Reaction Mechanisms (see p. 310)

A. Recognizing/Classifying as Radical, Cationic, or Anionic

1. Radical
   ▪ initiation requires both energy (either hv or Δ) and a weak, breakable heteroatom-heteroatom bond
      o   Cl-Cl, Br-Br, O-O (peroxide), N-Br, etc..

   ┌─────────────────────────────────────┐
   │ 2 Guides for That are Usually Reliable: │
   │ hv → radical mechanism   │
   │ peroxides → radical mechanism   │
   └─────────────────────────────────────┘

2. Anionic
   ▪ **a strong anion/base appears in the recipe**
   ▪ no strong acids should appear in the recipe
   ▪ mechanisms should involve anionic intermediates and reactants, not strongly cationic ones
      • (except for do-nothing spectators like metal cations)
   ▪ The first step in the mechanism will involve the strong anion/base that appears in the recipe

3. Cationic
   ▪ **a strong acid/electrophile appears in the recipe**
   ▪ no strong anion/base should appear in the recipe
   ▪ mechanisms should involve cationic intermediates and reactants, not strongly anionic ones
      • (except for do-nothing spectators like halide or hydrogen sulfate anions)
   ▪ The first step in the mechanism will involve the acid that appears in the recipe. The last step will often involve a deprotonation step. Often the main step occurs in between the proton-on and proton-off steps

B. Miscellaneous Mechanism Tips

   1. Keep track of hydrogens on reacting carbons
   2. **Each step in a mechanism must balance**
   3. The types of intermediates involved (cation, anion, or radical) should be consistent with the reaction classification above
      a. **If the reaction is cationic, don't show anionic intermediates**
      b. **If the reaction is anionic, don't show cationic intermediates**
   4. Usually conditions are ionic.
   5. **Use a reactive species, whether strong anion or an acid, to start the first step**
      a. **If acidic, first step will involve protonation of the organic**
      b. **If anionic, the first step will involve the anion attacking the organic.**
   6. While it isn't always easy to figure out what is a good mechanism, you should often be able to eliminate an unreasonable mechanism.

Some Arrow-Pushing Guidelines (Section 1.14)

1. Arrows follow <u>electron movement</u>.

2. Some rules for the appearance of arrows
    *   The arrow must begin from the electron source. There are two sources:
        a. An atom (which must have a lone pair to give)
        b. A bond pair (an old bond that breaks)
    *   An arrow must always point directly to an <u>atom</u>, because when electrons move, they always go to some new atom.

3. Ignore any Spectator Atoms. Any metal atom is always a "spectator"
    *   When you have a metal spectator atom, realize that the non-metal next to it must have negative charge

4. Draw all H's on any Atom Whose Bonding Changes

5. Draw all lone-pairs on any Atom whose bonding changes

6. **KEY ON BOND CHANGES**.   Any two-electron bond that changes (either made or broken) must have an arrow to illustrate:
    *   where it came from (new bond made) or
    *   an arrow showing where it goes to (old bond broken)

7. **Watch for Formal Charges and Changes in Formal Charge**
    *   If an atom's charge <u>gets more positive</u> Þ it's donating/losing an electron pair Þ <u>arrow must emanate from that atom or one of it's associated bonds.</u>   There are two "more positive" transactions:
        *   <u>When an anion becomes neutral.</u> In this case, an arrow will emanate from the atom. The atom has donated a lone pair which becomes a bond pair.
        *   <u>When a neutral atom becomes cationic.</u> In this case, the atom will be losing a bond pair, so the arrow should emanate from the bond rather than from the atom.

    *   If an atom's charge <u>gets more negative</u> Þ it's accepting an electron pair Þ <u>an arrow must point to that atom.</u> Ordinarily the arrow will have started from a bond and will point to the atom.

8. **When bonds change, but Formal Charge Doesn't Change, A "Substitution" is Involved**
    *   Often an atom gives up an old bond and replaces it with a new bond. This is "substitution".
    *   In this case, there will be an incoming arrow pointing directly at the atom (to illustrate formation of the new bond), and an outgoing arrow emanating from the old bond that breaks

4.16 Reactive Intermediates: Stability Patterns

- Shortlived, unstable, highly reactive intermediates
- Normally lack normal bonding

These are tremendously important:
1. They will be the **least stable intermediate** in any multistep mechanism
2. When formed, they are **products of the rate-determining step**
3. **Factors that stabilize them will speed up reaction rates**

Thus it is very important to know their stability patterns!

Class	Structure	Stability Pattern		
Carbocations	$-\overset{\vert}{\underset{\vert}{C}}\oplus$	Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbon Radicals	$-\overset{\vert}{\underset{\vert}{C}}\cdot$	Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbanions	$-\overset{\vert}{\underset{\vert}{C}}\colon\ominus$	Allylic > alkenyl (vinyl, aryl) > methyl > 1º > 2º > 3º	Electron Rich	Nucleophilic/ Basic

Notes
1. Both carbocations and radicals have the same pattern. So you don't need to memorize them twice!
2. Carbanions are almost exactly the reverse, except that being allylic is ideal for both.
3. All benefit from resonance (allylic).
4. Cations and radicals both fall short of octet rule. As a result, they are both electron deficient. Carbanions, by contrast, are electron rich.
5. Alkyl substituents are electron donors. As a result, they are good for electron deficient cations and radicals (3º > 2º > 1º > methyl) but bad for carbanions.
6. Alkenyl (vinyl or aryl) carbons are inherently a bit electron poor. This is excellent for carbanions, but terrible for cations or radicals.

Stability/Reactivity/Selectivity Principles

1. **Reactant Stability/Reactivity**: The <u>more stable the reactant</u>, the <u>less reactive</u> it will be. In terms of rates, this means that the <u>more stable the reactant,</u> the slower it will react. (The concept here is that the more stable the reactant, the more content it is to stay as is, and the less motivated it is to react and change into something different)
   **Key note:** Often the "reactant" that's relevant in this context will not be the original reactant of the reaction, but will be the "reactant" involved in the rate determining step.

   • **Basicity**
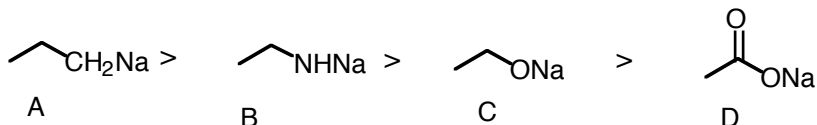
   $\sim\text{CH}_2\text{Na} >$ $\sim\text{NHNa} >$ $\sim\text{ONa} >$ $\underset{\text{O}}{\overset{\text{O}}{\sim}}\text{ONa}$
   A   B   C   D

   Why: As anion stability increases from A to D, the reactivity decreases

   • **Nucleophilicity**

   $\sim\text{CH}_2\text{Na} >$ $\sim\text{NHNa} >$ $\sim\text{ONa} >$ $\underset{\text{O}}{\overset{\text{O}}{\sim}}\text{ONa}$
   A   B   C   D

   Why: As anion stability increases from A to D, the reactivity decreases

   • **Nucleophilicity**

   $\sim\text{SeNa} >$ $\sim\text{SNa} >$ $\sim\text{ONa} >$ $\underset{\text{O}}{\overset{\text{O}}{\sim}}\text{ONa}$
   A   B   C   D
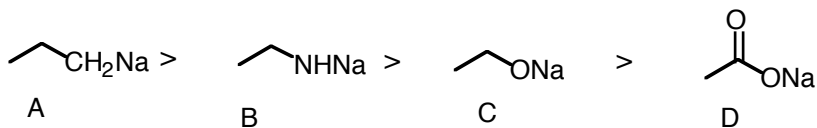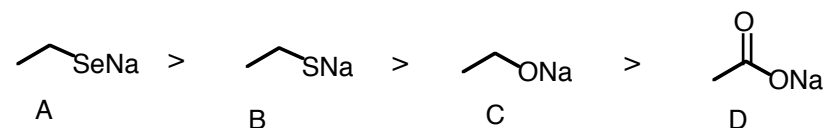
   Why: As anion stability increases from A to D, the reactivity decreases

   ---
   | |
   | • **Reactivity toward alkanes via radical halogenation** |
   | |
   | $F_2 > Cl_2 > Br_2 > I_2$ because $F\cdot > Cl\cdot > Br\cdot > I\cdot$ |
   | |
   | Why: Chlorine is more reactive the bromine because chlorine radical is less stable then bromine radical. |

   • **Electrophilicity (Reactivity in S_N2, S_N1, E2, E1 Reactions)**

   $\underset{}{\overset{}{\bigvee}}_\text{I}$ $>$ $\underset{}{\overset{}{\bigvee}}_\text{Br}$ $>$ $\underset{}{\overset{}{\bigvee}}_\text{Cl}$
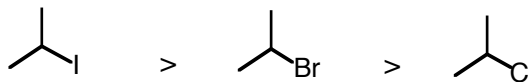
   Why: As carbon-halogen bond stability increases, the reactivity decreases

2. **Product Stability/Reactivity**: The more stable the product, the more favorable its formation will be. In terms of rates, this means that the more stable the product, the faster the reaction. (The concept here is that the more stable the product, the more favorable it will be to make that product.)

   Key note: Often the "product" that's relevant in this context will not be the final product of the reaction, but will be the "product" of the rate determining step.

   - Acidity
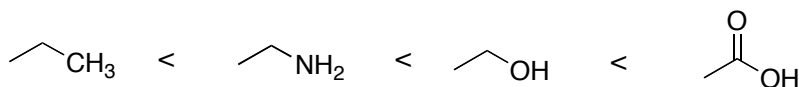
   Why: Because as the stability of the anion products increases from A to D, the reactivity of the parent acids increase
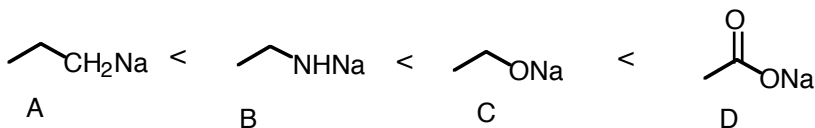
   - **Reactivity of alkanes toward radical halogenation**
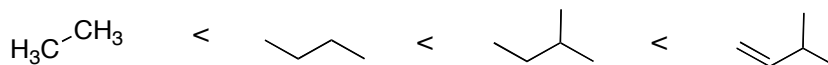
   Why: Because as the stability of the radical produced during the rate-determining-step increases, the reactivity of the parent alkane increases
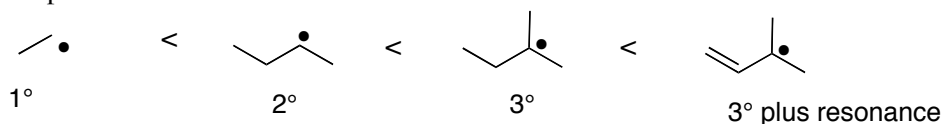
   - **S_N1, E1 Reactivity**
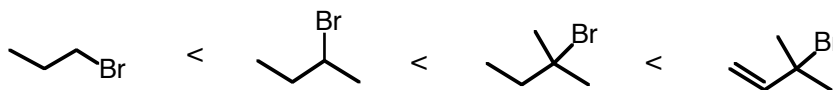
   Why: Because as the stability of the cation produced in the rate-determining step increases, the reactivity of the parent halide increases as well
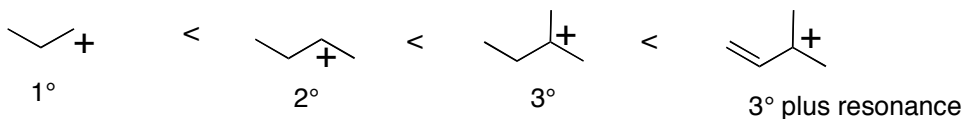
3. **Transition-State Stability/Reactivity**: The more stable the transition state, the faster the reaction will be. (The concept here is that the lower the transition state, the more easily it will be crossed.)

   - **S_N2 Reactivity**
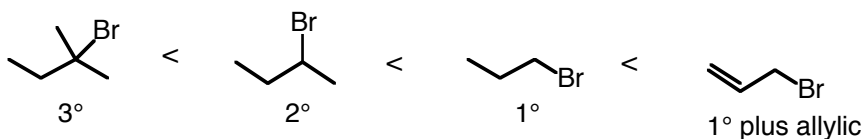
   Why: The pattern reflects the relative stability of the transition states. In the case of 3˚ versus 2˚ versus 1˚, the issue is steric congestion in the transition state. The transition states for the more highly substituted halides are destabilized. In the case of allylic halides, the transition state is stabilized for orbital reasons, not steric reasons.

Summary of Alcohol Syntheses, Ch. 10 (and Review of Old Ones).
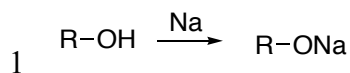
1   R–OH $\xrightarrow{\text{Na}}$ R–ONa

- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

2   R–OH $\xrightarrow[\text{2. R'-X}]{\text{1. Na}}$ R–O–R'

- Alkoxide formation-S_N2 route to ether
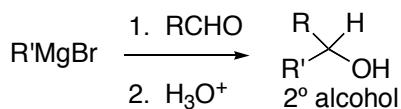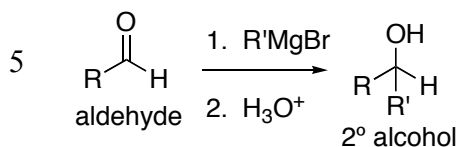- The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group

Mech?

3   R–Br $\xrightarrow{\text{Mg}}$ RMgBr

-Li is analogous for making RLi, which also act analogously.

-MgBr is spectator: $R^{\ominus}$ is key.

4   formaldehyde $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. R'MgBr}}$ 1° alcohol   R'MgBr $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. H}_2\text{CO}}$ 1° alcohol   1 carbon chain extension   Mech

5   aldehyde $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. R'MgBr}}$ 2° alcohol   R'MgBr $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. RCHO}}$ 2° alcohol   Mech
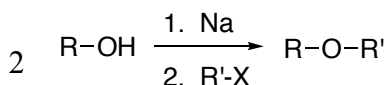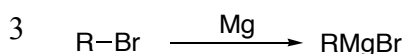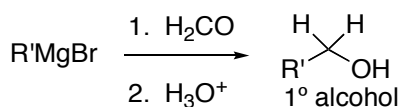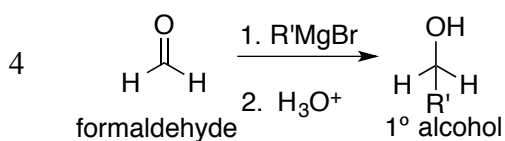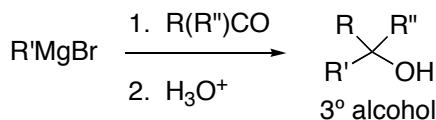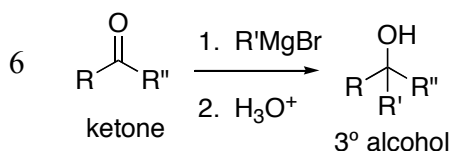
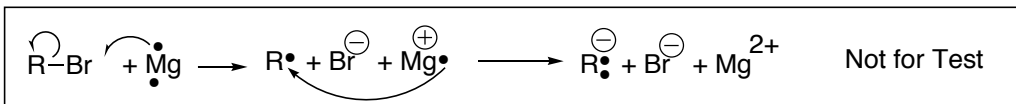**6**   ketone $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. R'MgBr}}$ 3° alcohol   R'MgBr $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. R(R'')CO}}$ 3° alcohol   All three R groups can be different.   Mech
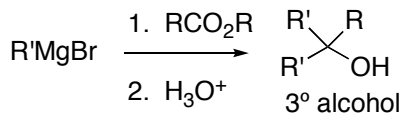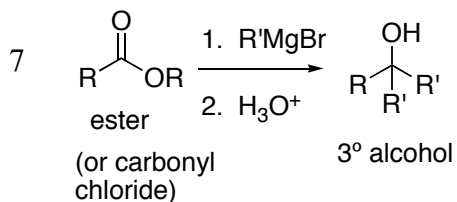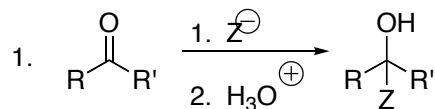
7   ester (or carbonyl chloride) $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. R'MgBr}}$ 3° alcohol   R'MgBr $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. RCO}_2\text{R}}$ 3° alcohol   At least 2 R groups must be the same   Mech

8 ethylene oxide $\xrightarrow[\text{2. } H_3O^+]{\text{1. R'MgBr}}$ R'—CH$_2$—CH$_2$OH 1° alcohol   R'MgBr $\xrightarrow[\text{2. } H_3O^+]{\text{1. }}$ R'—CH$_2$—CH$_2$OH 1° alcohol   2-Carbon chain extension   Mech

9 aldehyde $R\!-\!CHO$ $\xrightarrow[\text{CH}_3\text{OH}]{\text{NaBH}_4}$ or $\xrightarrow[\text{2. } H_3O^+]{\text{1. LiAlH}_4}$ R—CH(OH)—H 1° alcohol   Mech

10 ketone $R\!-\!CO\!-\!R''$ $\xrightarrow[\text{CH}_3\text{OH}]{\text{NaBH}_4}$ or $\xrightarrow[\text{2. } H_3O^+]{\text{1. LiAlH}_4}$ R—CH(OH)—R'' 2° alcohol   Mech

11 ester $R\!-\!CO\!-\!OR$ $\xrightarrow[\text{2. } H_3O^+]{\text{1. LiAlH}_4}$ R—CH(OH)—H 1° alcohol   NaBH$_4$ will not react with esters   Mech
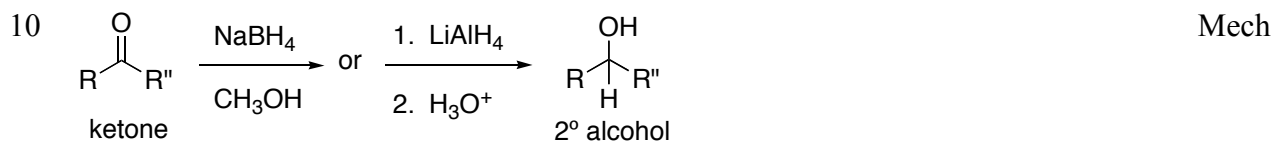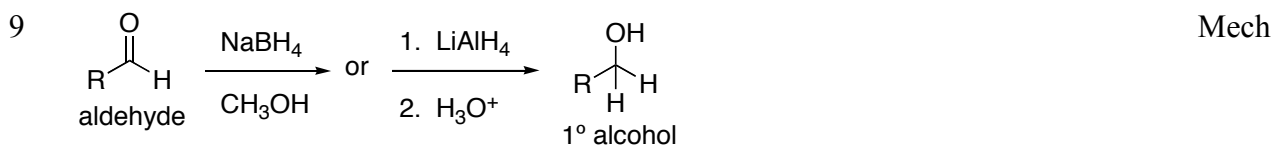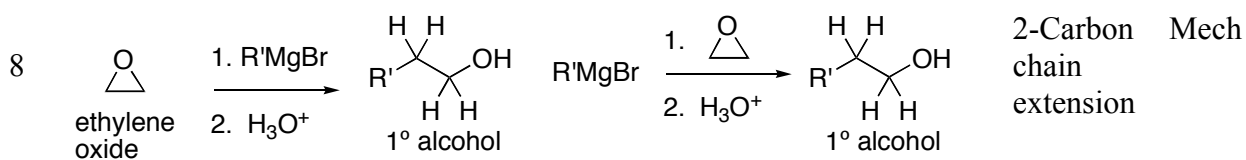
Review Routes to Alcohols

10 R—CH=CH$_2$ $\xrightarrow{\text{H}_2\text{O, H}^+}$ R—CH(OH)—CH$_3$ Markovnikov

11 R—CH=CH$_2$ $\xrightarrow[\text{2. NaBH}_4]{\text{1. Hg(OAc)}_2\text{, H}_2\text{O}}$ R—CH(OH)—CH$_3$ Markovnikov

12 R—CH=CH$_2$ $\xrightarrow[\text{2. H}_2\text{O}_2\text{, NaOH}]{\text{1. BH}_3\text{-THF}}$ R—CH$_2$—CH$_2$OH   anti-Markovnikov

13 R–X $\xrightarrow{\text{NaOH}}$ R–OH   S$_N$2 mech, needs 1° or 2° system and an excellent leaving group
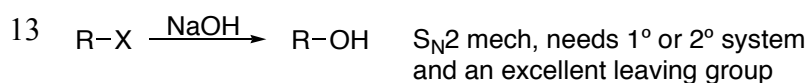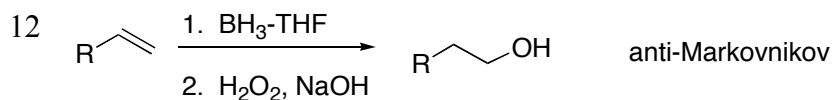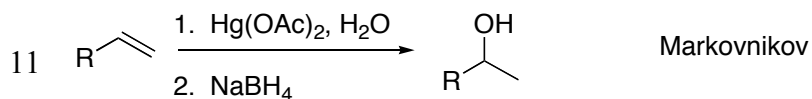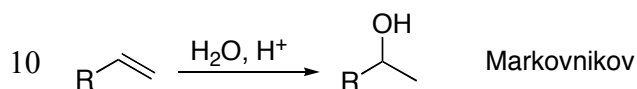
Summary of Mechanisms, Ch. 10

$R-Br + Mg \longrightarrow R\cdot + Br^{\ominus} + Mg^{\oplus}\cdot \longrightarrow R^{\ominus} + Br^{\ominus} + Mg^{2+}$ Not for Test

For Test:

1.

aldehyde
or ketone
or formaldehyde

$Z^{\ominus}$ may be $R^{\ominus}$ (RMgBr)

or $H^{\ominus}$ (NaBH$_4$ or LiAlH$_4$)

mech:

2.
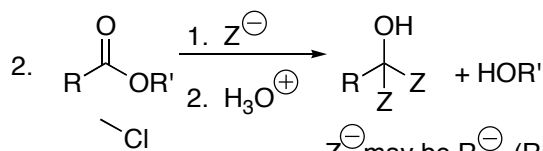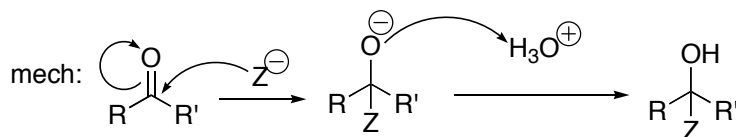
esters
or
acid chlorides

$Z^{\ominus}$ may be $R^{\ominus}$ (RMgBr)

or $H^{\ominus}$ (LiAlH4)

+ HOR'

mech:

3.

mech:
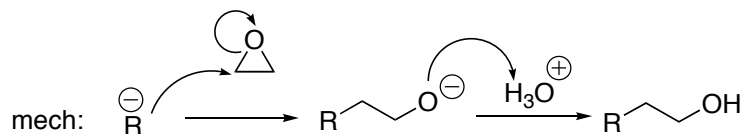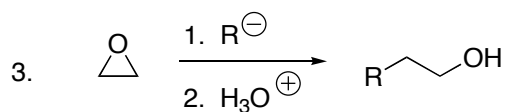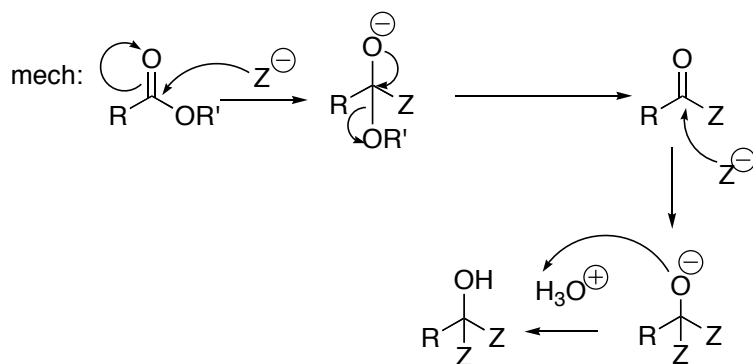
10.1,2 Intro, Classification

"**Alcohol**": OH attached to a saturated, sp^3, "alkyl" carbon

1º, 2º, 3º Alcohols: based on whether the carbon with the OH is 1º, 2º, or 3º
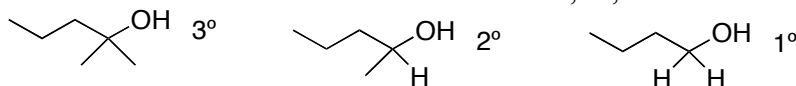
"**Phenol**": OH attached to an aromatic
-Note: phen**ol**, not phen**yl**

4-phenylbut-1-ene

phen**yl**, as substituent
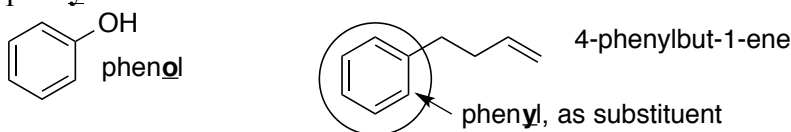
"Enol" or "vinyl alcohol": OH attached to an alkene

enol or vinyl alcohol
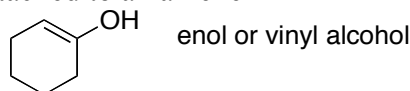
10.3 Nomenclature
A. IUPAC, when alcohol is priority functional group and is part of the core name: alkan-x-**ol**

B. Cycloalkanols: The OH-carbon is automatically Number 1. Don't need "-1-" in front of "ol".

C. **Alk**-x-**en-z-ol**. When an alkene is in the main carbon chain, you need two number descriptors, one for the alkene, the second for the alcohol.

D. Diols: alkane-x,y-**diol**

E. Functional Group Priority: CO_2H > C=O > OH > amine > alkene > halide

F. OH as a Substituent: "**Hydroxy**"

H. Substituted Phenols
  • IUPAC: use numbers, with OH carbon #1
  • Common:
      o **Ortho: 2-position, adjacent**
      o **Meta: 3-position, two carbons away**
      o **Para: 4 position**
  • Skill: be able to use or recognize either system

10.4 Physical Properties: Dominated by H-Bonding
Water solubility: water solubility decreases as hydrophobic R gets longer

10.8 Organometallics: RM (M = Metal) = $R^{\ominus} M^{\oplus}$

R−Br $\xrightarrow{\text{Mg}}$ RMgBr
"Grignard Reagent"

-Li is analogous for making RLi,
which also act analogously.

-MgBr is spectator: $R^{\ominus}$ is key.

R−Br $\xrightarrow{\text{2Li}}$ RLi + LiBr
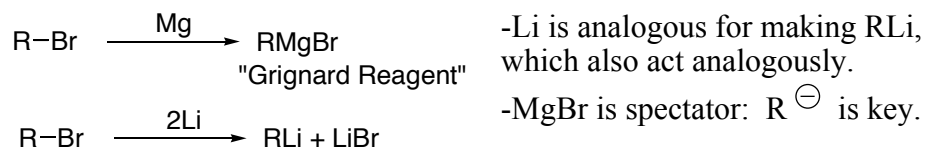
1. Key: This is the way to make $R^{\ominus}$, strong nucleophiles/bases
2. **View as carbanions: RMgBr = $R^{\ominus}$ Super Strong Bases and Nucleophiles**
    • The counterion metal is a spectator
    • Stability-reactivity principle: very unstable → very reactive
    • This great reactivity is very useful (as nucleophile)
3. Solvent and handling:
    • No water, alcohol, amines or acids allowed, or carbanion will just deprotonate them
        ○ $R^{\ominus} + H_2O →$ R-H + $HO^{\ominus}$ Destroys carbanion
    • If any chemicals with carbonyls are present, they too will react with the carbanion by nucleophile/electrophile reaction
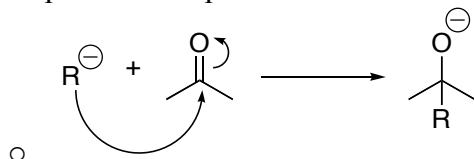
4. Two perspectives for dealing with organometallics in general and RMgBr in particular
    • Mechanistic Thinking: $R^{\ominus}$
    • Predict-the-product thinking: R-MgBr: easier to see source and substitution product.

R−Br $\xrightarrow{\text{Mg}}$ R−MgBr $\xrightarrow{\text{Electrophile}}$ R−Electrophile
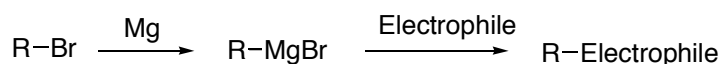
10.9 Addition of RMgBr to Carbonyl Compounds: Alcohols are Produced
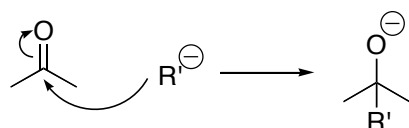
Exothermic Addition of Carbon or Hydrogen Anions:
    • σ bond (made) stronger than π bond (broken)
    • oxygen anion more stable than carbanion

Carbonyl is strongly electrophile
-much stronger even than a 1° alkyl iodide!
    1. Breakable π bond
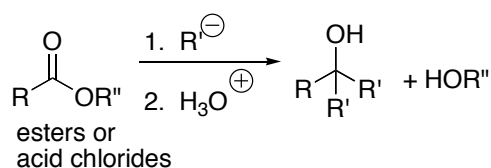   2. Carbonyl polarity
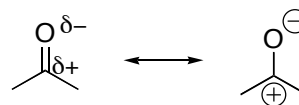
Reaction Mechanisms for Grignard Reactions

Formaldehyde, Aldehyde, or Ketone as Carbonyl Compound (Reactions 4, 5, and 6)
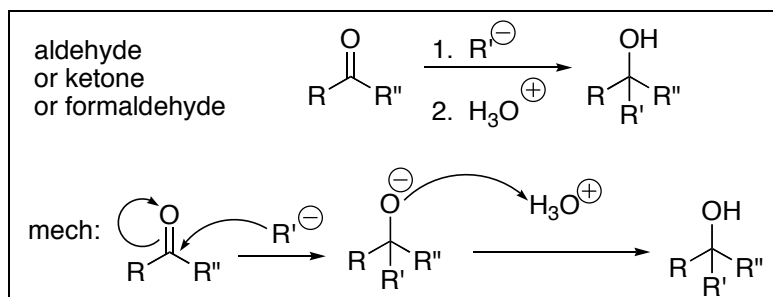
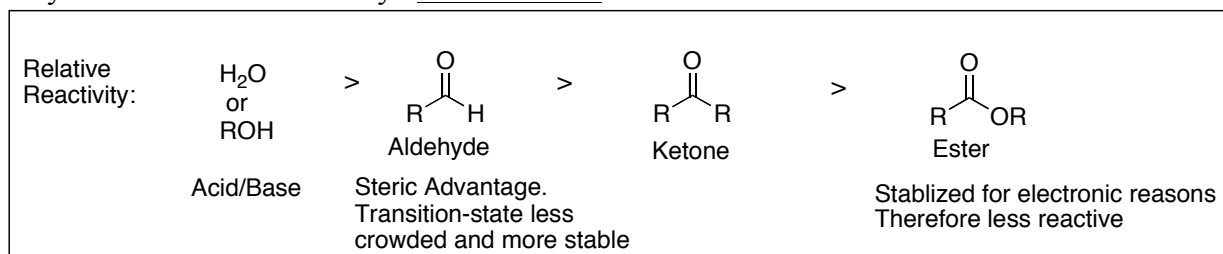1. Two simple steps:
    a. **Addition**
    b. **Protonation**
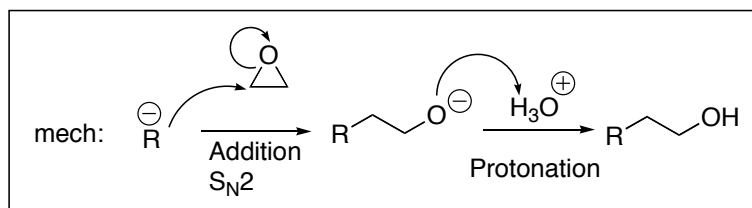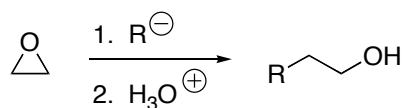2. RMgBr = R-MgBr = R $\ominus$ carbanion
    a. The $\oplus$ MgBr stuff is spectator, doesn't need to be drawn in

Esters or Acid Chlorides: More Complex, Needs to Explain Two Additions and More Bond Breakings
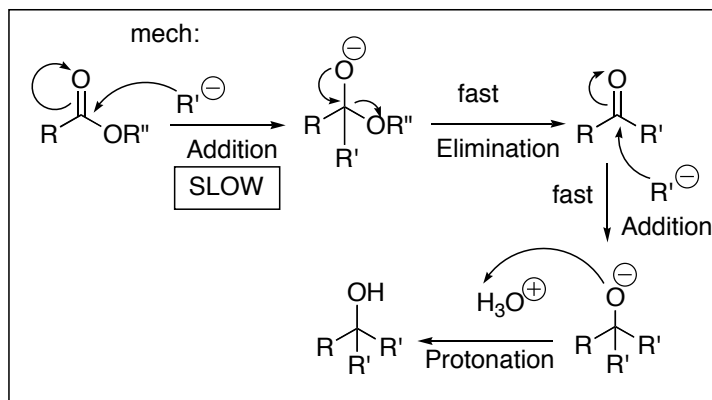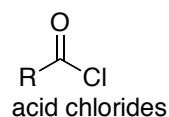
1. Four Step Mechanism:
    a. **Addition**
    b. **Elimination**
    c. **Addition**
    d. **Protonation**

Why? Kinetics and Reactivity. **MEMORIZE**.

