US04CHHE21 : ORGANIC CHEMISTRY

UNIT-II [B]: ALDEHYDES, KETONES, AMINE

Compiled By Dr. B. C. Dixit

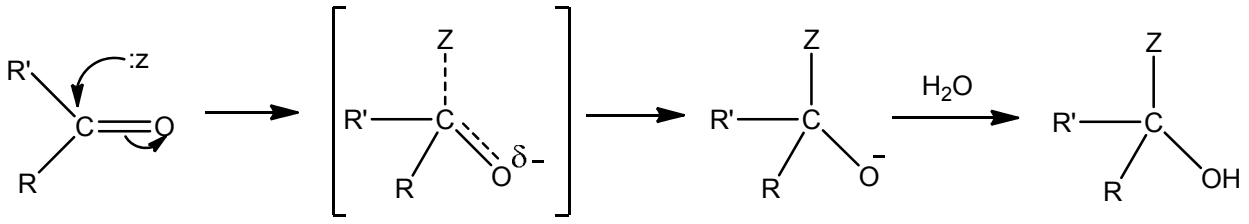
Reactions. Nucleophilic addition

The carbonyl group, C=O, direct the chemistry of aldehydes and ketones. It does this in two ways :
(a) by providing a site for nucleophilic addition, and
(b) by increasing the acidity of the hydrogen atoms attached to the alpha carbon.

Both these effects are quite consistent with the structure of the carbonyl group and due to the ability of oxygen to accommodate a negative charge.
The carbonyl group contains a carbon-oxygen double bond; since the mobile π-electrons are pulled strongly toward oxygen, carbonyl carbon is electron-deficient and carbonyl oxygen is electron-rich. Carbonyl carbon is a flat and relatively open and unhindered for nucleophilic attack from above or below the plan, in a direction perpendicular to the plane of the group.

The important step in these reactions is the formation of a bond to the electron-deficient (electrophilic) carbonyl carbon, the carbonyl group is most susceptible to attack by electron-rich, nucleophilic reagents (bases). [**Q. The typical reaction of aldehydes and ketones is nucleophilic addition].**

Nucleophilic addition



Reactant

Trigonal

Transition state

Becoming tetrahedral
Partial negative
charge on oxygen

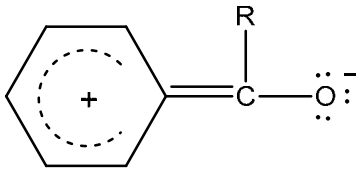
Product

Negative charge
on oxygen

In the reactant, carbon is trigonal. In the transition state, carbon has begun to acquire the tetrahedral configuration it will have in the product; the attached groups are thus being brought closer together. In the transition state, larger groups (R and R') will tend to create steric hindrance more than smaller groups.

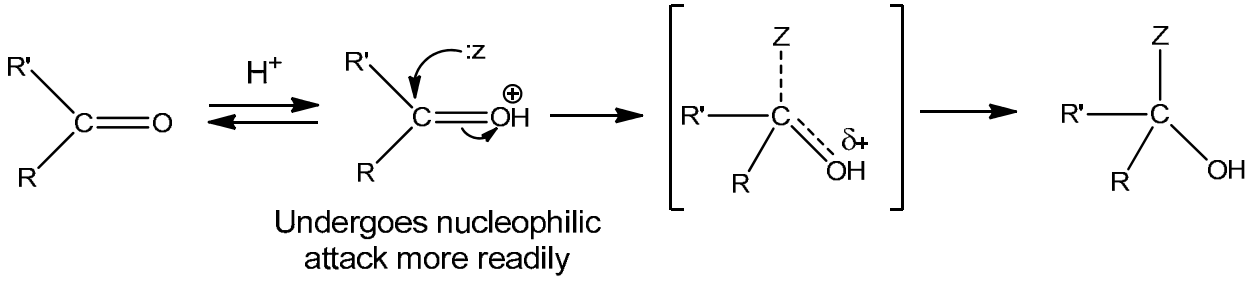
Q. Aldehydes generally undergo nucleophilic addition more readily than ketones.
This difference in reactivity is consistent with the transition states involved, and seems to be due to a combination of (i) electronic and (ii) steric factors. A ketone contains a second alkyl or aryl group where an aldehyde contains a hydrogen atom. A second alkyl or aryl group of a ketone is larger than the hydrogen of an aldehyde, and resists more strongly the crowding together in the transition state. An alkyl group releases electrons, and thus destabilizes the transition state by intensifying the negative charge developing on oxygen.

An aryl group has an electron-withdrawing inductive effect, and it stabilize the transition state and thus speed up reaction; however, it seems to stabilize the reactant even more, by resonance (contribution by I), and thus causes net deactivation.



If acid is present, hydrogen ion becomes attached to carbonyl oxygen. This prior protonation lowers the E_{act} for nucleophilic attack, since it permits oxygen to acquire the electrons without having to accept a negative charge.

Acid-catalyzed nucleophilic addition

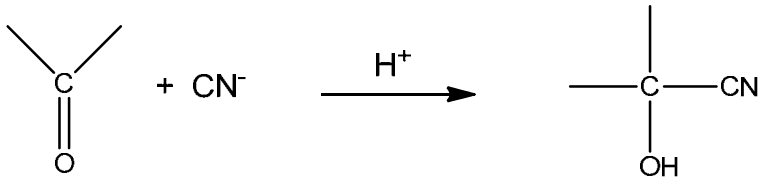


Thus nucleophilic addition to aldehydes and ketones can be catalyzed by acids (sometimes, by Lewis acids).

[Q. The typical reaction of aldehydes and ketones is nucleophilic addition]

Addition of cyanide

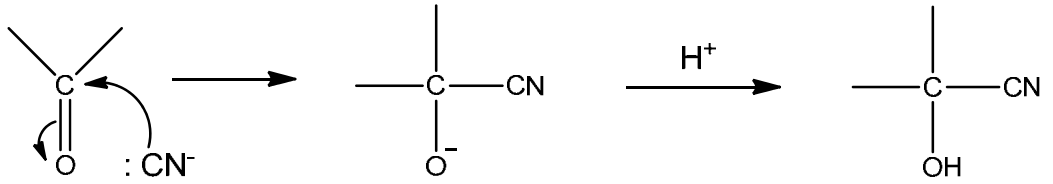
The HCN add to the carbonyl group of aldehydes and ketones to yield compounds known as cyanobydrins:



A cyanohydrin

The reaction is often carried out by adding mineral acid to a mixture of the carbonyl compound and aqueous sodium cyanide.

Addition appears to involve nucleophilic attack on carbonyl carbon by the strongly basic cyanide ion; subsequently (or possibly simultaneously) oxygen accepts a hydrogen ion to form the cyanohydrin product :

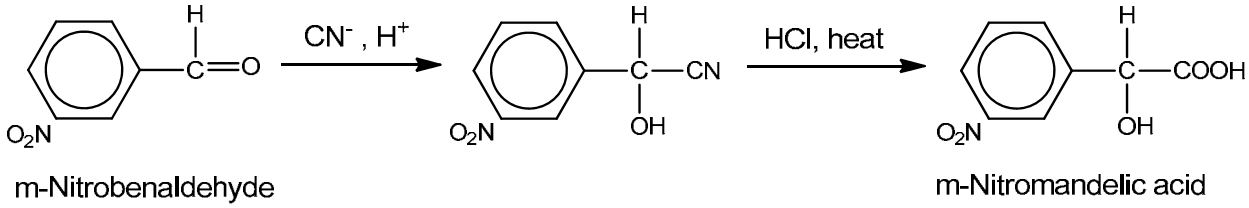


Nucleophilic reagent

A cyanohydrin

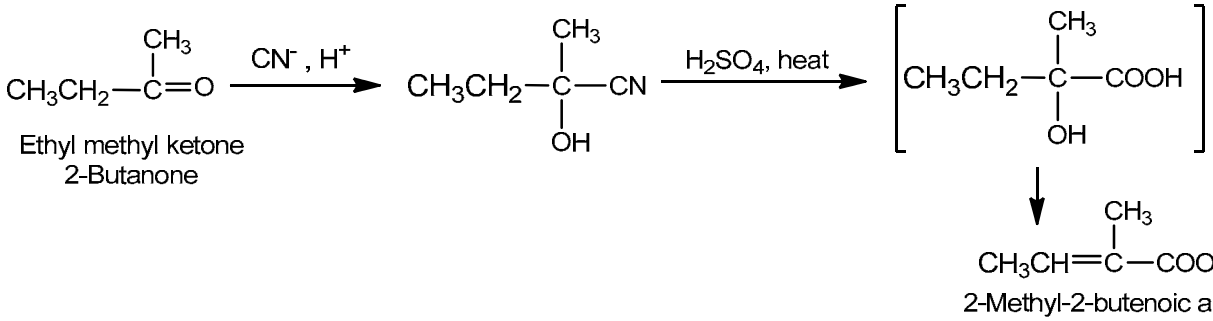
However, a highly acidic medium-in which the concentration of un-ionized HCN is highest-actually slow down reaction since HCN is a poor source of the very weak cyanide ion.

Cyanohydrins undergo hydrolysis to produces the products like α-hydroxy acids or unsaturated acids. For example:



m-Nitrobenaldehyde

m-Nitromandelic acid

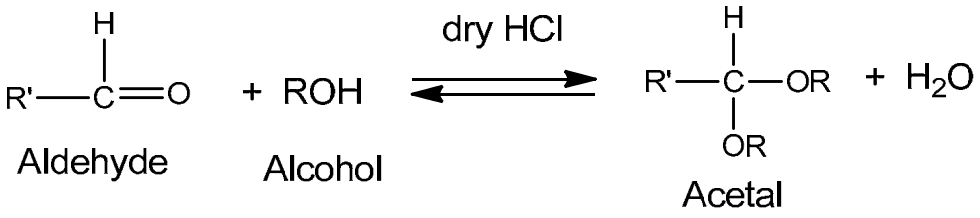


Ethyl methyl ketone
2-Butanone

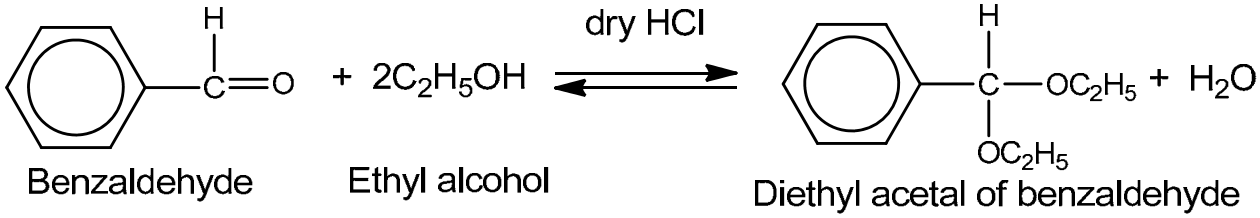
2-Methyl-2-butenoic acid

Addition of alcohols. Acetal formation

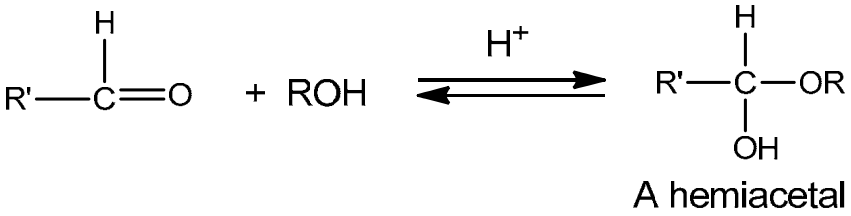
When alcohol is added to the carbonyl group of aldehydes in the presence of anhydrous acids it yield acetals :



The reaction is carried out by allowing the aldehyde to stand with an excess of the anhydrous alcohol and a little anhydrous acid, usually hydrogen chloride. In the preparation of ethyl acetals the water is often removed as it is formed by means of the azeotrope of water, benzene, and ethyl alcohol.

