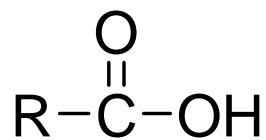
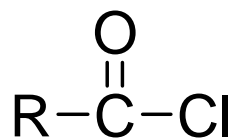


Ch.21 Carboxylic Acid Derivatives and Nucleophilic Acyl Substitution

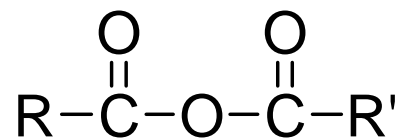
Carboxylic Acid Derivatives



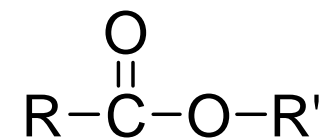
Carboxylic acid



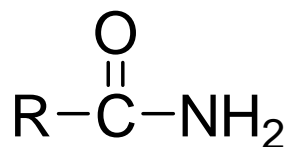
Carboxylic acid chloride



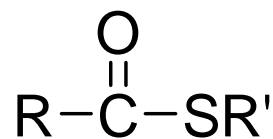
Acid anhydride



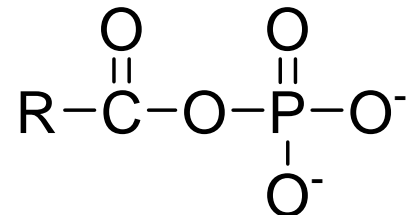
Ester



Amide



Thioester



Acyl phosphate



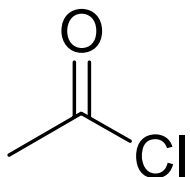
Nitrile

Nucleophilic Acyl Substitution

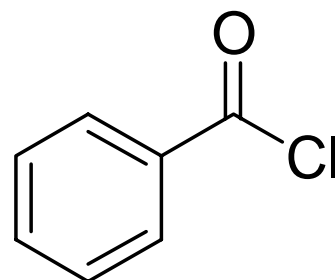


21.1 Nomenclature

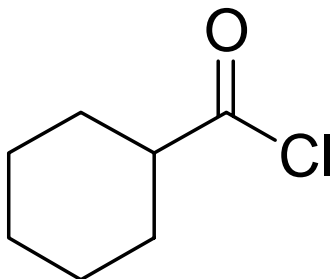
Acid Halides: RCOX -oic acid -yl
 -carboxylic acid -carbonyl



Acetyl chloride

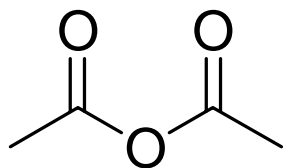


Benzoyl chloride

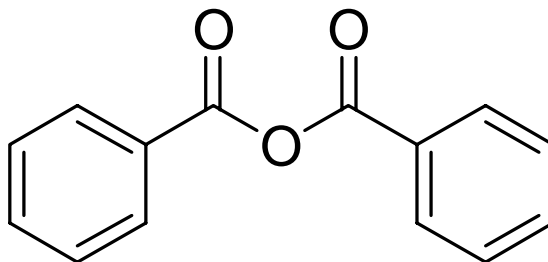


Cyclohexanecarbonyl chloride

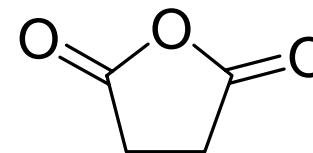
Acid Anhydrides: $\text{RCO}_2\text{COR}'$ acid anhydride



Acetic anhydride

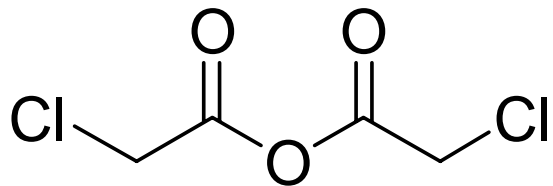


Benzoic anhydride

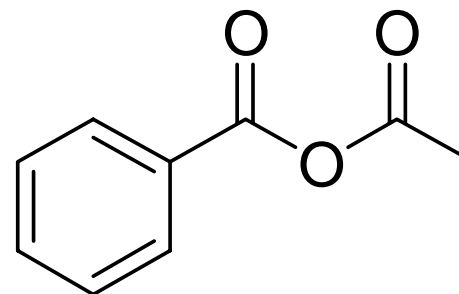


Succinic anhydride

- anhydride from substituted monocarboxylic acid: **bis-**
- unsymmetrical anhydride: cite two carboxylic groups alphabetically



Bis(chloroacetic) anhydride

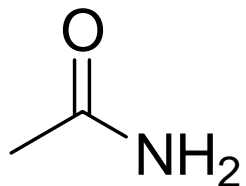


Acetic benzoic anhydride

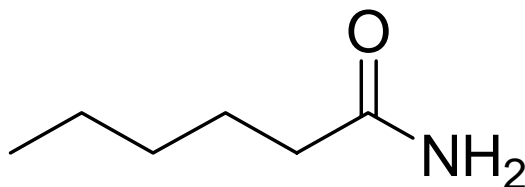
Amides: $RCONH_2$

-(o)ic acid amide

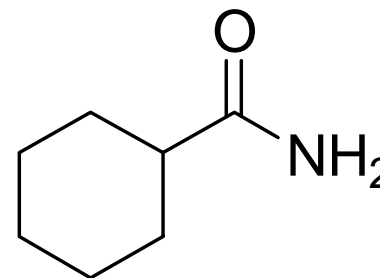
-carboxylic acid -carboxamide



Acetamide

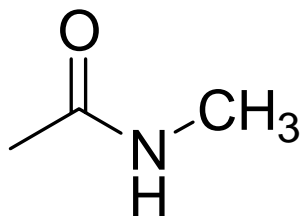


Hexanamide

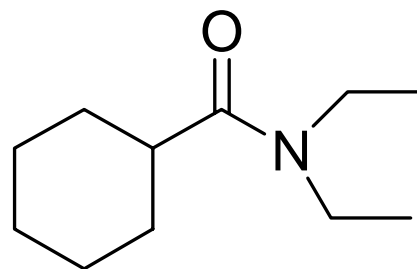


Cyclohexanecarboxamide

- substituted amide: *N*-alkyl----amide



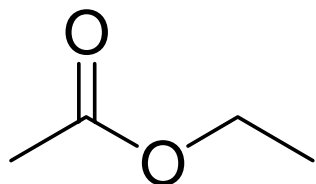
N-Methylacetamide



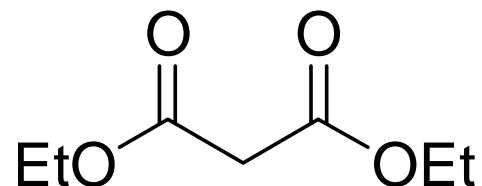
N,N-Diethylcyclohexanecarboxamide

Esters: $\text{RCO}_2\text{R}'$

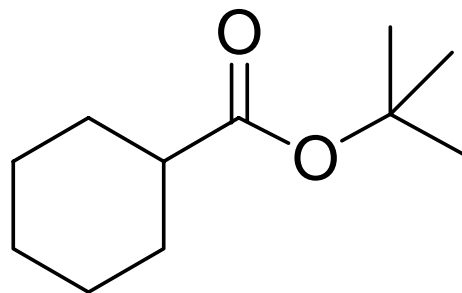
- name alkyl group attached to oxygen
then -ic acid -ate



Ethyl acetate



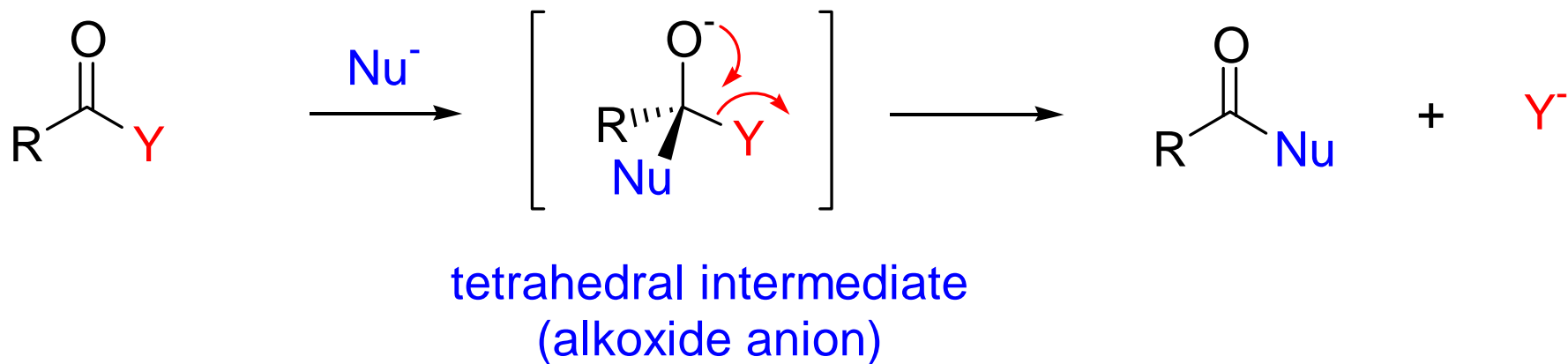
Diethyl malonate



tert-Butyl cyclohexanecarboxylate

21.2 Nucleophilic Acyl Substitution Reactions

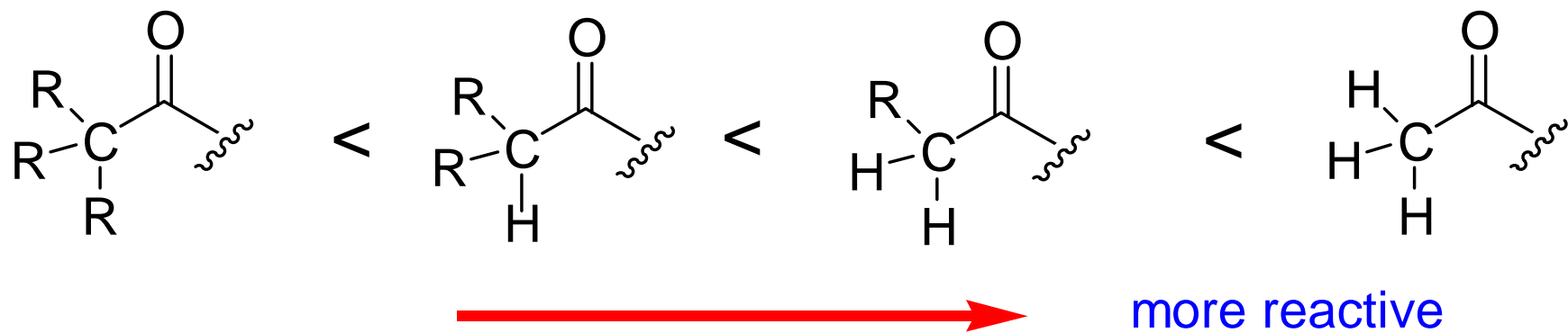
Nucleophilic acyl substitution: $Y = \text{OR}', \text{Cl}, \text{OCOR}', \text{NR}'_2$



- addition-elimination mechanism: different from $\text{S}_{\text{N}}2$ mechanism

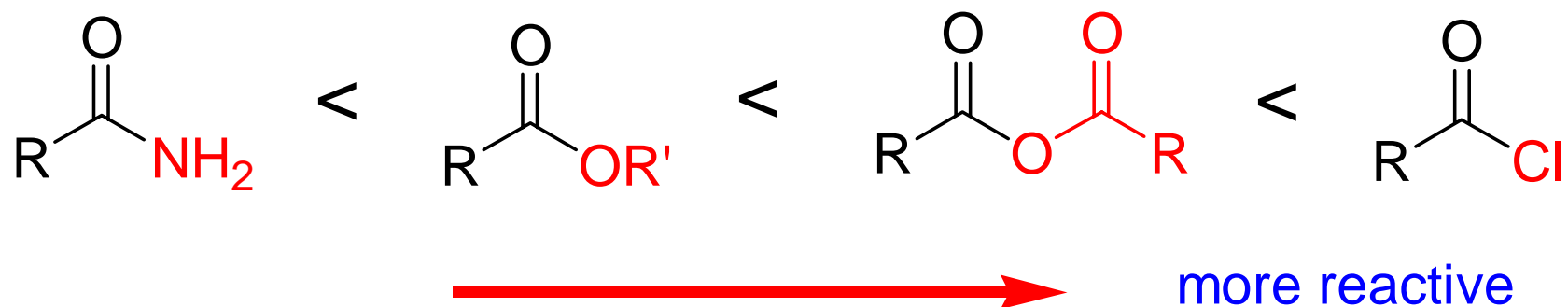
Relative Reactivity of Carboxylic Acid Derivatives

Steric effect:

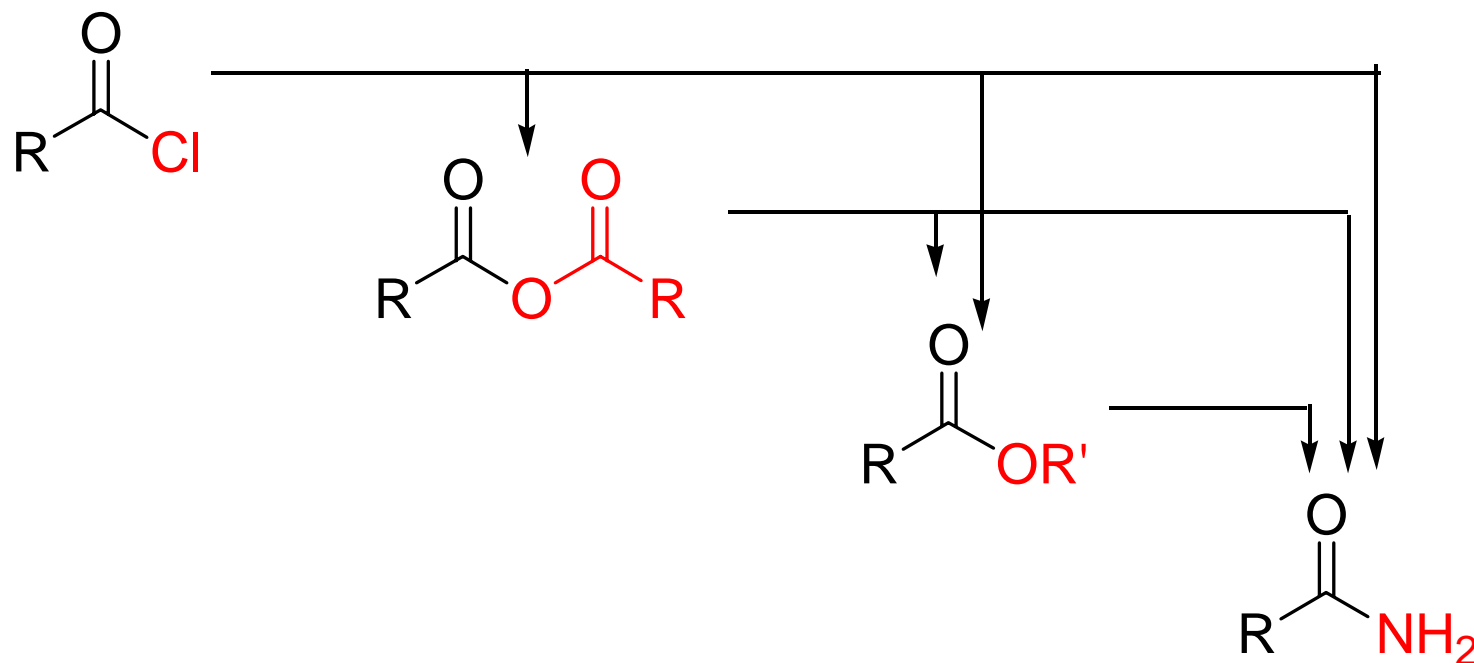


Electronical effect:

