Synthesis of Ketones and Aldehydes

#	Reaction	Ref
1	$Ph\diagdown OH \xrightarrow{PCC} Ph\diagdown CHO$	15.9
2	$\underset{Ph}{\overset{OH}{\diagup}} \xrightarrow{H_2CrO_4} Ph\overset{O}{\diagup}$	15.9
3	$Ph\diagdown \xrightarrow[\text{2. NaOH, }H_2O_2]{\text{1. }BH_3\cdot THF} Ph\diagdown OH \xrightarrow{PCC} Ph\diagdown CHO$	6.11
4	$Ph\diagdown \xrightarrow{H_2O, H^+} \underset{Ph}{\overset{OH}{\diagup}} \xrightarrow{H_2CrO_4} Ph\overset{O}{\diagup}$	6.9
5	$\xrightarrow[\text{2. Me}_2S]{\text{1. O}_3}$ +	6.20
6	$\underset{\text{Aldehyde}}{\overset{O}{Ph\diagdown H}} \xrightarrow[\text{2. }H^+]{\text{1. RMgBr}} \underset{H}{\overset{OH}{Ph\diagdown R}} \xrightarrow{H_2CrO_4} \underset{\text{Ketone}}{\overset{O}{Ph\diagdown R}}$	14.6
7	$\underset{\text{acid or ester}}{\overset{O}{Ph\diagdown OR}} \xrightarrow[\text{2. }H^+]{\text{1. LiAlH}_4} \underset{H}{\overset{OH}{Ph\diagdown H}} \xrightarrow{PCC} \underset{\text{aldehyde}}{\overset{O}{Ph\diagdown H}}$	19.13
8	$R\diagdown Br \xrightarrow{NaOH} R\diagdown OH \xrightarrow{PCC} R\diagdown CHO$	8.3
9	$\underset{Br}{\diagup} \xrightarrow{NaOH} \underset{OH}{\diagup} \xrightarrow{H_2CrO_4} \overset{O}{\diagup}$	8.3
10	$Ph-C\equiv C-H \xrightarrow[\substack{H_2SO_4 \\ \text{Markovnikov} \\ \text{Addition}}]{Hg^{2+}, H_2O} \left[\underset{\text{"enol"}}{\overset{OH}{Ph\diagup}}\right] \xrightarrow[\boxed{\text{MECH}}]{H^+, H_2O} \underset{\text{Ketone}}{\overset{O}{Ph\diagup}}$	9.12
11	$Ph-C\equiv C-H \xrightarrow[\substack{\text{2. NaOH, }H_2O_2 \\ \text{Anti-Markovnikov} \\ \text{Addition}}]{\text{1. (Sia)}_2BH} \left[\underset{\text{"enol"}}{Ph\diagdown OH}\right] \xrightarrow[\boxed{\text{MECH}}]{\overset{\ominus}{O}H, H_2O} \underset{\text{Aldehyde}}{Ph\diagdown CHO}$	9.12

#	Reaction	Ref
12	Ph–C(=O)–OH (acid) →[1. 2 RLi][2. H⁺, H₂O] [Ph–C(=O)–OLi] (carboxylate anion) → [LiO–C(OLi)–R with Ph] (tetrahedral dianion) →[acid] [HO–C(OH)–R with Ph] (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)	14.10
14	H–C₆H₅ + R–C(=O)–Cl →[AlCl₃] R–C(=O)–C₆H₅ Aromatic ketone (from the aryl group's perspective)	12.7
	R–C(=O)–Cl (acid chloride) →[Ar-H, AlCl₃] R–C(=O)–C₆H₅ Aromatic ketone (from the acyl group's perspective)	
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)	19.19
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	19.19

Reactions of Ketones and Aldehydes

19		14.6, 17.5

Anionic

Mech: Addition-Protonation. Strong nucleophile, Strongly anionic. Irreversible.

20		15.2, 17.5

Anionic

Mech: Addition-Protonation. Strong nucleophile, Strongly anionic. Irreversible.

21		17.7

Anionic

Mech: Addition-Protonation.   Medium nucleophile, Weakly anionic; literally buffered. Reversible.

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.	17.6

Anionic

Mech Forward: Addition-Protonation. Nucleophile, anionic mechanism. Reversible.
Mech Reverse: Deprotonation-Elimination. Anionic mechanism. Reversible.

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.	17.6

Cationic

Mech Forward: Protonation-Addition-deprotonation. Weakly nucleophile, cationic mechanism. Reversible.
Mech Reverse: Protonation-Elimination-deprotonation.   Cationic E1-type mechanism. Reversible.

| 24 | | 17.8,9 |

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 | | 17.10 |

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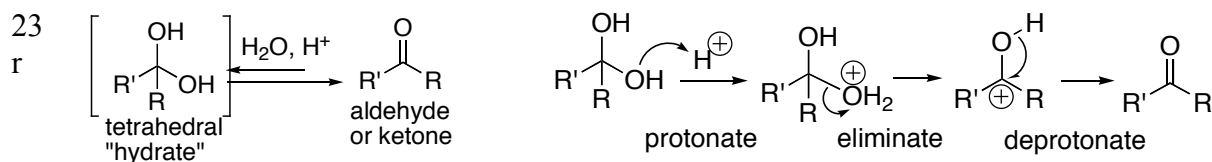- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.

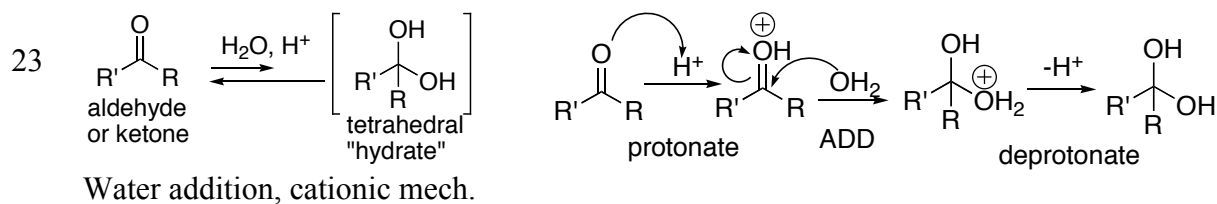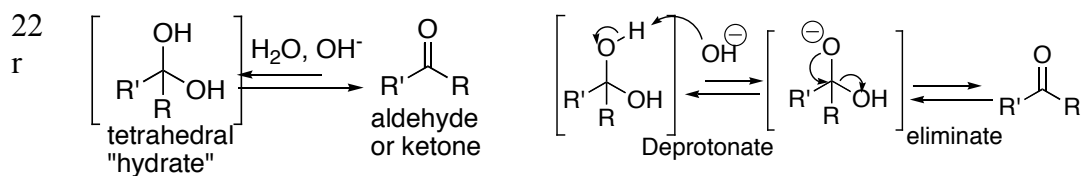| 26 | R'—CHO $\xrightarrow{\text{H}_2\text{CrO}_4 \text{ or Ag}^+ \text{ etc.}}$ R'—COOH | 17.15 |

