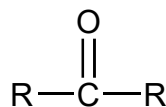


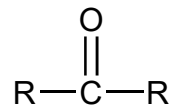
- I. Physical Properties (20.3)
- II. Preparation of RCO_2H (20.4)
 - A) oxidation of aldehydes and 1° alcohols (12.10) and ozonolysis of alkynes (9.9)
 - B) organometallic reagents + CO_2
 - C) hydrolysis of carboxylic acid derivatives (RCN , RCOLG) **SkillBuilder 20.1**
- III. Preparation of Carboxylic Acid Derivatives
 - A) features of the leaving group, LG (20.7)
 - B) acid halides (20.8)
 - C) anhydrides (20.9)
 - D) esters (20.10)
 - E) amides (20.12)
- IV. Reactions of Carboxylic Acids and Derivatives with Nucleophiles (20.11, 20.12)
 - A) reduction reactions of carboxylic acids and derivatives (12.4) **SkillBuilder 12.4**
 - B) organometallic reagents (12.6)
 - C) special reagents (if time allows)
- V. Synthesis (20.14) **SkillBuilder 20.2, SkillBuilder 20.3**
- VI. Nomenclature (20.1, 20.2)

Read on your own:
Spectroscopy (section 20.15)

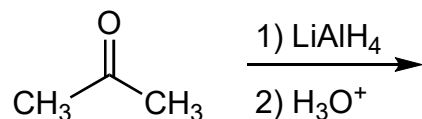
Review Reactions of Ketone/Aldehyde



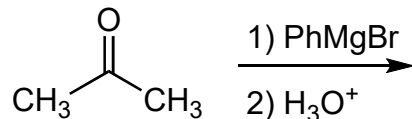
Carbonyl Reactivity:



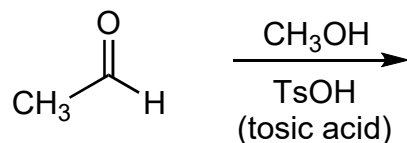
Nucleophile = hydride (reduction)



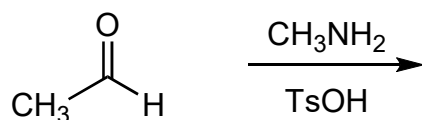
Nucleophile = Grignard

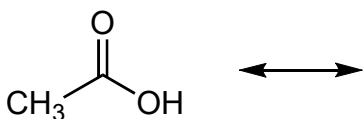


Nucleophile = alcohol



Nucleophile = amine

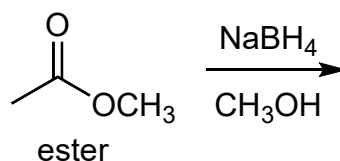
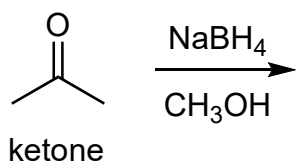




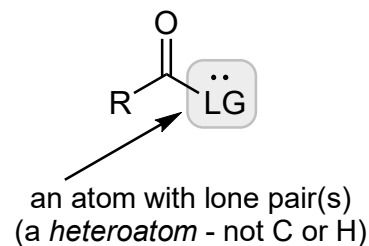
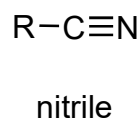
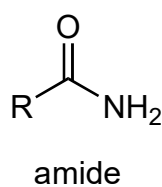
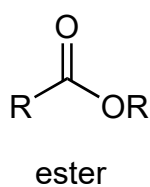
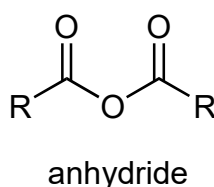
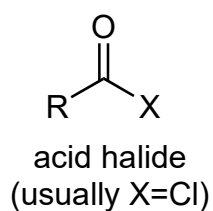
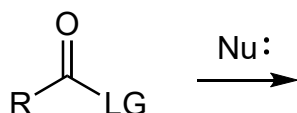
Carboxylic Acid

- OH group _____ electron density to carbonyl
- RCO_2H is _____ electron-rich than ketone/aldehyde
- ketone/aldehyde is more δ^+ , better electrophile (E^+)

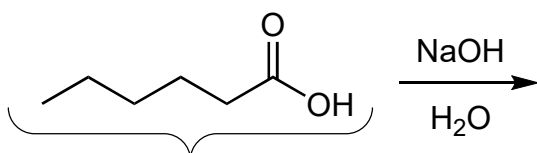
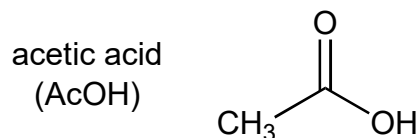
Ketone vs. Ester Reactivity

