

Block

**4****ORGANIC SYNTHESIS: SOME MORE  
APPROACHES**

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## Course Design Committee

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Prof. H. Surya Prakash Rao (Retd.),  
Department of Chemistry,  
Pondicherry University, Puducherry

Prof. Ashok Kumar Mishra,  
IIT Madras, Tamil Nadu

Prof. Tabrez Alam,  
Department of Chemistry, Jamia Millia  
Islamia, New Delhi

Prof. Ghanshayam Bez,  
North-Eastern Hill University,  
Shillong, Meghalaya

Prof. Sunil Sharma,  
Department of Chemistry,  
University of Delhi, Delhi

Dr. Pritam Mukhopadhyaya  
Department of Chemistry,  
Jawahar Lal Nehru University, New Delhi

**School of Sciences,  
IGNOU, New Delhi**

Prof. Sujatha Varma  
Prof. Sunita Malhotra  
Prof. B.I. Fozdar  
Prof. Javed A. Farooqi  
Prof. Sanjiv Kumar  
Prof. Lalita S. Kumar  
Prof. Kamalika Banerjee

### Block Preparation Team

Prof. Bharat Inder Fozdar  
(Units 14, 15, 16 & 17)  
School of Sciences,  
IGNOU, New Delhi-110068

Prof. J.M. Khurana (Retd.)(Editor)  
Department of Chemistry,  
University of Delhi, Delhi-110007

**Course Coordinator: Prof. Sunita Malhotra**

---

### Print Production

Mr. Rajiv Girdhar  
Assistant Registrar (Pub),  
MPDD, IGNOU, New Delhi

Mr. Hemant Kumar Parida  
Section Officer (Pub),  
MPDD, IGNOU, New Delhi

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## BLOCK 4: ORGANIC SYNTHESIS: SOME MORE APPROACHES

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So far in this course you have studied chemistry of heterocyclic compounds and various approaches of synthesis of organic compounds. Organic synthesis provides necessary amount of compounds useful to us as drugs, insecticides, pesticides, insect attractants, dyes etc. which are not available in sufficient quantities from nature. As a result, developing practical methods to synthesize organic molecules is the main focus of organic chemists. Improving efficiency in terms of the number of steps and/or the yields of these steps, or developing more sustainable methods involving green reagents, catalysts or solvents or a reduced energy requirement are typically ways to make synthetic routes more attractive. Such routes are likely to be adopted by chemists in academic world and industry, who are working towards producing target molecules. In this block our focus will be on alternative approaches for the synthesis of organic compounds. This block has four units. Unit 14 deals with the chemistry of enolates. This unit discusses enolate formation, alkylation and aldol reactions of enolates and their analogues such as imine anions and enamines. This unit also considers the stereochemistry of the alkylation and aldol reactions in some detail, including the use of chiral auxiliaries and enantioselective catalysts.

Unit 15 provides a general introduction to the chemistry of umpolung reactions. These methods allow us to develop alternative routes to traditional carbon-carbon bonds forming strategies for synthesis of organic compounds. Unit 16 deals with the chemistry of phase transfer catalysis. These reactions provide an alternate approach for the synthesis of organic molecules in two or more phases. There are number advantages that phase transfer catalysis offers over homogeneous alternatives. A last unit (Unit 17) of this block is on asymmetric synthesis. This unit presents the different types of asymmetric reactions. It sheds light on the origins of the enantio selectivities in order to facilitate better understanding of the mechanisms of the reactions.

### Expected Learning Outcomes

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After studying this course, you should be able to:

- list various methods for generating enols and enolates;
- explain the mechanism of nucleophilic addition reactions of enolates;
- understand the importance of enolate chemistry in stereoselective C-C bond formation;
- define term umpolung strategy;
- describe various approaches for developing umpolung reagents for the synthesis;
- apply umpolung strategy in construction of carbon-carbon bonds;
- define term phase transfer catalysis;
- explain mechanism of phase transfer catalysis processes;

- describe applications of phase transfer catalysis reactions in organic synthesis;
- state the significance of chirality in the organic compounds of biological importance;
- define and explain the significance of asymmetric synthesis in organic reactions; and
- describe the four generations of the strategies of asymmetric synthesis along with suitable examples and also the method used for absolute asymmetric synthesis.



# UNIT 14

## ENOLATES |

### Structure

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14.1	Introduction		Alkylation of $\alpha,\beta$ -unsaturated Ketones
	Expected Learning Outcomes		
14.2	Enols and Enolates		Alkylation of Aldehydes, Esters, Carboxylic acids and Amides
14.3	Generation of Enolates		Control of Enantioselectivity in Alkylation Reactions
	Regioselectivity and Stereoselectivity in Enolate Formation		Nucleophilic Addition of Enolates on Carbonyl Compounds
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
	Alkylation of Ketone Enolates	14.6	Terminal Questions
		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

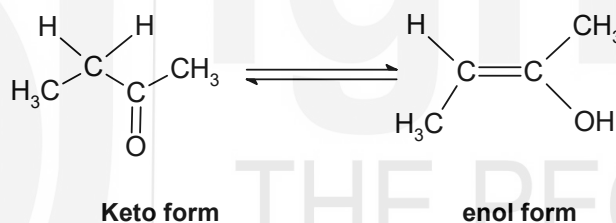
## Expected Learning Outcomes

After studying this unit you should be able to:

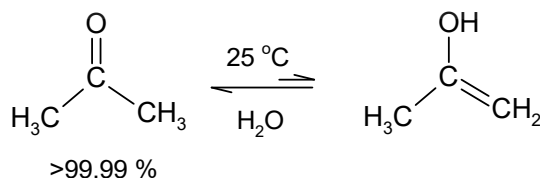
- list various methods for generating enols and enolates;
- describe various factors which control regioselectivity and stereoselectivity of enolate formation;
- explain the mechanism of nucleophilic addition reactions of enolates;
- understand the importance of enolate chemistry in stereoselective C–C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

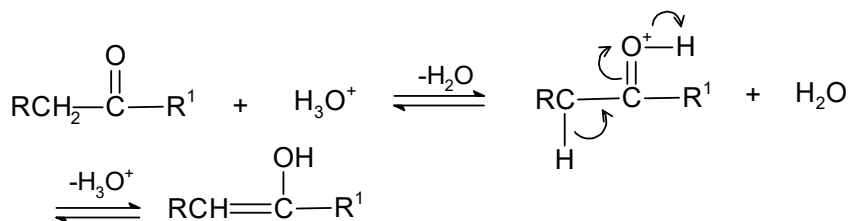


The process of converting between the keto and enol forms is called *tautomerism*. Tautomerism is rapid interconversion of structural isomers. In most of the cases, the equilibrium lies on the right with Keto form being the more stable. For example in aqueous solution of acetone at 25°C, concentration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

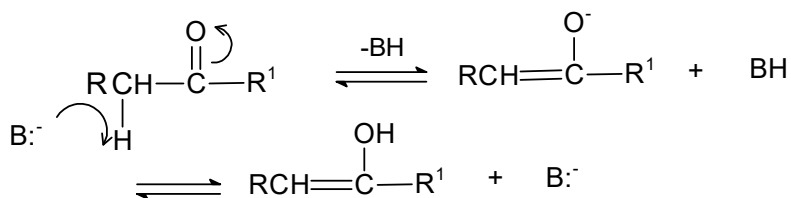


The equilibrium between carbonyl compounds and the corresponding enol form can be acid or base catalysed. This process occurs by a concerted mechanism in which protonation and deprotonation take place in single step.

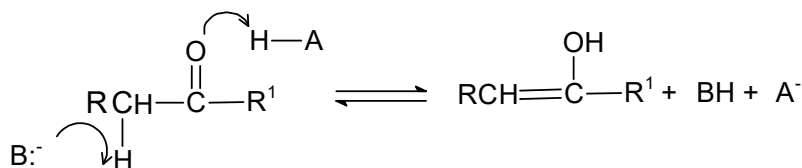
Acid catalysed:



## Base catalysed



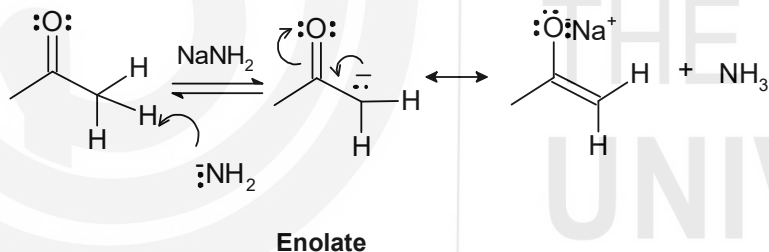
## Concerted



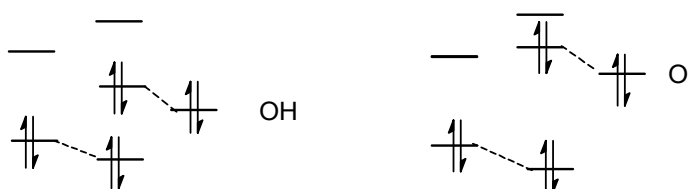
Once enols are formed, they are nucleophilic like simple alkenes by virtue of their  $\pi$  electrons, but they are more reactive than simple alkenes due to the presence of the hydroxyl group which participates as an electron donor during the reaction process. This can be shown by following resonance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

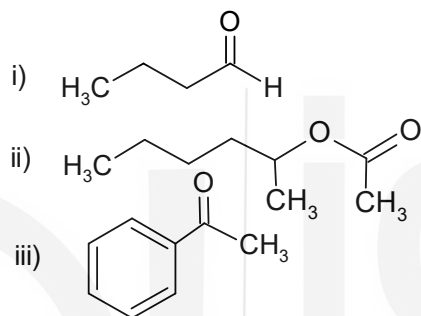


As mentioned earlier in most of cases, the keto-enolate equilibrium lies on the right because of the more stability of keto form. Typical strong bases such as hydroxide or alkoxide are only capable of forming, the enolates in very low

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:



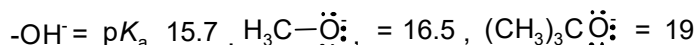
### SAQ 2

Why enolate anions are more reactive than enol form?

## 14.3 GENERATION OF ENOLATES

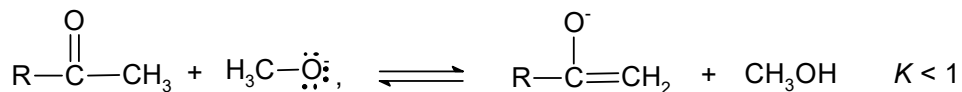
Acidity of the reactants having  $\alpha$ -hydrogen such as aldehydes or ketones determines which base can be used for generating enolates. For complete conversion, the base must be weaker acid than the reactants. In other words, the reagent must be a stronger base than the enolate anion of the reactant. 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,

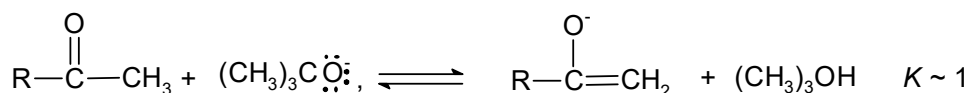


These bases are much less basic than the enolate ions. As a result, they convert only a small fraction of ketones, aldehydes or other carboxyl compound having  $\alpha$  hydrogen, to their corresponding enolates. Thus, by comparing the approximate  $pK_a$  values of the bases with those of the reactant 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.

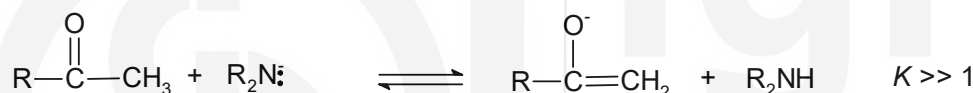


The slightly more basic tertiary alkoxides are comparable to the enolates in basicity, and a more favorable equilibrium will be established with such bases.



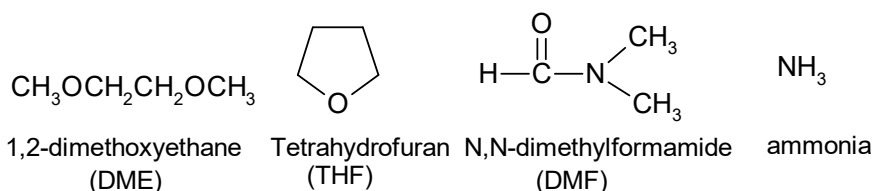
In DMSO, ketones such as acetone are slightly more acidic than in the simple alcohols. Therefore, use of alkoxide bases in DMSO favors enolate formation. All these typical bases besides providing low concentration of enolates, they are also potential nucleophiles in condensation and substitution reactions.

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.



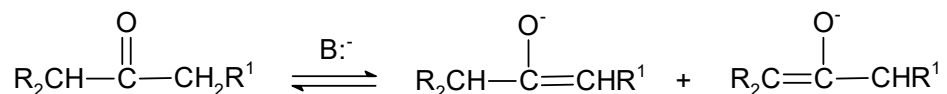
From above discussion it can be concluded that both bases and solvents play very important role in generation of enolates.

### SAQ 3

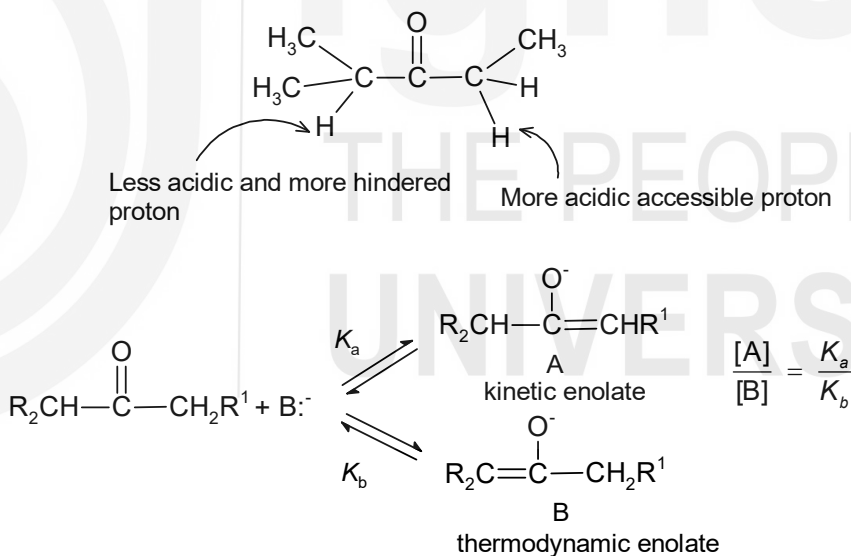
Why do we prefer aprotic solvents for generation of enolates?

### 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**.



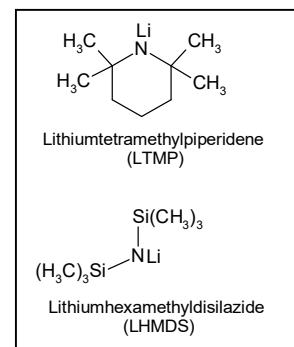
The regioselectivity of enolate formation can be controlled by following factors:

- Solvent
- Base
- Cation
- Temperature

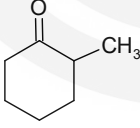
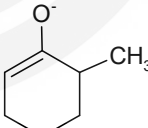
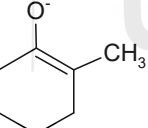
By controlling reaction conditions for the formation of an enolate, it is possible to obtain either kinetic or thermodynamic control enolate. Kinetic control enolate is usually a less substituted enolate. Conditions for kinetic control of enolate formation are those in which deprotonation is rapid, quantitative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

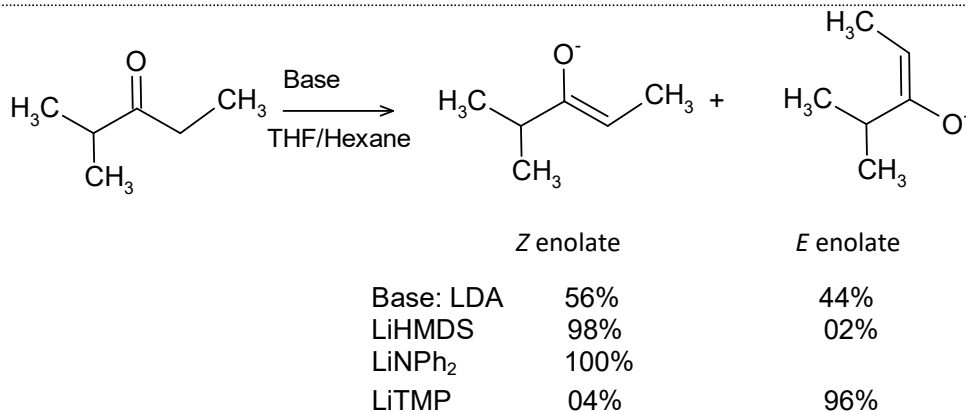
Aprotic solvents also favour the formation of kinetic product as protic solvents protonate oxygen which gives rise to the thermodynamically controlled enolate. Excess ketone also catalyses the equilibrium by proton exchange. Less hindered hydrogens also favour formation of kinetic enolates as they are 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.



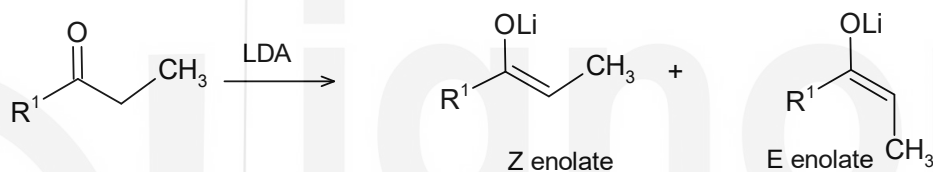
**Table 14.1: Composition of Enolate Mixture Formed under Kinetic and Thermodynamic Control**

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

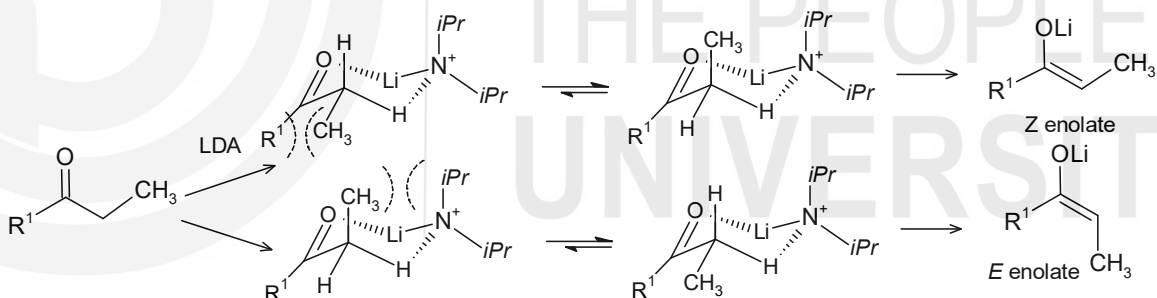
In addition to thermodynamic and kinetically formed enolates based on kinetic conditions as well as degrees of substitution of the double bond there is another characterization in enolates based on whether the alkyl group is on the same side of the double bond as the enolate oxygen or on the opposite 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:



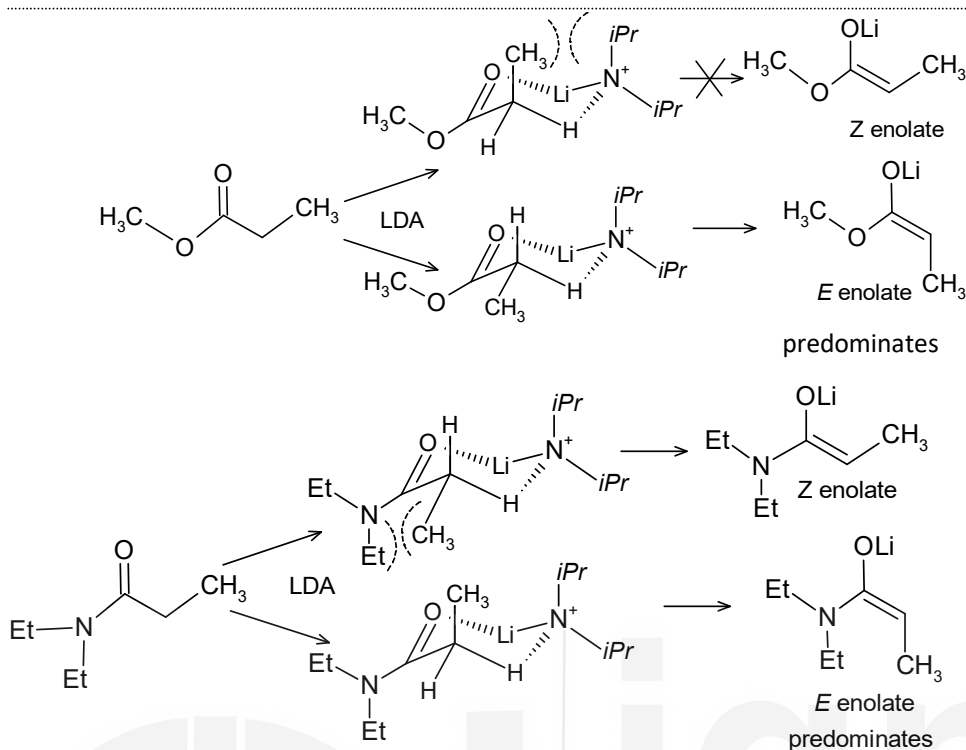
In a ketone shown above **Z-enolate** is favoured if **R<sup>1</sup>** is large but **E-enolate** is favoured if **R<sup>1</sup>** is small. Consider the transition states (TS) formed during the reaction as given below.



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

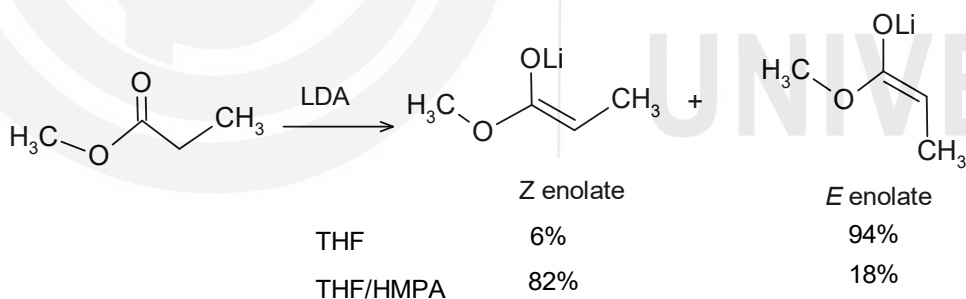
- if **R<sup>1</sup>** is large, this TS is destabilised by **R<sup>1</sup>**, **CH<sub>3</sub>** interaction and **Z** predominates
- if **R<sup>1</sup>** is small, 1,3-diaxial interaction is important as it destabilises this TS and **E** predominates. Therefore, bulky bases like LTMP favour the formation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

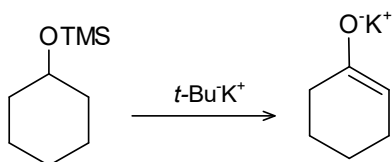
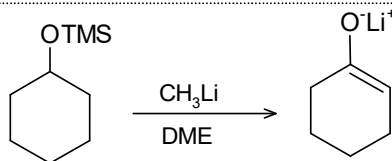
These arguments are good generalizations and many other factors also affect stereoselectivity of enolates. For example, use of the additive HMPA (hexamethylphosphoric triamide) reduces coordination and favours the thermodynamically more stable enolate.



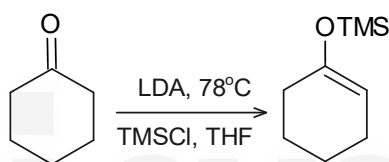
#### General observation

- 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.

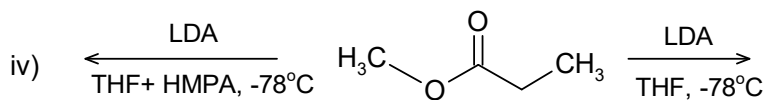
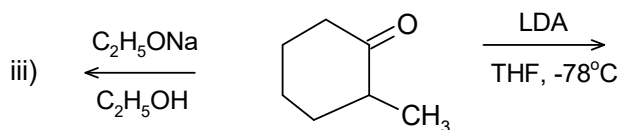
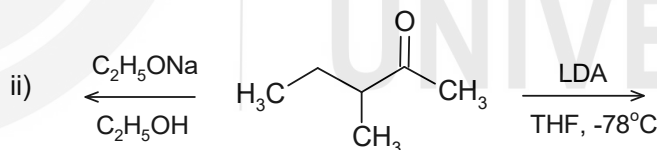
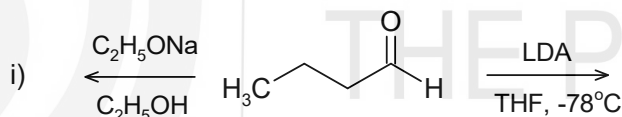


Trimethylsilyl enol ethers are readily prepared by trapping lithium enolate with TMSCl.



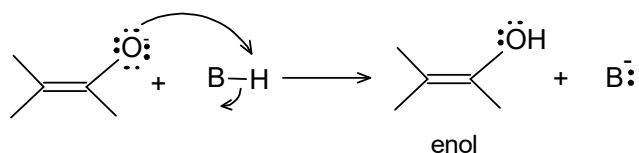
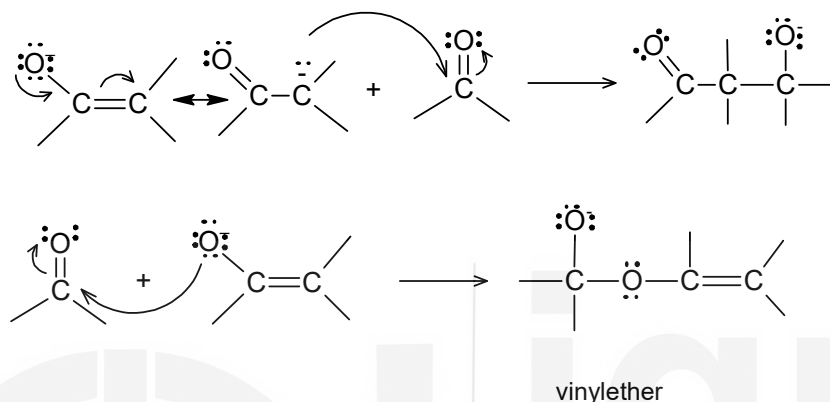
### SAQ 4

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



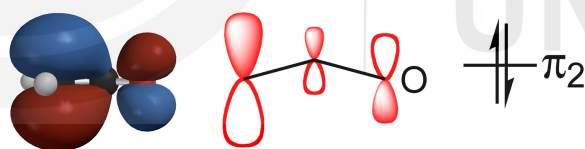
## 14.4 REACTIONS OF ENOLATES

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.

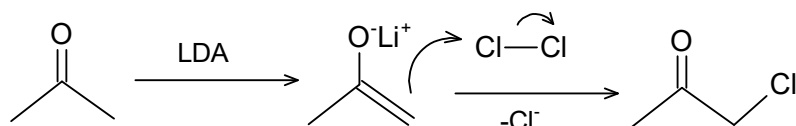
A soft electrophile is one in which the positive charge is able to spread over a larger area.



**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.

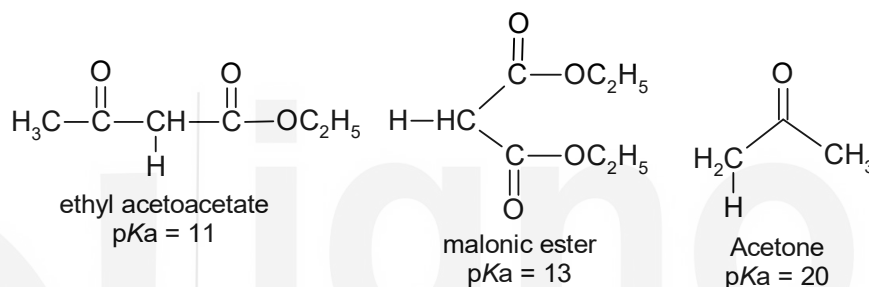


These reactions occur by a  $S_N2$  process. You have already studied such reaction in quite detail in your under graduate programme.

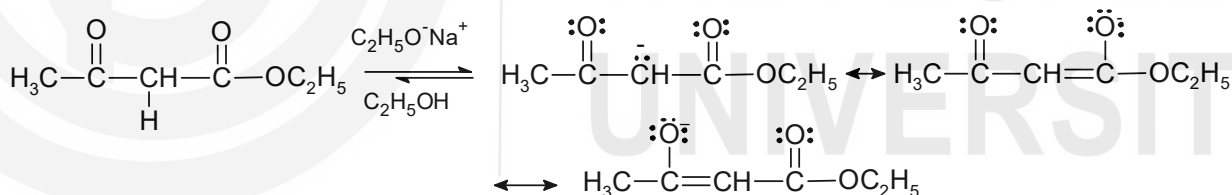
### 14.4.2 Enolate Alkylation: Reactions of Relatively Acidic Compounds

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.

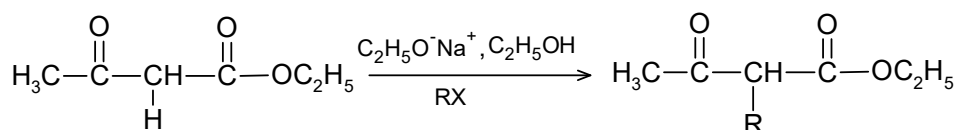
Two examples of this class extensively used in alkylation reactions are acetoacetic ester (ethyl acetoacetate) and malonic ester (diethyl malonate)



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.



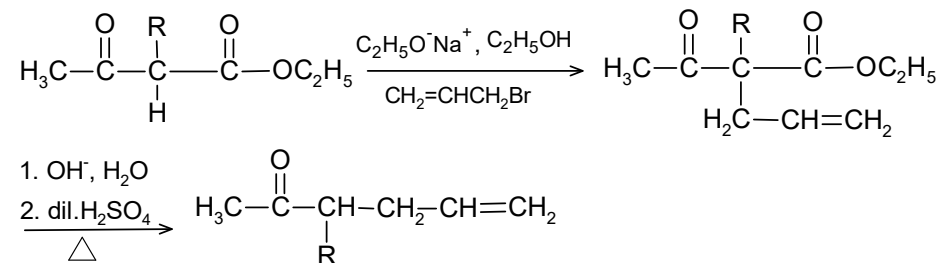
Similar resonating structures can also be drawn for malonic ester. The enolates formed by these esters undergo substitution reactions with alkyl halides.



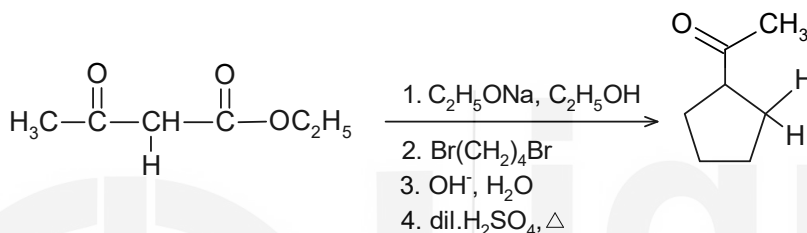
Above reaction illustrates the synthetic applications of acetoacetic and malonic esters in which two factors are important

- (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.

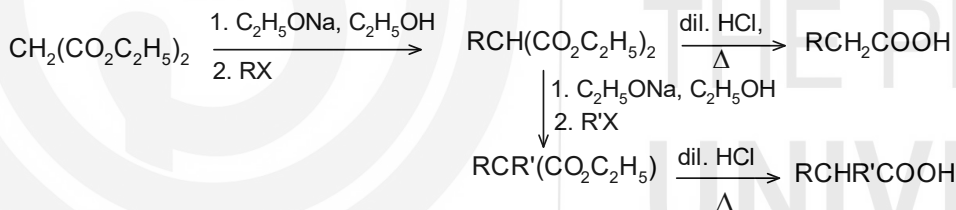
The monoalkyl acetoacetic ester may be treated with a base followed by addition of a different alkyl or allyl halide, alkaline hydrolysis (saponification) and decarboxylation (warming with dil. acids) gives a ketone that branched at the  $\alpha$ -carbon.



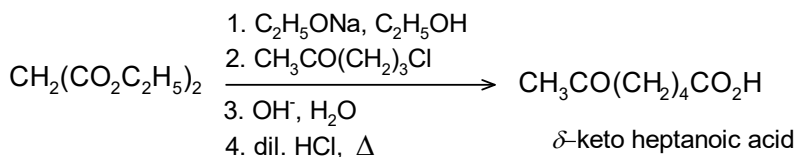
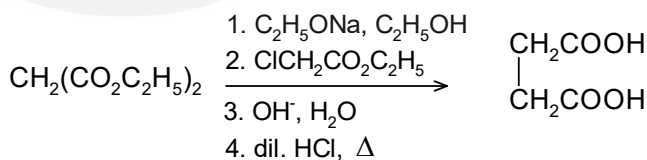
Cyclic products (3, 5, 6 and 7 carbon rings) can be formed if the dialkylation is done using dihaloalkane.



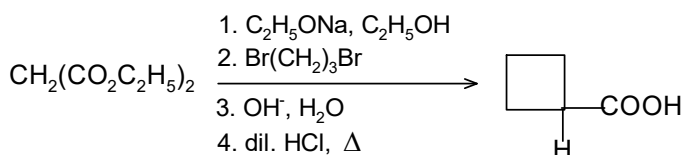
Malonic ester, like acetoacetic ester, when treated with base, generates the enolate ions which are also very reactive. Addition of alkylating agents followed by hydrolysis and decarboxylation gives carboxylic acids. Mono or dialkyl ethanoic acids are preferably prepared by this method.