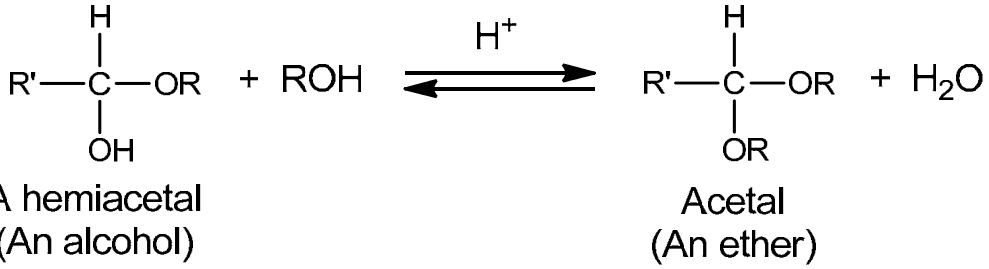


In alcoholic solution an aldehyde exists in equilibrium with a compound called a hemiacetal :

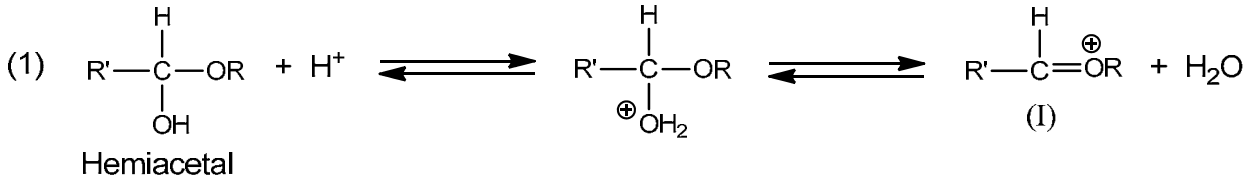


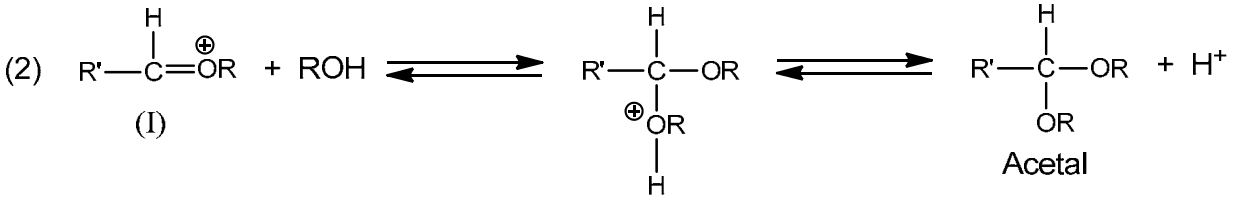
A hemiacetal is formed by the addition of the nucleophilic alcohol molecule to the carbonyl group; it is both an ether and an alcohol. However, hemiacetals are too unstable to be isolated.

In the presence of acid the hemiacetal, acting as an alcohol, reacts with more of the solvent alcohol to form the acetal, an ether:

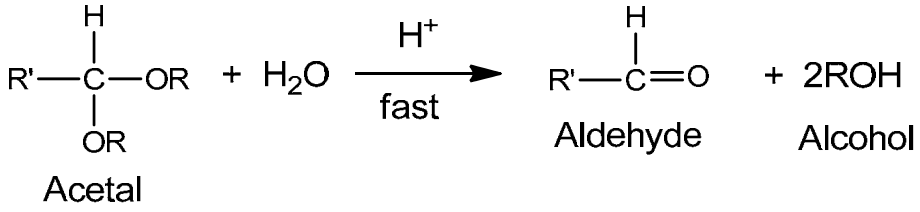


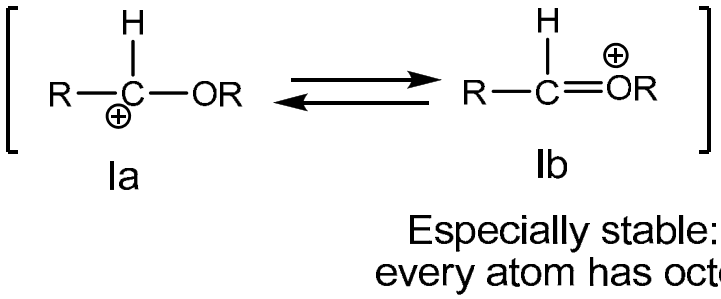
The reaction involves the formation (step 1) of the ion-I, which then combines (step 2) with a molecule of alcohol to yield the protonated acetal.





Acetal formation thus involves (a) nucleophilic addition to a carbonyl group, and (b) ether formation via a carbocation. Acetals have the structure of ethers and are cleaved by acids and are stable toward bases. Acetals differ from ethers, they undergo acidic cleavage and are rapidly converted into the aldehyde and alcohol by dilute mineral acids.



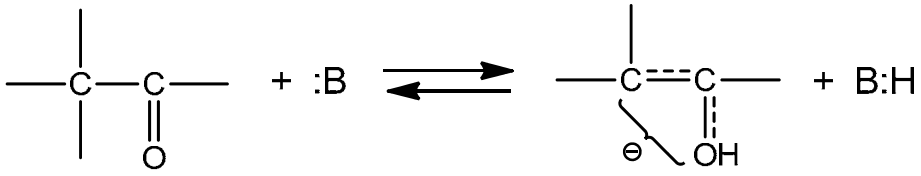


It proceeds via "carbocation", which is a hybrid of structures -Ia and -Ib. Contribution from **Ib**, in which every atom has an octet of electrons, makes this ion (oxonium ion) considerably more stable than ordinary carbocations.

Acidity of α-hydrogens

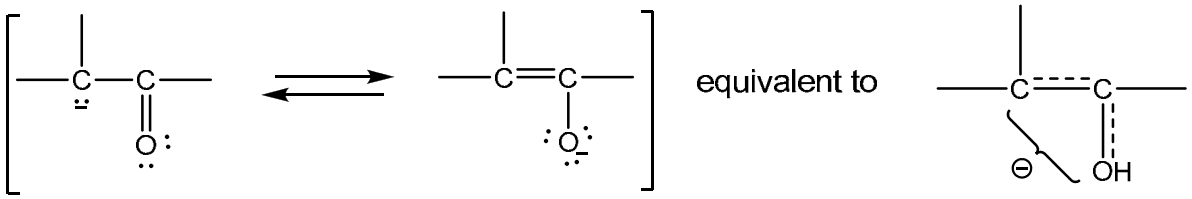
In aldehydes and ketones, the carbonyl group determines the chemistry of aldehydes and ketones. It provides a site at which nucleophilic addition can take place. But, like the carbon-carbon double bond and the benzene ring, the carbonyl can play another role, not as a functional group, but as a substituent. This carbonyl group strengthens the acidity of the hydrogen atoms attached to the α-carbon and, by doing this, it rise to a set of chemical reactions.

Ionization of an α-hydrogen



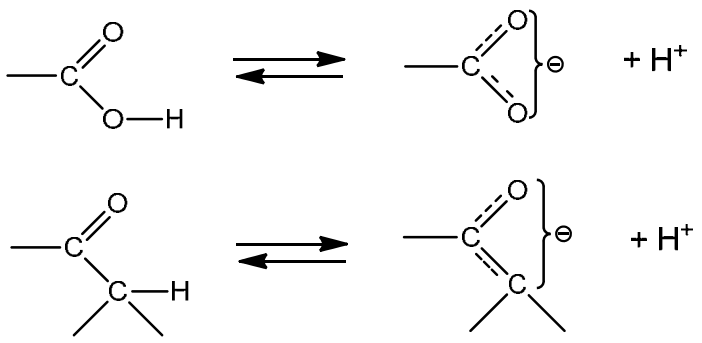
I

Aldehyde or ketone yields a carbanion-**I** and is a resonance hybrid of two structures, **II** and **III** due to presence of carbonyl group.



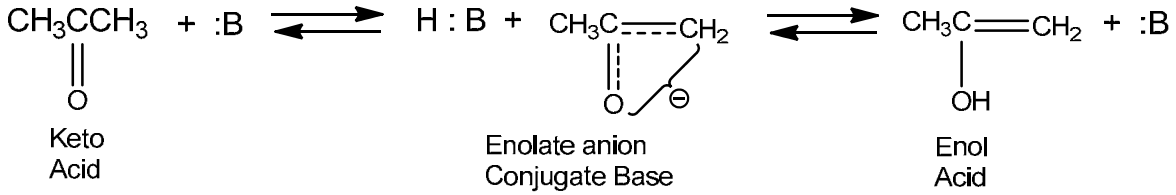
II III I

The carbonyl group thus increase the acidity of α-hydrogens by helping to accommodate the negative charge of the anion.



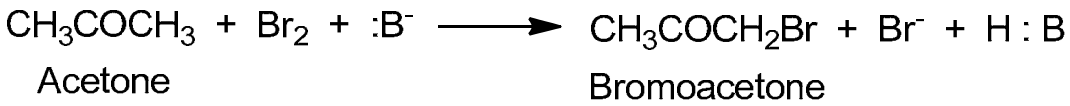
Resonance in **I** involves structures **II** and **III** of quite different stabilities, and hence is much less important than the resonance involving equivalent structures in a carboxylate ion. **[**Compared with the hydrogen of a -COOH group, the α-hydrogen atoms of an aldehyde or ketone are very weakly acidic; the important thing is that they are considerably more acidic than hydrogen atoms anywhere else in the molecule, and that they are acidic enough for significant-even though very low-concentrations of carbanions to be generated**]**.

We call **I** a carbanion since it is the conjugate base of a carbon acid, that is, an acid which loses its proton from carbon. A carbanion is stabilized by an adjacent carbonyl group, is often called an enolate anion, since the anion is, formally, the conjugate base not only of the keto form of the carbonyl compound but of the enol form as well. For example:



Base-promoted halogenation of ketones

Acetone reacts with bromine to form α-bromoacetone; in presence of bases (e.g., hydroxide ion, acetate ion, etc.).

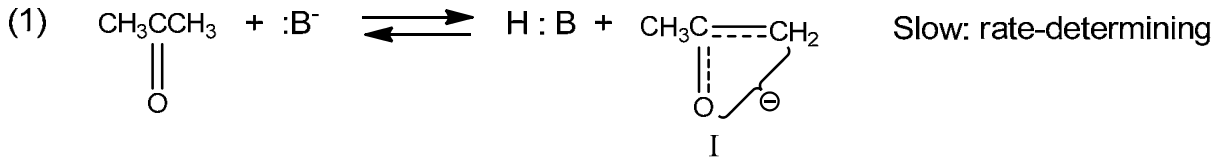


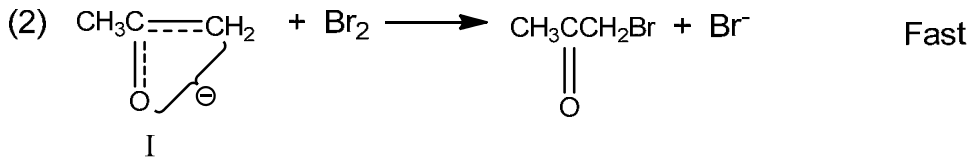
Kinetics studies shows that the rate of reaction depends upon the concentration of acetone, [acetone], and of base, [:B], but is independent on bromine [Br_2] concentration:

Rate = k [acetone] [:B]

it means that the reaction whose rate we are measuring does not involve Br_2.

The kinetics is quite consistent with the following mechanism. The base slowly abstracts a proton (step 1) from acetone to form carbanion-I, which then reacts rapidly with bromine (step 2) to yield bromoacetone. Step (1), generation of the carbanion, is the rate-determining step, since its rate determines the overall rate of the reaction sequence. As fast as carbanions are generated, they are rapidly react with bromine molecules.

