

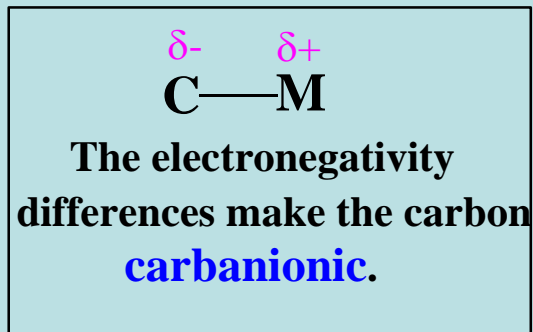
Chapter 12

ALCOHOLS FROM CARBONYL COMPOUNDS

Oxidation-Reduction and Organometallic Compounds

Organometallic Compounds

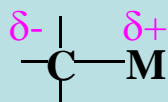
Organometallic compounds are characterized by the presence of a polarized carbon-metal bond:



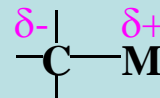
The degree of charge separation (polar character) in the carbon-metal bond depends on the metal, the structure around carbon, and the solvent.



Ionic bond
(Na⁺, K⁺)



Polar covalent
(Mg, Li)



Mostly covalent
(Pb, Sn, Hg)

Reactivity of Organometallics

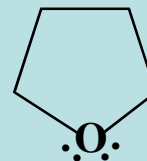
Their **reactivity** parallels the degree of **ionic character** in the carbon-metal bond. **Alkylsodium** and **alkylpotassium** reagents are very powerful bases that react explosively with water. **Organomercury** and **organolead** compounds are much more stable. **Organolithium** and **organomagnesium halides** are of intermediate reactivity. They require careful handling but find wide use in organic synthesis. All organometallics tend to be highly poisonous and harmful.

Preparation

Because of their high reactivity, most organometallic compounds are prepared and used in **solvents that are very inert to nucleophilic attack**. Ether solvents are typically used because of their good solubility properties for organometallics.



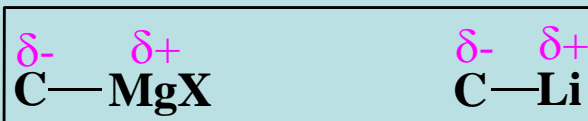
Diethyl ether (Et₂O)
"Ether"



Tetrahydrofuran
"THF"

Reactions of Organolithium and Organomagnesium Halides

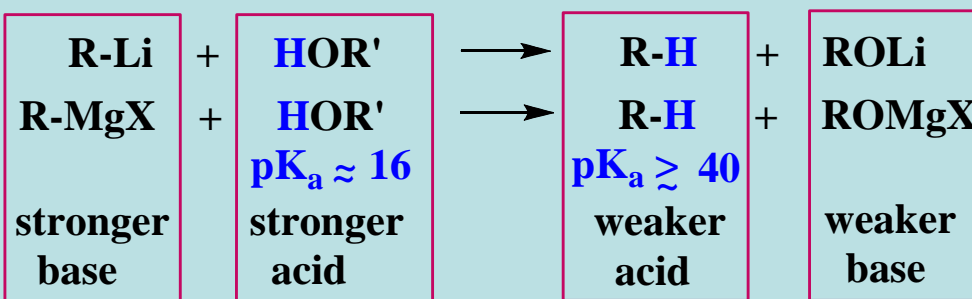
These organometallic reagents are **strong bases** and **good nucleophiles** in accord with the carbanionic character of the carbon atom:



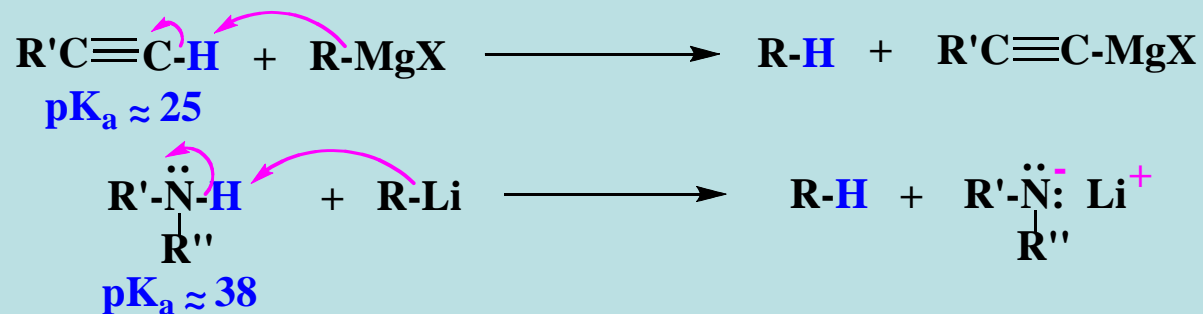
Reactions as Bases

With Water and Alcohols

(require caution)



With Weaker Acids



Preparation of Alkyl- and Aryllithiums

Organolithium compounds are prepared by reacting alkyl and aryl halides with two equivalents of lithium in a redox reaction:



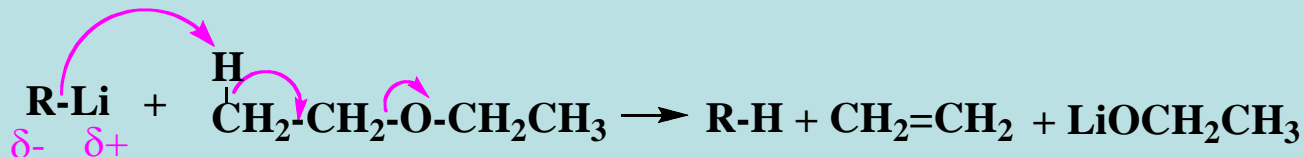
The reactivity order of R-X (or Ar-X) in this reaction is:



Note that this is in the reverse order of the C-X bond strengths.

Stability of R-Li Compounds

Organolithium (especially R-Li) compounds are exceptionally **strong bases** and react slowly with ethers in an E2 reaction:



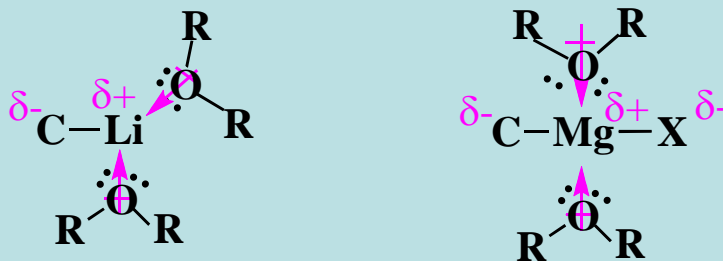
Therefore organolithium compounds prepared in ether solvents are typically used immediately. Organolithium compounds are relatively stable in hydrocarbon solvents under inert gases.

