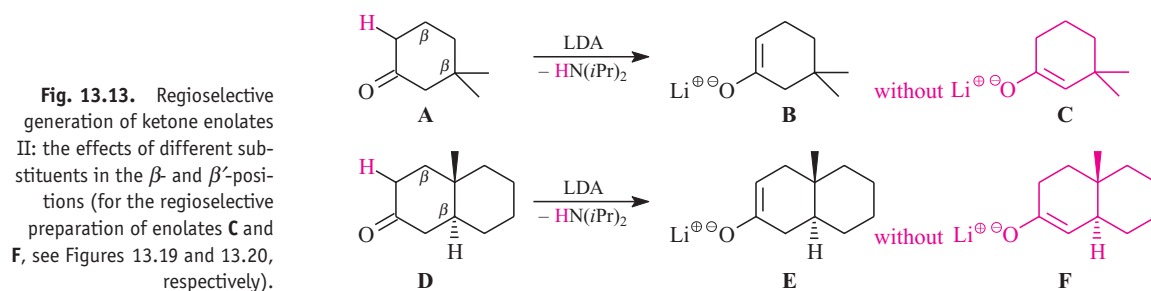
From the point of view of conformation cyclohexanones are more flexible than cyclohexanes. Therefore it *cannot* be generally assumed that hydrogen atoms in the α -position of cyclohexanones can be abstracted as protons only if they are pseudo-axially oriented. Accordingly, it is incorrect to say that removing them is never possible if their orientation is pseudo-equatorial. This situation is illustrated in Figure 13.12. The most favorable transition state (shown in the second line) corresponds (see above) to the pseudo-axial deprotonation, just as expected. The most stable transition state of the pseudo-equatorial deprotonation (shown in line 3), though, is higher in energy by only 2.8 kcal/mol and may—in the presence of suitable substituents, including bridging substituents—definitely become competitive.

An unsymmetrical ketone may even lead to the generation of one enolate in a selective fashion if the lack of symmetry is caused by the substitution patterns in the β - rather than α -positions. The difference in the β -positions may be due to the number or the kind of substituents there. This point is emphasized in Figure 13.13 with cyclohexanones that contain one (**D**) or two (**A**) β -substituents. In this case, deprotonation occurs preferentially on the side opposite to the location of the extra substituent; that is, the sterically less hindered acidic H atom reacts.

In the discussion of Figure 13.11, we mentioned that LDA abstracts acidic H atoms from the α -position of C,H-acidic compounds via a cyclic and six-membered transition state and that *the carbonyl group is an integral part of this six-membered ring*. This emphasis explains why the deprotonation of conjugated ketones with LDA yields the kinetic enolate (**A** in Figure 13.14) in a regioselective fashion instead of the thermodynamic enolate (**B** in Figure 13.14).

Stereocontrol in the Formation of Lithium Enolates

We have seen that LDA forms enolates of carbonyl compounds, carboxylic esters, and carboxylic amides via cyclic and six-membered transition states with the chair conformation. This geometry of the transition state for enolate formation has consequences if a stereogenic C=C double bond is generated.



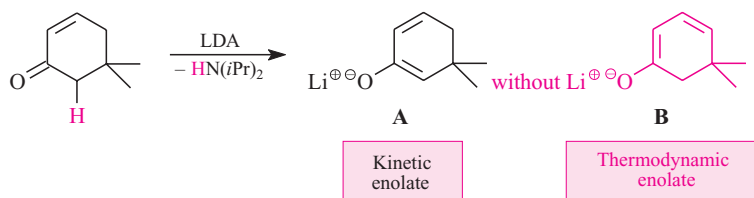


Fig. 13.14. Regioselective generation of ketone enolates **III**: the effects of conjugated versus nonconjugated substituents (for the regioselective preparation of enolate **B**, see Figure 13.21).

The reaction of unhindered aliphatic ketones with LDA yields more *E*- than *Z*-enolates. On the other hand, the *Z*-enolate is formed selectively if either a bulky aliphatic or a conjugating aromatic group is the inert group attached to the carbonyl carbon. Figure 13.15 shows how this *Z*-selectivity results from the differing steric demands in the potentially available transition states for deprotonation. The point is made using the example of an ethyl ketone with a sterically demanding substituent. Transition state **A** is so strongly destabilized by the 1,2-interaction indicated that deprotonation occurs exclusively via transition state **B** in spite of the repulsive 1,3-interaction in the latter.

Unhindered aliphatic ketones selectively yield *E*-enolates if they are deprotonated by a lithium amide via a transition state structure of type **A** of Figure 13.15. This occurs, for example, when the **B**-type transition state is destabilized because of the use of a base that is even more sterically demanding than LDA such as, for example, LTMP (for structure, see Figure 4.18). For example, diethyl ketone and LTMP form the *E*-enolate with *ds* = 87:13.

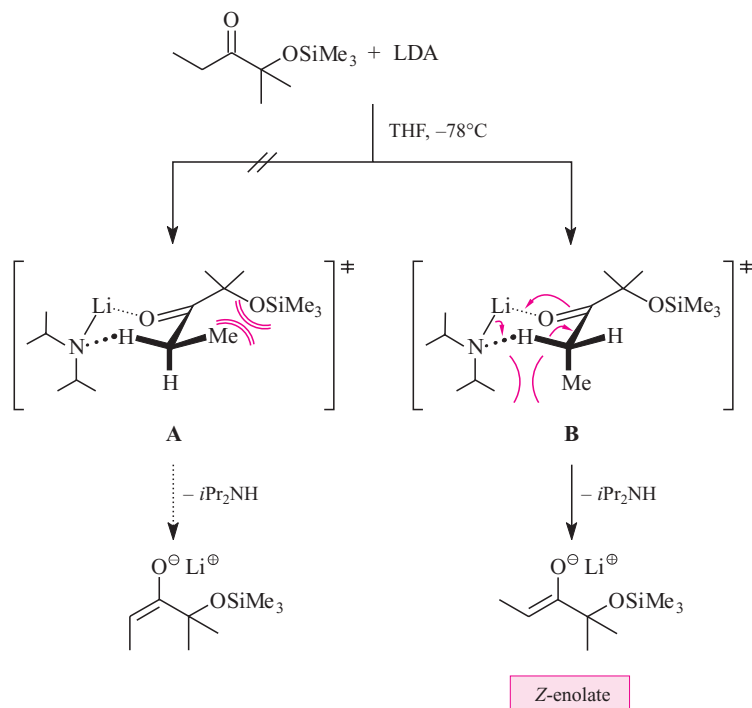


Fig. 13.15. Highly *Z*-selective generation of a ketone enolate. The transition state **A** is destabilized so strongly by 1,2-interactions that deprotonation occurs exclusively via transition state **B**. – Note: Don't let yourself be misled if it seems as though this is a deprotonation of H atoms lying almost in the plane of the C=O double bond. According to the discussion of Figure 13.12, this would be quite unfavorable due to the lack of $\sigma_{C-H}/\pi_{C=O}^*$ interaction. This is not true, though. For, if the transition states **A** and **B** displayed the same dihedral angle as a cyclohexane chair, the dihedral angle between the crucial C–H bond and the C=O bond in the transition states **A** and **B**, respectively, would amount to 60° each.

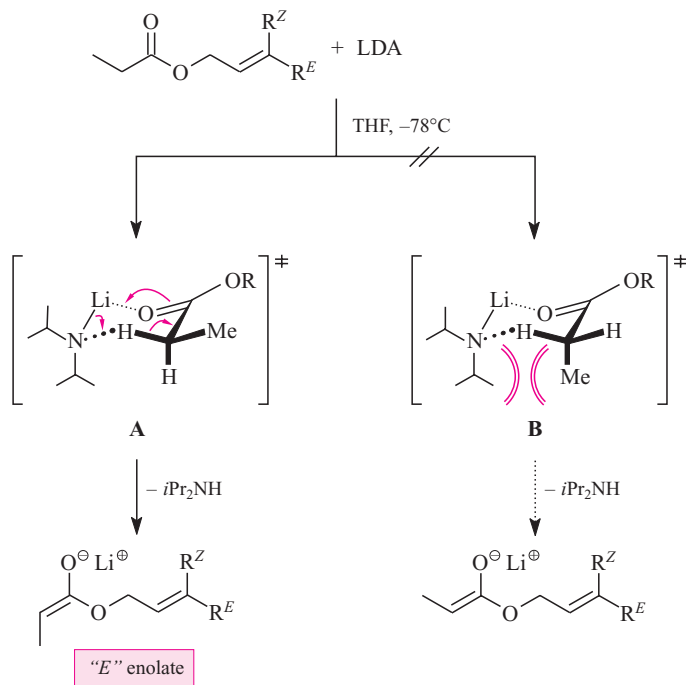


Fig. 13.16. Highly “*E*”-selective generation of ester enolates. The deprotonation of the ester occurs preferentially via the strain-free transition state **A**. – The caption of Figure 13.15 analogously applies to the dihedral angle between the C=O and the C–H bond that reacts (**A**) or does not react (**B**) with LDA.

Deprotonation of α -alkylated acetic acid esters (e.g., the propionic acid ester of Figure 13.16) with LDA at -78°C selectively yields the “*E*”-enolates. The quotation marks indicate that this application of the term is based on an extension of the *E/Z*-nomenclature: here, the Cahn–Ingold–Prelog priority of the $\text{O}^\oplus\text{Li}^\oplus$ substituent is considered to be higher than the priority of the OR group. The deprotonation of the ester shown in Figure 13.16 occurs via the strain-free transition state **A**. The alternative transition state **B** is destabilized by a 1,3-diaxial interaction.

“*Z*”-Enolates also are accessible from the same propionic acid esters with the same high stereoselectivity (Figure 13.17). This is a complete reversal of stereoselectivity in comparison to the deprotonation shown in Figure 13.16. This reversal is solely due to the change in solvent from THF to a mixture of THF and DMPU. The stereocontrol is again the result of kinetic control. In this solvent, the lithium of LDA coordinates with the oxygen atom of DMPU. Given the large excess of DMPU each lithium atom binds several equivalents of this ligand. Almost surely, in this way the lithium atom is fully coordinatively saturated by DMPU. Hence, in a mixture of THF and DMPU, LDA occurs as a “solvent-separated ion pair”. This is why the deprotonation in Figure 13.17 proceeds via an acyclic transition state. We may assume that the active base is the metal-free diisopropylamide anion of the above-mentioned solvent-separated ion pair. From these general conditions, we can derive structure **A** for the transition state of the “*Z*”-selective ester deprotonation. Its conformation corresponds to the most favorable transition state **B** of the gas-phase deprotonation of propionaldehyde, which also leads to the formation of a “*Z*”-enolate. The stereostructure of both transition states **A** and **B** benefits from the $\text{C-H}/\pi^*_{\text{C=O}}$ overlap. The importance of the $\text{C-H}/\pi^*_{\text{C=O}}$ overlap for the rapid depro-

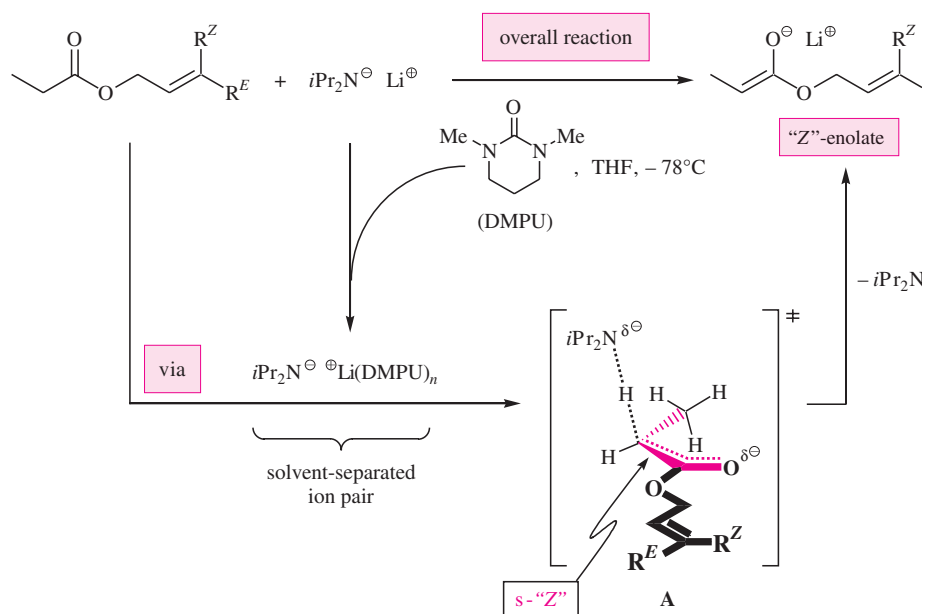
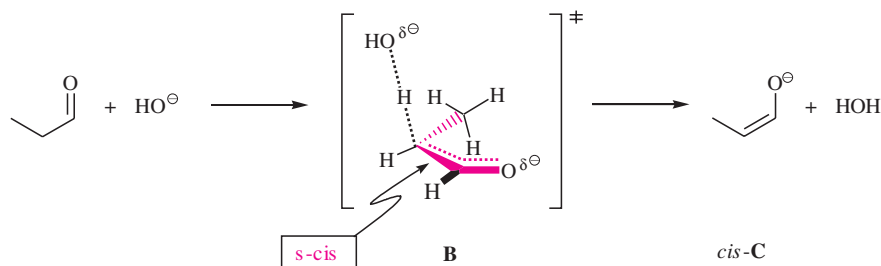


Fig. 13.17. Highly "Z"-selective generation of ester enolates in a THF/DMPU solvent mixture (DMPU, N,N' -dimethylpropyleneurea). The transition state **A** of this deprotonation with a metal-free diisopropylamide anion (in solution) corresponds to the calculated transition state **B** of the deprotonation of propionic aldehyde with a hydroxide anion (in the gas phase).



tonation of cyclohexanones was emphasized in connection with the discussion of Figure 13.12.

The generation of amide enolates by the reaction of carboxylic amides and LDA at $-78^\circ C$ occurs with complete stereoselectivity and yields the "Z"-enolate (Figure 13.18). This is just the opposite selectivity than in the case of the generation of ester enolates under the same conditions (Figure 13.16). The NR_2 group of an amide is branched and therefore sterically more demanding than the OR group of an ester. Hence, in the transition state for deprotonation, the NR_2 group of an amide requires more space than the OR group of an ester. Consequently, the propionic acid amide of Figure 13.18 as well as all other carboxylic amides cannot react via transition states **A**. Unlike transition state **A** of the analogous ester deprotonation (Figure 13.16), the 1,2-interaction would be *prohibitively* high. Therefore, carboxylic amides are deprotonated via **B**-type transition state structures in spite of the repulsive 1,3-interaction. Remember, it is due to this repulsive 1,3-interaction that these kinds of transition state structures (**B** in Figure 13.16) are *not involved* in the deprotonation of esters.

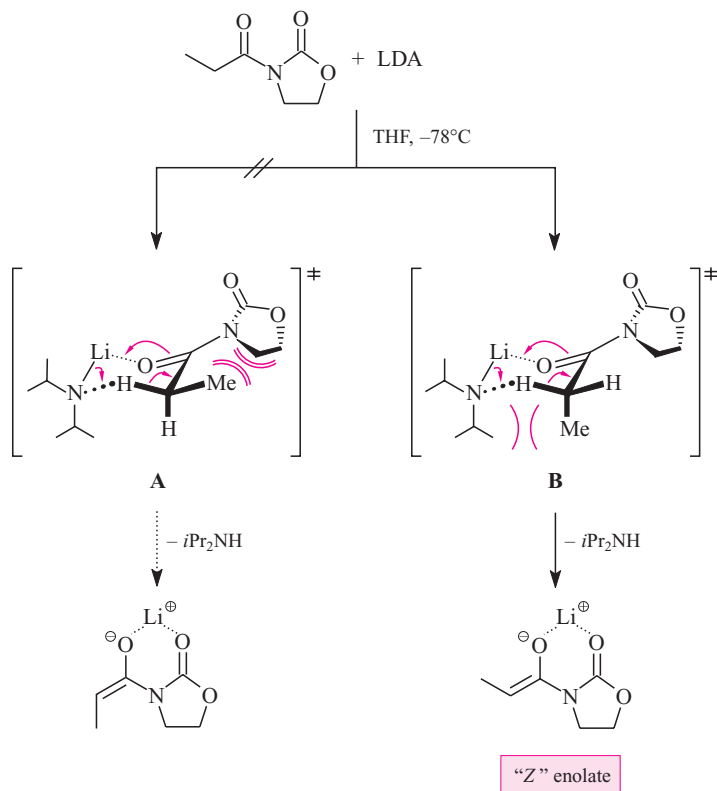


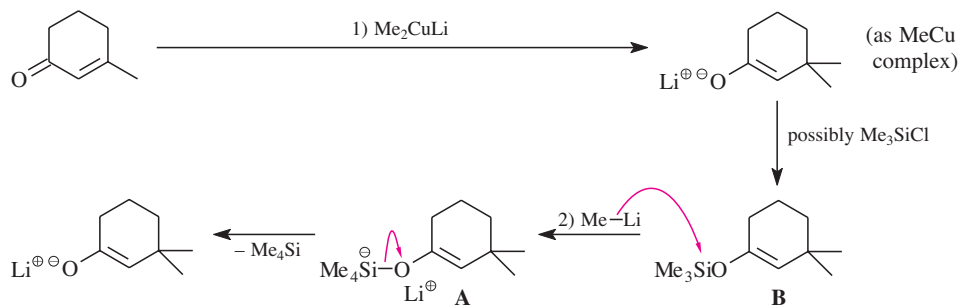
Fig. 13.18. Highly "Z"-selective generation of amide enolate.

13.1.3 Other Methods for the Generation of Enolates

Fig. 13.19. Generation of Cu-containing enolates from Gilman cuprates and their use as substrates for the preparation of Cu-free enolates via silyl enol ethers.

Figures 13.13 and 13.14 demonstrate that deprotonation might afford certain enolates with only *one* regioselectivity. However, there might be other reaction paths that lead to the other regioisomer (Figures 13.19–13.21).

One of these alternative synthetic paths consists of the addition of Gilman cuprates (for preparation, see Figure 10.43) to α,β -unsaturated ketones. In the discussion of this addition



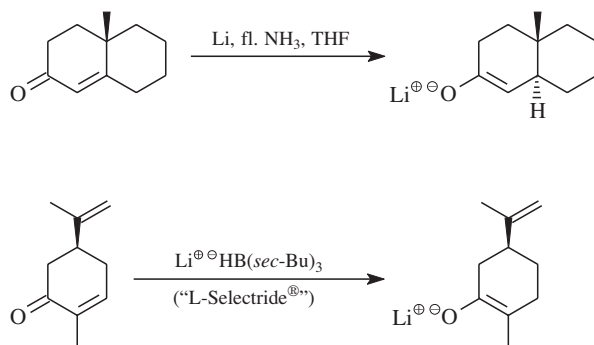


Fig. 13.20. Generation of enolates from α,β -unsaturated ketones via Birch reduction (top line) or by reduction with L-Selectride[®] (bottom line).

mechanism (Figure 10.46), it was pointed out that the enolates formed are associated with CuR . It is assumed that mixed aggregates are formed. As it turns out, the enolate fragments contained in such aggregates are significantly less reactive than CuR -free enolates. It is possible, however, to convert these CuR -containing enolates into the CuR -free lithium enolates. This conversion typically starts with the reaction between the CuR -containing enolate and Me_3SiCl to form a silyl enol ether such as **B** (Figure 13.19). The silyl enol ether reacts with MeLi via the silicate complex **A** (pentacoordinated Si center) to provide the Cu -free enolate.

Another way of obtaining enolates is the Birch reduction of α,β -unsaturated ketones (Figure 13.20, top; mechanism: in analogy to Figure 17.53). The transformation of α,β -unsaturated ketones into enolates using L-Selectride[®] proceeds via a different mechanism, namely the 1,4-addition of a hydride ion, with the result being indistinguishable, though, from the above (Figure 13.20, bottom).

Accordingly, trimethylsilyl enol ethers are enolate precursors (Figure 13.19). Fortunately, they can be prepared in many ways. For instance, silyl enol ethers are produced in the silylation of ammonium enolates. Such ammonium enolates can be generated at higher temperature by partial deprotonation of ketones with triethylamine (Figure 13.21). The incompleteness of this reaction makes this deprotonation reversible. Therefore, the regioselectivity of such deprotonations is subject to thermodynamic control and assures the preferential formation of the more stable enolate. Consequently, upon heating with Me_3SiCl and NEt_3 , α,β -unsaturated ketones are deprotonated to give 1,3-dienolates **A** with the O^- substituent in the 1-position.

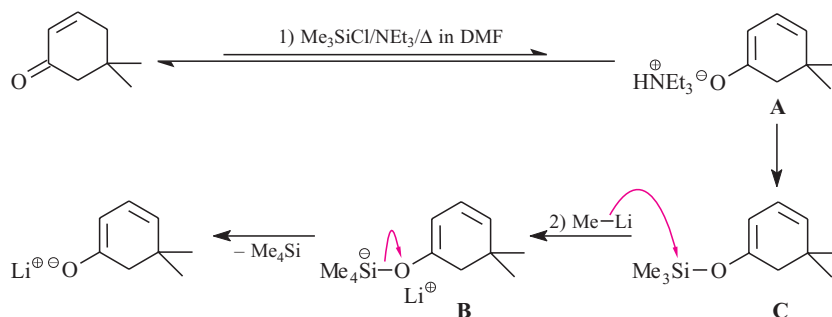


Fig. 13.21. Generation of enolates from silyl enol ethers.

This enolate is more stable than the isomeric 1,3-enolate in which the $\text{O}^\ominus$ substituent is in the 2-position; three resonance forms can be written for the former enolate while only two can be written for the latter. Me_3SiCl then reacts with the dienolate **A** at the oxygen atom. The dienol silyl ether **C** is obtained in this way. Silyl ether **C** reacts with MeLi —in analogy to the reaction **B** $\rightarrow$ **A** shown in Figure 13.19—via the silicate complex **B** to give the desired enolate. Note that the product enolate is not accessible by treatment of cyclohexanone with LDA (Figure 13.14).

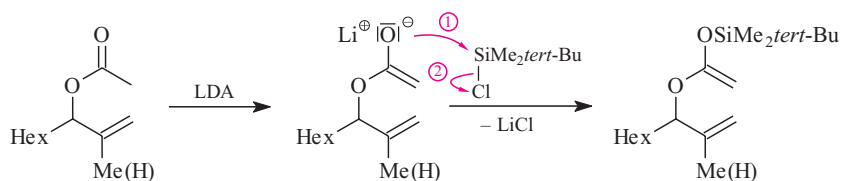
13.1.4 Survey of Reactions between Electrophiles and Enolates and the Issue of Ambidoselectivity

Enolates and aza enolates are so-called **ambident nucleophiles**. This term describes nucleophiles with two nucleophilic centers that are in conjugation with each other. In principle, enolates and aza enolates can react with electrophiles either at the heteroatom or at the carbanionic C atom. Ambidoselectivity occurs if one of these alternative modes of reaction dominates.