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

Acid-catalyzed elimination of a hydrate to a carbonyl

15

15 phase 1

"imine" → tetrahedral "aminol"

H⁺, H₂O MECH

Acid-catalyzed addition of water to an imine

protonate   add   deprotonate

15 phase 2

tetrahedral "aminol" → ketone

H⁺, H₂O MECH

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

protonate   eliminate   deprotonate

Review: Several Pertinent Mechanistic Principles

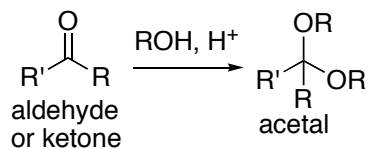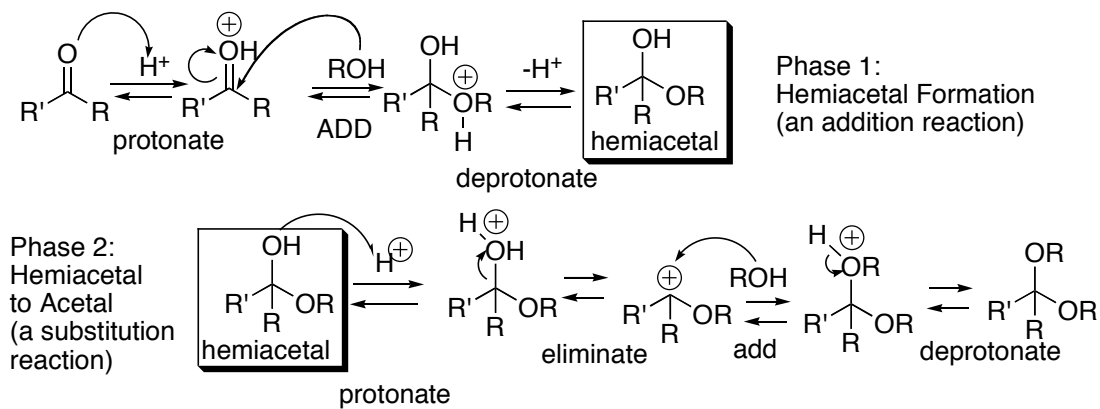1. **Recognize anionic mechanisms** (when a strong anion is involved)
   - In an anionic mechanism, a strong anion will drive the first step
   - In an anionic mechanism, intermediates should avoid positive charges
   - Recognize anionic species even when they are disguised by a cationic metal counterion.

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.

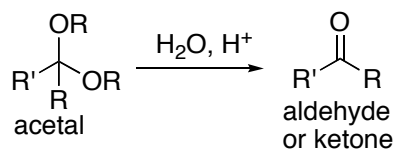## Some Mechanisms Associated with the Reactions of Aldehydes and Ketones

19 Grignard Addition of a Carbanion

20 aldehyde or ketone

Hydride addition.

21 HCN addition, anionic mech.

22 aldehyde or ketone tetrahedral "hydrate"

Water addition, anionic mech.

22 r tetrahedral "hydrate" aldehyde or ketone

23 aldehyde or ketone tetrahedral "hydrate"

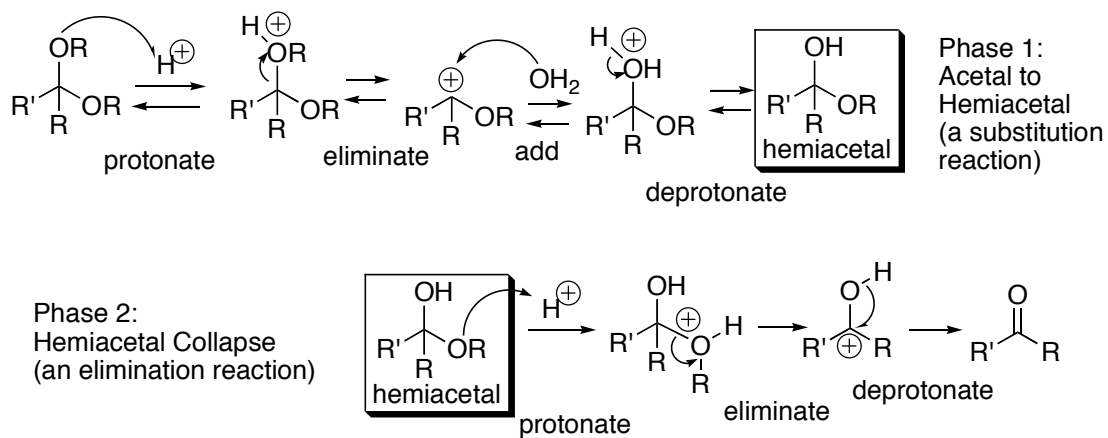Water addition, cationic mech.

