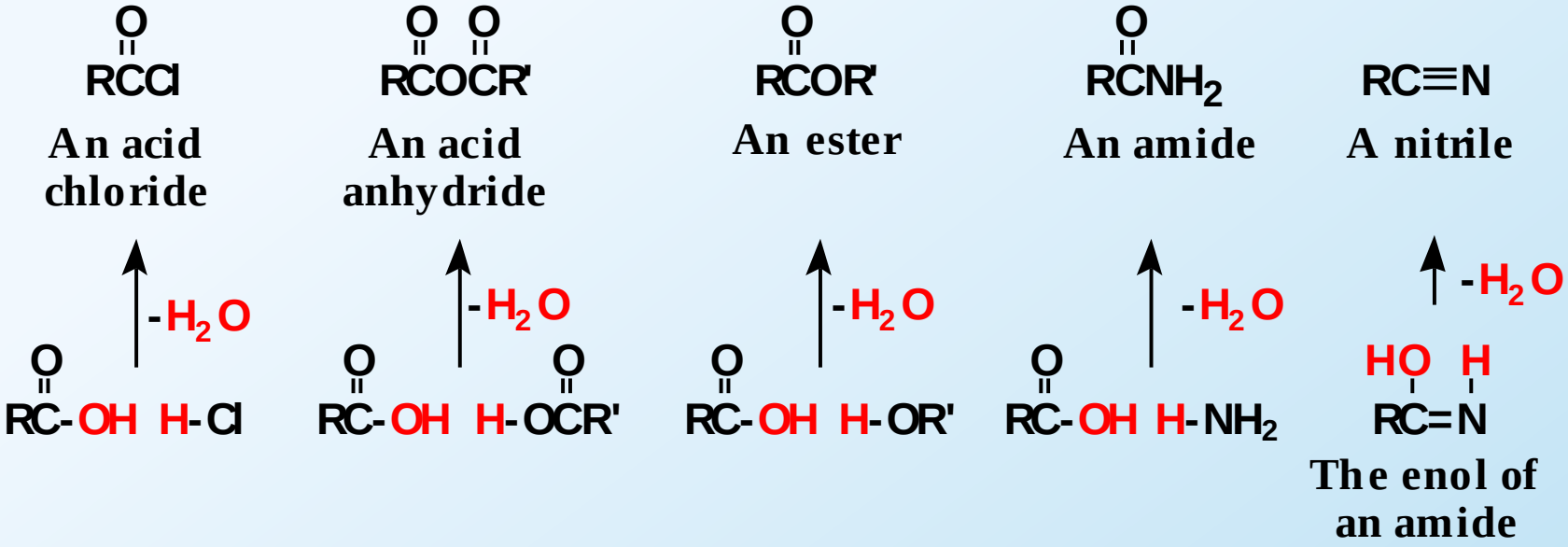
Carboxylic Acid Derivatives Synthesis and Reactions

Dr. Sapna Gupta

Reactivity of the Derivatives

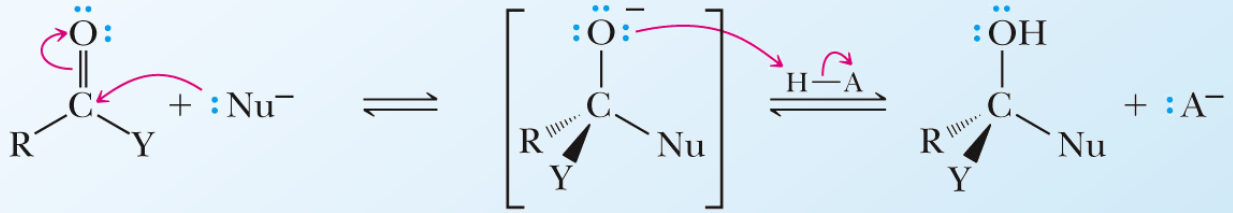
Here are all derivatives and their relationship to carboxylic acid.



Reactivity of the Derivatives

- Two kinds of reactions occur in acids:
  - **Nucleophilic addition**

Nucleophilic acyl addition (basic conditions):



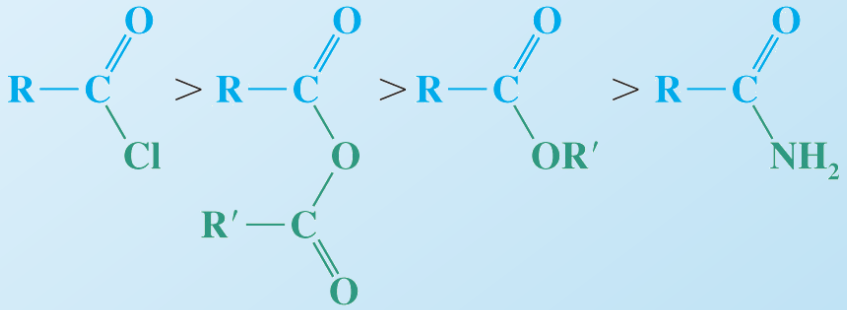
A carboxylic acid derivative

Tetrahedral carbonyl addition intermediate

Addition product

  - **Nucleophilic substitution**

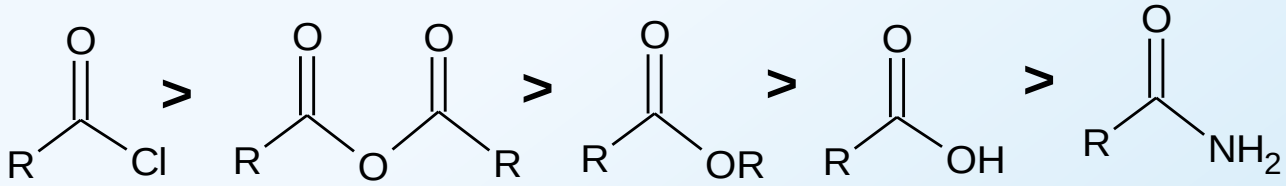
In leaving group ability:



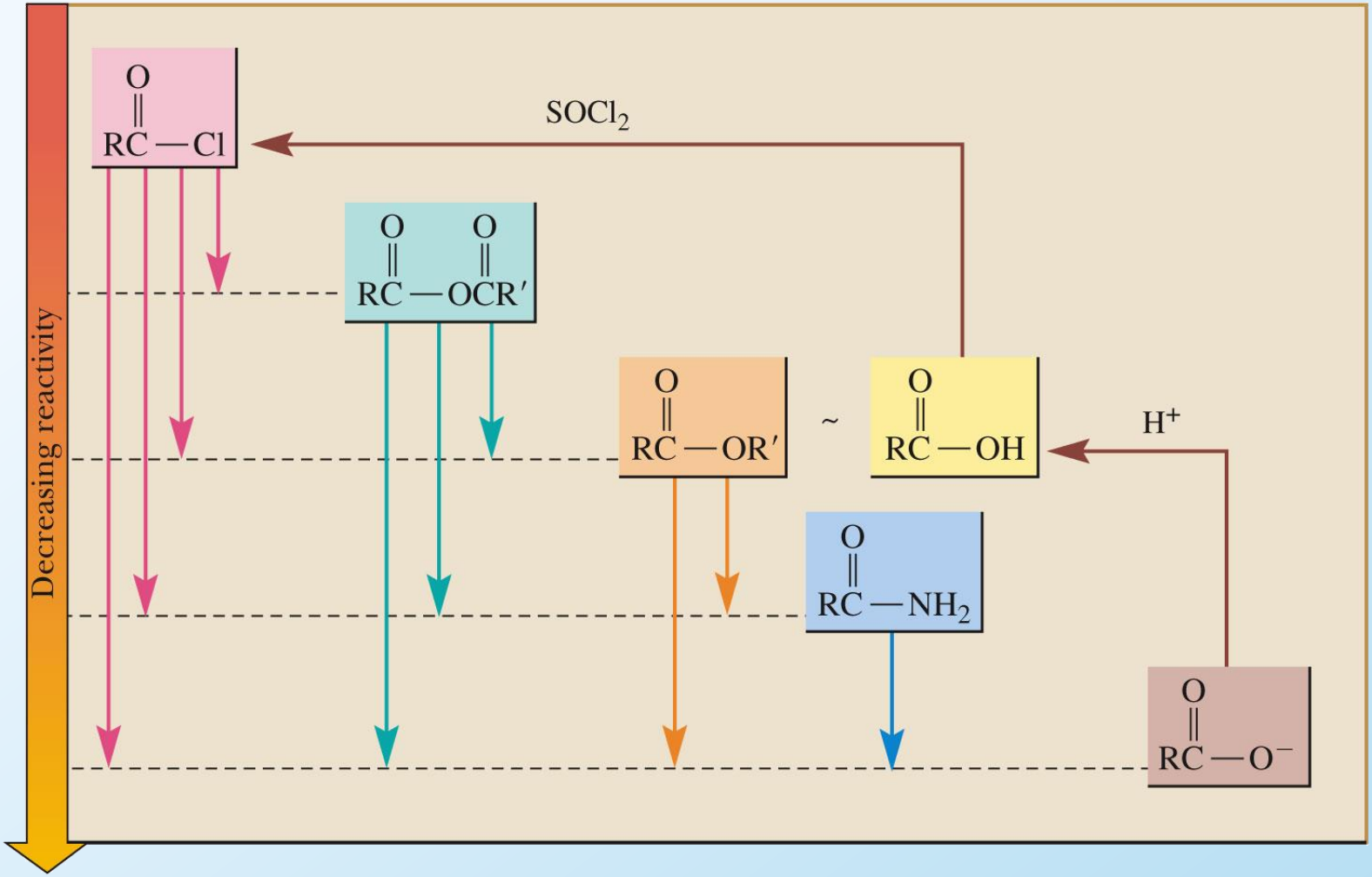
Acyl chloride **Acid anhydride** **Ester** **Amide**

