Alcohols
2-Synthesis

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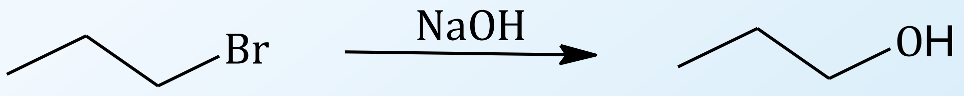
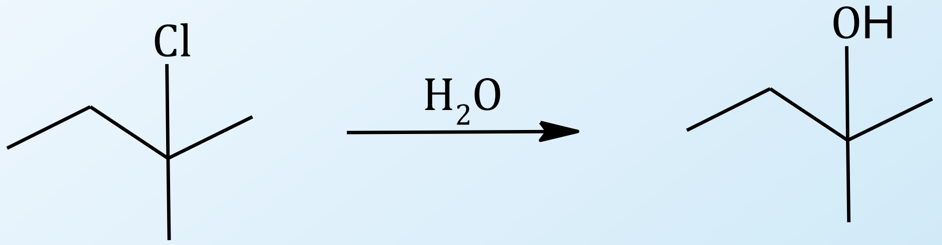
Synthesis of Alcohols – From Alkyl Halides

Alcohols can be synthesized from several functional groups. We will learn about them one by one.

1) **From Alkyl Halides/Substitution Reaction**: Nucleophilic substitution of OH^- on alkyl halide. The substitution can be S_N2 or S_N1.



S_N2 substitution – needs primary halide and strong nucleophile.



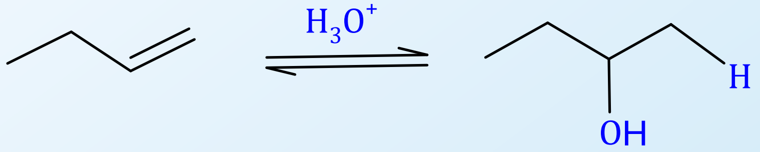
S_N1 substitution – needs tertiary halide and a weak nucleophile will also work.

Synthesis of Alcohols – From Alkenes - 1

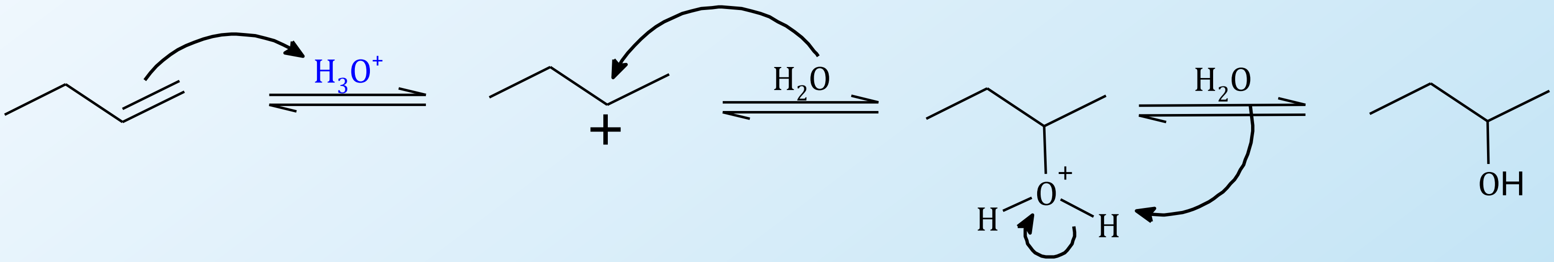
2) **From Alkenes/Addition Reactions**: There are many synthesis of alcohols from alkenes using a variety of reagents to give different types of alcohols.

a) Hydration of alkenes: This is carried out by water in acid solution (H_3O^+). A reversible reaction with Markovnikov regioselectivity. Rearrangement can also occur.

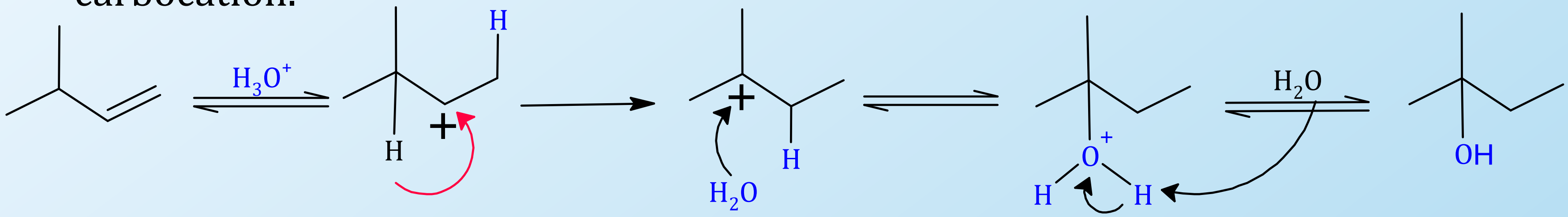
General Reaction:



General Mechanism:

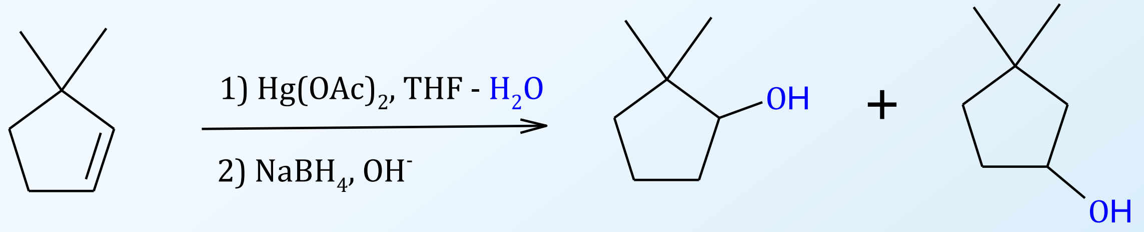


Rearrangement: The second step shows the **H-shift** to form a more stable carbocation.