Most enolates exhibit an ambidoselectivity toward electrophiles that depends on the electrophile and not on the substrate. The extent of the ambidoselectivity almost always is complete:

- 1) Only very few electrophiles react at the enolate *oxygen* of the enolates of aldehydes, ketones, esters, and amides, and these few electrophiles are
 - silyl chlorides (examples in Figures 13.19, 13.21, and 13.22)

Fig. 13.22. *O*-Silylation of an ester enolate to give a silyl ketene acetal. (The formation of the silicate complex in step 1 of the reaction is plausible but has not yet been proven.)



- Derivatives of sulfonic acids such as the *N*-phenylbisimide of trifluoromethane-sulfonic acid (examples: Figure 13.23, Side Note 13.3 and Figure 16.2). Note that alkenyl triflates are obtained in this way and these are the substrates of a variety of Pd-mediated C,C-coupling reactions (Chapter 16).
 - Derivatives of chlorophosphonic acid such as chlorophosphonic acid diamide (for example, see Figure 13.24) or chlorophosphonic acid esters (Figure 13.25).
- 2) Essentially all other electrophiles react with the enolate *carbon* of the enolates of aldehydes, ketones, esters, and amides (important examples are listed in Table 13.5).

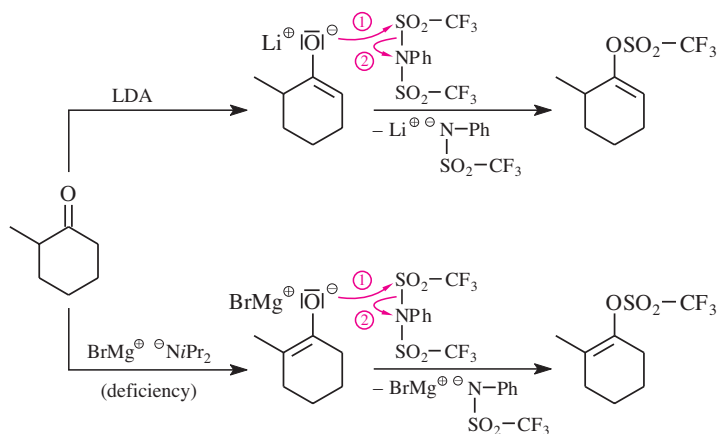


Fig. 13.23. *O*-Sulfonylations of regioisomeric ketone enolates to give an enol triflate (regarding the regiocontrol of the enolate formations cf. the discussion of Figure 13.11):

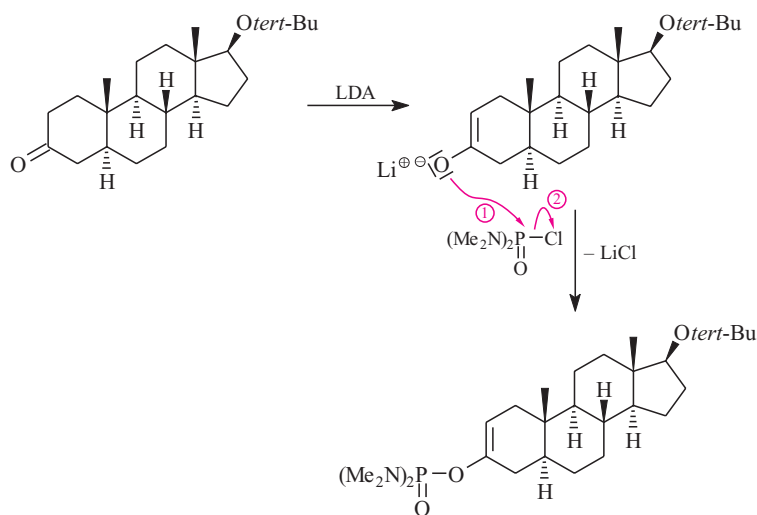


Fig. 13.24. *O*-Phosphorylation of a ketone enolate to afford an enol phosphonamide (see Figure 13.13, bottom row, regarding the regioselectivity of the enolate formation):

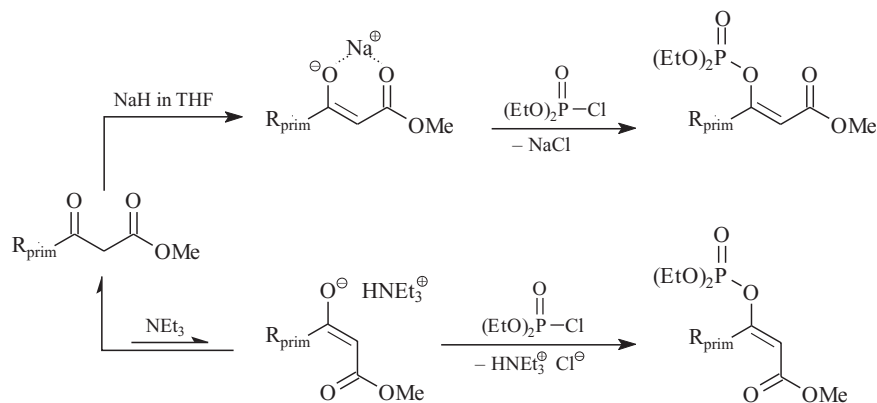
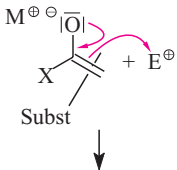
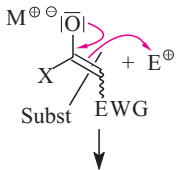
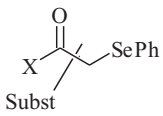
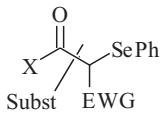
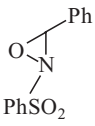
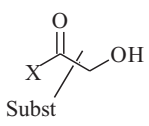
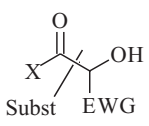
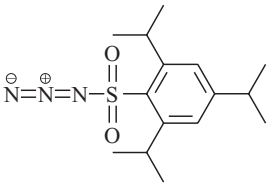
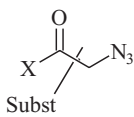
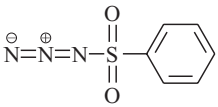
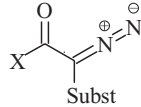
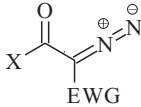
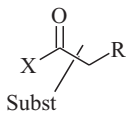
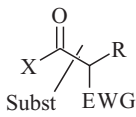
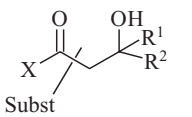
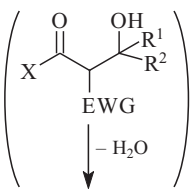
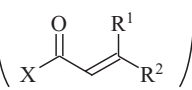
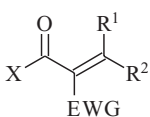
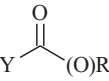
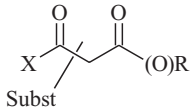
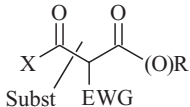
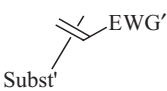
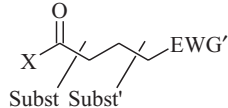
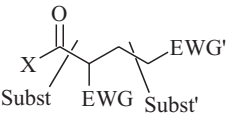


Fig. 13.25. *O*-Phosphorylation of a ketone enolate to afford an enol phosphate (see Figure 13.4 regarding the stereochemistry of the enolate formation).

Tab. 13.5 Electrophiles That React Ambidoselectively at the C Atom of Enolates Derived from Aldehydes, Ketones, Esters, and Amides

Electrophile			For details or applications in synthesis, sec ...
PhSe—SePh			Fig. 4.12
			—
			—
			Fig. 4.29, Fig. 15.42
RX			Section 13.2
			Section 13.3
	(für X = H, Alkyl oder Aryl auch →) 		Section 13.4
			Section 13.5
			Section 13.6

13.2 Alkylation of Quantitatively Prepared Enolates and Aza-enolates; Chain-Elongating Syntheses of Carbonyl Compounds and Carboxylic Acid Derivatives

All the reactions discussed in this section are S_N2 reactions with respect to the alkylating reagent. The most suitable alkylating reagents for enolates and aza enolates are therefore the most reactive alkylating reagents (Section 2.4.4), that is, MeI, $R_{\text{prim}}-X$, and especially $H_2C=CH-CH_2-X$ and $Ar-CH_2-X$ ($X = \text{Hal}, \text{OTs}, \text{OMs}$). Isopropyl bromide and iodide also can alkylate enolates in some instances. Analogous compounds $R_{\text{sec}}-X$ and $R_{\text{tert}}-X$ either do not react with enolates at all or react via E2 eliminations to afford alkenes.

13.2.1 Chain-Elongating Syntheses of Carbonyl Compounds

Acetoacetic Ester Synthesis of Methyl Ketones

An acetoacetic ester is an active-methylene compound and it can be deprotonated (Table 13.1) with one equivalent of NaOEt in EtOH to the sodium enolate **A** (Figure 13.26). As is depicted in Figure 13.26, **A** is *monoalkylated* by butyl bromide. This is possible even though the butylated sodium enolate **B** is already present while the reaction is still under way. The sodium enolate **B** is formed in an equilibrium reaction between not-yet-butylated enolate **A** and the butylation product **C**. **B** represents a nucleophilic alternative to unreacted enolate **A**. However, the butylated enolate **B** is sterically more demanding than the nonbutylated enolate **A**. The first butylation of **A** is thus faster than the second butylation reaction, that is, the butylation of **B**. This reactivity difference is not large enough to cause 100% monobutylation and 0% dibutylation. Still, the main product is the product of monobutylation **C**. Distillation is required to separate the monobutylation product from the dibutylation product and from unreacted substrate.

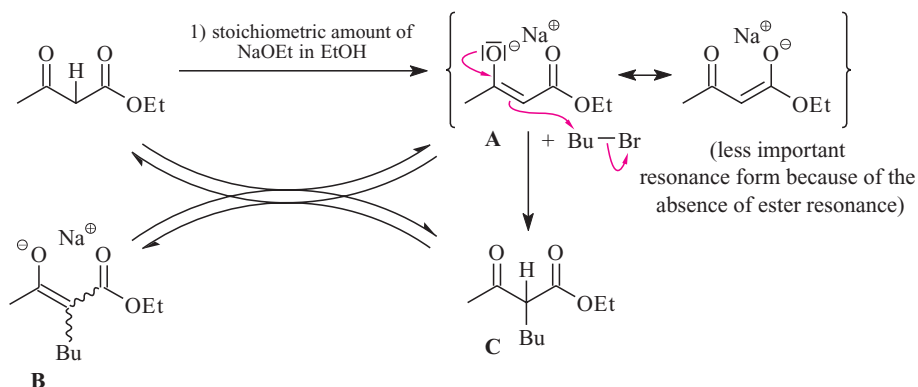


Fig. 13.26. Acetoacetic ester synthesis of methyl ketones I: preparation of an alkylated acetoacetic ester.

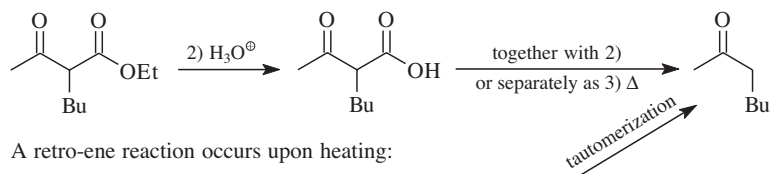
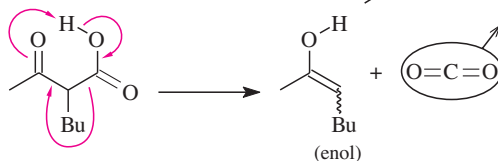


Fig. 13.27. Acetoacetic ester synthesis of methyl ketones II: hydrolysis of the alkylated acetoacetic ester/decarboxylation of the alkylated acetoacetic acid.



The butylated β -ketoester **C** of Figure 13.26 is not the final synthetic target of the *acetoacetic ester synthesis of methyl ketones*. In that context, the β -ketoester **C** is converted into the corresponding β -ketocarboxylic acid via acid-catalyzed hydrolysis (Figure 13.27; for the mechanism, see Figure 6.22). This β -ketocarboxylic acid is then heated either in the same pot or after isolation to effect decarboxylation. The β -ketocarboxylic acid decarboxylates via a cyclic six-membered transition state in which three valence electron pairs are shifted at the same time. The reaction product is an enol, which isomerizes immediately to a ketone (to phenyl methyl ketone in the specific example shown).

Other β -ketoesters can be converted into other ketones under the reaction conditions of the acetoacetic ester synthesis and with the same kinds of reactions as are shown in Figures 13.26 and 13.27. Two examples are provided in Figures 13.28 and 13.29. These β -ketoesters also are first converted into sodium enolates by reaction with NaOEt in EtOH, and the enolates are then reacted with alkylating reagents. The reaction shown in Figure 13.28 employs a β -ketoester that can be synthesized by a Claisen condensation (see Figure 13.57). The alkylating reagent employed in Figure 13.28 is bifunctional and reacts at both its reactive centers, thereby cross-linking two originally separate β -ketoester molecules. The new bis(β -ketoester) is hydrolyzed to afford a bis(β -ketocarboxylic acid), a twofold decarboxylation of which occurs subsequently according to the mechanism depicted in Figure 13.27. The reaction sequence of Figure 13.28 represents the synthesis of a diketone and illustrates the value of the acetoacetic ester synthesis to access a variety of alkyl ketones.

β -Ketoesters derived from cyclic five- or six-membered ketones are conveniently accessible via the Dieckmann condensation (for example, see Figure 13.58). Such β -ketoesters can be converted into cyclic ketones under the reaction conditions of the acetoacetic ester synthesis. Step 1 in Figure 13.29 shows how such a β -ketoester is allylated at its activated position. The allylation product **A** could be converted into the alkylated ketone **B** via a sequence comprising hydrolysis and decarboxylation. There exists, however, an alternative to achieve the special transformation of β -keto *methyl* esters ketones. It is shown in Figure 13.29. This alternative is based on the knowledge that good nucleophiles like the iodide ion or the phenylthiolate ion undergo an S_N2 reaction at the methyl group of the β -ketoester. The reaction is carried out at temperatures above 100 °C. The β -ketocarboxylate leaving group decarboxylates immediately under these conditions, producing the enolate of the desired ketone. This enolate is protonated to the ketone either by acidic contaminants of the solvent or later, during aqueous workup.

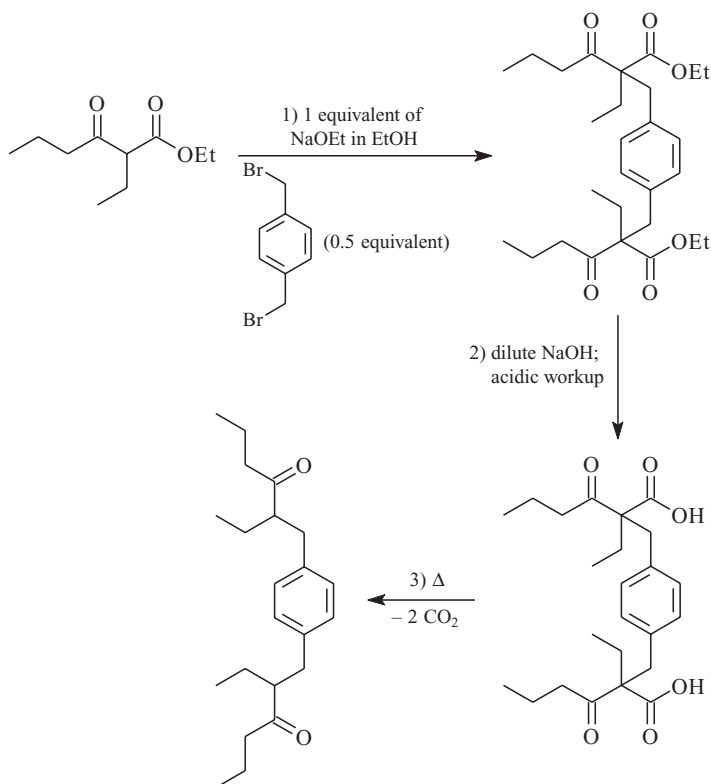


Fig. 13.28. Synthesis of complicated ketones in analogy to the acetoacetic ester synthesis I: generation of a diketone.

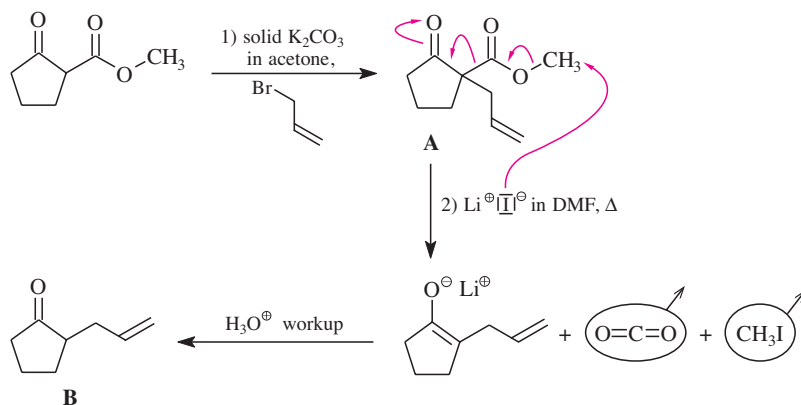


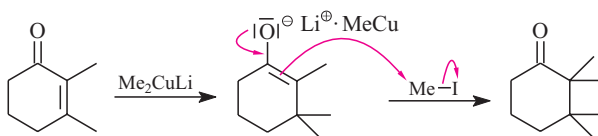
Fig. 13.29. Synthesis of complicated ketones in analogy to the acetoacetic ester synthesis II: generation of a cyclic ketone. In the first step, the β -ketoester is alkylated at its activated position. In the second step, the β -ketoester is treated with $\text{Li}^+ \text{I}^-$. $\text{S}_{\text{N}}2$ reaction of the iodide at the methyl group generates the β -ketocarboxylate ion as the leaving group. The β -ketocarboxylate decarboxylates immediately under the reaction conditions (temperature above 100°C) and yields the enolate of a ketone.

Alkylation of Ketone Enolates

Ester-substituted ketone enolates are stabilized, and these enolates can be alkylated (acetoacetic ester synthesis). Alkylation is, however, also possible for enolates that are not stabilized. In the case of the stabilized enolates, the alkylated ketones are formed in two or three steps, while the nonstabilized enolates afford the alkylated ketones in one step. However, the preparation of nonstabilized ketone enolates requires more aggressive reagents than the ones employed in the acetoacetic ester synthesis.

Figure 13.30 shows that even sterically hindered ketone enolates can be alkylated. The carbon atom in the β -position relative to the carbonyl carbon of an α,β -dialkylated α,β -unsaturated ketone can be converted into a quaternary C atom via 1,4-addition of an Gilman cuprate (for conceivable mechanisms, see Figure 10.46). As can be seen, a subsequent alkylation allows for the construction of another quaternary C atom in the α -position even though it is immediately adjacent to the quaternary center generated initially in the β -position.

Fig. 13.30. 1,4-Addition plus enolate alkylation—a one-pot process for the α - and β -functionalization of α,β -unsaturated ketones. Two quaternary C atoms can be constructed via addition of a Gilman reagent and subsequent alkylation with MeI.



Diastereoselective alkylations of enolates may occur if the enolate is chiral, i.e., surrounded by diastereotopic half-spaces. This was discussed in Section 3.4.1. In general, it is difficult to predict the preferred side of reaction of the alkylating reagent on such enolates. For cyclic enolates the situation is relatively simple, because these enolates always react from the less-hindered side. Hence, for the methylation of the enolate in Figure 13.31, the reaction with methyl iodide occurs equatorially, that is, from the side that is opposite to the axially oriented methyl group at the bridgehead.

Bisenolates such as compound **A** derived from the acetoacetic ester in Figure 13.32 react with one equivalent of alkylating reagent in a regioselective fashion to give the enolate **C**. This could be the result of product development control, since the isomeric alkylation product

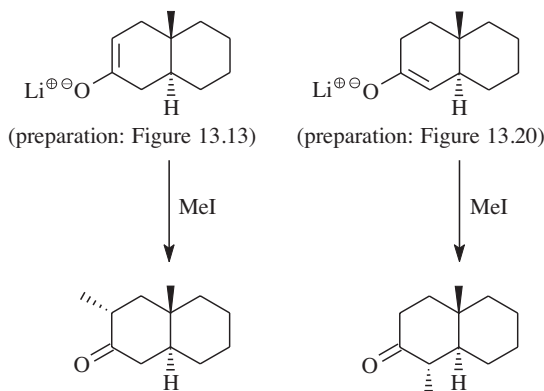


Fig. 13.31. Alkylation of a chiral ketone enolate. The reaction with methyl iodide occurs preferentially from the side opposite to the side of the axially oriented methyl group at the bridgehead carbon.

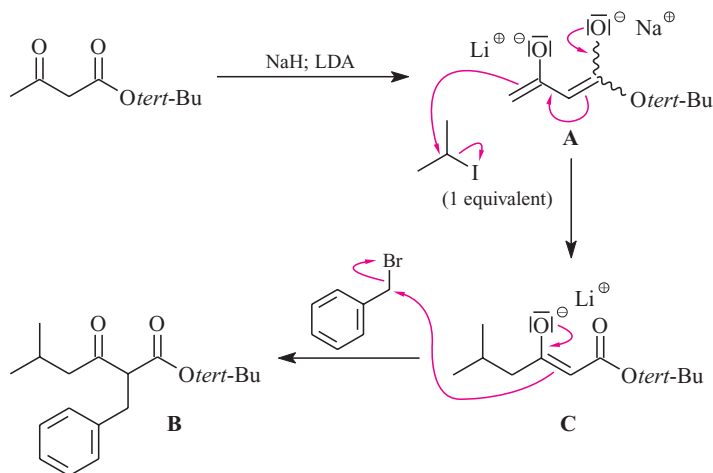


Fig. 13.32. Regiocontrolled bisalkylation of a bisenolate. The enolate **C** is formed with one equivalent of the alkylating reagent. **C** can be alkylated again, and **B** is formed in that way.

would be less stable. The enolate **C** resembles the nucleophile of the acetoacetic ester synthesis (Figure 13.26) and can be alkylated likewise. One can employ different alkylating reagents in the first and second alkylations to obtain a β -ketoester **B** with two new substituents. This product may feature a substitution pattern that could not be constructed via a Claisen condensation (Figures 13.57 and 13.59), as is true for the example presented in Figure 13.32.

Alkylation of Lithiated Aldimines and Lithiated Hydrazones

The quantitative conversion of aldehydes into enolates with lithium amides hardly ever succeeds because an aldol reaction (cf. Section 13.1.2) occurs while the deprotonation with LDA is in progress. Aldol additions also occur upon conversion of a small fraction of the aldehyde into the enolate with a weak base (Section 13.3.1). Hence, it is generally impossible to alkylate an aldehyde without the simultaneous occurrence of an aldol addition. There is only one exception: certain α -branched aldehydes can be deprotonated to their enolates in equilibrium reactions, and these enolates can be reacted with alkylating reagents to obtain tertiary aldehydes.