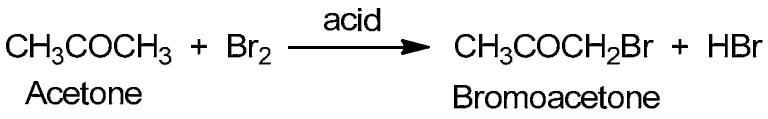




rate = k [acetone] [:B]

Acid-catalyzed halogenation of ketones. Enolization

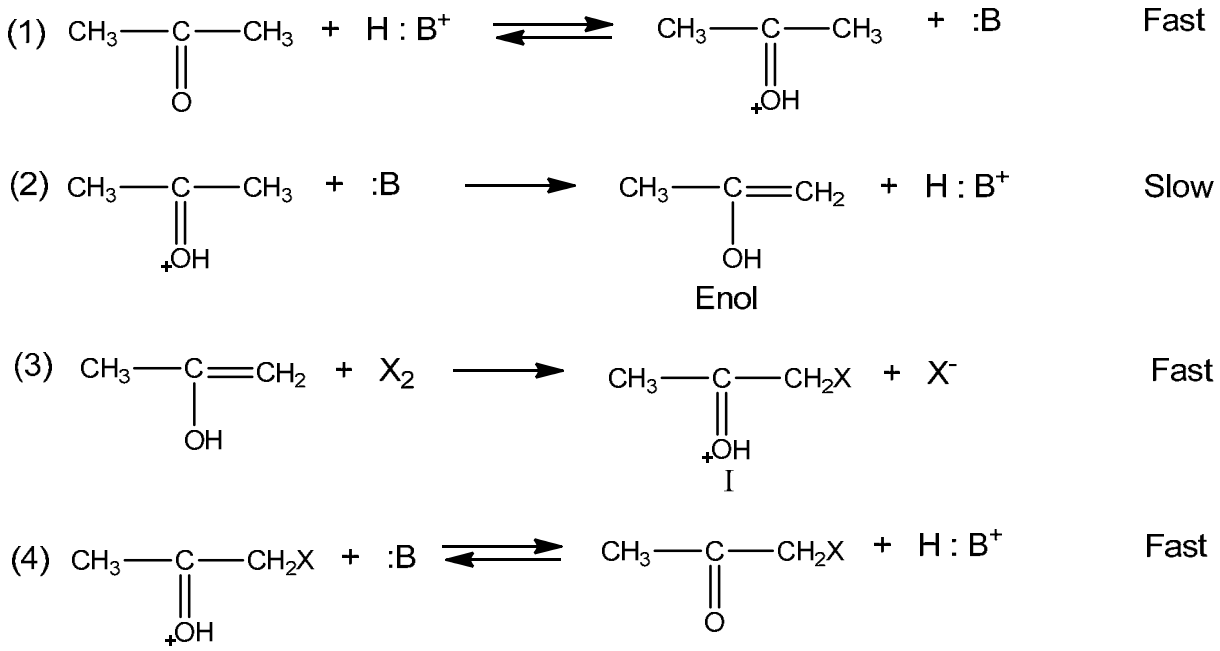
Acetone reacts with bromine to form α-bromoacetone; in presence of acid.



rate = k [acetone] [:B]

Here, the kinetics shows the rate of halogenation to be independent of halogen concentration, but dependent upon concentration of ketone and acid.

The rate-determining reaction here is the formation of the enol, which involves two steps: rapid, reversible protonation (step 1) of the carbonyl oxygen, followed by the slow loss of an α-hydrogen (step 2).

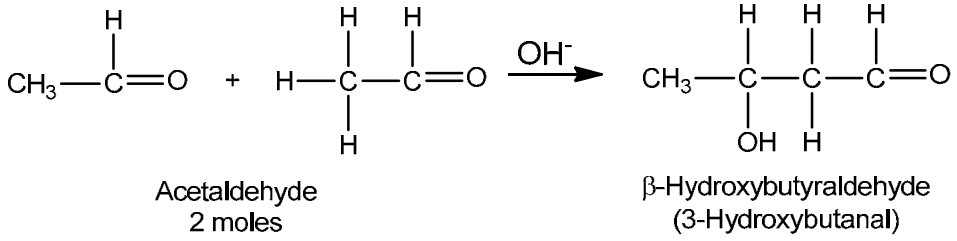


Once formed, the enol reacts rapidly with halogen (step 3) to form halogen substituted protonated ketone. From protonated ketone base abstract proton to give α-bromoacetone.

[**Q. Write reaction mechanism for acid/base promoted halogenations of ketones]**

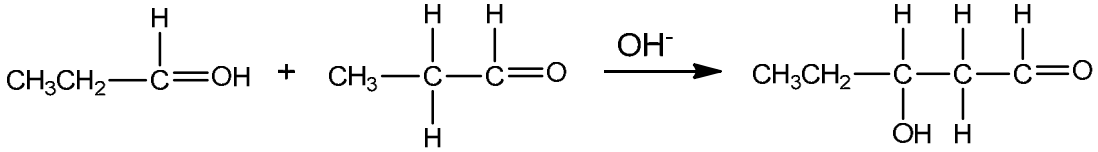
Aldol condensation :

Under the influence of dilute base or dilute acid, two molecules of an aldehyde or a ketone may combine to form a β-hydroxyaldehyde or β-hydroxyketone. This reaction is called the aldol condensation. In every case the product results from addition of one molecule of aldehyde (or ketone) to a second molecule in such a way that the α-carbon of the first becomes attached to the carbonyl carbon of the second. For example:



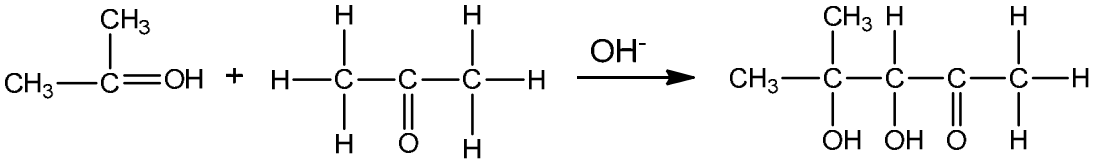
Acetaldehyde
2 moles

β-Hydroxybutyraldehyde
(3-Hydroxybutanal)



Propionaldehyde
2 moles

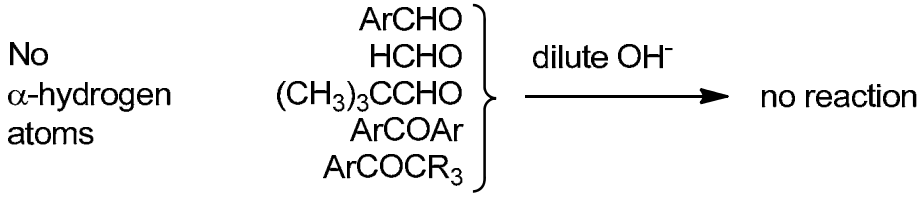
β-Hydroxy-α–methylvaleraldehyde
(3-Hydroxy-2-methylpentanal)



Acetaldehyde
2 moles

4-Hydroxy-4-methyl-2-pentanone

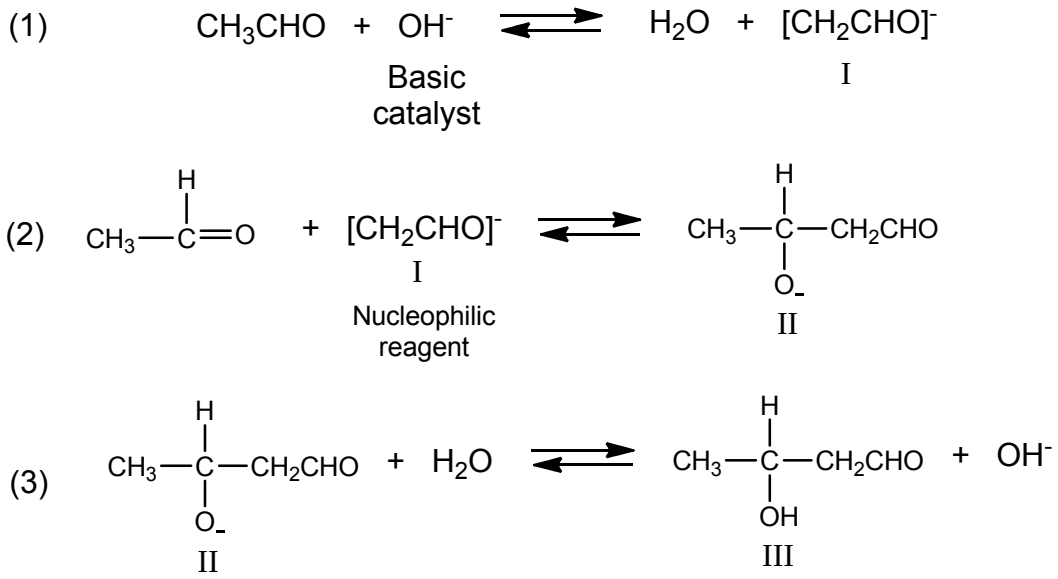
If the aldehyde or ketone does not contain an a-hydrogen, a simple aldol condensation cannot take place. For example:



(In concentrated base, however, such aldehydes may undergo the Cannizzaro reaction)

[**Q. Write reaction mechanism for Aldol condensation.]**

Mechanism :

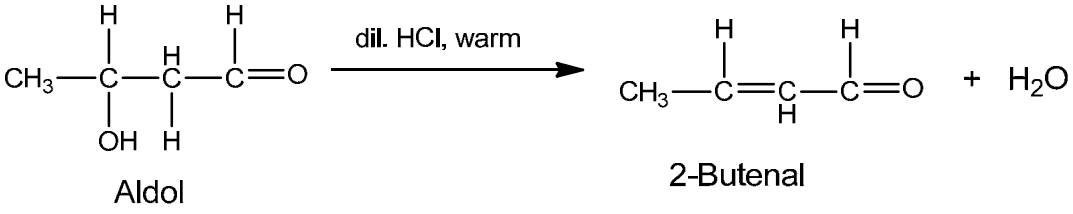


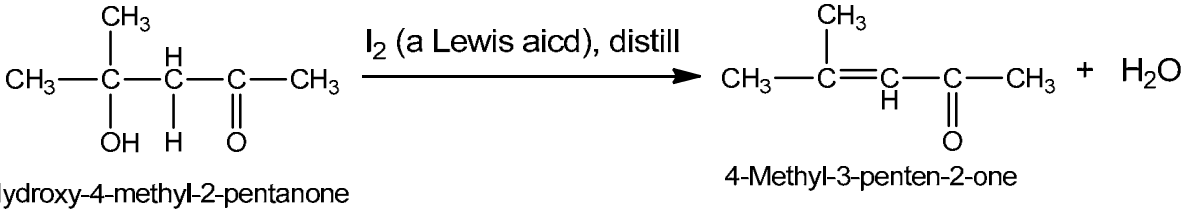
Hydroxide ion abstracts (step 1) a hydrogen ion from the α-carbon of the aldehyde to form carbanion-I, which attacks (step 2) on carbonyl carbon to form ion-II. Ion-II (an alkoxide) abstracts (step 3) a hydrogen ion from water to form the β-hydroxyaldehyde-III, regenerating hydroxide ion.

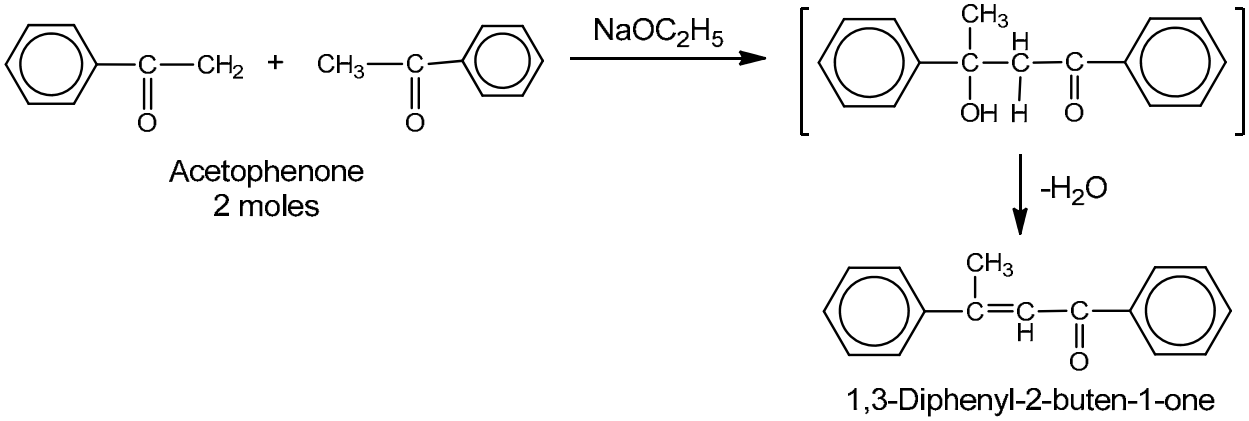
[The carbonyl group plays two roles in the aldol condensation. It not only provides the unsaturated linkage at which addition (step 2) occurs, but also makes the α-hydrogens acidic enough for carbanion formation (step 1) to take place**]**.