Interconversions of Acid Derivatives

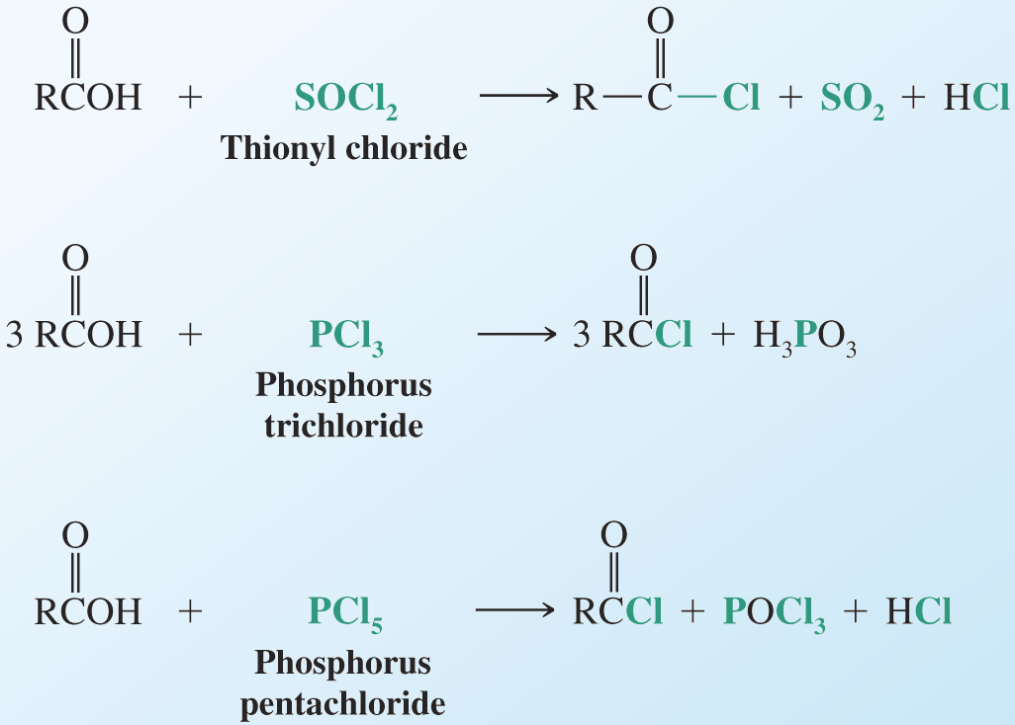
Most reactive



Least reactive

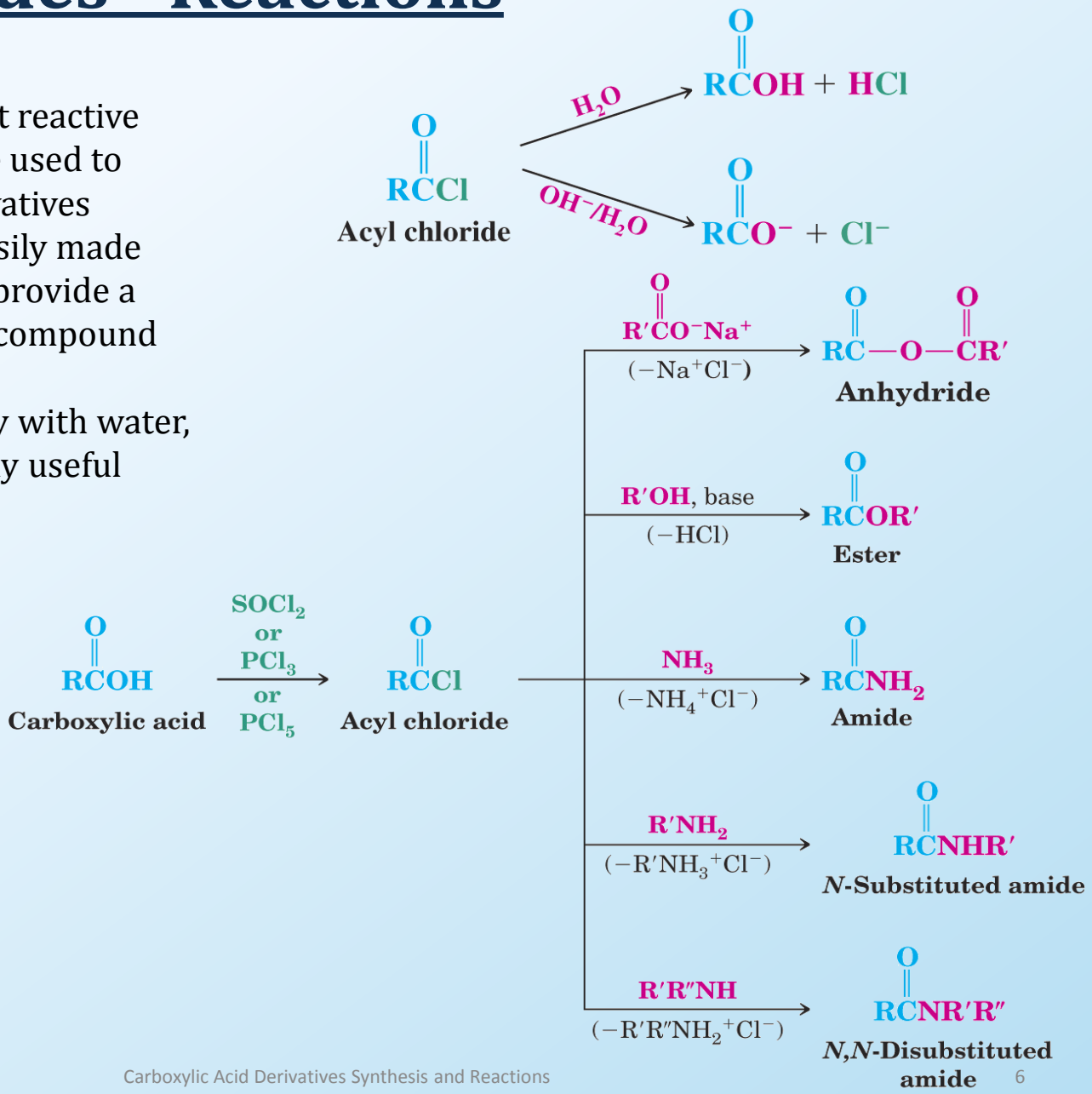


Acyl Chlorides- Synthesis



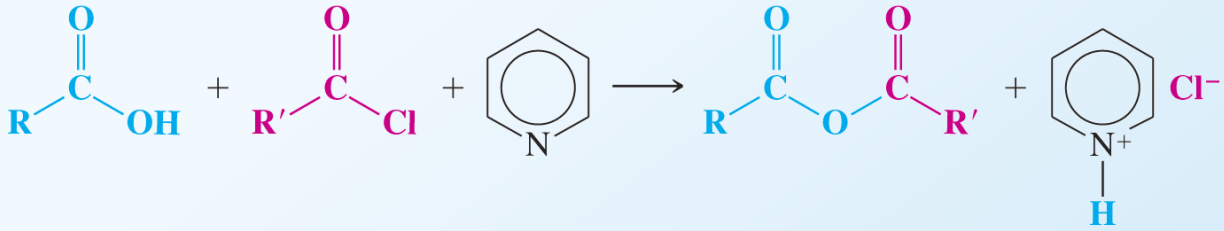
Acyl Chlorides - Reactions

- Acyl chlorides are the most reactive acyl compounds and can be used to make any of the other derivatives
- Since acyl chlorides are easily made from carboxylic acids they provide a way to synthesize any acyl compound from a carboxylic acid
- Acyl chlorides react readily with water, but this is not a synthetically useful reaction