Since very few aldehydes can be converted into an α -alkylated aldehyde directly, there are some “detours” available. Figure 13.33 shows such a detour for the conversion of an aldehyde (without α -branching) into an α -alkylated aldehyde. First, the aldehyde is reacted with a primary amine—cyclohexyl amine is frequently used—to form the corresponding aldimine. Aldimines can be deprotonated with LDA or *sec*-BuLi to give azaenolates. The success of the deprotonation with *sec*-BuLi demonstrates that aldimines are much weaker electrophiles than aldehydes: *sec*-BuLi would immediately add to an aldehyde.

The obviously low electrophilicity of the C=N double bonds of aldimines precludes the addition of the azaenolate to remaining aldimine in the course of aldimine deprotonation. The aldimine enolate is obtained quantitatively and then reacted with the alkylating reagent. This step results cleanly in the desired product, again because of the low electrophilicity of imines: as the alkylation progresses, azaenolate and the alkylation product coexist without reacting with each other, no aldol-type reaction, no proton transfer. *All* the azaenolate is thus converted

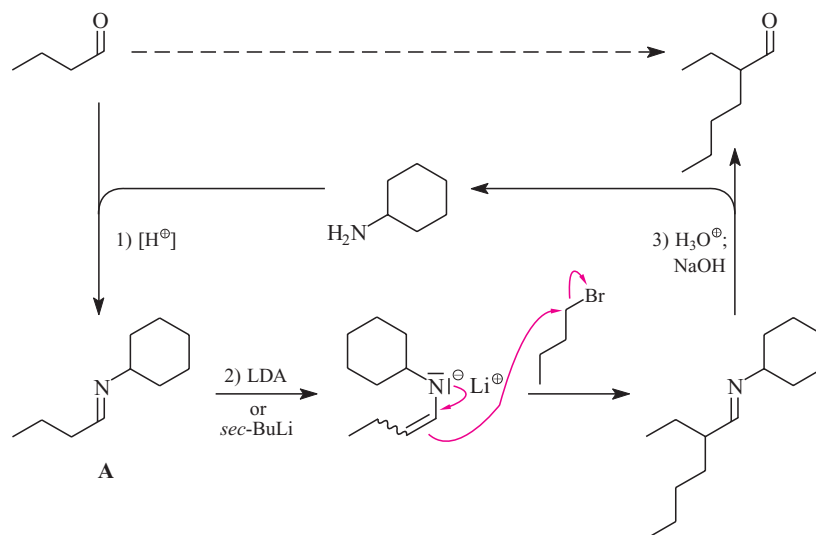


Fig. 13.33. α -Alkylation of an aldehyde via an imine derivative.

into the alkylated aldimine. In step 3 of the sequence of Figure 13.33, the imine is subjected to an acid-catalyzed hydrolysis, and the alkylated aldehyde results.

The formation of the alkylated aldimine in Figure 13.33 involves the generation of a stereo-center, yet without stereocontrol. The aldehyde derived from this aldimine consequently is obtained as a racemate. Figure 13.34 shows how a variation of this procedure allows for the enantioselective generation of the same aldehyde.

The “aldimine” of Figure 13.34 is a chiral and enantiomerically pure aldehydrazone **C**. This hydrazone is obtained by condensation of the aldehyde to be alkylated, and an enantiomerically pure hydrazine **A**, the *S*-proline derivative **S**-aminoprolinol methyl ether (SAMP). The hydrazone **C** derived from aldehyde **A** is called the SAMP hydrazone, and the entire reaction sequence of Figure 13.34 is the **Enders SAMP alkylation**. The reaction of the aldehydrazone **C** with LDA results in the chemoselective formation of an azaenolate **D**, as in the case of the analogous aldimine **A** of Figure 13.33. The $C=C$ double bond of the azaenolate **D** is *trans*-configured. This selectivity is reminiscent of the *E*-preference in the deprotonation of sterically unhindered aliphatic ketones to ketone enolates and, in fact, the origin is the same: both deprotonations occur via six-membered ring transition states with chair conformations. The transition state structure with the least steric interactions is preferred in both cases. It is the one that features the C atom in the β -position of the C,H acid in the pseudo-equatorial orientation.

The $N-Li$ bond of azaenolate **D** lies outside the plane of the enolate. The structure created via chelation is a rigid polycyclic species. In this structure, the 4 and 5 carbons of the pyrrolidine ring block one side of the azaenolate, resulting in facial selectivity during alkylation. The alkylation product **E** is formed preferentially with the *S*-configuration shown. Only traces of the *R*-configured product are formed.

The main and trace products are diastereoisomers, which can be completely separated by using chromatography. The separation affords a diastereomerically and enantiomerically pure SAMP hydrazone **E**.

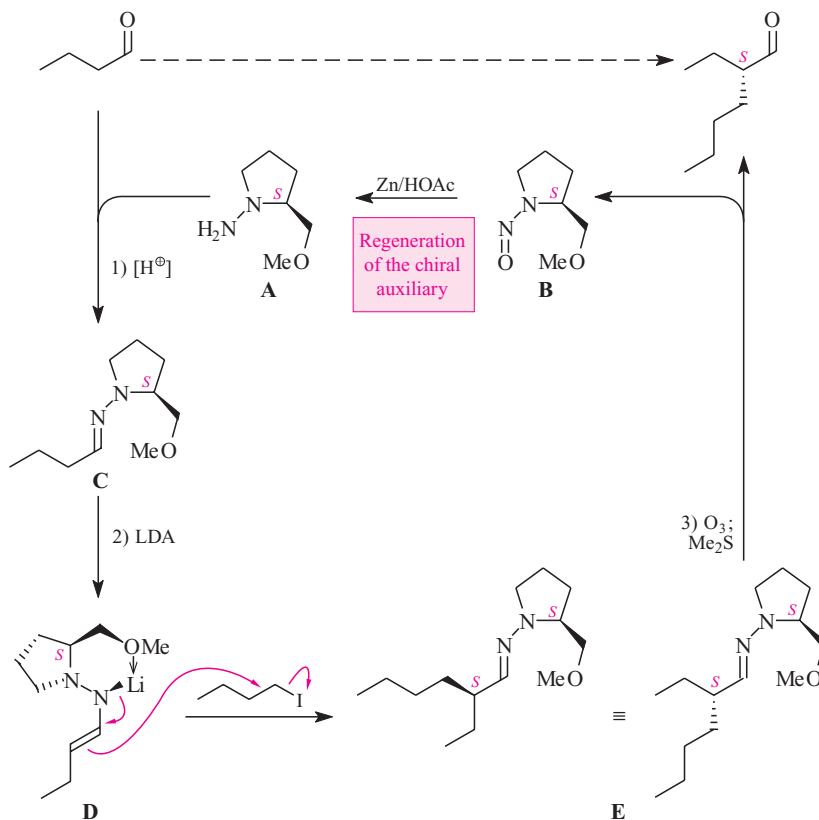


Fig. 13.34. Enders' SAMP method for the generation of enantiomerically pure α -alkylated carbonyl compounds; SAMP, (S)-aminoprolinol methyl ether = (S)-2-methoxymethyl-1-pyrrolidine, or S-1-amino-2-(methoxymethyl)pyrrolidine (which is the name according to IUPAC rules).

In the third step of the reaction sequence depicted in Figure 13.34, the hydrazone **E** is converted into the desired sterically homogeneous aldehyde. This transformation can be achieved, for example, by ozonolysis of the $\text{C}=\text{N}$ double bond. One of the products of ozonolysis is the desired enantiomerically pure α -butylated butanal. The other product of the ozonolysis also is valuable, since it is the nitroso derivative **B** of reagent **A**. The $\text{N}=\text{O}$ group of **B** can be reduced to give an amino group to regenerate **A** from **B**. The possibility of recycling valuable chiral auxiliaries greatly enhances the attractiveness of any method for asymmetric synthesis.

The strategy of Figure 13.34 also is suitable for the synthesis of enantiomerically pure α -alkylated ketones. Figure 13.35 shows a procedure for the synthesis of the S-configured 6-methyl-2-cyclohexenone. The desired S-configuration is achieved with the help of a so-called RAMP hydrazone **C**, which is a derivative of the R-aminoprolinol methyl ether **A**. In step 2 of the RAMP procedure, hydrazone **C** is deprotonated with LDA to give the azaenolate **D**. This deprotonation occurs with the same regioselectivity as the formation of the kinetic enolate **A** in the reaction of cyclohexenone with LDA. The common regioselectivities have the same origin. Deprotonations with LDA prefer cyclic transition state structures that are six-membered rings and include the heteroatom of the acidifying $\text{C}=\text{X}$ double bond ($\text{X} = \text{O}, \text{N}$).

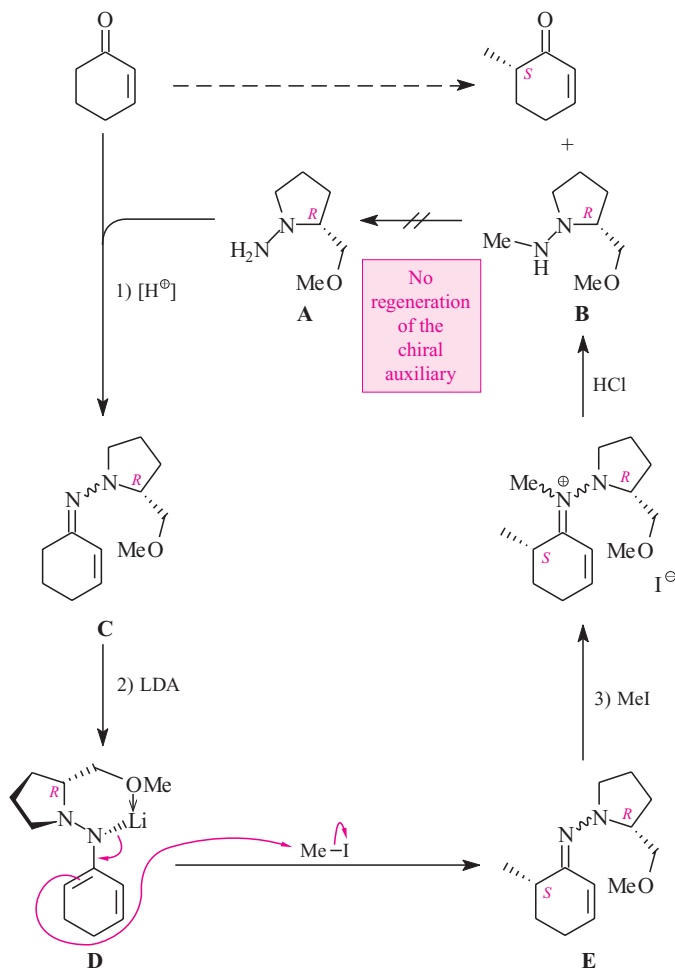


Fig. 13.35. Enders' RAMP method for the generation of enantiomerically pure α -alkylated carbonyl compounds; RAMP, (*R*)-aminoprolinol methyl ether or *R*-1-amino-2-(methoxymethyl)pyrrolidine. While hydrazones derived from ketones, such as compound **E**, are methylated at the doubly bound nitrogen, the methylation of the corresponding aldehyde-derived hydrazones preferentially occurs at the nitrogen atom of the heterocycle.

As with the azaenolate of Figure 13.34, the azaenolate **D** in Figure 13.35 contains a chelate. As before a preferred conformation of the azaenolate and a rigid structure results in high diastereoselectivity during alkylation. The kethdrazone **E** is formed with high diastereoselectivity and, after chromatographic separation, it is obtained in 100% stereochemically pure form.

To complete the reaction sequence of Figure 13.35, the desired alkylated ketone needs to be released from the kethdrazone. Ozonolysis cannot be used in the present case. Ozonolysis would cleave not only the $\text{C}=\text{N}$ double bond but also the $\text{C}=\text{C}$ double bond. Another method must therefore be chosen. The kethdrazone is alkylated to give an iminium ion. The iminium ion is much more easily hydrolyzed than the hydrazone itself, and mild hydrolysis yields the desired *S*-enantiomer of 6-methyl-2-cyclohexenone. The other product of hydrolysis is a RAMP derivative. This RAMP derivative carries a methyl group at the N atom and cannot be recycled to the enantiomerically pure chiral auxiliary **A** that was employed initially.

13.2.2 Chain-Elongating Syntheses of Carboxylic Acid Derivatives

Malonic Ester Synthesis of Substituted Acetic Acids

Malonic ester syntheses are the classical analog of acetoacetic ester syntheses of methyl ketones. Neither case requires the use of an amide base for the enolate formation, and in both cases alkoxides suffice to deprotonate the substrate completely. Malonic esters are active-methylene compounds just like acetoacetic ester and its derivatives.

One equivalent of NaOEt in EtOH deprotonates diethyl malonate completely to give the sodium enolate **A** (Figure 13.36). This enolate is monoalkylated upon addition of an alkylating reagent such as BuBr, and a substituted malonic ester **C** is formed. *During* the alkylation reaction, the substituted malonic ester **C** reacts to a certain extent with some of the enolate **A**, resulting in the butylated enolate **B** and unsubstituted neutral malonic ester. It is for this reason that the reaction mixture contains *two* nucleophiles—the original enolate **A** and the butylated enolate **B**. The alkylation of **A** with butyl bromide is much faster than that of **B**, since **A** is less sterically hindered than **B**. The main product is therefore the product of monoalkylation. Distillation can be used to separate the main product from small amounts of the product of dialkylation.

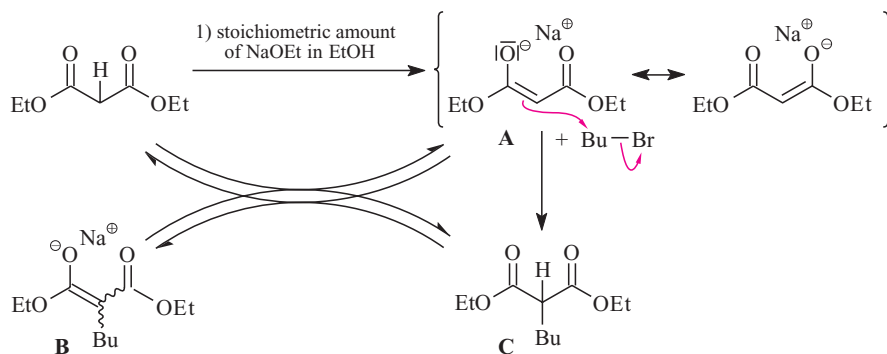


Fig. 13.36. Malonic ester synthesis of alkylated acetic acids I: preparation of alkylated malonic esters.

The butylated malonic ester **C** of Figure 13.36 is not the actual synthetic target of the *malonic ester synthesis of substituted acetic acids*. Instead, **C** is subjected to further transformations as shown in Figure 13.37. Ester **C** first is hydrolyzed with acid catalysis to afford the corresponding alkylated malonic acid (for the mechanism, see Figure 6.22). The alkylated malonic acid then is heated either directly in the hydrolysis mixture or after it has been isolated. This heating leads to decarboxylation. The mechanism of this decarboxylation resembles the mechanism of the decarboxylation of β -ketocarboxylic acids (see Figure 13.27), and it involves a cyclic, six-membered ring transition state in which three valence electron pairs are shifted at the same time. The primary products of this decomposition are carbon dioxide and the enol of the carboxylic acid. The enol immediately tautomerizes to give the carboxylic acid. This carboxylic acid—an alkylated acetic acid—represents the typical final product of a malonic ester synthesis.

Both acidic H atoms of a malonic ester can be replaced by alkyl groups. These dialkylated malonic esters are formed by successively removing the acidic protons with sodium alkoxide

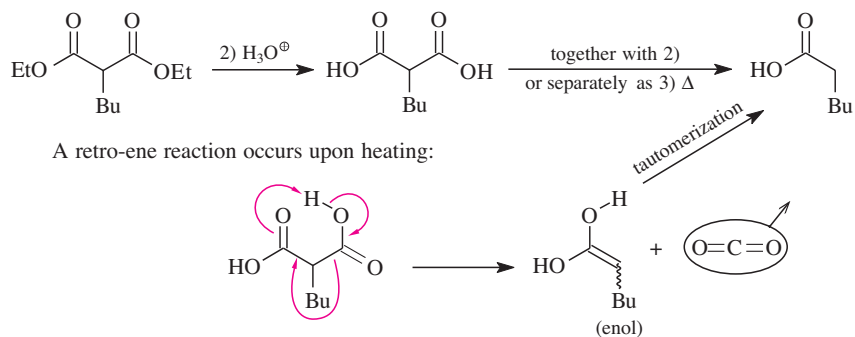


Fig. 13.37. Malonic ester synthesis of alkylated acetic acids II: hydrolysis and decarboxylation of the alkylated malonic ester.

and treatment of the enolates with an alkylating reagent. The subsequent hydrolysis and decarboxylation of these dialkylated malonic esters affords α,α -dialkylated acetic acids as another class of products accessible via the malonic ester synthesis.

If one employs *monofunctional* alkylating reagents in the alkylation of malonic esters, one obtains dialkylated acetic acids in which the two α -alkyl groups are not connected with each other. On the other hand, if one employs a *difunctional* alkylating reagent, the dialkylated acetic acid synthesized is a cycloalkane carboxylic acid. This is the case when the second alkylation occurs in an intramolecular instead of an intermolecular fashion. Over 100 years ago, Perkin employed this principle and succeeded at the synthesis of cyclopropane carboxylic acid (Figure 13.38), the first cyclopropane derivative ever made. Until that time, the synthesis of a cyclopropane was thought to be impossible because of its high Baeyer strain (“angular strain”).

Figure 13.39 shows that malonic ester syntheses can also lead to acetic acid derivatives with a heteroatom in the α -position. The benzylation of (acetamido)malonic acid diethyl ester

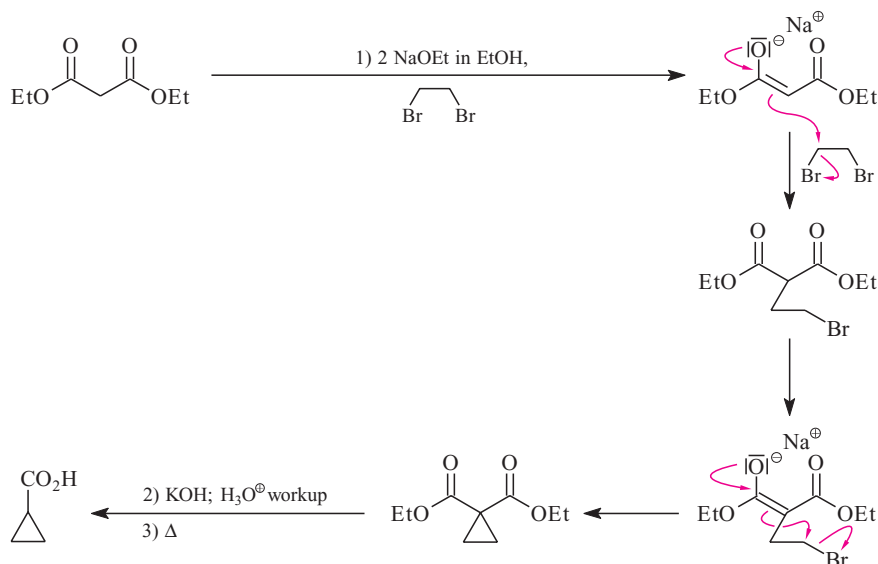


Fig. 13.38. Perkin's first cyclopropane synthesis via a malonic ester synthesis.

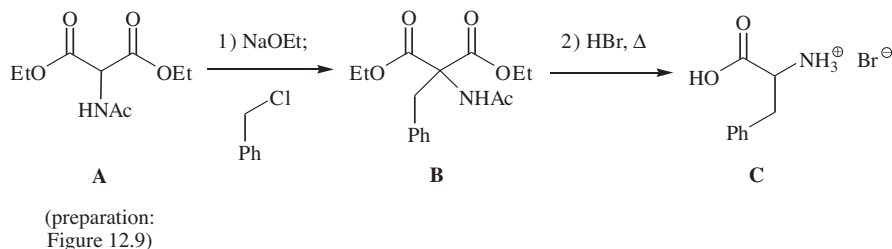


Fig. 13.39. Synthesis of an α -amino acid through malonic ester synthesis, here using the example of phenylalanine (in the form of its hydrobromide).

(**A**) produces the disubstituted malonic ester **B**. Hydrobromic acid hydrolyzes the ester functions of **B**—which, upon heating, is followed by the usual decarboxylation—as well as the acetamido group. The reaction product is the hydrobromide **C** of the α -amino acid phenylalanine.

Alkylation of Ester Enolates

Ester enolates are generated by the reaction between an ester and LDA at -78°C in THF, enolate formation usually being “*E*”-selective (Figure 13.16). The “*Z*”-enolate is obtained in analogous deprotonations of esters that carry an alkoxy group in the α -position relative to the $\text{C}=\text{O}$ double bond (Figure 13.40). Product development control is the reason for the latter stereochemical outcome: the “*Z*”-enolate and the lithium form an energetically favored five-membered chelate ring.

Many ester enolates can be alkylated, and this is irrespective of whether they are “*E*”- or “*Z*”-configured. The example of Figure 13.40 shows the butylation of a “*Z*”-configured α -oxygenated ester enolate. The butylated ester **B** is both a benzyl ester and benzyl ether. The two benzylic $\text{C}-\text{O}$ bonds in this compound can be removed subsequently by way of hydrogenolysis (see Figure 17.51). Overall, this reaction sequence represents a method that allows for the elongation of alkylating agents to α -hydroxycarboxylic acids **A**.

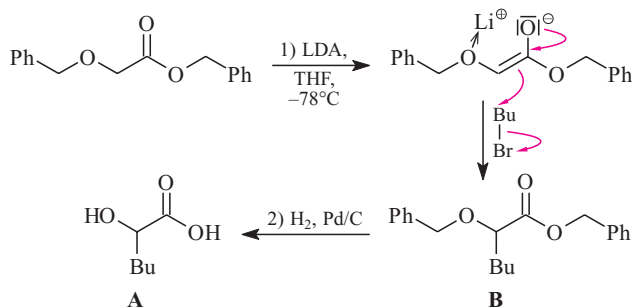


Fig. 13.40. Alkylation of an ester enolate for the preparation of an α -hydroxycarboxylic acid (for the preparation of enantiomerically pure α -hydroxy carboxylic acid through alkylation of an enantiomerically pure ester enolate cf. Figure 13.41). The initially formed benzyl ester **B** contains two benzylic $\text{C}-\text{O}$ bonds, which can be cleaved by means of hydrogenolysis.

Diastereoselective Alkylation of Chiral Ester and Amide Enolates: Generation of Enantiomerically Pure Carboxylic Acids with Chiral Centers in the α -Position

The alkylation of an *achiral* ester enolate to give an α -alkylated carboxylic ester can generate a new stereocenter. If so, this stereocenter is formed without stereocontrol. For such a sub-

strate, the two half-spaces above and below the enolate plane are enantiotopic. Consequently, the reaction of an achiral alkylating reagent occurs from both faces with the same rate constant (cf. discussion of Section 3.4.1). Thus, one obtains the alkylated ester as a racemic mixture. In the alkylation of an achiral amide enolate, the outcome is entirely analogous: the resulting α -alkylated amide either is achiral or a racemate.