One-Pot Reactions

Because of their reactivity and sensitivity to trace amounts of water, Grignard (organomagnesium) and organolithium reagents are seldom isolated. Typically, they are used in the same solvent in which they are prepared and are kept under an inert and dry atmosphere during their preparation and use.

The Role of Ether Solvents

Because they are Lewis bases, ethers interact with the electropositive metals in organometallic reagents, which promotes charge polarization in the C-M bond and increases reactivity.



The carbon centers in these organometallic reagents are very good nucleophiles in reactions with carbonyl compounds.

Organomagnesium Halides (Grignard Reagents)

The utility of these reagents was discovered by French chemist Victor Grignard in 1900. For the work, he received a Nobel Prize in 1912, and organomagnesium halides (RMgX and ArMgX) are referred to as "**Grignard reagents**" in his honor. They are prepared in an ether solvent in a manner similar to that used for organolithium reagents.



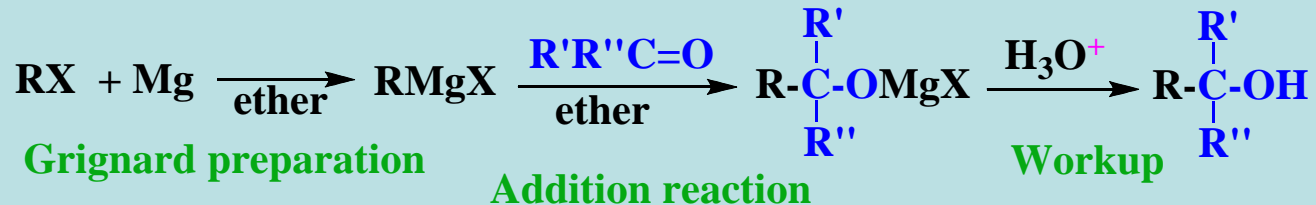
The reactivity order of R-X (or Ar-X) in the metallation reaction is:



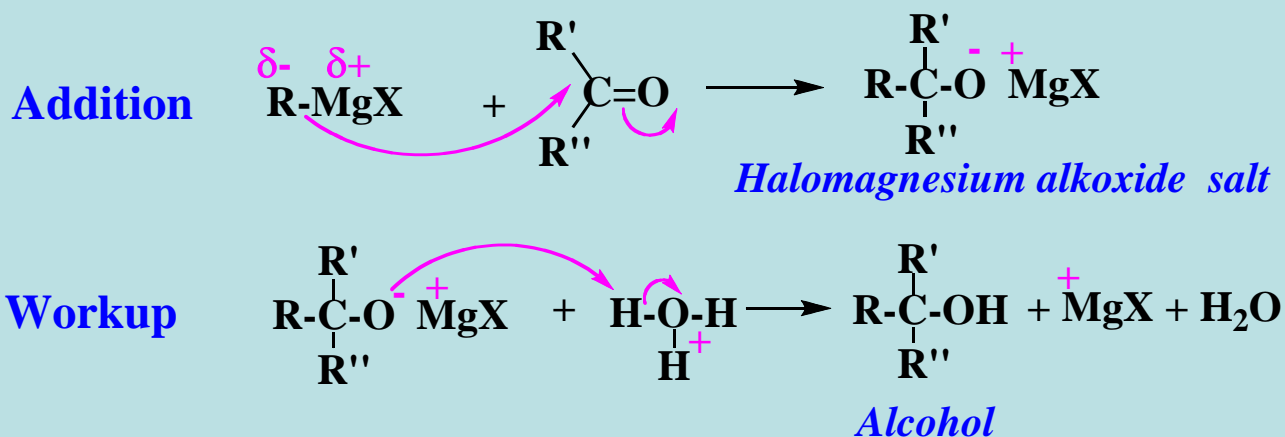
Aryl chlorides react very slowly, so aryl magnesium iodides and bromides are more often used in syntheses.

Reaction Conditions

Grignard reactions are run in **anhydrous (no water) ether solvents**. Typically, the alkyl or aryl Grignard reagent is prepared and then immediately reacted with a carbonyl compound (e.g., an aldehyde, ketone, or ester). After the reaction is over, the magnesium salt is converted to the alcohol product by addition of aqueous acid.

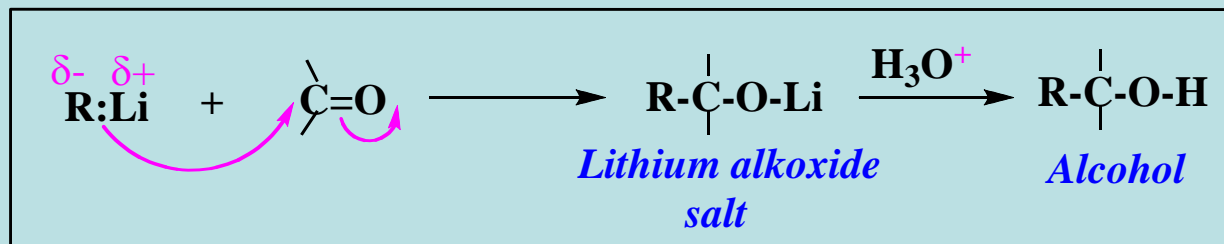


In more detail:



Organolithium Reagents

Organolithium reagents, R-Li, react with carbonyl compounds much as Grignard reagents do. Overall, RMgX and RLi reagents show **parallel reactivity**.