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

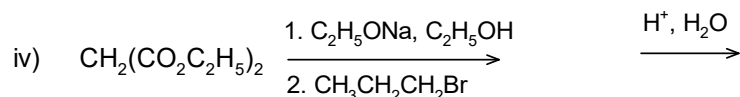
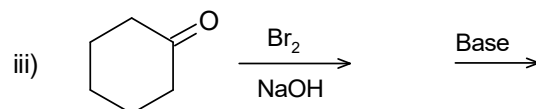
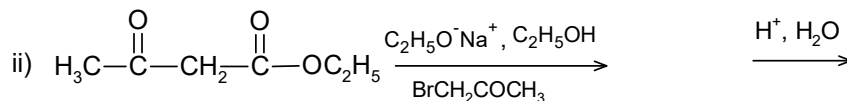
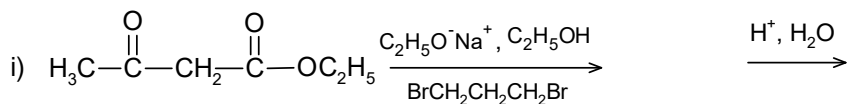


Alicyclic compounds have been prepared by the reaction of malonic ester with dihaloalkane.



## SAQ 5

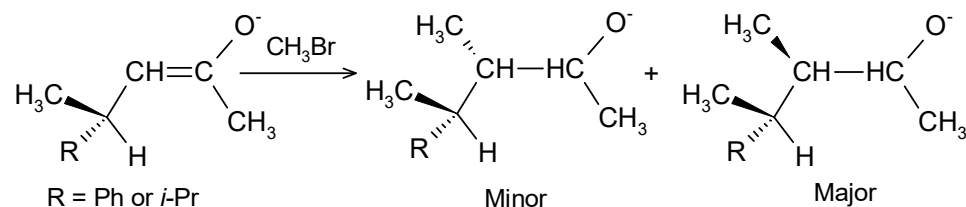
Predict the products of the following reactions



### 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.

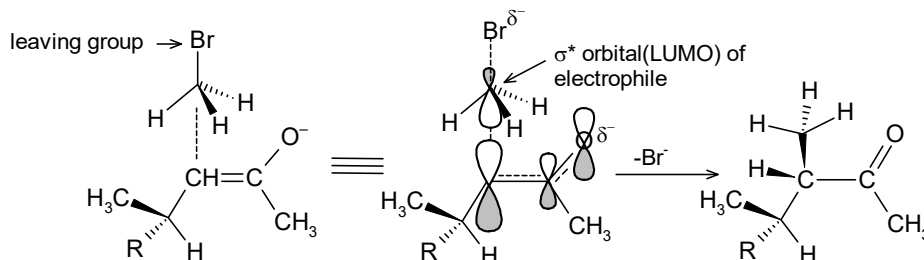
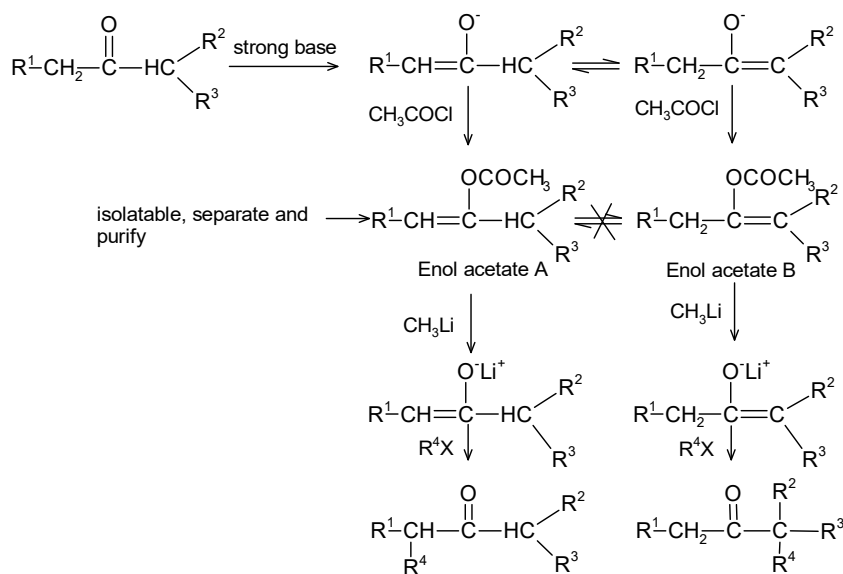


Fig. 14.2 : Attack of enolate on an electrophilic centre.

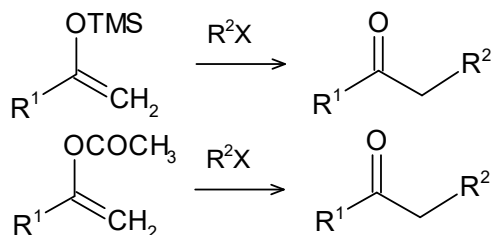
As mentioned earlier these reactions follow  $\text{S}_{\text{N}}2$  mechanism, therefore, these reactions are more feasible for  $1^\circ$  or  $2^\circ$ , as well as allylic or benzylic halides. In the case of  $3^\circ$  alkyl halides, we mainly observed  $\text{E}2$  elimination with enolate ion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

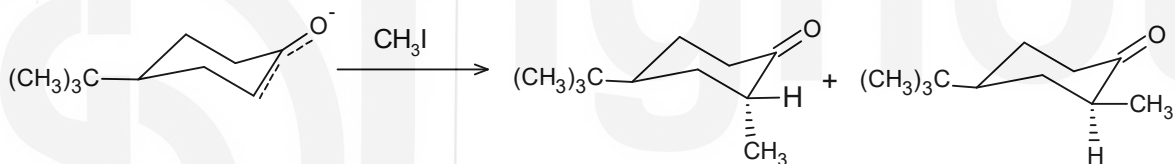


Both enol acetates and silyl enol esters can also be directly alkylated with alkyl halides in the presence of Lewis acids. Lewis acid forms a complex to the halogen atom making it a better leaving group.

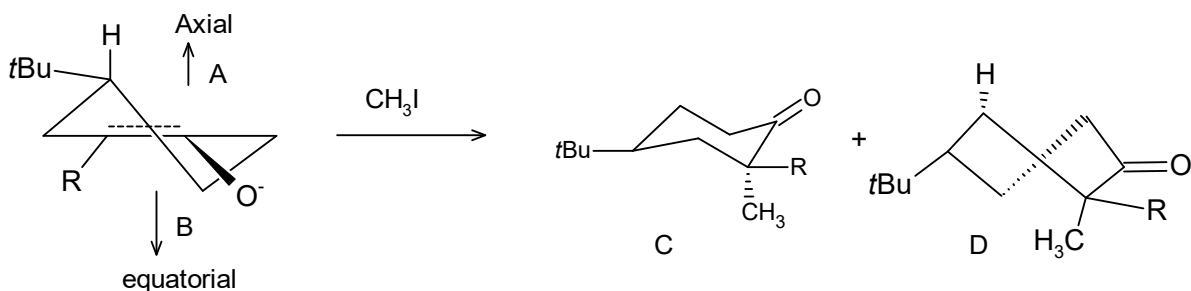
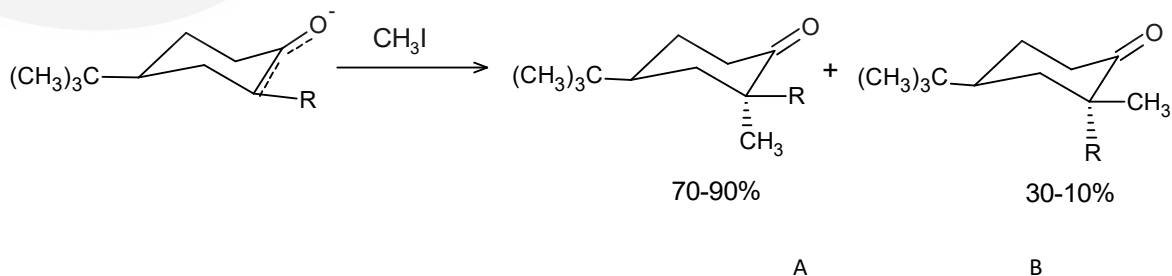


These reactions may follow  $S_N1$  reaction. Especially in case of tertiary alkyl halides, allylic and benzylic halides as all these system are capable of stabilising positive charge.

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.

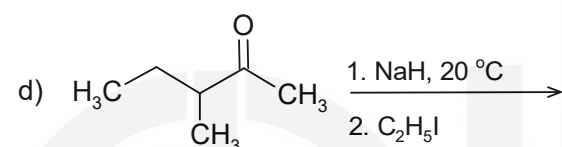
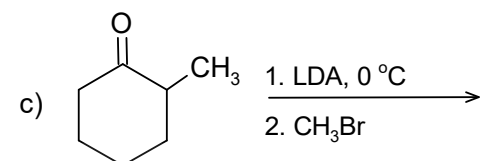
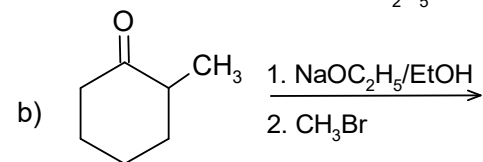
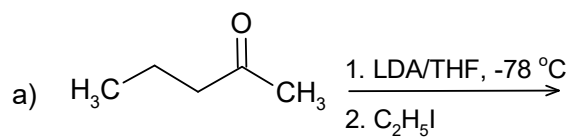


The introduction of an alkyl substituent at the  $\alpha$ -carbon in the enolate enhances stereoselectivity. This is due to a steric effect in the enolate. In such cases, the electrophile approaches from an axial trajectory preferably. This approach leads directly into chair-like product (A). Equatorial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



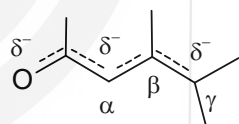
## SAQ 6

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

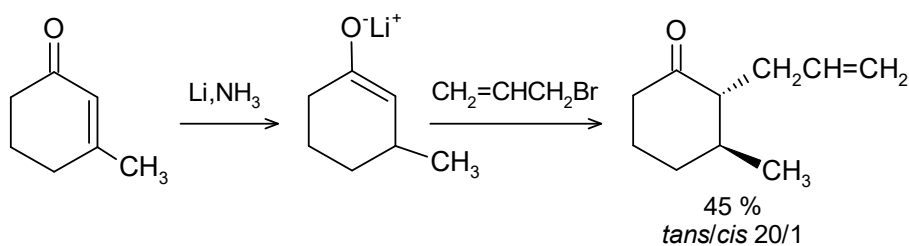
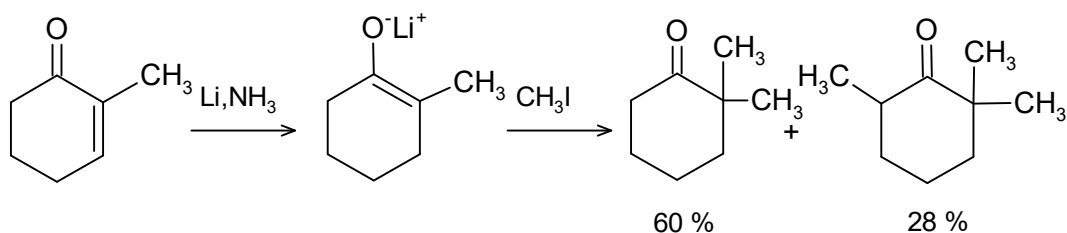


#### 14.4.4 Alkylation of $\alpha,\beta$ -unsaturated Ketones

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.

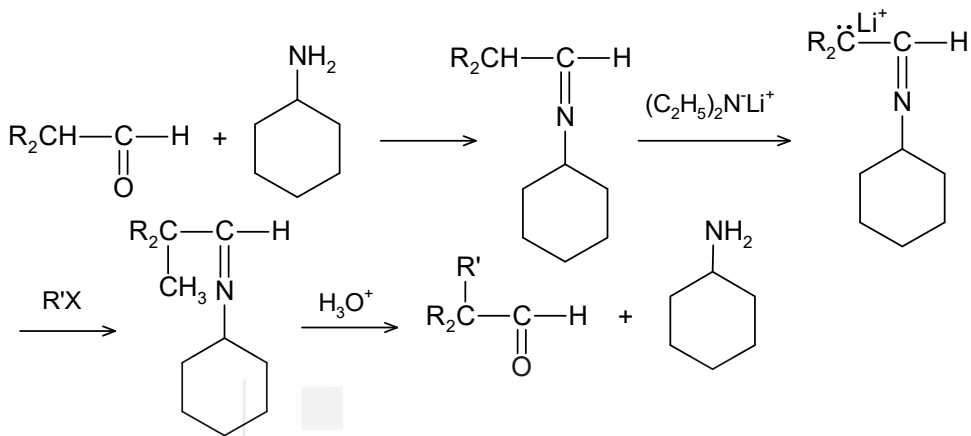


This selectivity may be due to the fact that  $\alpha$ -carbon has greater negative charge as compared with  $\gamma$  carbon.



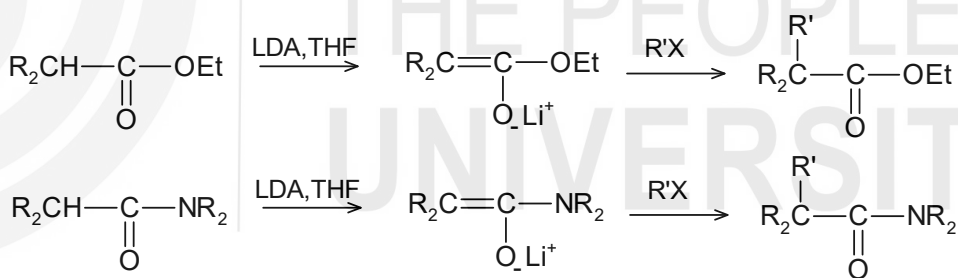
### 14.4.5 Alkylation of Aldehydes, Esters, Carboxylic Acids and Amides

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:

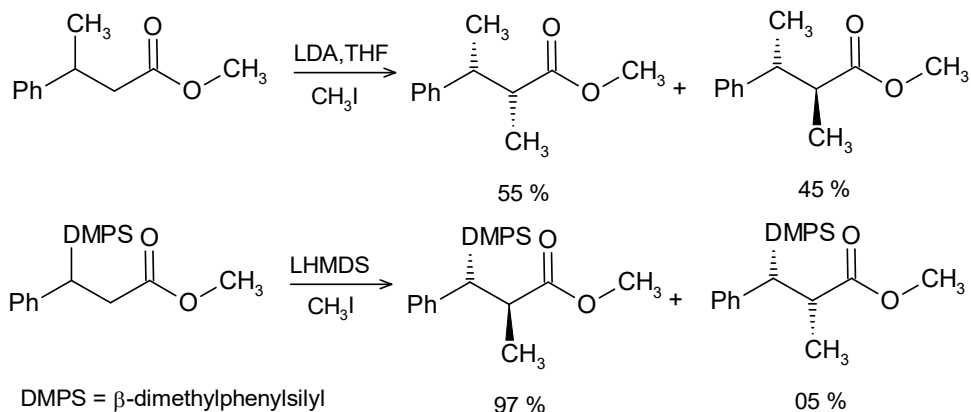


In above reaction, we have converted aldehyde to an imine and then this react with strong base to give an enolate type ion. Reaction of this ion with alkyl halide gives an  $\alpha$ -alkylated imine that can be hydrolyzed to give the  $\alpha$ -alkyl aldehydes.

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.

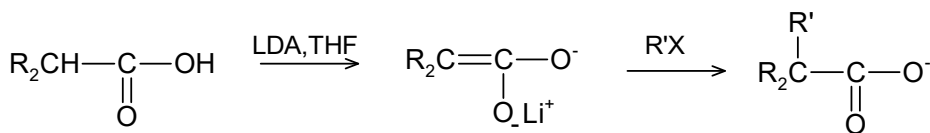


Similar to ketone, the stereochemistry of alkylation of esters and amides depends on steric factors mainly.



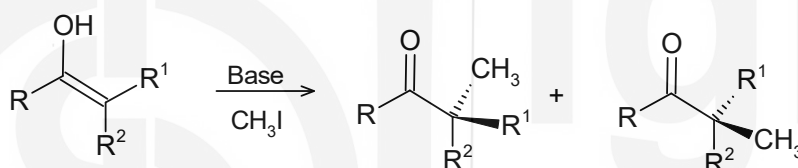
This stereoselectivity is the result of the conformation of the enolate and steric shielding by the silyl substituent. Such directive effect has been employed in stereoselective synthesis. In next section we will further elaborate this concept.

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

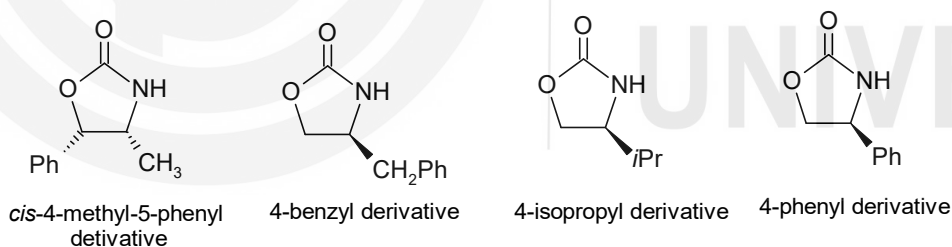


### 14.4.6 Control of Enantioselectivity in Alkylation Reactions

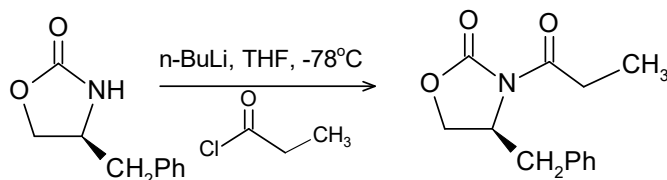
The alkylation of an enolate generate new stereogenic centre when  $\alpha$  substituents are nonidentical. In enantioselective synthesis, it is necessary to control the direction of approach and thus the configuration of the new stereocentre.



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.

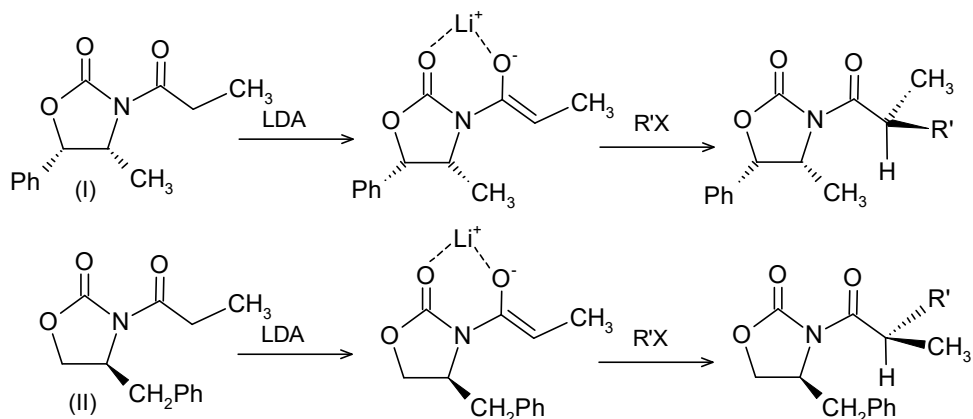


The 4-isopropyl and 4-benzyl oxazolidinones can be obtained from valine and phenylalanine, respectively. Other derivatives can also be synthesized easily. These chiral auxiliaries can be attached to an appropriate substrate by *N*-acylation reaction using *n*-BuLi as a base.

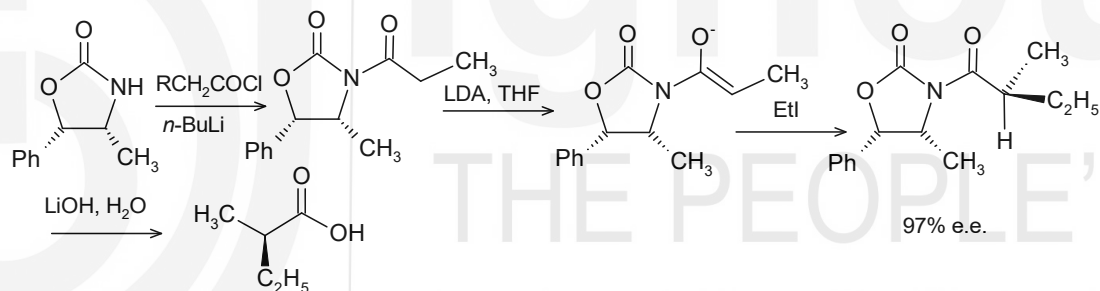


The above product with LDA generates mainly *z*-enolate. The electrophiles have a tendency to attack from the opposite face of the chiral controlling group at C<sub>4</sub> position of oxazolidinone ring. The high to excellent diastereoselectivity in

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

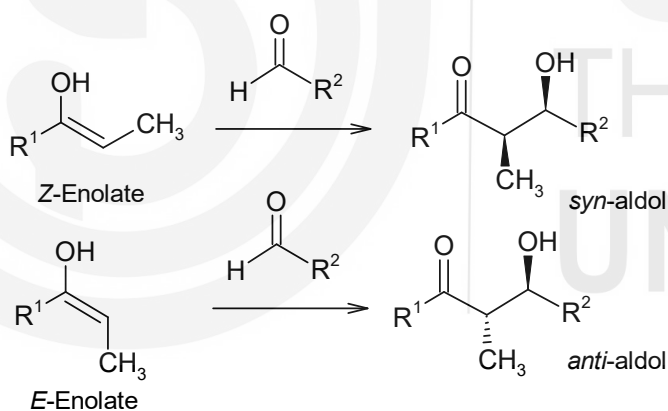
In earlier Sub-section we have described reaction of enolates with alkylating agents such as alkyl halides. In this Sub-section we will discuss chemistry of the nucleophilic attack by enolates on carbonyl groups of aldehydes or ketones.

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..

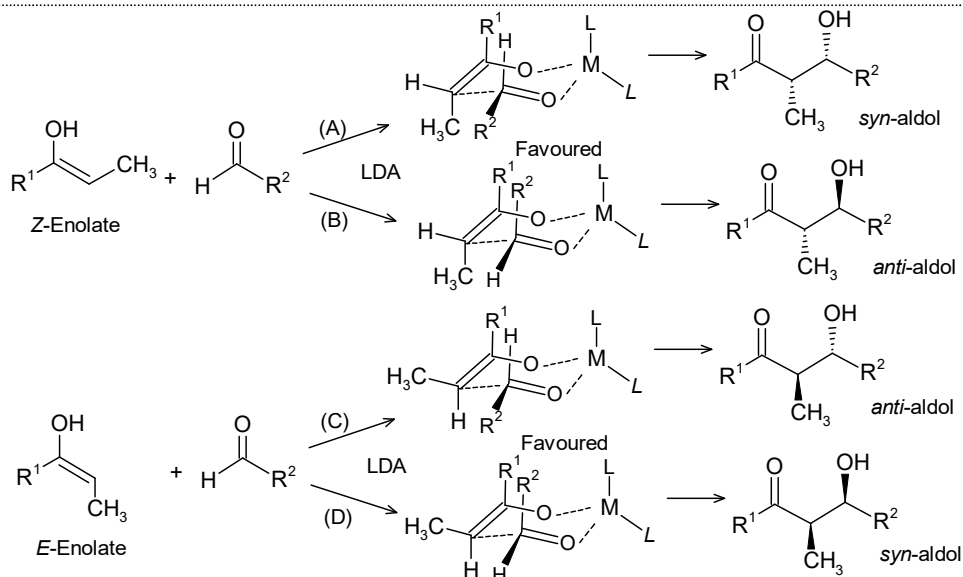
As we have discussed earlier, the enolates that participate in an aldol reaction can be formed under two types of conditions, either thermodynamic deprotonation or kinetic deprotonation. A thermodynamically formed enolate generally has the most substituted double bond or conjugated double bond and is 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.



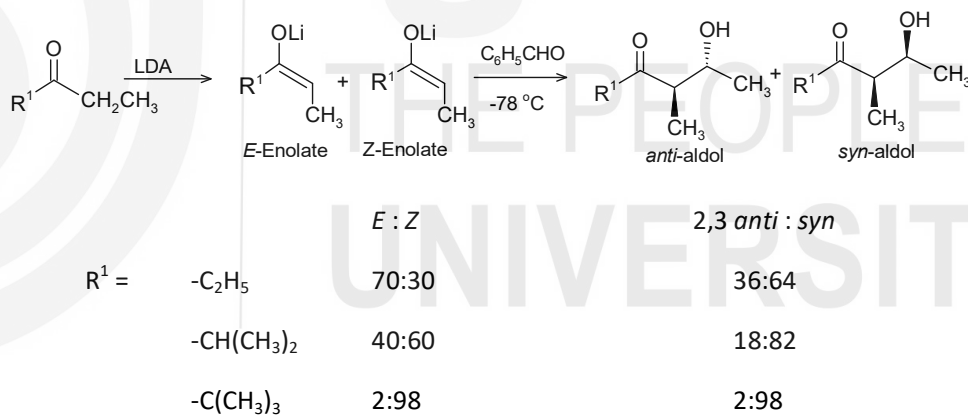
Generally the diastereoselectivity of an aldol reaction using thermodynamically formed *Z*-enolate is higher than for the kinetically formed *E*-enolates.

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  $\text{R}^1$  is axial and  $\text{R}^3$  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.



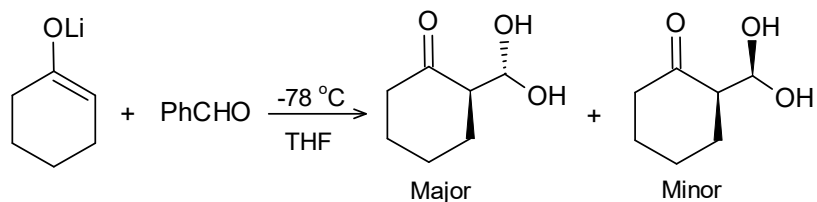
**Fig. 14.3:** Cyclic Transition model for *E*-enolates and *Z*-enolates;  $M = \text{Li}^+$  ion, Boron or any other metal ion.

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.



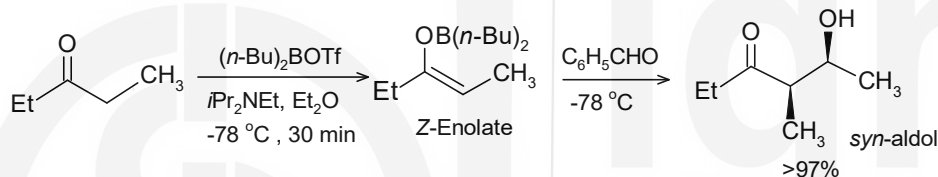
From these and many related examples the following generalizations can be made about stereoselection in aldol additions of lithium enolates.

- 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.

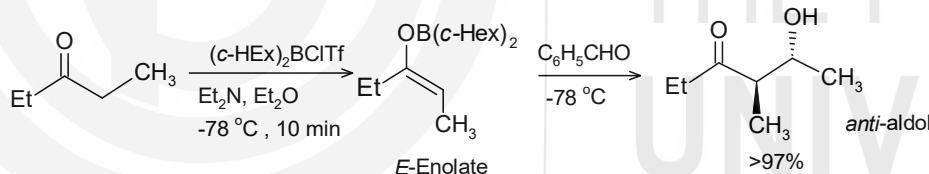
### Boron Enolates in Aldol Reactions

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.

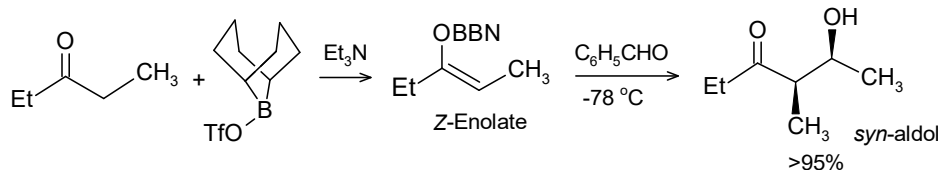
*Z*-Boron enolate can be prepared by the reaction of ketone with dialkylboron trifluoromethanesulfonate (triflate) and a tertiary amine. Use of boron triflates and a bulky amine favors the *Z*-enolate. The resulting aldol products are predominantly the *syn* product.



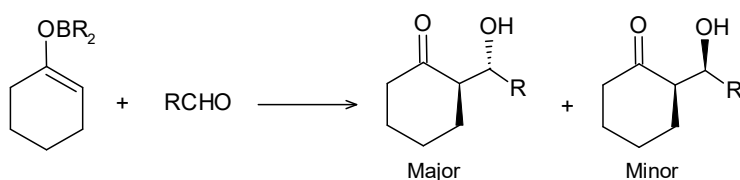
The combination of  $(c\text{-Hex})_2\text{BCl}$  and  $\text{Et}_3\text{N}$  provides the *E*-boron enolate preferentially. Bulkier group such as dicyclohexylboron chloride, favours formation of *E*-enolates.



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

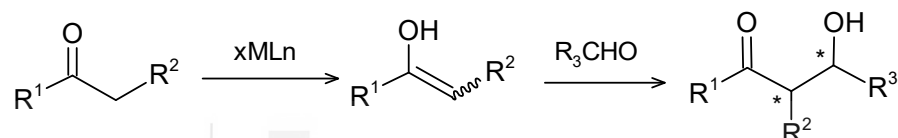


The *E*-boron enolate from cyclohexanone shows a preference for the *anti* aldol product. The ratio depends on the boron alkyl groups and is modest (2:1) with di-*n*-butylboron but greater than 20:1 for cyclopentyl-*n*-hexylboron.



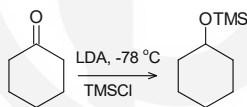
Beside Lithium and boron enolates aldol reactions can also be conducted using titanium, tin, and zirconium enolates.

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  $ML_n$  or added Lewis Acid.

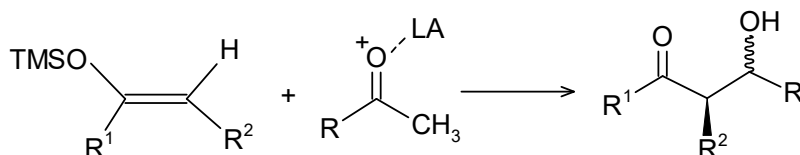
Silyl Enol Ethers can be readily formed by trapping a lithium enolate with TMSCl.



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.

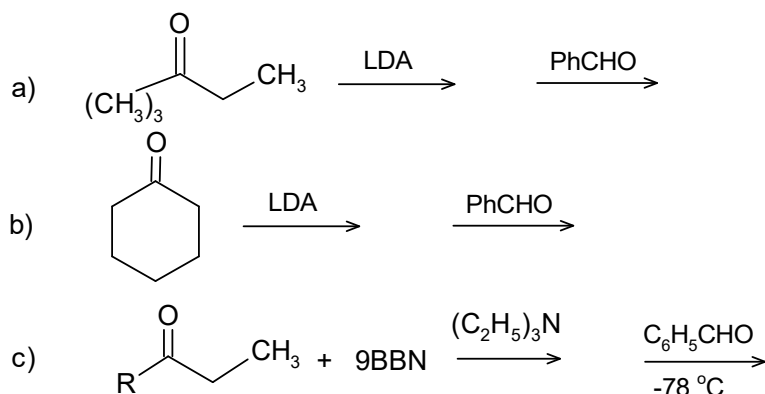


The reaction mechanism is quite different to that of lithium or boron enolates described above. These reactions proceed through an open T.S. Stereoselectivity of these reactions are usually low. But, the use of chiral Lewis acids in sub-stoichiometric quantities provides important methods for controlling 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  $LiClO_4$ .

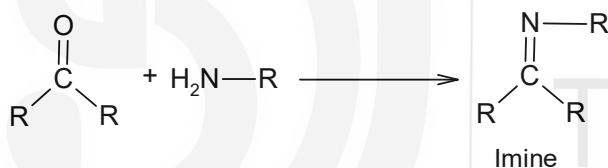
## SAQ 7

Complete following reaction and also indicate the major product.

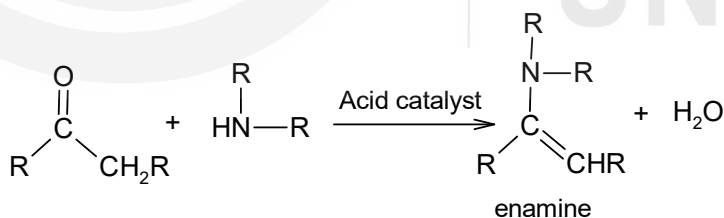


### 14.4.8 Nitrogen Analogs of Enols and Enolates: Enamines and Imines

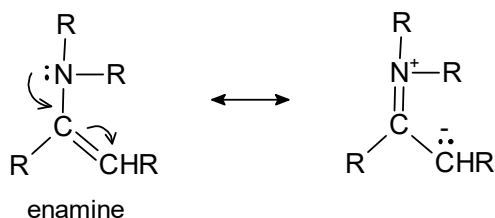
The nitrogen analogs of aldehyds and ketones are called imine or Schiff bases. The imine is prepared by the condensation of aldehyde or ketones with primary amines.