The situation changes when chiral ester enolates or chiral amide enolates are alkylated. There, the half-spaces on the two sides of the enolate planes of the substrates are diastereotopic, and alkylating reagents can react from one of the sides selectively (see discussion in Section 3.4.1). Stereogenic alkylations of such enolates therefore may take place diastereoselectively.

Side Note 13.4 presents the diastereoselective alkylation of a very special ester enolate in which one can easily understand what the stereocontrol observed is based upon. However, only *very* specific carboxylic acid derivatives are made accessible by those alkylations. Much more broadly applicable diastereoselective alkylations of chiral ester or amide enolates will be introduced in Figures 13.42 and 13.43. Figure 13.42 shows alkylations of a propionic acid ester—derived from an enantiomerically pure chiral alcohol—via the “*E*”- and “*Z*”-enolate. Figure 13.43 illustrates alkylations of two propionic acid amides, where in each case the N atom is part of an enantiomerically pure heterocycle, proceeding via the respective *Z*-configured amide enolates.

Side Note 13.4.
An Enolate Alkylation
with “Self-Reproduction
of Chirality”

Compound **A** (Figure 13.41) was introduced in Section 9.2.2 as “a kind of *O,O* acetal.” Here you will see how asymmetric synthesis may take advantage of the fact that the “acetal” carbon atom of this compound is a stereocenter that uniformly displays the absolute configuration given here. In the reaction with the base LDA, the compound **A** acts as an ester, i.e., it undergoes deprotonation to the ester enolate **B**. If the latter is alkylated, the bulky *tert*-butyl

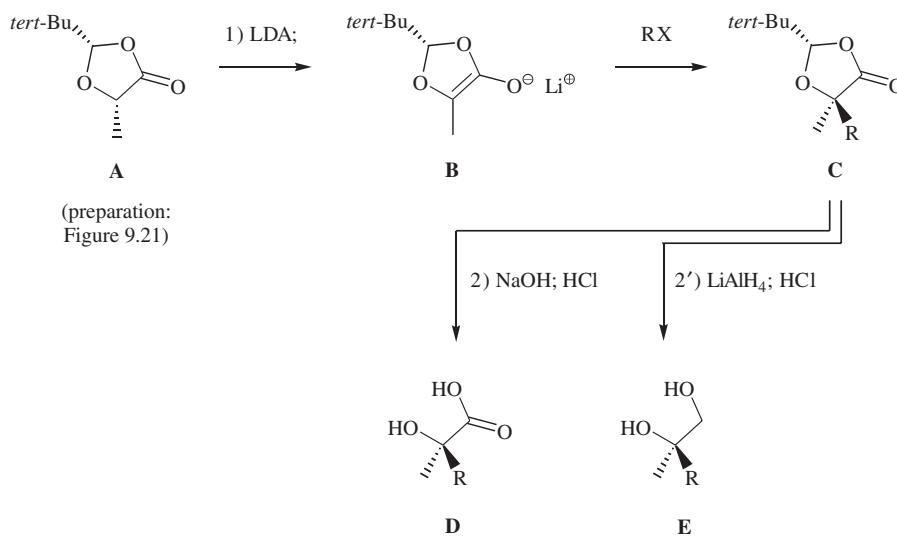


Fig. 13.41. Alkylation of an enantiomerically pure lactone enolate (**B**) for the preparation of enantiomerically pure α -alkyl- α -hydroxycarboxylic acids and enantiomerically pure 1,2-diols, respectively. In the lactone **C** the carboxyl group may react with water or with a hydride donor. In any case, the leaving group released is a hemiacetal anion that decomposes to pivalaldehyde and the α -alkyl- α -hydroxycarboxylic acid **D** or the enantiomerically pure 1,2-diol **E**.

residue at the “acetal” carbon atom ensures that the alkylating agent exclusively approaches the enolate from the opposite side of the molecule. This is why the alkylation products **C** are obtained with high diastereoselectivity. They may then be hydrolyzed to yield the enantiomerically pure α -hydroxy carboxylic acid **D** (or be reduced to the enantiomerically pure 1,2-diols **E**).

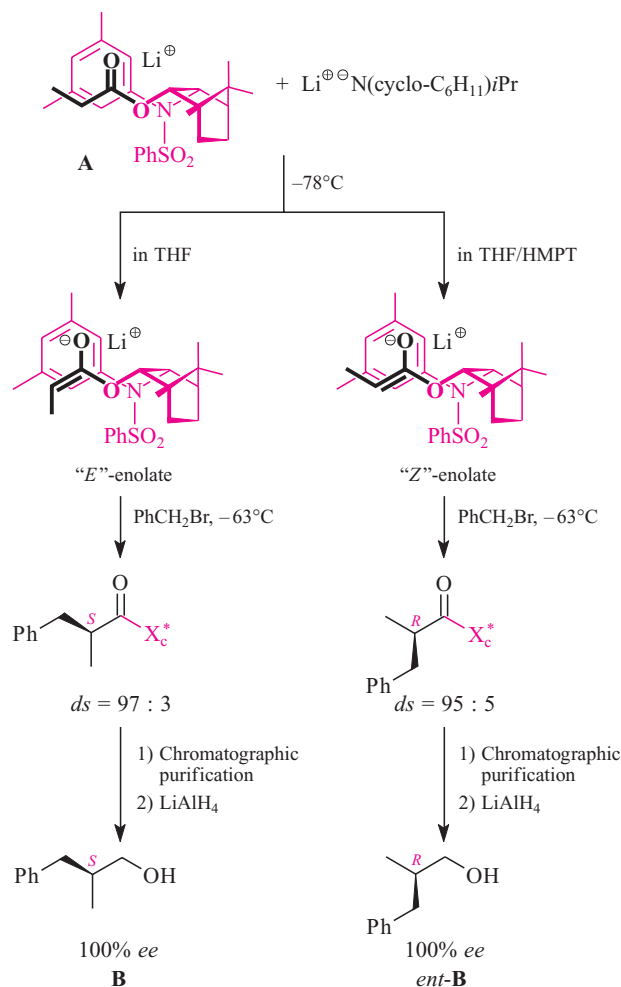
The lactic acid, which initiates the reaction sequence *S*-lactic acid $\rightarrow$ “acetal” **A** $\rightarrow$ enolate **B** $\rightarrow$ “acetal” **C** $\rightarrow$ *R* hydroxycarboxylic acid **D**, has a stereocenter with a well-defined absolute configuration that is destroyed in the enolate intermediate **B**, but finally restored in the hydroxycarboxylic acid **C**. This is why the principle concerning the stereochemistry of the key step (“acetal” **A** $\rightarrow$ enolate **B** $\rightarrow$ “acetal” **C**) is referred to as the “self-reproduction of chirality.”

Both enantiomers of camphor are commercially available. One of the camphor enantiomers can be converted into the enantiomerically pure, chiral alcohol contained in the propionic acid ester **A** in five steps. Ester **A** is employed in the **Helmchen synthesis** of Figure 13.42. The enantiomer of this ester can be obtained from the other camphor isomer. Each of these esters can be alkylated with high diastereoselectivity, as shown in Figure 13.42 for two alkylations of ester **A**. The highest selectivities are achieved if the ester is deprotonated at -78°C with lithium cyclohexyl isopropyl amide. This reagent is an amide base with a somewhat higher steric demand than LDA. The deprotonation with this reagent is a stereogenic reaction just like the LDA deprotonation of the propionic acid esters of Figures 13.16 and 13.17, and the same stereoselectivities result: in pure THF propionic acid ester **A** yields the “*E*”-enolate with high diastereoselectivity (Figure 13.42, left). In THF/HMPA mixtures, on the other hand, the reaction of the same propionic acid ester **A** with the same base occurs with complete reversal of stereochemistry, i.e., yields the “*Z*”-enolate (Figure 13.42, right). Accordingly, THF/HMPA mixtures have the same effect on the stereoselectivity of ester enolate formation as we discussed for THF/DMPU mixtures in the context of Figure 13.17. Fortunately, in *this* case the HMPA (carcinogenic) can be replaced by DMPU (not carcinogenic). This option was not known at the time when the investigations described in Figure 13.42 were carried out.

The chiral alcohol group in Figure 13.42 was chosen to differentiate as much as possible between the half-spaces on both sides of the enolate plane. One half-space should be left entirely unhindered while the other should be blocked as completely as possible. The reaction of the alkylating reagent then occurs preferentially, and in the ideal case exclusively, from the unhindered half-space. The stereostructures of the two ester enolates of Figure 13.42 therefore model the enolate moieties of the (early!) transition states of these alkylations. The part of the transition state structure that contains the alkylating reagent is not shown.

It is assumed that the preferred conformation of the substructure $\text{C}=\text{C}-\text{O}-\text{C}$ of the “*E*”-configured ester enolate in the preferred transition state of the alkylation is that depicted in the center of the left-hand column of Figure 13.42. In the projection shown, the alkylating reagent reacts with the enolate from the front side for the reasons just stated. The reaction occurs with a diastereoselectivity of 97:3. Chromatography allows for the complete separation of the main diastereoisomer from the minor diastereoisomer. Reduction of the main diastereoisomer (for the mechanism, see Section 17.4.3) affords the alcohol **B**, a derivative of *S*- α -benzyl propionic acid, with 100% *ee*. Hydrolysis of the benzylated esters without iso-

Fig. 13.42. Helmchen synthesis of enantiomerically pure α -alkylated carboxylic acids. The deprotonation of the propionic acid ester results in the “*E*”-enolate in the solvent THF and in the “*Z*”-enolate in the solvent mixture THF/HMPA. In these projections, both enolates react preferentially from the front. The “*E*”-enolate results in a 97:3 mixture of *S*- and *R*-configured α -benzylpropionic acid esters (X_c^* marks the chiral alkoxide group), while the “*Z*”-enolate results in a 5:95 mixture. Chromatographic separation and reduction of the $C(=O)-X_c^*$ groups afford alcohol **B** with 100% *ee* from the “*E*”-enolate and alcohol *ent*-**B** with 100% *ee* from the “*Z*”-enolate.



merization is impossible, however, so that optically active α -benzylpropionic acids cannot be obtained in this way. The center of the right-hand column of Figure 13.42 shows the assumed stereostructure of the substructure $\text{C}=\text{C}-\text{O}-\text{C}$ of the “*Z*”-configured ester enolate in the preferred transition state of the alkylation. In the chosen projection, the alkylating reagent again reacts from the front side. With a diastereoselectivity of 95:5, the benzylated ester that was the minor product in the alkylation of the “*E*”-configured ester enolate is now formed as the main product. Again, chromatography allows one to separate the minor from the major diastereoisomer. The main product is then reduced without any isomerization to afford the alcohol *ent*-**B** with an *ee* value of 100%.

Why are the benzylated esters of Figure 13.42 not obtained with higher diastereoselectivities than 95 or 97%, respectively? One possible reason lies in the failure of both the “*E*”- and the “*Z*”-enolate to form with perfect stereocontrol. Small contaminations of these enolates by just 5 or 3% of the corresponding enolate with the opposite configuration would explain the

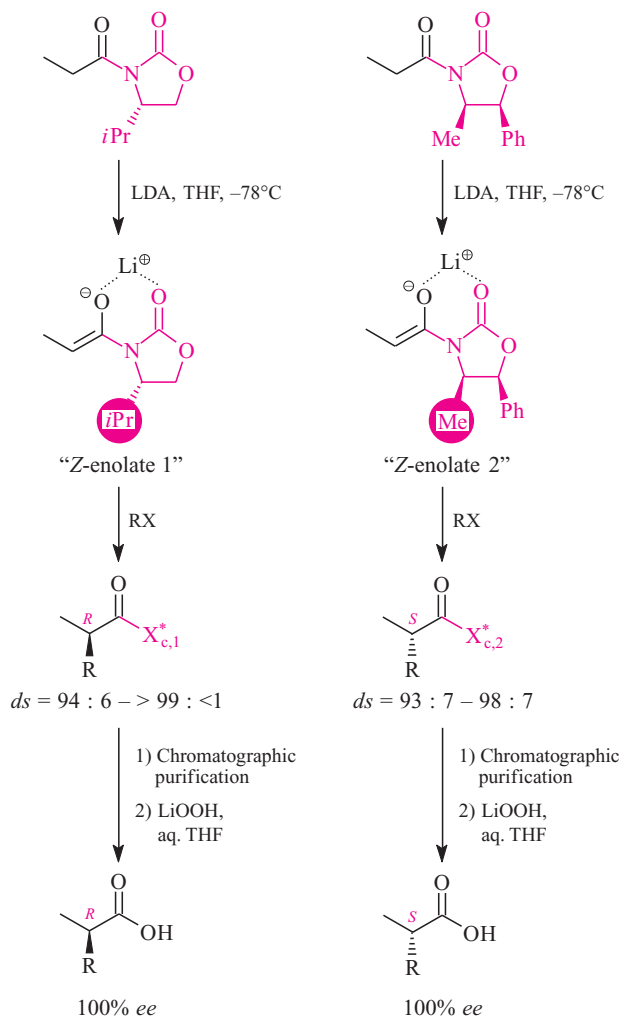


Fig. 13.43. Evans synthesis of enantiomerically pure α -alkylated carboxylic acids. The amides are derived from oxazolidinones and yield "Z"-enolates with high stereoselectivity. The alkylating agent reacts in both cases from the side that is opposite to the side of the substituent highlighted in red. Alkaline hydrolysis accelerated by hydrogen peroxide proceeds with retention of configuration and yields enantiomerically pure α -alkylated carboxylic acids; $X_{c,1}^*$ and $X_{c,2}^*$ are the chiral amide groups.

observed amounts of the minor diastereoisomers, even if every enolate were alkylated with 100% diastereoselectivity.

Only chiral propionic acid amides can be alkylated with still higher diastereoselectivity than chiral propionic acid esters. This is because according to Figure 13.18, the selectivity for the formation of a "Z"-configured amide enolate is higher than the selectivities that can be achieved in the conversion of esters to the "E"- and "Z"-enolates. The alkylation of the "Z"-configured lithium enolates of the two enantiomerically pure propionic acid amides in the **Evans synthesis** of Figure 13.43 proceeds with particularly high diastereoselectivity. These amide enolates contain an oxazolidinone ring, and the presence of this ring causes conformational rigidity of the enolates: lithium bridges between the enolate oxygen and the carbonyl O atom of the heterocycle to form a six-membered ring.

Both oxazolidinones in Figure 13.43 are selected such that the substituent marked by a red circle occupies one of the two half-spaces of the enolate. The oxazolidinone to the left in Fig-

ure 13.43 can be prepared from *S*-valine in two steps. The isopropyl group ensures that the most stable transition state for the alkylation of the “Z-enolate 1” involves reaction of the alkylating reagent from the front side (with respect to the selected projection). The alkylating agent thus reacts preferentially from the side opposite to the isopropyl group. Similar considerations apply to the most stable transition state structure of the alkylation of the oxazolidinone “Z-enolate 2” in Figure 13.43. This transition state results from the backside reaction of the alkylating agent (again with regard to the projection drawn). But again, this is a reaction from that side of the molecule that is opposite to the substituent marked by the red circle.

The alkylations of the oxazolidinone-containing amide enolate of Figure 13.43 occur with diastereoselectivities of 93:7 and > 99:1, respectively. The hydrogen peroxide-accelerated alkaline hydrolysis of these compounds occurs with complete retention of the previously established configuration at the α -stereocenter. To date, the Evans synthesis offers the most versatile access to enantiomerically pure α -alkylated carboxylic acids.

13.3 Hydroxyalkylation of Enolates with Carbonyl Compounds (“Aldol Addition”): Synthesis of β -Hydroxyketones and β -Hydroxyesters

An “aldol addition” involves the addition of the α -C atom of a carbonyl compound, a carboxylic acid, a carboxylic ester, or a carboxylic amide to the C=O double bond of an aldehyde or a ketone. The products of aldol additions are β -hydroxycarbonyl compounds (**aldols**), β -hydroxycarboxylic acids, β -hydroxycarboxylic esters, or β -hydroxycarboxylic amides.

13.3.1 Driving Force of Aldol Additions and Survey of Reaction Products

The addition of an alkaline earth metal enolate **A** to a carbonyl compound is always an exergonic process irrespective of whether the enolate is derived from a ketone, an ester, or an amide and whether the carbonyl compound is an aldehyde or a ketone (Figure 13.44, top). One of the reasons for this exergonicity lies in the fact that the alkaline earth metal ion is part of a chelate in the alkoxide **B** of the aldol addition product. The driving forces for the additions of alkaline earth metal enolates of esters and amides to carbonyl compounds are further increased because the aldol adducts **B** are resonance-stabilized, whereas the enolates are not.

Table 13.6 shows the various aldol adducts that can be obtained if one reacts a quantitatively formed ester enolate or a quantitatively formed (kinetic) ketone enolate with three representative carbonyl compounds. **Crossed aldol adducts** are adducts that result from the addition of the enolate of *one* carbonyl compound to the C=O double bond of a *second* carbonyl compound (center column in Table 13.6).

Tab. 13.6 Representative Aldol Adducts Formed by Addition of Ketone or Ester Enolates to Selected Carbonyl Compounds

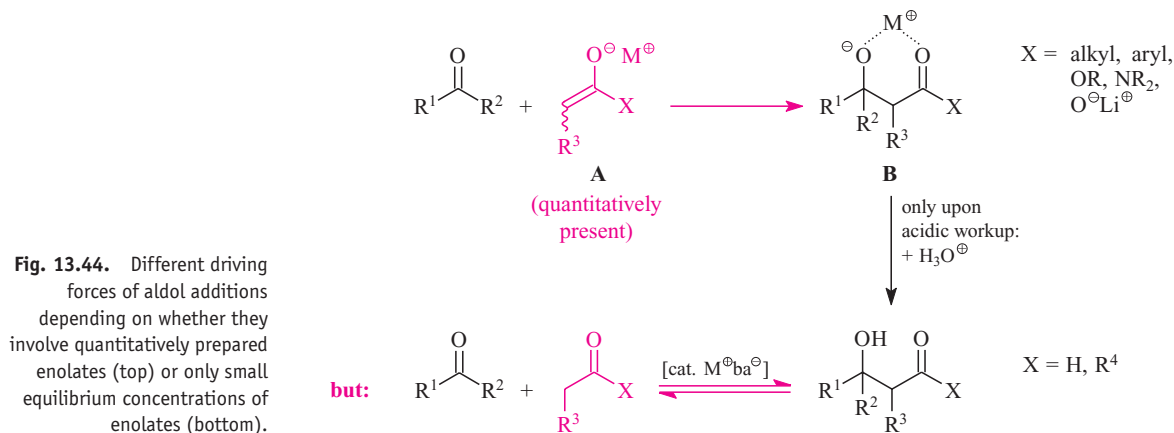
First: The starting material $\xrightarrow[\text{THF, } -78^\circ\text{C}]{\text{LDA}}$ Li-enolate Then: Addition of ...	e.g.	e.g.
e.g.		
e.g.		
e.g.		

↑
crossed aldol additions

In principle it also is possible to obtain the β -hydroxycarbonyl compounds directly in neutral form rather than in form of their alkoxides (Figure 13.44, bottom). This is accomplished by the reaction of one carbonyl compound or of a mixture of two carbonyl compounds with a catalytic amount of MOH or MOR. Aldehyde enolates and ketone enolates are then formed in small amounts (see the Rule of Thumb at the beginning of Section 13.1.2). These enolates add to the C=O double bond of the starting substrate molecules or, if a mixture of carbonyl compounds is employed, they add to the C=O double bond of the more reactive of the carbonyl compounds. The alkoxides **B** of the aldol adducts are formed initially but are converted immediately and quantitatively into the aldols by way of protonation.

This base-catalyzed aldol addition is an equilibrium reaction, and all steps of this reaction are reversible. The free enthalpy of reaction ΔG_r° of such aldol reactions is close to zero. In fact, ΔG_r° is negative only if there are “many H atoms” among the substituents R^1 , R^2 , and R^3 of the two reacting components (structures in Figure 13.44, bottom). Otherwise, the formation of the aldol adduct is endergonic because of the destabilization due to the van-der-Waals repulsion between these substituents. A base-catalyzed aldol addition between two *ketones*, therefore, is never observed.

Esters and amides are much weaker C,H acids than aldehydes and ketones. Neither the ester nor the amide is deprotonated to any significant extent if a base such as MOH or MOR



is added to a mixture of these esters or amides with a carbonyl compound. Hence, neither esters nor amides afford aldol adducts in base-catalyzed reactions.

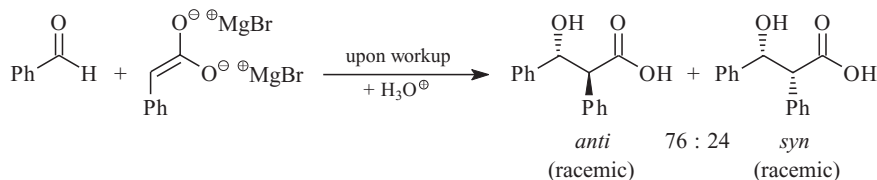
13.3.2 Stereocontrol

The preparation of aldol adducts may occur with simple diastereoselectivity. A definition of the term was given in Section 11.1.3. In a slightly different formulation, simple diastereoselectivity means that a single relative configuration is established at two neighboring C atoms that become stereocenters for the following reasons: (1) Both C atoms were sp^2 -hybridized in the reactants; one was part of a nonhomotopic $\text{C}=\text{X}$ double bond and the other was part of a nonhomotopic $\text{C}=\text{Y}$ double bond. (2) The formation of a σ -bond between these C atoms causes them to be sp^3 -hybridized in the reaction product.

The simple diastereoselectivity of aldol reactions was first studied in detail for the **Ivanov reaction** (Figure 13.45). The Ivanov reaction consists of the addition of a carboxylate enolate to an aldehyde. In the example of Figure 13.45, the diastereomer of the β -hydroxycarboxylic acid product that is referred to as the *anti*-diastereomer is formed in a threefold excess in comparison to the *syn*-diastereoisomer. Zimmerman and Traxler suggested a transition state model to explain this selectivity, and their transition state model now is referred to as the **Zimmerman–Traxler model** (Figure 13.46). This model has been applied ever since with good success to explain the simple diastereoselectivities of a great variety of aldol reactions.

The key idea of the Zimmerman–Traxler model is that aldol additions proceed via six-membered ring transition state structures. In these transition states, the metal (a magnesium

Fig. 13.45. The Ivanov reaction. For the generation of the carboxylate enolate see Figure 13.10.



cation in the case of the Ivanov reaction) coordinates both to the enolate oxygen and to the O atom of the carbonyl compound. By way of this coordination, the metal ion guides the approach of the electrophilic carbonyl carbon to the nucleophilic enolate carbon. The approach of the carbonyl and enolate carbons occurs in a transition state structure with a chair conformation. C—C bond formation is fastest in the transition state with the maximum number of pseudo-equatorially oriented and therefore sterically unhindered substituents.