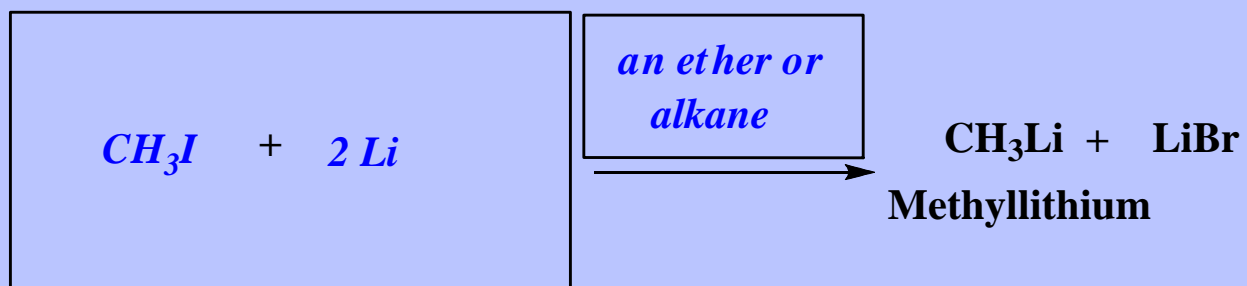
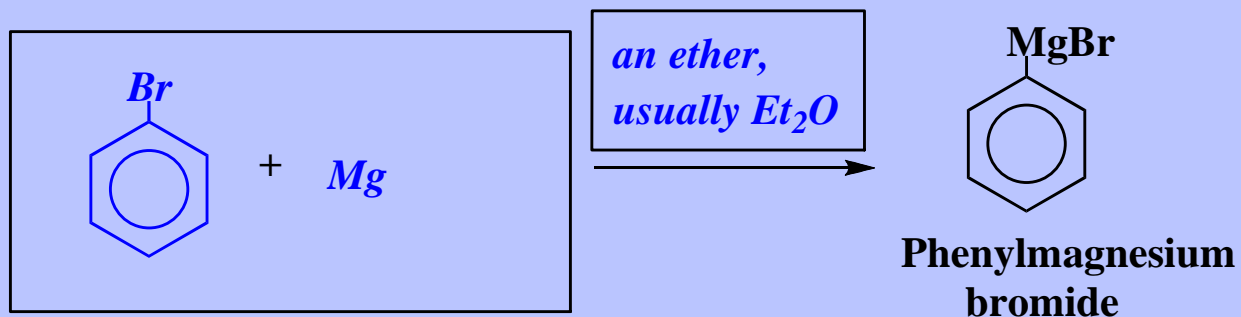


Organolithium reagents are also **very strong bases** and must be prepared and used in anhydrous ether or hydrocarbon solvents.

They usually are more reactive than the corresponding Grignard reagents.

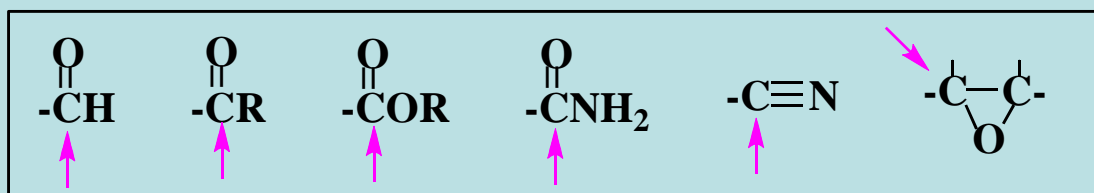
Quiz 12.05

Provide the missing reagents and solvents for the preparation of the following organometallic reagents.



Grignard Reagents Are Nucleophiles

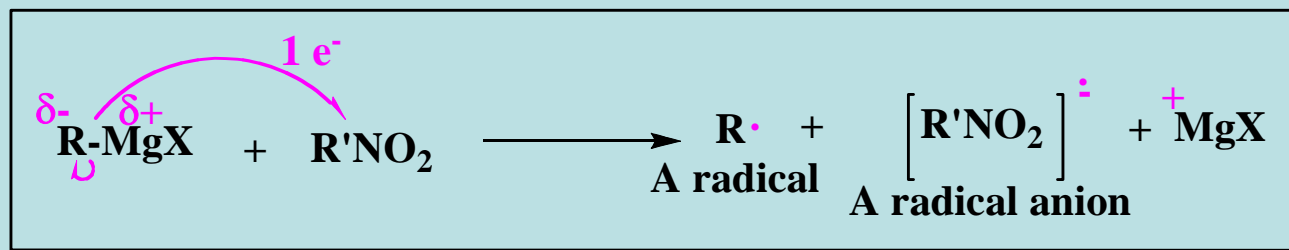
Grignard reagents react with a number of functional groups as **nucleophiles**. If these groups are present during the preparation or reaction of a Grignard reagent, they **all** will offer sites of attack.



Grignard Reagents Are Reducing Agents

In the usual Grignard reactions, considered above, the electrophilic carbon in the carbonyl compound or other substrate attacked is reduced (its oxidation number is reduced).

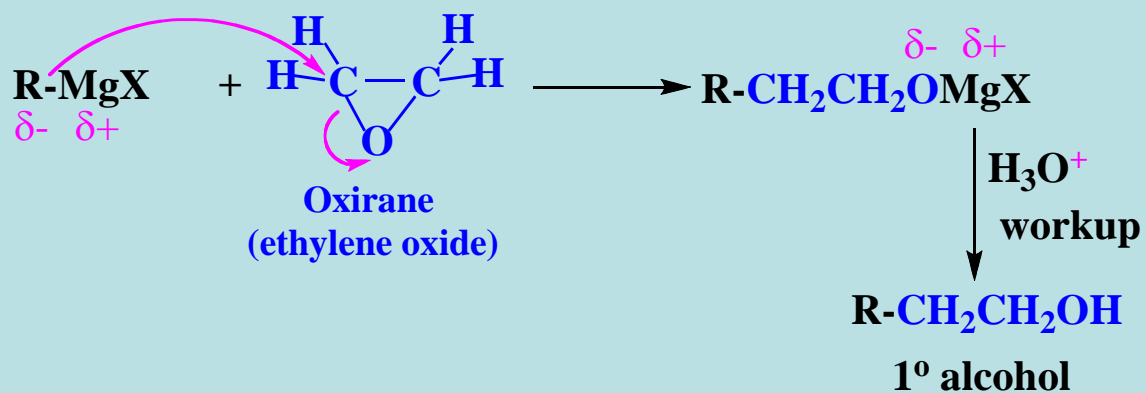
Grignard reagents can also react, e. g. with the **nitro group (-NO₂)**, by an apparent electron transfer reaction (redox reaction) that generates free radicals:



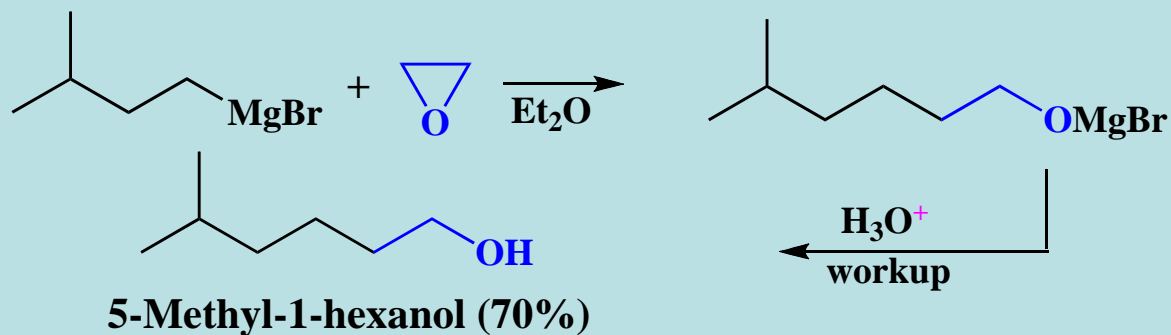
Nucleophilic Additions of Grignard Reagents

