

# UMPOLUNG REACTIONS

## Structure

---

|                                  |                         |
|----------------------------------|-------------------------|
| 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

---

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

---

After studying this unit, you should be able to:

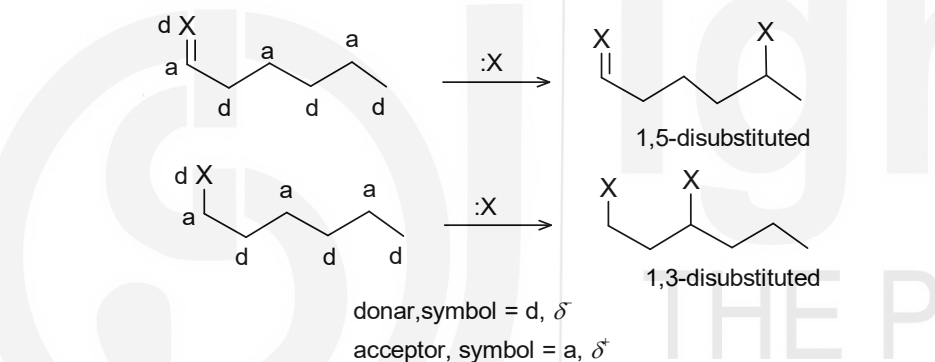
- ❖ define term umpolung strategy;
- ❖ describe various approaches for developing umpolung reagents for the synthesis;
- ❖ list and explain various types of umpolung reactions using carbonyl umpolung, homoenolates and  $\alpha$ -electrophiles;
- ❖ apply umpolung strategy in construction of carbon-carbon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

## 15.2 TYPES OF UMPOLUNG REACTIONS

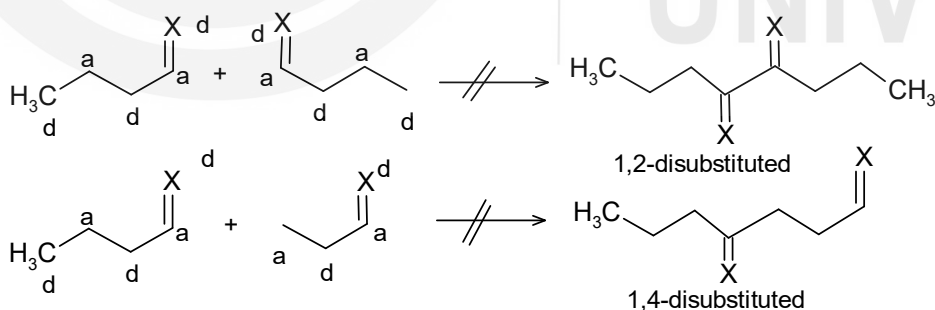
Before going in detail let us define term umpolung.

### 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:**

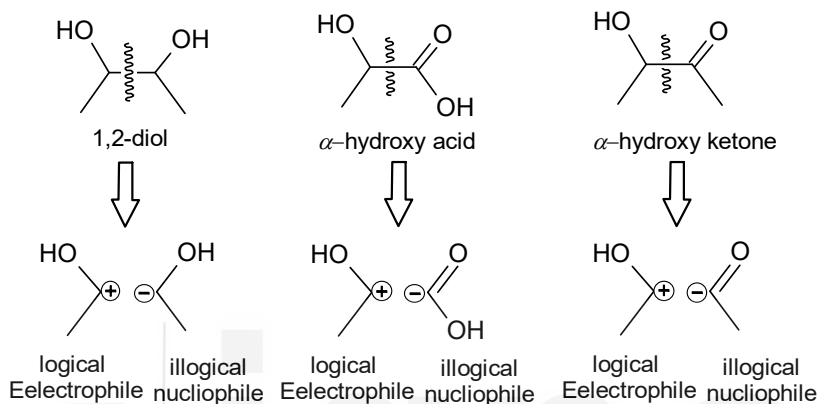
The charge on the synthon coincides with the natural polarity imparted by the functional group present.

**Illogical synthons:**

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

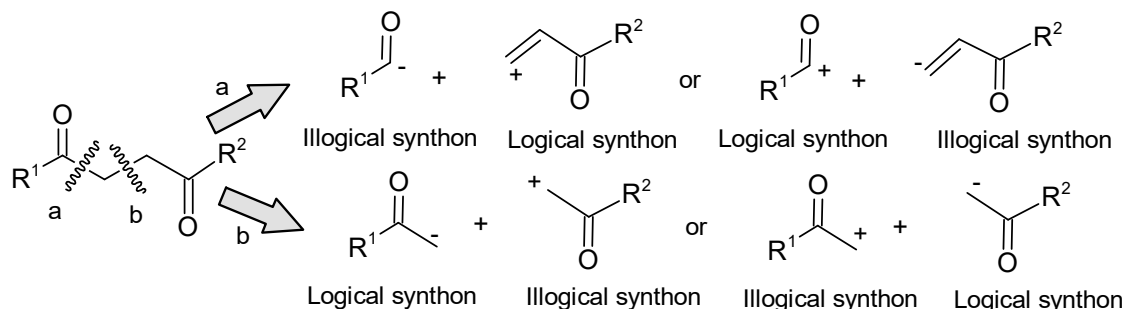
Thus, logical synthons are often also called natural synthons and illogical synthons are known as unnatural synthons. The synthetic equivalent representing a logical electrophilic synthon is called a 'logical' electrophile while an illogical electrophilic synthon is represented by an 'illogical' electrophile.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

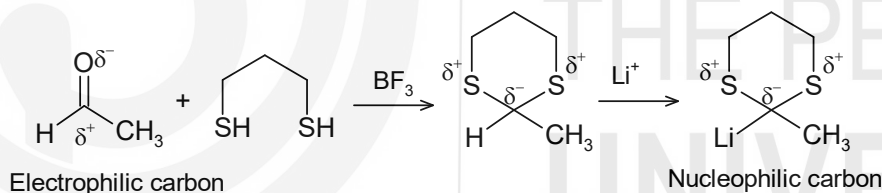
### 15.2.1 Carbonyl Umpolung Strategies

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:

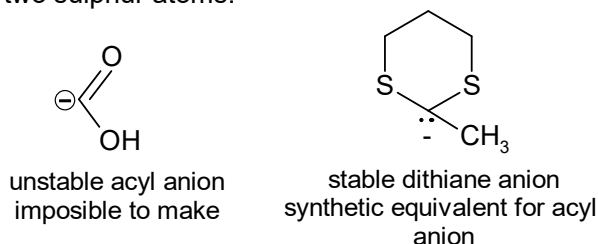
1. Dithiane (sulphur umpolung)
2. Cyanide ion
3. Nitronate anion
4. Cyanohydrins
5. Metalated enol derivatives
6. *t*-Butylhydrazone
7. Lithium acetylide
8. Intermediates in thiazolium salt catalysed reaction

#### 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:

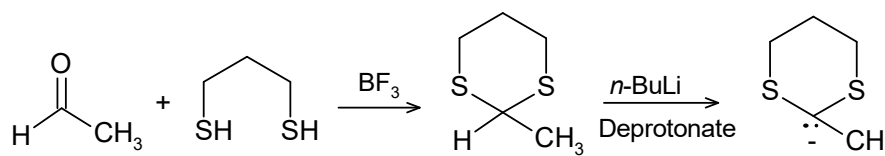


Dithianes are also used as protecting group in many transformations similar to acetals. They are also a classic example of polarity inversion i.e. umpolung. Usually the oxygen atom in the carbonyl group is more electronegative than the carbon atom and therefore the carbon atom of carbonyl group acts 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.



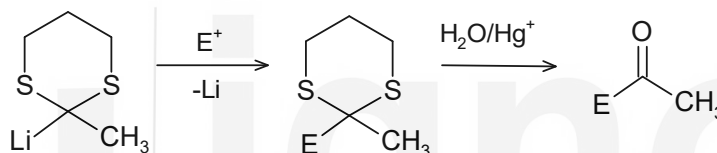
**1,3-Dithiane anion is the synthetic equivalent of an acyl anion**

**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).



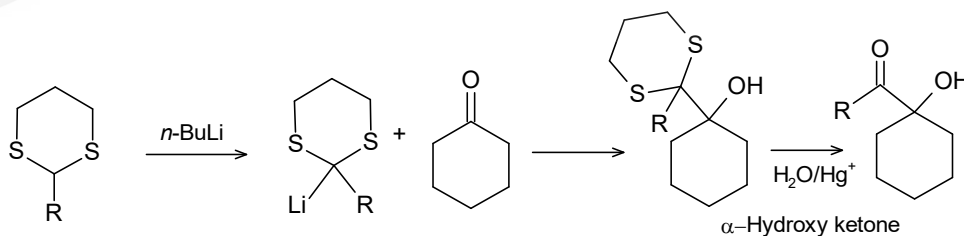
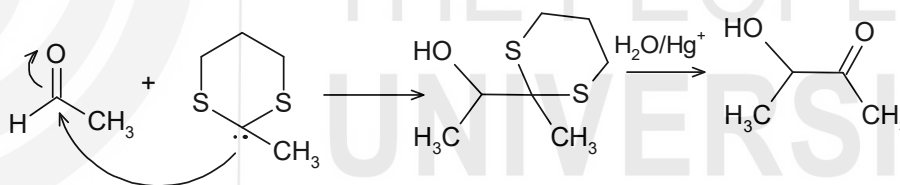
### Reactions of Dithianes:

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:

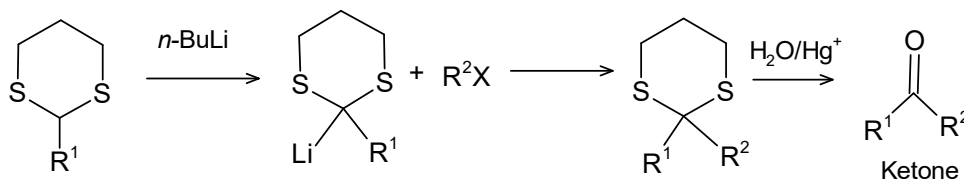


1,3-Dithianes and other sulphur compounds have found considerable applications in multistep syntheses. Few examples of synthetic sequences that employ acyl anion equivalents are given below:

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



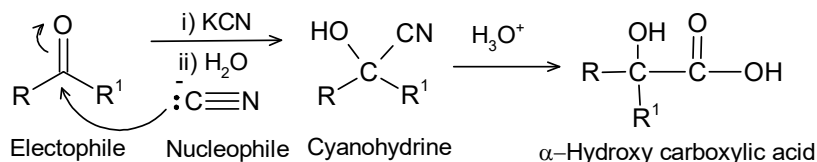
**Reaction with alkyl halide:** Aldehydes and ketones can be prepared using 1,3-dithiane and alkylhalide.



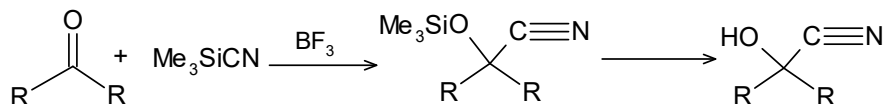
Similar to 1,3-dithianes other sulphur compounds can also be used to generate acyl anion equivalent.



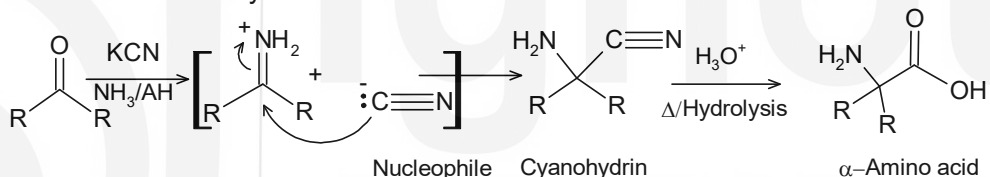
how the synthesis of an  $\alpha$ -hydroxycarboxylic acid can be achieved by addition of cyanide to a ketone or an aldehyde followed by hydrolysis of the resulting cyanohydrin,



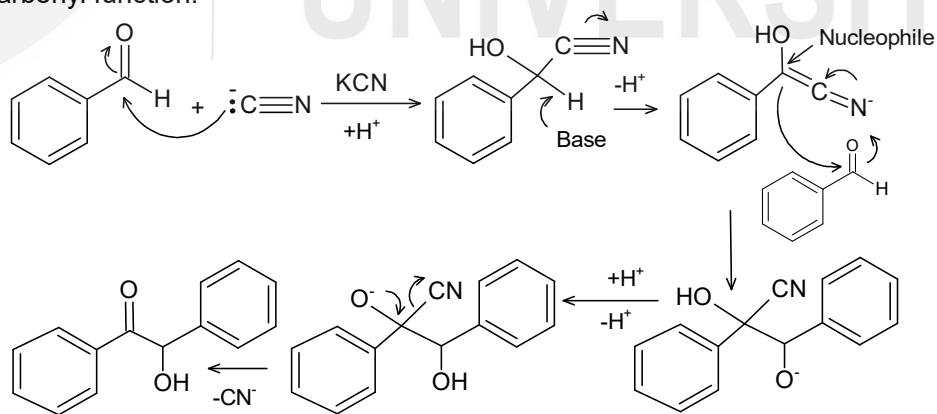
This sometimes has problems with forcing the reaction to the product side, and a competing benzoin condensation, so the reaction is usually performed by trimethylsilyl cyanide and a Lewis acid.



