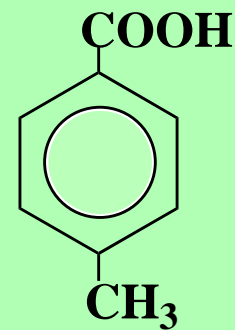
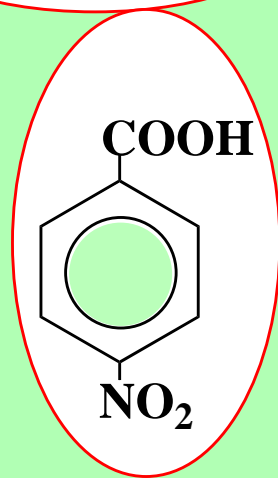
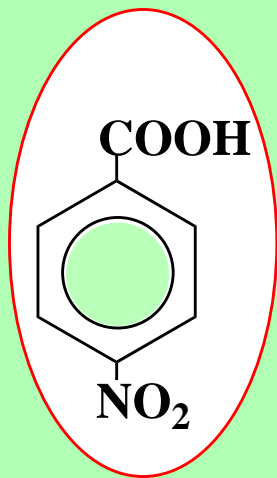
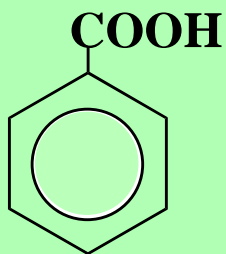
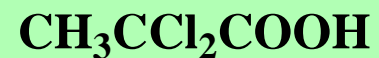
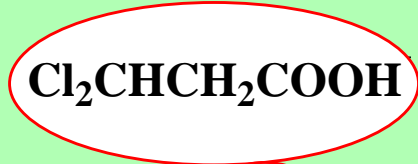


Quiz 18.02

In each pair of compounds below, circle the stronger carboxylic acid.

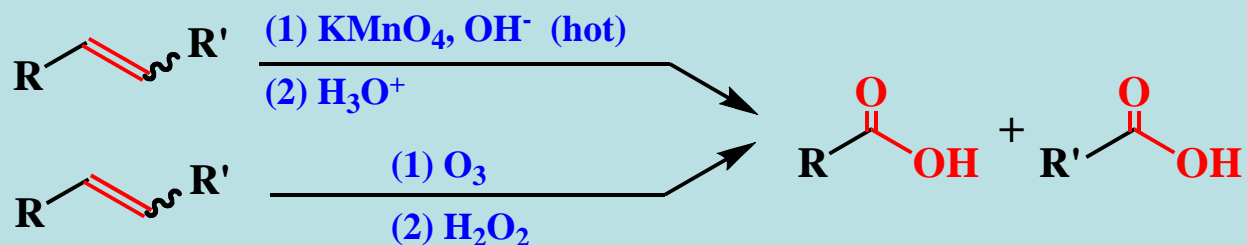


What is the mistake on this slide?

Preparation of Carboxylic Acids

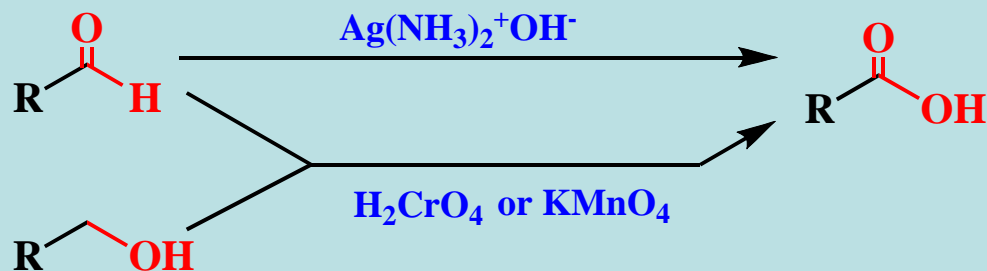
Oxidation of Alkenes

Alkenes can be oxidatively cleaved to carboxylic acids by use of either KMnO_4 or ozone.



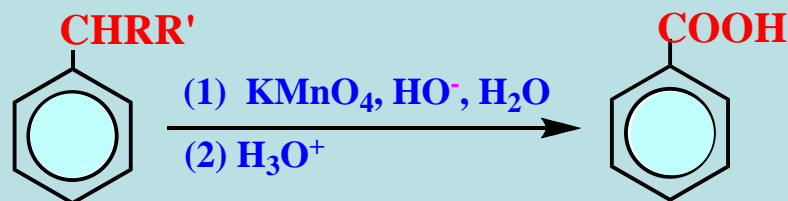
Oxidation of Aldehydes and 1° Alcohols

Aldehydes are easily oxidized to carboxylic acids, even by mild oxidants such as $\text{Ag}(\text{NH}_3)_2^+\text{OH}^-$, which is used in the Tollens' test for distinguishing aldehydes from ketones. Stronger reagents such as chromic acid (H_2CrO_4) or KMnO_4 can oxidize either aldehydes or 1° alcohols to carboxylic acids.



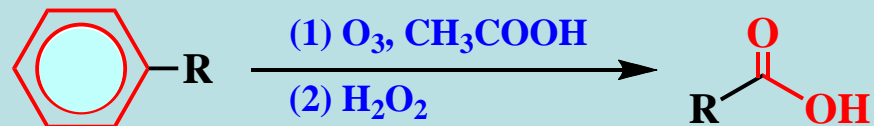
Oxidation of Alkylbenzenes

Vigorous oxidation by KMnO_4 of primary and secondary (but not tertiary) alkyl groups directly attached to a benzene ring produces aromatic acids.



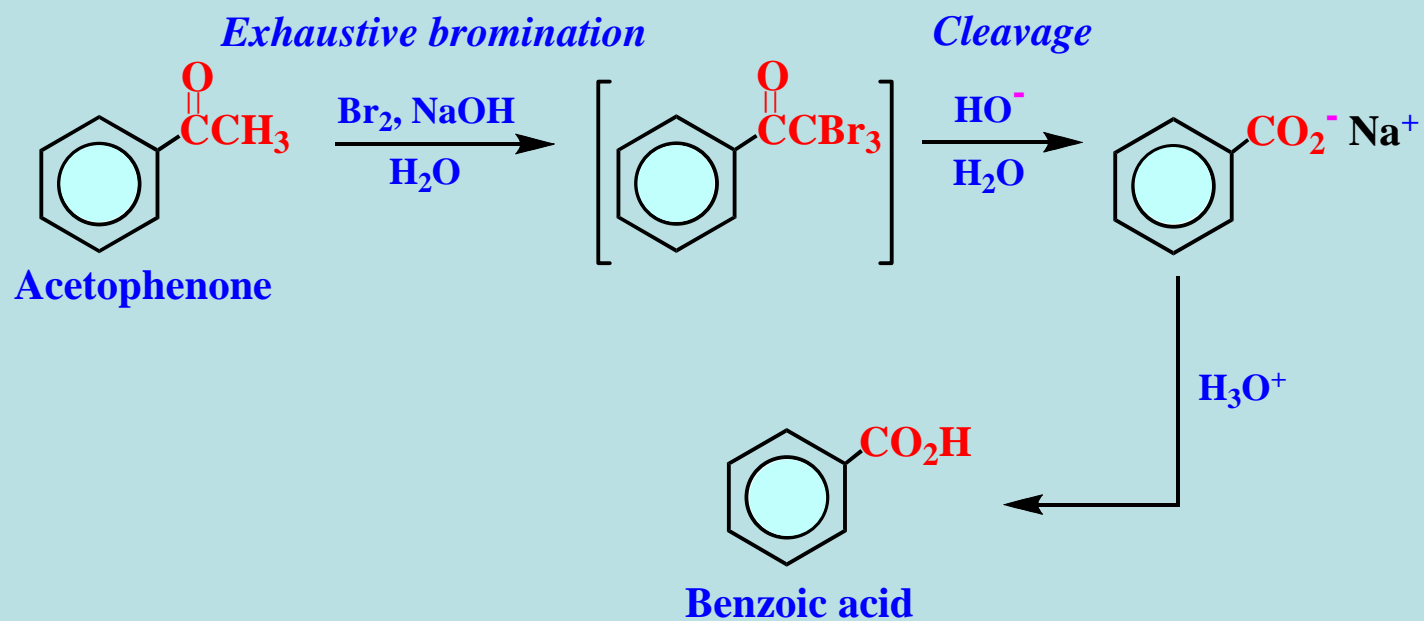
Oxidation of Alkylbenzenes

The benzene ring of an alkylbenzene can be converted to a carboxyl group by ozonolysis.