Ethylene Oxide Mechanism

Grignards in Synthesis: Provide Precursors.
- **Think backwards from Targets to Reactants.**
- Identify possible Grignards and Grignard acceptors
- **Pattern:**
    - **3° alcohol, all three attachments different ← Ketone Precursor**
    - **3° alcohol, two (or more) of the attachments identical ← Ester**
    - **2° alcohol ← Aldehyde**
   - **1° alcohol ← Formaldehyde or ethylene oxide**

10.10 Restrictions on Grignard Reactions
- RMgBr = R$^{\ominus}$ carbanion, highly unstable, highly reactive.
- Unstable in the presence of:
    1. OH's (get proton transfer reaction)
    2. Carbonyls (get Grignard-type nucleophilic addition)

10.11 Alcohols by Reduction of Carbonyls: H$^{\ominus}$ Addition

9

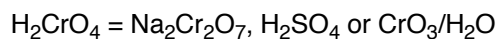Mech

10

Mech

11

NaBH$_4$ will   Mech
not react with
esters
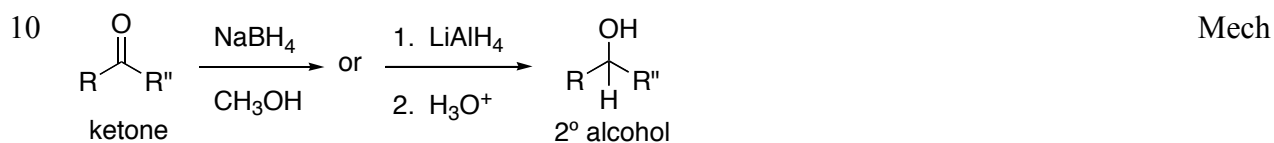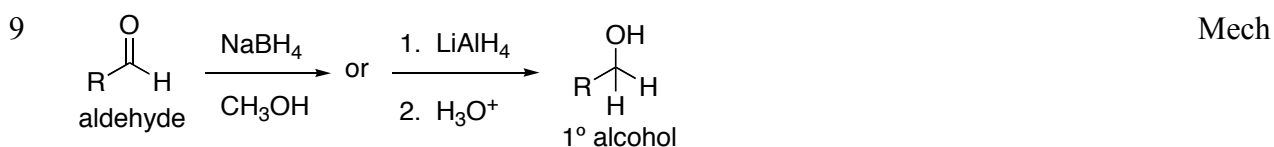
Mechanism
Aldehydes and Ketones
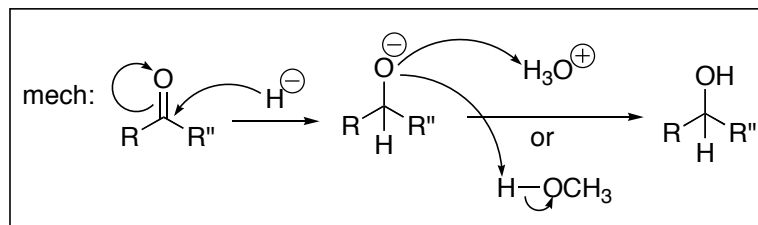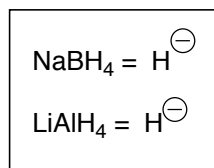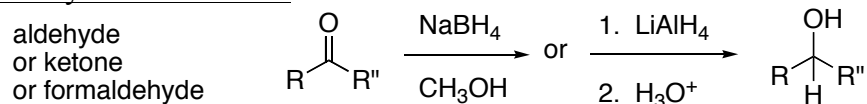
Esters
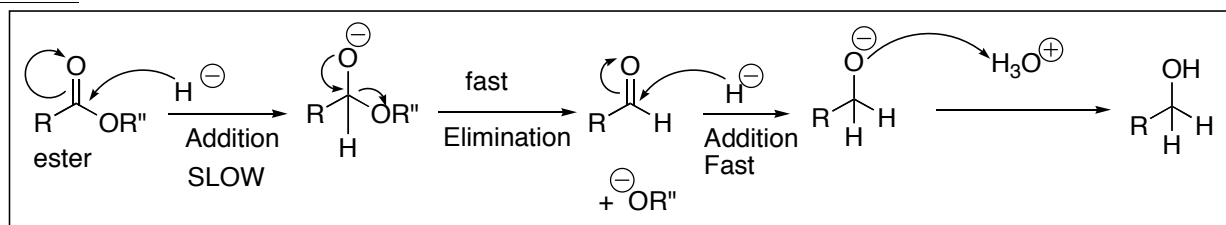
Cyclic Esters
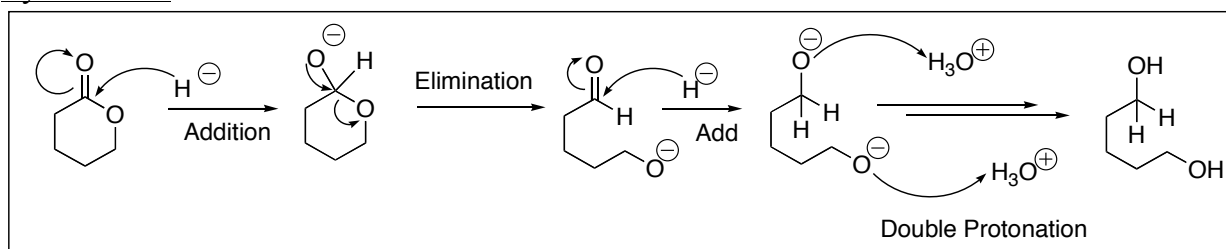
Notes:
- Mechanisms are exactly like with Grignard reactions
- LiAlH$_4$ and NaBH$_4$ function as hydride anions H $\ominus$
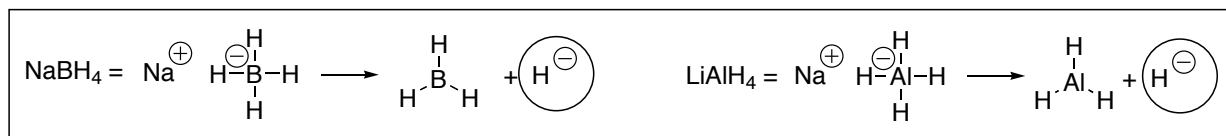
LiAlH$_4$ is much stronger, NaBH$_4$ much weaker
1. **Selective reduction**: if both an ester and an aldehyde/ketone are present:
   - LiAlH$_4$ reduces both
   - NaBH$_4$ selectively reduces the aldehyde/ketone but leaves the ester untouched
2. **LiAlH$_4$ is strong enough to react with and be destroyed by water or alcohol; NaBH$_4$ isn't**
$$LiAlH_4 + H_2O \rightarrow H_2(gas) + LiOH + AlH_3 + heat$$

3. LiAlH$_4$ is strong enough to react with esters, NaBH$_4$ isn't

Summary of Alcohol Reactions, Ch. 11.
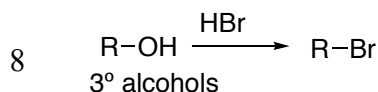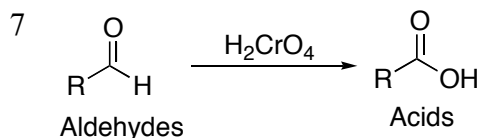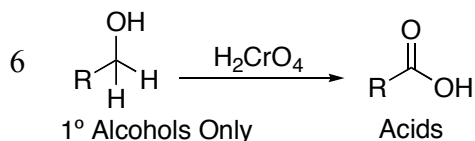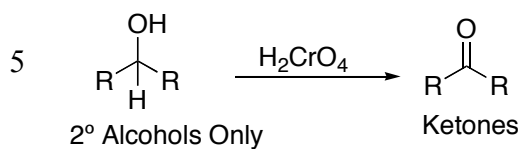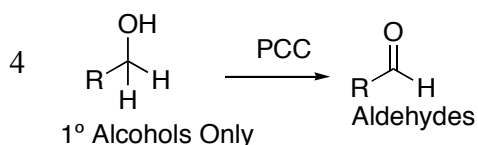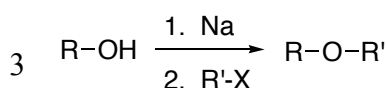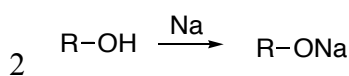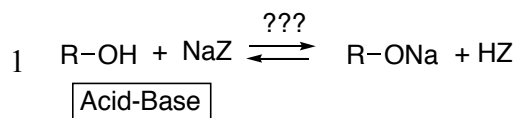
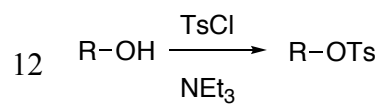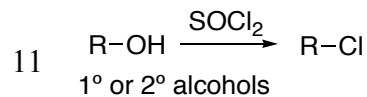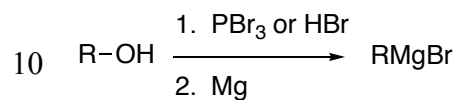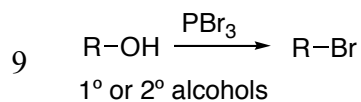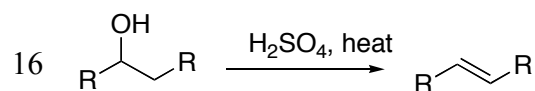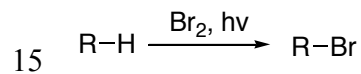|	
1 R–OH + NaZ $\rightleftharpoons$ R–ONa + HZ (???) **Acid-Base**	• Deprotonation by a base. • Controlled by relative stability of RO$^{\ominus}$ versus Z$^{\ominus}$. • Consider relative electronegativity and whether either anion is resonance stabilized.
2 R–OH $\xrightarrow{\text{Na}}$ R–ONa	• Potassium (K) analogous. • Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.
3 R–OH $\xrightarrow[\text{2. R'-X}]{\text{1. Na}}$ R–O–R'	• Alkoxide formation-S_N2 route to ether • The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group
4 (OH, 1° Alcohols Only) $\xrightarrow{\text{PCC}}$ Aldehydes	• Key access to aldehydes, which are useful for more Grignard chemistry. • Note difference between PCC and H_2CrO_4 • PCC does not react with 2° alcohols very rapidly
5 (OH, 2° Alcohols Only) $\xrightarrow{H_2CrO_4}$ Ketones $H_2CrO_4 = Na_2Cr_2O_7, H_2SO_4$ or CrO_3/H_2O	• Key access to ketones. • PCC does not react very fast with 2° alcohols
6 (OH, 1° Alcohols Only) $\xrightarrow{H_2CrO_4}$ Acids	• Note difference between • PCC and H_2CrO_4 when reacting with 1° alcohols.
7 Aldehydes $\xrightarrow{H_2CrO_4}$ Acids	
8 R–OH $\xrightarrow{\text{HBr}}$ R–Br (3° alcohols) **Mech: Be able to draw!**	• HI, HCl analogous • Converts alcohol into a bromide that can be used in Grignards, E2 reactions • Cation mechanism • Usually not method of choice for 1°, 2° alcohols

9    $R-OH \xrightarrow{\text{PBr}_3} R-Br$

1° or 2° alcohols

- Converts alcohol into a bromide that can be used in Grignards, E2, S_N2 reactions
- Inversion of stereochem
- Not good for 3° alcohols

10   $R-OH \xrightarrow[\text{2. Mg}]{\text{1. PBr}_3 \text{ or HBr}} RMgBr$

- Quick 2-step conversion of alcohol into a nucleophilic Grignard

11   $R-OH \xrightarrow{\text{SOCl}_2} R-Cl$

1° or 2° alcohols

- Retention of stereo!

12   $R-OH \xrightarrow[\text{NEt}_3]{\text{TsCl}} R-OTs$

- Tosylates are super leaving groups, better even than iodides.
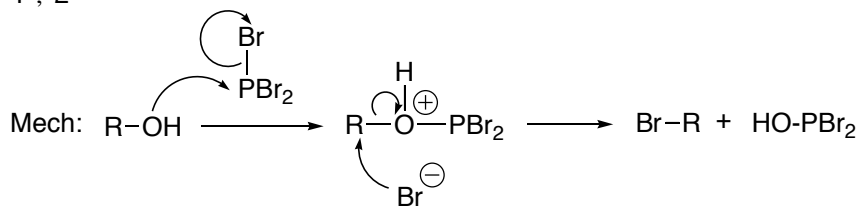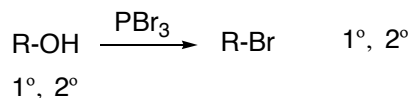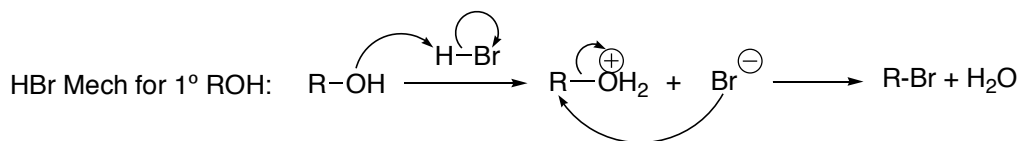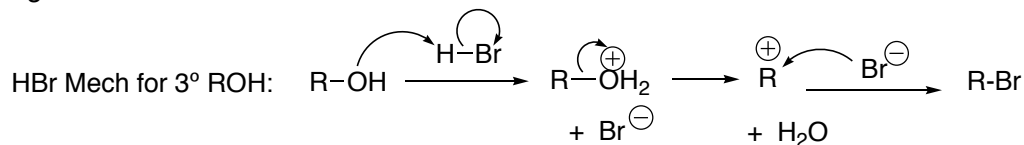- Tosylates are well suited to S_N2 and E2 reactions.

Review Reactions

-

13   $R\diagup\!\!\diagdown \xrightarrow{\text{HBr}} R\diagdown\!\!\overset{\text{Br}}{\diagup}$

- Markovnikov addition

14   $R\diagup\!\!\diagdown \xrightarrow[\text{peroxides}]{\text{HBr}} R\diagdown\!\!\diagup\!\!\diagdown^{\text{Br}}$

- anti-Markovnikov addition

15   $R-H \xrightarrow{\text{Br}_2,\ hv} R-Br$

- Radical mechanism, 3° > 2° > 1°

16   $\underset{R}{\overset{\text{OH}}{\diagdown}}\!\!\diagup\!\!R \xrightarrow{\text{H}_2\text{SO}_4,\ \text{heat}} R\diagup\!\!\diagdown^{R}$

- Zaytsev elimination

Mechanisms for ROH → RBr Reactions

R-OH $\xrightarrow{\text{HBr}}$ R-Br   3° mostly, sometimes 1°
3°

HBr Mech for 3° ROH: R−OH $\longrightarrow$ R−$\overset{+}{O}H_2$ $\longrightarrow$ $\overset{+}{R}$ $\xrightarrow{\quad Br^{\ominus}\quad}$ R-Br
                                                    H−Br
                                          + Br$^{\ominus}$ + H$_2$O

HBr Mech for 1° ROH: R−OH $\longrightarrow$ R−$\overset{+}{O}H_2$ + Br$^{\ominus}$ $\longrightarrow$ R-Br + H$_2$O
                                                    H−Br

R-OH $\xrightarrow{\text{PBr}_3}$ R-Br   1°, 2°
1°, 2°

Mech: R−OH $\longrightarrow$ R−$\overset{\overset{H}{|}}{O}$−PBr$_2$ $\longrightarrow$ Br−R + HO-PBr$_2$
                              Br
                              |
                              PBr$_2$
                              Br$^{\ominus}$
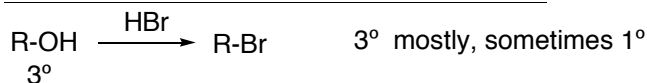
Ch. 11 Reactions of Alcohols

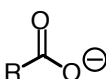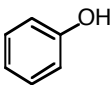## A. Conversion to Alkoxides. Acidity of Alcohols and Phenols (10.6)

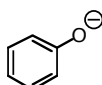"alkoxide" = RO$^{\ominus}$ anion

1	R−OH + NaZ $\underset{}{\overset{???}{\rightleftharpoons}}$ R−ONa + HZ Acid-Base	1. Deprotonation by a base. 2. Controlled by relative stability of RO$^{\ominus}$ versus Z$^{\ominus}$. 3. Consider relative electronegativity and whether either anion is resonance stabilized.

- Alcohols are weak acids → can be ionized by stronger bases
- goes to the right (alkoxide) only if resulting RO$^{\ominus}$ is more stable than B$^{\ominus}$
- ex. $^{\ominus}$NH$_2$, $^{\ominus}$CH$_3$ (nitrogen or carbon anions)

   •

Acidity Table

Class	Structure	Ka	Acid Strength	Anion	Base Strength	Base Stability
Strong Acids	H-Cl	10^{2}		Cl $^{\ominus}$		
Carboxylic Acid	$R\overset{O}{\underset{OH}{\parallel}}$	10^{-5}		$R\overset{O}{\underset{O^{\ominus}}{\parallel}}$		
Phenol	OH	10^{-10}		O$^{\ominus}$		
Water	H_2O	10^{-16}		HO $^{\ominus}$		
Alcohol	ROH	10^{-18}		RO $^{\ominus}$		
Amine (N-H)	RNH_2	10^{-33}		RNH $^{\ominus}$		
Alkane (C-H)	RCH_3	10^{-50}		RCH_2 $^{\ominus}$		

Notes/skills:
1. Be able to rank acidity.
2. Memorize/understand neutral OH acidity ranking: $RCO_2H > H_2O > ROH$
    •   Reason: **resonance** stabilization of the **anion**
    •   Alkoxide is **destabilized** relative to hydroxide by **electron donor** alkyl group
3. Predict deprotonation (acid/base) reactions
    •   Any weak acid **will be** deprotonated by a **stronger base (lower** on table)
    •   Any weak acid **will not be** deprotonated by a **weaker base (higher** on table)
4. Predict ether/water extraction problems
    •   If an organic chemical is neutral and stays neutral, it will stay in ether layer
    •   If an organic chemical is ionized (by an acid-base reaction), it will extract into the aqueous layer

---

Key: a proton transfer will happen only if it results in a more stabilized anion

Key anion stability factors:
•   Electronegativity (oxygen > nitrogen > carbon)
•   Resonance. Carboxylate, phenoxide yes > hydroxide, alkoxide no
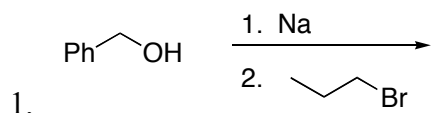•   Donor/withdrawer factor: hydroxide > alkoxide (electron donor destabilizes anion)

A2. Alkoxide formation by redox reaction with sodium or potassium (or other metals) (10.6B)

2	R–OH $\xrightarrow{\text{Na}}$ R–ONa $\left.\begin{array}{c} \\ \\ \end{array}\right\}$ R–O$^{\ominus}$ R–OH $\xrightarrow{\text{K}}$ R–OK	• Potassium (K) analogous. • Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

- Key source of nucleophilic/basic alkoxides
- Alkoxides are used all the time as S_N2 nucleophilies and E2 bases

B. **2-Step Conversion of Alcohols into Ethers via the Alkoxides (10.6B)**

3	R–OH $\xrightarrow[\text{2. R'-X}]{\text{1. Na}}$ R–O–R'	• Alkoxide formation-S_N2 route to ether • The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group

1. Ph⌒OH $\xrightarrow[\text{2.} \diagdown\diagup\diagdown\text{Br}]{\text{1. Na}}$

C. Oxidation of Alcohols to Carbonyl Compounds (11.1-4)
Summary: 2 Oxidants

1. **PCC = mild   1° alcohols → aldehydes**
   - "**P**yridinium **c**hloro**c**hromate": soluble in water-free dichloromethane
   - Mild, selective for 1° over 2° alcohols, and when 1° alcohols are used stops at aldehyde

2. **H_2CrO_4 = strong**
   a. **2° alcohols → ketones**
   b. **1° alcohols → carboxylic acids**
   c. 3° alcohols → no reaction
   d. aldehydes → carboxylic acids
   - H_2CrO_4 = CrO_3 + H_2O or Na_2Cr_2O7 + H_2SO_4 (make in the reaction flask)
   - Always made and used in the presence of some water
   - Very strong, when 1° alcohols are used goes 1° RCH_2OH → RCHO → RCO_2H without stopping at aldehyde

Jones Test H_2CrO_4 for Alcohols (11-2C) (test responsible)
- H_2CrO_4 (Jones Reagent) is clear orange
- Treatment of an unknown with Jones reagent:
  o Solution stays clear orange → no 1° or 2° alcohol present (negative reaction)
  o Solution gives a green/brown precipitate → 1° or 2° alcohol present (positive reaction)
  o 3°, vinyl, and aryl alcohols do not react. Nor do ketones, ethers, or esters.

-

General Recognition of Oxidation/Reduction in Organic Chemistry
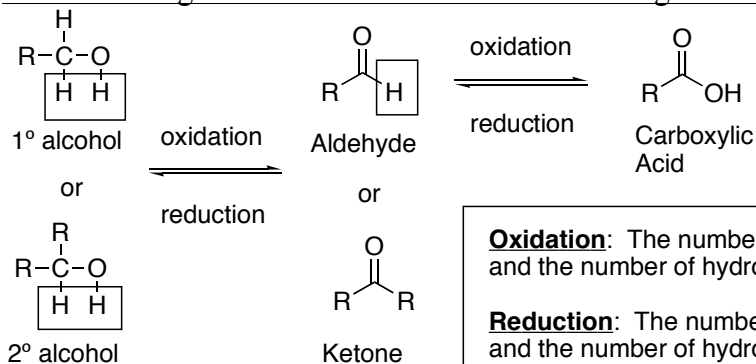
Oxidation: The number of oxygen bonds to a carbon increases, and the number of hydrogens bonded to a carbon decreases

Reduction: The number of oxygen bonds to a carbon is reduced, and the number of hydrogens bonded to a carbon increases.

More General: # of bonds to heteroatoms versus to hydrogens

11.3, 11.4 Other methods for Oxidizing Alcohols. (No test)
There are lots of other recipes used for oxidizing alcohols (and for other oxidation reactions)
1. $KMnO_4$
2. CuO
3. "Jones": H_2CrO_4 with acetone added to temper reactivity
4. Collins: H_2CrO_4 with pyridine added to temper reactivity
5. "Swern": $(COCl)_2$ and $(CH_3)_2S=O$ then NEt_3

In General: Recognizing Oxidizing versus Reducing Agents

Oxidizing Agents: Often have:
- Highly Oxidized Metals or Nonmetals
- Extra Oxygen

Reducing Agents: Often involve:
- Hydrides in Formulas
- Highly Reduced Metals
- Metals + H_2
- Metals + acid

OsO_4 (+8)
$KMnO_4$ (+7)
CrO_4 (+6)
H_2CrO_4 (+6)
HNO_4 (+5)
$H_2O_2 \rightarrow H_2O$
$RCO_3H \rightarrow RCO_2H$
$O_3 \rightarrow O_2$

$LiAlH_4$
$NaBH_4$
Li, Na, K, Mg, Zn, Al, etc.
Pd/H_2, Pt/H_2, Ni/H_2 etc.
Zn/HCl, Fe/HCl, $Zn/Hg/HCl$, etc..

- The ability to qualitatively recognize when a transformation involves an oxidation or reduction can be very helpful.
- The ability to recognize a reactant as an oxidizing agent or a reducing agent can be very helpful
- Often on standardized tests!

11.7-9 Conversion of Alcohols to Alkyl Halides
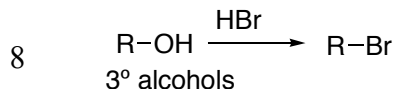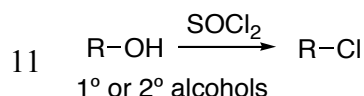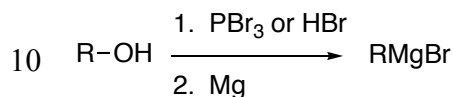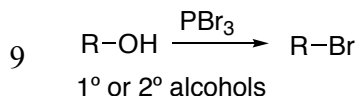
8

$$R-OH \xrightarrow{\text{HBr}} R-Br$$

3° alcohols

| Mech: Be able to draw! |

- HI, HCl analogous
- Converts alcohol into a bromide that can be used in Grignards, E2 reactions
- Cation mechanism
- Usually not method of choice for 1°, 2° alcohols

9

$$R-OH \xrightarrow{\text{PBr}_3} R-Br$$

1° or 2° alcohols

- Converts alcohol into a bromide that can be used in Grignards, E2, S_N2 reactions
- **Inversion of stereochem**
- Not good for 3° alcohols

10

$$R-OH \xrightarrow[\text{2. Mg}]{\text{1. PBr}_3 \text{ or HBr}} RMgBr$$

- Quick 2-step conversion of alcohol into a nucleophilic Grignard

11

$$R-OH \xrightarrow{\text{SOCl}_2} R-Cl$$

1° or 2° alcohols

- Retention of stereo!
- Section 11-9

Summary:

Class	R-Br	R-Cl
1° ROH	PBr$_3$	SOCl$_2$
2° ROH	PBr$_3$	SOCl$_2$
3° ROH	**HBr**	**HCl**
Vinyl or Aryl	Nothing works	Nothing works

Mechanism for H-X reactions with 3° Alcohols: Cationic (Test Responsible)

HBr Mech for 3° ROH:
$$R-OH \longrightarrow R-\overset{+}{O}H_2 \longrightarrow \overset{+}{R} \xrightarrow{Br^-} R\text{-Br}$$
$$+ \; Br^- \qquad + \; H_2O$$
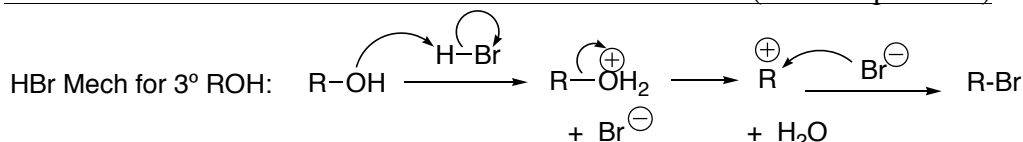
Notes:
1. Memorize the 3° alcohol mechanism (test responsible)
    a. Protonate
    b. Leave to give Cation. This is the slow step for 3° alcohols
    c. Capture
2. Analogous with HI or HCl
3. S_N1 type: carbocation-forming step is the rate-determining step, so R+ stability key
    - 3° alcohols fastest
    - 2° alcohols are way slower
    - 1° alcohols (or vinyl/aryl) can't react at all via this mechanism, because 1° R+ are too unstable.
4. HBr can also react with 1° ROH to give 1° RBr, although it is not often the method of choice
    - The mechanism is different, but rather interesting (not test responsible)
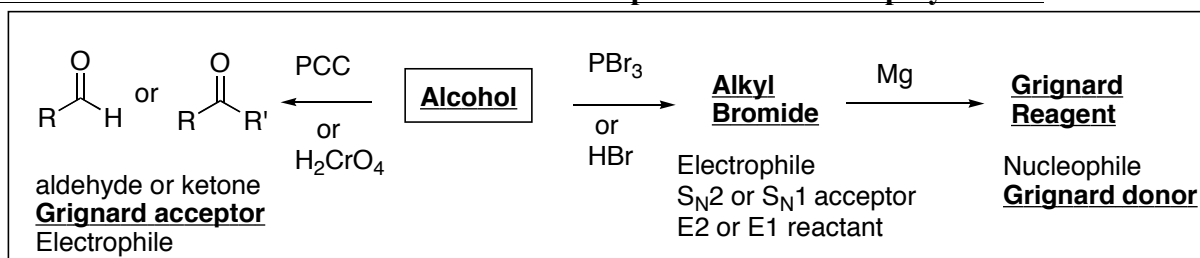
HBr Mech for 1° ROH:
$$R-OH \longrightarrow R-\overset{+}{O}H_2 \; + \; Br^- \longrightarrow R\text{-Br} + H_2O$$
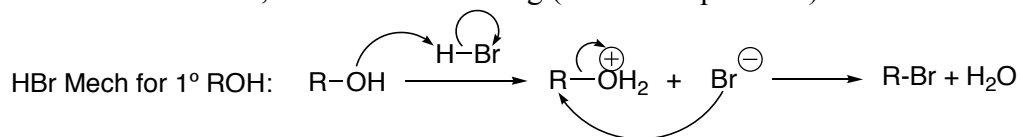
Reaction of 1° and 2° Alcohols with PBr₃ (Section 11-8)

- Default recipe for 1° and 2° alcohols

Mech:

$R-OH$
1°, 2° → $R-O-PBr_2$ → $Br-R$ + $HO-PBr_2$
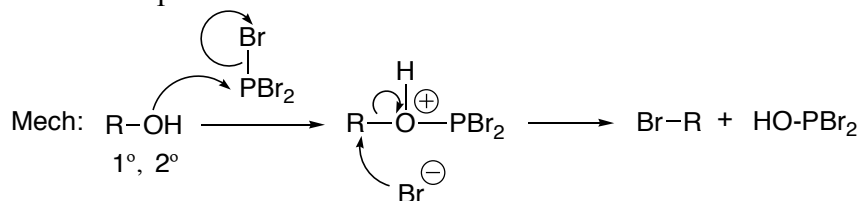
- PBr₃ is an exceptional electrophile, and reacts even with neutral alcohols
- The first step activates the oxygen as a leaving group.
- The second step involves an S_N2 substitution
  - **stereochemical inversion occurs if chirality is present (common for 2° alcohols)**
- Because the second step is an S_N2 substitution, the reaction fails for 3° ROH

Conversions of Alcohols into Other Reactive Species in Multi-Step Syntheses

aldehyde or ketone
Grignard acceptor
Electrophile

Alcohol

Alkyl Bromide
Electrophile
S_N2 or S_N1 acceptor
E2 or E1 reactant

Grignard Reagent
Nucleophile
Grignard donor

1. oxidation can convert an alcohol into a carbonyl = **Grignard acceptor   (electrophile)**
2. PBr₃/Mg or HBr/Mg can convert an alcohol into RMgBr = **Grignard donor (nucleophile)**
3. PBr₃ or HBr can convert an alcohol into RBr, capable of normal substitution and elimination reactions.

Retrosynthesis Problems (In which you decide what to start from):
1. Focus on the functionalized carbon(s)
2. Try to figure out which groups of the skeleton began together, and where new C-C bonds will have been formed
3. When "breaking" it up into sub-chunks, try to make the pieces as large as possible
4. Be careful that you aren't adding or substracting carbons by mistake

Normal Synthesis Design: In which you are given at least one of the starting Chemicals. **Tips**:
- Identify where the reactant carbons are in the product
- Working backwards helps.

Unknowns and Chemical Tests (Sections 11-2C, 11-7)
1. H$_2$/Pt test for alkenes
2. Br$_2$ test for alkenes
3. **Jones reagent (H$_2$CrO$_4$) Test for 1° or 2° alcohols**
   - 3° alcohols do not react
   - 2° alcohols keep the same number of oxygens but lose two hydrogens in the formula
   - 1° alcohols lose two H's but also add one oxygen
4. **Lucas Test: HCl/ZnCl$_2$ for 3° or 2° alcohols**

R-OH $\xrightarrow{\text{HCl/ZnCl}_2 \text{ in water}}$ R-Cl   via R$^{\oplus}$ 3° > 2° >>>> 1°

3° >	2° >>>	1°
<1 min	1-5 min	never

Why? R$^{\oplus}$ stability: 3° R$^{\oplus}$ >   2° R$^{\oplus}$ >>> 1° R$^{\oplus}$
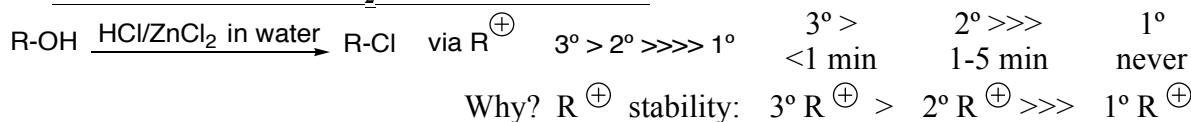
- 3° alcohols are fastest
- 1° alcohols don't react at all
- R$^{\oplus}$ stability is the key

- Test is based on **solubility**: The R-Cl product is nonpolar and water insoluble, so it separates out from water. Alcohols are quite soluble especially in highly acidic water.