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 acy anion, this undergoes a subsequent 1,2-addition to a carbonyl function.



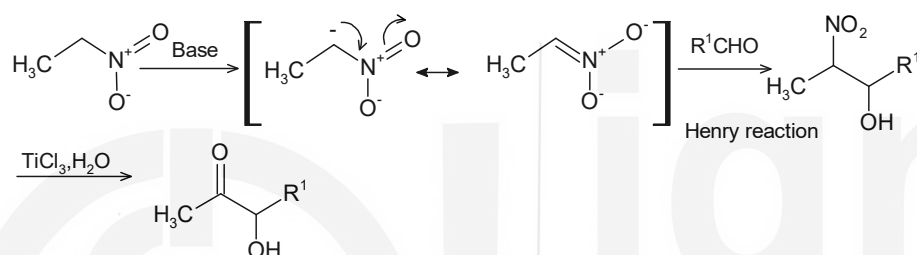
The net result of the benzoin reaction is that a bond has been formed between two carbons that are normally electrophiles.

### SAQ 3

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

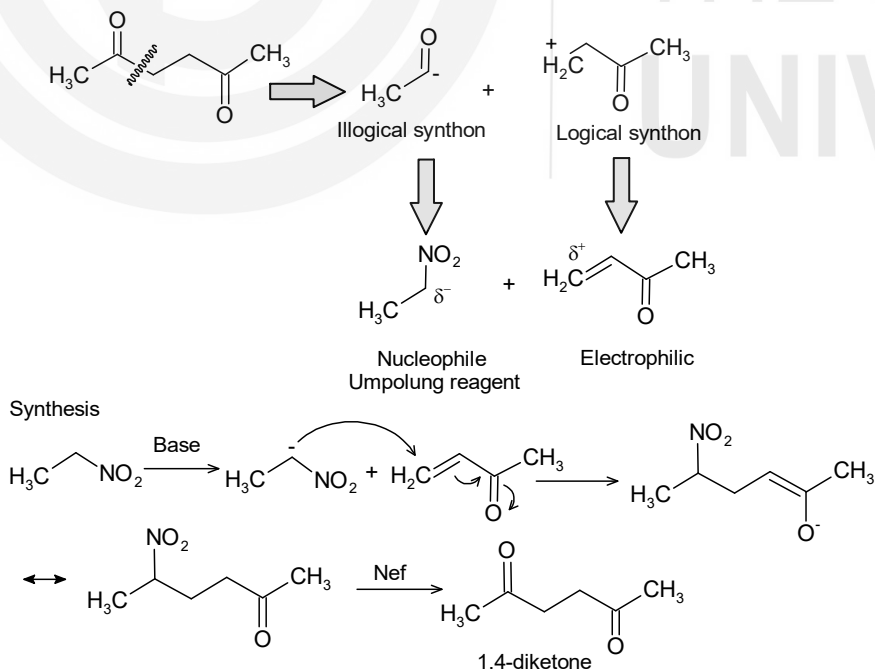
### 3. Nitronate anion

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.



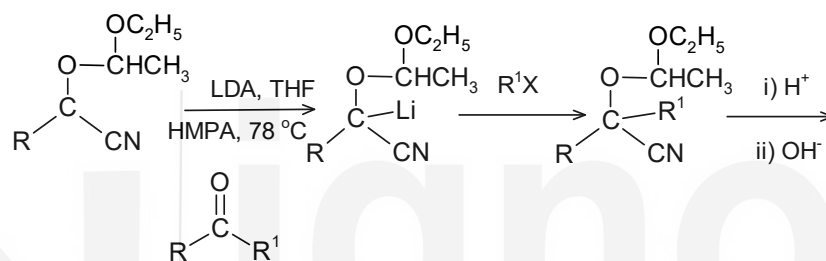
In both the examples final products are 1,2-disubstituted and 1,4-disubstituted which otherwise are difficult to achieve or we have to use many steps to obtain final target molecules.

## SAQ 4

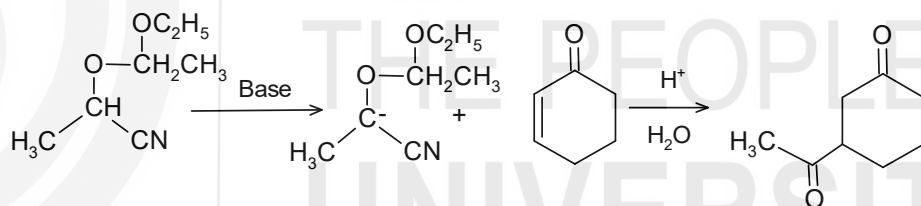
Using Henry and Nef reaction how you will prepare 3-hydroxy-2-butanone.

## 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 ethoxyethylether. 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.

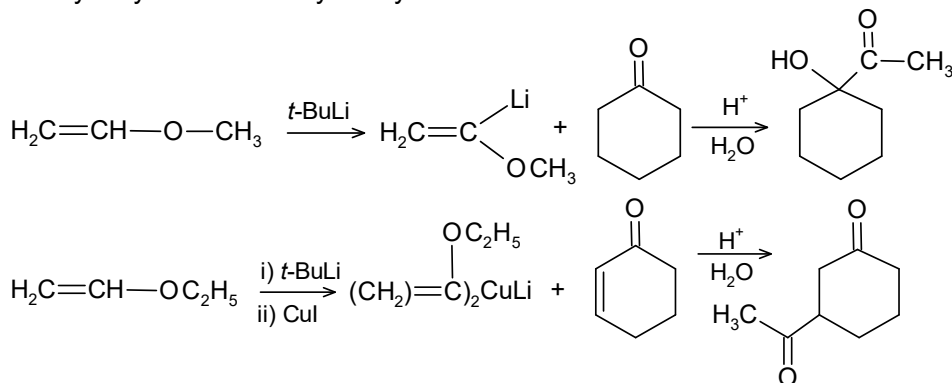


This method can be used for introducing an acetyl group at the  $\beta$ -position of cyclohexenone which is otherwise it is difficult to achieve by natural reactivity of functional groups.



