

# UNIT 14

## ENOLATES

### Structure

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	Expected Learning Outcomes		
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14.3	Generation of Enolates		Control of Enantioselectivity in Alkylation Reactions
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14.4	Reactions of Enolates		Nitrogen Analogs of Enols and Enolates: Enamines and Imines
	Halogenation		
	Enolate Alkylation: Reactions of Relatively Acidic Compounds	14.5	Summary
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		14.7	Answers

### 14.1 INTRODUCTION

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In your earlier classes you have studied about the construction of the molecular framework of organic molecules by carbon-carbon bond formation. Various types of electrophilic and nucleophilic reagents can be used for this purpose. In this unit our focus will be on nucleophilic reactions in which intermediates such as enolates, imine anions and enamines are involved. We will discuss these intermediates considering following points:

- generation of enolates
- the effect of the reaction conditions on the structure and reactivity of the enolates.
- the regioselectivity and stereoselectivity of enolates.
- generation and reactions involving nitrogen analogs of enolates, i.e. imines and enamines

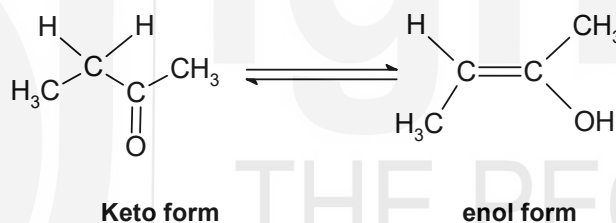
## Expected Learning Outcomes

After studying this unit you should be able to:

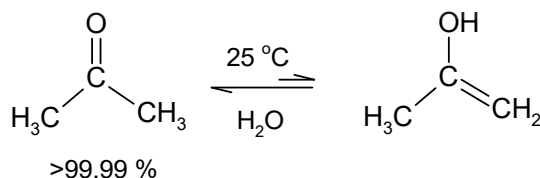
- list various methods for generating enols and enolates;
- describe various factors which control regioselectivity and stereoselectivity of enolate formation;
- explain the mechanism of nucleophilic addition reactions of enolates;
- understand the importance of enolate chemistry in stereoselective C-C bond formation; and
- describe significance of aldol reaction in synthetic organic chemistry.

## 14.2 ENOLS AND ENOLATES

Enols are isomers of aldehydes or ketones in which an alpha ( $\alpha$ ) hydrogen has been removed and placed on the oxygen atom of the carbonyl group. These molecules have a C=C and an OH group, so they are called an ene/ol i.e. enols.

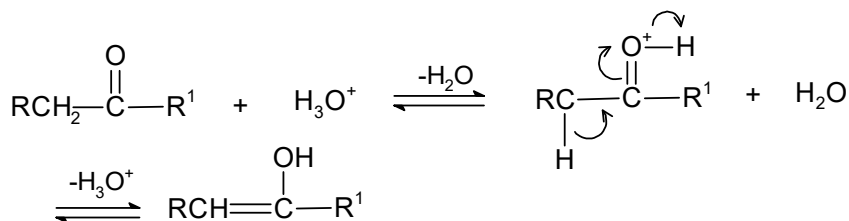


The process of converting between the keto and enol forms is called *tautomerism*. Tautomerism is rapid interconversion of structural isomers. In most of the cases, the equilibrium lies on the right with Keto form being the more stable. For example in aqueous solution of acetone at 25°C, concentration of enol form is almost negligible.

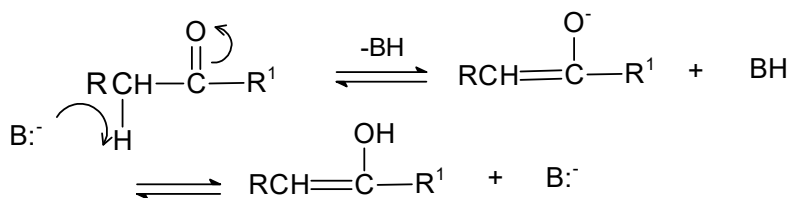


The equilibrium between carbonyl compounds and the corresponding enol form can be acid or base catalysed. This process occurs by a concerted mechanism in which protonation and deprotonation take place in single step.

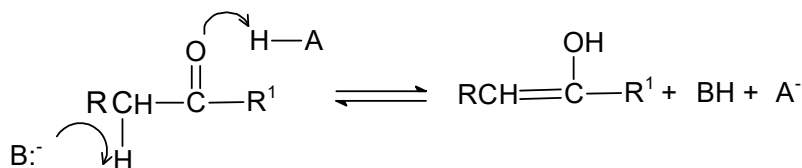
Acid catalysed:



## Base catalysed



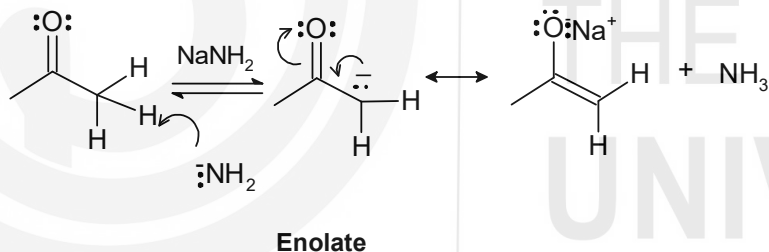
## Concerted



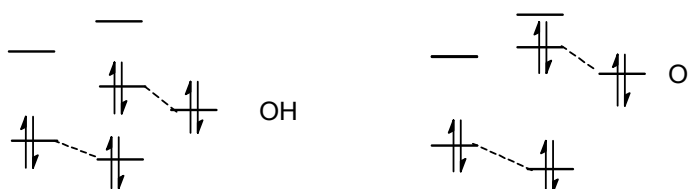
Once enols are formed, they are nucleophilic like simple alkenes by virtue of their  $\pi$  electrons, but they are more reactive than simple alkenes due to the presence of the hydroxyl group which participates as an electron donor during the reaction process. This can be shown by following resonance structures:



In strong basic conditions,  $\alpha$ -hydrogen of an aldehydes or ketone can be removed to generate resonance stabilized enolate anion or enolate.



Enolate anions are more reactive than enols. The relative lower reactivity of enols is due to the presence of proton of OH group, which decreases the electron density of the enol relative to the negative charge on oxygen of enolate. This relative reactivity of enol and enolate can also be explained on the basis of Molecular Orbital (MO) theory. Both  $-\text{OH}$  and  $-\text{O}^-$  donor substituent raise the energy of the  $\pi$  HOMO of enolate, but  $-\text{O}^-$  group being a better donor raises this energy little higher.

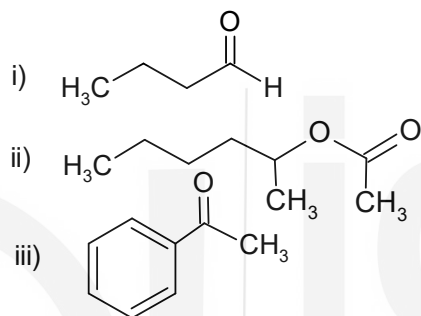


As mentioned earlier in most of cases, the keto-enolate equilibrium lies on the right because of the more stability of keto form. Typical strong bases such as hydroxide or alkoxide are only capable of forming, the enolates in very low

concentration. This leaves a significant concentration of the electrophilic carbonyl which can react with the base or the enolate. Thus aqueous base conditions used for the aldol condensation are not suitable because of the very low concentration of enolate formation from simple carbonyl compounds. Further, bases like hydroxide or alkoxide are also good nucleophiles. Therefore, they induce competing reactions such as  $S_N2$  and E2. Thus it becomes necessary to achieve complete conversion of aldehydes or ketone reactants to their enolate forms for their nucleophilic addition reactions. In the next section we will study various methods to generate enolates in high concentration.

### SAQ 1

Write enol forms of following compounds:



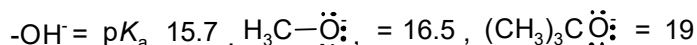
### SAQ 2

Why enolate anions are more reactive than enol form?

## 14.3 GENERATION OF ENOLATES

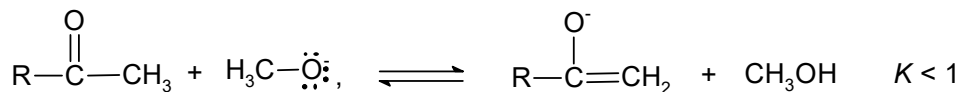
Acidity of the reactants having  $\alpha$ -hydrogen such as aldehydes or ketones determines which base can be used for generating enolates. For complete conversion, the base must be weaker acid than the reactants. In other words, the reagent must be a stronger base than the enolate anion of the reactant. Beside these, solvents and other coordinating or chelating agents also have strong effect on the formation of enolates. Let us now explain all these points using some examples.

The  $pK_a$  values of the  $\alpha$ -C-H of acetone and other similar ketones are about 20 ( $K_a = 10^{-20}$ ) while the  $pK_a$  of typical base like,

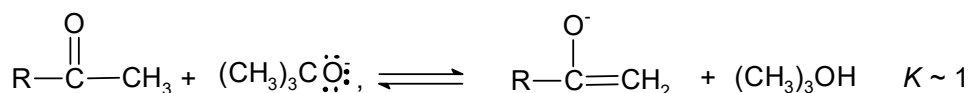


These bases are much less basic than the enolate ions. As a result, they convert only a small fraction of ketones, aldehydes or other carboxyl compound having  $\alpha$  hydrogen, to their corresponding enolates. Thus, by comparing the approximate  $pK_a$  values of the bases with those of the reactant of interest, it is possible to estimate the position of the acid-base equilibrium for a given reactant-base combination.

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

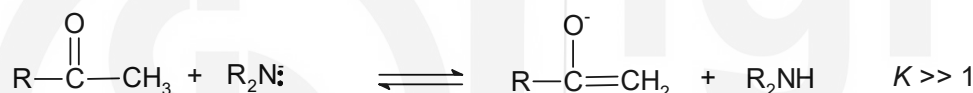


The slightly more basic tertiary alkoxides are comparable to the enolates in basicity, and a more favorable equilibrium will be established with such bases.



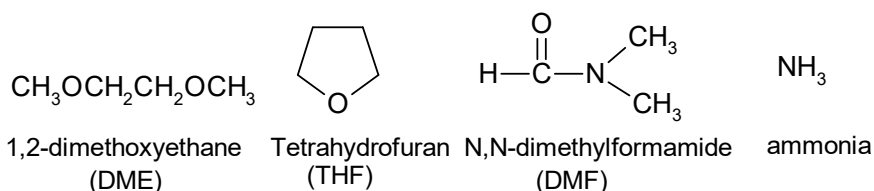
In DMSO, ketones such as acetone are slightly more acidic than in the simple alcohols. Therefore, use of alkoxide bases in DMSO favors enolate formation. All these typical bases besides providing low concentration of enolates, they are also potential nucleophiles in condensation and substitution reactions.

For the amide bases, such as NaH, NaNH<sub>2</sub>, ((CH<sub>3</sub>)<sub>2</sub>CH)<sub>2</sub>NLi (lithium diisopropylamide (LDA) (pK<sub>a</sub> ~ 36, the equilibrium can be shifted to right K<sub>a</sub>(B-H) << K<sub>a</sub>(C-H), and complete formation of the enolate occurs.



All these bases have higher pK<sub>a</sub>. The pK<sub>a</sub> difference between acetone and LDA is 20 on the other hand it is 1 in case of acetone and tertiary alkoxides.

Solvents also play important role in generation of enolates. Solvent like water and alcohols act as acids and they can protonate enolates. Therefore, solvents not having acidic protons are preferred for achieving high concentration of enolates. Aprotic solvents such as dimethyl sulphoxide (DMSO), 1,2-dimethoxyethane (DME), tetrahydrofuran (THF) *N,N*-dimethylformamide (DMF) and liquid NH<sub>3</sub> are commonly used.



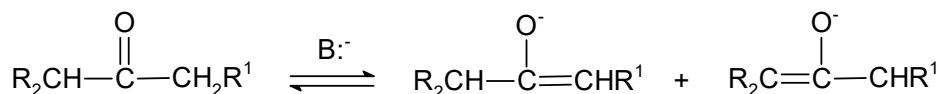
From above discussion it can be concluded that both bases and solvents play very important role in generation of enolates.