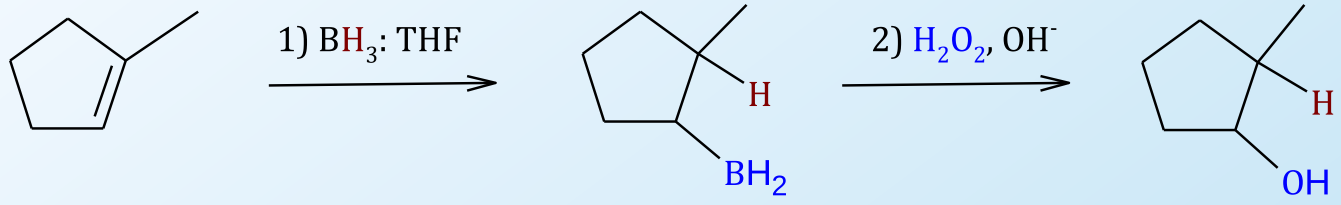


Synthesis of Alcohols –From Alkenes - 2

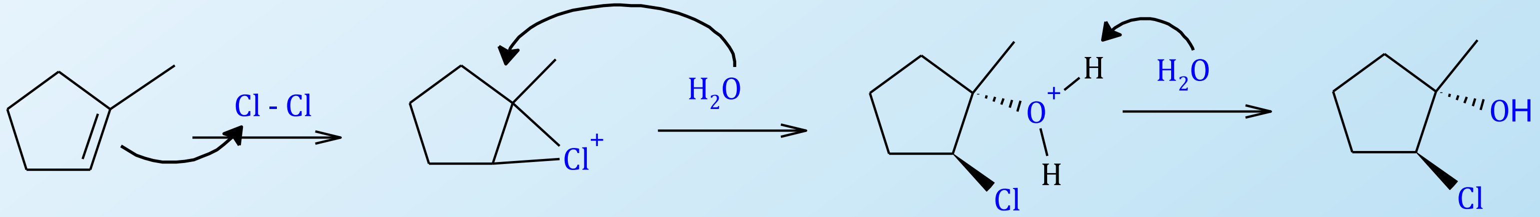
b) <u>Oxymercuration – demercuration:</u> Markovnikov addition which occurs without rearrangement.



c) <u>Hydroboration:</u> Uses borane to form anti-Markovnikov's alcohol.



d) <u>Halohydrin</u>: Addition of halide and alcohol. Markovnikov's addition and **<u>anti</u>** addition, i.e., the two groups are added on opposite sides.

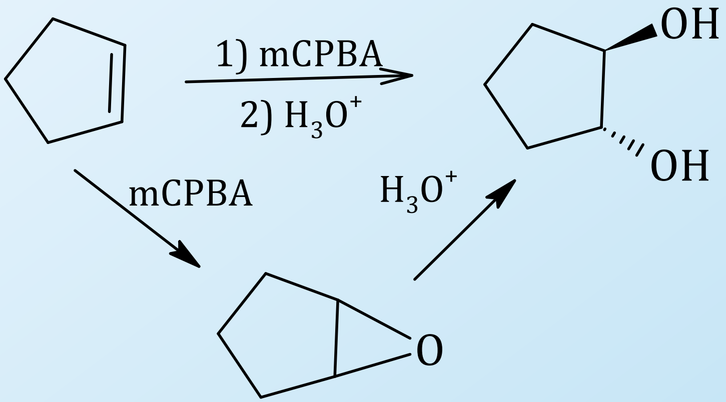


Synthesis of Alcohols –From Alkenes - 3

e) Making **syn** diols: Either OsO_4 or $KMnO_4$ will give cis 1,2 diols (glycols).

Both these reagents give **syn** diols i.e. addition of alcohols on same side.

f) Making **anti** diols: Ring opening of an epoxide with water under acid or base catalyzed conditions gives the trans diol. (We will cover more in the ether chapter). The epoxide ring opening causes **anti** addition of alcohols groups.

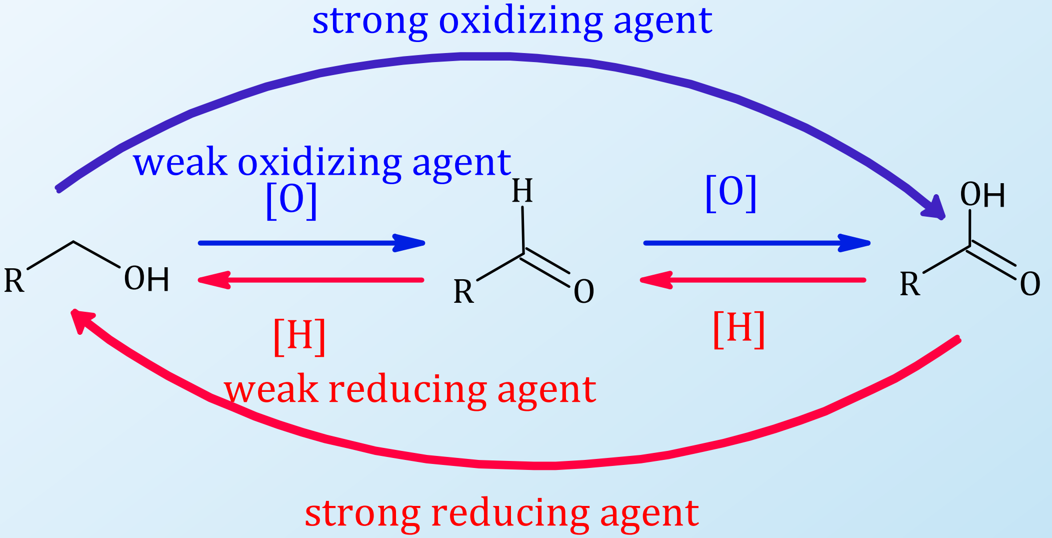


Synthesis of Alcohols – From Carbonyls

3) **From Carbonyls/Reduction**: Alcohols can be made by reduction of aldehydes, ketones, carboxylic acids and carboxylic esters.