To Oxiranes (Epoxides)

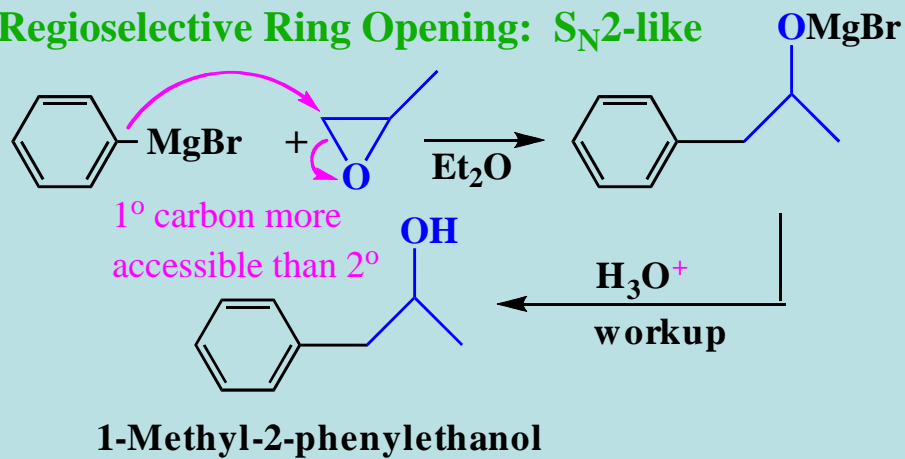
These three-membered cyclic ethers are highly reactive towards nucleophiles because of the ring strain. Ordinary ethers do not react in the same manner.



Oxirane Examples



Regioselective Ring Opening: S_N2-like

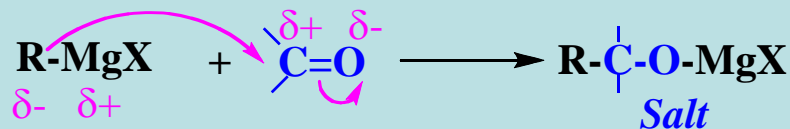


Nucleophilic Additions of Grignard Reagents

To Carbonyl Compounds: Syntheses of Alcohols

The reaction with carbonyl compounds is perhaps the most useful synthetic application of Grignard reagents .

Overall mode of the addition:

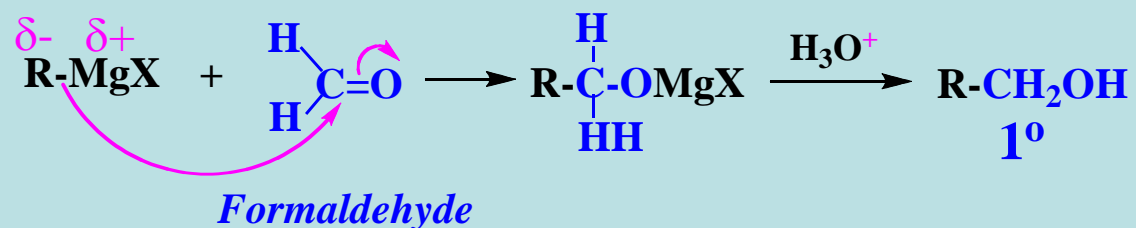


The nucleophile adds to the electropositive carbon and the metal adds to the electronegative oxygen.

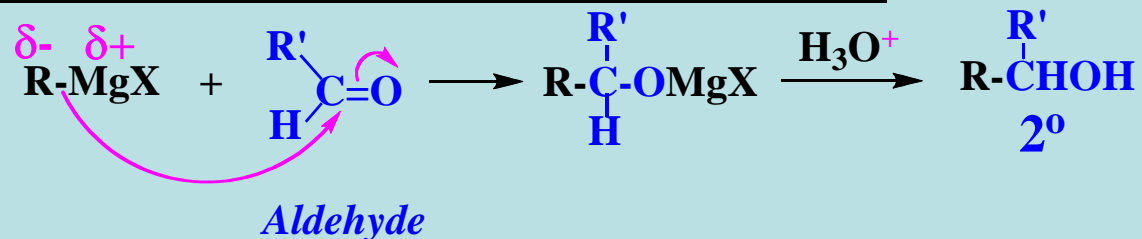
Alcohols from Aldehydes and Ketones

By proper choice of the Grignard and carbonyl compounds, a great variety of **1°**, **2°**, and **3° alcohols** may be synthesized.