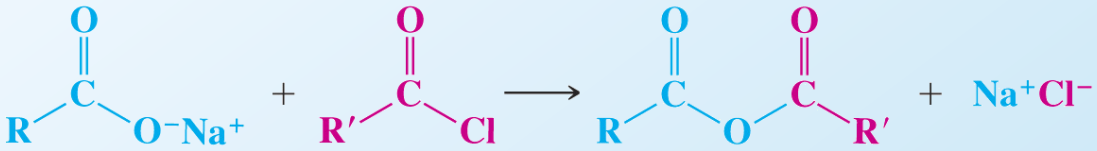


Anhydrides - Synthesis

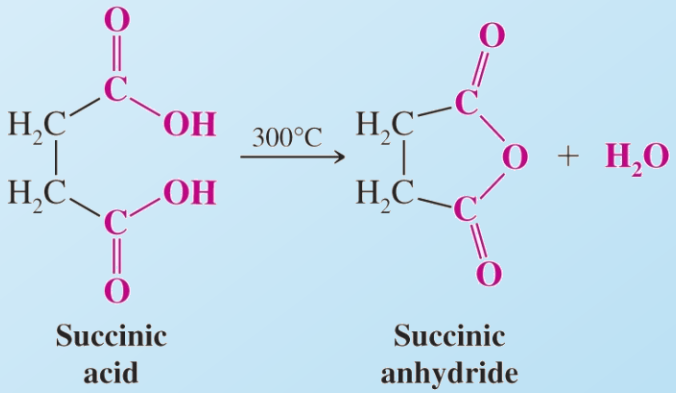
1) **Acid chlorides** + **carboxylic acids** to form mixed or symmetrical anhydrides. It is necessary to use a base such as pyridine



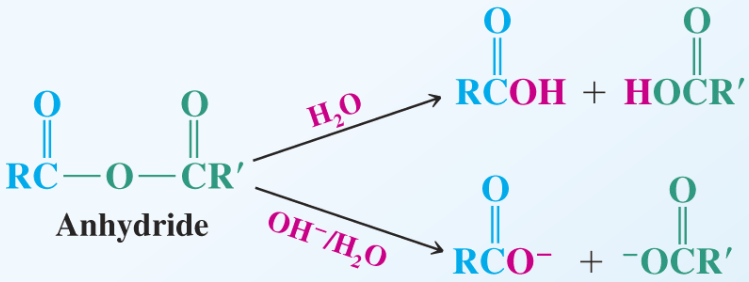
2) **Sodium carboxylates + acid chlorides** to form anhydrides.

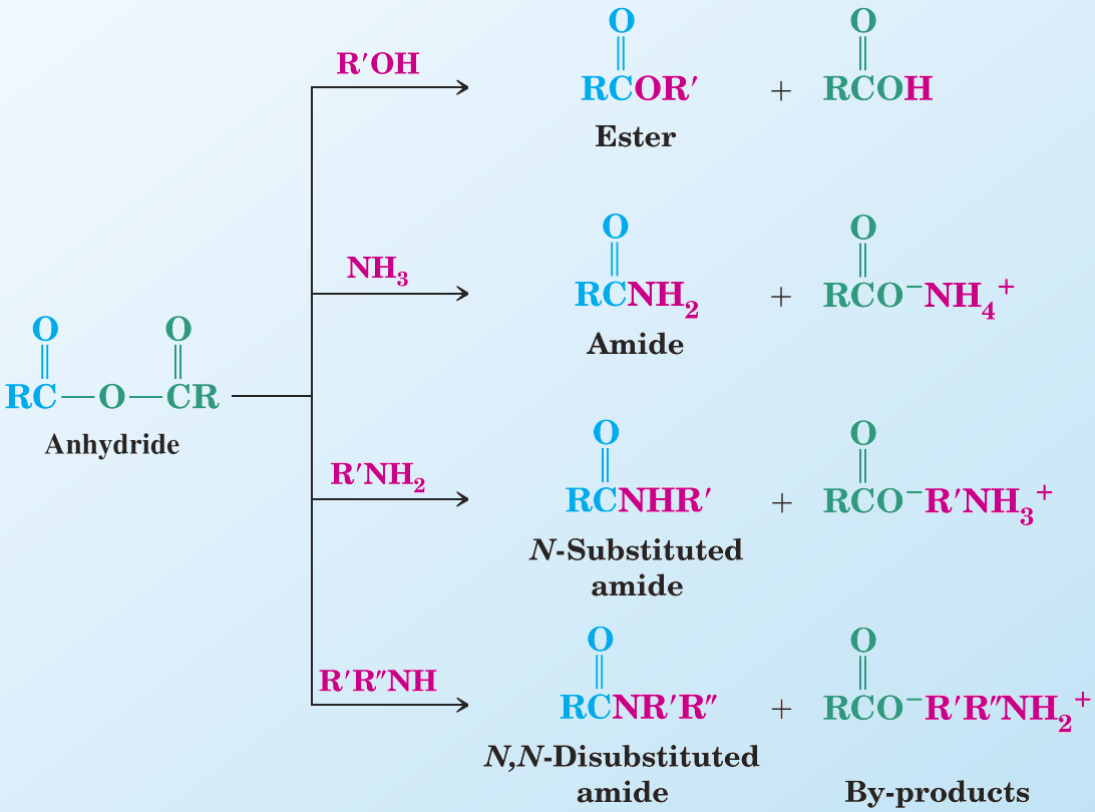


3) **Cyclic anhydrides** with 5- and 6-membered rings can be synthesized by heating the appropriate diacid



Anhydrides - Reactions

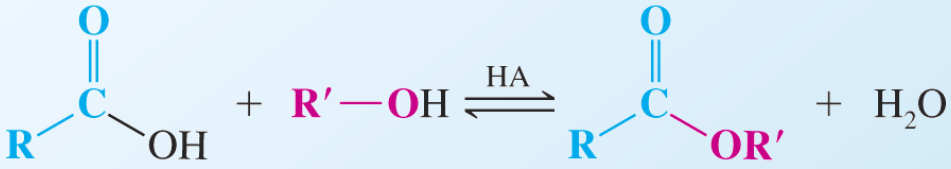


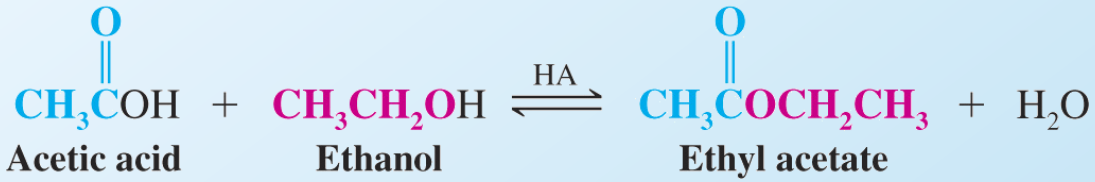


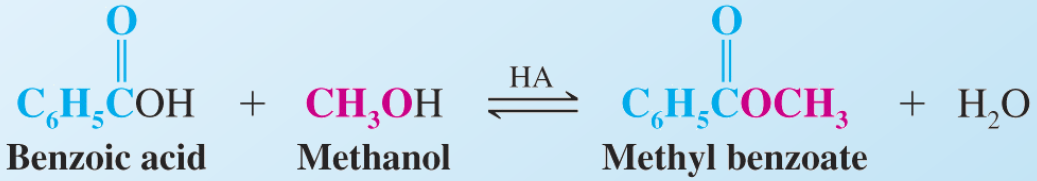
Esters - Synthesis

- Acid catalyzed reaction of alcohols and carboxylic acids to form esters is called Fischer esterification
- Fischer esterification is an equilibrium process
- Ester formation is favored by use of a large excess of either the alcohol or carboxylic acid and by removal of water.

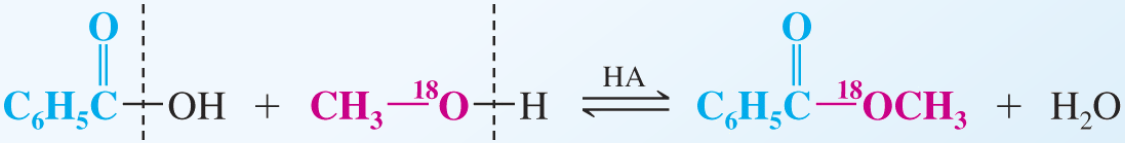
From Acids

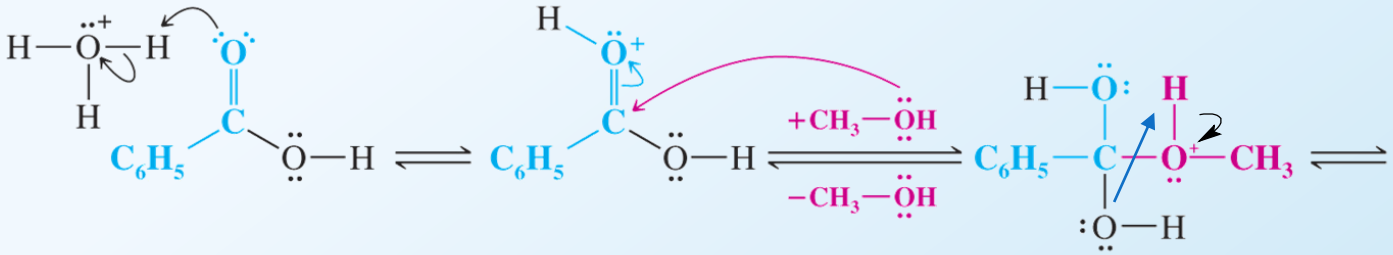






Mechanism of Esterification

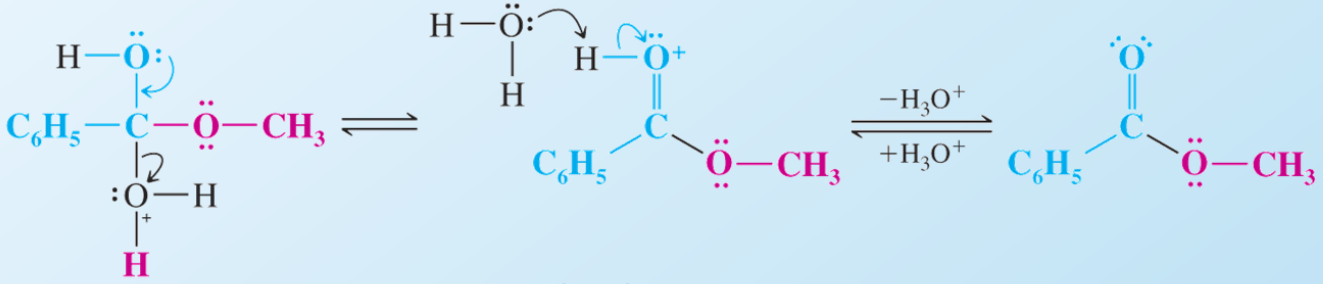




The carboxylic acid accepts a proton from the strong acid catalyst.