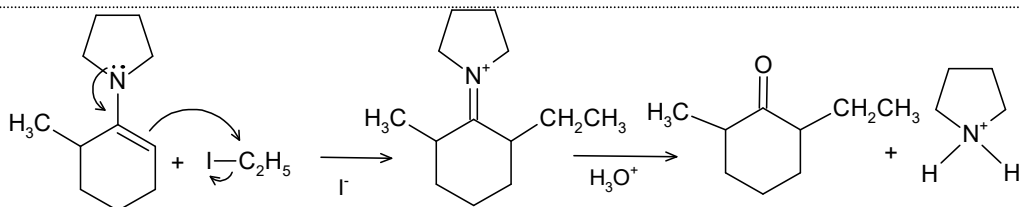
When we use secondary amines, they react with aldehydes or ketones having  $\alpha$ -hydrogen in the presence of acidic catalyst to give enamines.



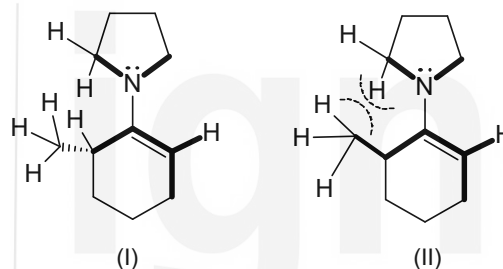
The  $\beta$ -carbon atom of an enamine is a nucleophilic site because of conjugation with the nitrogen atom similar to enolate ion.



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

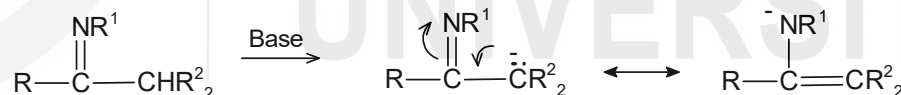


In above example of alkylation reaction of pyrrolidine enamine, the less substituted enamine is formed mainly by the reaction of 2-methyl cyclohexanone with pyrrolidine because of the steric factor and more acidity of the C-H on the less substituted carbon. Less substituted enamine is a mixture of two 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.

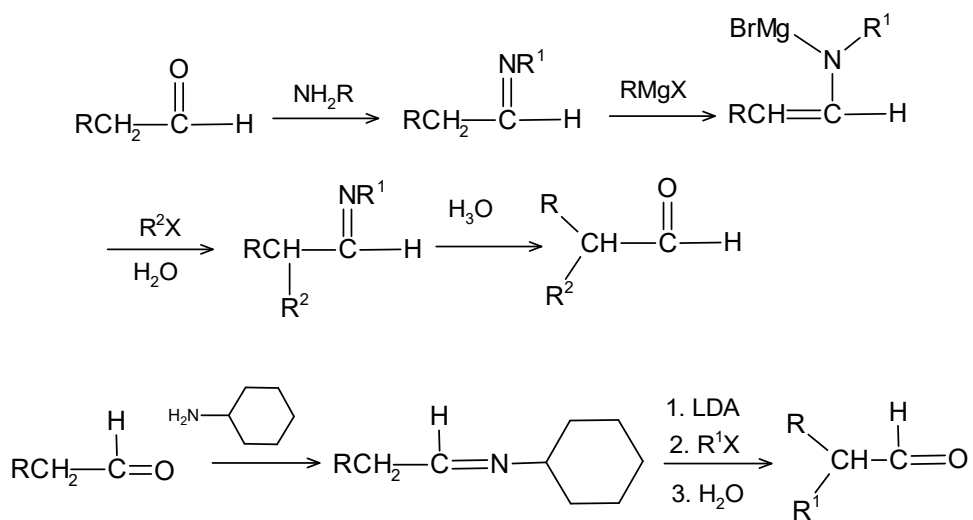


The imine ion resulting from alkylation can be hydrolysed to prepare 2,6-disubstituted cyclohexanone.

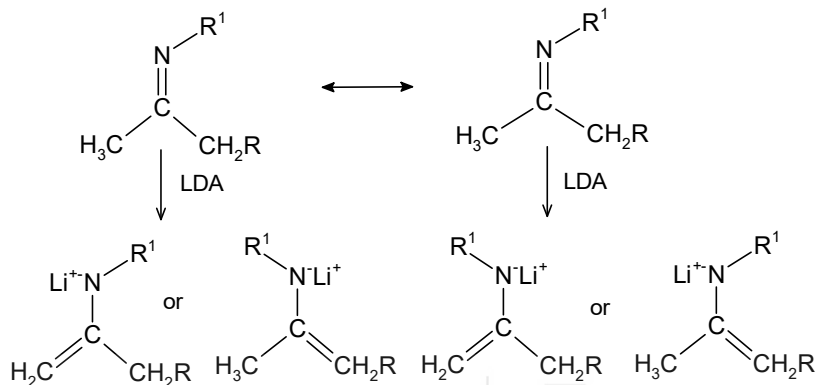
Imines can also be deprotonated at the  $\alpha$ -carbon by strong bases to give the nitrogen analogs of enolates. Grignard reagents and lithium amides can be used for deprotonation. These anions are referred to as imine anions. Imine anions are also more nucleophilic than enolates and can be alkylated.



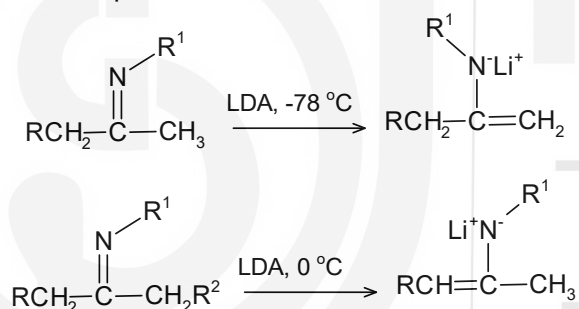
One application of imine anions is for the alkylation of aldehydes.



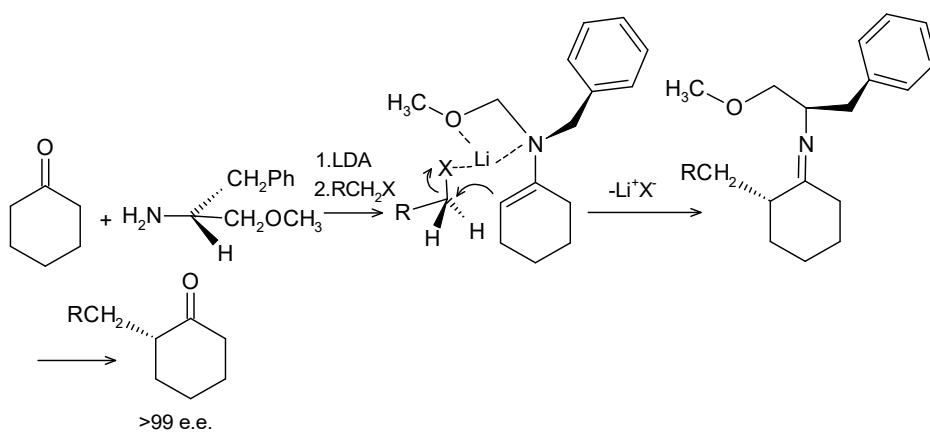
Ketone imine anions can also be alkylated. The prediction of the regioselectivity of lithioimine formation is somewhat more complex than the case of kinetic ketone enolate formation. One of the complicating factors is that there are two imine stereoisomers, each of which can give rise to two regioisomeric 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.



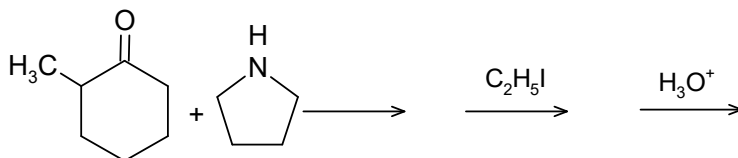
Beside the factors discussed above other factors such as the state of aggregation and solvation also control regioselectivity of ketimines. One of the important applications of the imine anions is that they can be prepared from enantiomerically pure amines. When imines derived from chiral amines are 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.

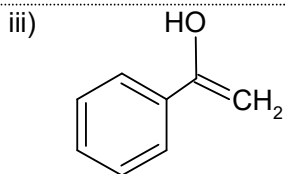
## 14.6 TERMINAL QUESTIONS

- 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.

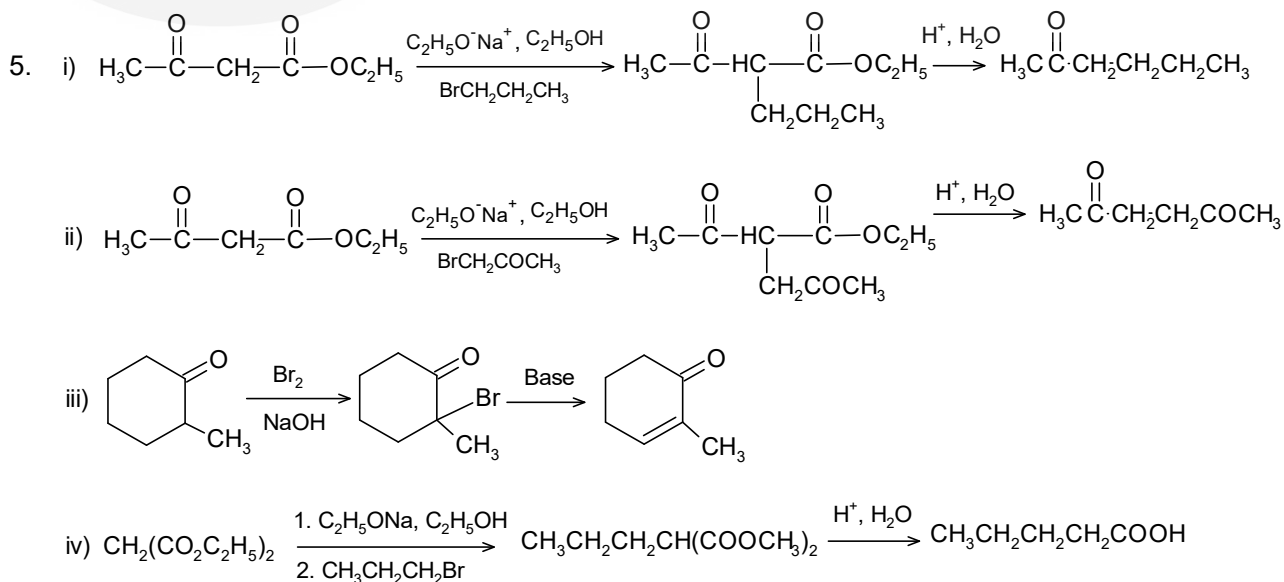
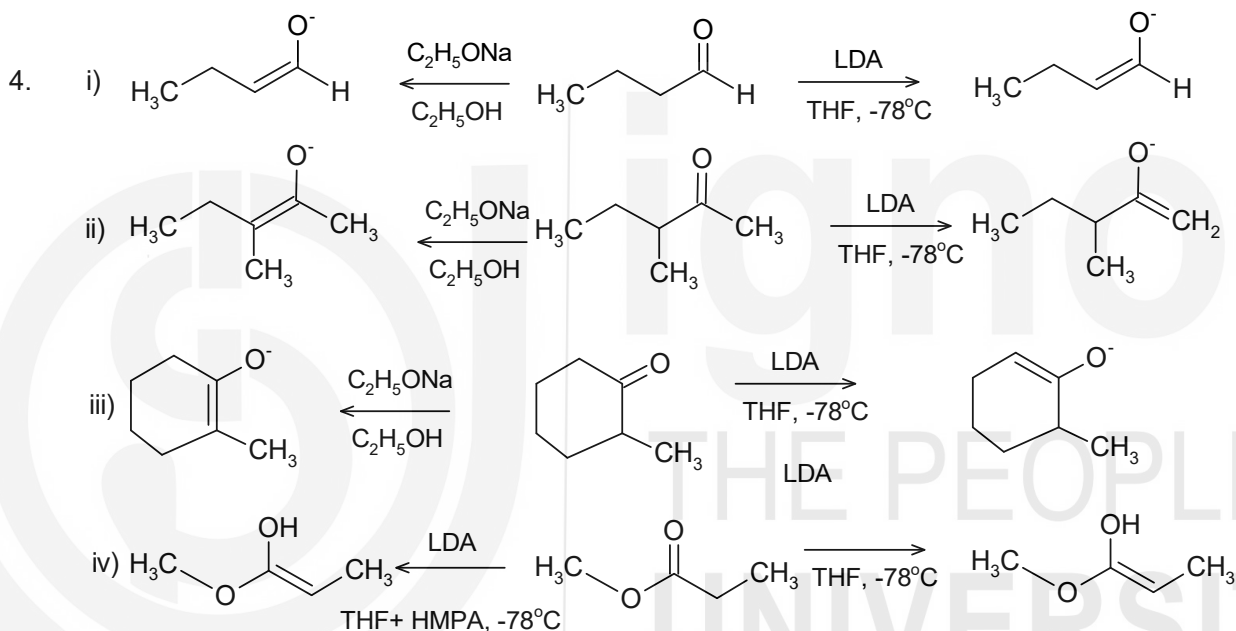
## 14.7 ANSWERS

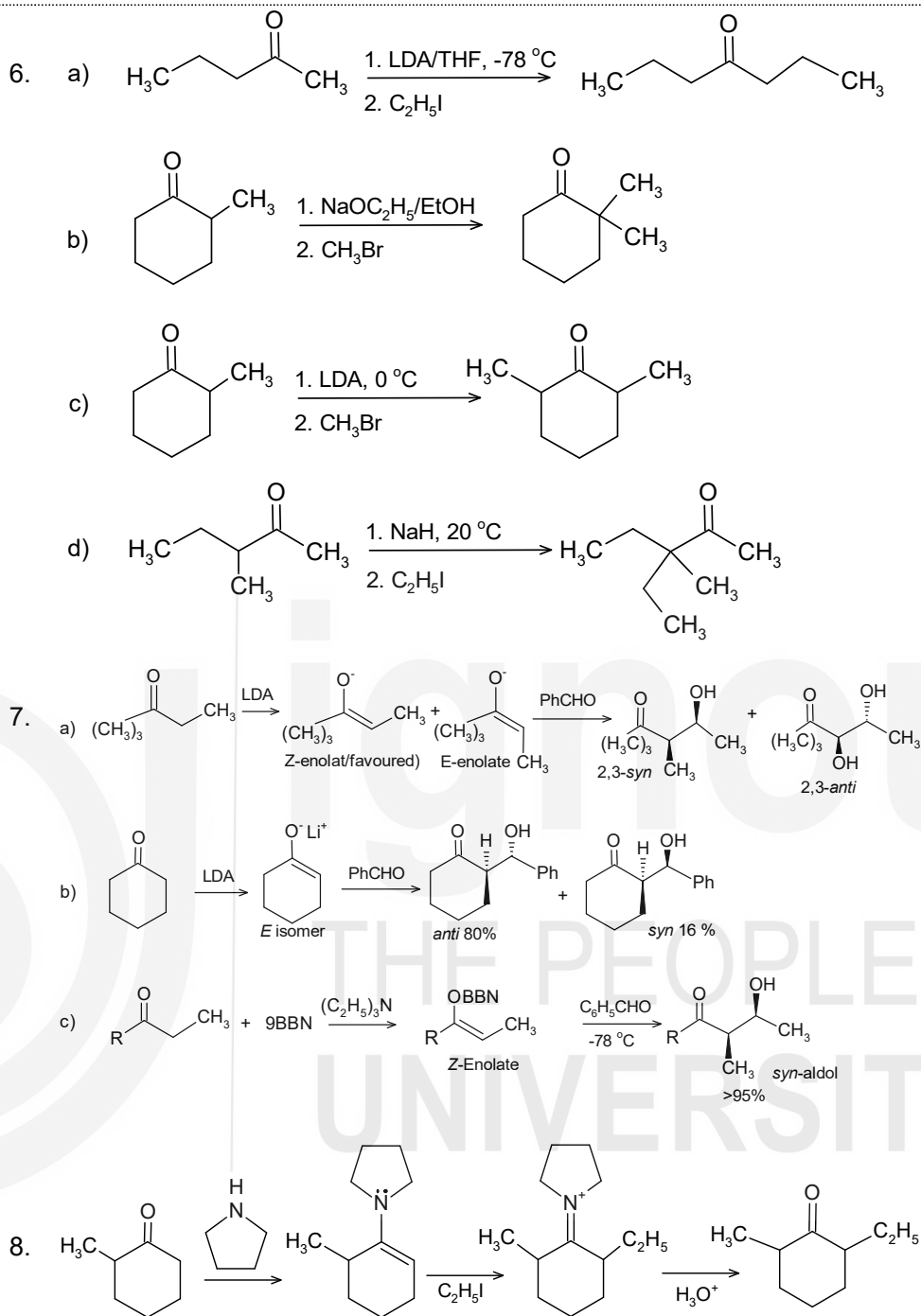
### Self Assessment Questions

- -



- 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.
- 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.

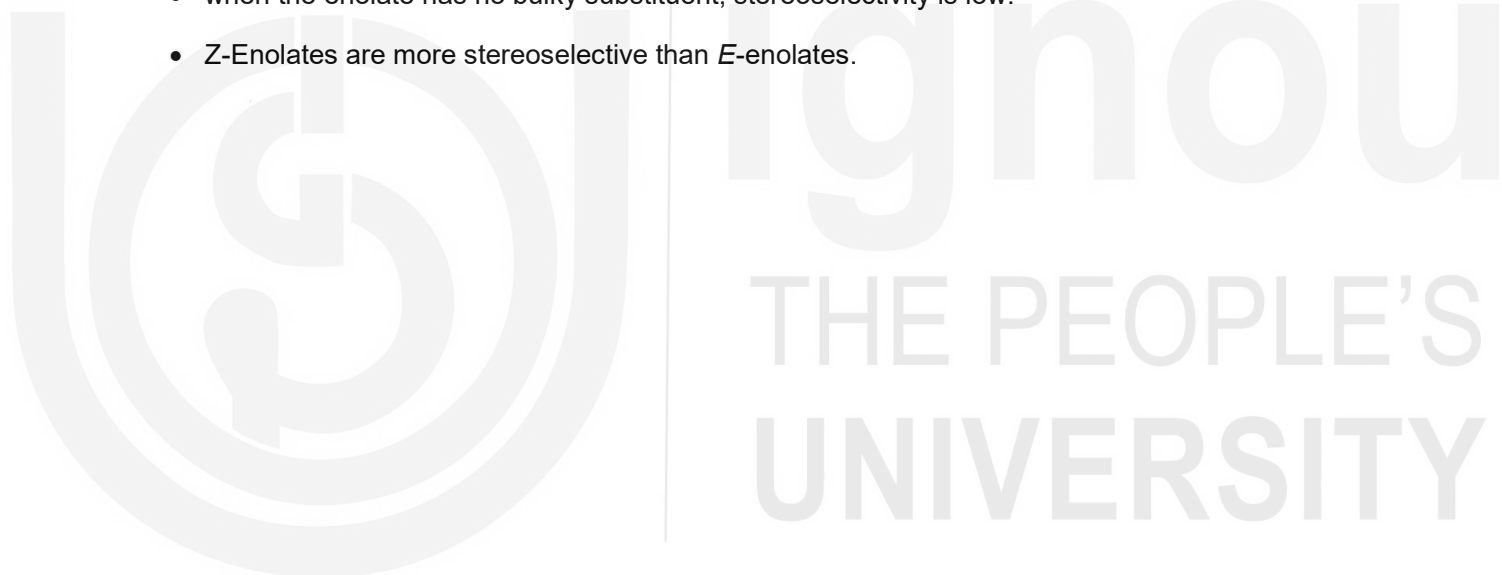




### Terminal Questions

- 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.



# UMPOLUNG REACTIONS

## Structure

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15.1 Introduction	$\alpha$ -Electrophiles
Expected Learning Outcomes	15.3 Summary
15.2 Types of Umpolung Reactions	15.4 Terminal Questions
Carbonyl Umpolung Strategies	15.5 Answers
Homoenolates	

## 15.1 INTRODUCTION

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In the previous unit, you have learnt about chemistry of enolates. You have learnt about the important role of enolates in organic synthesis especially in construction of new carbon-carbon bonds. In this approach carbon-carbon bond is formed by the reaction of nucleophilic enolate and electrophilic carbon centre of compounds such as alkyl halides and carbonyl compounds. Despite the great importance of such synthetic strategies, there is still a continuous demand for more efficient carbon-carbon bond formation techniques for useful synthesis of small and complex molecules. In this unit, we will discuss an alternative approach for the construction of carbon-carbon bonds using umpolung strategy.

In the next unit we would take up the applications of phase transfer catalysis in organic synthesis.

## Expected Learning Outcomes

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After studying this unit, you should be able to:

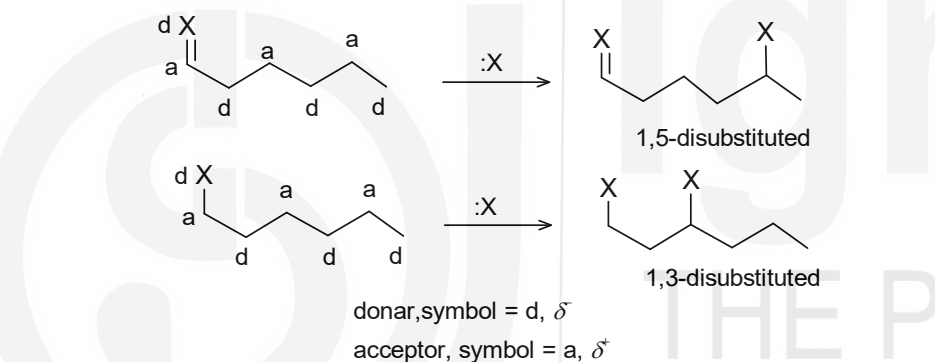
- ❖ define term umpolung strategy;
- ❖ describe various approaches for developing umpolung reagents for the synthesis;
- ❖ list and explain various types of umpolung reactions using carbonyl umpolung, homoenolates and  $\alpha$ -electrophiles;
- ❖ apply umpolung strategy in construction of carbon-carbon bonds.

## 15.2 TYPES OF UMPOLUNG REACTIONS

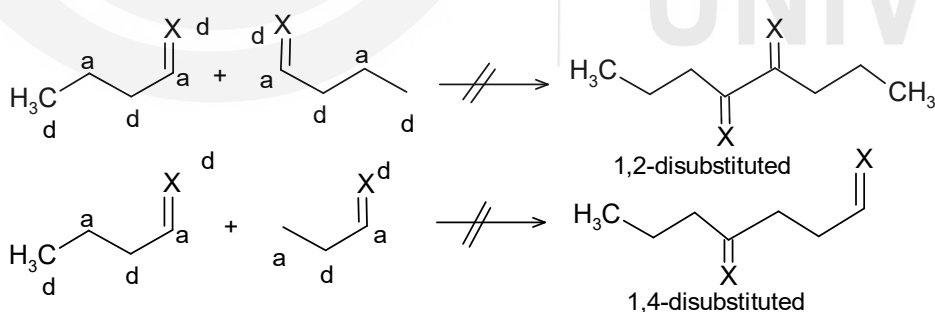
Before going in detail let us define term umpolung.

### What is Umpolung?

The reactions most frequently used for carbon-carbon bond formation are polar in nature. Generally, electronegative hetero atoms such as nitrogen, oxygen and the halogens impose an alternating positive and negative polarity on carbon skeleton, in other words these charges create donor and acceptor reactivity pattern. This alternating pattern of donor (**d**) and acceptor (**a**) atoms implies that in principle 1, (2*n*+1) substituted products can be formed through nucleophilic attack at the acceptor carbons (see Fig.15.1). The same bond-making approach would fail for odd substitution products because the two atoms making a bond have a non-complementary relationship. Hence, formation of synthetic targets with 1, (2*n*)-disubstituted substitution patterns is difficult to achieve using traditional reactivity pattern owing to the charge affinity mismatch (see Fig. 15.2). This mismatched bonding relationship is commonly referred to as dissonant.



**Fig. 15.1: An alternating donor and acceptor reactivity pattern on the carbon skeleton framework for 1, (2*n*+1) disubstituted patterns.**



**Fig. 15.2: An alternating donor and acceptor reactivity pattern on the carbon skeleton framework for 1, (2*n*) disubstituted patterns.**

Access to 1, (2*n*)-disubstituted patterns necessitates a change in polarity from acceptor to donor at the 2*n* carbon atom positions. This process of polarity inversion is termed *umpolung* (polarity inversion) and was introduced by D. Seebach together with E. J. Corey and has proven to be a useful theoretical tool in organic synthesis for the construction of simple and complex molecular targets. In this unit our focus will be on various methods for creating opposite reactivity in 1, (2*n*)-positions of a carbon framework. These methods allow us

to develop alternative routes to traditional carbon-carbon bonds forming strategies for synthesis of organic compounds.

**Logical synthons:**

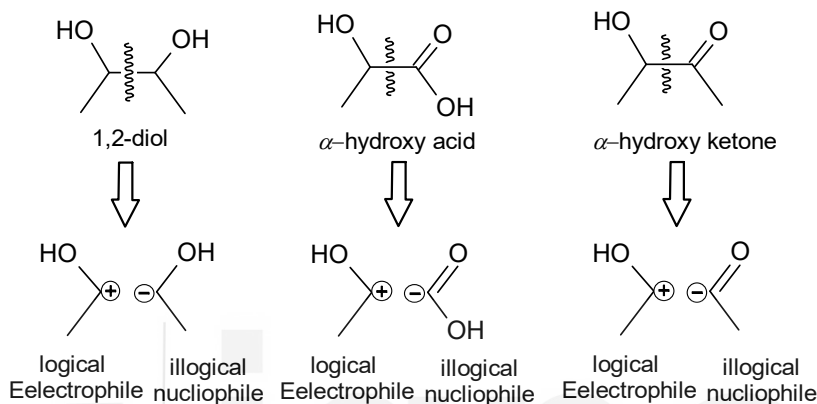
The charge on the synthon coincides with the natural polarity imparted by the functional group present.

**Illogical synthons:**

The charge on the synthon is opposite to the natural polarity imparted by the functional group present.

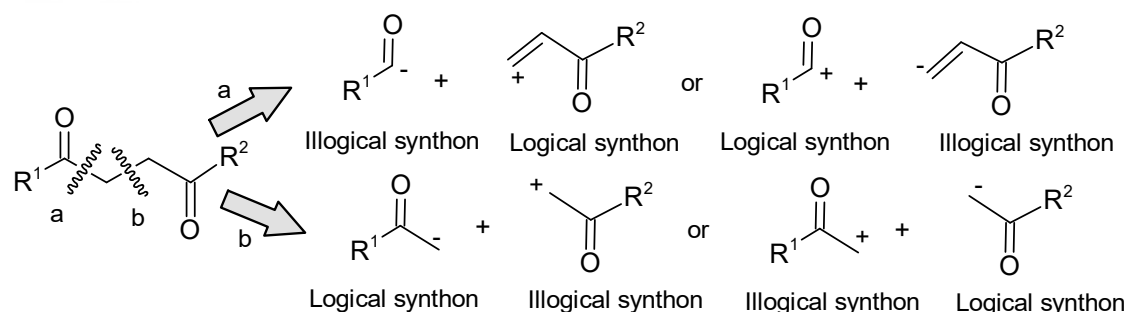
Thus, logical synthons are often also called natural synthons and illogical synthons are known as unnatural synthons. The synthetic equivalent representing a logical electrophilic synthon is called a 'logical' electrophile while an illogical electrophilic synthon is represented by an 'illogical' electrophile. The same pattern is followed for nucleophilic synthons.

For better understanding of umpolung let's carry out retrosynthetic analysis of the 1,2-disubstituted deoxygenated compounds such as 1,2-diol,  $\alpha$ -hydroxy ketone and  $\alpha$ -hydroxy acid (Fig. 15.3). As mentioned in earlier, the normal reactivity does not enable us to construct 1,2-disubstituted products. Then question arises, how we can synthesise such products?



**Fig. 15.3: Retrosynthesis pathway for 1,2-dioxygenated target molecules**

Using retrosynthetic analysis we may identify synthetic equivalent groups. We call such groups as synthons that correspond structurally to a subunit of the target molecule. In these cases disconnection does not result in a logical electrophile and nucleophile. In both the cases negative charged carbonyls i.e. acyl anions are illogical synthons. Since carbon centre of carbonyls are normally electrophilic in nature a reversal of polarity (umpolung) must occur in order to accomplish the synthesis of 1,2-diol,  $\alpha$ -hydroxy acid and  $\alpha$ -hydroxy ketone. In this case acyl anion can be an umpolung equivalent of the electrophilic positive charge carbonyl (acylium cation). Similarly, retrosynthetic analysis of 1,4-diketone also results in logical and illogical synthons. Thus, synthesis of target compound requires either an acyl anion equivalent reacting with a logical  $\beta$ -carbonyl electrophile or a normal  $\alpha$ -carbonyl nucleophile reacting with illogical  $\alpha$ -carbonyl electrophile.



Now, in next sub-section, we will explore various strategies for the reversal of the polarity of carbon atom of carbonyl group.

**SAQ 1**

Carry out retrosynthetic analysis of 1-Hydroxy-1-phenyl-2-butanone and name the synthons as logical or illogical synthon.

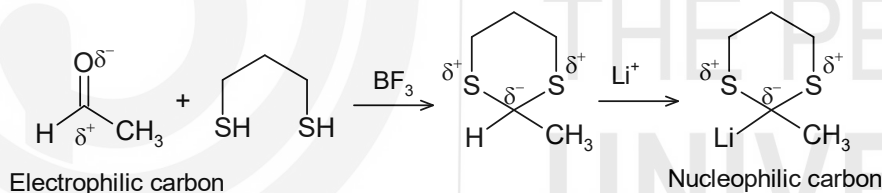
### 15.2.1 Carbonyl Umpolung Strategies

Owing to the great importance of carbonyl groups in synthesis, a substantial effort has been dedicated to developing nucleophilic equivalents for introduction of acyl groups. There are several synthetic equivalents for the acyl anions as given below:

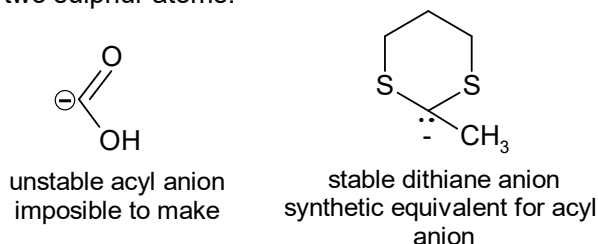
1. Dithiane (sulphur umpolung)
2. Cyanide ion
3. Nitronate anion
4. Cyanohydrins
5. Metalated enol derivatives
6. *t*-Butylhydrazone
7. Lithium acetylide
8. Intermediates in thiazolium salt catalysed reaction

#### 1. Dithiane (sulphur umpolung)

Sulphur compounds are useful in inducing carbonyl umpolung reactivity. Dithianes are for most purposes simply the sulphur version of acetals. They can be prepared by the reaction of aldehyde or ketone with alkyl or aryl dithiols in presence of Lewis acid in an appropriate solvent. This can be represented by following reaction:

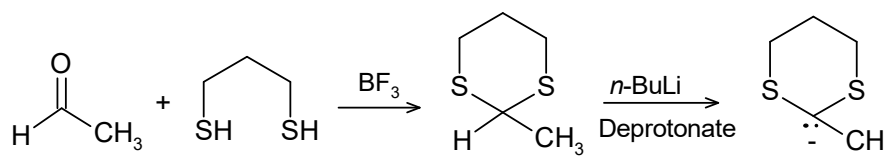


Dithianes are also used as protecting group in many transformations similar to acetals. They are also a classic example of polarity inversion i.e. umpolung. Usually the oxygen atom in the carbonyl group is more electronegative than the carbon atom and therefore the carbon atom of carbonyl group acts as an electrophile. When the carbonyl group is converted into a dithiane or a thioacetal, the polarity of carbon atom is reversed. In synthon terminology the ordinary carbonyl group is an acyl cation and the dithiane is a masked acyl anion. In dithianes the reversal of polarity i.e. umpolung is achieved because of the anion stabilizing ability due to the inductive withdrawal of electron density by the two sulphur atoms.



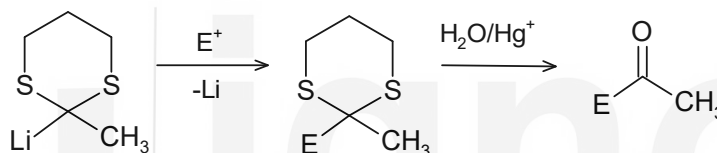
**1,3-Dithiane anion is the synthetic equivalent of an acyl anion**

**Preparation of 1,3-dithiane anion:** 1,3-Dithiane is an important umpolung reagent. To make a 1,3-dithiane anion, an aldehyde is first converted to a thioacetal by reaction with 1,3-propanedithiol and a Lewis acid such as  $\text{BF}_3$ . The resulting thioacetal is then deprotonated with a strong base such as an *n*-butyl lithium to generate 2-lithio-1,3-dithiane (a masked acyl anion).