Oxidative Cleavage of Methyl Ketones

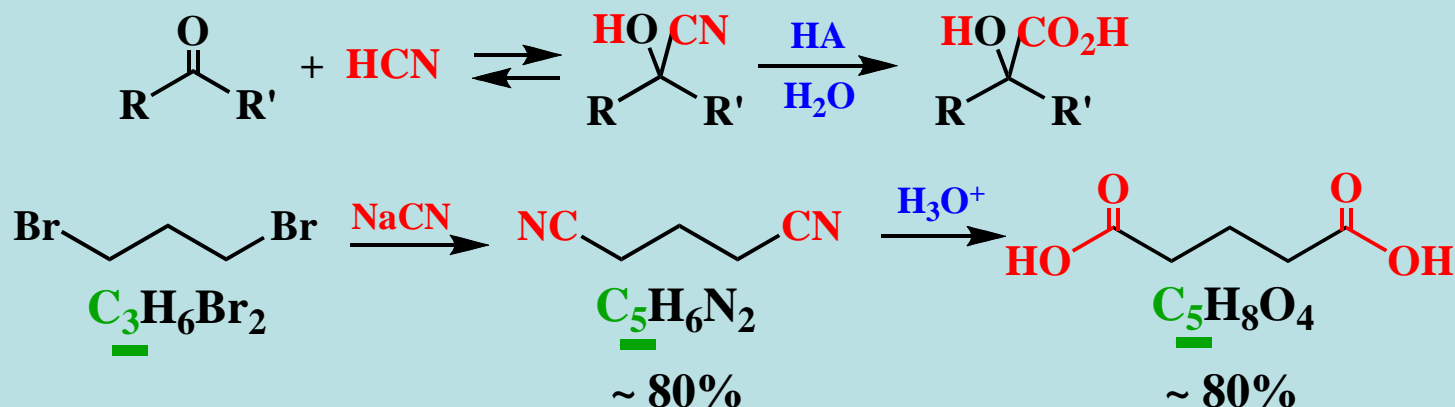
The **haloform reaction** converts methylketones to carboxylic acids (on acidification of the product).



Hydrolysis of Cyanohydrins and Other Nitriles

Cyanohydrins, prepared by addition of HCN to aldehydes or ketones, can be hydrolyzed to α -hydroxy acids.

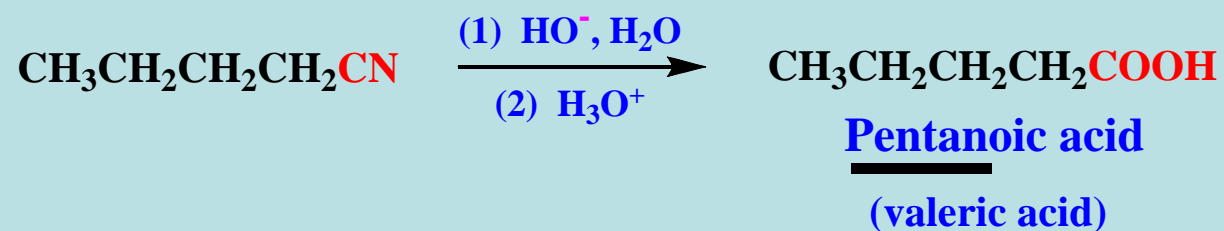
Nitriles can also be prepared by nucleophilic substitution reactions of 1° alkyl halides with sodium cyanide. Hydrolysis then provides a carboxylic acid of increased chain length.



Because of the elimination-promoting basicity of cyanide ion, the $\text{S}_{\text{N}}2$ reaction proceeds in good yield only with CH_3X and 1° halides. Aryl halides (except for those with *o*- or *p*-nitro groups) do not readily undergo nucleophilic substitution reactions.

Hydrolysis of nitriles may be carried out under either basic or acidic conditions.

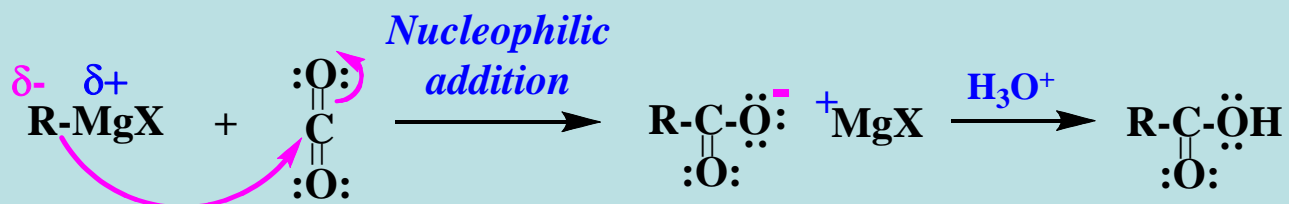
An Example: The Synthesis of Pentanoic Acid from 1-Bromobutane



Carbonation of Grignard Reagents

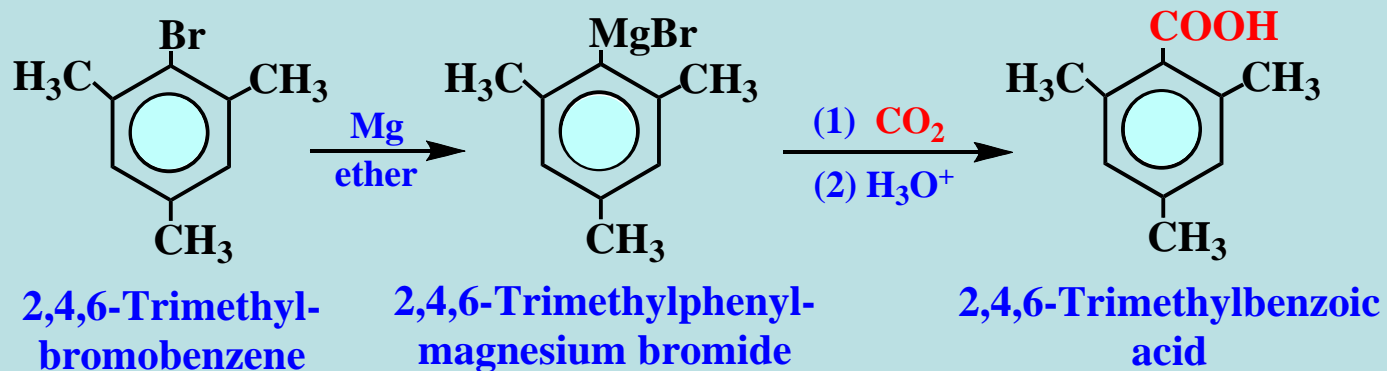
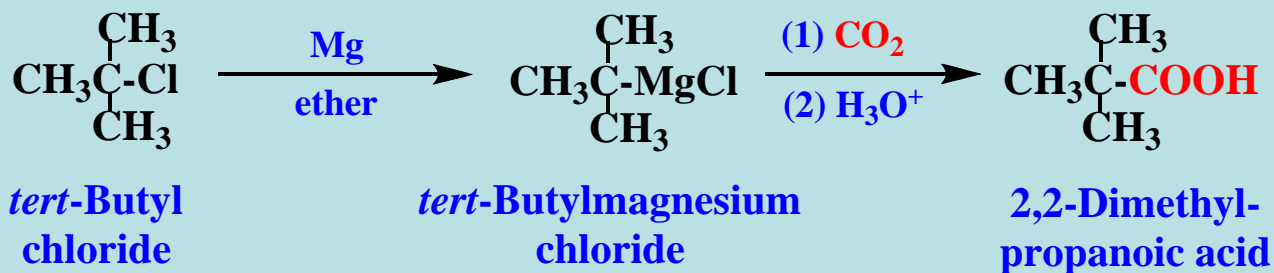
A more general way to prepare carboxylic acids from alkyl or aryl halides is by carbonation (reaction with CO_2) of the corresponding Grignard reagents.

The **strongly nucleophilic** organomagnesium reagents add to CO_2 to produce magnesium carboxylates. Acidification of these salts yields the carboxylic acids.



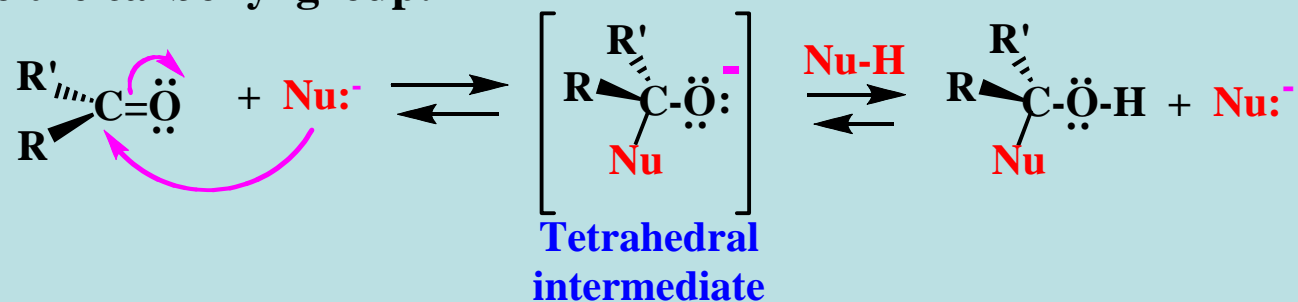
All alkyl (1° , 2° , 3°) and aryl Grignard reagents undergo the carboxylation reaction. This reaction is accomplished by either bubbling dry gaseous CO_2 through an ether solution of the Grignard reagent or by pouring the Grignard reagent onto crushed dry ice (solid CO_2).

