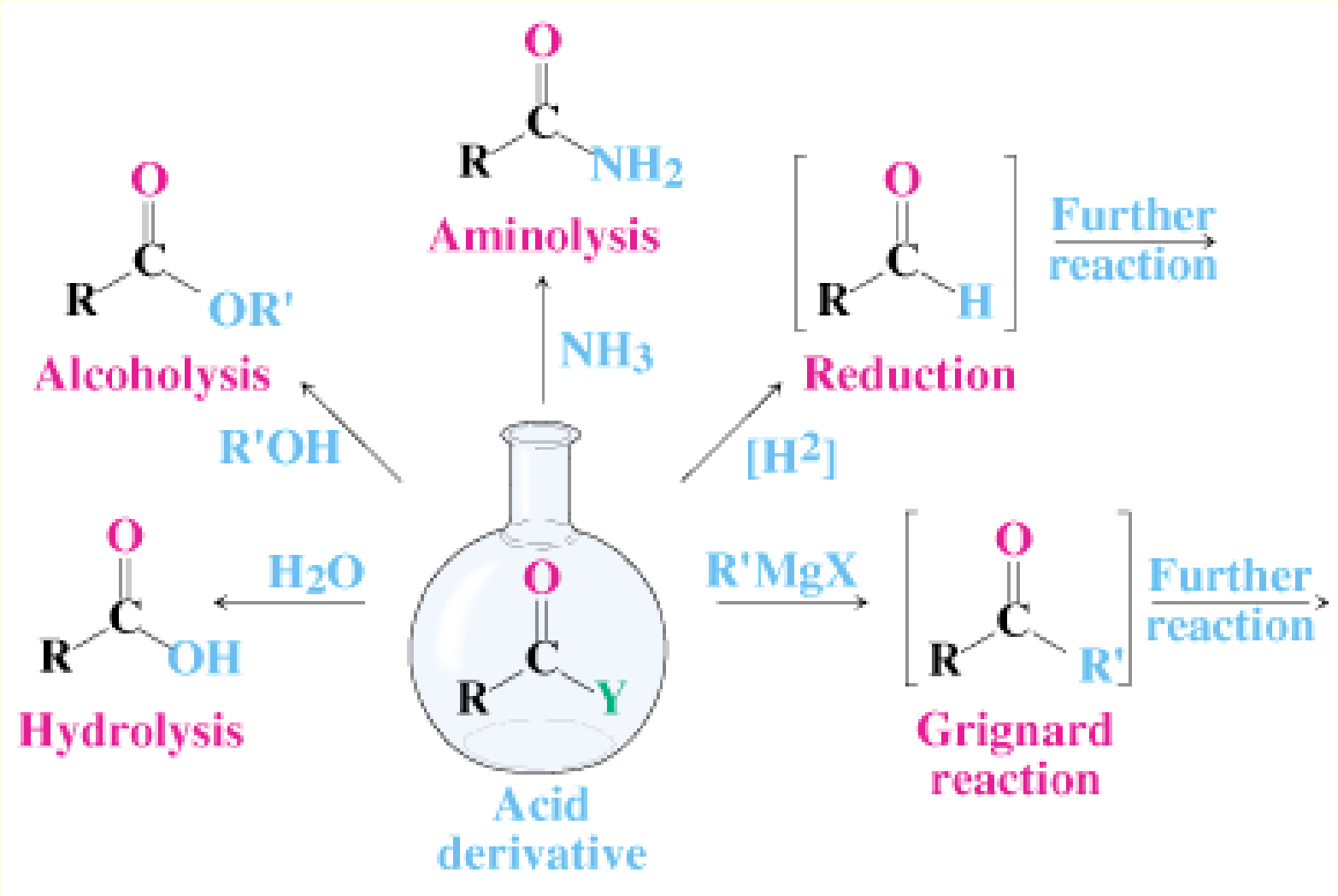
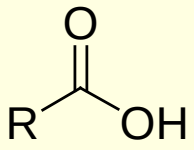
Chapter 21: Carboxylic Acid Derivatives and Nucleophilic Acyl Substitution Reactions

General Reactions of Carboxylic Acid Derivatives

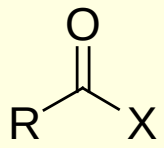


Carboxylic Compounds

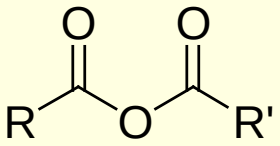
- Acyl group bonded to Y, an electronegative atom or leaving group
- Includes: Y = halide (acid halides), acyloxy (anhydrides), alkoxy (esters), amine (amides), thiolate (thioesters), phosphate (acyl phosphates)



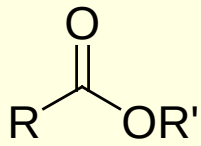
Carboxylic Acid



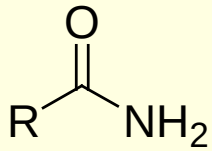
X = Cl, Br
Acid Halides



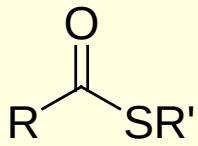
Acid Anhydride



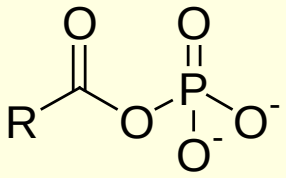
Ester



Amide



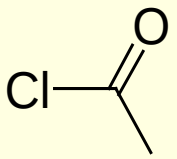
Thioester



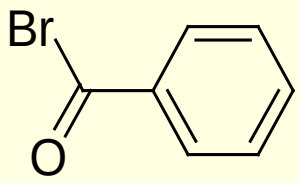
Acyl Phosphate

Naming Carboxylic Acid Derivatives

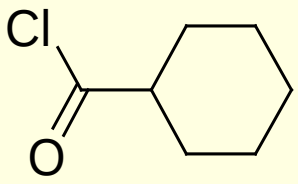
- Acid Halides, RCOX
  - Derived from the carboxylic acid name by replacing the -*ic acid* ending with -*yl* or the -*carboxylic acid* ending with –*carbonyl* and specifying the halide



Acetyl Chloride



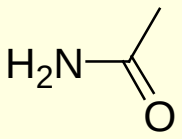
Benzoyl Bromide



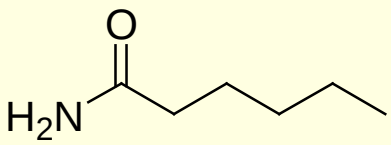
Cyclohexanecarbonyl chloride

Naming Amides, $RCONH_2$

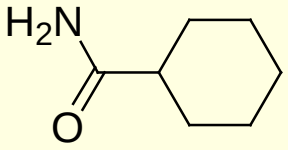
- With unsubstituted —NH_2 group. replace -*oic acid* or -*ic acid* with -*amide*, or by replacing the -*carboxylic acid* ending with –*carboxamide*
- If the N is further substituted, identify the substituent groups (preceded by “N”) and then the parent amide



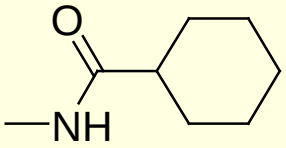
Acetamide



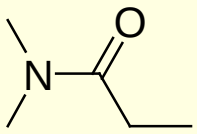
Hexanamide



Cyclohexanecarboxamide



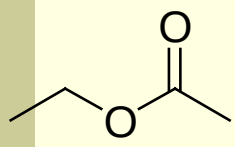
N-Methyl-cyclohexamide



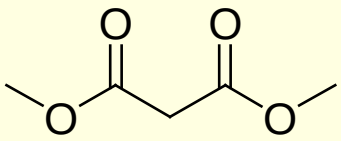
N,N-Dimethyl-propamide

Naming Esters, RCO_2R'

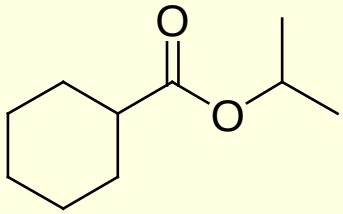
- Name R' and then, after a space, the carboxylic acid (RCOOH), with the "*-ic acid*" ending replaced by "-*ate*"