- strongly polarized derivatives are more reactive
- leaving group ability

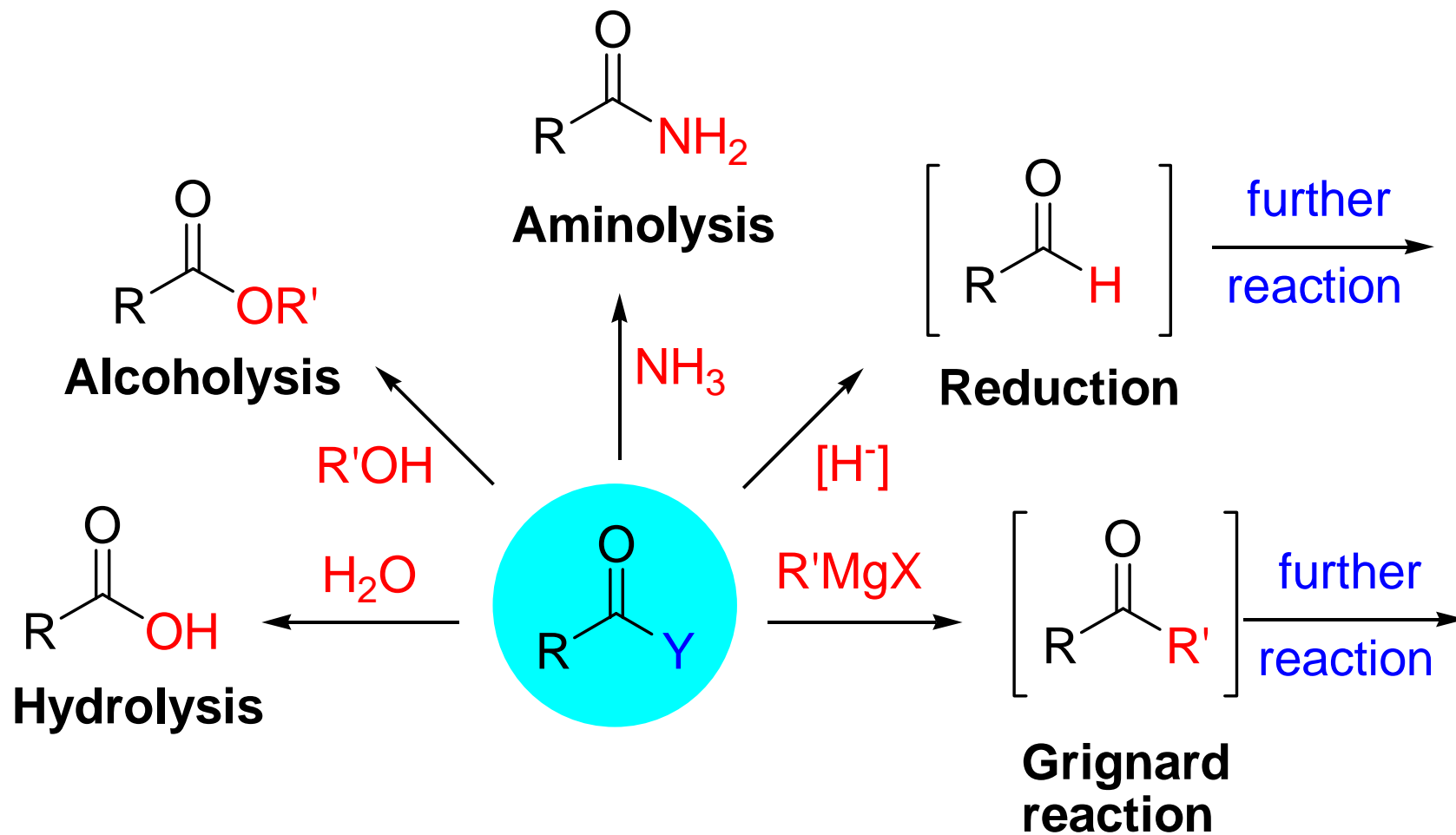


Conversion of a more reactive derivatives to less a reactive derivatives; but reverse direction is not possible

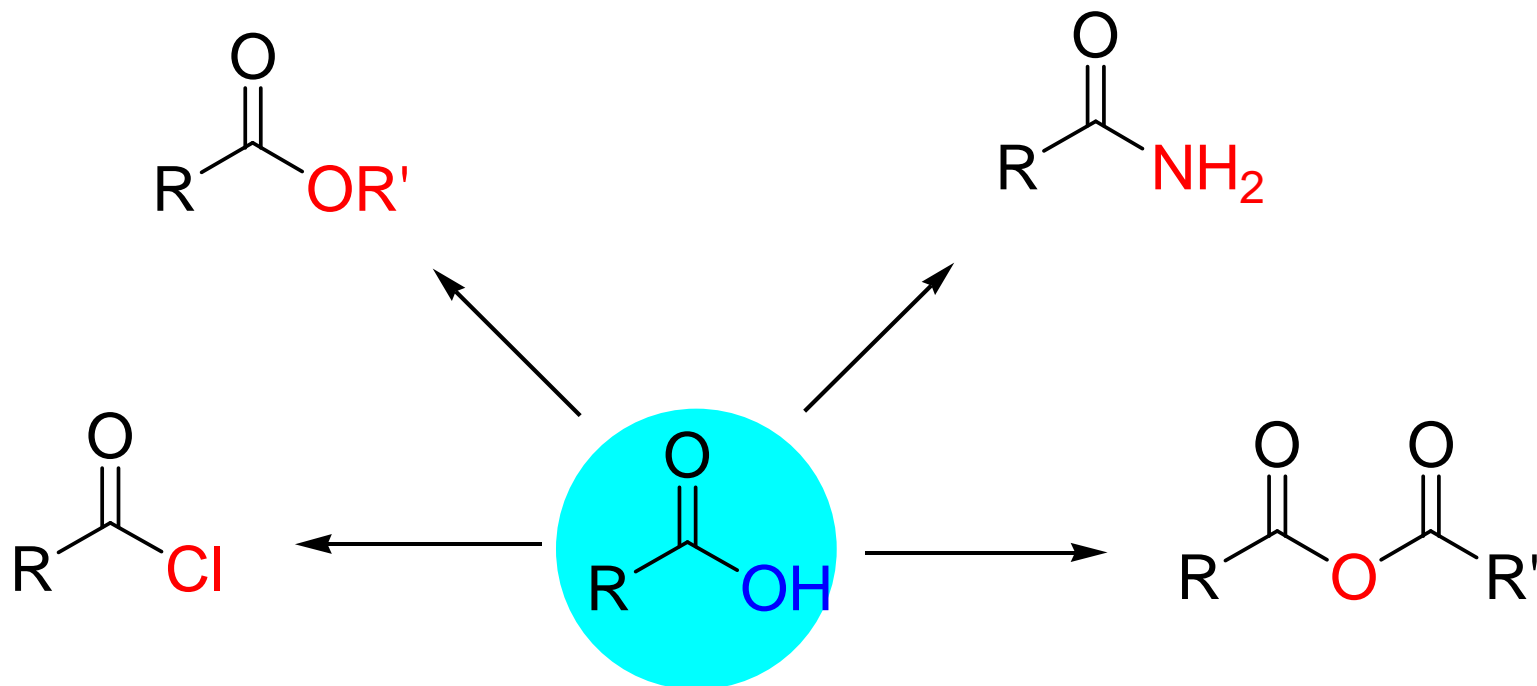


- only ester and amides are commonly found in nature
- acid chloride and acid anhydride undergo nucleophilic attack by water

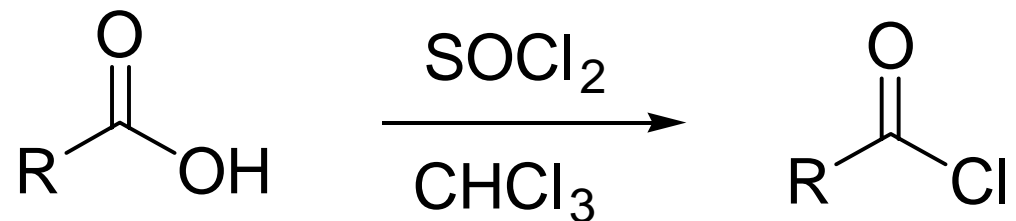
Kinds of Nucleophilic Acyl Substitutions



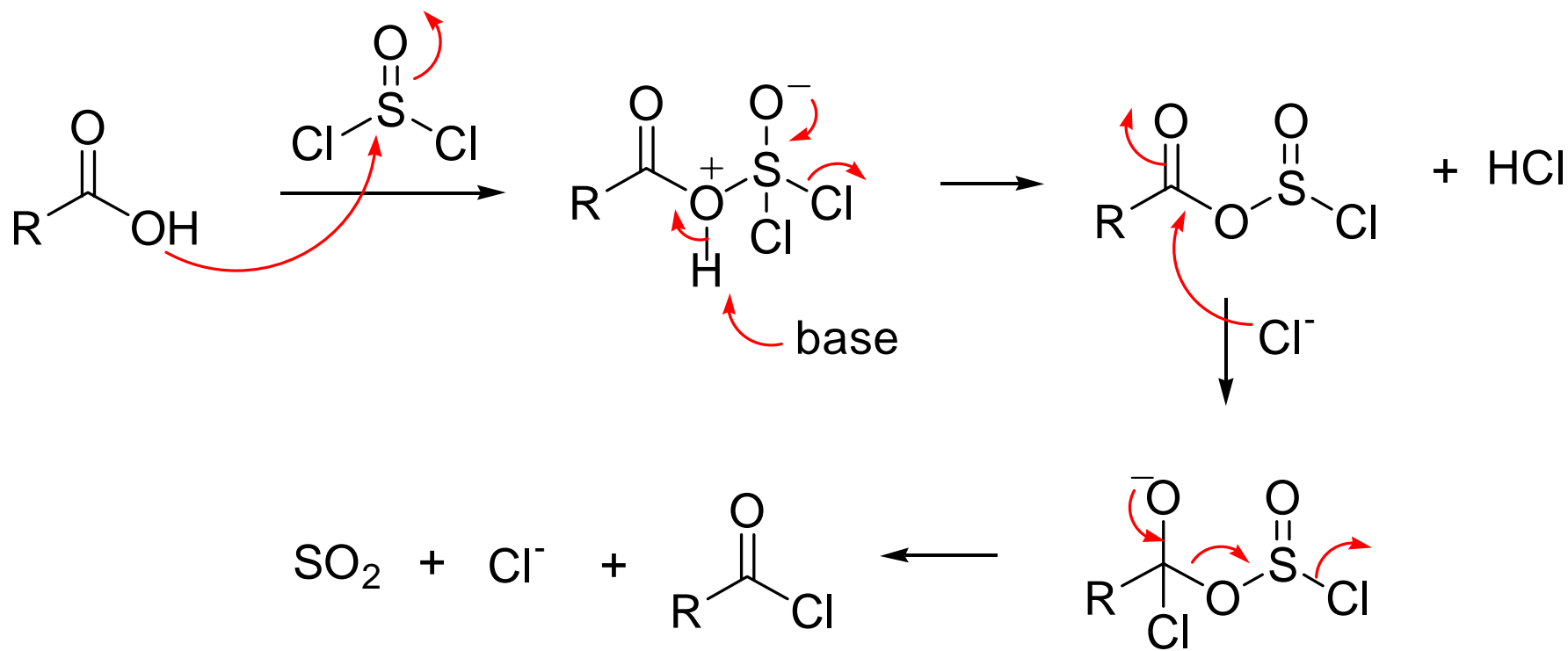
21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids



Conversion to acid chloride

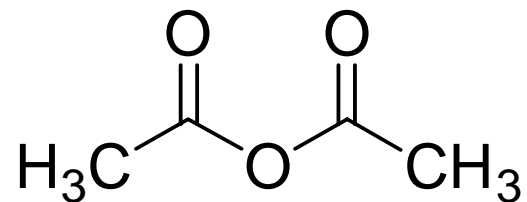


mechanism:



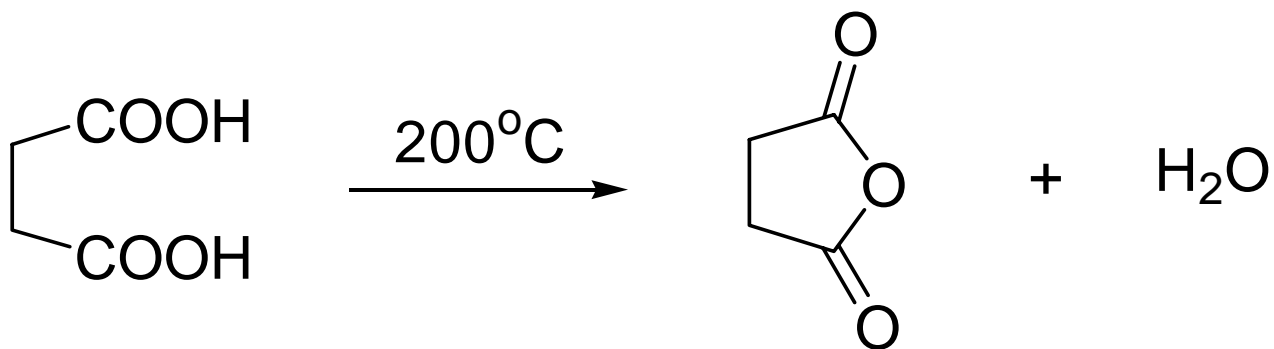
Conversion to acid anhydride:

- acyclic anhydrides are difficult to prepare
- acetic anhydride is commonly used



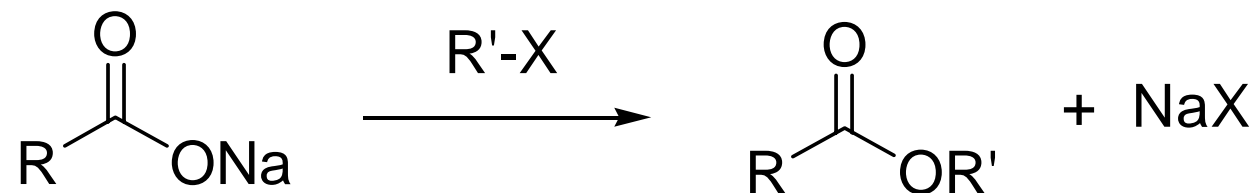
Acetic anhydride

- 5, 6-membered cyclic anhydrides are obtained by high temperature dehydration

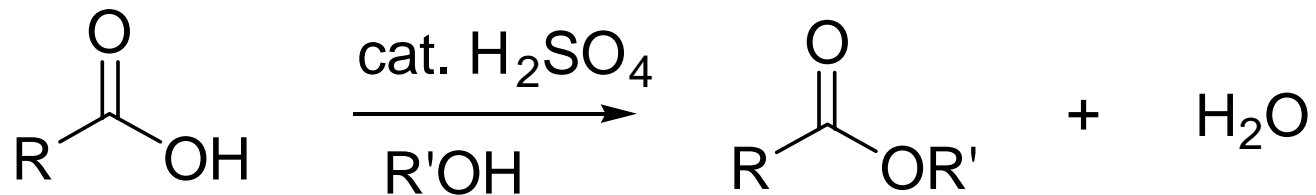


Conversion to esters:

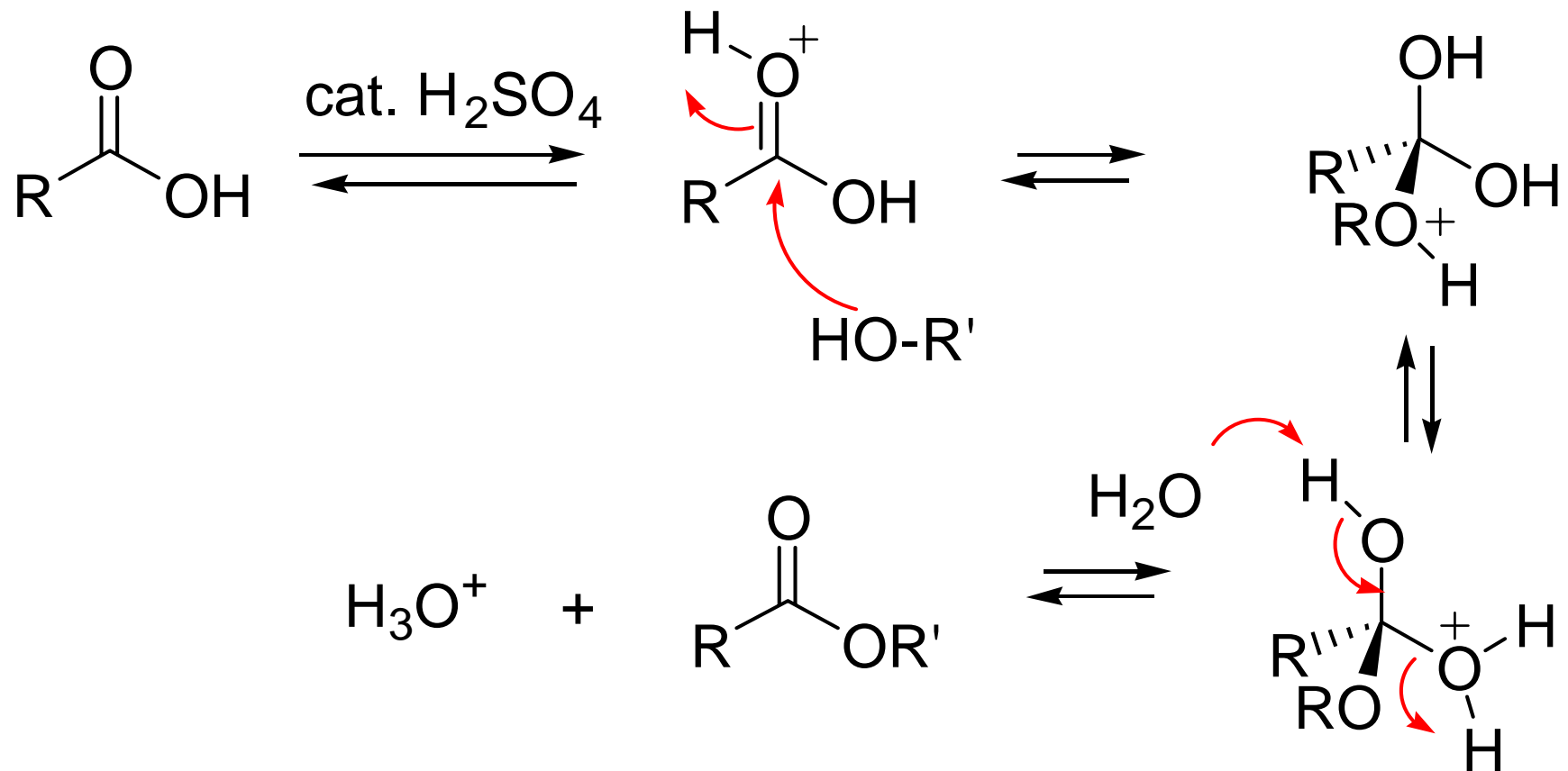
Alkylation of carboxylates with 1° alkyl halides