Organic reduction reactions add the equivalent of H_2 to a molecule OR removal of oxygen. The chart below shows the redox sequence from alcohol to acid. Alcohols can be made from aldehyde or ketone using a weak reducing agent, or from carboxylic acid and ester using a strong reducing agent.

(*Note: we will cover oxidation of alcohol when we do reactions of alcohols*)

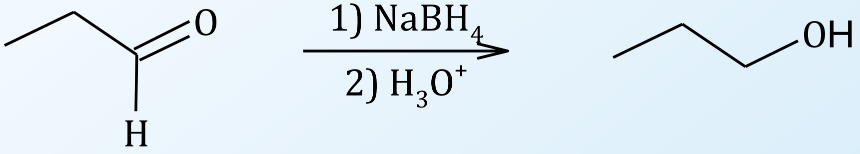


Weak reducing agent: sodium borohydride – $NaBH_4$.

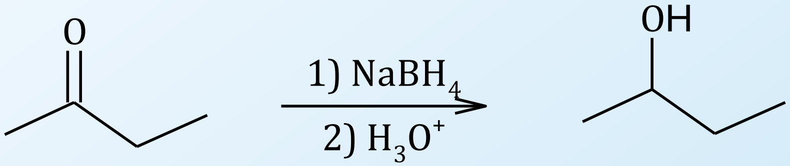
Strong reducing agent: lithium aluminum hydride, $LiAlH_4$. Very reactive.

Synthesis of Alcohols – From Aldehyde and Ketone

An aldehyde (terminal group) will always primary alcohols while a ketone (internal group) will give a secondary alcohol. <u>Note:</u> When writing the reagents for this reaction don't write $NaBH_4$, H_3O^+ - those two chemicals cannot be used together. They have to be used one step at a time, hence the step 1 and step 2.

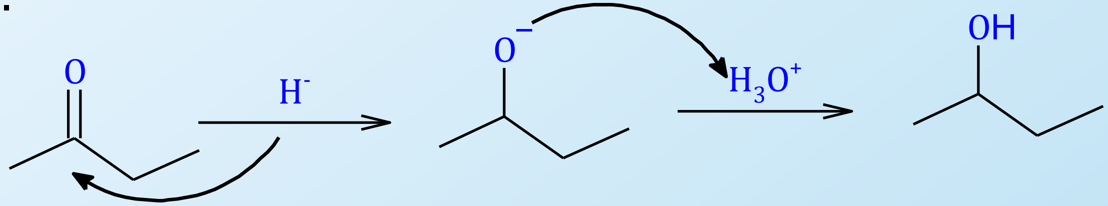


1° alcohol



2° alcohol

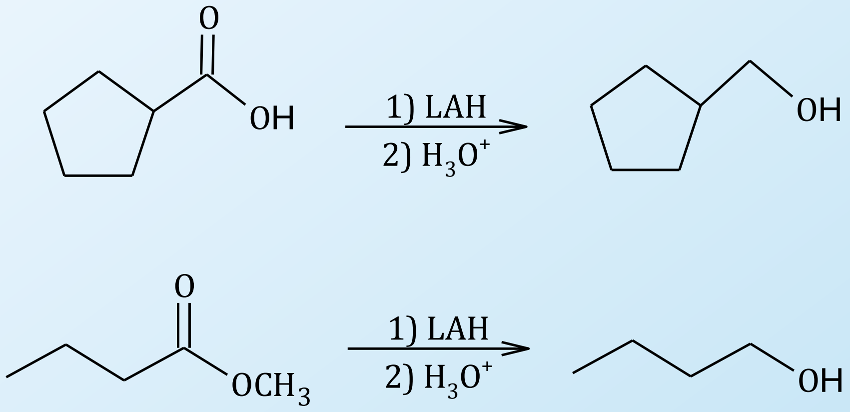
Mechanism involves the hydride nucleophile attacking the electropositive C of the carbonyl and the oxide formed will get protonated in the second step in presence of a weak acid.



Synthesis of Alcohols – From Acid and Ester

Carboxylic acids and esters can be reduced to give primary alcohols. Although carboxylic acid is clearly a terminal group, while ester is an internal group, both will still result in only generating a 1° alcohol.

- $LiAlH_4$ (also written as LAH) is used because $NaBH_4$ is not effective, the former is stronger.
- It is better to reduce esters and not acids because acids have the acidic proton which can react with the strong nucleophile, H^-, of $LiAlH_4$.