### SAQ 3

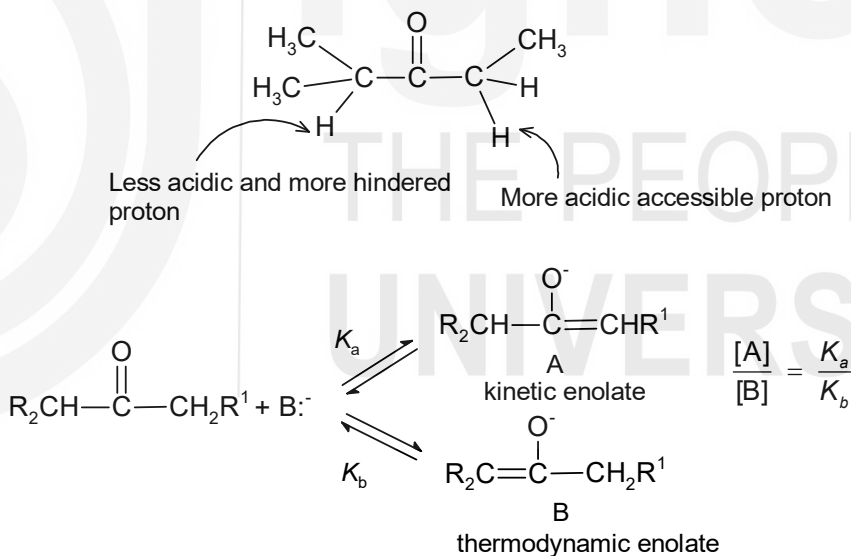
Why do we prefer aprotic solvents for generation of enolates?

### 14.3.1 Regioselectivity and Stereoselectivity in Enolates Formation

Deprotonation from the  $\alpha$ -position of carbonyl compounds is the basic method for the generation of enolates. An unsymmetrical dialkyl ketone can form two regioisomeric enolates on deprotonation. Consider following substituted ketone:



In this example, there are two sites of deprotonation leading to two different types of enolates. Although it may not be possible to generate only one type of enolate, but experimental conditions can be created to favor one of the regioisomers. The composition of an enolate mixture is regulated by kinetic or thermodynamic factors. The enolate ratio is determined by the relative rates of the competing proton abstraction reactions. In the example given below, secondary protons are more accessible protons for deprotonation. Deprotonation of these protons will give **kinetic control** product. On the other hand deprotonation of tertiary proton leads to more stable enolate because of higher degree of substitution of the double, thus formation of stable enolate is **thermodynamically controlled**.



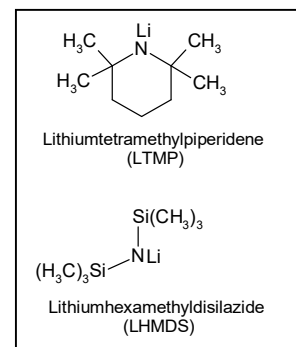
The regioselectivity of enolate formation can be controlled by following factors:

- Solvent
- Base
- Cation
- Temperature

By controlling reaction conditions for the formation of an enolate, it is possible to obtain either kinetic or thermodynamic control enolate. Kinetic control enolate is usually a less substituted enolate. Conditions for kinetic control of enolate formation are those in which deprotonation is rapid, quantitative and

irreversible. This can be achieved by using very strong base such as LDA or LiHMDS in an aprotic solvent such as DMSO in absence of excess ketone. Lithium ion is better counter ion than sodium or potassium as it maintain a tighter coordination at oxygen and reduce the rate of proton exchange.

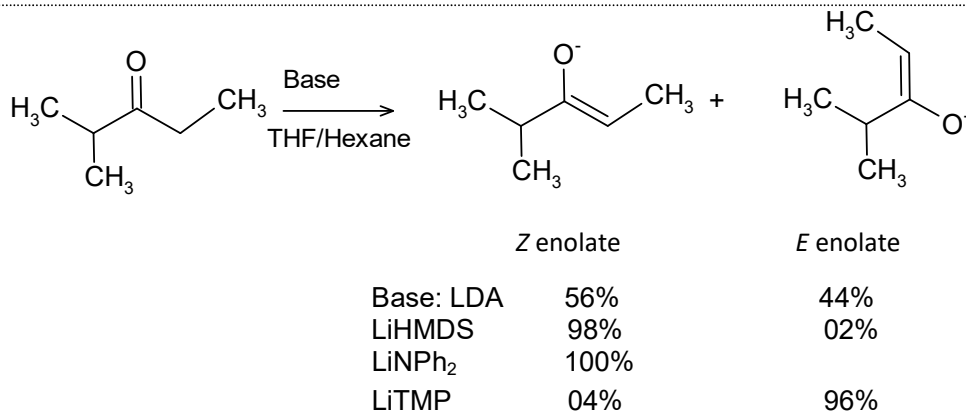
Aprotic solvents also favour the formation of kinetic product as protic solvents protonate oxygen which gives rise to the thermodynamically controlled enolate. Excess ketone also catalyses the equilibrium by proton exchange. Less hindered hydrogens also favour formation of kinetic enolates as they are more acidic and their removals are faster than removal of more hindered hydrogen. Higher temperature, weaker base and protic solvent such as ROH favour formation of thermodynamic enolates. The equilibrium ratios of enolates for some ketone-enolate systems are also shown in Table 14.1.



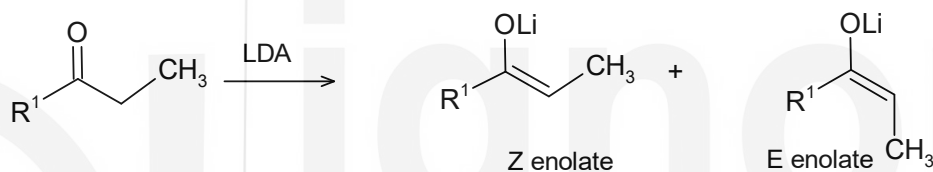
**Table 14.1: Composition of Enolate Mixture Formed under Kinetic and Thermodynamic Control**

$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{CH}_3$ Kinetic (LDA, 0°C)	 71%      13% Z form      16% E Form
$\text{CH}_3(\text{CH}_2)_3\text{C}(=\text{O})\text{CH}_3$ Kinetic (LDA, -78°C) Thermodynamic (KH, 20°C)	 100%      46% Z form      12% E Form 42%
$(\text{CH}_3)_2\text{CHC}(=\text{O})\text{CH}_3$ Kinetic (KHMDS, -78°C) Thermodynamic (KH, 20°C)	 99%      1%      12% 88%
 Kinetic (LDA, 0°C) Thermodynamic (NaH, 20°C)	 99%      1% 26%      74%

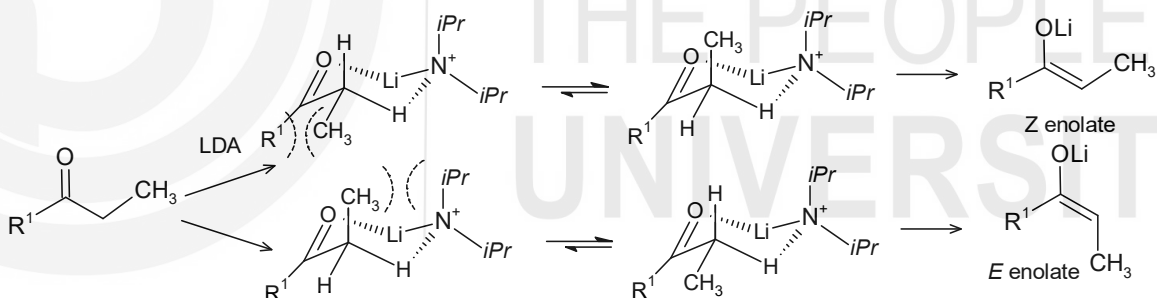
In addition to thermodynamic and kinetically formed enolates based on kinetic conditions as well as degrees of substitution of the double bond there is another characterization in enolates based on whether the alkyl group is on the same side of the double bond as the enolate oxygen or on the opposite side. If the alkyl group is on the same side of the double bond as the oxygen this is referred to as the *Z* (*zusammen* = together) configuration, this configuration is generally more stable. If the alkyl group is on the opposite side of the double bond from the oxygen this is referred to as the *E* (*entgegen* = opposite) configuration and is generally less stable. The ratio of *E* & *Z* isomers depends on the nature of base used for enolate formation and nature of substituents. Consider the formation of enolates using variety of bases in kinetic control condition.



From above example it can be inferred that LiHMDS generally provides the *Z* enolate as the major product and LTMP being a very bulky gives the *E* enolate as the major product. Such stereoselectivity can be explained on the basis of chair-like transition state. Consider following example:



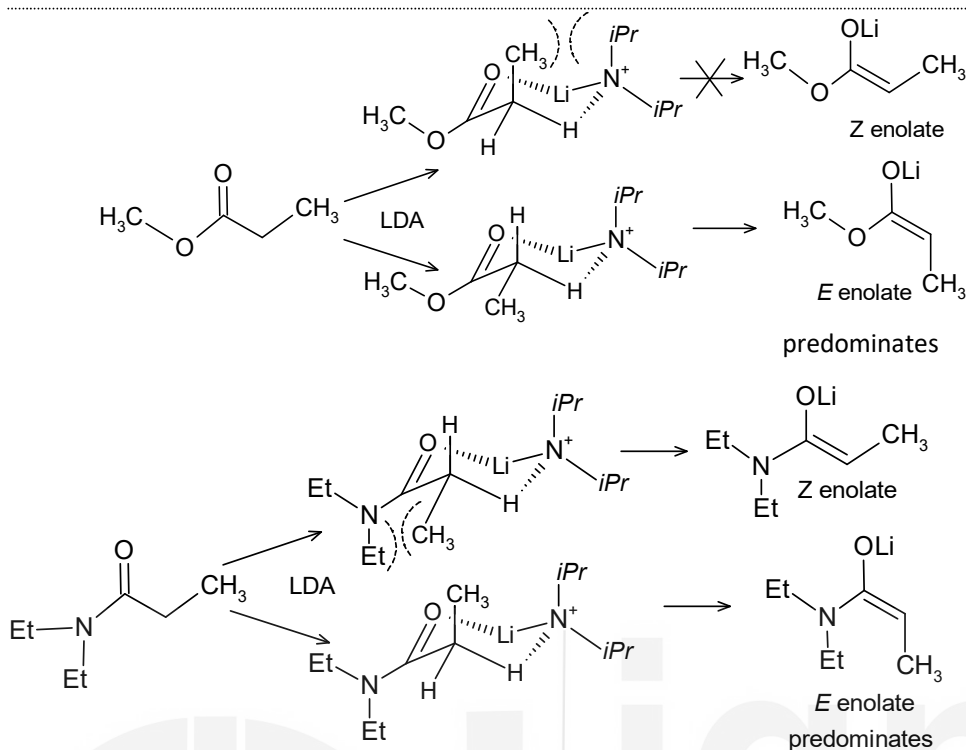
In a ketone shown above **Z-enolate** is favoured if **R<sup>1</sup>** is large but **E-enolate** is favoured if **R<sup>1</sup>** is small. Consider the transition states (TS) formed during the reaction as given below.



The interactions shown above are important for determining the stereochemical outcome of the reaction.

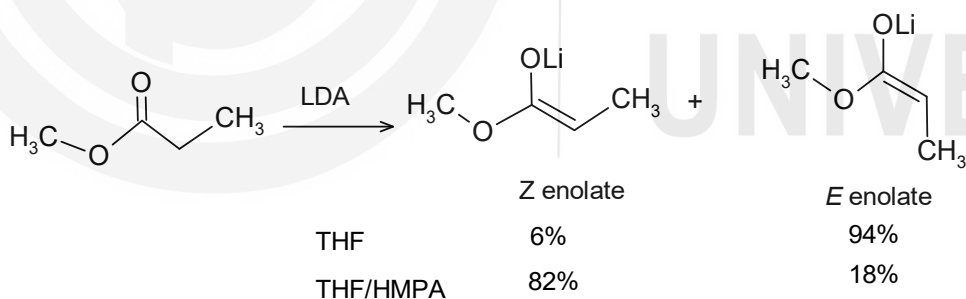
- if **R<sup>1</sup>** is large, this TS is destabilised by **R<sup>1</sup>**, **CH<sub>3</sub>** interaction and *Z* predominates
- if **R<sup>1</sup>** is small, 1,3-diaxial interaction is important as it destabilises this TS and *E* predominates. Therefore, bulky bases like LTMP favour the formation of *E*-Enolate

Esters and amide also form enolates on treatment with strong bases. In these cases  $\alpha$ -proton is less acidic than in a ketone. In case of esters, the formation of *E* enolates is favoured whereas tertiary amides tend to form *Z* enolates. This again can be explained by formation of cyclic transition states as shown below:



You can see in case of esters 1, 3 diaxial interactions discourage the formation of Z-enolate. On the other hand in substituted amides its substituent and the  $-\text{CH}_3$  interaction discourages formation of E-enolate.

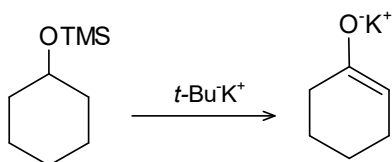
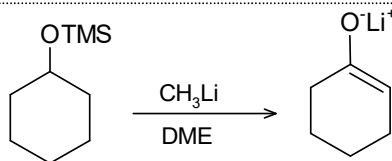
These arguments are good generalizations and many other factors also affect stereoselectivity of enolates. For example, use of the additive HMPA (hexamethylphosphoric triamide) reduces coordination and favours the thermodynamically more stable enolate.