## 5. Metalated enol derivatives

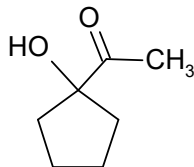
$\alpha$ -Lithiovinyl ethers which are also known as protected enols are another examples of acyl anion equivalents. They can be metalated with Li and corresponding cuprate. These reagents are capable of adding the  $\alpha$ -alkoxyvinyl group to electrophilic centers. Subsequent hydrolysis can generate 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.

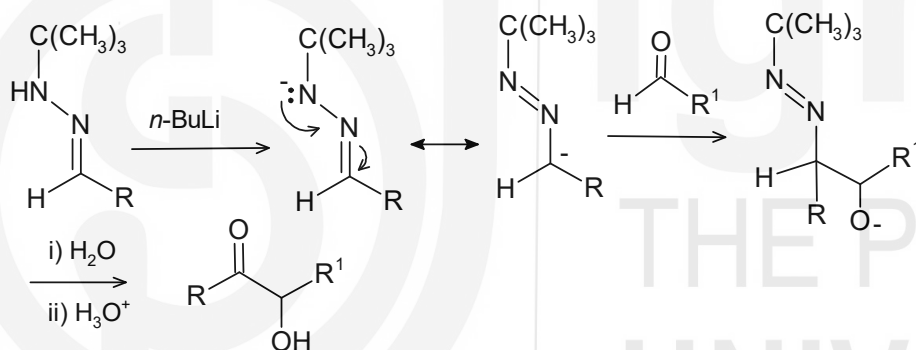
### SAQ 5

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.

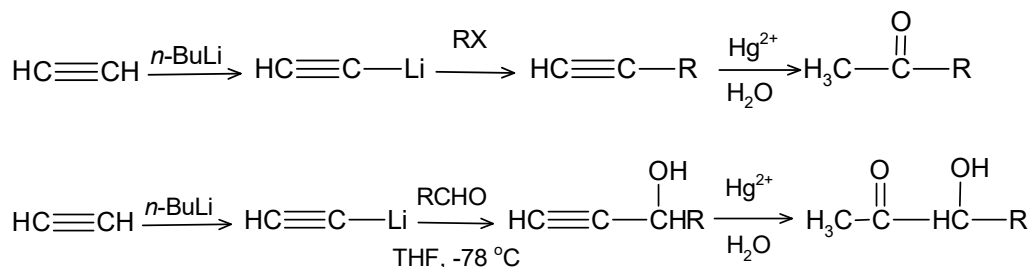


### SAQ 6

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

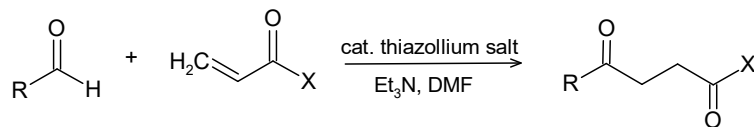
### 7. Acyl Anions Derived from Lithium acetylene

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.

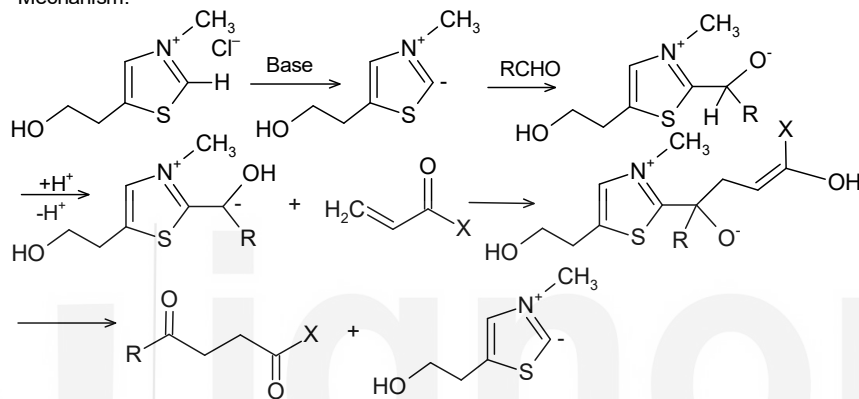


### 8. Intermediates in thiazolium salt catalysed reaction

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)

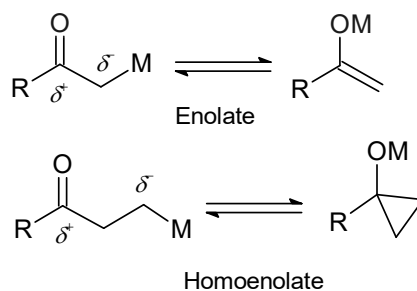
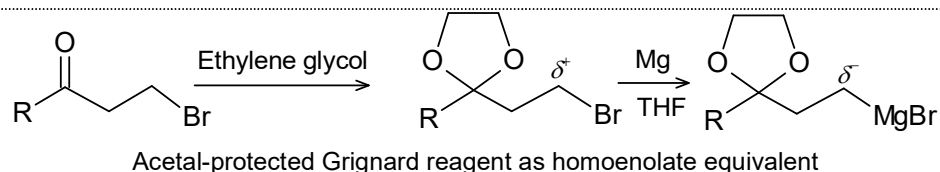
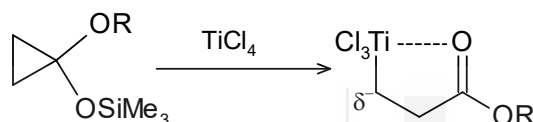


Fig. 15.4: Comparison of enolate and homoenolate.

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.

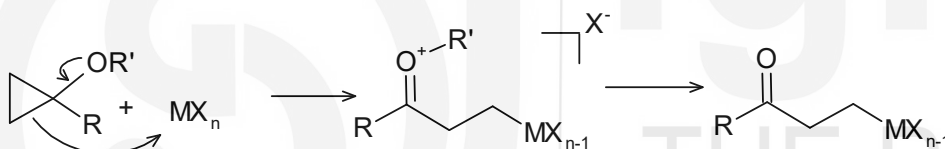


In such reactions we have to protect carbonyl group before reactions with metal ions. Homo-enolates can also be readily prepared via treatment of siloxycyclopropanes with an appropriate metal halide source. Overall, this method utilizes the lessening of ring strain in cyclopropanes towards the formation 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.

