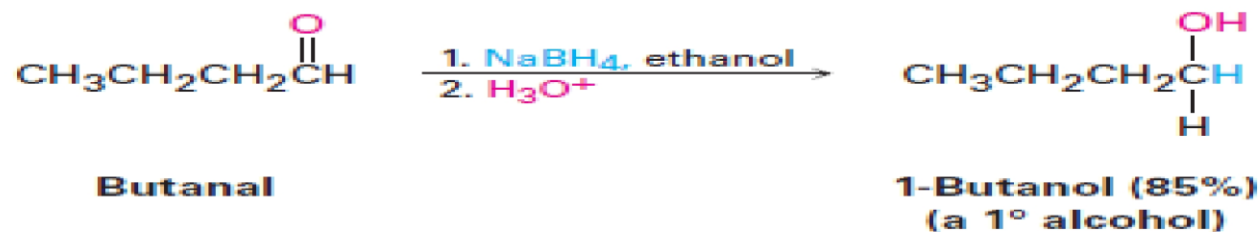
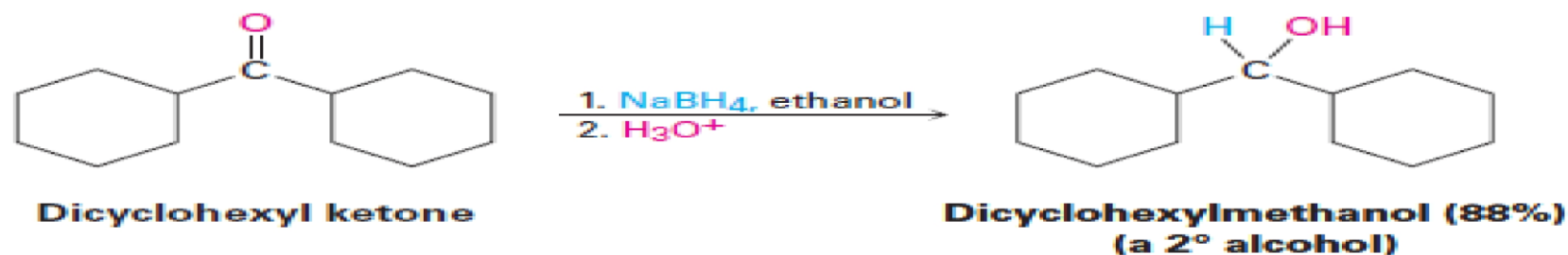


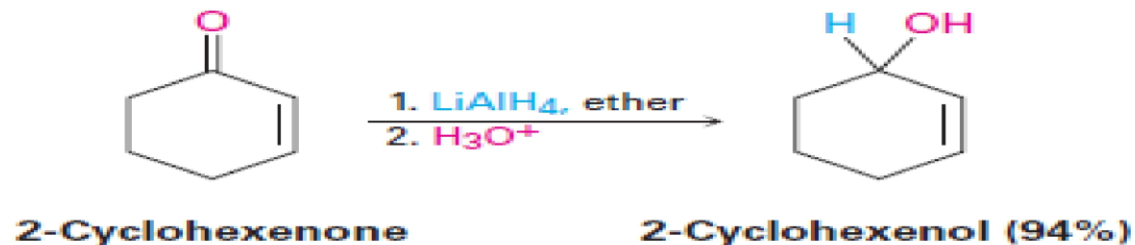
Aldehyde reduction



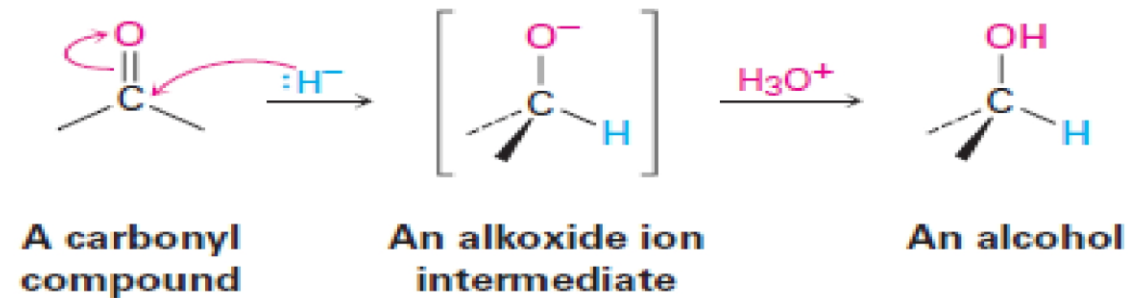
Ketone reduction



Lithium aluminum hydride, LiAlH_4 , is another reducing agent often used for reduction of aldehydes and ketones. A grayish powder that is soluble in ether and tetrahydrofuran, LiAlH_4 is much more reactive than NaBH_4 but also more dangerous. It reacts violently with water and decomposes explosively when heated above 120°C .