Syntheses Using the Grignard Carbonation Reaction

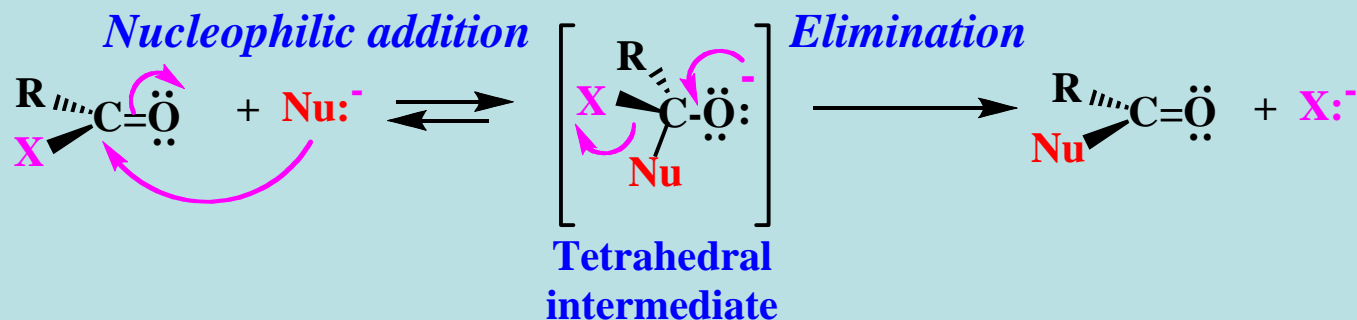


Nucleophilic Addition-Elimination at Acyl Carbon

Aldehydes and ketones undergo **nucleophilic additions** to the carbonyl group:

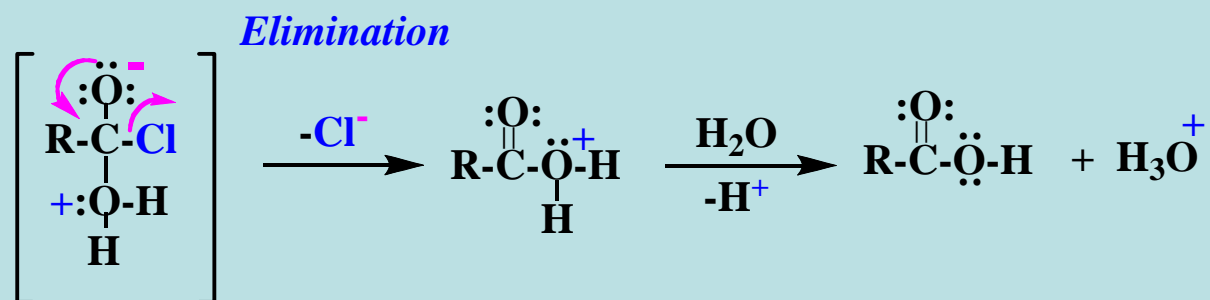
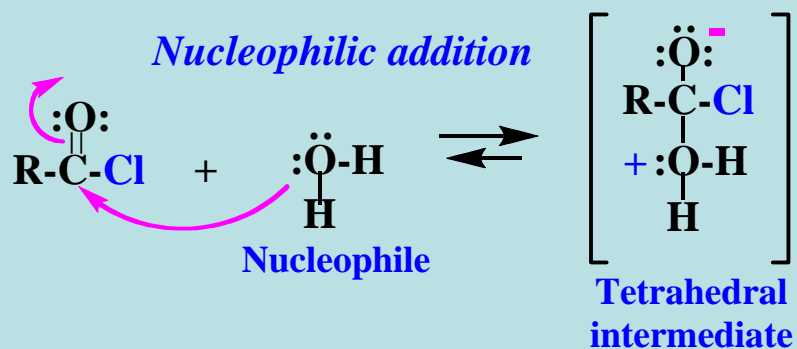


A typical reaction of carboxylic acids and their derivatives is **nucleophilic addition-elimination**. The first step is nucleophilic addition to the carbonyl to give a tetrahedral intermediate, but the presence of a good **leaving group (X)** at this site results in an elimination that regenerates the trigonal carbonyl.



This reaction mechanism is employed in many biological systems, and biochemists call them **acyl transfer reactions**.

Example: Hydrolysis of an Acyl Chloride

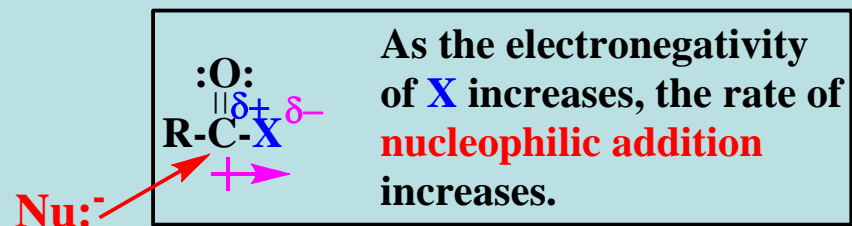


This reaction proceeds well because of the **great reactivity** of the acyl chloride towards nucleophilic addition and the **good leaving group ability** of Cl^- in the cleavage step.

Important Factors in the Addition-Elimination Reaction

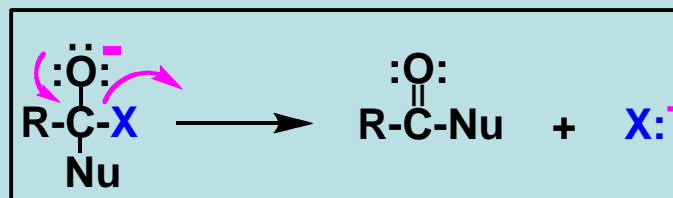
Reactivity of the Acyl Carbon

Electronic influences that increase the **electropositive character** of the acyl carbon enhance the rate of nucleophilic addition.



Stability of the Leaving Group

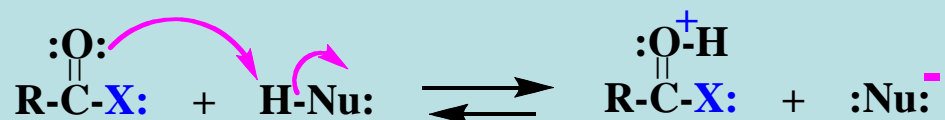
As the stability of X:- increases, it becomes a better leaving group.



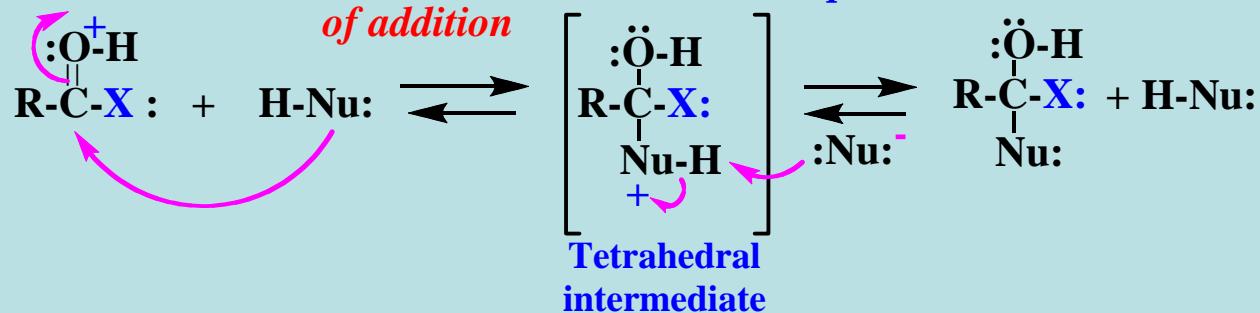
Acid Catalysis

Acid catalysis is important in both the **addition** and **elimination** steps.

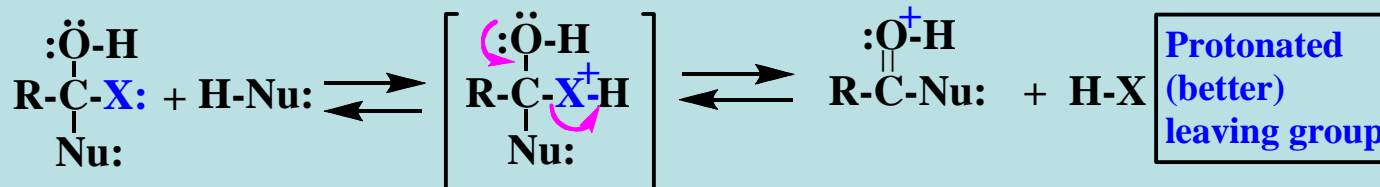
Protonation of the carbonyl



Provides electrophilic catalysis of addition

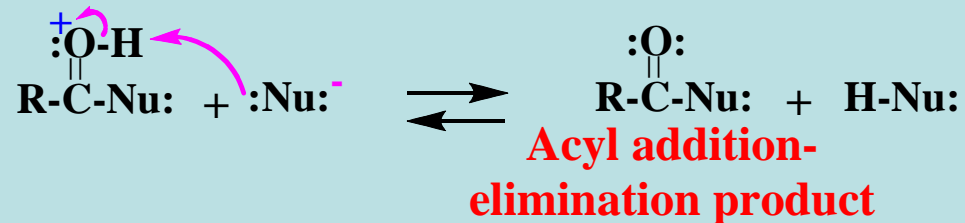


Protonation of leaving group



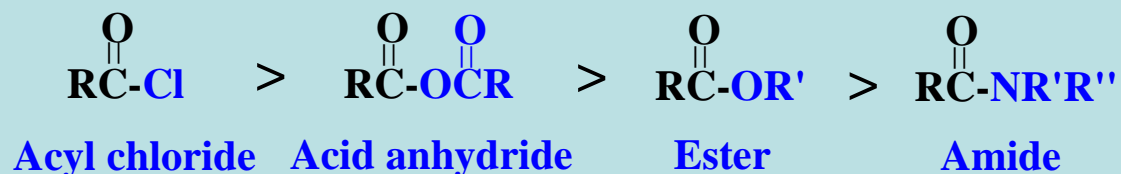
Electrophilic catalysis of elimination

Deprotonation

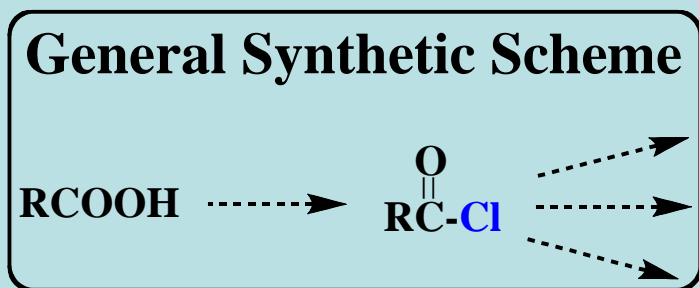


Relative Reactivity of Acyl Compounds

The basicity of the leaving group can explain the relative reactivity of acid derivatives below. The weaker the basicity of the **leaving group**, the more reactive the acid derivative.