23 r tetrahedral "hydrate" aldehyde or ketone
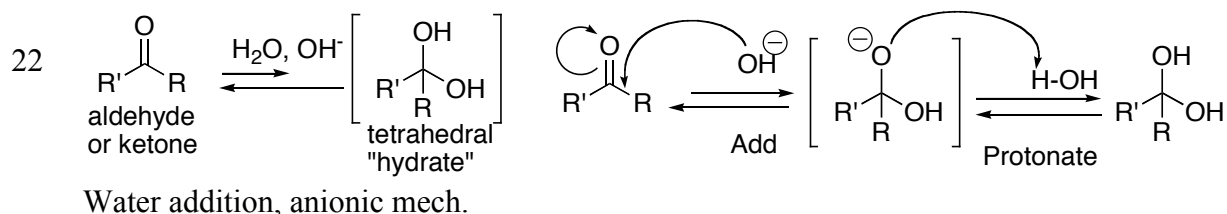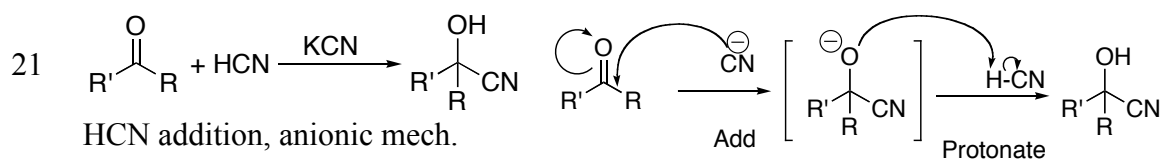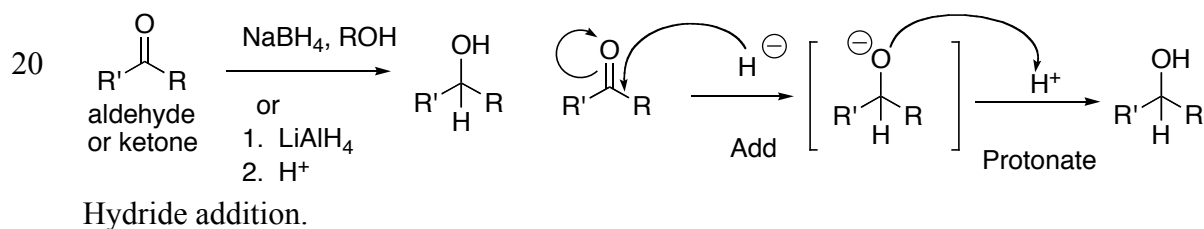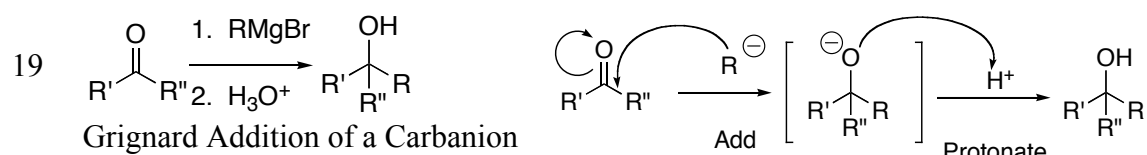
24

Acetal formation

24r

Acetal hydrolysis.

25

ZNH$_2$, H$^+$

aldehyde
or ketone

imine

Imine Formation

Phase 1:
Aminol Formation
(an addition reaction)

protonate   ADD   aminol   deprotonate

Phase 2:
Aminol
to Imine
(an elimination
reaction)

aminol

protonate   eliminate   deprotonate   imine

25r

H$_2$O, H$^+$
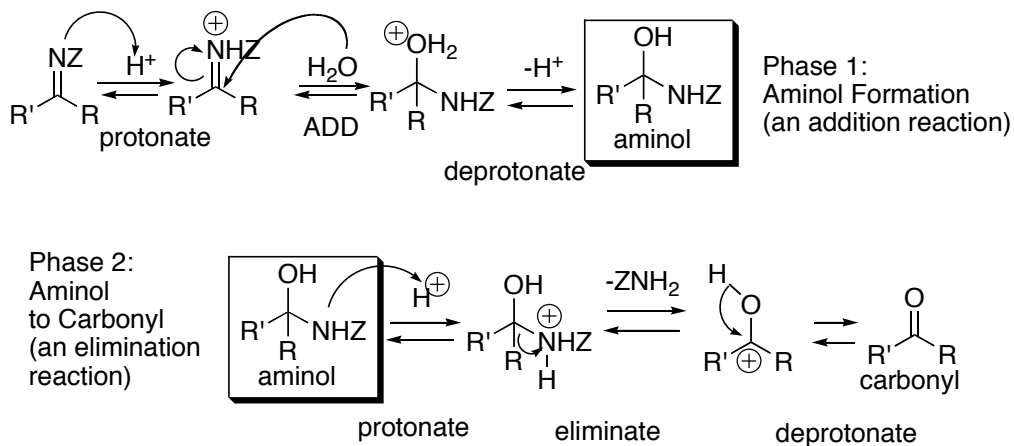
imine

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   −ZNH$_2$

protonate   eliminate   deprotonate   carbonyl

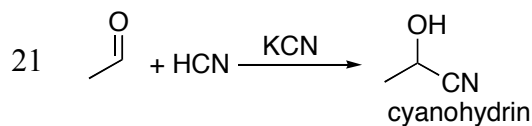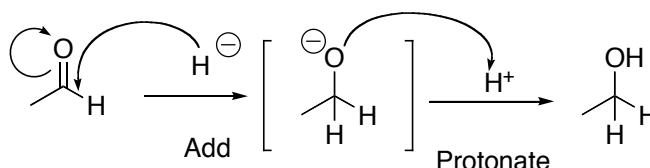## Classification of Mechanisms Associated With Ketone/Aldehyde Reactions.

- 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.
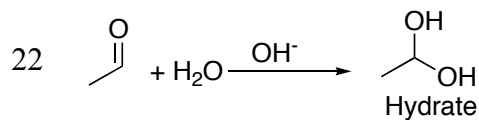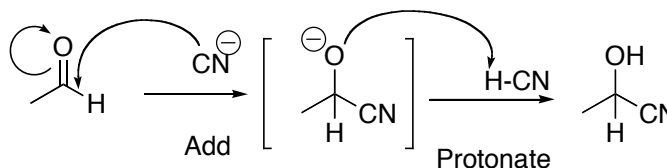
ADDITION REACTIONS.
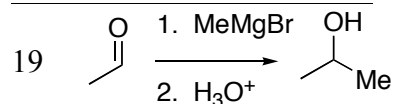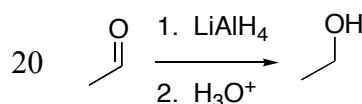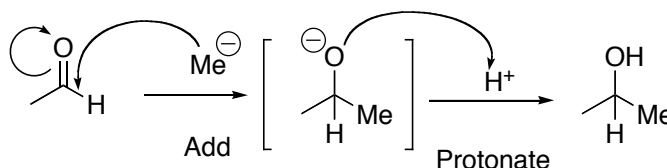
19 Grignard Addition of a Carbanion
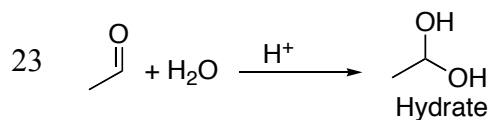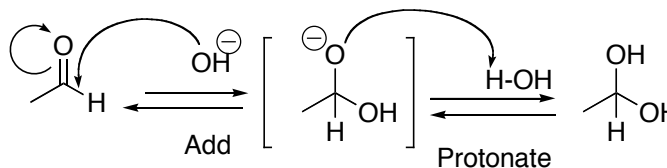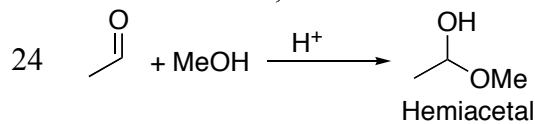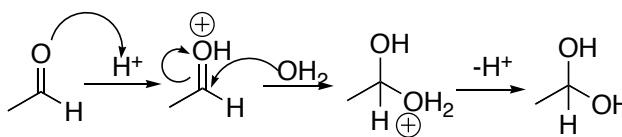
20 Hydride addition.