The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.

A proton is lost at one oxygen atom and gained at another.

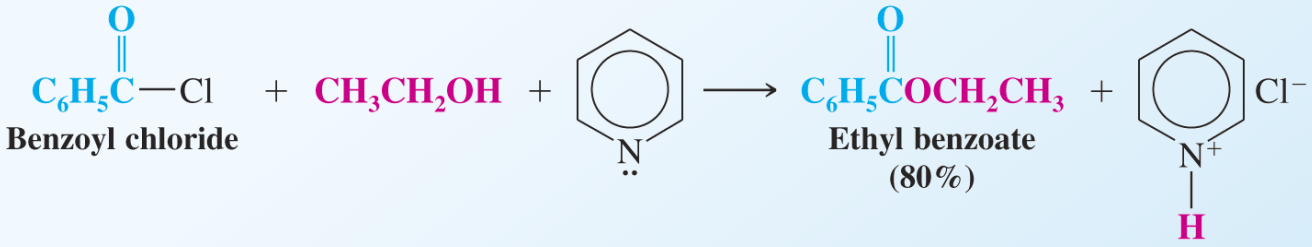


Loss of a molecule of water gives a protonated ester.

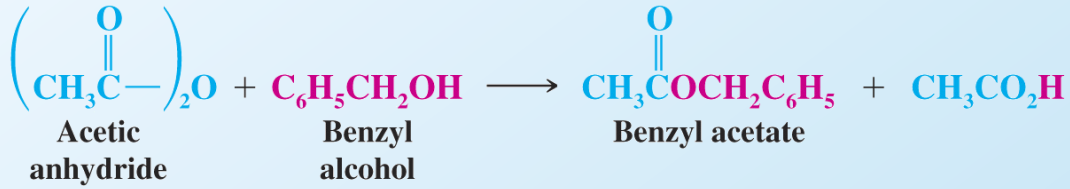
Transfer of a proton to a base leads to the ester.

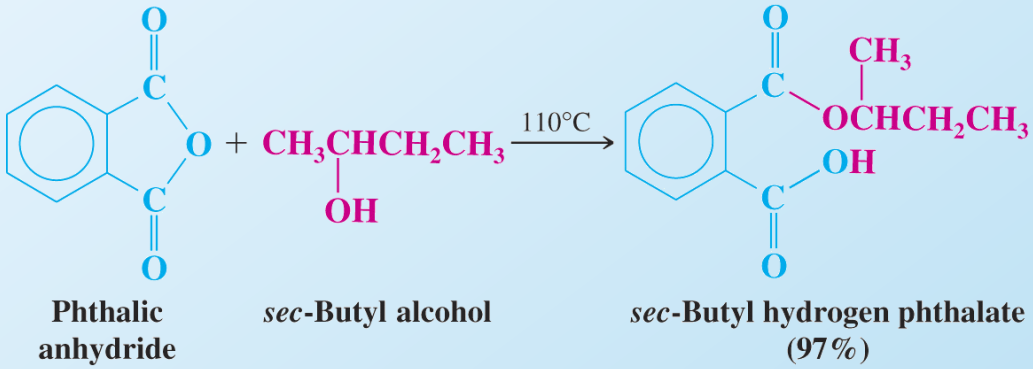
Esters - Synthesis

From Acyl Chlorides



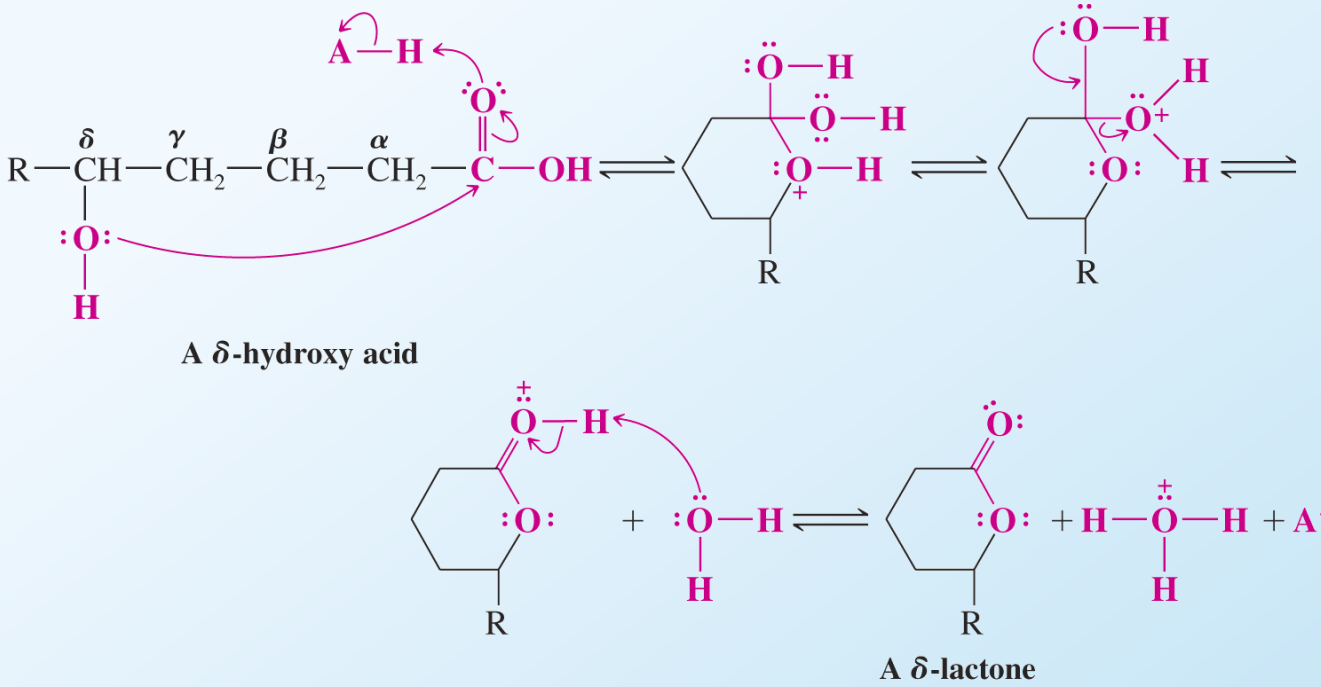
From Acid Anhydrides



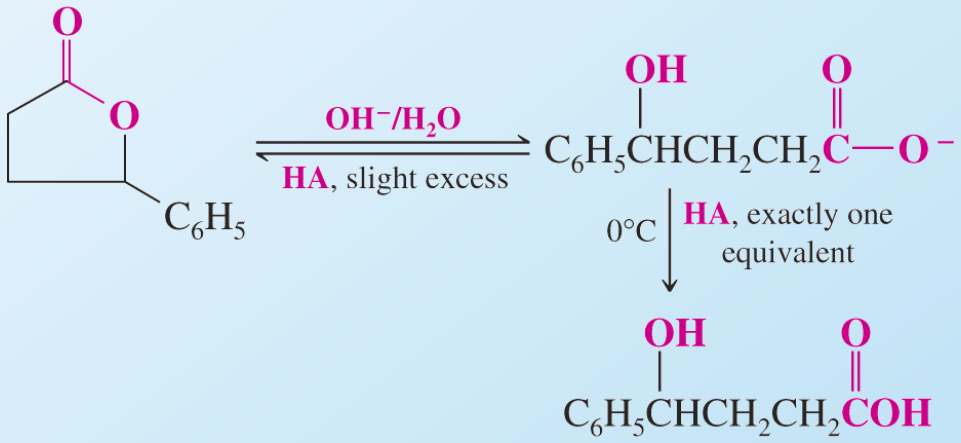


Lactones

Synthesis

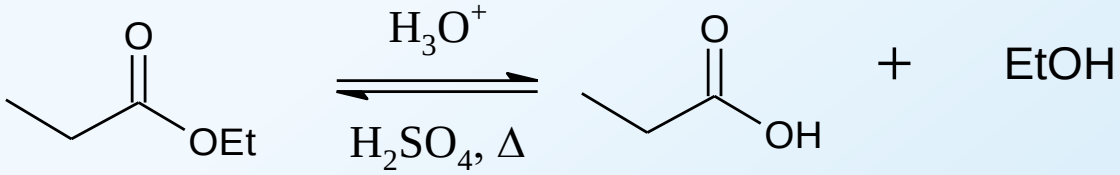


Hydrolysis



Esters - Reactions

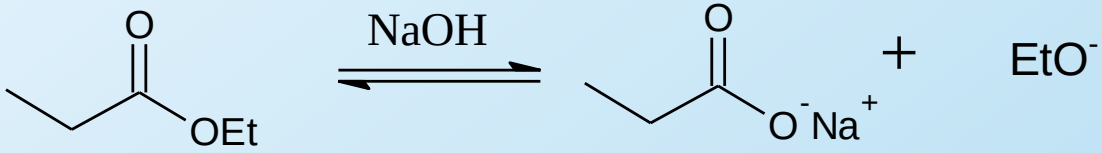
Hydrolysis: Acids can be acid hydrolyzed to give acid and alcohol.