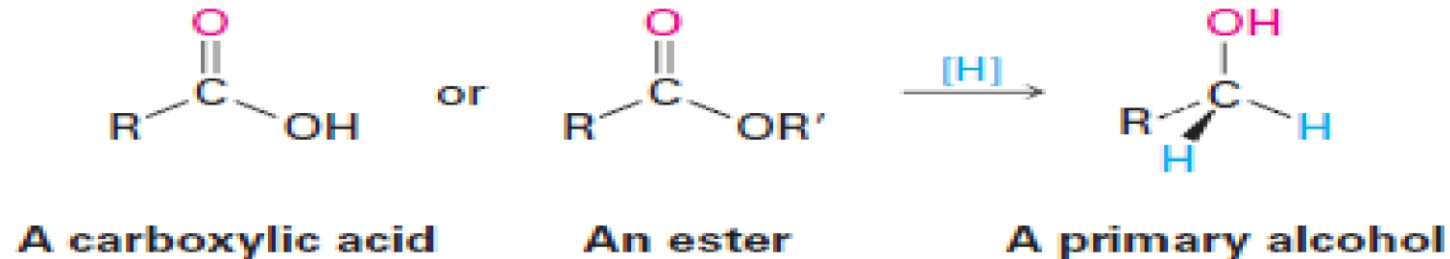


For the moment, we'll simply note that they involve the addition of a nucleophilic hydride ion (:H^-) to the positively polarized, electrophilic carbon atom of the carbonyl group. The initial product is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step to yield the alcohol product.



Reduction of Carboxylic Acids and Esters

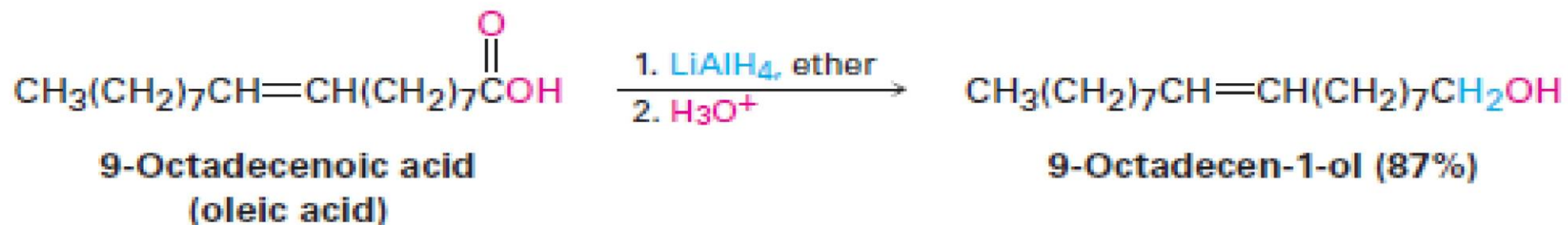
Carboxylic acids and esters are reduced to give primary alcohols.



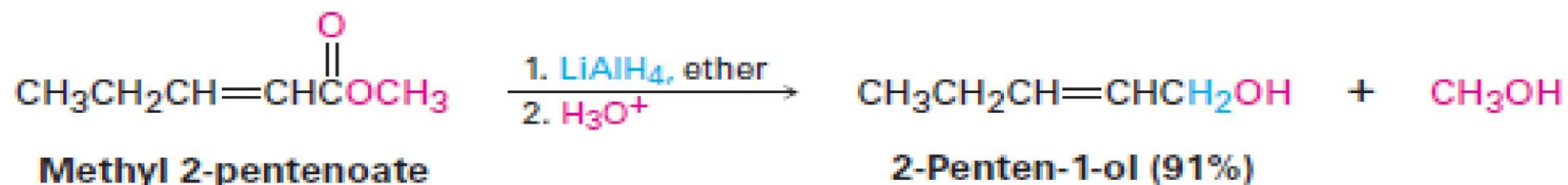
These reactions aren't as rapid as the reductions of aldehydes and ketones. NaBH_4 reduces esters very slowly and does not reduce carboxylic acids at all. Instead,

carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent LiAlH_4 . All carbonyl groups, including acids, esters, ketones, and aldehydes, are reduced by LiAlH_4 . Note that one hydrogen atom is delivered to the carbonyl carbon atom during aldehyde and ketone reductions but that two hydrogens become bonded to the former carbonyl carbon during carboxylic acid and ester reductions.