21 HCN addition, anionic mech.

22 Water addition, anionic mech.

23 Water addition, cationic mech.

24 Alcohol addition, cationic mech.
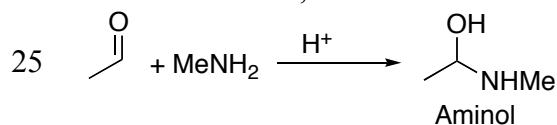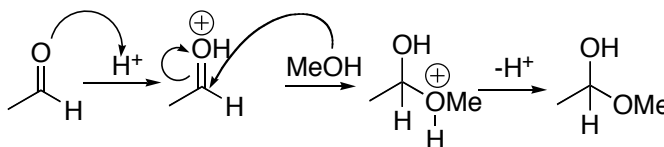
25 Amine addition, cationic mech.
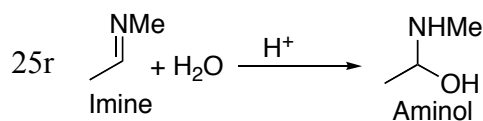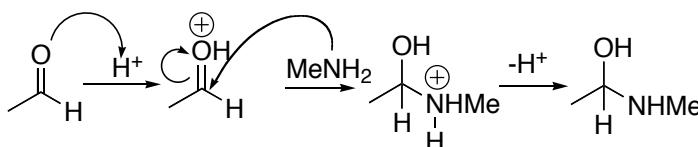
25r Water addition to imine, cationic mech

Elimination Reactions.

22r	Tetrahedral "hydrate" → aldehyde or ketone, H_2O, OH^-	Deprotonate → eliminate
23r	Tetrahedral "hydrate" → aldehyde or ketone, H_2O, H^+	protonate → eliminate → deprotonate
24r	Tetrahedral "hemiacetal" → aldehyde or ketone, H_2O, H^+	protonate → eliminate → deprotonate
25r	Tetrahedral "aminol" → aldehyde or ketone, H_2O, H^+	protonate → eliminate → deprotonate
25b	Tetrahedral "aminol" → imine, H_2O, H^+	protonate → eliminate → deprotonate

Substitution Reactions.

24b	"hemiacetal" → "acetal", ROH, H^+; protonate → eliminate → add ROH → deprotonate
24r	"acetal" → "hemiacetal", HOH, H^+; protonate → eliminate → add → deprotonate

A. Nomenclature (Section 17.1)
1. Aldehydes:
   a. IUPAC: Alkan**al**
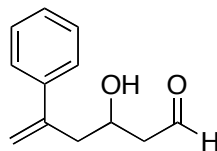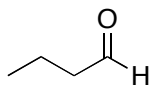
   • Note: carbonyl takes precedence over alcohols (hydroxy), aromatics, alkenes, halides.
   • Aldehyde carbon is always #1, so needs no number (don't forget to count that carbon!)

   b. Aldehydes are often written as RCHO

CH₃CHO   PhCHO
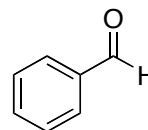
   c. Common Names: (Memorize)

2. Ketones:
   a. IUPAC: alkan-x-**one**

Need number, remember to number!!
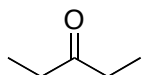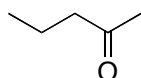
   b. Common Names: (Memorize)
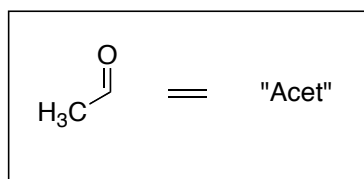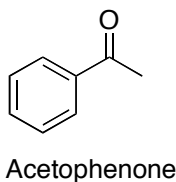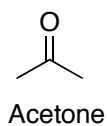
"Acet"

Acetone
Acetophenone
Acetaldehyde
Acetic Acid
Acetic Anhydride

3. Carbonyls as Substituents: **Alkanoyl**
*   needed when there are higher priority functional groups present, such as carbonylic acids
*   alkanoyl assumes the carbonyl is on the 1st, connecting carbon of the alkyl substituent
*   Not for test: (x-oxoalkyl) when the carbonyl is not on the connecting carbon.
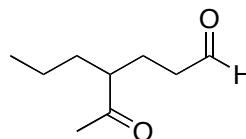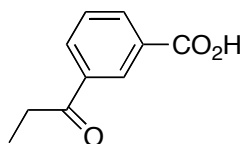
Common Names:
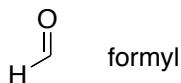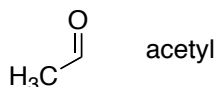
formyl   acetyl

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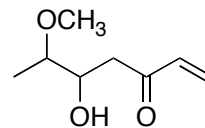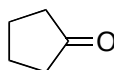1. **Core name versus Substituents.** Which part of the molecule can be included in the core name, and which parts need to treated as substituents?

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..)

|	$\underset{\underset{O}{|}}{C}$	$\underset{\underset{O}{|}}{C}$	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)
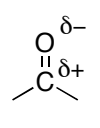
4. **Punctuation**
*   Hyphenate numbers and stereochemical descriptors
*   Parenthesize stereochemical descriptors: (R)/(S), (E)/(Z)
*   Do not put any spaces for molecular-style names
*   Do put spaces for ionic style names

Ionic style:
NaCl: PhCO$_2$H: PhCO$_2$CH$_3$

C. Properties of Carbonyls (Sections 17.2,3)

$O^{\delta-}$ $\overset{\|}{\underset{\delta+}{C}}$	• 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

Many Ketones and Aldehydes have Famous, Nice Smells
   • Vanilla, almond extract, cinnamon, spearmint, pistachio, butter, camphor, etc.

