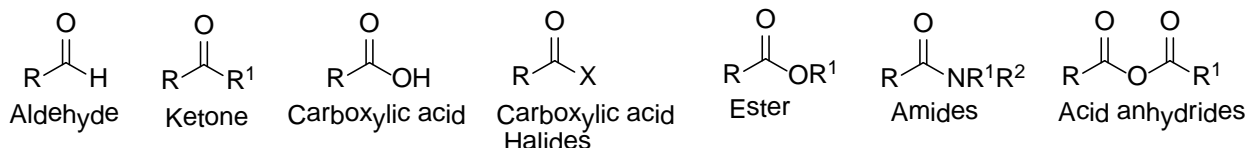


Module 6 Carbonyl Compounds

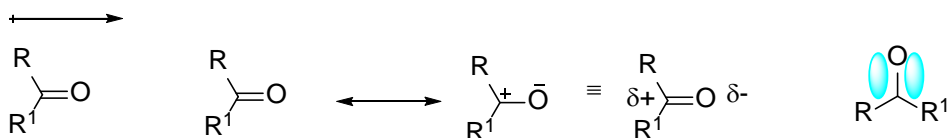
Lecture 13 Carbonyl Compounds I

6.1 Introduction

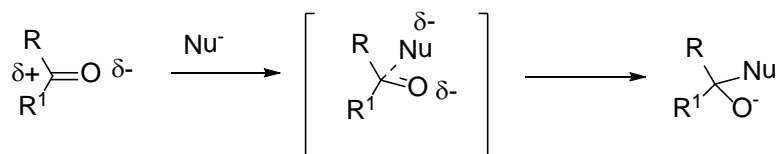
Carbonyl compounds are compounds that contain the carbonyl group, which include aldehydes, ketones, carboxylic acid and its derivatives.



They have dipolar moment as oxygen is more electronegative than carbon. This implies that the carbonyl carbon is slightly positively charged and the carbonyl oxygen is slightly negatively charged. This makes the former susceptible to nucleophilic attack while the latter should be susceptible to attack by electrophiles.



In simple nucleophilic addition reaction, where the rate limiting step is the attack by nucleophile (Nu^-), the rate of the reaction will reduce with electron donating R groups and enhance with electron withdrawing R groups. This is on account of the fact that the positive charge on carbonyl carbon is neutralized progressively on going to the transition state for nucleophilic addition.

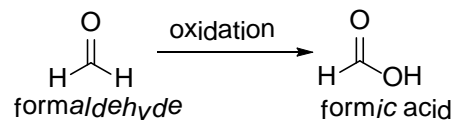


Thus it is further expected that the factors which may cause the delocalization of the positive charge on the carbonyl carbon will render the nucleophilic addition slow. Such factors include conjugation with aromatic rings, double bonds and groups containing unshared pair of electrons. As the addition reaction proceeds, the trigonal carbon is

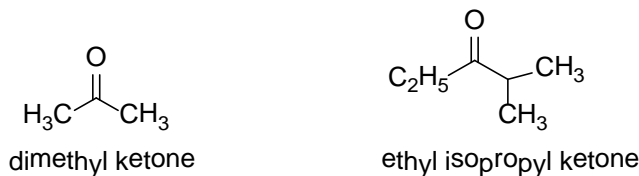
converted to saturated carbon, any increase in steric bulk in the R groups is expected to hinder the rate of the reaction. Thus, carbonyl compounds containing sterically bulky groups tend to react slowly and more reversibly.

6.2 Aldehydes and Ketones

Trivially, aldehydes are usually named after the acids they form on oxidation. The *-ic* in the name of the acid is then replaced by *aldehyde* to get the name of the aldehyde.

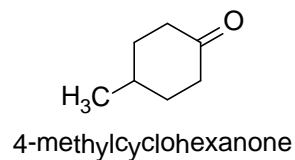
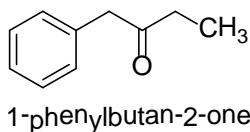
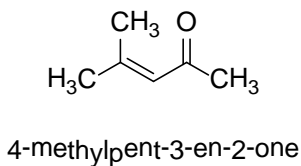
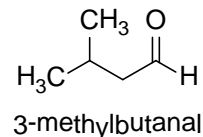
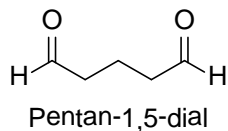
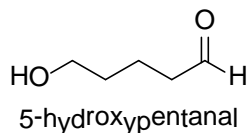


On the other hand, ketones are named by using the names of the groups attached with the carbonyl group and then adding ketone after the name of groups.

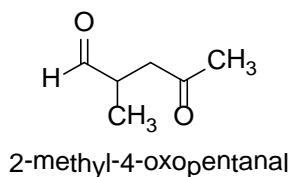


In the *IUPAC* system, aldehydes and ketones are named according to the following procedure:

- The name of the parent hydrocarbon (alkane or alkene or alkyne) is determined while counting the carbonyl carbon as a methyl group for aldehydes and as a methylene group for ketones. The substituents are named as it is done for the hydrocarbon while considering the position of aldehyde as 1-position. For both aldehydes and ketones, the naming is done as in alkanes but keeping in mind the priority sequence and rule of lowest locants.
- The name of the alkane is modified to *alkanal* for an aldehyde. In case of ketones, the name is modified to *alkanone*. The position of the carbonyl group is denoted as numerical prefix to *-one*.



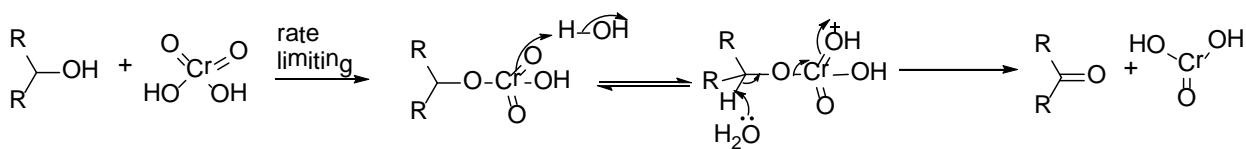
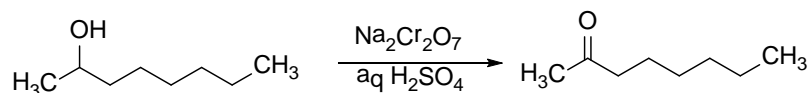
- In cases where both the aldehyde and keto functionalities are present in the same molecule, the aldehyde gets preference and the molecule is suffixed with an –al. The position of the keto group is denoted by a numerical prefix and is denoted by used of the word *oxo*.



6.2.1 Common Methods for Preparation Aldehydes and Ketones

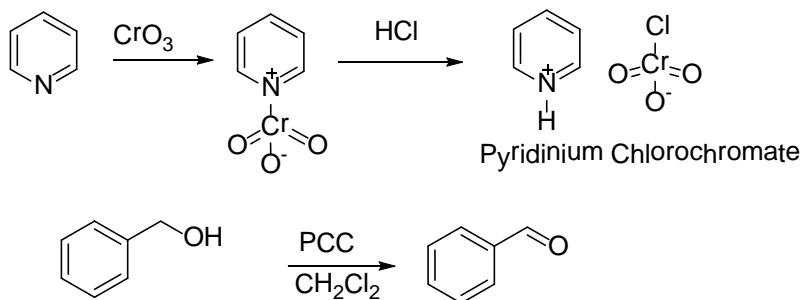
6.2.1.1 Oxidation of Alcohols

Ketones may be prepared by the oxidation of secondary alcohols in the presence of acid dichromate (Scheme 1). The reaction probably proceeds via the rate limiting formation of a chromate ester followed by decomposition of the ester to give the products.



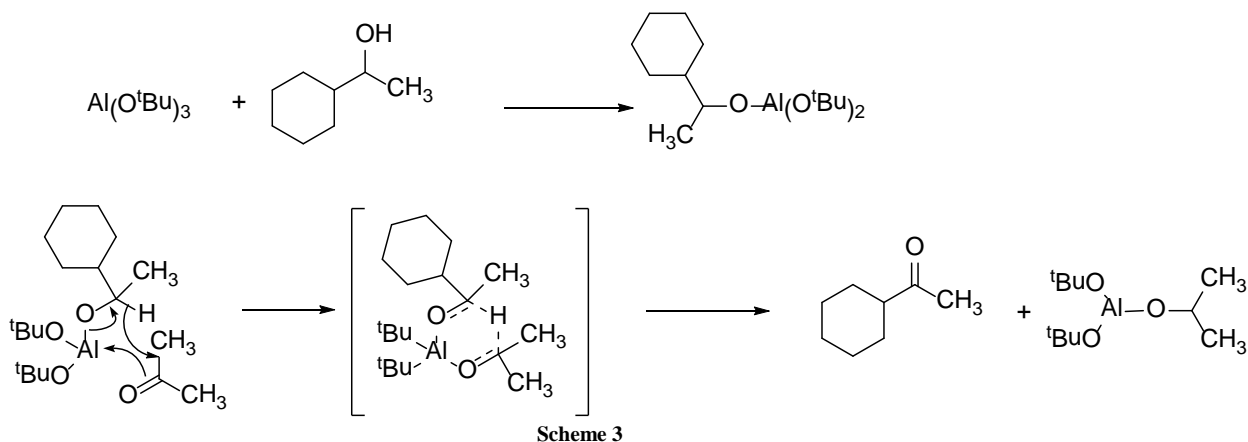
Scheme 1

In case of primary alcohol, this process may lead to oxidation of the alcohol to carboxylic acid. This problem is overcome by attenuating the oxidizing power of chromic acid based reagents to generate a milder oxidizing agent. The two most popular oxidizing agents for oxidizing primary alcohols to aldehydes are *pyridinium chlorochromate* (PCC) and *pyridinium dichromate* (PDC). These reagents are prepared by the treatment of chromic acid with pyridine (Scheme 2).



Scheme 2

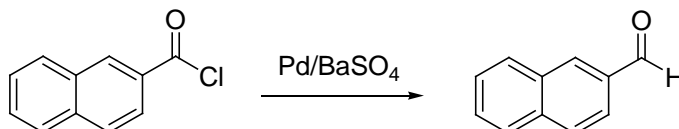
The ketones may also be generated from the secondary alcohols using aluminium t-butoxide in the presence of acetone (Scheme 3). The secondary alcohol is refluxed with the reagent in an excess of acetone. This reagent is particularly helpful in oxidation of unsaturated alcohol as only the alcoholic OH is oxidized.



Scheme 3

6.2.1.2 Reduction of Acid Chloride

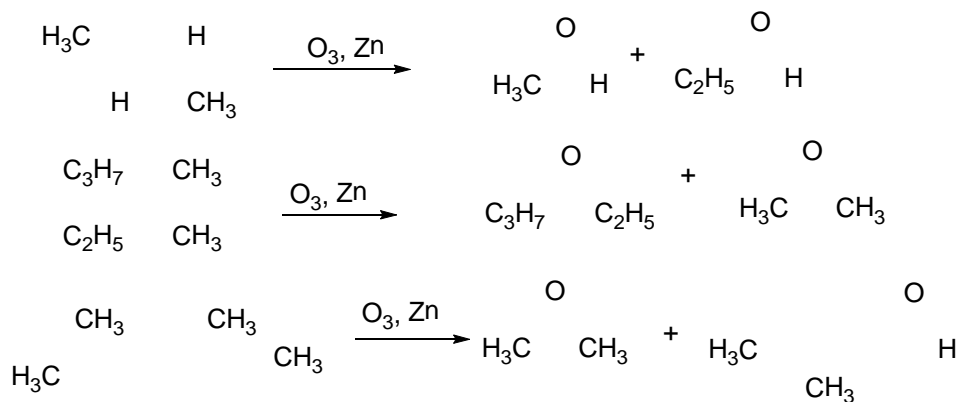
Aldehydes can be prepared by the reduction of acid chloride with hydrogen in xylene using a palladium catalyst suspended on barium sulphate (*Rosenmund reduction*) (Scheme 4). This process demonstrates the control of chemoselectivity by poisoning of the catalyst. The role of barium sulphate is to prevent the reaction from proceeding further to alcohol.



Scheme 4

6.2.1.3 Oxidative Cleavage of Alkenes

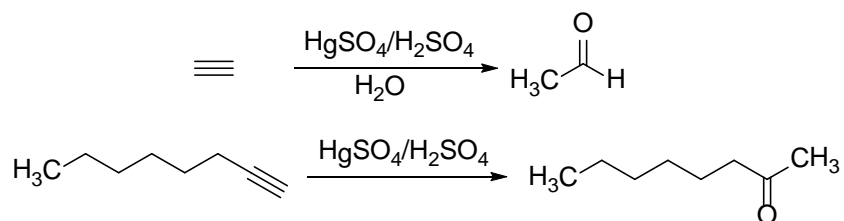
Both aldehydes and ketones may be formed by ozonolysis of suitable alkenes (Scheme 5). The ozonolysis of alkenes of the type RCH=CHR¹ leads to the formation of aldehydes while the tetrasubstituted alkenes will give ketones as product.



Scheme 5

6.2.1.4 Hydration of Alkynes

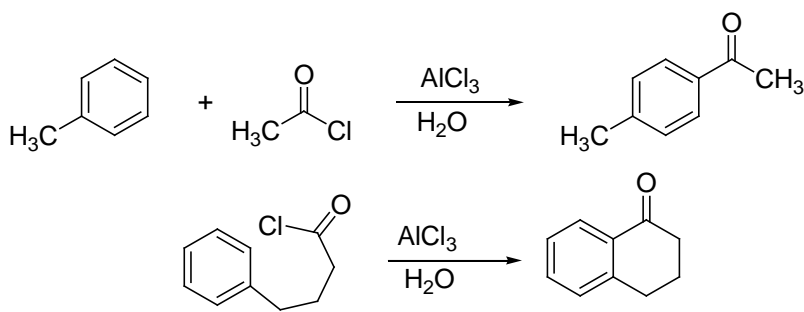
The hydration of alkynes by the mercuration-demercuration procedure can be utilized to prepare acetaldehyde and ketones (Scheme 6). The hydration of acetylene gives acetaldehyde while the hydration of any other alkyne leads to formation of ketones.



Scheme 6

6.2.1.5 Acylation of Arenes

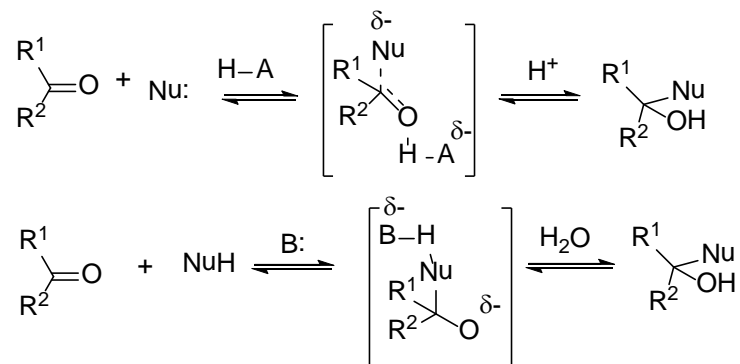
Friedel Craft acylation may be used to prepare alkyl aryl ketones or diaryl ketones (Scheme 7). In this process, an arene is usually treated with an acid halide or acid anhydride in the presence of a Lewis acid catalyst. This reaction is an example of aromatic electrophilic substitution.