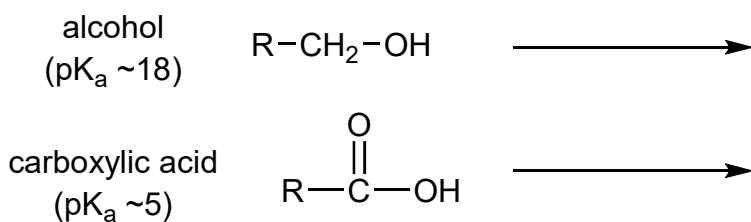
**Carboxylic Acid Derivatives**

General structure:

**General Reactions of Carboxylic Acid Derivatives**

- overall, a substitution reaction
- *acyl substitution* mechanism described as "addition-elimination"
- has both acid- and base-catalyzed mechanisms

I. Physical Properties of Carboxylic Acids (20.3)insoluble in neutral H_2O , but soluble in basic H_2O (aq. NaOH)



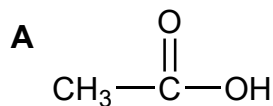
**** In basic conditions (HO^-/RO^-), RCO_2H becomes RCO_2^- ****

Why are pK_a 's so different? Look at conjugate bases!

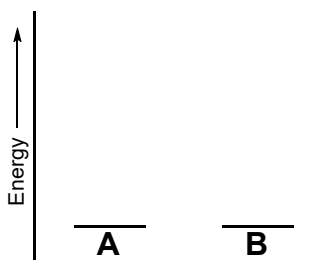
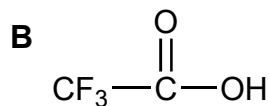


**** Something that will stabilize the conjugate base will make a stronger acid ****

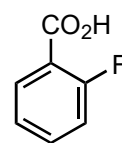
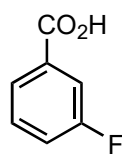
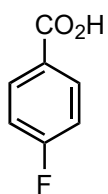
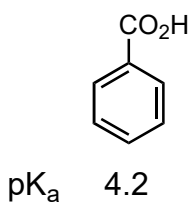
Which is the stronger acid?



vs.



Note: Inductive effects decrease with distance

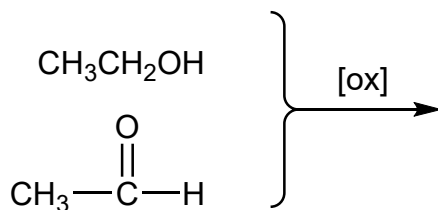


II. Preparation of Carboxylic Acids, RCO₂H (20.4)

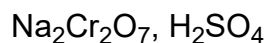
20-4

A) Preparation of RCO₂H by oxidation

Oxidation of aldehydes or primary alcohols

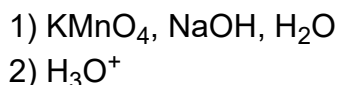


oxidizing agents [ox]



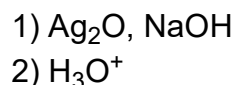
(chromic acid)
(Jones)

or



(permanganate)

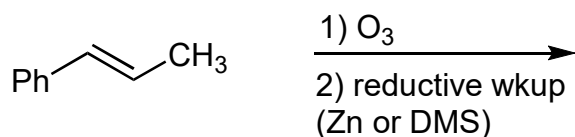
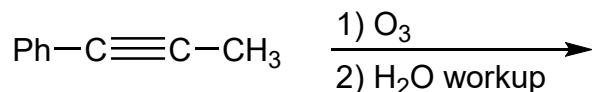
or



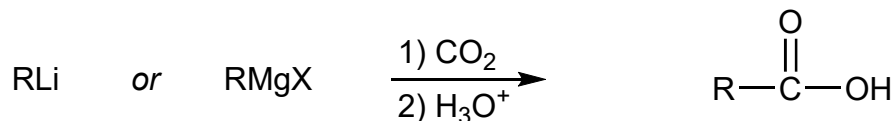
(Tollens)

**** Note: basic reaction conditions require acidic workup to get *neutral* carboxylic acid product ****

Oxidation of alkenes or alkynes (ozonolysis)



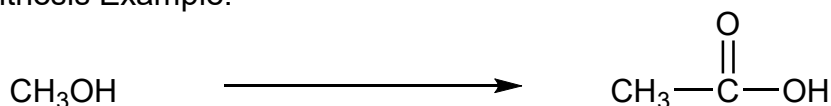
B) Preparation of RCO₂H from Organometallic Reagents

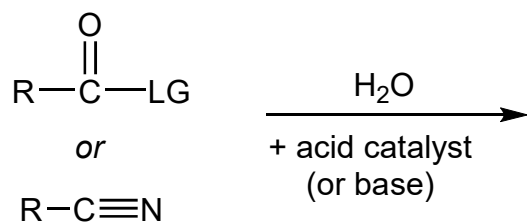


**** use in synthesis:
new C-C bond! ****

mechanism:

Synthesis Example:

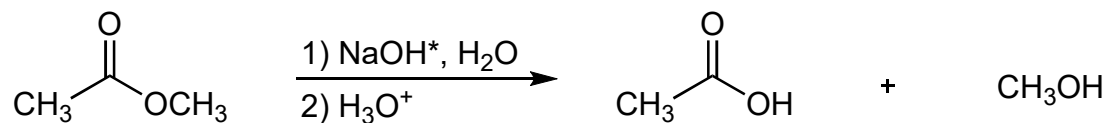




**** All carboxylic acid derivatives give RCO_2H (or RCO^-) upon hydrolysis ****



Ester example:



***Base-promoted** (not "catalyzed" because base is consumed)

Hydrolysis mechanism (base-promoted):

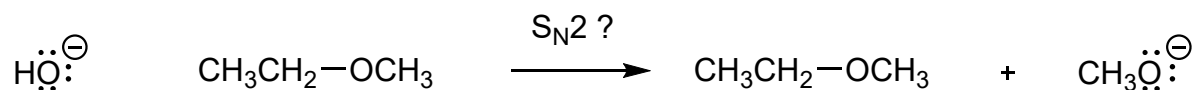


Overall, this is a substitution reaction

Nu: =

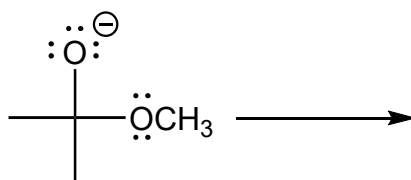
LG =

-- RO^- is bad LG for $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$



-- RO^- is okay LG for collapse of CTI

charged tetrahedral
intermediate (CTI)
(2 groups with lone pairs)

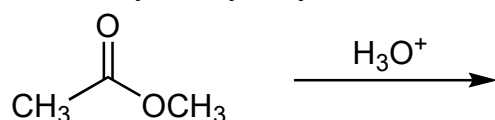


Base-promoted ester hydrolysis is called "saponification" (makes soap)

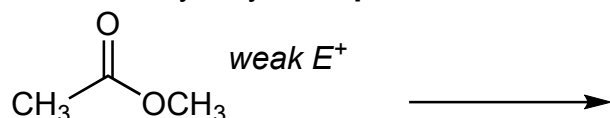
20-6

History: animal fat + wood ash \longrightarrow soap!

Acid-catalyzed hydrolysis mechanism...no \ominus charges!



Note: ester hydrolysis **requires** acid or base (not neutral H_2O)



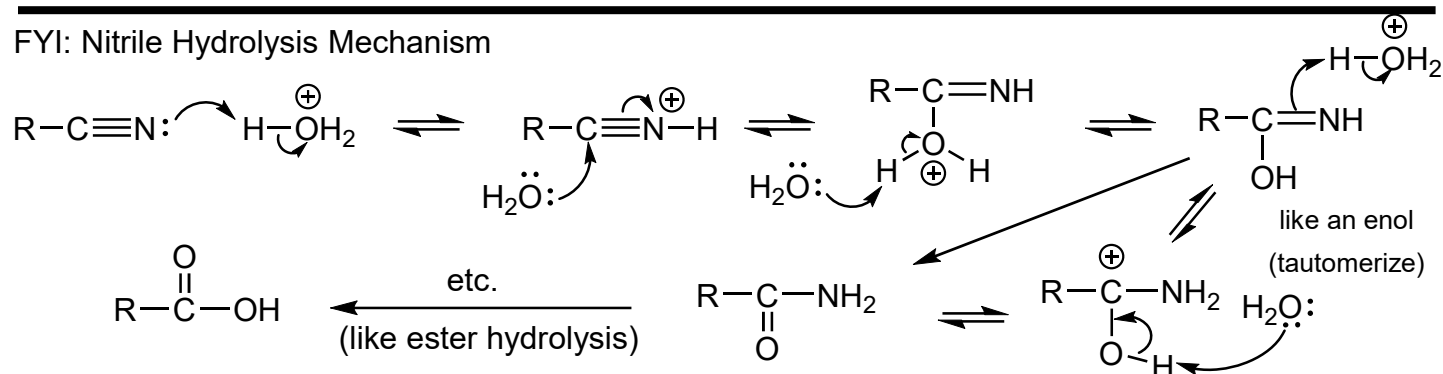
$\text{H}_2\ddot{\text{O}}:$ weak Nu:

In basic conditions:
strong Nucleophile (Nu^-)

In acidic conditions:
strong Electrophile (E^+)

Try SkillBuilder 20.1

FYI: Nitrile Hydrolysis Mechanism



Use of nitriles in synthesis

$:\text{C}\equiv\text{N}^-$ is a good nucleophile

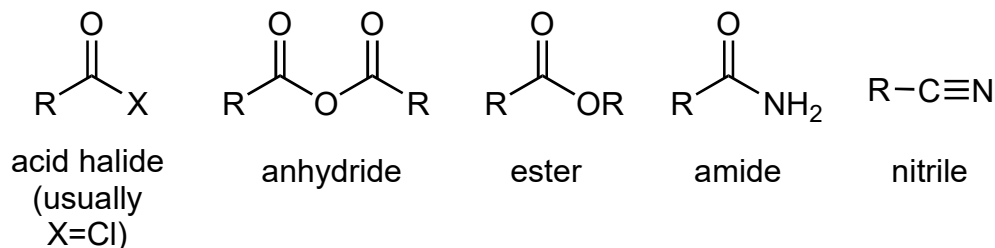
Example:



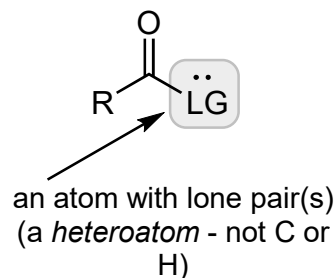
III. Preparation of Carboxylic Acid Derivatives

20-7

Carboxylic Acid Derivatives

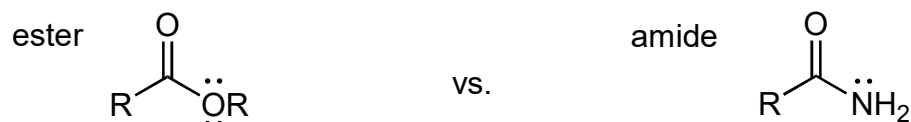


General structure:



A) features of the leaving group, LG (20.7)

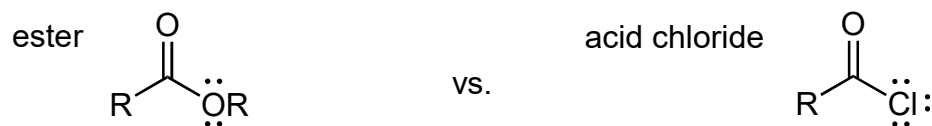
Which is the better electrophile/ E^+ , an ester or an amide?



inductive effects: ** Oxygen is more electronegative than nitrogen

resonance effects:

Which is the better electrophile/ E^+ , an ester or an acid chloride?



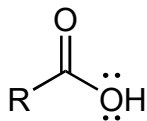
inductive effects: ** Both oxygen and chlorine atoms withdraw electron density

resonance effects:

Which is the better electrophile/ E^+ , a carboxylic acid or an anhydride?

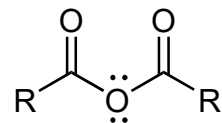
20-8

carboxylic acid



vs.

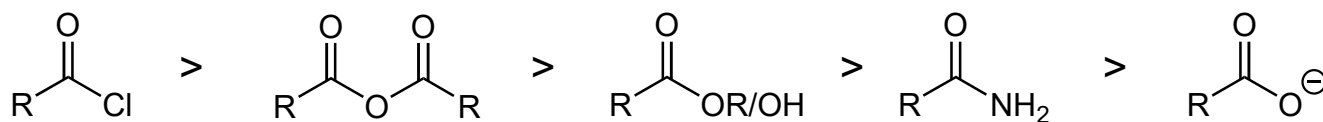
anhydride



inductive effects: ** Both have oxygen atoms withdrawing electron density

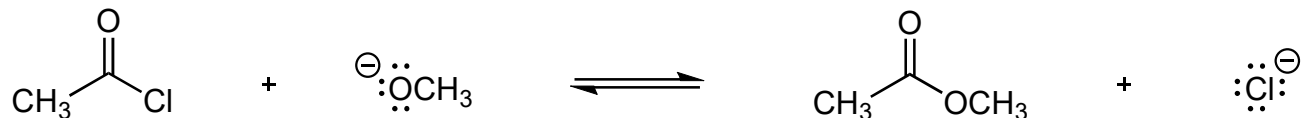
resonance effects:

Summary: Order of Electrophilicity and Leaving Group Ability

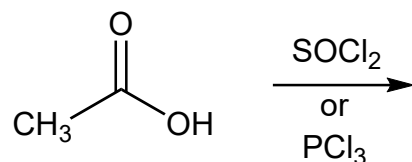


LG:

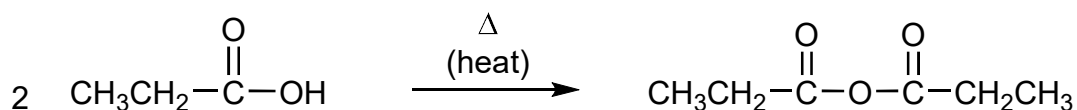
Carboxylic Acid Derivative Interconversion



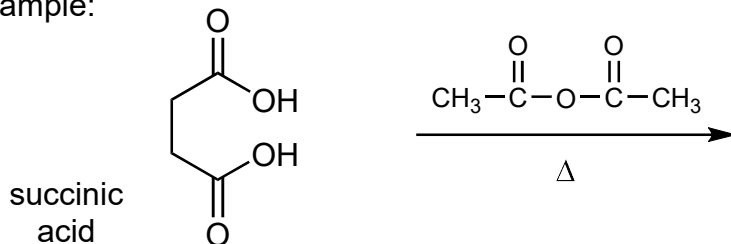
****Can use acid chloride to make any other derivative!**** (so, how do we make the acid chloride?!)