D. Synthesis of Ketones/Aldehydes: Review Routes, Handout Reactions 1-9 (Sections 17.4 and earlier book sections)

From Alcohols

1

2
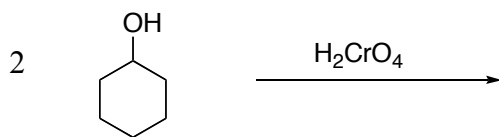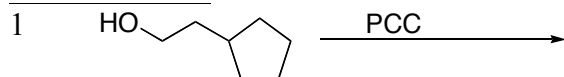
From Alkenes via Alcohols or Oxidative Cleavage

3

4

5
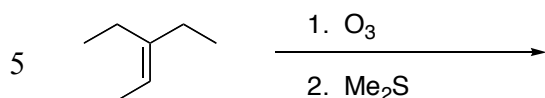
From Carbonyl via Alcohols

6

7

From Halides via Alcohols

8

9

E. **New Syntheses of Ketones/Aldehydes: Handout Reactions 10-18**

From Alkynes (Section 9.12)

10   Ph−C≡C−H $\xrightarrow[\substack{H_2SO_4 \\ \text{Markovnikov} \\ \text{Addition}}]{Hg^{2+}, H_2O}$ $\left[\substack{OH \\ Ph} \right]$ "enol" $\xrightarrow{H^+, H_2O}$ **MECH** $\substack{O \\ Ph}$ Ketone
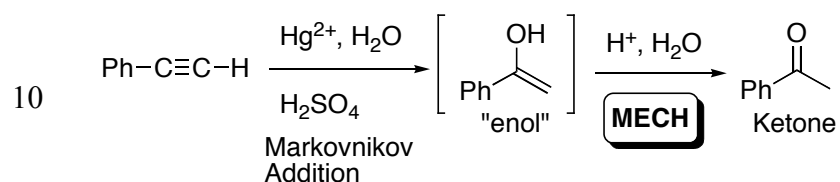
Two Phases:
   1. The first phase is analogous to oxymercuration of an alkene
       a. It involves Hg^{2+} and water
       b. H-OH adds across the π-bond
       c. Markovnikov addition: OH adds to the more substituted end of alkyne
       d. NaBH$_4$ is actually not required
   2. Phase 2: The "enol" produced in the first phase is unstable and rapidly converts to the carbonyl
   •   Phase 2: Mechanism Responsible.

Mechanism: (Acid-Catalyzed enol → carbonyl)
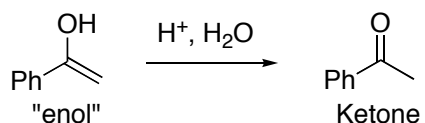
New Bonds   Broken Bonds

Acid Conditions:
1. Use H+ in first step
2. Cationic intermediates
3. At some point deprotonate to return to neutral.

11   Ph−C≡C−H   1. (Sia)$_2$BH   →   [Ph〜OH "enol"] $^{\ominus}$OH, H$_2$O **MECH**   Ph〜O Aldehyde

2. NaOH, H$_2$O$_2$
Anti-Markovnikov Addition

Two Phases:
   1. The first phase is analogous to hydroboration of an alkene
         a. H-OH adds across the π-bond
         b. It involves a borane
         c. Anti-Markovnikov addition: OH adds to the less substituted end of alkyne
         d. (Sia)$_2$BH ~ BH$_3$-THF, but is much bulkier in order to ensure high anti-Markovnikov orientation and to ensure that it stop after one addition and leaves the second π-bond untouched. (BH$_3$ works but is less selective)

   2. Phase 2: The "enol" produced in the first phase is unstable and rapidly converts to the carbonyl
   • Phase 2: Mechanism Responsible.

Mechanism: (Base-Catalyzed enol → carbonyl)

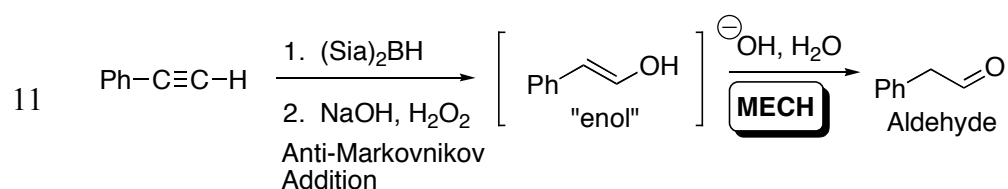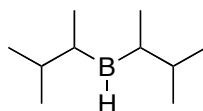New Bonds   Broken Bonds

Base Conditions:
1. Use base (hydroxide) in first step
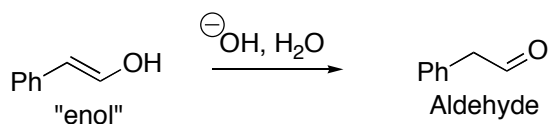2. Cationic intermediates
3. At some point deprotonate to return to neutral.

a. Hg^{2+}, H_2O / H_2SO_4

b. Hg^{2+}, H_2O / H_2SO_4

c.   1. $(Sia)_2BH$
       2. NaOH, H_2O_2

d.
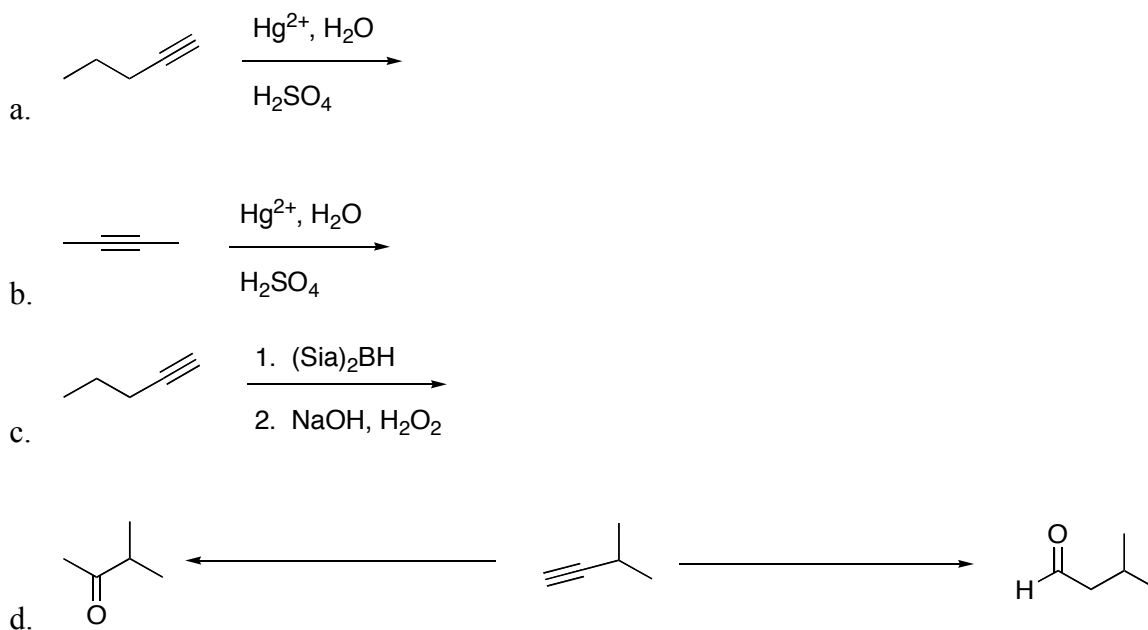
Remember:
1. Enols quickly convert to carbonyls
2. Remember these two reactions mainly as Markovnikov or anti-Markovnikov addition of H-OH addition to alkyne