Scheme 7

6.2.2 Reactions of Aldehydes and Ketones

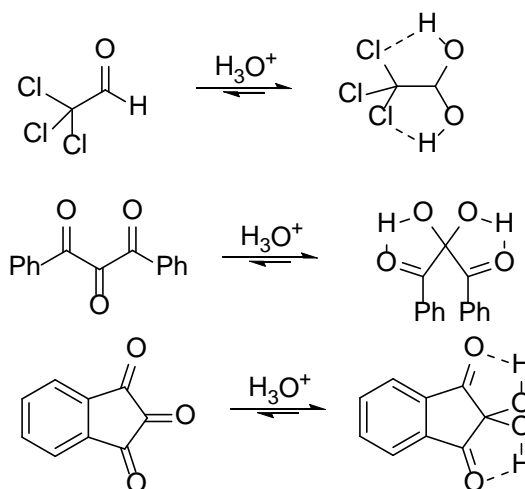
The nucleophilic addition to the carbonyl group is the most important reaction of aldehydes and ketones. Several nucleophiles such as water, alcohols, cyanide etc attack the carbonyl carbon. But, it should be noted that all adducts of this addition reaction are not stable and many reaction are readily reversible. The reaction can be catalyzed by the presence of both acids and bases. The mechanisms are given below.



Since in both cases, the amount of negative charge increases in transition state, so it is expected that electron withdrawing substituents in the carbonyl compound will enhance the rate of reaction.

6.2.2.1 Hydration

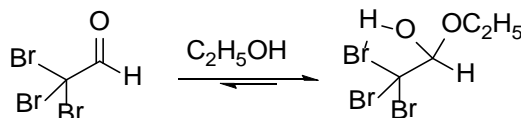
The addition of water to aldehydes and ketones seems insignificant as the reaction is usually reversible with the equilibrium lying largely to the left. However, in some cases the hydrate may be stabilized due to various reasons. Thus, powerful electron withdrawing effect on the carbonyl carbon may facilitate hydration thereby moving the equilibrium to the right. Thus, trichloroethanal, diphenylpropantrione and ninhydrin readily form their corresponding hydrates (Scheme 9). Further stabilization is also provided by the hydrogen bonding interactions.



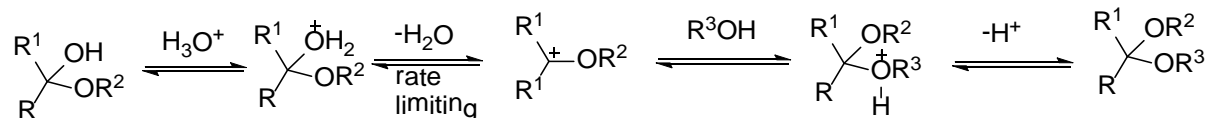
Scheme 9

6.2.2.2 Acetal Formation

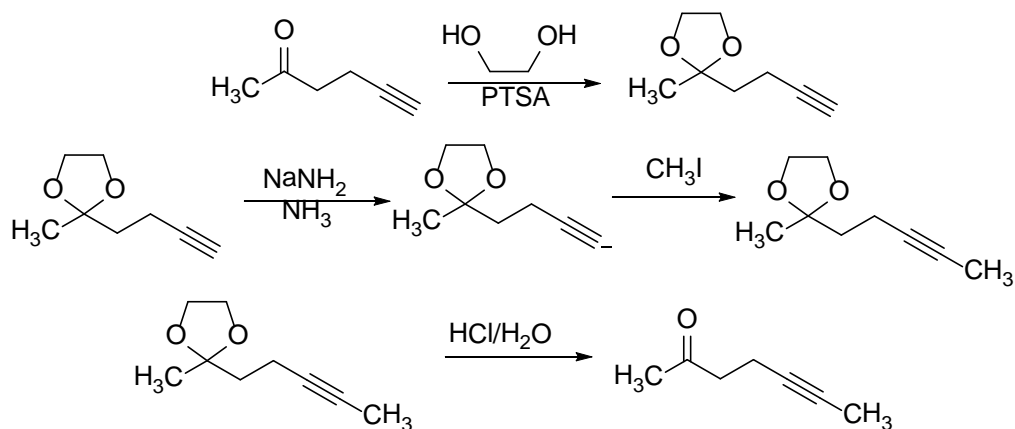
The reactions of aldehydes with one equiv of alcohols yield hemiacetals. The reaction follows the same pattern as with hydration and stable hemiacetals can be isolated by using aldehydes possessing electron withdrawing groups.



Hemiacetals may react with one more equiv of alcohol to form acetals. The reaction requires specific acid catalysis indicating that the loss of water as the slow rate determining step.



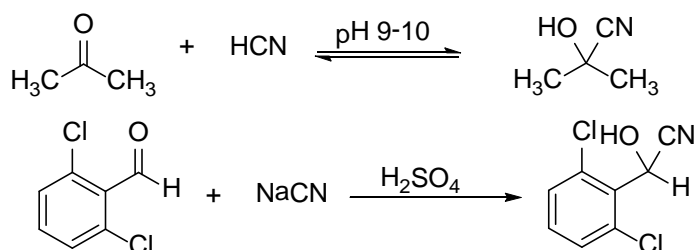
This reaction is not very feasible with ketones however, ketones do react with 1,2-diols to form cyclic acetals (Scheme 10). The fact that the reaction can be made to go with 1,2-diols but not with simple alcohols (ROH) is due to the entropy factor for the former being more favourable than that for the latter, which involves a decrease in the number of molecules on going from starting material to product. The acetals are not susceptible to hydrolysis by a base and thus are used as a protecting group.



Scheme 10

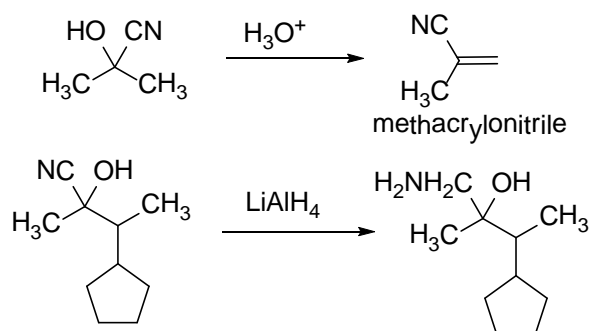
6.2.2.2 Cyanohydrin Synthesis

The addition of cyanide leads to the formation of cyanohydrins, a class of molecules with interesting synthetic application. The formation of cyanohydrin is also a reversible reaction and the equilibrium can be shifted to the right by using an acid or base as catalyst. In this case the rate limiting step is the attack of the nucleophile. This reaction proceeds quantitatively for aldehydes and simple ketones but not so for aryl alkyl ketones and diaryl ketones (Scheme 11).



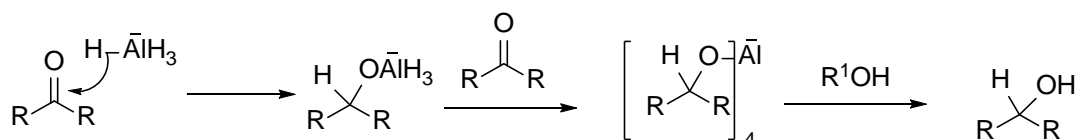
Scheme 11

As told above the cyanohydrin moiety is of synthetic importance and it can be easily transformed into other important functionalities. Thus, the OH group can undergo several functional group transformations such as oxidation and dehydration. Similarly, the cyano group can be reduced to amines or oxidized to carboxylic acids.

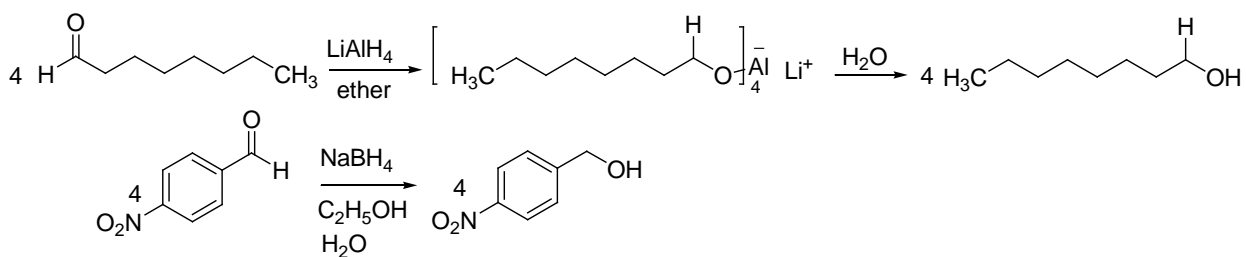
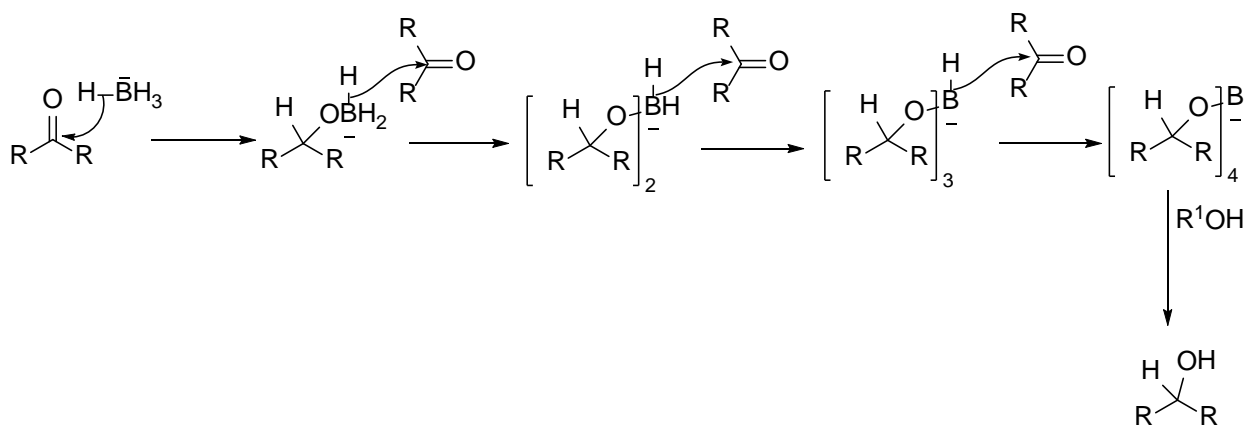


6.2.2.3 Reduction

The attack of hydride ion on the carbonyl group, i.e., the reduction of aldehydes and ketones may be seen as nucleophilic addition but the actual pathway is quite complicated. Lithium aluminium hydride is a very powerful reducing agent and easily reduces both aldehydes and ketones to their corresponding alcohols. The reaction involves irreversible hydride transfer to the carbonyl compound to form an aluminium complex (1) which then further reacts with another three molecules of ketone to form the complex (2) which on treatment with aprotic solvent gives the product.



A much weaker reducing agent is sodium borohydride which may be used in protic solvents. It is less reactive than lithium aluminium hydride thereby allowing more selective reductions. The pathway for reduction is however similar to that of lithium aluminium hydride (Scheme 12).



Scheme 12

There are variety of reducing agents can be derived from these hydride ion donors. Several reducing agents are known tailor made to suit the purpose of selective reduction of one group while keeping the other unaffected.

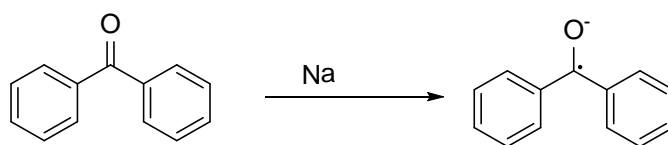
In the above mentioned reduction protocols, the transfer of hydride ion is irreversible but a reversible hydride transfer to a carbonyl compound is also possible. This reaction known as *Meerwein-Pondorf-Verley* reduction is similar to the previously mentioned Oppenauer oxidation protocol for preparation of ketones.

Module 6 Carbonyl Compounds

Lecture 14 Aldehydes and Ketones I

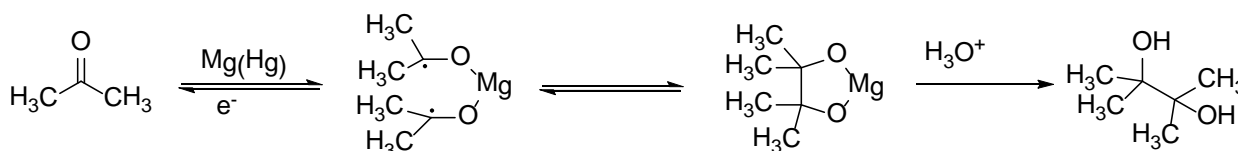
6.2.2.3 Reduction

The reduction of aldehydes and ketones may be carried out by electrons generated from more electropositive elements under certain conditions (Scheme 1). Such electrons may act as a nucleophile and add to the carbonyl group to yield a radical anion often as ion pair with the metal cation. The blue colour generated by the aromatic ketones on reaction with sodium in the absence of air is an example of formation of such a radical.



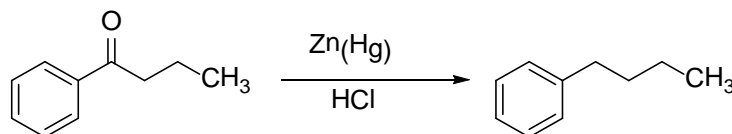
Scheme 1

The radical so formed can couple with a similar radical to form a 1,2-diol (pinacol) (Scheme 2). The reaction is however usually carried out using amalgamated magnesium.



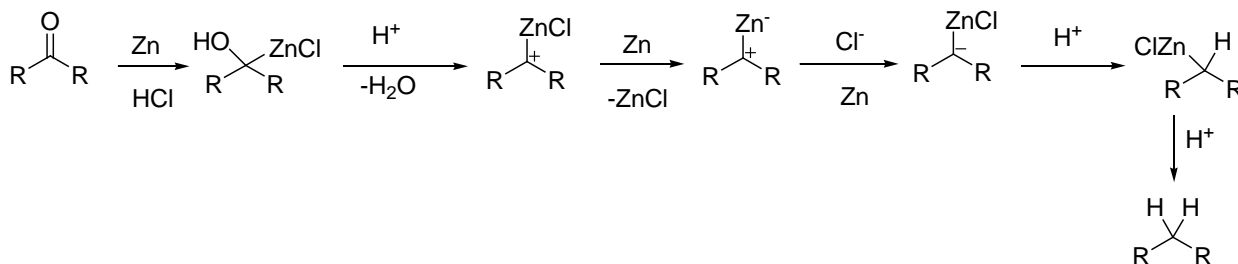
Scheme 2

Another example of this phenomenon is the famed *Clemmensen reduction* (Scheme 3). In this reaction, a ketone (usually) is treated with amalgamated zinc and hydrochloric acid.