Dehydration of aldol products

The β-hydroxy aldehydes and β-hydroxy ketones obtained from aldol condensations are dehydrated very easily; resulting in to carbon-carbon double bond between the α- and β-carbon atoms. For example:

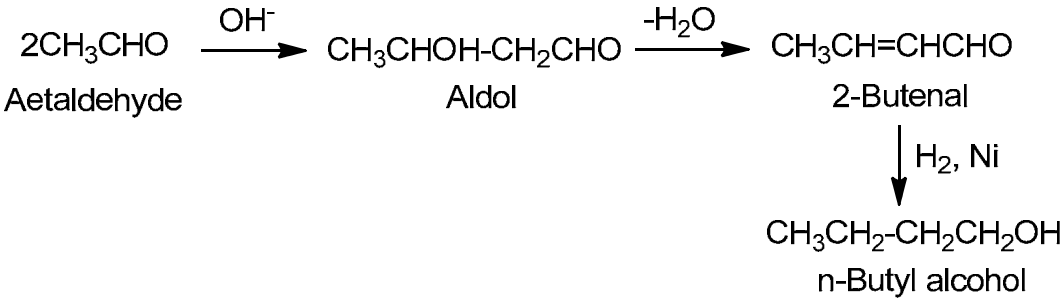




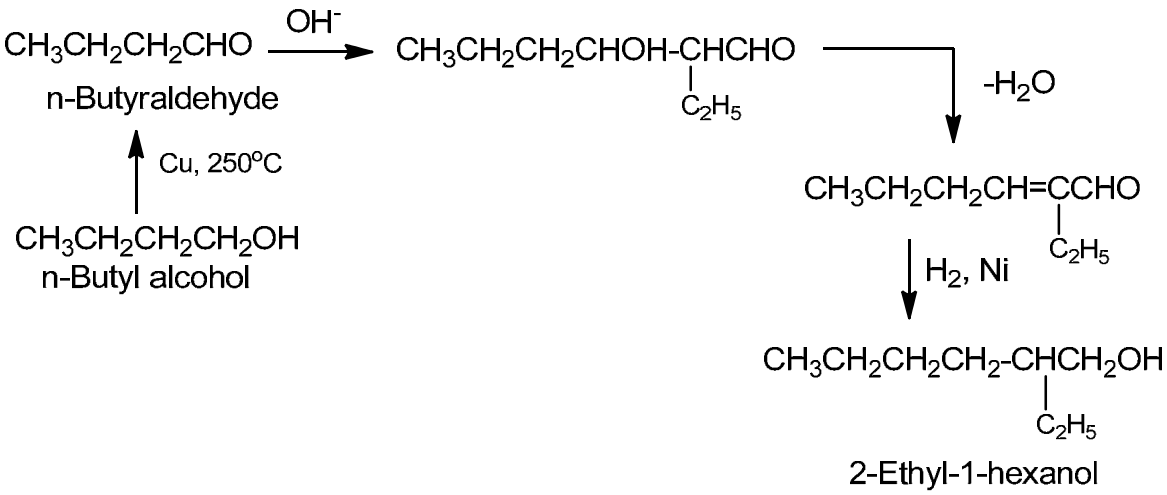


Use of aldol condensation in synthesis

Catalytic hydrogenation of α,β-unsaturated aldehydes and ketones yields saturated alcohols, addition of hydrogen occurring both at carbon-carbon and at carbon-oxygen double bonds. It is for the purpose of ultimately preparing saturated alcohols that the aldol condensation is often carried out. For example, n-butyl alcohol and 2-ethyl-1-hexanol are both prepared on an industrial scale in this way:

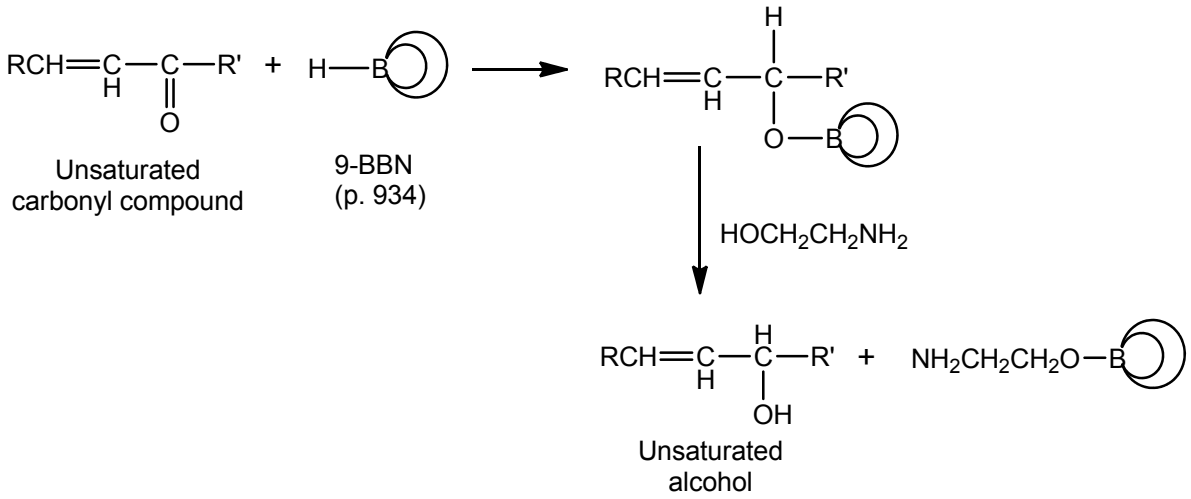


(i)



(ii)

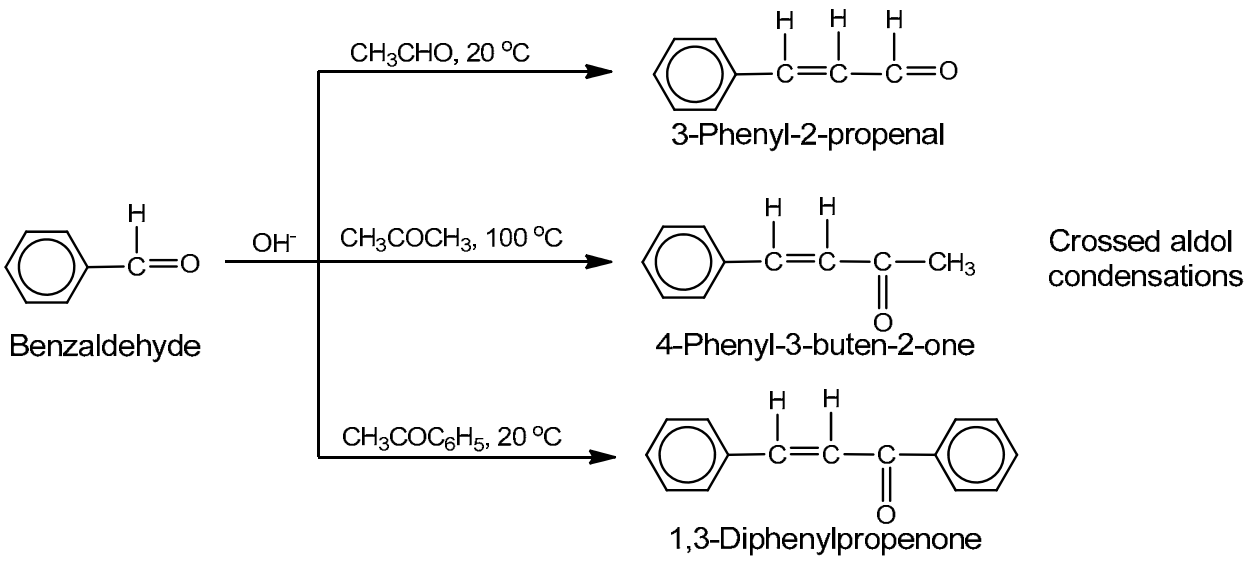
To prepare an unsaturated alcohol from an α,β-unsaturated aldehyde or ketone, we need a reagent that reduces only the carbonyl group and leaves the carbon-carbon double bond intact. A reagent that, selectively attacks one of several different functional groups is called a ***chemoselective reagent***. This particular job can be done by the hydroborane known as 9-BBN.



Crossed aldol condensation

An aldol condensation between two different carbonyl compounds so called crossed aldol condensation is not always feasible in the laboratory, since a mixture of the four possible products may be obtained.

Under certain conditions, a good yield of a single product can be obtained from a crossed aldol condensation: (a) one reactant contains no α-hydrogens and therefore is incapable of condensing with itself (e.g., aromatic aldehydes or formaldehyde); (b) this reactant is mixed with the catalyst; and then (c) a carbonyl compound that contains α-hydrogens is added slowly to this mixture.


CH3CHO, 20 °C
3-Phenyl-2-propenal
OH-
CH3COCH3, 100 °C
Benzaldehyde
4-Phenyl-3-buten-2-one
CH3COC6H5, 20 °C
1,3-Diphenylpropenone
Crossed aldol condensations

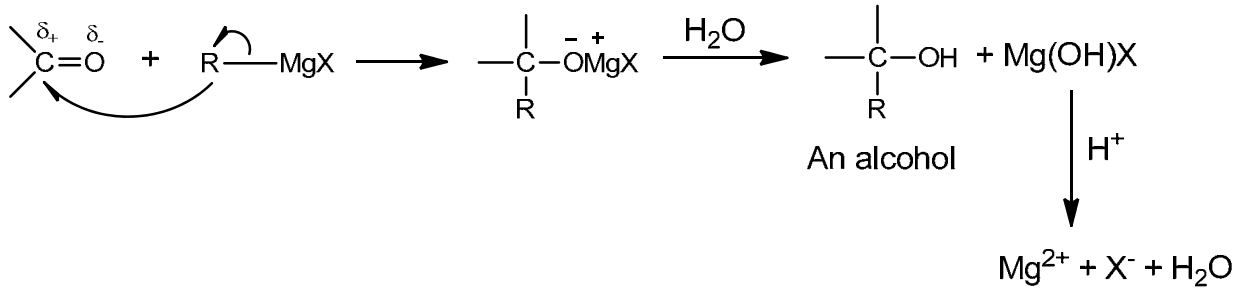
Addition of Grignard reagents :

The Grignard reagent has the formula RMgX, and is prepared by the reaction of metallic magnesium with the appropriate organic halide. This halide can be alkyl (1^o, 2^o, 3^o), allylic, arylalkyl (e.g., benzyl), or aryl (phenyl or substituted phenyl). The halogen may be –Cl, -Br, or –I. (Arylmagnesium chlorides must be made in the cyclic ether tetrahydrofuran instead of diethyl ether.)

$$RX + Mg \xrightarrow{\text{anhydrous ether}} RMgX$$

A Grignard reahent

One of the most important uses of the Grignard reagent lies in its reaction with aldehydes and ketones. The carbon-magnesium bond of the Grignard reagent is a highly polar bond, carbon being negative relative to electropositive magnesium. It is not surprising, then, that in the addition to carbonyl compounds, the organic group becomes attached to carbon and magnesium to oxygen. The product is the magnesium salt of the weakly acidic alcohol and is easily converted into the alcohol itself by the addition of the stronger acid, water.



Since the Mg(OH)X thus formed is a gelatinous material difficult to handle, dilute mineral acid (HCl, H_2SO_4) is commonly used instead of water, so that water-soluble magnesium salts are formed.