From Carboxylic Acids

12   Ph—C(=O)—OH   1. 2 RLi
     acid   2. H^+, H_2O [Ph—C(=O)—OLi]   → [LiO—C(Ph)(R)—OLi]   acid   → [HO—C(Ph)(R)—OH] H^+, H_2O Ph—C(=O)—R   18.9
                                      carboxylate   tetrahedral   tetrahedral   **MECH**   ketone
                                      anion   dianion   "hydrate"

a.   1. 2 MeLi
       2. H^+, H_2O

b. HO   1. 2 PhLi
        2. H^+, H_2O

c.   ————→
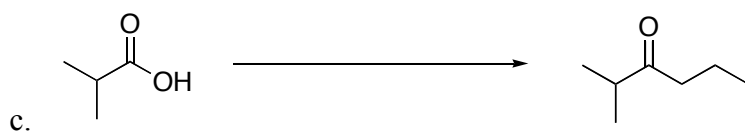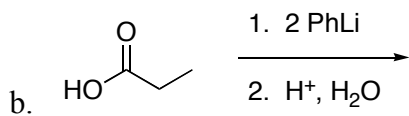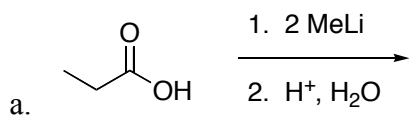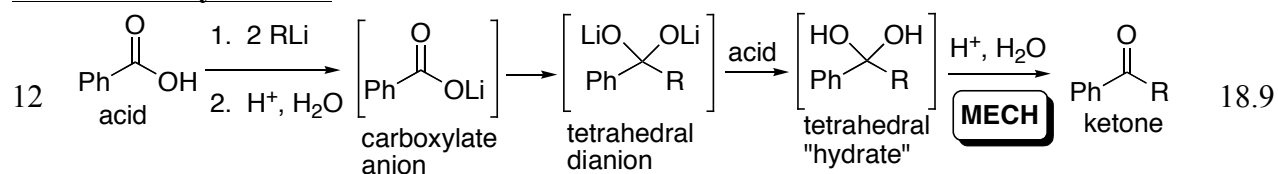
Mechanism: Key new Mechanism Step is the **acid-catalyzed hydrolysis of the tetrahedral hydrate** to the ketone
- Tetrahedral anion is stable until acid/water is added
- Tetrahedral hydrate rapidly "dehydrates" to ketone

From Acid Chlorides (Section 14.10, 19.4)

13 acid chloride   ketone   18.11

14   Aromatic ketone
                                      (from the aryl group's perspective)   18.11

acid chloride   Aromatic ketone
                                      (from the acyl group's perspective)
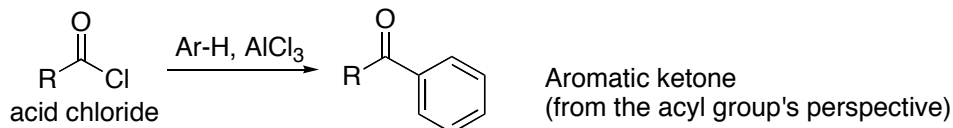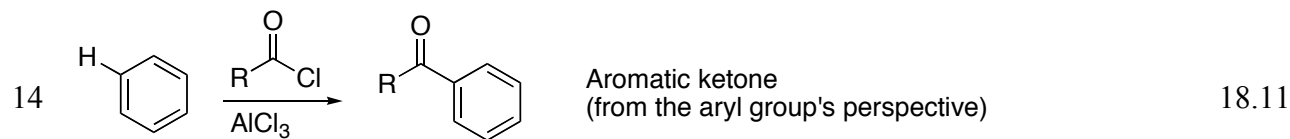
- No mechanism responsibility for reaction 13
- Reaction 14, mechanisms from chapter 17, Semester 1, Test 4
- R$_2$CuLi is a special, mild carbanion equivalent. Some special properties enable it to stop at ketone. (RMgBr would not stop at ketone, but would add again to give 3° alcohol)

a.

b.
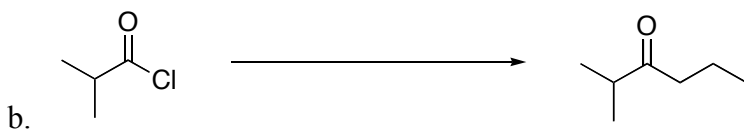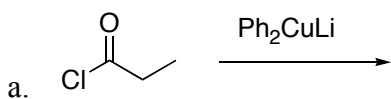
From Nitriles (Section 19.19)

15   Ph–CN $\xrightarrow[\text{2. H}^+,\text{ H}_2\text{O}]{\text{1. RMgBr}}$ $\begin{bmatrix} \text{Ph} \diagup \text{R} \\ \text{N}\ominus \end{bmatrix}$ $\xrightarrow{\text{H}^+}$ $\begin{bmatrix} \text{Ph} \diagup \text{R} \\ \text{NH} \\ \text{"imine"} \end{bmatrix}$ $\xrightarrow{\text{H}^+,\text{ H}_2\text{O}}$ **MECH** $\begin{bmatrix} \text{Ph} \diagdown \diagup \text{R} \\ \text{HO} \quad \text{NH}_2 \\ \text{tetrahedral} \\ \text{"aminol"} \end{bmatrix}$ $\xrightarrow{\text{H}^+,\text{ H}_2\text{O}}$ **MECH** $\boxed{\begin{array}{c} \text{Ph} \diagdown \diagup \text{R} \\ \text{O} \\ \text{ketone} \end{array}}$ 18.10