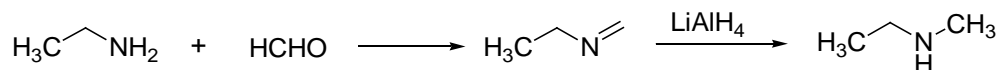
Scheme 3

Several pathways have been proposed for this reaction. However, the understanding of the mechanism of this reaction is still unclear. A probable mechanism is depicted in Scheme 4.



Scheme 4

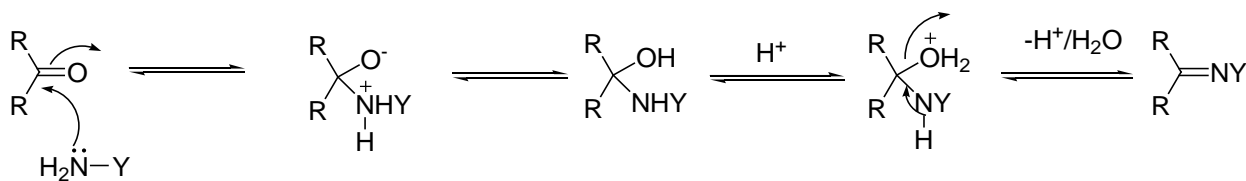
Another application of this protocol is methylation of primary amines. The alkylation of amine often leads to polyalkylated amines. In case of methylation, the methylation can be stopped after one methyl group is added to the amine by treating it with formaldehyde to form an enamine followed by reduction (Scheme 5).



Scheme 5

6.2.2.4 Condensation

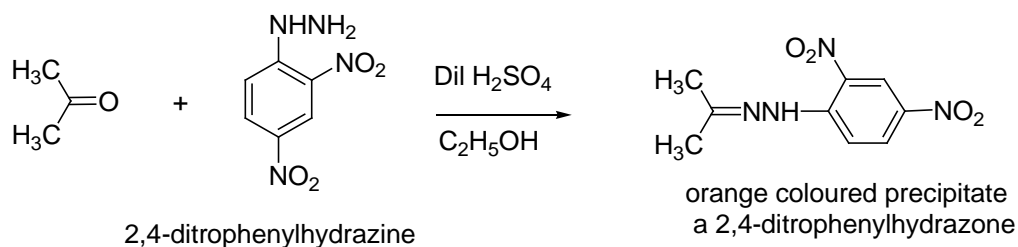
The aldehydes and ketones undergo another class of reactions which may be called addition elimination reaction or condensation reactions. In these reactions, they react with a reagent to form an adduct, which may then under suitable conditions undergo elimination of a water molecule to form the product. The most common reactions involve an attack by nucleophiles like hydroxylamine, phenyl hydrazine and its derivatives and semicarbazide and its derivatives. The general pathway for this reaction may be given as:



The strong nucleophiles such as hydroxylamine do not require assistance by any catalyst, however, weaker nucleophiles such as semicarbazone and its derivatives require general acid catalysis to activate the keto group. Thus, it may be expected that in basic and neutral solutions, the elimination of water is the rate limiting slow step which in an acidic solution, the attack of the nucleophile is the rate limiting step. The table below gives the names of the products of some common ammonia derivatives and ketones.

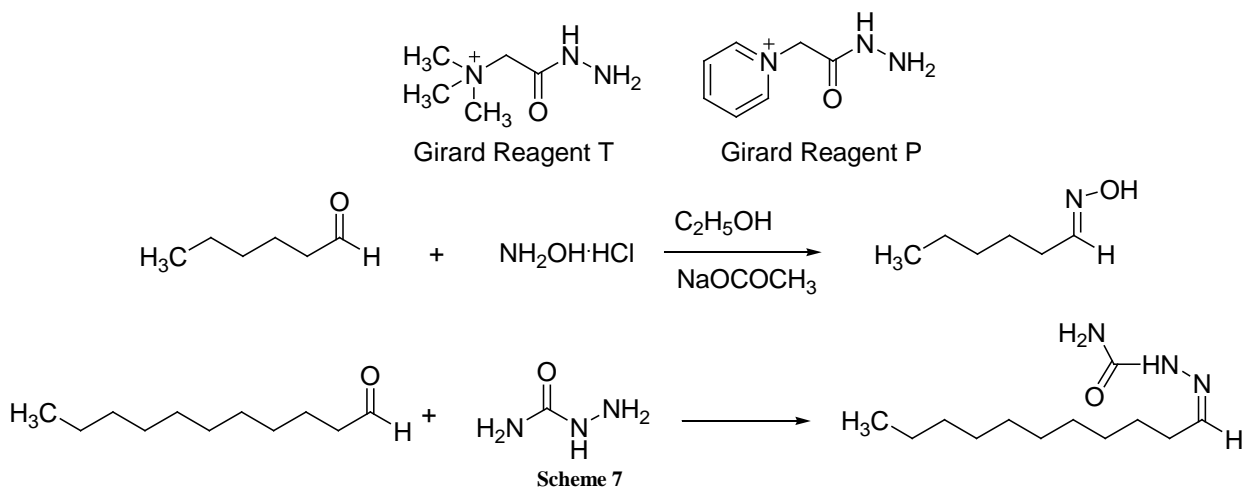
Ammonia derivative	Carbonyl derivative
Hydroxylamine	Oxime
Hydrazine	Hydrazone
Semicarbazide	Semicarabazone

The most famous application of this category is the formation of 2,4-dinitrophenylhydrazone derivatives of ketones which are used to determine the presence of keto functionality (Scheme 6).

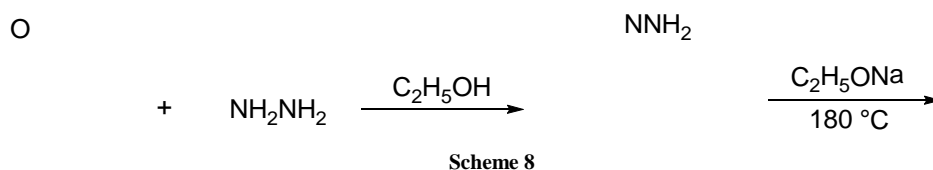


Scheme 6

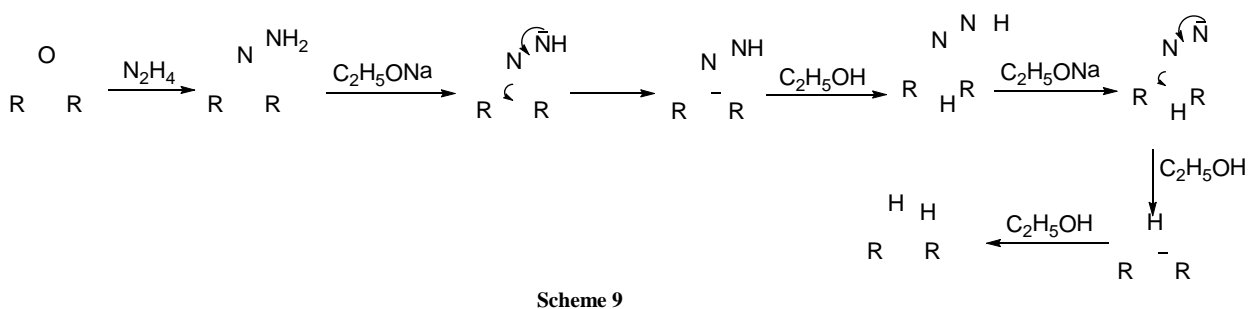
Similarly, Girard's reagent T and Girard's reagent P are used in purification of carbonyl compounds (Scheme 7).



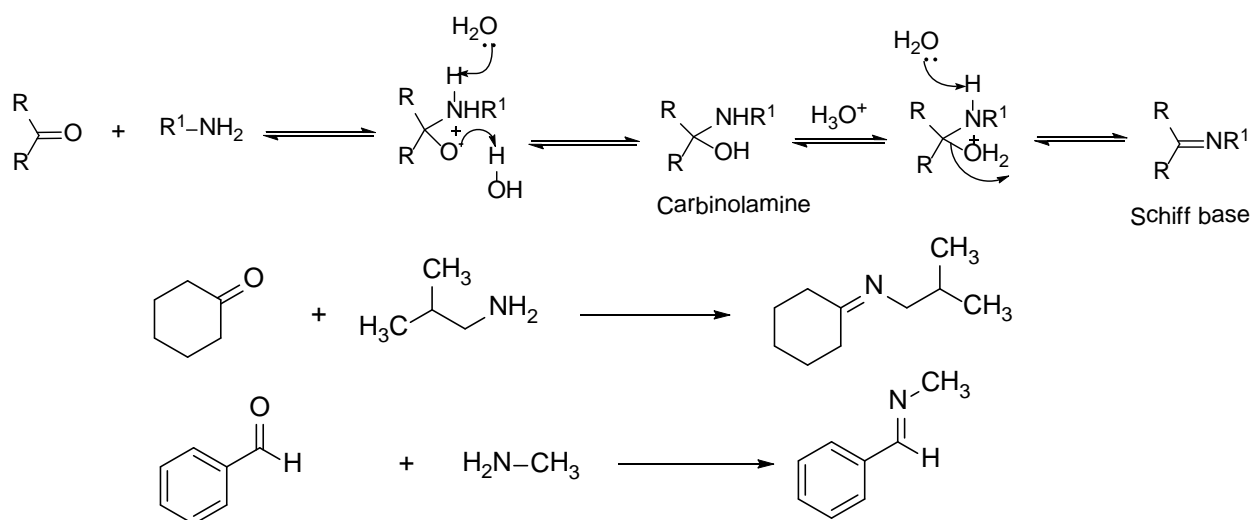
The *Clemensen* reduction discussed previously cannot be used acid sensitive carbonyl compounds. A method known as *Wolff Kishner* reduction may be employed in such circumstances (Scheme 8). The protocol involves the synthesis of the corresponding hydrazone from the ketone followed by reduction.



The reaction is believed to proceed in the following manner (Scheme 9).

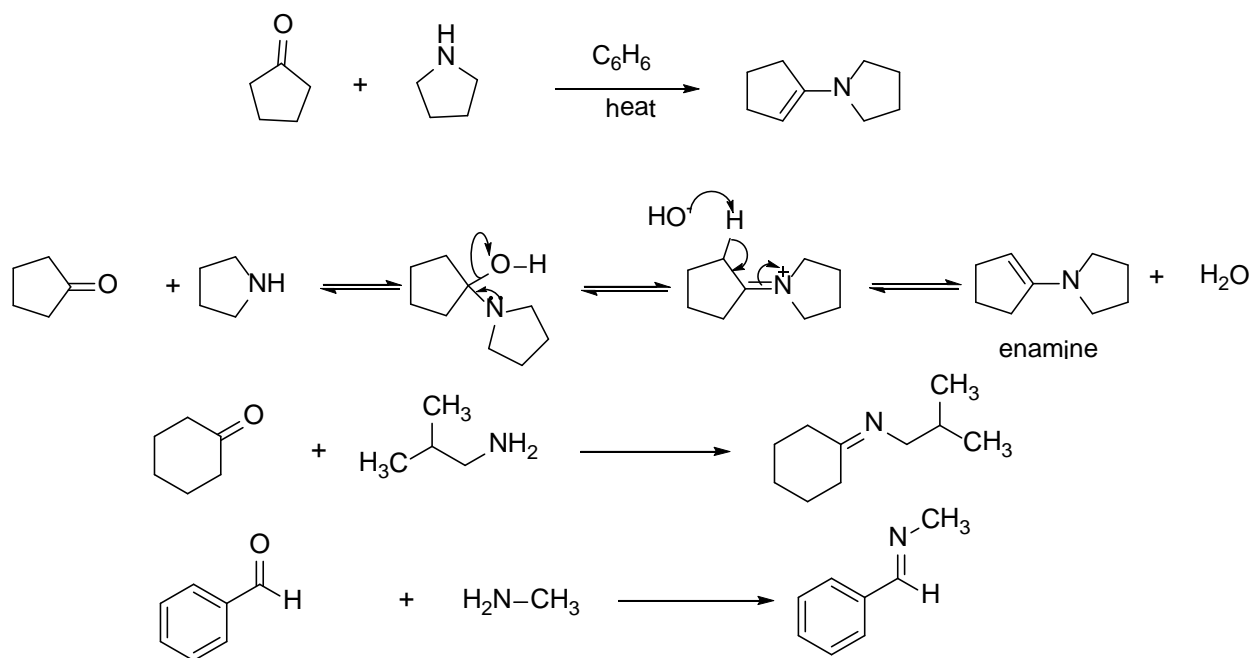


Another type of reactions is the reaction of aldehydes and ketones with substituted amines (Scheme 10). Primary amines react with carbonyl compounds to give an imine (also called Schiff base). As shown above, the initial addition of the amine generates a carbinol amine which then undergoes β -elimination to give the imine as product. The reaction requires acid catalysis for the elimination step. However, the pH of the solution has to be maintained properly since a very low pH will result in protonation of the nucleophile amine.



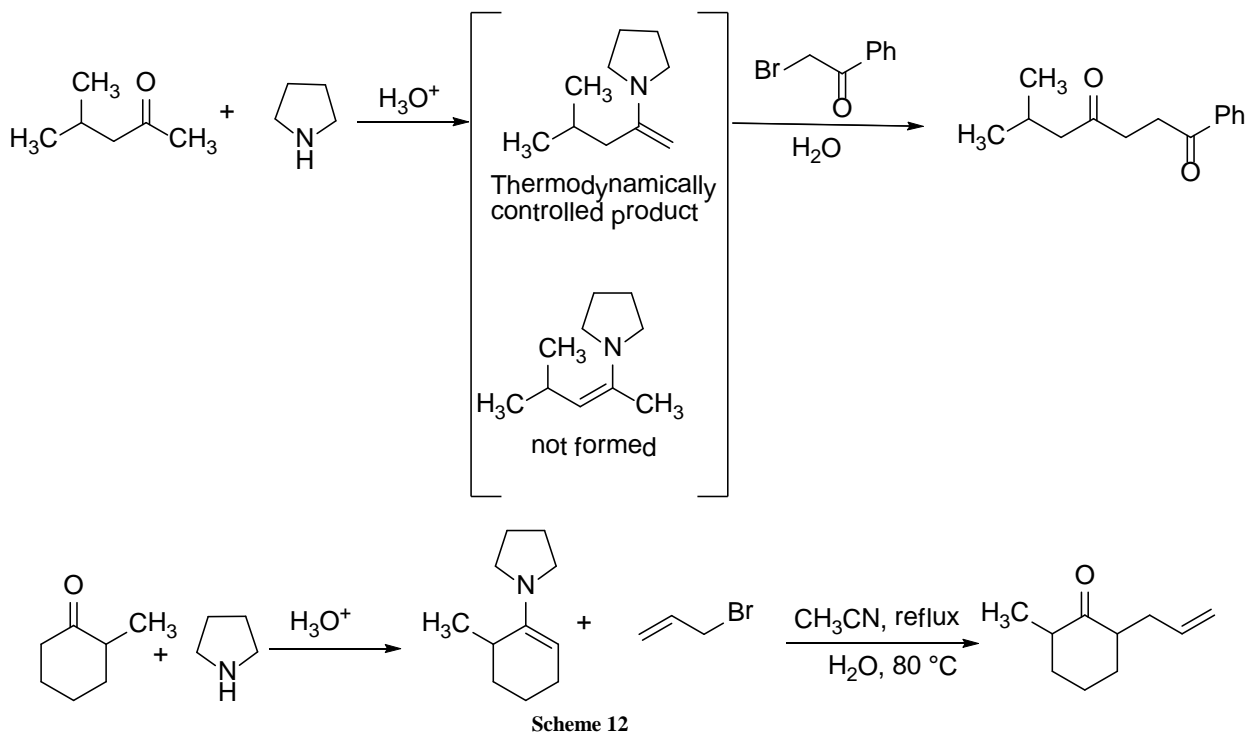
Scheme 10

Secondary amines may also participate in this reaction (Scheme 11). They add to aldehydes and ketones to form a carbinol amine which on dehydration leads to formation of an enamine. The pathway of the reaction is similar to the pathway shown above for the reaction of ketones with primary amines. The formation of enamine is of some synthetic importance as it is commonly used as an intermediate in many synthetic protocols.