The application of the Zimmerman–Traxler model to the specific case of the Ivanov reaction of Figure 13.45 is illustrated in Figure 13.46. The reaction proceeds preferentially through

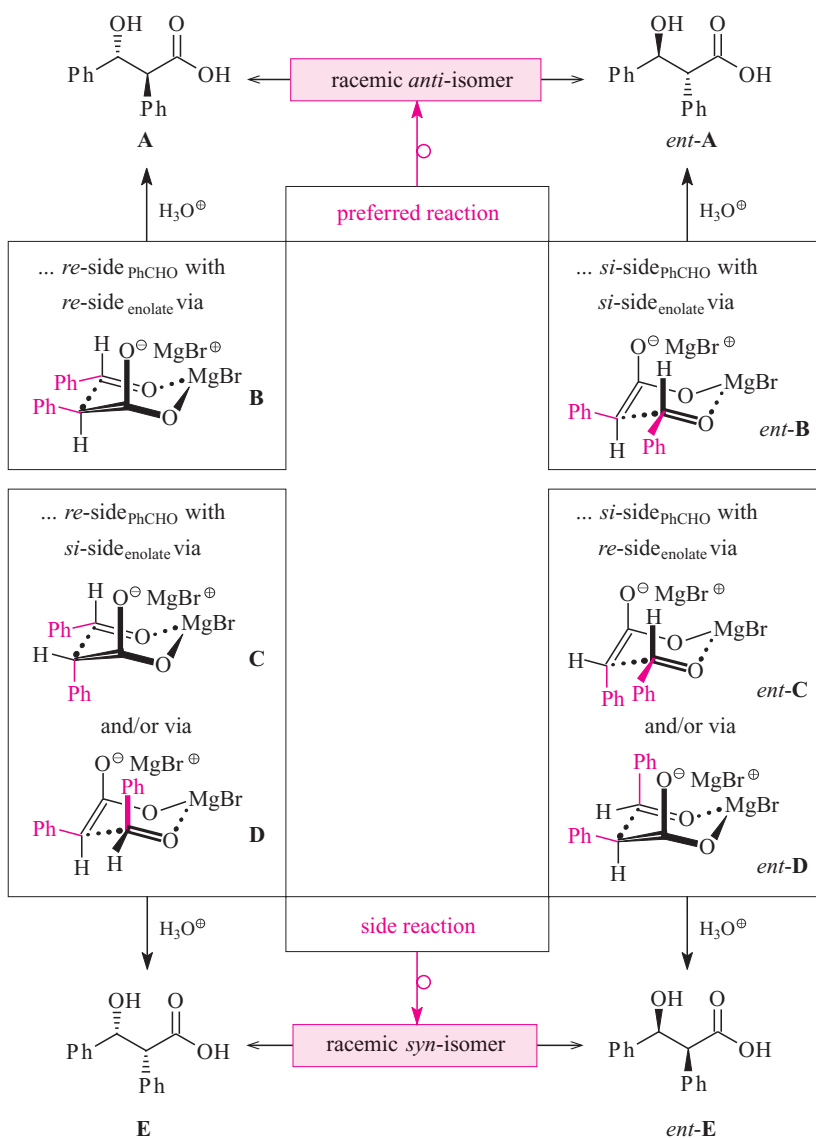


Fig. 13.46. Explanation of the *anti*-selectivity of the Ivanov reaction of Figure 13.45 by means of the Zimmerman–Traxler model. The stereo-descriptors *Re* and *Si* are defined as follows. Suppose you are looking down on the plane of an alkene, in which an sp^2 -hybridized C atom is connected to three different substituents. You are on the *Re* side of the double bond if the Cahn–Ingold–Prelog priorities of these substituents decrease going clockwise, and on the *Si* side otherwise.

transition state **B** and its mirror image *ent*-**B** and results in the formation of a racemic mixture of the enantiomers **A** and *ent*-**A** of the main diastereoisomer. Both phenyl groups are pseudo-equatorial in these transition states. All other transition state structures are less stable because they contain at least one phenyl group in a pseudo-axial orientation. For example, the phenyl group of the enolate is in a pseudoaxial position in transition state **C** and its mirror image *ent*-**C**. In transition state **D** and its mirror image *ent*-**D**, the phenyl groups of the benzaldehyde occupy pseudo-axial positions. The latter transition state structures are therefore just as disfavored as the pair **C** and *ent*-**C**. In fact, the *syn*-configured minor product of the Ivanov reaction, a racemic mixture of enantiomers **E** and *ent*-**E**, must be formed via the transition states **C** and *ent*-**C** or via **D** and *ent*-**D**, but it is not known which path is actually taken.

The *anti* adducts **A**/*ent*-**A** also could, in principle, result via the pair of transition states that contain *both* phenyl groups in pseudo-axial positions. This reaction path might contribute a small amount of the *anti* adduct, but this is rather improbable.

Lithium enolates of ketones and esters also add to aldehydes by way of Zimmerman–Traxler transition states. However, the Li—O bond is weaker and longer than the Mg—O bond. The lithium-containing transition state structures thus are less compact than those containing Mg. Therefore, in a Li-containing Zimmerman–Traxler transition state, a pseudo-axial and thus unfavorably positioned aldehyde substituent suffers only a weak *gauche* interaction with the skeleton of the six-membered ring. In fact, this destabilization generally is too small to render such a transition state structure inaccessible. Hence, the addition of lithium enolates to aldehydes only occurs with high diastereoselectivity if the aldehyde substituent does not assume a pseudo-axial position as the consequence of *another* destabilizing interaction.

Heathcock identified such a destabilizing interaction in the 1,3-diaxial interaction of the aldehyde substituent with a substituent at the C atom to which the enolate oxygen is attached. In spite of the relatively long Li—O distance, this 1,3-interaction can be sufficiently strong if the substituent of the aldehyde is extremely bulky. In that case, and only in that case, the aldehyde group is forced into the pseudo-equatorial orientation also in a lithium-containing Zimmerman–Traxler transition state. If, in addition, the lithium enolate of the aldehyde contains a homogeneously configured C=C(O[−]) double bond, a highly diastereoselective aldol addition of a lithium enolate occurs. Two configurationally homogeneous lithium enolates with suitably bulky substituents are the *Z*-configured ketone enolate of Figure 13.47 with its Me₂C(OSiMe₃) group and the “*E*”-configured ester enolate of Figure 13.48 with its (2,6-di-*tert*-butyl-4-methoxyphenyl)oxy group.

The ketone enolate **A** of Figure 13.47 is generated in a *Z*-selective fashion (as we saw in Figure 13.15). The bulky and branched enolate substituent destabilizes the Zimmerman–Traxler transition state **C** by way of the discussed 1,3-diaxial interaction, while the transition state structure **B** is not affected. Hence, the aldol addition of enolate **A** occurs almost exclusively via transition state **B**, and the *syn*-configured aldol adducts **D** (Figure 13.47) are formed with a near-perfect simple diastereoselectivity. The acidic workup converts the initially formed trimethylsilyloxy-substituted aldol adducts into the *hydroxylated* aldol adducts.

It is for good reason that the bulky ketone substituent of enolate **A** contains a Me₃SiO group, which is carried on into the *syn*-configured aldol adduct: its acid-catalyzed hydrolysis affords an OH group in the α -position of the C=O double bond. Such an α -hydroxycarbonyl compound can be oxidatively cleaved with sodium periodate to afford a carboxylic acid (cf. Section 9.1.1). The mechanism of this oxidation is described later in connection with Fig-

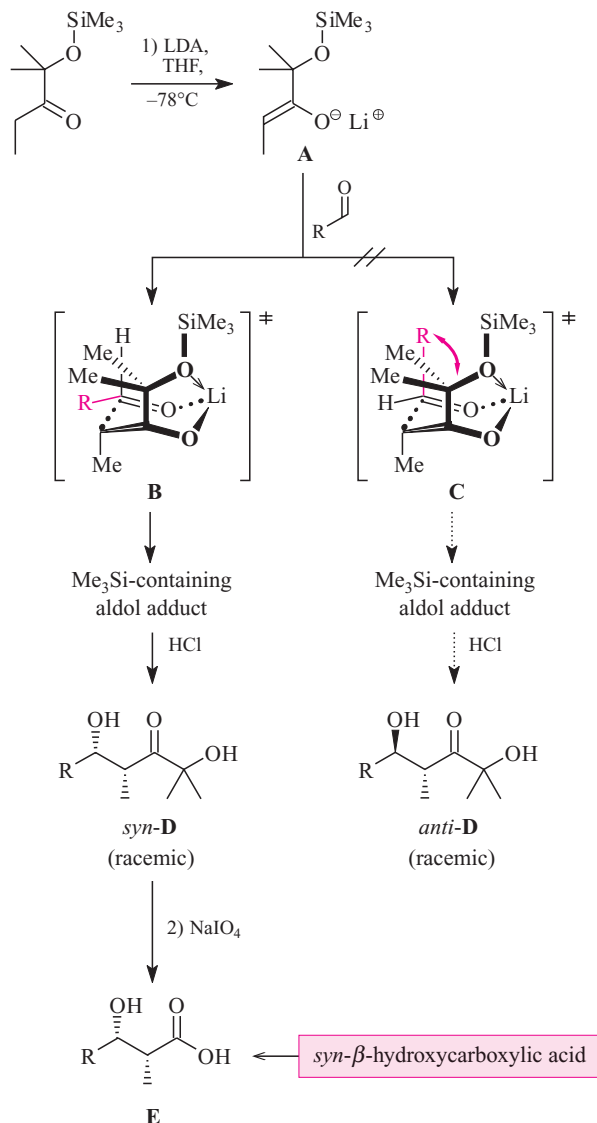


Fig. 13.47. *syn*-Selectivity of the aldol addition with a Heathcock lithium enolate including a mechanistic explanation. The Zimmerman–Traxler transition state **C** is destabilized by a 1,3-diaxial interaction, while the Zimmerman–Traxler transition state **B** does not suffer from such a disadvantage. The reaction thus occurs exclusively via transition state **B**.

ure 17.23. It involves the oxidation of the corresponding hydrate of the carbonyl compound. The hydrate of the α -hydroxycarbonyl compound is formed in an equilibrium reaction. This oxidation converts the *syn*-configured aldol adduct **D**—which contains a synthetically less useful ketone substituent—into a synthetically more valuable *syn*-configured β -hydroxycarboxylic acid, **E**.

The aldol addition of Figure 13.47 can also be carried out in such a fashion that the crude silyl ether-containing aldol adducts are treated directly with periodic acid without prior aqueous workup. In that case, the silyl ether and α -hydroxyketone cleavages both occur in one operation.

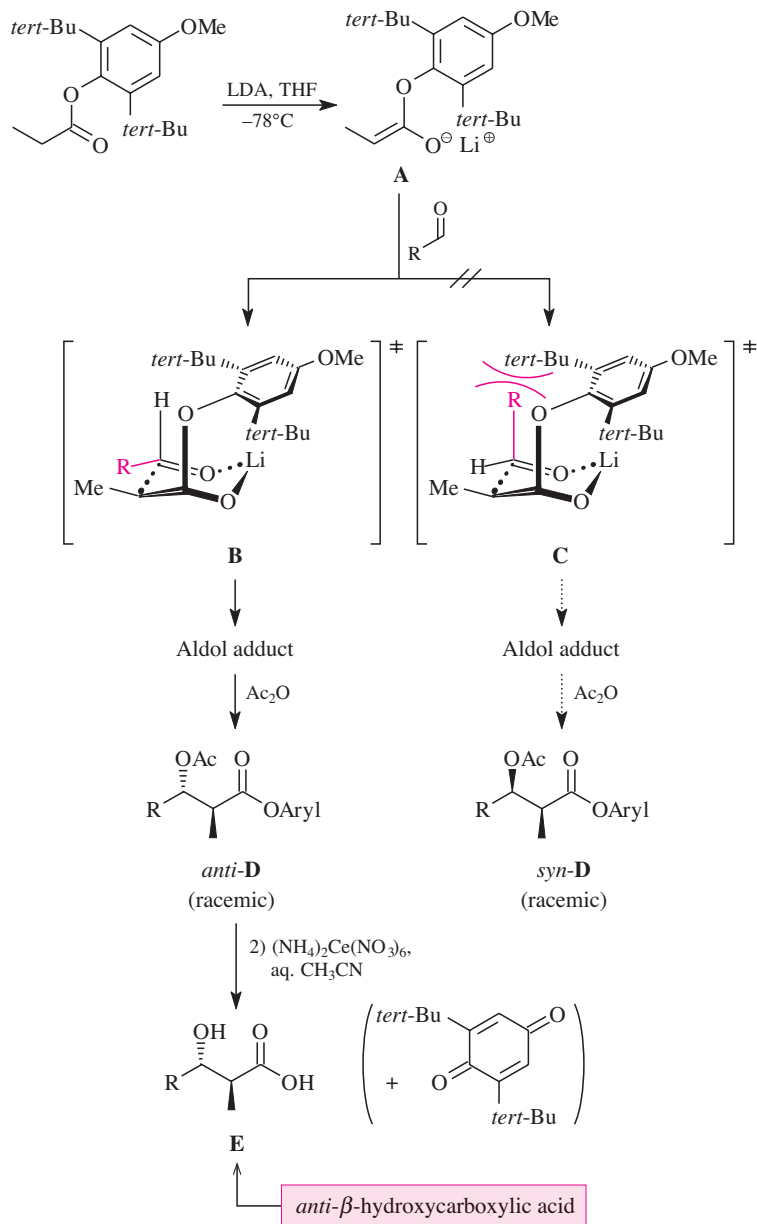


Fig. 13.48. *anti*-Selectivity of the aldol addition with a Heathcock lithium enolate including a mechanistic explanation. The Zimmerman–Traxler transition state **C** is destabilized by a 1,3-diaxial interaction, while the Zimmerman–Traxler transition state **B** does not suffer from such a disadvantage. The reaction thus occurs exclusively via transition state **B**.

Anti-configured β -hydroxycarboxylic acids are accessible via the reaction sequence depicted in Figure 13.48. The ester enolate **A** is generated by using LDA in THF with the usual “*E*”-selectivity (see Figure 13.16). The enolate contains a phenyl group with two *ortho*-attached *tert*-butyl groups. A phenyl substituent with such a substitution pattern must be twisted out of the plane of the enolate. This is true also in the Zimmerman–Traxler transition

states **B** and **C**. One of the *tert*-butyl groups ends up directly on top of the chair structure. Being forced into this position above the ring, the *tert*-butyl group necessarily repels the non-hydrogen substituent of the aldehyde in transition state structure **C**. The associated destabilization of **C** does not occur in the diastereomeric transition state **B**. The aldol addition of Figure 13.48 thus proceeds exclusively via **B**, and perfect simple diastereoselectivity results.

The reaction mixture of Figure 13.48 is worked up such that it yields the β -*acetoxycarboxylic acid* esters **D** instead of the β -*hydroxycarboxylic acid* esters. These products are obtained with diastereoselectivities $ds > 98:2$; and this is independent of the nature of the aldehyde employed. The acetoxiesters **D** are prepared instead of the hydroxiesters because the latter would not survive the ester cleavage still to come. The problem is that this ester group cannot be taken off by way of hydrolysis because it is so bulky. However, it can be removed via oxidation with ceric ammonium nitrate, a quinone being the leaving group. The resulting β -hydroxycarboxylic acids **E** retain the high *anti*-stereochemistry established in **C**.

13.4 Condensation of Enolates with Carbonyl Compounds: Synthesis of Michael Acceptors

13.4.1 Aldol Condensations

An **aldol reaction** is a reaction between two carbonyl compounds in which one carbonyl compound plays the role of a nucleophile while the other carbonyl compound acts as an electrophile. The term “aldol reaction” covers two types of reactions, aldol additions (see Section 13.3) and aldol condensations. The aldol reactions that lead to β -hydroxycarbonyl compounds belong to the class of aldol *additions*. Aldol *condensations* start from the same substrates but result in α,β -unsaturated carbonyl compounds (Figure 13.49).

Aldol reactions often proceed as aldol condensations if the participating aldehyde or ketone enolates **C** are formed only in equilibrium reactions, i.e., incompletely (Figure 13.49). Under these reaction conditions an aldol addition occurs first: it leads to the formation of **D** proceeding by way of the mechanism shown in Figure 13.44 (bottom). Then an $E1_{cb}$ elimination takes place: in an equilibrium reaction, aldol **D** forms a small amount of enolate **E**, which eliminates NaOH or KOH.

If a stereogenic double bond is established by this $E1_{cb}$ elimination, one usually observes a *trans*- or an *E*-selectivity. This experimental finding could have two origins: (1) product development control (Section 4.1.3), if the stereoselectivity occurs under kinetic control, or (2) thermodynamic control. Thermodynamic control comes into play if the *cis,trans*- or *E,Z*-isomeric condensation products can be interconverted via a reversible 1,4-addition of NaOH or KOH. In the *trans*- or *E*-isomer of an α,β -unsaturated carbonyl compound the formyl or acyl group may lie *unimpeded* in the plane of the C=C double bond. This geometry allows one to take *full advantage* of the resonance stabilization $\{C=C-C=O \leftrightarrow {}^{\oplus}C-C=C-O^{\ominus}\}$.

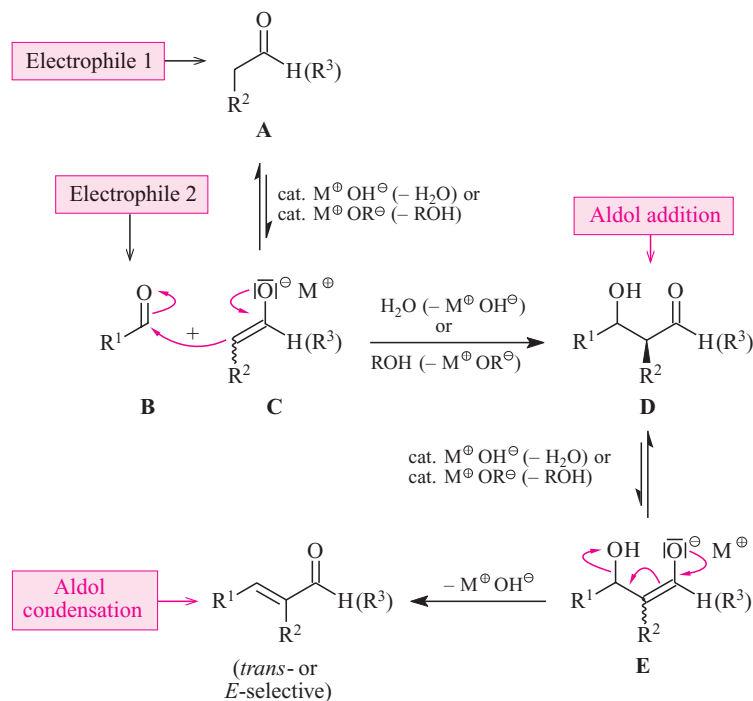


Fig. 13.49. Mechanisms of base-catalyzed aldol reactions: aldol addition (steps 1 and 2) and aldol condensation (up to and including step 4).
 $\text{M}^+ = \text{Na}^+ \text{ or } \text{K}^+$

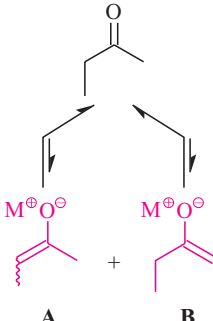
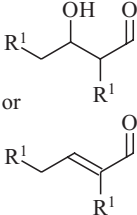
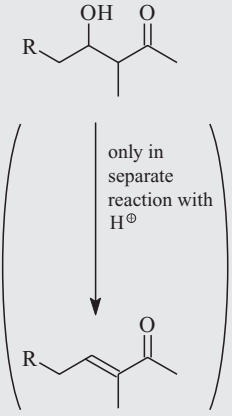
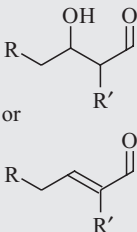
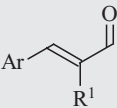
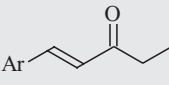
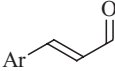
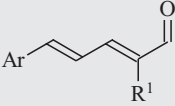
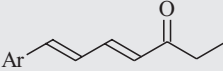
On the other hand, in the *cis*- or *Z*-isomer of an α,β -unsaturated carbonyl compound the formyl or acyl group interferes to such an extent with the substituent at the other end of the $\text{C}=\text{C}$ double bond that a planar geometry is no longer possible and the resonance stabilization consequently is reduced.

As with MOH - or MOH -catalyzed aldol additions ($\text{M} = \text{Na}$ or K ; Figure 13.44), MOH - or MOH -catalyzed aldol condensations ($\text{M} = \text{Na}$ or K) can be carried out only with aldehyde or ketone enolates, not with ester or amide enolates. The reason for this is the same as discussed before, namely, that ester and amides are less acidic than carbonyl compounds and the amounts of enolate they form with the bases mentioned are much too small.

According to Figure 13.44, ketones often do not engage in base-catalyzed aldol *additions* because of a lack of driving force. Hence, ketones also are less suitable electrophiles than aldehydes in aldol condensations. However, for ketones, too, the elimination step is irreversible and they can therefore form α,β -unsaturated carbonyl compounds. It is not always possible to isolate the α,β -unsaturated carbonyl compounds thus formed. If the $\text{C}-\beta$ atom is not sterically hindered, these products can act as electrophiles and add any residual ketone enolate; the α,β -unsaturated carbonyl compound acts as a Michael acceptor in this case (Section 13.6.1).

A broad spectrum of α,β -unsaturated carbonyl compounds becomes accessible in this way because a great variety of aldehydes is suited for aldol condensation. Table 13.7 exemplifies the broad scope by way of the reactions of an aldehyde enolate (center) and of the enolate of an unsymmetrical ketone (right). The right column of Table 13.7 also shows that the regioselectivity of the aldol condensation of the ketone is not easy to predict. Subtle substituent

Tab. 13.7 Representative α,β -Unsaturated Carbonyl Compounds Generated by Aldol Condensations of Carbonyl Compounds with Selected Aldehydes ($M^{\oplus} = Na^{\oplus}$ or $K^{\oplus}$)

Carbonyl compound $\xrightleftharpoons[\text{cat. } M^{\oplus} OR^{\ominus}]{\text{cat. } M^{\oplus} OH^{\ominus}}$ starting material Electrophile		
		
	Mixtures of  (R, R' = R¹, R²)	
		
		

↑ ↑
crossed aldol reactions

effects decide whether in a given case the thermodynamic enolate **A** or the kinetic enolate **B** (present in much smaller amounts) is responsible for the reaction. The thermodynamic enolate leads to the aldol addition, while the kinetic enolate leads to the aldol condensation.

Only one of the aldol condensations of Table 13.7 (top, center) concerns the reaction of a carbonyl compound *with itself*. In all other reactions of Table 13.7, the α,β -unsaturated carbonyl compounds are formed by two different carbonyl compounds. Such aldol condensations are referred to as **crossed aldol condensations** (cf. the discussion of crossed aldol additions in Section 13.3.1).