Transesterifcation: One ester can be converted to another in presence of an alcohol and a catalyst.

Write the mechanism on your own! (start with protonating the carbonyl of the ester; the OCH_3 will be the leaving group.)

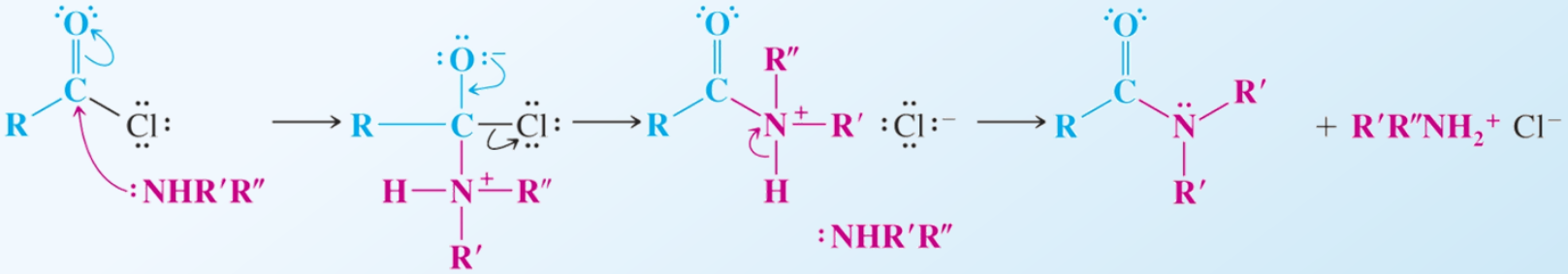
Saponification: Treatment of ester with strong base. Used mostly to prepare soaps.



Amides - Synthesis

(*Note: do mechanism for lactams on your own*)

From Acyl Chlorides



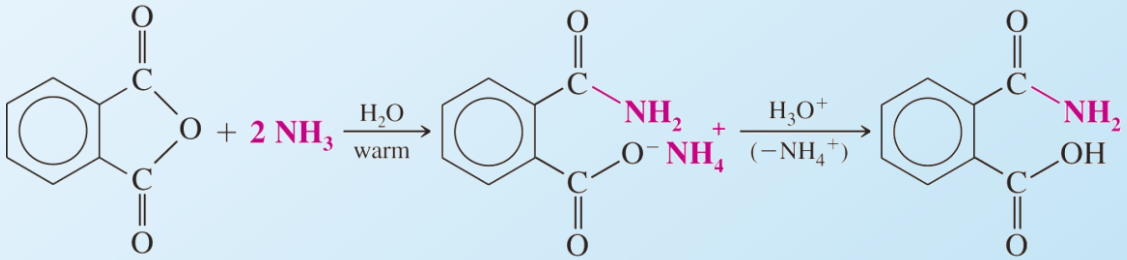
Reactant

Ammonia; R′, R″ = H
1° Amine; R′ = H, R″ = alkyl, aryl
2° Amine; R′, R″ = alkyl, aryl

Product

Unsubstituted amide; R′, R″ = H
N-Substituted amide; R′ = H, R″ = alkyl, aryl
N,*N*-Disubstituted amide; R′,R″ = alkyl, aryl

From Anhydrides



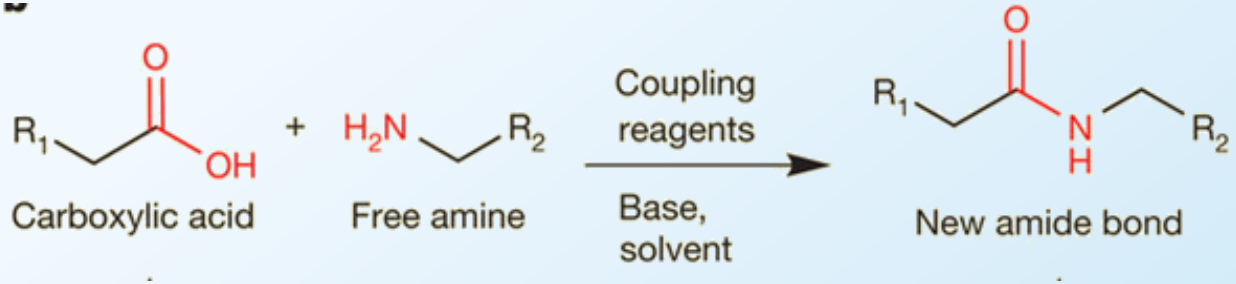
Phthalic anhydride

Ammonium phthalamate (94%)

Phthalamic acid (81%)

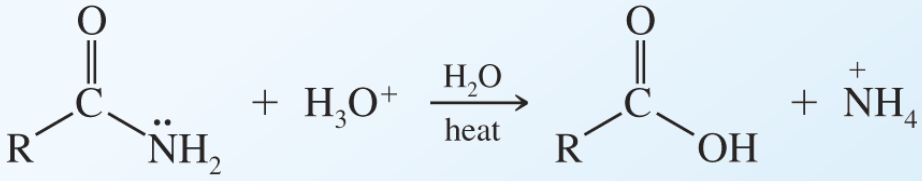
Amides - Synthesis

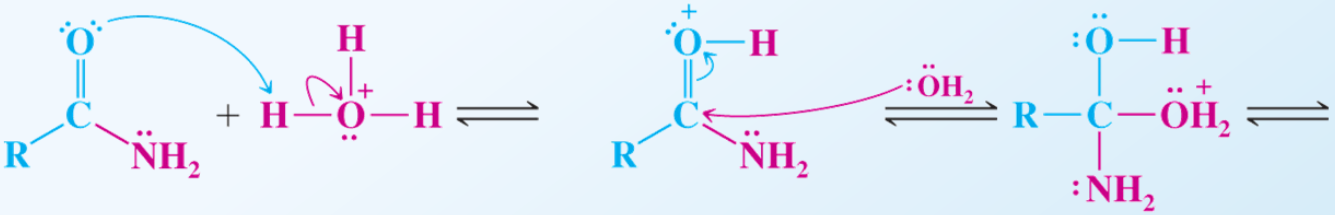
From Carboxylic Acid



Amides - Reactions

Hydrolysis

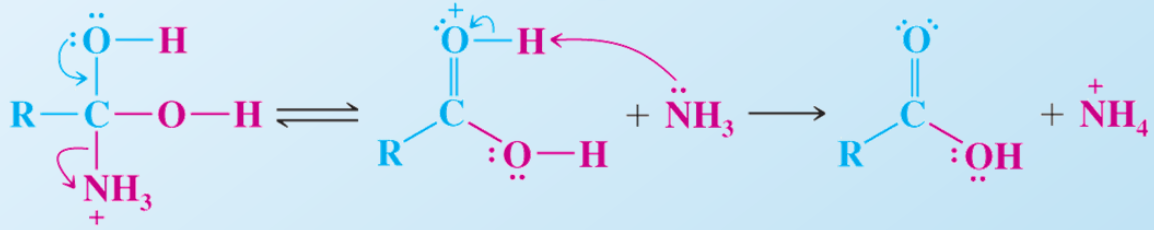




The amide carbonyl accepts a proton from the aqueous acid.

A water molecule attacks the protonated carbonyl to give a tetrahedral intermediate.

A proton is lost at one oxygen and gained at the nitrogen.

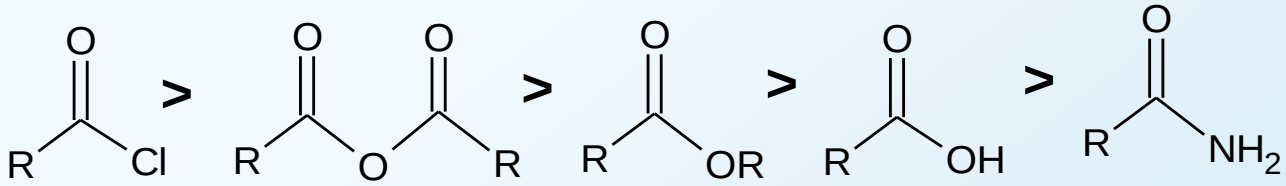


Loss of a molecule of ammonia gives a protonated carboxylic acid.