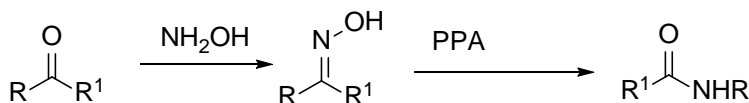


Scheme 11

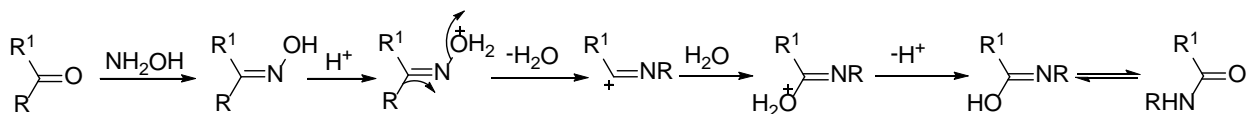
One of the uses is in the selective alkylation as shown below. In this case, only the least hindered enamine is formed. This is because the enamine formation is thermodynamically controlled and, hence, the less substituted enamine is formed slowly. Thus, the alkylation takes place on that side only (Scheme 12).



The hydrazone derivatives of ketones undergo a rearrangement to form N-substituted amides in the presence of acidic reagents like H_2SO_4 , PCl_5 , BF_3 etc. This is known as **Beckmann** rearrangement (Scheme 13).



The reaction is believed to proceed in the following manner. It is the group *trans* to hydroxyl group that always migrates under these conditions (Scheme 14).

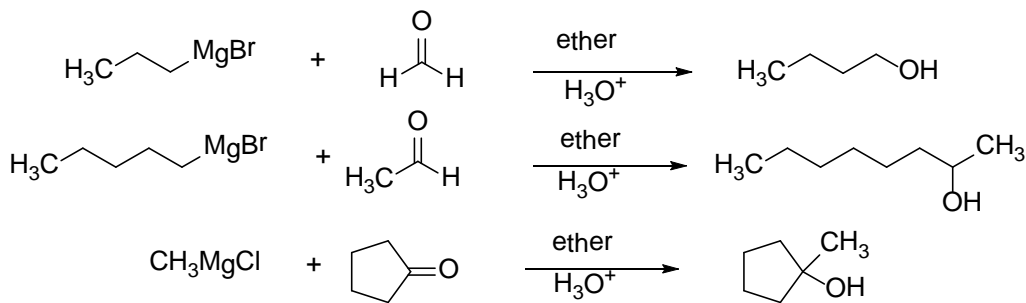


Scheme 14

6.2.2.5 1.2-Addition Reaction

The reaction of carbonyl compounds with organometallic reagents is of unique importance in organic chemistry. These organometallic reagents are nucleophilic in nature and, thus, can attack on the carbonyl carbon. Though almost all classes of carbonyl compound react with aldehydes and ketones with varying results, in this section, only the reactions of aldehydes and ketones are discussed here.

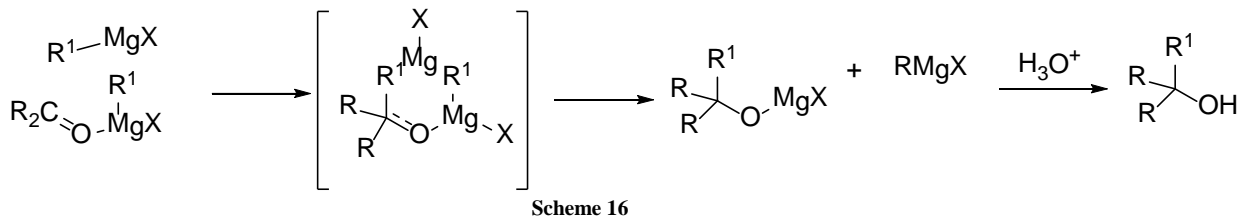
Both aldehydes and ketones react with Grignard reagents to form an alcohol. Formaldehyde forms a primary alcohol as a result of this reaction while the rest of the aldehydes all form secondary alcohols. Similarly, the ketones form tertiary alcohols (Scheme 15).



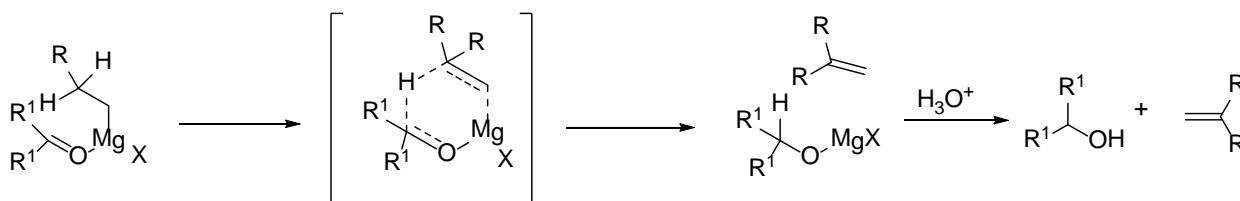
Scheme 15

The actual composition of the Grignard reagents and the pathway of the reaction is a debatable issue, but it is clear that the Grignard reagents usually form associated structures among themselves (Scheme 16). This has been found to depend on the nature

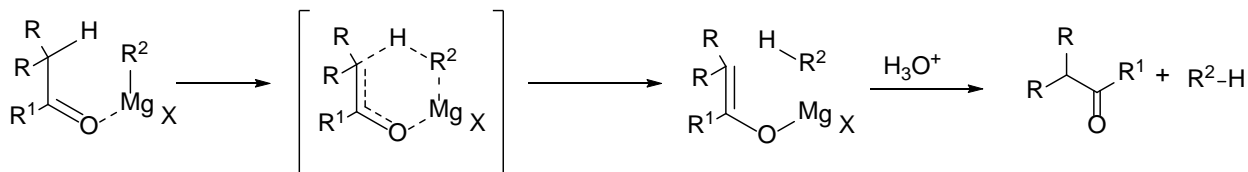
of the groups in the Grignard reagent as well as the solvent. It is believed that the reaction proceeds through a cyclic transition state involving the Grignard reagent, the carbonyl compound and the solvent molecules.



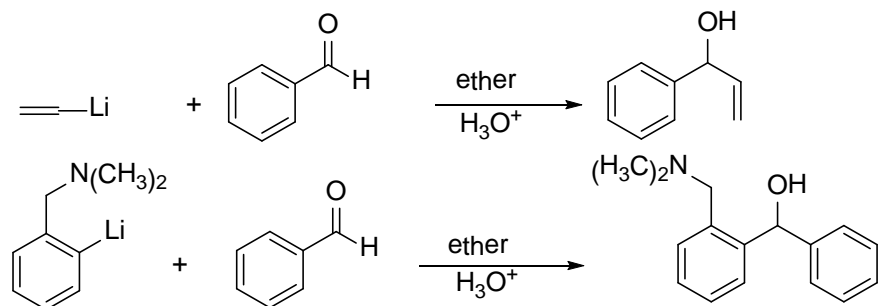
However, when there are hydrogen atoms on the β -carbon of the Grignard reagent, then they tend to reduce the carbonyl compound, they themselves being oxidized to alkenes.



Similarly, sterically hindered ketones having hydrogen atoms on their α -carbons tend to be converted to enols, the Grignard reagent is reduced to form an alkane.



Another class of widely used organometallic reagents which act as a nucleophile are the organolithium reagents. The organolithium reagents are usually harder bases than the Grignard reagents and therefore show a greater reactivity.



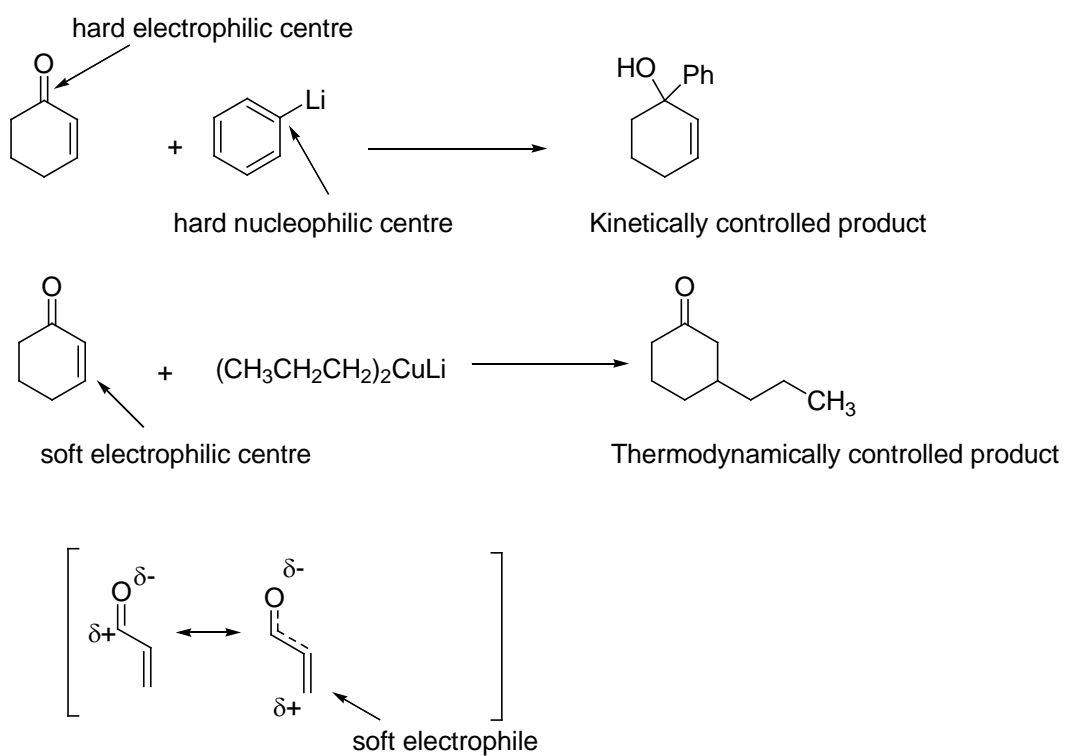
However, due to their higher reactivity, they are not prone to the side reactions occurring due to steric crowding as in Grignard reagents.

Module 6 Carbonyl Compounds

Lecture 15 Aldehydes and Ketones II

6.2.2.6 1,4-Addition Reaction

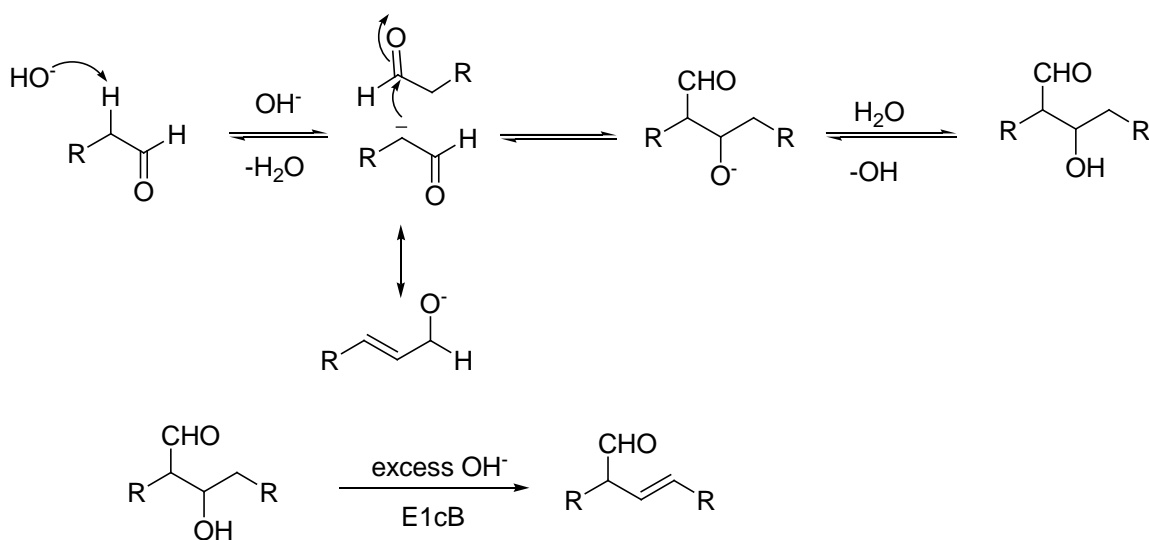
The organocopper reagents are much softer nucleophiles and when they are used as a nucleophile for an α,β -unsaturated carbonyl compound, it results in not a 1,2 addition but rather 1,4-addition (Scheme 1). This is explained by the thermodynamic control of the reaction. A hard nucleophile like organolithium reagents instead react under kinetic control.