Carboxylic acid reduction

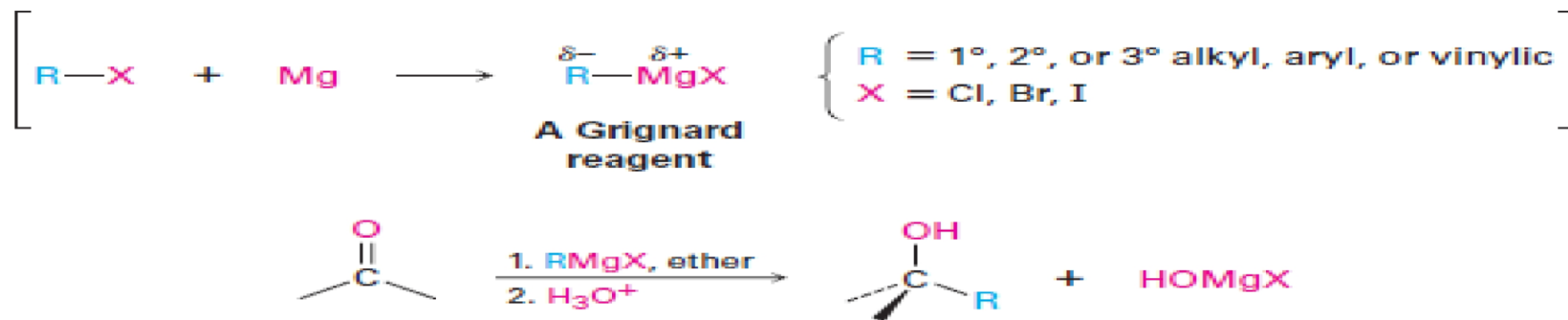


Ester reduction



Alcohols from Carbonyl Compounds: Grignard Reaction

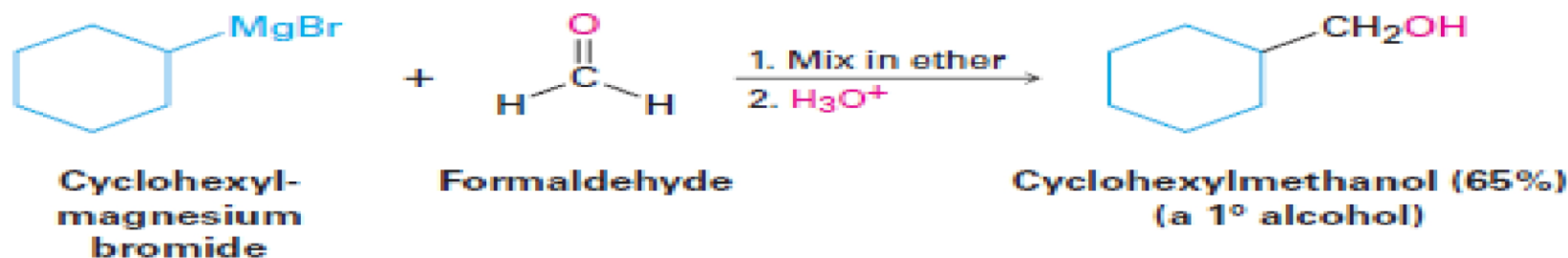
Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium, react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the $\text{C}=\text{O}$ bond, Grignard reaction involves addition of a carbanion nucleophile ($\text{R}^- + \text{MgX}$).



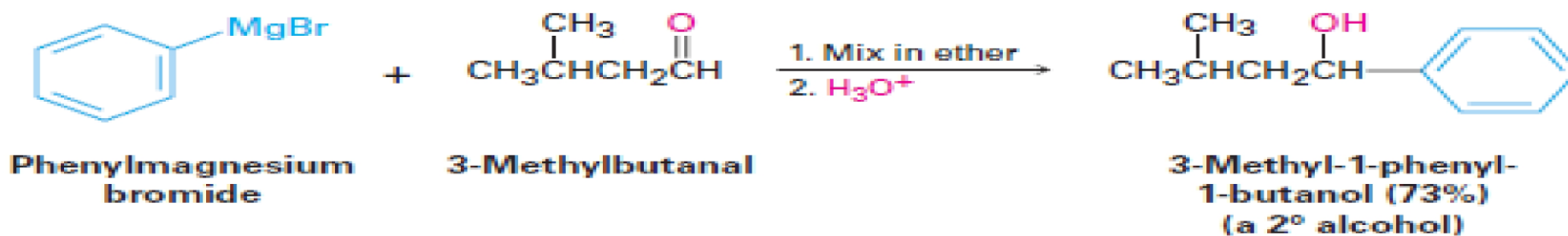
The reaction of Grignard reagents with carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, this reaction is worth understanding for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction *does* have an indirect biological counterpart, that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon–carbon bonds.

As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $\text{H}_2\text{C}=\text{O}$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.