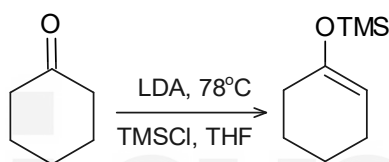
#### General observation

- LHMDS generally provides the Z enolate as major product
- LTMP (very bulky) affords the E enolate as the major product
- LDA gives intermediate result
- Use of HMPA as a strong Lewis basic donor-co-solvent can reverse selectivity.

Enolates can also be prepared by other methods than deprotonation of  $\alpha$ -hydrogen. For example enolates can be obtained by the cleavage of trimethylsilyl enol ether or enol acetate by methyl lithium. Alkoxides can also be used to cleave silyl enol ethers and enol acetates.

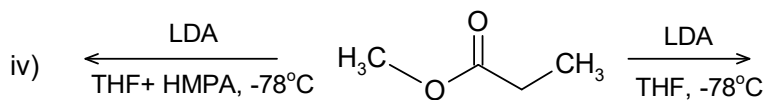
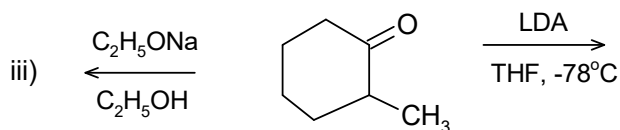
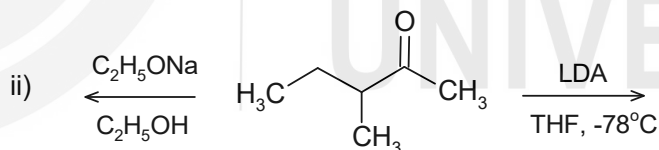
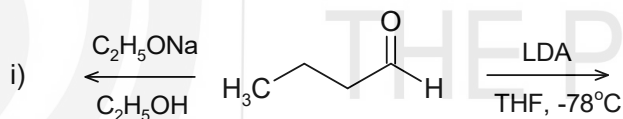


Trimethylsilyl enol ethers are readily prepared by trapping lithium enolate with TMSCl.



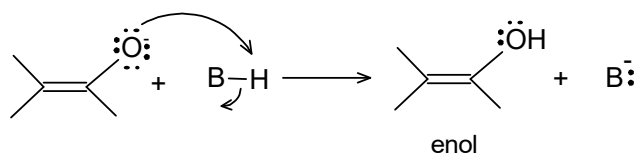
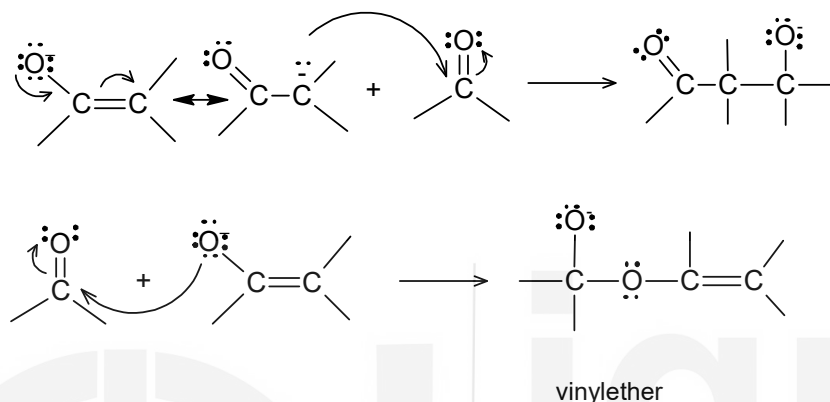
### SAQ 4

Draw the enolate formed when following compounds are treated in the specified condition given in each case.



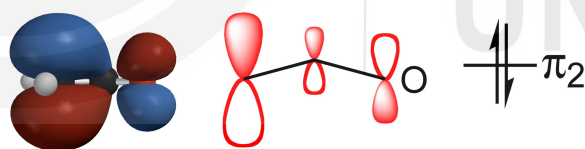
## 14.4 REACTIONS OF ENOLATES

The enolates are ambident nucleophiles and they can react either by oxygen or carbon ends.

**Acid-base reaction:****Nucleophilic-Electrophilic reaction:**

Soft electrophiles such as carbon electrophiles tend to interact with carbon centre and hard electrophile such as  $H^+$  prefer to interact with oxygen. This can also be explained on the basis of MO theory. The highest occupied molecular orbital (HOMO) of enolate is delocalized between carbonyl oxygen and  $\alpha$ -carbon. Both sides can act as nucleophilic centres but the carbon centre is a better nucleophile because the HOMO is distorted towards carbon centre and negative charge is centred on oxygen (see Fig. 14.1). Thus reactions which are dominated by charges and electrostatic interactions occur at the oxygen and reactions which are dominated by orbital interaction occur at the  $\alpha$ -carbon.

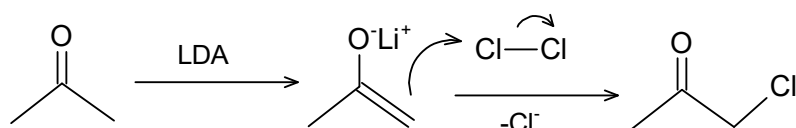
A soft electrophile is one in which the positive charge is able to spread over a larger area.



**Fig. 14.1:** The charge density map of the highest occupied molecular orbital (HOMO).

**14.4.1 Halogenation**

In these reactions, halogens are the electrophiles that react with the nucleophilic enolate.

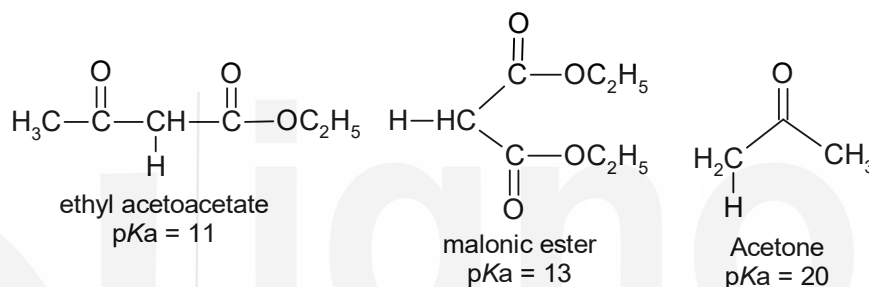


These reactions occur by a  $S_N2$  process. You have already studied such reaction in quite detail in your under graduate programme.

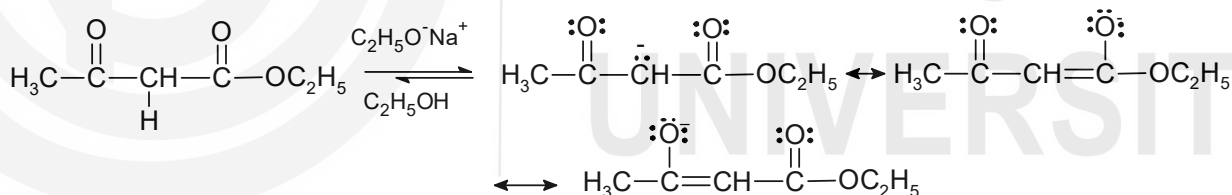
### 14.4.2 Enolate Alkylation: Reactions of Relatively Acidic Compounds

Malonic esters and  $\beta$ -ketoesters are relatively acidic compounds. These compounds generate enolate equivalent mild reaction conditions using metal alkoxides as base. The presence of two electron withdrawing substituents facilitates formation of the enolates. Enolate alkylation reactions occur by a  $S_N2$  process, therefore primary alkyl halides, allylic halides and benzylic halides are most reactive alkylating agents. Secondary alkyl halides react more slowly and give only moderate yields because of competing elimination reactions. Tertiary halides give mainly elimination products.

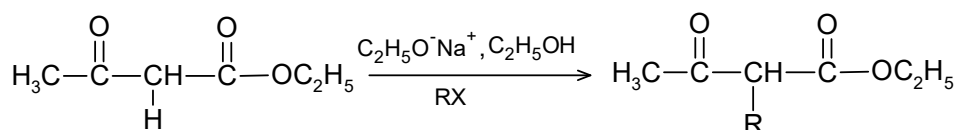
Two examples of this class extensively used in alkylation reactions are acetoacetic ester (ethyl acetoacetate) and malonic ester (diethyl malonate)



In both cases,  $\alpha$ -hydrogen is alpha to two carbonyl groups, the negative charge on the anions which are formed on deprotonation (enolates) can be delocalized by both the  $\text{C}=\text{O}$  groups. Such hydrogens are more acidic than that of a ketone. Therefore these enolates can be generated in high concentration even using alkoxide bases in alcoholic solvents.



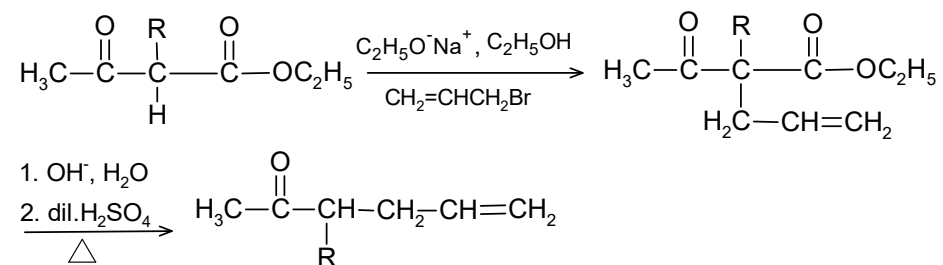
Similar resonating structures can also be drawn for malonic ester. The enolates formed by these esters undergo substitution reactions with alkyl halides.



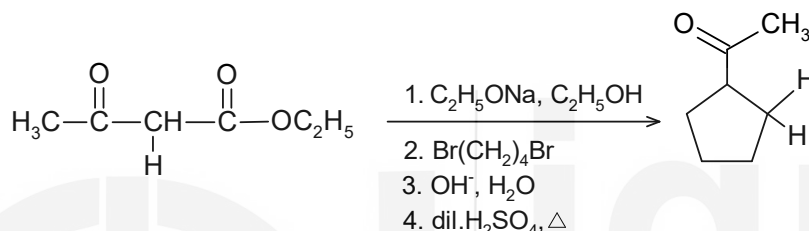
Above reaction illustrates the synthetic applications of acetoacetic and malonic esters in which two factors are important

- (i) enolate can be generated using mild bases such as metal alkoxides.
- (ii) Higher nucleophilic reactivity of the enolates in displacing halogen from alkyl halides and similar alkylating agents, and
- (iii) Extreme ease of decarboxylation of  $\beta$ -ketoacids.

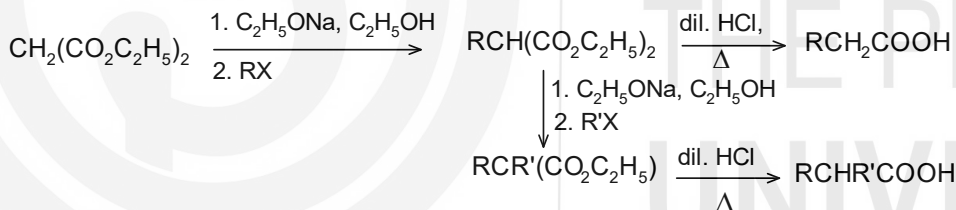
The monoalkyl acetoacetic ester may be treated with a base followed by addition of a different alkyl or allyl halide, alkaline hydrolysis (saponification) and decarboxylation (warming with dil. acids) gives a ketone that branched at the  $\alpha$ -carbon.



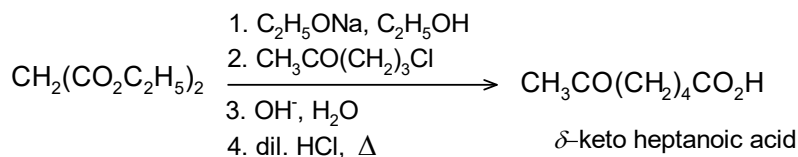
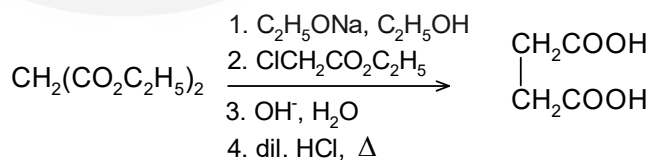
Cyclic products (3, 5, 6 and 7 carbon rings) can be formed if the dialkylation is done using dihaloalkane.



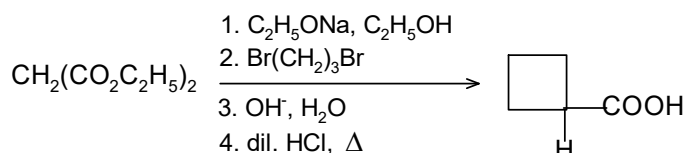
Malonic ester, like acetoacetic ester, when treated with base, generates the enolate ions which are also very reactive. Addition of alkylating agents followed by hydrolysis and decarboxylation gives carboxylic acids. Mono or dialkyl ethanoic acids are preferably prepared by this method.