Nitrile

16   Ph–Br $\xrightarrow[\begin{array}{l}\text{2. RMgBr}\\\text{3. H}^+,\text{ H}_2\text{O}\end{array}]{\text{1. KCN}}$ Ph–CN $\xrightarrow{\text{Steps 2 + 3}}$ Ph $\diagdown\diagup$ R, O   18.10

Primary Bromide   Nitrile
                         Intermediate
                         (after step 1)

a.   CN $\diagup$ $\xrightarrow[\text{2. H}^+,\text{ H}_2\text{O}]{\text{1. MeMgBr}}$

b.   NC $\diagdown\diagup$ $\xrightarrow[\text{2. H}^+,\text{ H}_2\text{O}]{\text{1. PhMgBr}}$

c. $\diagup$Br $\longrightarrow$ $\longrightarrow$ (2-methyl-3-hexanone structure)

Mechanism: Acid-Catalyzed Hydrolysis of C=NH
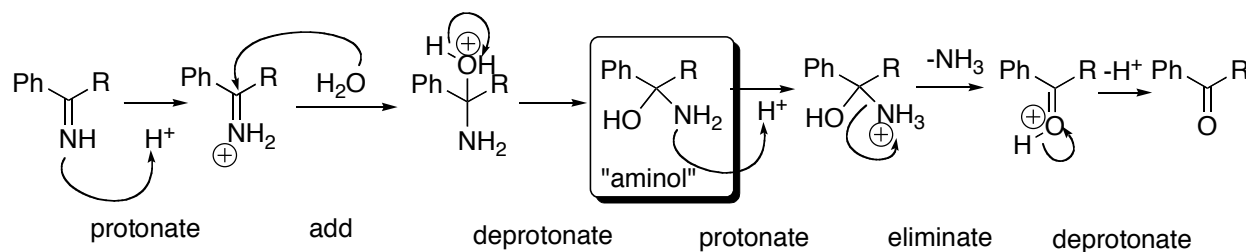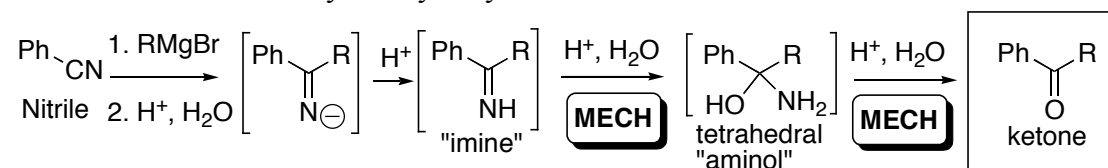
Ph–CN $\xrightarrow[\text{2. H}^+,\text{ H}_2\text{O}]{\text{1. RMgBr}}$ $\begin{bmatrix} \text{Ph} \diagup \text{R} \\ \text{N}\ominus \end{bmatrix}$ $\xrightarrow{\text{H}^+}$ $\begin{bmatrix} \text{Ph} \diagup \text{R} \\ \text{NH} \\ \text{"imine"} \end{bmatrix}$ $\xrightarrow{\text{H}^+,\text{ H}_2\text{O}}$ **MECH** $\begin{bmatrix} \text{Ph} \diagdown \diagup \text{R} \\ \text{HO} \quad \text{NH}_2 \\ \text{tetrahedral} \\ \text{"aminol"} \end{bmatrix}$ $\xrightarrow{\text{H}^+,\text{ H}_2\text{O}}$ **MECH** $\boxed{\begin{array}{c} \text{Ph} \diagdown \diagup \text{R} \\ \text{O} \\ \text{ketone} \end{array}}$

Nitrile

protonate   add   deprotonate   protonate   eliminate   deprotonate

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
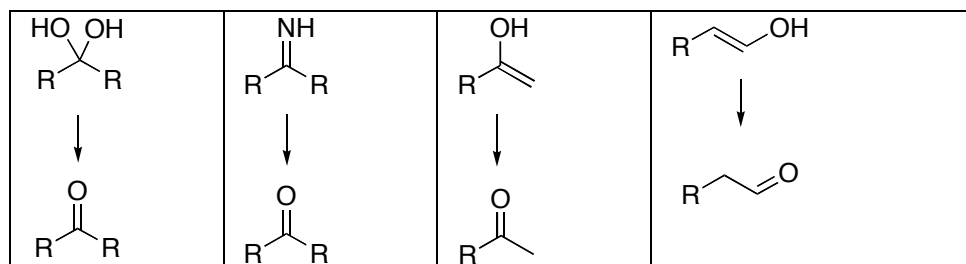
F. General Reactivity of Ketones and Aldehydes: Addition Reactions (Section 17.5,6)
**Key: Are reaction conditions anionic/basic or cationic/acidic (or perhaps buffered in between?)**