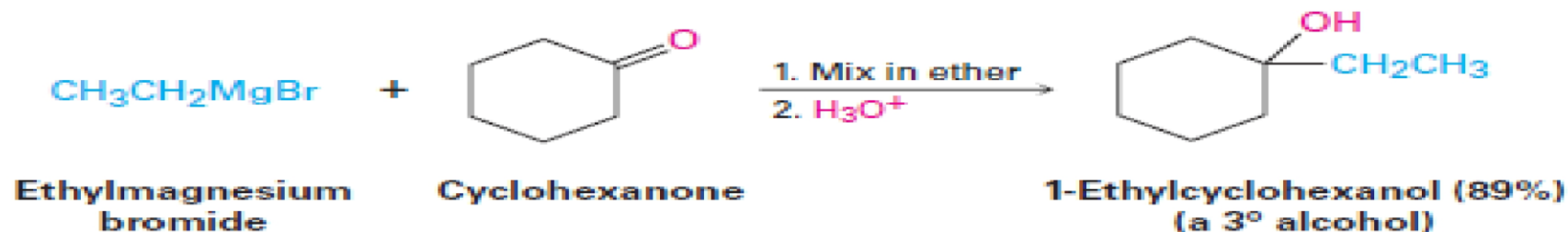
Formaldehyde reaction



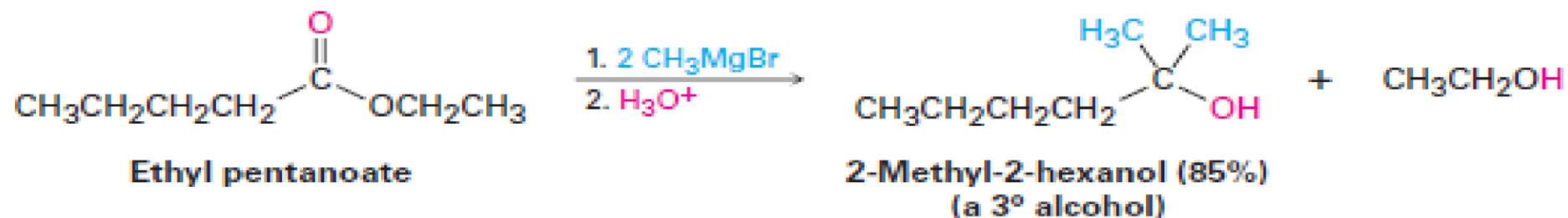
Aldehyde reaction



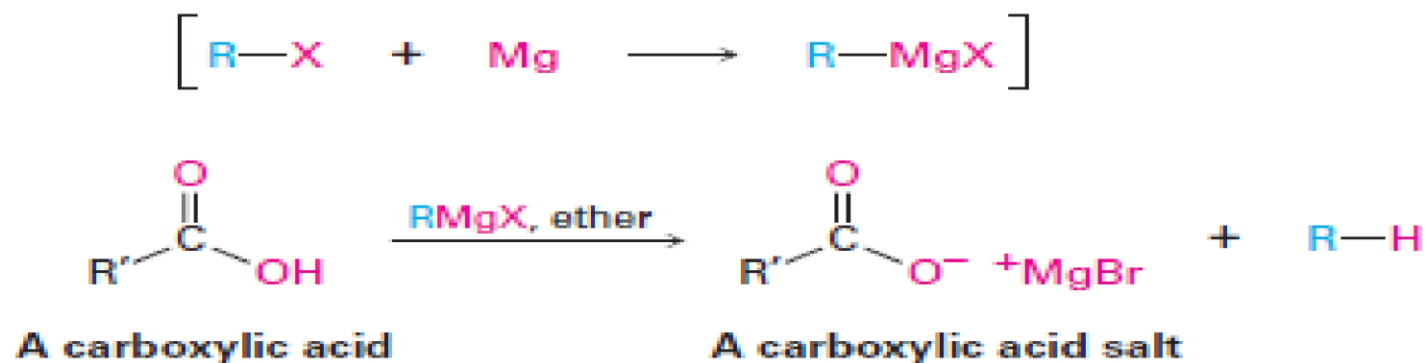
Ketone reaction



Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as LiAlH_4 reduction of an ester adds two hydrogens.



Carboxylic acids don't give addition products with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid.