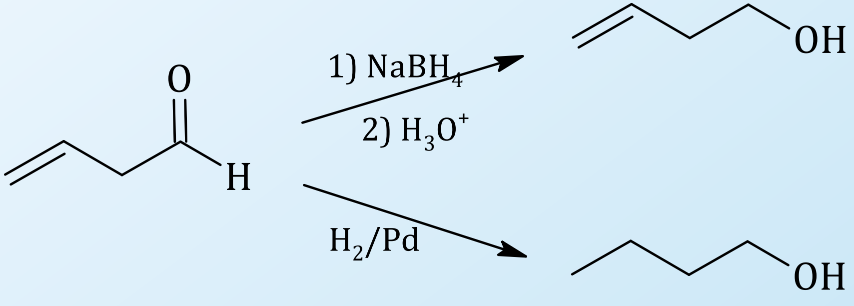
1° alcohol

1° alcohol

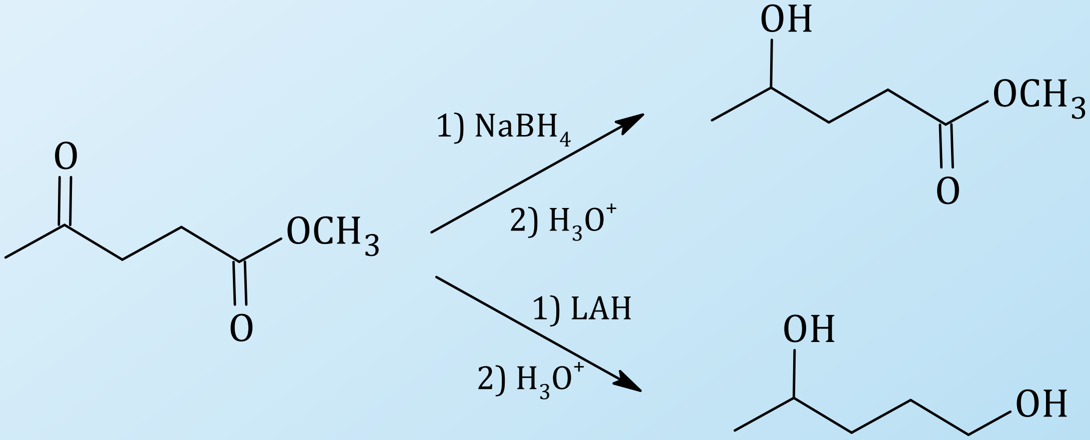
Synthesis of Alcohols – Reduction Examples

When there are more one functional groups on a molecule, then you have to choose the reducing agent carefully so you reduce only the group you want to otherwise you may reduce other groups well.

If there is an alkene and aldehyde, and you want to reduce only aldehyde, you cannot use hydrogenation – it will reduce both carbonyl and alkene.



LAH is the strongest reagent and can reduce both aldehyde/ketone and carboxylic acid, so if you want to reduce only aldehyde then use a weak reducing agent $NaBH_4$.



Synthesis of Alcohols – From Carbonyls Using Grignard Reagents - 1

Organometallic reagents are formed from the reaction of a metal with alkyl halide. The alkyl group bonded to the metal is an anion – carbonanion.

$R – Li$ $R\text{-}MgX$ R_2CuLi

Lithium reagents are most ionic due to the most electropositive nature of lithium. This makes the carbonanion the most negative and thus a strong nucleophile. Magnesium is little less electropositive and lastly the copper lithium reagents. Lithium reagents are most reactive and the least are the dialkylcuprate reagents (they offer more controlled reactions).

Synthesis of Alcohols – Making Grignard Reagent

Making the Grignard reagent (GR): Organometallics can be made by treating alkyl halides with the metals. Reactions should be done in moisture free environment since the carbonanions formed are very reactive with water.

$$R - X + Mg \longrightarrow R - MgX$$

R = alkyl halide and X is any halide except F

Grignard regents are strong bases thus will react with water or alcohols, which is why alcohols are not used as solvents in Grignard synthesis. (Ethers are used as solvents)

Reaction with water or alcohol

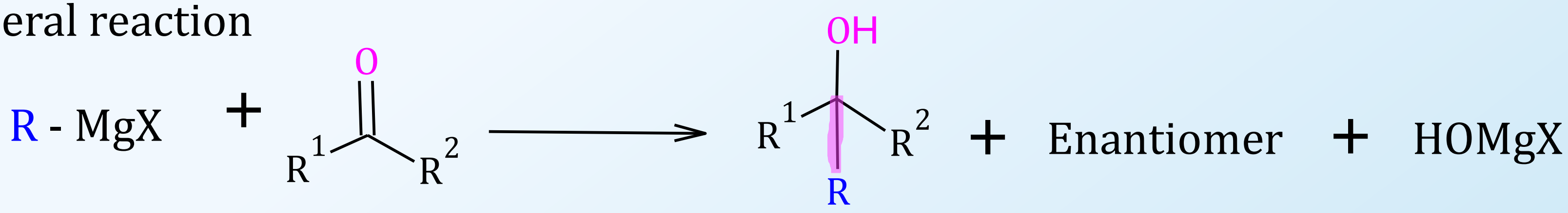
$$CH_3CH_2 - MgBr + HOH \longrightarrow CH_3CH_2\text{-}H + Mg^{2+} + OH^- + Br^-$$

stronger base *weaker base*

$$CH_3CH_2 - MgBr + HOCH_3 \longrightarrow CH_3CH_2\text{-}H + Mg^{2+} + CH_3O^- + Br$$

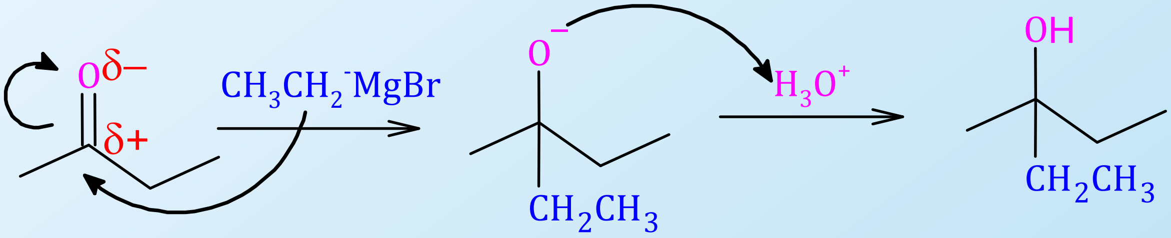
Synthesis of Alcohols – Grignard Reagents –2 General Mechanism

General reaction



The interesting thing to note here is the new carbon – carbon bond formation (highlighted in pink) using GR. In these reactions se synthesize an alcohol group, and we can also add carbons during this reaction to form a larger molecule.

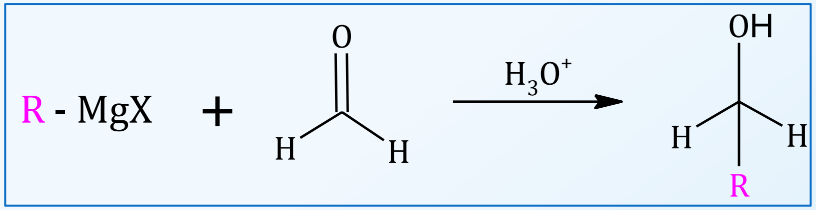
General mechanism involves the carbonanion of the Grignard attacking the electropositive carbon of carbonyl to form a tetrahedral carbon, and an oxide. In the next step acid is added to protonate the oxide to give the alcohol. Again, note that this is a two step reaction like reduction with hydrides.