Section 11-5 Conversion of Alcohols to "Tosylates", and their use as Exceptional Leaving Groups in S$_N$2, S$_N$1, E2, and E1 Reactions
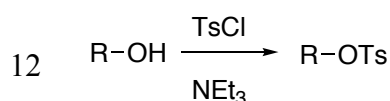
12   R–OH $\xrightarrow[\text{NEt}_3]{\text{TsCl}}$ R–OTs

> - Tosylates are super leaving groups, better even than iodides.
> - Tosylates are well suited to S$_N$2 and E2 reactions.
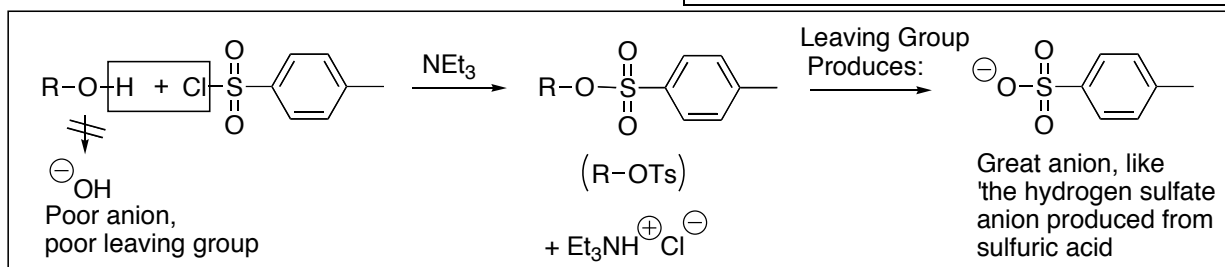
Notes:
1. Tosylates are easy to form
2. "Toluene sulfonate"
3. Tosylate anion is really stable, comparable to the anion from sulfuric acid
   - Thanks to electronegative sulfur and the resonance/charge sharing with the other oxygens
4. Whereas a normal OH has a poor leaving group (hydroxide anion), conversion to the tosylate provides a super good leaving group.
5. Leaving Group Reactivity: Better than the best of the halides
   - OTs >> I > Br > Cl
6. Tosylates are highly reactive toward S$_N$2, S$_N$1, E2, and E1 Reactions
7. Triethylamine is used as an HCl scavenger in the tosylate formation
   - Often a weaker amine base called pyridine is used, to avoid unintentionally providing E2 on the tosylate

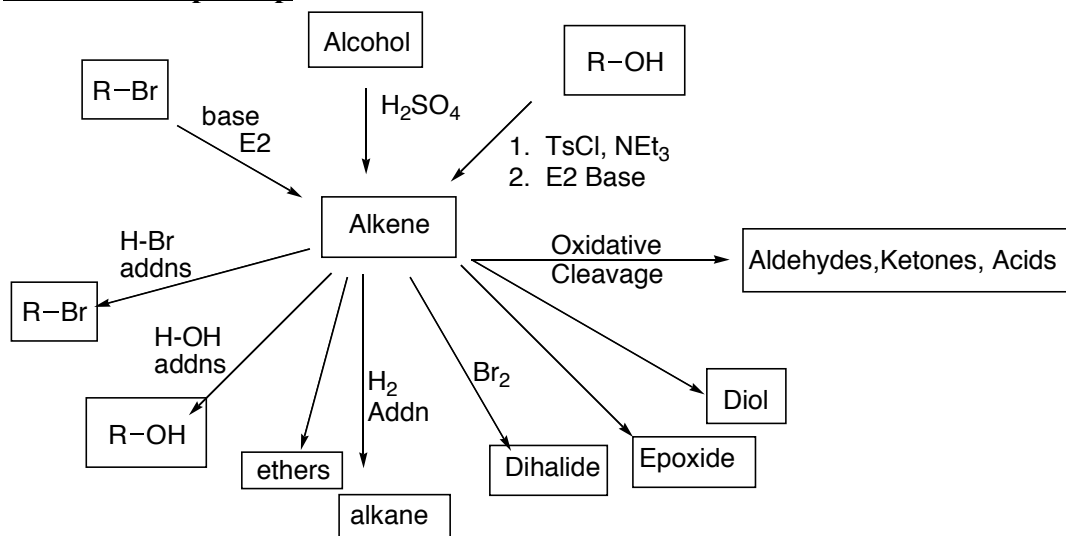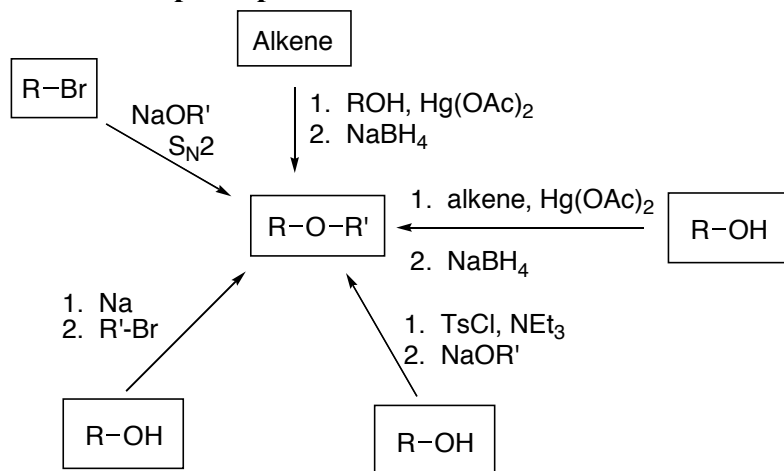## Reaction of 1º and 2º Alcohols with SOCl₂ (Section 11-9)

- Default recipe for chlorination of 1º and 2º alcohols
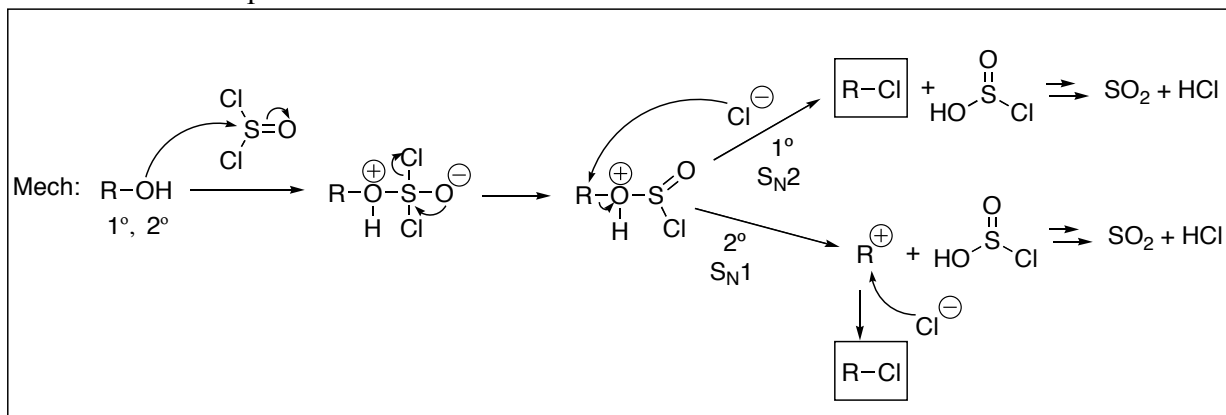
- Mechanism: Not for test responsibility
- The chloride that captures the cation is normally on the same side of the molecule on which the oxygen began, and often captures the cation very rapidly from that same side
- This results in a very unusual **retention of stereochemistry.**

REVIEW.   Bromoalkane Concept Map

Alkene

1°, 2° ROH

Alkane

HBr, peroxides
(anti-Mark)
or
HBr (Mark)

PBr$_3$

3° ROH

Br$_2$, hv

HBr

R−Br

Mg

Z $\ominus$

S$_N$2

E2
(normal
or
bulky base)

R−MgBr

Grignard
Acceptors

R−Z

ethers

alcohols

Alkene

1°, 2°, 3° ROH

etc.

Alcohol Concept Map

ROH

ROH

ROH

Alkenes

1. PBr$_3$ or HBr
2. Mg
3. Grignard
    Acceptor

1. Oxidize
   (PCC or
   H$_2$CrO$_4$)
2. RMgBr

1. TsCl
2. NaOH
   (inverts
   stereo)

Mark or
AntiMark
HOH

Aldehyde,
Ketone,
Ester

NaOH
S$_N$2

NaBH$_4$
or
LiAlH$_4$

R-Br

1. Mg
2. Grignard Acceptor
   (aldehyde, ketone, ester, epoxide)

RMgBr

Aldehyde,
Ketone,
Ester

R-Br

Alcohol

3. H$_3$O$^+$

PBr$_3$

1. TsCl
2. Base

1° or 2° R-Br

SOCl$_2$

1° or 2° R-Cl

HBr

Alkene

H$_2$SO$_4$

3° R-Br

PCC

1. Oxidize
   (PCC or
   H$_2$CrO$_4$)
2. RMgBr

1.PBr$_3$ or HBr
2. Mg
3. Grignard
   Acceptor

Alkene

Aldehyde

H$_2$CrO$_4$

H$_2$CrO$_4$

1. Na
2. RBr

1. TsCl
2. NaOR

1. TsCl
2. NaOH

Ketone

Acid

Ether

Ether

Alcohol
(inversion)

Alcohol

Alcohol

Alkene Concept Map

Ether Concept Map

Short Summary of 1H-NMR Interpretation

For fuller explanation, see: http://web.mnstate.edu/jasperse/Chem355/H-NMR.doc.pdf

I. Number of Signal Sets

II. Integration   These **must be simple whole-number ratios** (2:1, 3:1, 3:2, etc..)

III. "Chemical Shifts" of the Signal Sets (when only one functional group is at play)

9's (9.0-10.0)	**Aldehyde** sp^2 hybridized C-H's
7's (6.5-8.4)	**Aromatic** sp^2 hybridized C-H's
5's (4.8-6.8)	**Alkene** sp^2 hybridized C-H's

3's (2.8-4.5)　　**Oxygenated** or **Halogenated** sp^3 hybridized C-H's (halogenated and nitrogenated alkyl C-H's will also come in this window, although no candidates for today's lab). Oxygenated sp^3–carbons are routinely present for the following functional groups that contain oxygen single bonds:
    a. **alcohols**,
    b. **ethers**, or
    c. **esters**

2's (1.8-2.8)　　**Allylic** sp^3 hybridized C-H's (sp^3 hybridized C-H's that has a double bond attached to the sp^3 hybridized C). Allylic signals routinely appear when one of the following double-bonded functional groups is present:
    a. **carbonyls**, (ketones, esters, aldehydes, acids, amides)
    b. **alkenes**, or
    c. **aromatics**

1's (0.7-2.0)　　sp^3 hybridized C-H's, with **no attached Functional Groups**
    a. **Note:** Many molecules with non-functional alkyl portions will give a lot of signal in this area.

0-12 (anywhere!)　　**Alcohol/Acid** O-H hydrogens (N-H hydrogens likewise)
    a. **alcohols**,
    b. **carboxylic acids**

1. Recognize OH's..
2. Check each of the zones. Each one gives you a yes or no answer about the presence of absence of the featured group.
3. End-Check: Check that the functional groups indicated by your chemical shift information match with the structure you believe you actually have! If not, structure needs correction!
4. The regions are somewhat approximate, and have some spillover.
5. For multi-functional complex molecules, there are more complex ways for a C-H to come in some of the above window. For example, an sp^3-hybridized C-H with two attached oxygens can come in the 5's, or an sp^3-hybridized C-H that is doubly allylic can come in the 3's. In other words, the impact of functional groups is roughly additive.

IV. Splitting
- ❑ **N-1 Rule:**   **N lines → N-1 neighbor H's** (H's directly attached to carbons attached to the C-H group causing the signal)
  - • The N-1 Rule is useful when <u>working from spectrum to actual structure</u>
- ❑ **N+1 Rule:**   **N neighbor H's → N+1 lines**
  - • The N+1 Rule is useful when <u>working from structure to actual spectrum</u>

Note: OH hydrogens don't participate in splitting (normally)

Short Summary of C13-NMR Interpretation

1. **Count how many lines** you have. **This will tell you how many types of carbons** you have. (Symmetry equivalent carbons will give a single line.)
    a. Each "unique"carbon gives a separate line.
    b. Symmetry duplicates give the same line.
    c. If there are more carbons in your formula than there are lines in your spectrum, it means you have symmetry.

2. **Check diagnostic frequency windows** ("chemical shift windows") of the lines **to provide yes-or-no answers regarding the presence or absence of key functional groups** in your molecule.

    220-160   C=O carbonyl carbons, sp^2 hybridized
    160-100   C alkene or aromatic carbons, sp^2 hybridized
    100-50   C-O oxygen-bearing carbons, single bonds only, sp^3 hybridized
    50-0   C alkyl carbons, no oxygens attached, sp^3 hybridized

3. **Check Splitting**. C13 NMR's are often acquired as "decoupled" spectra, in which each carbon signal appears as a singlet. However, at the cost of extra time and/or complexity it is also possible to get "coupled" C13 NMR's with splitting. These splitting values are very useful, and follow the N+1/N-1 rules (the number of lines is one greater than the number of attached H's). (Other experimentally preferable but conceptually complex "HSQC" two-dimensional NMR experiments can provide the same information more quickly.)
    Quartert (q) CH_3
    Triplet (t) CH_2
    Doublet (d)   CH
    Singlet (s) C (no attached hydrogens).
    • Note: The use of DEPT NMR or other techniques can also be used to establish whether carbons are CH_3, CH_2, CH, or carbons without any attached hydrogens.

4. **Signal Height/Size**
    a. Carbons without any attached H's are short.   This is common for carbonyls (aldehydes are the only carbonyl carbons that have hydrogens attached) and for substituted carbons in a benzene ring.
    b. Symmetry duplication multiplies signal height (if you have two copies of a carbon, the line will probably be taller than normal!)

5. **Aromatics, Symmetry, and C-13 Signals**. Most aromatics have symmetry, and both the number of aromatic lines and the splitting of the aromatic lines can be indicative of the substitution pattern on a benzene. Mono- and para-disubstituted benzenes have symmetry.

    4 lines s, d, d, d   Monosubstituted benzene. (Has symmetry).
    4 lines s, s, d, d   Para-disubstituted benzene. (Has symmetry).
    6 lines s, s, d, d, d, d Ortho- or meta-disubstituted benzene. (Has no symmetry).

Summary of IR (Infrared) Interpretation

1. **Check for Diagnostic Signals**
    3500-3200   OH or NH
    1800-1640   C=O
    3500-2500 + 1800-1640 CO_2H
2. **Further Information in the "Carbonyl Zone"**
    <1700   Unsaturated C=O
    >1700   Saturated C=O
    1720-1700   Saturated ketones, aldehydes, acids
    1750-1735   Saturated ester

The four facets of 1H NMR spectroscopy:

1. The <u>number of signal sets</u> (Section 13.6)
   - Symmetry-duplicate hydrogens give the same signal sets
2. <u>Chemical shifts</u> reflect the chemical environment of each type of hydrogen
   a. Whether attached to an sp^3 or and sp^2 carbon
   b. What kind of functional groups might be attached to the carbon on which the hydrogen is attached.
   c. Whether attached to carbon versus to oxygen or nitrogen
   - The <u>integration</u> of each signal set reflects how many hydrogens are responsible.
   a. 3H → CH_3 group (or 2H and 1H groups superimposed)
   b. 2H → CH_2 group (or two nonequivalent 1H groups superimposed)
   c. 1H → CH or OH group
3. The <u>splitting</u> provides information about H's on neighbor carbons
   a. N lines → N-1 "neighbor" H's (when working from spectrum to structure)
   b. N neighbors → N+1 lines (when predicting spectrum from structure)

Summary of Steps in Beginner 1H NMR Interpretation:

1. If provided with a chemical formula, calculate elements of unsaturation
2. **Count how many signal sets** you have.
   - This will tell you how many types of hydrogen-bearing carbons you have.
3. Check the **integration** of each signal set.
   - 3H → CH_3 group   2H → CH_2 group   1H → CH or OH group
   - The above are true if there isn't any accidental overlapping
   - Clean CH_3 or CH_2 signal sets will normally have reasonable shape symmetry
   a. But if you have a complex, unsymmetric 3H, do not assume it's really a CH_3.
   - Effective recognition and integration of signal sets can help you know how many CH_3's and CH_2's you have in your molecule
4. **Check diagnostic "chemical shift" windows** of the lines
5. Check the **splitting** of each signal set.
6. Try to find any sure things that you can as soon as you can.
7. Try to use integration to find any clean 3H signals that indicate CH_3 groups. Then use splitting and/or chemical shifts to track down what the CH_3 group is connected to, etc..

Other Practical Tips
1. Try to recognize any easy and obvious sure-thing components, for example:
   a. Aryl groups (chemical shift in the 7's, a 4H or 5H integral depending on whether di- or mono-substituted)
   b. CH_3 methyl groups (based on clean 3H integration)
   c. Isopropyl groups (6H doublet)
   d. Alcohol OH: integrates for only 1H, and normally doesn't have the splitting that a CH hydrogen does
2. Try to work from end(s) toward the middle
   - If you know you have a CH_3 group, you can write it down for sure, and then try to figure out via splitting and/or chemical shifts what it's connected to, etc.
3. Recognizing "end groups" can give you an idea whether you have a straight chain or have branching
   - CH_3, Cl, Br, OH, C_6H_5

The Number of Signal Sets (Section 13-6)
1. Nonequivalent H's have different chemical environments and give different signals
2. Symmetry-equivalent H's have the same chemical environment and give the same signal
    *   Thus the number of signal sets tells you how many different types of hydrogens are present
3. On an **achiral** molecule (alkenes and rings excepted), hydrogens on a common carbon will be equivalent.
    *   all three H's on a CH_3 group will be equivalent
    *   both H's on a CH_2 group will be equivalent.
4. For chiral molecules, substituted rings, and alkenes, cis-trans relationships can often make the two hydrogens in a CH_2 group non-equivalent
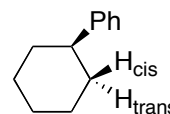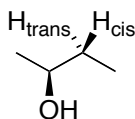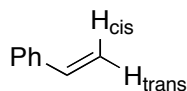
5. **Beware of overlaps!**
    *   Often two signal sets will show at about the same place. If you think you have a CH_3 group when in fact it's overlapping CH_2 and CH signals, you can get very confused…
    *   Overlaps normally don't have the clean symmetry that a clean signal set has
6. **Beware of Symmetry Duplication**
    *   Isopropyl groups are most common, and t-butyl groups on occasion
        o   Integrations of 6H or 9H can help recognize these

Integration   (Section 13-7)
1. When there is symmetry duplication of a hydrogen, the resulting signal will be multiplied accordingly!
2. Technical notes:
    a. The key is not the signal height, but rather the signal **area**.
    b. The signal **area** is measured by "integration lines". Make sure to differentiate integration marks, and what they mean, from signal lines themselves.

3. The relative areas of the signal-set integrals directly correlates the ratios of H's

*   The integrals **must be simple whole-number ratios** (2:1, 3:1, 3:2, etc..)
4. Clean sets involving equivalent H's give clean, symmetric signal sets:
    a. 1H → CH or OH
    b. 2H → CH_2
    c. 3H → CH_3
    d. 6H → 2 equivalent CH_3 groups
    e. 5H in aryl region → monosubstituted benzene (even if not clean set)
    f. 4H in aryl region → disubstituted benzene (even if not clean set)
5. Unsymmetrical messy sets involving overlapping signal sets: (these will routinely not look nice and symmetric…)
    a. 3H → CH_2 overlapping an OH or CH
    b. 4H   → two overlapping but not exactly equivalent CH_2 groups; or a CH_3 overlapping an OH or CH
    c. 5H →   common in the 7's, for 5 overlapping arene H's; also common in the 1's, when a CH_3 and CH_2 overlap
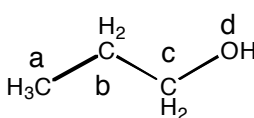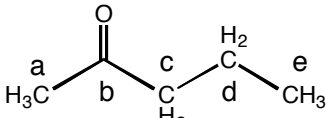
Splitting   (Section 13.8)
- But the splitting tells us something else that is really useful: what kind of CH groups are attached to the group of interest! Splitting tells us nothing about the group itself, but it does provide great information about neighbor groups.

Rules of "Splitting"
- ❑ **N-1 Rule: N lines → N-1 neighbor H's** (H's directly attached to carbons attached to the C-H group causing the signal)
  - The N-1 Rule is useful when working from spectrum to actual structure
- ❑ **N+1 Rule: N neighbor H's → N+1 lines**
  - The N+1 Rule is useful when predicting a spectrum for a structure

---

N+1 Rule (Given structure, how many lines a spectrum should give)

| Neighbors | 2 | 3+2 | 2 | 0 | | Neighbors | 0 | - | 2 | 2+3 | 2 |
| Lines | 3 | 6 | 3 | 1 | | Lines | 1 | - | 3 | 6 | 3 |

(Notice: OH doesn't split...)

N-1 Rule (Given spectrum, how many neighbors a structure should have)

| Lines | 1 (s)inglet | | Lines | 2 (d)oublet |
| Neighbors | 0 | | Neighbors | 1 |

| Lines | 3 (t)riplet | | Lines | 4 (q)uartet |
| Neighbors | 2 | | Neighbors | 3 | etc. |

---

1. Neighbor C-H hydrogens participate in splitting (always)
2. Neighbor OH hydrogens usually don't participate in splitting (~75% of the time). But sometimes they do (about 25% of the time).
   - They can have widely varying and rapidly changing hydrogen-bonding arrangements
3. Splitting from H's further distant than neighbor carbons sometimes occurs, but usually the amount of splitting is too small to worry about
4. Splitting nicknames:
   - 1 line = singlet (s)   2 lines = doublet (d)   3 lines = triplet (t)
   - 4 lines = quartet (q)   5 lines = pentet (p)   >5 lines = multiplet (m)
5. Limitation to the N-1/N+1 rules: it is only reliable if all of the neighbor hydrogens are equivalent. However, the rules actually are accurate only if the neighbor H's are equivalent.
   - The rule can break down when some of the neighbor H's differ significantly from each other
   - The more nonequivalent the neighbor hydrogens, the less the N-1/N+1 rules apply
     - Neighbor hydrogens on acyclic and sp^3 carbons tend to be pretty similar
     - Alkenes or aldehyde hydrogens (on sp^2 carbons) tend to split rather differently than hydrogens on sp^3 carbons
     - Splitting involving cis versus trans hydrogens on rings or alkenes tend to split rather differently from each other and from hydrogens on acyclic sp^3 systems.
     - Chiral centers can mess up the splitting even on acyclic systems

"Chemical Shifts" of the Signal Sets (Section 13.5)
- The following apply when only one functional group is impacting
- If two or more are impacting, then signal sets can appear outside of these windows

1's (0.7-2.0) sp^3 hybridized C-H's, with **no attached Functional Groups**
- **Note:** Many molecules with non-functional alkyl portions will give a lot of signal in this area.
- **This is the default place for** sp^3 **C-H's, when no functional group is shifting them to higher number**

2's (1.8-3.1)   **Allylic** sp^3 hybridized C-H's (sp^3 hybridized C-H's that has a double bond attached to the sp^3 hybridized C). Allylic signals routinely appear when one of the following double-bonded functional groups is present:
- +1 Adjustment factor
- **carbonyls**, (ketones, esters, aldehydes, acids, amides)
- **alkenes**, or
- **aromatics**

3's (2.8-4.5)   **Oxygenated** sp^3 hybridized C-H's (halogenated and nitrogenated alkyl C-H's will also come in this window, although no candidates for today's lab). Oxygenated sp^3–carbons are routinely present for the following functional groups that contain oxygen single bonds:
- +2 Adjustment factor
- **alcohols**, (usually signal in 3's)
- **ethers**, (usually signal in 3's) or
- **esters** (usually signal in low 4's)
- **More general: heteroatom substituents (O, Cl, Br, I) usually have a +2 adjustment factor, N a +1.5-2.0 adjustment factor.**

5's (4.8-6.8)   **Alkene** sp^2 hybridized C-H's

7's (6.5-8.4)   **Aromatic** sp^2 hybridized C-H's

9's (9.0-10.0)   **Aldehyde** sp^2 hybridized C-H's

0-12 (anywhere!)   **Alcohol/Acid** O-H hydrogens (N-H hydrogens likewise)
- **alcohols**, (normally 1.5-3.0)
- **carboxylic acids** (usually 10-12)

1. Replacement of H by more electronegative atom/group "deshields" a proton and moves it "downfield", to a higher number
    a. "methine" (CH) → "methylene" (CH$_2$) → "methyl" (CH$_3$) (case "a" vs "b" vs "c")
        • sequential replacement of hydrogens by more electronegative carbons moves the signal "downfield"
    b. See the electronegativity pattern as you go from: H (0.9) – C (1.2) – N (2.6) – I (3.2) – Br (3.3) – Cl (3.4) to O (3.5) (case "a" vs "b" vs "g" vs "i-l")
        • sequential replacement of hydrogens (or carbons) by any more electronegative substituents moves a signal "downfield"
    c. See the electronegativity pattern between amine (2.7) versus amide (3.2) (case "g" vs "h"), and alcohol/ether oxygen (3.5) versus ester oxygen (4.1) (case "l" vs "m")
        • the electron-withdrawing carbonyl attachment on the nitrogen or oxygen makes it effectively more electronegative and moves the signal "downfield"

| a. 0.90 | b. 1.20 | c. 1.55 | d. 2.00 | e. 2.45 | f. 2.55 |

| g. 2.65 | h. 3.20 | i. 3.15 | j. 3.35 | k. 3.40 | l. 3.53 | m. 4.08 |
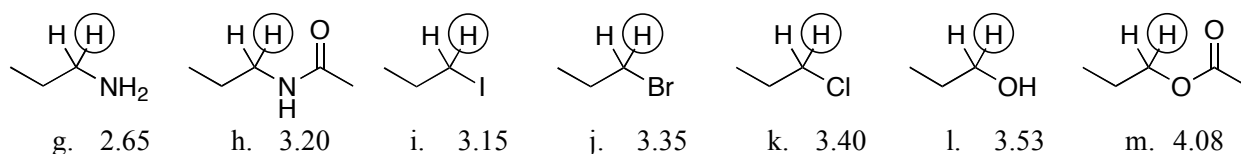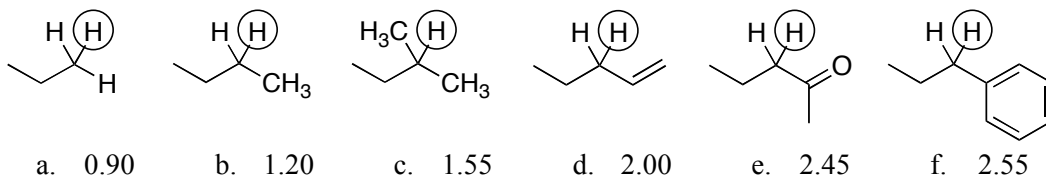
2. The allylic factor has the same basis: sp^2 carbons are more electronegative than sp^3 carbons, so replacing an sp^3 with an sp^2 "deshields"

| 1.20 | 2.00 | 2.45 |
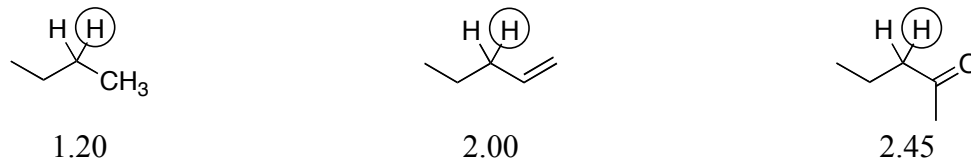
3. An electron-withdrawing carbonyl on a heteroatom makes the heteroatom effectively more electronegative.   So ester versus ether and amide versus amine has the same electronegativity basis.

| 2.65 | 3.20 | 3.53 | 4.08 |
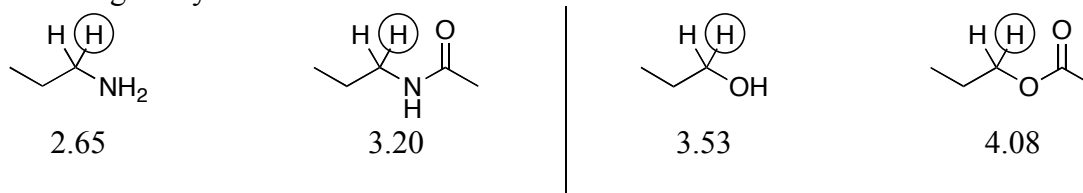
4. Additivity values can be used to predict chemical shifts when two or more functional groups are acting

Vinyl	Carbonyl ("Acyl")	Aryl	Amino	Amido	Halo	Hydroxy/ Alkoxy	Carbonyloxy
0.8	1.2	1.3	1.5	2	2.2	2.3	2.8

- Default reference points: CH_3 0.90 CH_2 1.20   CH 1.50
- Memorize the following qualitative additivity values:
    a. Double-bonded carbons (vinyl, acyl, aryl) → +1
    b. Oxygen or Halogen → +2

5. Strong hybridization effect: hydrogens on sp^2 carbons routinely above 5, those on sp^3 carbons normally come below 5.
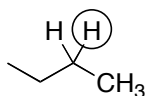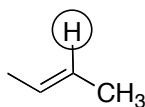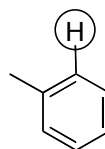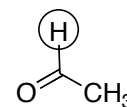
| 1.20 | 5.4 | 7.1 | 9.7 |

6. Functional Groups further away have reduced but sometimes significant impact.
   - Direct "α" attached functional groups have a large impact
   - When the functional group is "β" it makes a difference, but not large
   - When the functional group is "γ" or further, it makes no difference
   - Sometimes a couple of "β" substituents can add up and push a signal set out of it's normal window
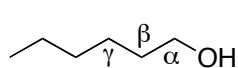
α-CH_2 3.5
β-CH_2 1.3
γ-CH_2 1.2

Key: The impact of two or more functional groups can sometimes deceptively push a signal into a window that you assume means something else
   - A signal in the 3's normally implies an oxygenated (or halogenated) carbon. But it could also result from a double allylic carbon with two carbonyls attached.
   - A signal in the 5's is normally implies an alkene, but it might also result from an sp^3-hybridized carbon that has two oxygen attachments.
   - Etc.

7. **Recognize OH's.**.
   a. An OH can come anywhere, and can easily cause you to make a mistaken conclusion about a feature group.
   b. Three recognition factors for OH signals:
      1. They always **integrate for 1H**, never for 2H or 3H
      2. They **lack sharp splitting**, and often **appear as singlets, often somewhat broad**..
      3. They come anywhere, but often in the 1.5-3.0 range
      4. If you have an OH signal, of course you will also have some C-H signals in the 3.0-4.5 area.

Standard Summary Format and Predicting H-NMR's   There is a standard summary report format for H-NMR's which addresses **chemical shift, integration, and splitting**. Normally an **interpretation**/correlation with the actual structure is also included.

> Ex: $CH_3OCH_2CH_2CH_2C(O)CH_3$ (I'll number the carbons from left to right…)

> Standard report format (approximate chemical shift range, integration, splitting, and interpretation of which signal correlates to which group in the structure…)
> > 3's, 3H, s (CH_3-1)
> > 3's, 2H, t (CH_2-2)
> > 1's, 2H, p (CH_2-3)
> > 2's, 2H, t (CH_2-4)
> > 2's, 3H, s (CH_3-6)

Review + Summary
   1. Use your formula to count elements of unsaturation
   2. Count **how many signal sets** you have.
   3. Check the **integration** of each signal set.
      * 3H → CH_3 group   2H → CH_2 group   1H → CH or OH group
   4. Check the **splitting** of each signal set.
      * N lines → N-1 neighbor hydrogens
   5. Check **"chemical shift" windows** of the lines to provide information regarding the **presence or absence of key functional groups** in your molecule.
      ❑ Beware of misinterpreting overlapping signals
      ❑ Beware of being confused by signal sets caused by OH's or caused by two or more functional groups impacting chemical shift
      ❑ Steps 4 and 5 are definitely interchangeable
   6. **Use "tracking" to work from known components (normally CH₃ end groups, or C₆H₅ end group, or OH end groups) down the chain**
      * **Integration** can tell whether it's a CH_3, CH_2, or CH causing a particular signal set
      * **Chemical shift** and/or **splitting** can then tell you what else may be **attached**
         a. **Chemical shift** tells if a **functional group** is attached
         b. **Splitting** tells what **CH, CH2, or CH3** groups are attached
   7. **End-Check: Check that the structure you believe you actually have would give the number of signal sets you have, the chemical shifts you have, the integrations you have, and the splittings that you have. If not, your structure needs to be corrected!**

^{13}C NMR (Sections 13.13,14)
- ^{13}C is NMR active, ^{12}C is not
- Signals are much weaker, C-13 spectra are harder to get
    - C-13 gives about 1/10,000th as strong a signal as H-NMR
    - Because the natural abundance is only 1%, and the inherent sensitivity is only 1%
- A result is that for C-13 NMR, one or more of the following is usually true:
    1. Take longer
    2. Not as clean a baseline
    3. Higher sample/solvent concentration used
    4. Data processing tricks used in order to shorten the process. These often result in:
        - Loss of splitting information ("decoupled" C-13 NMR's in lab…)
        - Loss of integration information (our C-13 NMR's in lab…)

Summary of C-13 NMR Interpretation:
1. **Count how many lines** you have in a decoupled carbon spectrum. **This will tell you how many types of carbons** you have. (Symmetry equivalent carbons can at times cause the number of lines to be less than the number of carbons in your structure.)
2. **Check diagnostic frequency windows** ("chemical shift windows") of the lines **to provide yes-or-no answers regarding the presence or absence of key functional groups** in your molecule.
3. If **splitting** information is provided via a coupled carbon spectrum, or a DEPT NMR spectrum is provided, or a phase-sensitive 2-dimensional NMR is provided, use tools like these to decide which carbons are CH$_3$, CH$_2$, CH, and no-H C's.