Fisher esterification: acid-catalyzed, HCl, H₂SO₄

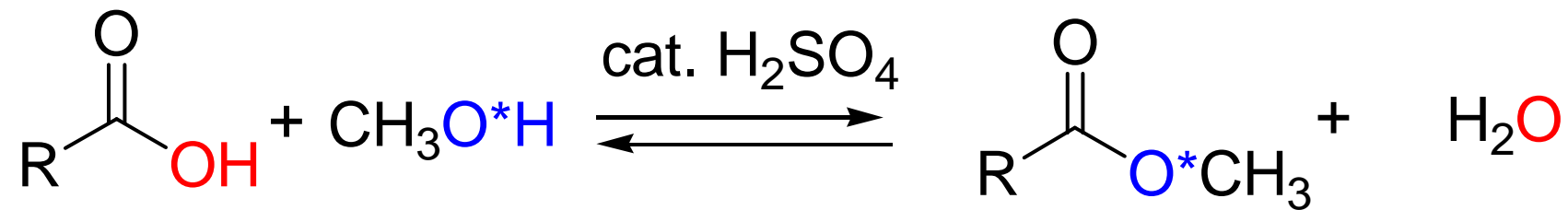


mechanism

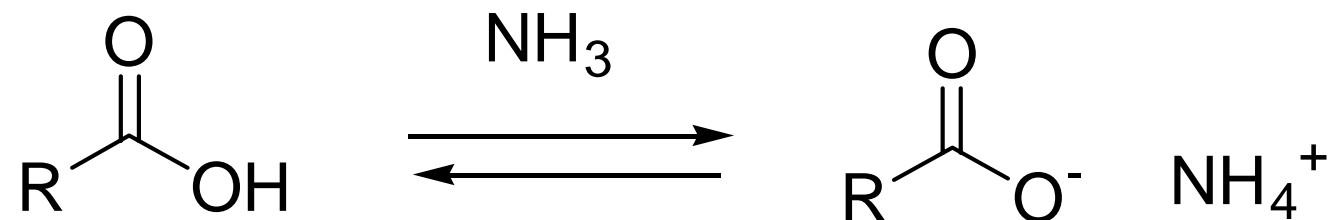


- reversible process: use excess of alcohol for complete esterification

- substitution of OH by OR'



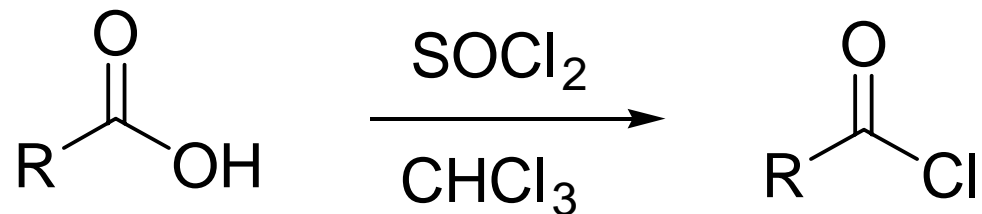
Conversion to amide



- amines are base: direct conversion to an amide is **not possible**

21.4 Chemistry of Acid Halides

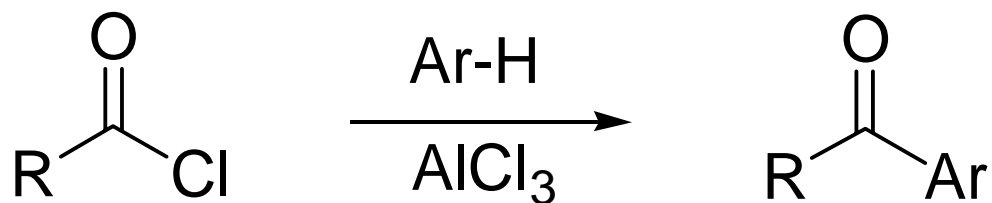
Preparation



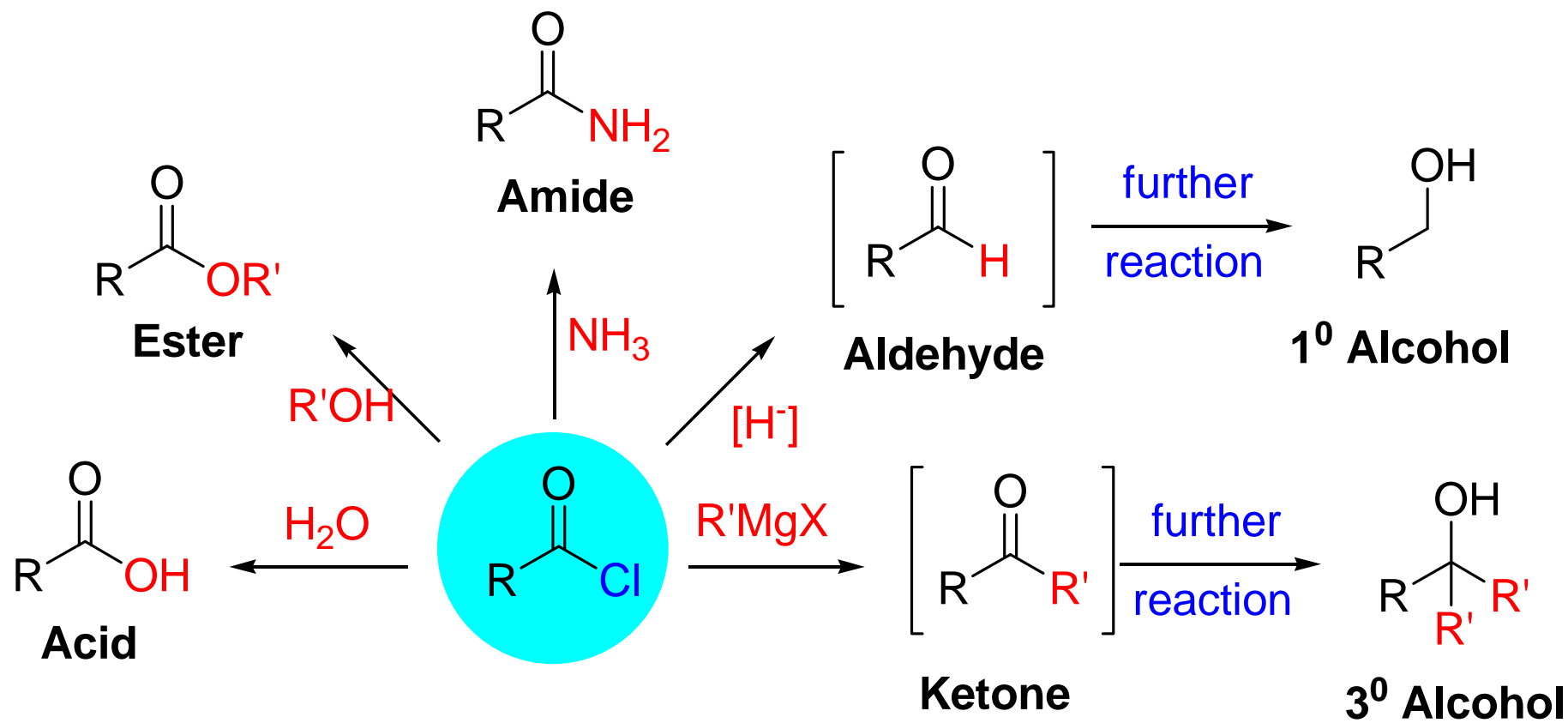
acid bromide, acid iodide: unstable

Reactions

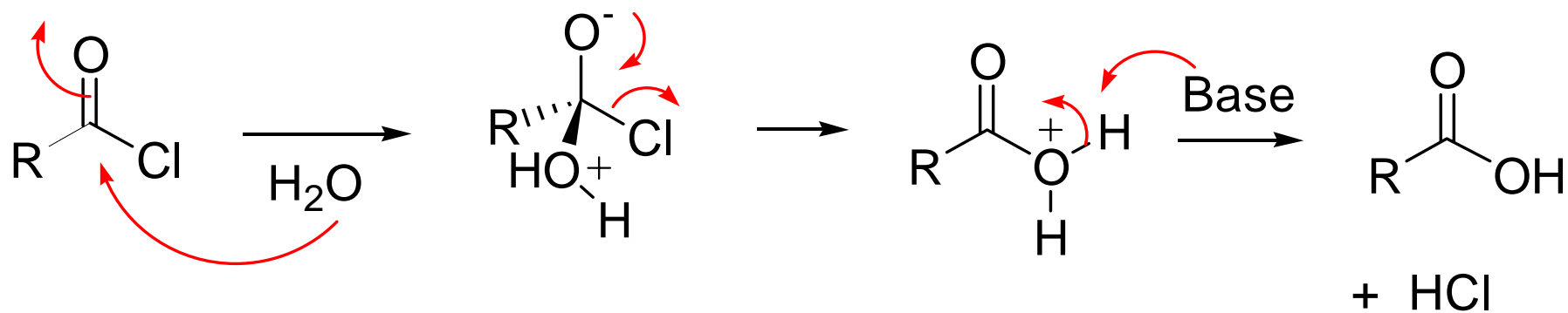
Friedel-Craft acylation:



Reactions

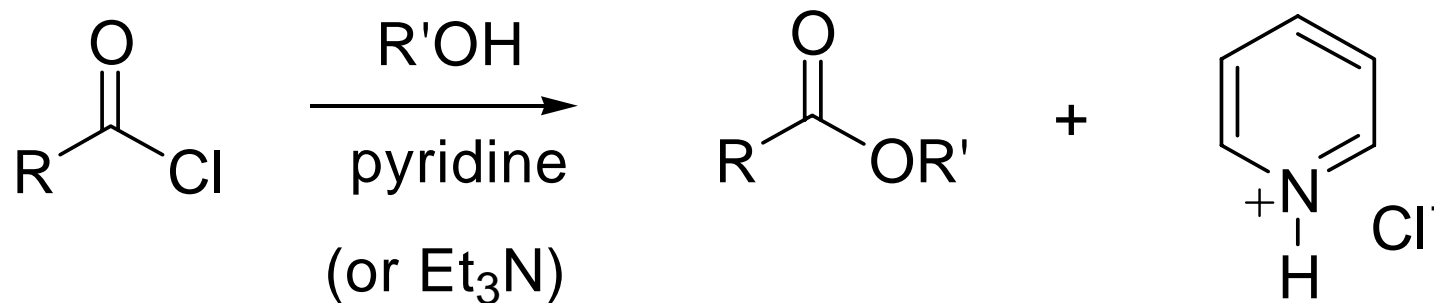


Hydrolysis:

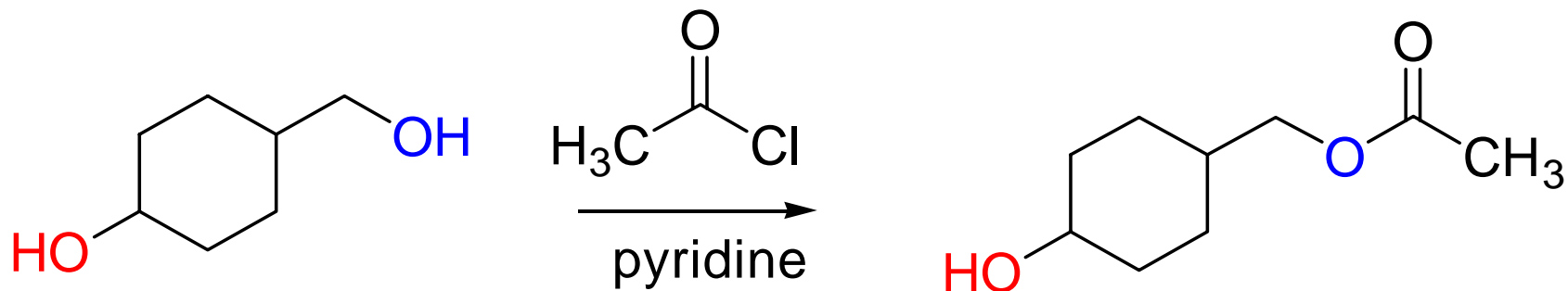


- use base (pyridine, NaOH) to neutralize HCl

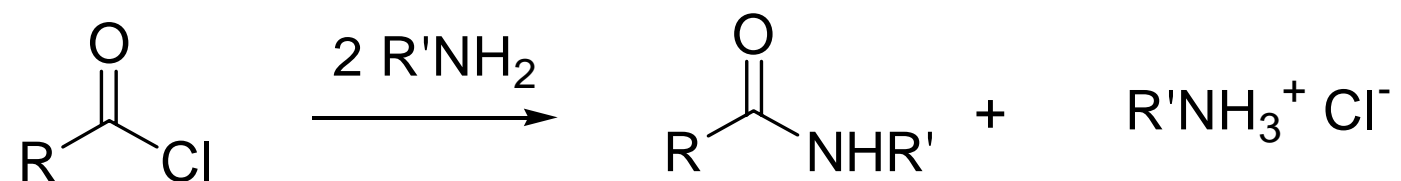
Alcoholysis: Ester formation



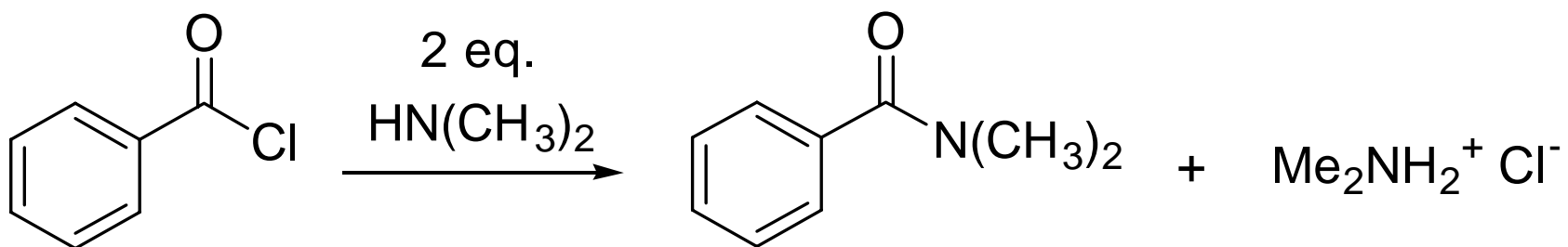
- use base (pyridine, Et₃N) to neutralize HCl formed
- reactivity: 1° > 2° > 3° alcohol
- selective esterification of unhindered alcohol