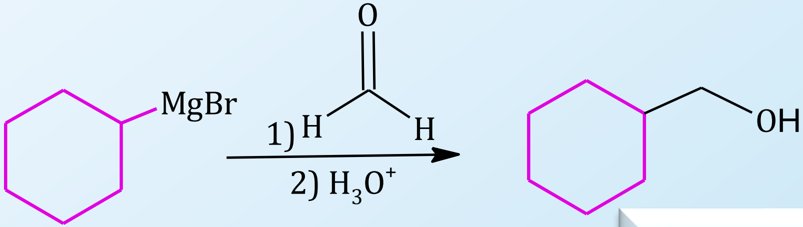


Synthesis of Alcohols – From Aldehyde and Ketone Using Grignard Reagents - 3

Example

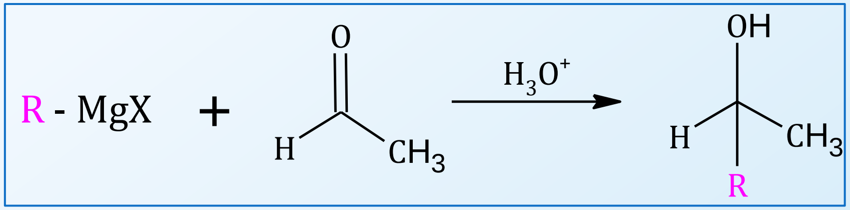
Synthesis of 1° alcohol from formaldehyde (HCHO)

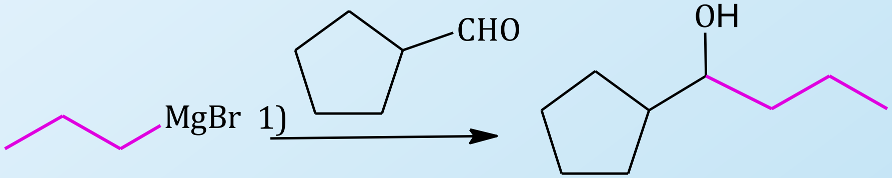




1° alcohol

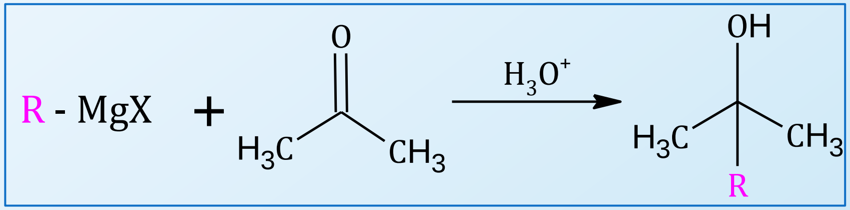
Synthesis of 2° alcohol from any other aldehyde