Ethyl Acetate



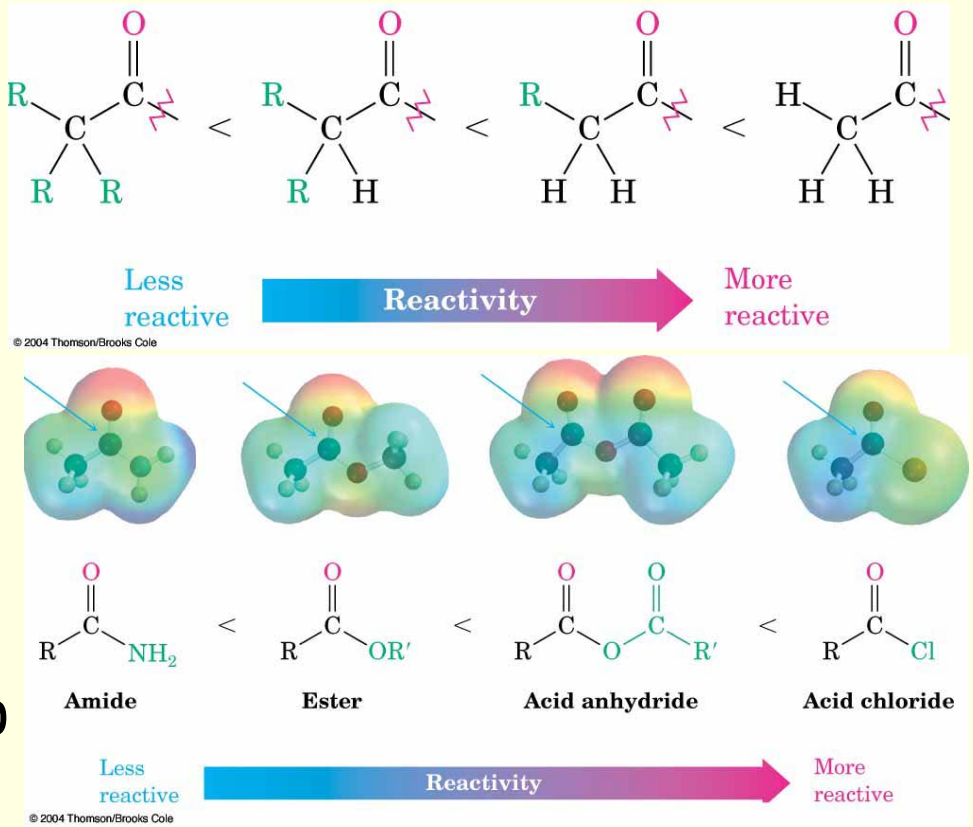
Dimethyl malonate



Cyclohexanecarboxylic acid isopropyl ester

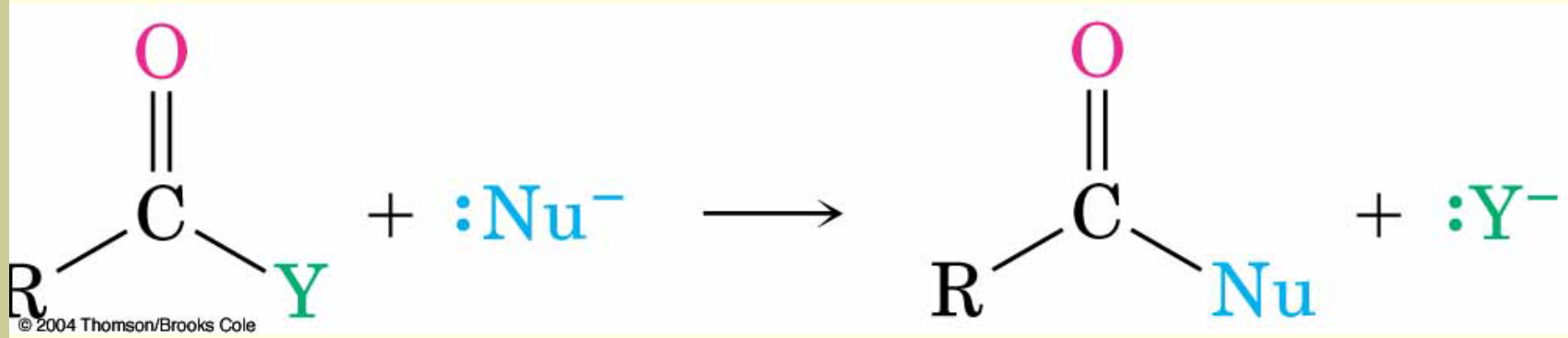
Relative Reactivity of Carboxylic Acid Derivatives

- Nucleophiles react more readily with unhindered carbonyl groups
- More electrophilic carbonyl groups are more reactive to addition (acyl halides are most reactive, amides are least)
- The intermediate with the best leaving group decomposes fastest



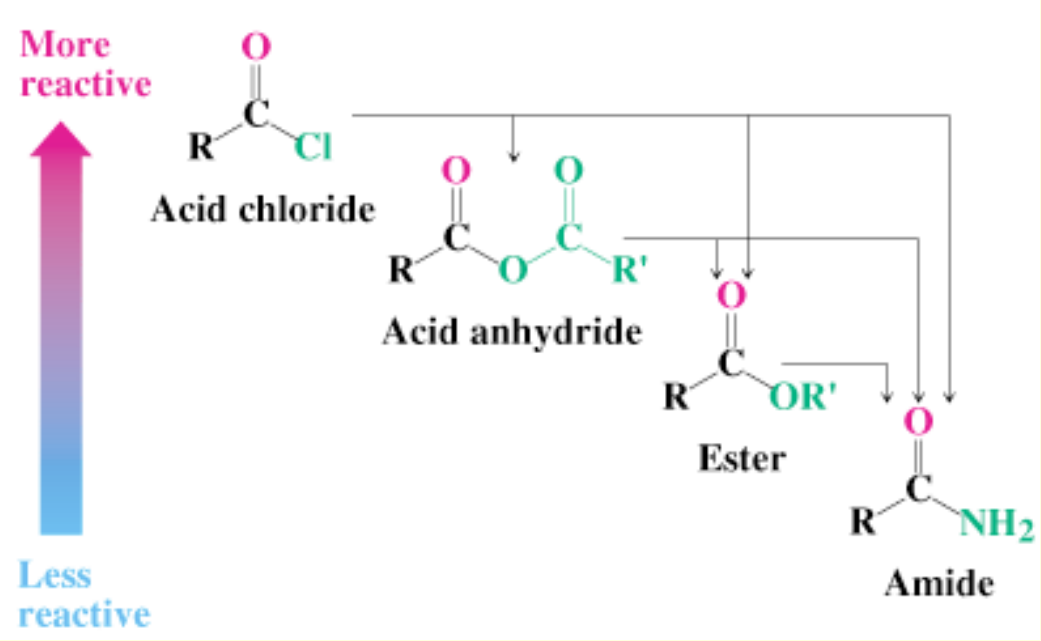
General Reaction Pattern

- Nucleophilic acyl substitution



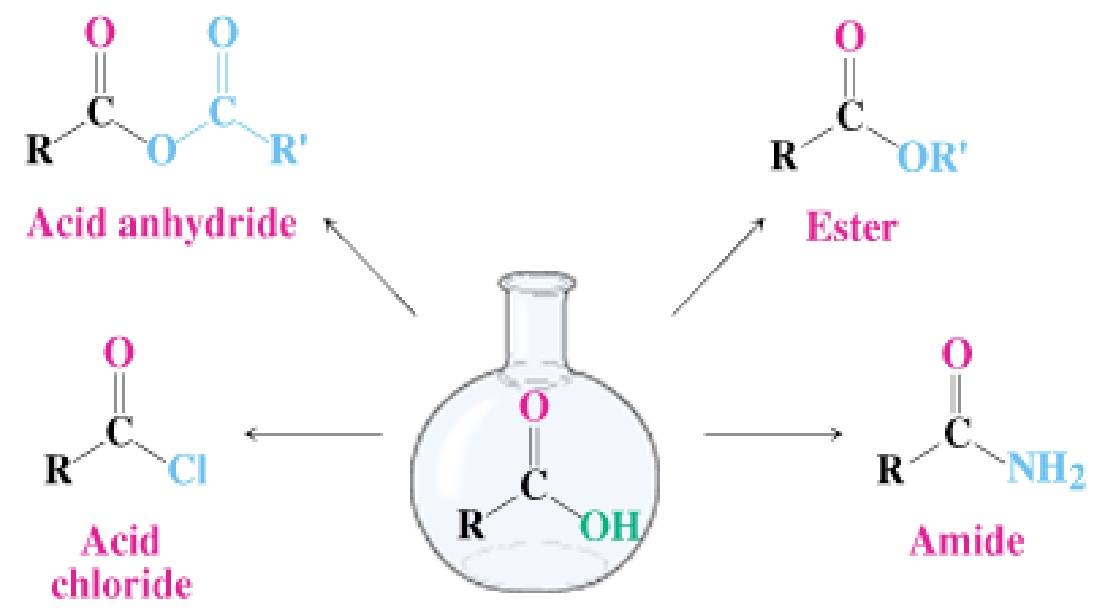
Substitution in Synthesis

- We can readily convert a more reactive acid derivative into a less reactive one
- Reactions in the opposite sense are possible but require more complex approaches