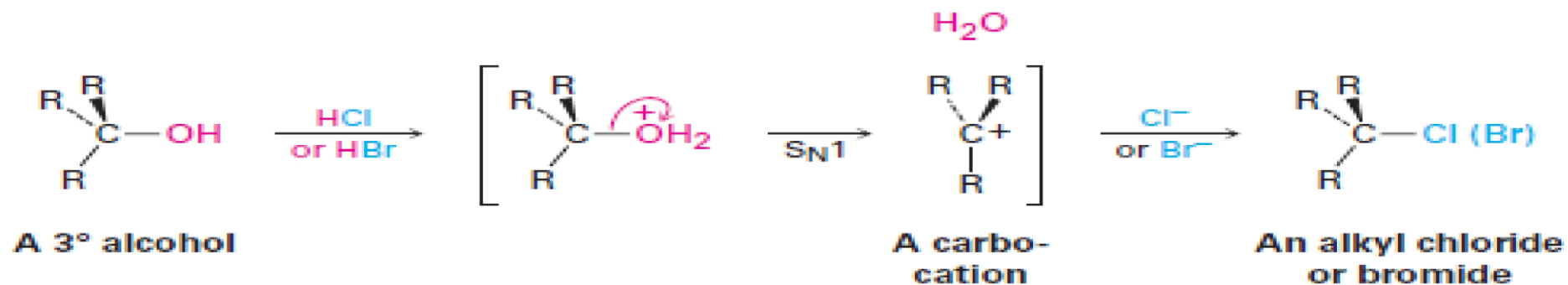
Reactions of Alcohols

Several reactions of alcohols their conversion into alkyl halides and tosylates and their dehydration to give alkenes in albeit without mechanistic details.

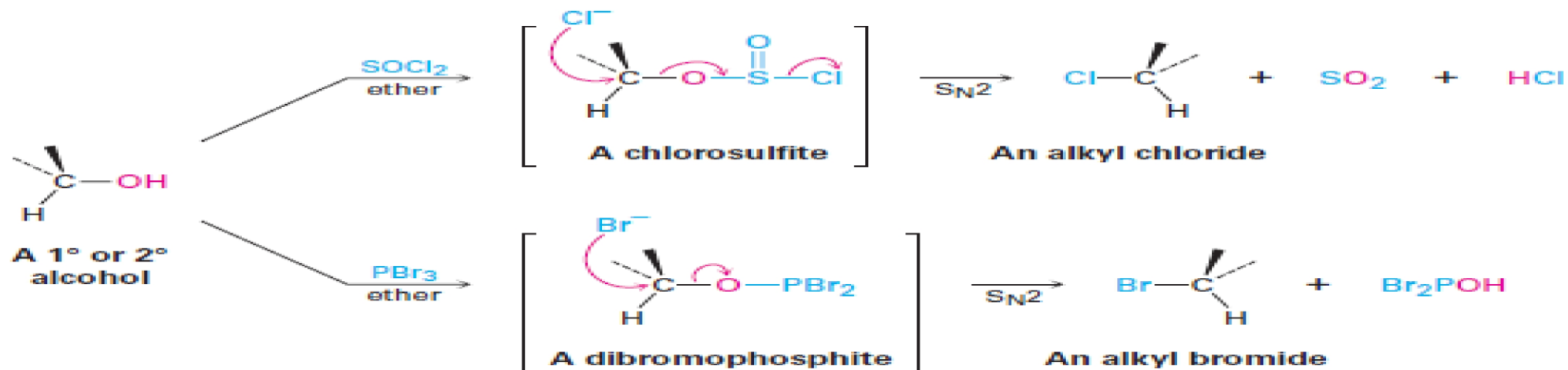
Conversion of Alcohols into Alkyl Halides

Tertiary alcohols react with either HCl or HBr at 0 °C by an S_N1 mechanism through a carbocation intermediate. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into halides by treatment with either $SOCl_2$ or PBr_3 through an S_N2 mechanism.

The reaction of a tertiary alcohol with HX takes place by an S_N1 mechanism when acid protonates the hydroxyl oxygen atom. Water is expelled to generate a carbocation, and the cation reacts with nucleophilic halide ion to give the alkyl halide product.



The reactions of primary and secondary alcohols with SOCl_2 and PBr_3 take place by S_{N}^2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_{N}^2 reactions, but reaction of an alcohol with SOCl_2 or PBr_3 converts the $-\text{OH}$ into a much better leaving group, either a chlorosulfite ($-\text{OSOCl}$) or a dibromophosphite ($-\text{OPBr}_2$), which is readily expelled by backside nucleophilic substitution.



One of the most important reasons for using tosylates in S_{N}^2 reactions is stereochemical. The S_{N}^2 reaction of an alcohol via an alkyl halide proceeds with *two* inversions of configuration one to make the halide from the alcohol and one to substitute the halide and yields a product with the same stereochemistry as the starting alcohol.

The S_N2 reaction of an alcohol via a tosylate, however, proceeds with only one inversion and yields a product of opposite stereochemistry to the starting alcohol. **Figure 17-5** shows a series of reactions on the *R* enantiomer of 2-octanol that illustrates these stereochemical relationships.