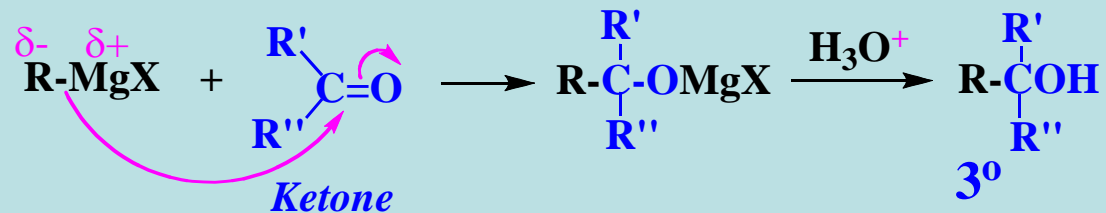
1° Alcohols from Formaldehyde



2° Alcohols from Aldehydes

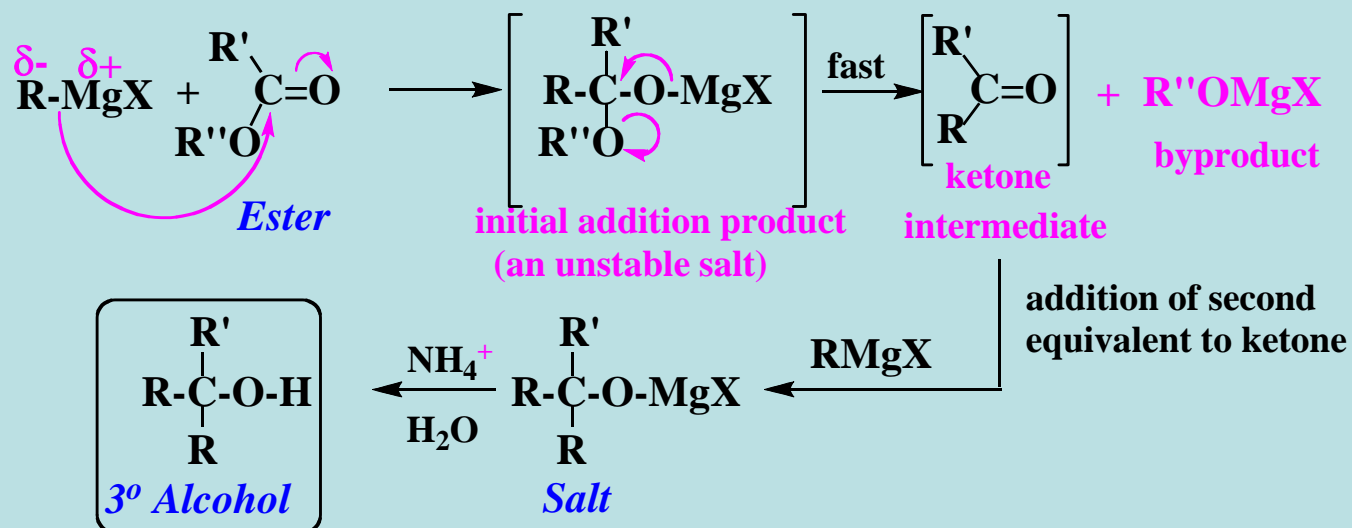


3° Alcohols from Ketones

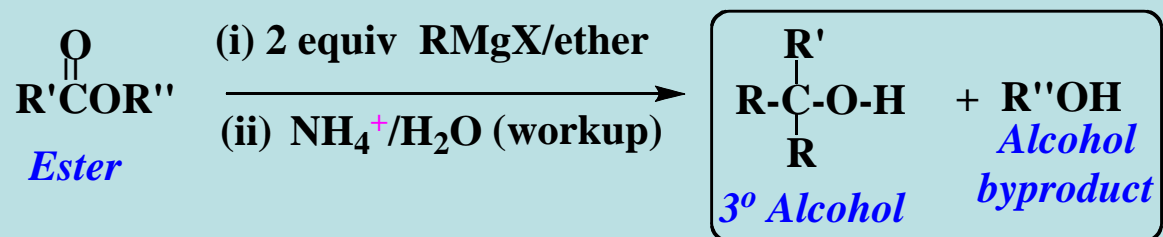


3° Alcohols from Esters

Two equivalents of Grignard reagent add to esters in sequential steps, leading to 3° alcohols.

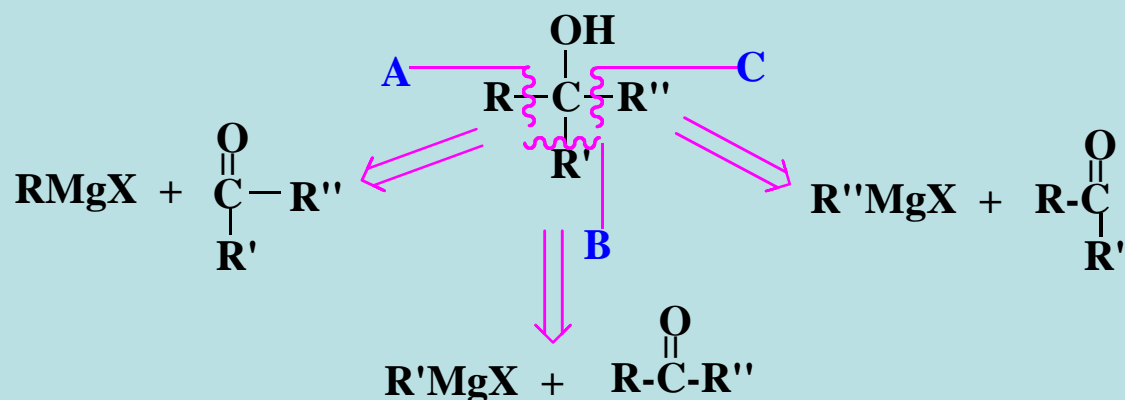


Overall:



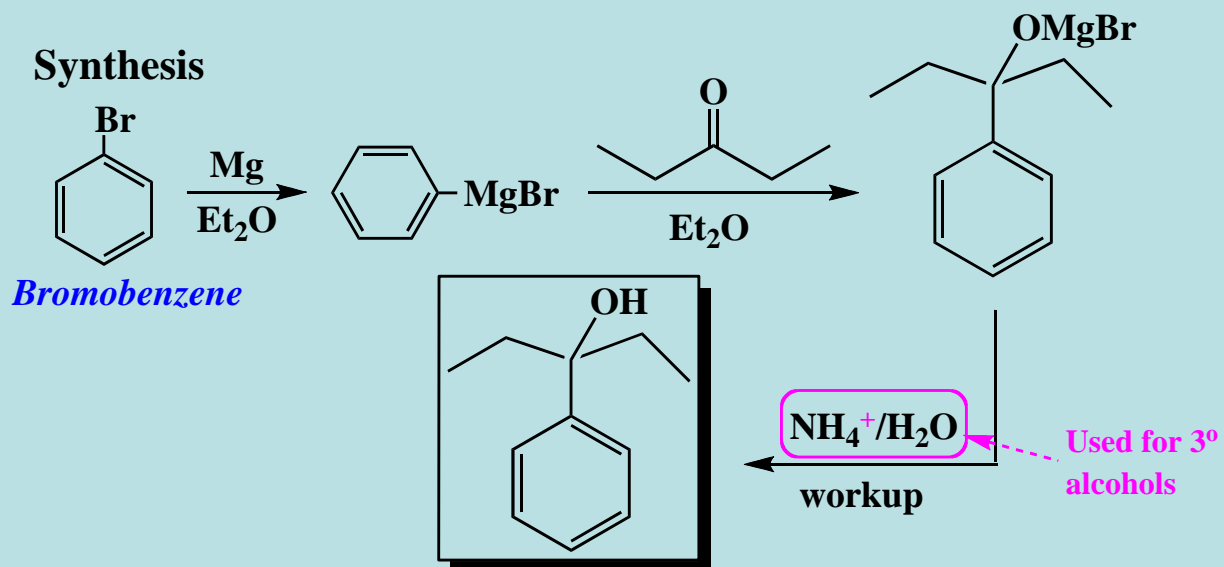
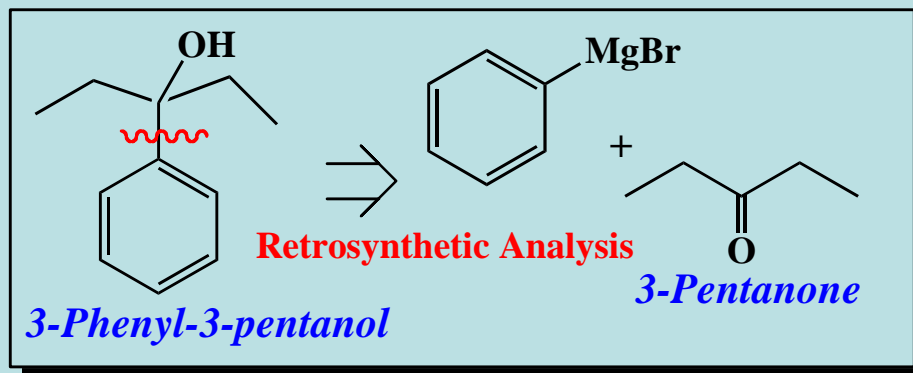
Planning a Grignard Synthesis