1. **Chemical Shifts: Where do the Lines Come?**

220-160   C=O carbonyl carbons, sp^2 hybridized

> 160-180 → typically ester
> - for formulas that have two oxygens, being able to recognize ester group helps a ton
> 180-220 → other carbonyls (ketone, aldehyde, carboxylic acid, amide)

160-100   C alkene or aromatic carbons, sp^2 hybridized

> - If a molecule has alkene or aromatic, it's usually easy to tell which it is based on chemical formula or on the number of lines in the 100-160 zone (2 for alkene, usually more for aromatics

100-50   C-O oxygen-bearing carbons, single bonds only, sp^3 hybridized
80-30   C-N nitrogen bearing carbons, single bonds only, sp^3 hybridized
80-30   C-X halogen bearing carbons, single bonds only, sp^3 hybridized
50-0   C alkyl carbons, no oxygens attached, sp^3 hybridized

> - This is the default zone for sp^3 carbons with no attached heteroatoms
> - Allylic carbons still fall into the 50-0 zone, unlike in H-NMR where allylic hydrogens are distinct

- Halogens or nitrogens complicate things a bit, because they can appear on either side of the 50-divider.
- But for formulas involving only C, H, and O, the 50-divider is very, very useful.

Using the "Oxygen Zones" for Oxygenated Systems

			220-160 Zone	100-50 Zone
One-Oxygen Formulas	Ketone, Aldehyde		180-220	
	Alcohol			One
	Ether			Two
Two-Oxygen Formulas	Acid		180-220	
	Ester		160-180	One
	Aldehyde/Ketone And Alcohol		180-220	One
	Aldehyde/Ketone And Ether		180-220	Two

2. **Splitting** in a coupled carbon NMR spectrum.
   - C13 NMR's are normally acquired as "decoupled" spectra, in which each carbon signal appears as a singlet, for reasons of speed and simplicity.
   - However, at the cost of extra time and at the expense of some simplicity, it is also possible to get "coupled" C13 NMR's with splitting. The C-13 atoms are split by directly attached hydrogens.
   - These splitting values are very useful, and follow the N+1/N-1 rules (the number of lines is one greater than the number of attached H's).

Quartert (q)	CH_3
Triplet (t)	CH_2
Doublet (d)	CH
Singlet (s)	C (no attached hydrogens)

   - Coupled C-13 has at last two drawbacks:
     1. The signal to noise ratio and thus the sensitivity is a lot worse.
     2. Overlap: With coupled C-13 NMR, there are a lot more lines, and overlapping of lines becomes normal and confusing for non- simple molecules.

3. **Aromatics, Symmetry, Splitting**. Most aromatics have symmetry, and both the number of aromatic lines and the splitting of the aromatic lines can be indicative of the substitution pattern on a benzene. Mono- and para-disubstituted benzenes have symmetry.

4 lines	s, d, d, d	Monosubstituted benzene. (Has symmetry)
4 lines	s, s, d, d	Para-disubstituted benzene. (Has symmetry)
6 lines	s, s, d, d, d, d	Ortho- or meta-disubstituted benzene. (Has no symmetry)

4. **Signal Height/Size**   Unlike 1H-NMR, where integration is really important, signal size is not very important in C-13 NMR.
    a. Signal amplification tricks (to save time) compromise accurate integration
    b. Even when lines have equal area, a narrower one looks much taller than a fatter one
    c. Two patterns that can be somewhat helpful.
        1. Carbons without any attached H's are short. Common in:
        2. Symmetry duplication multiplies signal height (if you have two copies of a carbon, the line will probably be taller than normal!)

Problem Solving and C-13

Alone	In Support with H-NMR
1. Calculate EU 2. Symmetry? Check lines versus formula 3. Look for Obvious Things • Oxygen zones, aryl zone… 4. Use Splitting 5. Look for ends groups • Methyl, phenyl, OH, halogen	Look for obvious things 1. Carbonyls? (any, and if so ester or aldehyde?) 2. Oxygen zones? 3. Aromatic or alkene, and if so with what kind of substitution pattern? 4. Symmetry? 5. CH_3, CH_2, CH count

Infrared Spectroscopy (Chapter 12, Nice Summary in Section 12-11)
• Much more complex than NMR
• In IR, two typical uses:
    a. Functional Group Identification: focus on a few key zones (our use)
    b. "Fingerprint" matchups of unknowns to knowns (we won't do)

Major Bands that are of some Functional Group Interest
3500-2700   N-H, O-H, C-H single bonds
2300-2100   CN, CC triple bonds
1800-1580   C=O, C=N, C=C double bonds

Practical Feature Groups
1. O-H/N-H Zone (except when O-H is a carboxylic acid O-H): 3500-3200
    • **Alcohol Recognition**
    • Amines or amides
    • Note: when looking at an actual spectrum, focus in specifically on the 3500-3200 range, don't just look generally around 3000
        o Because every organic molecule will have a big C-H signal around 2900-3000
        o That is *not* interesting or informative, and should *not* be mistaken for proof of alcohol
    • In contrast to alcohol O-H, carboxylic acid O-H signals are extremely broad, ranging somewhere within 3500-2200

2. Carbonyl Zone: Around 1710 ± 80
    • Very strong signal
    • First thing to check
    1700 rule
    • carbonyls >1700 are "saturated": no attached double-bonded carbons
    • carbonyls <1700 are "unsaturated": an sp^2 attached carbon (i.e. alkene or aromatic)

Saturated, >1700

Unsaturated, <1700
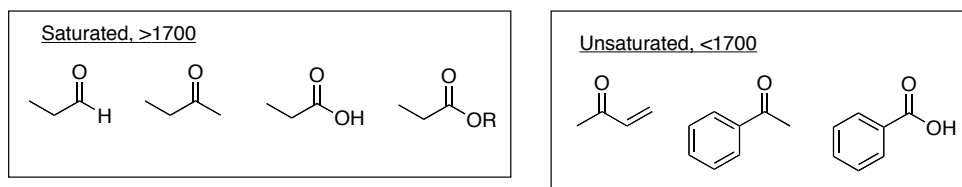
Esters versus Ketones/Aldehydes/Acids
- Saturated esters 1735-1750
- Saturated ketones/aldehydes/acids: 1700-1720

Carboxylic Acids (versus hydroxy ketones)
- Acid has both a carbonyl in the ~1700 zone and a broad hydroxyl spread somewhere in the 3500-2200 zone
- A formula with two oxygens that has one as ketone and one as alcohol would give a carbonyl in the ~1700 zone but a tighter alcohol O-H in the 3500-3200 zone
- Very useful for quick recognition of carboxylic acids

Using the "Oxygen Zones" for Oxygenated Systems

			Carbonyl Zone	Hydroxyl Zone
One-Oxygen Formulas	Ketone, Aldehyde		1700-1720 (if saturated, <1700 if not)	
	Alcohol			3500-3200
	Ether			
Two-Oxygen Formulas	Acid		1700-1720 (if saturated, <1700 if not)	3500-3200 (**broad**)
	Ester		1735-1750 (if saturated)	
	Aldehyde/Ketone And Alcohol		1700-1720 (if saturated, <1700 if not)	3500-3200 (**broad**)
	Aldehyde/Ketone And Ether		1700-1720 (if saturated, <1700 if not)	

Summary of IR (Infrared) Interpretation	
Check for Diagnostic Signals	
3500-3200	OH or NH
1800-1641	C=O
3500-2500 + 1800-1640	CO_2H
Further Information in the "Carbonyl Zone"	
<1700	Unsaturated C=O
>1700	Saturated C=O
1720-1701	Saturated ketones, aldehydes, acids
1750-1735	Saturated ester

Jasperse Organic II NMR Problems

1. C_3H_7Cl
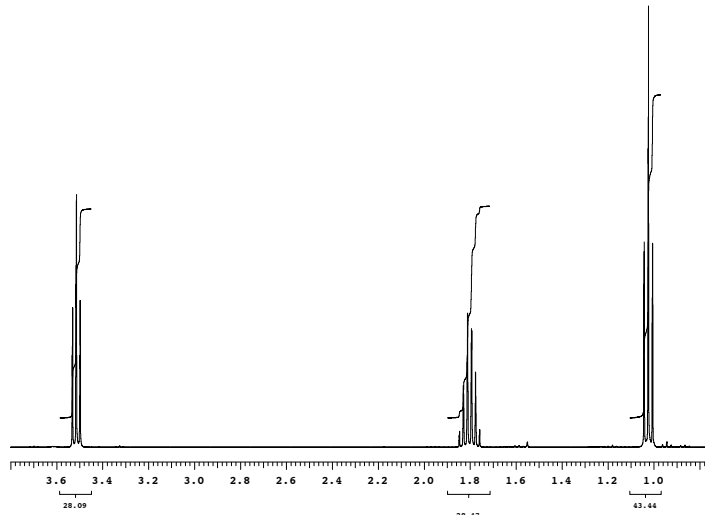
2. $C_5H_{10}O$
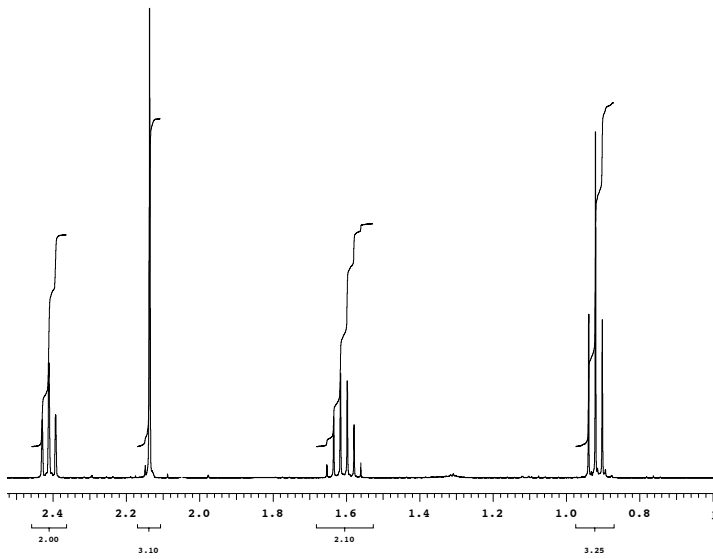
3. $C_4H_8O_2$
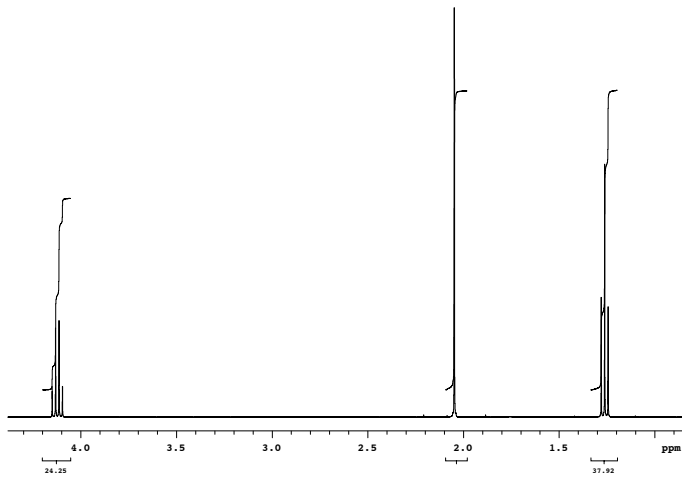
4. C_8H_{10}
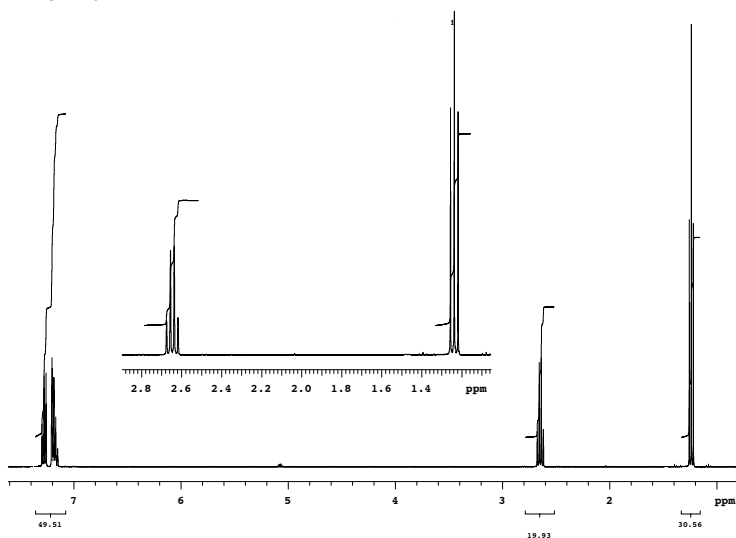
5. $C_5H_{10}O$
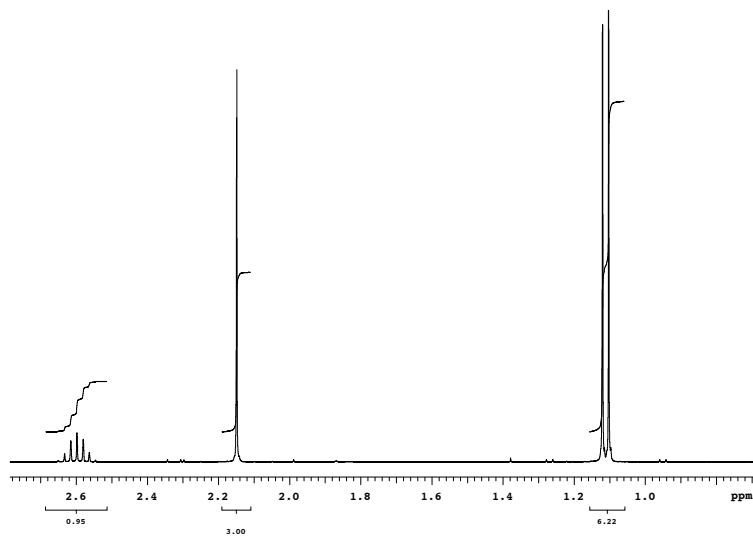
6. Predict the Spectrum for:

a.

b.
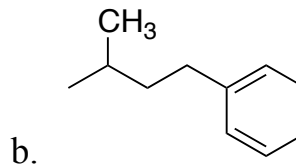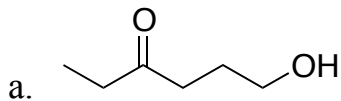
7. Identify the Structure from the Shorthand NMR (nongraphic)
   C_4H_8O
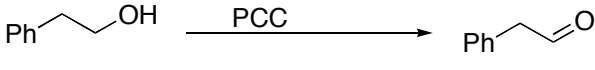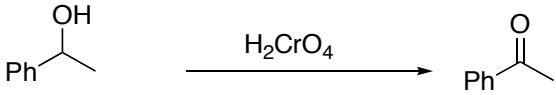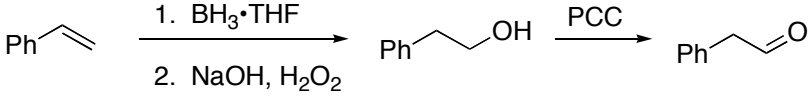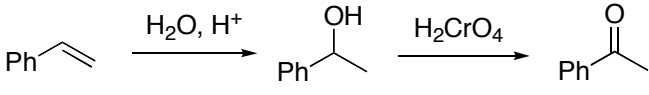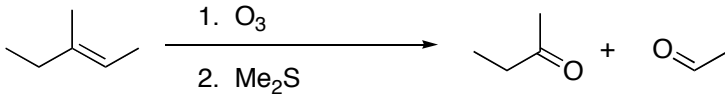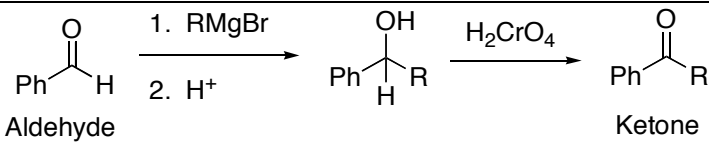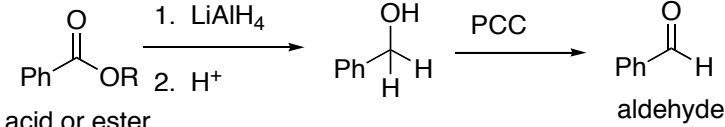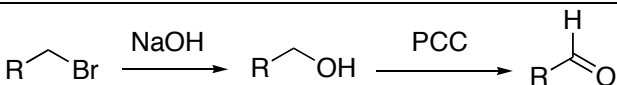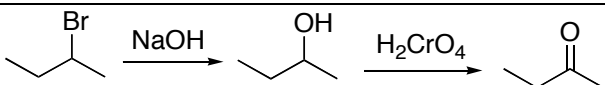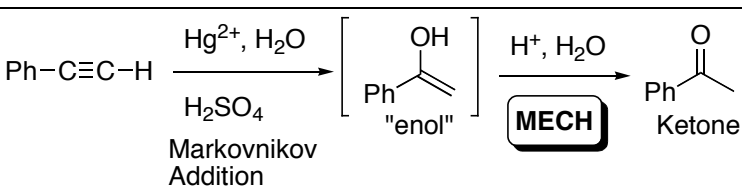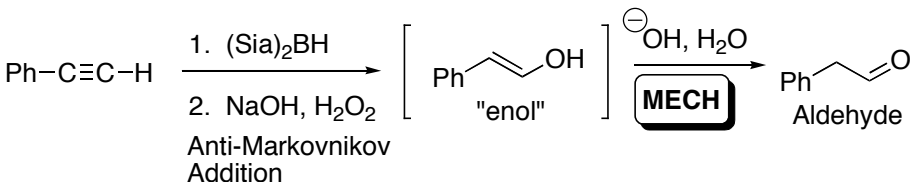
   1.05, triplet, 3H
   2.13, singlet, 3H
   2.47, quartet, 2H

Synthesis of Ketones and Aldehydes

1	Ph⌒⌒OH →(PCC) Ph⌒CHO	11.2
2	Ph-CH(OH)-CH₃ →(H₂CrO₄) Ph-CO-CH₃	11.2
3	Ph-CH=CH₂ →(1. BH₃•THF, 2. NaOH, H₂O₂) Ph⌒⌒OH →(PCC) Ph⌒CHO	8.7
4	Ph-CH=CH₂ →(H₂O, H⁺) Ph-CH(OH)-CH₃ →(H₂CrO₄) Ph-CO-CH₃	8.4
5	→(1. O₃, 2. Me₂S) methyl ethyl ketone + acetaldehyde	8.15
6	Ph-CHO (Aldehyde) →(1. RMgBr, 2. H⁺) Ph-CH(OH)(R) →(H₂CrO₄) Ph-CO-R (Ketone)	10.9
7	Ph-CO-OR (acid or ester) →(1. LiAlH₄, 2. H⁺) Ph-CH(OH)(H) →(PCC) Ph-CHO (aldehyde)	10.11
8	R⌒Br →(NaOH) R⌒OH →(PCC) R-CHO	6.8
9	CH₃CH₂-CHBr-CH₃ →(NaOH) CH₃CH₂-CH(OH)-CH₃ →(H₂CrO₄) CH₃CH₂-CO-CH₃	6.8
10	Ph−C≡C−H →(Hg²⁺, H₂O, H₂SO₄, Markovnikov Addition) [Ph-C(OH)=CH₂ "enol"] →(H⁺, H₂O, MECH) Ph-CO-CH₃ Ketone	9.9F
11	Ph−C≡C−H →(1. (Sia)₂BH, 2. NaOH, H₂O₂, Anti-Markovnikov Addition) [Ph-CH=CH-OH "enol"] →(⁻OH, H₂O, MECH) Ph-CH₂-CHO Aldehyde	9.9F

12	Ph–C(=O)–OH (acid) →[1. 2 RLi][2. H⁺, H₂O] [Ph–C(=O)–OLi] carboxylate anion → [LiO–C(Ph)(R)–OLi] tetrahedral dianion →[acid] [HO–C(Ph)(R)–OH] tetrahedral "hydrate" →[H⁺, H₂O][MECH] Ph–C(=O)–R ketone	18.9
13	Ph–C(=O)–Cl (acid chloride) →[R₂CuLi] Ph–C(=O)–R ketone	18.11
14	(benzene, H) + R–C(=O)–Cl →[AlCl₃] R–C(=O)–Ar Aromatic ketone (from the aryl group's perspective) R–C(=O)–Cl (acid chloride) →[Ar-H, AlCl₃] R–C(=O)–Ar Aromatic ketone (from the acyl group's perspective)	18.11
15	Ph–CN (Nitrile) →[1. RMgBr][2. H⁺, H₂O] [Ph–C(R)=N⁻] →[H⁺] [Ph–C(R)=NH "imine"] →[H⁺, H₂O][MECH] [Ph–C(R)(OH)(NH₂) tetrahedral "aminol"] →[H⁺, H₂O][MECH] Ph–C(=O)–R ketone	18.10
16	Ph–CH₂–Br (Primary Bromide) →[1. KCN][2. RMgBr][3. H⁺, H₂O] Ph–CH₂–CN Nitrile Intermediate (after step 1) →[Steps 2 + 3] Ph–CH₂–C(=O)–R	18.10

Reactions of Ketones and Aldehydes

19	**Anionic** Mech: Addition-Protonation. Strong nucleophile, Strongly anionic. Irreversible.	18.12, 10.9
20	**Anionic** Mech: Addition-Protonation. Strong nucleophile, Strongly anionic. Irreversible.	18.12, 10.11
21	**Anionic** Mech: Addition-Protonation. Medium nucleophile, Weakly anionic; literally buffered. Reversible.	18.15
22	"Hydrates" are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilbrium their aldehyde or ketone. **Anionic** Mech Forward: Addition-Protonation. Nucleophile, anionic mechanism. Reversible. Mech Reverse: Deprotonation-Elimination. Anionic mechanism. Reversible.	18.14
23	"Hydrates" are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilbrium with their aldehyde or ketone. **Cationic** Mech Forward: Protonation-Addition-deprotonation. Weakly nucleophile, cationic mechanism. Reversible. Mech Reverse: Protonation-Elimination-deprotonation. Cationic E1-type mechanism. Reversible.	18.14

24		18.18, 18.19

Cationic
Mech Forward: Protonation-Addition-deprotonation (hemiacetal)   Protonation-elimination-addition-deprotonation   (acetal).   Weak   nucleophile,   cationic mechanism. Reversible.

Mech Reverse: Protonation-Elimination-Addition-deprotonation. (hemiacetal) protonation-elimination-deprotonation (aldehyde or ketone). Reversible.

Notes:
- Reactions are reversible
- The "hemiacetal" is an intermediate, and can never be isolated
- The acetal <u>can</u> be isolated.
- Equilibrium considerations (LeChatelier's principle) apply. When water is plentiful, things go to the left. When water is scarce or removed, and alcohol is abundant, things drive to the right.
- Use H_2O/H^+ to hydrolyze an acetal back to an aldehyde or ketone
- Use $MeOH/H^+$ to convert an aldehyde to an acetal
- Use $HOCH_2CH_2OH/H^+$ to convert a ketone to an acetal
- Aldehydes or ketones can be temporarily "protected" as their acetals, then later "deprotected" by hydrolysis

25		18.16, 18.17

Cationic
Mech Forward: Protonation-Addition-deprotonation (aminol)   Protonation-elimination- deprotonation (imine).   Mild nucleophile, cationic mechanism, buffered conditions. Reversible. Note: sometimes addition precedes protonation, or is concerted with protonation.

Mech Reverse: Protonation-Addition-deprotonation (aminol)   Protonation-elimination- deprotonation (aldehyde or ketone). Reversible.

Notes:
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.

Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.

26	$\underset{R'}{\overset{O}{\parallel}}\!\!\!\diagdown\!\!H$ $\xrightarrow{\text{H}_2\text{CrO}_4 \text{ or Ag}^+ \text{ etc.}}$ $\underset{R'}{\overset{O}{\parallel}}\!\!\!\diagdown\!\!OH$	18.20
	No Mech Responsibility	
	"Tollens test" is a common chemical test for aldehydes. Ag$^+$ undergoes redox reaction with aldeydes to produce shiny Ag metal, or a "silver mirror".	

Ch. 18 Mechanisms
Some New Mechanisms Associated with the Syntheses of Aldehydes and Ketones

10

Enol to Carbonyl, Acid Catalyzed

11

Enol to Carbonyl, Base Catalyzed

12

tetrahedral
"hydrate"

Acid-catalyzed elimination of a
hydrate to a carbonyl

15

15 phase 1

"imine"

H$^+$, H$_2$O **MECH**

tetrahedral "aminol"

Acid-catalyzed addition of water to an imine

protonate   add   deprotonate

15 phase 2

tetrahedral "aminol"

H$^+$, H$_2$O **MECH**

ketone

Acid-catalyzed elimination of amine from an aminol to give a carbonyl

protonate   eliminate   deprotonate

Review: Several Pertinent Mechanistic Principles

1. **Recognize anionic mechanisms** (when a strong anion is involved)
   - In an anionic mechanism, a strong anion will drive the first step
   - In an anionic mechanism, intermediates should avoid positive charges
   - Recognize anionic species even when they are disguised by a cationic metal counterion.

2. **Recognize cationic mechanisms**
   - Recipes that involve acid will be cationic
   - In a cationic mechanism, the first step will routinely involve protonation
   - In a cationic mechanism, the last step will frequently involve deprotonation to return to neutral
   - Normally the main step or steps are sandwiched in between the protonation and deprotonation events

3. Focus on bonds made and broken
4. Draw in hydrogens on carbons whose bonding changes
5. Keep track of lone pairs on reacting centers (in your head if not on paper)
6. Always draw in formal charges where appropriate
7. Arrows show electron flow, from giver to receiver
8. A good mechanism illustrates not only where electrons go as bonds change, but also the timing of bond changes. Avoid drawing bond changes that occur at different times as if they occur in the same step, i.e. as if they were concerted.

Some Mechanisms Associated with the Reactions of Aldehydes and Ketones

19 Grignard Addition of a Carbanion

R'C(=O)R" →(1. RMgBr 2. H₃O⁺)→ R'C(OH)(R)R"

20 Hydride addition.

aldehyde or ketone →(NaBH₄, ROH or 1. LiAlH₄ 2. H⁺)→ R'CH(OH)R

21 HCN addition, anionic mech.

R'C(=O)R + HCN →(KCN)→ R'C(OH)(CN)R

22 Water addition, anionic mech.

aldehyde or ketone ⇌(H₂O, OH⁻)⇌ tetrahedral "hydrate" R'C(OH)(OH)R

22 r

tetrahedral "hydrate" R'C(OH)(OH)R ⇌(H₂O, OH⁻)⇌ aldehyde or ketone R'C(=O)R

23 Water addition, cationic mech.

aldehyde or ketone R'C(=O)R ⇌(H₂O, H⁺)⇌ tetrahedral "hydrate" R'C(OH)(OH)R

23 r

tetrahedral "hydrate" R'C(OH)(OH)R ⇌(H₂O, H⁺)⇌ aldehyde or ketone R'C(=O)R

24

Acetal formation

24r

Acetal hydrolysis.

25

ZNH_2, H^+

aldehyde
or ketone

imine

Imine Formation

Phase 1:
Aminol Formation
(an addition reaction)

protonate   ADD

deprotonate

aminol

Phase 2:
Aminol
to Imine
(an elimination
reaction)

aminol

protonate   eliminate   deprotonate

$-H_2O$

imine

25r

H_2O, H^+

imine

aldehyde
or ketone

Imine Hydrolysis

Phase 1:
Aminol Formation
(an addition reaction)

protonate   ADD

deprotonate

aminol

Phase 2:
Aminol
to Carbonyl
(an elimination
reaction)

aminol

protonate   eliminate   deprotonate

$-ZNH_2$

carbonyl

Classification of Mechanisms Associated With Ketone/Aldehyde Reactions.
- There may seem to be a dizzying number of mechanisms this chapter. But all of them simplify into some combination of acid- or base-catalyzed **addition reaction**, **elimination reaction** and/or **substitution reaction**.
- To predict what product forms that can be isolated, you will need to know when an addition is all that happens, and when an addition is followed by elimination or substitution.
- Many reactions are reversible, and are controlled by equilibrium principles, so you ought to be able to go in either direction.
- The sequencing of many of the mechanistic steps is dependent on whether you are under acidic (cationic) conditions or basic (anionic) conditions.

ADDITION REACTIONS.
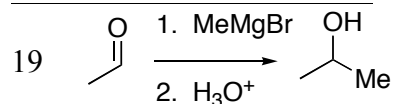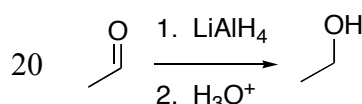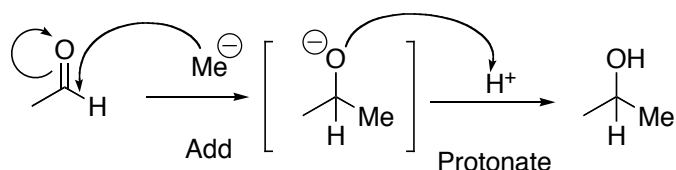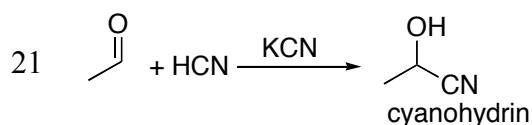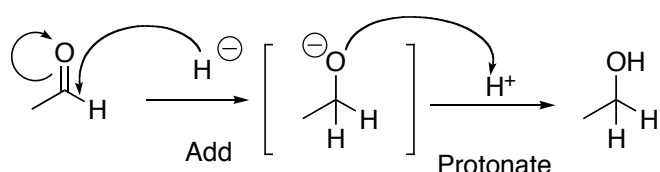
19 Grignard Addition of a Carbanion

20 Hydride addition.

21 HCN addition, anionic mech.
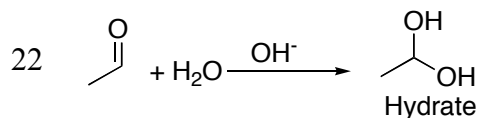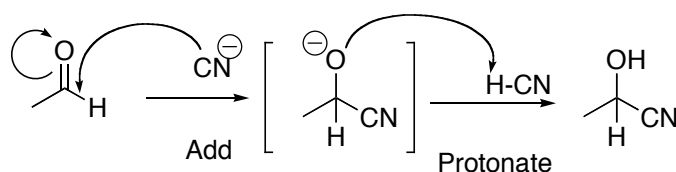
22 Water addition, anionic mech.
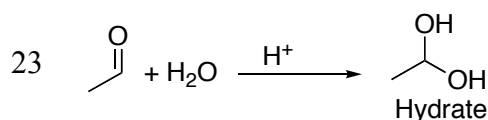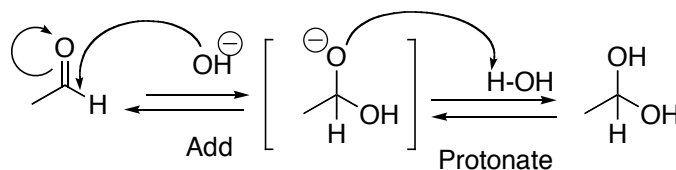
23 Water addition, cationic mech.
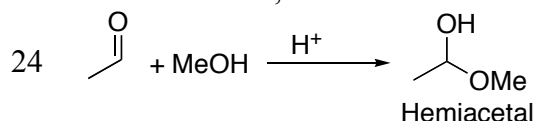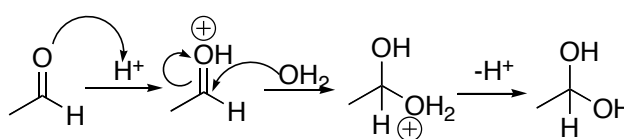
24 Alcohol addition, cationic mech.
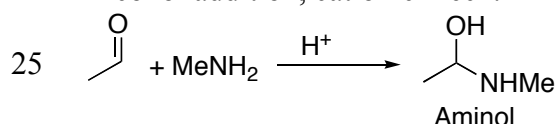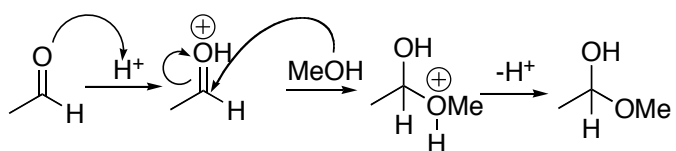
25 Amine addition, cationic mech.
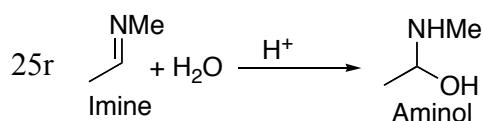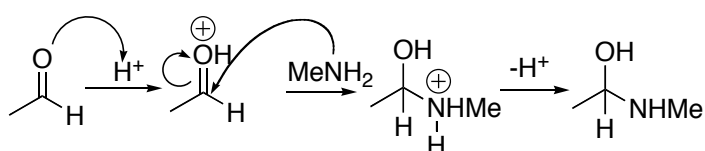
25r Water addition to imine, cationic mech

Elimination Reactions.