In general, a less reactive acyl compound can be prepared from more reactive acyl compounds. The reverse is usually difficult and, when possible, requires special reagents.

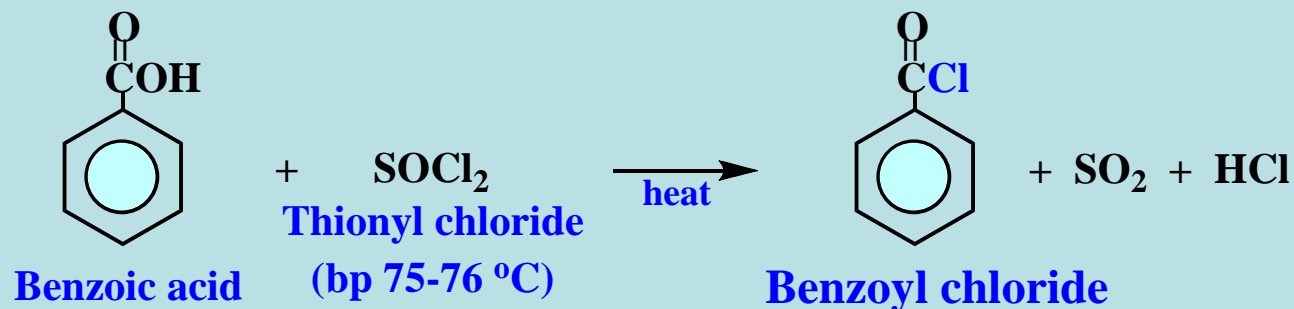


Synthesis of Acyl Chlorides

Because of their reactivity, acyl chlorides must be prepared under conditions that exclude exposure to good nucleophiles like water. Common reagents that convert carboxylic acids into acyl chlorides are phosphorus trichloride (PCl_3) phosphorus pentachloride (PCl_5), and thionyl chloride (SOCl_2).

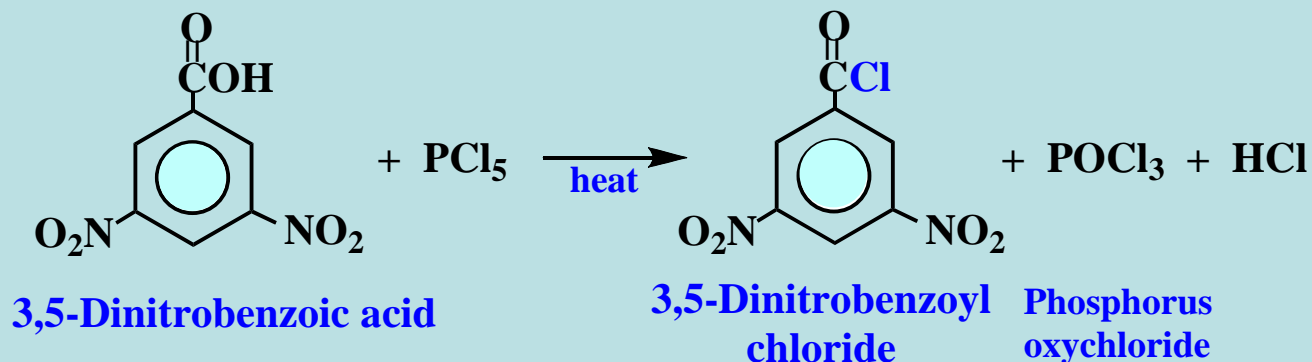
Typical Synthetic Procedures

The carboxylic acid is heated with the reagent, with or without the presence of an inert solvent.



Thionyl chloride is an especially convenient reagent because the byproducts are gases and easily removed. Excess thionyl chloride is easy to remove by distillation.

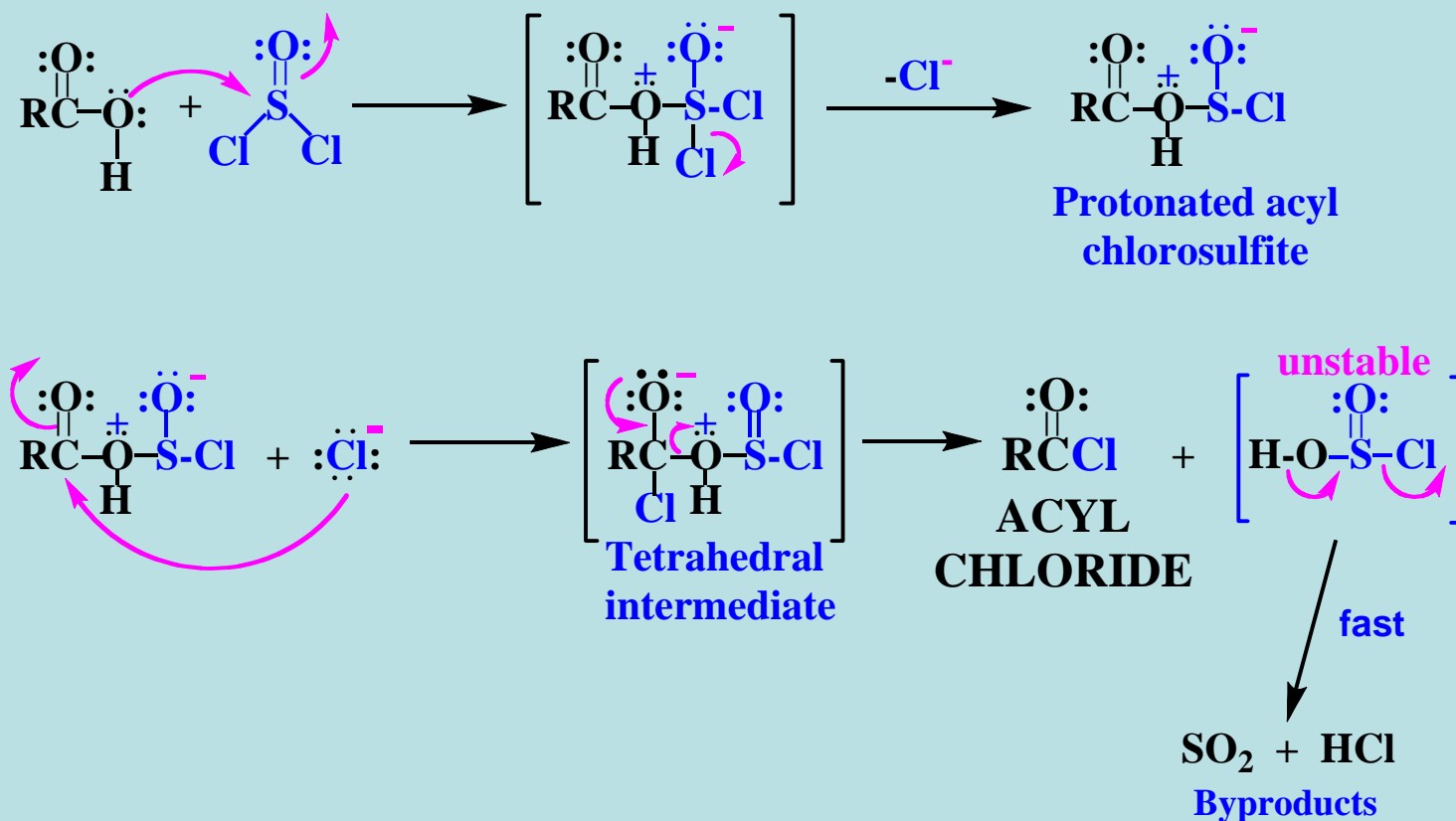
Use of Phosphorus Pentachloride



The acyl chlorides are usually isolated and purified, often by distillation. They are reasonably stable in the absence of water and other nucleophiles.