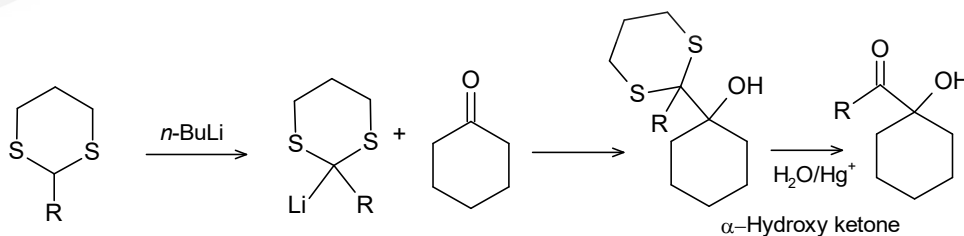
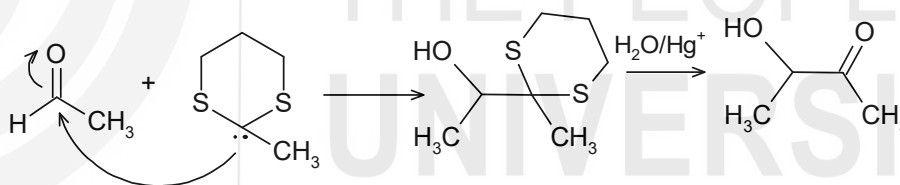
### Reactions of Dithianes:

The lithio derivative of 1,3-dithiane is a reactive nucleophile toward electrophiles such as alkyl halides, carbonyl compounds. The final product can be hydrolysed with  $\text{Hg}^{2+}$  in aqueous medium. Final reaction can be represented as:

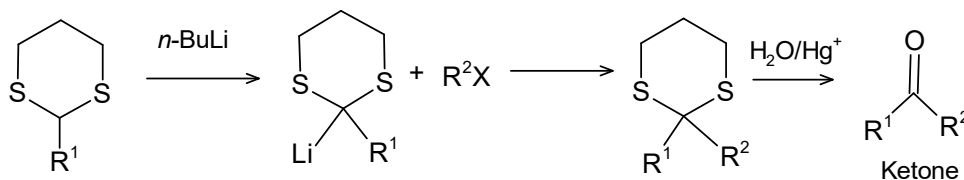


1,3-Dithianes and other sulphur compounds have found considerable applications in multistep syntheses. Few examples of synthetic sequences that employ acyl anion equivalents are given below:

**Reaction with carbonyl compound:**  $\alpha$ -Hydroxy ketones can be prepared using 1,3-dithiane and ketone.



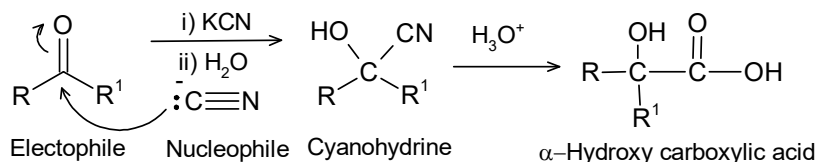
**Reaction with alkyl halide:** Aldehydes and ketones can be prepared using 1,3-dithiane and alkylhalide.



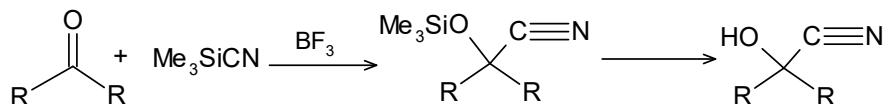
Similar to 1,3-dithianes other sulphur compounds can also be used to generate acyl anion equivalent.



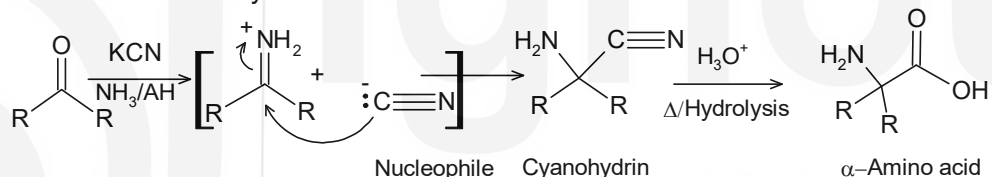
how the synthesis of an  $\alpha$ -hydroxycarboxylic acid can be achieved by addition of cyanide to a ketone or an aldehyde followed by hydrolysis of the resulting cyanohydrin,



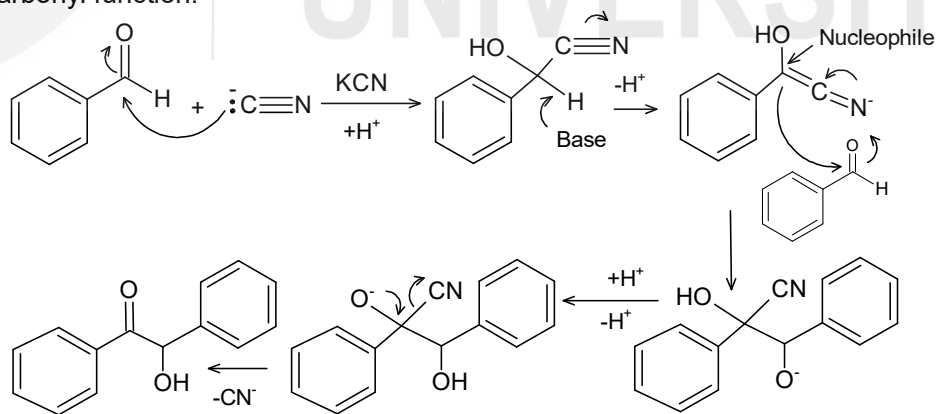
This sometimes has problems with forcing the reaction to the product side, and a competing benzoin condensation, so the reaction is usually performed by trimethylsilyl cyanide and a Lewis acid.



Let's take up some related reactions, such as the Strecker amino acid synthesis, and the benzoin condensation. In the Strecker amino acid synthesis cyanide is once again used as a synthetic equivalent for the carboxyl group, but it attacks an imine rather than a carbonyl, the imine is formed *in situ* by combining ammonia with a ketone or an aldehyde, and hydrolysis of the nitrile affords the carboxylic acid.



Benzoin condensation is another classical example of polarity inversion (umpolung). In this case cyanide ion act as nucleophilic catalyst, deprotonation of the acidic  $\alpha$ -proton generates a nitrile stabilized anion which act as equivalent to acyl anion, this undergoes a subsequent 1,2-addition to a carbonyl function.



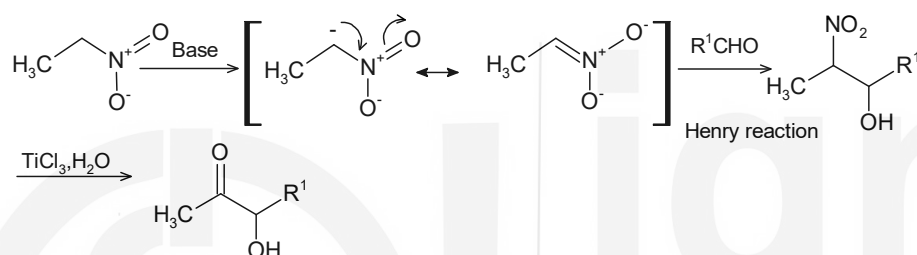
The net result of the benzoin reaction is that a bond has been formed between two carbons that are normally electrophiles.

### SAQ 3

How do you prepare 2-hydroxypropanoic acid? Write all the steps involved in its synthesis.

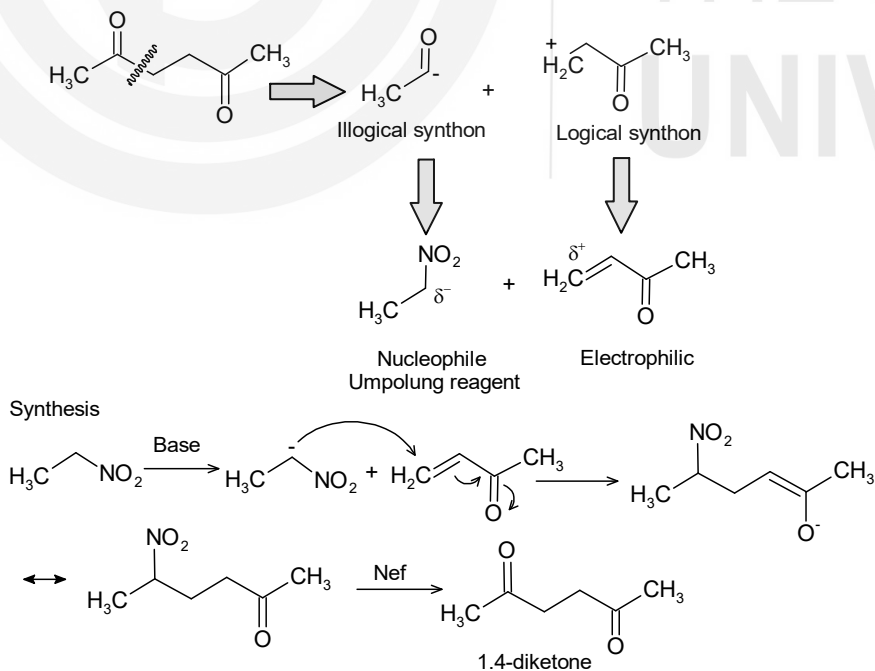
### 3. Nitronate anion

Generally, carbon-carbon bond formation at the  $\alpha$ -position of a ketone is performed by the reactions of enolates and enamines with carbon electrophiles. The umpolung reaction of the  $\alpha$ -carbon on a carbonyl structure for formation of carbon-carbon bond using a carbon nucleophile can be achieved using **Henry and Nef reactions**. These reactions are common example of 1,2-addition and 1,4-addition of nitroalkanes. The  $\alpha$ -hydrogens of nitroalkanes are appreciably acidic due to resonance stabilization of the anion  $^-\text{CH}_2\text{NO}_2$ ,  $\text{p}K_{\text{a}}$ : 10.2. The anions derived from nitroalkanes give typical nucleophilic addition reactions with aldehydes and ketones. Finally nitro group of the product is converted to carbonyl group using acidic conditions. The later conversion is called Nef reaction. Henry-Nef reactions are one of the examples of "umpolung" reactivity in which nitronate anion functions as an umpolung reagent and it is equivalent to acyl anion. The Nef reaction is an excellent way to convert nitronates into carbonyl compounds.



#### In preparation of 1,4-dicarbonyl compounds

You have seen earlier that retrosynthetic analysis of 1,4-diketone results in logical and illogical synthons. Thus for the synthesis of 2,5-hexadiketone we have to look for umpolung reagent for illogical synthon. In this case nitronate anion can be used as umpolung reagent.



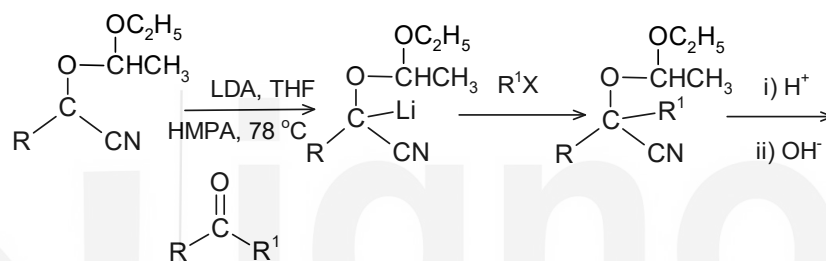
In both the examples final products are 1,2-disubstituted and 1,4-disubstituted which otherwise are difficult to achieve or we have to use many steps to obtain final target molecules.

## SAQ 4

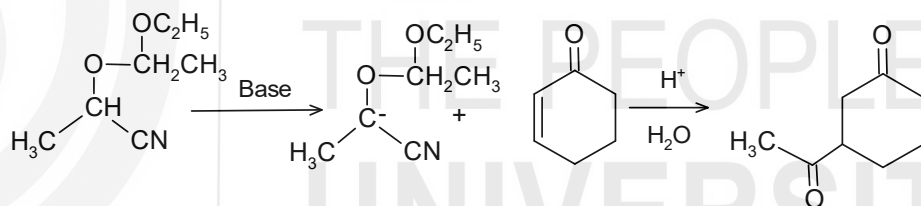
Using Henry and Nef reaction how you will prepare 3-hydroxy-2-butanone.

## 4. Cyanohydrins

Protected cyanohydrins, when deprotonated by a suitable base, are synthetic equivalents of the acyl anion. They display 'umpolung' reactivity as the normally electrophilic carbonyl carbon is transformed into a nucleophile. This method involves a three-step sequence in which an aldehyde is converted to an O-protected cyanohydrin as its ethoxyethyl ether. The  $\alpha$ -alkoxynitrile is then deprotonated with LDA, generating a nucleophilic carbanion. After carbon-carbon bond formation, the carbonyl group can be regenerated by hydrolysis of the cyanohydrin.

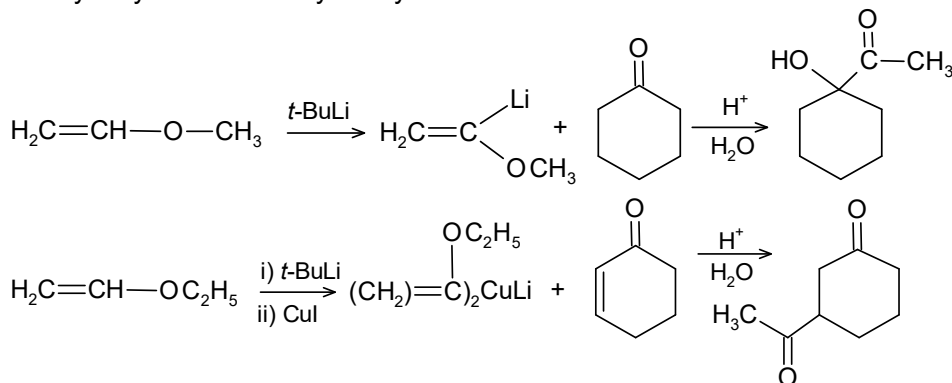


This method can be used for introducing an acetyl group at the  $\beta$ -position of cyclohexenone which is otherwise it is difficult to achieve by natural reactivity of functional groups.



## 5. Metalated enol derivatives

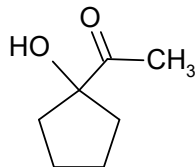
$\alpha$ -Lithiovinyl ethers which are also known as protected enols are another examples of acyl anion equivalents. They can be metalated with Li and corresponding cuprate. These reagents are capable of adding the  $\alpha$ -alkoxyvinyl group to electrophilic centers. Subsequent hydrolysis can generate the carbonyl group and complete the nucleophilic acylation at electrophilic carbonyl carbon. One of the big advantages of enol ether products is that they are hydrolysed under very mildly acidic conditions.



Lithiation of vinyl thioethers and vinyl carbamates also provides acyl anion equivalents.

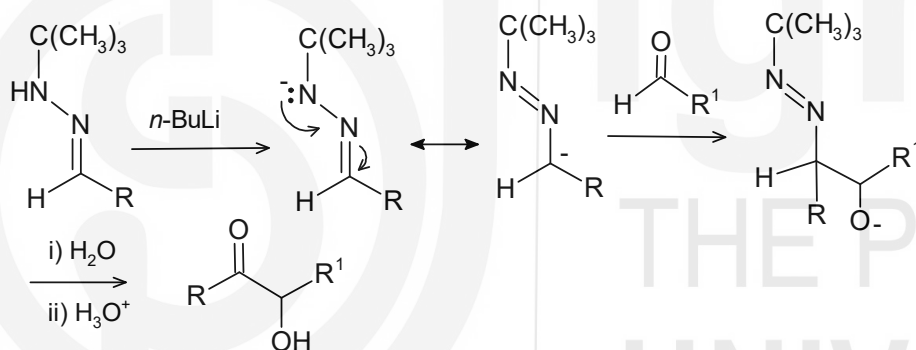
### SAQ 5

Write the steps involved in the synthesis of following compound using  $\alpha$ -lithiovinyl ether.



### 6. *t*-Butyl hydrazones

Carbon centre of hydrazones which are formed by condensation of *t*-butyl hydrazine with aldehydes or ketones behaves as nucleophile on reaction with strong base such as *n*-butyl lithium. Carbanion so formed can react with aldehydes/ketones and alkyl halides. After carbon-carbon bond formation, the carbonyl group can be regenerated by hydrolysis of the final product.

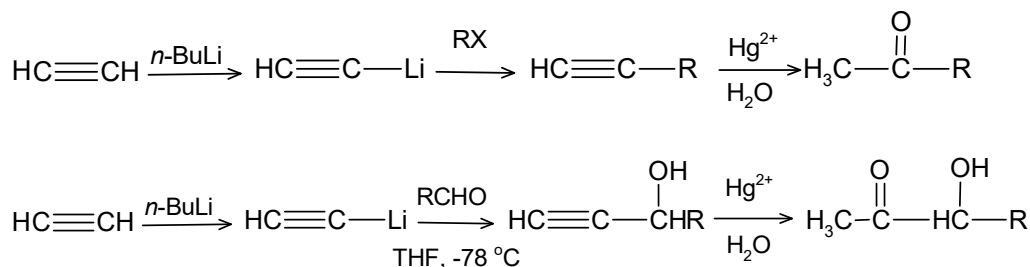


### SAQ 6

Using *t*-butyl hydrazine, write the steps for the preparation of a 4-ketoacid.

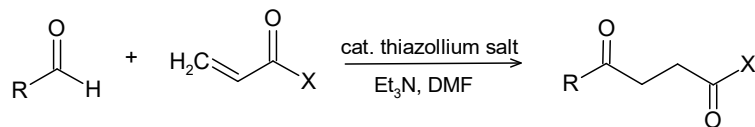
### 7. Acyl Anions Derived from Lithium acetylene

Lithium acetylene is also considered equivalent to acyl anion. It can undergo nucleophilic reactions with a primary alkyl halide (bromide or iodide) or with aldehydes or ketones to produce the corresponding monosubstituted acetylenes or alkynyl alcohols. Mercuric ion-catalyzed hydration of these furnishes methyl ketones and methyl  $\alpha$ -hydroxy ketones, respectively.

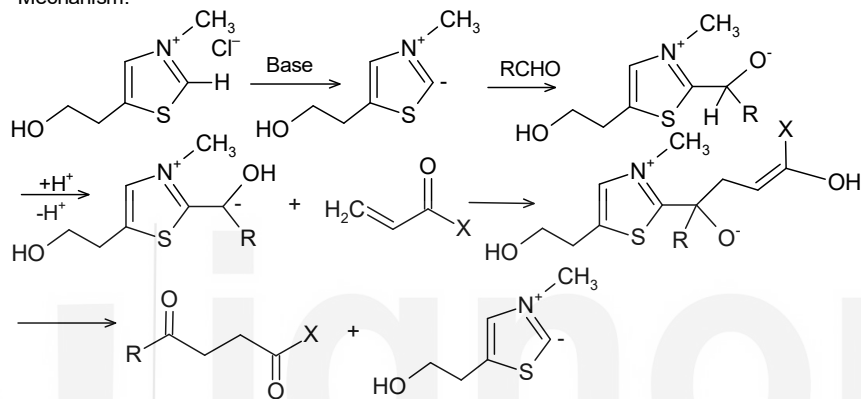


### 8. Intermediates in thiazolium salt catalysed reaction

In the presence of base, quaternary thiazolium salts are converted to the ylide, which acts as catalyst for aliphatic, aromatic, and heterocyclic aldehydes to generate acyl anion equivalent. This can add to  $\alpha,\beta$ -unsaturated ketones, esters, and nitriles.  $\text{Et}_3\text{N}$  or  $\text{NaOAc}$  are preferred bases and DMF, dioxane, or even alcohols can function as solvent.



Mechanism:



### 15.2.2 Homo-enolates

Carbon-carbon bond formation at the  $\alpha$ -position of carbonyl compounds is mostly based on aldol-type processes, whereas bond formation at the  $\beta$ -position is usually achieved by another classical reaction, the Michael addition. The latter reaction exploits the electrophilic nature of the  $\beta$ -carbon of an  $\alpha,\beta$ -unsaturated carbonyl compound. Umpolung equivalent of  $\alpha,\beta$ -unsaturated carbonyl compound is called homoenolate. Negatively polarised  $\beta$ -carbon of homoenolates opens up many interesting synthetic possibilities. By definition they must exhibit nucleophilic character at the carbon  $\beta$ -to a carbonyl group or a moiety that can be transformed into a carbonyl group (Fig. 15.4)

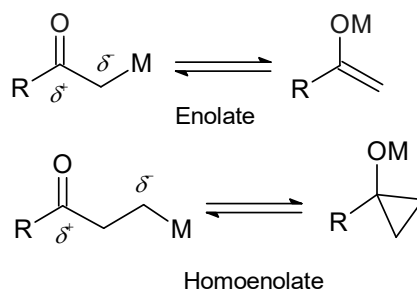
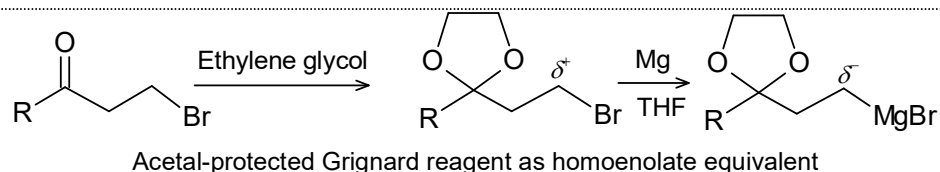
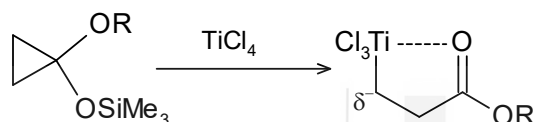


Fig. 15.4: Comparison of enolate and homoenolate.

These reagents similar to acyl anion equivalent, are used for carbon-carbon bond formation with electrophiles such as alkyl halide and carbonyl compounds. Unlike enolates, the carbonyl group of homoenolate is incapable of stabilizing a  $\beta$ -negative charge; indirect methods are required for the generation of homoenolates. Generally, for making  $\beta$ -carbon as nucleophilic center, an organometallic is needed. A common way to do this is to use a  $\beta$ -bromo acetal.

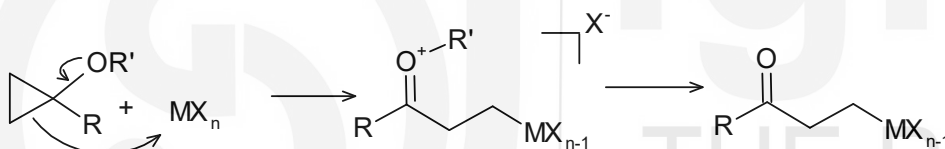


In such reactions we have to protect carbonyl group before reactions with metal ions. Homo-enolates can also be readily prepared via treatment of siloxycyclopropanes with an appropriate metal halide source. Overall, this method utilizes the lessening of ring strain in cyclopropanes towards the formation of various homo-enolate equivalents. Such species do work as the nucleophilic homo-enolate anion of alkyl propionate. Variety of metals can be used to form such homo-enolates such as titanium, magnesium, zinc, palladium, nickel, copper, mercury and tin metals. Preparation of cyclopropanol-derived titanium(IV) homo-enolate is shown below.

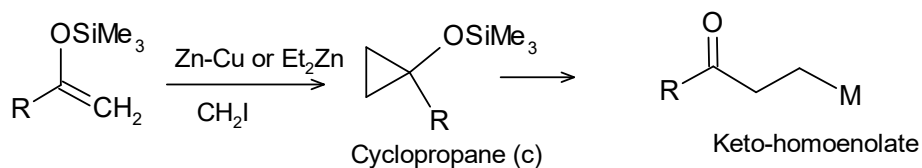
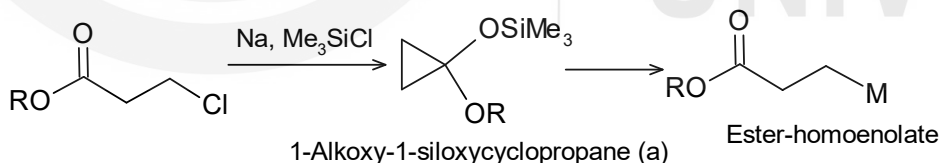


#### Cyclopropanol-derived metal homo-enolate equivalents

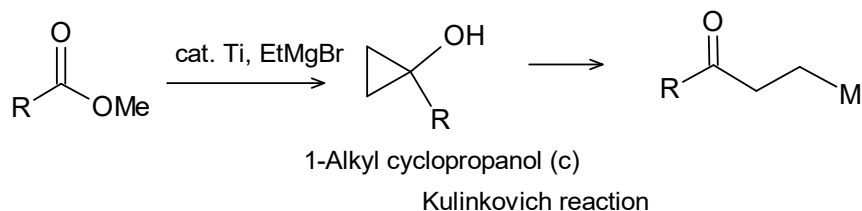
Following mechanism can be proposed for ring penning of cyclopropanol derivatives.



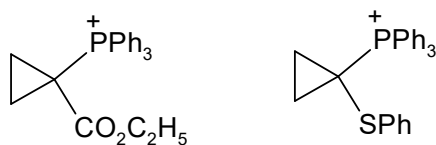
The cyclopropanol derivatives used as homo-enolate precursors can be categorized into three types, that is, 1-alkoxy-1-siloxycyclopropanes (**a**) for ester homo-enolates and 1-alkyl/aryl-1-siloxycyclopropanes (**b**) and cyclopropanols (**c**) for keto-homo-enolates.



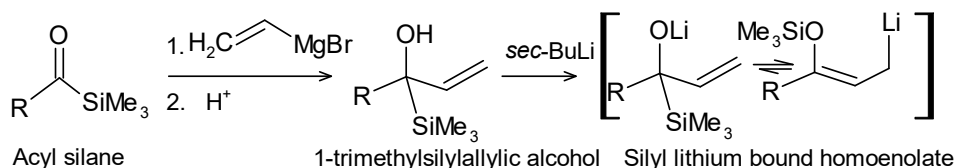
#### Simmons-Smith reaction



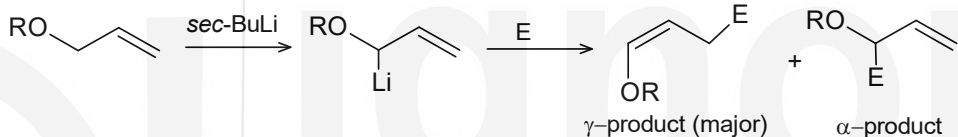
Cyclopropyl phosphonium ions equivalent to homoenolates have also been developed along these lines.



Homoenolates can also be prepared by the reaction of acyl silane with a vinyl Grignard reagent in two step reaction.



Homoenolate can also be prepared by the metalation of allylic ethers with *sec*-butyllithium in THF at low temperature.

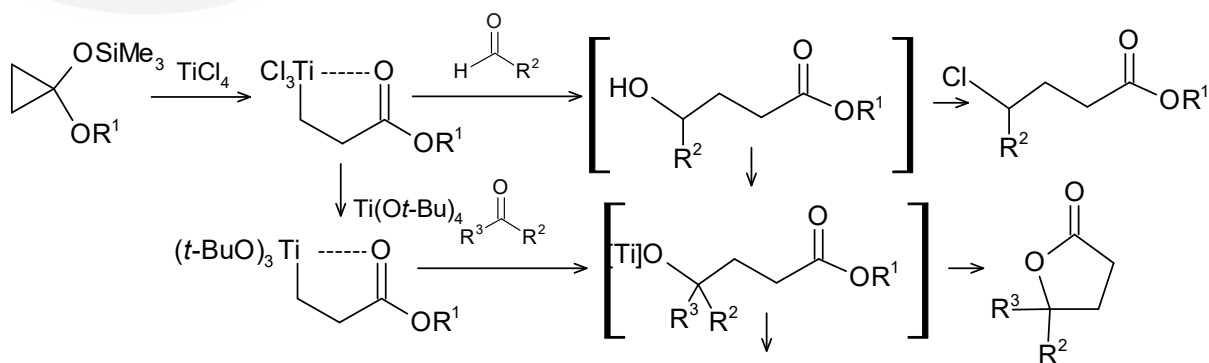


Homoenolate, provide us a one-carbon-extended homolog of enolate, can also be attractive reactive species, as it could react with electrophiles to afford  $\beta$ -substituted ketones.

These reagents involve delocalized allylic anions, which gives rise to the possibility of electrophilic attack at either the  $\gamma$ - or  $\alpha$ -position of the allylic group. In most cases, the  $\gamma$ -attack that is necessary for the anion to function as a propanal homoenolate is dominated.

Beside these common methods many other types of homoenolates has been developed in past. All these reagents are reactive toward electrophiles such as alkyl halides and carbonyl compounds. Some representative conversion using homoenolate reagents are given below:

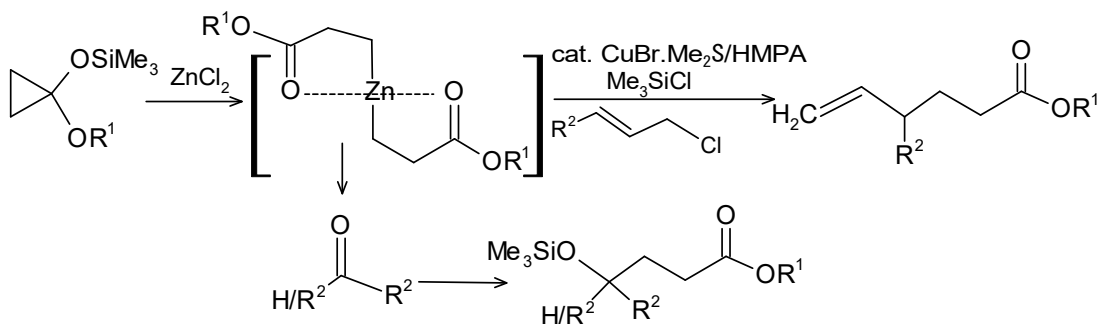
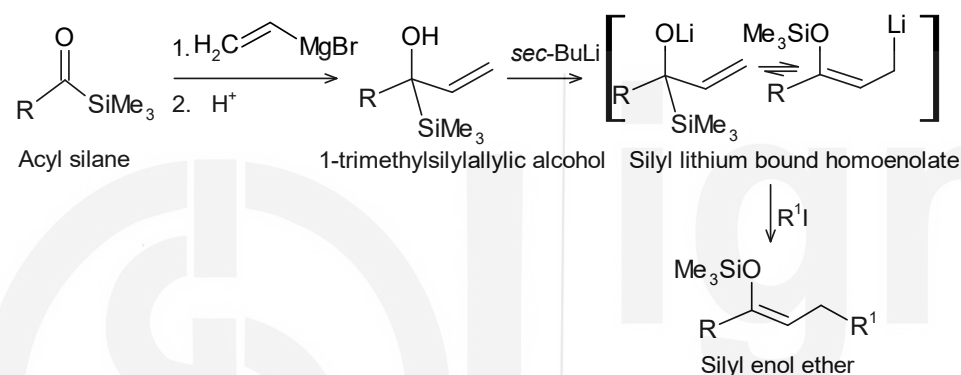
#### Reactions of Titanium Ester-homoenolate:



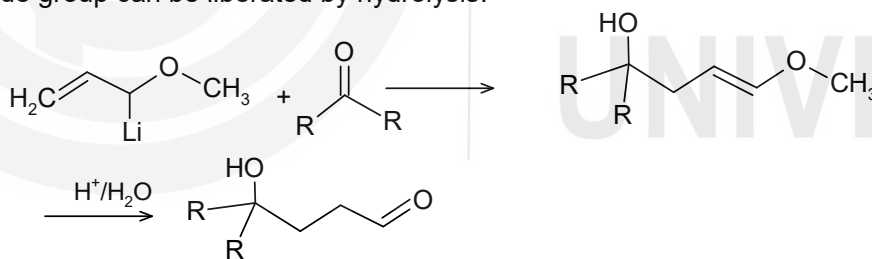
The  $\text{TiCl}_3$ -homoenolate is less reactive. It reacts only with aldehydes to afford  $\gamma$ -chloroesters through *in situ* chlorination of the initial adducts but not with ketones. The reactivity of this reaction can be enhanced by exchanging chloride ligand of this homoenolate with an alkoxide using  $\text{Ti}(\text{OR})_4$  which makes the homoenolate more nucleophilic, thus reacting with ketones to give  $\gamma$ -lactones.

**Reactions of Zinc Ester-homoenolate:**

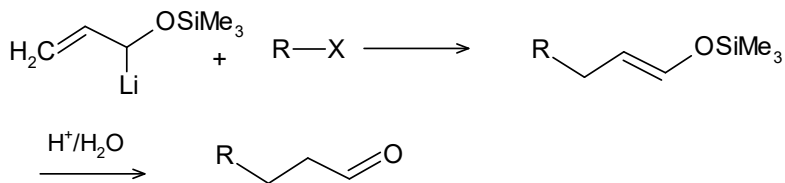
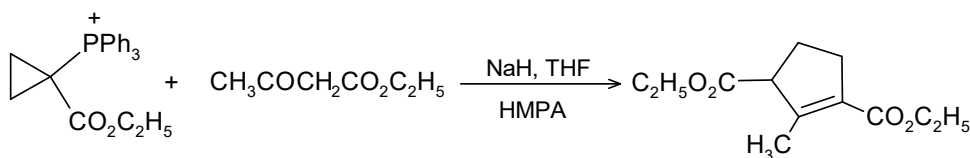
The zinc homoenolate worked as a good alkyl nucleophile towards various electrophiles with or without transition metals.

**Reactions of Silyl lithium bound homoenolate:****Reactions of 2-methoxypropyllithium:**

The lithiation product of allyl methyl ether serves as a nucleophile and the aldehyde group can be liberated by hydrolysis.

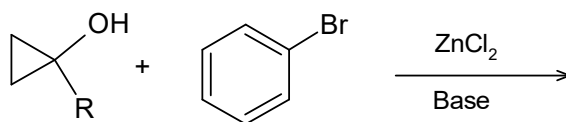


Above reaction can be modified by using trimethylsilyl ether.