Scheme 1

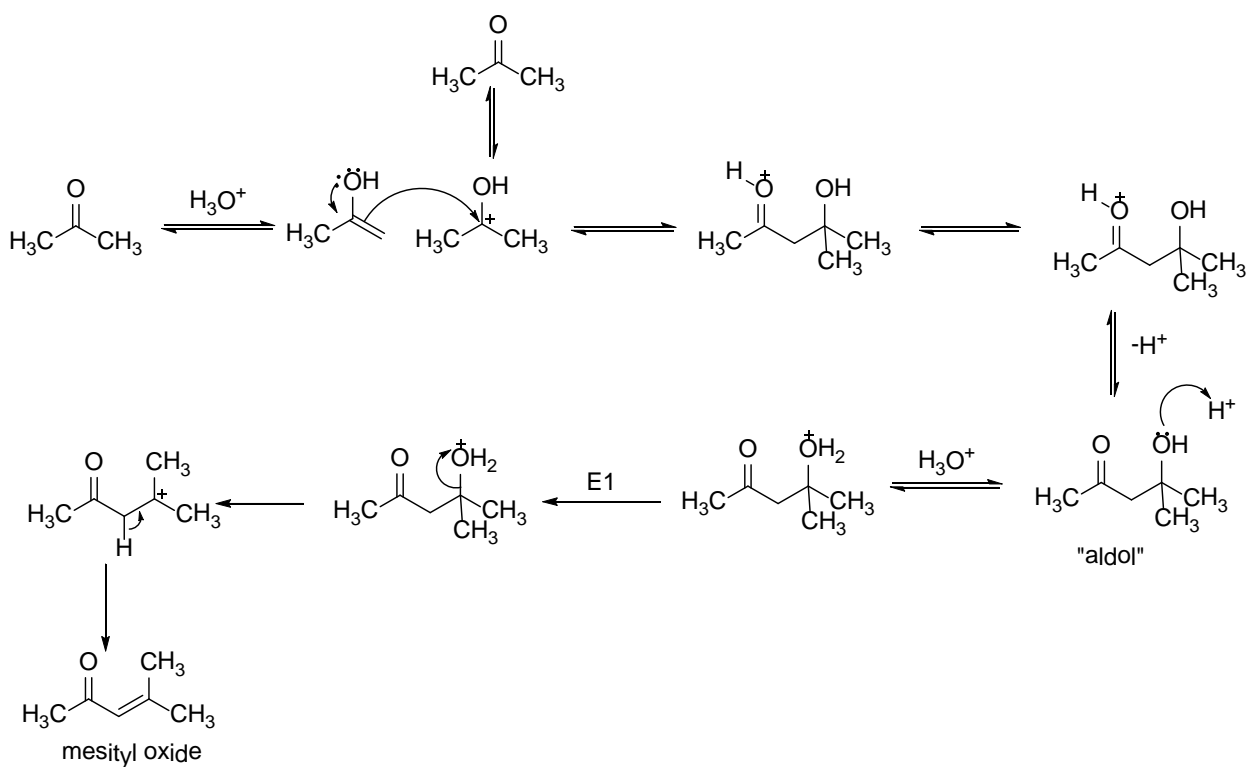
6.2.2.7 Aldol Reactions

This reaction also involves the attack of a nucleophile, but the nucleophile is a carbanion generated from an aldehyde or ketone. This evidently requires a base to abstract a proton from the carbonyl compound to generate the carbanion. The carbanion so generated may now attack another molecule of aldehyde or ketone to generate a β -hydroxy carbonyl compound which may be dehydrated under suitable conditions to generate an α,β -unsaturated carbonyl compound (Scheme 2). The reaction is almost complete for aldehydes but in case of even simple ketones, the reaction almost completely lies to the left. The reason for such an observation lies in the reversibility of the formation of the carbanion. In such cases, where the attack of the carbanion the carbonyl compound is slower than the reprotonation of the carbonyl compound, the product will be formed only in small amounts. The reaction can be made to proceed quantitatively, if one of the products is removed continuously thereby pulling the reaction to the right.



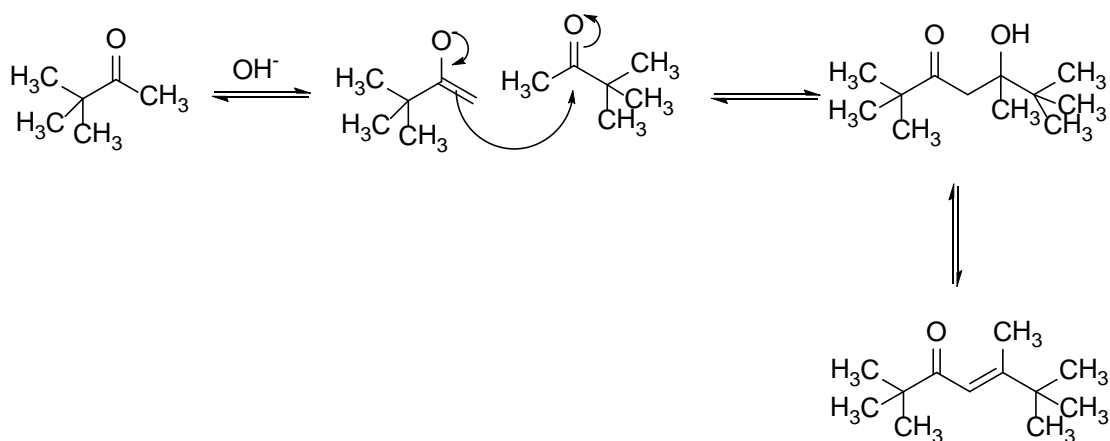
The β -hydroxy compound so formed may undergo elimination in the presence of excess of base to generate an α,β -unsaturated carbonyl compound. The reaction is evidently dependent on both the concentration of the base and the β -hydroxy carbonyl compound and is found to proceed by E1cB pathway.

It is to be noted that this reaction is essentially a reaction involving the enolate ions. Since enol formation from an aldehyde or ketone is feasible even in acid solution, so this reaction can be carried out using an acid as a catalyst. The reaction now follows a completely different pathway and almost always leads to the formation of the dehydrated product. Here, the carbonyl compound forms an equilibrium concentration of enol which then attacks the protonated form of the carbonyl compound to give the “aldol” which may undergo elimination by E1 pathway to give the α,β -unsaturated carbonyl compound (Scheme 3).



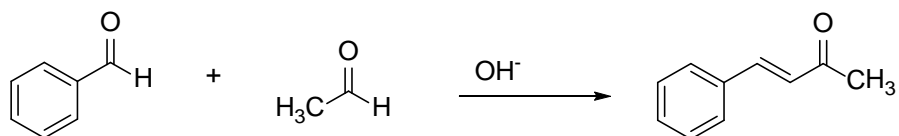
Scheme 3

A further complication may arise on subjecting unsymmetrical ketones to aldol reaction. Now, there are two potential enols/enolates that could be formed and hence a mixture of products will be obtained. These rules out any synthetic utility for such reaction. However, in certain ketones, one side may be blocked by group so that it can enolize in one specific direction. Some examples of such ketones are t-butyl ketones, acetophenone and its derivatives and lactones (Scheme 4).



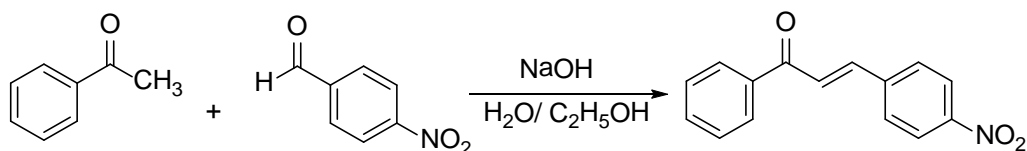
Scheme 4

An aldol reaction may also be carried out between an aldehyde and a ketone or between two different aldehydes and ketones. Such a reaction is called a cross aldol reaction. Now in cases where both the coupling partners possess α -H are not of any synthetic value as four different products may be produced. However, where one of the coupling partners is only capable of enolizing and is more electrophilic than the other partner, the aldol reaction may be fruitful in giving only one preferential product. Thus, the **Claisen-Schmidt** condensation of aromatic aldehydes with aliphatic aldehydes or methyl ketones using a base may be considered as of this type (Scheme 5).

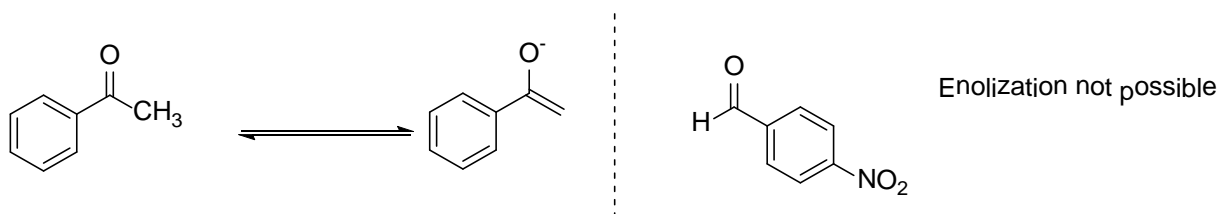


Scheme 5

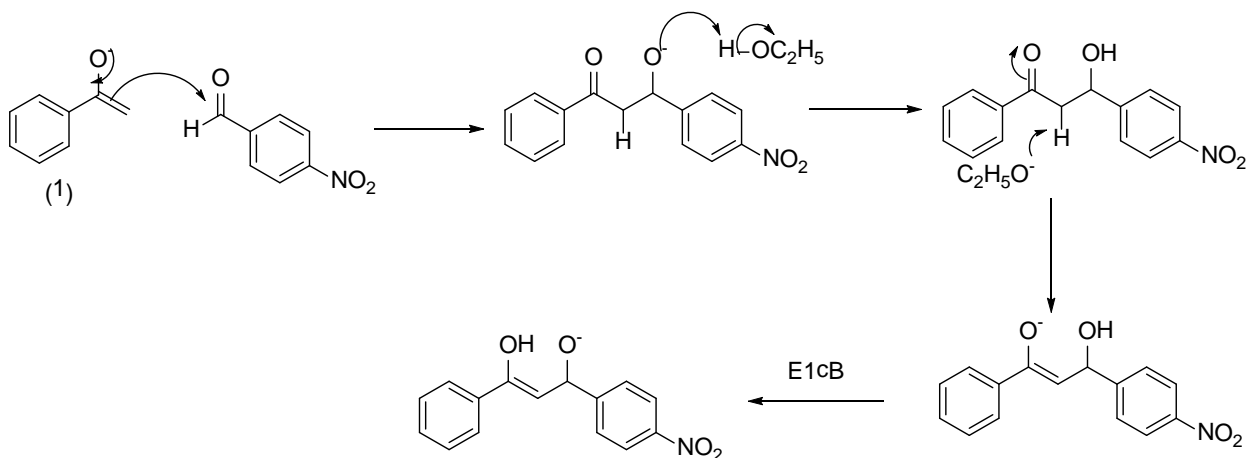
Similarly the importance of high electrophilicity of the non enolizing partner can be understood from the following example.



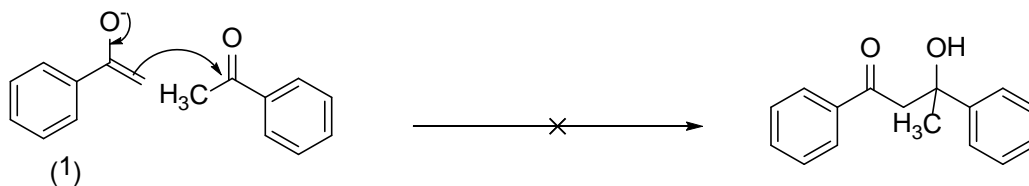
The reaction proceeds via the usual base catalyzed pathway. In the first step, the enolizable partner undergoes enolization in the presence of the base.



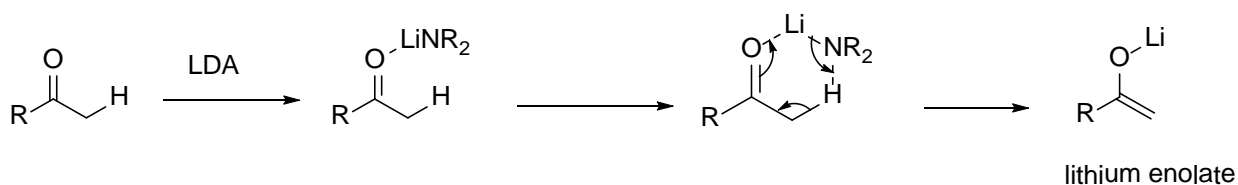
Next, the enolate attacks the electrophile benzaldehyde to form an aldol which then dehydrates by E1cB pathway.



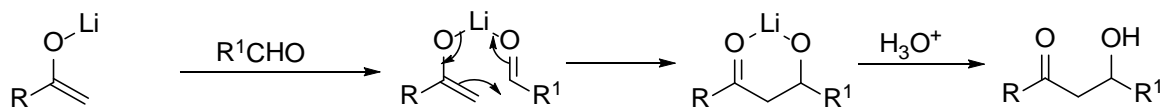
The enolate (1) formed in this step could attack another molecule of unenolized ketone but did not since ketones are less reactive than aldehydes. Thus, the enolate chooses to attack the better electrophile (4-nitrobenzaldehyde).



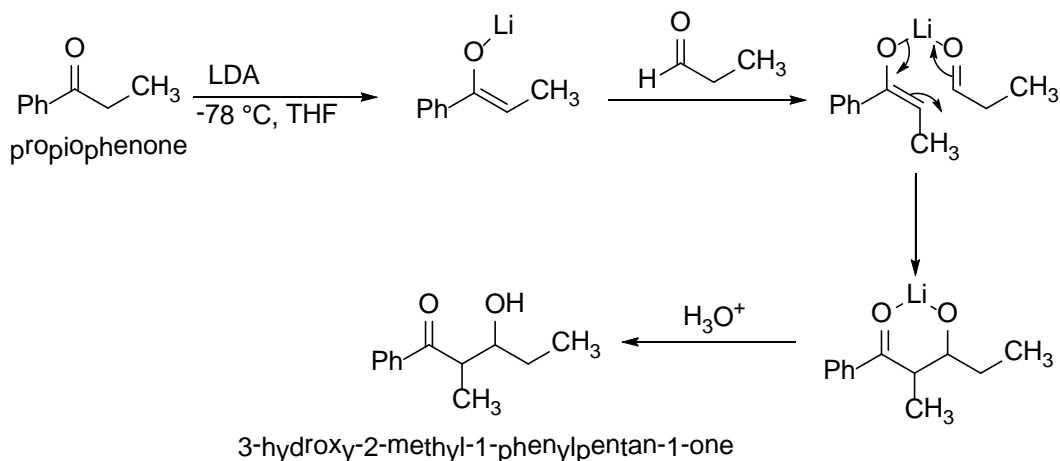
Lithium enolates derived from carbonyl compounds in THF at low temperature by using lithium diisopropylamide (LDA) as base. The reaction is kinetically controlled and therefore converted fast enough to prevent the enolate to react with a molecule of unenolized carbonyl compound.



Now, if a second carbonyl compound is added, then it also complexes with the lithium cation allowing the aldol reaction to take place from a six membered transition state.

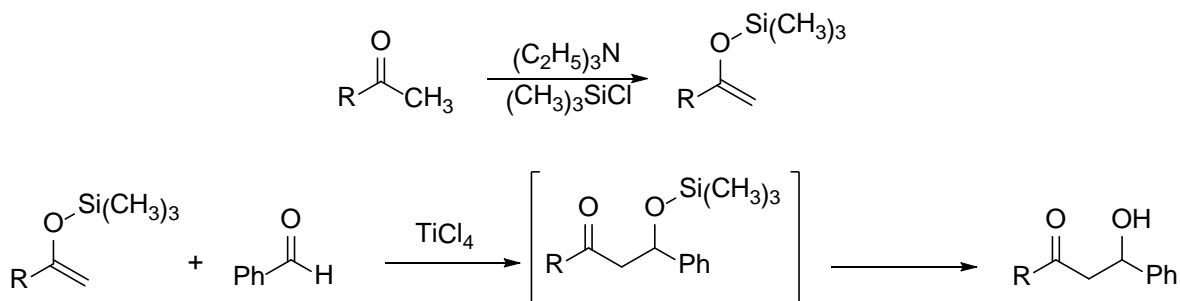


The reaction works well even if the electrophilic partner is an enolizable aldehyde. Thus, the lithium enolate of propiophenone can react with propan-1-al to form 3-hydroxy-2-methyl-1-phenylpentan-1-one selectively even when propan-1-al is an enolizable aldehydes (Scheme 6). But it must be noted that the reaction is actually carried out in two steps. In the first step, lithium enolate of propiophenone is formed, then, the electrophilic partner is added.