Of course, it is the goal of a crossed aldol condensation to produce a single α,β -unsaturated carbonyl compound. One has to keep in mind that crossed aldol condensations may result in up to four constitutionally isomeric condensation products (starting from two aldehydes or an aldehyde and a symmetric ketone) or even in eight constitutional isomers (starting with an aldehyde and an unsymmetrical ketone). These maximum numbers of structural isomers result if both starting materials

- can react as electrophiles and as nucleophiles
- can react with molecules of their own kind as well as with other molecules. The product variety is further increased if
- unsymmetrical ketones can react via two regioisomeric enolates.

Crossed aldol condensations occur *with chemoselectivity* only if some of the foregoing options cannot be realized. The following possibilities exist.

Chemoselectivity of Crossed Aldol Condensations

- 1) *Ketones* generally react only as nucleophiles in crossed aldol additions because the addition of an enolate to their C=O double bond is thermodynamically disadvantageous (Figure 13.44).
- 2) *Benzaldehyde, cinnamic aldehyde, and their derivatives* do not contain any α -H atoms; therefore, they can participate in crossed aldol additions only as electrophiles.
- 3) *Formaldehyde* also does not contain an α -H atom. However, formaldehyde is such a reactive electrophile that it tends to undergo multiple aldol additions instead of a simple aldol condensation. This type of reaction is exploited in the pentaerythritol synthesis.

These guidelines allow one to understand the following observations concerning crossed aldol condensations that proceed via the mechanism shown in Figure 13.49.

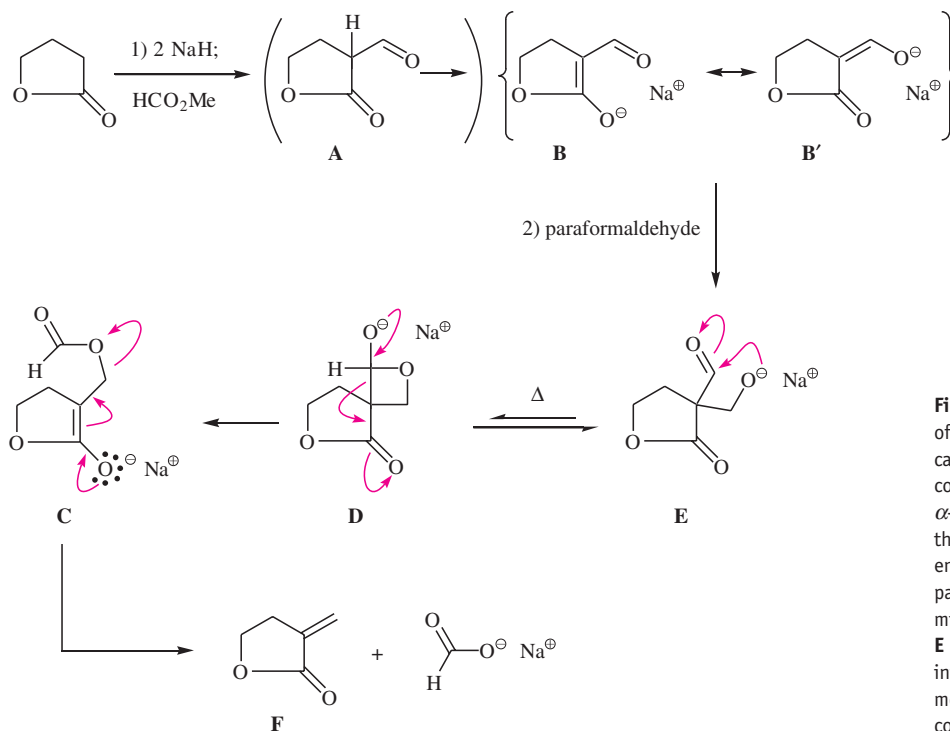
- 1) Crossed aldol condensations between *benzaldehyde or cinnamic aldehyde or their derivatives* *ketones* pose no chemoselectivity problems. The least sterically hindered ketone, acetone, may condense with benzaldehyde, cinnamic aldehyde, and their derivatives with both enolizable positions if an excess of the aldehyde is employed.
- 2) Crossed aldol condensations between *aliphatic aldehydes and ketones* succeed only in two steps via the corresponding crossed aldol adducts. The latter can be obtained by adding the aldehyde dropwise to a mixture of the ketone and base. The aldol adducts subsequently must be dehydrated with acid catalysis.
- 3) Crossed aldol condensations between *aliphatic aldehydes* on the one hand and *benzaldehyde or cinnamic aldehyde or their derivatives* on the other also are possible. The reaction components can even be mixed together. The aldol adducts are formed without chemo-

selectivity, as a mixture of isomers, but their formation is reversible. The $E1_{cb}$ elimination to an α,β -unsaturated carbonyl compound is fast only if the newly created $C=C$ double bond is conjugated to an aromatic system or to another $C=C$ double bond already present in the substrate. This effect is due to product development control. All the starting materials thus react in this way via the most reactive aldol adduct.

- 4) Chemoselective crossed aldol condensations between *two different C,H-acidic aldehydes* are impossible. There is only a single exception, and that is the intramolecular aldol condensation of an unsymmetrical dialdehyde.

Ester enolates and aldehydes normally undergo aldol *additions*, as illustrated in the example of Figure 13.48, but not aldol *condensations*. Of course, these aldol *adducts* can subsequently be dehydrated to furnish aldol *condensates*. This Side Note, however, is intended to show that certain ester enolates may also undergo aldol *condensations* in a single step upon reaction with certain aldehydes.

Figure 13.50 outlines how esters in general (not shown) and especially lactones (shown) can be prepared for a one-step aldol condensation with an aldehyde: they are exposed to a mixed (“crossed”) Claisen condensation with formic acid methyl ester (cf. Figure 13.59, first line). Like all Claisen condensations (Section 13.5.1), this also first leads to the formation of the enolate of the acylated ester. Unlike other Claisen condensations, this enolate is *isolated*. Resonance form **B** identifies it as a formylated ester- or lactone enolate and resonance form



Side Note 13.5. Aldol Condensations of Ester Enolates

Fig. 13.50. α -Methylenation of an ester (in this special case: of a lactone) via aldol condensation of the resulting α -formylated ester enolate (in this special case: a lactone enolate) $\mathbf{B} \leftrightarrow \mathbf{B}'$ with paraformaldehyde. Here, the migration of the formyl groups $\mathbf{E} \rightarrow \mathbf{C}$ is considered to proceed intramolecularly, but an intermolecular process is equally conceivable.

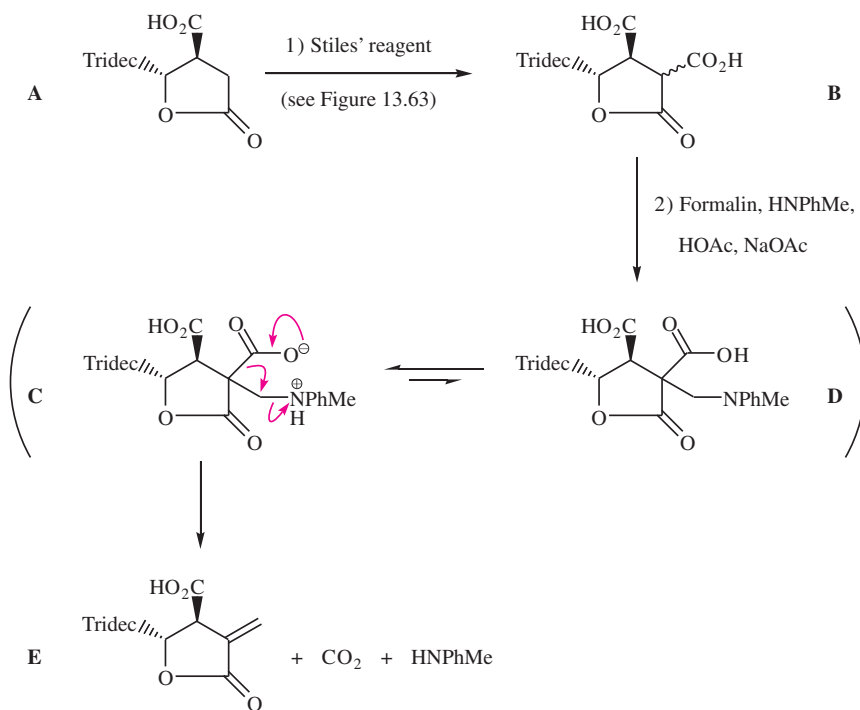


Fig. 13.51. α -Methylation of a lactone via Mannich reaction (cf. Figure 12.14 and 12.15) of the α -carboxylated lactone enolate or lactone enol derived thereof. Another approach to α -methylation of not only lactones, but normal carboxylic acid esters, is presented in Figure 13.50.

B' as an ester- or lactone-substituted aldehyde enolate. Such enolates undergo condensations with all kinds of aldehydes, including paraformaldehyde. An *adduct E* is formed initially, acylating itself as soon as it is heated. The reaction could proceed intramolecularly via the tetrahedral intermediate **D** or intermolecularly as a retro-Claisen condensation. In both cases, the result is an acyloxy-substituted ester enolate. In the example given in Figure 13.50, this is the formyloxy-substituted lactone enolate **C**. As in the second step of an E1_{cb} elimination, **C** eliminates the sodium salt of a carboxylic acid. The α,β -unsaturated ester (in Figure 13.50: the α,β -unsaturated lactone) remains as the aldol *condensation* product derived from the initial ester (here, a lactone) and the added aldehyde (here, paraformaldehyde).

Figure 13.51 shows a trick that allows the reaction of lactones with formaldehyde to yield the corresponding aldol condensation product in a single step. These lactones are first carboxylated with (methoxymagnesium)monomethyl carbonate. Figure 13.63 shows how this leads to the carboxylated lactone **B** shown here. The fact that only lactones can be activated in this manner is due to their elevated C,H acidity compared to normal esters (cf. Figure 13.7). In the second reaction of Figure 13.51, a change probably occurs from enolate to enol chemistry, since next a Mannich reaction (see Figures 12.14, 12.15) takes place to furnish the lactone **D**. This lactone is an amino acid and, like all amino acids, occurs as a zwitterion (Formula **C**). Upon heating, this zwitterion undergoes fragmentation—just like the pyridinium carboxylate in the last step of a decarboxylating Knoevenagel condensation (**F** $\rightarrow$ **G**, Figure 13.56) or like the sulfinat ion in the last step of the Julia–Kocienski olefination (**E** $\rightarrow$ **F**, Figure 11.23). Thus, the α -methylene lactone **E** is formed.

13.4.2 Knoevenagel Reaction

A Knoevenagel reaction is a condensation reaction between an active-methylene compound (or the comparably C,H-acidic nitromethane) and a carbonyl compound. The product of a Knoevenagel reaction is an alkene that contains two geminal acceptor groups (**B** in Figure 13.52) or one nitro group (**B** in Figure 13.53).

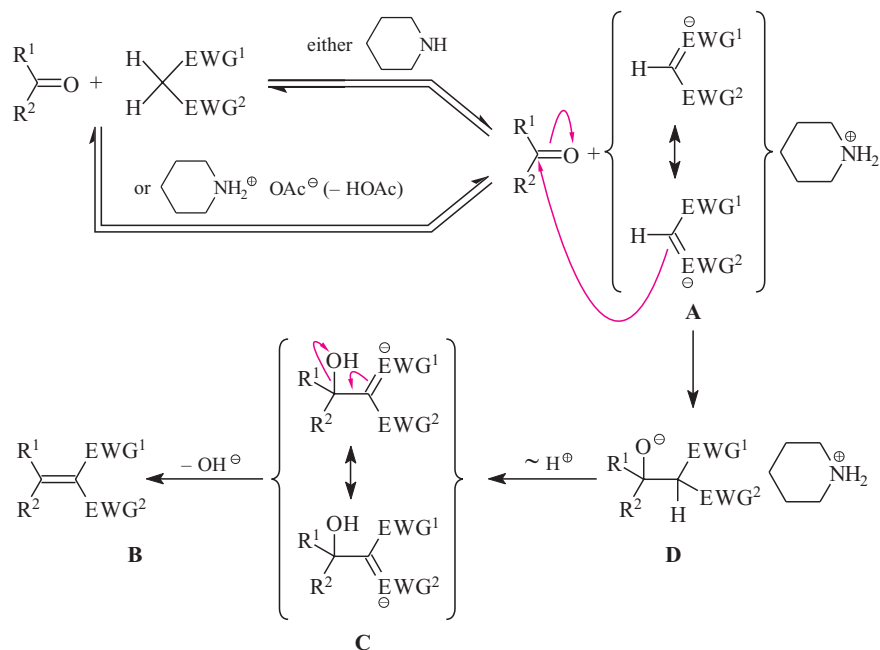
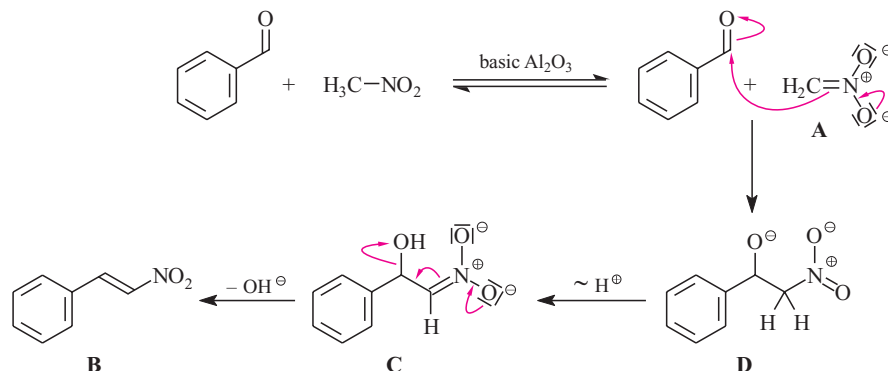


Fig. 13.52. Mechanism of the Knoevenagel reaction of active-methylene compounds; $\sim H^+$ indicates the migration of a proton.

Knoevenagel reactions are carried out in mildly basic media—in the presence of piperidine, for example—or in neutral solution—catalyzed by piperidinium acetate, for example. The basicity of piperidine or of acetate ions, respectively, suffices to generate a sufficiently high equilibrium concentration of the ammonium enolate of the active-methylene compound (**A** in Figure 13.52) or to generate a sufficiently high equilibrium concentration of the ammonium nitronate of the nitroalkane (**A** in Figure 13.53). The rather high acidity of the nitroalkanes (Table 13.1) alternatively allows the formation of nitroalkenes by way of reaction of nitroalkanes with aldehydes in the presence of basic aluminum oxide powder as base.

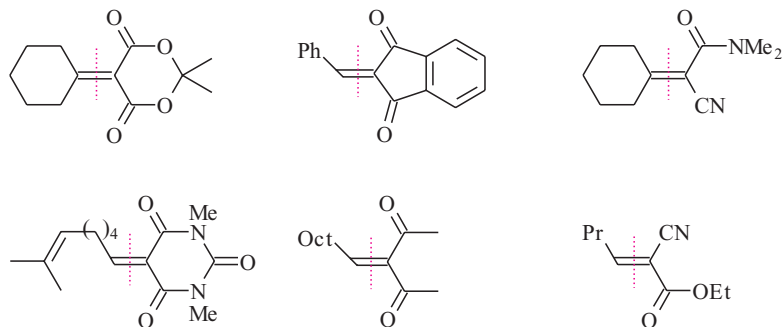
The enolate **A** or the nitronate **A**, respectively, initially adds to the $C=O$ double bond of the aldehyde or the ketone. The primary product in both cases is an alkoxide, **D**, which contains a fairly strong C,H acid, namely, of an active-methylene compound or of a nitroalkane, respectively. Hence, intermediate **D** is protonated at the alkoxide oxygen and the C- β atom is deprotonated to about the same extent as in the case of the respective starting materials. An OH-substituted enolate **C** is formed (Figures 13.52 and 13.53), which then undergoes an $E1_{cb}$ elimination, leading to the condensation product **B**. The Knoevenagel condensation and the aldol condensation have in common that both reactions consist of a sequence of an enolate hydroxyalkylation and an $E1_{cb}$ elimination.

Fig. 13.53. Mechanism of a Knoevenagel reaction with nitromethane. Alkaline aluminum oxide powder is sufficiently basic to deprotonate nitromethane. The small amount of the anion generated from nitromethane suffices for the addition to aldehydes to proceed. The elimination of water via an $E1_{cb}$ mechanism follows quickly if a conjugated $C=C$ double bond is formed, as in the present case.



The Knoevenagel reaction can be employed for the synthesis of a wide variety of condensation products—as shown in Figure 13.54—because the carbonyl component as well as the active-methylene component can be varied.

Fig. 13.54. Products of Knoevenagel condensations and their indication of their potential synthetic origin. The left molecule halves stem from the carbonyl compounds and the right fragments come from the active-methylene compounds.



Side Note 13.6. Knoevenagel Synthesis of Conjugated (Mono-) Carboxylic Acids

Malonic acid itself can react with aldehydes in the presence of piperidine by way of a Knoevenagel condensation. A decarboxylation occurs after the condensation, and this decarboxylation cannot be avoided. Figure 13.55 shows how the overall reaction can be employed for the synthesis of cinnamic or sorbic acid. This reaction sequence occurs under much milder conditions than the **Perkin synthesis of cinnamic acids**. (The Perkin synthesis consists of the condensation of aromatic aldehydes with acetic acid anhydride in the presence of sodium acetate.)

Mechanistic details about the decarboxylating Knoevenagel condensations between malonic acid and the unsaturated aldehydes of Figure 13.55 are given in Figure 13.56. There is no problem in assuming that the respective aldehyde itself is the electrophile in this Knoevenagel reaction. But it is also possible that the piperidinium salt derived thereof acts as the electrophile. This is why a question mark hovers above the first step of the mechanism in Figure 13.56. There is also a question as to the exact nature of the nucleophile. Certainly the

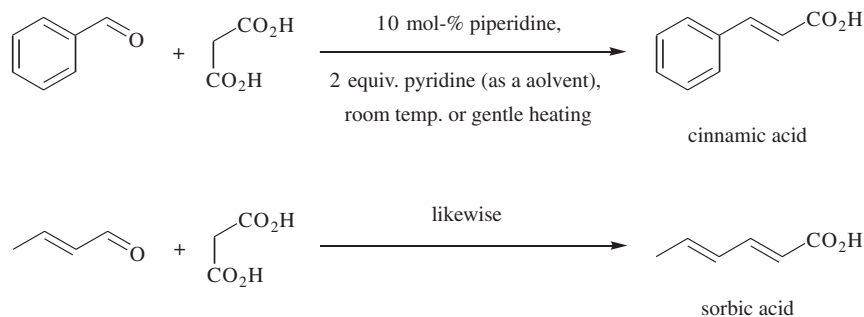


Fig. 13.55. A Knoevenagel reaction “with a twist”: preparation of cinnamic acid and sorbic acid.

nucleophile has to be a species with an enolate carbon. The conceivable candidates include the malonic acid enolate **D** (malonic acid “monoanion”) or the malonic acid “dianion”. The malonic acid “trianion” cannot be generated by bases that are as weak as piperidine or pyridine. The nucleophilicity of the resulting enolates increases greatly in this order, while their concentrations in the corresponding deprotonation equilibria decrease drastically. The *combined* effect of nucleophilicity and abundance determines which nucleophile initiates the Knoevenagel condensation. It is therefore important to know the concentrations of the various species.

It can be assumed that the small amount of piperidine in the reaction mixture is completely protonated by malonic acid because piperidine is more basic than pyridine. Hence, only the less basic pyridine is available for the formation of the malonic acid enolate **D** from free malonic acid and for the formation of the malonic acid “dianion” from the malonic acid monocarboxylate **C**. The pK_a value of malonic acid *with regard to its C,H acidity* should be close to the pK_a value of malonic acid diethyl ester ($pK_a = 13.3$). The pK_a value of malonic acid monocarboxylate **C** *with regard to its C,H acidity* should be larger by at least a factor 10. Hence, the concentration of the malonic acid enolate **D** in the reaction mixture must be by many orders of magnitude higher than that of any malonic acid “dianion.” Due to the advantages associated with this enormous concentration **D** could be the actual nucleophile in Knoevenagel condensations.

On this basis, Figure 13.56 presents a plausible mechanism for the transformations depicted in Figure 13.55. This mechanism is based on the assumption that the malonic acid enolate **D** initially reacts with benzaldehyde or crotonaldehyde just as the enolates of the active-methylene compounds. Thus, the malonic acid enolate and its unsaturated aldehydic reaction partners should first react to furnish the alkylidene malonic acids **B**. If pyridine were added to **B** in an equilibrium reaction (in terms of a Michael addition), the pyridinium-substituted malonic acid enolate **E** would be formed. This should undergo exergonic proton transfer to give the pyridinium carboxylate **F**. This zwitterion **F** could undergo fragmentation in the same way as described for the zwitterion **C** in Figure 13.51 to furnish the α,β -unsaturated carboxylic acids **G** as well as pyridine and carbon dioxide.

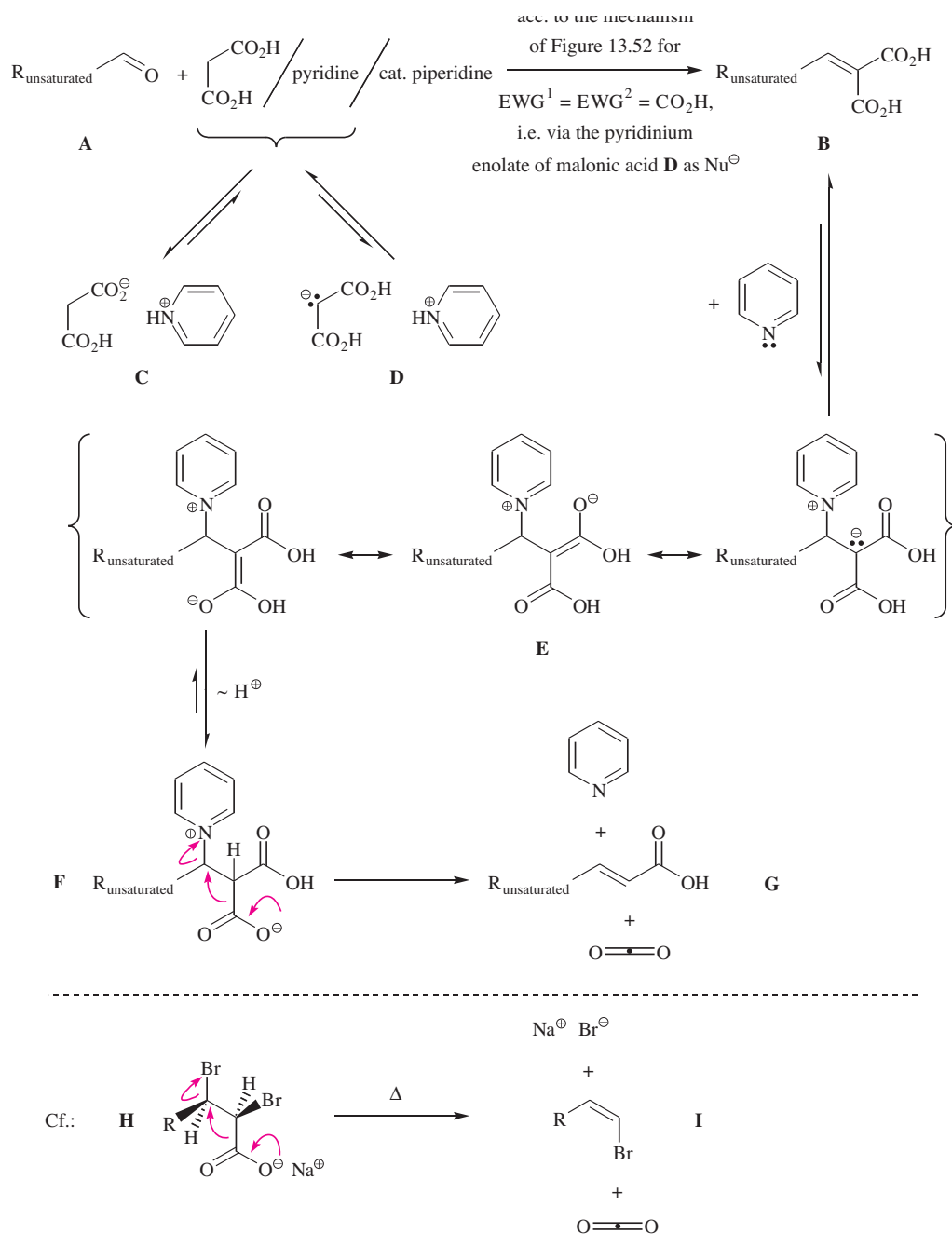


Fig. 13.56. Mechanism of the Knoevenagel condensations in Figure 13.55. The C,H(!)-acidic reaction partner is malonic acid in the form of the malonic acid enolate **D** (malonic acid “monoanion”). The decarboxylation proceeds as a fragmentation of the pyridinium-substituted malonic acid carboxylate **F** to furnish the α,β -unsaturated ester (**G**) and pyridine. This fragmentation resembles the decomposition of the sodium salts **H** of α,β -dibrominated carboxylic acids to yield the α,β -unsaturated bromides **I** and sodium bromide.