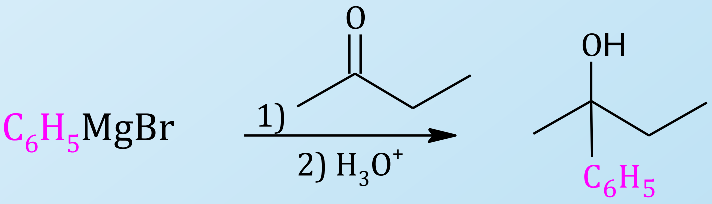




2° alcohol

Synthesis of 3° alcohol from ketones

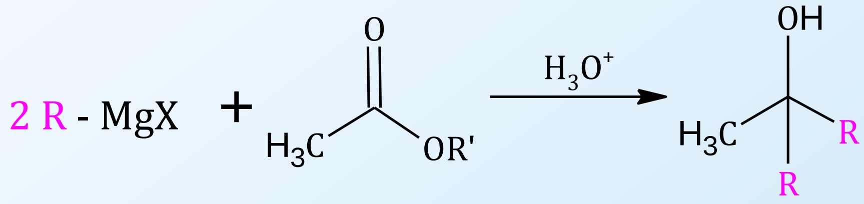


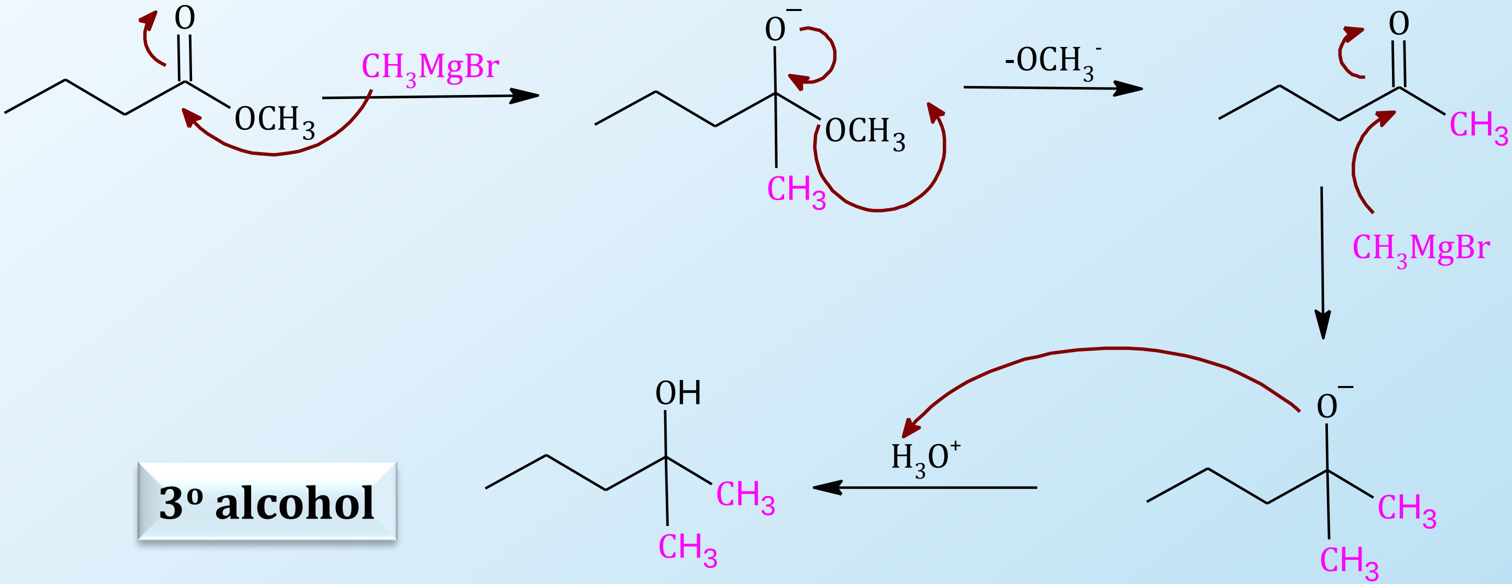


3° alcohol

Synthesis of Alcohols – From Esters Using Grignard Reagents - 4

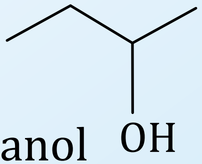
- Esters give tertiary alcohols in which *two* alkyl substituents come from the Grignard reagent.
- Grignard reagents do not add to carboxylic acids – they undergo an acid-base reaction, generating the hydrocarbon of the Grignard reagent.



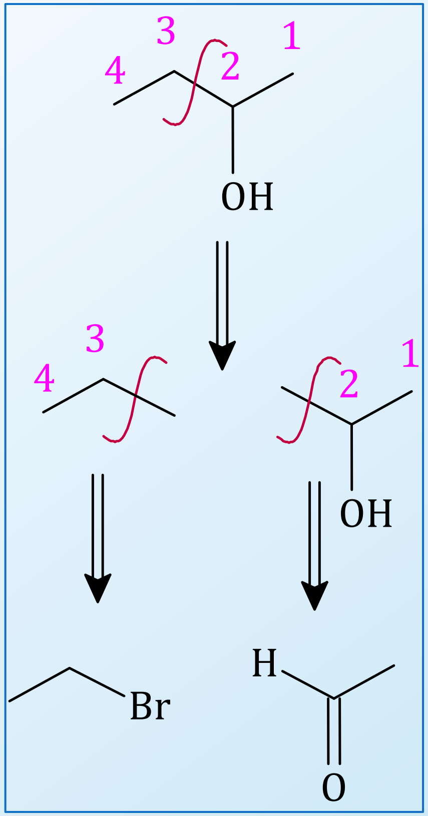


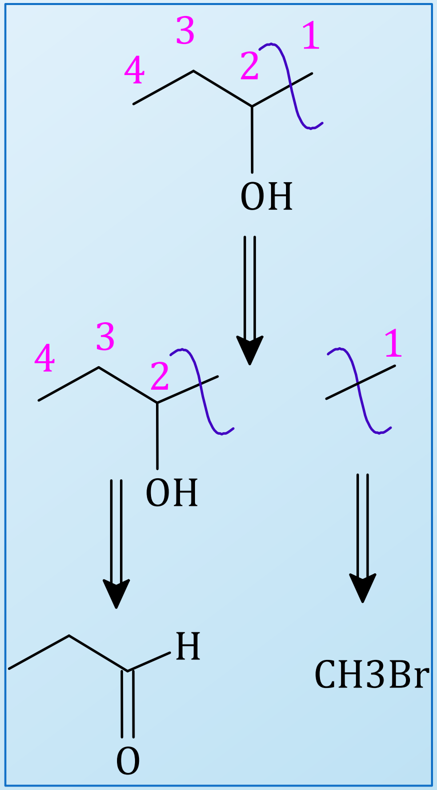
3º alcohol

Worked Example: Synthesizing a secondary alcohol: 2-butanol.

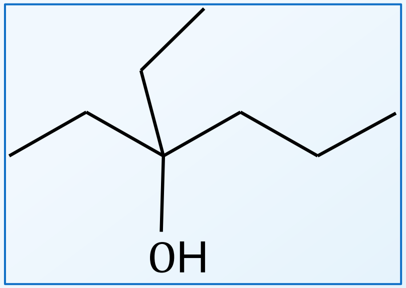


- The starting material should be an aldehyde + alkyl halide because 2-butanol is a 2^o alcohol. There are two routes since the alcohol is asymmetric.
- The fragment with oxygen will come from aldehyde and the one without oxygen will be made from the Grignard reagent.
- I have numbered the carbons so you can see fragmentation.





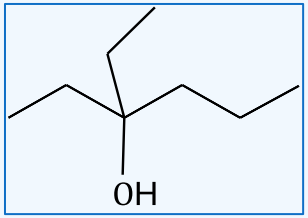
Worked Example: Synthesize the alcohol: 3-ethylhexan-3-ol.



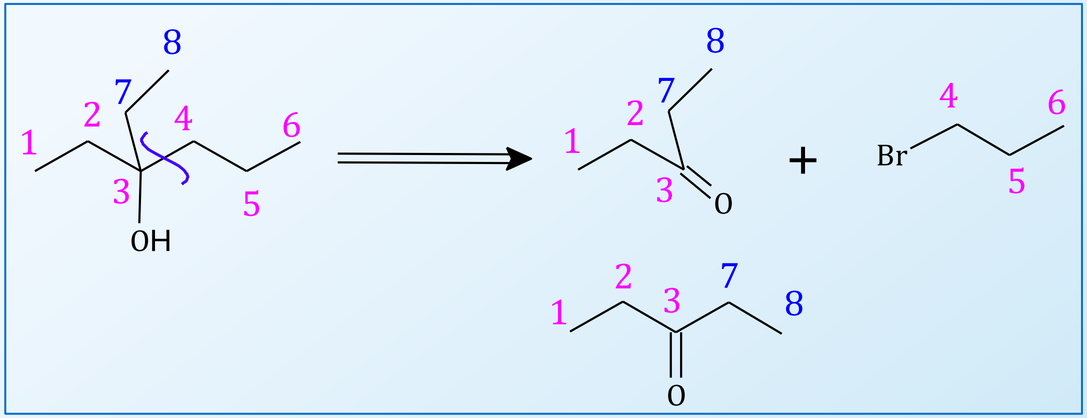
- The starting material should be a ketone because it is a 3^{o} alcohol. It can also be an ester because two of the fragments (ethyl) are identical.
- There are two routes that start with ketones.
- I have numbered the carbons so you can see fragmentation.
- Go to the next slide to see the retrosynthesis