Dicarboxylic acids and keto acids can be prepared using malonic ester.

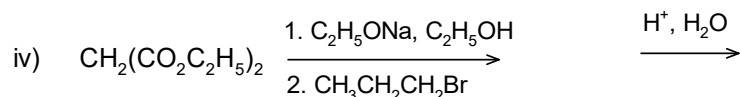
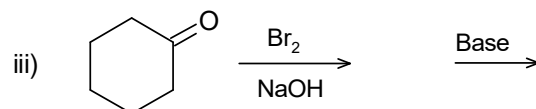
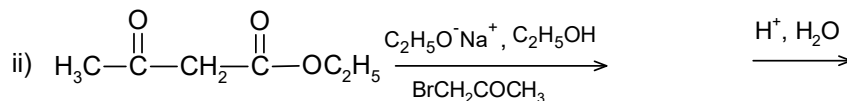
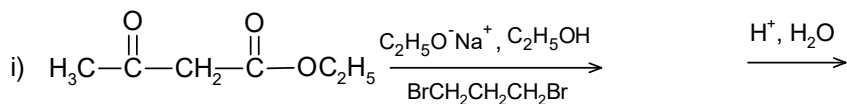


Alicyclic compounds have been prepared by the reaction of malonic ester with dihaloalkane.



## SAQ 5

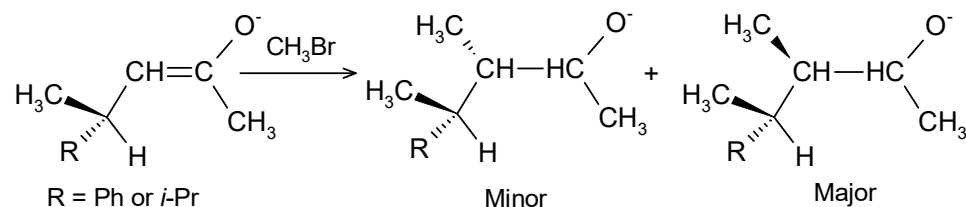
Predict the products of the following reactions



### 14.4.3 Alkylation of Ketone Enolates

Alkylations of ketone enolates are usually more useful than alkylation of aldehyde enolates. With aldehydes, it is difficult to avoid condensation reactions because  $\alpha$ -carbon of aldehydes are better electrophile. We have seen earlier that selective enolate formations are possible in case of unsymmetrical ketones. It is also possible to develop reaction conditions for stoichiometric formation of both kinetically and thermodynamically controlled enolates. All these factors permit us to use of enolate alkylation reactions in multi step synthesis of complex molecules. One of the important aspects of the alkylation reaction is that we can achieve stereoselectivity. The alkylation has a stereo electronic preference for approach of the electrophile perpendicular to the plane of the enolate, because the  $\pi$  electrons are involved in bond formation. A major factor in determining the stereoselectivity of ketone enolate alkylations is the difference in steric hindrance on the two faces of the enolate. The electrophile approaches from the less hindered of the two faces and the degree of stereoselectivity depends on the steric differentiation. Numerous examples of such effects have been observed. For analyzing the stereoselectivity of enolate alkylation reactions let us consider following example.

Consider a  $\beta,\beta$ -disubstituted enolate, in this case alkylation usually takes place *anti* to the larger substituent, R.



Major : Minor

R = Ph                      60 : 40

R = *i*-pr                    75 : 25

In such cases the major factors which decide approach of electrophile are the conformation of the enolate, the stereoelectronic requirement for an approximately perpendicular trajectory, the steric preference for the least hindered path of approach, and minimization of torsional strain. In above case R being a bulky group, electrophile will preferably approach anti to R group. In Fig. 14.2 we have shown trajectory of approach of the enolate and alkyl halide.

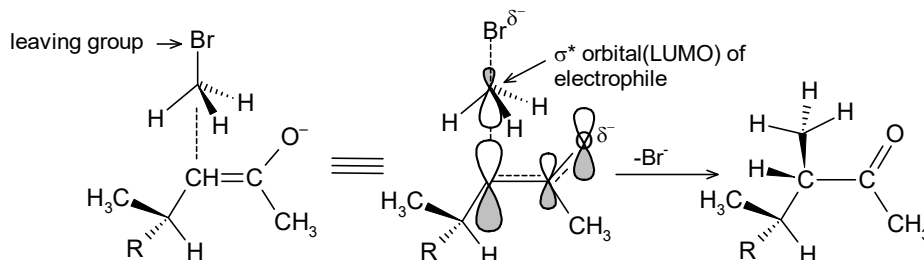
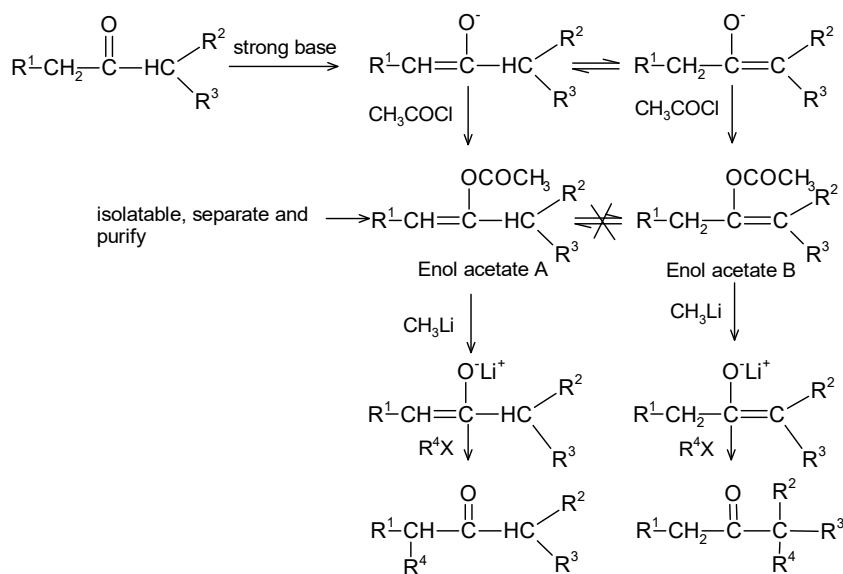


Fig. 14.2 : Attack of enolate on an electrophilic centre.

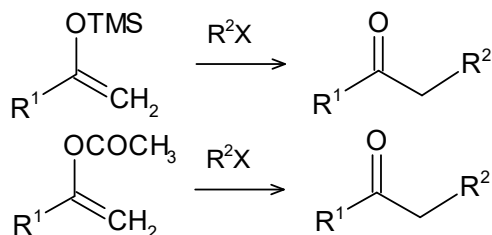
As mentioned earlier these reactions follow  $\text{S}_{\text{N}}2$  mechanism, therefore, these reactions are more feasible for  $1^\circ$  or  $2^\circ$ , as well as allylic or benzylic halides. In the case of  $3^\circ$  alkyl halides, we mainly observed  $\text{E}2$  elimination with enolate ion serving as the base.

Some elimination can occur even in  $1^\circ$  and  $2^\circ$  alkyl halides. This can be reduced by replacing halogen group with better leaving groups ( $\text{L} = \text{OSO}_2\text{R}$ ,  $-\text{OTs}$ , etc.).

Regioselectivity in alkylation of unsymmetrical ketones can be achieved by preparing regioselective enolate intermediates using reaction conditions as discussed earlier. This can also be achieved by preparing enol acetates and silyl enol ethers. Both enol acetate and silyl ethers are readily formed by trapping enolates with acetyl chloride and  $\text{TMSCl}$ , respectively. The isomers of enol acetates and silyl enol ethers can be separated using physical methods and their pure forms then converted to lithium enolate on treatment with methyl lithium. Alkylation reaction of each lithium enolate gives the corresponding  $\alpha$ -alkylated carbonyl compound (see example below).

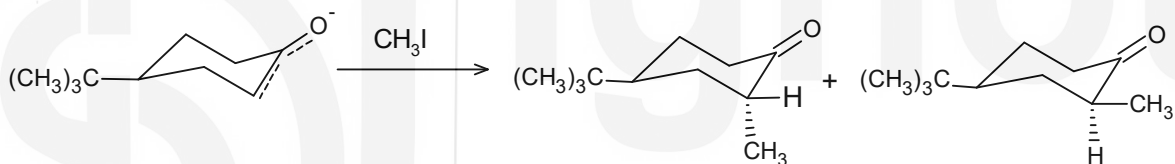


Both enol acetates and silyl enol esters can also be directly alkylated with alkyl halides in the presence of Lewis acids. Lewis acid forms a complex to the halogen atom making it a better leaving group.

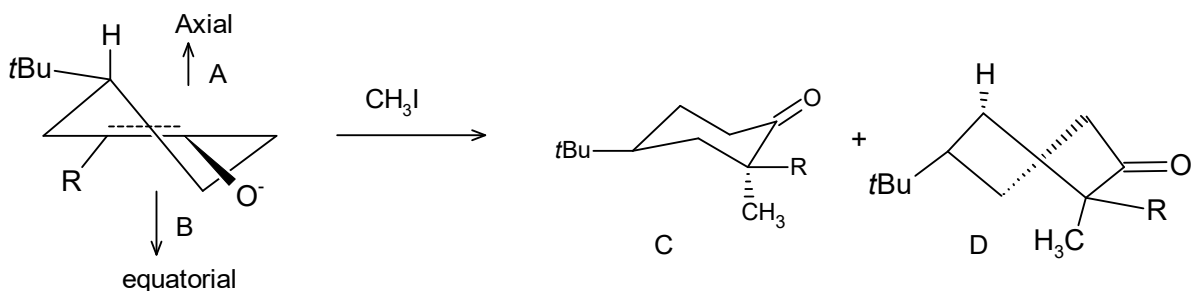
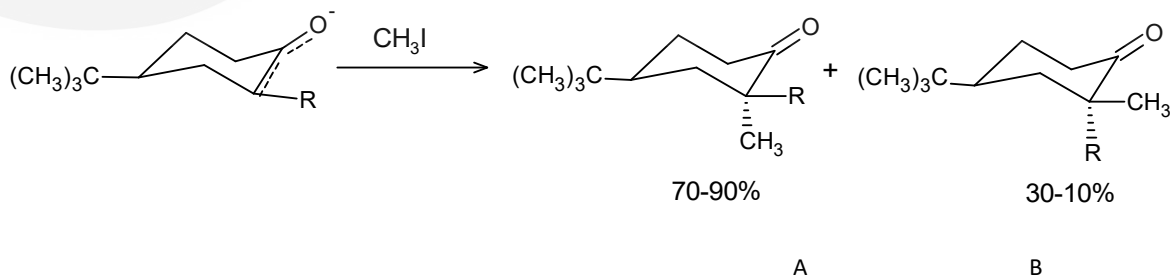


These reactions may follow  $S_N1$  reaction. Especially in case of tertiary alkyl halides, allylic and benzylic halides as all these system are capable of stabilising positive charge.

In cyclic system, ring conformation and nature of substituents are the dominant factor. In case of 4-*t*-butylcyclohexanone, there is little steric differentiation for *cis* and *trans* approaches of electrophile. The alkylation product is a nearly 1:1 mixture of the *cis* and *trans* isomers.

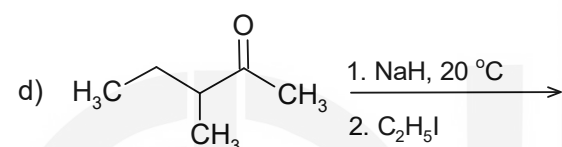
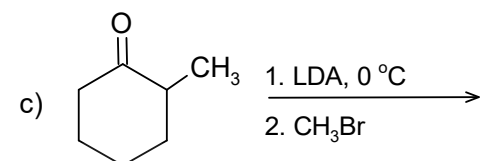
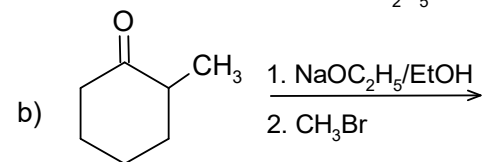
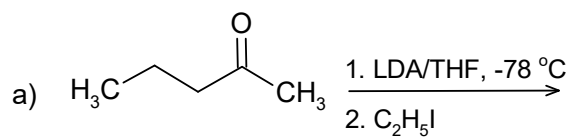


The introduction of an alkyl substituent at the  $\alpha$ -carbon in the enolate enhances stereoselectivity. This is due to a steric effect in the enolate. In such cases, the electrophile approaches from an axial trajectory preferably. This approach leads directly into chair-like product (A). Equatorial approach leads to a higher energy twisted-boat conformation (see structure D) which finally leads to structure B.