Retrosynthetic analysis is very helpful in designing an alcohol synthesis that incorporates a Grignard reaction. The alcohol product may be **deconstructed** in several ways.

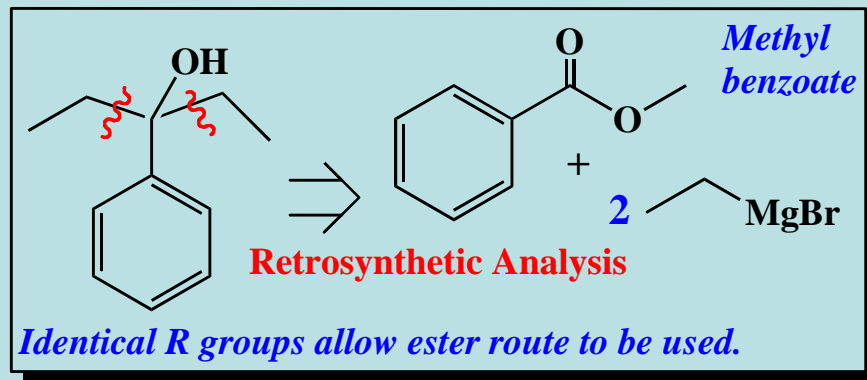


The path selected often is determined by the availability of the required starting compounds.

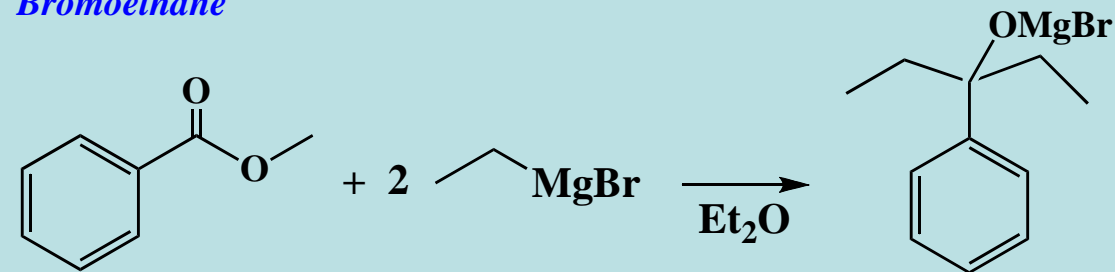
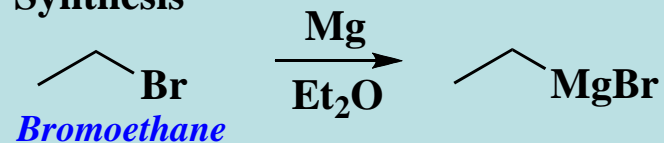
Synthesis Goal: 3-Phenyl-3-pentanol



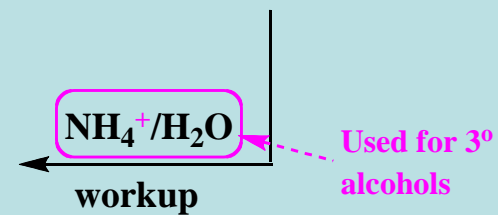
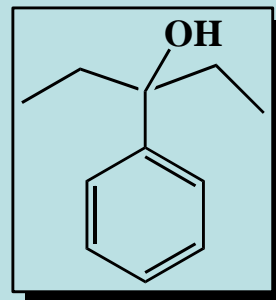
An Alternative Synthesis of 3-Phenyl-3-pentanol