Using Ketone *Step 1: Fragment at carbon with alcohol group.*
Step 2: Use appropriate ketone and Grignard reagent.

Using Ester *Use appropriate ester and two moles of Grignard reagent.*

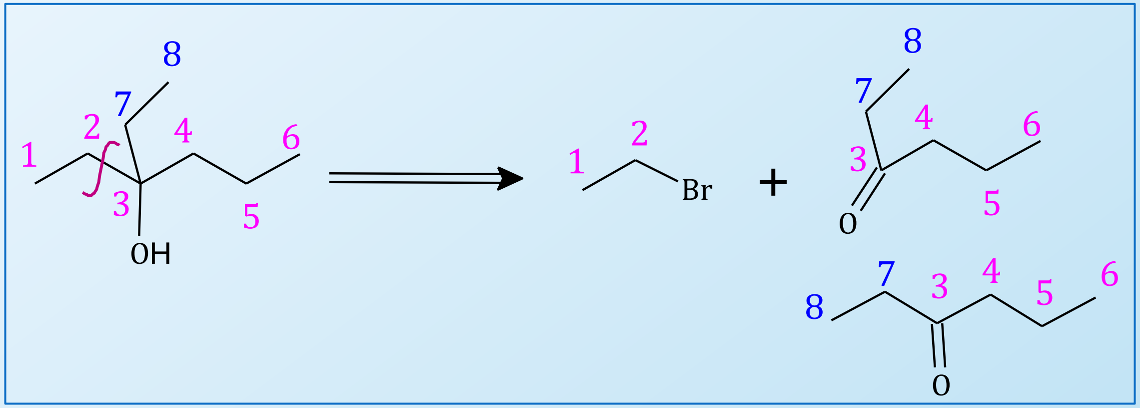


Fragment at carbon with alcohol group.



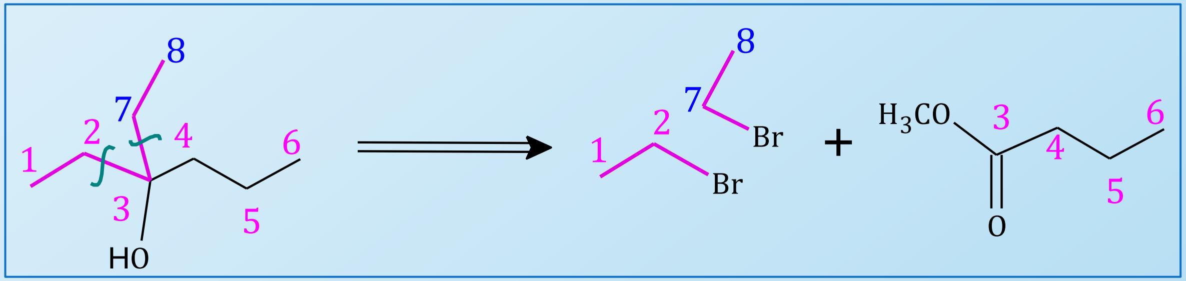
Using Ketone

Use appropriate ketone and Grignard reagent.



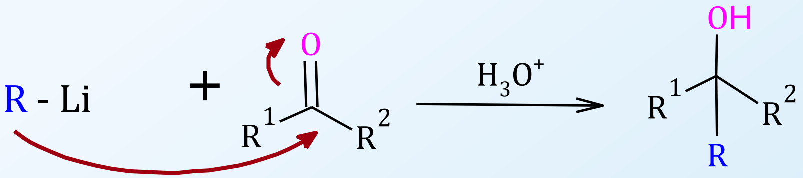
Using Ester

Use appropriate ester and two moles of Grignard reagent.



Using Lithium and Alkynide Reagents

- For both the reagents, starting material can be any carbonyl according to what is needed – 1^{o}, 2^{o} or 3^{o} alcohol.
- Organolithium reagents are similar to Grignard regents.



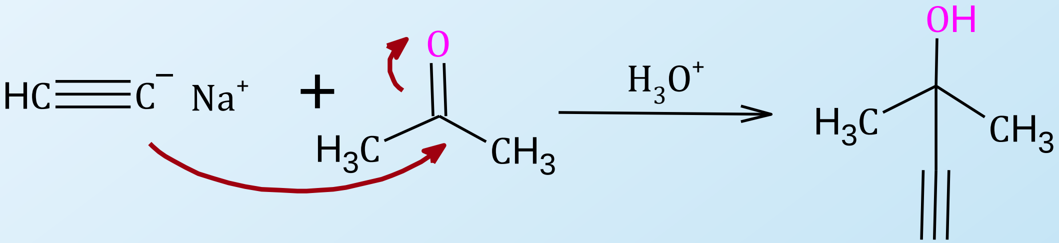
Organolithium reagent

Aldehyde or ketone

1^{o}, 2^{o} or 3^{o} alcohol

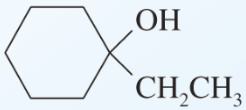
- Alkynide ions will also react with carbonyls to give alcohols, and now in addition to the alcohol group there will also be an alkyne group.