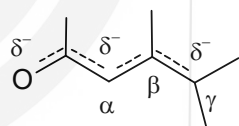
## SAQ 6

Predict the product(s) for each of the following alkylation reactions:

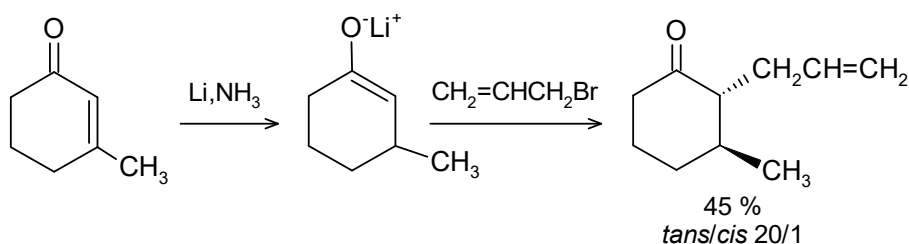
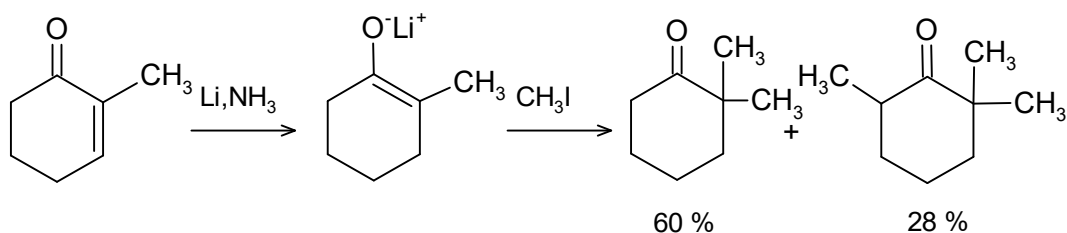


#### 14.4.4 Alkylation of $\alpha,\beta$ -unsaturated Ketones

In the case of  $\alpha,\beta$ -unsaturated ketones, there are three potential sites from where electrophile attack on the enolate can take place. These are oxygen, the  $\alpha$ -carbon, and the  $\gamma$  carbon. The  $\alpha$  site is kinetically favourable for the electrophilic attack.

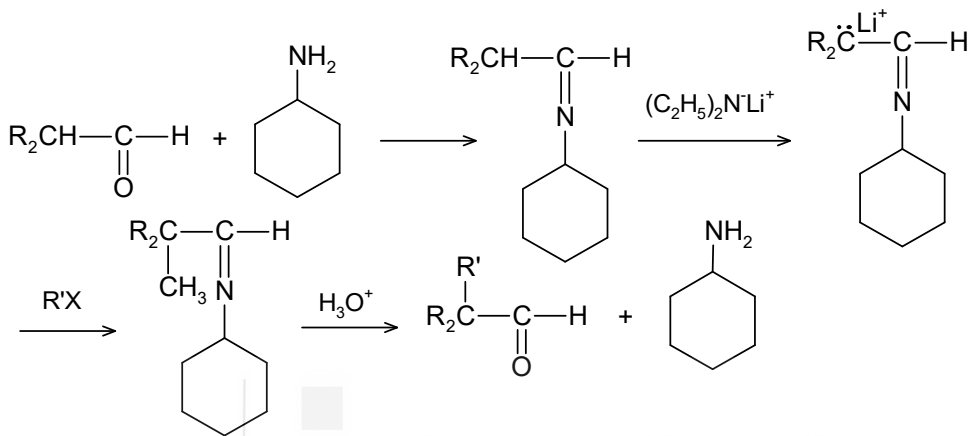


This selectivity may be due to the fact that  $\alpha$ -carbon has greater negative charge as compared with  $\gamma$  carbon.



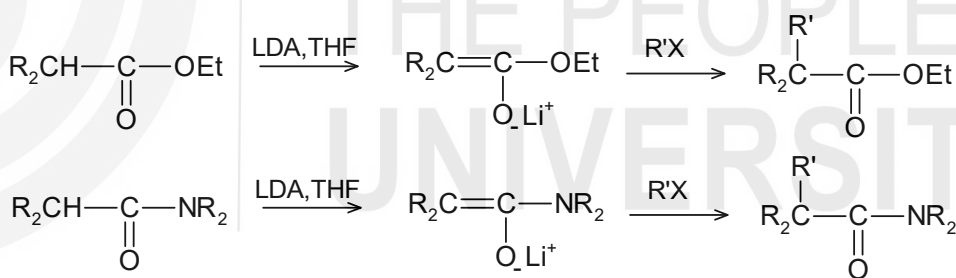
### 14.4.5 Alkylation of Aldehydes, Esters, Carboxylic Acids and Amides

As mentioned earlier alkylation of ketones has wider applications in synthetic chemistry. Since direct alkylation of aldehydes leads to condensation reactions mainly in presence of base, we can use the indirect approach as shown below:

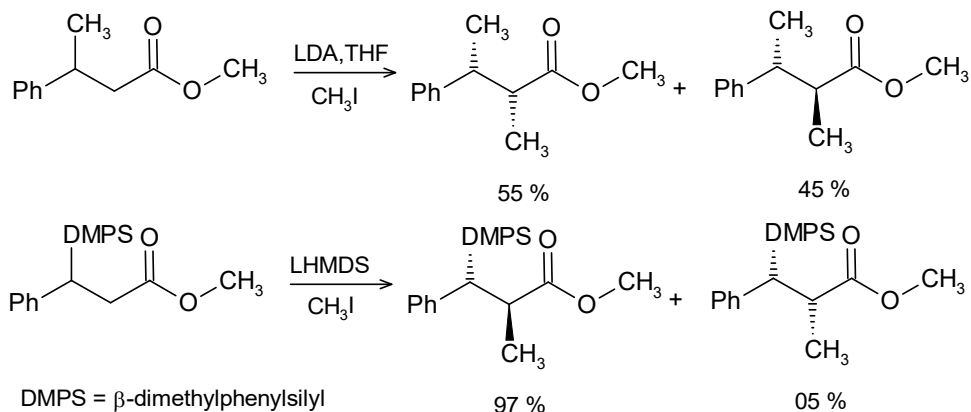


In above reaction, we have converted aldehyde to an imine and then this react with strong base to give an enolate type ion. Reaction of this ion with alkyl halide gives an  $\alpha$ -alkylated imine that can be hydrolyzed to give the  $\alpha$ -alkyl aldehydes.

Both esters and amides can also be alkylated. Unlike ketones, they give one enolate ion on reaction with base and they are less reactive than aldehydes in aldol reactions.

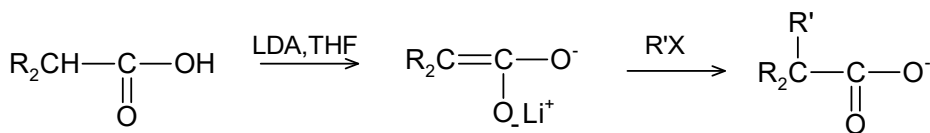


Similar to ketone, the stereochemistry of alkylation of esters and amides depends on steric factors mainly.



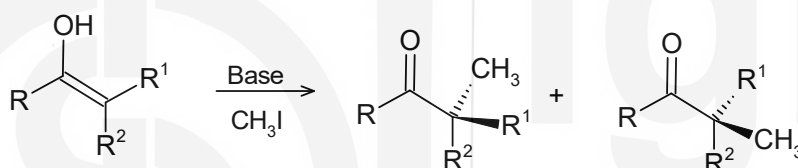
This stereoselectivity is the result of the conformation of the enolate and steric shielding by the silyl substituent. Such directive effect has been employed in stereoselective synthesis. In next section we will further elaborate this concept.

Strong bases convert carboxylic into enolate dianion. This dianion will react with haloalkane to give the  $\alpha$ -alkylated carboxylic ion.

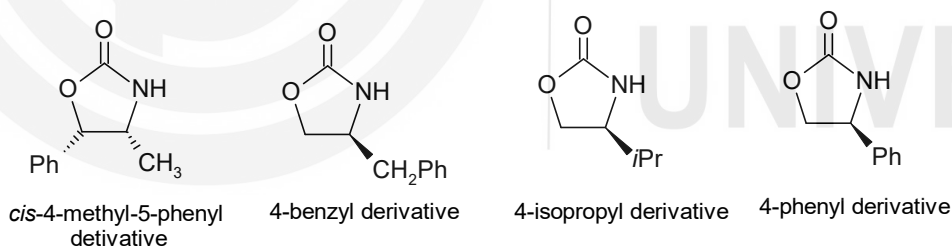


### 14.4.6 Control of Enantioselectivity in Alkylation Reactions

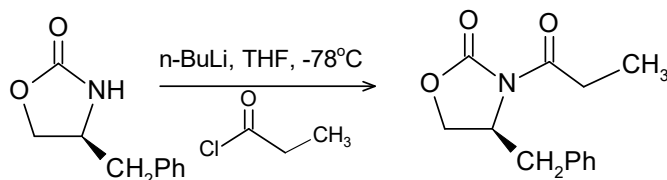
The alkylation of an enolate generate new stereogenic centre when  $\alpha$  substituents are nonidentical. In enantioselective synthesis, it is necessary to control the direction of approach and thus the configuration of the new stereocentre.



Enantioselective enolate alkylation can be achieved using chiral auxiliaries such as oxazolidinones. Many other chiral auxiliaries have been developed in past, but here we will consider some examples of oxazolidinones.

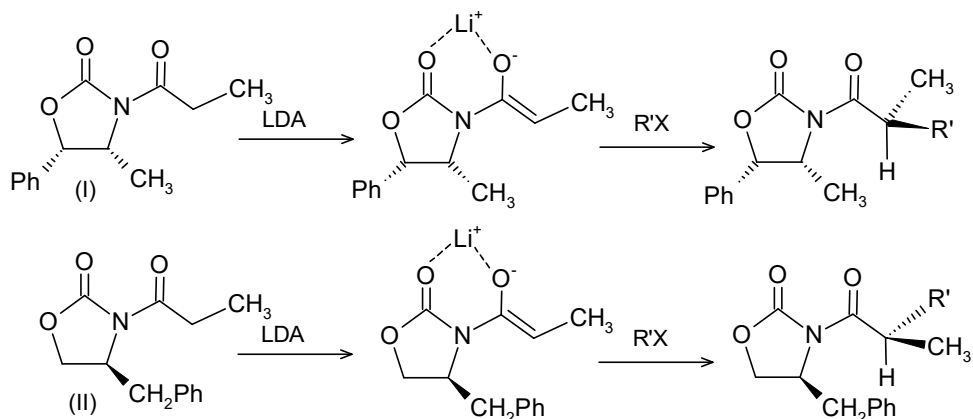


The 4-isopropyl and 4-benzyl oxazolidinones can be obtained from valine and phenylalanine, respectively. Other derivatives can also be synthesized easily. These chiral auxiliaries can be attached to an appropriate substrate by *N*-acylation reaction using *n*-BuLi as a base.

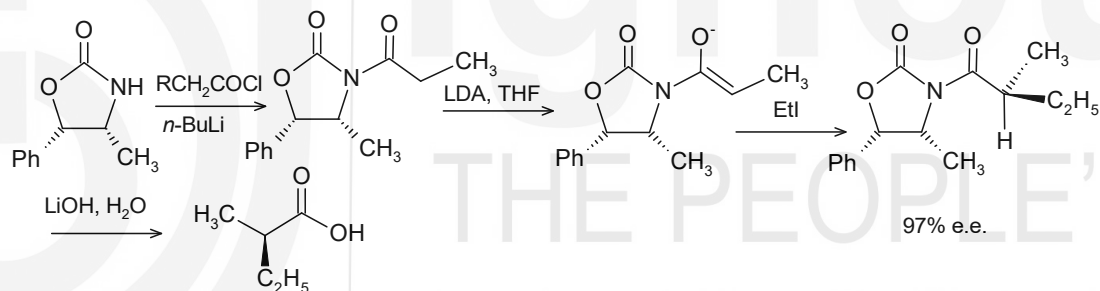


The above product with LDA generates mainly *z*-enolate. The electrophiles have a tendency to attack from the opposite face of the chiral controlling group at C<sub>4</sub> position of oxazolidine ring. The high to excellent diastereoselectivity in

alkylation reactions of oxazolidinones as chiral auxiliary has been well established.



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



#### 14.4.7 Nucleophilic Addition of Enolates on Carbonyl Compounds

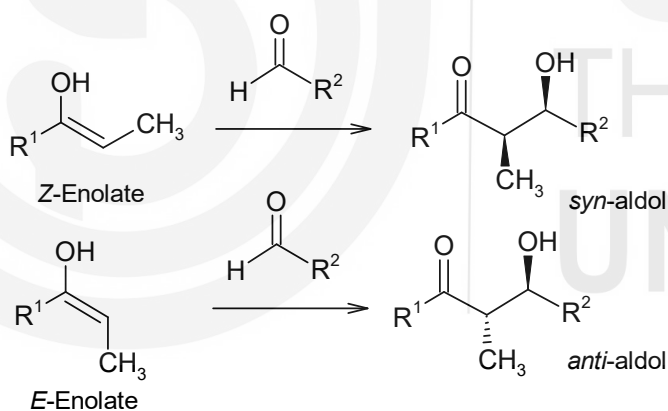
In earlier Sub-section we have described reaction of enolates with alkylating agents such as alkyl halides. In this Sub-section we will discuss chemistry of the nucleophilic attack by enolates on carbonyl groups of aldehydes or ketones.