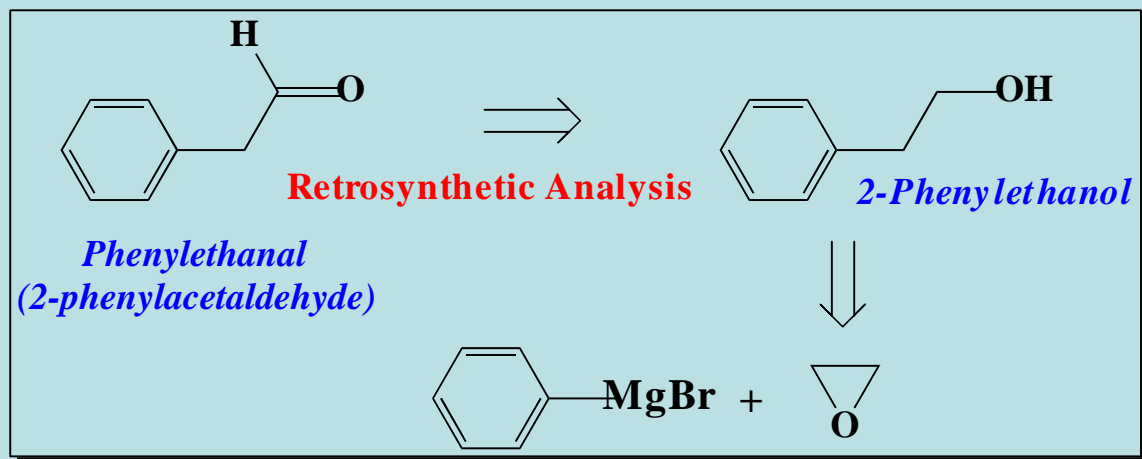
Synthesis



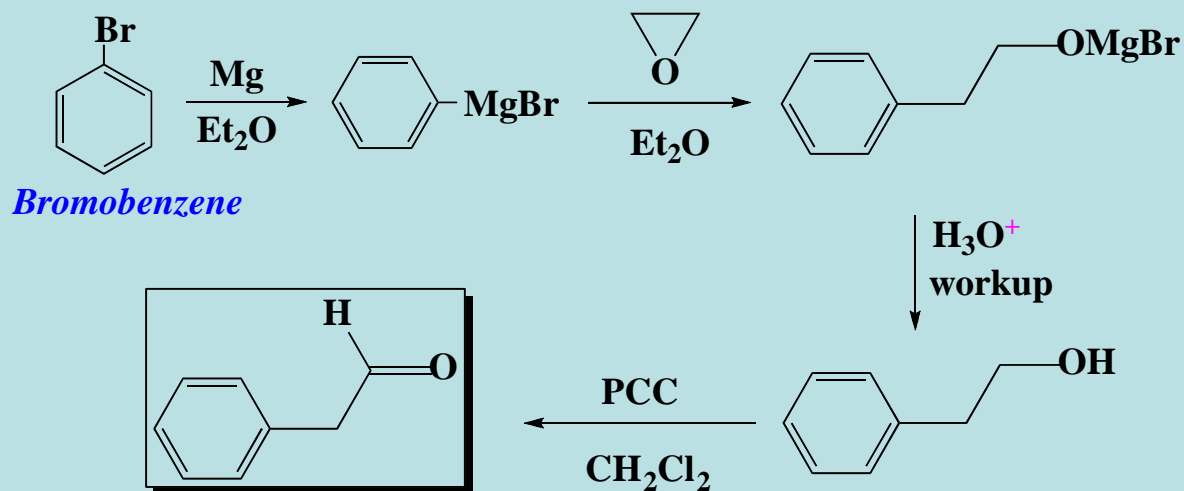
Methyl benzoate



Synthesis Example: Phenylethanal

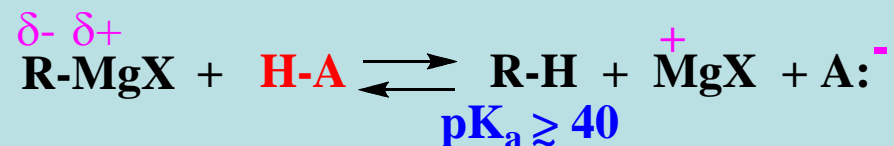


Synthesis

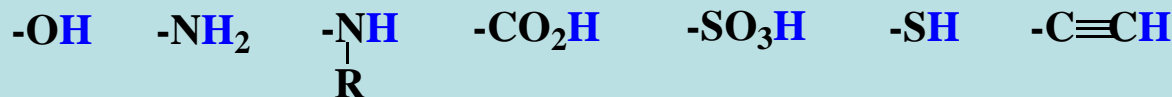


Some Limitations of the Grignard Reagents

Grignard reagents are very strong bases and will remove H^+ from any **H-A** with a $\text{pK}_a < 35$.



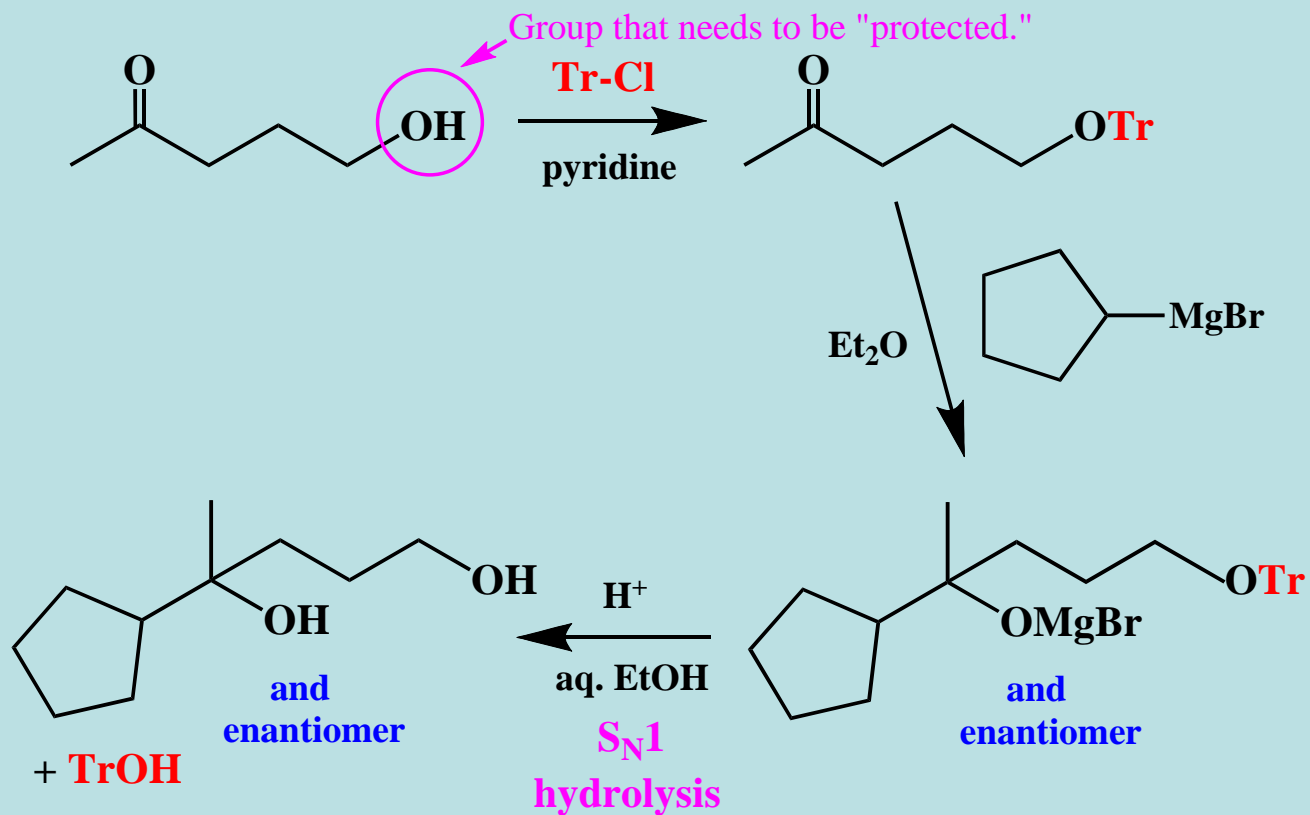
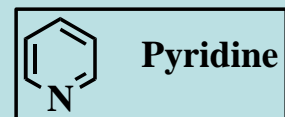
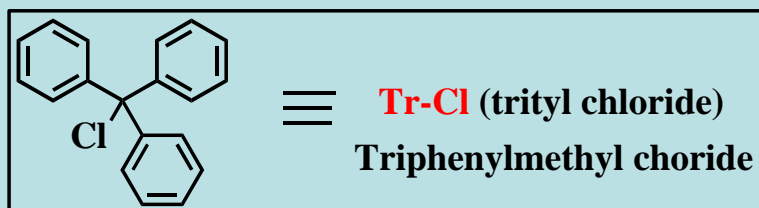
Because of this strong basicity, the following functional groups also cannot be present during a Grignard reaction.