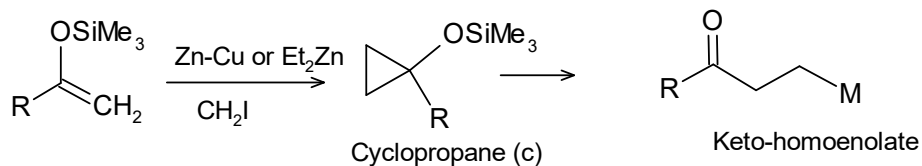
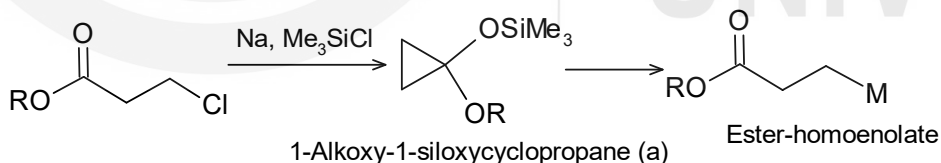


#### Cyclopropanol-derived metal homo-enolate equivalents

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

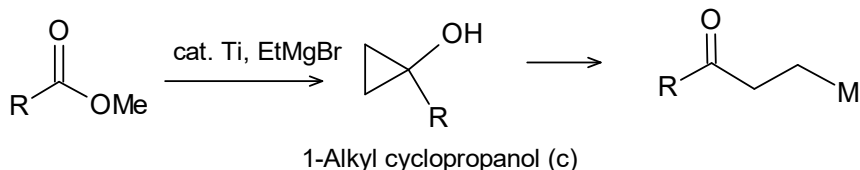


The cyclopropanol derivatives used as homo-enolate precursors can be categorized into three types, that is, 1-alkoxy-1-siloxycyclopropanes (**a**) for ester homo-enolates and 1-alkyl/aryl-1-siloxycyclopropanes (**b**) and cyclopropanols (**c**) for keto-homo-enolates.



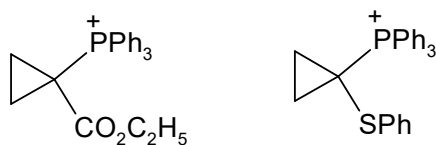
#### 1-Alkyl-1-siloxycyclopropane (b)

Simmons-Smith reaction

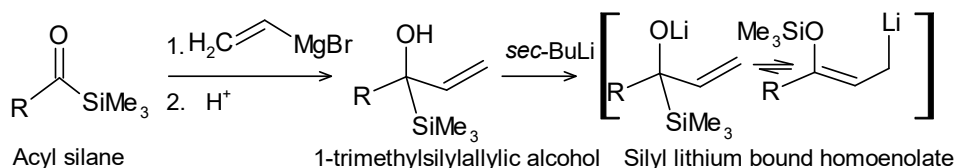


Kulinkovich reaction

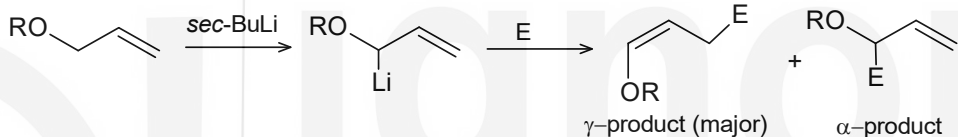
Cyclopropyl phosphonium ions equivalent to homoenolates have also been developed along these lines.



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.

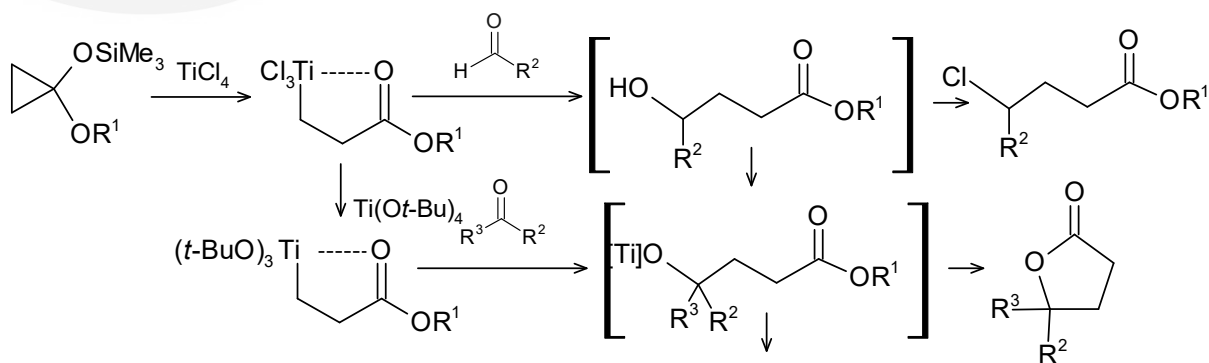


Homoenolate, provide us a one-carbon-extended homolog of enolate, can also be attractive reactive species, as it could react with electrophiles to afford  $\beta$ -substituted ketones.

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:

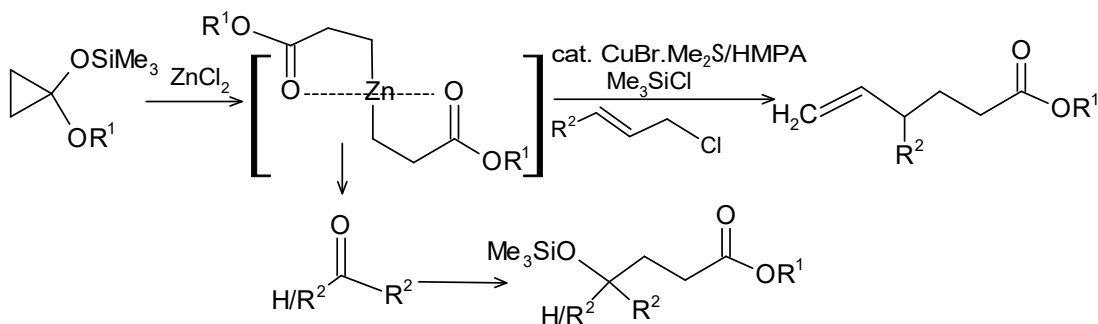
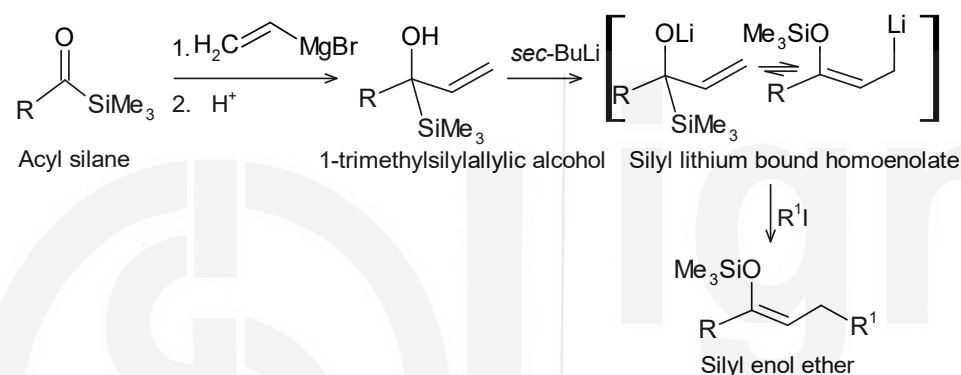
#### Reactions of Titanium Ester-homoenolate:



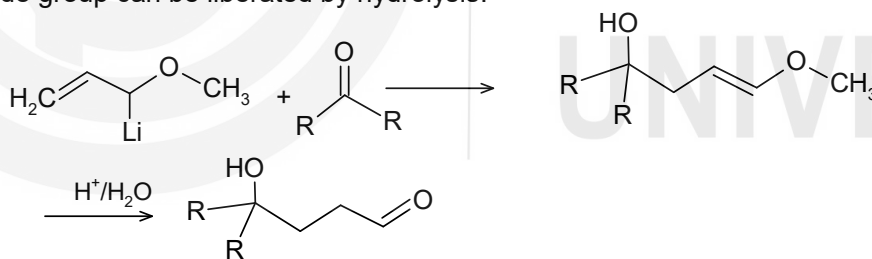
The  $\text{TiCl}_3$ -homoenolate is less reactive. It reacts only with aldehydes to afford  $\gamma$ -chloroesters through *in situ* chlorination of the initial adducts but not with ketones. The reactivity of this reaction can be enhanced by exchanging chloride ligand of this homoenolate with an alkoxide 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:**

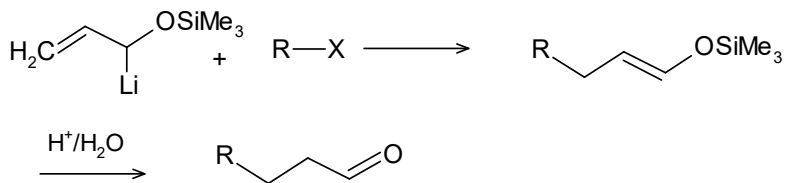
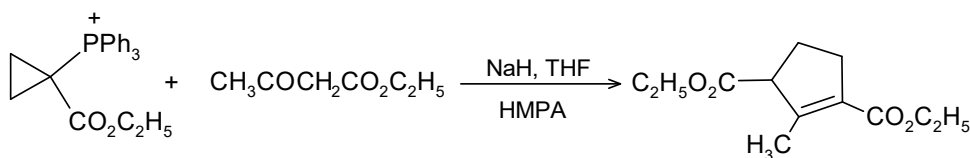
The zinc homoenolate worked as a good alkyl nucleophile towards various electrophiles with or without transition metals.

**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.

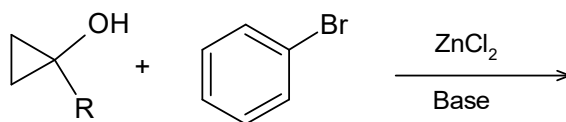


Above reaction can be modified by using trimethylsilyl ether.

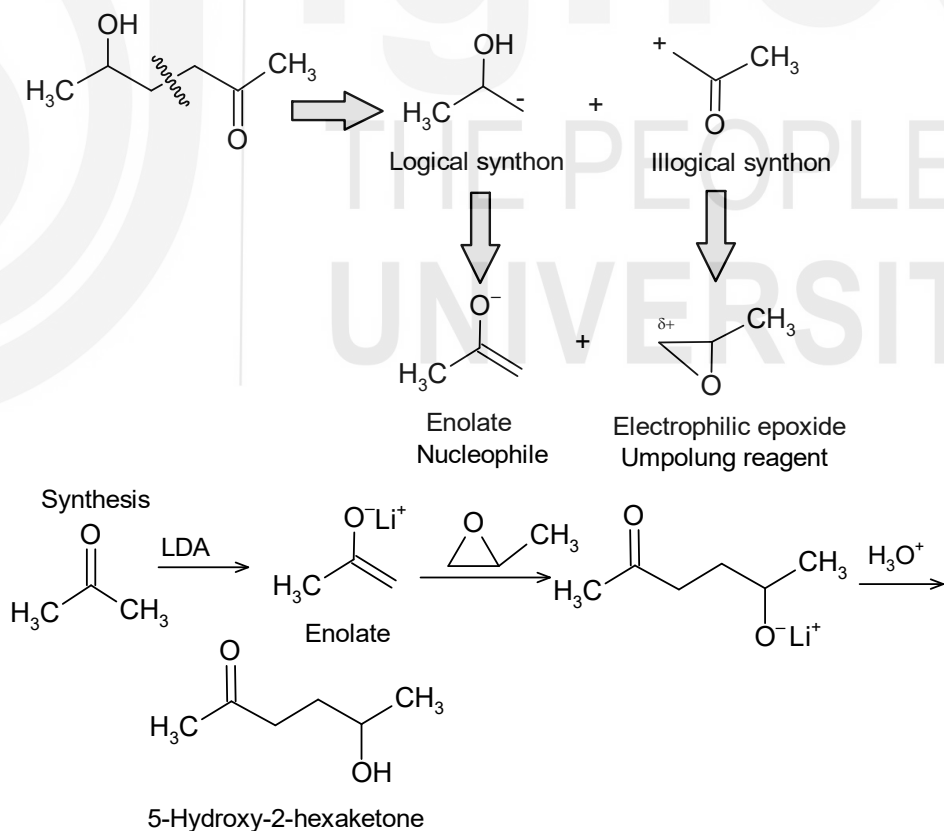
**Reactions of cyclopropyl phosphonium ions:**

## SAQ 7

Complete following reaction:

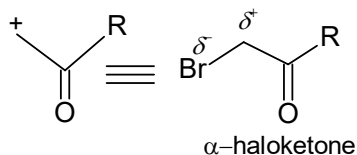
15.2.3  $\alpha$ -Electrophiles

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.