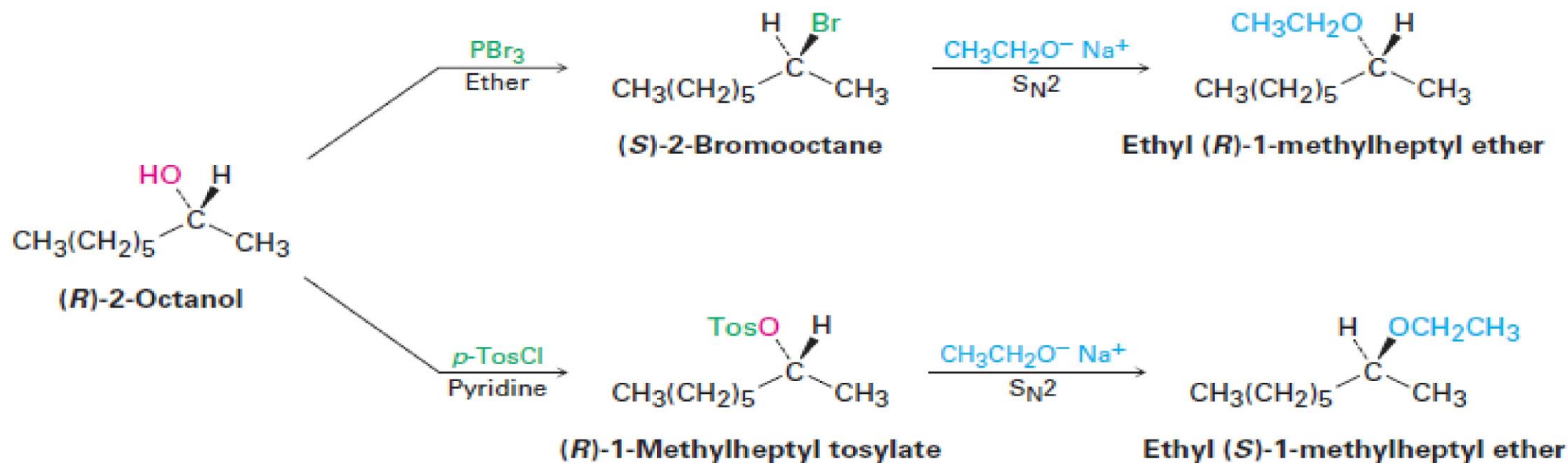
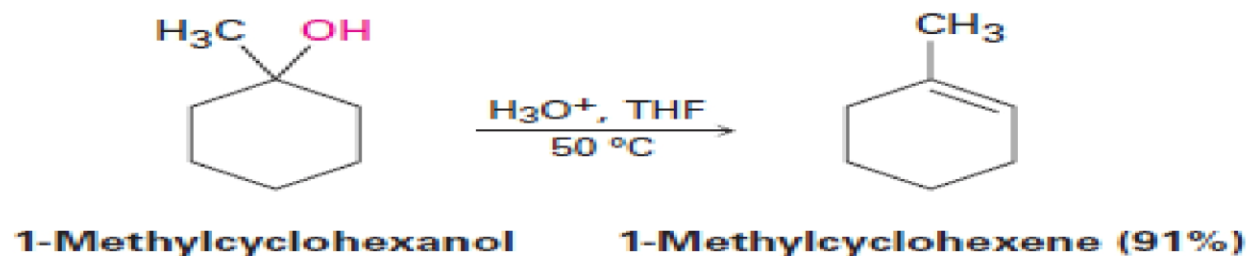


Figure 17-5 Stereochemical consequences of S_N2 reactions on derivatives of (*R*)-2-octanol. Substitution through the halide gives a product with the same stereochemistry as the starting alcohol; substitution through the tosylate gives a product with opposite stereochemistry to the starting alcohol.

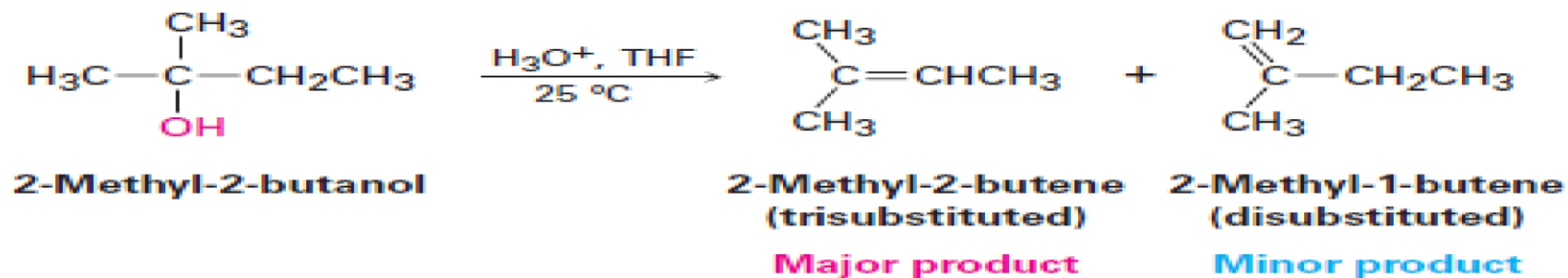
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. Because of the usefulness of the reaction, a number of ways have been devised for carrying out dehydrations.