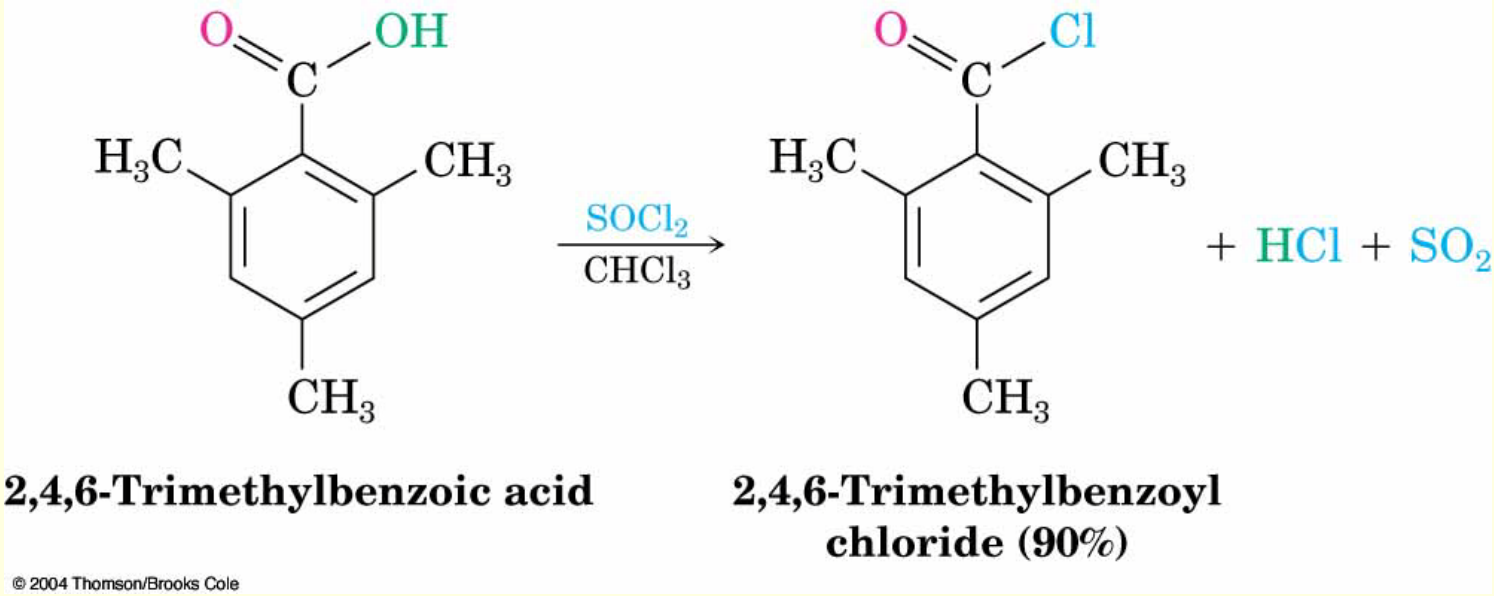
Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

- Must enhance reactivity
- Convert —OH into a better leaving group
- Specific reagents can produce acid chlorides, anhydrides, esters, amides



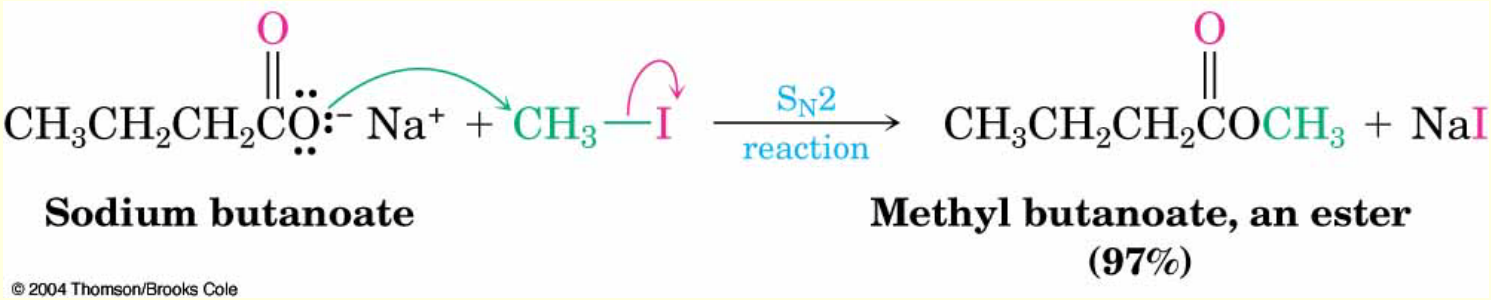
Conversion of Carboxylic Acids into Acid Chlorides

- Reaction with thionyl chloride, $SOCl_2$



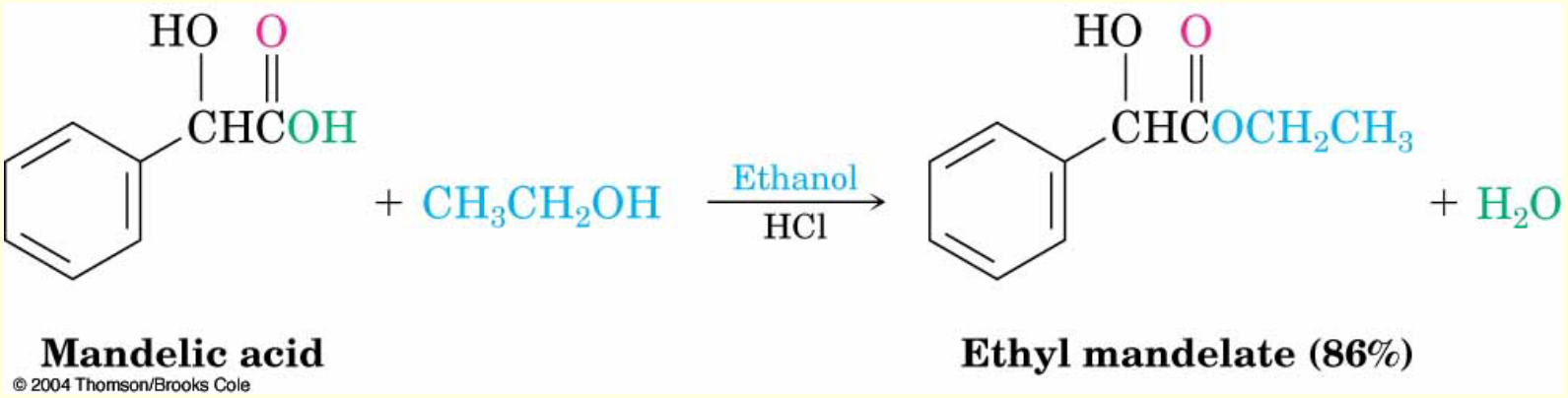
Conversion of Carboxylic Acids into Esters

- Methods include reaction of a carboxylate anion with a primary alkyl halide



Fischer Esterification

- Heating a carboxylic acid in an alcohol solvent containing a small amount of strong acid produces an ester from the alcohol and acid

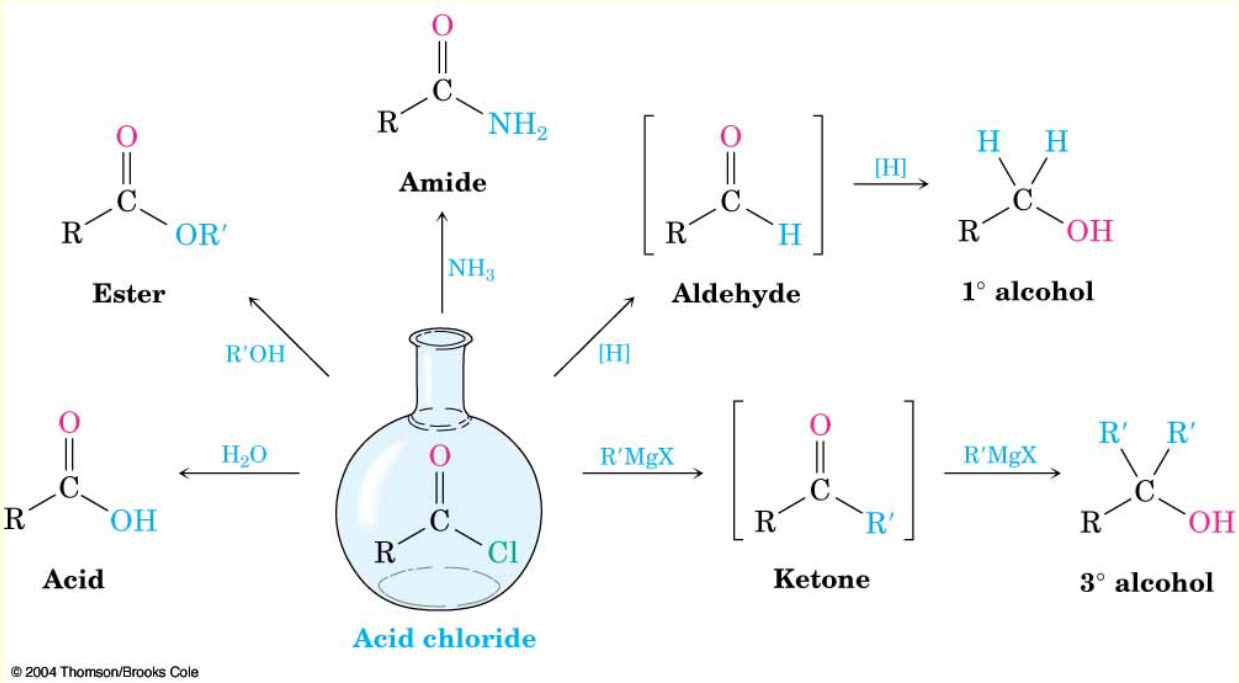


Chemistry of Acid Halides

- Acid chlorides are prepared from carboxylic acids by reaction with $SOCl_2$
- Reaction of a carboxylic acid with PBr_3 yields the acid bromide