The nucleophilic addition reactions of enolate on carbonyl compounds are most useful methods for carbon-carbon bond formation. Some important examples of such reactions are the aldol reaction, the Robinson annulation, the Claisen condensation, carbon acylation methods, the Wittig reaction and other olefination methods. Here our focus will be on aldol reactions.

An aldol reaction is the nucleophilic attack on a carbonyl group by an enol or enolate to create a beta hydroxy carbonyl compound. If the reaction is followed by dehydration, it results in the formation of a double bond and the reaction is called an aldol condensation. The aldol reaction is the most important reaction for lengthening a carbon chain that contains chiral centers. In most cases, this can be achieved by using enolates of smaller metal ions such as lithium, boron, titanium, tin, and zirconium etc..

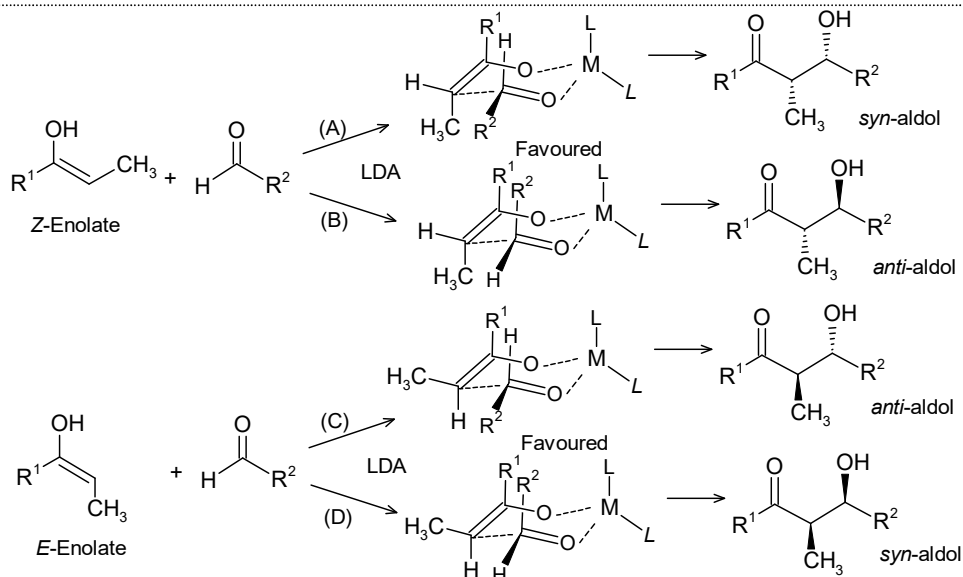
As we have discussed earlier, the enolates that participate in an aldol reaction can be formed under two types of conditions, either thermodynamic deprotonation or kinetic deprotonation. A thermodynamically formed enolate generally has the most substituted double bond or conjugated double bond and is more stable because of the substitution. The kinetically formed enolate is formed by the removal of the most easily (accessible) proton and they are generally less substituted. If the thermodynamic product is desired, then a larger or more loosely held counter ion such as sodium or potassium is used as this allows for proton exchange and the reaction is done in a protic solvent at warmer temperatures and the enolate is allowed to come to equilibrium with its most stable form. When the kinetically deprotonated enolate is desired, a smaller more tightly bound counter ion such as lithium or boron is used as this decreases the rate of proton exchange, and an aprotic solvent and cold temperatures (generally from  $-80^{\circ}\text{C}$  to  $-35^{\circ}\text{C}$ ) are also used. Usually a sterically hindered strong base is employed which cannot act as a nucleophile.

As mentioned earlier, these enolates may be *E*-enolate or *Z*-enolate based on whether the alkyl group is on the same side of the double bond as the enolate oxygen or on the opposite side. In aldol reactions, it is observed that *Z*-enolates predominantly give *syn* addition whereas the *E*-enolate predominantly gives the *anti* addition product. The *anti* and *syn* isomers are called diastereomers and these terms refer to the orientation of the  $\alpha$  and  $\beta$  substituents and are with respect to the lowest energy conformation of the molecule.



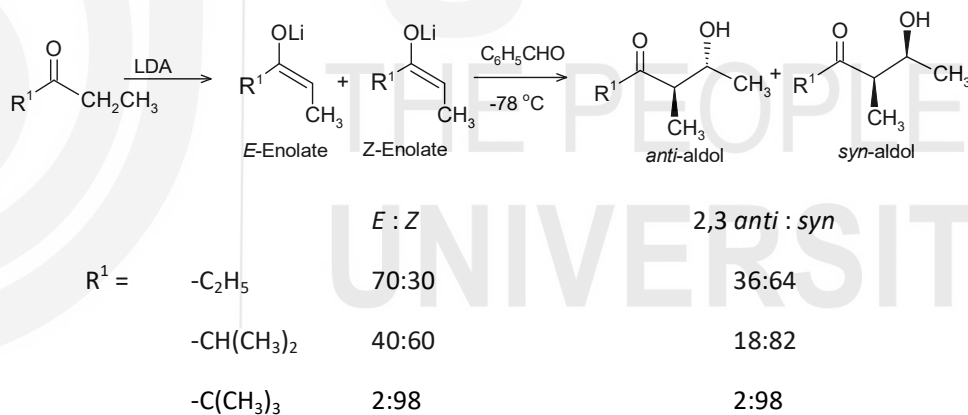
Generally the diastereoselectivity of an aldol reaction using thermodynamically formed *Z*-enolate is higher than for the kinetically formed *E*-enolates.

Formation of *syn* and *anti* products of aldol reaction can be understood on the basis of cyclic chair model of transition state. (See Fig. 14.3). The stability of the transition states is mostly governed by the 1,3 diaxial interactions. In the case of the most favorable pathway for the reaction of the *Z*-enolate and an aldehyde, the 1,3 interactions are better if R<sup>1</sup> is axial and R<sup>3</sup> is equatorial [TS A (Fig. 14.3)] rather than both groups being axial the alkyl groups [TS B (Fig. 14.3)]. For the most favorable reaction pathway for the *E*-enolate the same 1,3 interactions prevail TS C rather than TS D (Fig. 14.3). Thus, aldol reactions are stereospecific with respect to the *E*- or *Z*-configuration of the enolate. The *E*-enolate gives the *anti* aldol product, whereas the *Z*-enolate gives the *syn*-aldol.



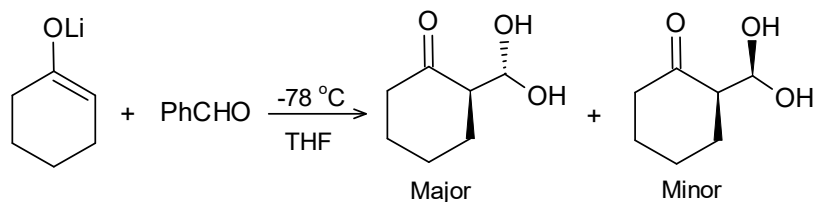
**Fig. 14.3:** Cyclic Transition model for *E*-enolates and *Z*-enolates;  $M = \text{Li}^+$  ion, Boron or any other metal ion.

Diastereoselection is best when using smaller metal ions such as lithium and boron that form short metal-oxygen bonds as this gives a tighter transition state and maximizes steric interactions. The steric interaction can further be increased by using one bulky group in enolate. Now consider following example.



In this case ketone enolates with more bulky substituents show an increasing stereoselectivity in the order: ethyl < *i*-propyl < *t*-butyl.

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



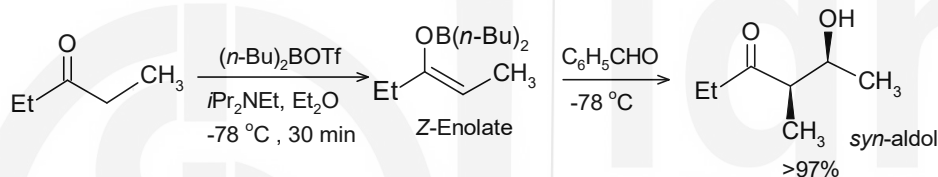
From these and many related examples the following generalizations can be made about stereoselection in aldol additions of lithium enolates.

- The chair TS model provides a basis for analyzing the stereoselectivity observed in aldol reactions of ketone enolates having one bulky substituent. The preference is *Z*-enolate→*syn* aldol; *E*-enolate→*anti* aldol.
- When the enolate has no bulky substituent, stereoselectivity is low.
- *Z*-Enolates are more stereoselective than *E*-enolates.

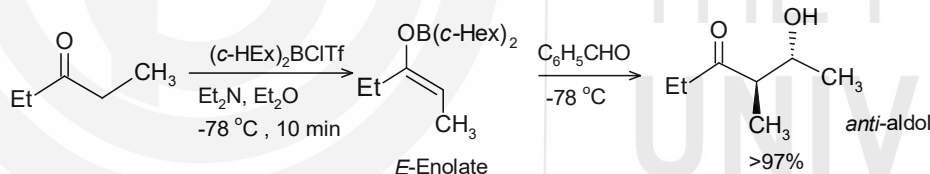
### Boron Enolates in Aldol Reactions

Stereoselectivity of aldol reaction of boron enolates is also predicted on the basis of cyclic TS similar to that for lithium enolates and the same relationship exists between enolate configuration and product stereochemistry. Boron enolates much more stereoselective than lithium enolates. The shorter B-O bond compared to Li-O bond leads to a tighter cyclic T.S. and accounts for the improved stereoselectivity.

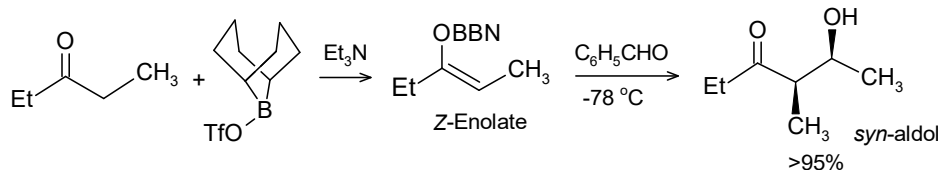
*Z*-Boron enolate can be prepared by the reaction of ketone with dialkylboron trifluoromethanesulfonate (triflate) and a tertiary amine. Use of boron triflates and a bulky amine favors the *Z*-enolate. The resulting aldol products are predominantly the *syn* product.



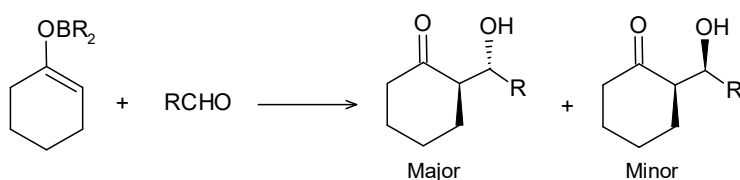
The combination of  $(c\text{-Hex})_2\text{BCl}$  and  $\text{Et}_3\text{N}$  provides the *E*-boron enolate preferentially. Bulkier group such as dicyclohexylboron chloride, favours formation of *E*-enolates.



Though 9-BBN (9-borabicyclononane) looks bulky, but most of it is 'tied-back' behind boron thus allowing formation of the *Z*-enolate.

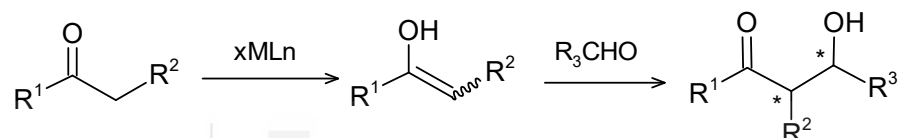


The *E*-boron enolate from cyclohexanone shows a preference for the *anti* aldol product. The ratio depends on the boron alkyl groups and is modest (2:1) with di-*n*-butylboron but greater than 20:1 for cyclopentyl-*n*-hexylboron.



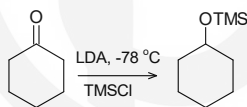
Beside Lithium and boron enolates aldol reactions can also be conducted using titanium, tin, and zirconium enolates.

Similar to alkylation reactions, we can also create facial discrimination in aldol reactions by using either the aldehyde or the enolate, or both, as chiral entities (substrate control). Also as in to alkylation reactions, this can also be achieved by attaching chiral auxiliaries to the carbonyl compound before enolization and then removing after the reaction (auxiliary control). Beside these approaches, using chiral ligands at the metal centre also provides an alternative approach to controlling the stereochemical outcome of aldol reactions (reagent control). In Fig. 14.4 we have summarized all three commonly used approaches for achieving stereochemical outcome of aldol reactions.