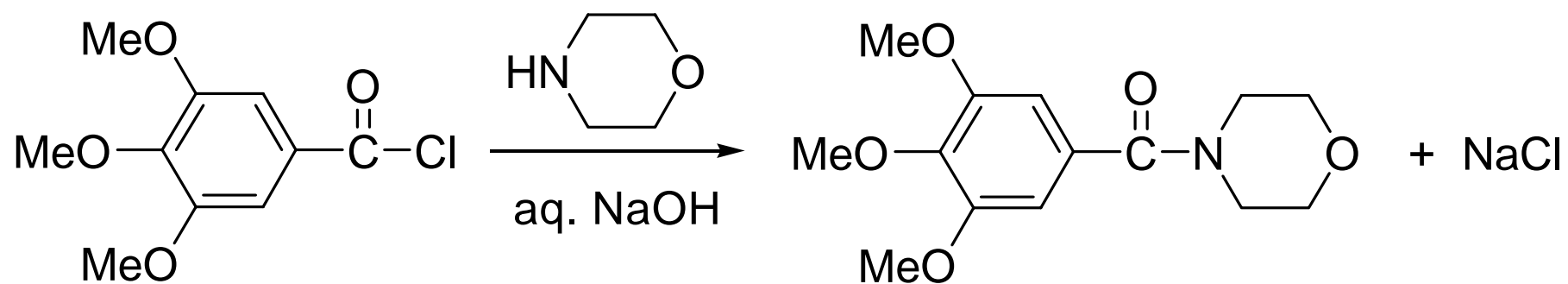
Aminolysis



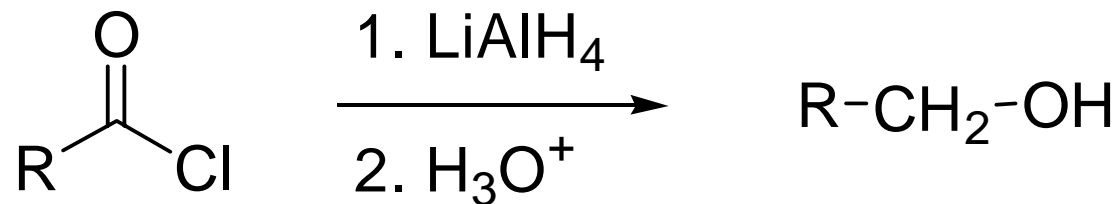
- use 2 equiv. of amine



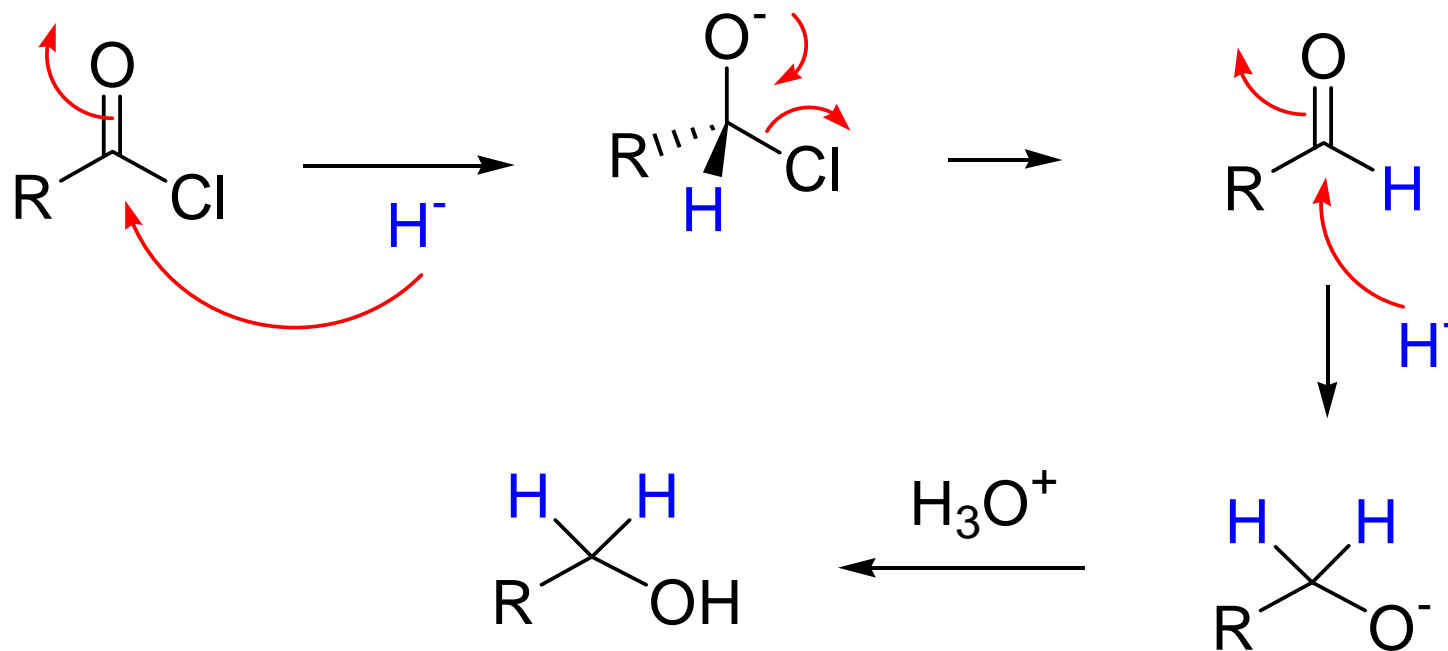
- for valuable amines; use external bases



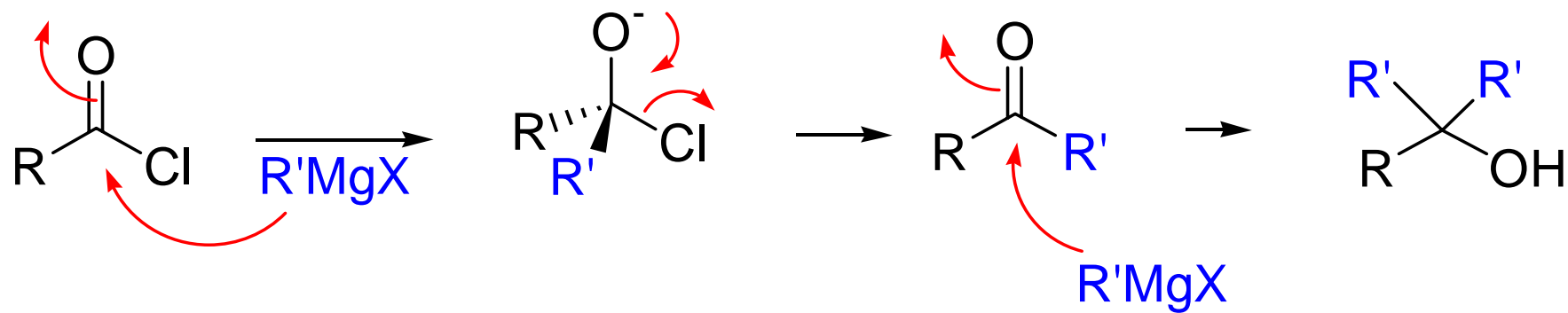
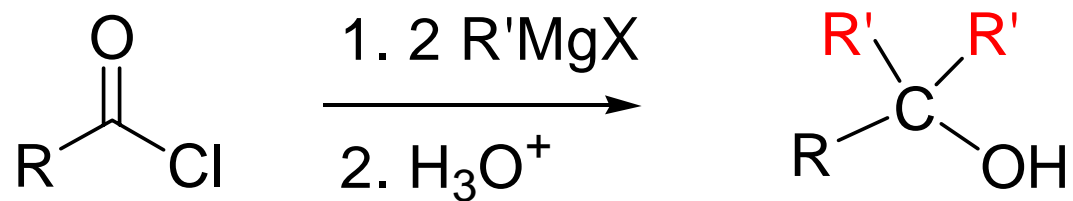
Reduction:



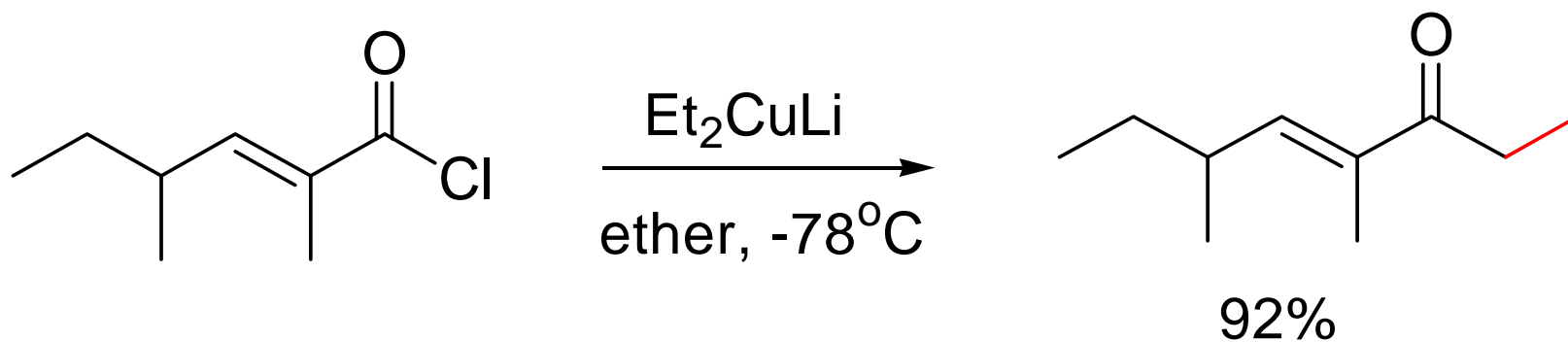
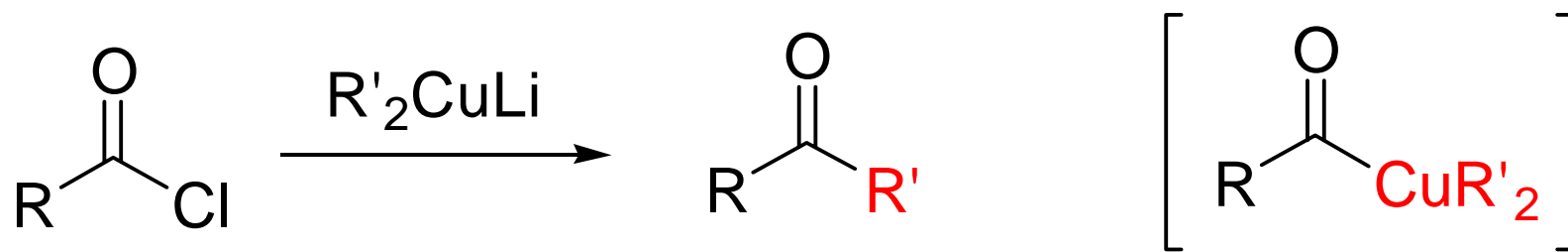
- little practical value: acid is more readily available and reduced to alcohol



Reaction of acid chloride with organometallic reagents



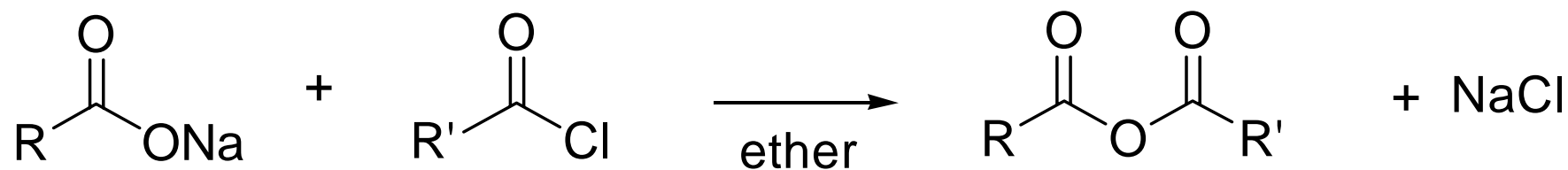
Diorganocopper reagent: Gilman reagent



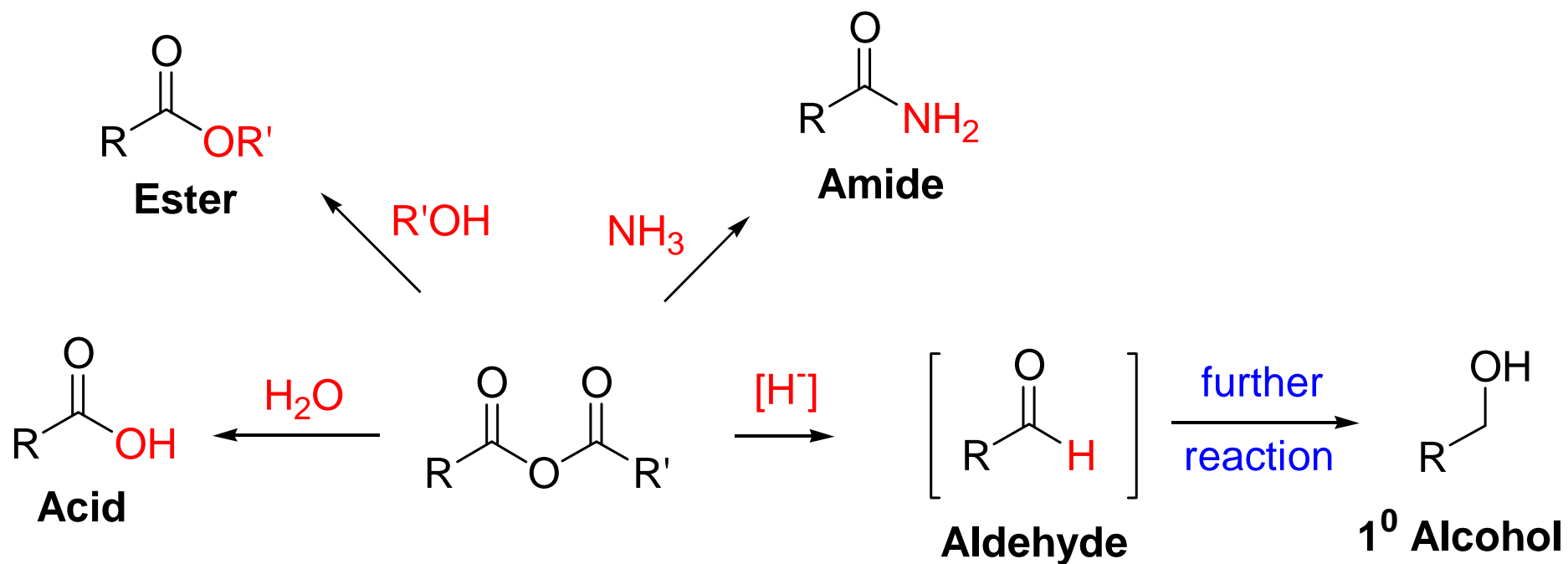
- diorganocopper reaction occurs only with acid chlorides
- carboxylic acid, ester, anhydride, amide do not react with diorganocopper reagents

21.5 Chemistry of Acid Anhydride

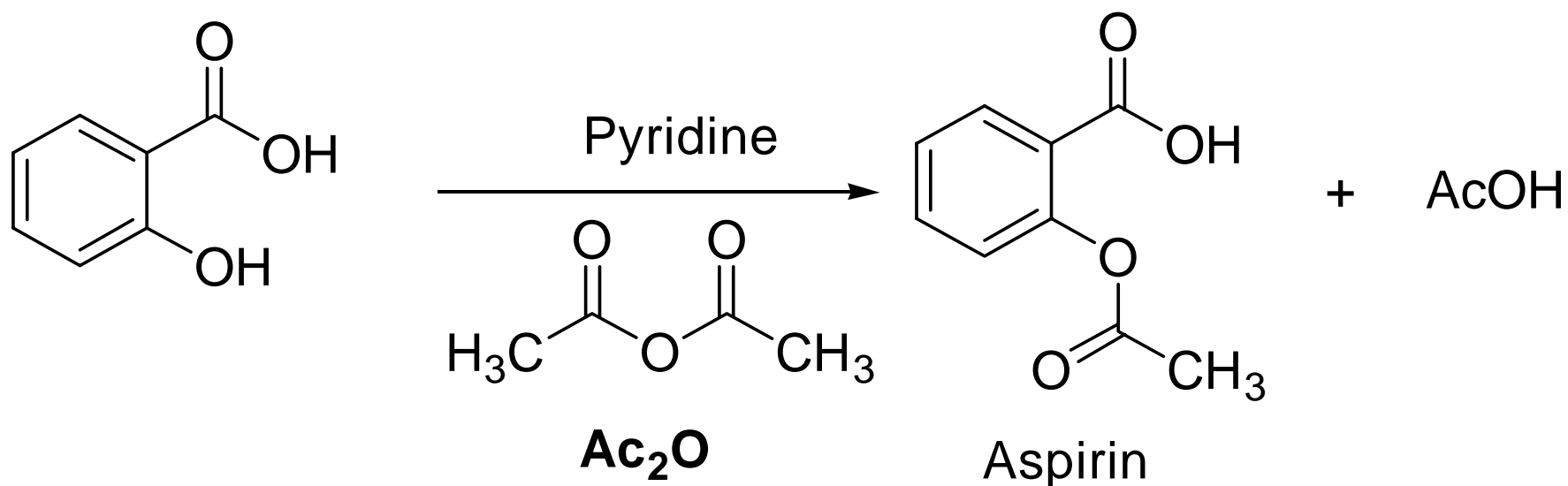
Preparation

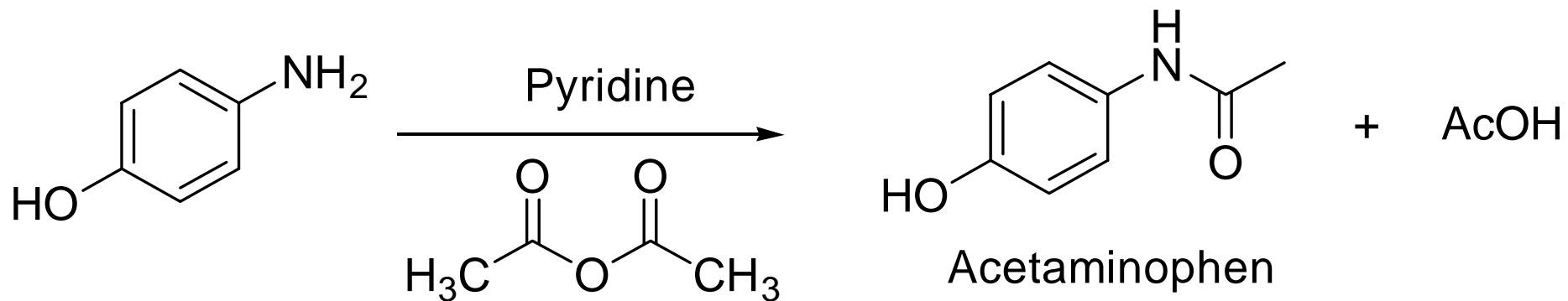


Reactions



- Acetic anhydride is commonly used
- selective reaction is possible if two functional groups have different reactivity