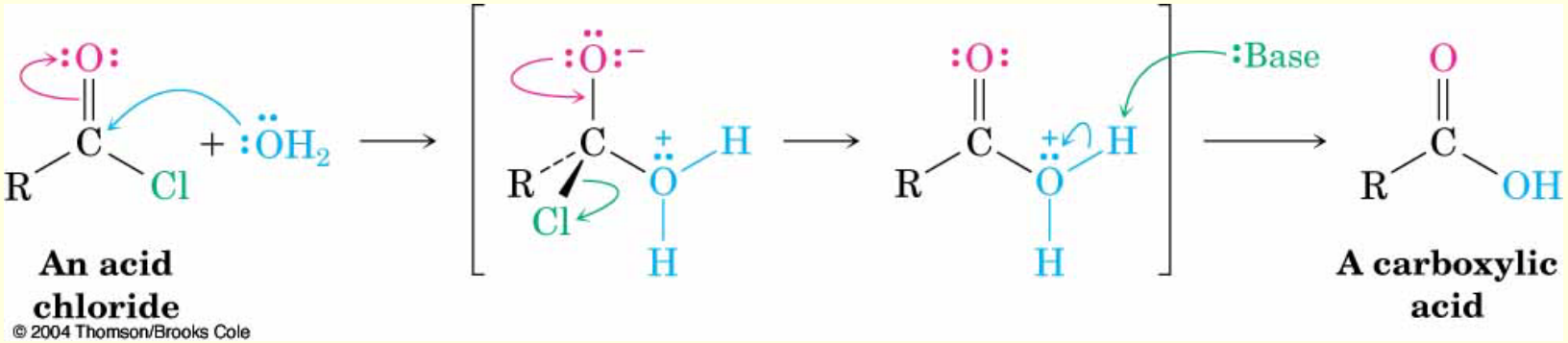
Reactions of Acid Halides

- Nucleophilic acyl substitution
- Halogen replaced by —OH, by —OR, or by —NH_2
- Reduction yields a primary alcohol
- Grignard reagent yields a tertiary alcohol



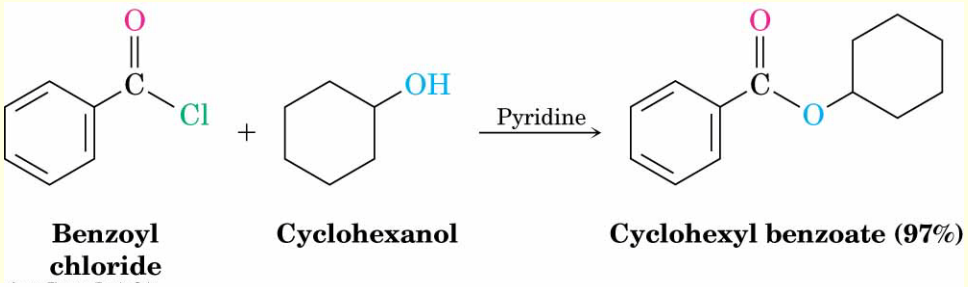
Hydrolysis: Conversion of Acid Halides into Acids

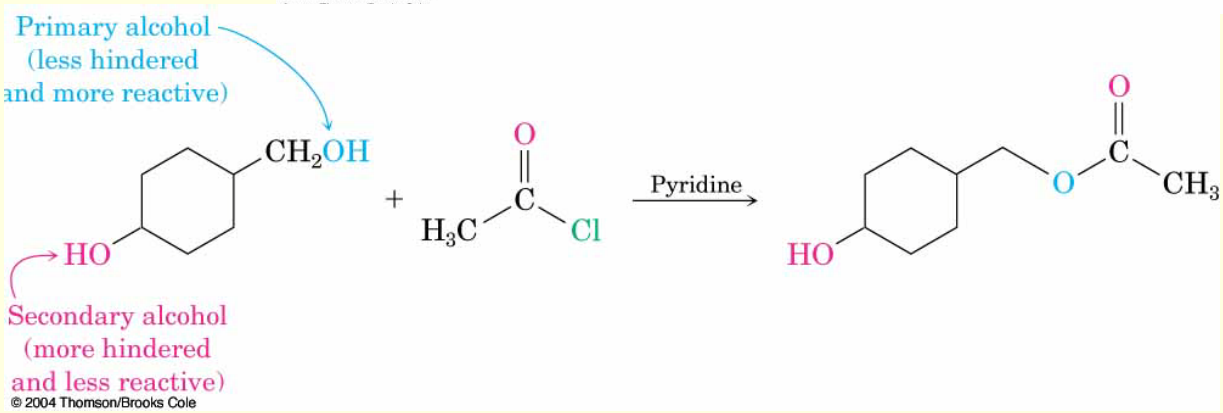
- Acid chlorides react with water to yield carboxylic acids
- HCl is generated during the hydrolysis: a base is added to remove the HCl



Conversion of Acid Halides to Esters

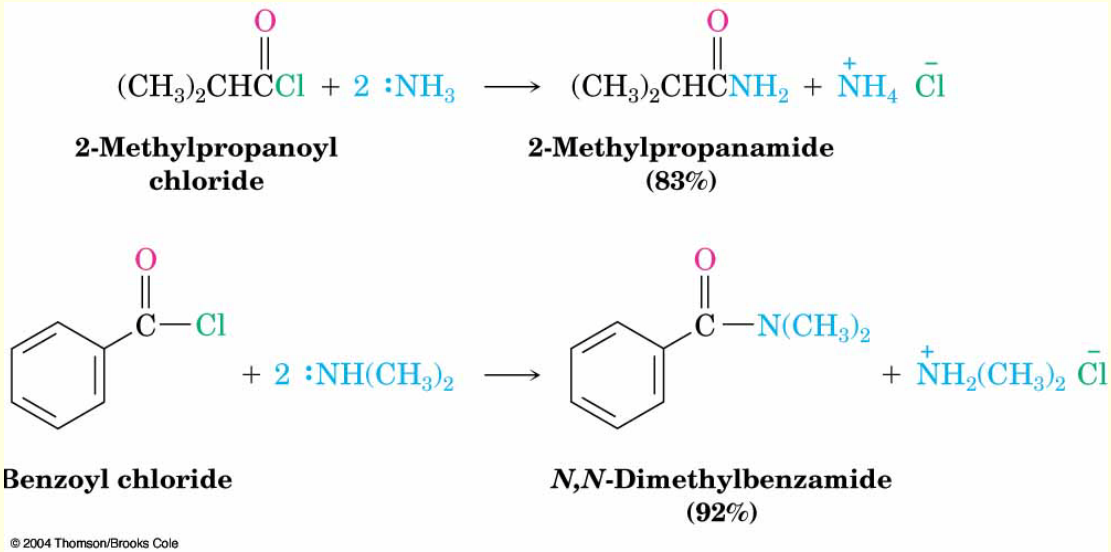
- Esters are produced in the reaction of acid chlorides react with alcohols in the presence of pyridine or NaOH
- The reaction is better with less steric bulk





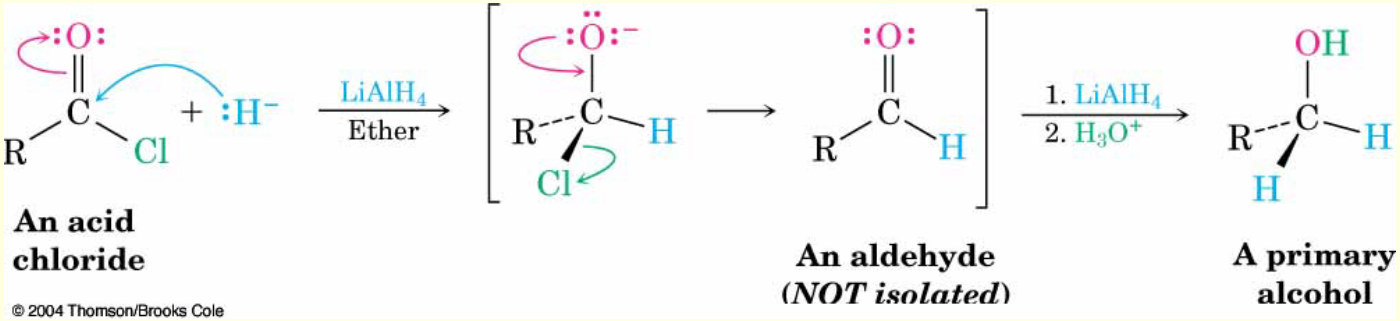
Aminolysis: Conversion of Acid Halides into Amides