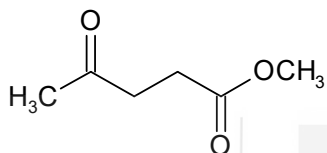
In above reaction unsymmetrically substituted epoxide is an umpolung reagent. Ring opening of such epoxide depends on the reaction conditions. They tend to react with anionic nucleophile at the less hindered carbon of the ring. Under acidic condition more substituted carbon is attacked.  $\alpha$ -

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.

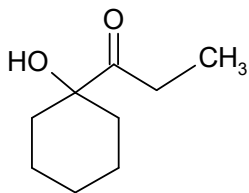


## 15.3 SUMMARY

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

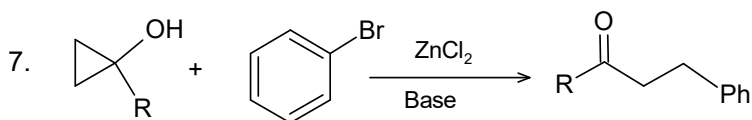
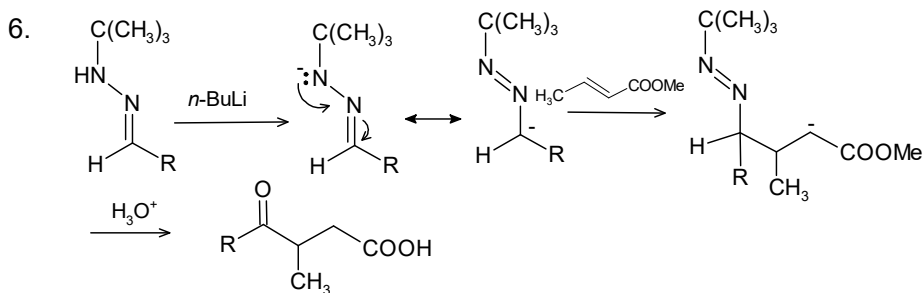
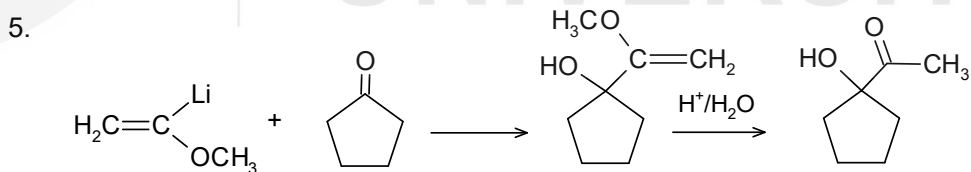
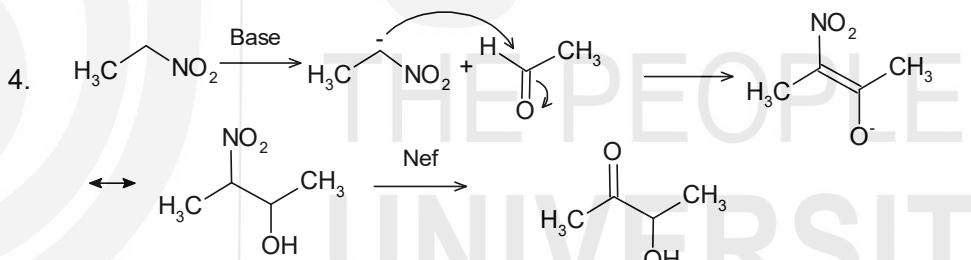
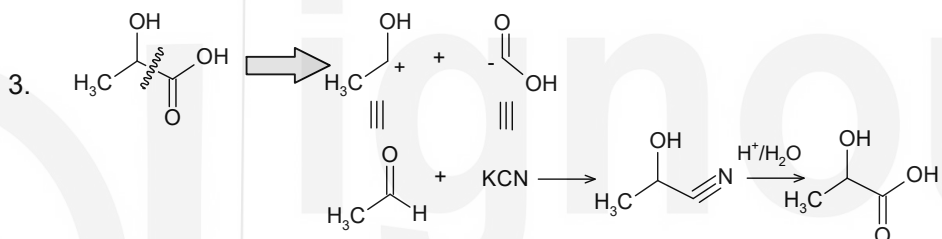
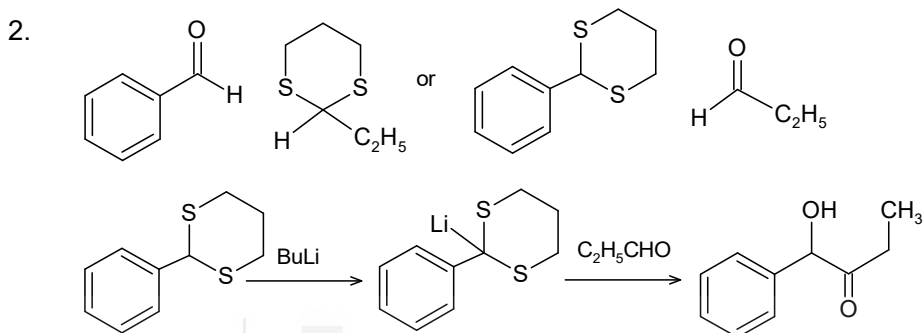
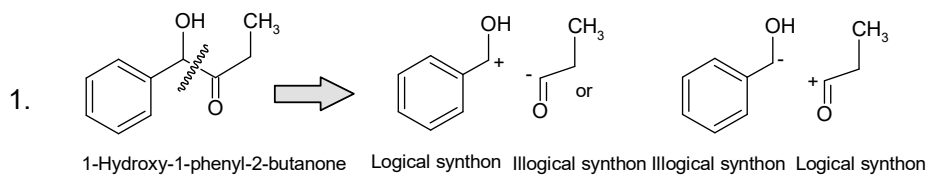
1. Identify synthons of following compound. Write steps involved in its synthesis:



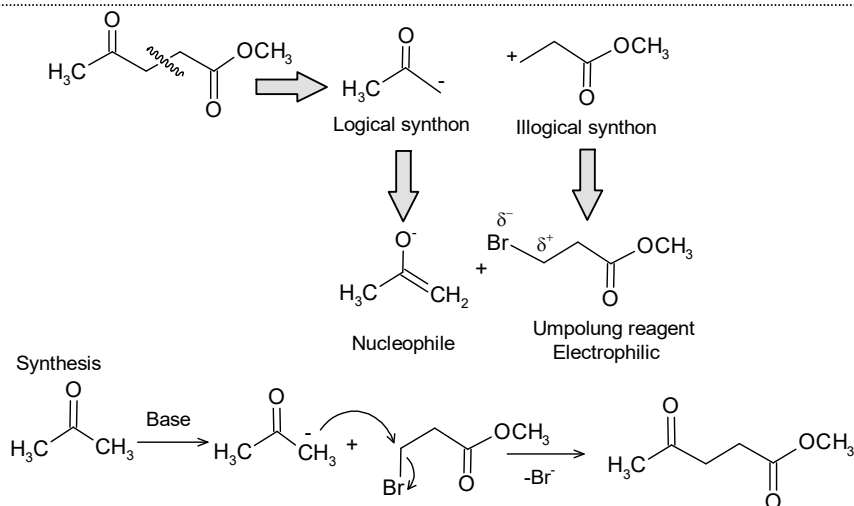
2. Explain the role of sulphur compounds in the preparation of acyl equivalent.
3. How you will convert aldehydes into ketones using 1,3-dithiane.
4. Identify synthons for the synthesis of a  $\gamma$ -hydroxy carbonyl compound. Write the steps involved in its synthesis.
5. Describe homoenolates with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

## 15.5 ANSWERS

## Self Assessment Questions

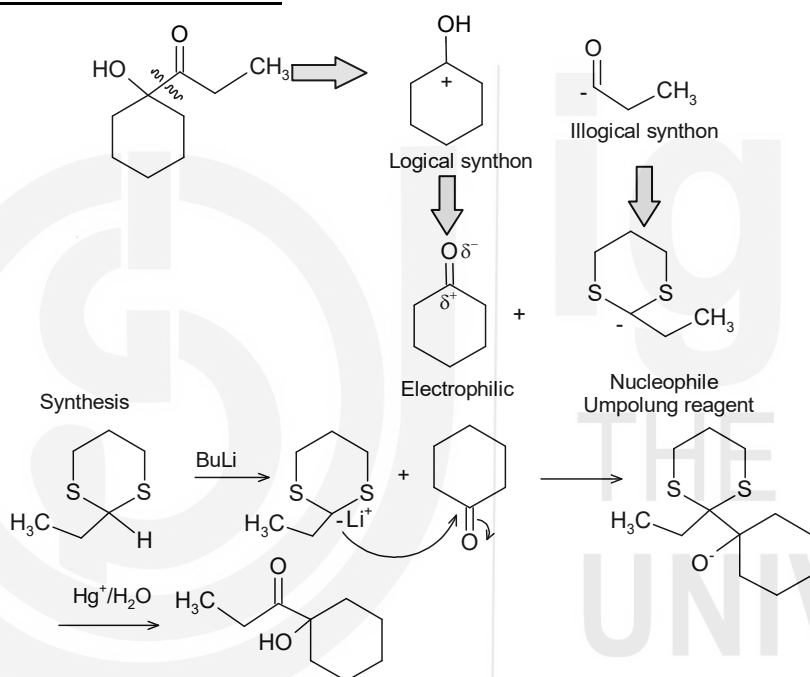


8.

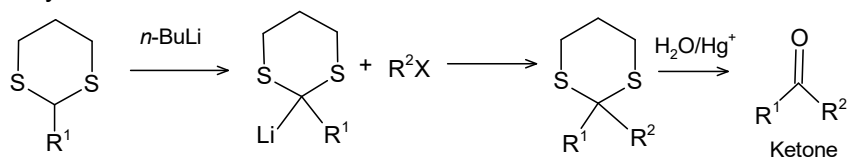


### Terminal Questions

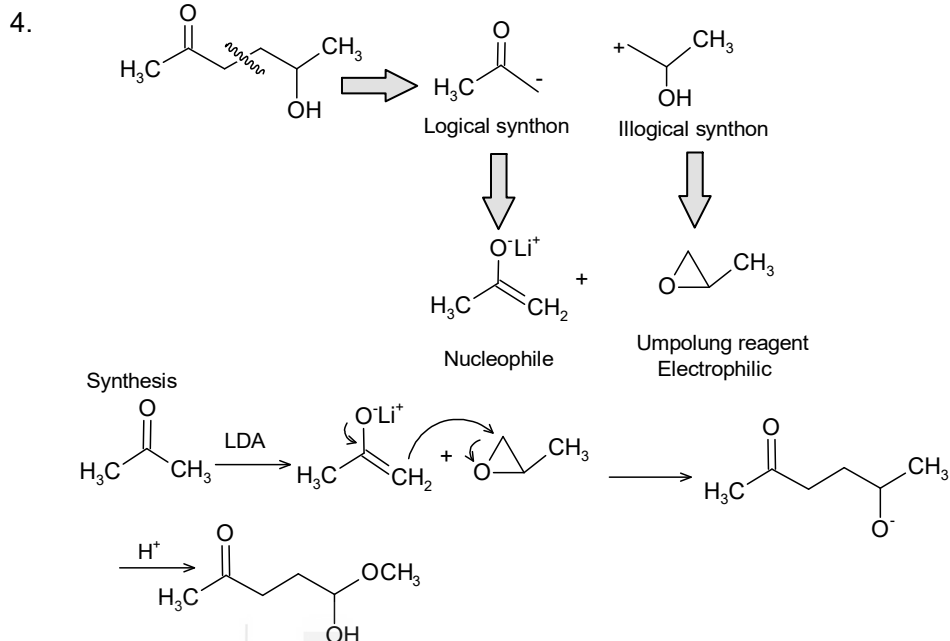
1.



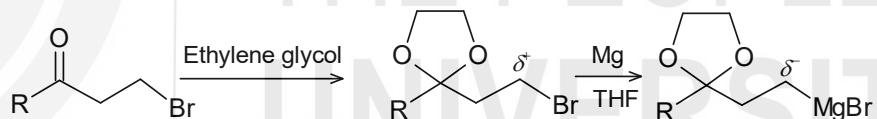
2. Ordinarily the oxygen atom in the carbonyl group is more electronegative than the carbon atom and therefore the carbon atom of carbonyl group acts as an electrophile. When the carbonyl group is converted into a dithiane or a thioacetal, the polarity of carbon atom is reversed. In synthon terminology 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.



$\text{R}^1 = \text{H/R}$



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.