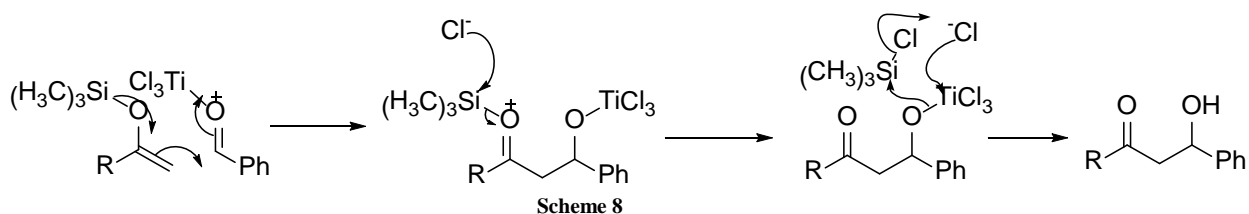
Scheme 6

Similarly, silylenol ethers generated from ketones may also be used as the nucleophilic partner in aldol reactions. The silylenol ether can be prepared from its parent carbonyl compound by forming a small equilibrium concentration of enolate ion with weak base such as a tertiary amine and trapping the enolate with the very efficient oxygen electrophile $(\text{CH}_3)_3\text{SiCl}$. The silylenol ether is stable enough to be isolated but is usually used immediately without storing. Lewis acid catalyst is needed to get the aldol reaction to work, and a Ti(IV) compound such as TiCl_4 is the most popular (Scheme 7).



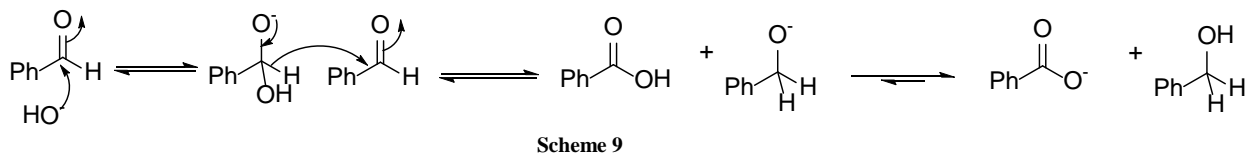
Scheme 7

In this reaction, the aldehyde presumably coordinates with the Lewis acid TiCl_4 which then undergoes a nucleophilic attack by the silylenol ether to form the aldol product (Scheme 8). The reaction pathway probably involves a six membered cyclic transition state as shown below.

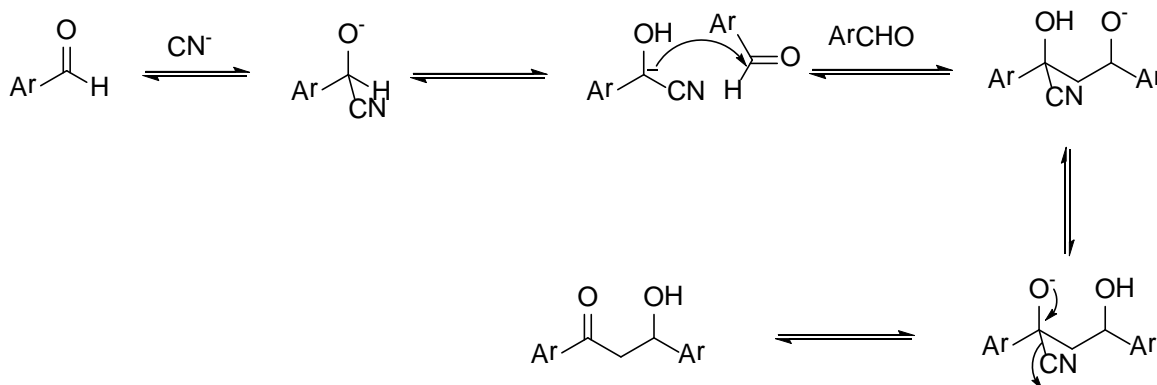


6.2.2.8 Benzoin Condensation

A reaction similar in nature with the aldol reaction but occurs in the presence of a very concentration of base and with substrates lacking an α -H like benzaldehyde, formaldehyde etc. This reaction involves a hydride transfer from one molecule of aldehyde to other leading to an overall disproportionation where one molecule of aldehyde is oxidized to carboxylic acid where as the other is reduced to an alcohol (Scheme 9).



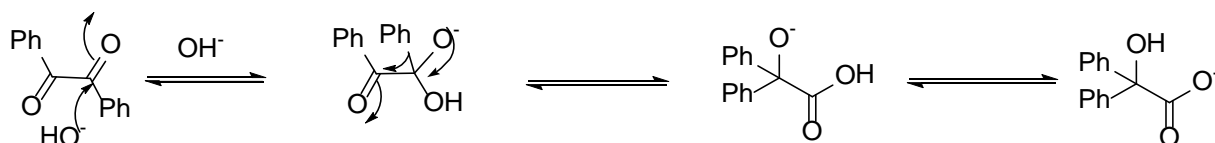
Aromatic aldehydes in the presence of catalytic amount of cyanide as a nucleophile may undergo **benzoin condensation** where cyanide first attacks a molecule of aldehyde to form an intermediate. Next, an intramolecular hydride transfer takes place followed a carbanionic attack on another aldehyde molecule. The intermediate so formed undergoes elimination of cyanide to form α -hydroxyketone (Scheme 10).



Scheme 10

Cyanide is considered ideal for catalysing this reaction due to (1) its ability to act as a nucleophile, (2) its ability to act as a leaving group and (c) its ability through electron withdrawal to increase the acidity of the C-H bond and to stabilize the carbanion.

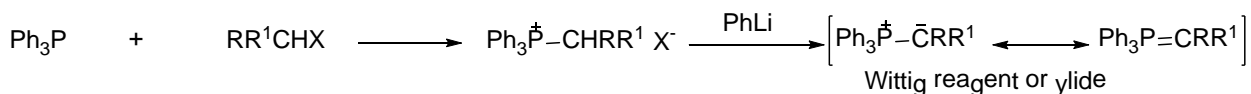
When benzaldehyde is used as reactant in the above reaction the product is called benzoin and hence the reaction has been named **benzoin condensation**. These α -hydroxyketones may be easily oxidized to the 1,2-diketones which under the action of hydroxylic base undergo rearrangement to form benzilic acid (Scheme 11).



Scheme 11

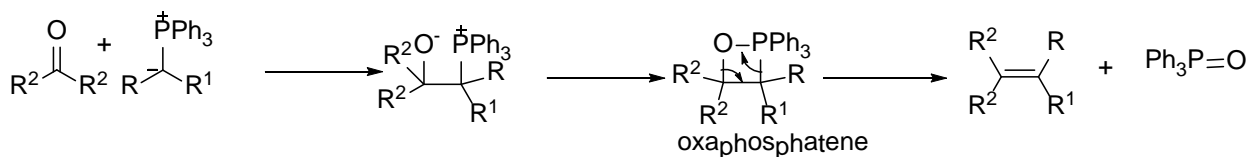
6.2.2.9 Wittig Reaction

The **Wittig reaction** is one of the most important reactions of the carbonyl group and is an important synthetic route to alkenes. It involves the addition of a phosphonium ylide to a carbonyl group of an aldehyde or a ketone. The ylide is actually a carbanion having an adjacent heteroatom. Such species are generated by the reaction of an alkyl halide and triaryl phosphine to yield a salt followed by abstraction of a proton from it by a very strong base (Scheme 12).



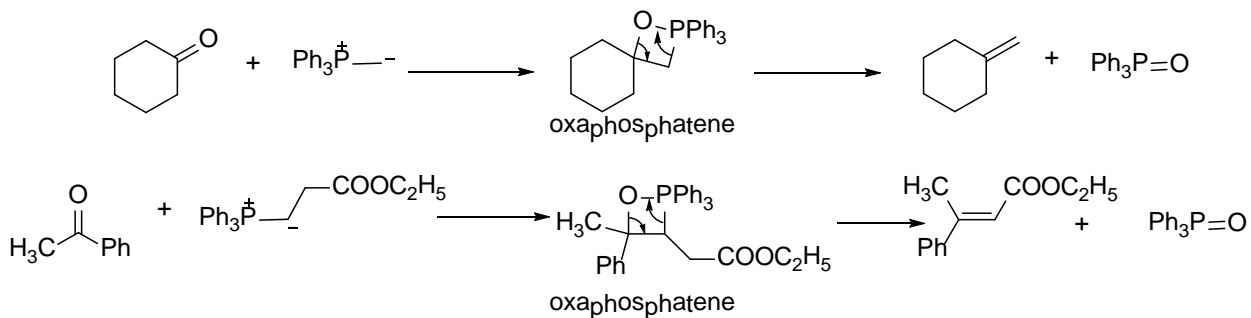
Scheme 12

The Wittig reagent or ylide then reacts with the carbonyl compound to probably form an oxaphosphatene intermediate which undergoes elimination to generate the alkene (Scheme 13).



Scheme 13

This reaction is particularly valuable to insert methylene groups in exocyclic positions and for the preparation of β,γ -unsaturated carboxylic acids and their derivatives (Scheme 14).

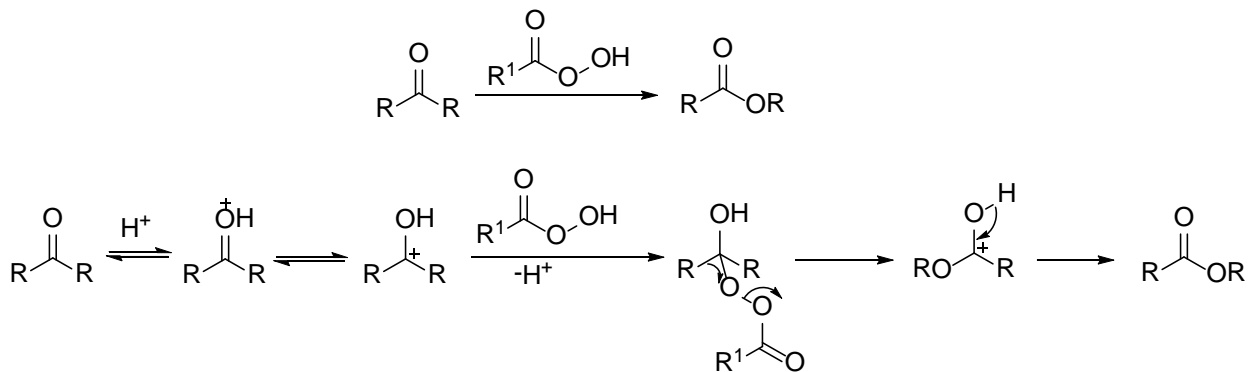


Scheme 14

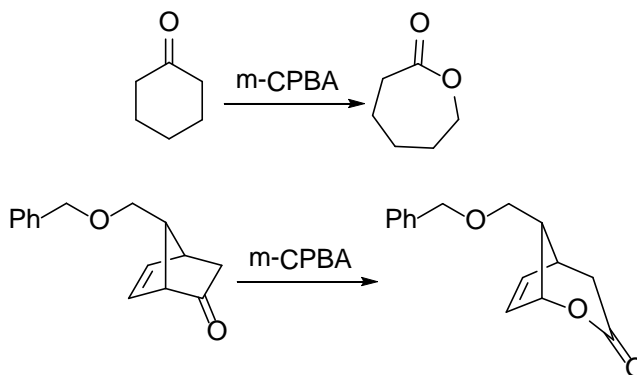
It should be noticed that normally stabilized ylides give the E-alkene while non-stabilized alkenes give the Z-alkene.

6.2.2.10 Baeyer Villiger Oxidation

When ketones are treated with peracids, they rearrange to form esters, the reaction is known as *Baeyer Villiger* oxidation. Carboxylates are not such good leaving groups, but the oxygen–oxygen single bond is very weak and monovalent oxygen cannot bear to carry a positive charge so that, once the peracid has added, loss of carboxylate is concerted with a rearrangement driven, by formation of a carbonyl group (Scheme 15).



The tendency of migration in this case of a group depends more on less the order in which the groups are able to stabilize a positive charge. Thus, tertiary alkyl is best in migrating followed by secondary alkyl, phenyl and methyl (Scheme 16).



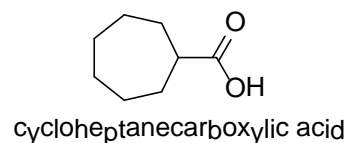
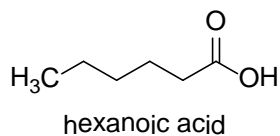
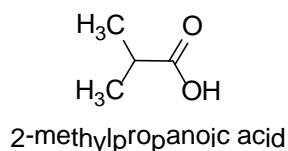
Module 6 Carbonyl Compounds

Lecture 16 Carboxylic Acid and its Derivatives

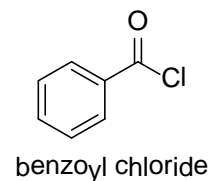
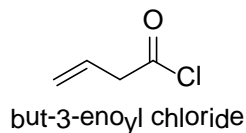
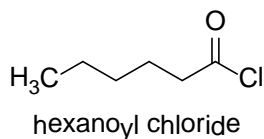
The carboxylic acid and its derivatives are important classes of compounds in organic chemistry.

- The carboxylic acids are named by first finding out the name of parent alkane while counting the carboxyl carbon too. Then, the suffix oic acid is added to it.

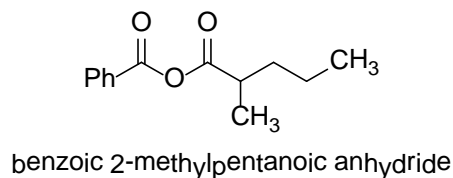
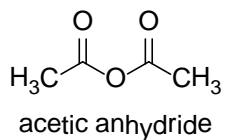
Some examples are given below.



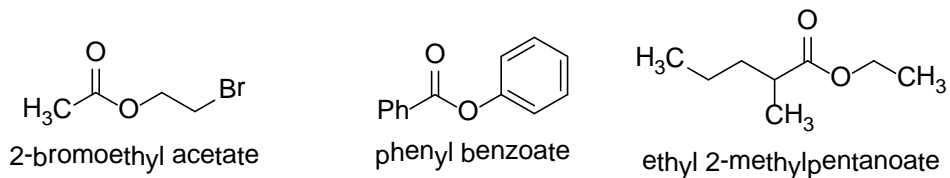
- The acid chlorides are named after the carboxylic acid from which they are derived. The *-ic acid* in the IUPAC name is replaced by *-yl halide*. Some examples are given below.



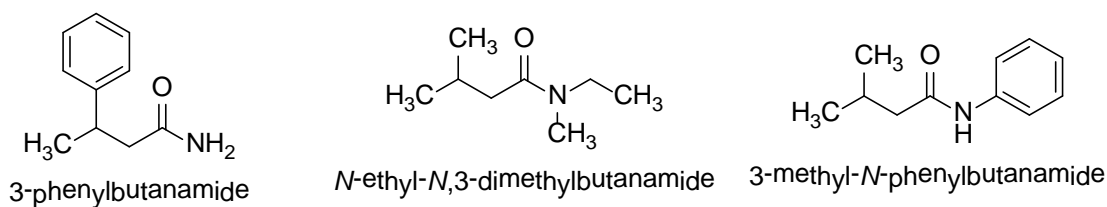
- In an acid anhydride, when both the acyl groups are same, the word acid in the carboxylic acid is replaced by anhydride but, if the two acyl groups are different, the names of carboxylic acids are written in alphabetical order.