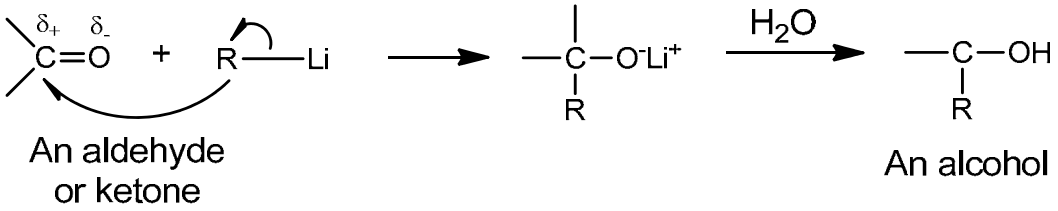
Grignard reagents are the classical reagents for such syntheses. Increasingly, however, organolithium compounds are being used instead, chiefly because they are less prone to unwanted side reactions. Organolithium can be prepared in the same way as Grignard reagents, by reaction of the metal with organic halides.

$$RX + 2Li \xrightarrow{\text{anhydrous ether}} RLi + LiX$$

An organolithium

Because lithium is more electropositive than magnesium, carbon-lithium bonds are more polar than carbon-magnesium bonds; carbon is more negative-more carbanion-like and organolithium are in general somewhat more reactive than Grignard reagents.

Organolithiums react with aldehydes and ketones in the same manner that we have shown for Grignard reagents, and yield the same kinds of products.

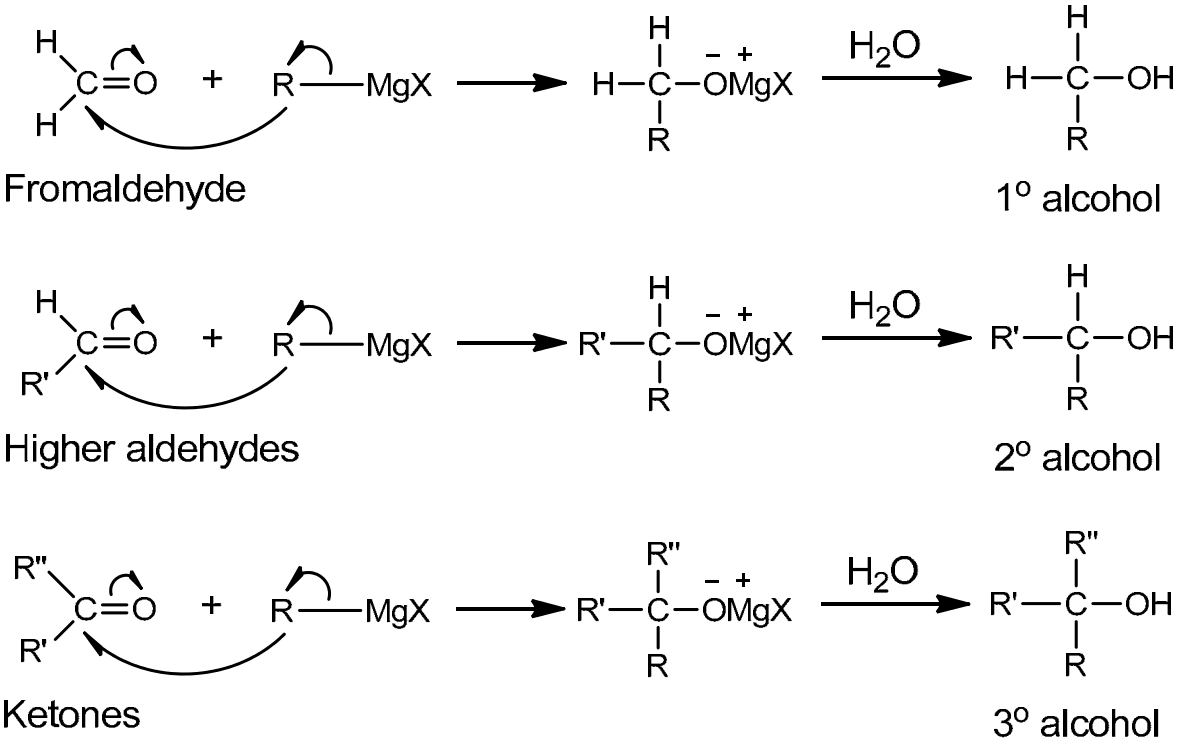


Using Grignard synthesis, two small organic molecules are convert into a bigger one. It will results in to formation of carbon-carbon bond. The Grignard reaction is thus an example of the typical reaction of aldehydes and ketones: nucleophilic addition.

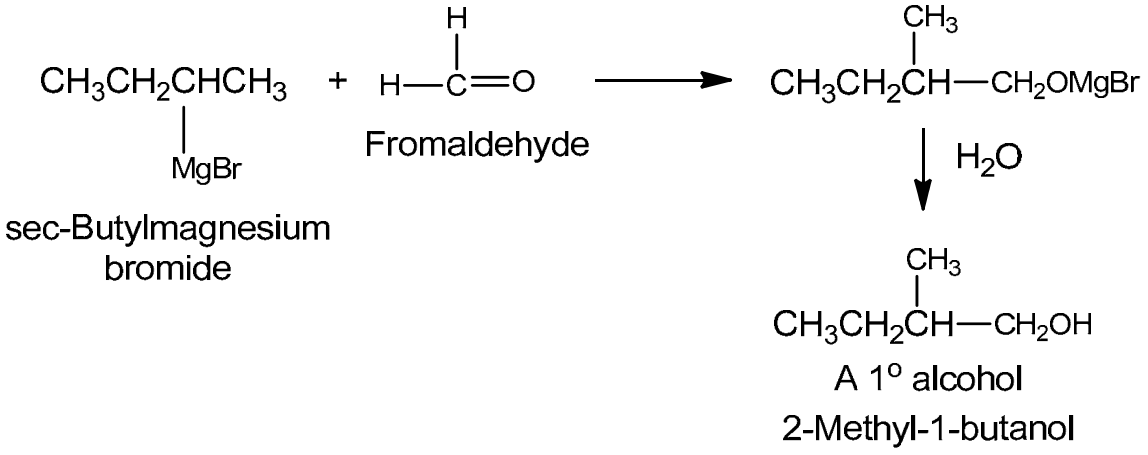
Grignard synthesis not only involve formation of a carbon-carbon bond, but the product contains the highly versatile group, -OH. And now it open the way for further synthesis, and the building of still bigger and more complicated structures.

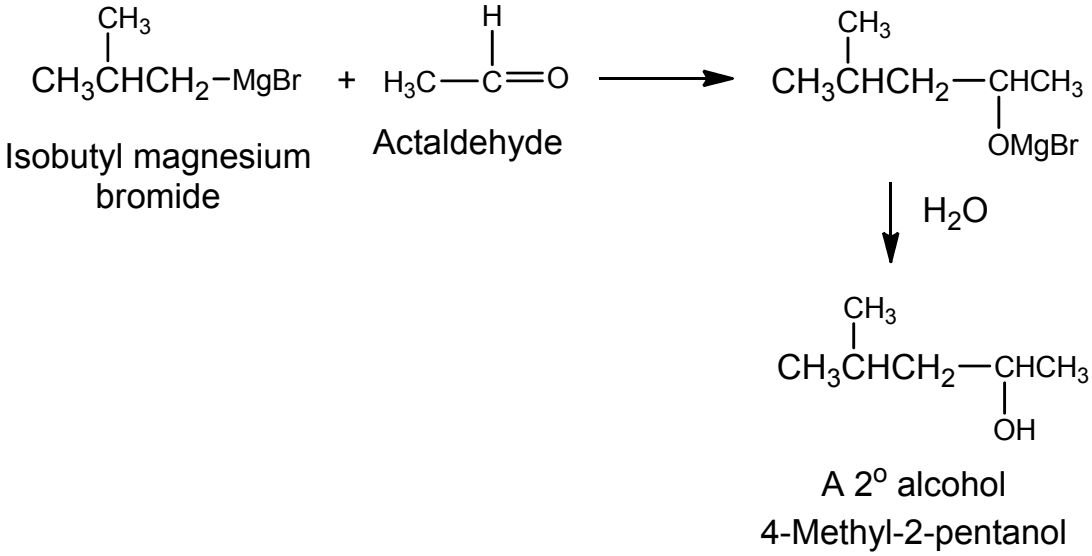
Products of the Grignard synthesis

The class of alcohol that is obtained form a Grignard synthesis depends upon the type of carbonyl compound used: formaldehyde, HCHO, yields primary alcohols; other aldehydes, RCHO, yield secondary alcohols; and ketones, R_2CO, yield tertiary alcohols.



The carbonyl carbon bears the –OH group in the product; and the number of hydrogens defines the alcohol as primary, secondary, or tertiary. For example:



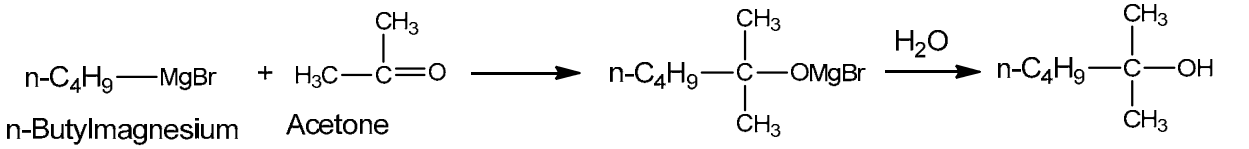


Isobutyl magnesium bromide

Actaldehyde

A 2° alcohol

4-Methyl-2-pentanol



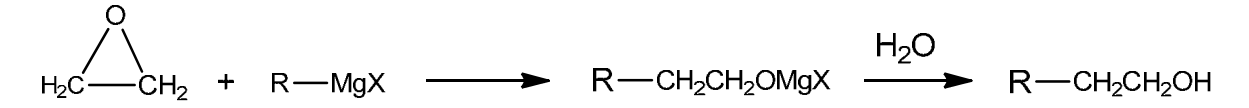
n-Butylmagnesium bromide

Acetone

A 3° alcohol

2-Methyl-2-hexanol

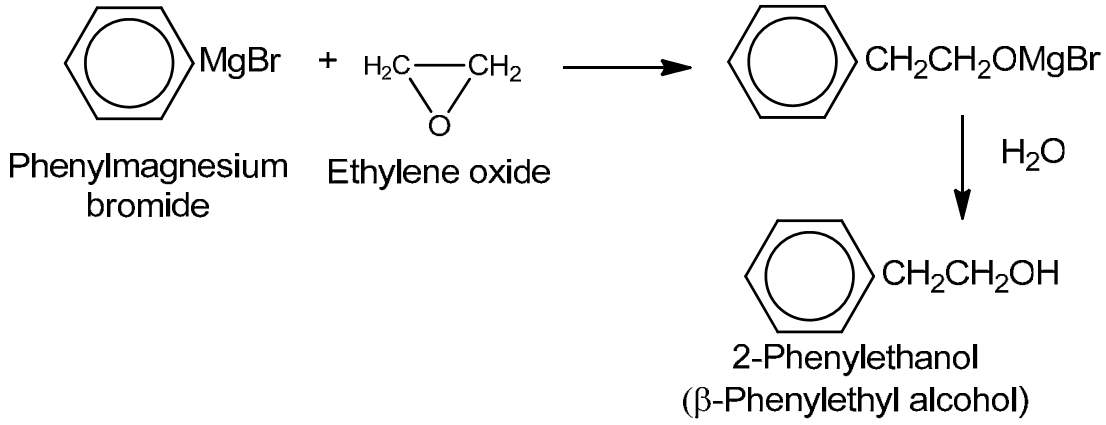
One can utilizes ethylene oxide to make primary alcohols containing two more carbons than the Grignard reagent. Here, too, the organic group becomes attached to carbon and magnesium to oxygen, this time with breaking of a carbon-oxygen σ-bond in a highly strained three-membered ring.