22r	
23r	
24r	
25r	
25b	

Substitution Reactions.

| 24b | |
| 24r | |

A. Nomenclature (Section 18-3)
1. Aldehydes:
   a. IUPAC: Alkan**al**
   - Note: carbonyl takes precedence over alcohols (hydroxy), aromatics, alkenes, halides.
   - Aldehyde carbon is always #1, so needs no number (don't forget to count that carbon!)
   b. Aldehydes are often written as RCHO
   c. Common Names: (Memorize)
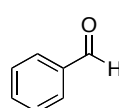
2. Ketones:
   a. IUPAC: alkan-x-**one**

   > **Need number, remember to number!!**
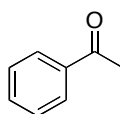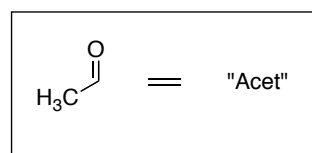
   b. Common Names: (Memorize)

B. General Review of Basic Nomenclature Principles
1. **Core name versus Substituents.** Which part of the molecule can be included in the core name, and which parts need to treated as substituents?

2. **Ranking of Functional Group Priority.**
   - when 2 or more functional groups are present, the priority functional group is included in the core name, and the core numbering is based on the priority group
   - Many common names incorporate two functional groups (benzoic acid, phenol, etc..)
   -

	$\overset{O}{\underset{O}{\overset{||}{C}}}$	$\overset{O}{\overset{||}{C}}$	OH	NH$_2$	Aryl	Alkene
Families	Acids Esters	Ketones Aldehydes				
Core Name	Alkanoic acids	alkan**al** alkan- x-**one**	alkan-x-**ol**	alkan-x- **amine**		alk-x-**ene**
Substituent		alkanoyl or (x-oxoalkyl)	hydroxy	amino	Phenyl	

   -
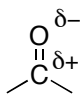
3. **Remember Descriptors**
   - Position of functional groups
   - Position of substituents
   - Stereochemical descriptors (cis/trans, E/Z, R/S)

4. **Punctuation**
   - Hyphenate numbers and stereochemical descriptors
   - Parenthesize stereochemical descriptors: (R)/(S), (E)/(Z)
   - Do not put any spaces for molecular-style names
   - Do put spaces for ionic style names

C. **Properties of Carbonyls (Sections 18.2, 4)**

$O^{\delta-}$ $\overset{\|}{\underset{C}{C}}{}^{\delta+}$	• Strongly polar • Sp^2, flat, ~120° angles • Can H-bond water (impacting water solubility) • But cannot H-bond self (impacting boiling point)

For molecules of similar weight:
1. Boiling Point: Alcohols (H-bonding) >>> ketones (polar) > ethers (less polar) > alkanes (nonpolar)
   • Large difference between alcohols and ketones because of H-bonding
2. Water solubility: Alcohols > ketones > ethers >>> alkanes (nonpolar)
   • The difference between alcohols and ketones is much smaller, since both can H-bond to water's hydrogens

Note: Many groups can "hydrolyze" to carbonyls
• A carbon with two heteroatoms attached, single-bonded or double-bonded
• A carbon with one heteroatom and one π-bond
• Often base or acid or some special acid assistant helps
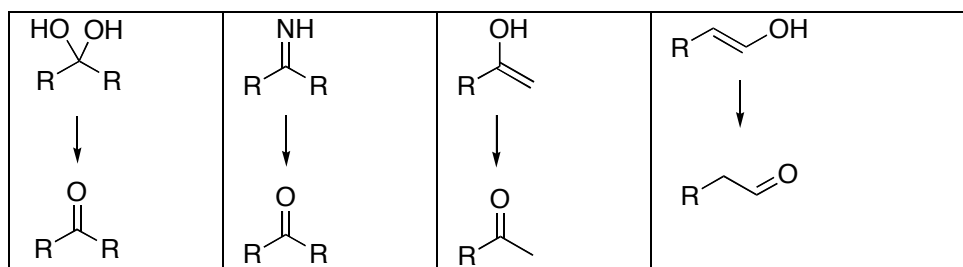
F. General Reactivity of Ketones and Aldehydes: Addition Reactions (Section 18.12)
Key: Are reaction conditions anionic/basic or cationic/acidic (or perhaps buffered?)
1. **Anionic Conditions** (when a strong anion is involved)
   a. General principles review for strongly anionic/basic conditions apply
      1. In an anionic mechanism, a strong anion will drive the first step
      2. In an anionic mechanism, intermediates should avoid positive charges
      3. Recognize anionic species even when they are disguised by a cationic metal counterion.

   b. Anionic additions to ketones
      1. Strong nucleophile required (R $^\ominus$, H $^\ominus$, HO $^\ominus$, …)
         • Intermediates have negative charge
      2. Addition first, protonation second
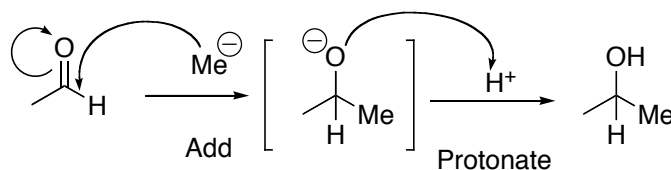
2. **Cationic Conditions** (acid is involved)
   a. General principles review for acid/cartionic conditions apply
      - Recipes that involve acid will be cationic
      - In a cationic mechanism, the first step will routinely involve protonation
      - In a cationic mechanism, the last step will frequently involve deprotonation to return to neutral
   - Normally the main step or steps are sandwiched in between the protonation and deprotonation events
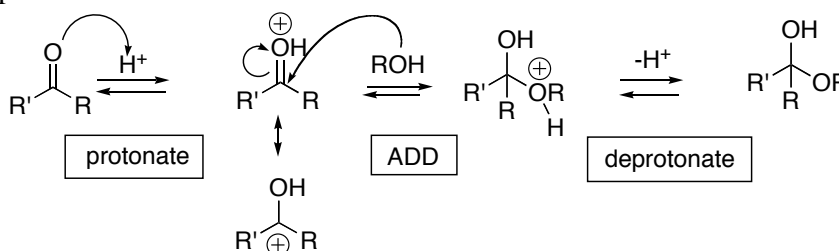
   b. Cationic additions to ketones
      1. Weak, neutral nucleophile involved (ROH, HOH…)
      2. Intermediates have positive charge
      3. **Protonation first, addition second**
         - Weak nucleophile is not strong enough to add to neutral carbonyl
         - Protonation activates the carbonyl as an electrophile
      4. A deprotonation step is routinely required following addition, to get back to neutral
      5. Addition is normally reversible
         - Nucleophile can come back off
         - Nucleophile is normally a reasonable leaving group

3. **Buffer Conditions** (both weak acid and weak base/nucleophile are present at same time)
   - RNH_2/H^+, KCN/HCN…
   - Reversibility again applies
   - Whether addition comes before protonation, or protonation precedes addition depends on the exact case

4. **Anion Conditions**: Nucleophilic addition versus deprotonation (enolate chemistry)
   - Sometimes an anion will function as a base and remove a proton rather than functioning as a nucleophile and adding to the carbonyl
   - Comparable to S_N2 versus E2 reactions
   - Anion size will again factor, with bulky bases more likely to deprotonate and smaller ones to add
   - Chapter 22 will deal with the deprotonation pathway, followed by nucleophilic attack on electrophiles
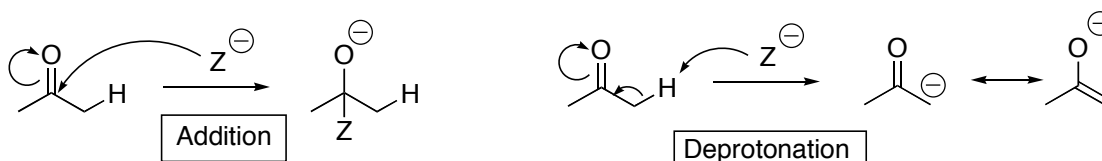
Equilibrium and Acetals
1. Normally favors the carbonyl, especially for ketones
2. Push to the acetal side by using excess alcohol
3. Push to carbonyl side by using excess water
4. **Equilibrium improves greatly for cyclic acetals.**
5. **Hemiacetals have a favorable equilibrium if and only if a 5- or 6-ring hemiacetal can form.**   (This is central to carboyhydrate/sugar chemistry.)

Hemiacetals, mixed acetals, and Sugar/Carbohydrate Chemistry (interest, not test)
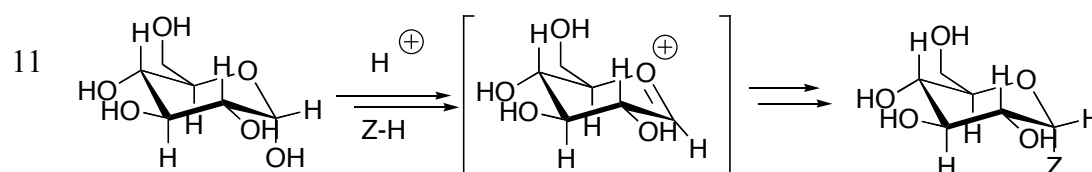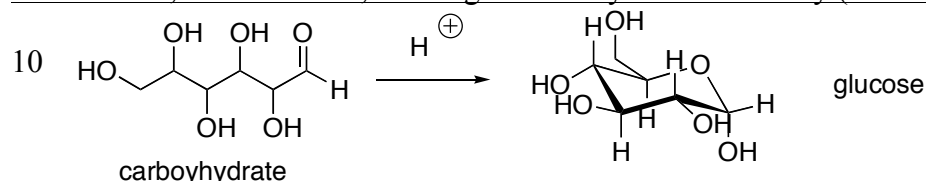
Notes:
1. Acetal or hemiacetal carbons have two single-bond oxygens
2. When thinking about an acetal being hydrolyzed, the carbon with two single-bond oxygens hydrolyzes to a carbonyl
3. Acetal or hemiacetal carbons are **highly reactive as S_N1 substrates** thanks to cation stabilization by oxygen donor
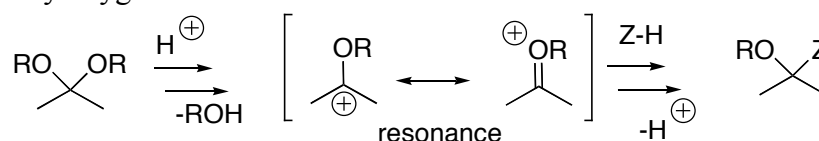
4. Carbohydrates exist as hemiacetals or acetals
5. Carbohydrates can polymerize or make complex derivatives via substitution at their acetal carbons

Acetals as Protecting Groups in Synthesis (Section 18-19)
1. Reactivity: Aldehydes > Ketones >> Esters
    a. Aldehydes versus Ketones Why:
        • Sterics, ketones are more cluttered and additions make things worse
        • Electronics, ketones are more stable with two electron-donating groups
    b. Ketones versus Esters Why:
        • Electronics, the conjugation stabilizes esters
2. **Selective protection**:
    a. Methanol can be used to protect an aldehyde, while a ketone or ester will go untouched.
    b. Ethylene glycol can be used to protect a ketone, while an ester will be untouched.

Addition of H_2N-Z Reagents (Sections 18-16,17)
1. C=N species can sometimes be hydrolyzed back to carbonyls by H_2O/H^+
2. 2,4-DNP derivatives are easily made and usually crystalline

   a. reaction of an unknown with DNPH to make a solid DNP-derivative is proof of
      aldehyde or ketone
   b. The melting point of DNP-derivatives permits identification
   c.

Oxidation of Aldehydes (Section 18.20)
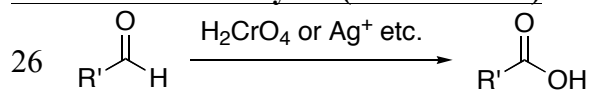
26
$$R' \overset{O}{\underset{}{\parallel}} H \xrightarrow{H_2CrO_4 \text{ or } Ag^+ \text{ etc.}} R' \overset{O}{\underset{}{\parallel}} OH$$

18.20

No Mech Responsibility

"Tollens test" is a common chemical test for aldehydes. Ag^+ undergoes redox reaction with aldeydes to produce shiny Ag metal, or a "silver mirror".

Tollens reagent: $Ag(NH_3)_2^+$ Chemical test for **aldehydes**
   •   A silver mirror forms

Chem 360-Jasperse   **Chapter 22 (Enolate Chemistry) Reaction Summary**

PROTON as ELECTROPHILE

1.
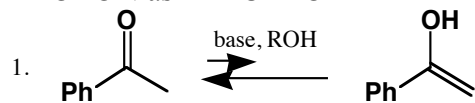
-Base-catalyzed keto-enol equilibrium
-know mech (either direction)
-know impact of substituents on enol concentration

2.
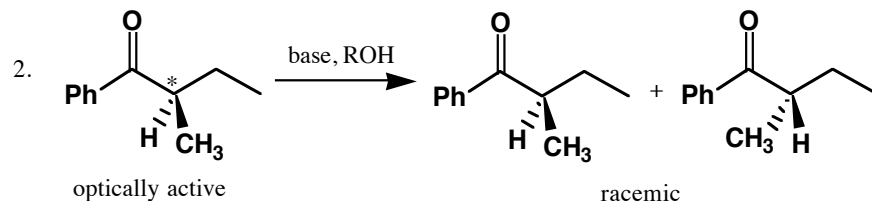
-Racemization of α-chiral optically active carbonyls
-Mech

HALOGEN as ELECTROPHILE

3.
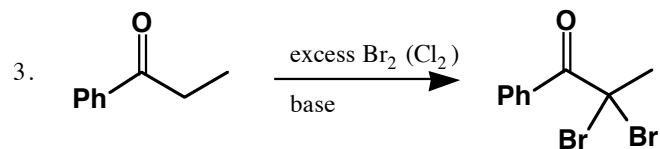
-Base catalyzed halogenation
-with excess halogen, all α-hydrogens get replaced
-Mech

4.
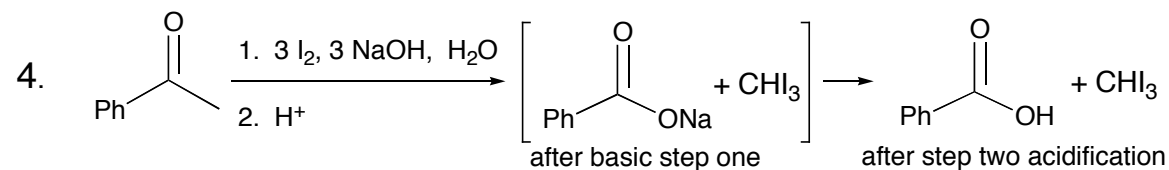
-Iodoform reaction.
-chemical test for methyl ketones

ALKYL HALIDE as ELECTROPHILE

6.

$$\text{Z-C(=O)-CH}_3 \xrightarrow[\text{2. R-X}]{\text{1. LDA}} \text{Z-C(=O)-CH}_2\text{-R}$$
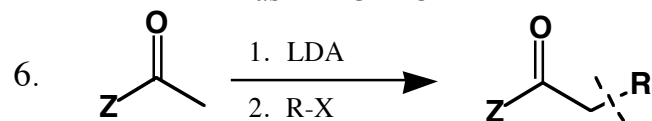
-Enolate alkylation
-strong LDA base required to completely deprotonate carbonyl
-Mech
-Ketones, Esters, Amides, Aldehydes: doesn't matter which kind of carbonyl
-unsymmetrical ketones give isomer problems
-S_N2 alkylation restricts R-X to active ones

7.

$$\xrightarrow[\text{2. R-X}]{\text{1. NaOR}} \xrightarrow[]{\text{H}_3\text{O}^+, \text{heat}}$$
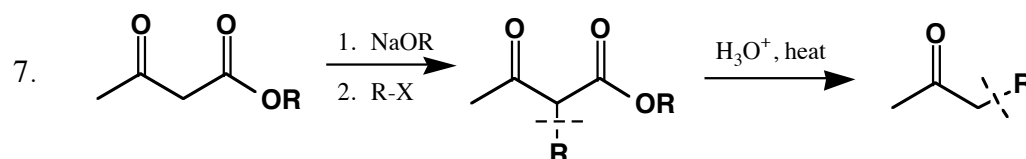
-Enolate alkylation of 1,3-ketoester
-alkoxide base strong enough to completely generate enolate
-Mech for alkylation
-S_N2 alkylation restricts R-X
-position of alkylation is unambiguous
-acid-catalyzed hydrolysis/decarboxylation

8.

$$\xrightarrow[\text{2. R-X}]{\text{1. NaOR}} \xrightarrow[]{\text{H}_3\text{O}^+, \text{heat}}$$
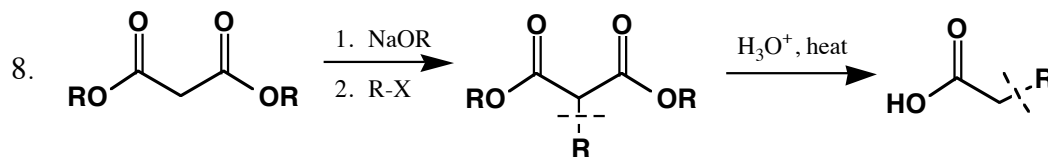
-Enolate alkylation of 1,3-diester
-alkoxide base strong enough to completely generate enolate
-Mech for alkylation
-S_N2 alkylation restricts R-X
-acid catalyzed hydrolysis/decarboxylation
-Final product is an ACID (Diester →Acid)
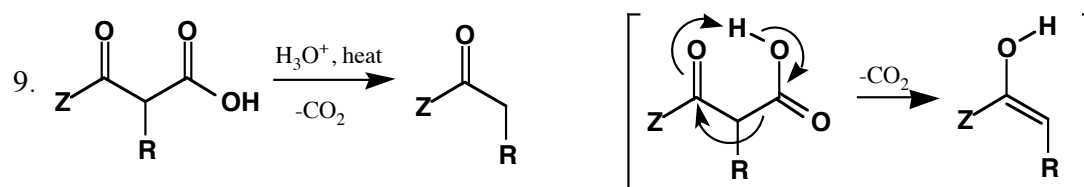
9.

$$\xrightarrow[\text{-CO}_2]{\text{H}_3\text{O}^+, \text{heat}} \qquad \left[\quad \xrightarrow[]{\text{-CO}_2} \quad \right]$$

-decarboxylation of a 1,3-carbonyl acid
-"Z" can be anything so that you end with a ketone, aldehyde, or acid at the end
-know the mechanism for the decarboxylation, and acid-catalyzed enol to carbonyl isomerization
-rate will be impacted by stability of the enol intermediate

ALDEHYDE/KETONE as ELECTROPHILE

10.
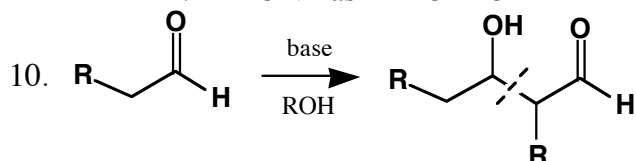
-Aldol Reaction
-Mech

11.
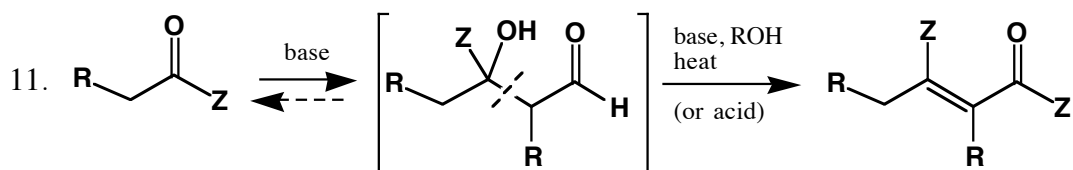
-Aldol Condensation
-Ketones as well as Aldehydes can be used
-In ketone case, unfavorable aldol equilibrium is still drawn off to enone
-In Aldehyde case, can stop at aldol if you don't heat
-Mech
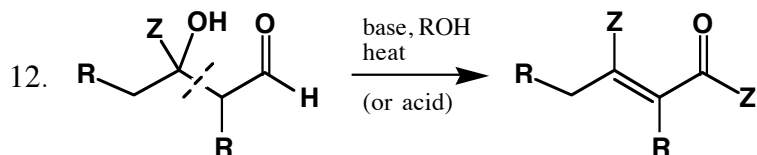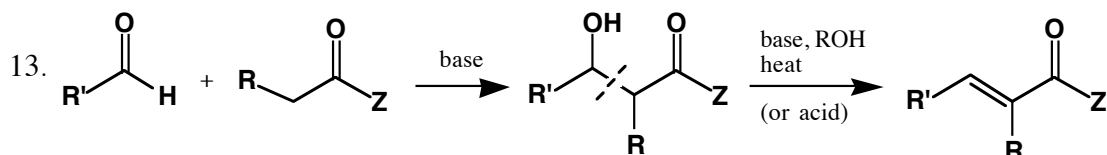
12.

-Aldol dehydration
-Mech under basic conditions

13.

-Crossed Aldol (2 different carbonyls)
-Many variations, but there must be some differentiation so that one acts selectively as the enolate and the other as the electrophile
-Mech

14.
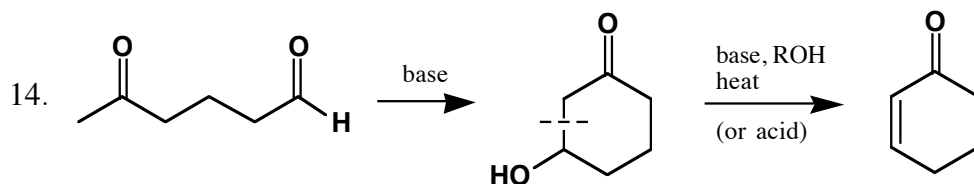
-Intramolecular aldol
-Mech
-many variations
-Normally only good for 5, 6-membered rings

ESTER as ELECTROPHILE
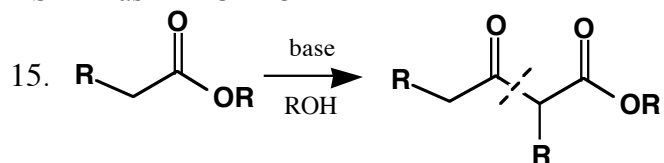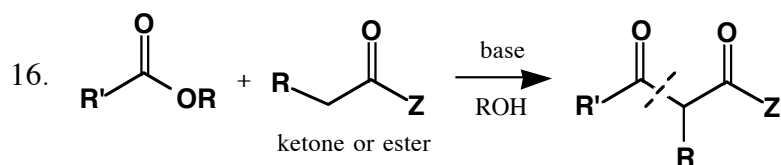
15.

-Claisen Reaction
-Mech
-Produces 1,3-ketoester

16.

ketone or ester

-Crossed Claisen
-May include cyclic Claisen reactions
-If the "enolate" carbonyl is a ketone, get a 1,3-diketone
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester
-Mech

WITTIG REACTION

19.

-Mech

20.
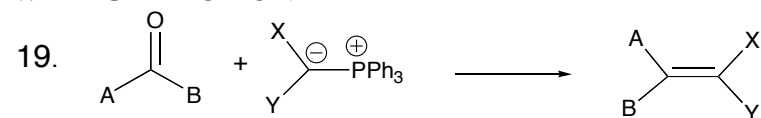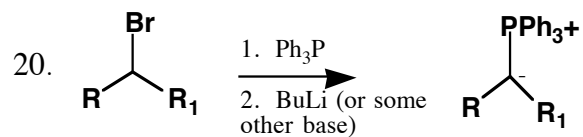
-Mech

Chem 360-Jasperse   **Chapter   22   (Enolate   Chemistry)   Reaction   Mechanisms Summary**
- Note: in many of these reactions, I simply write in "base". But for specific reactions, you need to recognize and specify the actual base that does the work.

PROTON as ELECTROPHILE
Ketone to Enol
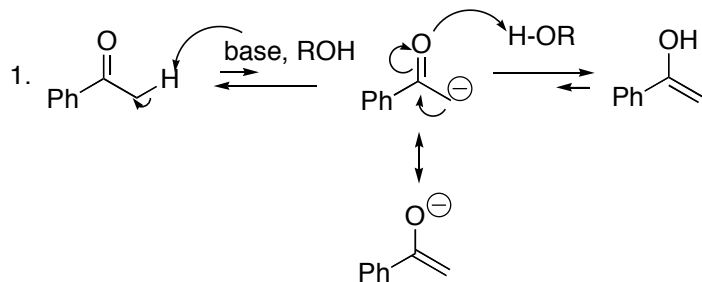
Enol Back to Ketone:
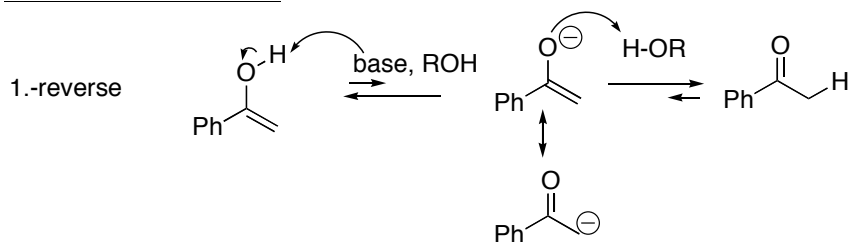
Deprotonation/Reprotonation to Racemize an optically active α-chiral center

optically active   racemic   enantiomer or original. Protonation from the front gives enantiomer, from the back gives the original. The result is a 50/50 racemic mixture.
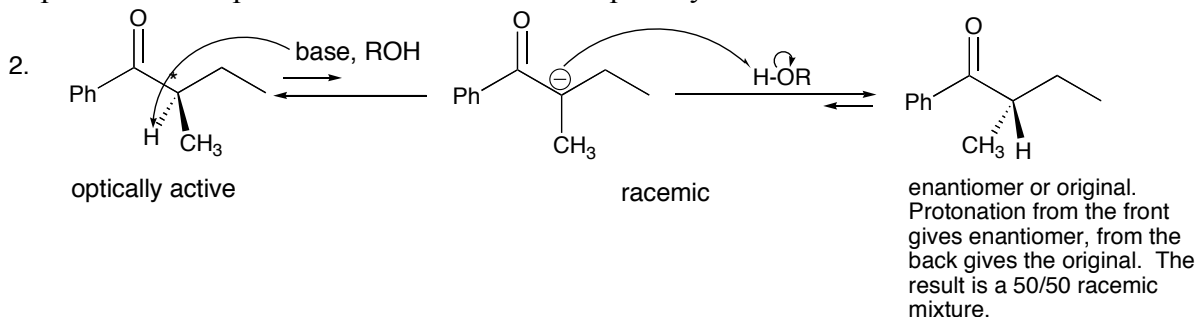
HALOGEN as ELECTROPHILE
Base catalyzed halogenation. Sequential deprotonation/halogenation until all the α-hydrogens are replaced.
- Note: addition of an electronegative, electron-withdrawing halogen stabilizes subsequent anion formation. As a result, the bromoketone formed after the first substitution is actually more acidic and therefore more reactive than the original ketone. For this reason you can't just stop with a single halogenation under base conditions. (But you can under acid conditions, via an enol rather than enolate mechanism.)
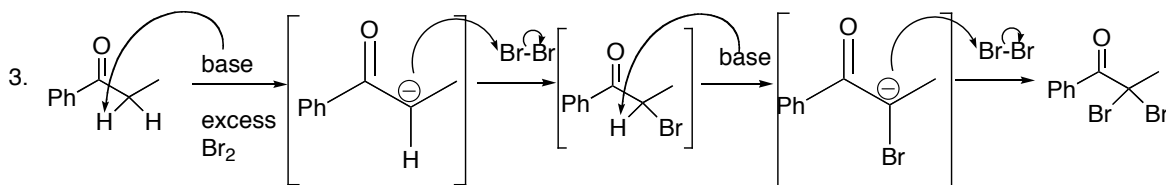
ALKYL HALIDE as ELECTROPHILE
With Strong LDA as Base, using a Monocarbonyl

6.
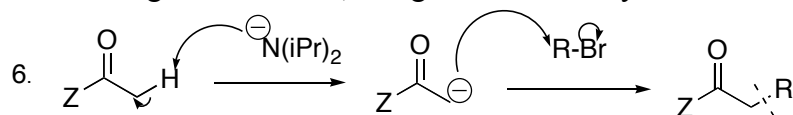
1. Z can be anything: works for ketones, esters, aldehydes, esters,…
2. "LDA" is lithium diisopropylamine, provides the nitrogen anion shown
3. strong LDA base required to completely deprotonate carbonyl. The base strength
    enables the enolate to form completely, no equilibrium or reversibility issues.
4. unsymmetrical ketones give isomer problems. If there are α-hydrogens on both left
    and right side of ketone, which will get deprotonated selectively?
5. S_N2 alkylation restricts R-X to active ones (ideally primary or allylic/benzylic…)
6. Sequencing: the LDA must be added first, allowing the enolate to form completely;
    then the alkyl halide is added subsequently. If you add the halide at the beginning, it
    reacts with LDA
7. LDA deprotonates the carbonyl rather than adding to the carbonyl carbon for steric
    reasons

Using 1,3-Dicarbonyls, Such that Weaker Oxygen Bases are Strong Enough
 Strong LDA as Base, using a Monocarbonyl
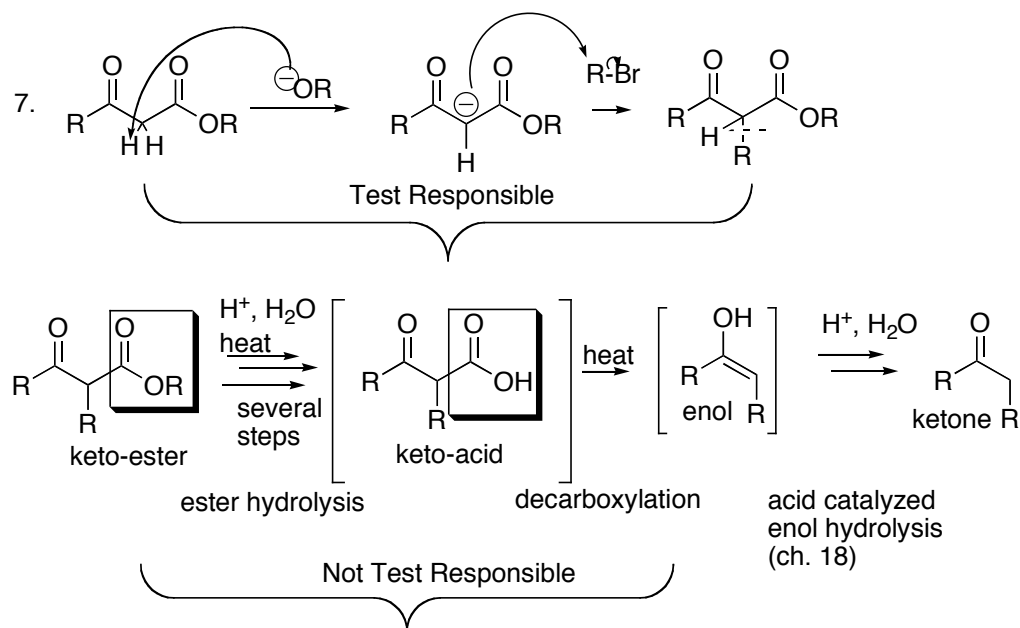
7.

Test Responsible

-alkoxide base strong enough to completely generate enolate
-S_N2 alkylation restricts R-X
-acid-catalyzed hydrolysis/decarboxylation
-not test responsible for the acid/catalyzed ester hydrolysis or the keto-acid decarboxylation
mechanisms
-you are responsible for the acid-catalysis enol hydrolysis (not detailed here, but was in Ch.
18)

8.

Test Responsible

ester-ester → ester hydrolysis → acid-acid → decarboxylation → enol R → acid catalyzed enol hydrolysis (ch. 18) → acid

Not Test Responsible

-alkoxide base strong enough to completely generate enolate
-S_N2 alkylation restricts R-X
-acid-catalyzed hydrolysis/decarboxylation
-not test responsible for the acid/catalyzed ester hydrolysis or the keto-acid decarboxylation mechanisms
-you are responsible for the acid-catalysis enol hydrolysis (not detailed here, but was in Ch. 18)

9.
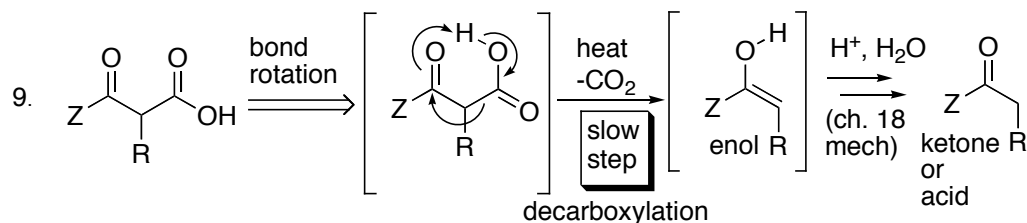
Not Fully Test Responsible. But must know that ENOL is key intermediate that forms in the slow step.
What is good for the enol (and it's alkene) accelerates the decarboxylation

-decarboxylation of a 1,3-carbonyl acid
-"Z" can be anything so that you end with a ketone, aldehyde, or acid at the end
-rate will be impacted by stability of the enol intermediate (more highly substituted enol alkene is better; conjugated enol alkene will form faster....)
-since the mechanism depends on the conversion of the left carbonyl into an enol, decarboxylations are limited to 1,3-carbonyl acids. If you have a 1,2-carbonyl acid or a 1,4-carbonyl acid (etc), the formation of an enol will not be possible and the decarboxylation will not occur

ALDEHYDE/KETONE as ELECTROPHILE

Simple Aldol Reaction, giving a β-hydroxy-carbonyl. In which the same carbonyl functions as both enolate precursor and electrophile.
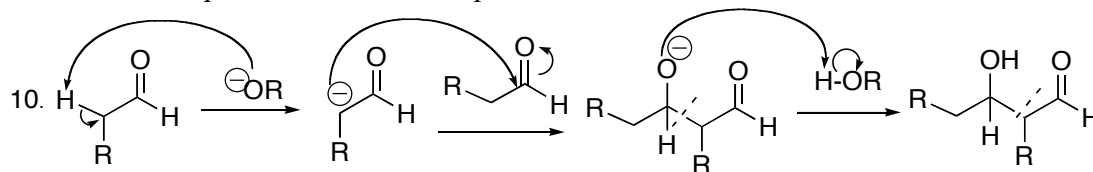
-Deprotonate-react-protonate
-Notice in this case that it's the same carbonyl that functions as both the enolate precursor but also as the electrophile.