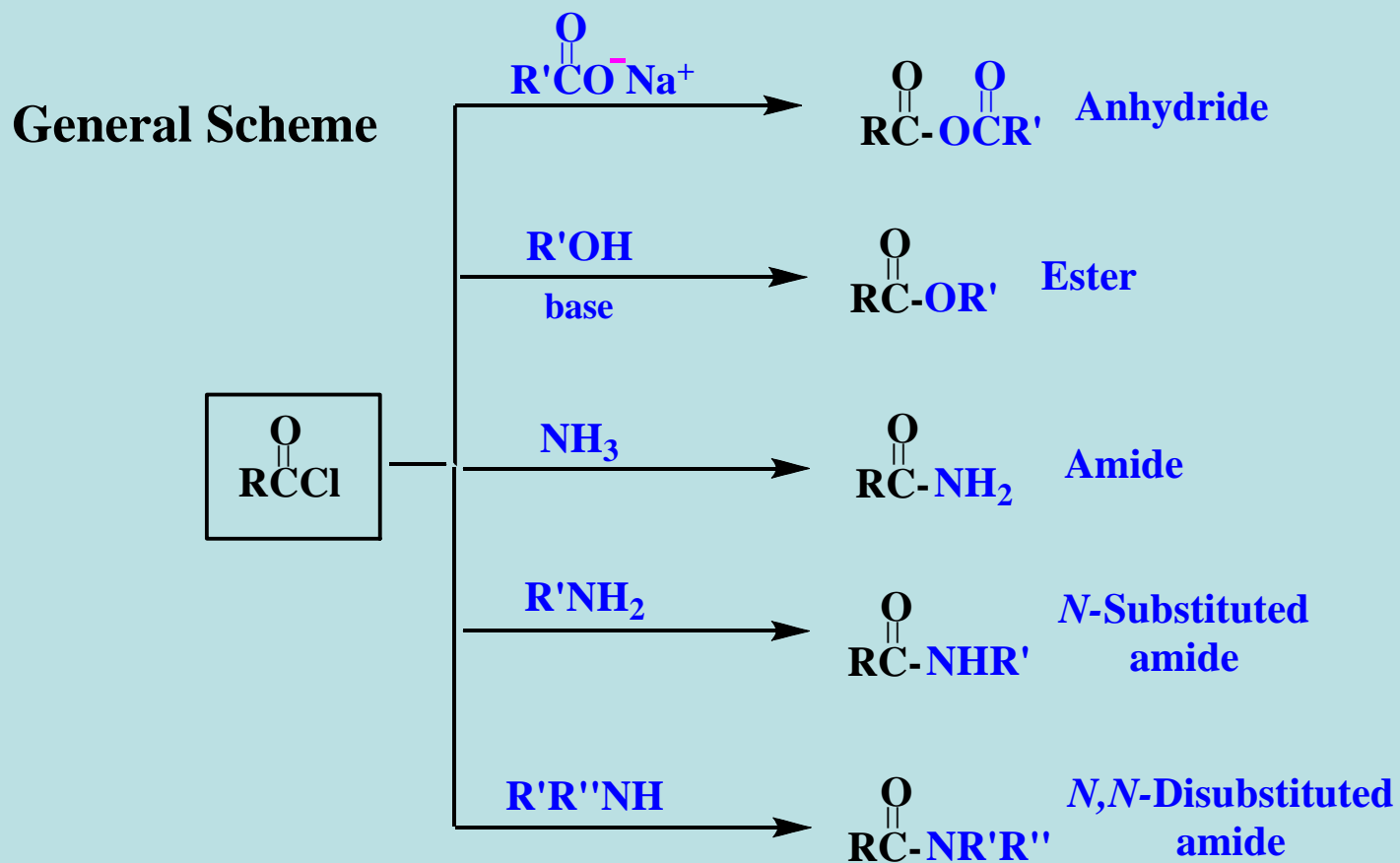
Both SOCl₂ and PCl₅ are strong electrophiles that transform the hydroxyl into a much better leaving group, thereby promoting substitution at the acyl carbon.

Mechanism for Acyl Chloride Synthesis Using Thionyl Chloride



Reactions of Acyl Chlorides

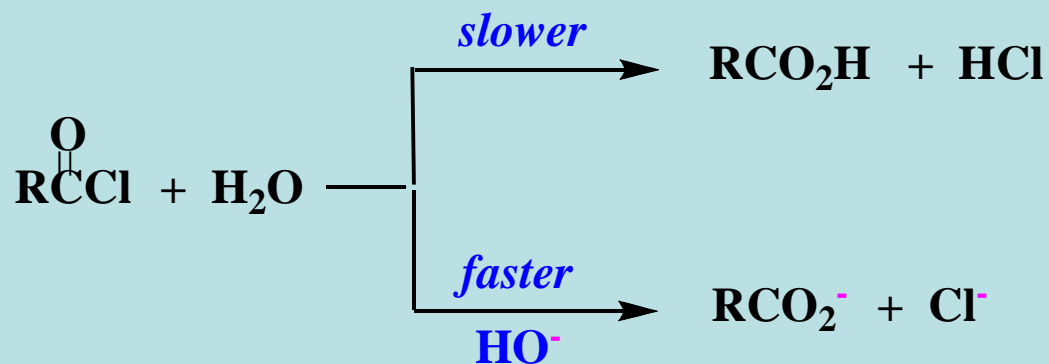
Acyl chlorides are easily converted into other acyl compounds (acid anhydrides, esters, amides, etc.) by reaction with the appropriate nucleophile.



Hydrolysis of Acyl Chlorides

Hydrolysis converts acyl chlorides into carboxylic acids. Note that reaction with water yields HCl as a byproduct. Alkaline hydrolysis proceeds faster than acid hydrolysis.

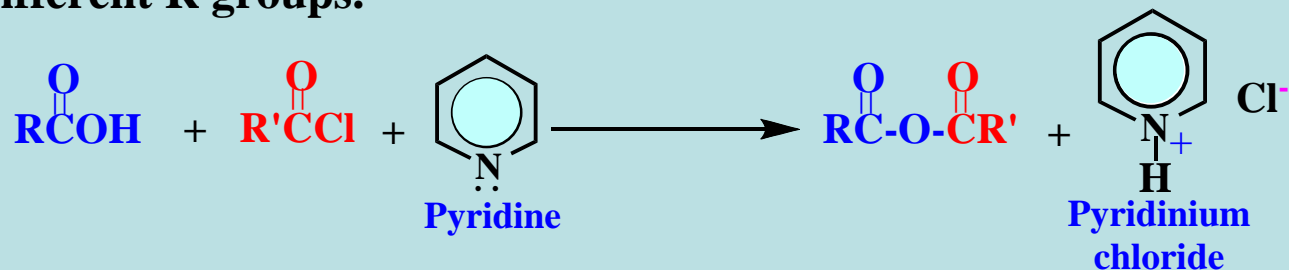
These reactions are rarely useful; usually they are accidental and need to be guarded against.



Carboxylic Acid Anhydrides

Synthesis

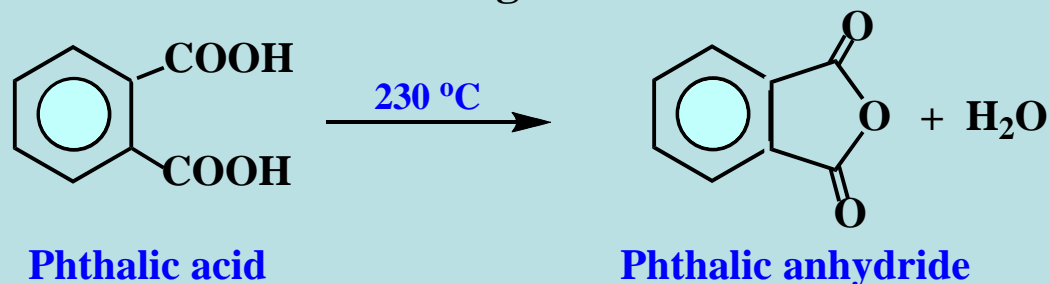
The reaction of a carboxylic acid and an acyl chloride in the presence of **pyridine** (a base) gives carboxylic acid anhydrides that may contain different R groups.