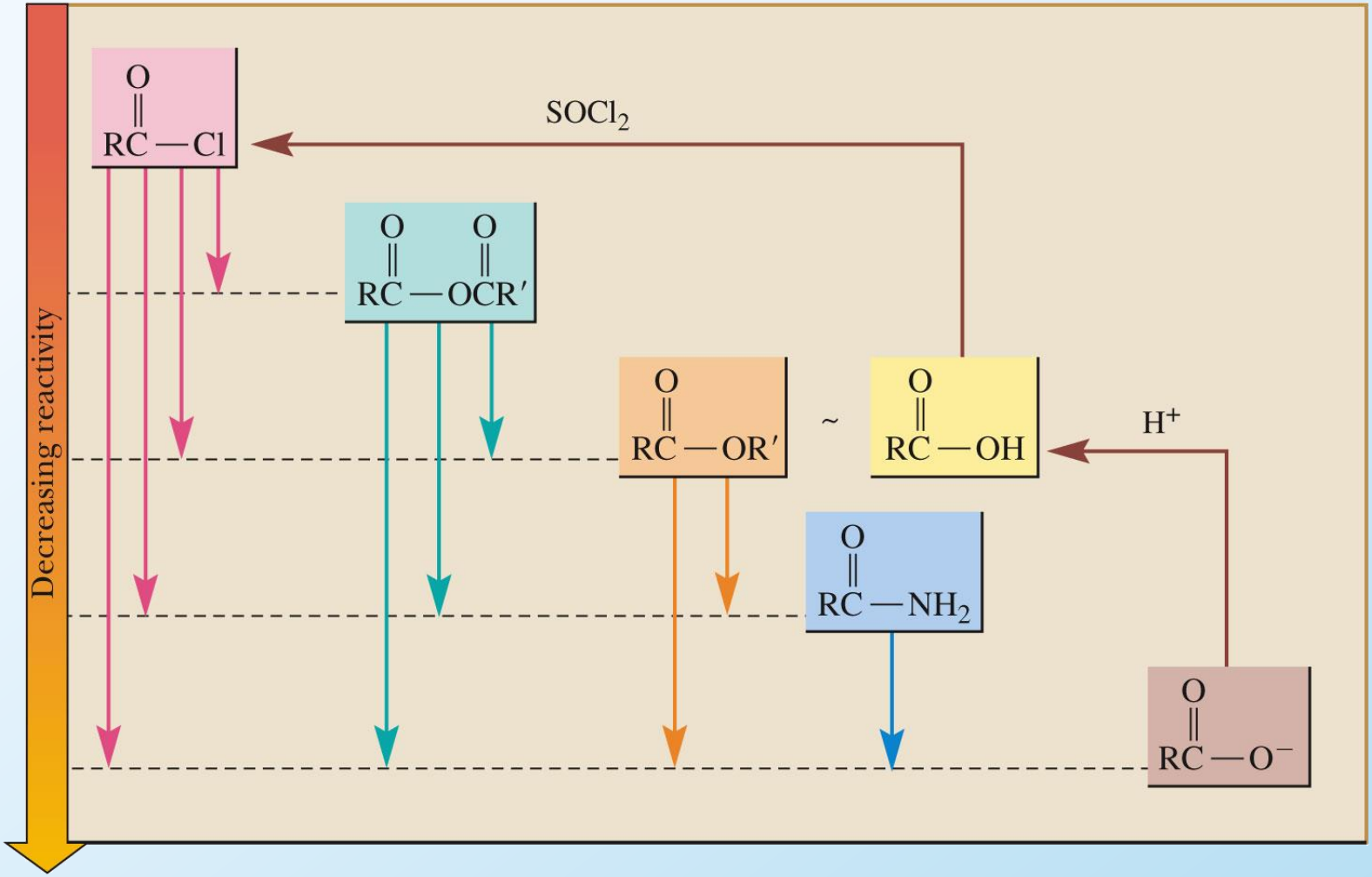
Transfer of a proton to ammonia leads to the carboxylic acid and an ammonium ion.

Interconversions of Acid Derivatives

Most reactive

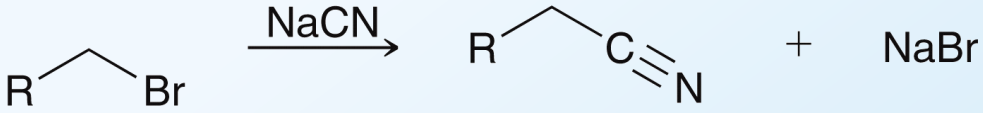


Least reactive

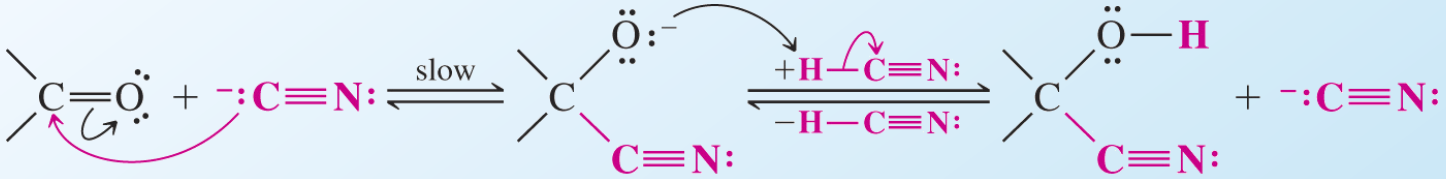


Nitriles - Synthesis

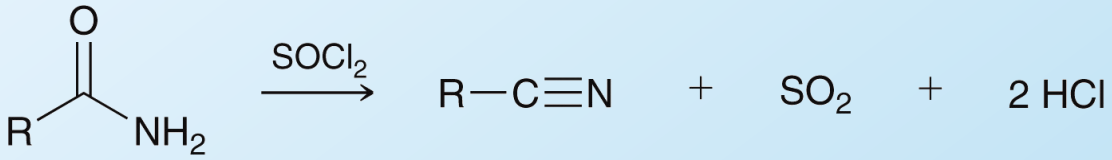
- **From Alkyl Halides** (SN2 reaction)



- **From Aldehydes and Ketones**

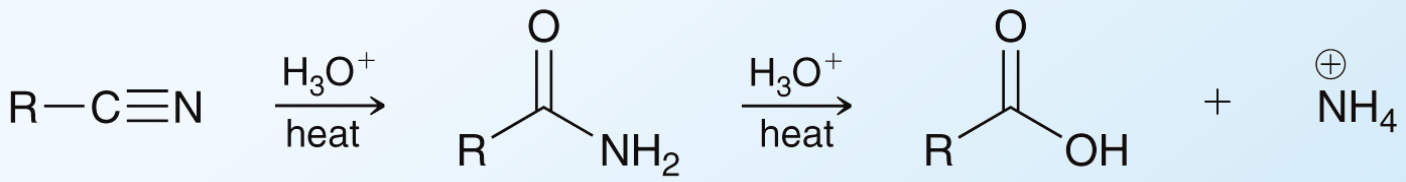


- **From dehydration of amides**



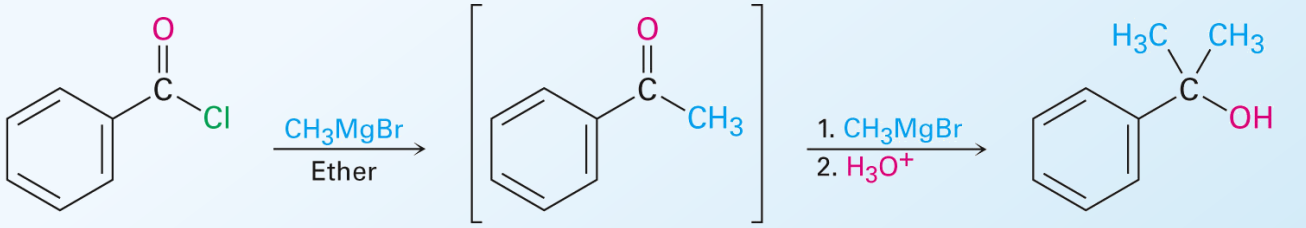
Reactions - Nitriles (as Acid Derivative)

- **Hydrolysis** gives carboxylic acid



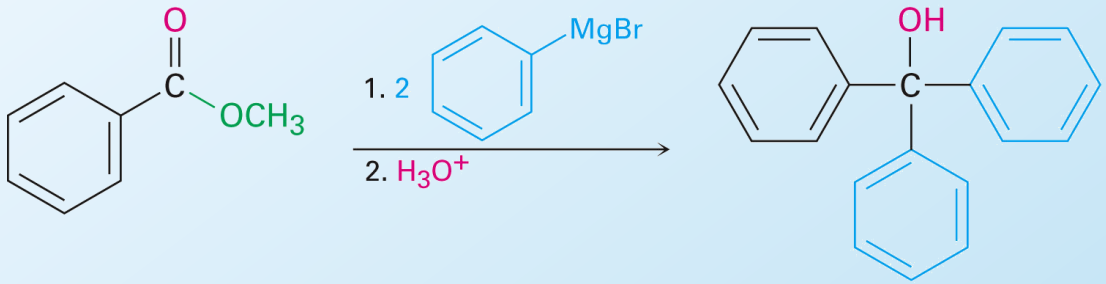
Other Reactions of Carboxylic Acid Derivatives – With Grignard Reagent