**Fig. 14.4:** Substrate control if stereoinduction from  $R^1$ ,  $R^2$  or  $R^3$ ; Auxiliary control if stereoinduction from  $R^1$  = a chiral auxiliary; Reagent control if stereoinduction from  $MLn$  or added Lewis Acid.

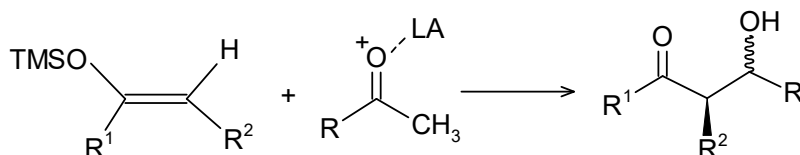
Silyl Enol Ethers can be readily formed by trapping a lithium enolate with TMSCl.



For mixed aldol reactions, enolates of esters, thiol esters, amides, and imides, including several that serve as chiral auxiliaries can be prepared similar to those for ketones. Lithium, boron, titanium, and tin derivatives have all been widely used in the synthesis.

#### Silyl Enol Ethers in Aldol Reactions (Mukaiyama Aldol Reaction)

The Mukaiyama aldol reaction refers to Lewis acid-catalyzed aldol addition reactions of silyl enol ethers. Silyl enol ethers are much less nucleophilic than boron or lithium enolates and do not react directly with aldehydes. Therefore, Lewis acid such as  $TiCl_4$  is used to increase the electrophilicity of carbonyl group to allow aldol reaction.

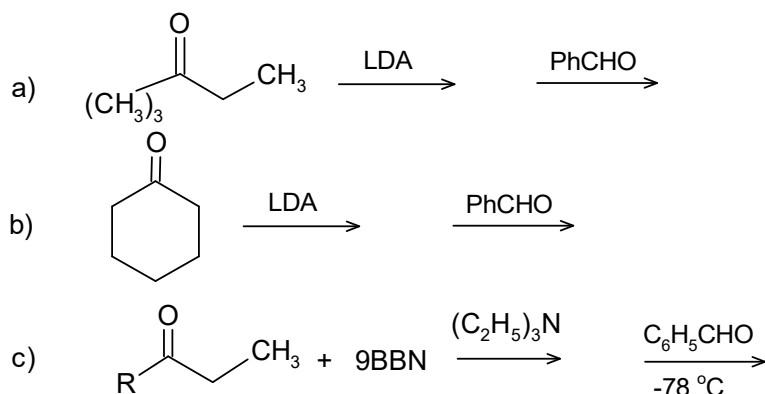


The reaction mechanism is quite different to that of lithium or boron enolates described above. These reactions proceed through an open T.S. Stereoselectivity of these reactions are usually low. But, the use of chiral Lewis acids in sub-stoichiometric quantities provides important methods for controlling the stereoselectivity of these reactions and thus these reactions are rapidly becoming a very useful method.

Beside  $TiCl_4$ , and  $SnCl_4$  quite a number of other Lewis acids can be used for Mukaiyama aldol reaction, including  $Bu_2Sn(O_3SCF_3)$ ,  $Bu_3SnClO_4$ ,  $Sn(O_3SCF_3)$ ,  $Zn(O_3SCF_3)$  and  $LiClO_4$ .

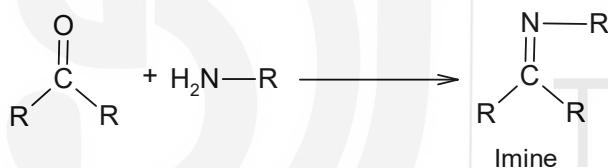
## SAQ 7

Complete following reaction and also indicate the major product.

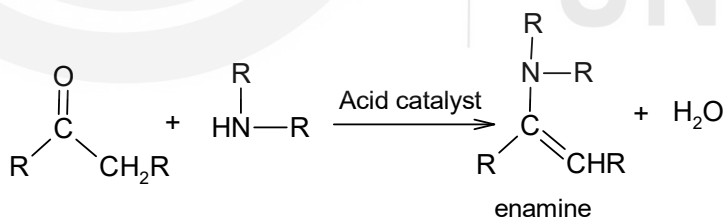


### 14.4.8 Nitrogen Analogs of Enols and Enolates: Enamines and Imines

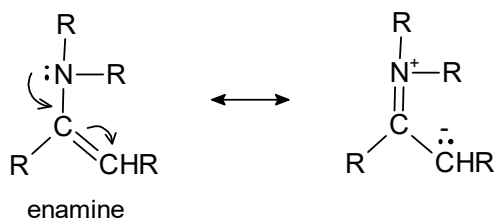
The nitrogen analogs of aldehyds and ketones are called imine or Schiff bases. The imine is prepared by the condensation of aldehyde or ketones with primary amines.



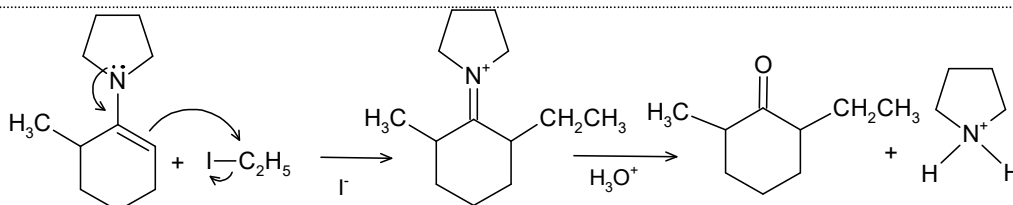
When we use secondary amines, they react with aldehydes or ketones having  $\alpha$ -hydrogen in the presence of acidic catalyst to give enamines.



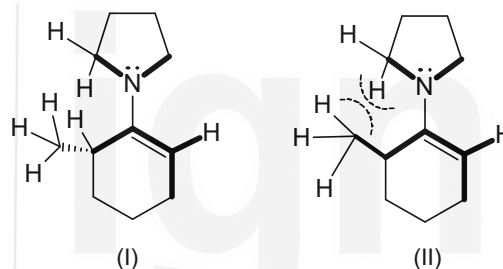
The  $\beta$ -carbon atom of an enamine is a nucleophilic site because of conjugation with the nitrogen atom similar to enolate ion.



The nucleophilicity of the  $\beta$ -carbon atom, permits enamines to be used for alkylation reaction similar to enolates.

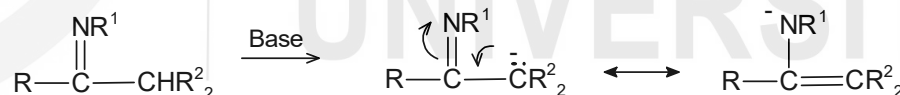


In above example of alkylation reaction of pyrrolidine enamine, the less substituted enamine is formed mainly by the reaction of 2-methyl cyclohexanone with pyrrolidine because of the steric factor and more acidity of the C-H on the less substituted carbon. Less substituted enamine is a mixture of two isomers (I) and (II). The isomer (I) is predominant because of the steric effect. Conjugation between the nitrogen atom and the  $\pi$  orbitals of the double bond favors coplanarity of the bonds that are darkened in the structures. In isomer (I) the methyl group adopts a quasi-axial conformation to avoid steric interaction with the amine substituents. A serious nonbonded repulsion in (I) destabilizes this isomer.

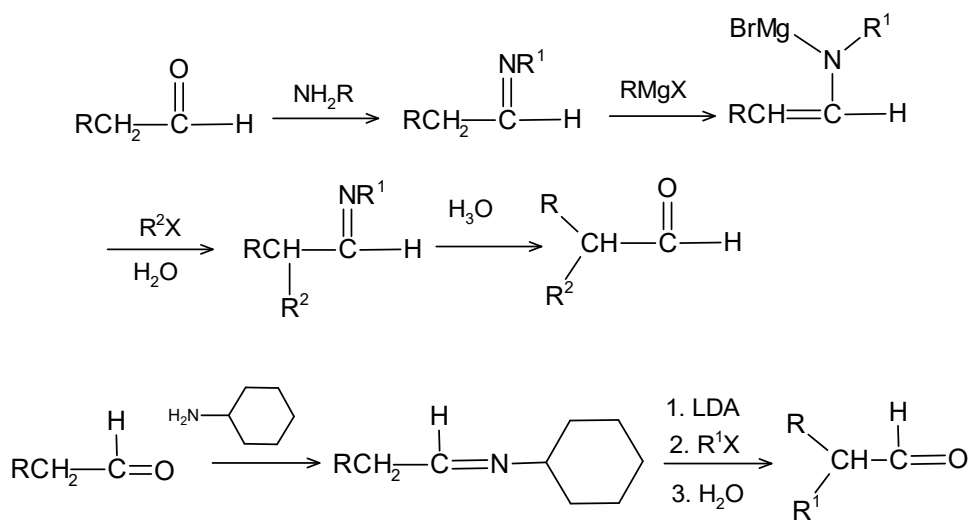


The imine ion resulting from alkylation can be hydrolysed to prepare 2,6-disubstituted cyclohexanone.

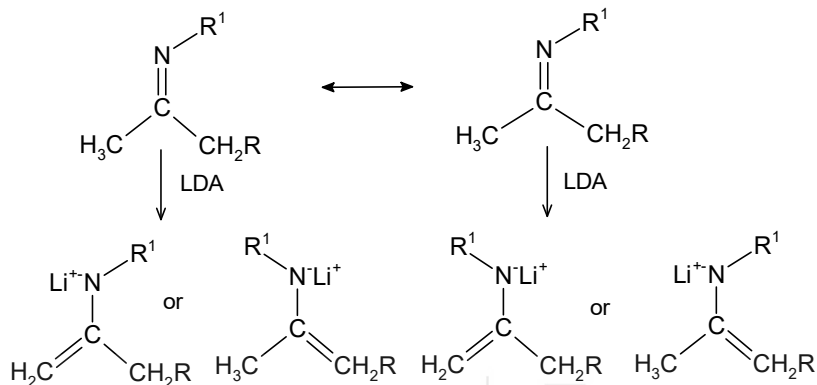
Imines can also be deprotonated at the  $\alpha$ -carbon by strong bases to give the nitrogen analogs of enolates. Grignard reagents and lithium amides can be used for deprotonation. These anions are referred to as imine anions. Imine anions are also more nucleophilic than enolates and can be alkylated.



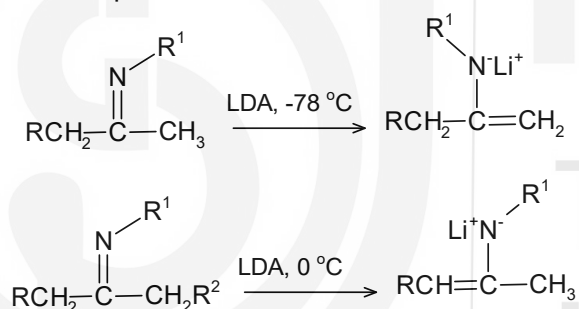
One application of imine anions is for the alkylation of aldehydes.



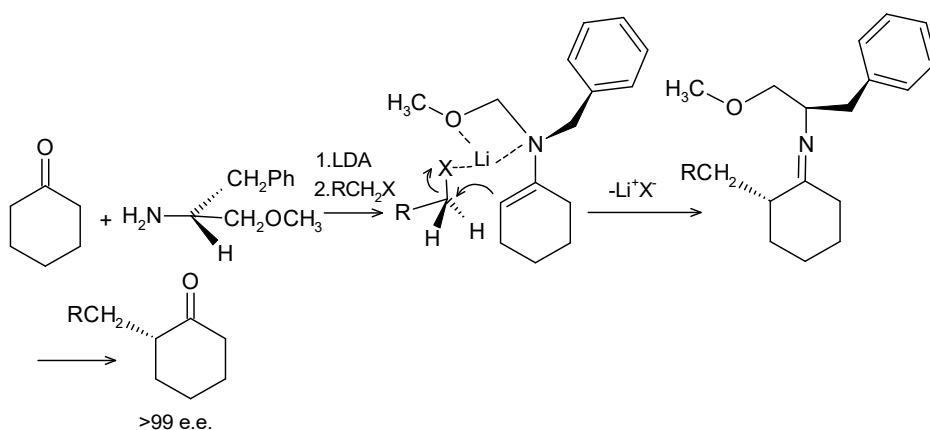
Ketone imine anions can also be alkylated. The prediction of the regioselectivity of lithioimine formation is somewhat more complex than the case of kinetic ketone enolate formation. One of the complicating factors is that there are two imine stereoisomers, each of which can give rise to two regioisomeric imine anions. The isomers in which the nitrogen substituent  $R^1$  is *syn* to the double bond are the more stable.