Ethylene oxide

A 1° alcohol: two carbons added

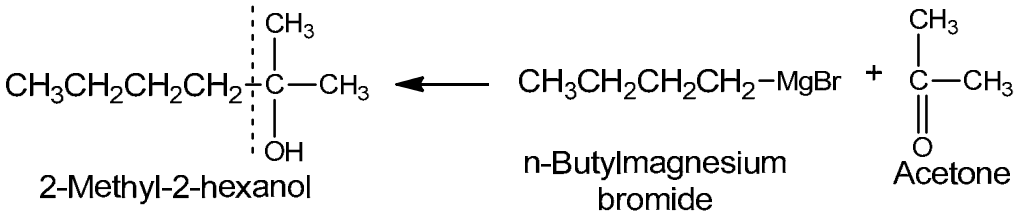
For example :

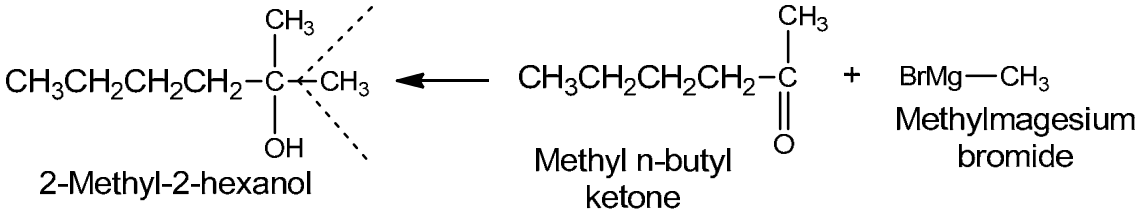


Planning a Grignard synthesis

How do we decide which Grignard reagent and which carbonyl compound to be used in preparing a particular alcohol? We have only to look at the structure of the alcohol we want to prepare. Of groups attached to the carbon bearing the –OH group, one must come from the Grignard reagent, the other two (including any hydrogens) must come form the carbonyl compound.

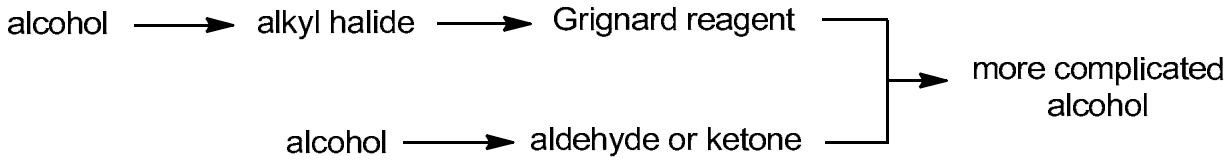
Most alcohols can be obtained from more than one combination of reagents; we usually choose the combination that is most readily available. Consider, for example, the synthesis of **2-methyl-2-hexanol:**



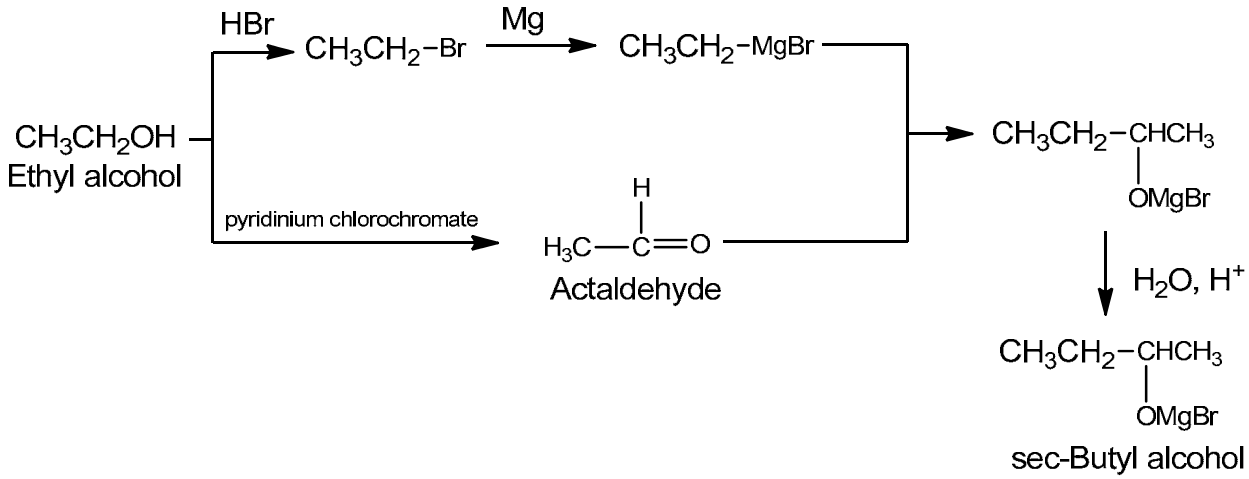


As shown, we could make this either from the four-carbon Grignard reagent and acetone, or from the methyl Grignard reagent and the six-carbon aliphatic ketone. Which combination do we pick? As we shall see below, it depends upon which reactants are more readily available.

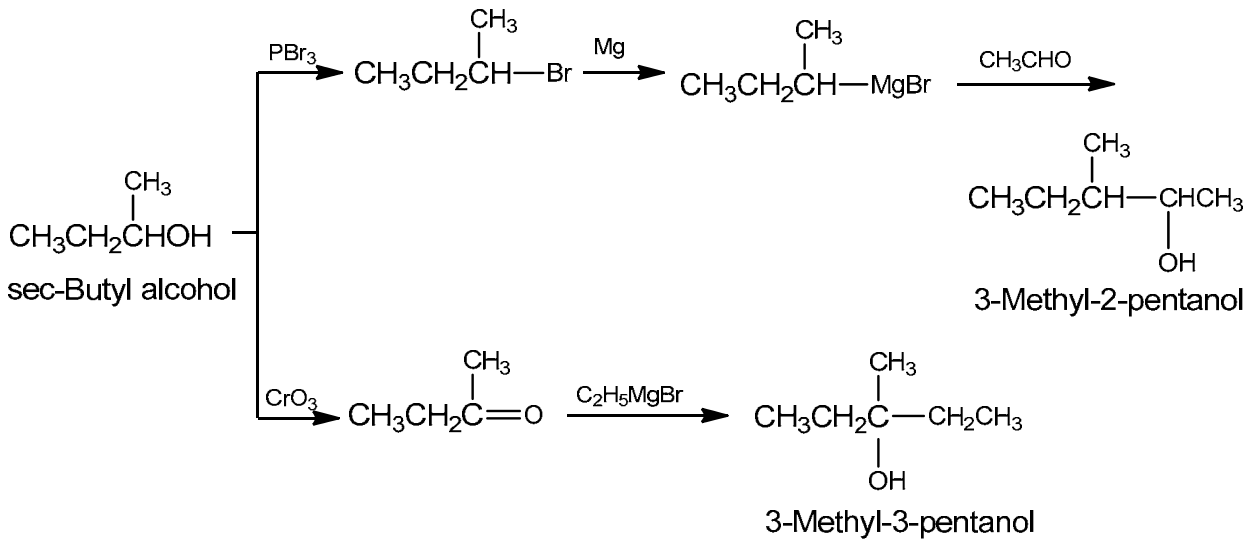
Let us look at this matter of how we obtain the reactants for Grignard syntheses. We know that aldehydes and ketones are most often made from alcohols. We know that Grignard reagents are made from organic halides and that these, too, are most often made from alcohols. Finally, we know that the simple alcohols are among our most readily available compounds. We have available to us, then, a synthetic route leading from simple alcohols to more complicated ones.



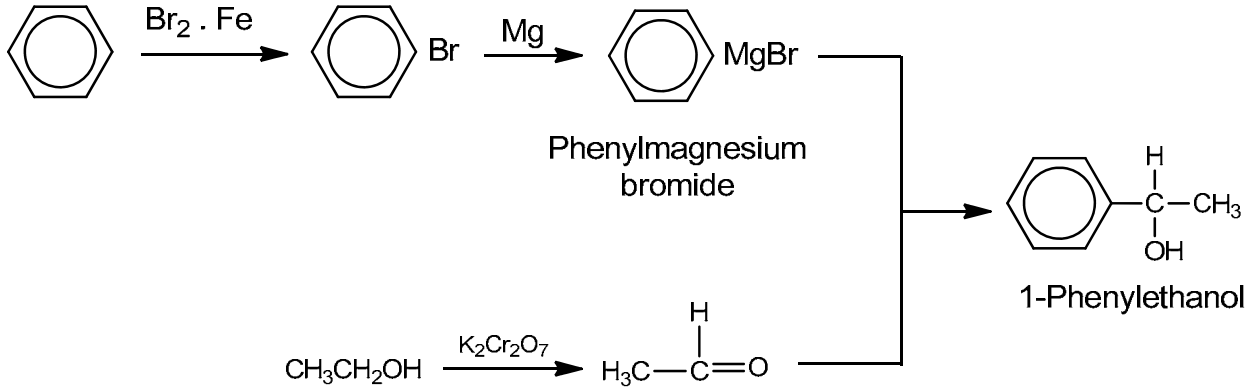
As a simple example, consider conversion of the two-carbon **ethyl alcohol into the four-carbon sec-butyl alcohol:**



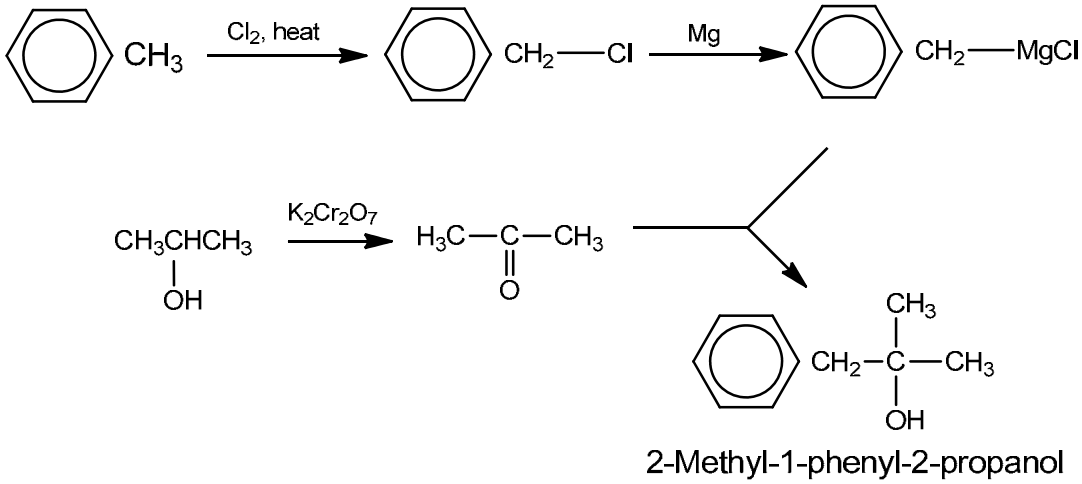
Using the **sec-butyl alcohol**, we could prepare even **larger alcohols**:



Even starting from benzene we can make, 1-phenylethanol.

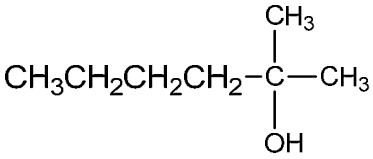


And from toluene we can make 2-methyl-1-phenyl-2-propanol.



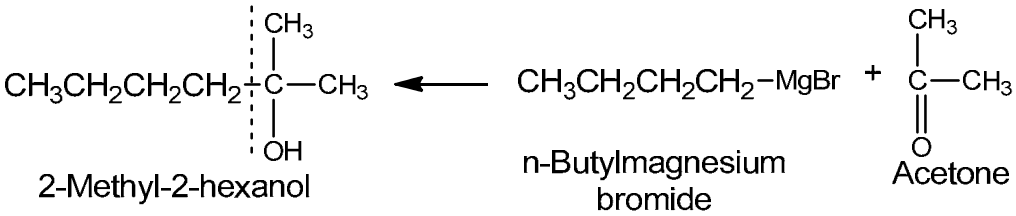
In almost every organic synthesis it is best to work backwards from the compound we want (RETRO SYNTHESIS). There are relatively few ways to make a complicated **alcohol**; there are relatively few ways to make the **Grignard reagent** or the aldehyde or ketone; and so on back to our primary starting materials.