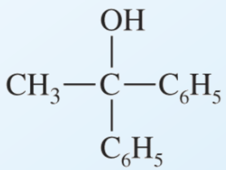
$$HC\equiv CH \xrightarrow{NaNH_2} HC\equiv C^- \; Na^+$$



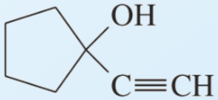
Examples

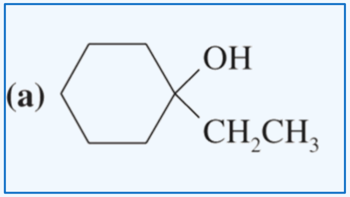
Synthesize the following alcohols using the appropriate alkyl halide.

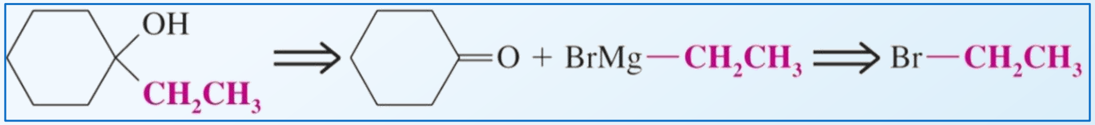
(a)


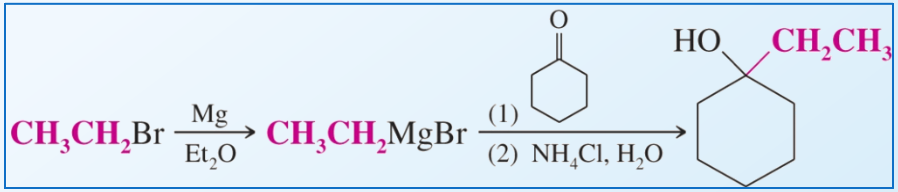
(b)


$$CH_3-\overset{\overset{\large OH}{|}}{\underset{\underset{\large C_6H_5}{|}}{C}}-C_6H_5$$

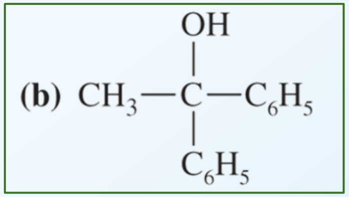
(c)




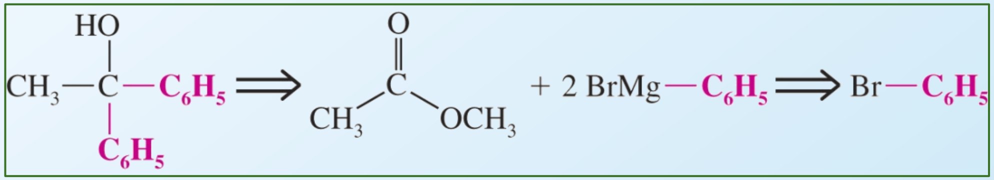




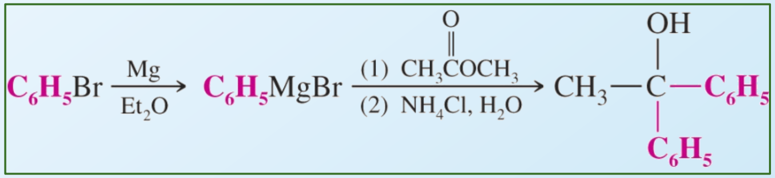
$CH_3CH_2Br \xrightarrow[Et_2O]{Mg} CH_3CH_2MgBr \xrightarrow[(2)\ NH_4Cl,\ H_2O]{(1)}$



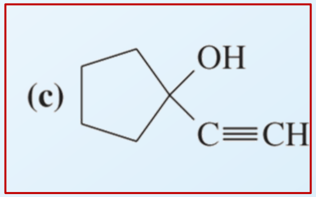
(b) $CH_3-\overset{\overset{\large OH}{|}}{\underset{\underset{\large C_6H_5}{|}}{C}}-C_6H_5$

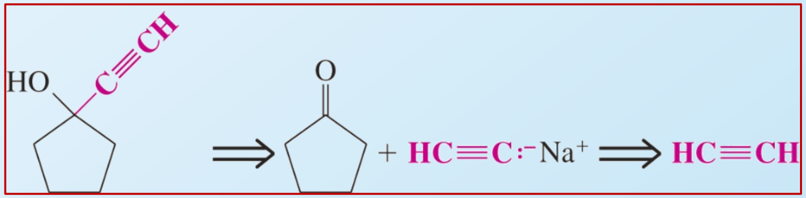


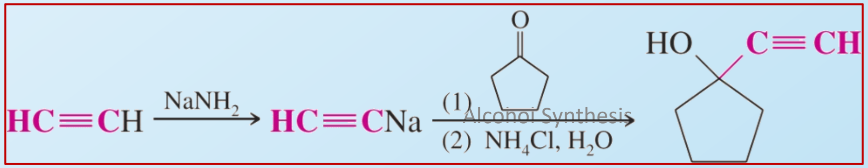
$CH_3-\overset{\overset{\large HO}{|}}{\underset{\underset{\large C_6H_5}{|}}{C}}-C_6H_5 \Longrightarrow CH_3\overset{O}{\overset{\|}{C}}OCH_3 + 2\ BrMg-C_6H_5 \Longrightarrow Br-C_6H_5$



$C_6H_5Br \xrightarrow[Et_2O]{Mg} C_6H_5MgBr \xrightarrow[(2)\ NH_4Cl,\ H_2O]{(1)\ CH_3\overset{O}{\overset{\|}{C}}OCH_3} CH_3-\overset{\overset{\large OH}{|}}{\underset{\underset{\large C_6H_5}{|}}{C}}-C_6H_5$







$HC{\equiv}CH \xrightarrow{NaNH_2} HC{\equiv}CNa \xrightarrow[(2)\ NH_4Cl,\ H_2O]{(1)}$

Key Concepts

Synthesis

- From alkenes of alcohols
- Of diols
- Reduction of carbonlys
- Using Grignard reagents and other organometallic reagents.