One method that works particularly well for tertiary alcohols is the acid catalyzed reaction. For example, treatment of 1-methylcyclohexanol with warm, aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.

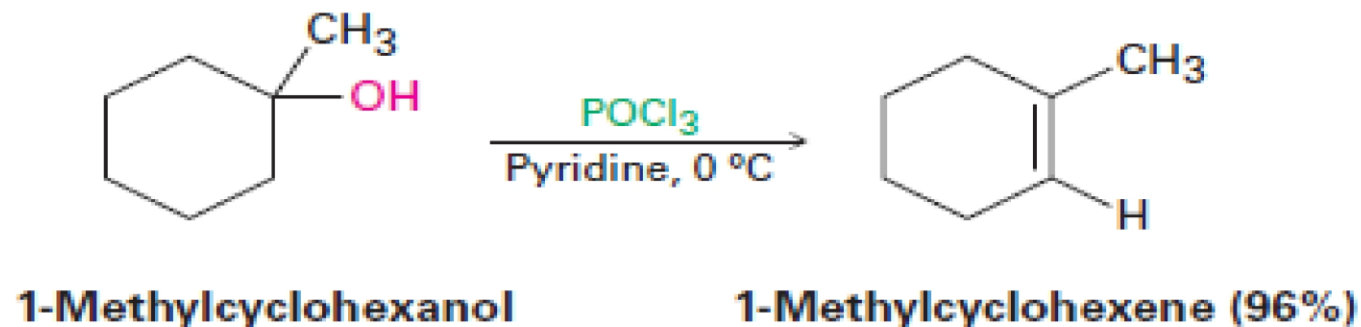


Acid-catalyzed dehydrations usually follow Zaitsev's rule and yield the more stable alkene as the major product. Thus, 2-methyl-2-butanol gives primarily 2-methyl-2-butene (trisubstituted double bond) rather than 2-methyl-1-butene (disubstituted double bond).



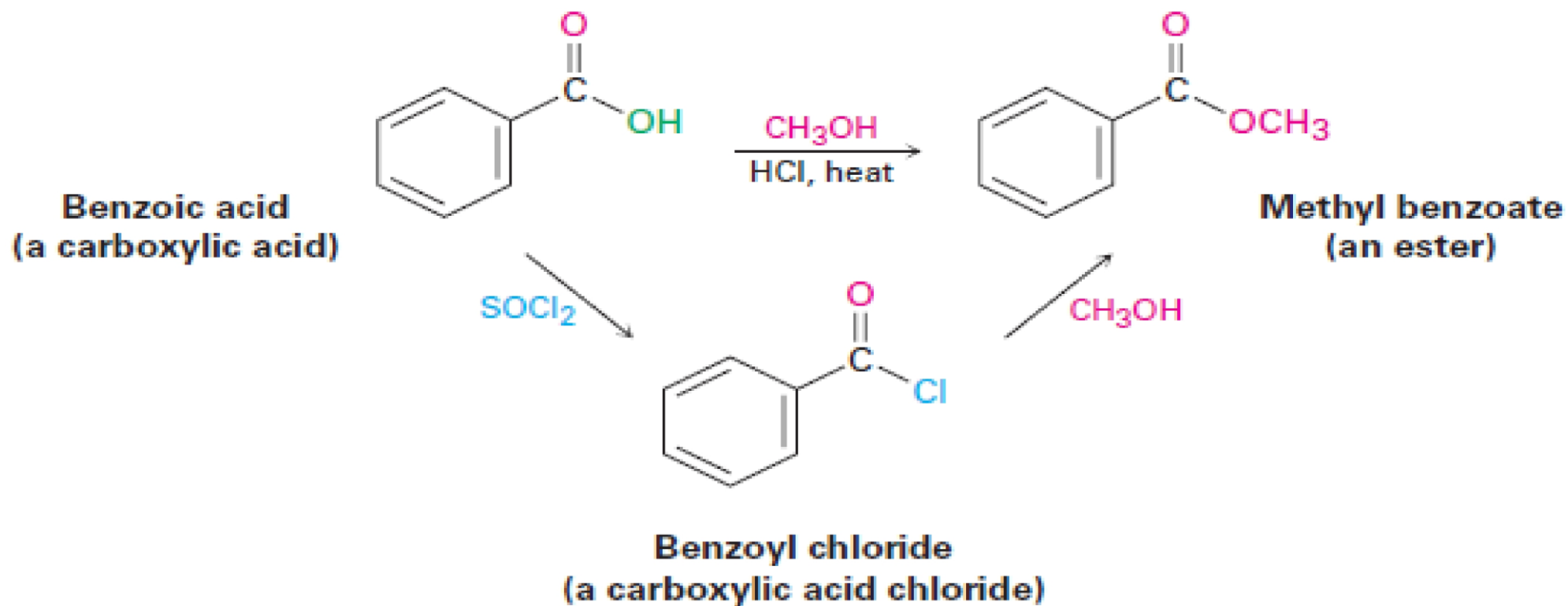
This reaction is an E₁ process and occurs by the three step mechanism. Protonation of the alcohol oxygen is followed by unimolecular loss of water to generate a carbocation intermediate and final loss of a proton from the neighboring carbon atom to complete the process. As with most E₁ reactions, tertiary alcohols react fastest because they lead to stabilized, tertiary carbocation intermediates.