Alternatively, carboxylate salts may be reacted with acyl chlorides:

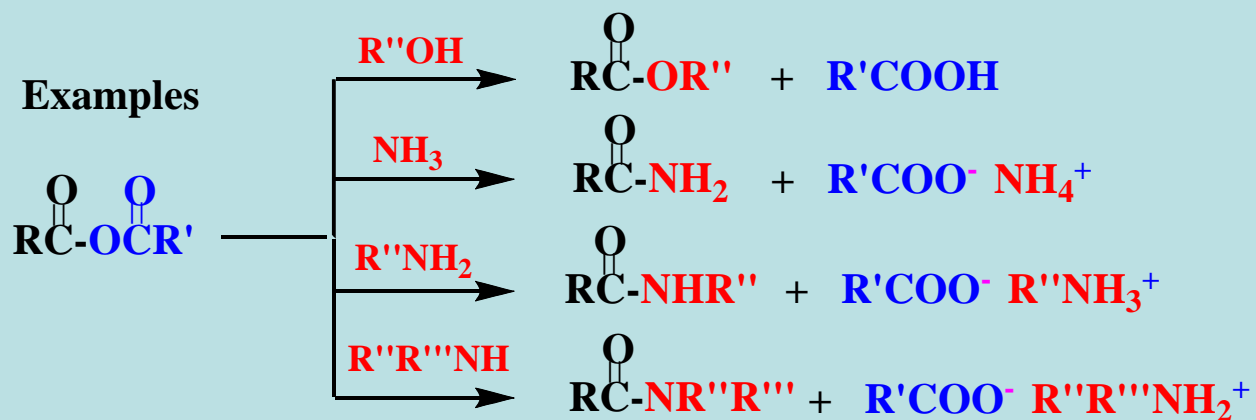
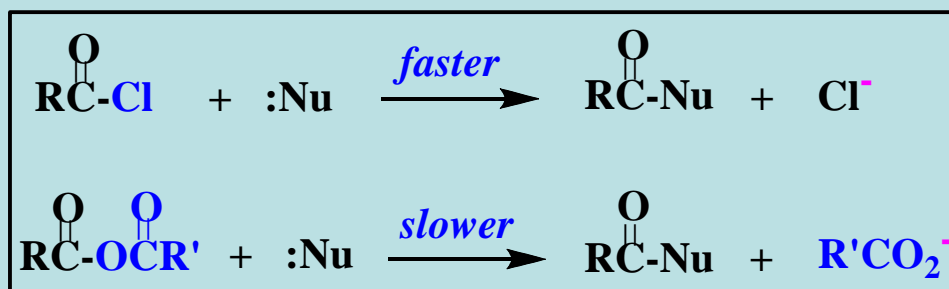


On heating, dicarboxylic acids yield cyclic anhydrides, if they have 5- or 6-membered rings.



Reactions of Carboxylic Acid Anhydrides

Carboxylic acid anhydrides and acyl chlorides show parallel patterns of reactions. The latter react **faster** because of the better leaving group ability of Cl^- .

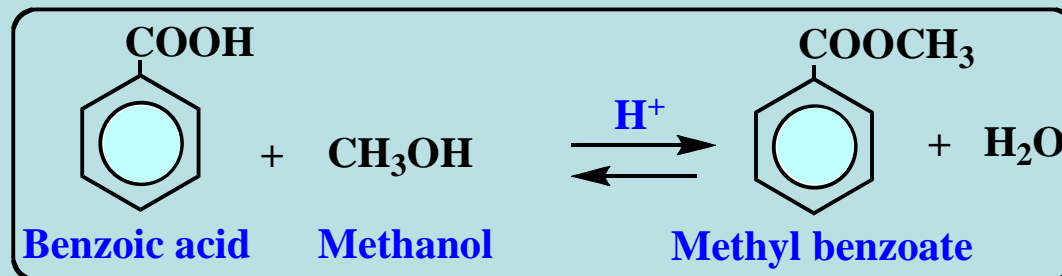


Esters

Synthesis of Esters

Direct Esterification of Carboxylic Acids

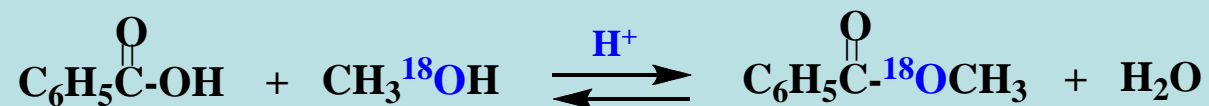
Carboxylic acids and alcohols react in the presence of a small amount of strong acid to give esters.



Esterifications are **acid-catalyzed equilibrium reactions**. Catalytic amounts of concentrated sulfuric acid or hydrochloric acid are used. Usually a large excess of the alcohol (10- or 15-fold) is used to drive the equilibrium to the product side. Product formation can also be promoted by removing the water as it is formed.

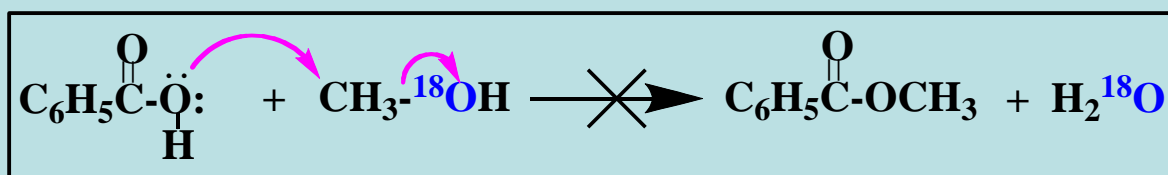
Mechanistic Studies by Isotopic Labeling

Insight into the key bonding changes during esterification was obtained by studies using **isotopically enriched** methanol.

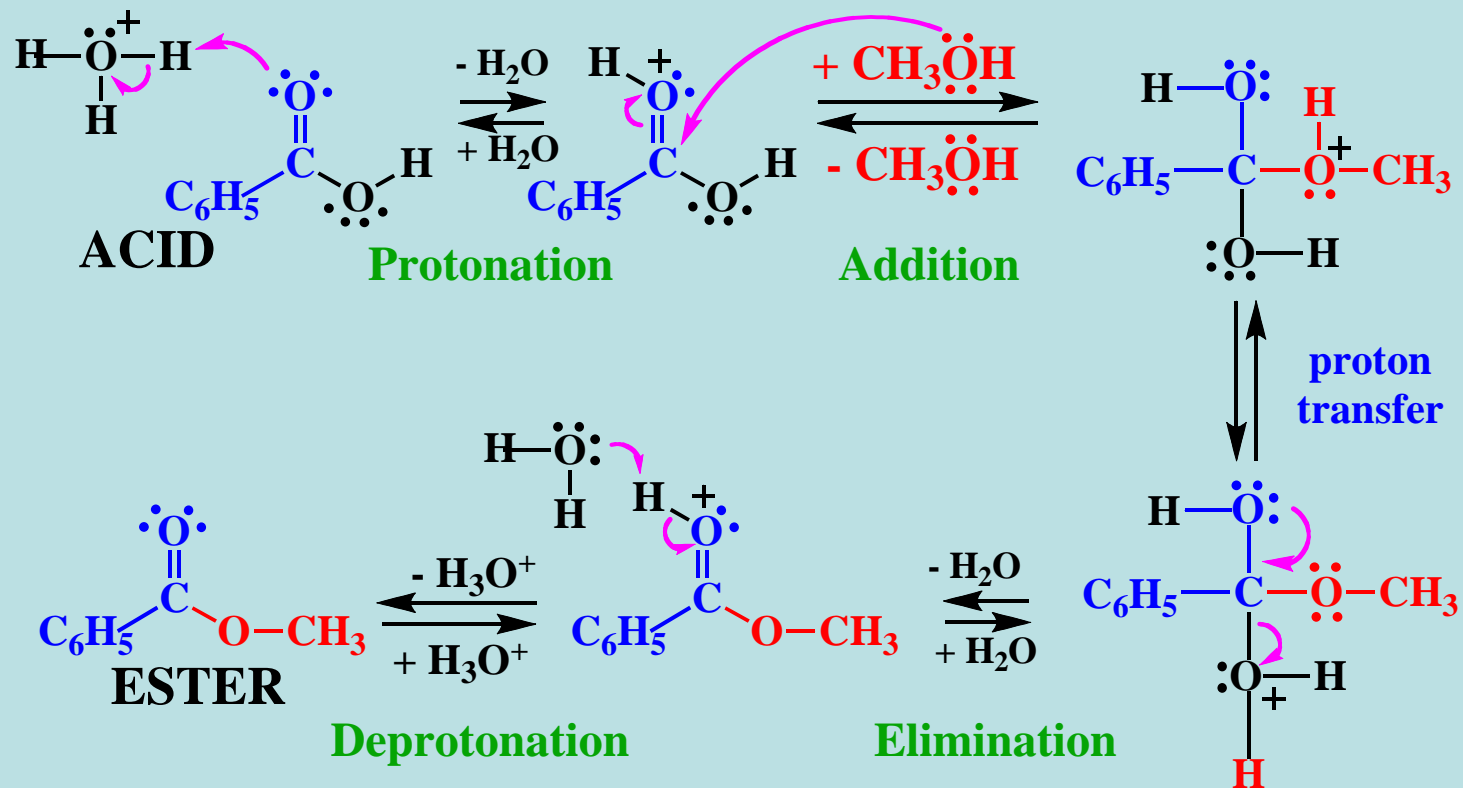


All the isotopic label appears in the methoxy oxygen.

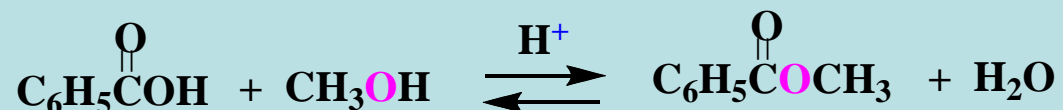
This result rules out an $\text{S}_{\text{N}}2$ mechanism:



The Mechanism of Acid-Catalyzed Esterification

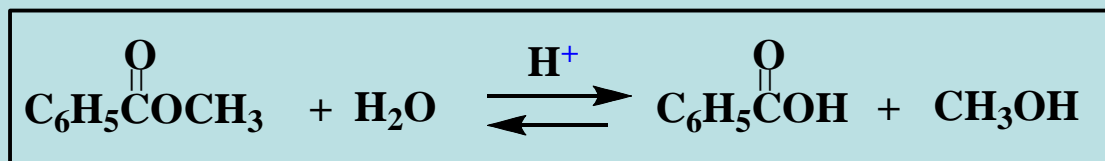


This mechanism for esterification is consistent with the incorporation of the **isotopic label**:



A Mechanism for Acid-Catalyzed Hydrolysis of Esters

Since every step is reversible, the reverse of the esterification scheme is the mechanism for the **acid-catalyzed hydrolysis** of esters.