- **With acyl chlorides** – gives tertiary alcohols



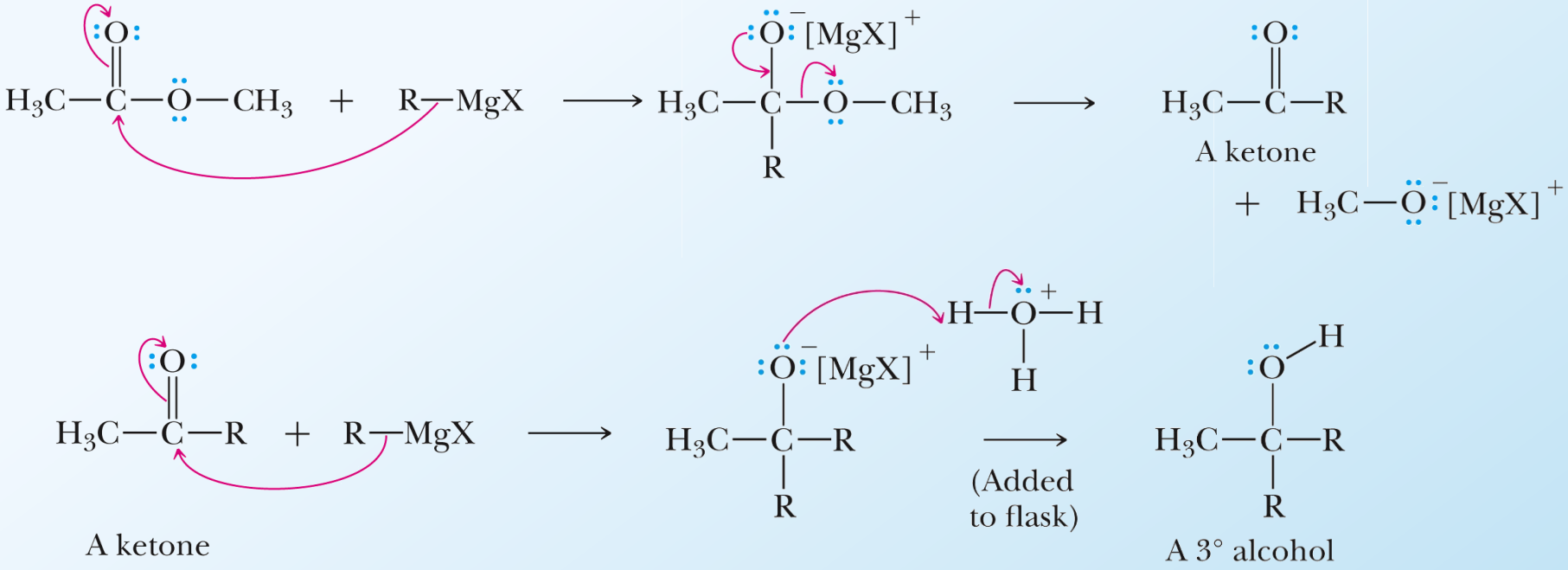
Benzoyl chloride | **Acetophenone** ***(Not isolated)*** | **2-Phenyl-2-propanol (92%)**

- **With esters** – gives tertiary alcohols (*write mechanism*)



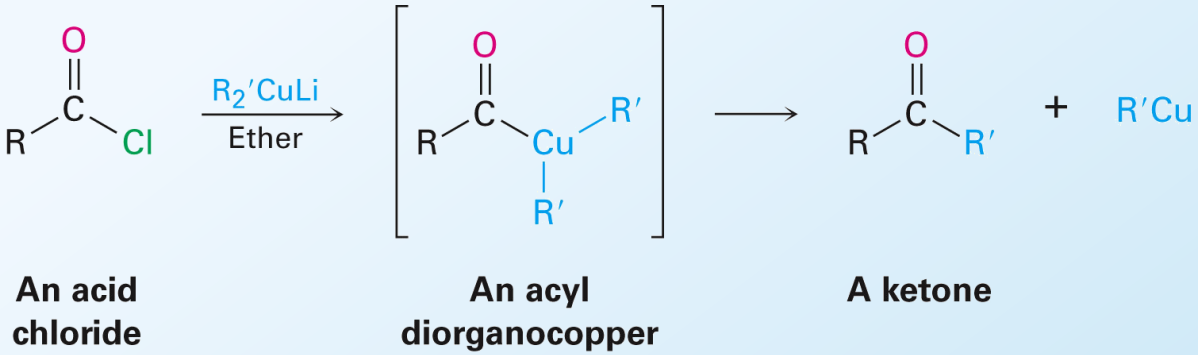
Methyl benzoate | **Triphenylmethanol (96%)**

Other Reactions of Carboxylic Acid Derivatives – With Grignard Reaction (Ester – Mechanism)