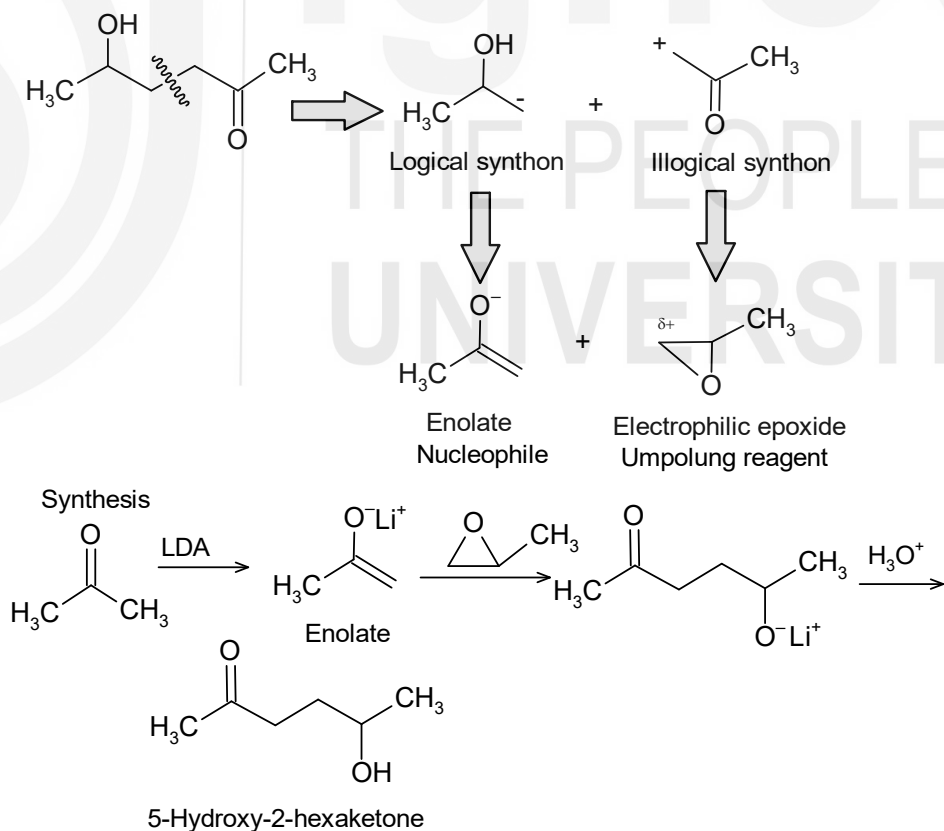
**Reactions of cyclopropyl phosphonium ions:**

## SAQ 7

Complete following reaction:

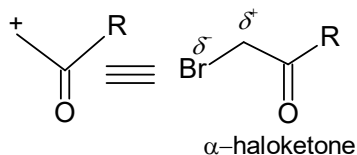
15.2.3  $\alpha$ -Electrophiles

Generally, carbon–carbon bond formation at the  $\alpha$ -position of a ketone is performed by the reactions of enolates and enamines with carbon electrophiles. The umpolung reaction of the  $\alpha$ -carbon on a carbonyl structure is an attractive reaction because it allows the direct introduction of various types of substituents into the  $\alpha$ -position through the use of nucleophiles. For further illustration, consider again retrosynthetic analysis of 1,4-dioxy compound results in logical and illogical synthons. Thus for the synthesis of 5-hydroxy-2-hexaketone we have to look for umpolung reagent for illogical synthon. In this case epoxide can be used as umpolung reagent.



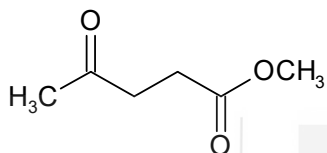
In above reaction unsymmetrically substituted epoxide is an umpolung reagent. Ring opening of such epoxide depends on the reaction conditions. They tend to react with anionic nucleophile at the less hindered carbon of the ring. Under acidic condition more substituted carbon is attacked.  $\alpha$ -

Halogenated carbonyl compounds can also be used for umpolung reactions at  $\alpha$ -carbon atoms.



### SAQ 8

Identify synthons for the compound shown below. Write all the steps involved in its synthesis.

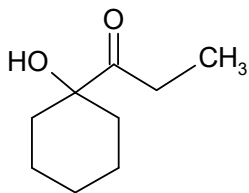


## 15.3 SUMMARY

In this unit we have discussed umpolung reactions. These reactions provide an alternate approach for the synthesis of organic molecules. Umpolung strategies are very effective for the organic synthesis which are otherwise non-accessible reactivity patterns. Umpolung chemistry reverses the “normal” traditional reactivity patterns imposed by heteroatoms in alkyl chains. It is not only academically interesting but synthetically useful as well. In this unit we have covered wide variety of reactions related to carbonyl umpolungs, homoenolates and  $\alpha$ -carbon electrophiles.

## 15.4 TERMINAL QUESTIONS

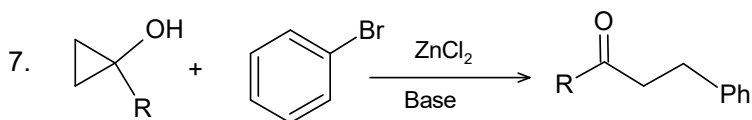
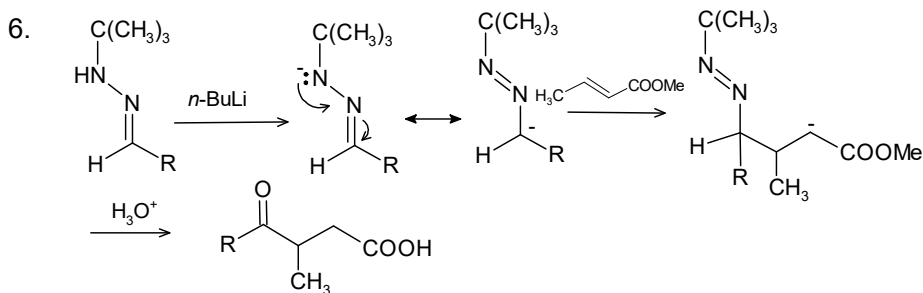
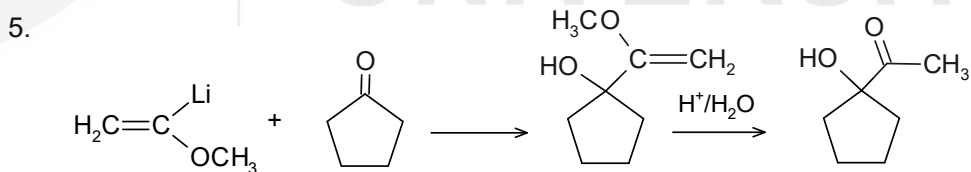
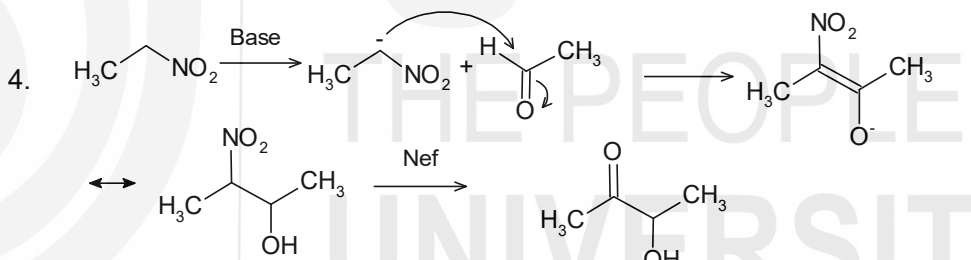
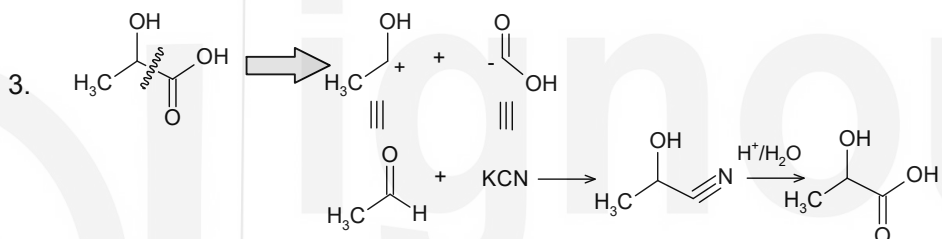
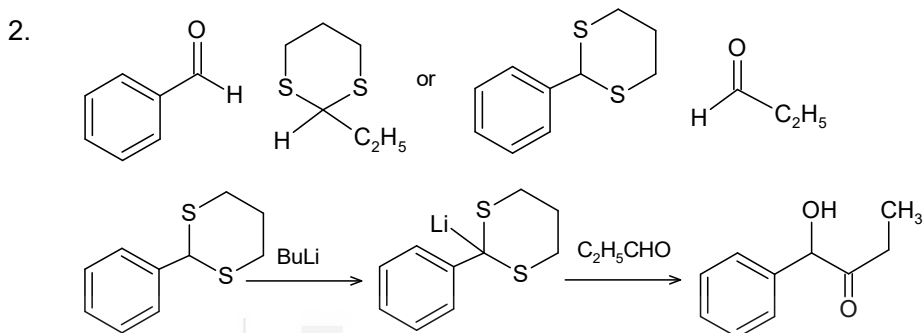
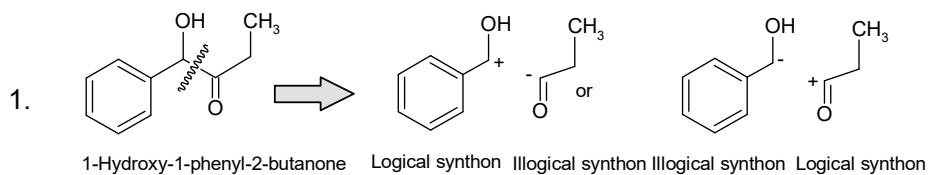
1. Identify synthons of following compound. Write steps involved in its synthesis:



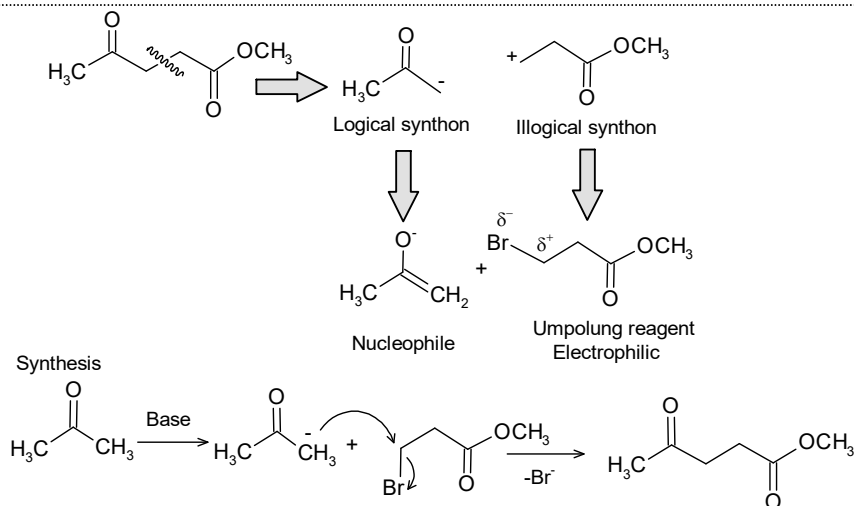
2. Explain the role of sulphur compounds in the preparation of acyl equivalent.
3. How you will convert aldehydes into ketones using 1,3-dithiane.
4. Identify synthons for the synthesis of a  $\gamma$ -hydroxy carbonyl compound. Write the steps involved in its synthesis.
5. Describe homoenolates with suitable examples.

## 15.5 ANSWERS

## Self Assessment Questions

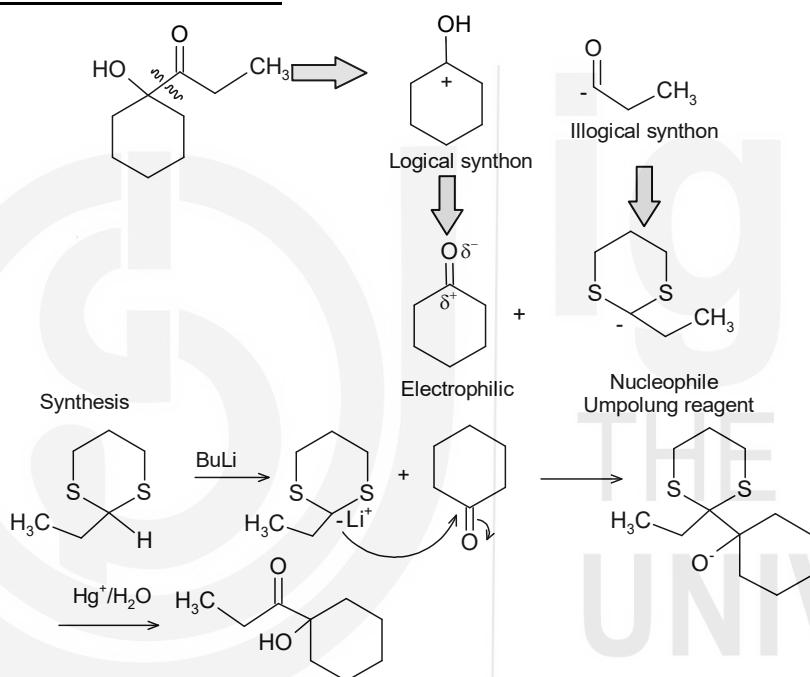


8.

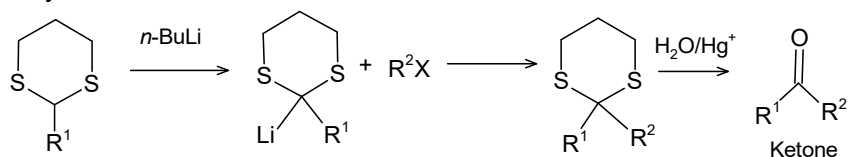


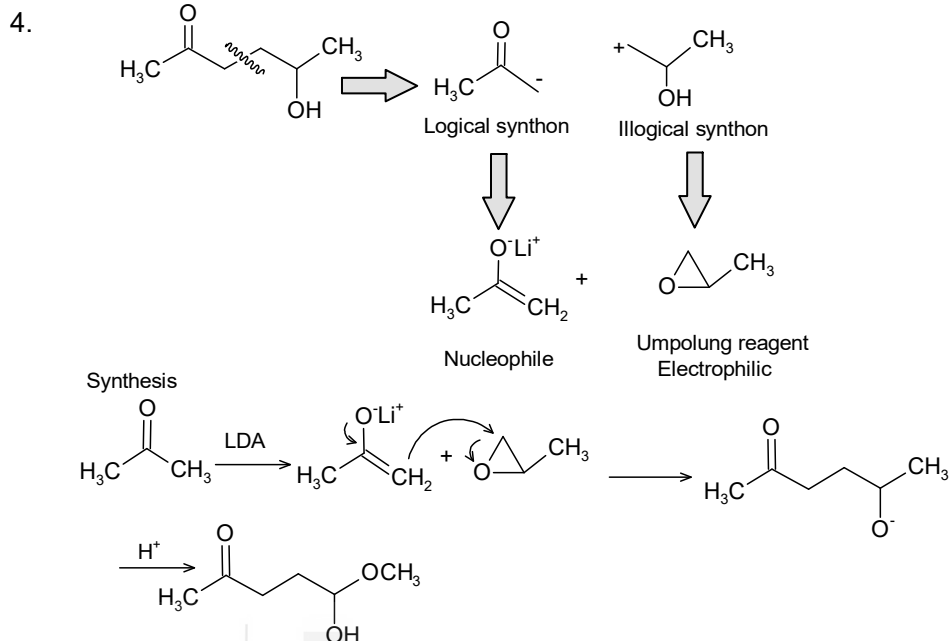
### Terminal Questions

1.

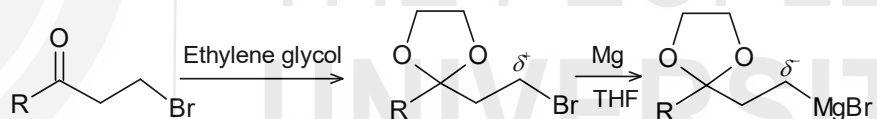


2. Ordinarily the oxygen atom in the carbonyl group is more electronegative than the carbon atom and therefore the carbon atom of carbonyl group acts as an electrophile. When the carbonyl group is converted into a dithiane or a thioacetal, the polarity of carbon atom is reversed. In synthon terminology the ordinary carbonyl group is an acyl cation and the dithiane is a masked acyl anion. In dithianes, the reversal of polarity i.e. umpolung, is achieved because of the anion stabilizing ability by the two sulphur atoms by the inductive withdrawal of electron density.
3. Aldehydes can be converted to ketones using 1,3-dithiane and alkylhalide.

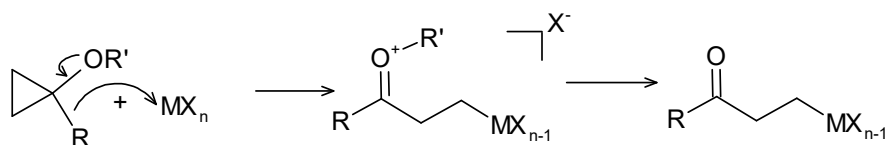

 $R^1 = H/R$



5. Homoenolates are one-carbon-extended homologs of enolates. These can also be attractive reactive species, as it could react with electrophiles to afford  $\beta$ -substituted ketones. While enolate can be accessed by deprotonating the  $\alpha$ -position of the corresponding carbonyl compound with an appropriate base, the preparation of homoenolate cannot be performed in an analogous fashion because selective deprotonation of the  $\beta$ -C-H bond is difficult as it is less acidic than the  $\alpha$ -C-H bond. Generally, for making  $\beta$ -carbon as nucleophilic center, an organometallic is needed. A common way to do this is to use a  $\beta$ -bromo acetal.



Another category of homoenolates are cyclopropanol derivatives. They have been widely recognized as viable precursors to metal homoenolate, as the cleavage of the strained cyclopropane ring and the formation of a strong C=O bond constitute substantial driving forces.



# UNIT 16

## PRINCIPLE AND APPLICATIONS OF PHASE TRANSFER CATALYSIS

### Structure

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16.1 Introduction	16.4 Applications of Phase transfer Catalysis
Expected Learning Outcomes	16.5 Summary
16.2 Types of Phase Transfer Catalyst	16.6 Terminal Questions
16.3 Mechanisms of Phase Transfer Catalysis	16.7 Answers

### 16.1 INTRODUCTION

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In the previous unit you have learnt about chemistry of umpolung reactions. You have learnt about the important role of umpolung strategies in organic synthesis. These methods provide alternative approaches for the construction of new carbon-carbon C-C bonds. In this unit we will discuss another alternative approach to traditional chemical reactions which are generally conducted in a homogeneous medium. There are chemical agents which can facilitate the transport of reactants and reagents between two or more different immiscible phases. Such agents are referred as the phase transfer catalysts (PTC) or simply catalyst and the process or action by which a catalyst increases the reaction rate is called catalysis. Generally, this process involves the transport of ions between phases facilitated by the formation of a catalyst-reagent ion pair. After the intermediate ion-pair has crossed the phase boundary, this reactive ion-pair can participate in a number of different chemical reactions. Finally, the catalyst may be regenerated after the complete transportation of the reactant/reagent to complete the reaction.

Phase transfer acatalytic reactions are performed in a combination of phases; the most common are liquid-liquid and liquid-solid phase reactions. In

the case of liquid-liquid phase transfer reactions, one phase is generally a non-polar organic solvent and the other phase is a polar solvent, typically an aqueous solution. Most often, a reagent is transferred from the aqueous phase

into the organic phase by the phase transfer catalyst. Solid-liquid phase transfer reactions are similar in most respects with the exception that one phase remains a solid and may be immobilized on any polymer support. The majority of phase transfer catalytic processes involve reactions of interest taking place in the organic phase. Although in certain cases this trend may be reversed and the desired reaction will proceed in the aqueous or solid phase. Phase transfer catalysts have wider application in the chemical industry as phase transfer catalysis processes offer the advantage of mild reactions conditions and acceleration of the reactions rates. They also provide high yield, solvent flexibility, and simplistic product isolation and minimize chemical waste. Therefore, phase transfer catalysis is an ideal tool for the adoption of green chemistry principles into organic synthesis.

### Expected Learning Outcomes \_\_\_\_\_

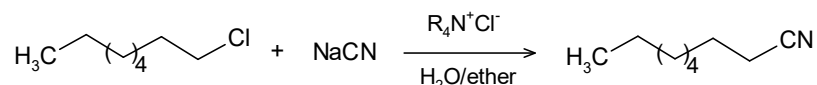
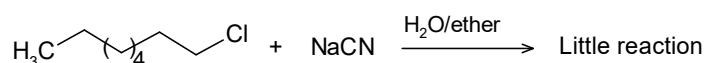
After studying this unit, you should be able to:

- ❖ define term phase transfer catalysis;
- ❖ explain mechanism of phase transfer catalytic processes;
- ❖ describe various reactions conducted in the presence of phase transfer catalyst; and
- ❖ describe applications of phase transfer catalysis reactions in organic synthesis.

## 16.2 TYPES OF PHASE TRANSFER CATALYSTS

The concept of phase transfer catalysis was first described by Starks in which various alkyl halides in an organic solvent underwent  $S_N2$  displacement reactions by cyanide ions in aqueous solution catalyzed by a quaternary ammonium or phosphonium salt. These catalysts allowed for the transport of anion, normally insoluble in an organic solvent, to react with a suitable electrophile in the organic phase. This catalyst-reagent ion pair is sufficiently reactive to displace a halide from alkyl halide.

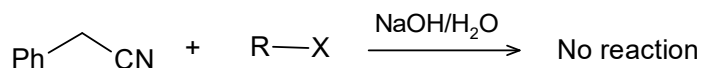
Let us start our discussion with some familiar examples to understand their role in organic synthesis. For example, consider  $S_N2$  reaction of 1-chlorooctane with sodium cyanide. In this case, 1-chlorooctane is poorly soluble in the aqueous cyanide solution, and the sodium cyanide does not dissolve well in the organic solvent such as ether. Because of this, 1-chlorooctane and sodium cyanide solution form two separate layers. Heating of this two phase mixture under reflux and vigorous stirring for 1-2 days shows little reaction. But, when an appropriate quaternary ammonium salt such as tetrahexylammonium chloride is added, the substitution occurs rapidly in near 100% in 2-3h.



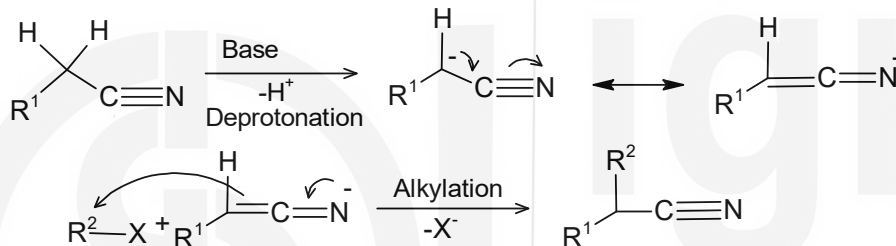
100 % yield in 2-3 Hr.

In this process the ammonium salt acts as phase transfer catalyst, transfers the cyanide into the organic phase and activates the transferred cyanide for the reaction with the alkyl halide. It also transfers the displaced chloride anions back to the aqueous phase to start a new catalytic cycle

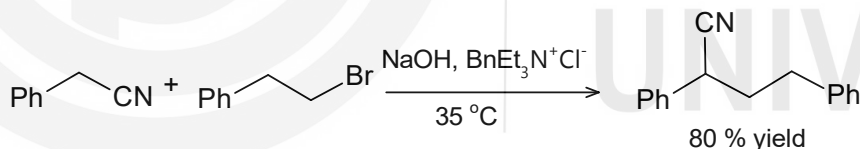
Consider another example of alkylation reaction of nitriles. No reaction occurs when a mixture of 2-phenylacetonitrile (benzyl cyanide), an alkyl halide and 50% aq. NaOH are vigorously stirred.



The nitrile group is similar to the carbonyl group increases acidic character of  $\alpha$ -hydrogens, but the acidity of the  $\alpha$ -hydrogen is much less (nitrogen is less electronegative than oxygen). Thus for deprotonation of nitriles, we require strong base such as  $\text{NaNH}_2$  or metal alkyls such as  $\text{BuLi}$ . With sodium hydroxide, the nitrile does not get deprotonated completely for alkylation and only a small amount of anion is formed.

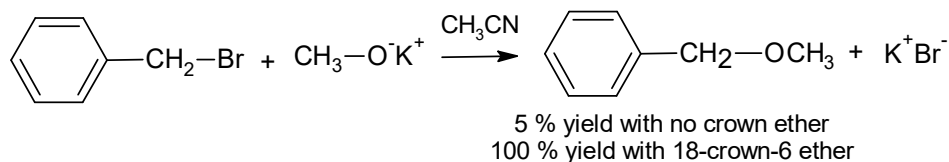


Upon addition of tetraalkylammonium chloride (benzyltriethylammonium chloride  $\text{BnEt}_3\text{N}^+\text{Cl}^-$ ) in a catalytic amount, usually 1% molar, an exothermic reaction occurs and produces phenylalkylacetonitrile in high yield.

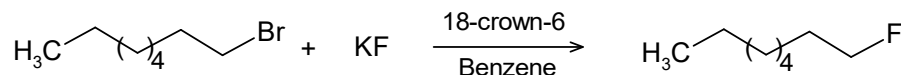


The above reaction is carried out in a two-phase mixture (water + an immiscible organic solvent) to prevent the hydroxide and 2-phenylethyl bromide reacting together to give 2-phenyl ethanol. The hydroxide stays in the aqueous layer, and the other reagents stay in the organic layer. A tetraalkylammonium chloride works as a phase transfer catalyst and allows sufficient hydroxide to enter the organic layer to deprotonate the nitrile.

Beside the quaternary ammonium and phosphonium salts (which together known as onium salts), crown ethers are also used as phase transfer catalysts. In the examples shown below, it illustrates how crown ether increases the rate of substitution reaction in the preparation of the benzyl methyl ether in acetonitrile (methyl cyanide) which does not dissolve the ionic compound. Here, the crown ether works as cation complexing agent, which surrounds and solvate the potassium ion and therefore enhances the reactivity of anionic nucleophile, cyanide ions.



Similarly, in the presence of 18-crown-6, potassium fluoride is soluble in benzene and acts as a reactive nucleophile to give product in high yields.



The phase transfer catalyst used can be either soluble or insoluble in one of the two phases. Soluble catalysts include quaternary ammonium and phosphonium salts, polyethylene glycol and its derivatives, crown ethers and cryptands, and polymeric analogs. Insoluble catalysts include polymer-bound derivatives of soluble catalysts, or species which show negligible solubility in either phase and exists as a separate third phase. No one class of catalyst can be applied to all reactions amenable to phase transfer catalysis processes. In this unit our focus will be mainly on soluble phase transfer catalysts.

The various types of phase transfer catalysts are phosphonium and quaternary ammonium salts, crown ethers, cryptands, polyethylene glycols (PEG), etc. Table 16.1 summarizes some of the properties of frequently used phase transfer catalysts.

**Table 16.1: Commonly used phase transfer catalysts**

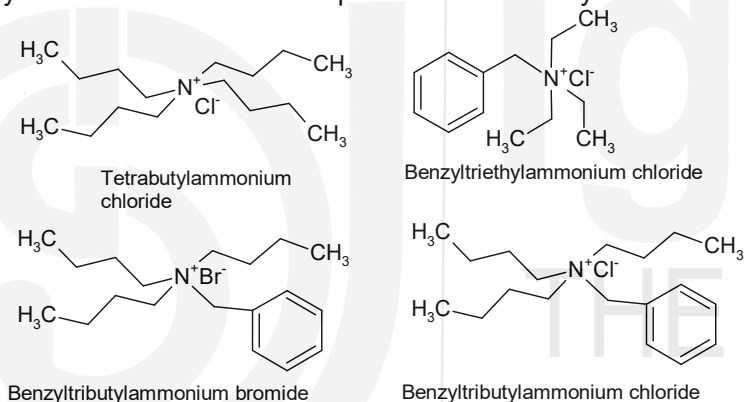
Catalyst	Stability and Activity	Use and Recovery
Ammonium salts	Moderately stable in basic conditions and up to 100°C. Decomposition by Hofmann elimination under basic conditions. Moderately active.	Widely used. Recovery is relatively difficult.
Phosphonium salts	Thermally more stable than ammonium salts, although less stable under basic conditions.	Widely used. Recovery is relatively difficult.
Crown ethers	Stable and very active catalysts both under basic conditions and at higher temperatures up to even 150-200°C.	Often used. Recovery is difficult and causes environmental issues due to their toxicity.
Cryptands	Stable and highly reactive, excluding the presence of strong acids.	Used sometimes despite high costs and toxicity, due to higher reactivity.
Polyethylene glycols	Lower activity but more stable than quaternary ammonium salts.	Often used and especially larger quantities of catalyst cause no problems. Reasonably easy to recover.

Let us discuss these catalysts in some detail.

**Quaternary ammonium salts:**

Quaternary ammonium cations have the ability to transfer the anionic reactants as non-solvated ion-pairs from aqueous media into organic media. The resultant effect is to increase the rate of the organic reaction by enhancing the reactivity of the anionic species and increasing the interaction rate with the organic substrate. Side reactions are frequently eliminated so that the overall yield of the desired product is increased. In the earlier examples we have shown how the quaternary ammonium salts increase the rate of reaction of a substitution reaction and also its yields. These catalysts are very cost effective and hence they are most widely used in the industry also.

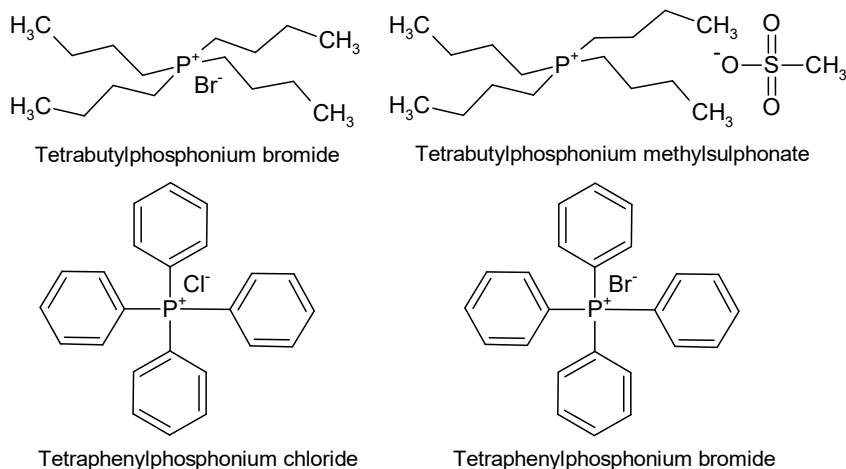
Quaternary ammonium salts are chemical compounds having nitrogen in their skeleton and large hydrocarbon groups enough to convey good solubility in nonpolar solvents. In other words, the cations are highly lipophilic. Quaternary ammonium salts form ion pair with different anions. When these phase transfer catalysts are added, the lipophilic cations are transferred to the nonpolar phase and anions are attracted from the water to the organic phase to maintain electrical neutrality. The anions are weakly solvated in the organic phase and therefore exhibit enhanced nucleophilicity. Fig. 16.1 shows the commonly used ammonium salts as phase transfer catalysts.



**Fig. 16.1: Commonly used ammonium salts as phase transfer catalysts.**

**Phosphonium Salts:**

These are analogous to the ammonium salts. The only difference is that instead of nitrogen, it contains phosphorous. Some commonly used phosphonium salts as phase transfer catalysts are shown in Fig. 16.2.

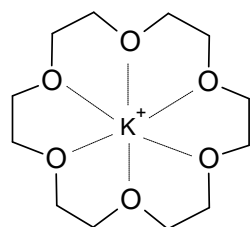


**Fig. 16.2 Phosphonium salts used as phase transfer catalysts.**

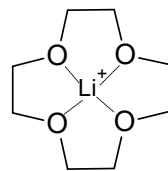
**Crown ethers and Cryptands:**

Macrocyclic and macrobicyclic polydentate ligands as crown ethers and cryptands are commonly used as phase transfer catalysts. The crown ethers and cryptands are a family of cyclic polyethers (Fig.16.3). These compounds can solubilize salts in nonpolar solvents by complexing with the cation in the cavity of the crown ether. In solution, the anions become more reactive as nucleophiles because they are weakly solvated. Regardless of their great activity as successful phase transfer catalysts, crown ethers and cryptands are not practicable for most industrial purposes due to their high costs and toxicity.