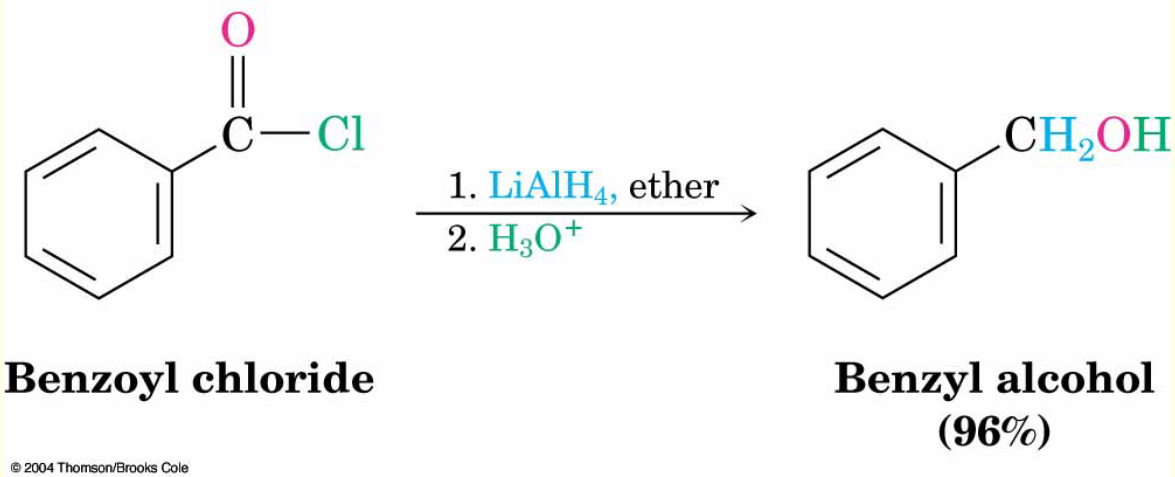
- Amides result from the reaction of acid chlorides with NH_3, primary (RNH_2) and secondary amines (R_2NH)
- The reaction with tertiary amines (R_3N) gives an unstable species that cannot be isolated
- HCl is neutralized by the amine or an added base



Reduction: Conversion of Acid Chlorides into Alcohols

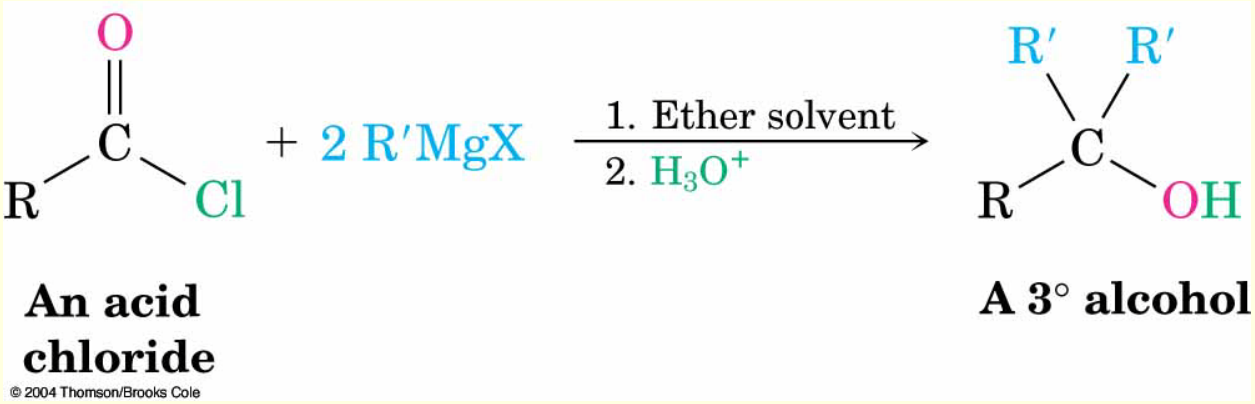
- $LiAlH_4$ reduces acid chlorides to yield aldehydes and then primary alcohols

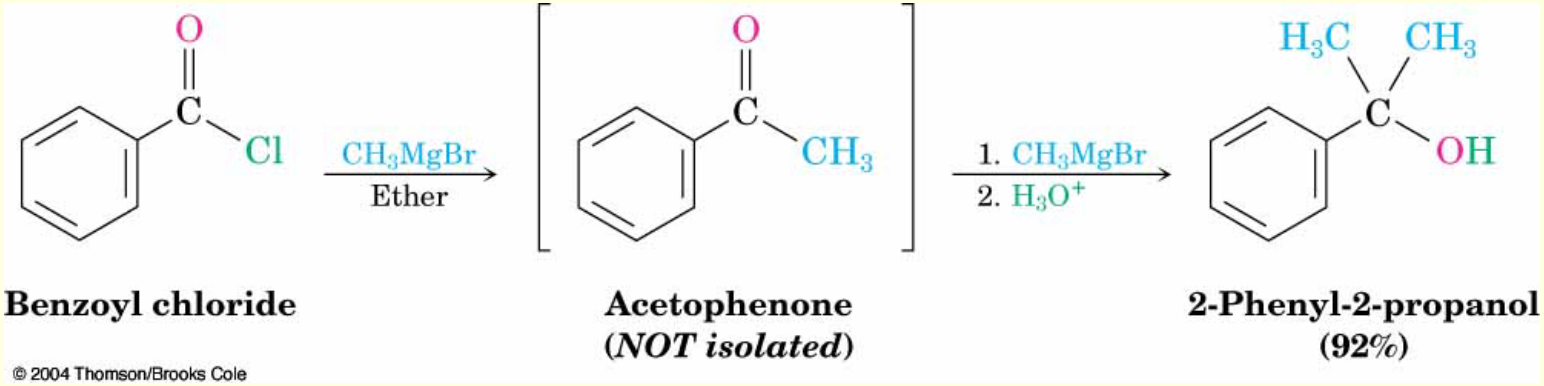




Reaction of Acid Chlorides with Organometallic Reagents

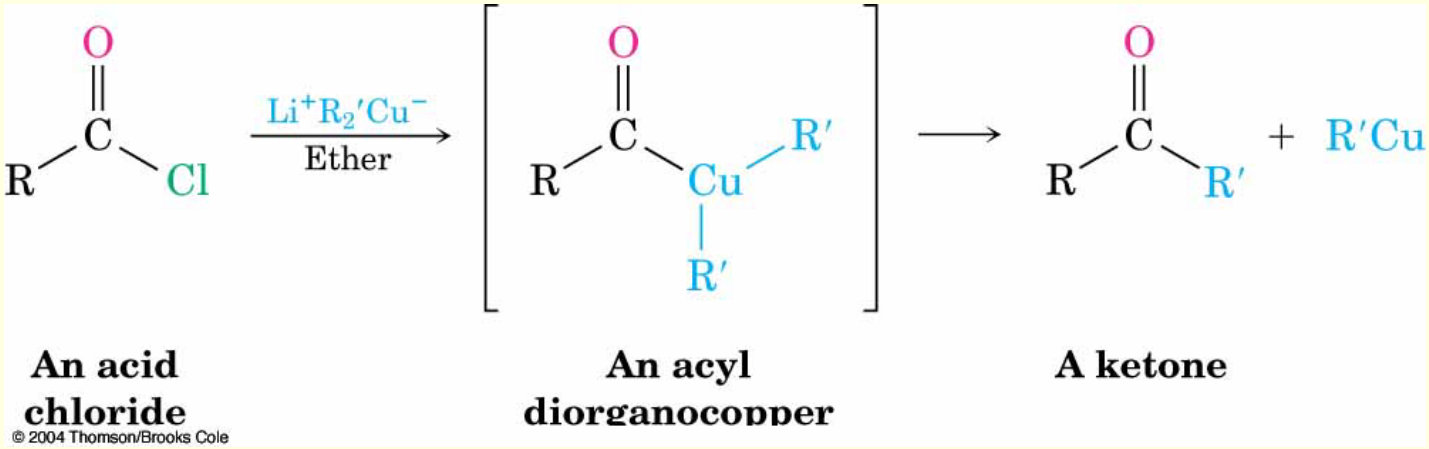
- Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same





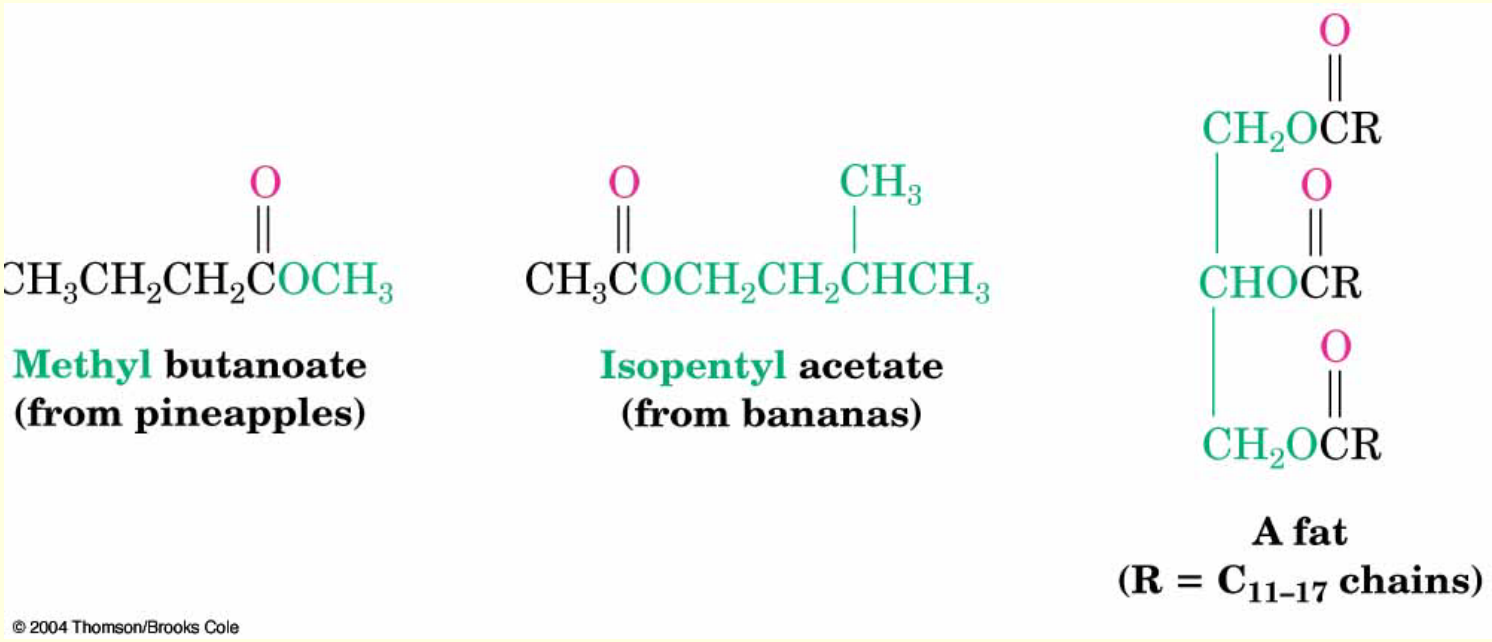
Formation of Ketones from Acid Chlorides

- Reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $Li^+ R_2Cu^-$
- Addition produces an acyl diorganocopper intermediate, followed by loss of R′Cu and formation of the ketone



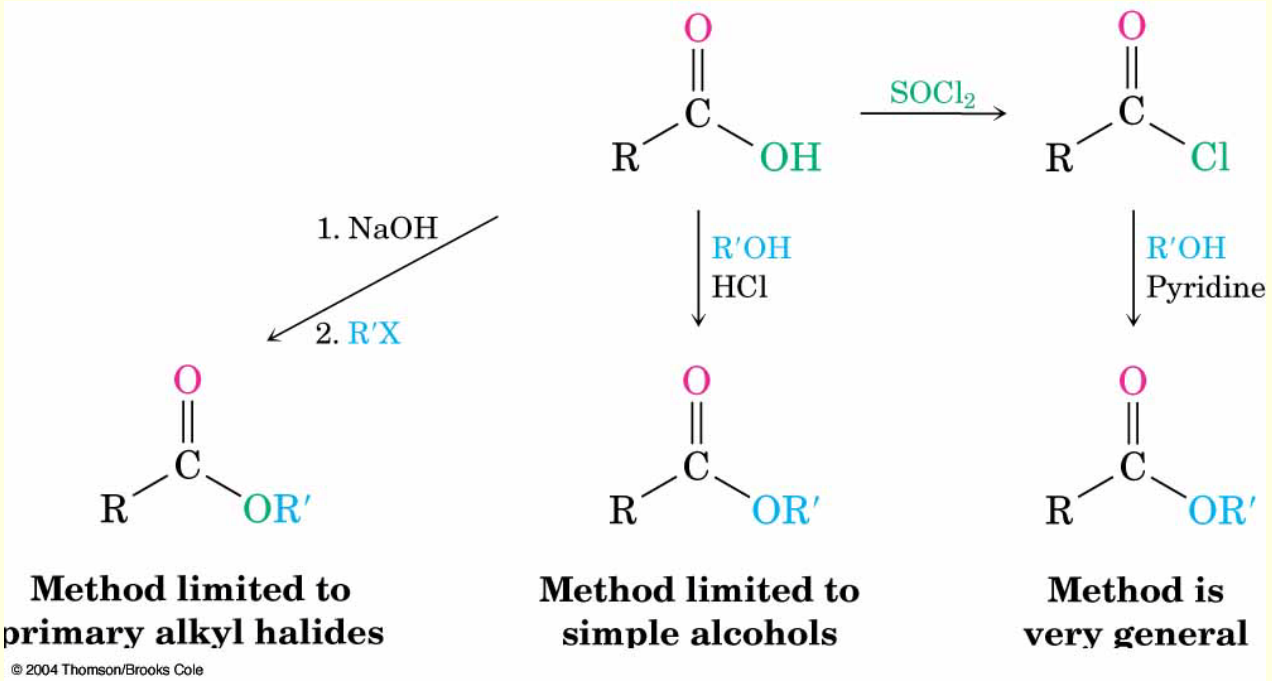
Chemistry of Esters

- Many esters are pleasant-smelling liquids: fragrant odors of fruits and flowers
- Also present in fats and vegetable oils



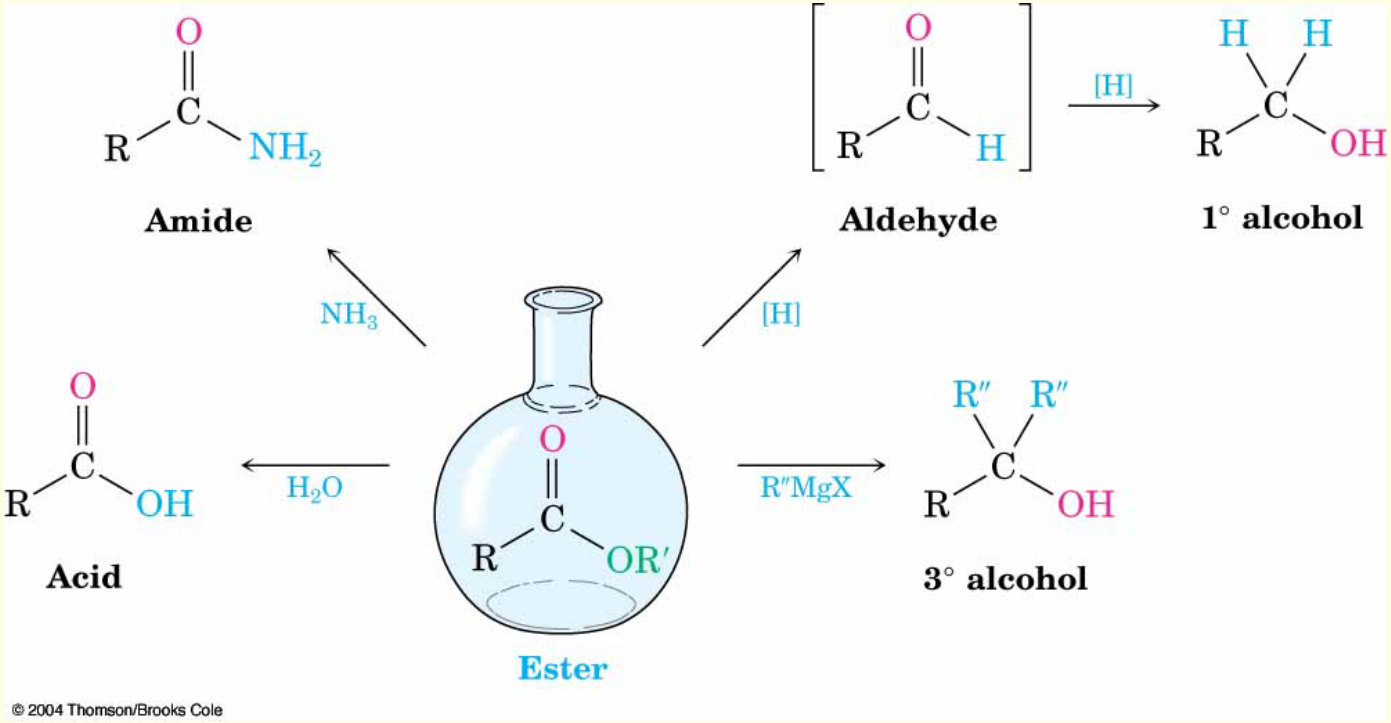
Preparation of Esters

- Esters are usually prepared from carboxylic acids



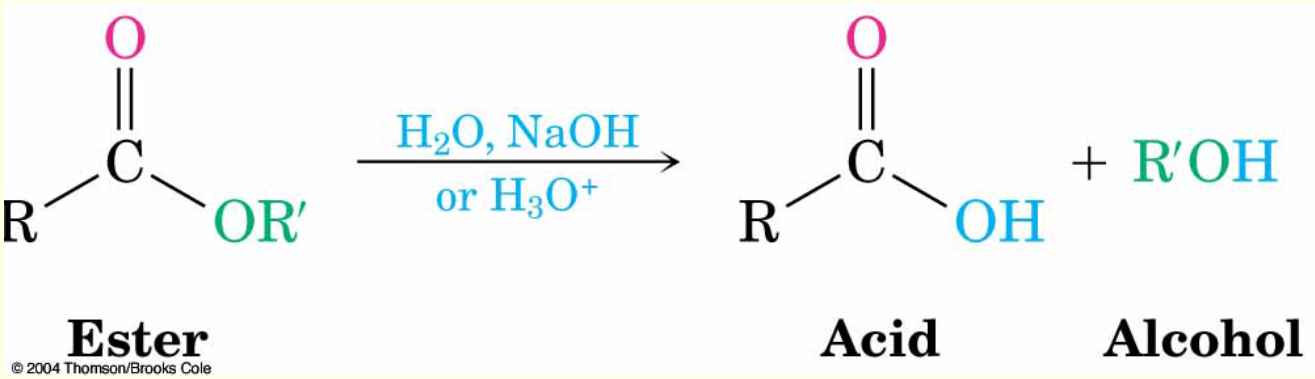
Reactions of Esters

- Less reactive toward nucleophiles than are acid chlorides or anhydrides
- Cyclic esters are called lactones and react similarly to acyclic esters