Other Reactions of Carboxylic Acid Derivatives – with Copper Reagents

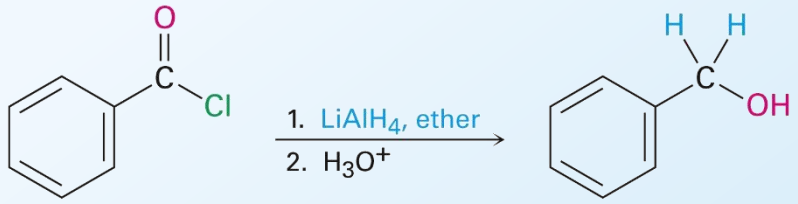
- **Acyl chlorides** – give ketones



Other Reactions of Carboxylic Acid Derivatives - Reduction

Of Acyl chlorides

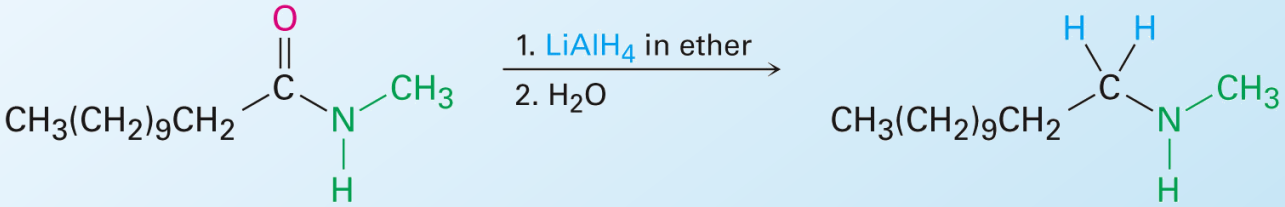
Give 1° alcohols



Benzoyl chloride **Benzyl alcohol (96%)**

Of Amides

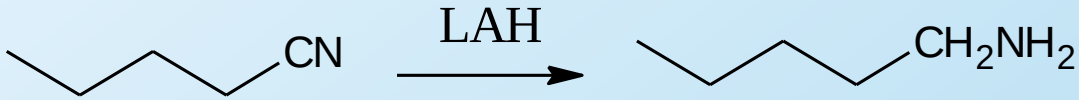
Give amines



***N*-Methyldodecanamide** **Dodecylmethylamine (95%)**

Of Nitriles

Give amines

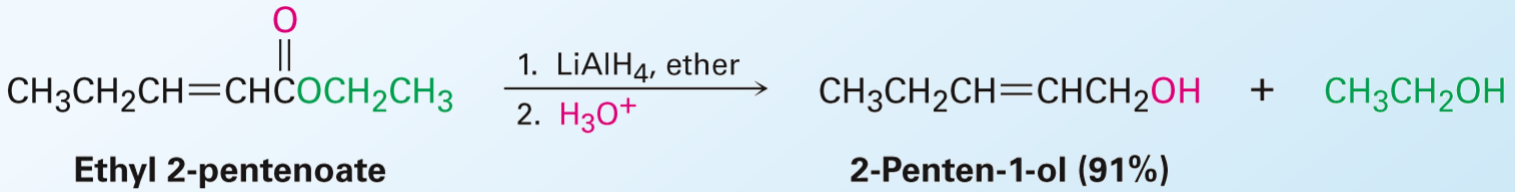


Other Reactions of Carboxylic Acid Derivatives - Reduction

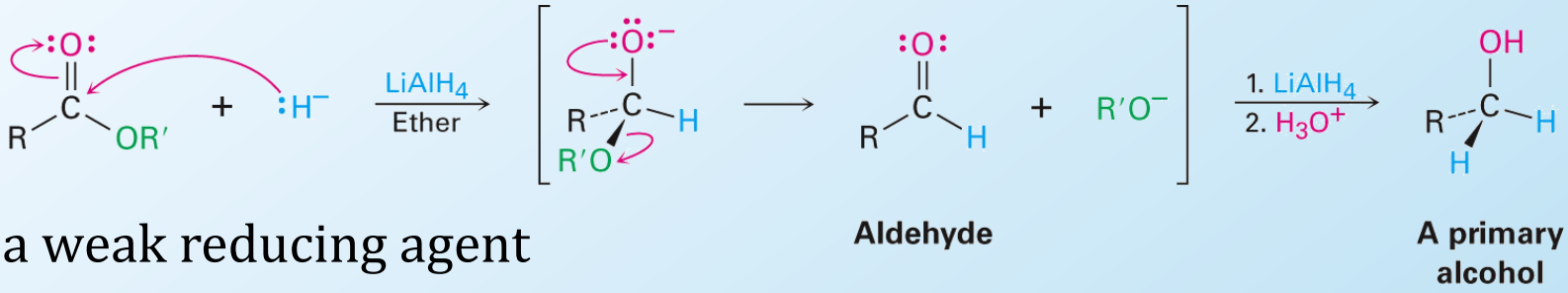
Of Esters

With strong reducing agent

Give 1° alcohols

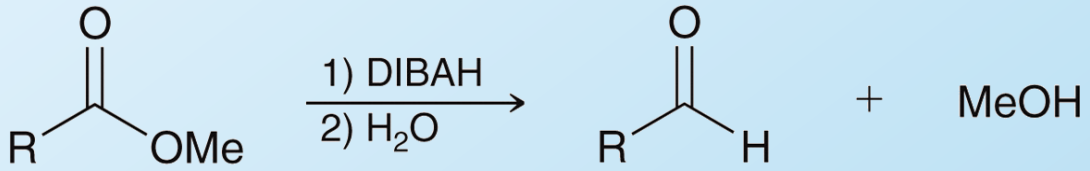


Mechanism

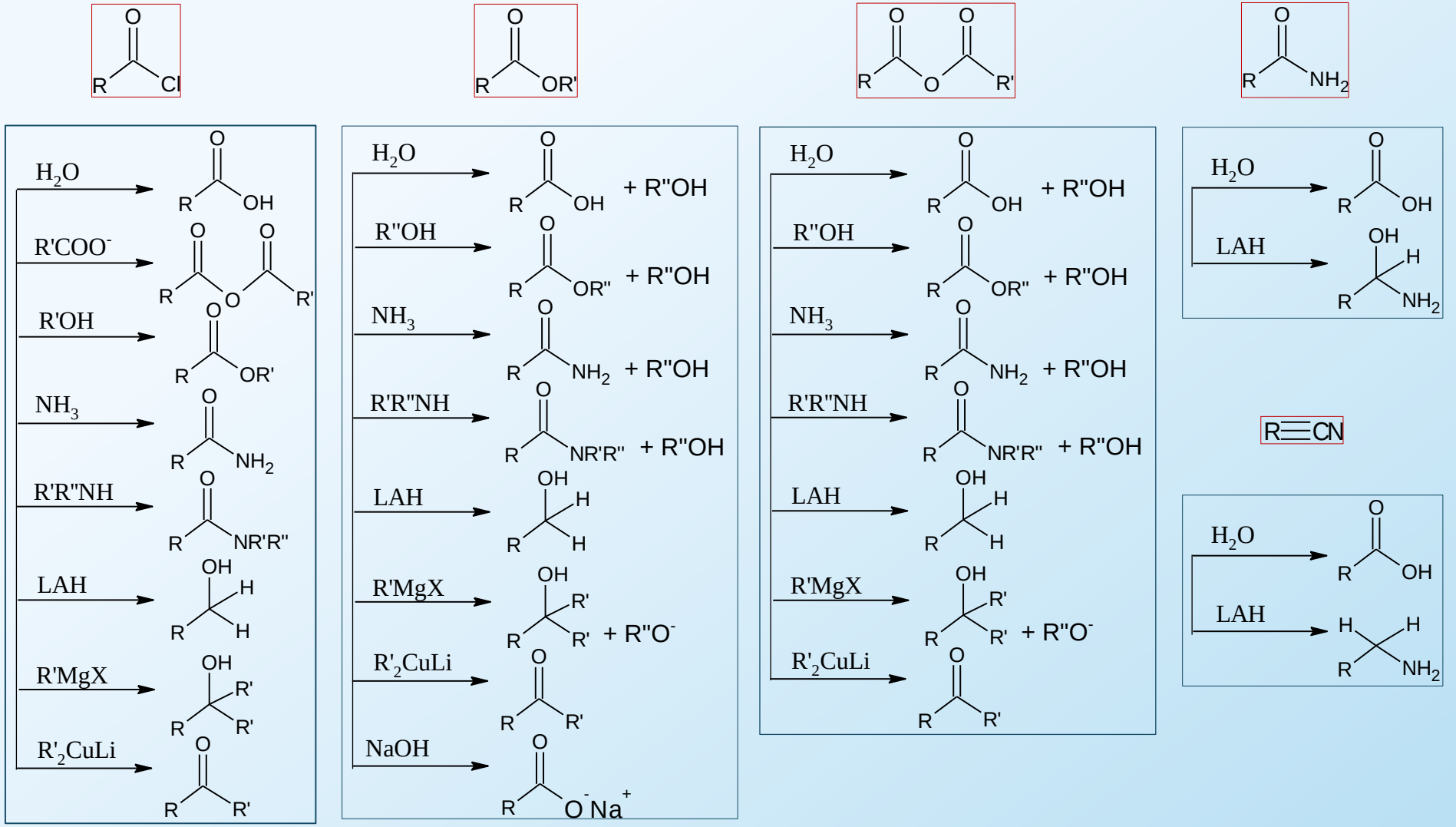


Using a weak reducing agent

Give aldehydes

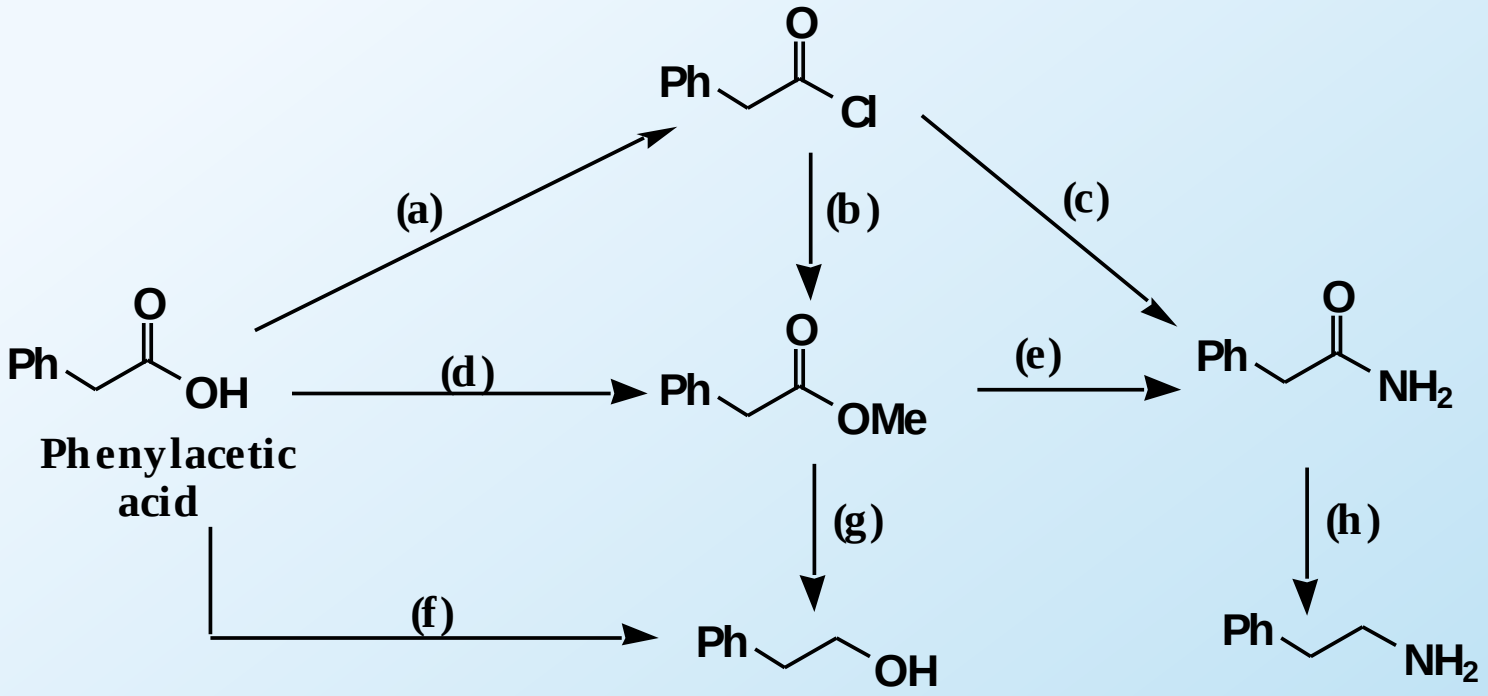


All Reactions



Interconversions - Practice

Problem: Show reagents and experimental conditions to bring about each reaction.



Key Concepts

- Synthesis and Reactions of all derivatives
- Mechanism of esterification