- In esters the alkyl group and the acyl group are specified independently. The name of the alkyl group is first written followed by the name of the acyl group. The name is suffixed by with an *oate*.



- When naming amides, the -oic in the name of the acid is replaced with -amide. In case of substitution on the nitrogen atom, they are prefixed before the name as N-. The substituents are always written in an alphabetical order. Some examples are provided below.



6.3 Reactions

The reactivity of the carboxylic acid derivatives towards nucleophilic attack follows the order:

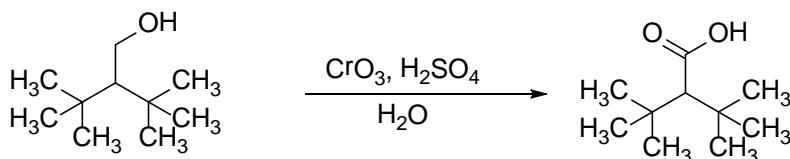


This order of reactivity of carboxylic acid derivatives towards nucleophilic acyl substitution can be explained on the basis of the electron donating properties of the substituent attached to the acyl group. The greater the electron donating power of this group, the slower is the rate.

6.4 Carboxylic Acid Synthesis

6.4.1 Oxidation of Alcohols

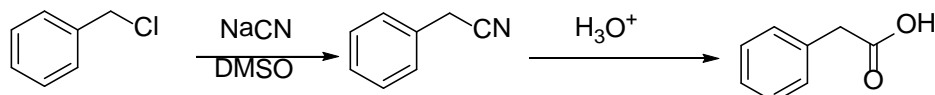
Carboxylic acids are normally prepared from primary alcohols by oxidation using oxidizing agents such as KMnO_4 and chromic acid (Scheme 1).



Scheme 1

6.4.2 Hydrolysis of Nitriles

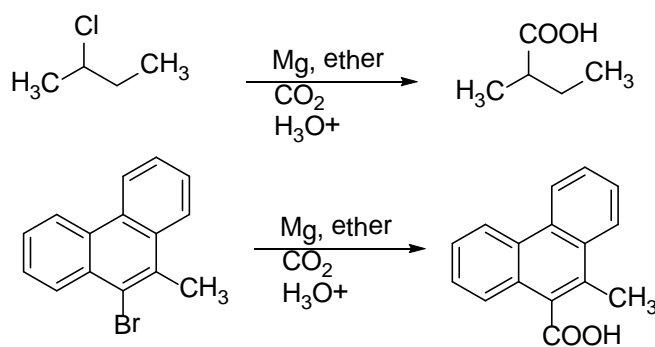
Another method of preparation of carboxylic acids involves the hydrolysis of nitriles by an acid or a base (Scheme 2).



Scheme 2

6.4.2 Grignard Reaction

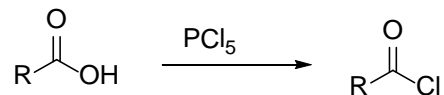
The action of dry ice on Grignard reagent leads to the formation of carboxylic acids (Scheme 3).



Scheme 3

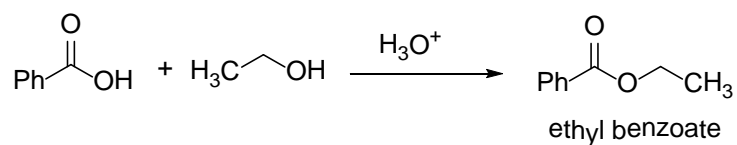
6.5 Acid Chloride Synthesis

The acyl chlorides may be generated from carboxylic acids by heating them with phosphorus trichloride or phosphorus pentachloride.



6.6 Ester Synthesis

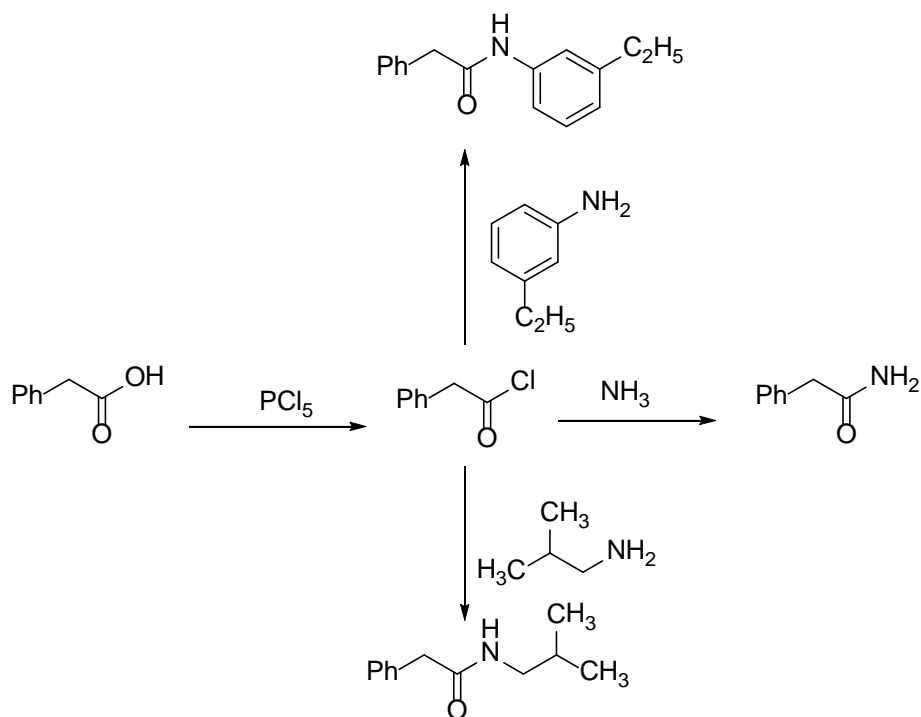
The carboxylic acids can be converted to corresponding esters by treating them with an alcohol in the presence of an acid or a base as a catalyst (Scheme 4). The reaction may be reversible and suitable precautions are to be employed to obtain satisfactory yields.



Scheme 4

6.7 Amide Synthesis

The carboxylic acid chlorides or acyl chlorides can be converted into amides by treating with ammonia. Treatment with an aliphatic or aromatic amine results in formation of corresponding N-substituted amide (Scheme 5).

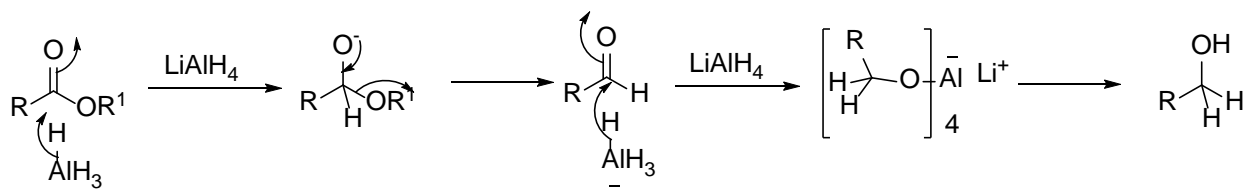


Scheme 5

6.8 Reactions

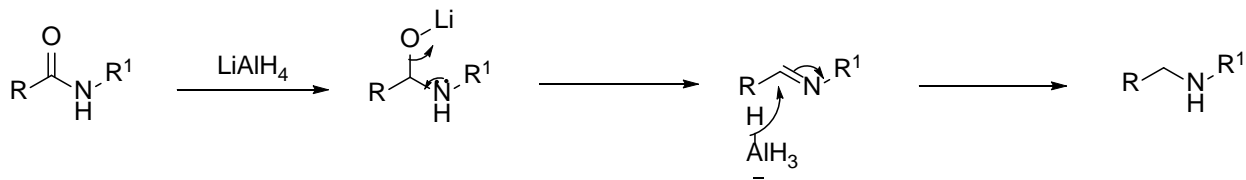
6.8.1 Reduction

The reduction of carboxylic acids and its derivatives is an important reaction and can be carried out with variety of reagents. However, the reagents need to be varied according the class of compounds to be reduced. The pathway followed by the reaction remains more or less the same as discussed under reduction of aldehydes and ketones with hydride transfer reagents. As an example, esters can be reduced to alcohols using lithium aluminium hydride as a reducing agent according to the pathway shown in Scheme 6.



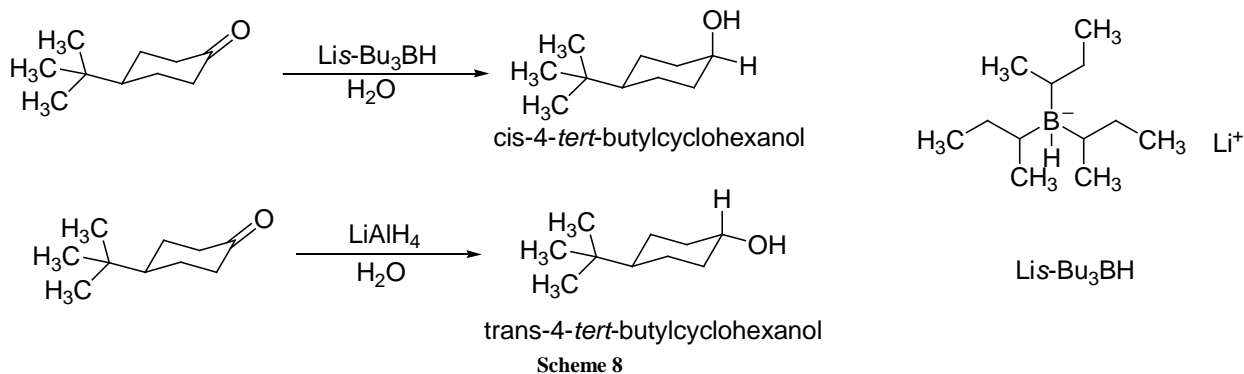
Scheme 6

Similarly the reduction of amides is believed to proceed via an imine intermediate (Scheme 7).



Scheme 7

In order to achieve selective reduction or to generate a reducing agent which can induce stereoselectivity to a reduction reaction, the two major hydride sources aluminium hydride and borohydride are suitably modified and their counter cations are also changed. In an example of such type, lithium tri-*sec*-butylborohydride (L-selectride) reduces 4-*t*-butyl cyclohexanone to the corresponding *cis*-alcohol while reduction by lithium aluminium hydride gives predominantly *trans*-alcohol (Scheme 8).

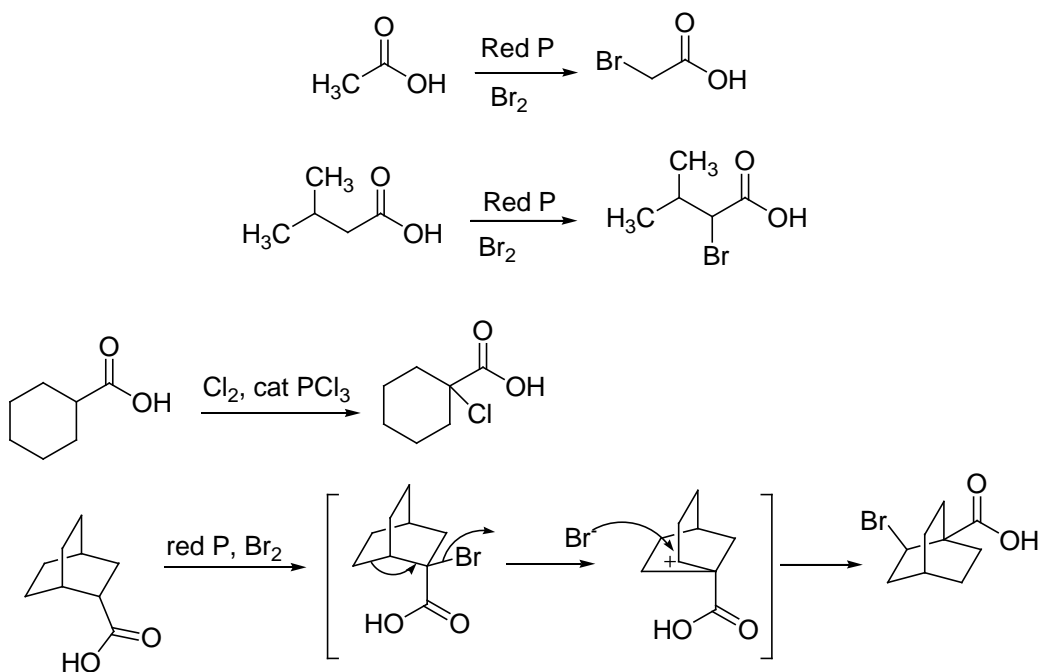


The selectivity of the reducing agents is given below.

Reducing agent	Imine	Aldehyde	Ketone	Ester	Amide	Carboxylic acid
NaCNBH ₃	Reduced	Slowly reduced	Slowly reduced	Not reduced	Not reduced	Not reduced
NaBH ₄	-	Reduced	Reduced	Slowly reduced	Not reduced	Not reduced
LiBH ₄	-	Reduced	Reduced	Not reduced	Not reduced	Not reduced
LiAlH ₄	-	Reduced	Reduced	Reduced	Reduced	Slowly reduced
BH ₃	-	Slowly reduced	Slowly reduced	Slowly reduced	Reduced	Reduced

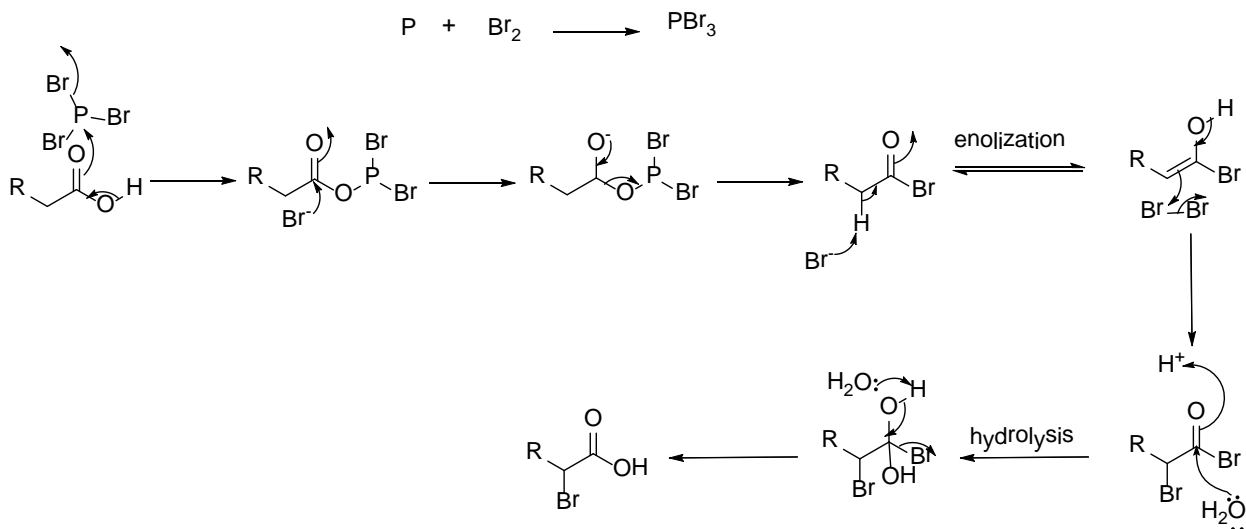
6.8.2 Halogenation

The carboxylic acids can be halogenated in α -position by treating with red phosphorus and halogens (Scheme 9). This is usually called **Hell-Vollhard-Zelinsky** reaction, which is an important process from the perspective of synthetic chemistry.