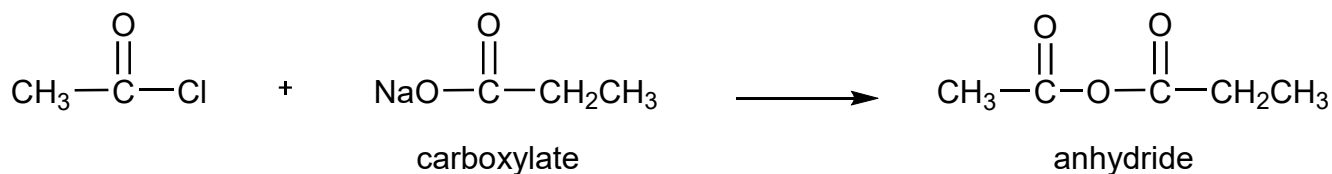
a) Dehydration of carboxylic acids (to prepare symmetrical anhydrides)



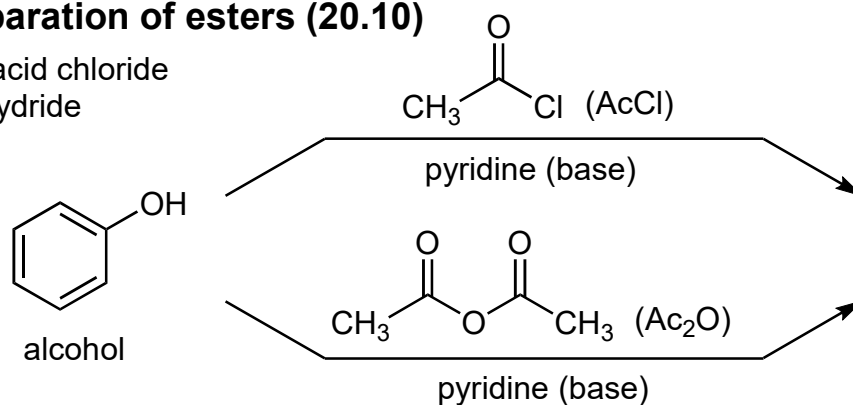
Example:



b) From an acid chloride (to make a mixed anhydride)



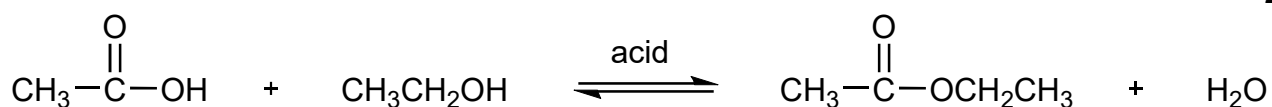
b) From an acid chloride
or an anhydride



**** called an "acylation" reaction ****

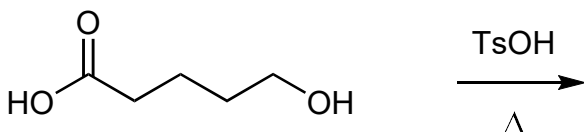
b) Preparation of esters from carboxylic acids (Fischer Esterification)

20-10

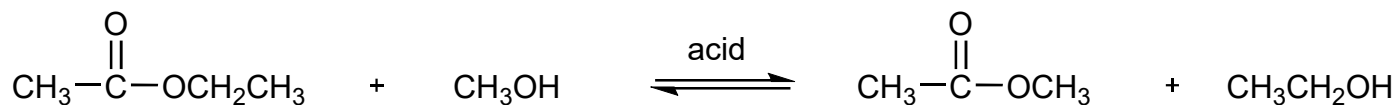
acid (HA) = H₂SO₄, TsOH, HCl (not H₃O⁺)

mechanism? addition/elimination! (exact reverse of hydrolysis)