13.5 Acylation of Enolates

13.5.1 Acylation of Ester Enolates

A **Claisen condensation** is the acylation of an ester enolate by the corresponding ester. By deprotonating an ester with MOR, only a small concentration of the ester enolate is generated and this enolate is in equilibrium with the ester (cf. Table 13.1). The mechanism of the Claisen condensation is illustrated in detail in Figure 13.57 for the example of the condensation of ethyl butyrate. Both the deprotonation of the ester to give enolate **A** and the subsequent acylation of the latter are reversible. This acylation occurs via a tetrahedral intermediate (**B** in Figure 13.57) just like the acylations of other nucleophiles (Chapter 6). The equilibrium between two molecules of ethyl butyrate and one molecule each of the condensation product **C** and ethanol does not lie completely on the side of the products. In fact, Claisen condensations go to completion only

- if a stoichiometric amount of alkoxide is present, or
- if a stoichiometric amount of alkoxide can be generated from the one equivalent of alcohol liberated in the course of the Claisen condensation and a stoichiometric amount of Na or NaH.

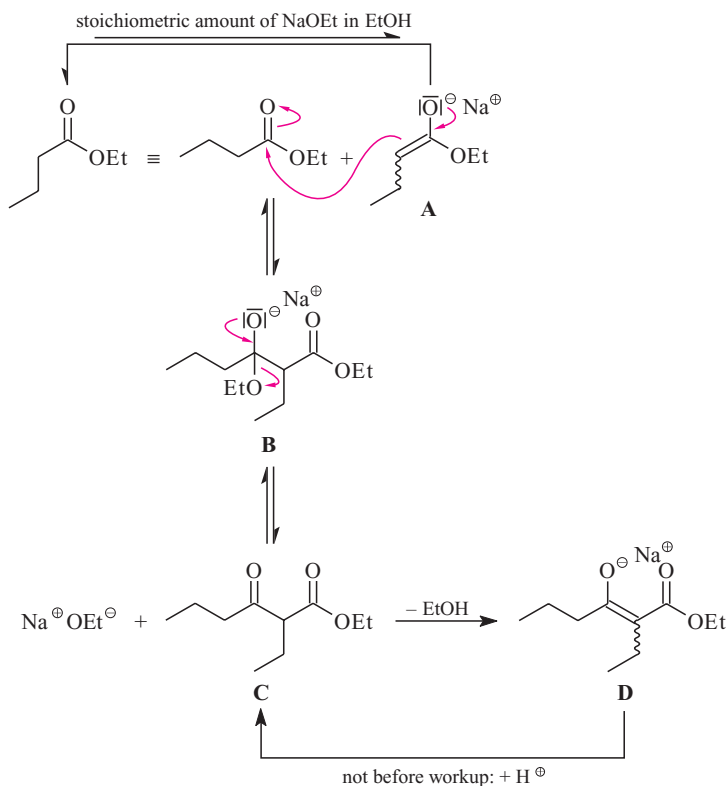


Fig. 13.57. Mechanism of a Claisen condensation. The deprotonation step $\text{Na}^+\text{OEt}^- + \text{C} \rightarrow \text{D} + \text{EtOH}$ is irreversible, and it is for this reason that eventually all the starting material will be converted into the enolate **D**.

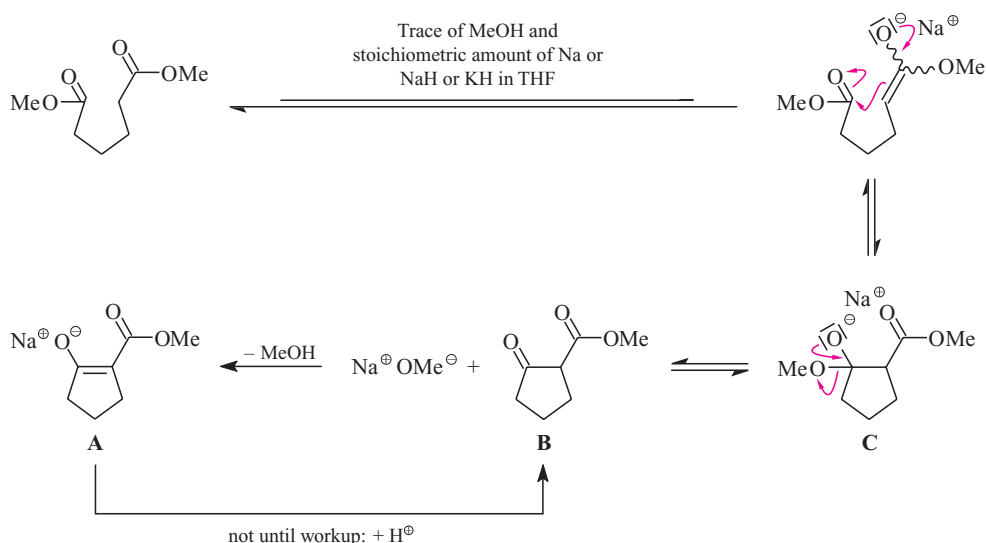
What is the effect of the stoichiometric amount of strong base that allows the Claisen condensation to proceed to completion? The β -ketoester **C**, which occurs in the equilibrium, is an active-methylene compound and rather C,H-acidic. Therefore, its reaction with the alkoxide to form the ester-substituted enolate **D** occurs *with considerable driving force*. This driving force is strong enough to render the deprotonation step $\mathbf{C} \rightarrow \mathbf{D}$ essentially irreversible. Consequently, the overall condensation also becomes irreversible. In this way, all the substrate is eventually converted into enolate **D**. The neutral β -ketoester can be isolated after addition of one equivalent of aqueous acid during workup.

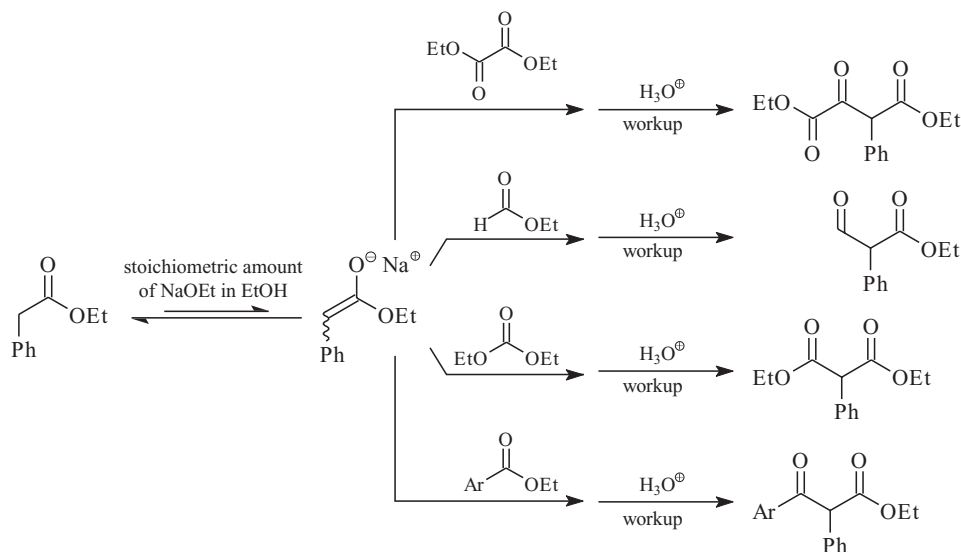
Intramolecular Claisen condensations, called **Dieckmann condensations**, are ring-closing reactions that yield 2-cyclopentanone carboxylic esters (Figure 13.58) or 2-cyclohexanone carboxylic esters. The mechanism of the Dieckmann condensation is, of course, identical to the mechanism of the Claisen condensation (Figure 13.57). To ensure that the Dieckmann condensation goes to completion, the presence of a stoichiometric amount of base is required. As before, the neutral β -ketoester (**B** in Figure 13.58) is formed in a reversible reaction under basic conditions. However, the back-reaction of the β -ketoester **B** to the diester is avoided by deprotonation to the substituted enolate **A**. This enolate is the thermodynamic sink to which all the substrate eventually is converted. The β -ketoester **B** is regenerated in neutral form again during workup with aqueous acid.

Acylation of ester enolates with different esters are called **crossed Claisen condensations** and are carried out—just like normal Claisen condensations—in the presence of a stoichiometric amount of alkoxide, Na, or NaH. Crossed Claisen condensations can in principle lead to four products. In order that only a single product is formed in a crossed Claisen condensation, the esters employed need to be suitably differentiated: one of the esters must be prone to enolate formation, while the other must possess a high propensity to form a tetrahedral intermediate (see example in Figure 13.59).

The use of an ester without acidic α -H atoms ensures that this ester can act only as the electrophile in a crossed Claisen condensation. Moreover, this nonenolizable ester must be at least

Fig. 13.58. Mechanism of a Dieckmann condensation. The Dieckmann condensation is an intramolecular Claisen condensation.





as electrophilic as the other ester. This is because the larger fraction of the latter is present in its nondeprotonated form; that is, it represents a possible electrophile, too, capable of forming a tetrahedral intermediate upon reaction with an enolate.

Accordingly, crossed Claisen condensations occur without any problems if the acylating agent is a better electrophile than the other, nondeprotonated ester. This is the case, for example, if the acylating agent is an oxalic ester (with an electronically activated carboxyl carbon) or a formic ester (the least sterically hindered carboxyl carbon).

Crossed Claisen condensations can be chemoselective even when the nonenolizable ester is *not* a better electrophile than the enolizable ester. This can be accomplished by a suitable choice of reaction conditions. The nonenolizable ester is mixed with the base and the enolizable ester is added slowly to that mixture. The enolate of the enolizable ester then reacts mostly with the nonenolizable ester for statistical reasons; it reacts much less with the nonenolized form of the enolizable ester, which is present only in rather small concentration. Carbonic acid esters and benzoic acid esters are nonenolizable esters of the kind just described.

Under different reaction conditions, esters other than the ones shown in Figure 13.59 can be employed for the acylation of ester enolates. In such a case, one *quantitatively* deprotonates *two* equivalents of an ester with LDA or a similar amide base. This is exemplified by the upper part of Figure 13.60, starting from two equivalents of acetic acid *tert*-butylester. Then 1.0 equivalent of the ester serving as the acylating agent is added. In the example given in Figure 13.60 (top), this may be any carboxylic acid methyl ester. The acylation product is a β -ketoester **B**, and thus a stronger C,H acid than the conjugate acid of the ester enolate employed. Therefore, the initially formed β -ketoester **B** reacts immediately in an acid/base reaction with the second equivalent of the ester enolate. The β -ketoester **B** protonates this ester enolate, consumes it completely and thereby is itself converted into the conjugate base, i.e., the enolate **C**. The β -ketoester **B** is reconstituted upon acidic workup.

In some acylations it may even be necessary to employ three equivalents of the ester enolate. The example at the bottom of Figure 13.60 is such a case: with its free OH group the acy-

Fig. 13.59. Crossed Claisen condensation. Although the tautomers of the acylation products shown are not the major tautomer except for the third case from the top, they are presented because they show best the molecules from which these products were derived.

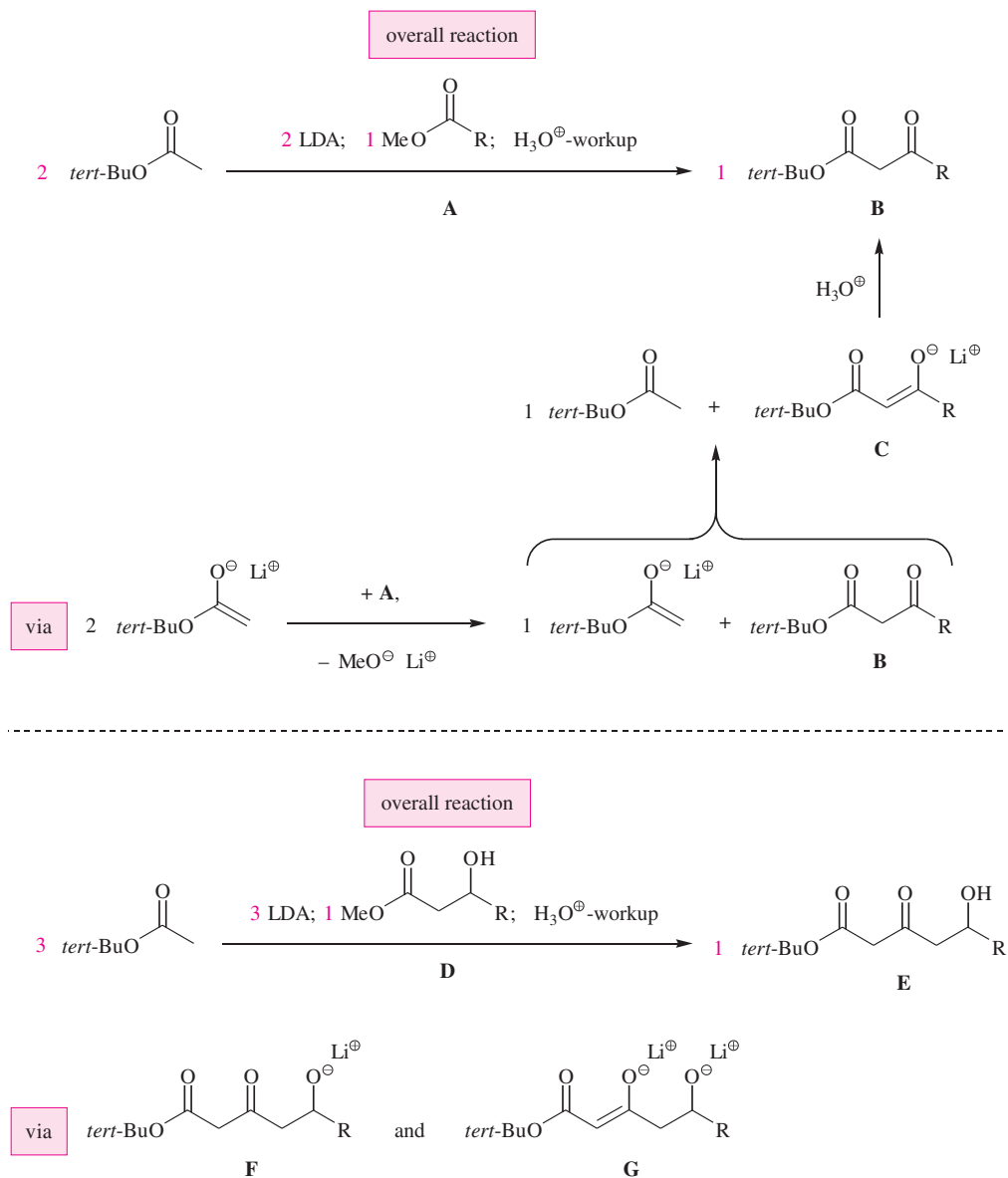


Fig. 13.60. Crossed ester condensation via acylation of a quantitatively prepared ester enolate. Three equivalents of ester enolate must be employed because the acylating ester contains a free OH group with an acidic H atom: one for the deprotonation of the OH group of the substrate, one for the substitution of the MeO group, and one for the transformation of the C,H-acidic substitution product into an enolate.

lating β -hydroxyester **D** protonates the first equivalent of the enolate of the acetic acid *tert*-butyl ester to furnish *tert*-butyl acetate. The second equivalent of the ester enolate undergoes a crossed Claisen condensation with the anion of the β -hydroxyester **D** that is present at this point. The resulting β -ketoester **F** protonates the third equivalent of the *tert*-butyl acetate ester enolate thereby forming its conjugate base, the enolate **G**. Only upon acidic workup does the latter afford the neutral Claisen condensation product, the δ -hydroxy- β -ketoester **E**.

A procedure that may be used to carboxylate lactone enolates is described in Figure 13.63.

13.5.2 Acylation of Ketone Enolates

Remember what we discussed in the context of Figure 13.44: *ketones* usually do not undergo aldol additions if they are deprotonated to only a small extent by an alkaline earth metal alkoxide or hydroxide. The driving force behind that reaction simply is too weak. In fact, only a very few ketones can react with themselves in the presence of alkaline earth metal alkoxides or alkaline earth metal hydroxides. And if they do, they engage in an aldol condensation. Cyclopentanone and acetophenone, for example, show this reactivity.

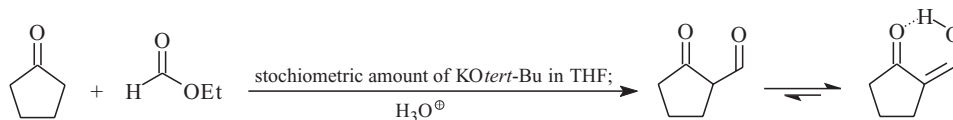
The relative inertness of ketone enolates toward ketones makes it possible to react non-quantitatively obtained ketone enolates with esters instead of with ketones. These esters—and reactive esters in particular—then act as acylating reagents.

In contrast to ketones, aldehydes easily undergo a base-catalyzed aldol reaction (Figure 13.44), and this reaction may even progress to an aldol condensation (Section 13.4.1). It is therefore not possible to acylate aldehyde enolates that are present only in equilibrium concentrations. Any such enolates would be lost completely to an aldol reaction.

Oxalic esters (for electronic reasons) and formic esters (because of their low steric hindrance) are reactive esters that can acylate ketone enolates formed with NaOR in equilibrium reactions. Formic esters acylate ketones to provide formyl ketones (for example, see Figure 13.61). It should be noted that under the reaction conditions the conjugate base of the active-methylene formyl ketone is formed. The neutral formyl ketone is regenerated upon acidic workup.

Most other carboxylic acid derivatives can acylate only ketone enolates that are formed quantitatively. In these reactions, the acylation product is a β -diketone, i.e., an active-methylene compound. As a consequence it is so acidic that it will be deprotonated quantitatively. This deprotonation will be effected by the ketone enolate. Therefore, a complete acylation of this type can be achieved only if two equivalents of the ketone enolate are reacted with one equivalent of the acylating agent. Of course, proceeding in that manner would mean an unacceptable waste in the case of a valuable ketone.

Fig. 13.61. Acylation of a ketone enolate with a formic ester to generate a formyl ketone. The ketone enolate intermediate (not shown) is formed in an equilibrium reaction.

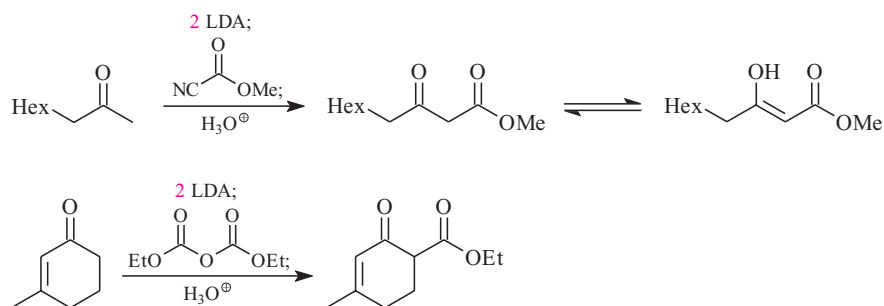


Against Wastefulness: A Practical Hint Regarding the Acylation of Ketone Enolates

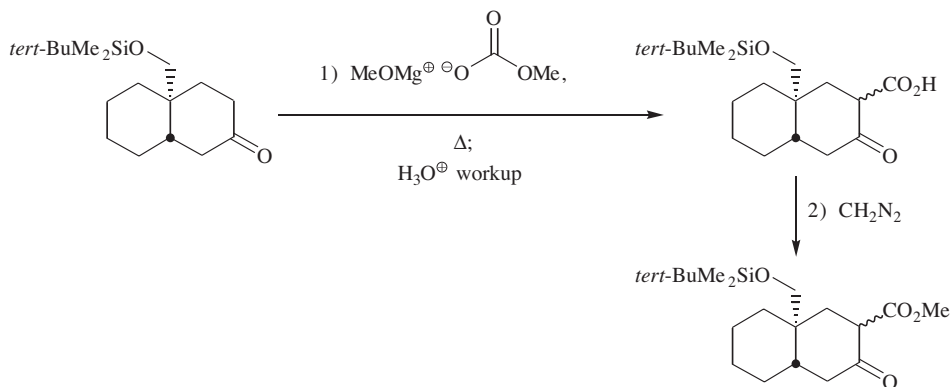
The following protocol requires no more than the stoichiometric amount of a ketone enolate to achieve a complete acylation. An ester is added dropwise to a 1:1 mixture of one equivalent each of the ketone enolate and LDA. The acidic proton of the β -diketone, which is formed, then is abstracted by the excess equivalent of LDA rather than by the ketone enolate.

The protocol described also can be used for the acylation of ketone enolates with carbonic acid derivatives (Figure 13.62). Especially good acylating agents are cyanocarboxylic acid methyl ester (Mander's reagent, Figure 13.62, top) and dialkyl pyrocarbonates (bottom). Usually it is not possible to use dimethyl carbonate for the acylation of ketone enolates because dimethyl carbonate is a weaker electrophile than cyanocarboxylic acid methyl ester or diethyl pyrocarbonates.

Fig. 13.62. Acylation of ketone enolates with carbonic acid derivatives. Especially good acylation reagents are cyanocarboxylic acid methyl ester (top) and dialkyl pyrocarbonates (bottom).