Aldol Condensation, giving an enone.   In which the initial aldol product undergoes dehydration.
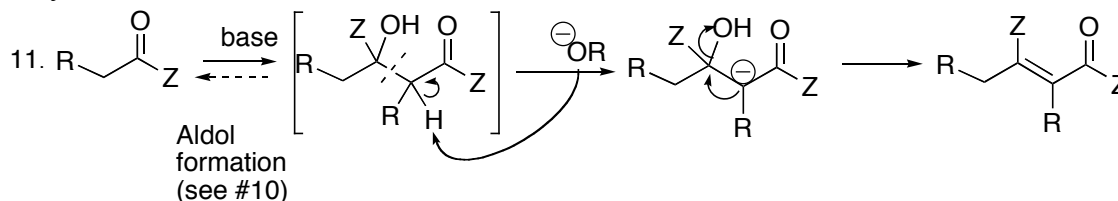
-The aldol product is formed as shown in mechanism 10. But under extended opportunity or heat, the product β-hydroxy group is eliminated to give the enone.
-The elimination mechanism involves deprotonation to enolate, followed by hydroxide extrusion
-Ketones as well as Aldehydes can be used
-In ketone case, unfavorable aldol equilibrium is still drawn off to enone
-In Aldehyde case, can stop at aldol if you don't heat and/or if you stop quickly enough

General Dehydration of β-hydroxy Carbonyls to Give α,β-unsaturated carbonyls
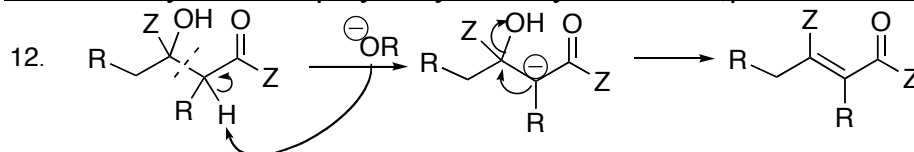
-Aldol dehydration
-Mech under basic conditions
- β-hydroxy Carbonyls can also eliminate water to give enones under acid conditions, via a different mechanism.

Crossed Aldol Reaction, in Which One carbonyl compound serves selectively as the Enolate Precursor and a different one (usually aldehyde) as the electrophile
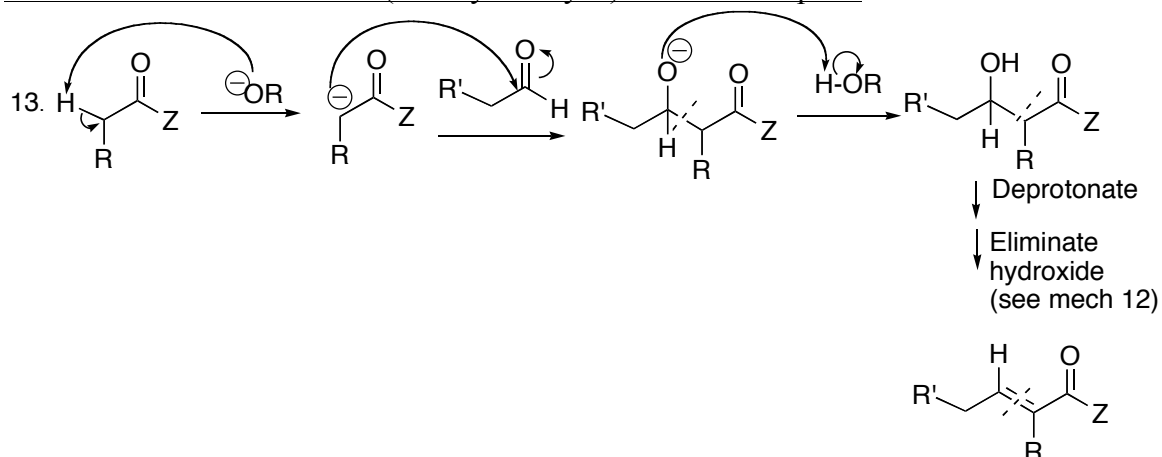
-Crossed Aldol (2 different carbonyls)
-Many variations, but there must be some differentiation so that one acts selectively as the enolate and the other as the electrophile
-because aldehydes are so much more reactive as electrophiles, and because ketones are so much weaker as electrophiles and even when they do function as electrophiles the addition is reversible, crossed aldols between ketones and aldehydes work well, with the ketone reacting as the enolate and the aldehyde as the electrophile.
-The mechanisms for the addition and also the subsequent possibly dehydration are essentially the same as for reactions 10-12.

Aldol Cyclization: Basically a crossed aldol reaction in which both carbonyls are tied together, and in which aldol reaction results in formation of a cyclic rather than an acylic β-hydroxy carbonyl
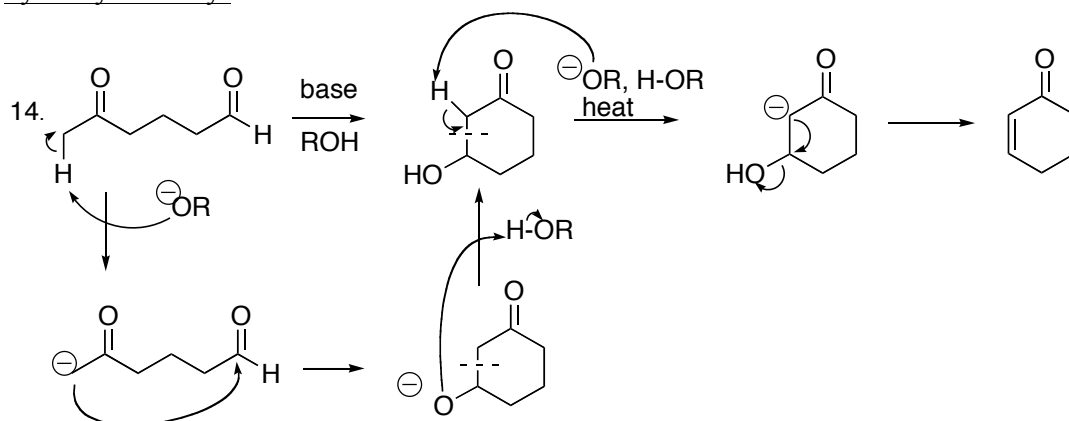
-Intramolecular aldol
-many variations
-Normally only good for 5, 6-membered rings
-There are often multiple α-hydrogens that can give multiple different enolates. But since enolate formation is reversible, reaction proceeds via the enolate that can:
react with the best electrophile. (Aldehyde rather than a ketone), and react to give the best ring size (5 or 6 membered rings >>> 7-membered rings >> 3-, 4-, or ≥8-membered rings)

ESTER as ELECTROPHILE
<u>Simple Claisen Reaction</u>, giving a β-ketoester. In which the same ester functions as both enolate precursor and electrophile.

15.
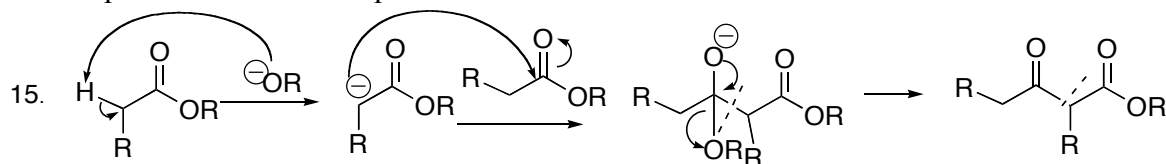
-Produces 1,3-ketoester
-The alkoxide used as base should match the R-group found in the ester. For example, if the ester OR group is OMe, then the base should be NaOMe/MeOH. If the ester OR group is OEt, then NaOEt/EtOH should be used, etc.
-Following enolate addition, the tetrahedral intermediate is *not* stable, and eliminates alkoxide to regenerate the carbonyl.
-Note: Under basic reaction conditions, the keto-ester is normally deprotonated to a stabilized enolate. Following acidic workup, the enolate is reprotonated to give the actual keto-ester product. The enolate formation is actually crucial, because it "protects" the ketone from nucleophilic attack.
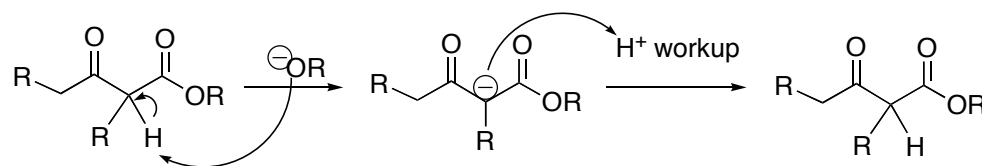
<u>Crossed Claisen Reaction</u>, giving either a β-ketoester or a 1,3-diketone. In which either a ketone or an ester functions as the enolated precursor, and a different ester functions as electrophile.

16.
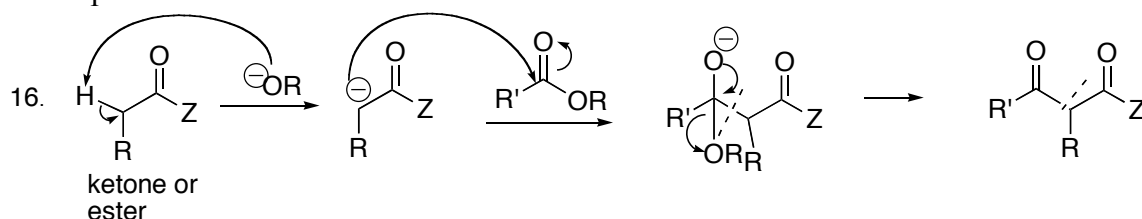
ketone or
ester

-Crossed Claisen
-If the "enolate" carbonyl is a ketone, get a 1,3-diketone
-When ketones and esters are mixed, the ketone usually functions as the enolate and the ester as the electrophile, because a) the ketone is more acidic, so makes enolate more easily, and b) addition/elimination to the ester is irreversible, whereas addition to ketone is reversible
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester. These work best if only one of the esters has α-hydrogens, so that you have just one enolate available.
-May include cyclic Claisen reactions (see example below)

WITTIG REACTION

19.

(and $O{=}PPh_3$)

20.
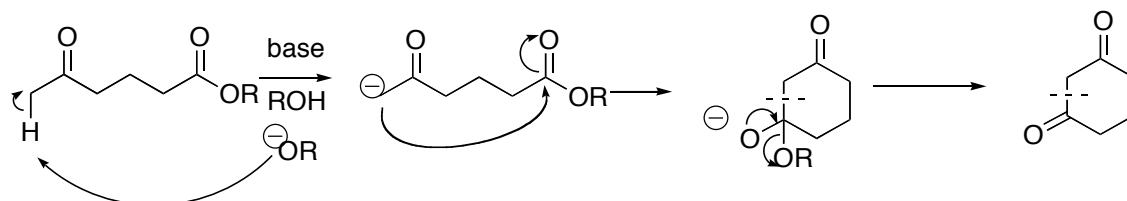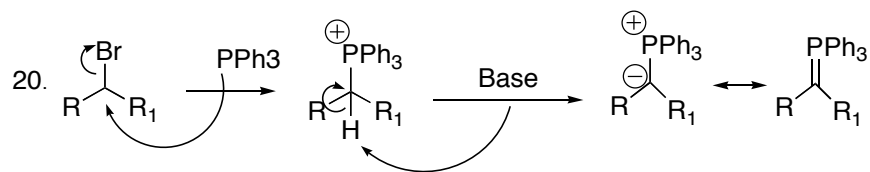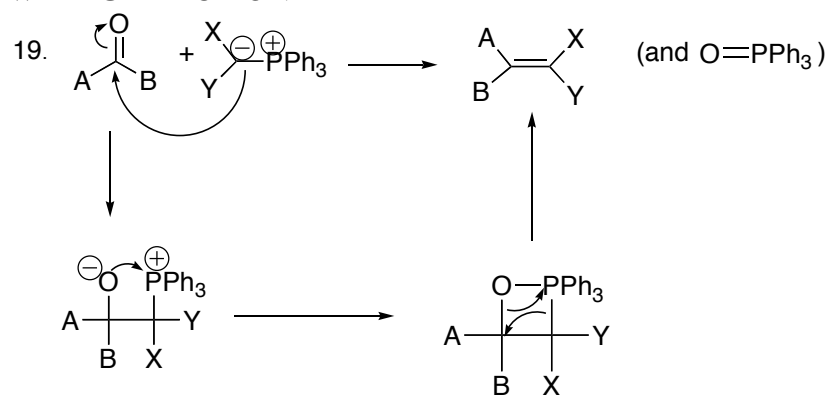
Ch. 22 Additions and Condensations of Enols and Enolate Ions

TYPICAL MECHANISM: Via ENOLATE Anion

Z = H (Aldehyde)
Z = R (Ketone)
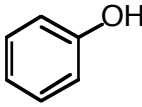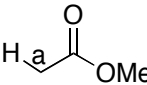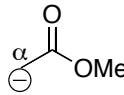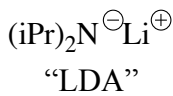Z = OR (Ester)
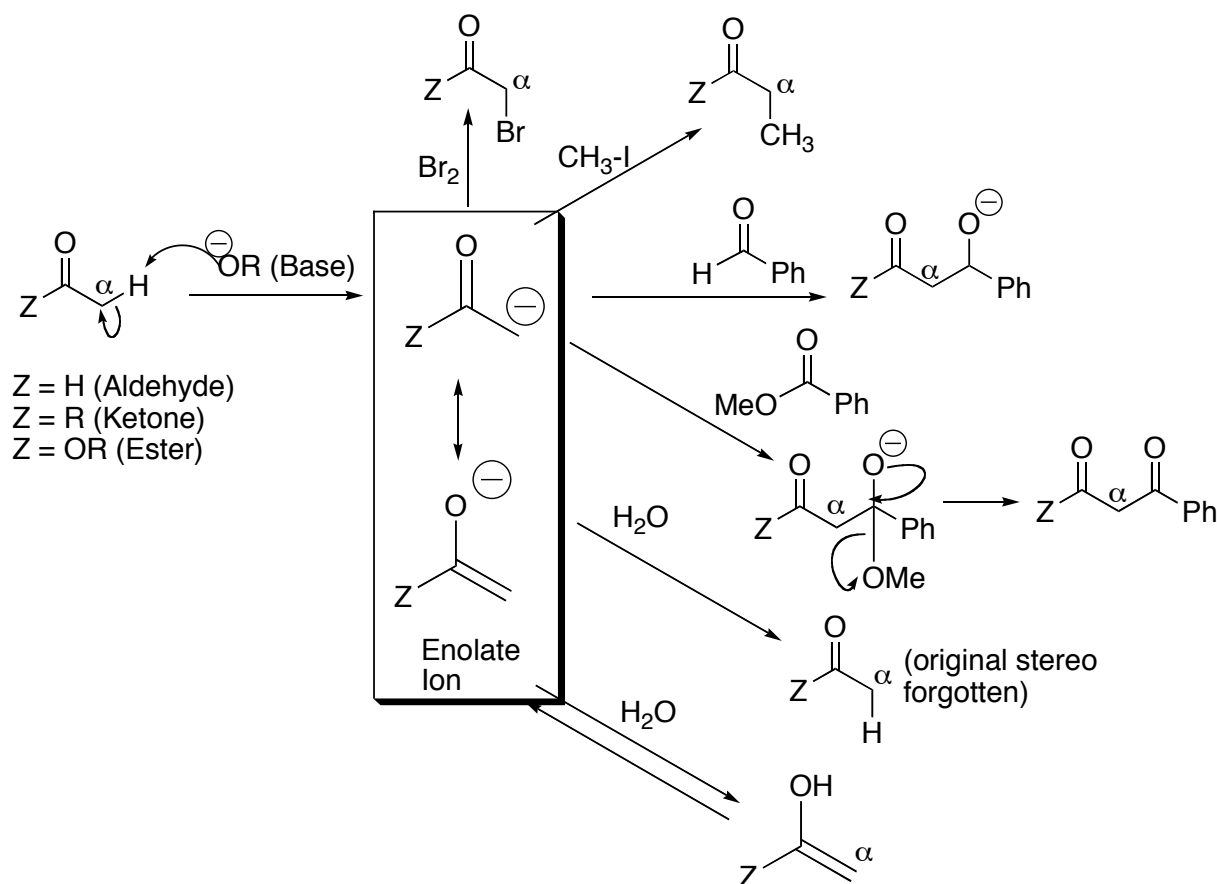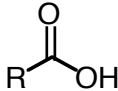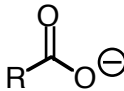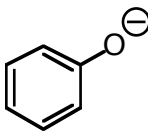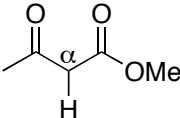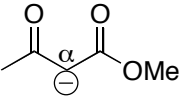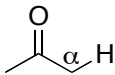
Under base conditions, a carbonyl compound with an α-hydrogen can be deprotonated to give a resonance-stablized, delocalized "enolate" anion, which is nucleophilic at the α-carbon.
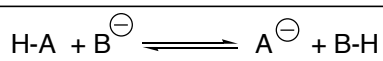
- Normal C-H bonds are very non-acidic. But C-H bonds α to a carbonyl are much more acidic because the resulting anion is resonance stabilized and is shared by the oxygen.

$K_a = 10^{-20}$ $K_a = 10^{-50}$

Stabilized   Unstabilized
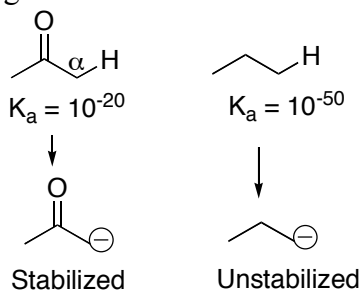
- The α-carbon has two other attachments in addition to the carbonyl and the H shown in this page. The other attachments will remain attached as spectators, and need to be accounted for in drawing products.
- α-Hydrogens are only slightly less acidic than is water or alcohol hydrogens

- **B: Acid/Base Considerations (Sections 22.2, 15) Acidity Table**

Class	Structure	Ka	Acid Strength	Anion	Base Strength
Strong Acids	H-Cl	10^2		Cl⁻	
Carboxylic Acid	R—C(=O)—OH	10^{-5}		R—C(=O)—O⁻	
Phenol	(phenol) OH	10^{-10}		(phenoxide) O⁻	
1,3-Dicarbonyl	CH₃—C(=O)—CαH—C(=O)—OMe	10^{-12}		CH₃—C(=O)—Cα⁻—C(=O)—OMe	
Water	HOH	10^{-16}		HO⁻	
Alcohol	ROH	10^{-17}		RO⁻	
Ketones and Aldehydes	CH₃—C(=O)—CαH	10^{-20}		CH₃—C(=O)—Cα⁻	
Ester	H—Cα—C(=O)—OMe	10^{-24}		⁻Cα—C(=O)—OMe	
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^-Li^+$ "LDA"	
Alkane (C-H)	RCH_3	10^{-50}		RCH_2^-	

$$H\text{-}A + B^- \rightleftharpoons A^- + B\text{-}H$$ Relative stability of anions dictates equilibrium

Notes to remember
1. Carbonyls acidify α-H's (anion stabilized)
2. 1,3-Dicarbonyls are much more acidic than monocarbonyls (anion is more stabilized)
3. Ketones are more acidic than esters
4. A "lower" anion on the chart can favorably deprotonate any acid that's "higher" on chart. Because any acid-base equilibrium will always favor the more stable anion.
5. **"LDA" is strong enough to completely deprotonate ketones, esters, or 1,3-dicarbonyls**
6. NaOH, NaOR can **completely** deprotonate a 1,3-dicarbonyl (but not ketones or esters)
7. NaOH, NaOR do **not** completely deprotonate ketones or esters, but do provide a usable equilibrium supply of the enolate that can procede to product in some reactions.

The Iodoform Reaction:
*   A Chemical Test for methyl ketones (unknowns problems)
*   A synthetic technique for converting methyl ketones to carboxylic acids

E. Enolate Alkylation: Alkyl Halides or Tosylates as Electrophiles

Alkylation of Monocarbonyls: Use strong, bulky LDA [LiN(iPr)$_2$] as base
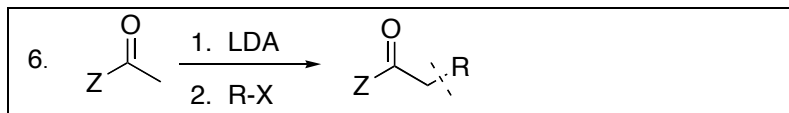
1. S$_N$2 alkylation reaction restricts R-X (or ROTs) to active, 1° electrophile
2. Ketones, Esters, Amides, Aldehydes all work, so long as they have an α-hydrogen that can be deprotonated
    *   For unsymmetrical ketones, isomer problems can occur (which enolate forms?)
3. Predict the products: Attach the electrophile R group to the α-carbon
    *   This is a substitution reaction: α-C-H + R-X → α-C-R
4. Mechanism: Deprotonate first, add the electrophile second

    *   Treat LDA as $^{\ominus}$NR$_2$

For Monocarbonyls, why must we use LDA as base, rather than a normal oxygen base (NaOH or NaOCH$_3$) or a simpler Nitrogen base (NaNH$_2$)?

$\boxed{\textbf{LDA is strong and bulky}}$

1. Base Strength: the LDA base must be strong enough to **completely** deprotonate the carbonyl before the electrophile is added
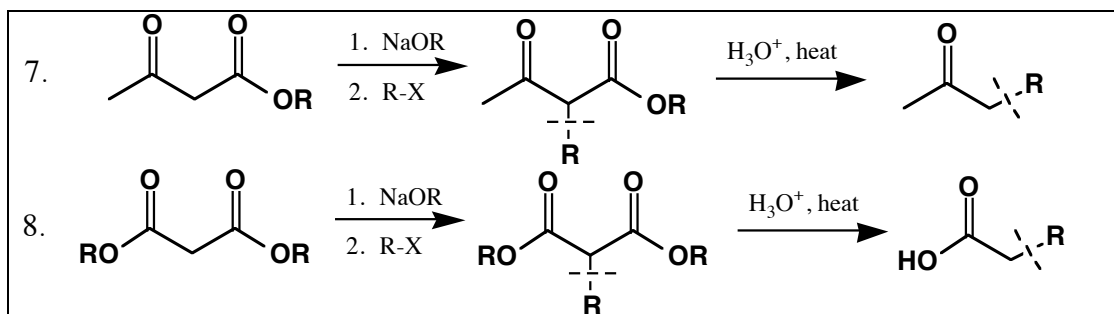   *   With oxygen bases, the equilibrium favors the oxygen anion rather than the enolate, and it's just the oxygen anion which attacks the electrophile

2. Base size: A bulky base favors deprotonation over nucleophilic attack
    *   Comparable to E2 versus S$_N$2 competition
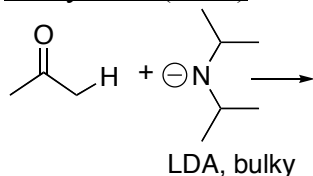
Bulky Base (LDA)   Small Base
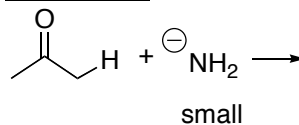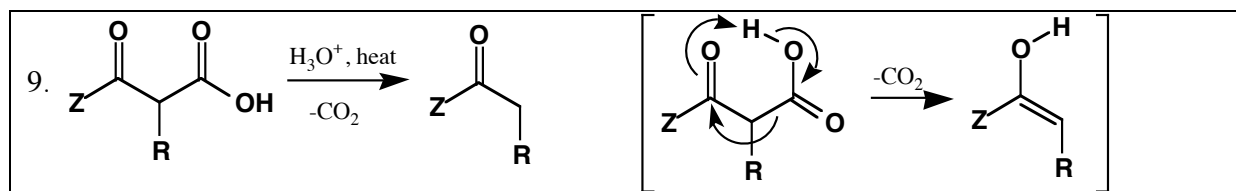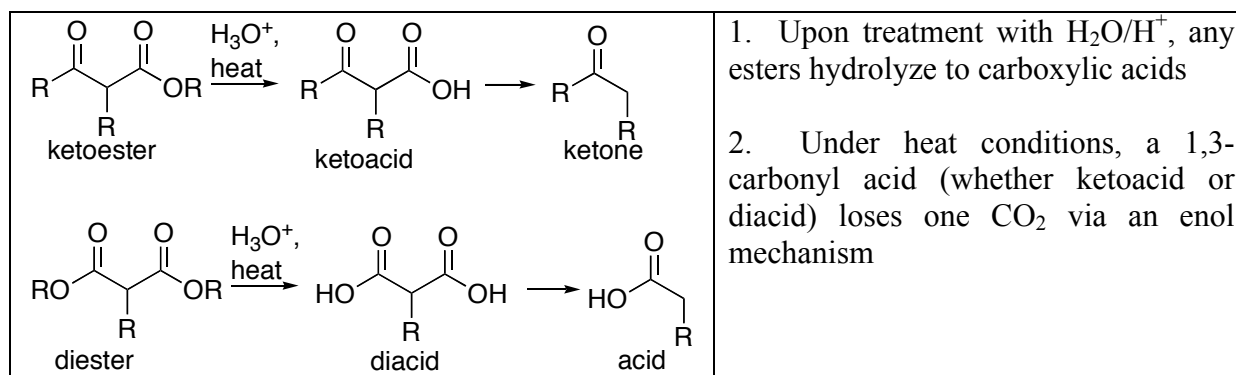
Alkylation of 1,3-dicarbonyls: Now oxygen bases are fine

Stage One: Alkylation of a 1,3-Dicarbonyl
1. S_N2 alkylation reaction restricts R-X (or ROTs) to active, 1° electrophile
2. The dicarbonyl can be a 1,3-diketone, a 1,3 ketoester, or a 1,3-diester
3. Predict the products: Attach the electrophile R group to the α-carbon
4. Position of alkylation is unambiguous: in between the two carbonyls
5. Mechanism: Deprotonate first, add the electrophile second

   •   ⊖ OR bases are fine, no need for LDA

Stage Two: Acid/water hydrolysis of any esters, and decarboxylation of 1,3-carbonyl acids

1. Upon treatment with H_2O/H^+, any esters hydrolyze to carboxylic acids

2. Under heat conditions, a 1,3-carbonyl acid (whether ketoacid or diacid) loses one CO_2 via an enol mechanism

1. Decarboxylation of a 1,3-carbonyl acid
2. "Z" can be anything so that you end with a ketone, aldehyde, or acid at the end
3. Mechanism responsibility
   a. Be able to write the acid-catalyzed enol to carbonyl isomerization (see chapter 18)
   b. Know that an enol is involved in the rate-determining step
      •   -rate will be impacted by stability of the enol intermediate
         1. conjugation of the enol alkene will help
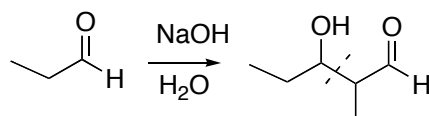   2. hydrogen-bonding of the enol O-H will help

F. Aldehydes or Ketones as Electrophiles: The Aldol Reaction (22.7-11)
The basic aldol reaction: in which the same aldehyde functions as both enolate and electrophile, and in which a β-hydroxyaldehyde is produced.
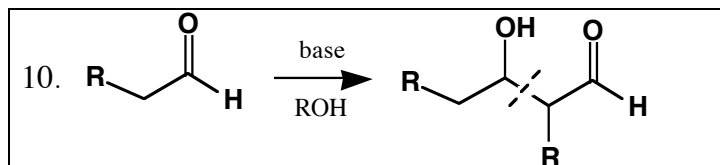

1. Try to draw the mechanism for the following.

Aldol Condensation: In which a β-hydroxycarbonyl is formed but then is pushed on via loss of H and OH to produce an "enone" (α,β-unsaturated carbonyl)
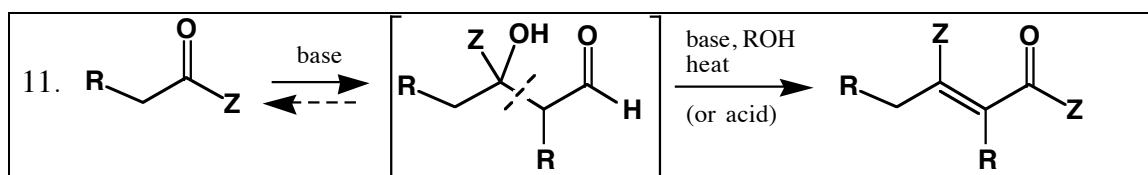
a. Elimination is irreversible
b. Ketones as well as Aldehydes can be used
   • In ketone case, unfavorable aldol equilibrium is still drawn off to enone
c. In Aldehyde case, can stop at aldol if you don't heat
   • To force toward the enone, give extra time or extra heat

General Process for Dehydration of β-Hydroxy Carbonyl Compounds
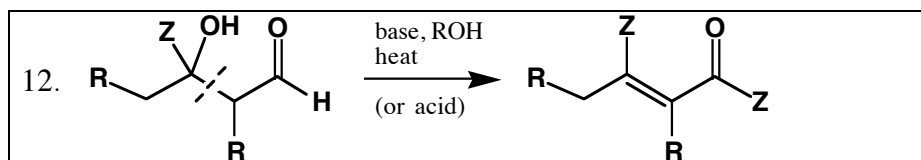
Crossed Aldol Reactions: Using 2 Different Carbonyls, One of Which Functions as Neutral Electrophile (normally an aldehyde) and the Other as the Nucleophilic Enolate
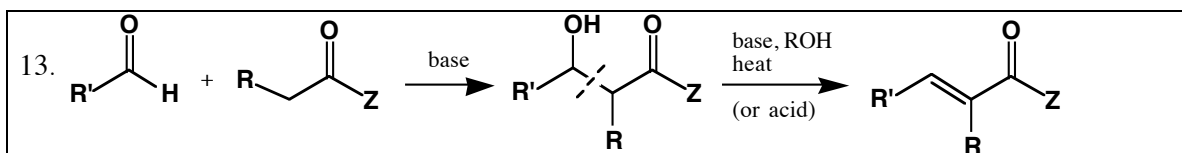
a. Mechanisms required
b. Many variations, but there must be some differentiation so that one carbonyl acts selectively as the enolate and the other as the electrophile
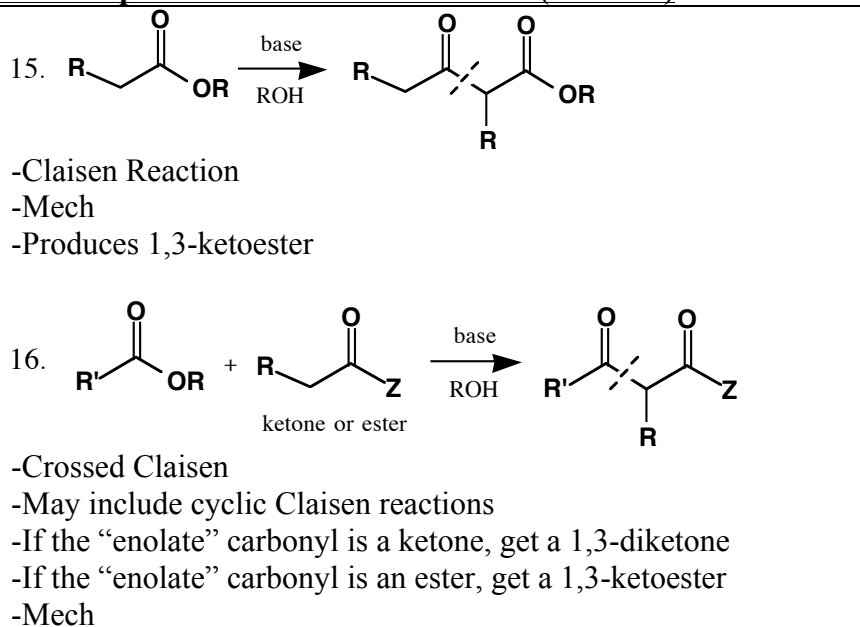
1. If one carbonyl lacks any α-hydrogens, it can't be converted to nucleophile and can only function as electrophile
2. Aldehydes are much better electrophiles than ketones
   - When ketones do function as electrophiles in aldol reactions, the reactions usually just reverses itself anyway