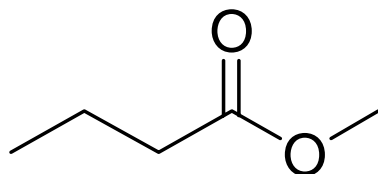




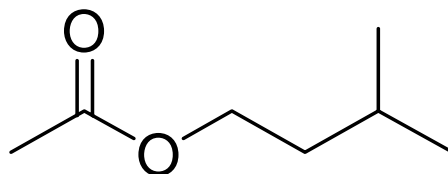
- AcCl: highly reactive, HCl (NaCl) as by-product
- Ac₂O/pyr: moderate reactivity, AcOH (AcONa) as by-product

21.6 Chemistry of Esters

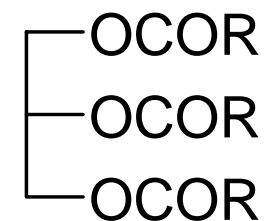
- fragrant odors of fruits and flowers



from pineapples



from banana

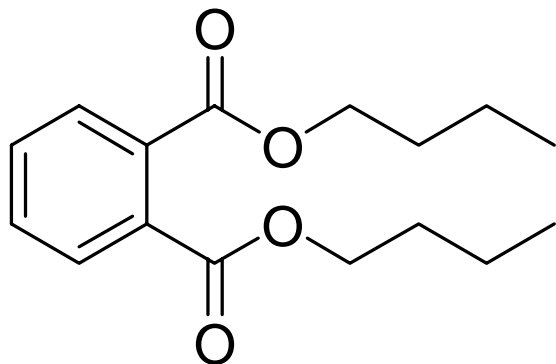


A fat

(R = C₁₁₋₁₇ chains)

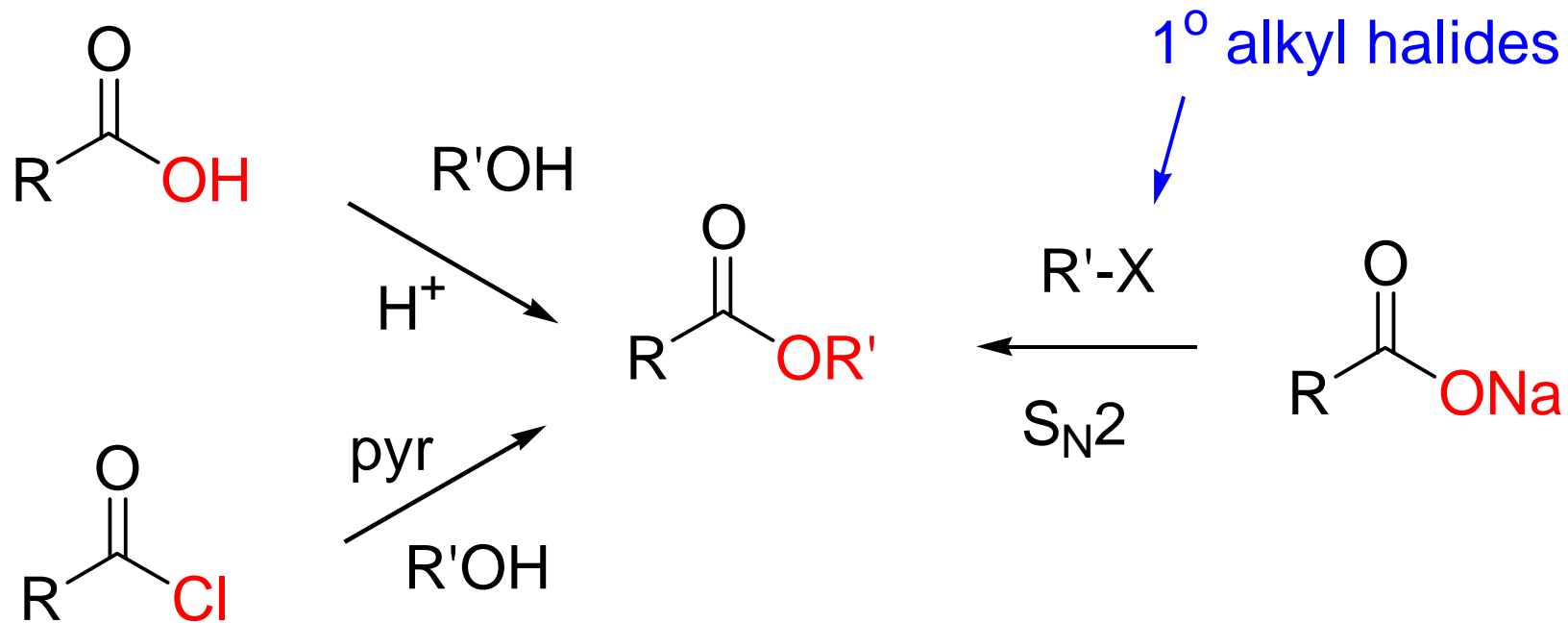
industrial use

- Ethyl acetate (solvent)
- dialkyl phthalate (plasticizer: keep polymers from becoming brittle)

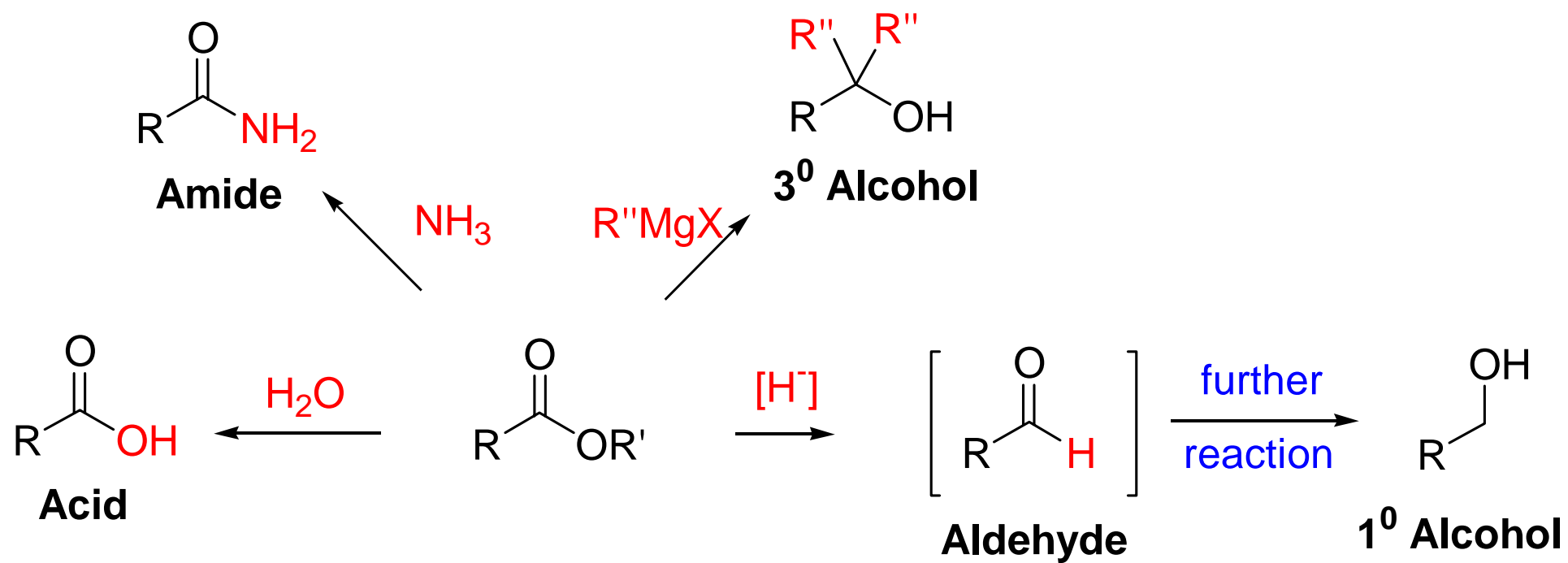


Dibutyl phthalate (a plasticizer)

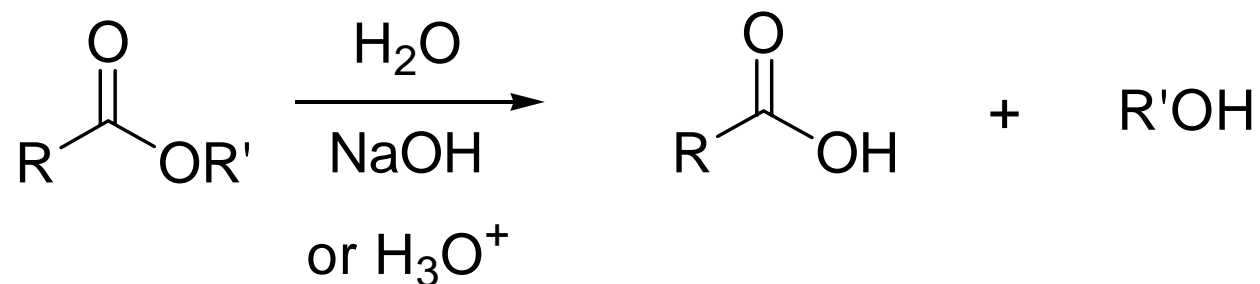
Preparation of esters



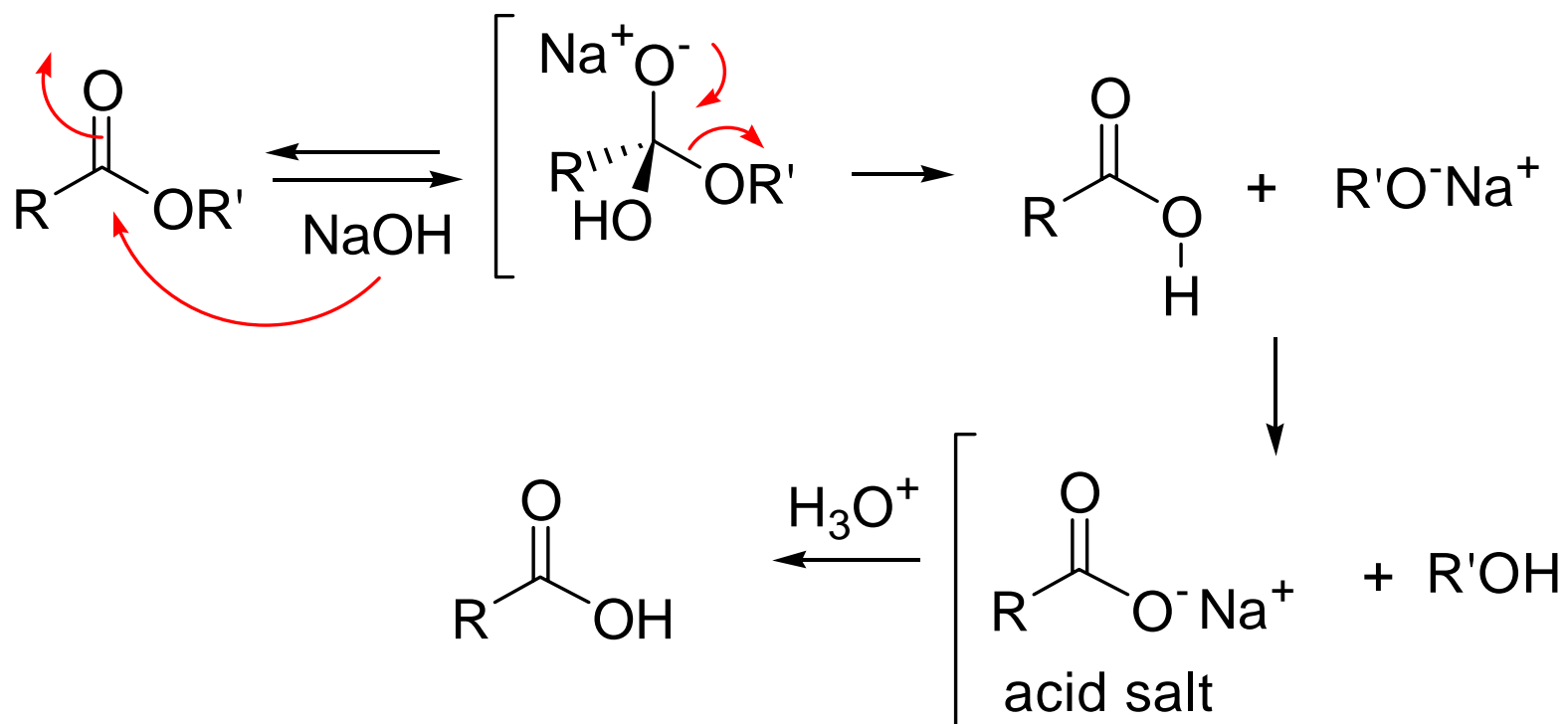
Reactions of esters



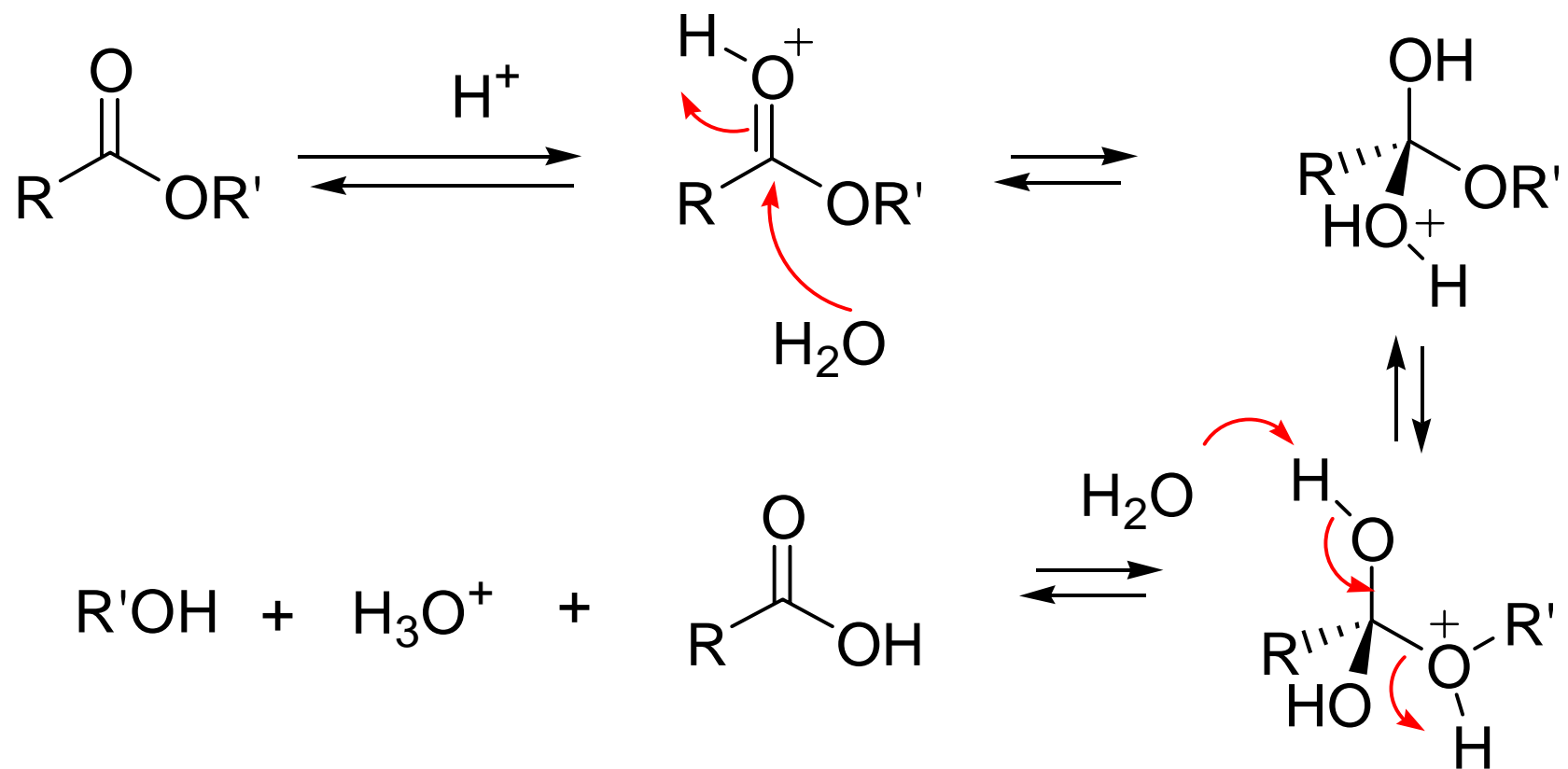
Hydrolysis:



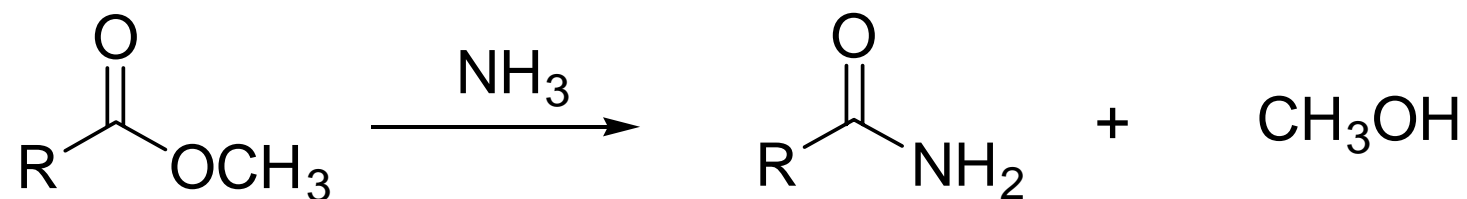
Saponification: basic hydrolysis



Acid-catalyzed hydrolysis: reversible



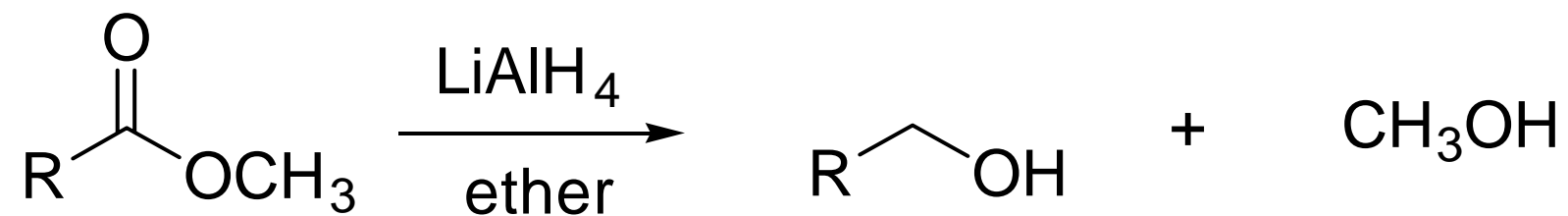
Aminolysis: not often used, acid chloride method is commonly used

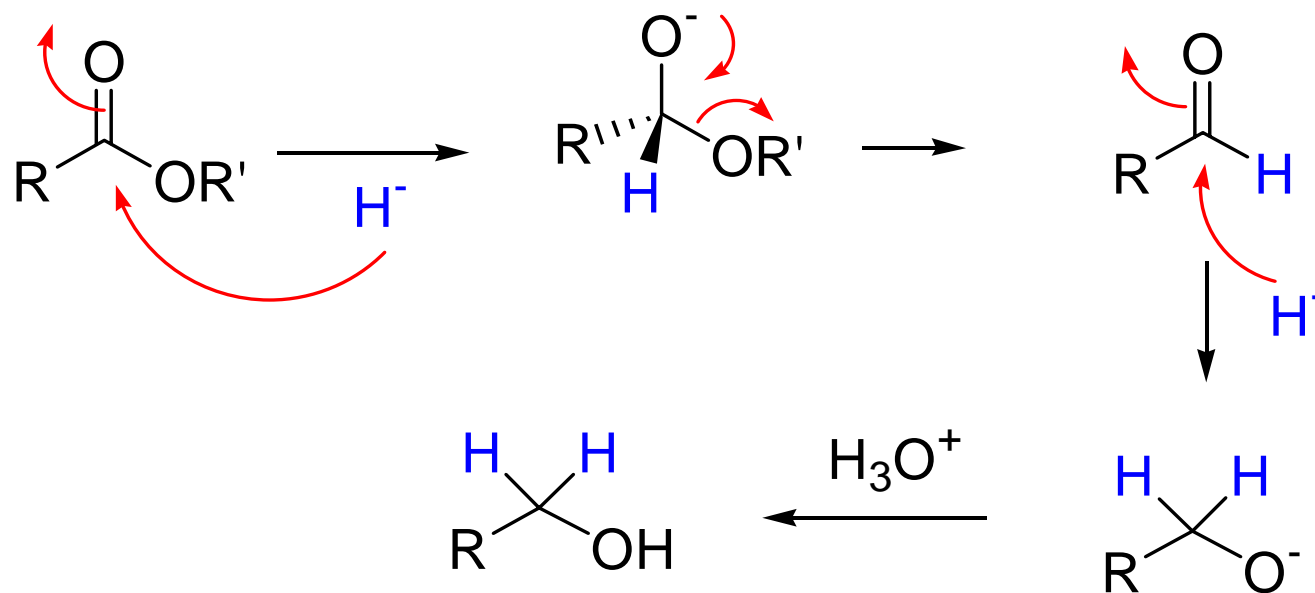


not so reactive to amine

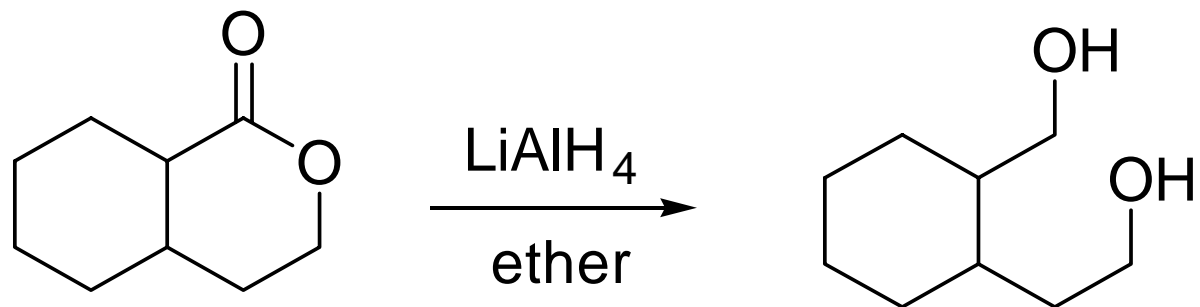
Reduction: LiAlH_4

- NaBH_4 cannot reduce ester under normal condition

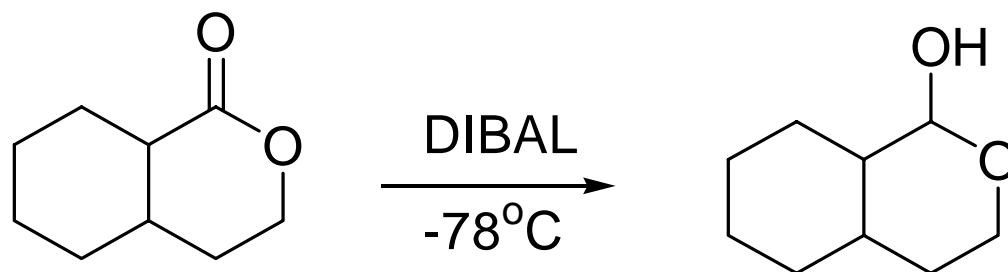
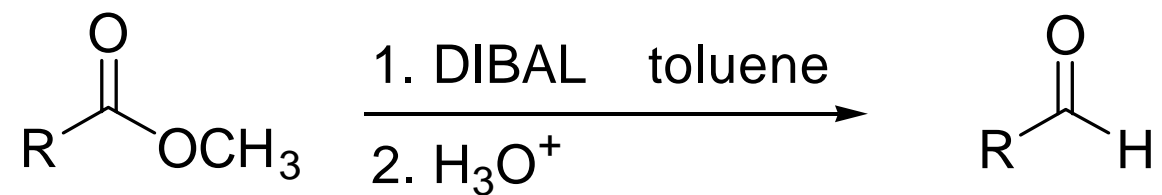




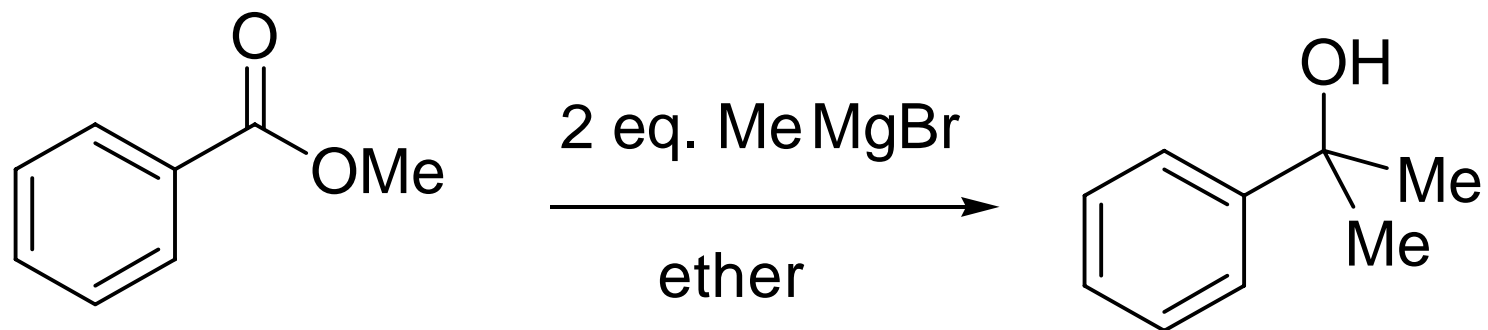
- intermediate aldehyde is more reactive than ester



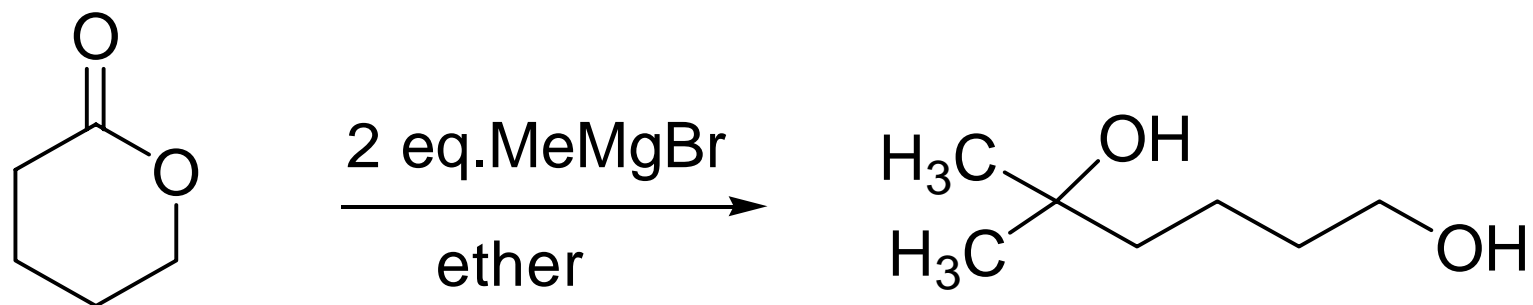
- intermediate aldehyde can be isolated by **DIBALH** (*i*-Bu₂AlH)



Grignard addition: add 2 equivalent of RMgX,
yield 3° alcohol product

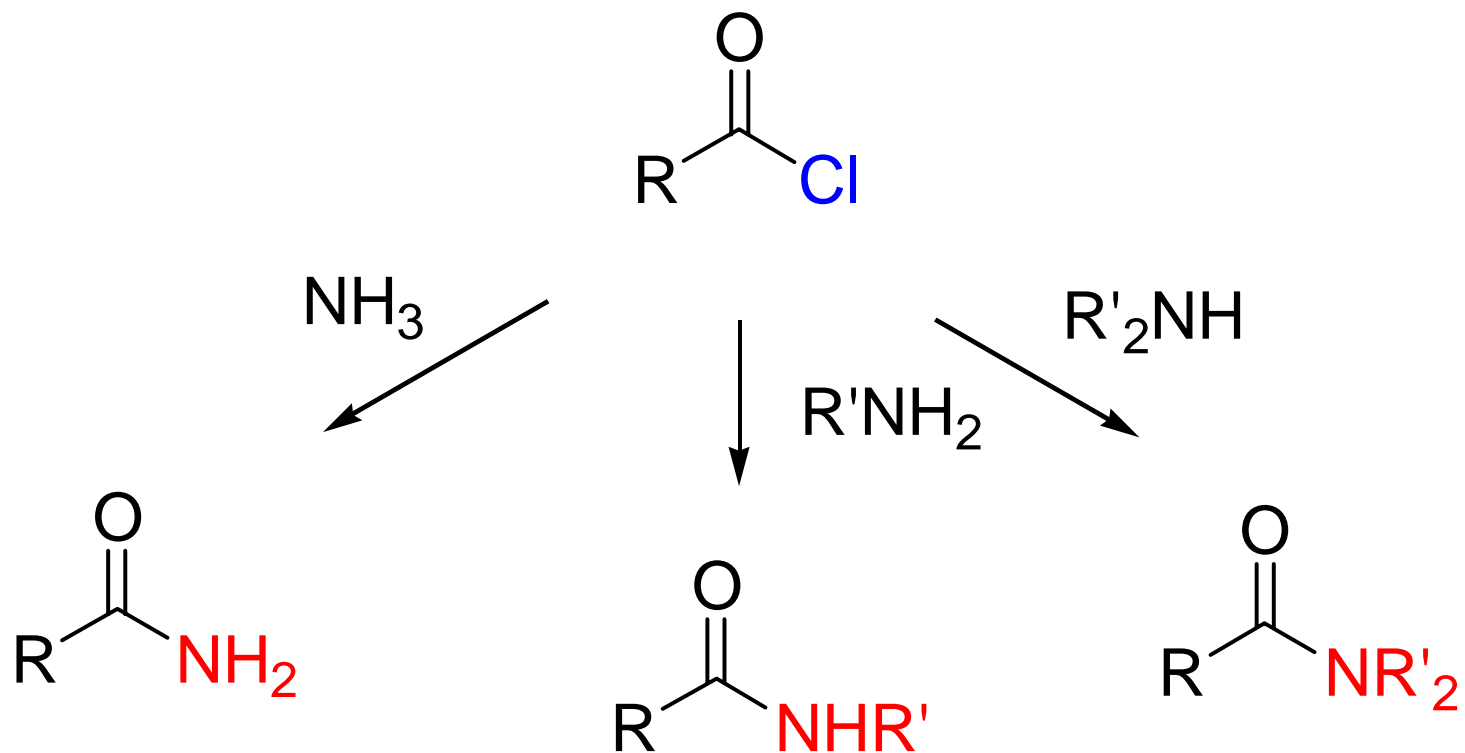


- intermediate ketone is more reactive than ester



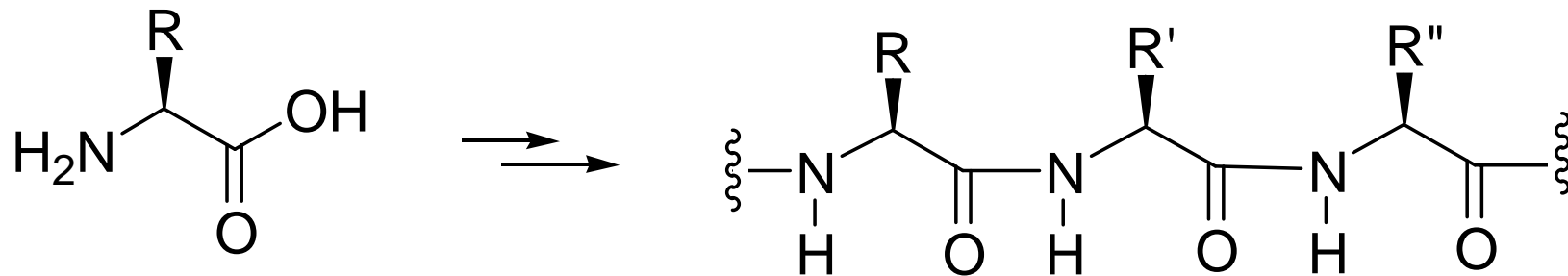
21.7 Chemistry of Amides

Preparation



Reactions

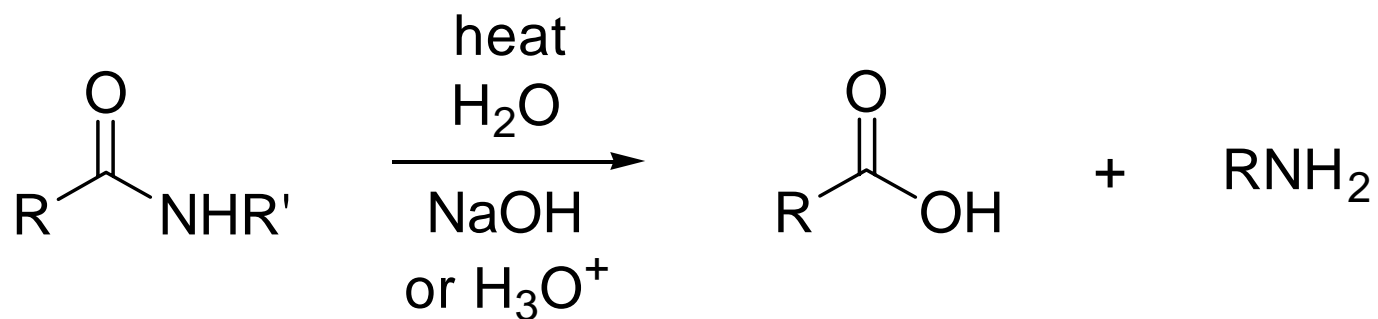
- amide bonds are stable, used for protein building