Let us suppose (and this is quite reasonable) that we have available all alcohols of four carbons or fewer, and that we want to make, say, 2-methyl-2-hexanol. Let us set down the structure of this target molecule, and see what we need to make it.



2-Methyl-2-hexanol

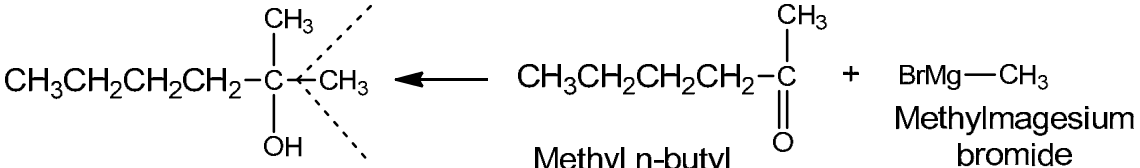
Since it is a tertiary alcohol, we must use a Grignard reagent and a ketone. Using the same approach as before, there are two possibilities:



2-Methyl-2-hexanol

n-Butylmagnesium bromide

Acetone

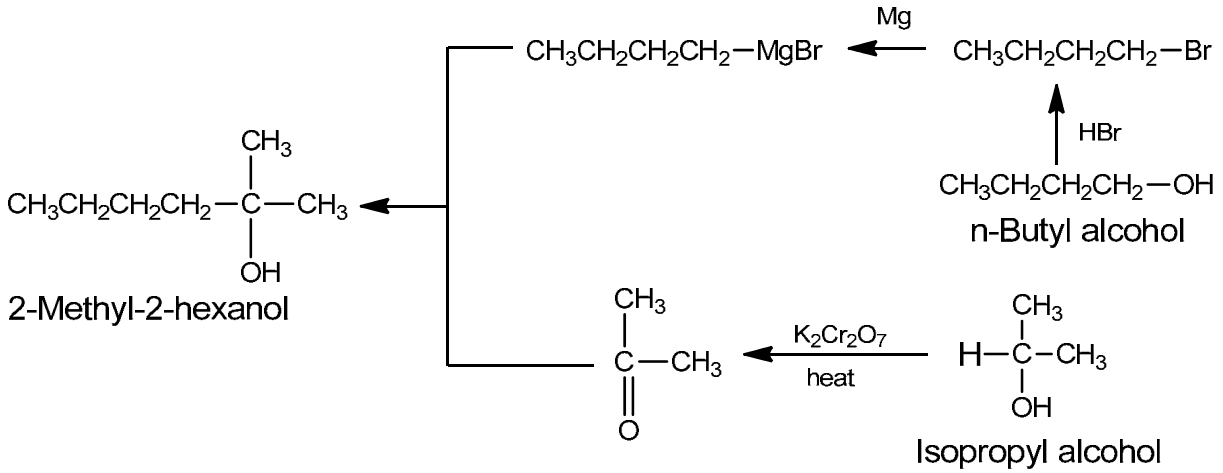


2-Methyl-2-hexanol

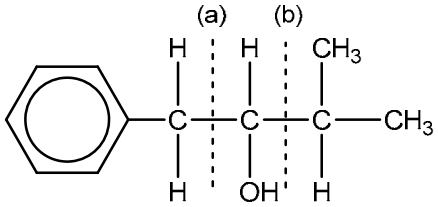
Methyl n-butyl ketone

Methylmagesium bromide

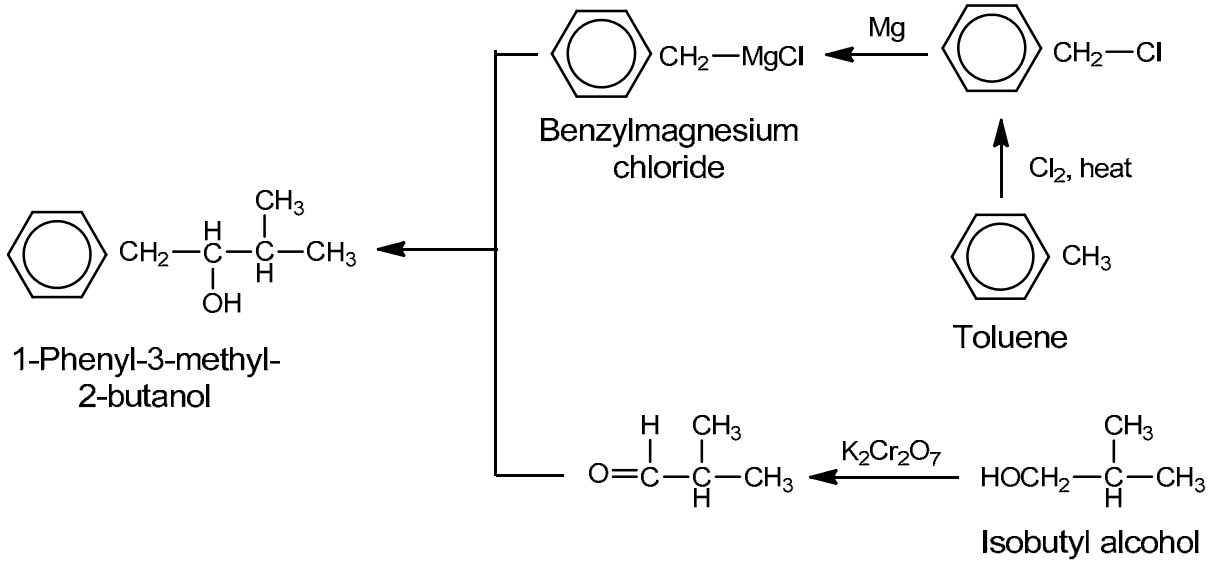
Of these two possibilities we would select the one involving the four-carbon Grignard reagent and the three-carbon ketone. The Grignard reagent can be made only from the corresponding alkyl halide, n-butyl bromide, and that in turn most likely from an alcohol, n-butyl alcohol. Acetone requires, can be prepared from isopropyl alcohol. Putting together all in the entire synthesis, we have the following sequence:



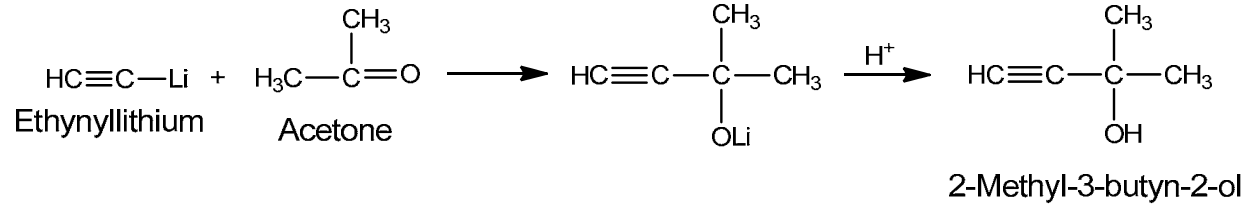
We can prepare 3-methyl-1-phenyl-2-butanol using starting materials toluene and isobutyl alcohol.

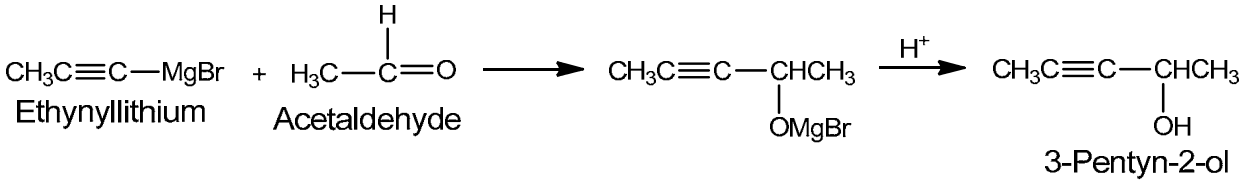


Synthesis can be written as :



When lithium acetylides and alkynyl Grignard reagents add to aldehydes and ketones it give alcohols. For example:

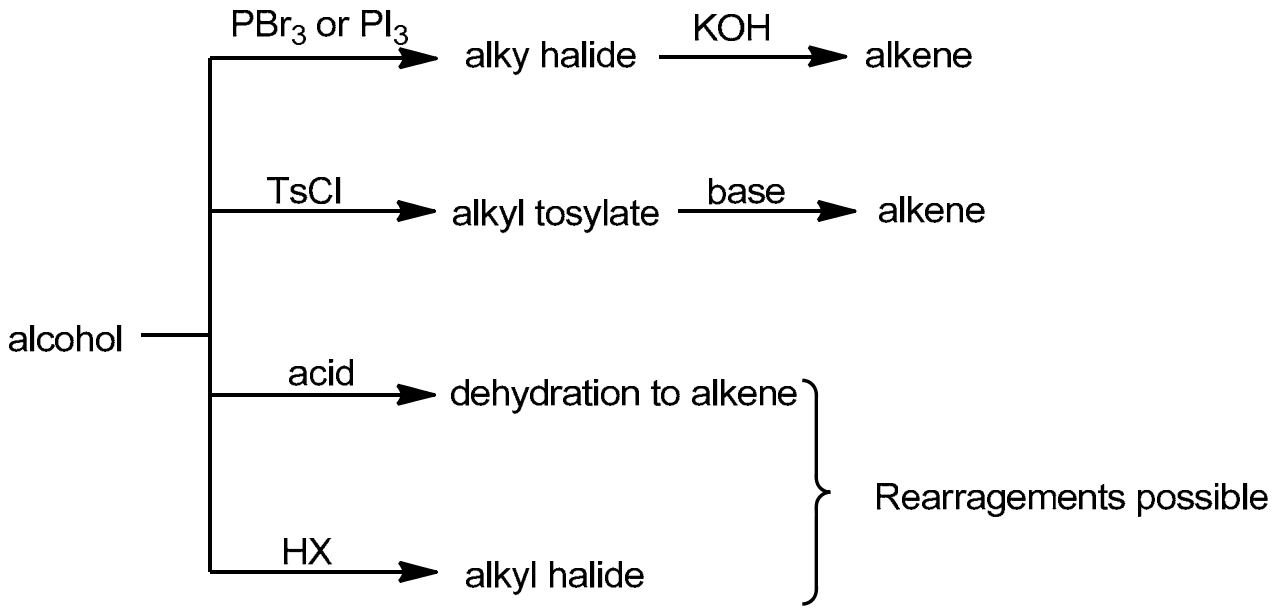




We have now formed compounds that contain not only-OH, but a second highly reactive group, the carbon-carbon triple bond. The triple bond can be converted with a high degree of stereoselectivity into a double bond; and at this double bond there can occur various addition reactions, to yield a wide variety of products-each of which also contains the -OH group.

Syntheses using alcohols

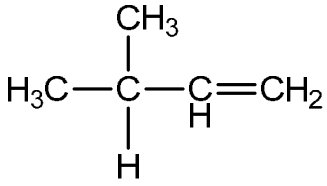
The alcohols can be converted into other kinds of compounds having the same carbon skeleton; from complicated alcohols we can make complicated aldehydes, ketones, acids, halides, alkenes, alkynes, alkanes, etc. Alkyl halides are prepared from alcohols by use of hydrogen halides or phosphorus halides. Alkenes are prepared from alcohols either by direct dehydration or by dehydro halogenation of intermediate alkyl halides; to avoid rearrangement we often select dehydrohalogenation of halides even though this route involves an extra step, Or, sometimes better, we use elimination from alkyl sulfonates.