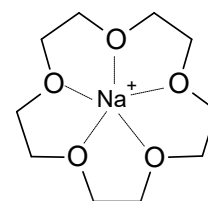
Crown ethers are specific for the cation they bind, and this is related to the size of the cavity. As show above, 18-crown-6 binds  $K^+$  preferentially, but smaller crown ethers can bind  $Li^+$  or  $Na^+$



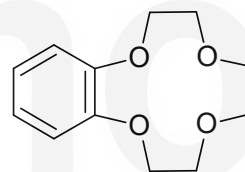
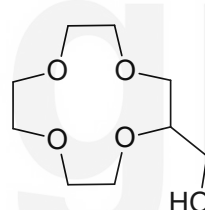
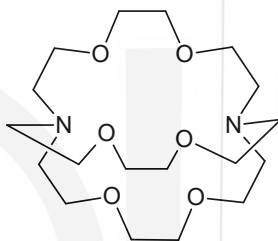
18-Crown-6 complex



12-Crown-4 complex



15-Crown-5 complex

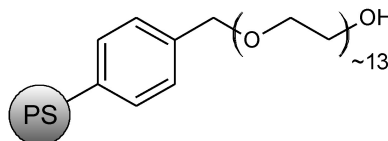


[2.2.2] Cryptand (2-Hydroxymethyl)-12-Crown-4-ether Benzo-12-Crown-4-ether

**Fig. 16.3: Crown ethers and Cryptand used as phase transfer catalyst.****Polyethylene glycols:**

Polyethylene glycols (PEGs) and their derivatives are also extensively utilized as phase transfer catalysts. Although they are less active than quaternary ammonium salts and crown ethers, they are comparatively inexpensive and environmentally friendly. Polyethylene glycols are nontoxic, stable, easy to regain and easily biodegradable, and are available without difficulty. They are generally used as immobilized phase transfer catalyst on insoluble polymer backbones.

For reactions with hydroxide transfer step in solid-liquid systems in polar solvents, polyethylene glycols acts as a highly efficient phase transfer catalyst with occasionally better activities than crown ethers. Water solubility makes them poor catalysts meant for liquid-liquid systems, even though in certain instances the polyethylene glycols can produce a third catalyst-rich phase and become active phase transfer catalyst. For example polymer-support poly ethylene glycol is shown below which is extensively used in organic synthesis.

**Polymer-Supported Poly(Ethylene Glycol) 600**

**SAQ 1**

In what way phase transfer catalyst are different from homogenous catalysts?

**SAQ 2**

What are the different types of phase transfer catalysts?

## 16.3 MECHANISMS OF PHASE TRANSFER CATALYSIS

Two competing mechanisms are thought to exist for PTC processes:

1. Extraction Mechanism
2. Interfacial Mechanism

### 1. Extraction Mechanism

The extraction mechanism, first proposed by Starks in the early 1970's, postulates that the phase-transfer catalyst can transport counter ions between the aqueous and organic phases. For example, the chloride displacement of 1-chlorooctane with cyanide ion in presence of tetraalkylammonium ( $R_4N^+$ ) and/or phosphonium salts ( $R_4P^+$ ),  $Q^+$  (Fig. 16.4). First, the phase-transfer catalyst exchanges its native counter ion for a cyanide anion in the aqueous phase. Second, the newly formed ion pair,  $Q^+CN^-$ , must then be extracted into the organic phase by crossing the interface where the equilibrium of this transfer is determined by the properties of the ion pair. The  $Q^+CN^-$  ion pair is then poised to react with 1-chlorooctane in the organic phase, and this step is referred to as the intrinsic reaction. In this case, the intrinsic reaction regenerates the catalyst, but the original ion pair,  $Q^+Cl^-$ , must be extracted back into the aqueous phase to complete the catalytic cycle. The sequences of steps that transport cyanide into the organic phase are referred to as transfer steps.

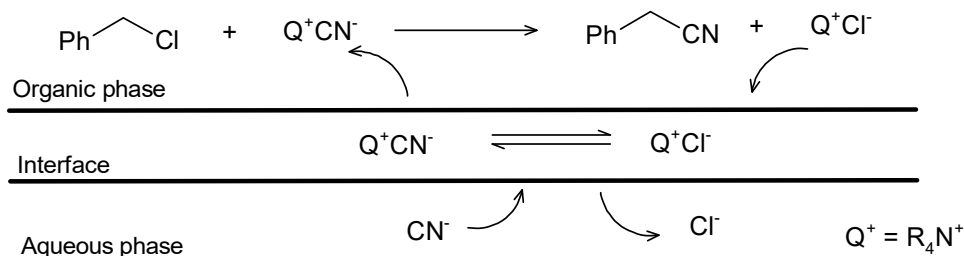
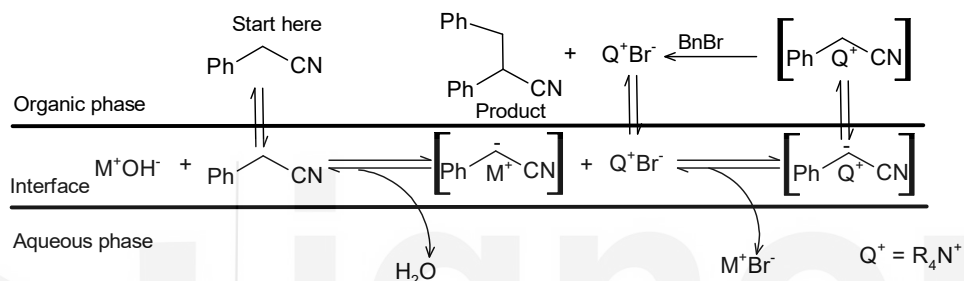


Fig. 16.4: Starks extraction mechanism.

### Interfacial Mechanism

The second mechanism is referred to as the Makosza interfacial mechanism. This mechanism is postulated from the observation that highly lipophilic tetraalkylammonium salts showed limited or no aqueous solubility yet still remained highly active catalysts. As an example, the PTC alkylation of

phenylacetonitrile with benzyl bromide and aqueous hydroxide base illustrates the Makosza interfacial mechanism (Fig. 16.5). **Unlike the Starks extraction mechanism,  $Q^+$ , does not enter the aqueous phase.** First, phenylacetonitrile migrates to the interfacial layer where it undergoes deprotonation by a hydroxide anion, which is also present in the interface. The resulting nitrile anion is formed in the interface layer. This intermediate is too polar to be extracted into the organic phase and too basic to persist in the aqueous phase. Concurrently,  $Q^+Br^-$  will exist in equilibrium between the organic phase and interfacial layer. Once at the interface,  $Q^+Br^-$  can undergo an ion exchange with the nitrile anion. The resulting ion pair is now sufficiently lipophilic to be extracted into the organic phase and participate in the intrinsic reaction, in this case an alkylation with benzyl bromide.



**Fig.16.5: Makosza interfacial mechanism for phenylacetonitrile alkylation.**

Given the several phase equilibria which transverse the interfacial layer, the rate determining step of a particular interfacial PTC process often involves an intermediate at the interphase. Therefore, an interfacial PTC mechanism is strongly dependent on the interfacial surface area between the bulk phases. For this reason, efficient agitation methods (e.g. stirring speed) are necessary for a PTC reaction operating under an interfacial mechanism.

Both these mechanisms are probably correct depending on the quaternary catalyst, with the first being more likely with small to medium sized quaternary cations, while the second is more correct for medium and large quaternary cations. For asymmetric PTC, most catalyst employed remains in the organic phase with transfer occurring at the interface (2nd mechanism).

## 16.4 APPLICATIONS OF PHASE TRANSFER CATALYSIS

Phase-transfer catalysis (PTC) is a powerful tool to carry out many organic reactions in a practical fashion, both in the laboratory and on the industrial scale. Significant cost savings and major process improvements can be achieved in reactions performed in water–organic solvent mixtures. Particularly striking is the possibility of replacing expensive solvents and dangerous bases that require strictly anhydrous conditions with aqueous bases and apolar, environmentally friendly, easily recyclable solvents. During the last decade notable results, both in terms of yields and stereoselectivity, were obtained in various reactions performed in the presence of chiral, nonracemic quaternary ammonium salts.

PTC is particularly useful for reactions of organic anions with nonpolar organic reactants. They are also applicable for numerous reactions in which anions

are intermediates for generating other active species such as carbenes, nitrenes and organometallic reagents.

Reactions have been reported in the following areas:

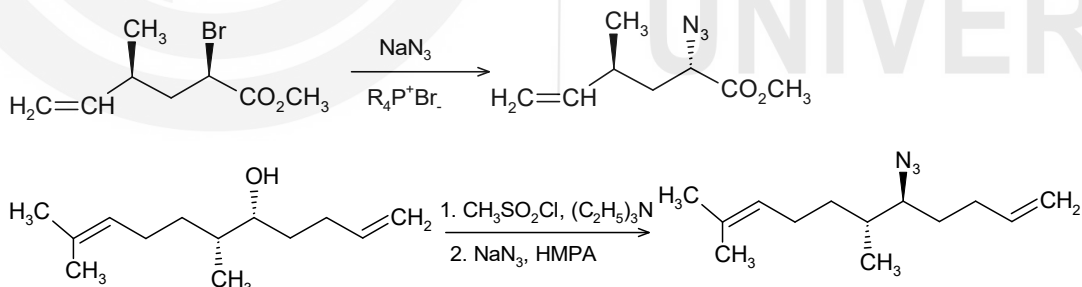
- i) Nucleophilic Substitutions
- ii) Alkylations
- iii) Carbene reactions
- iv) Oxidations and reductions
- v) Aldol and related condensations

Here we are reporting some representative examples from the literature.

### Nucleophilic substitutions

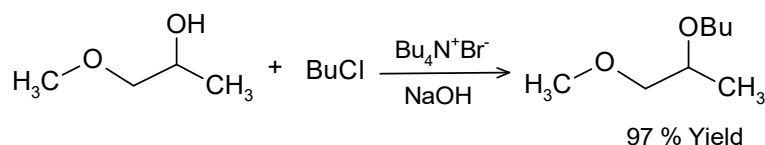
The objective in selecting the reaction conditions for a preparative nucleophilic substitution is to enhance the mutual reactivity of the leaving group and nucleophile so that the desired substitution occurs at a convenient rate and with minimal competition from other possible reactions. Phase transfer catalysis provides an alternative approach of achieving this objective. In earlier example of nucleophilic substitution of cyano group, you have seen how it was difficult to replace halogen group by cyano group in normal reaction conditions. But this transformation can be completed in very less time under phase transfer conditions. Phase transfer catalyst such as crown ethers, quaternary ammonium and phosphonium salts surround and solvate the cation and therefore enhance the reactivity of anion nucleophile. Now consider few more examples of nucleophilic substitution reactions under phase transfer condition:

1. Phase transfer conditions can be used for the preparation of azides

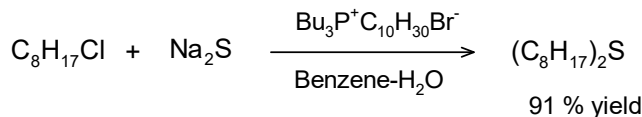
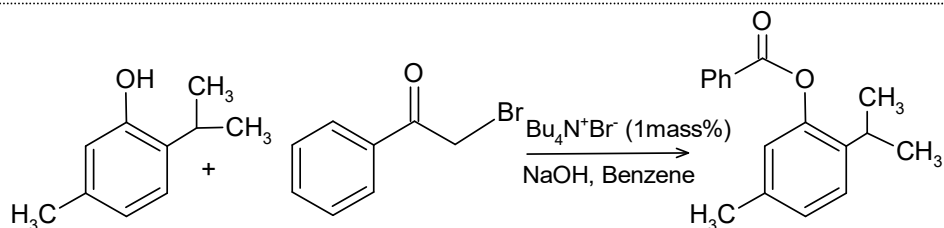


### Alkylations

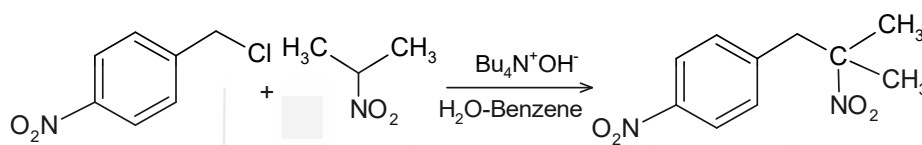
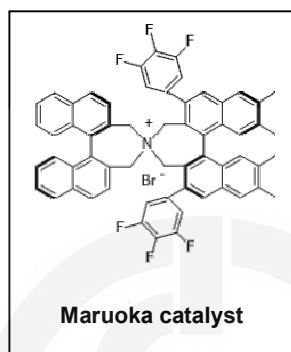
Alkylations are the most common application of phase transfer catalysts. We have already discussed alkylation of nitriles. Alcohols can also be alkylated using quaternary ammonium salts to give dialkyl ethers.



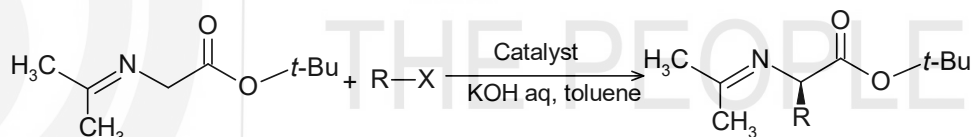
Similarly phenols can also be alkylated using phase transfer catalyst.



Nitroalkanes can be alkylated in a single step with hydroxide as a base in phase transfer conditions. This keeps the  $\text{HO}^-$  and the electrophile apart, preventing alcohol formation.

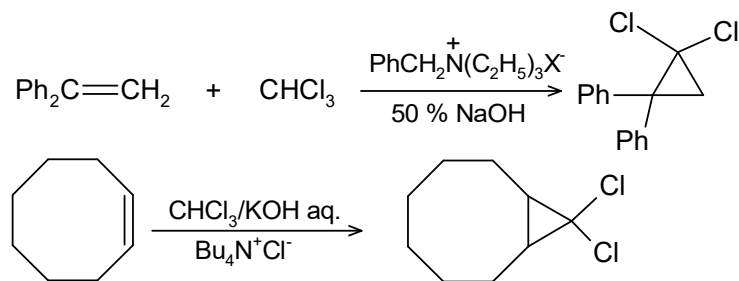


Phase transfer catalyzed processes can also give enantioenriched products by the action of chiral, nonracemic catalyst. Such processes are referred to as asymmetric phase-transfer catalysis (APT) reactions. For example consider the asymmetric phase-transfer catalysis by the Maruoka catalyst. In this case protected glycine can be alkylated enantioselectively using very small amounts of the chiral quaternary ammonium salt.



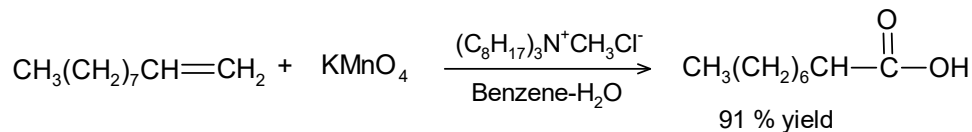
### Carbene reactions

Phase transfer catalysis has proved to be effective in generation of carbenes by  $\alpha$ -elimination of haloalkanes. Both tetraalkylammonium salts and crown ethers can be used to promote  $\alpha$ -elimination reactions of chloroform and other haloalkanes. The carbenes can be trapped by alkenes to form dichlorocyclopropanes.



### Oxidation

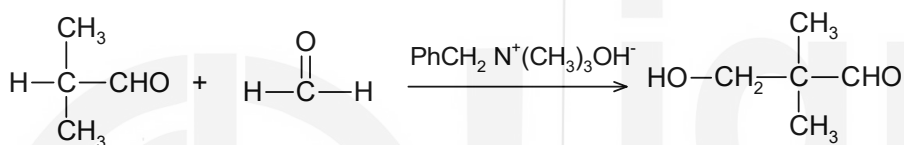
Phase-transfer catalysis is particularly useful in oxidation reactions because the oxidizing agents are insoluble in most organic solvents, while the substrates are generally insoluble in water.



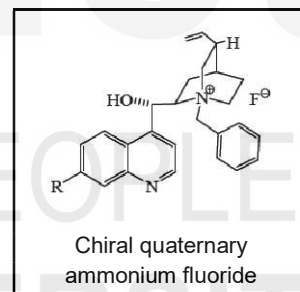
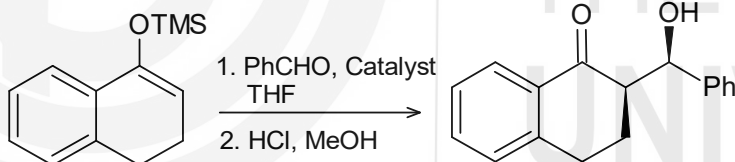
Benzylic and allylic alcohols have been selectively oxidized to the aldehydes in presence of saturated alcohols by the use of potassium manganate ( $\text{KMnO}_4$ ) under phase-transfer conditions.

### Aldol and related condensations

Aldol product can be obtained in high yields using phase transfer catalyst. For example 3-Hydroxy-2,2-dimethylpropanal (hydroxypivaldehyde) (HPA) is a precursor intermediate for the synthesis of neopentyl glycol (NPG) can be prepared by aldol condensation of isobutyraldehyde and formaldehyde at 20 °C using benzyltrimethylammonium hydroxide, a basic phase transfer catalyst in almost quantitative yield with ~100% selectivity.

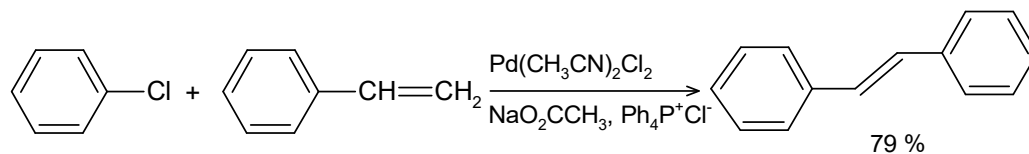


The asymmetric aldol products can be prepared using chiral phase transfer catalysts. In this reaction given below, silyl enol ether reacts with benzaldehyde using chiral quaternary ammonium fluoride as a catalyst and the silylated aldol is hydrolyzed with hydrochloric acid to give the aldol product.

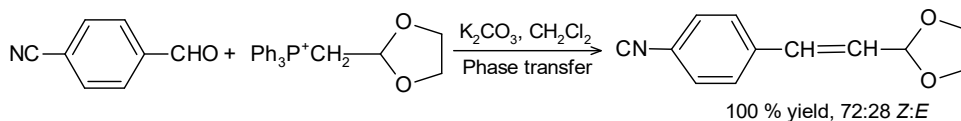


### Heck reaction

Aryl chlorides are not very reactive under normal Heck reaction conditions but reaction can be achieved by addition of phase transfer catalyst, tetraphenylphosphonium salts with  $\text{Pd}(\text{OAc})_2$  or  $\text{PdCl}_2$  as the catalysts.

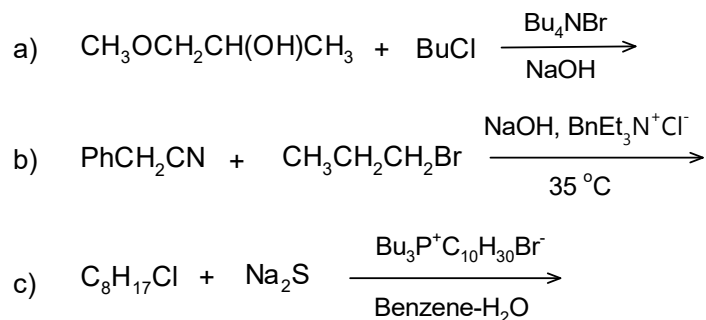


### Wittig Reaction



## SAQ 3

Complete following reactions:



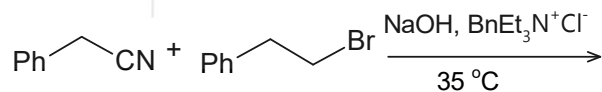
## 16.5 SUMMARY

In this unit we have discussed chemistry of phase transfer catalysis. These reactions provide an alternate approach for the synthesis of organic molecules in two or more phases. There are number of advantages that phase transfer catalysis offers over homogeneous alternatives:

- Usually the reactions under phase transfer conditions require mild reaction conditions thus involves inexpensive reagents (NaOH, KOH,  $\text{K}_2\text{CO}_3$  etc. instead of NaH, KHMDS *t*-BuOK, etc.).
- The reactions are relatively easy to perform and are highly scalable.
- Phase transfer catalytic processes are consistent with the principles of green chemistry, for this reason industrial applications are growing.

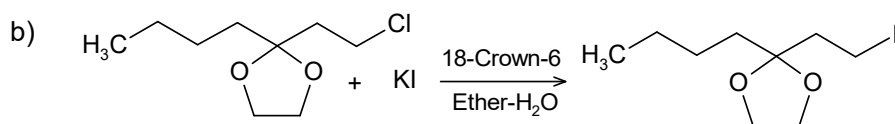
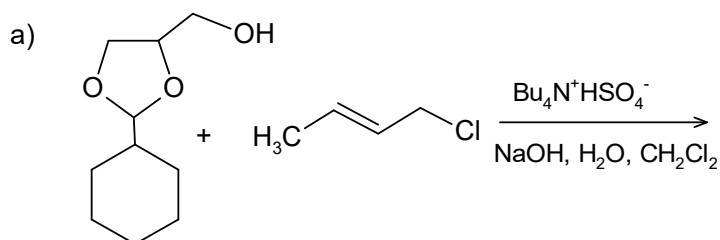
## 16.6 TERMINAL QUESTIONS

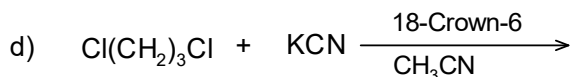
1. Complete the following reaction and write its mechanism.



2. Discuss the role of crown ethers in the phase transfer reactions.

3. Complete following reactions:

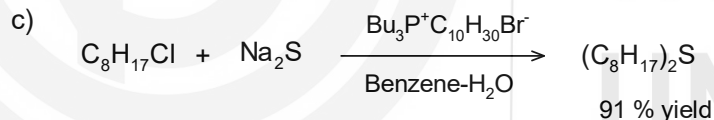
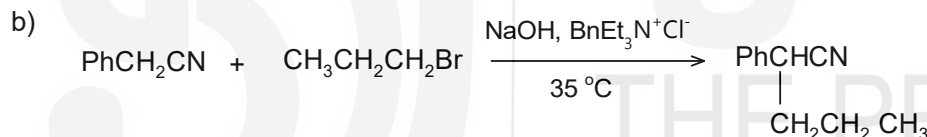




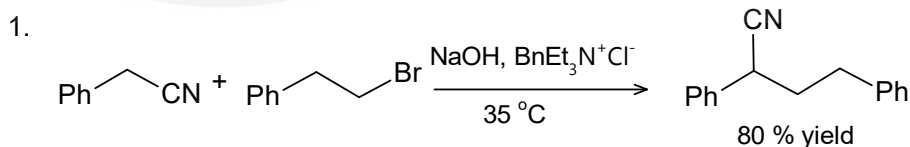
## 16.7 ANSWERS

### Self Assessment Questions

- Homogeneous catalysts are those which exist in the same phase (gas or liquid) as the reactants, while phase transfer catalyst may be soluble in one or two phases and facilitates the migration of a reactant from one phase into another phase where reaction occurs. Typically, phase transfer catalysis involves the use of phase transfer catalyst such as onium salts and crown ethers placed in a two-phase liquid-liquid system.
- Common phase transfer catalysts are onium salts (ammonium and phosphonium salts), crown ethers (macrocyclic polyethers), cryptands (aza-macrobicyclic ethers), and polyethylene glycols (PEG), etc..

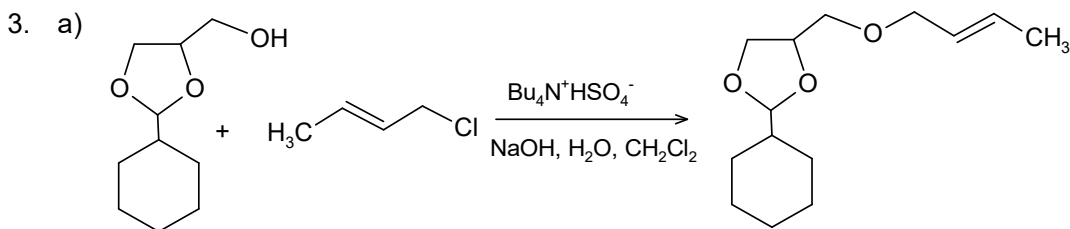


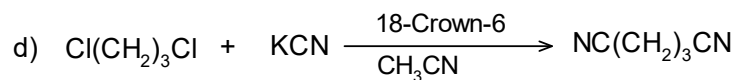
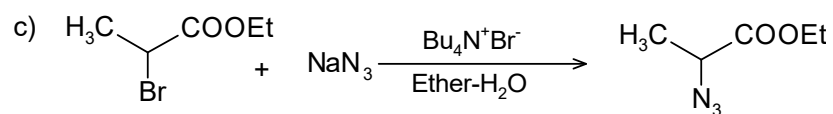
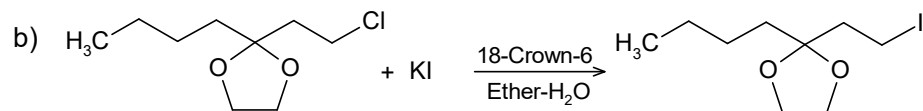
### Terminal Questions



Its mechanism is similar to Interfacial Mechanism.

- Crown ethers can solubilize salts in nonpolar solvents by complexing the cation in the cavity of the crown ether. In solution, the anions become more reactive as nucleophiles because they are weakly solvated.





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# UNIT 17

## ASYMMETRIC SYNTHESIS |

### Structure

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17.1 Introduction	What is Asymmetric Synthesis
Expected Learning Outcomes	First-Generation or Chiron Approach
17.2 Significance of Chirality	Second-Generation or Auxiliary-Controlled Methods
17.3 Stereochemical Terminology	Third-Generation or Reagent-Controlled Methods
17.4 Selectivity in Asymmetric Synthesis	Fourth-Generation or Catalyst-Controlled Methods
Chemoselectivity	Absolute Asymmetric Synthesis
Regioselectivity	17.6 Summary
Stereoselectivity	17.7 Terminal Questions
Stereospecificity	17.8 Answers
17.5 Methodologies for Asymmetric Synthesis	

### 17.1 INTRODUCTION

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In the previous units of the last block of this course, you have studied some important concepts and reactions involved in the synthesis of organic compounds. These included umpolung reactions and reactions with enolates and phase transfer catalysis. You know that the stereochemistry of organic compounds is very crucial and significant when it comes to synthesising organic compounds which may be useful for therapeutic uses. There comes the applications of optically active compounds in which the stereochemistry is one of the most significant aspects. This is true, especially knowing the different biological activity of the isomers of a compound.

You have studied the important stereochemical aspects of organic compounds in the first two blocks of the Semester I course, 'Stereochemistry and Intermediates' (MCH-012). In view of the biological significance and applications in pharmacology, the present unit deals with the strategy of synthesis for chiral compounds or the optically active compounds. You will study about the significance of chirality in organic compounds after which some important and relevant terms that you have studied in your first semester

course are given for a recall and ready reference. The concept of selectivity is very important in the synthetic reactions pertaining to the formation of chiral compounds. It has been discussed in detail in the unit. Finally the evolution or the development of various strategies in the asymmetric synthesis of chiral compounds has been discussed. This particular section includes the four generations of asymmetric synthesis and the method for absolute asymmetric synthesis.

Thus this happens to be the last unit of this block as well as the last unit of the second semester course in organic chemistry.

### Expected Learning Outcomes

After studying this unit you should be able to:

- ❖ state the significance of chirality in the organic compounds of biological importance;
- ❖ define some of the common terms used to identify the stereochemistry of the substrates and the products involved in the organic reactions;
- ❖ define and explain the significance of selectivity in organic reactions;
- ❖ differentiate between stereoselectivity and stereospecificity;
- ❖ explain diastereoselectivity and enantioselectivity in organic reactions;
- ❖ define and explain the significance of asymmetric synthesis in organic reactions; and
- ❖ describe the four generations of the strategies of asymmetric synthesis along with suitable examples and also the method used for absolute asymmetric synthesis.

## 17.2 SIGNIFICANCE OF CHIRALITY

In the organic chemistry course of Semester I, you must have come across a number of terms that are commonly used when we talk about the stereochemical aspects of a molecule. You would have realised that the most basic term is **chirality** and the chiral molecules. You are aware that for the past many years, stereochemistry, dealing with the three-dimensional behaviour of chiral molecules, has become a significant area of research in modern organic chemistry. The chirality is of prime significance as it is one of the features of a molecule that is responsible for the formation of two or more isomers. You should be able to recall the existence of two types of isomers called the enantiomers and the diastereoisomers. You are also aware that most of the biological macromolecules of living systems occur in nature in one enantiomeric form only. For instance, all the naturally occurring amino acids except glycine possess chirality, with L-amino acids prevalent in proteins. Similarly, sugars like glucose and fructose exhibit chirality, with D-glucose being the primary energy source for living organisms. The nucleic acids which are the building blocks of DNA and RNA consist of chiral nucleotide units that encode genetic information.

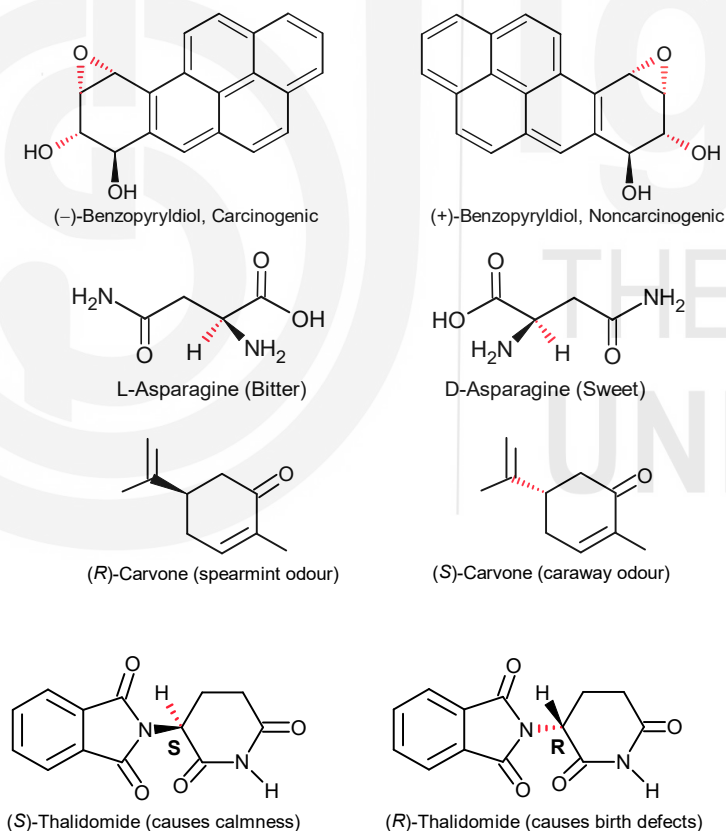
The presence of chiral centers introduces the possibility of stereochemical variation within a molecule, giving rise to mirror-image forms called the enantiomers.

A biologically active chiral compound interacts with the target molecule or the site in a chiral manner, and the two isomers of the molecule may behave very differently. If we consider the biological activities of chiral compounds in general, these may show the following types of actions:

- Only one enantiomer is biologically active, the other one does not show significant bioactivity.
- Both the enantiomers have almost similar bioactivity.
- The enantiomers show entirely different activity.

Thus, one of the isomer may be therapeutically effective, while the other may be either ineffective or even toxic. Many of you might have studied about the drug thalidomide used for treating the morning sickness in pregnant females in late 50s. The drug was supposed to cause relief till it was found to lead to births of babies with deformities. It was discovered much later that the two isomers of this drug have a very different effect, one causes relief while the other is truly devastating. Several of the pairs of such isomers that behave almost in an opposite manner are given in Fig. 17.1 along with their stereochemistry and the effect caused by them.

the *S* enantiomer of thalidomide can fit the active site of a specific enzyme (like a “key” for a specific “lock”) producing the desired effect (sedative). On the other hand, the *R* enantiomer cannot interact with the same site due to a different arrangement of atoms (3D shape). As a consequence, it fits a different enzyme active pocket triggering a different biological effect (toxic).



**Fig. 17.1: Some isomers showing different behaviours.**

The solution to the problem posed by two isomers interacting with biological receptors differently could be solved by selectively synthesising the desired isomer minimising the formation of undesired ones. This selective method of synthesis is called the **asymmetric synthesis**. The asymmetric synthesis enables the synthesis of complex molecules in a highly efficient and sustainable manner.

It was mentioned in the introduction to this unit that our main aim is to introduce different strategies of asymmetric synthesis. However, in the next section we would first recall a few of the most common terms used while dealing with asymmetric molecules, many of which you are already familiar with. We are sure that at this point of time you would like to have a relook into the units of stereochemistry studied in the first semester.

### 17.3 STEREOCHEMICAL TERMINOLOGY

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Let us recall some of the terms with their simplest definitions as these will be used often as per the context. These are given below.

- **Asymmetric compounds:** The compounds do not possess symmetry. These may exist as enantiomers as well as diastereoisomers.
- **D or L:** The absolute configurations assigned to a molecule through experimental chemical correlation with the configuration of *d*- or *l*-glyceraldehyde. However, the designations **R** and **S** are preferred.
- ***d* or *l*:** These indicate dextrorotatory or levorotatory molecules according to the experimentally determined rotation of the plane of monochromatic plane polarized light to the right or left respectively.
- **Diastereoisomers:** These are the stereoisomers with two or more chiral centres which are not mirror images of one another.
- **Diastereomeric excess:** It is the percentage proportion of the major diastereomer produced minus the minor diastereomer produced and is represented as *de*.
- **Dissymmetric compounds:** The compounds which do not have an alternating axis of symmetry and usually exist as enantiomers.
- **Enantiomeric excess:** The percentage by which one enantiomer is in excess to the other and generally represented as *ee*. It is commonly expressed as a percentage.
- **Enantiomers:** These stereoisomers are nonsuperimposable mirror images of each other. These were also called the optical isomers.
- **Erythro/Threo:** The term *erythro* refers to a configuration with identical or similar substituents on the same side of the vertical chain in Fischer projection. The *threo* isomer has these substituents on the opposite sides.
- **Heterochiral or Enantioenriched:** A chiral molecule when present in excess as one enantiomer but not in exclusion of the other enantiomer, it is called heterochiral or enantioenriched.
- **Homochiral or Enantiopure:** A chiral molecule present as only one of the two possible isomers it is called the homochiral or enantiopure.
- **Optical activity:** It is the experimentally observed rotation of the plane of monochromatic plane polarized light by a molecule using a polarimeter. The rotation may be in the right or left direction.
- **Racemic mixtures or Racemates:** The mixture of two enantiomers in equal amounts leads to a racemic mixture.