Other functional groups, like carbonyl and epoxy, that will react with nucleophiles cannot be present if they will compete with a Grignard reaction to be employed at another site in the molecule.

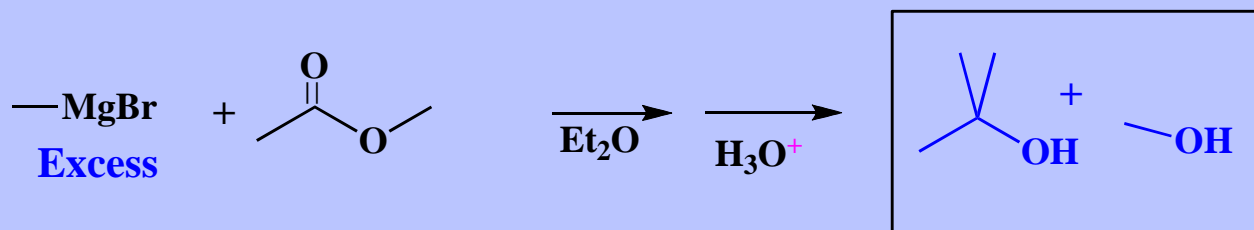
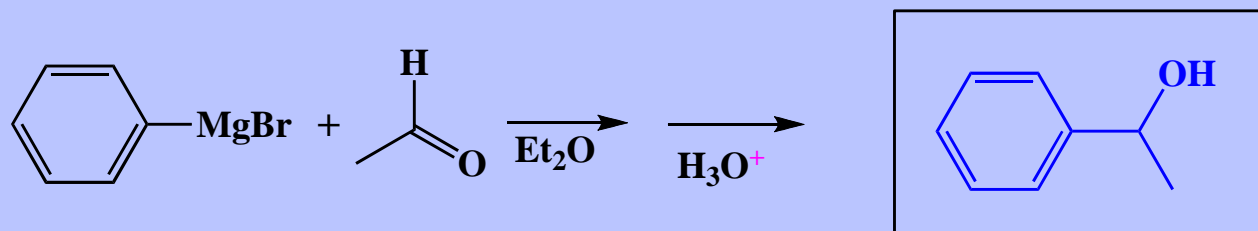
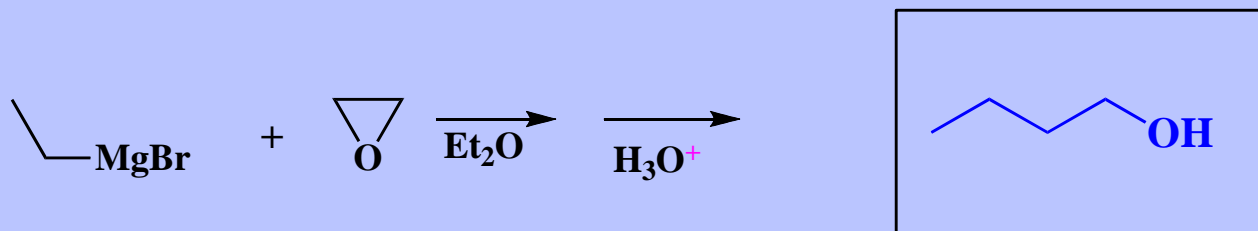
Sometimes interfering groups can be "**protected.**"

Use of the Trityl Protecting Group in a Grignard Reaction



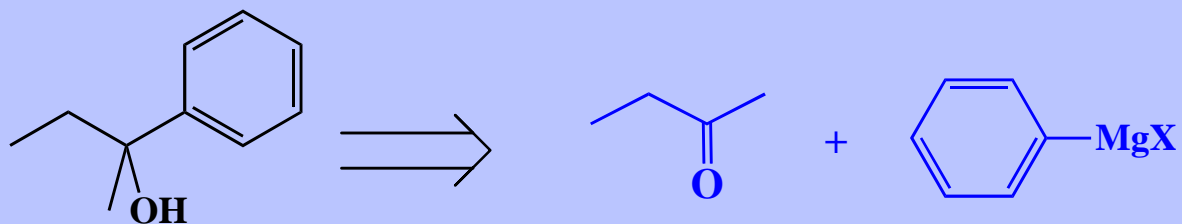
Quiz 12.06

Indicate the organic products of the following Grignard reactions.

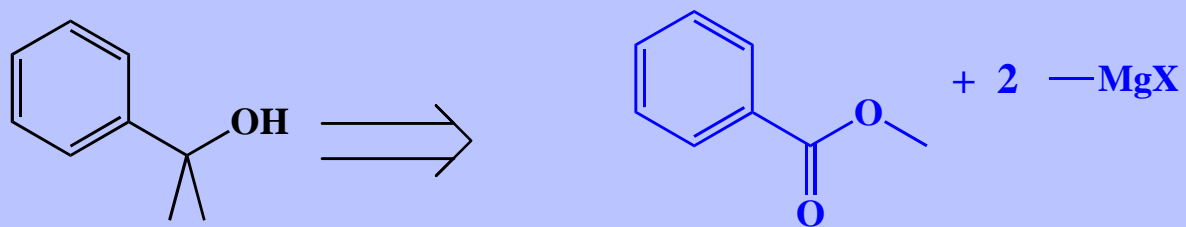


Quiz 12.07

Provide retrosynthetic analyses of the following alcohols in accord with the **stated guidelines**.



From an alkanone



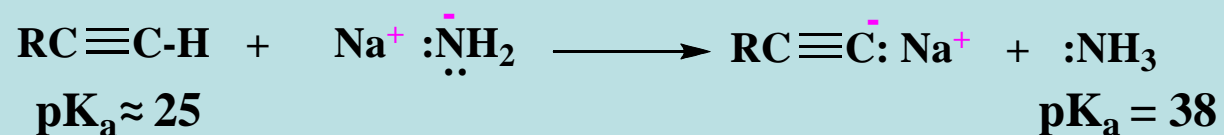
From an ester

Organosodium Compounds

Because of their very great reactivity, $R:^- Na^+$ compounds often undergo side reactions and have limited synthetic value. One notable exception are the sodium alkynides, $RC \equiv C:^- Na^+$.

Preparation

These organosodium compounds can be prepared by proton exchange between terminal alkynes and sodium amide:



An Example of a Sodium Alkynide Addition Reaction