Amino acids

A protein (polyamide)

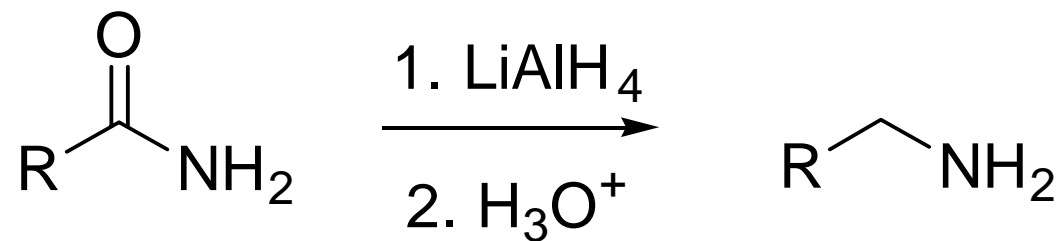
Hydrolysis: require severe conditions, synthetically not useful



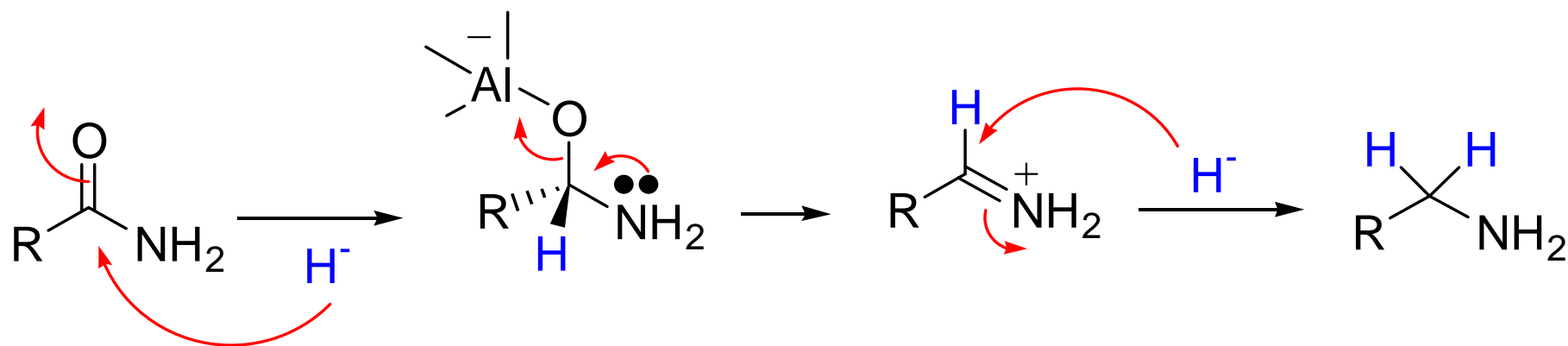
slow
(inefficient)

Reduction: LiAlH_4

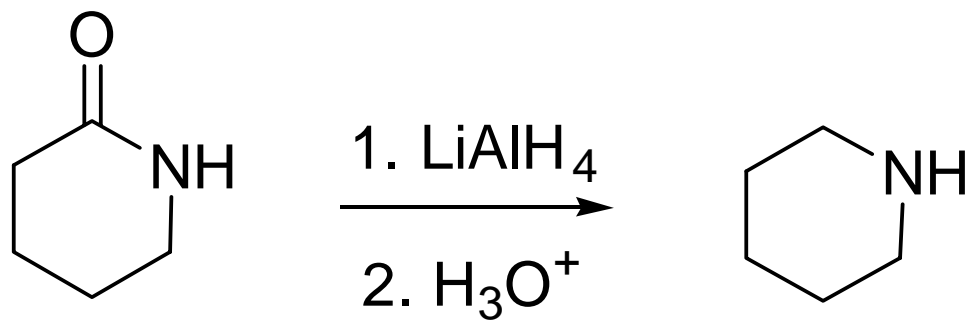
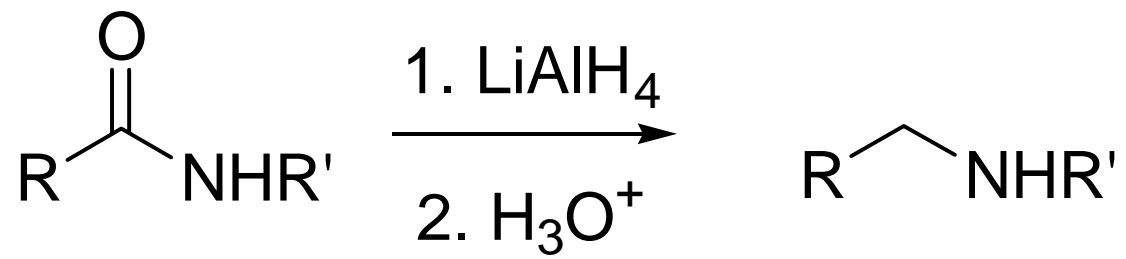
- NaBH_4 cannot reduce amides



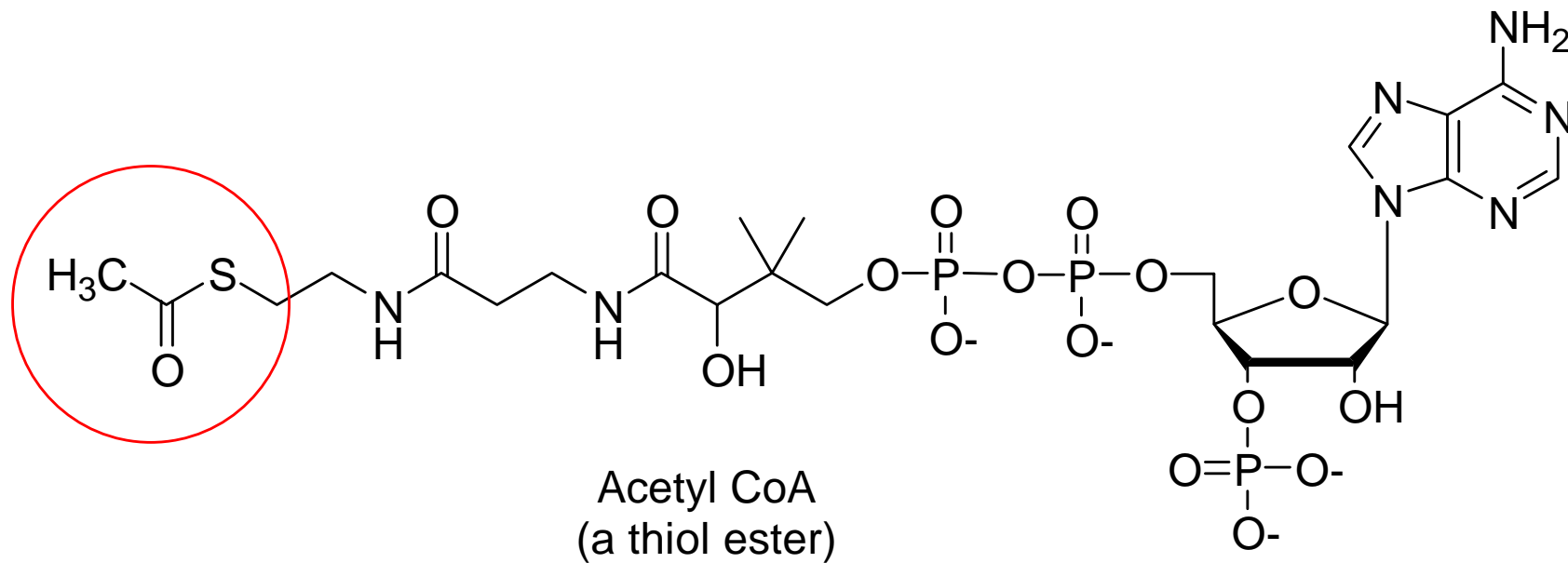
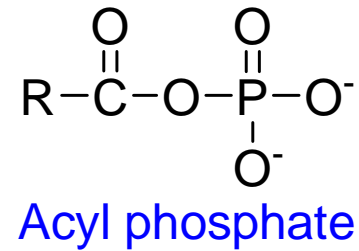
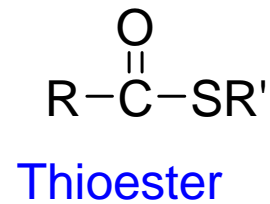
mechanism

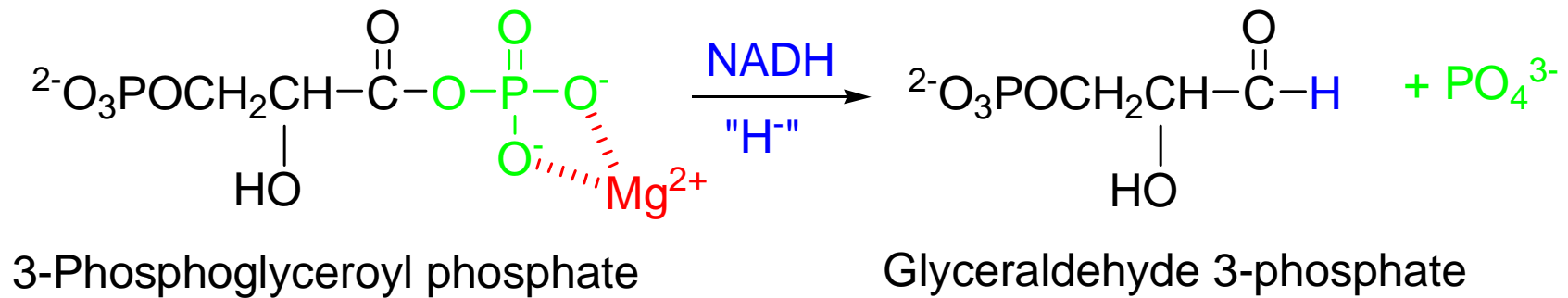
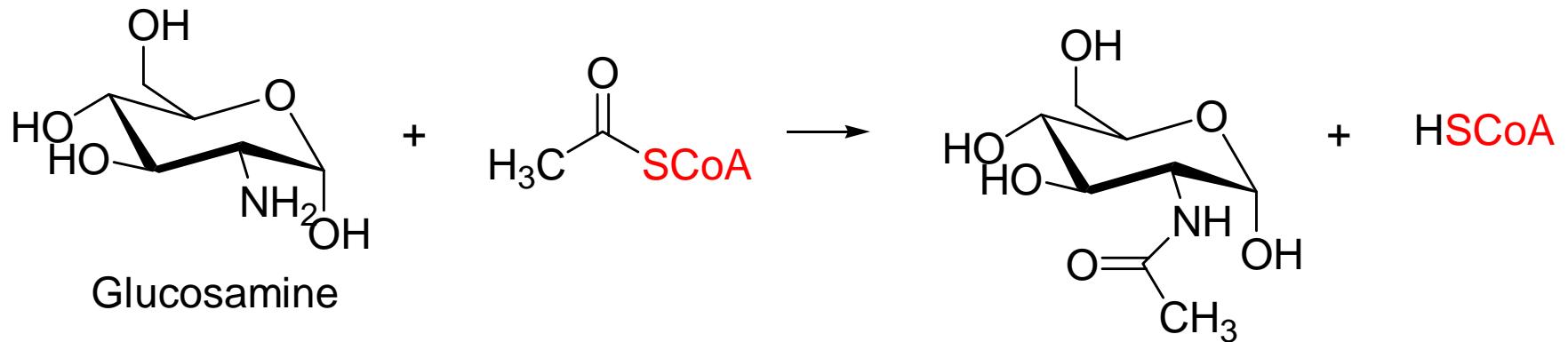
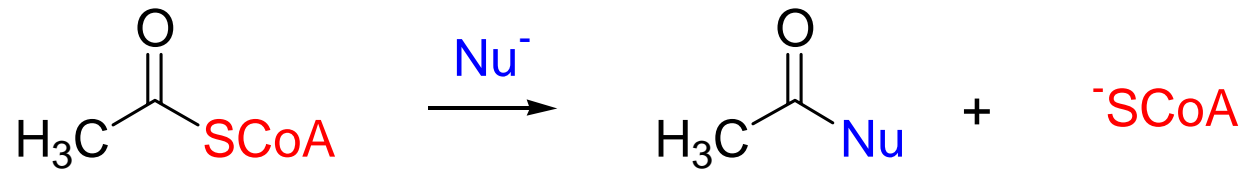


- oxygen atom leaves as an aluminate anion



21.8 Thiol Esters and Acyl Phosphate: Biological Carboxylic Acid Derivatives

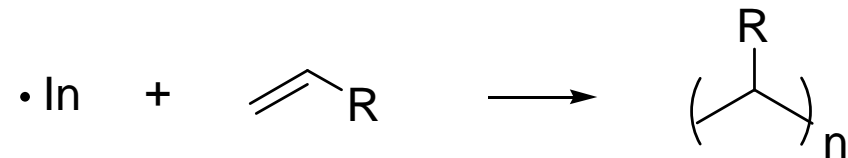




21.9 Polymers and Polyesters: Step-Growth Polymers

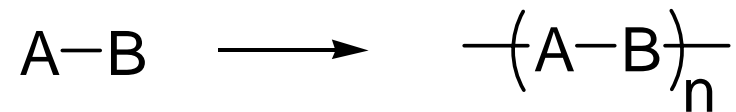
Chain-growth polymers:

chain-reaction process of one type of monomer

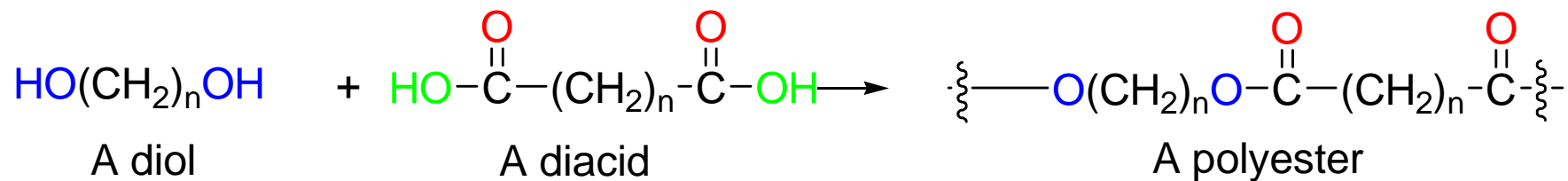
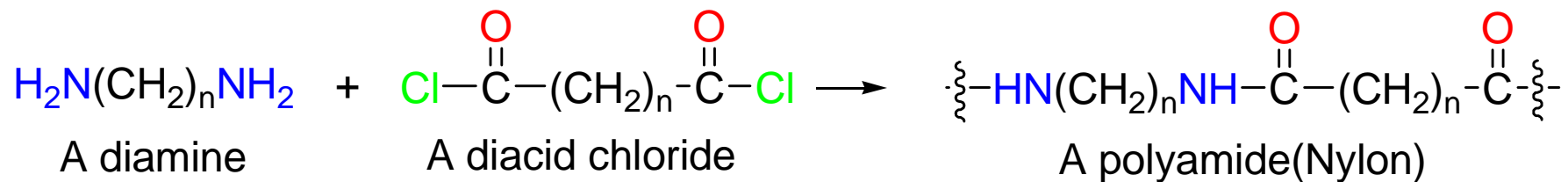


Step-growth polymers:

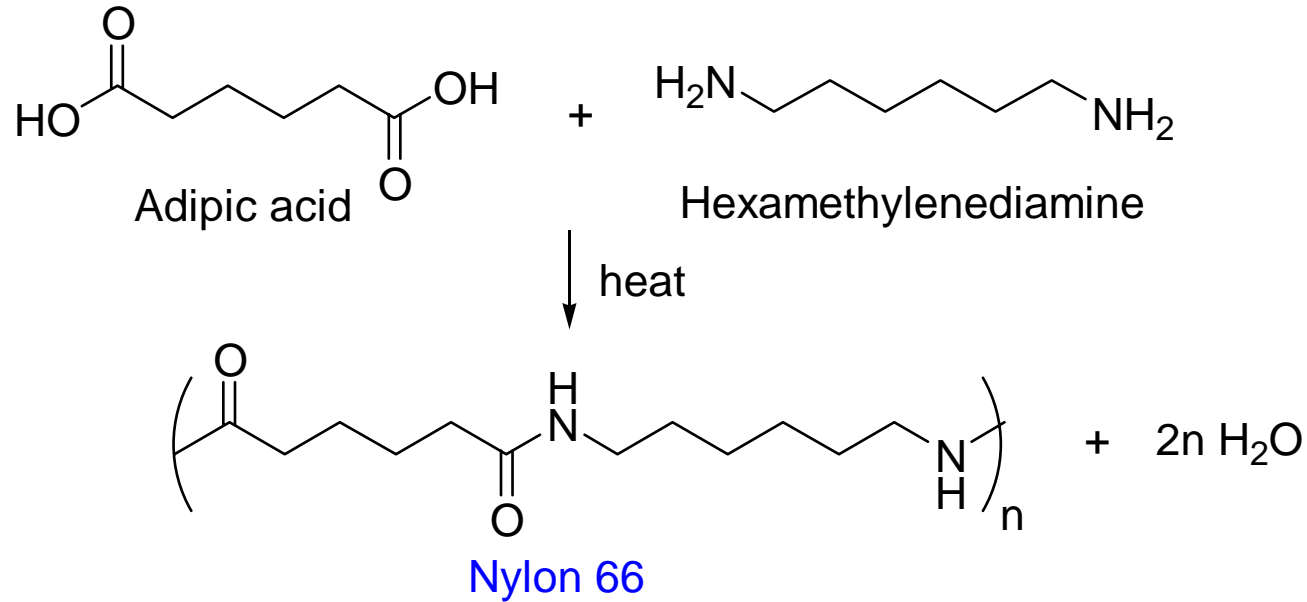
polymerization between two difunctional molecules