Regioselectivity of ketimines depends on the  $\alpha$ -substituents and N-substituents. For example, in methyl ketimines deprotonation of methyl is favoured when reaction is carried out using LDA at  $-78^\circ\text{C}$ . With larger N-substituents, deprotonation at  $25^\circ\text{C}$  occurs *anti* to the nitrogen substituent.



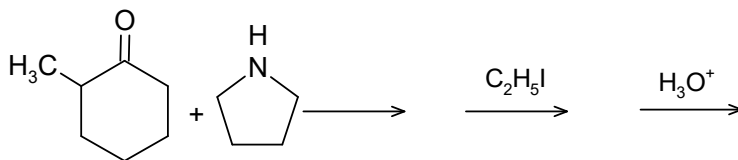
Beside the factors discussed above other factors such as the state of aggregation and solvation also control regioselectivity of ketimines. One of the important applications of the imine anions is that they can be prepared from enantiomerically pure amines. When imines derived from chiral amines are alkylated, the new carbon-carbon bond is formed with a bias for one of the two possible stereochemical configurations. Hydrolysis of the imine then leads to enantiomerically enriched ketone.



The important aspects of above reaction are: (1) formation of rigid structure due to the chelation of the methoxy group with the lithium ion; (2) the interaction of the lithium ion with the bromide leaving group, and (3) the steric effect of the benzyl group, which makes the underside the preferred direction of approach for the alkylating agent.

### SAQ 8

Complete following reaction:



## 14.5 SUMMARY

You have now seen how enols and enolates are generated. There was a detail discussion how to achieve regioselectivity and stereo selectivity in alkylation and aldol reactions. We have also briefly covered reactions of imine, enamine and silyl enol ethers.

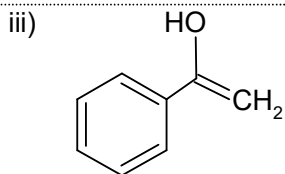
## 14.6 TERMINAL QUESTIONS

- What are the reaction conditions needed to generate kinetic control enolates?
- Starting with either acetoacetic ester or malonic ester how are the following compounds prepared:
  - 5-Methyl-2-hexanone
  - 3-methyl-2-hexanone
  - 2-Methyl butanoic acid
  - Allylethanoic acid
- How you will control stereochemical outcome of enolate formation.
- Write the factors which control stereoselectivity in aldol reactions of ketones.

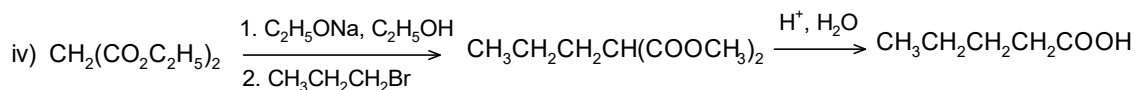
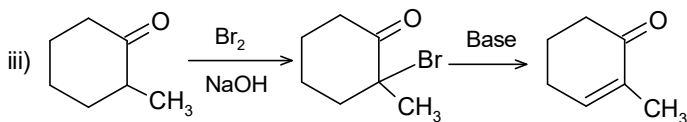
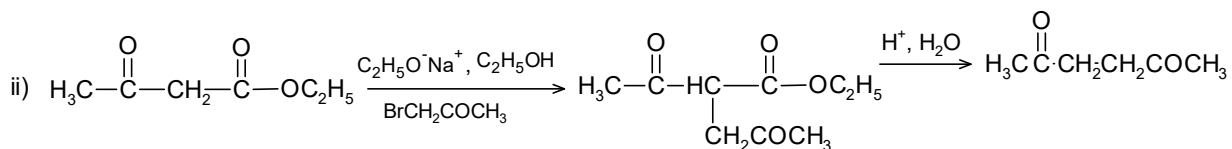
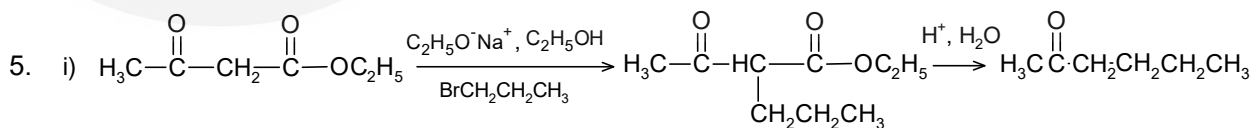
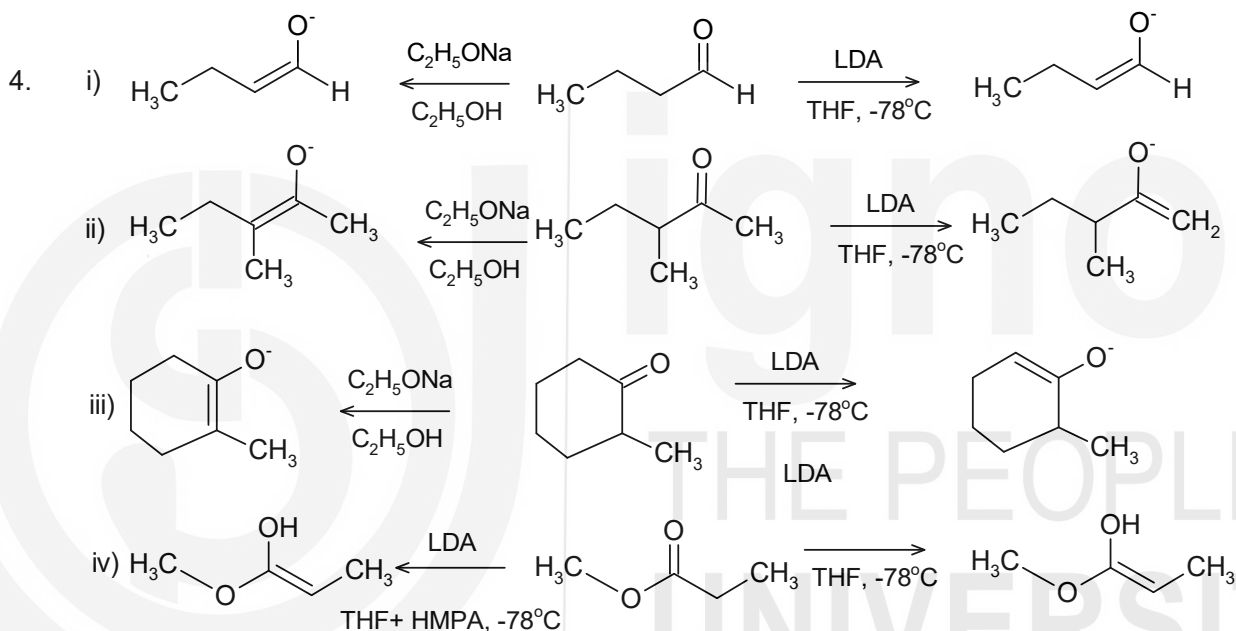
## 14.7 ANSWERS

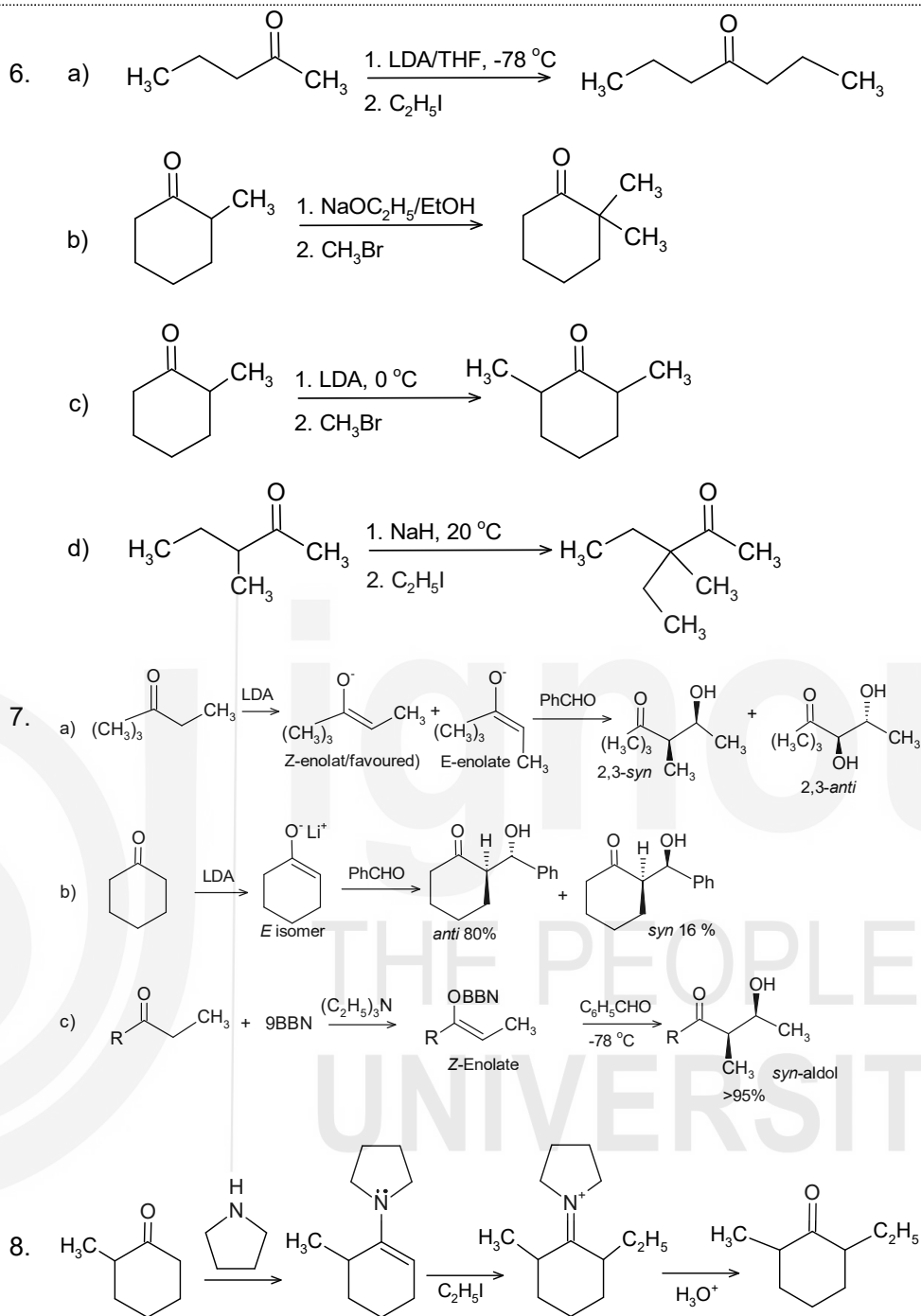
### Self Assessment Questions

- -



2. Enolate anions are more reactive than enols. The relative lower reactivity of enols is due to the presence of proton of OH group, which decreases the electron density of the enol relative to the negative charge oxygen of enolate.
3. Protic solvent like water and alcohols act as acids and they can protonate enolates. Therefore, solvents, not having acidic protons, are preferred for achieving high concentration of enolates.





### Terminal Questions

- Following conditions favour the formation of kinetic enolate: Proton attached to  $\alpha$  Carbon should be less substituted, strong base like LDA, low temperature, and aprotic solvent.
- Treatment of acetoacetic ester with: 1.  $\text{NaOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH} + (\text{CH}_3)_2\text{CHCH}_2\text{Br}$ ; 2.  $\text{OH}^-/\text{H}_2\text{O}$ ; 3.  $\text{H}_3\text{O}^+$
  - Treatment of acetoacetic ester with: 1.  $\text{NaOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH} + \text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$ ; 2.  $\text{NaOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH} + \text{CH}_3\text{Br}$ ; 3.  $\text{OH}^-/\text{H}_2\text{O}$ ; 4.  $\text{H}_3\text{O}^+$
  - Treatment of malonic ester with: 1.  $\text{NaOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH} + \text{CH}_3\text{CH}_2\text{Br}$ ; 2.  $\text{NaOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH} + \text{CH}_3\text{Br}$ ; 3.  $\text{OH}^-/\text{H}_2\text{O}$ ; 4.  $\text{H}_3\text{O}^+$

- d) Treatment of malonic ester with: 1.  $\text{NaOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH}$  + Allyl chloride;  
2.  $\text{OH}^-/\text{H}_2\text{O}$ ; 3.  $\text{H}_3\text{O}^+$
3. Following reaction conditions may be used to control stereochemical outcome of enolate formations:
- LHMDs generally provides the *Z* enolate as major product
  - LTMP (very bulky) affords the *E* enolate as the major product
  - LDA gives intermediate result
  - Use of HMPA as a strong Lewis basic donor-co-solvent can reverse selectivity.
4. Following factors control stereoselectivity in aldol additions via lithium enolates and boron enolates.
- aldol reactions of ketone enolates having one bulky substituent. The preference is *Z*-enolate  $\rightarrow$  syn aldol; *E*-enolate  $\rightarrow$  anti aldol.
  - when the enolate has no bulky substituent, stereoselectivity is low.
  - *Z*-Enolates are more stereoselective than *E*-enolates.