Ring-Forming Aldol Reactions
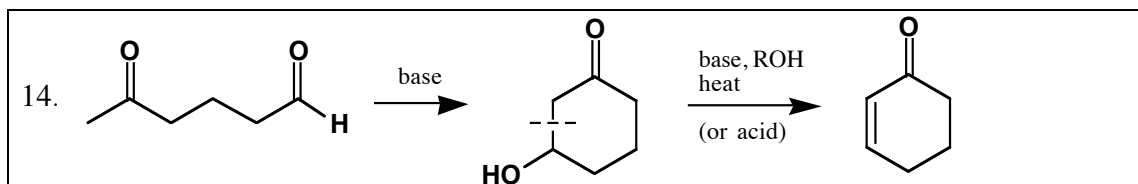
a. Intramolecular crossed aldol reactions
b. Electrophile: if one of the carbonyls is an aldehyde, it will function as the electrophile
c. Normally only good for 5, 6-membered rings
   - If more than one enolate can form, use the one that could produce a 5- or 6-ring

G. Esters as Electrophiles. The Claisen Reaction. (22.12-14)

-Claisen Reaction
-Mech
-Produces 1,3-ketoester

-Crossed Claisen
-May include cyclic Claisen reactions
-If the "enolate" carbonyl is a ketone, get a 1,3-diketone
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester
-Mech

Mechanism: enolate formation – addition to ester carbonyl – elimination of alkoxy anion

1. Draw the mechanism for the following reaction. (Claisen reaction).
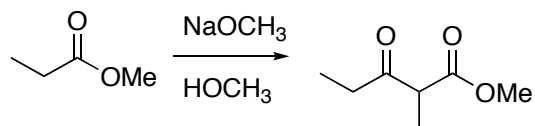
Notes
a. Product: β-keto ester (or ketone). The β-carbonyl was an ester, and the α-carbon was enolate

H. The WITTIG REACTION. A process involving carbonyls making alkenes. (18.13)
*   Very Powerful route to alkene synthesis
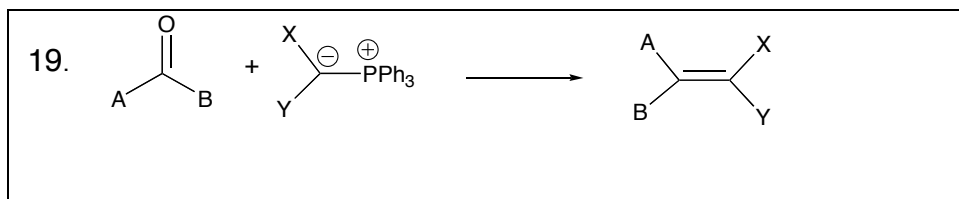
a. The carbonyl can be an aldehyde or a ketone
b. Phosphorus "ylide": a molecule with adjacent positive and negative charge, but overall neutral
c. The ylide carbon is strongly nucleophilic

Ylide Preparation:
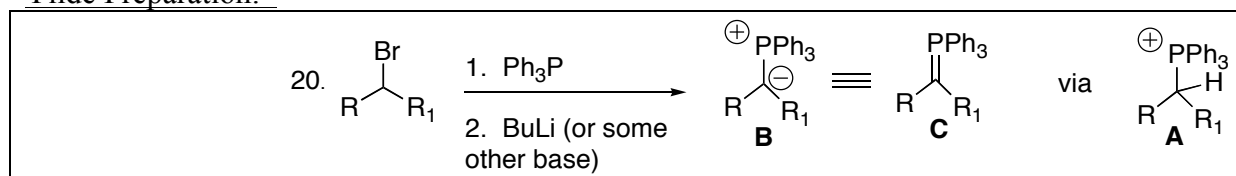
a. PPh_3 is a decent nucleophile, produces phosphonium salt (**A**)
b. The phosphonium salts **A** are weakly acidic and can be deprotonated by strong base (LDA also works) to produce Wittig reagent **B**
c. Wittig Reagent B is really in resonance with version C
    *   **B** helps explain why the carbon is so nucleophilie
    *   **C** is good for predicting alkene products

General Routes to Make Alkenes
*   **Wittig Reactions**.
    o   Very general
    o   Useful for making more elaborate organics, because two subcomponents can be coupled to make a larger product.
    o   Technically longer and more difficult than an aldol condensation, so should not be used to make enones when an aldol condensation could be used instead.
*   **Aldol Condensations**.
    o   Great for making enones (α,β-unsaturated carbonyls). But limited to making enones.
    o   If you see an enone target, make via aldol condensation.
    o   Useful for making more elaborate organics, because two subcomponents can be coupled to make a larger product.
*   **Elimination reactions** (from either halides or alcohols).
    o   Not useful for building up carbon chain lengths. Simply involves transforming one functional group into another.
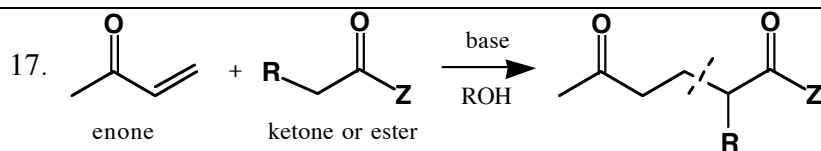
I. Enones as Electrophiles (22.18-19) Michael Reactions/β-Addition (Not for Test)

General: Enones as Electrophiles. Nucleophiles that attack enones must choose between:
- Carbonyl addition
- β-Addition
    o   this isn't bad, as it results in enolate formation

Carbonyl addition normally dominates with:	β- addition normally dominates with:
  • RMgBr • RLi • NaBH$_4$ • LiAlH$_4$ • LiCCR	• enolates of dicarbonyls • sometimes enolates of monocarbonyls (but not always) • Cuprates (R$_2$CuLi) Prep: 2RBr $\xrightarrow[\text{2. 1 CuI}]{\text{1. 4 Li}}$ R$_2$CuLi

-"Michael Addition
-1,5 dicarbonyls are well suited for ring-forming aldol or Claisen reactions

Reactions of Amines

1. **Reaction as a proton base** (Section 19-5 and 19-6)
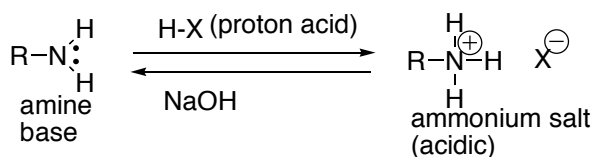
- Mechanism: Required (protonation)
- Reverse Mechanism: Required (deprotonation)
- Amines are completely converted to ammonium salts by acids
- Ammonium salts are completely neutralized back to amines by bases
- Patterns in base strength: Reflect stabilization/destabilization factors for both the amine and the ammonium
 - N lone pair: $sp^3 > sp^2 > p$
  - For sp^3 nitrogens, $3° > 2° > 1°$

2. **Reaction with Ketones or Aldehydes** (Section 18-16,17 and 19-10)
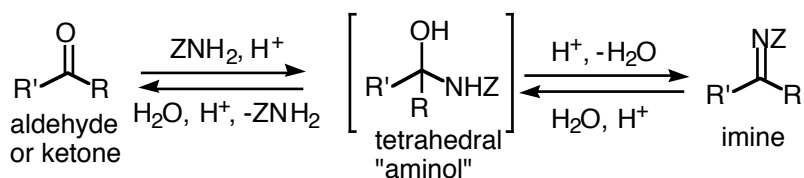
Notes:
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H's on nitrogen → 2°, 3° amines can't do this

1. **Alkylation of 1° Alkyl Halides** (Section 19-12, 19-21A)
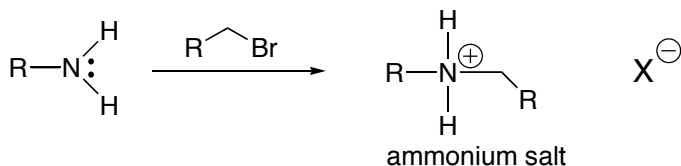
- **3a. Polyalkylation** is routine.
  - o With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below) .
    - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.
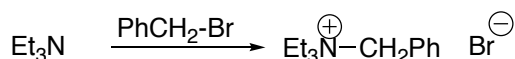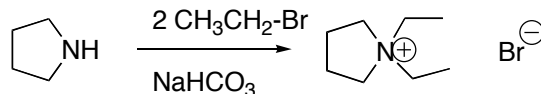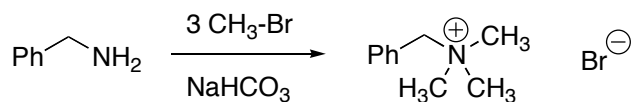

- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.
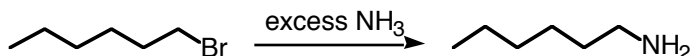

2. **Acylation with Acid Chlorides** to From Amides: (Section 19-13, 20-15)
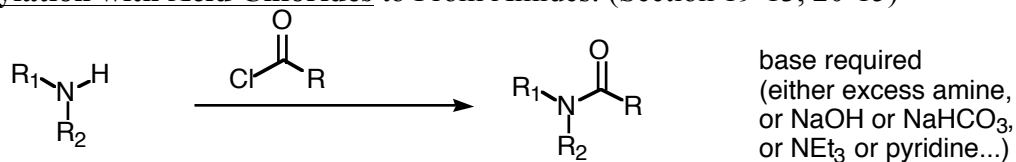
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1°, 2°, or NH_3 all react well.
- But 3° amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

4b. **Acylation with Carboxylic Acids** to From Amides: (Section 20-12)
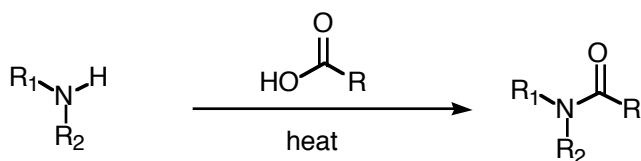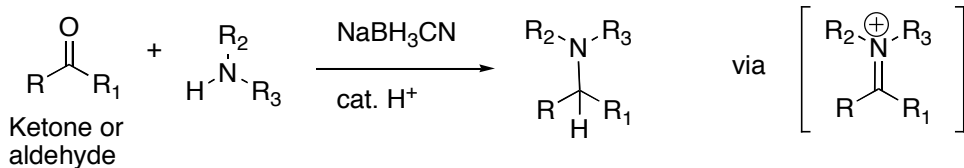

- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid → amide is routine, and is facilitated by complex enzyme mechanisms

3. **Substitution for Aromatic Amines via the Diazonium Salts** ("The Sandmeyer Reaction") (Section 19-17, 18)
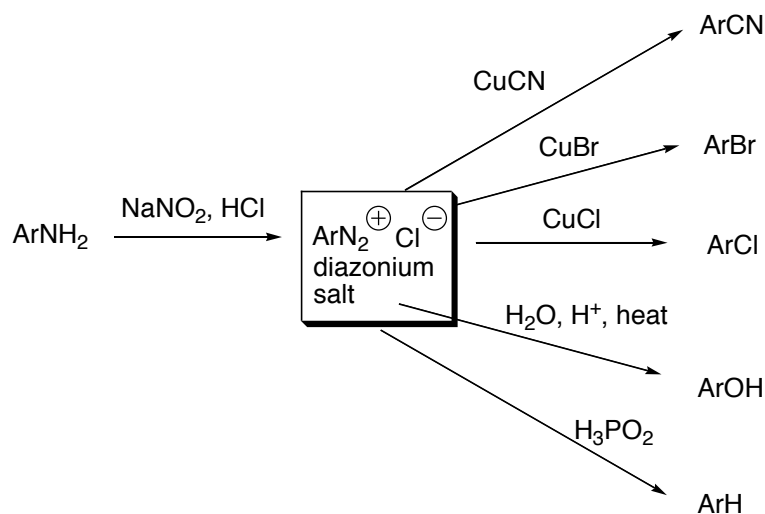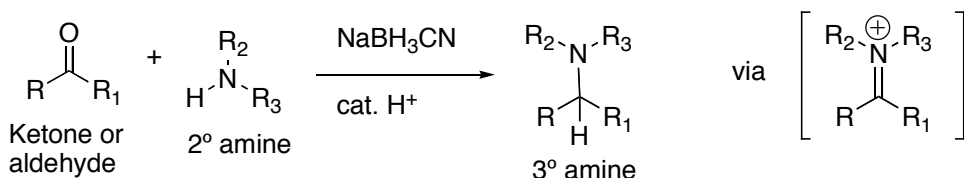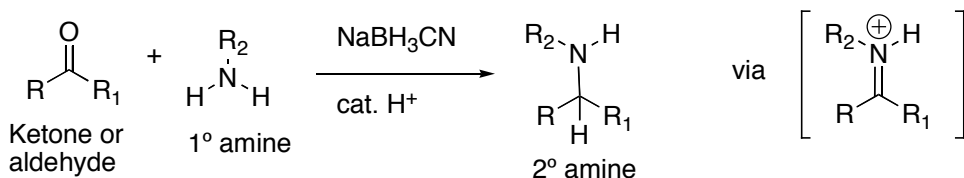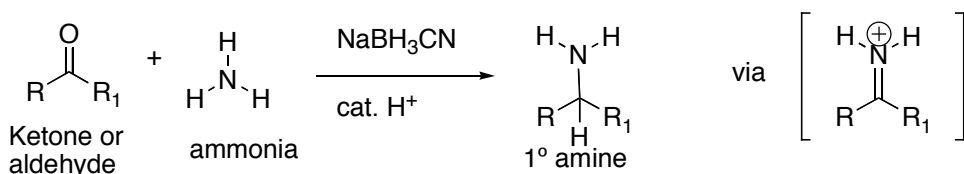

- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2, a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven't been able to make before.

Synthesis of Amines

6. **From Aldehydes or Ketones: Reductive Amination** (Section 19-19)

- Access: 1°, 2°, or 3° Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R_2 and/or R_3 can be either a carbon or a hydrogen. Thus:
  - $NH_3 \rightarrow 1°\ RNH_2$
  - $1°\ RNH_2 \rightarrow 2°\ R_2NH$
  - $2°\ R_2NH \rightarrow 3°\ R_3N$
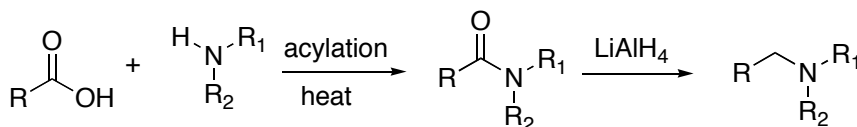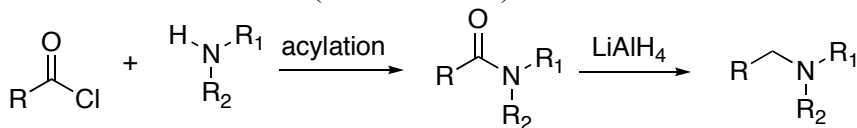 - $3°\ R_3N$ don't react

7. **Via Amides**: (Section 19-20)
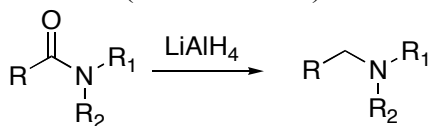
- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- R_1 and R_2 can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
  - $RCONH_2 \rightarrow 1°\ RCH_2NH_2$
  - $RCONHR \rightarrow 2°\ RCH_2NHR$
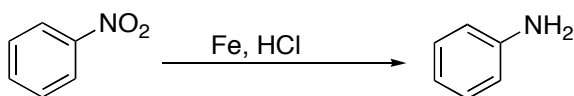 - $RCONR_2 \rightarrow 3°\ RCH_2NR_2$

8. **From Amines via Amides**: (Section 19-20)


- Access: 1°, 2°, or 3° Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

9. **Reduction of nitro compounds**: (section 19-21C)


- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
    - Pd/H$_2$, Ni/H$_2$, Pt/H$_2$,
    - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1° Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A) (See reaction 3).
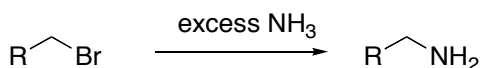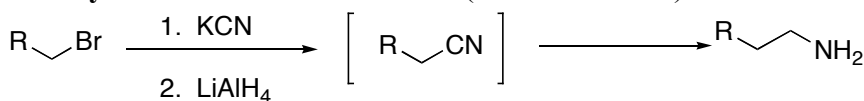

- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH$_3$ prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 19-21B)
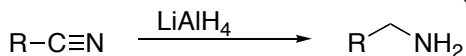
- Access: 1° amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-21B)

- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!

Summary of Amine Syntheses

Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH, H^+ $NaBH_3CN$,	1º, 2º, or 3º Amines	
2	#7, #8	Amides	$LiAlH_4$	1º, 2º, or 3º Amines	
3	#7, #8	Amines (via Amide)	1. RCOCl (or RCO_2H, heat) 2. $LiAlH_4$	1º $ArNH_2$	
4	#7, #8	Acid Chlorides or Acids (via Amide)	1. RNH_2 2. $LiAlH_4$		
5	#9	$ArNO_2$	Fe/HCl	1º $ArNH_2$	
6	#10	1º RCH_2Br	NH_3 (excess)	1º only, with CH_2 next to nitrogen	Original carbon chain is not extended
7	#12	1º RCH_2Br (via nitrile)	1. KCN or NaCN 2. $LiAlH_4$	1º only, with CH_2 next to nitrogen	Original carbon chain is extended by one carbon
8	#11	RCH_2CN	$LiAlH_4$	1º only, with CH_2 next to nitrogen	

Mechanisms
1. Protonation
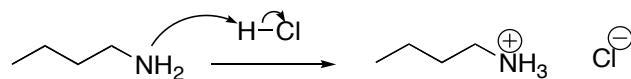
1.-Reverse. Deprotonation
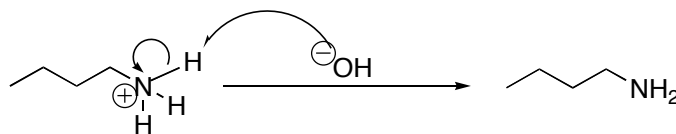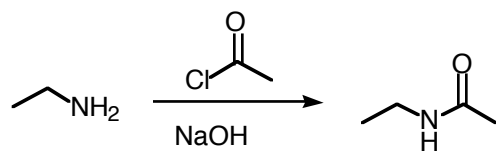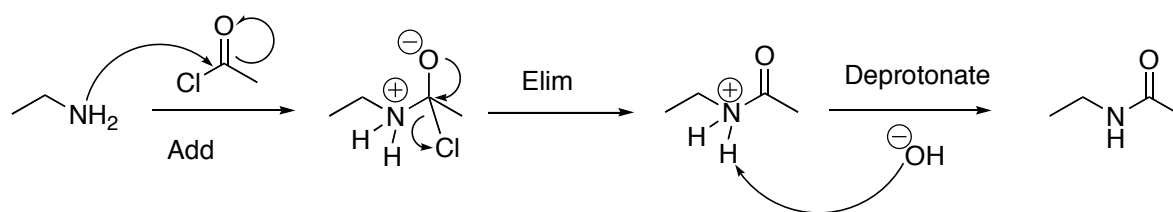

3. Polyalkylation

Ex:
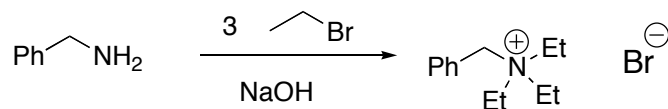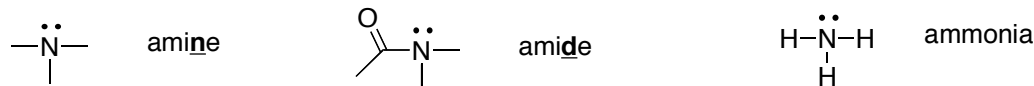

Mech:
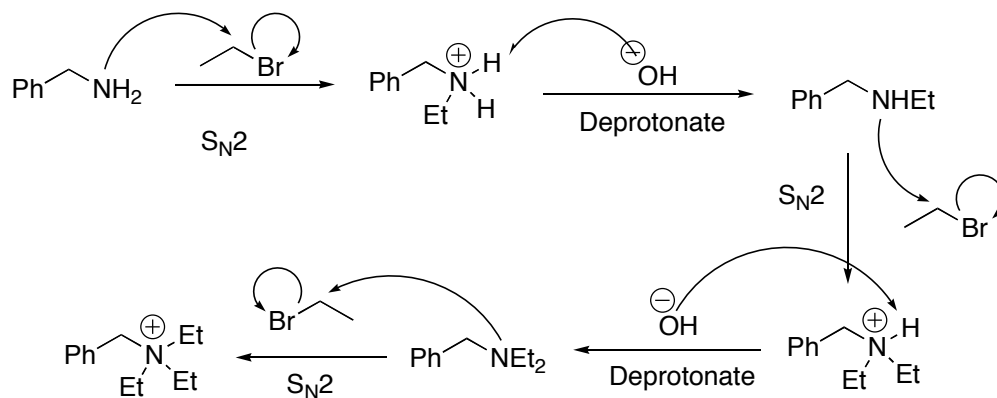
3b. Monoalkylation
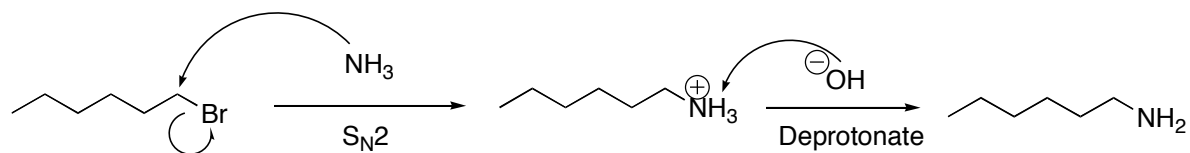
4. Acylation

Ex:

Mech: 3 steps: Addition-Elimination-Deprotonation

Chapter 19 Amines
A. Miscellaneous
19.1 Intro, Terms
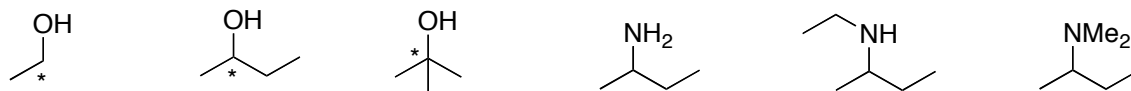
Amines versus Amides

—N̈—   ami**ne**   amide   H–N̈–H   ammonia

1°, 2°, 3° classification: based on how many of the three nitrogen attachments are carbons:

R–N̈–H   R–N̈–H   R–N̈–R
  H   R   R
1° Amine   2° Amine   3° Amine
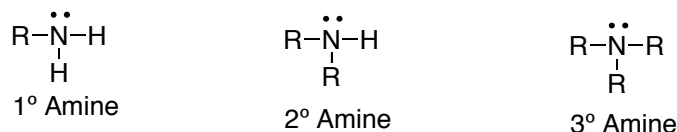
Note: 1°, 2°, 3° has a different sense than with alcohols.
1. In an alcohol, it's based on how many carbon groups are attached to the hydroxy-bearing carbon.
▪ The alcohol oxygen always has one carbon group.
2. But in amines, it's how many carbon groups are attached to the nitrogen itself.
▪ Because the nitrogen could have 0, 1, 2, or 3 carbon groups attached.

OH   OH   OH   NH₂   NH   NMe₂

Amines versus Ammoniums: Neutral versus protonated/cationic

H–N̈–H   ammonia   H–N⁺–H   ammonium
  H   H

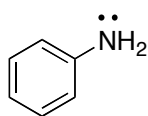—N̈—   ami**ne**   ⇌ (H⁺ / -H⁺)   —N⁺—   ammonium   R–N⁺–R   quaternary ammonium
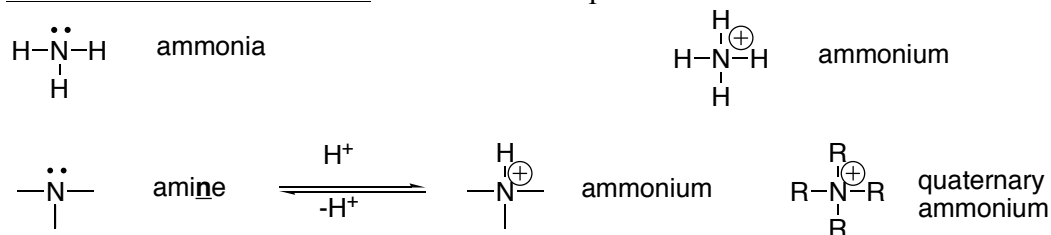
19.2 Formal **Amine Nomenclature**: alkan-x-amine, N-alkylalkan-x-amine, etc.
1. For core name, choose longest C-chain to which nitrogen is attached, and call it alkan-x-amine (including for alkan-1-amines)
   - Number from end nearer N
   - Be sure to specify with a number which **carbon** has the nitrogen
     - The nitrogen does **not** count as a number itself.
2. Substituents on the <u>nitrogen</u> (rather than on carbon) are designated as "N-"
   - Unlike substituents on a carbon, which are always designated by the carbon's number
   - The "N-" does not factor into alphabetizing. Ex: "N-ethyl" goes before "3-methyl"
3. NH_2 as a <u>Substituent</u>: "Amino"
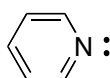
<u>Common Naming</u> (for simple amines): Alkylamine, dialkylamine, trialkylamine….

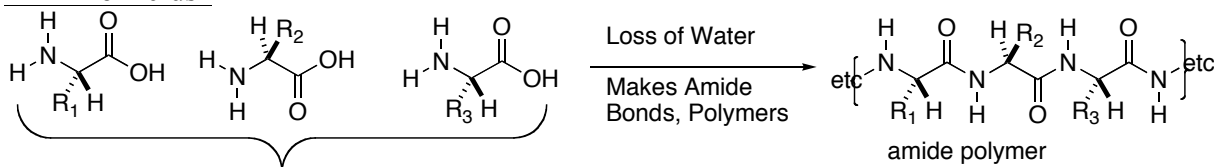<u>Three Common Amine Names to Memorize (Review from Aromatics Chapter)</u>

Aniline   Pyridine   Pyrrole

"Amino Acids"

Loss of Water

Makes Amide
Bonds, Polymers

amide polymer
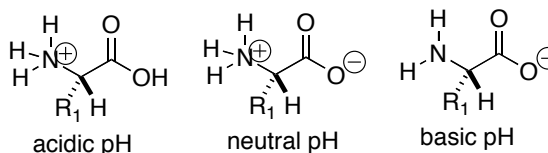"protein"
"polypeptide"

-The major natural amino acids all have "S" configuration
-20 major natural amino acids
-Under neutral conditions, the amine actually deprotonates the acid to give not an "amino acid" but actually an "ammonium carboxylate"
-The side groups "R" can be acid, basic, hydrophilic, or hydrophobic.
-The sequence or R groups on thepolymer essentially spells out the biological activity of the protein.

acidic pH   neutral pH   basic pH

<u>Test Keys:</u>
1. Understand that amino acids are the building blocks for polymeric proteins, and that the biological information is specified by the identity and sequence of the side groups

2. Understand what form an "amino acid" exists in, depending on whether the conditions are acidic, neutral, or basic pH
   - Is the nitrogen neutral (base form) or protonated and cationic (acid form)?
   - Is the carboxylic acid anionic (base form) or protonated and neutral (acid form)?

   a. Acidic pH: both are in protonated acid forms   Overall Charge: POSITIVE

   b. Neutral pH: one in acid form, the other in base form Overall Charge: NEUTRAL
      - Both are in ionic form, since amine is more basic than carboxylate (when formed when protonating the "basic pH" form), and carboxylic acid is more acidic than ammonium, when deprotonating the "acid pH" form.

   c.   Basic pH: both are in deprotonated base form   Overall Charge: NEGATIVE

Structure and Hybridization
1. **N atoms** are typically either sp^3 hybridized (normal) or sp^2 hybridized
    a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
    b. sp^2 in either of two cases:
        ▪ N atom is itself double bonded
        ▪ N atom is conjugated to a double bond

2. **N lone pair** is either:
    a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
    b. sp^2 when the N atom is itself double bonded
        ▪ the p orbital is used to make the double bond
        ▪ the lone pair is left in an sp^2 hybrid
    c. p when the N atom is conjugated to a double bond but is not itself double bonded
        ▪ the lone pair sits in the p orbital so that it can overlap with the adjacent p orbital/π bond

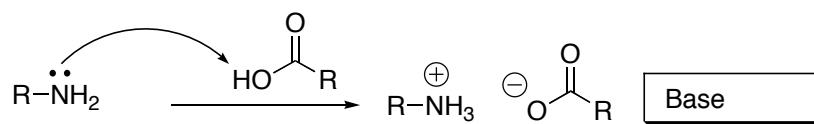**Practice**: For the nitrogens on page 10, identify the lone pair hybridization and bond angles.

19.3 Physical Properties

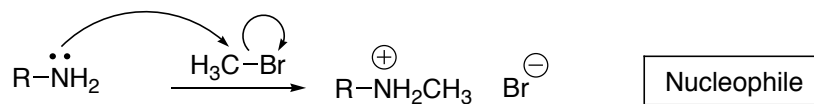Key: hydrogen bond strength depends on acidity of the hydrogen and basicity of the N or O

1. **Water Solubility**: All amines hydrogen-bond water → impacts solubility
    a. Because R_3N---HOH bond is stronger (due to amine lone-pair basicity) than ROH---HOH, amines tend to better H-bond water and are more soluble than oxygen analogs
    b. Based on basicity of substate (the acidity of water's hydrogen is common)

2. **Boiling Point:** 1° and 2° amines hydrogen bond themselves, but 3° amines don't
    a. Boiling point for similar mw amines: 1°, 2° amines > 3° amines
    b. amines generally have lower boiling points than analogous oxygen compounds
        • Boiling point for similar mw: RCO_2H > RCH_2OH > RCH_2NH_2
    c. for boiling point, the weaker acidity of the N-H hydrogens weakens the hydrogen-bonding strength more than the greater basicity of the Nitrogen lone pair.

3. Amines stink! (ammoniums don't)

Keys:
1. H-bonding: Is there any at all?
2. How relatively strong is the H-bonding?
3. What impacts H-bonding strength?
What impact will extra carbons have?

B. Basicity of Amines: Reactivity of the Nitrogen Lone Pair (19.5,6)

R–NH$_2$ $\xrightarrow{\text{HO} \overset{O}{\underset{}{\parallel}} R}$ R–NH$_3^{\oplus}$ $^{\ominus}$O–C(=O)R | Base |

•The nitrogen lone pair dominates amine reactivity

R–NH$_2$ $\xrightarrow{\text{H}_3\text{C–Br}}$ R–NH$_2$CH$_3^{\oplus}$ Br$^{\ominus}$ | Nucleophile |

R–NH$_2$ $\xrightarrow{\text{Oxidizing Agent}}$ R–NH$_2^{\oplus}\cdot$ | Reducing Agent |

•Trends in base strength, nucleophile strength, and redox strength follow similar patterns, based on lone pair stability/reactivity
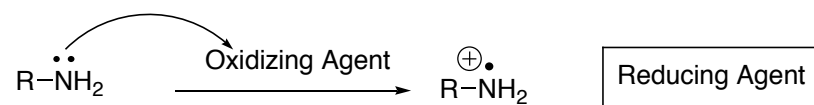
Neutral amine bases are stronger than:
1. Neutral oxygens (water, alcohol, ketones…)
2. Carboxylate anions (resonance stabilized)

Neutral amine bases are weaker than:
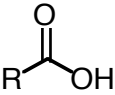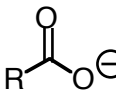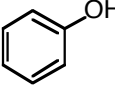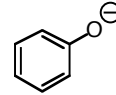1. Anionic hydroxide or alkoxides
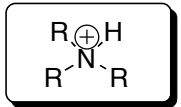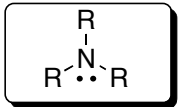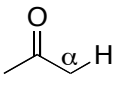2. Anionic nitrogen or carbon bases

Quick Checklist of Acid/Base Factors
1. **Charge**
2. **Electronegativity**
3. **Resonance/Conjugation**
4. **Hybridization**
5. **Impact of Electron Donors/Withdrawers**
6. **Amines/Ammoniums**

- When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.
- When a neutral acids are involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.

Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases

Class	Structure	Ka	Acid Strength	Base	Base Strength	
Strong Acids	H-Cl, H_2SO_4	10^2		$Cl^{\ominus}$, $HO-\overset{O}{\underset{O}{S}}-O^{\ominus}$		**S**mell **A**wful!
Hydronium	H_3O^+, ROH^+ cationic	10^0		H_2O, HOR neutral		**H**umans
Carboxylic Acid	$R{-}C(=O){-}OH$	10^{-5}		$R{-}C(=O){-}O^{\ominus}$		**C**uz
Phenol	OH (on benzene)	10^{-10}		$O^{\ominus}$ (on benzene)		**P**eople
Ammonium Ion (Charged)	$R{-}\overset{\oplus}{N}H{-}R{,}R$ Charged, but only weakly acidic!	**10^{-12}**		$R{-}\overset{..}{N}{-}R{,}R$ Neutral, but basic!		**A**gainst
Water	HOH	10^{-16}		$HO^{\ominus}$		**W**orking
Alcohol	ROH	10^{-17}		$RO^{\ominus}$		**A**re
Ketones and Aldehydes	$CH_3{-}C(=O){-}\alpha H$	10^{-20}		$CH_3{-}C(=O){-}\alpha^{\ominus}$		**K**ingdoms
Amine (N-H)	$(iPr)_2N{-}H$	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$		**A**nimal
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$		**A**ll

More Detailed Discussion of Acid/Base Patterns/Factors to remember

1. Charge

> • **All else equal, cations are more acidic than neutrals, and anions more basic than neutrals. (See Table 19.2)**

   • Nonfactor on Table 19.1, since all of the "acids" have the same charge (neutral), and all of the "bases" have the same charge (anions)
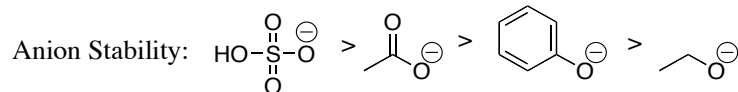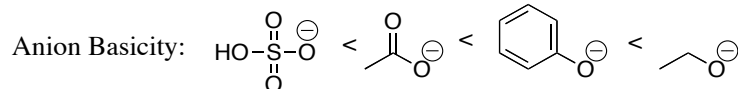
2. Electronegativity:
   • Acidity: H-C $<$ H-N $<$ H-O $<$ H-X (halogen)
   • Basicity: C$^{\ominus}$ $>$ N$^{\ominus}$ $>$ O$^{\ominus}$ $>$ X$^{\ominus}$
   • Anion Stability: C$^{\ominus}$ $<$ N$^{\ominus}$ $<$ O$^{\ominus}$ $<$ X$^{\ominus}$
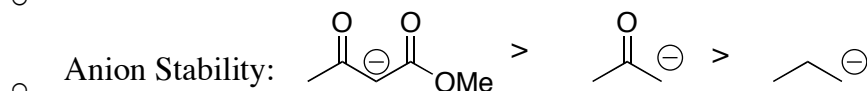
3. Resonance/Conjugation:
   • Oxygen Series:
     Acidity: sulfurice acid $>$ carboxylic acid $>$ phenol $>$ alcohol

     Anion Basicity: HO–S(=O)(=O)–O$^{\ominus}$ $<$ CH$_3$C(=O)O$^{\ominus}$ $<$ PhO$^{\ominus}$ $<$ EtO$^{\ominus}$

     Anion Stability: HO–S(=O)(=O)–O$^{\ominus}$ $>$ CH$_3$C(=O)O$^{\ominus}$ $>$ PhO$^{\ominus}$ $>$ EtO$^{\ominus}$

   • Carbon Series:
     o Acidity: 1,3-dicarbonyl $>$ ketone (monocarbonyl) $>$ alkane

       o Anion Basicity: [CH$_3$C(=O)–CH$^{\ominus}$–C(=O)OMe] $<$ [CH$_3$C(=O)–CH$_2^{\ominus}$] $<$ [CH$_3$CH$_2^{\ominus}$]

       o Anion Stability: [CH$_3$C(=O)–CH$^{\ominus}$–C(=O)OMe] $>$ [CH$_3$C(=O)–CH$_2^{\ominus}$] $>$ [CH$_3$CH$_2^{\ominus}$]

   • Nitrogen Series:
     o Acidity: amide $>$ amine

       o Anion Basicity: [CH$_3$C(=O)–NH$^{\ominus}$] $<$ [CH$_3$CH$_2$–NH$^{\ominus}$]

       o Anion Stability: [CH$_3$C(=O)–NH$^{\ominus}$] $>$ [CH$_3$CH$_2$–NH$^{\ominus}$]
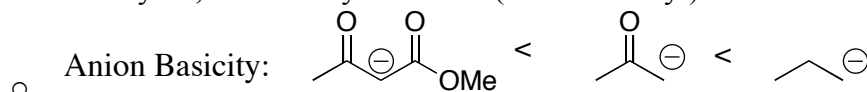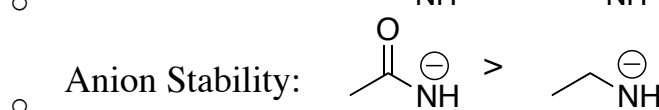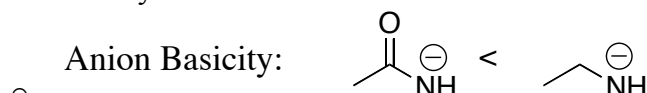
> • Note: Resonance is often useful as a tiebreaker (oxyanion versus oxyanion, etc.)
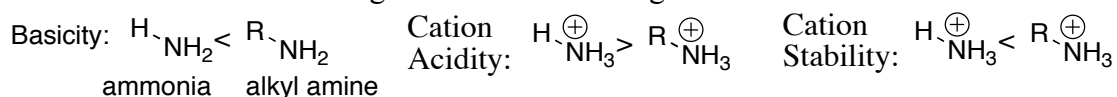> • NOTE: Resonance can sometimes (not always) trump electronegativity or charge.

Electroneg.   [CH$_3$C(=O)–CH$^{\ominus}$–C(=O)CH$_3$] $\underset{basicity}{\overset{stability}{\rightleftarrows}}$ [EtO$^{\ominus}$] $\underset{basicity}{\overset{stability}{\rightleftarrows}}$ [CH$_3$CH$_2$C(=O)CH$^{\ominus}$...] $\underset{basicity}{\overset{stability}{\rightleftarrows}}$ [$^{\ominus}$HN–CH$_2$CH$_3$]

Charge   [CH$_3$CH$_2$NH$_2$] $\underset{basicity}{\overset{stability}{\rightleftarrows}}$ [CH$_3$C(=O)O$^{\ominus}$]   [CH$_3$CH$_2$OH] $\underset{basicity}{\overset{stability}{\rightleftarrows}}$ [HO–S(=O)(=O)–O$^{\ominus}$]
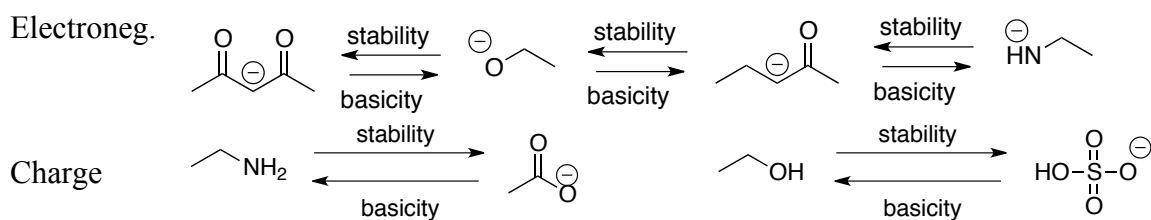
4. Hybridization:
   - For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$

   Neutral Nitrogen Series

   Carbanion Series

   Oxygen Anion Series
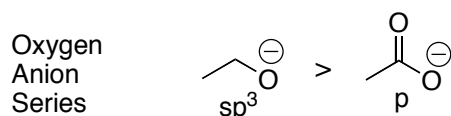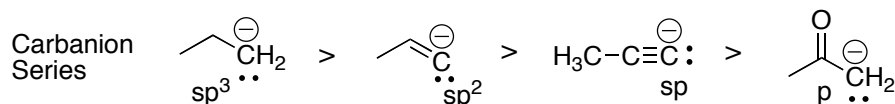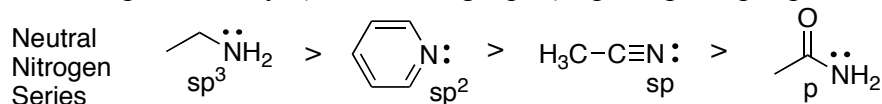
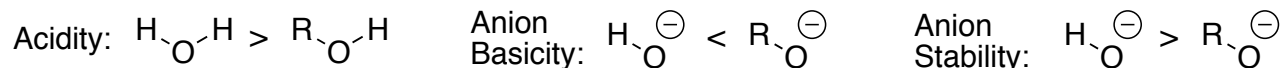   - This means that for acidity, alkynes > alkenes > alkanes

5. Electron donating/electron withdrawing substituents:
   - Electron withdrawing substituents will stabilize negatively charged anions, but will destabilize positively charged cations.
     o This means a withdrawer will increase the acidity of a neutral acid because it will stabilize the resulting anion.
     o This means a withdrawer will decrease the basicity of a neutral base because it will destabilize the resulting cation
   - Electron donating substituents will stabilize positively charged cations, but will destabilize negatively charged anions.
     o This means a donor will increase the basicity of a neutral base because it will stabilize the resulting cation. The resulting cation will be less acidic.

   Basicity: $H{-}NH_2 < R{-}NH_2$ Cation Acidity: $H{-}\overset{+}{N}H_3 > R{-}\overset{+}{N}H_3$ Cation Stability: $H{-}\overset{+}{N}H_3 < R{-}\overset{+}{N}H_3$
   ammonia   alkyl amine

     o This means a donor will decrease the acidity of a neutral acid because it will destabilize the resulting anion, and will increase the basicity of the anion

   Acidity: $H{-}O{-}H > R{-}O{-}H$ Anion Basicity: $H{-}\overset{-}{O} < R{-}\overset{-}{O}$ Anion Stability: $H{-}\overset{-}{O} > R{-}\overset{-}{O}$

6. Ammonium Cations as Acids and Neutral Amines as Bases
   - Neutral amines are more basic than any neutral oxygen (electronegativity factor)
   - Neutral amines are less basic than most anionic oxygens, including alkoxides, hydroxides (charge factor)
   - However, neutral amines are more basic than highly resonance-stabilized carboxylate anions (in this case, resonance factor trumps the charge factor).

Table 9.3 Relative Basicity of Different Classes of Neutral Nitrogen Compounds.
General Amine Basicity Patterns.

a. Relative basicity correlates Lone pair hybridization: sp^3 (entries 5-8) $> sp^2$ (entry 4) $> p$ (entries 1-3) (hybridization factor)

b. Within the sp^3 amines, increasing alkyl substitution increases basicity (entries 5-8): $3° > 2° > 1° > NH_3$ (electron donating group factor)

- Note: The **acidity of conjugate ammonium cations (conjugate acids relative to the amines) is directly and inversely related to the basicity of the neutral amines**.

- Key: remember patterns (a) and (b) above. That should help you solve relative basicity problems.   If given ammoniums, draw the related conjugate neutral amines, rank them as bases, and realize that the strongest amine base relates to the weakest ammonium acid.

- You should be able to handle any ranking problems involving either amines as bases or their conjugate ammoniums as acids. This should include relative to non-nitrogen acids and bases.

Synthesis of Carboxylic Acids

1. **From 1° Alcohols and Aldehydes: Oxidation** (Section 11-2B and 18-20)
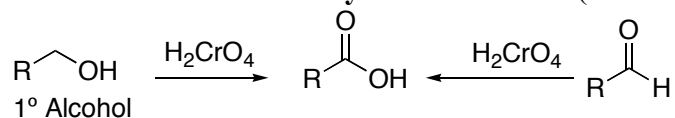
- No mechanism required for the reaction

2. **From Alkenes: Oxidative Cleavage**: (Section 8-15A and 9-10)
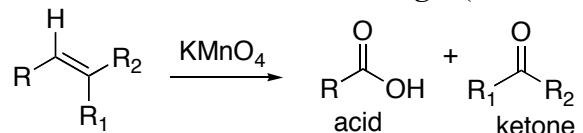
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH$_2$ would give an acid and carbonic acid (H$_2$CO$_3$), etc..

3. **From Aromatics**: **Oxidation of Alkylbenzenes** (Section 17-14A)
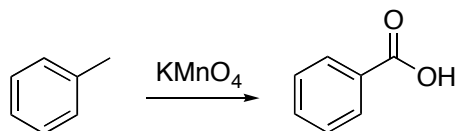
- No mechanism required for the reduction
- While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 22)
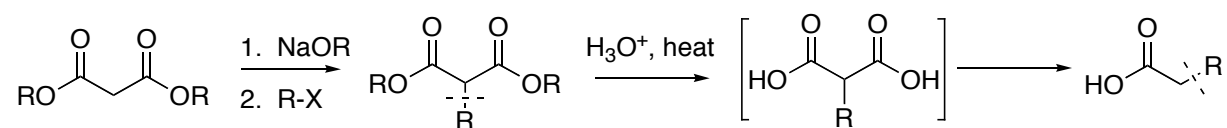
- Mechanism: Deprotation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)

5. **From Grignard Reagents: Via Carboxylation**: (Section 20-8B)

R-MgX $\xrightarrow[\text{2. H}^+]{\text{1. CO}_2}$ R-CO$_2$H
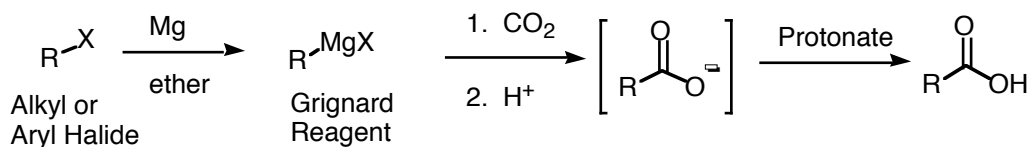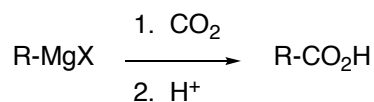
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1°, 2°, or 3°
- Mechanism required. (From Grignard on.)

6. **From Nitriles: Hydrolysis** (Section 20-8C)

R−C≡N $\xrightarrow{\text{H}^+, \text{H}_2\text{O}}$
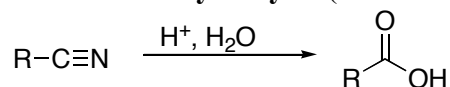
- Mechanism not required.

7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**
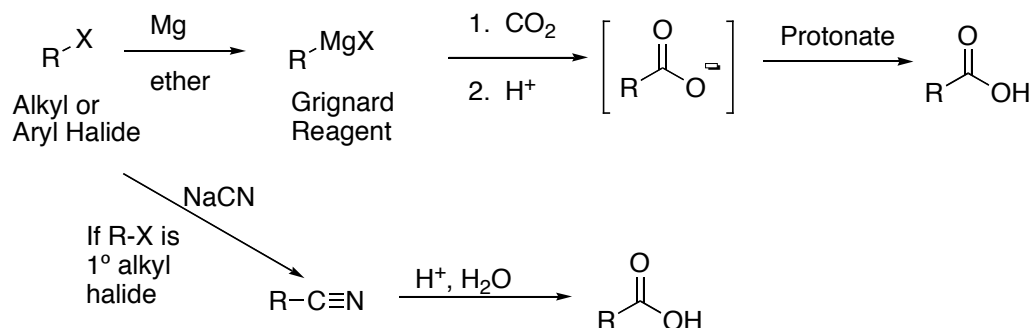
- Formation/Hydrolysis of Nitriles Requires a 1° Alkyl Halide to begin, since the formation of the nitrile proceeds via S$_N$2
- Reaction via the Grignard has no such limitation
- For 1° alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive Grignard reagents

8. **From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis** (Section 20-8C)
   a) "Downhill" hydrolysis: From acids or anhydrides with NEUTRAL WATER alone
   - **mechanism required: addition-elimination-deprotonation**
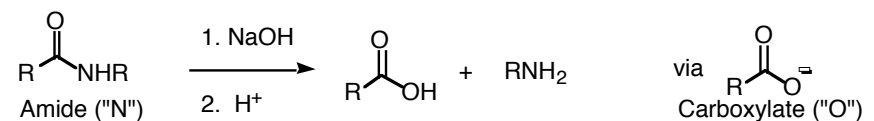

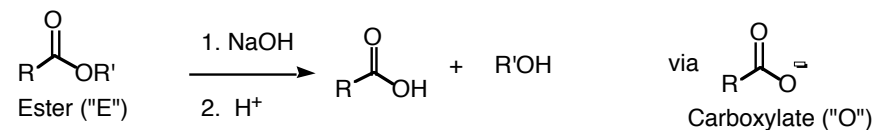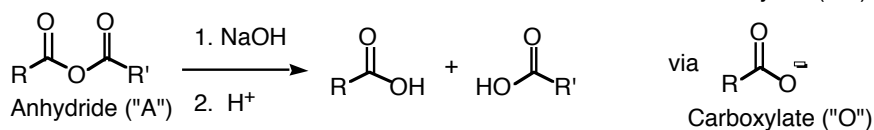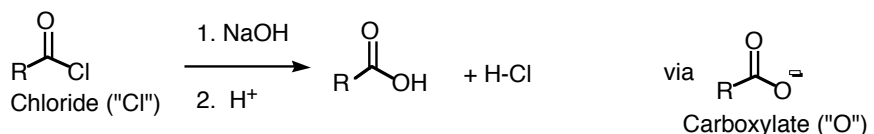Chloride ("Cl")

Anhydride ("A")
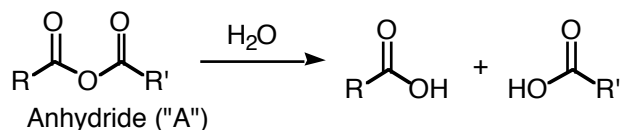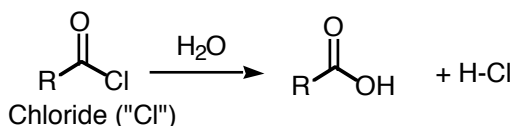
   b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)
   - **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to acid)**
   - These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester


Ester ("E")

via   hemiacetal

   c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H$^+$ workup
   - **mechanism required: addition-elimination-deprotonation (to carboxylate intermediate) followed by protonation**
   - Since the reaction with NaOH is always downhill, all of these reactions work

Chloride ("Cl")   2. H$^+$ + H-Cl   via   Carboxylate ("O")

Anhydride ("A") 2. H$^+$ via   Carboxylate ("O")

Ester ("E")   2. H$^+$ + R'OH   via   Carboxylate ("O")

Amide ("N")   2. H$^+$ + RNH$_2$ via   Carboxylate ("O")

Reactions of Carboxylic Acids

9. **Reaction as a proton Acid** (Section 20-4, 20-5)
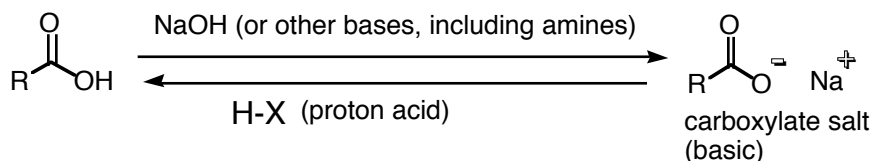
- Mechanism: Required (deprotonation)
- Reverse Mechanism: Required (protonation)
- Carboxylic acids are completely converted to carboxylate salts by base
- Carboxylate salts are completely neutralized back to carboxylic acids by strong acid
- The resonanance stabilization makes carboxylates much more stable than hydroxide or alkoxide anions, which is why the parents are carboxylic "acids"
- Carboxylic acids are more acidic than ammonium salts
- Patterns in acid strength: Reflect stabilization/destabilization factors on the carboxylate
    - Electron donors destabilize the carboxylate anion, so make the parent acid less acidic
    - Electron withdrawers stabilize the carboxylate anion, so make the parent acid more acidic

10. **Conversion to Acid Chlorides** (Section 20-11, 21-5)
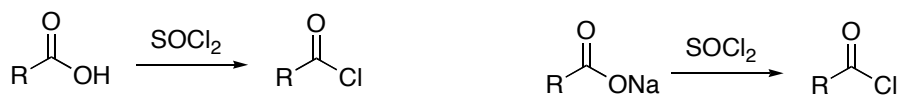
- Mechanism: Not Required
- Easy (but smelly) reaction. Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product.   So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.
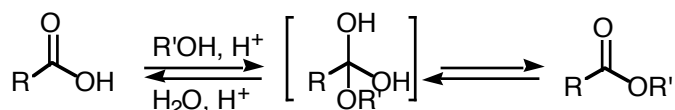
11. **Indirect Conversion to Anhydrides**
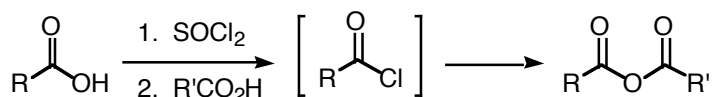
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction

## 12. Direct Conversion to Esters (Sections 20-10-12, 21-5)

- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester
- This is a "lateral" reaction, neither uphill nor downhill energetically
- This is the exact reverse of reaction 8b

13. Indirect Conversion to Esters via Acid Chlorides (Sections 20-10-12, 21-5)
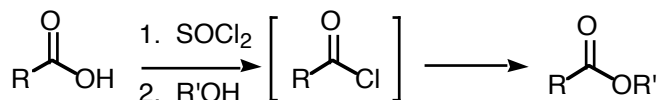
- mechanism required **for acid chloride to ester conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the ester is a "downhill" reaction energetically.

14. Direct Conversion to Amides
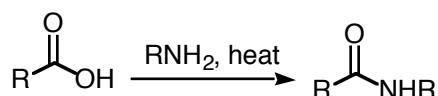
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly even at mild biological temperatures.

15. Indirect Conversion to Amides
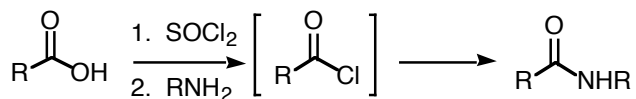
- mechanism required **for acid chloride to amide conversion: addition-elimination-deprotonation**
- This reaction sequence works very well in the laboratory

16. **Reduction to Primary Alcohol** (Sections 10-11, 20-14)

- **mechanism not required**

17. **Alkylation to Form Ketones** (Section 18-19, 20-15)

- **mechanism not required**

18. **Interconversions of Acids and Acid Derivatives** (Section 21-5 and many others)
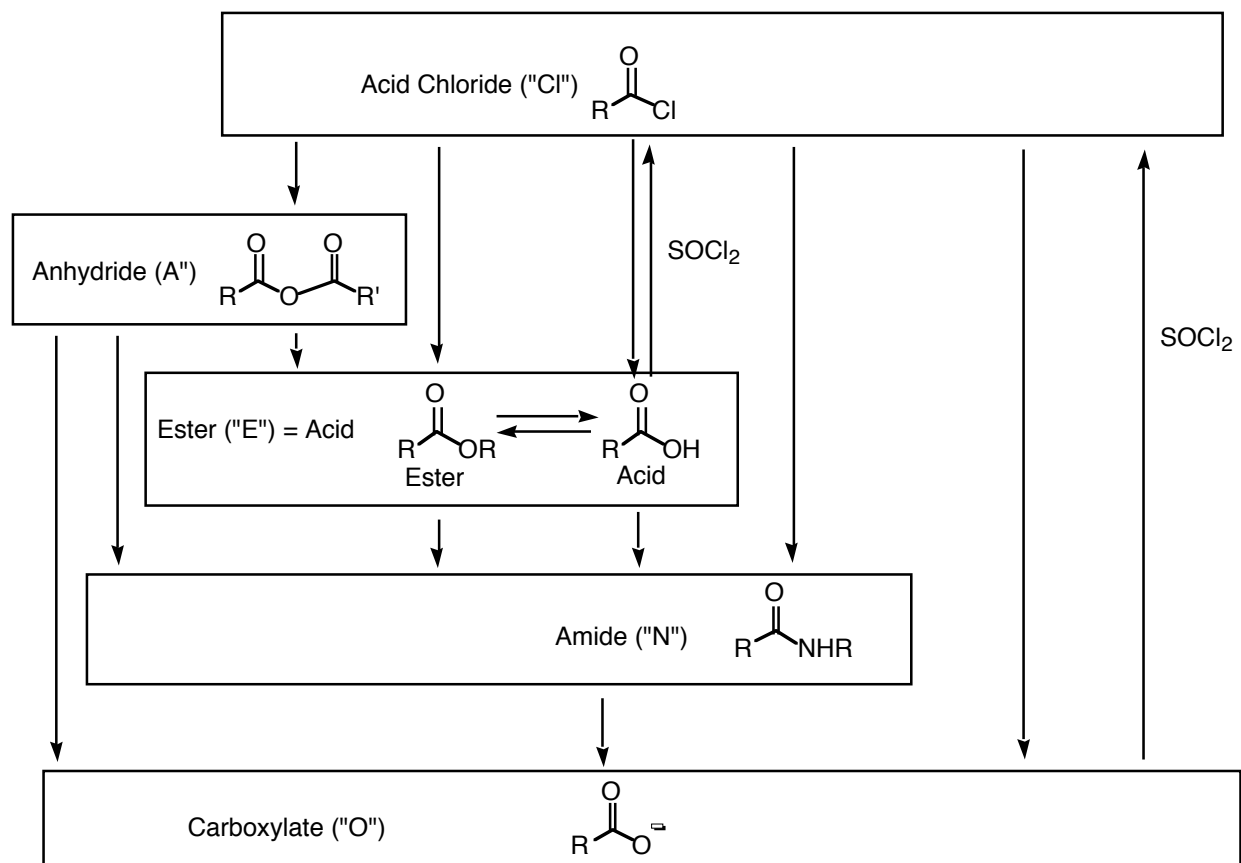
- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with SOCl$_2$ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)

Mechanisms
A. Miscellaneous
5. **From Grignard Reagents: Via Carboxylation**:
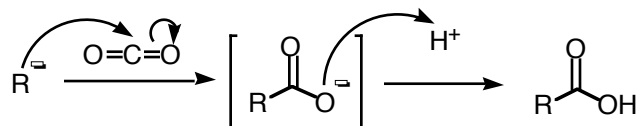
- exactly like any Grignard reaction

9. Reaction as a Proton Acid
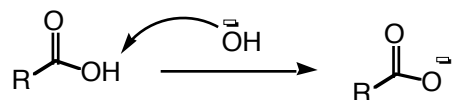
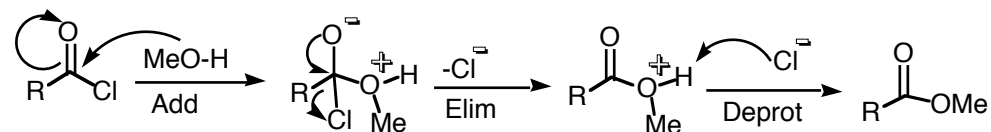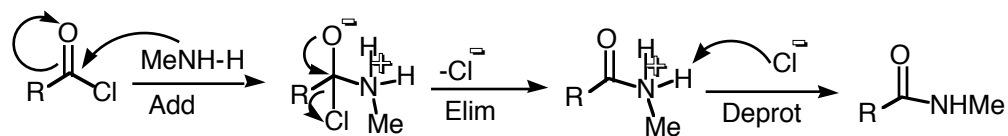### B.   Any "Downhill" Interconversions (8a, 8c, 11, 13, 15, 18):   All Proceed by Addition-Elimination-Deprotonation

General
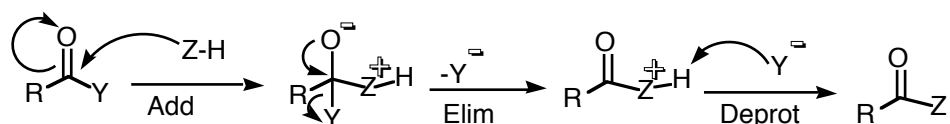
Examples
Reaction 8a
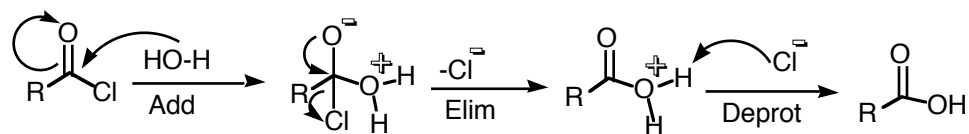
Reaction 8c (Note: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)
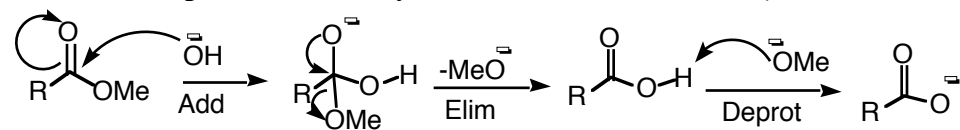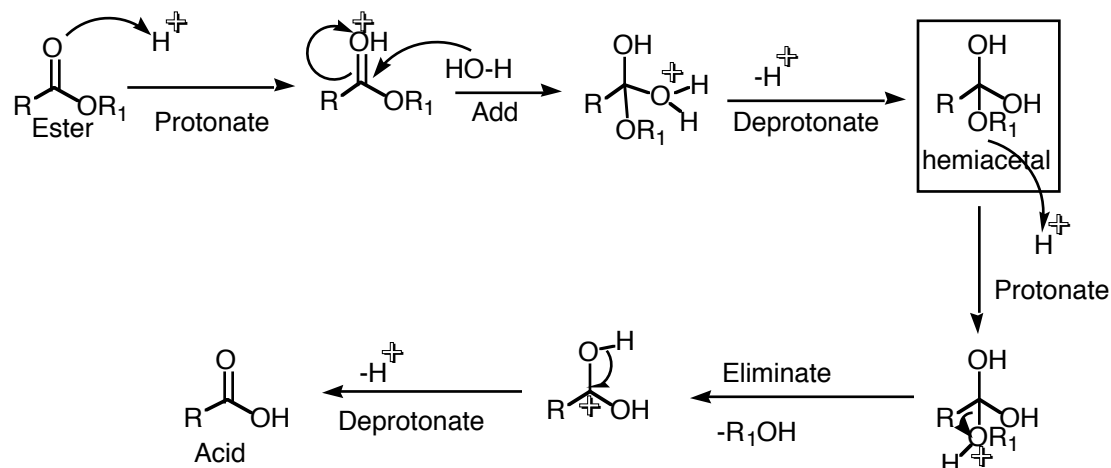

Reaction 13

Reaction 15

C. "Lateral" Interconversions (8b/12): Acid-Catalyzed conversion from Ester to Acid (8b) or From Acid to Ester (12): (ACID WATER)
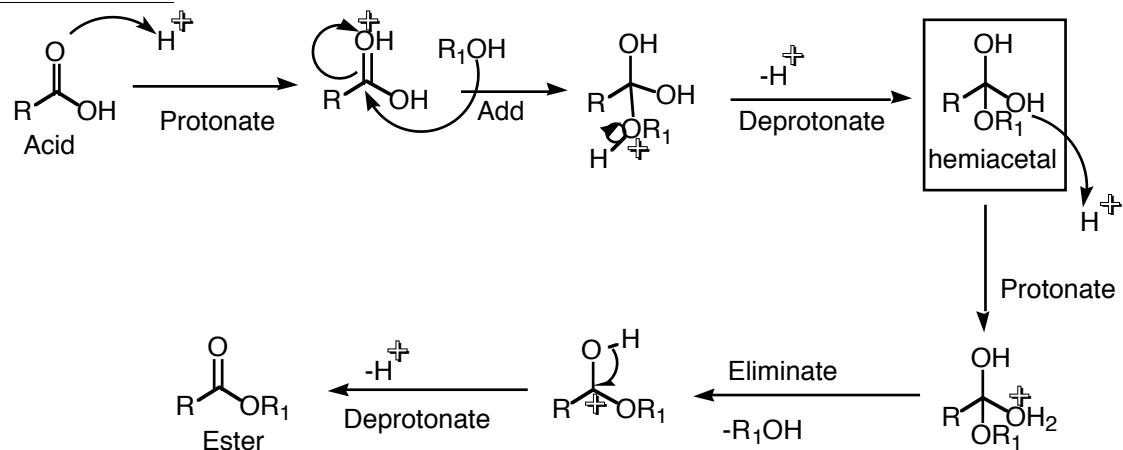
- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**
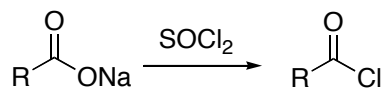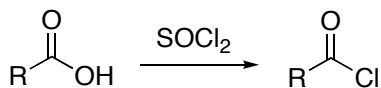
Examples
Reaction 8b: Ester to Acid

Reaction 12: Acid to Ester

<u>Acid Chlorides: Preparation and Uses (Sections 20.11 and 21.5)</u>

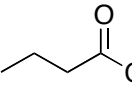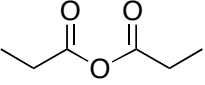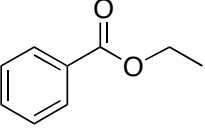10. **Conversion of acids or Carboxylates to Acid Chlorides**
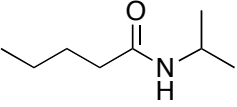

- Mechanism: Not Required
- Easy (but smelly) reaction.
  - o Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product.   So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

Ch. 21 Carboxylic Acid Derivatives:

- o Cl   chloride
- o A   anhydride
- o E   ester
- o N   amide
- o O: carboxylate

Structure, Names, Notes
- all are subject to hydrolysis
- All hydrolyze to acids (actually, to carboxylate anion) upon treatment with $NaOH/H_2O$
- Some (Cl and A) hydrolyze to acids under straight water treatment
- Esters hydrolyze to acids under acid catalysis

	General		Example	
	Alkanoyl chloride		Butanoyl chloride	• High reactivity • Named as if ionic
	Alkanoic Anhydride		Propanoic anhydride	
	Alkyl Alkanoate		Ethyl Benzoate	Named as if ionic
	Alkanamide		N-isopropyl pentanamide	