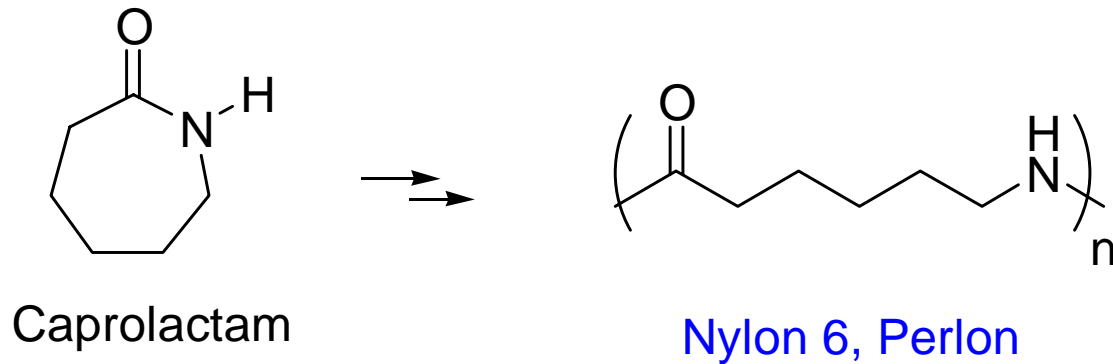
Step-growth polymers:



Nylons: polyamide = diamine + diacid

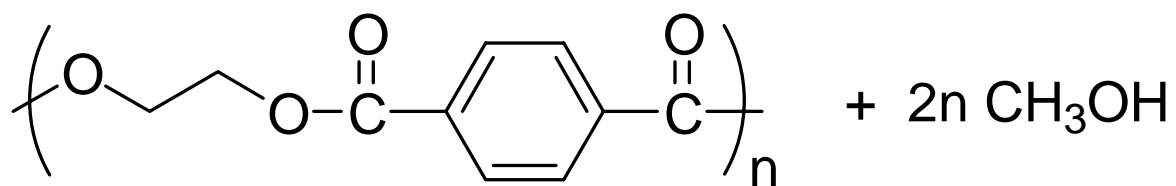
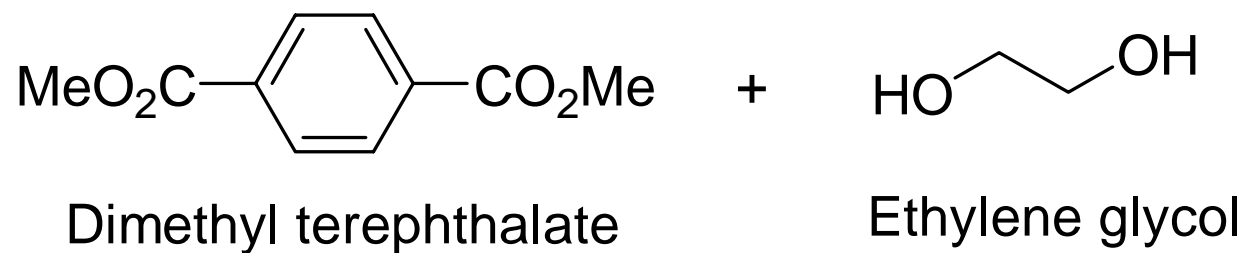


Fibers,
clothing,
tire cord,
bearings



Fibers,
large cast articles

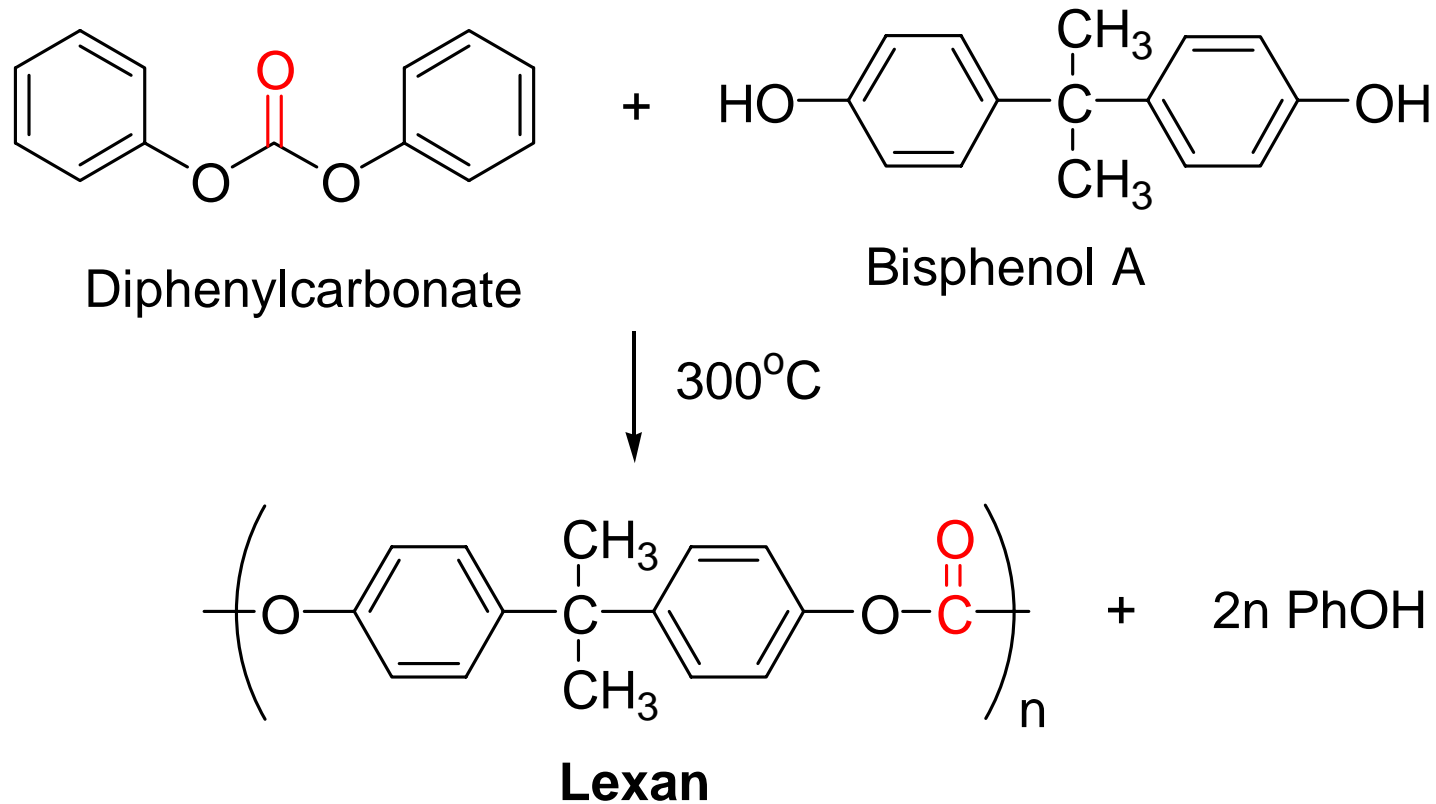
Polyesters: dialcohol + diacid



Polyester, Dacron, Mylar

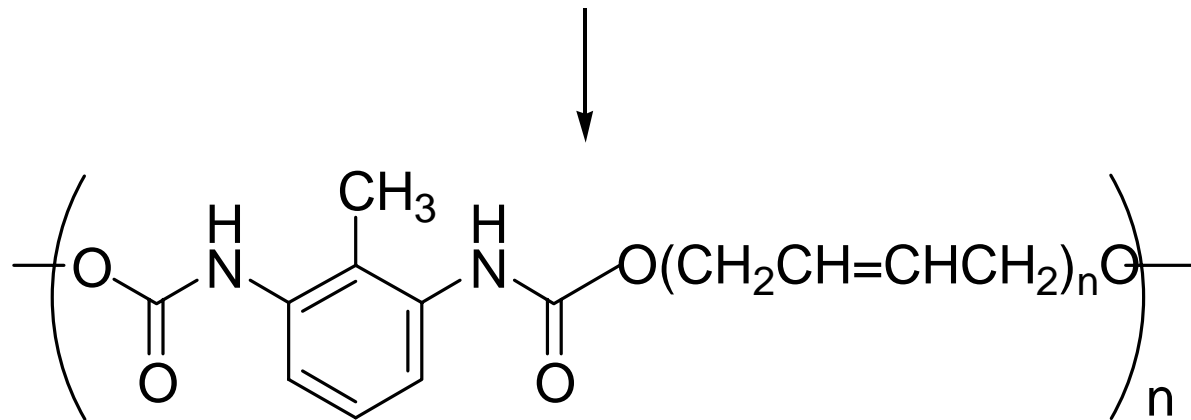
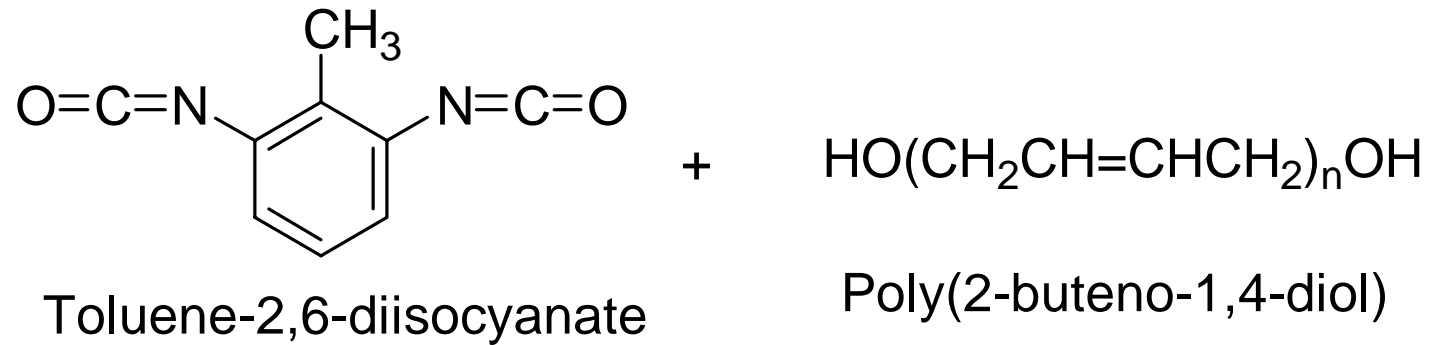
Fibers,
clothing,
tire cord,
film

Polycarbonate: dialcohol + carbonate



- high impact strength; machinery housing, telephone, safety helmet

Polyurethane: dialcohol + diisocyanate



Spandex

- foams, fibers, coatings

21.10 Spectroscopy of Carboxylic Acid Derivatives

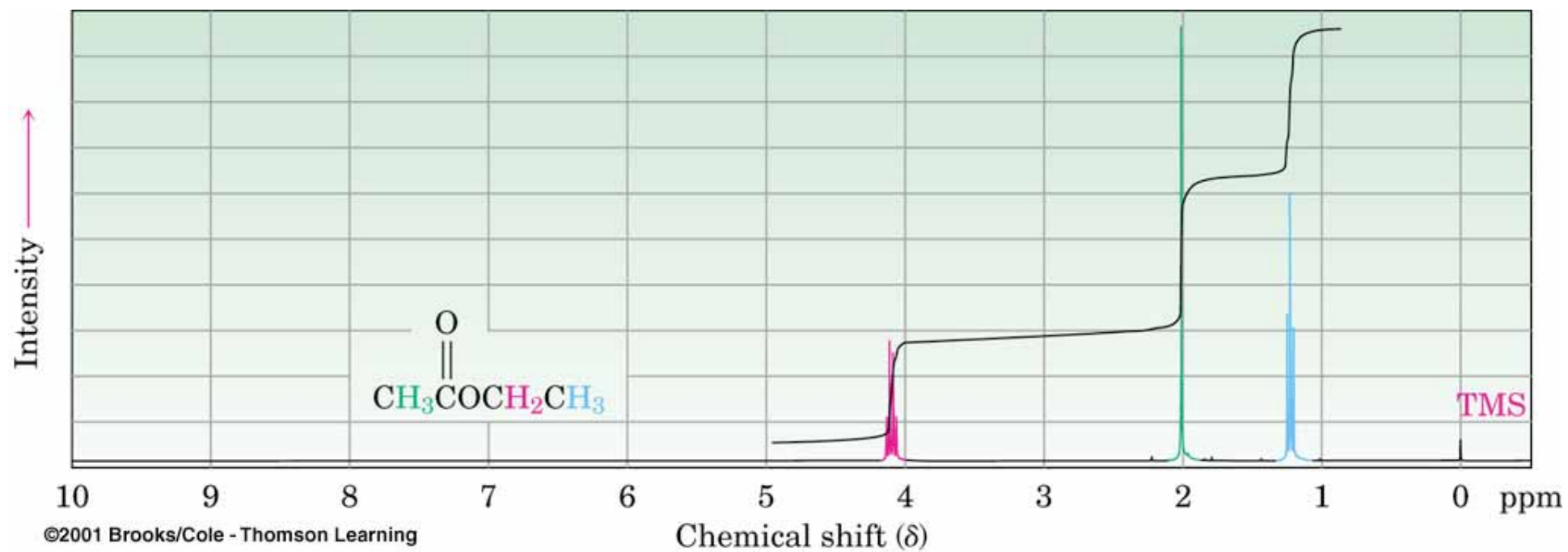
IR Spectroscopy

CO	1650-1850 cm^{-1}
RCOCl	1800 cm^{-1}
RCOOR'	1735 cm^{-1}

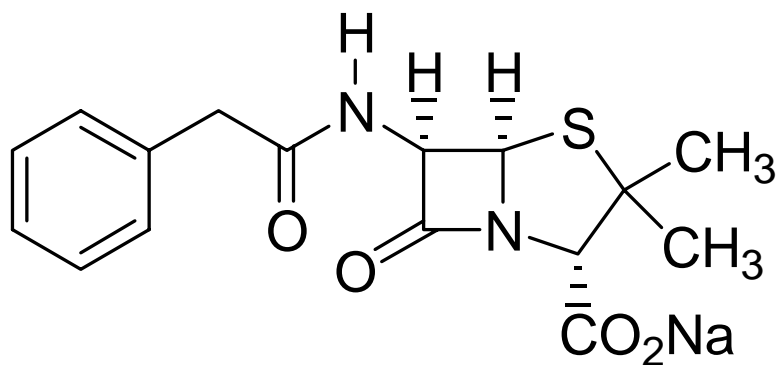
NMR Spectroscopy

^1H NMR	CHCOY	~ 2 ppm,
^{13}C NMR	acid derivatives	160-180 ppm
	aldehyde, ketone	200 ppm

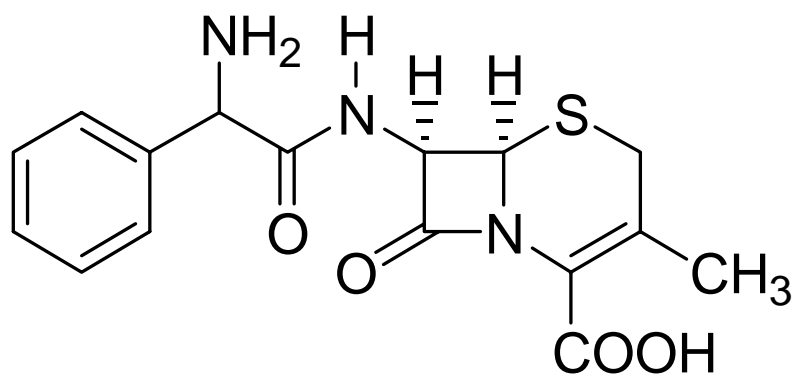
^1H NMR Spectrum



β -lactam antibiotics: four membered lactam ring
; block bacterial cell wall synthesis



Penicillin G

Cephalexin
(a cephalosporin)

Problem Sets

Chapter 21

32, 36, 37, 42, 53, 62