- **Stereoisomers:** These are the molecules consisting of the same types and same number of atoms with the same connections but different configurations.
- **Syn/Anti:** These are prefixes that indicate the relative positions of substituents with respect to the defined plane of a ring. Thus it is *syn* for the same side and *anti* for the opposite side.
- **Meso compounds:** These are the compounds which have two or more centres of dissymmetry but have plane (s) of symmetry because of which these do not show optical activity. These compounds do not exist as enantiomers.
- **Racemisation:** The process of converting an optically active molecule to a 50:50 mixture of the two.
- **Prochirality:** The existence of an achiral precursor that gives rise to chiral products.
- **Pro-R and Pro-S:** It is the presence of heterotopic ligands present in the prochiral molecule. If the newly created chiral centre has the *R*-configuration, that ligand is referred to as pro-*R*; while pro-*S* refers to the ligand replacement that creates an *S*-configuration.
- **Re and Si:** If the CIP priority of the three ligands, a, b and c is assigned as  $a > b > c$ , the face that is oriented clockwise toward the viewer is called *Re*, while the face with a counter clockwise orientation of a, b and c is called *Si*.

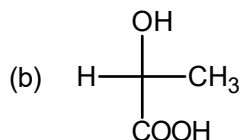
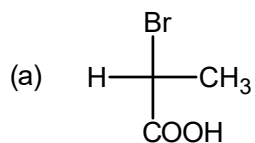
We mentioned about the selectivity of formation of a major product in case of a reaction where there is a possibility of formation of more than one product.

The selectivity in asymmetric synthesis has certain guiding principles that give the clue to the formation of a particular product. It is of different types, viz., chemoselectivity, regioselectivity and stereoselectivity. Further, the stereoselectivity is of two types, viz., enantioselectivity and diastereoselectivity. In the following section you will study about these selectivities. Before proceeding you may try to answer the following SAQ and revise some concepts studied in the previous course regarding stereochemistry.

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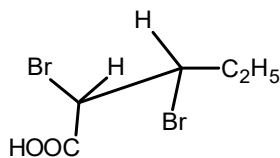
### SAQ 1

Specify *R/S* configuration showing the priorities assigned to various groups.



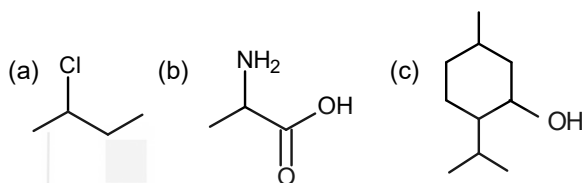
## SAQ 2

Designate the following compound as erythro or threo.



## SAQ 3

Indicate the number of chiral centres or the asymmetric carbons in the following compounds



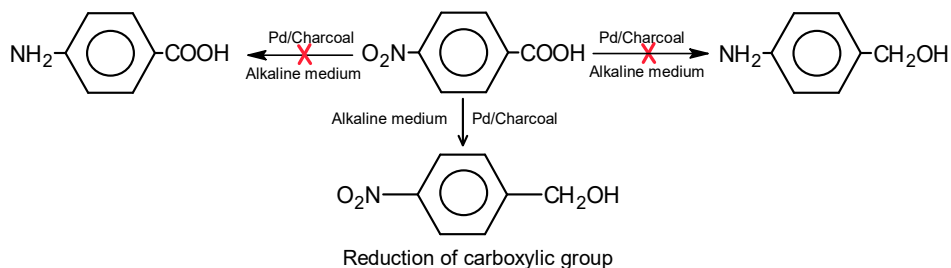
## 17.4 SELECTIVITY IN ASYMMETRIC SYNTHESIS

The selectivity in asymmetric synthesis can be attained by selecting appropriate starting materials, reagents, solvents, reaction conditions. As mentioned above, selectivity is mainly of three types i.e., **Chemoselectivity**, **Regioselectivity** and **Stereoselectivity** about which you will study in the following subsections.

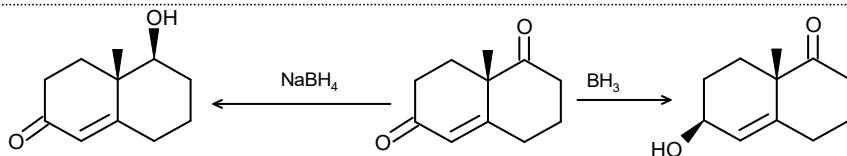
## 17.4.1 Chemoselectivity

Chemoselectivity is the selectivity between two different groups and indicates the group which takes part in the reaction. In other words, if in a bifunctional compound the reagent reacts preferentially with one of the functional groups, the reaction is called **chemoselective**. There are a number of reactions that depict chemoselectivity. Some of the reactions that are self explanatory are given below.

- **Reduction of carboxylic group in presence of nitro group:** The carboxylic group is reduced in preference to the  $\text{NO}_2$  group.

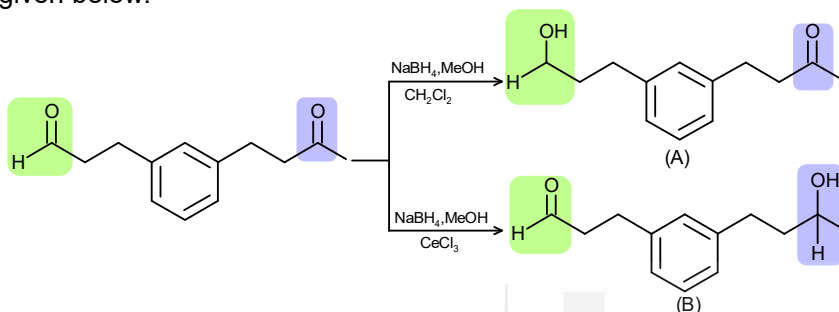


- **Selective reduction of a carbonyl group when two similar groups are present:** The reduction reaction varies with the reagent used.



### Chemoselective reduction of the aldehyde group with sodium borohydride and ceric chloride:

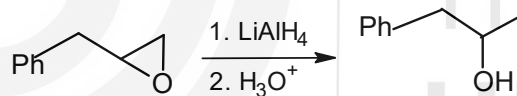
The reaction with  $\text{NaBH}_4$  in methanol at low temperature reduces the aldehyde group to form product (A) and in the presence of  $\text{CeCl}_3$  the keto group is reduced to give product (B). The reactions are given below.



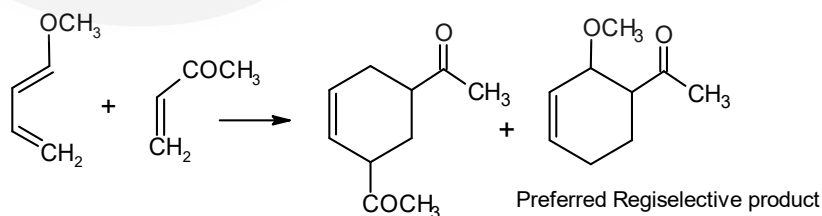
In the following subsection you will observe some reactions depicting regioselectivity.

### 17.4.2 Regioselectivity

Regioselectivity indicates the part or the site in the molecule where the reaction takes place in that group. We can say that it is the selectivity between two positions in a system with similar reactivity or where there is a possibility of reaction on both the sites. For example, in the epoxide shown below,  $\text{LiAlH}_4$  attacks the carbon from the less hindered side to form the alcohol.



The Diels Alder reaction shows a similar type of regioselectivity as given below.

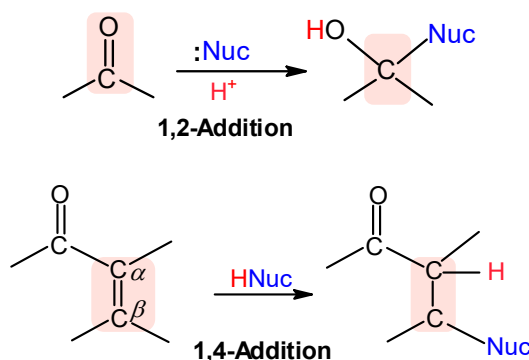


Thus it can be said that a **regioselective** reaction is selective for the formation of one **constitutional isomer** ("regioisomer"). The word regioselective arises from the word 'regio' arising from the Latin word "*regionem*," which means 'direction'. Some of the reactions showing regioselectivity are as follows. You will see that most of these examples might be familiar to you.

### 1,2- Addition versus 1,4-Addition in $\alpha, \beta$ -unsaturated Carbonyl compounds

Let us recall here that the nucleophiles may attack either at the carbonyl carbon, as in the case of aldehyde, ketone or carboxylic acid derivative, or at

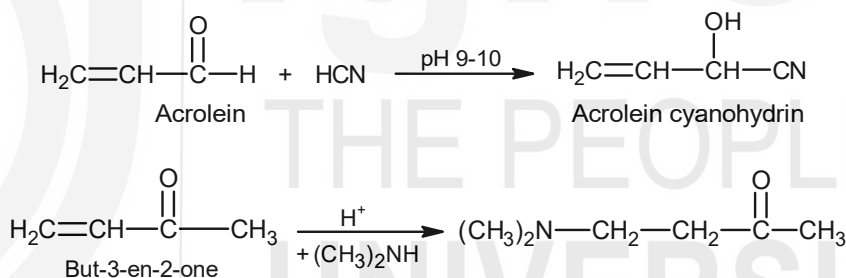
the beta-carbon. These two modes of reaction are referred to as 1,2-addition and 1,4-addition, respectively. The two reactions can be depicted in a general manner as follows.



A number of factors govern the direction of addition of nucleophiles to  $\alpha, \beta$ -unsaturated aldehydes and ketones, some of these are given below.

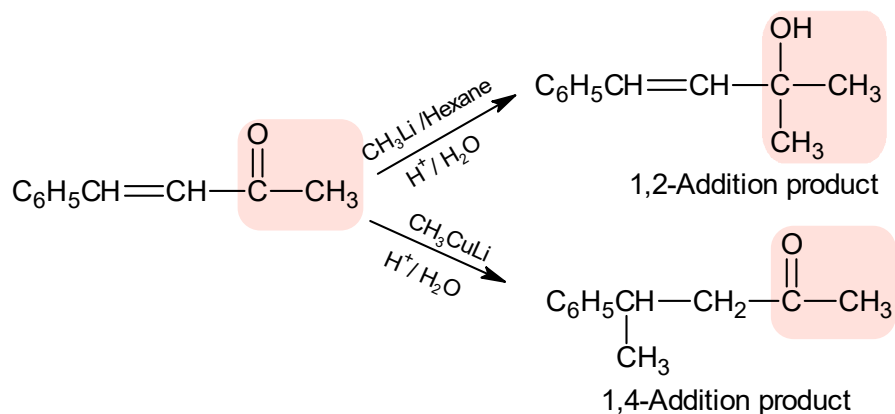
### Reactivity of carbonyl group

Since the aldehyde groups are much more reactive than ketones towards nucleophiles, so majority of the addition reactions are 1,2-addition reactions in the case of aldehydes. On the other hand, in the case of unsaturated ketones, which are less reactive than aldehydes, the results are 1, 4-additions. The reaction with an aldehyde and a ketone is given below.



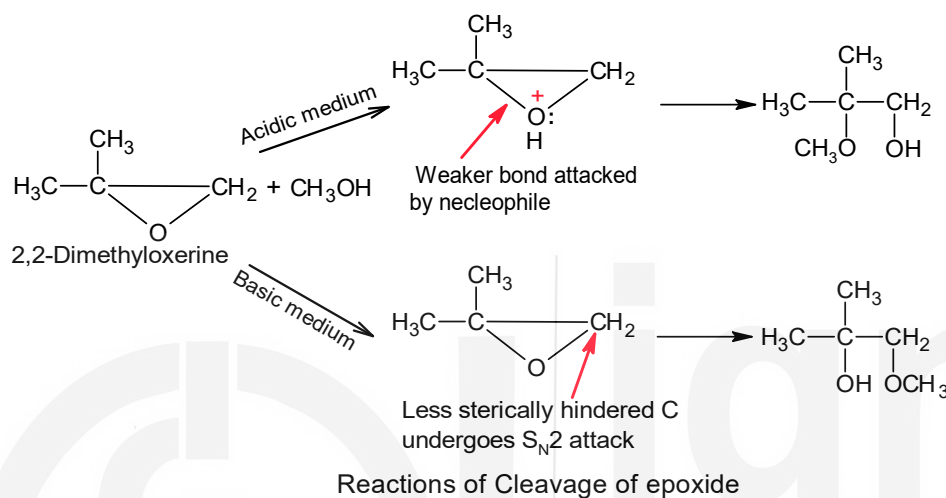
### Reactivity of the reagent

Here you can see how  $\alpha, \beta$ -unsaturated aldehydes and ketones may form different products in presence of different reagents. For example, in the following reaction the ketone gets reduced in presence of organolithium to give a 1, 2-addition product. While in case of the presence of organocuprate reagent ( $\text{RCuLi}$ ), we get a 1,4-addition product.



### Regioselectivity in the cleavage of epoxides

Try to observe the cleavage of epoxide in acidic medium and in basic medium as per the reactions. It can be seen that the carbon oxygen bond breaks and the ring opening takes place in the reaction of cleavage of epoxide. The question is which side of the bond would break? It has been observed that in the basic medium, the nucleophile i.e.,  $\text{OCH}_3$  group attacks at the less substituted and less hindered carbon by a  $\text{S}_{\text{N}}2$  mechanism. In the acidic medium the nucleophile attacks from the side of the weaker bond. These observations are depicted in the following two reactions.



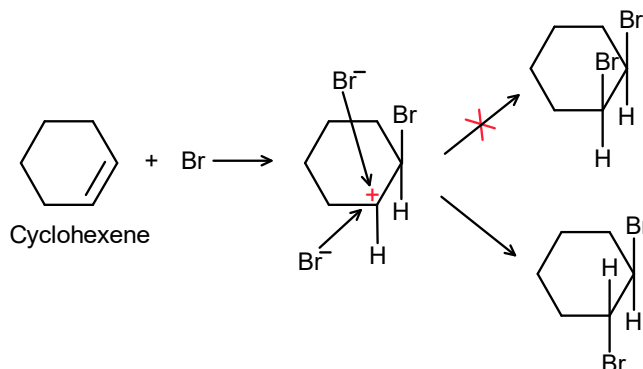
In the following subsection let us understand the stereoselectivity in reactions.

#### 17.4.3 Stereoselectivity

You must have come across many reactions where multiple stereoisomers may be the products. If the stereoisomers are not formed in equal amounts, the reaction is described as being **stereoselective**. Stereoselectivity indicates the way that group reacts to give a product preferentially. In other words it is the stereoselectivity in the formation of predominantly or exclusively one stereoisomer in a reaction where more than one stereoisomers are possible.

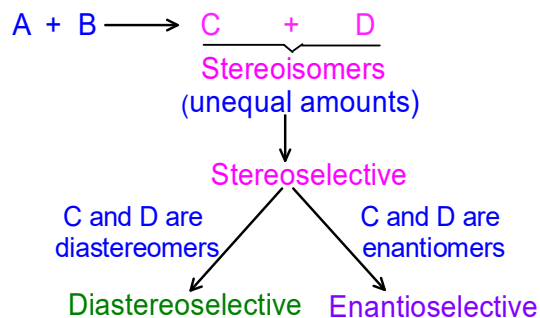
For example, formation of 1, 2-dibromocyclohexane by the addition of bromine to cyclohexene. As can be seen in the following reaction, one stereoisomer is formed selectively over the other stereoisomer.

Stereoselectivity arises when there is a possibility of formation of stereoisomers. The reactant may or may not have a chiral centre in a stereoselective reaction

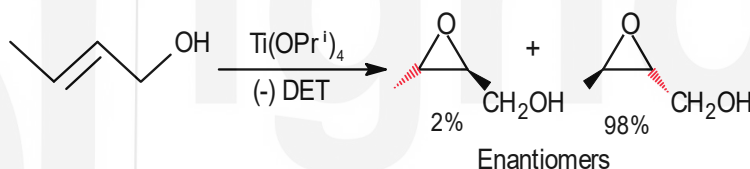


Stereoselectivity in the addition of bromine to cyclohexene

The stereoisomers can be enantiomers or the diastereoisomers. Therefore the stereoselectivity leads to **enantioselectivity** or **diastereoselectivity** depending upon whether the product is a diastereomer or an enantiomer that is being produced selectively. The formation of a diastereoselective or an enantioselective product can be depicted in a general manner as follows.

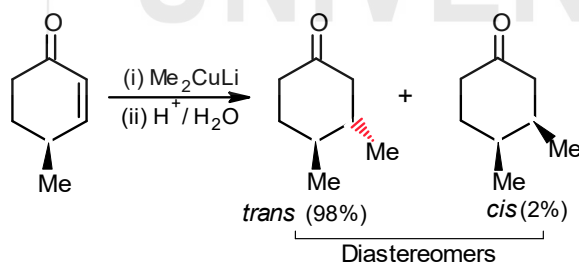


The formation of an enantiomer predominantly or exclusively is called the **enantioselectivity**. Let us understand enantioselectivity by an example. In the following reaction, epoxidation of the unsaturated alcohol, butenol, takes place stereoselectively in presence of a titanium catalyst and optically active reagent viz., diethyl tartrate. The result is the formation of one product in good amount.



#### Enantioselectivity in a reaction

The formation of one diastereomer predominantly or exclusively is called the **diastereoselectivity**. For example, the reaction of  $\alpha$ - $\beta$ -unsaturated ketone with the Gilman reagent which is written below. The reaction leads to the formation of alkylated diastereomers with *trans* product in predominant amount.



#### Diastereoselectivity in a reaction

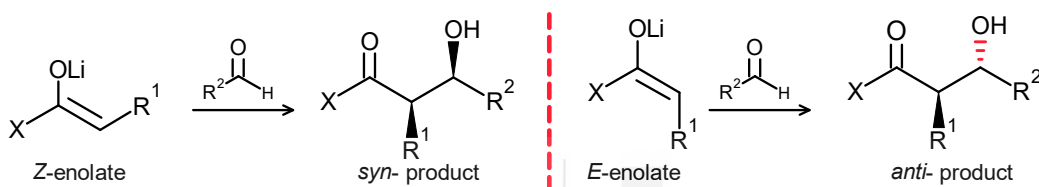
When stereoselectivity results in the formation of an excess of one enantiomer over the other from an achiral or racemic substrate it is sometimes called **asymmetric induction**. In the context of stereoselectivity, we come across another term called **stereospecificity**. You would like to revise the concept of stereospecificity vis-à-vis stereoselectivity in the following subsection.

### 17.4.4 Stereospecificity

A reaction in which there are two or more starting stereoisomers and two or more product stereoisomers. One of the starting isomers produces one

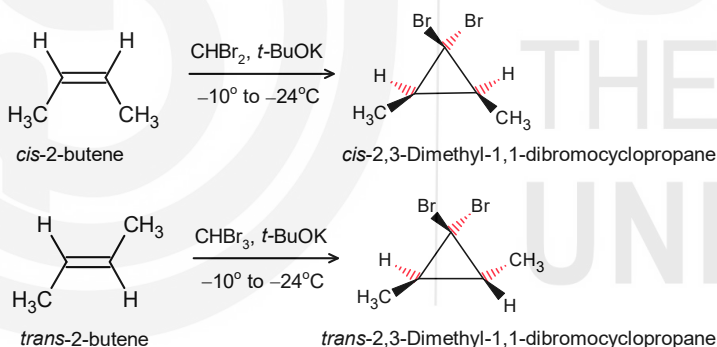
product isomer, while the other starting isomer produces the other product isomer. These are **stereospecific reactions**. It can be stated that a stereospecific reaction is the reaction in which the configuration of the substrate influences the configuration of the product. You are very well familiar with the nucleophilic substitution reaction by  $S_N2$  mechanism. In fact, *any stereospecific reaction is also stereoselective*. However, *all the stereoselective reactions are not essentially stereospecific*.

An appropriate example of a stereospecific reaction is the aldol condensation, where lithium or other enolates of *Z*- geometry form *syn*- diastereomers as products, while the *E*- enolates form *anti*- products.



### Streospecificity in aldol condensation

Another example of a stereospecific reaction is addition of bromine to *cis*-2-butene to form *cis*-2,3-dimethyl-1,1-dibromocyclopropane. In this reaction dibromocarbene reacts stereospecifically to form a *cis*- product starting from *cis*- butene, while the *trans*-2,3-dimethyl-1,1-dibromocyclopropane is formed from *trans*- butene. The reactions are as follows.

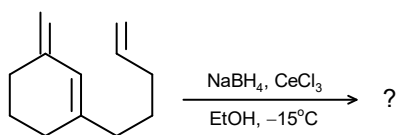


It is already mentioned that the use of biologically important compounds has the requirement of specifying the stereochemistry very categorically. You will learn the reasons of this requirement and then the various strategies used for this purpose.

Before proceeding to the next section, try to answer the following SAQ.

### SAQ 4

Complete the following reaction and indicate the type of selectivity in the reaction.



## SAQ 5

Fill in the blank spaces with appropriate words.

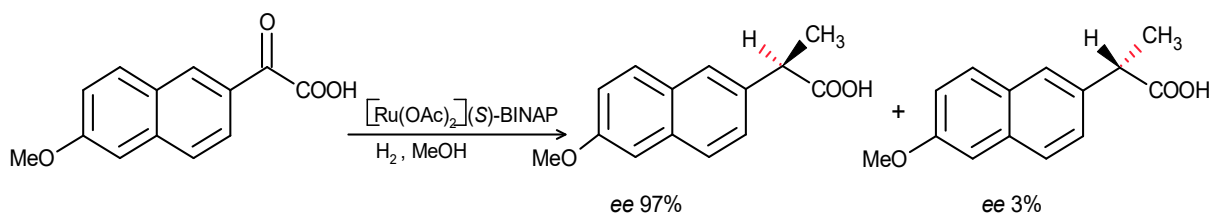
- The reaction in which an alkyne reacts preferentially in the presence of alkenes is called a .....reaction.
- The addition of a strong acid to a double bond forming selectively one constitutional isomer over the other as per Markownikoff's rule is an example of a .....reaction.
- The preference for partial hydrogenation of alkynes with  $\text{Na}/\text{NH}_3$  to give *trans* alkenes is an example of a .....reaction.
- The reaction in which the configuration of the substrate influences the configuration of the product is a .....reaction.

## 17.5 METHODOLOGIES FOR ASYMMETRIC SYNTHESIS

In the above sections, you have studied the importance of synthesising the enantiopure compounds. It can be inferred that chirality is one of the central concepts when it comes to synthesising optically active compounds. This type of synthesis is called the asymmetric synthesis. Before proceeding to the different strategies of asymmetric synthesis, let us explain what asymmetric synthesis is.

### 17.5.1 What is Asymmetric Synthesis

Asymmetric synthesis as defined by Morrison and Mosher, is a reaction in which an achiral unit in the form of a substrate molecule is converted into a chiral unit in such a manner that unequal amounts of stereoisomers are produced. For example, in the following reaction we can clearly see that the amount of one of the enantiomer is obtained almost to the full extent.



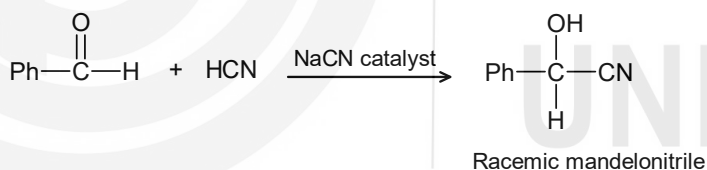
In view of the above definition, you might have come across a number of reactions where an achiral unit gets converted to a chiral one. Some of the reactions of this kind which you have seen in the previous section also, have been given in Table 17.2.

Table 17.2: Some reactions which form chiral centres

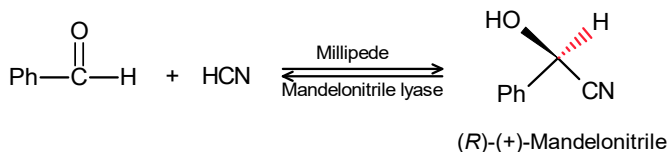
Hydrogenation of C=C, C=O bonds	$\text{R}_1\text{C}(\text{O})\text{R}^2 \xrightarrow{\text{reducing agent}} \text{R}_1\text{CH}(\text{OH})\text{R}^2$
Hydroboration of C=C bonds	$\text{R}_1\text{C}(\text{R}^2)\text{C}(\text{R}^3)\text{R}^4 \xrightarrow[\text{ii) H}_2\text{O}_2]{\text{i) BH}_3} \text{R}_1\text{CH}(\text{OH})\text{C}(\text{R}^3)\text{R}^4$
Addition of Grignard reagent to C=O	$\text{R}_1\text{C}(\text{O})\text{R}^2 \xrightarrow[\text{ii) acid workup}]{\text{i) RMgBr} \rightarrow \text{R}_1\text{C}(\text{OH})(\text{R})\text{R}^2$
Dihydroxylation of C=C bonds	$\text{R}_1\text{C}(\text{R}^2)\text{C}(\text{R}^3)\text{R}^4 \xrightarrow[\text{ii) hydrolysis}]{\text{i) OsO}_4} \text{R}_1\text{C}(\text{OH})\text{C}(\text{OH})\text{R}^4$
Aldol reaction	$\text{R}_1\text{C}(\text{O}^-)\text{C}(\text{R}^2)\text{R}^3 \xrightarrow[\text{(aldehyde)}]{\text{RCHO}} \text{R}_1\text{C}(\text{O})\text{C}(\text{R}^2)\text{C}(\text{H})(\text{OH})\text{R}$

**Asymmetric synthesis** is a synthetic process during which one or more new elements of chirality is introduced during a functional group transformation. As we have been studying, in asymmetric synthesis, the reactions are either highly enantioselective (high ee) or enantiospecific (100% ee). The difference between a normal synthesis and an asymmetric synthesis can be rationalised from the following two reactions.

#### Racemic Reaction



#### Asymmetric Reaction



The asymmetric synthesis has become an important subject for research and the researcher has to keep in mind the nature of the chiral molecule when designing biologically active compounds. There are two main guiding **principles** for asymmetric synthesis. These are as follows.

1. The substrate should have a prochiral unit that may be enantiotopic or diastereotopic groups or faces.
2. The substrate or the reagent or the solvent or the catalyst must be chiral for preferential formation of a stereoisomer over the other in an asymmetric synthesis.

*It is strongly advised to revise the stereochemistry blocks of the MCH-012 course to understand the product formation in asymmetric synthesis. Some of the important concepts like Cram's rule, Prelog's rule need to be revisited.*

There are four main strategies or categories or methods in the development of asymmetric synthesis. These are listed below.

- First-generation or substrate-controlled methods
- Second-generation or auxiliary-controlled methods
- Third-generation or reagent-controlled methods
- Fourth-generation or catalyst-controlled methods

You will learn about these along with representative examples in the following subsections.

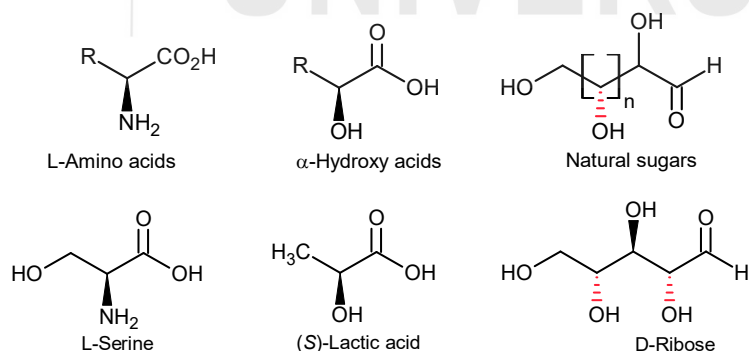
### 17.5.2 First-Generation or Chiron Approach

The first generation approach involves the formation of a new stereogenic centre in a substrate under the influence of an adjacent stereogenic group already present. It essentially involves the presence of a chiral substrate therefore, called the **Chiron approach**. The general reaction may be represented as follows.



In the reaction S represents the substrate, R the reagent, P the product and X the stereogenic group. The chirality is represented by an asterisk.

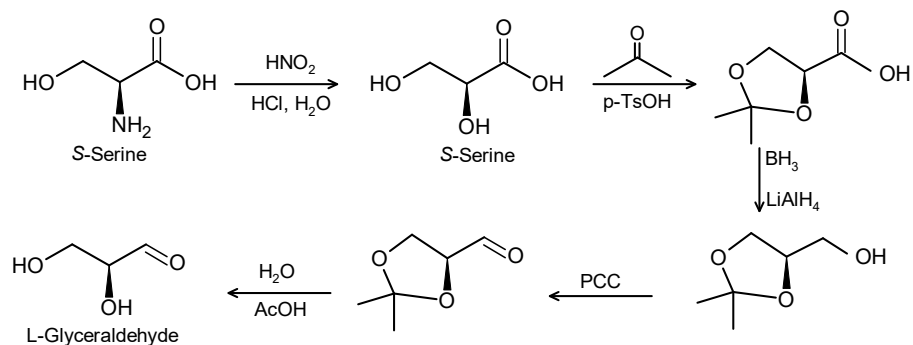
In the first generation asymmetric synthesis the starting molecule should be chiral and should be in an enantiomerically pure form as is evident from the reaction given above. That is why these methods are also called the **substrate controlled** methods. It is reasonable to think that the starting materials of this type are available only in nature. This approach is also called the **chiral pool approach** for this reason. You are aware of a number of naturally occurring biomolecules and the secondary metabolites like, simple sugars, amino acids, terpenes, steroids, alkaloids etc. which are all chiral. The structures of some of these are given as follows.



The guiding principle of this method is that the chiral centre(s) in the starting material are generally but not always preserved in the product. The new chiral centres can be generated through substitution or addition reactions.

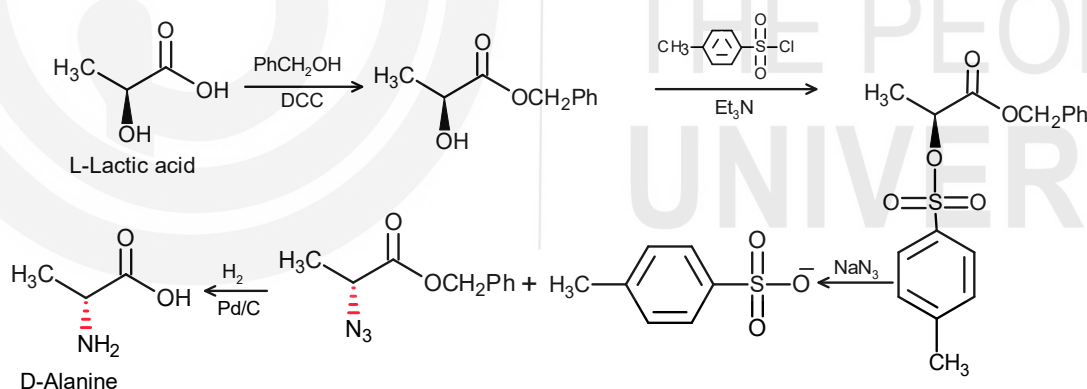
An example of this approach can be observed in the synthesis of L-glyceraldehyde, the unnatural sugar, from the natural amino acid L-serine. You will recall that the naturally occurring carbohydrates belong to the D configuration. As per the requirement of this method the amino acid used here

is chiral and also it is inexpensive. Therefore, this method is quite helpful in achieving the target molecule. You may note that there is retention of configuration in the diazotization-hydrolysis reaction. The sequence of reactions that follows is given below.



The first generation approach is very useful in carrying out the substitution reactions. For example, the functional group in a chiral pool substrate like, L-lactic acid can be converted into a good leaving group, e.g., a tosylate and the unusual product i.e., D-alanine can be achieved. Here again you would recall that the naturally occurring amino acids have L-configuration whereas the chiral pool approach can lead to the formation of unnatural amino acid with D-configuration.

You can observe that in this reaction  $\text{S}_{\text{N}}2$  substitution on the tosylate with  $\text{NaN}_3$  leads to inversion of configuration at the chiral centre. The sequence of reactions is given below.



The chiron approach has some advantages and a few limitations. These are listed below.

### Advantages of Chiron approach

The chiron approach has the following advantages for asymmetric synthesis.

- It ensures the choice of suitable starting material from the chiral pool available in nature.
- It preserves or enhances the enantiomeric excess i.e., the formation of an enantiomer in larger amounts.
- It can avoid racemisation through careful selection of reaction conditions.

### Disadvantages of Chiron approach

This approach faces a few shortcomings too, which are:

- The molecules readily available from the chiral pool like, amino acids, terpenes, etc. have limited variation in structure.
- The chiral pool molecules have limitation in terms of the specific requirement of a product.
- A multi-step synthesis is required to obtain the target molecule due to restriction in the variation in the structure of the chiral substrate.
- This approach requires stoichiometric amounts of the starting molecule which may not be available and may be expensive too.

You can study the second generation asymmetric synthesis after answering the following SAQ.

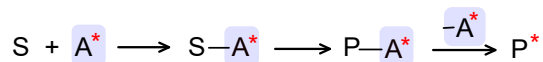
### SAQ 6

With reference to chiral pool asymmetric synthesis, choose the correct sentence in the following.