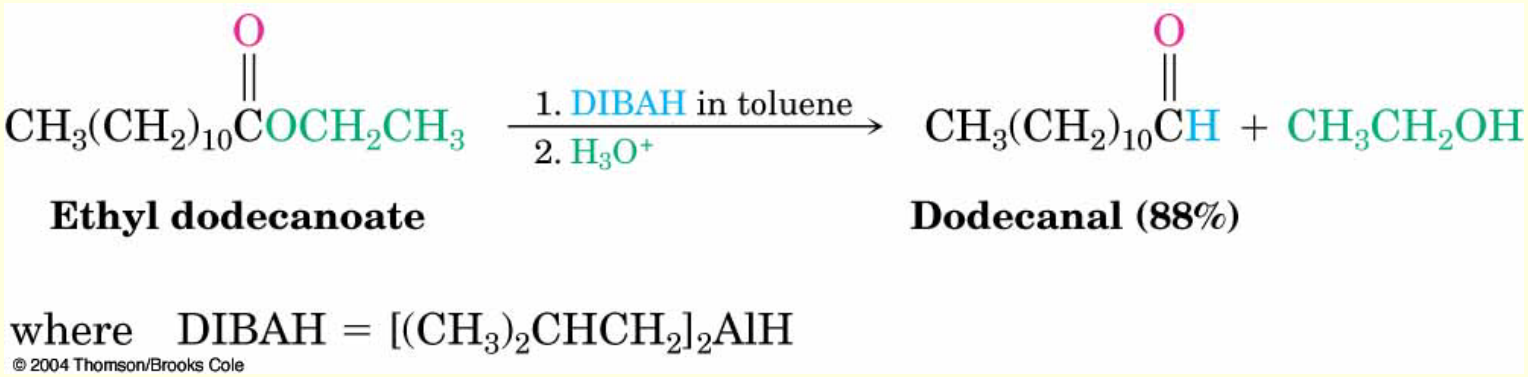
Hydrolysis: Conversion of Esters into Carboxylic Acids

- An ester is hydrolyzed by aqueous base or aqueous acid to yield a carboxylic acid plus an alcohol



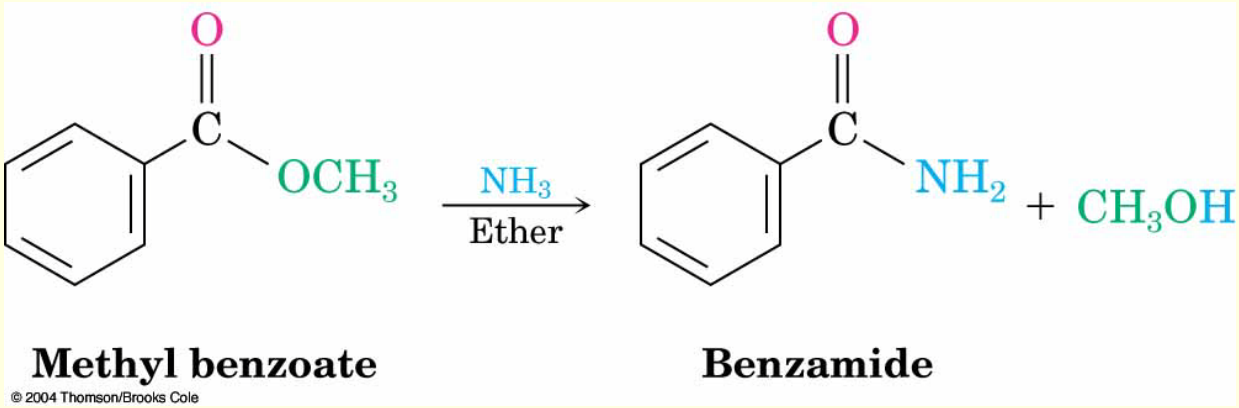
Acid Catalyzed Ester Hydrolysis

- The usual pathway is the reverse of the Fischer esterification



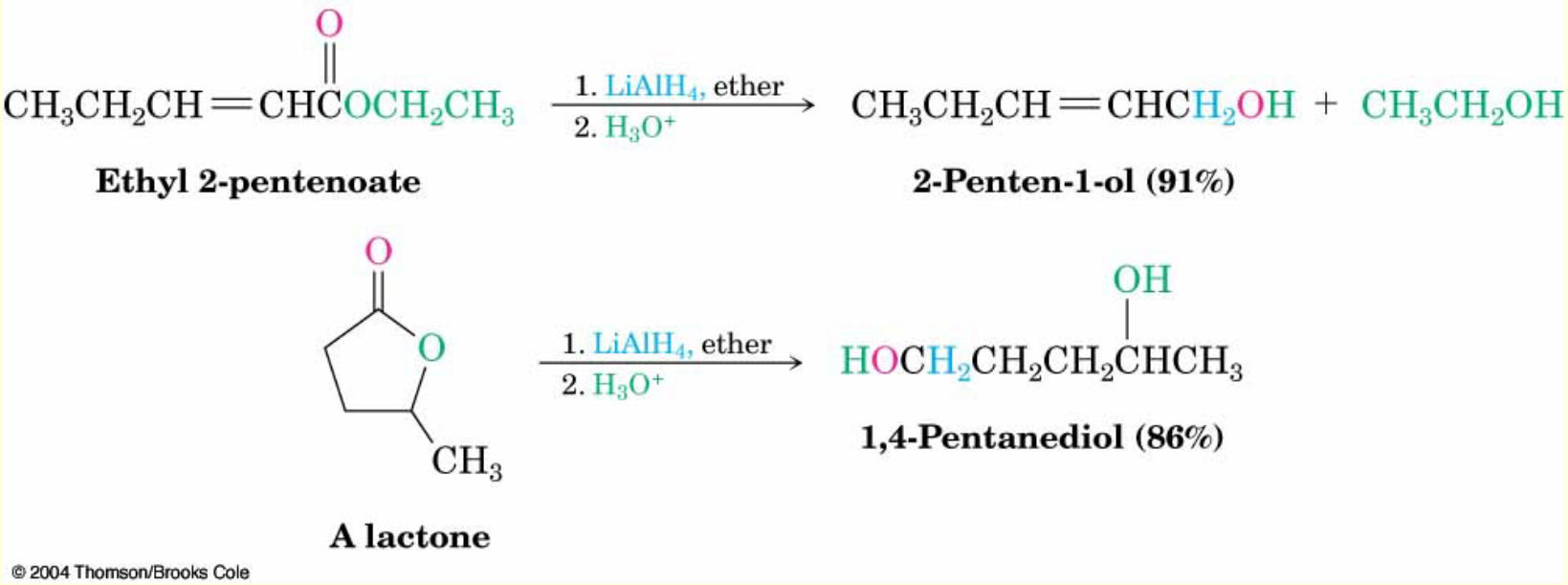
Aminolysis of Esters

- Ammonia reacts with esters to form amides



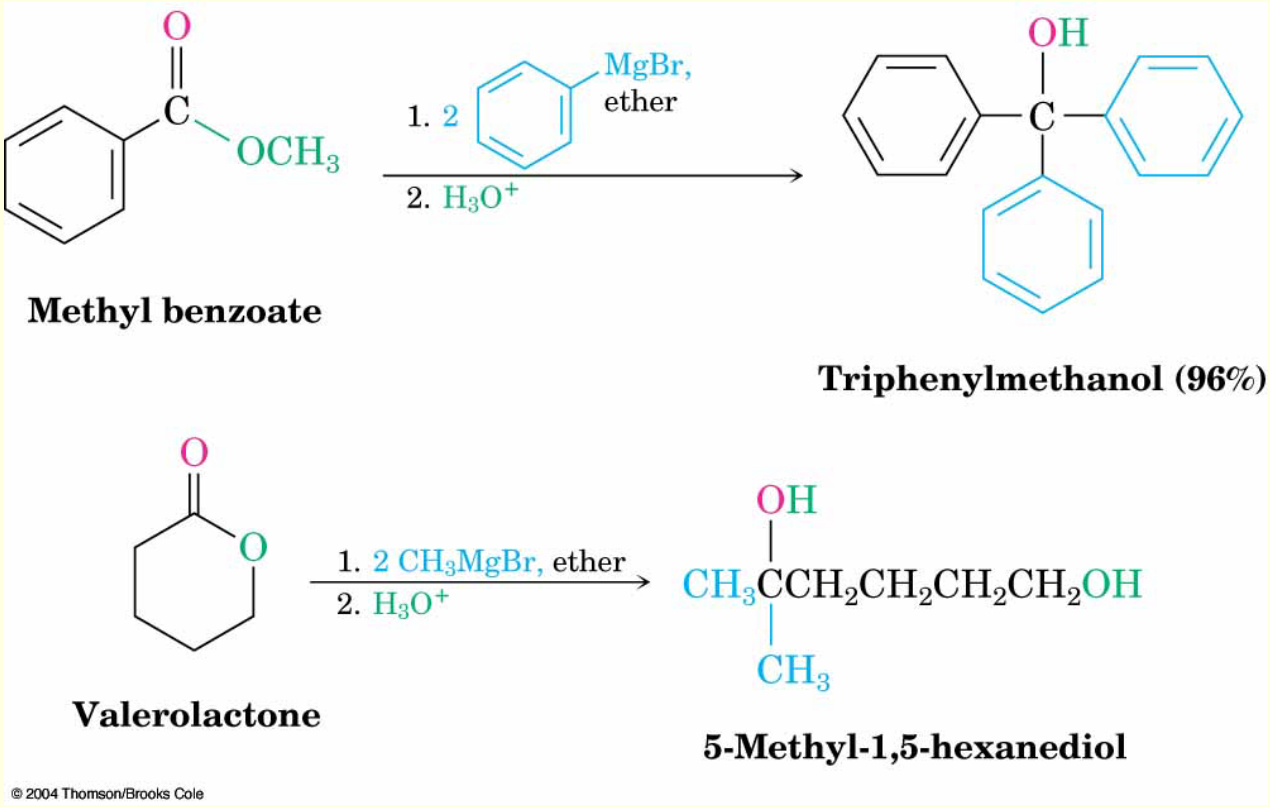
Reduction: Conversion of Esters into Alcohols