The direction of the reaction is controlled by the relative concentrations of water versus alcohol.

Steric Factors in Direct Esterification

The rate of esterification slows down as **bulky groups** are introduced into the structure near the carbonyl group of the acid or in the alcohol.



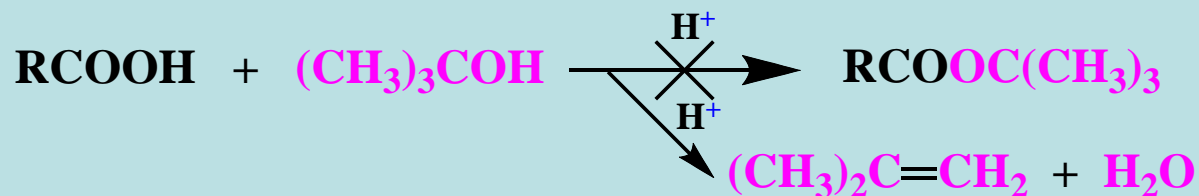
Relative reactivity of RCOOH



Relative reactivity of R'OH



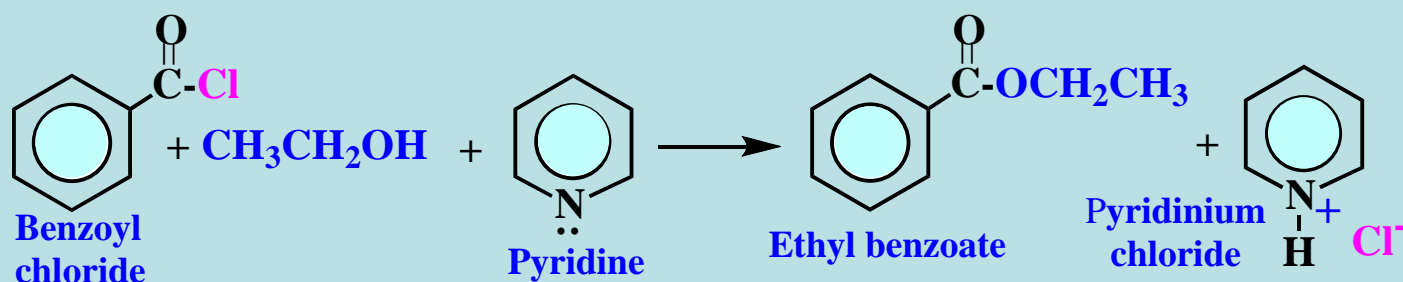
In the presence of strong acids, **tertiary alcohols** tend to dehydrate rather than undergo esterification reactions.



Sterically hindered esters have to be prepared by other methods.

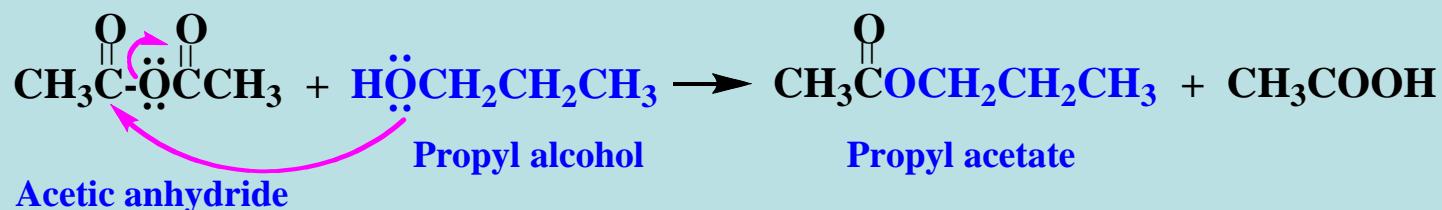
Esters from Acyl Chlorides

The reaction of alcohols with acyl chlorides gives esters. No acid catalysis is needed, but a tertiary amine, usually pyridine, is usually added to capture the HCl formed and drive the reaction to completion. These bases also appear to enhance the reactivity of acyl halides.

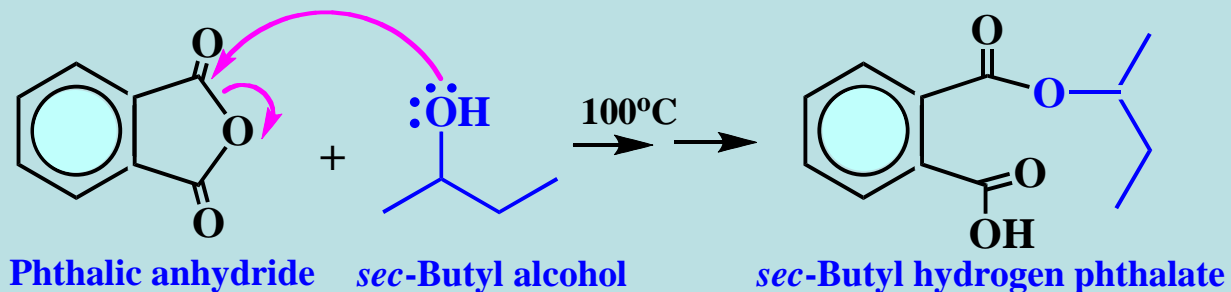


Esters from Carboxylic Acid Anhydrides

Alcohols react with acid anhydrides to give esters. As seen earlier, acyl chlorides and carboxylic acid anhydrides often undergo similar nucleophilic substitution reactions at the acyl carbon.

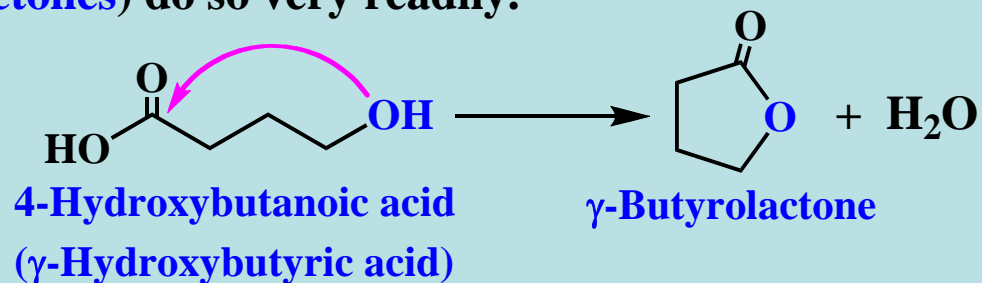


Cyclic Anhydrides Undergo Similar Reactions



Intramolecular Esterification: **Lactone** Formation

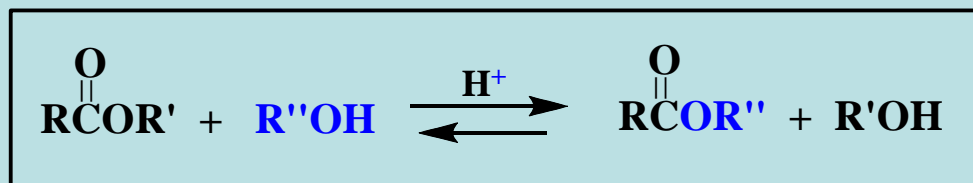
Carboxylic acids that contain alcohol functions that can react intramolecularly to form 5- or 6-membered cyclic esters (**lactones**) do so very readily.



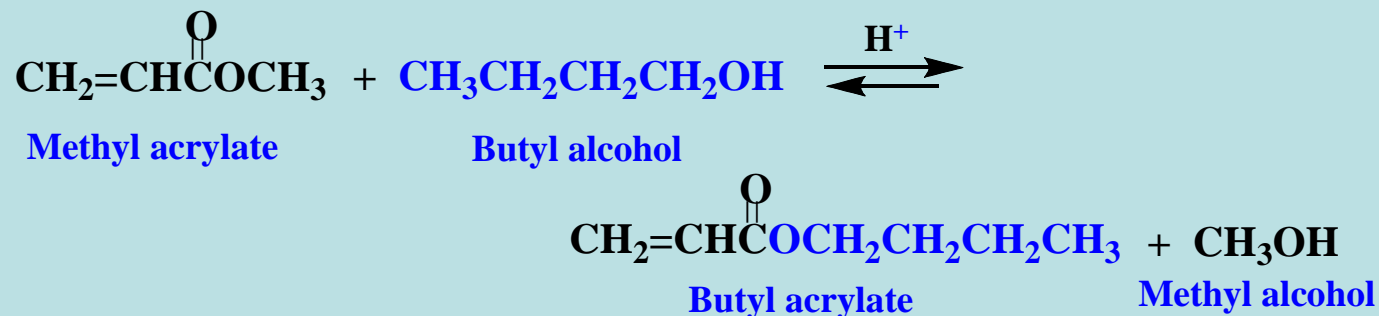
A trace of strong acid catalyst hastens the conversion.