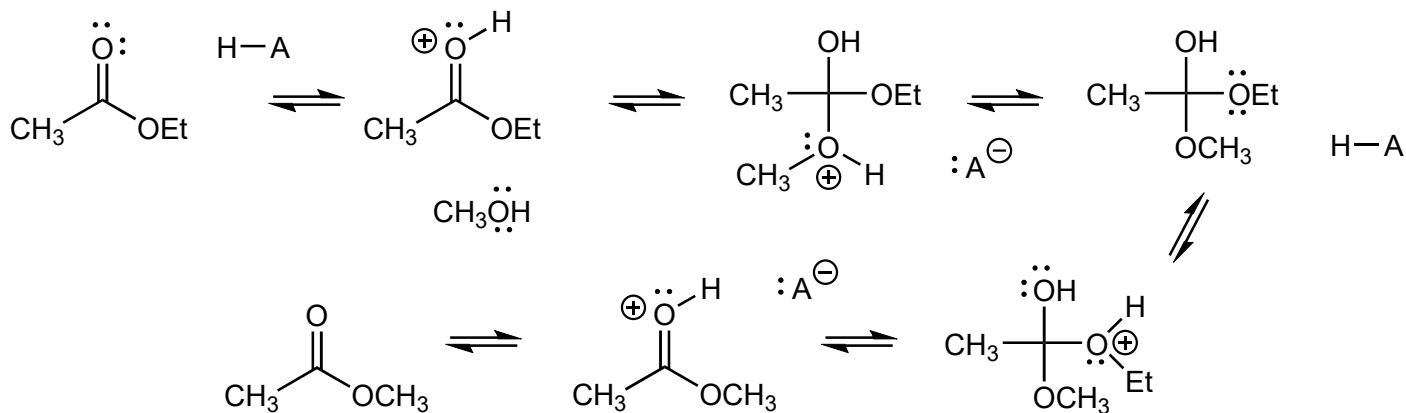
Example: Predict the Product



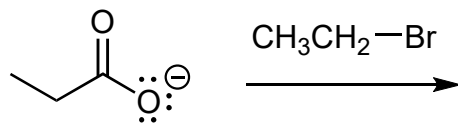
c) Preparation of esters by transesterification



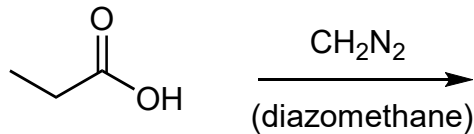
mechanism (add curved arrows): *equilibrium can be shifted by removal of ROH or excess ROH*



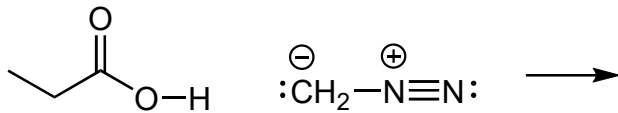
d) Preparation of esters by S_N2 with carboxylate



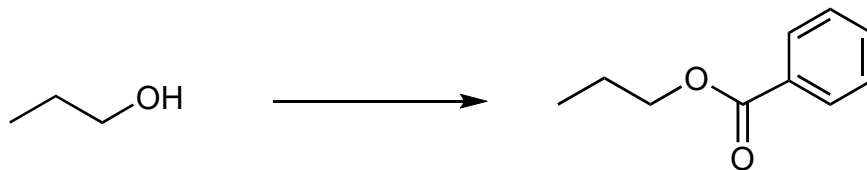
Example: using diazomethane to make a methyl ester



mechanism



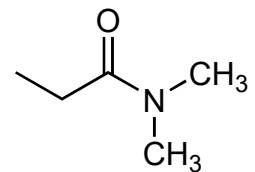
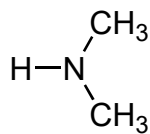
Example: Transform



III. E) Preparation of amides (20.12)

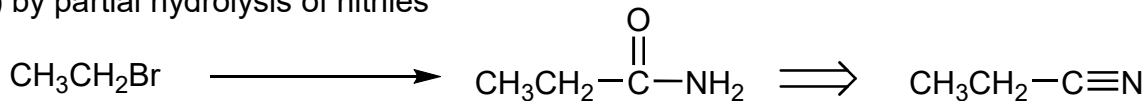
a) from an acid chloride
or an anhydride

often use TWO
equivalents of amine to
react with acid byproduct

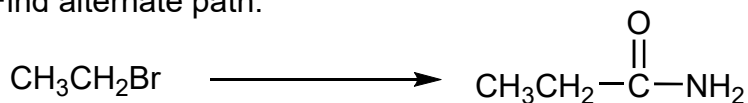


(+ HCl)
or (+ $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$)

b) by partial hydrolysis of nitriles

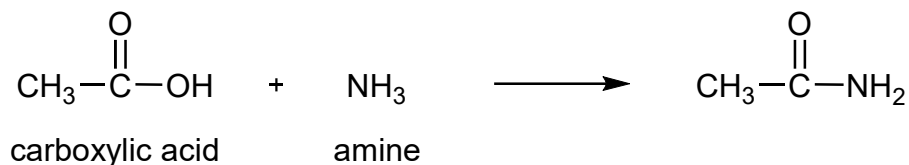


Find alternate path:



c) Amides cannot be easily prepared from RCO_2H directly!

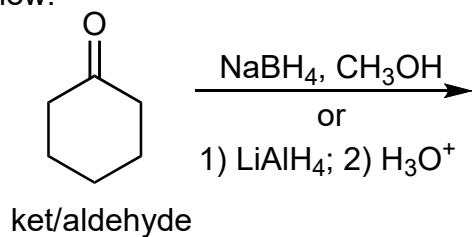
20-12



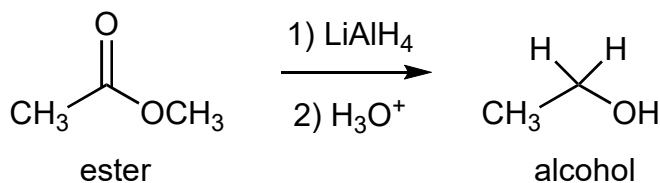
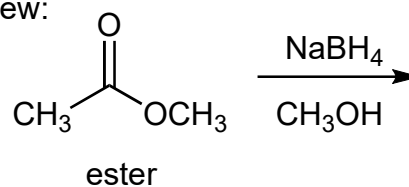
IV. Reactions of Carboxylic Acids and Derivatives with Nucleophiles (20.11-12)