- Reaction with $LiAlH_4$ yields primary alcohols



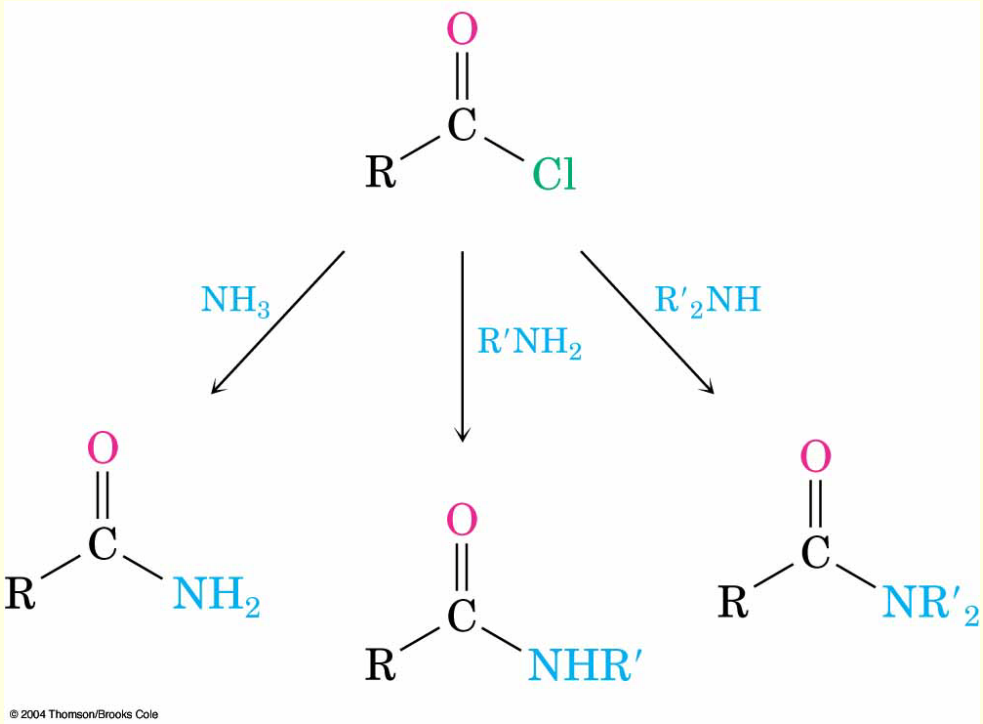
Reaction of Esters with Grignard Reagents

- React with 2 equivalents of a Grignard reagent to yield a tertiary alcohol



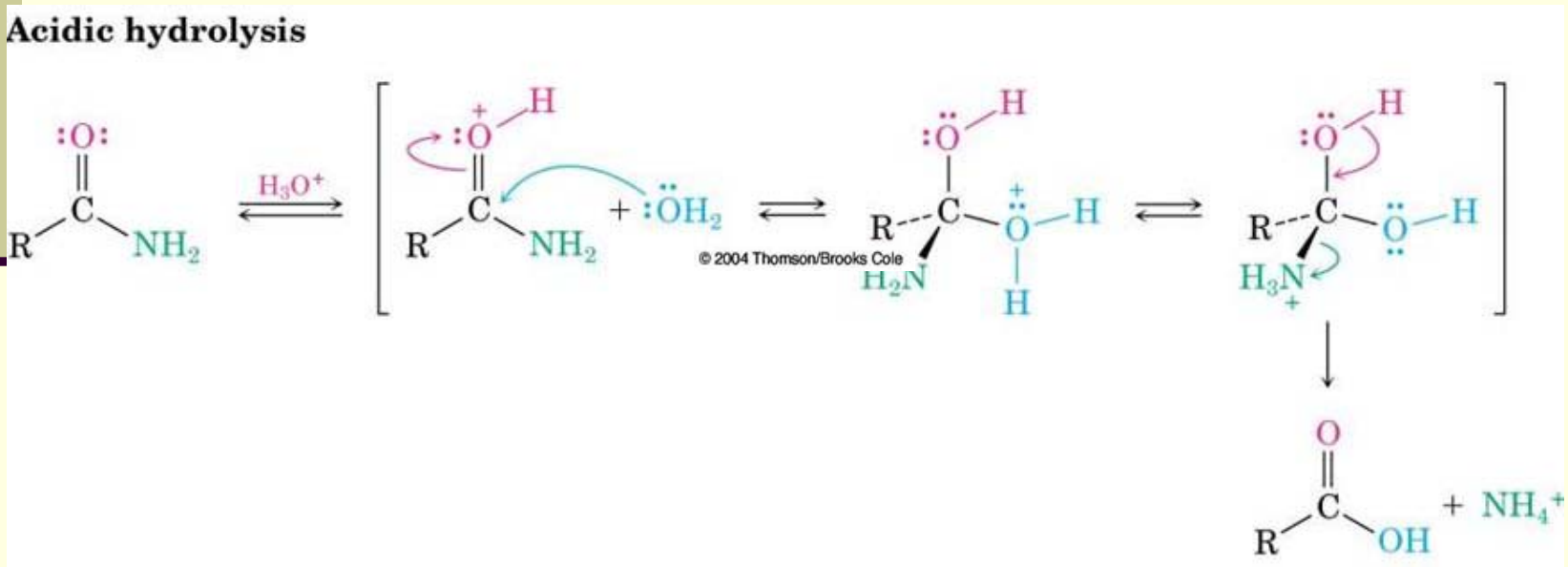
Chemistry of Amides

- Prepared by reaction of an acid chloride with ammonia, monosubstituted amines, or disubstituted amines



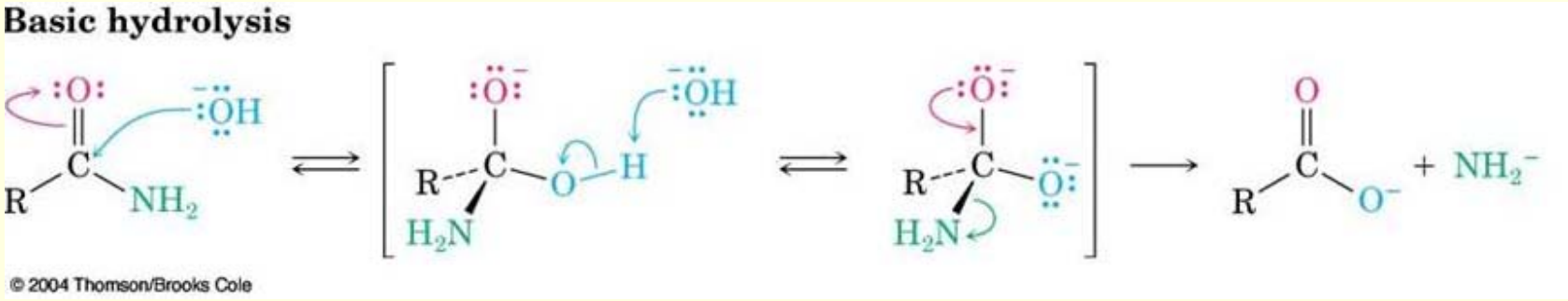
Reactions of Amides

- Heating in either aqueous acid or aqueous base produces a carboxylic acid and amine
- Acidic hydrolysis by nucleophilic addition of water to the protonated amide, followed by loss of ammonia



Basic Hydrolysis of Amides

- Addition of hydroxide and loss of amide ion



Reduction: Conversion of Amides into Amines

- Reduced by $LiAlH_4$ to an amine rather than an alcohol
- Converts C=O $\rightarrow$ CH_2