Transesterification

This is a process whereby the ester of one alcohol may be converted into the ester of a second alcohol by the equilibrium:



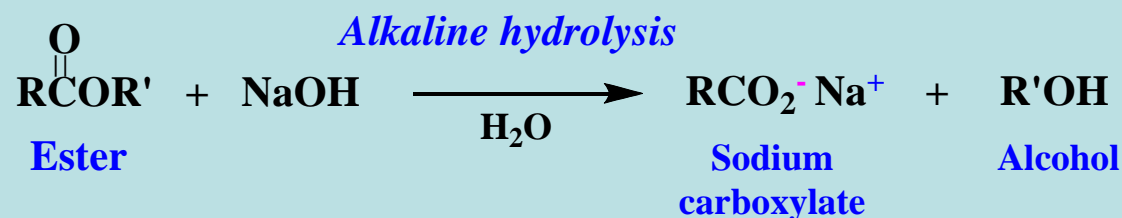
An example



The equilibrium is shifted to the product side by using an excess of butyl alcohol and/or distilling out the lower boiling methanol from the reaction mixture.

Base-Promoted Hydrolysis of Esters: Saponification

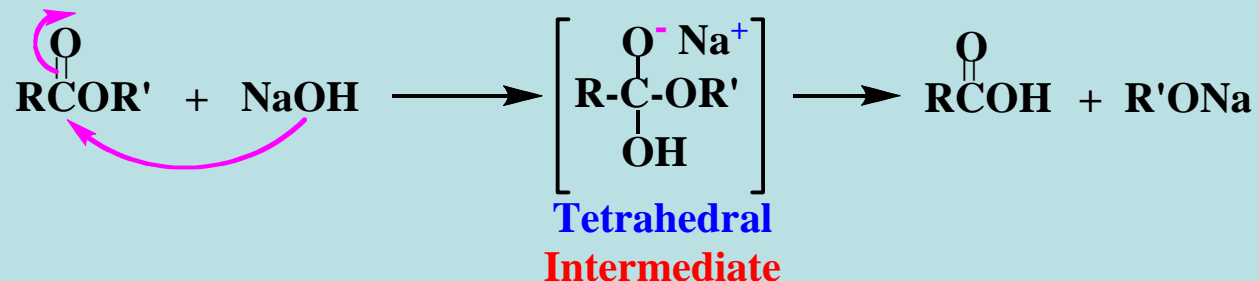
Base-promoted hydrolysis of esters is called **saponification** (from the Latin *sapo*, soap) because traditional soap-making involves the alkaline hydrolysis of fats (esters of glycerol).



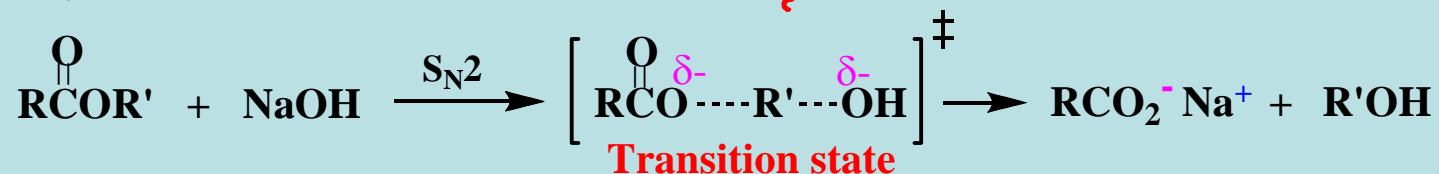
In the case of soaps, the R in the carboxylate ion typically is a straight-chain alkyl containing eleven to seventeen carbon atoms.

Two Possible Mechanisms for the Alkaline Hydrolysis of Esters

(1) *Addition-Elimination*: $\text{RC}(=\text{O})\text{-}\xi\text{-OR}'$



(2) *S_N2 Nucleophilic Substitution*: $\text{RCO}(=\text{O})\text{-}\xi\text{-R}'$



To distinguish between these possibilities, information on the mechanism was obtained by carefully designed experiments using **stereochemical and isotopic probes**.

Some Observations

Kinetic Studies

The rate of alkaline hydrolysis follows the **second-order**

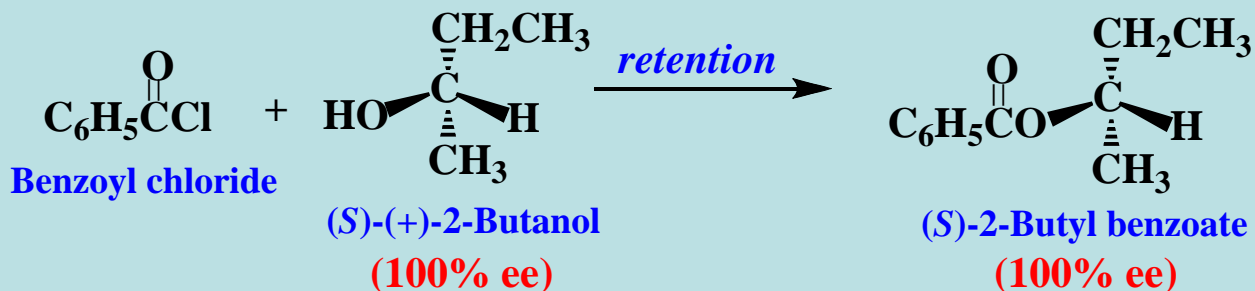
rate expression:

$$\text{rate} = k [\text{RCO}_2\text{R}'] [\text{HO}^-]$$

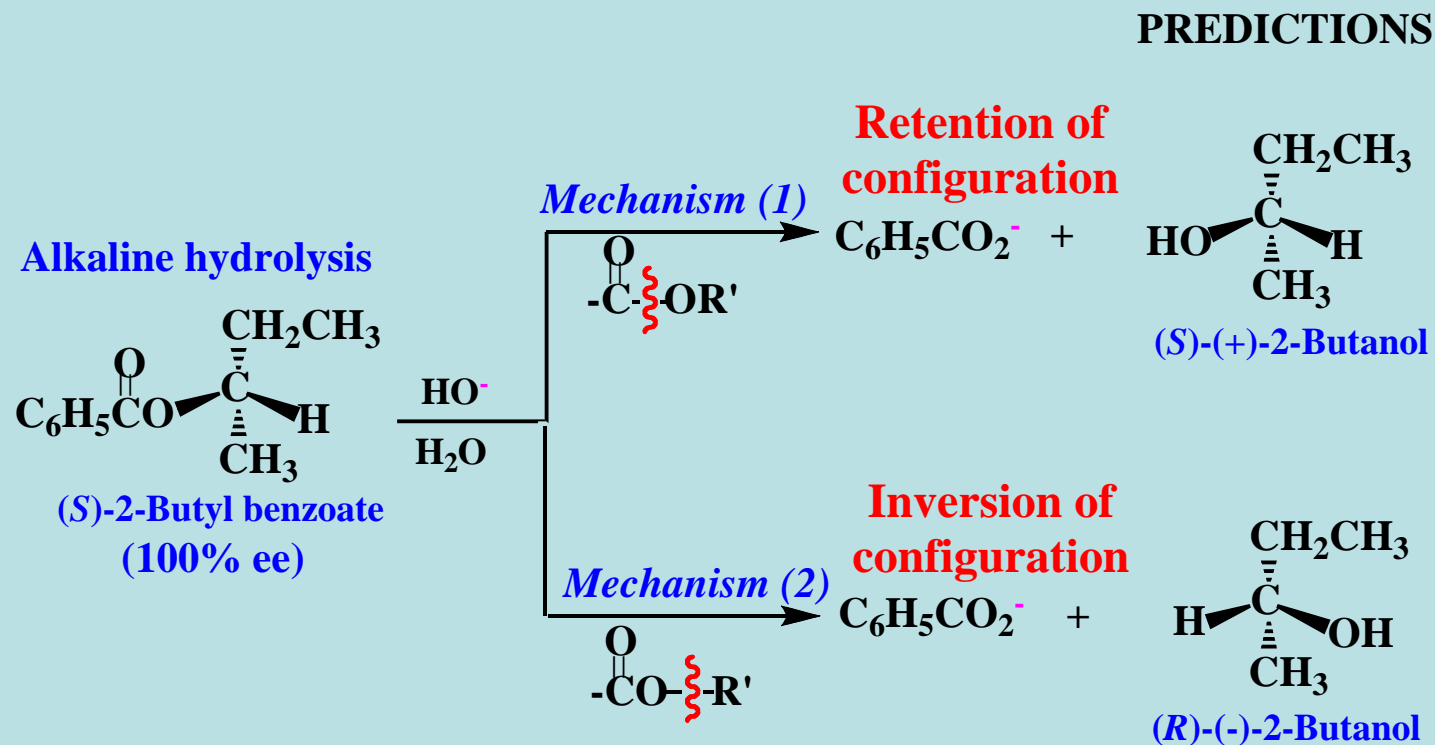
Since this result is consistent with either mechanism, it cannot elucidate the operating pathway for alkaline hydrolysis.

Stereochemical Probe

An ester with a **stereocenter** at the alkyl carbon can serve as a **stereochemical probe** of the mechanism. Such a probe molecule may be synthesized by the following stereospecific reaction.



Predictions of Stereochemical Outcomes



Stereochemical Outcome

Alkaline hydrolysis of (S)-2-butyl benzoate produced only (S)-(+)-2-butanol which is consistent with mechanism (1), cleavage at the acyl carbon.