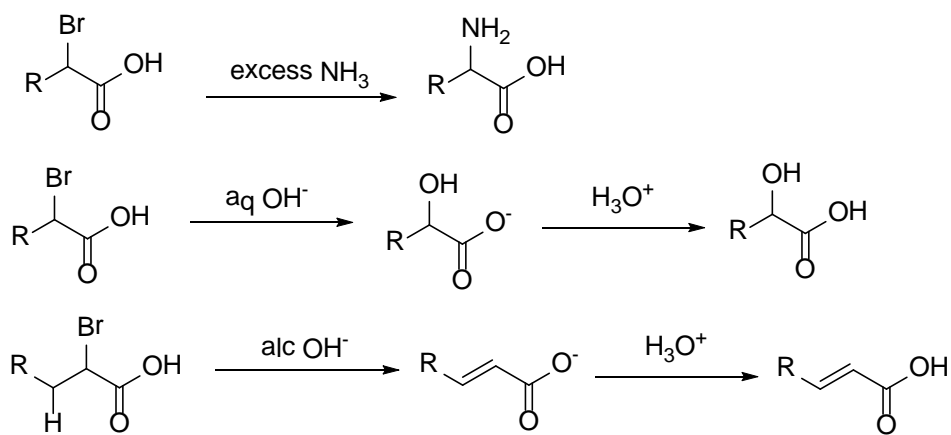


Scheme 9

The reaction is believed to proceed by an acyl halide intermediate (Scheme 10). The role of phosphorus is to ultimately convert a little of the acid to acid chloride which then undergoes halogenation at α -position.

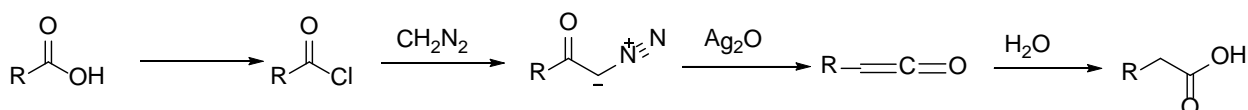


The α -haloacids so generated may be used as intermediates for the preparation of α -amino acids, α -hydroxy acids and α,β -unsaturated acids (Scheme 11).



6.8.3 Arndt Eistert Synthesis

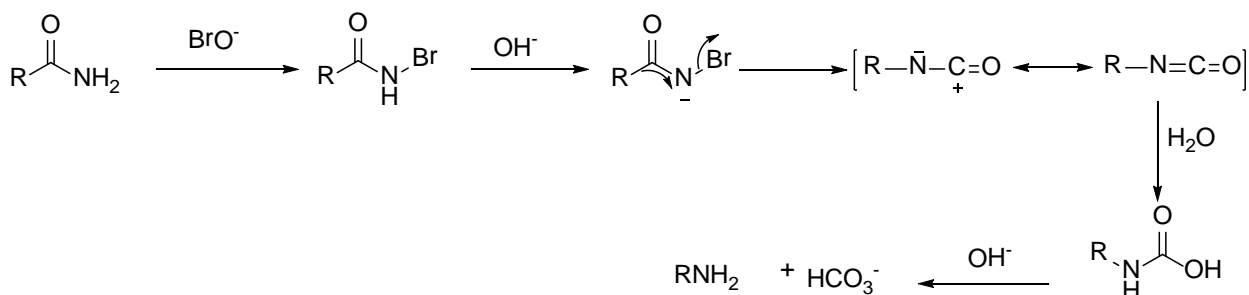
In order to go up by one carbon in the linear chain of a carboxylic acid, a protocol called *Arndt Eistert synthesis* may be employed (Scheme 12). In this protocol the homologation of a carboxylic acid is achieved by first converting the acid to acyl chloride which is then treated with diazomethane. The diazoketene so formed is treated with moist silver oxide to form a ketene which can be easily hydrolyzed to obtain the next higher carboxylic acid.



Scheme 12

6.8.4 Hoffman Rearrangement

An important reaction for the amides is the so called *Hoffman* reaction (Scheme 13). In this reaction, an amide is converted to an amine containing one less carbon. The reaction is carried out by treating the amide with an alkaline solution of sodium hypobromite.

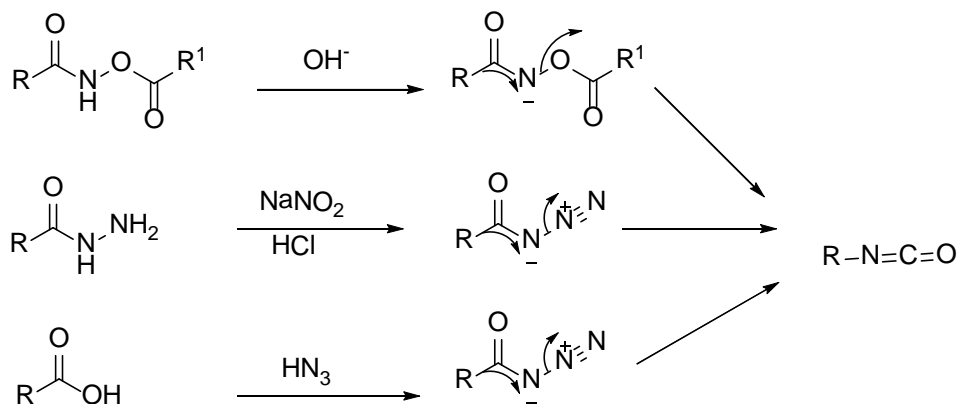


Scheme 13

The isocyanate formed in this reaction is the key intermediate and can be found in other related rearrangement reactions of carboxylic acid and its derivatives. This isocyanate intermediate undergoes addition of water to form a hydroxamic acid which decomposes under the reaction conditions to give an amine. This reaction involves a concerted step of the removal of the bromide along with the migration of the R group which migrates with retention of configuration.

6.8.5 Lossen, Curtius and Schmidt Rearrangements

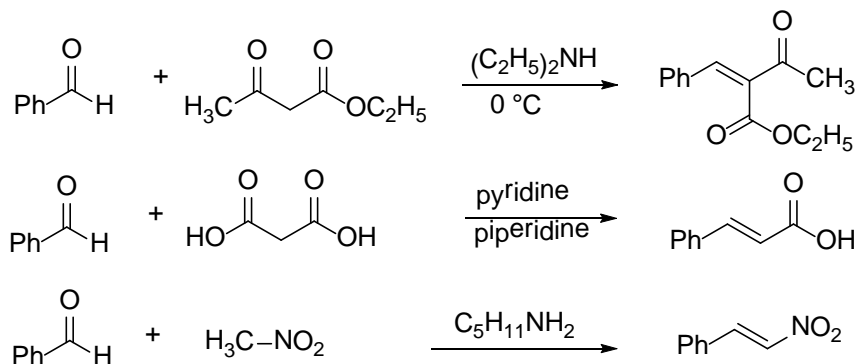
The *Lossen rearrangement* involves treatment of O-acyl derivatives of hydroxamic acids with base causing the departure of $R^1CO_2^-$ as leaving group (Scheme 14). The other related reactions, *Curtius* and *Schmidt* reactions involve acid hydrazides and carboxylic acids as the starting point. In both cases, nitrogen is the leaving group from the intermediate azide



Scheme 14

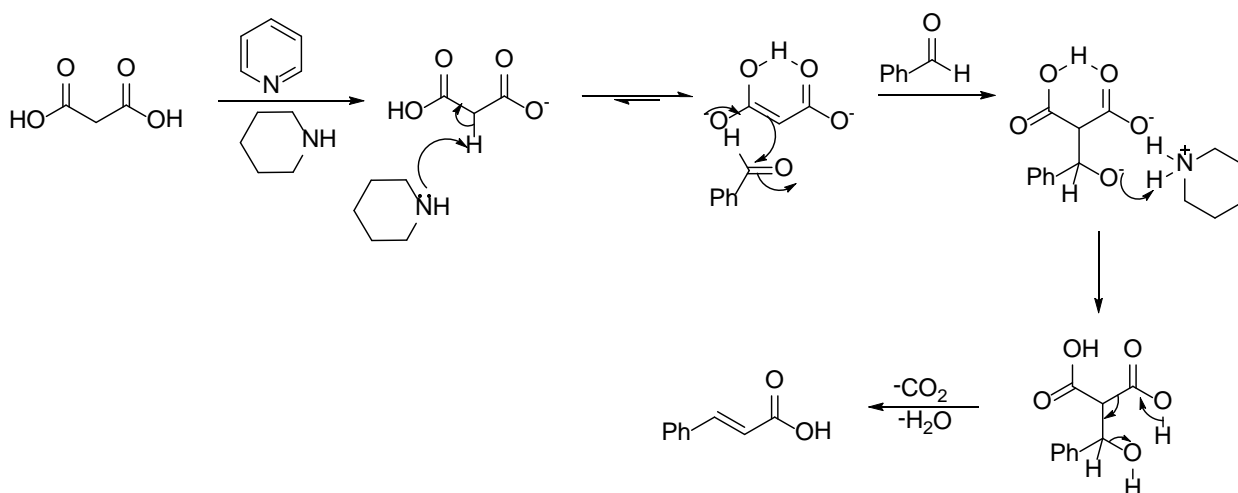
6.8.6 Knoevenagel Reaction

In *Knoevenagel reaction*, the carbanion generated from an ester may attack an aldehyde or a ketone to undergo a condensation reaction to form a α,β -unsaturated acid or ester (Scheme 15). Usually a secondary amine like piperidine used as base. Knoevenagel reactions may be extended to other compounds containing an active methylene groups such as nitroalkanes. Some examples are given below.



Scheme 15

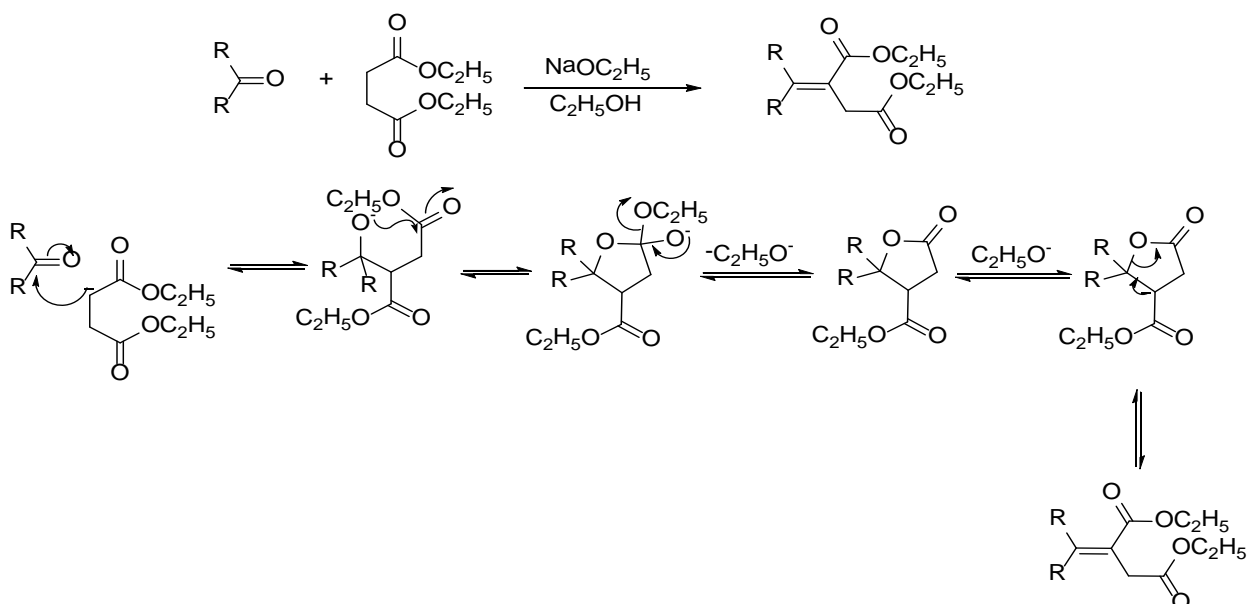
When the active methylene group is sandwiched between carboxylic acid groups, it often undergoes decarboxylation as shown in Scheme 16.



Scheme 16

6.8.7 Stobbe Condensation

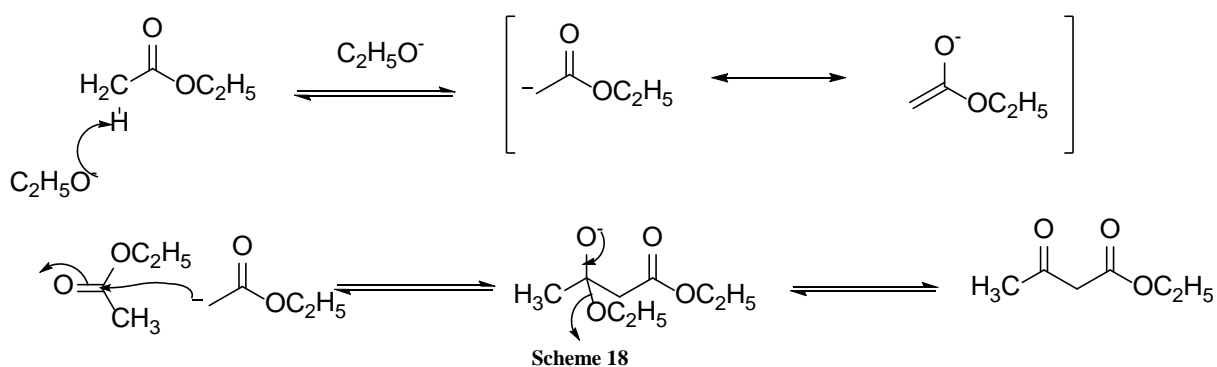
It involves the condensation dialkyl succinate with carbonyl compounds (Scheme 17). The reaction is usually carried out using bases such as sodium ethoxide and sodium hydride.



Scheme 17

6.8.8 Claisen Condensation

When the carbanion generated from an ester reacts with another molecule of ester, the reaction is known as *Claisen ester condensation* (Scheme 18). The reaction is usually carried out using sodium ethoxide as a base in ethanol. This reaction is reversible in nature and can be induced irreversible by using extremely strong base like triphenylmethanide. Furthermore, crossed Claisen condensations between two esters are useful only when one of the esters does not possess an α -H.



An intramolecular version of this reaction known as *Dieckmann cyclization* is also possible where medium sized rings are formed in this reaction.