- A mixture of both the enantiomers is obtained.
- The natural chiral molecules are good for single step synthesis.
- A chiral reagent is required during chiral pool synthesis.
- The products are formed with almost 100% enantiomeric excess.

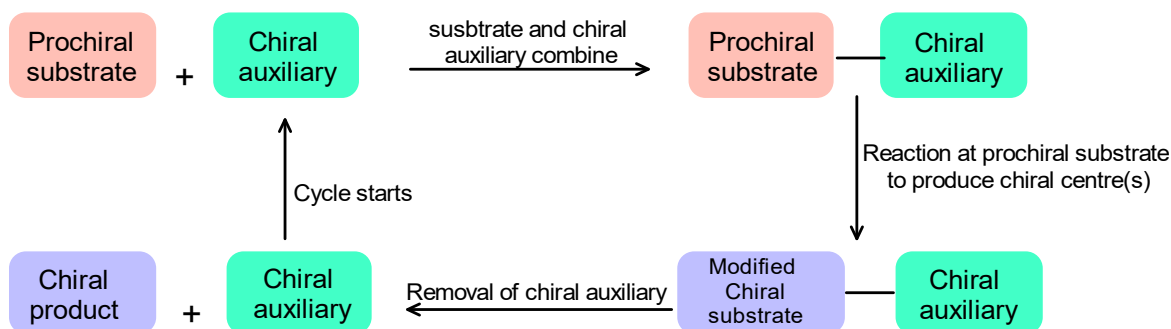
### 17.5.3 Second-Generation or Auxiliary-Controlled Methods

In this approach an achiral substrate is made chiral by attachment of a '**chiral auxiliary**'. A chiral auxiliary is a chiral molecular unit that can be temporarily incorporated in an achiral substrate to form one of the enantiomers. Chiral auxiliaries are optically active compounds and introduce chirality in otherwise achiral starting materials. This second generation synthesis is called **auxiliary-controlled** for this reason only. In the following general reaction, A with asterisk mark represents the chiral auxiliary and the sequence can be represented as given below.

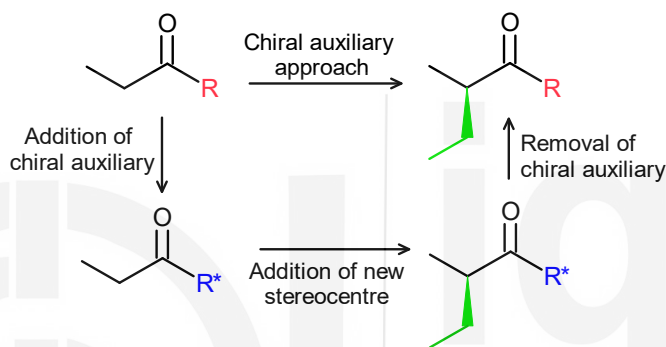


The chiral auxiliary participates in the reaction to get the product with the introduction of chirality in the product formed. This initial step produces a chiral substrate for the subsequent reaction. The attached auxiliary becomes responsible for the creation of another stereocentre in the next step. Thus, the reaction happens to be diastereoselective rather than enantioselective. In the final step the auxiliary is removed to give the desired chiral product. The stereochemistry of the new chiral centre can be rationalized based on steric considerations of the chiral auxiliary.

A better way of representing the whole sequence is given below.



Putting the above schematic process in the form of a reaction, we get the following.



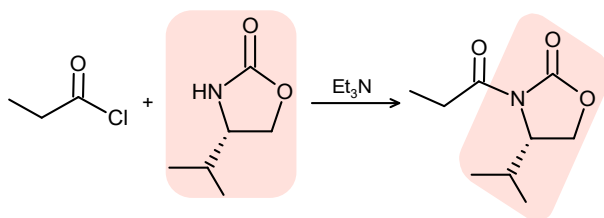
### Qualities of a Good Chiral Auxiliary

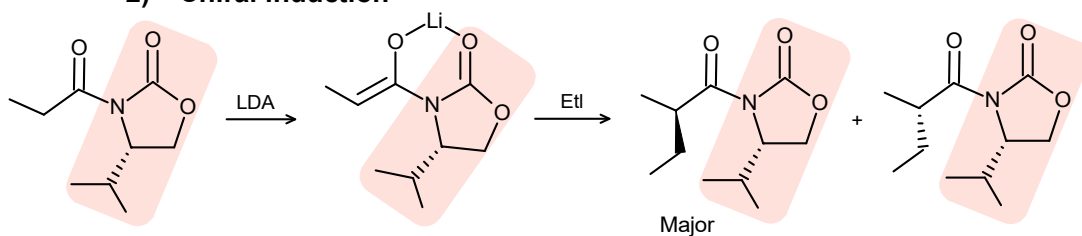
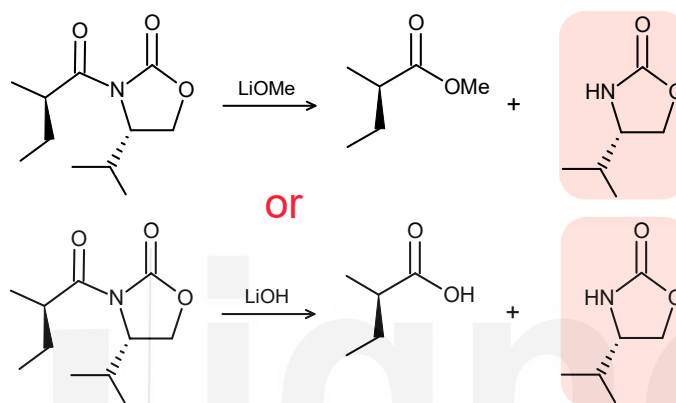
A chiral auxiliary should have the following properties being employed in an asymmetric synthesis.

- It should be available in both the enantiomeric forms
- It should be easy and quick to synthesise.
- It may be added readily to an achiral substrate.
- It should lead to high enantiomeric excess.
- It should be easily removable from the substrate under mild conditions.
- It should be recoverable and reusable.

A good example of chiral auxiliary mediated reaction is enantioselective alkylation of enolate with ethyl iodide in presence of triethyl amine and lithium diisopropylamide (LDA). It is given in a stepwise manner below.

#### 1) Installation of auxiliary



**2) Chiral induction****3) Removal of auxiliary**

The chiral auxiliary method has both advantages and disadvantages. These are given below.

**Advantages of Chiral Auxiliaries**

- The reaction using a chiral auxiliary leads to high enantiomeric excess.
- The product diastereomers formed can be separated by the use of simple methods like, chromatography and crystallisation.
- The chiral auxiliaries can be reused i.e., the method is cost effective.

**Disadvantages of Chiral Auxiliaries**

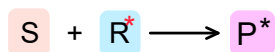
- Both the enantiomers of a chiral auxiliary are usually not readily available. Generally, one enantiomer is more expensive than the other.
- The chiral auxiliaries may not be available commercially and have to be synthesized for use.
- The synthesis of chiral auxiliaries may involve number of steps.
- The chiral auxiliary has to be removed once the reaction is completed.
- A stoichiometric amount of the chiral auxiliary is usually required.

In the following subsection, you will study the third generation method and reason out its utility in comparison to the two previous methods.

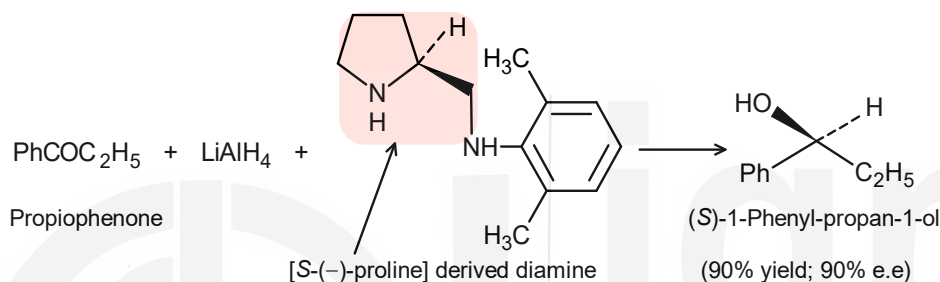
**17.5.4 Third-Generation' or Reagent-Controlled Methods**

The effectiveness of the auxiliary approach may be enhanced by the use of a chiral reagent, which converts the achiral substrate directly into a chiral

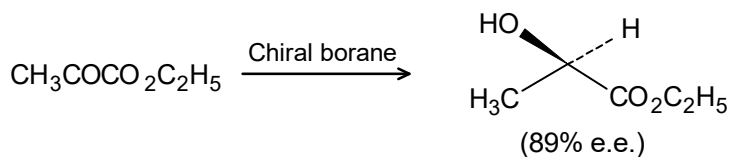
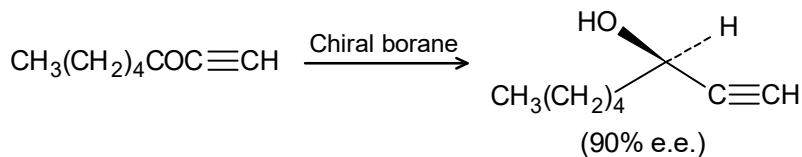
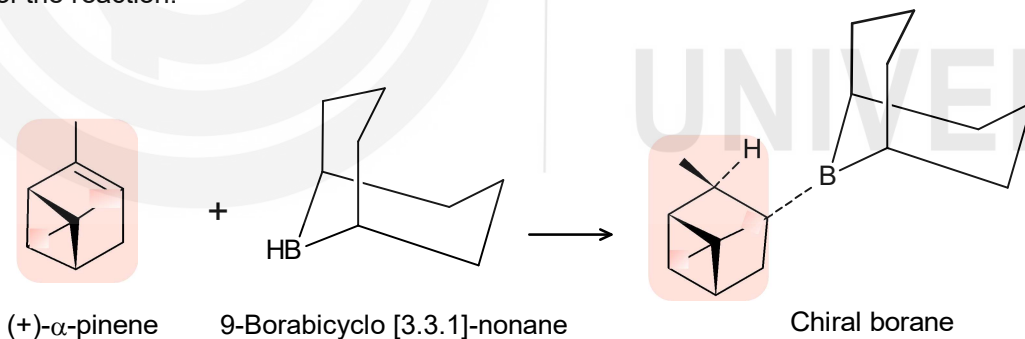
product. In the reagent controlled approach the chirality is based on the reagent instead of the substrate. The chiral reagent is used in stoichiometric quantities in the reaction. The most important point of difference which may be counted as a disadvantage here is that the reagent gets used in the reaction and cannot be recovered for reuse.



Let us understand this by the reaction using lithium aluminium hydride as the reducing agent. The reducing agent is treated with a chiral diamine or amino alcohol to create a reagent that will lead to asymmetric reduction. For example, reduction of propiophenone with lithium aluminium hydride in the presence of the proline-derived diamine gives (*S*)-1-phenyl-propan-1-ol with high selectivity.



In another case the hydroboration of a terpene like (+)- $\alpha$ -pinene forms a chiral borane with 9-borabicyclo[3.3.1]nonane (9-BBN) that reduces a number of ketones with high enantiomeric excess. As you would notice the hydride used in the reaction comes from 9-BBN and the  $\alpha$ -pinene molecule becomes the chiral carrier of the hydride. The pinene molecule gets regenerated at the end of the reaction.



### Advantages of chiral reagent

It does not require attaching or removing the chiral group (*c.f.* chiral auxiliaries). Therefore, if the reagent is commercially available, there are less synthetic steps.

### Disadvantages of chiral reagent

- There is no scope to improve the % enantiomeric excess of the product.
- The method requires stoichiometric amounts of reagent and hence the chirality which means 1 mole of reagent is required for every 1 mole of substrate.
- Not very efficient in chirality.

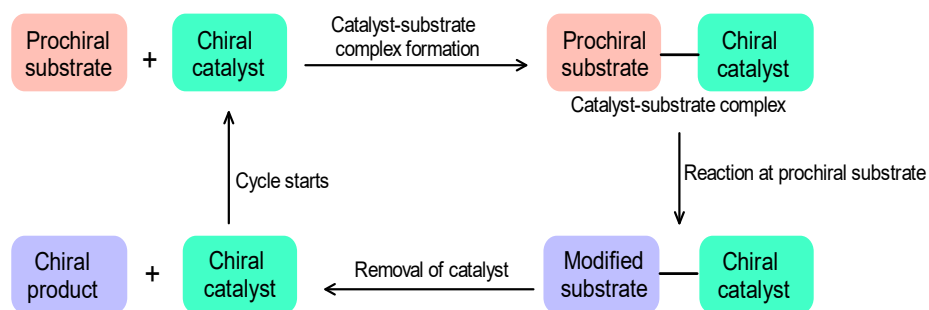
You would agree that use of chiral reagents does not prove to be an economically viable method. The best method employed as of today happens to be the use of chiral catalysts as you would understand after studying the fourth generation method which follows in the next subsection.

### 17.5.5 Fourth-Generation or Catalyst-Controlled Methods

You studied that in the third generation asymmetric synthesis a chiral reagent is used. In view of the disadvantage of nonreusable reagent the fourth generation methods involves the use of a nonchiral reagent but a **chiral catalyst**. The only condition required here is that the substrate should be prochiral i.e., the ability to become chiral in one simple transformation. The most common prochiral units that give rise to new chiral centres are the trigonal carbon atoms of alkenes and carbonyl groups, which become tetrahedral by addition reactions. The reaction is as simple as represented below.



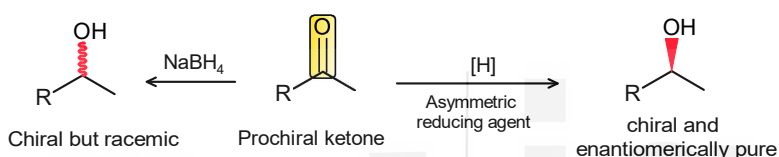
When a prochiral substrate is transformed into an enantiopure product using a chiral catalyst, the process is referred to as **asymmetric catalysis**. The process of chiral catalysis can be represented by the scheme given below. You would observe that it has a similarity to the scheme given for chiral auxiliary based synthesis.



The advantage of utilising a catalytic method lies in the fact that only small quantities of chiral catalyst are necessary to generate substantial quantities of chiral product called the **chiral amplification**. This does not require any additional steps.

The chiral catalyst controlled reactions can be well understood by looking into some of the examples. You might be familiar with a good number of these. One of the simplest transformations we could imagine of a prochiral unit into a chiral one is the reduction of an unsymmetrical ketone. Although chiral auxiliary strategies have been used to make this type of reaction asymmetric, conceptually the simplest way of getting the product as a single enantiomer would be to use a chiral reducing agent—in other words, to attach the chiral influence not to the substrate (as we did with chiral auxiliaries) but to the reagent.

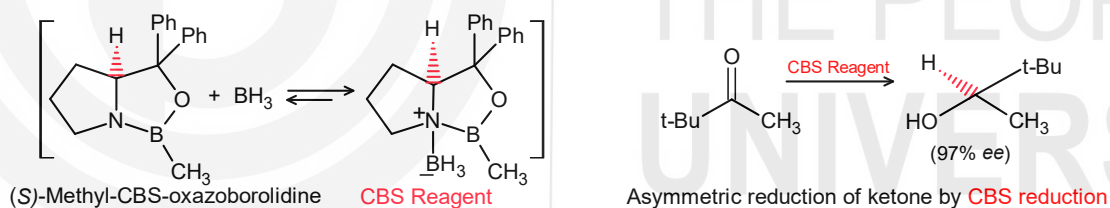
It is observed that addition of sodium borohydride to a ketone occurs equally from both *Re*- and *Si*- faces resulting into a chiral but racemic product. It implies that for the asymmetric reduction of a ketone we need to replace the usual  $\text{NaBH}_4$  with some chiral reducing agent. This can be represented in a general manner as follows.



#### Re and Si faces:

Using CIP rules if the substituents rank high priority to low priority clockwise then this is the *Re*-face. If they rank high priority to low priority anti-clockwise then this is the *Si*-face.

The enantioselective reduction of prochiral ketones to chiral alcohols can be carried out using a borohydride complexed with a difunctional chiral ligand like the one created by **Corey-Bakshi-Shibata** group of scientists. The reaction carried out by them is known by the name **CBS reduction**. The reducing agent is formed by binding (*S*)-2-methyl-CBS-oxazaborolidine to diborane in a reversible manner. The reducing agent reacts with a ketone to give an alcohol with good enantiomeric excess as per the following reaction.



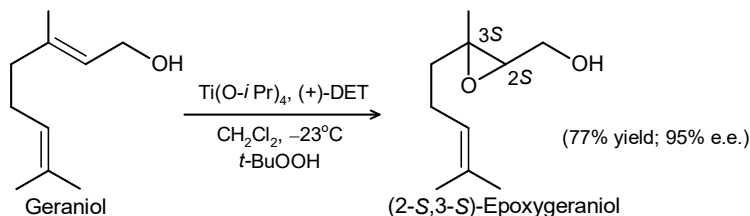
The energies of the diastereomeric transition states for reduction from either the *Re*- or *Si*-face are not equal. Therefore, the Lewis acidic boron orients the hydride attack from the *Si*-face of the carbonyl group.

You might be familiar with another very important asymmetric synthesis accomplished using chiral catalysts by **K. B. Sharpless** for **asymmetric epoxidation reaction** and also the **asymmetric aminohydroxylation**. These stereoselective oxidation reactions have multifold applications in synthetic organic chemistry.

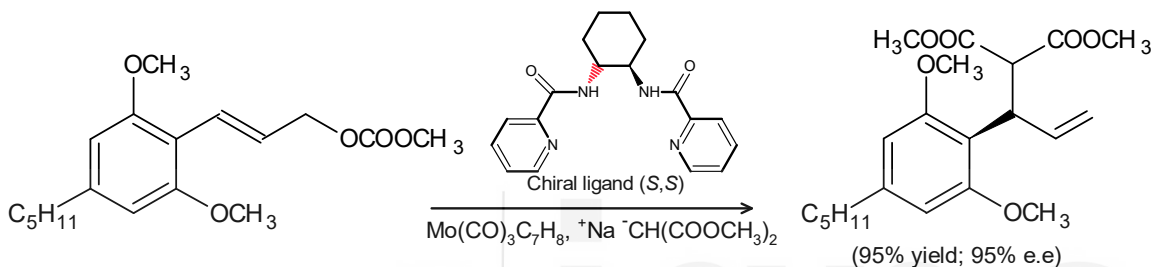
**Sharpless asymmetric epoxidation** is an enantioselective epoxidation of an allylic alcohol with *tert*-butyl hydroperoxide (*t*-BuOOH), titanium tetraisopropoxide  $[\text{Ti}(\text{O}-i\text{Pr})_4]$  and (+)- or (–)-diethyl tartrate [(+)- or (–)-DET] that produces optically active epoxide from achiral allylic alcohol. The reaction is diastereoselective for a substituted allylic alcohol. The formation of chiral epoxides is an important step in the synthesis of many natural products because epoxides can be easily converted into diols and ethers.

In 2001, K. B. Sharpless won the Nobel Prize in Chemistry for his work on asymmetric aminohydroxylation and asymmetric epoxidation.

For example, asymmetric epoxidation of geraniol gives (2*S*,3*S*)-epoxygeraniol in 77% yield and 95% ee.



Similarly the hydrogenation of alkenes in presence of a chiral molybdenum catalyst,  $[\text{Mo}(\text{CO})_3\text{C}_7\text{H}_8]$  forms a branched product with a very good yield and enantiomeric excess.

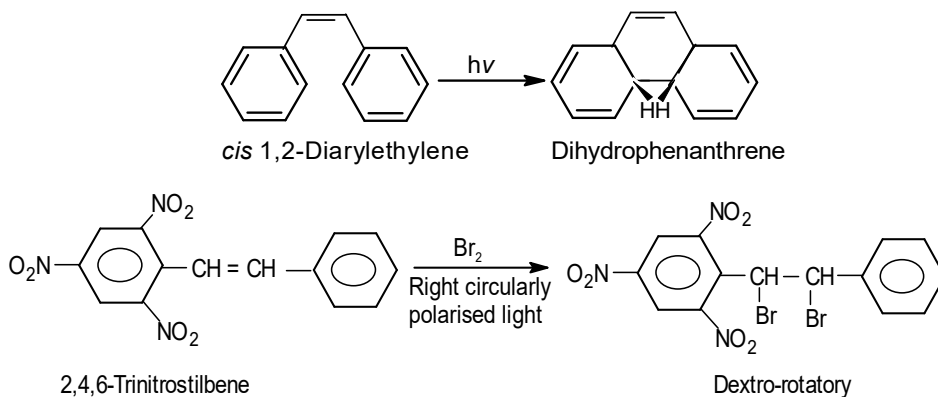


After studying the main approaches of asymmetric synthesis, you would be interested in getting acquainted to the approach called as absolute asymmetric synthesis. In the next subsection let us understand in brief about this approach.

### 17.5.6 Absolute Asymmetric Synthesis

The asymmetric approaches studied so far involved presence of a chiral moiety to begin with whether it was a reagent, substrate, catalyst or an auxiliary. These approaches are put into the category of **partial asymmetric synthesis**. In the second category of approach we do not use any chiral moiety to begin with but the result is formation of a chiral compound.

The synthesis of optically active products from achiral substances, without the use of optically active reagents is known as **absolute asymmetric synthesis**. If circularly polarised light is used to initiate a photochemical reaction of achiral reagents, a chiral product richer in one enantiomer can be obtained. For example, as 1, 2-diarylethylene forms dihydrophenanthrene in presence of light. In another example, 2,4,6-trinitrostilbene gives a dibromo addition product in presence of bromine and right circularly polarised light. The product obtained is dextro-rotatory.



You can assess a general understanding of the various strategies or approaches and a couple of reactions belonging to those approaches by trying to answer the following SAQ.

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### SAQ 7

Match the terms given in column (A) with the explanation given in column (B).

- |                                     |  |
|-------------------------------------|--|
| a) Asymmetric induction             | 1 Titanium tetraisopropoxide chiral catalyst |
| b) First generation synthesis       | 2 Use of chiral auxiliary                    |
| c) Second generation synthesis      | 3 Use of chiral reagent                      |
| d) Third generation synthesis       | 4 Chiron approach                            |
| e) Fourth generation synthesis      | 5 Creation of a new chiral centre            |
| f) Sharpless asymmetric epoxidation | 6 Chiral catalyst                            |
- 

## 17.6 SUMMARY

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Let us summarise the main concepts dealt in this unit regarding asymmetric synthesis in organic chemistry.

The three-dimensional behaviour of chiral molecules has become a significant area of research in modern organic chemistry. Chirality is of prime significance as it is one of the features of a molecule that is responsible for the formation of two or more isomers. It is because most of the drugs of therapeutic importance are chiral in nature, it becomes essential to synthesise with desired configuration.

A number of the basic terms which relate to the stereochemistry and the stereochemical reactions should be known with clarity and these have been recalled in the unit for the ready reference. These have been covered in the Semester I course on Stereochemistry and Reactive Intermediates.

The selectivity of formation of one isomer over the other is central to the asymmetric synthesis. The selectivity in asymmetric synthesis can be attained by selecting appropriate starting materials, reagents, solvents, reaction conditions. The selectivity is mainly of three types i.e., Chemoselectivity, Regioselectivity and Stereoselectivity.

The chemoselectivity is the selectivity in the formation of one product by the reaction with one functional group from the substrate that has two or more, similar or different functional groups present. The chemoselectivity can be very well explained with molecules having two keto groups in which the reduction takes place differently for both the groups based on the type of the reagent used.

The molecules may show selectivity between two positions present with similar reactivity. It is called the regioselectivity. A regioselective reaction is the selective formation of one constitutional isomer.

The stereoselectivity arises when there is a possibility of formation of stereoisomers. The reactant may or may not have a chiral centre in a

stereoselective reaction. The stereoisomers can be enantiomers or the diastereoisomers. Therefore the stereoselectivity leads to enantioselectivity or diastereoselectivity depending upon whether the product is a diastereomer or an enantiomer that is being produced selectively.

The reactions in which there are two or more starting stereoisomers which give rise two or more product stereoisomers, one of the starting isomers produces one product isomer, while the other starting isomer produces the other product isomer. These are called stereospecific reactions. All the stereospecific reactions are also stereoselective. However, all the stereoselective reactions are not essentially stereospecific.

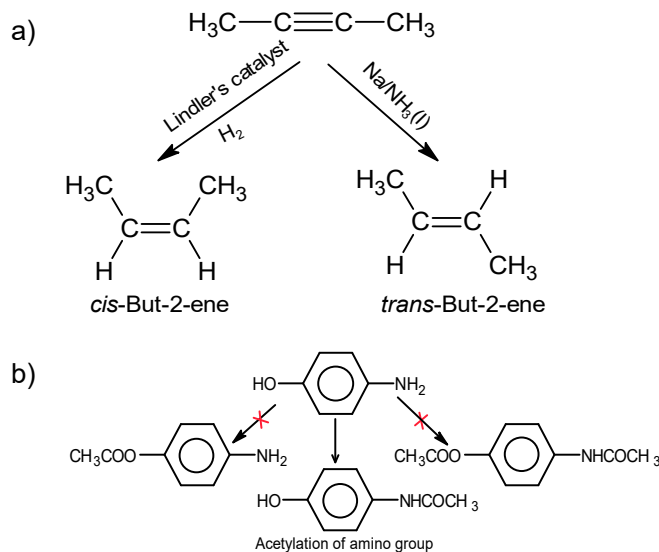
Asymmetric synthesis is a synthetic process during which one or more new elements of chirality is introduced during a functional group transformation. In asymmetric synthesis, the reactions are either highly enantioselective (high *ee*) or enantiospecific (100% *ee*).

There are four main approaches in the development of asymmetric synthesis. The first-generation or substrate-controlled methods is also called the chiron approach as it makes use of a chiral substrate from natural sources. The second-generation or auxiliary-controlled methods use a chiral auxiliary for generating another chiral centre and the auxiliary can be removed after the reaction is complete. The third-generation or reagent-controlled methods are improvised in making use of a chiral reagent. The fourth-generation or catalyst-controlled methods belong to the modern approach of asymmetric synthesis and involves a number of chiral catalyst based synthetic approaches.

Besides the partial asymmetric synthetic approaches there is an absolute asymmetric synthetic approach that does not involve any chiral substrate or the reagent. The method makes use of circularly polarised light for the synthesis of optically active compounds.

## 17.7 TERMINAL QUESTIONS

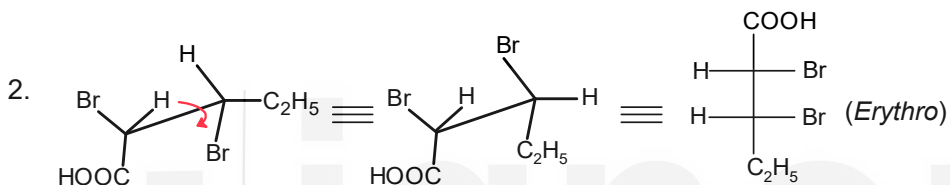
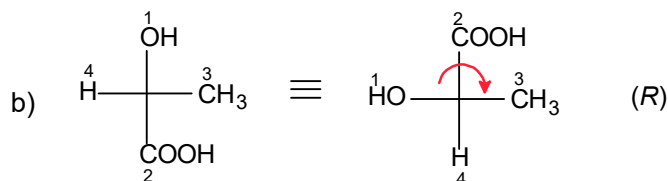
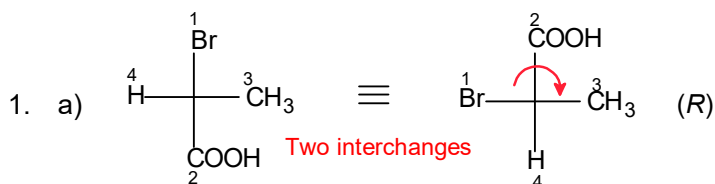
1. What type of selectivity is depicted by the following reactions? Explain.



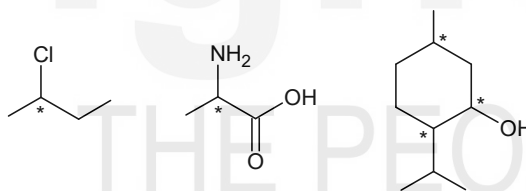


## 17.8 ANSWERS

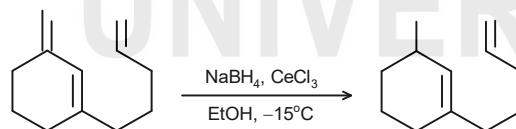
### Self Assessment Questions



3. a) and b) have one each and c) has three chiral centres. The chiral carbons are depicted below.



4. Selective reduction of a double bond, showing chemoselectivity



5. a) chemoselective  
 b) regioselective  
 c) stereoselective  
 d) stereospecific
6. d) is the correct option
7. a) - 5    b) - 4    c) - 2    d) - 3    e) - 6    f) - 1

### Terminal Questions

1. a) Regioselectivity: reagent based  
 b) Chemoselectivity: one functional group reacting with priority

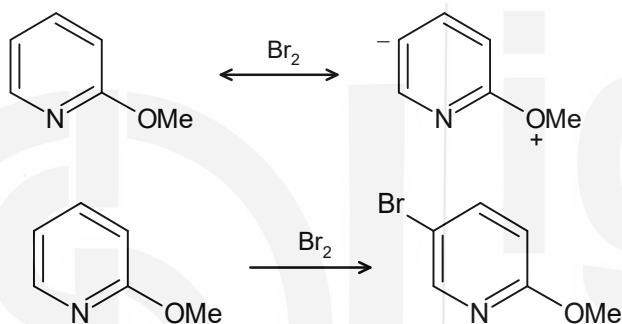
## 2. Advantages

- choice of suitable starting material from chiral pool in nature
- enhances the enantiomeric excess
- can avoid racemisation by selection of reaction conditions

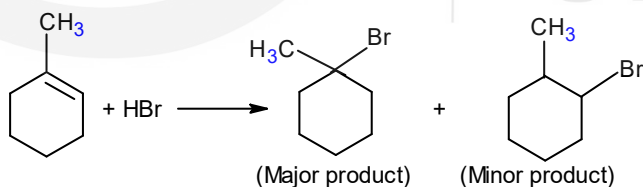
## Disadvantages

- chiral pool molecules have limited variation in structure.
- Are not able to fulfil specific requirement of product formation
- Requires a multi-step synthesis
- Lack of availability of stoichiometric amounts of the starting molecules

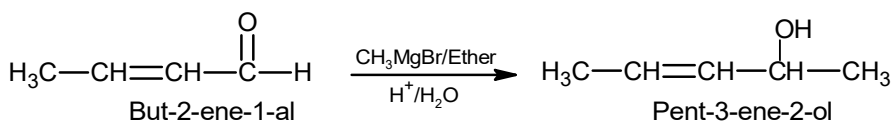
3. a) Pyridine is electron poor (imine-type heterocycle), and the resonance structure has the charge at the 5-position (para to OMe and meta to N). That is why it forms the bromo compound at position 5 showing regioselectivity.



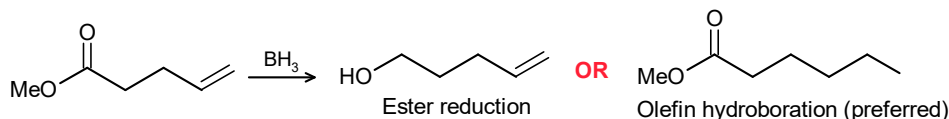
- b) In the addition of HBr to 1-methylcyclohexene, 1-bromo-1-methylcyclohexane is obtained as the major product and 1-bromo-2-methylcyclohexane is formed as the minor product. The +I effect of the methyl group is responsible for the creation of a positive charge at carbon adjacent to the methyl group and attack of bromide ion at that carbon. This is also an example of regioselectivity.



4. The reaction will result in the reduction of the aldehyde group by 1,2-addition reaction and shows chemoselectivity

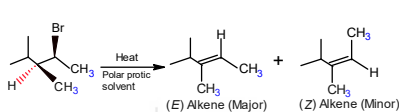


5. Hydroboration is favoured

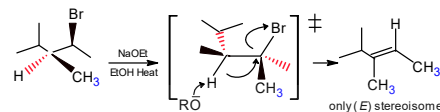


6.a) **Stereospecific Reactions**

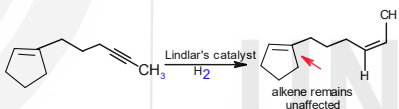
- The reaction in which stereochemistry of reactant completely determines the stereochemistry of the product without any other option
- Give a specific product from specific reactants.
- Final product depends upon the stereochemistry of reactants.

**Stereoselective Reactions**

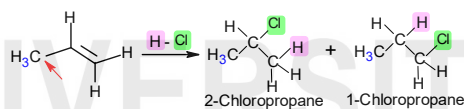
- The reaction in which there is a choice of pathway. The product stereoisomer is formed by a reaction pathway which is more favourable than other available.
- Can result in multiple products.
- Selectivity of the reaction pathway depends on difference in steric effect and electronic effect.

b) **Chemoselectivity**

- The reactions are selective for one functional group over another.
- Reagent reacts with one functional group only.
- The molecule has more than one functional group.

**Regioselectivity**

- The reactions are selective for the formation of one stereoisomer or constitutional isomer over another.
- Reagent attacks at any of the sites.
- The molecule has two or more sites of reactivity.



- 7.
- Chiral pool
  - Chiral catalyst
  - Chiral substrate
  - Chiral auxiliary