A) Reaction with hydride nucleophile (a reduction reaction) (12.4)

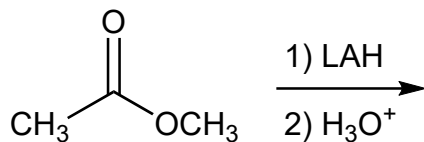
Review:

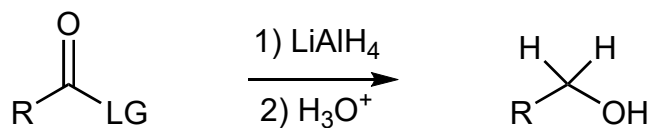


Review:



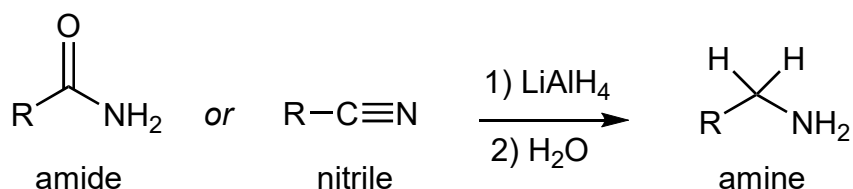
mechanism:





R = OH, OR, Cl, OCOR

alcohol

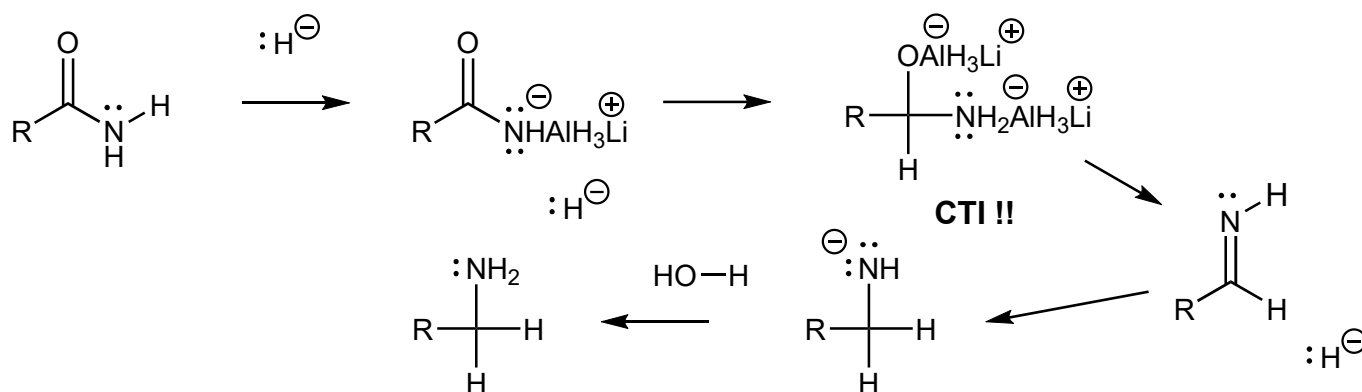


amide

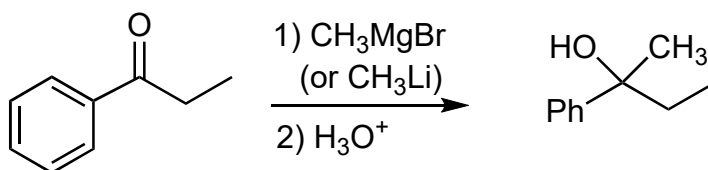
nitrile

amine

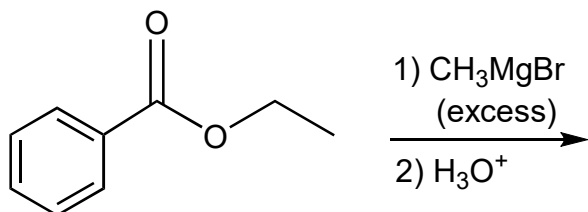
FYI mechanism for hydride reduction of amides (add missing arrows)

**B) Reaction with Grignard nucleophile (12.6, 20.11)**

Review:

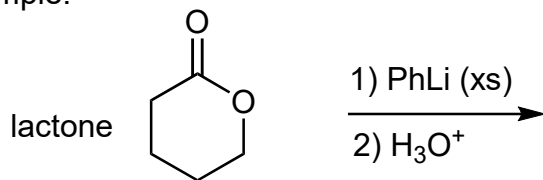
ketone or
aldehyde

ester



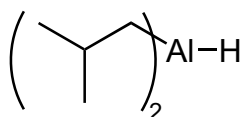
Example:

20-14

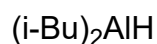


C) FYI: Special hydride and organometallic reagents

Diisobutylaluminum hydride (20.11) DIBAL or DIBAH



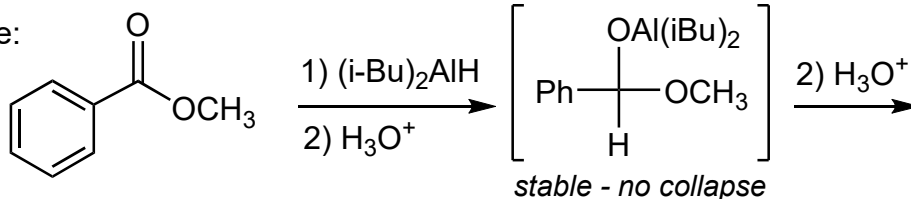
or



** less reactive, more selective than LiAlH₄

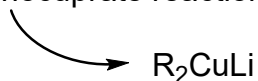
** adds only one equivalent of hydride to ester

Example:



reagents with similar reactivity: Li(t-BuO)₃AlH and NaBH₃CN

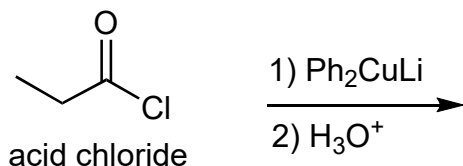
Organocuprate reactions with acid chlorides (20.8)



** organometallic reagent that is less reactive than RMgBr

** adds only one equivalent of "R" to acid chloride

Example:



**** if product is less reactive than starting material, it's possible to stop the reaction ****

Organic Chemistry II CHM 3150, Dr. Laurie S. Starkey, Cal Poly Pomona

Chapter 20 Summary (Klein), Carboxylic Acids & Their Derivatives

- I. Physical Properties (20.3)
 - A) water solubility of RCO_2H and RCO_2Na
 - B) acidity of RCO_2H (see pK_a Table 3.1)
 - i) look at inductive and/or resonance effects to stabilize the conjugate base
- II. Preparation of RCO_2H (20.4)
 - A) oxidation of aldehydes and 1° alcohols (12.10) and ozonolysis of alkynes (9.9)
 - i) $\text{Na}_2\text{Cr}_2\text{O}_7$, H_2SO_4 (chromic acid, Jones)
 - ii) KMnO_4 , NaOH , H_2O (permanganate)
 - iii) Ag_2O , NaOH , H_2O (Tollens test for aldehydes)
 - B) organometallic reagents + CO_2
 - C) hydrolysis of carboxylic acid derivatives, RCN or RCOLG
 - i) *Addition of H_2O /Elimination of LG = acyl substitution*
 - ii) acid- and base-catalyzed mechanisms (**SkillBuilder 20.1**)
 - iii) saponification reaction: lipids, fats, oils and soaps
 - iv) nitrile hydrolysis (20.13) and its use in synthesis (19.10)
- III. Preparation of Carboxylic Acid Derivatives
 - A) features of the leaving group, LG (20.7)
 - i) electrophilicity trends and leaving group ability: compare derivatives!
 - B) acid halides (20.8)
 - C) anhydrides (20.9)
 - D) esters (20.10)
 - E) amides (20.12)
- IV. Reactions of Carboxylic Acids and Derivatives with Nucleophiles (20.11, 20.12)
 - A) reduction reactions of carboxylic acids and derivatives (12.4)
 - i) adds 2 equiv. of LiAlH_4 (LAH) to give an alcohol (N.R. with NaBH_4)
 - ii) mechanism (Mechanism 12.3, **SkillBuilder 12.4**)
 - a) addition of LAH (" H^- " nu:) to $\text{C}=\text{O}$ carbon (E^+)
 - b) collapse of CTI to eliminate LG
 - c) addition of 2nd equiv. of LAH
 - d) protonation of O^- by H_3O^+ workup to give alcohol product
 - iii) exception: LAH reduction of amides and nitriles give amine products
 - B) organometallic reagents (12.6, Mechanism 12.5)
 - i) adds 2 equiv. of RMgX or RLi to give an alcohol product
 - ii) mechanism: same as above but carbon nu: (" R^- ") instead of hydride, " H^- "
 - C) FYI: special reagents (cuprates, modified LAH)
- V. Synthesis (20.14, **SkillBuilder 20.2**, **SkillBuilder 20.3**)
- VI. Nomenclature (20.1, 20.2)
 - A) alkanonic acid (RCO_2H)
 - B) alkanoyl halide (RCOX)
 - C) alkanonic anhydride (RCO_2COR)
 - D) alkyl' alkanooate ($\text{RCO}_2\text{R}'$)
 - E) alkanamide (RCONH_2), *N*-alkyl'alkanamide (RCONHR')
 - F) alkanenitrile (RCN)