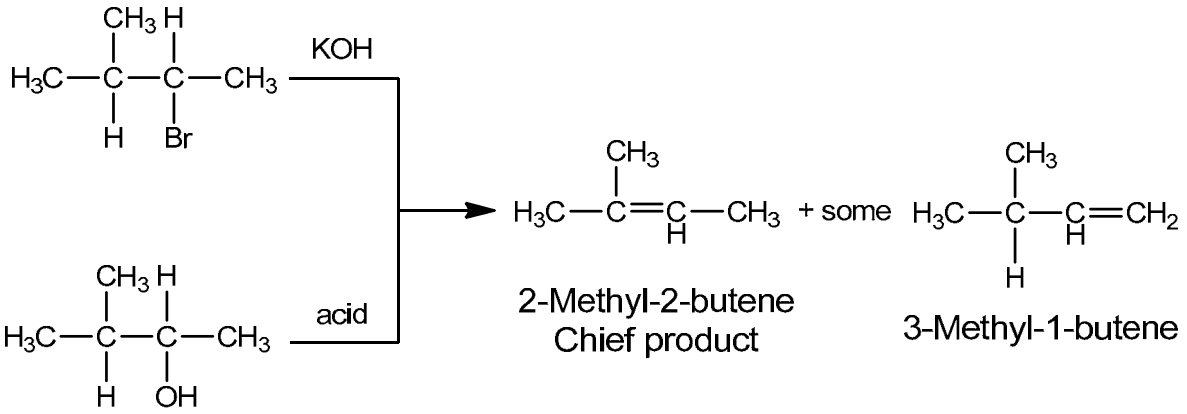
Alkanes, are best prepared from the corresponding alkenes by hydrogenation, so that we have a route from complicated alcohols to complicated alkanes.

Complicated aldehydes and ketones are made by oxidizing complicated alcohols. By reaction with Grignard reagents these aldehydes and ketones can be converted into even more complicated alcohols, and so on.

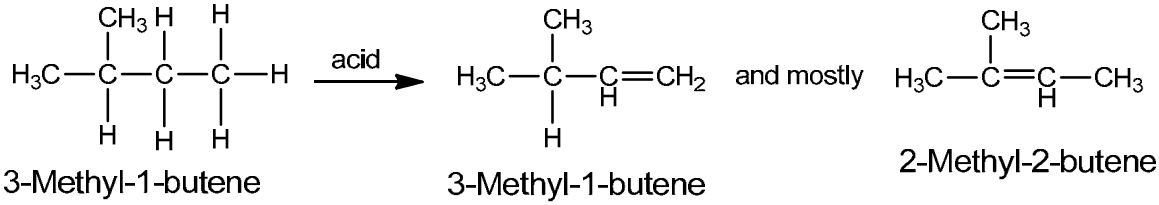
3-methyl-1-butene could be prepared by dehydrohalogenation of an alkyl halide of the same carbon skeleton, or by dehydration of an alcohol.



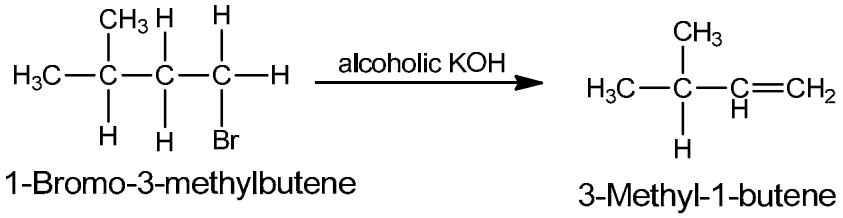
3-Methyl-1-butene



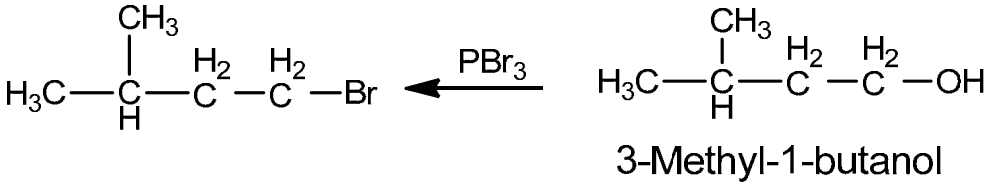
We would select, a compound with the functional group attached to C-1. Even so, if we were to use the alcohol, there would be extensive rearrangement to yield, again, the more stable 2-methyl-2-butene:



Only dehydrohalogenation of 1-bromo-3-methylbutane would yield the desired product in pure form:

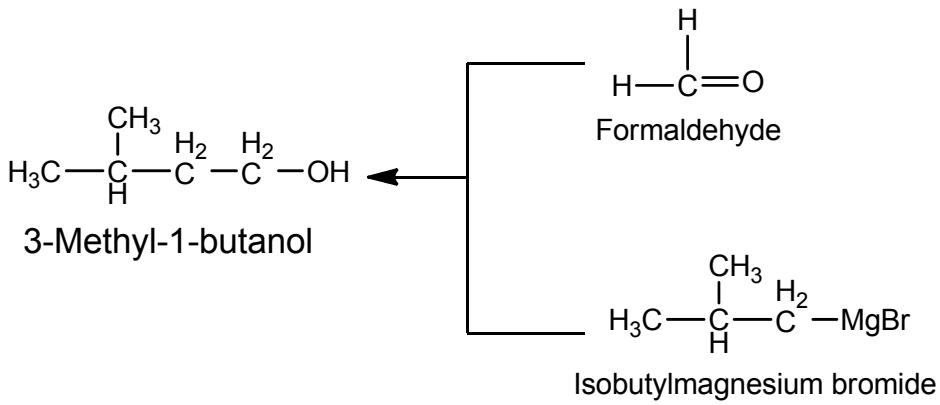


As usual, we would prepare the halide from the corresponding alcohol, in this case 3-methyl-1-butanol using either hydrogen bromide or PBr_3.

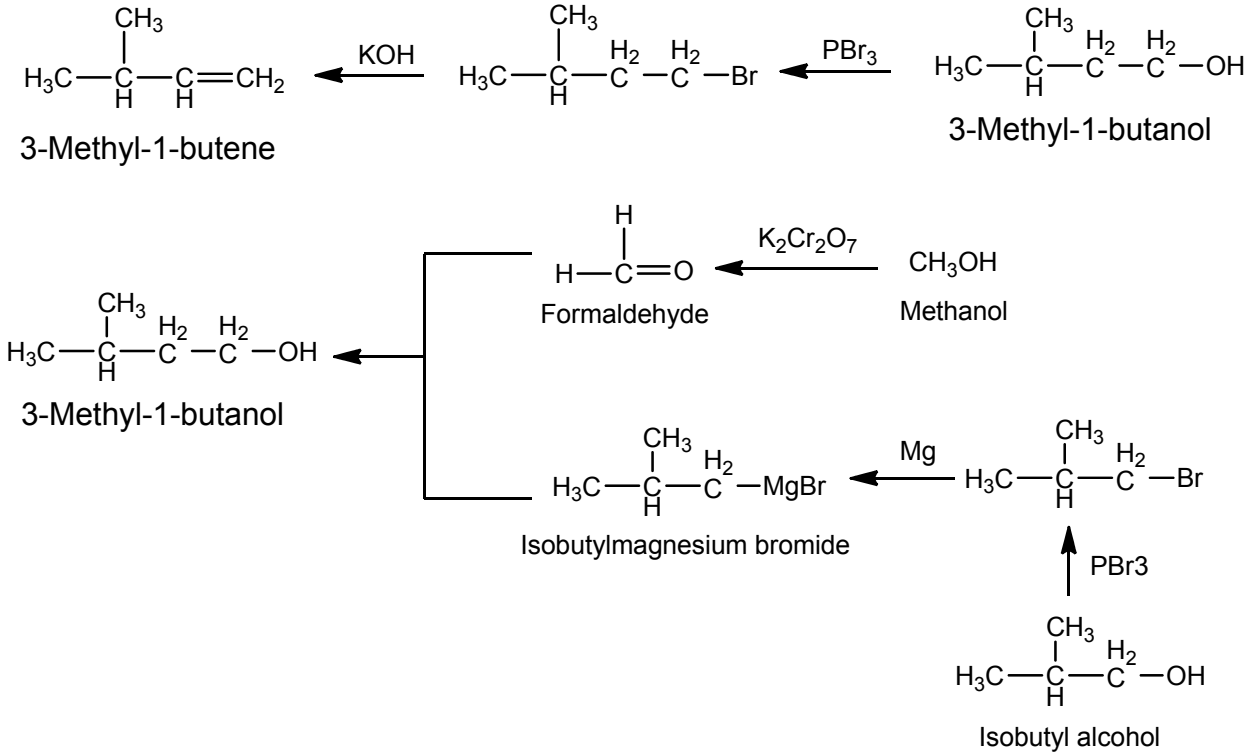


Now, how do we make 3-methyl-1-butanol? It can be prepared by the reaction of a Grignard reagent with formaldehyde. The necessary Grignard reagent is

isobutylmagnesium bromide, which we could have prepared from isobutyl bromide, and that in turn from isobutyl alcohol.



The formaldehyde is made by oxidation of methanol. The entire sequence, from which we could expect to obtain quite pure 3-methyl-1-butene, is the following:



Q. What is Grignard reagents ? What are its limitations?

Limitations of the Grignard synthesis

The very reactivity that makes a Grignard reagent so useful strictly limits how we may use it. We must keep this reactivity in mind when we plan the experimental conditions of

the synthesis, when we select the halide that is to become the Grignard reagent, and when we select the compound with which it is to react.

i) Any compound containing hydrogen attached to an electronegative element-oxygen, nitrogen, sulfur, or even triply bonded carbon-is acidic enough to decompose a Grignard reagent.

ii) A Grignard reagent reacts rapidly with oxygen and carbon dioxide, and with nearly every organic compound containing a carbon-oxygen or carbon-nitrogen multiple bond.

iii) During reaction between a Grignard reagent and an aldehyde, alkyl halide, aldehyde, and the ether used as solvent must be dried and freed of the alcohol from which each was made.

iv) Grignard reagent will not even form in the presence of water.

v) Our apparatus must be completely dry before we start.

vi) We must protect the reaction system from the water vapor, oxygen, and carbon dioxide of the air, water vapor can be kept out by use of calcium chloride tubes, and oxygen and carbon dioxide can be swept out of the system with dry nitrogen.

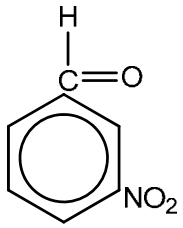
Having done all this we may hope to obtain a good yield of product-providing we have properly chosen the halide and the aldehyde.

vii) We cannot prepare a Grignard reagent from a compound (e.g., $HOCH_2CH_2Br$) that contains, in addition to halogen, some group (e.g., -OH) that will react with a Grignard reagent; if this were tried, as fast as a molecule of Grignard reagent formed it would react with the active group (-OH) in another molecule to yield an undesired product ($HOCH_2CH_2$-H).

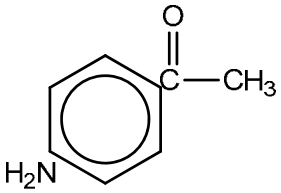
viii) We must be particularly watchful in the preparation of an arylmagnesium halide, in view of the wide variety of substituents that might be present on the benzene ring. Carboxyl (-COOH), hydroxyl (-OH), amino ($-NH_2$), and $–SO_3H$ all contain hydrogen attached to oxygen or nitrogen, and therefore are so acidic that they will decompose a Grignard reagent.

ix) Grignard reagent adds to the carbonyl group (C=O), and we shall learn that it adds similarly to -COOR and -C≡N groups. The nitro ($-NO_2$) group oxidizes a Grignard reagent. It turns out that only a comparatively few groups may be present in the halide molecule from which we prepare a Grignard reagent; among these are -R, -Ar, -OR, and -Cl (of an aryl chloride).

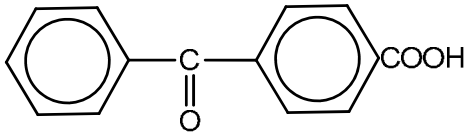
x) An aldehyde (or other compound) with which a Grignard reagent is to react may not contain other groups that are reactive toward a Grignard reagent. For example, a Grignard reagent would be decomposed before it could add to the carbonyl group of :



m-Nitrobenzaldehyde



p-Aminoacetophenone



p-Benzoylbenzoic acid

The kind of precautions described here must be taken in any kind of organic synthesis: we must not restrict our attention to the group we happen to be interested in, but must look for possible interference by other functional groups.