Secondary alcohols can be made to react, but the conditions are severe (75% H₂SO₄, 100 °C) and sensitive molecules don't survive. To circumvent the need for strong acid and allow the dehydration of secondary alcohols in a gentler way, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride (POCl₃) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0 °C.



Conversion of Alcohols into Esters

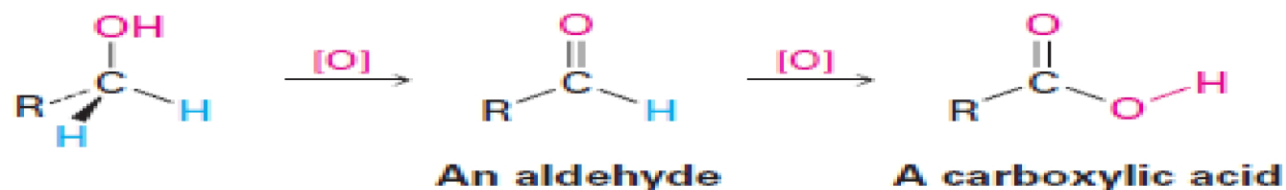
Alcohols react with carboxylic acids to give esters, a reaction that is common in both the laboratory and living organisms. In the laboratory, the reaction can be carried out in a single step if a strong acid is used as catalyst. More frequently, though, the reactivity of the carboxylic acid is enhanced by first converting it into a carboxylic acid chloride, which then reacts with the alcohol.



Oxidation of Alcohols

Perhaps the most valuable reaction of alcohols is their oxidation to give carbonyl compounds the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols yield aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols don't normally react with most oxidizing agents.

Primary alcohol



Secondary alcohol

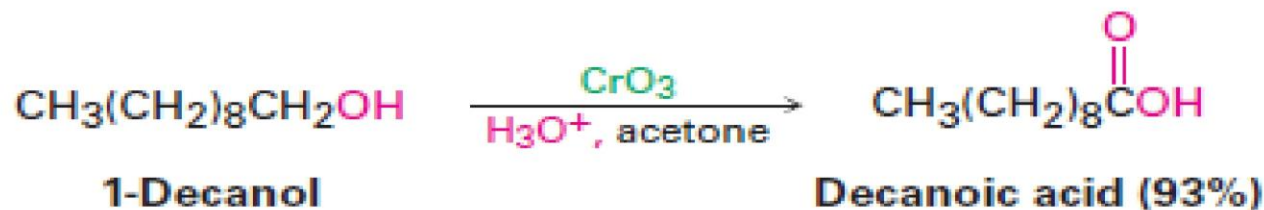


Tertiary alcohol



The oxidation of a primary or secondary alcohol can be accomplished by any of a large number of reagents, including KMnO_4 , CrO_3 , and $\text{Na}_2\text{Cr}_2\text{O}_7$. Which reagent is used in a specific case depends on such factors as cost, convenience, reaction yield, and alcohol sensitivity.

Most commonly used oxidizing agents, such as chromium trioxide (CrO_3) in aqueous acid, oxidize primary alcohols directly to carboxylic acids. An aldehyde is involved as an intermediate in this reaction but can't usually be isolated because it is further oxidized too rapidly.



Secondary alcohols are easily oxidized to give ketones. For a large-scale oxidation, however, an inexpensive reagent such as $\text{Na}_2\text{Cr}_2\text{O}_7$ in aqueous acetic acid might be used.