A carbonic acid derivative which, surprisingly, also proves to be suitable for the acylation of ketone enolates, is Stiles' reagent, i.e., (methoxymagnesium) monomethyl carbonate. In Section 8.2, you saw how this reagent can be obtained. Ketone enolates are carboxylated by Stiles' reagent to furnish a β -keto carboxylic acid, as shown by the reaction equation below. As this keto acid is initially obtained as the (methoxymagnesium) carboxylate, such an acylation can easily proceed without the extra equivalents of enolate or base mentioned above.



The reaction of the β -keto carboxylic acid resulting from the acidic workup of this carboxylation with diazomethane affords the corresponding β -ketoester (method: Figure 2.33).

Incidentally, lactones are also sufficiently C,H-acidic to be carboxylated by (methoxymagnesium) monomethyl carbonate. Figure 13.63 illustrates how this approach can be used to form an α -carboxylated lactone **B** and what the reaction mechanism might look like. An α -carboxylated lactone can react either with diazomethane to give an α -(methoxycarbonylated) lactone (not shown), or undergo a tandem reaction (consisting of Mannich reaction and fragmentation) to yield an α -methylene lactone (see Figure 13.51).

Weinreb amides are acylating agents that react according to the general mechanism outlined in Figure 6.4. Thus, the acylation product is not released from the tetrahedral intermediate as long as nucleophile is still present. Accordingly, the acylation of a ketone enolate by a Weinreb amide does not immediately result in the formation of the β -ketocarbonyl compound. Instead, the reaction proceeds just as an addition reaction and a tetrahedral intermediate is formed stoichiometrically (e.g., **C** in Figure 13.64). This tetrahedral intermediate is not an active-methylene compound but a donor-substituted (O^- substituent!) ketone. This intermediate therefore cannot act as a C,H acid with the ketone enolate or, in the present case, not even

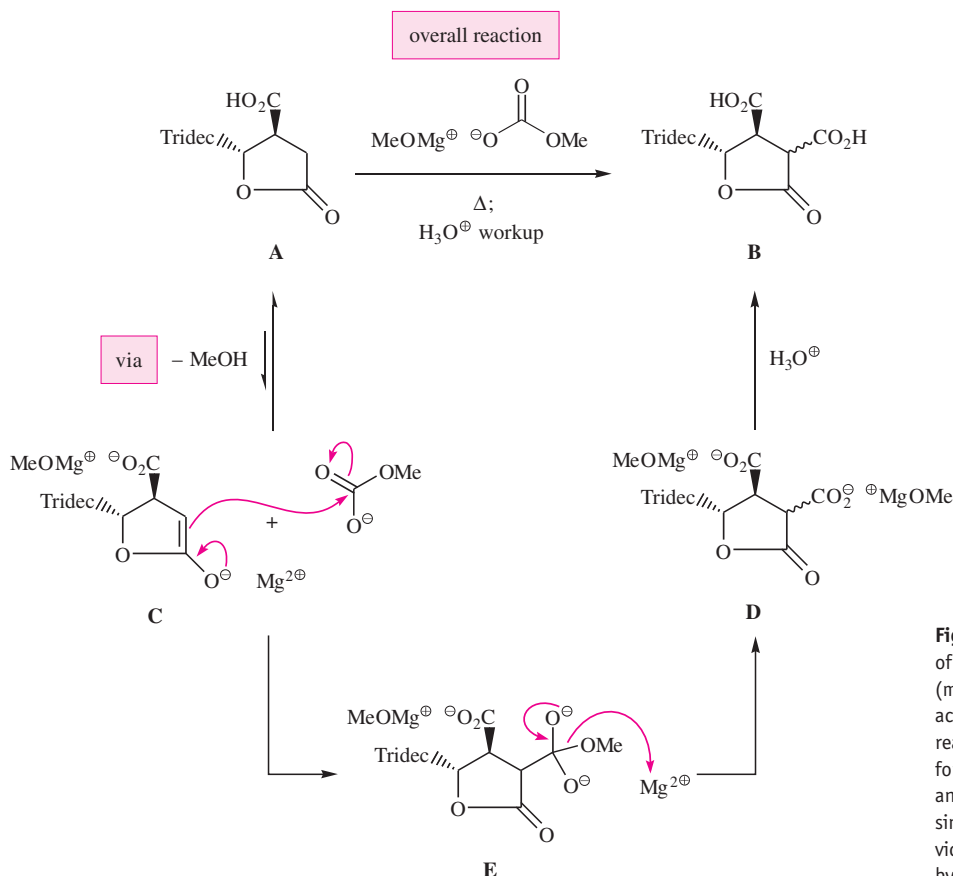


Fig. 13.63. α -Carboxylation of a lactone enolate with (methoxymagnesium) carbonic acid monomethyl ester ("Stiles' reagent"). In the C,C bond-forming step (**C** $\rightarrow$ **E**) this anion acts as an electrophile, since it is steered into close vicinity to the enolate carbon by a Mg^{2+} cation.

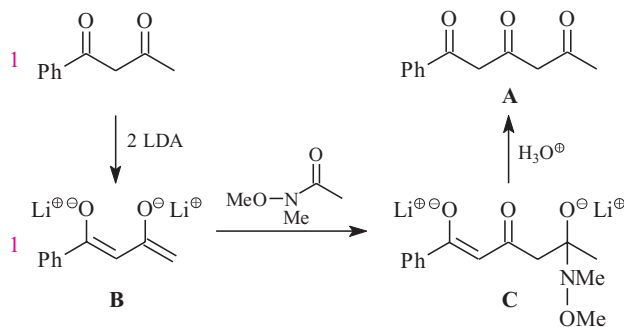


Fig. 13.64. Acylation of a bis(ketone enolate) with one equivalent of a Weinreb amide.

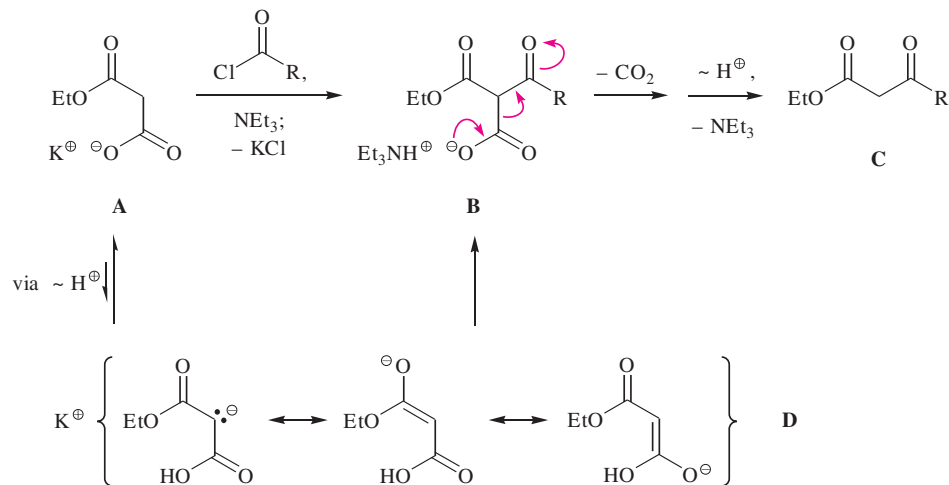
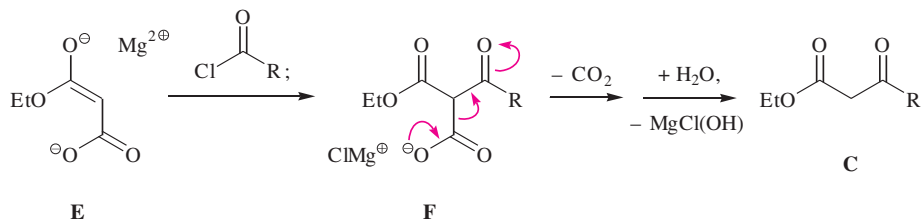
with the bis(ketone enolate) **B**. For reasons discussed in the context of Figure 6.42, the tetrahedral intermediate **C** is stable until it is protonated upon aqueous workup. Only then is the acylation product formed.

13.5.3 Acylation of the Enolates of Active-Methylene Compounds

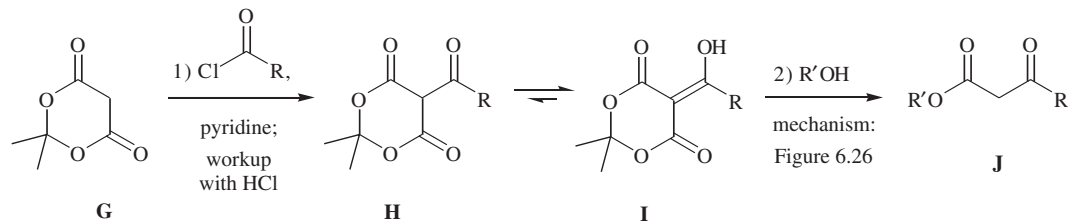
When the enolate of an active-methylene compound undergoes acylation with a carboxylic acid chloride, an “active-methyne” compound is formed initially (Figure 13.65, 13.66). If the electron acceptors therein are solely acyl- or (alkoxycarbonyl) groups, the substructure mentioned suffers from steric hindrance and substantial electrostatic repulsion forces. “Active-methyne” compounds with such a substitution pattern will react to alleviate this destabilization.

This can occur through loss of an acyl- or (alkoxycarbonyl) group and formation of an active-methylene compound. Figure 13.65 shows three variants of how this principle can be exploited to synthesize β -ketoesters from acid chlorides. Naturally, the destabilization of “active-methyne” compounds is also removed if *two* of the three acyl- or (alkoxycarbonyl) groups are eliminated, leaving behind a compound with just *one* C=O double bond. Figure 13.66 presents two methods for the chain-elongating synthesis of ketones from carboxylic acid chlorides that are based on this principle.

The “active-methyne” compounds, which derive from the acylation of the enolates of active-methylene compounds with carboxylic acid chlorides, eliminate the extra acceptor(s) in an additional step or immediately *in situ*. The defunctionalizations involved include one or two decarboxylations depending on the nature of the reactants and subsequent processing steps (Figures 13.66 and 13.67)

Variant 1:**Variant 2:**

(preparation: Figure 13.10)

Variant 3:

(preparation: Figure 9.21)

Fig. 13.65. Acylation of various malonic diester or malonic half-ester enolates with carboxylic acid chlorides. Spontaneous decarboxylation of the acylation products to furnish β -ketoesters (see variants 1 and 2) and transformation of the acylation products into β -ketoesters by way of alcoholysis/decarboxylation (see variant 3).

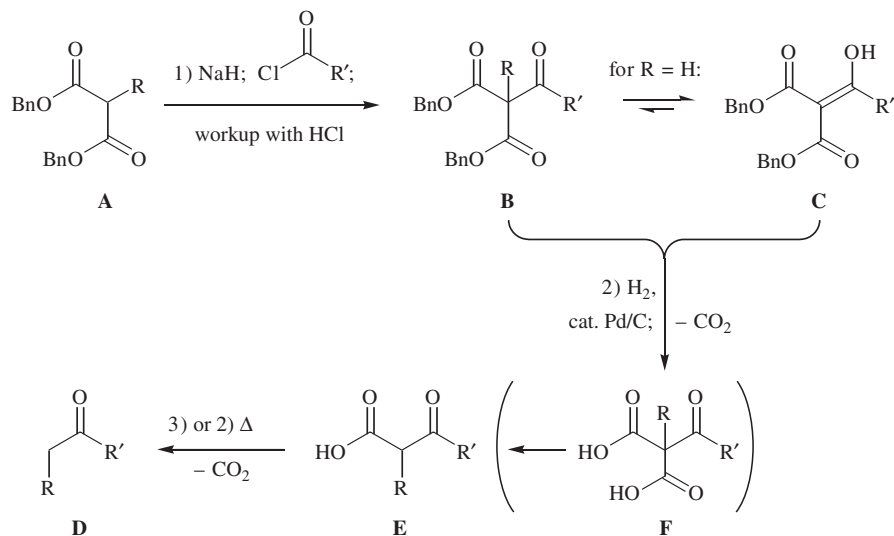
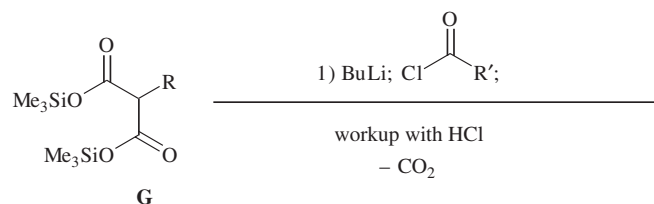
Variant 1:

Fig. 13.66. Acylation of two different malonic diester enolates with carboxylic acid chlorides. Transformation of the acylation products into ketones by heating after debenzylation (see variant 1) or just heating (variant 2).

Variant 2:

13.6 Michael Additions of Enolates

13.6.1 Simple Michael Additions

A Michael addition consists of the addition of the enolate of an active-methylene compound, the anion of a nitroalkane, or a ketone enolate to an acceptor-substituted alkene. Such Michael additions can occur in the presence of catalytic amounts of hydroxide or alkoxide. The mechanism of the Michael addition is shown in Figure 13.67. The addition step of the reaction initially leads to the conjugate base of the reaction product. Protonation subsequently gives the product in its neutral and more stable form. The Michael addition is named after the American chemist Arthur Michael.

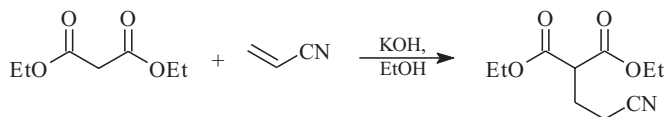
Acceptor-substituted alkenes that are employed as substrates in Michael additions include α,β -unsaturated ketones (for example, see Figure 13.68), α,β -unsaturated esters (Fig-

Fig. 13.69. Michael addition to an α,β -unsaturated ester.



Beyond the scope discussed so far, Michael additions also include additions of stoichiometrically generated enolates of ketones, SAMP or RAMP hydrazones, or esters to the C=C double bond of α,β -unsaturated ketones and α,β -unsaturated esters. These Michael additions convert one kind of enolate into another. The driving force stems from the C—C bond formation, not from differential stabilities of the enolates. It is important that the addition of the preformed enolate to the Michael acceptor is faster than the addition of the resulting enolate to another molecule of the Michael acceptor. If that reactivity order were not true, an anionic polymerization of the Michael acceptor would occur. In many Michael additions, however, the enolate *created* is more hindered sterically than the enolate *employed* as the starting material, and in these cases Michael additions are possible without polymerization.

Fig. 13.70. Michael addition to an α,β -unsaturated nitrile.



13.6.2 Tandem Reactions Consisting of Michael Addition and Consecutive Reactions

If a Michael addition of an enolate forms a *ketone enolate* as the primary reaction product, this enolate will be almost completely protonated to give the respective ketone. The reaction medium is of course still basic, since it still contains $\text{OH}^\ominus$ or $\text{RO}^\ominus$ ions. The Michael adduct, a ketone, is therefore reversibly deprotonated to a small extent.

This deprotonation may reform the ketone enolate that was the intermediate en route to the Michael adduct. However, the regioisomeric ketone enolate also can be formed. Figures 13.71–13.74 show such enolate isomerizations **B** $\rightarrow$ **D**, which proceed via the intermediacy of a neutral Michael adduct **C**. This neutral adduct is a 1,5-diketone in Figure 13.71, a δ -ketoaldehyde in Figure 13.72, and a δ -ketoester in Figure 13.73.

The new enolate carbon is located in position 6 of intermediate **D**. In this numbering scheme, position 1 is the C=O double bond of the keto group (Figures 13.71, 13.72), the aldehyde group (Figure 13.73), or the ester group (Figure 13.74). Because of the distance between the enolate position and the C=O double bond, a bond might form between C1 and C6:

- Enolate **D** of Figure 13.71 can undergo an aldol reaction with the C=O double bond of the ketone. The bicyclic compound **A** is formed as the condensation product. It is often possible to combine the formation and the consecutive reaction of a Michael adduct in a one-pot reaction. The overall reaction then is an annulation of a cyclohexenone to an enolizable ketone. The reaction sequence of Figure 13.71 is the **Robinson annulation**, an extraordinarily important synthesis of six-membered rings.

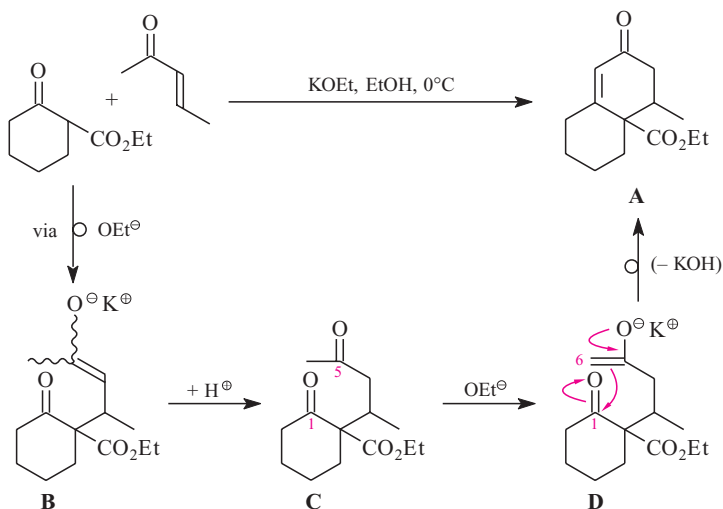


Fig. 13.71. Tandem reaction I, consisting of a Michael addition and an aldol condensation: Robinson annulation reaction for the synthesis of six-membered rings that are condensed to an existing ring.

- The enolate **D** in Figure 13.72 also undergoes an aldol condensation with a ketonic C=O double bond, furnishing the bicycle **A** as the condensation product. Here also, the formation and further reaction of the Michael adduct **C** can be combined in a one-pot reaction. As in the immediately preceding and following example, the final product is a cyclohexenone, but not one that would have been derived from an annulation. Despite the different number of C atoms that the respective reactants contribute to the resulting six-ring skeleton, a reaction like the one presented in Figure 13.72 is sometimes referred to as a **3+3 Robinson annulation** and thus distinguishes this one from the **2+4 Robinson annulations** shown in Figure 13.71.

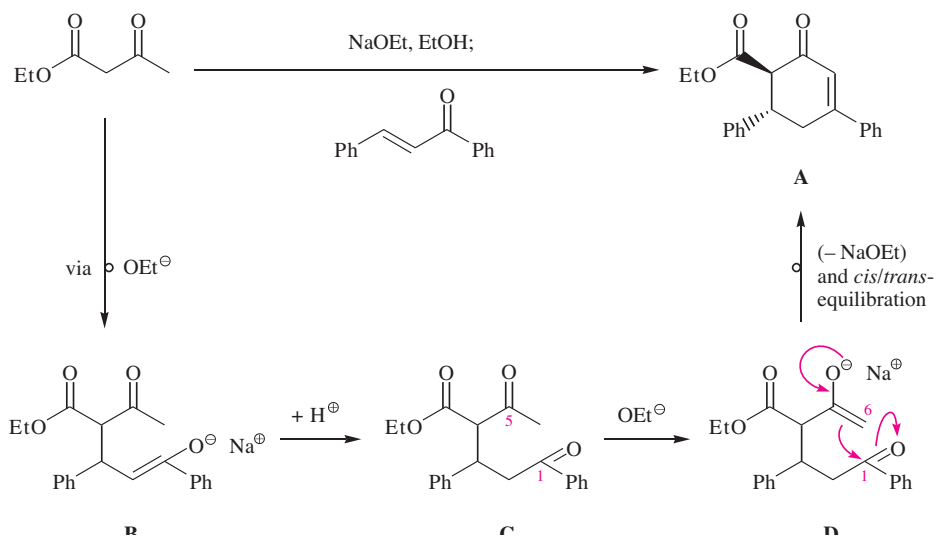


Fig. 13.72. Tandem reaction II, consisting of Michael addition and aldol condensation.

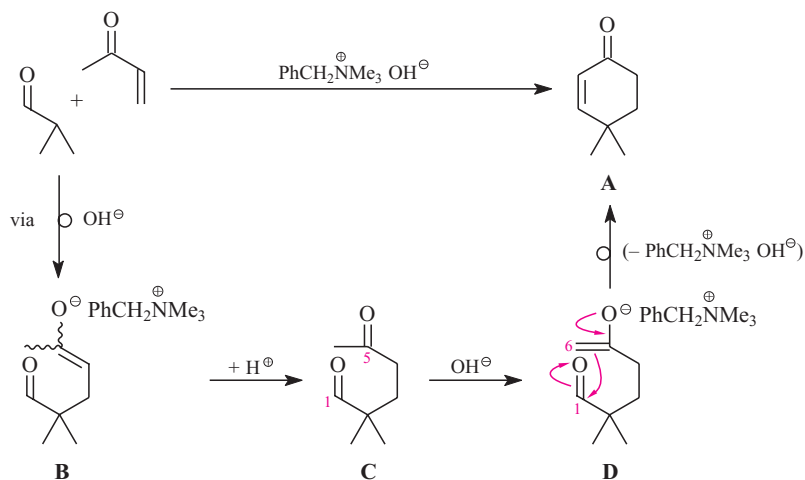


Fig. 13.73. Tandem reaction III, consisting of Michael addition and aldol condensation.

- Enolate **D** of Figure 13.73 undergoes an aldol condensation with the C=O double bond. The enone **A** is the condensation product. This reaction represents a six-membered ring synthesis even though it is not a six-ring annulation.
- Enolate **D** of Figure 13.74 is acylated by the ester following the usual mechanism. The bicyclic compound **A** is a product, which contains a new six-membered ring that has been annulated to an existing ring.

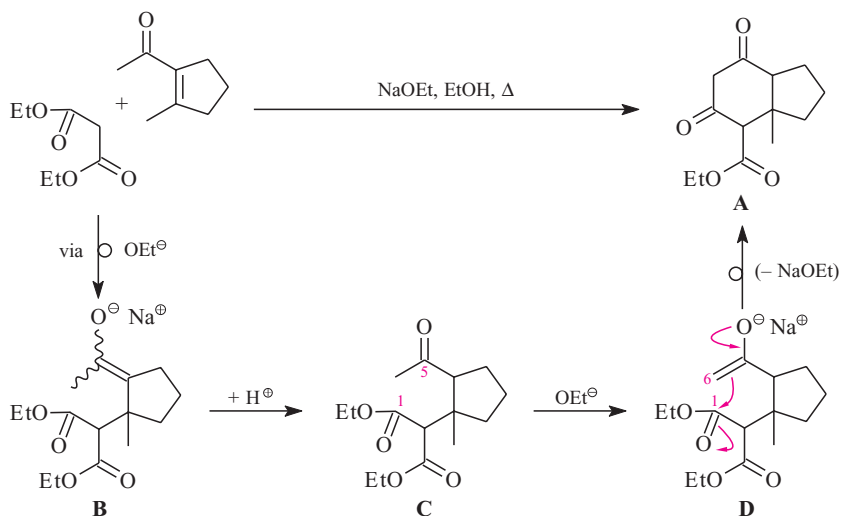


Fig. 13.74. Tandem reaction, consisting of a Michael addition and an enolate acylation (the major tautomer of the reaction product is not shown).

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