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**
        3. Addition is normally irreversible
            *   Addition is often strongly exothermic
            *   The proton source is often added in a separate laboratory step, because often the anion and the proton are incompatible
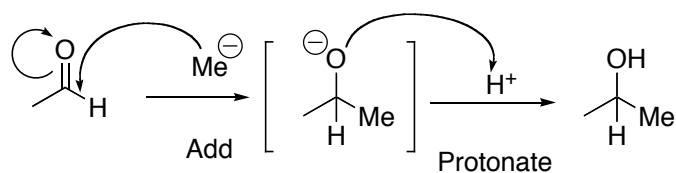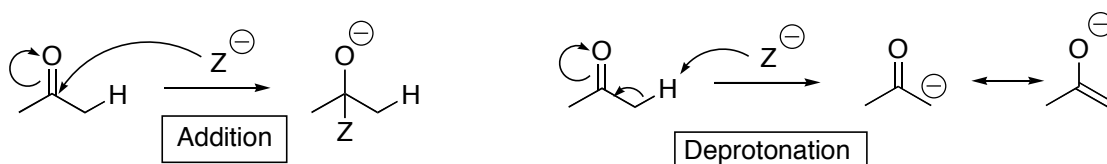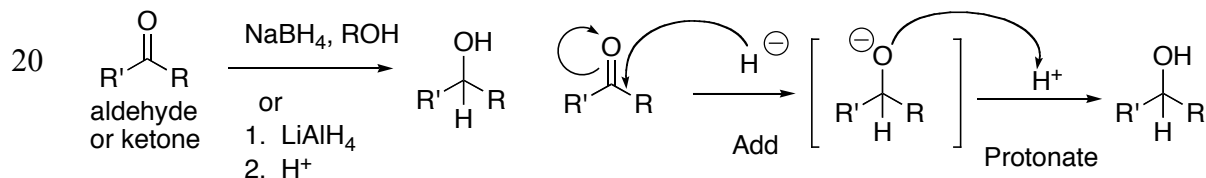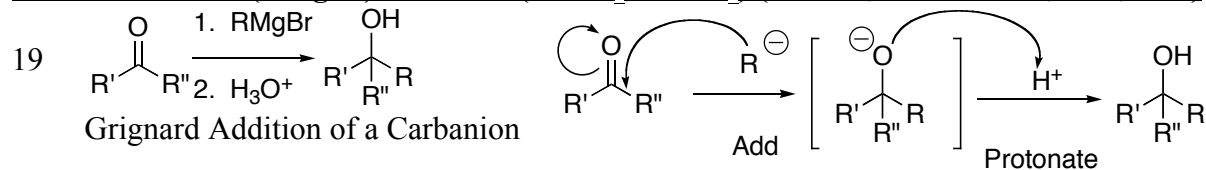
2. **Cationic Conditions** (acid is involved)
   a. General principles review for acid/cationic conditions apply
      - Recipes that involve acid will be cationic
      - In a cationic mechanism, the first step will routinely involve protonation
      - In a cationic mechanism, the last step will frequently involve deprotonation to return to neutral
      - Normally the main step or steps are sandwiched in between the protonation and deprotonation events
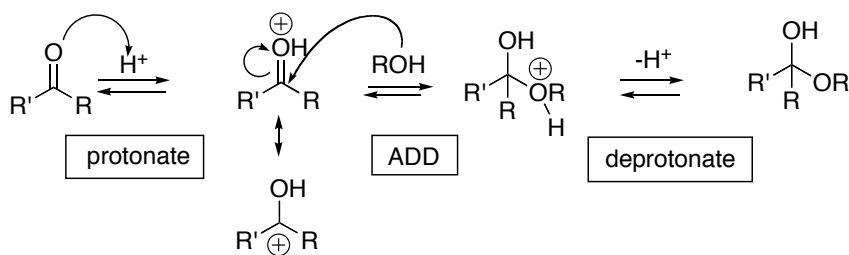
   b. Cationic additions to ketones
      1. Weak, neutral nucleophile involved (ROH, HOH…)
      2. Intermediates have positive charge
      3. **Protonation first, addition second**
         - Weak nucleophile is not strong enough to add to neutral carbonyl
         - Protonation activates the carbonyl 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
   - 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
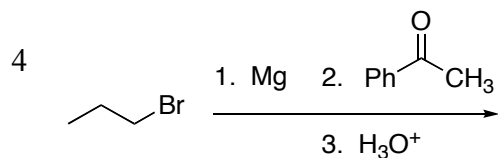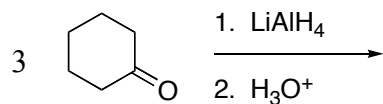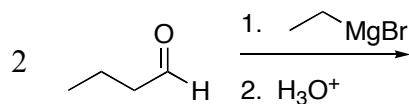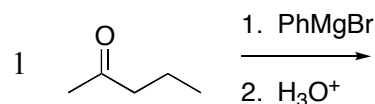
Addition of R $^{\ominus}$ (RMgBr) and H $^{\ominus}$ (NaBH$_4$, LiAlH$_4$) (Review, Section 17.5, 14.6, 15.2)

19

1. RMgBr
2. H$_3$O$^+$

Grignard Addition of a Carbanion

Add

Protonate

20

NaBH$_4$, ROH

or

1. LiAlH$_4$
2. H$^+$

aldehyde
or ketone

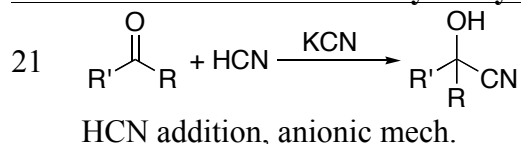Hydride addition.

Add

Protonate

Note: For RMgBr and LiAlH$_4$, the basicity of the reagent is too strong to permit a proton source to be present at the same time. Thus the proton source must be added in a subsequent laboratory step. The NaBH$_4$ is weaker, both as a nucleophile but also as a base.
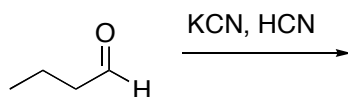
Draw products from the following reactions.
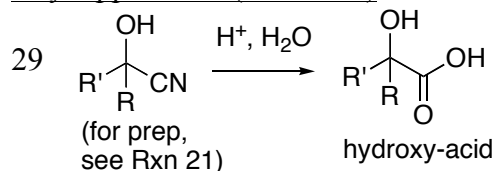
1°, 2° or
3°?

1

1. PhMgBr

2. H$_3$O$^+$

2

1.   MgBr

2. H$_3$O$^+$

3

1. LiAlH$_4$

2. H$_3$O$^+$

4

1. Mg   2. Ph   CH$_3$

Br

3. H$_3$O$^+$

5

Br

OH

6. Draw the mechanism for reaction 1 above.

## Addition of HCN to make "Cyanohydrins" (Section 17.7): Anionic Mechanism

21   R'–C(=O)–R + HCN —KCN→ R'–C(OH)(CN)–R

HCN addition, anionic mech.

Draw the product and mechanism for the following:

CH₃CH₂CH₂–C(=O)–H   —KCN, HCN→

Mechanistic notes
1. Addition first, protonation second
2. ⊖CN is a good nucleophile, HCN a decent acid
3. KCN/HCN represents a **buffer situation**: weak base/weak acid, not obvious which dominates. But in this case the anion does and it proceeds via anionic mechanism.
4. ⊖CN is actually used as a catalyst: after the HCN donates proton, the ⊖CN is regenerated
5. In reality, KCN/HCl or KCN/H₂SO₄ is often used
   • Easier to put together and handle
6. Reaction is reversible
   • Strongly favors product cyanohydrin, unless a strongly hindered ketone is used
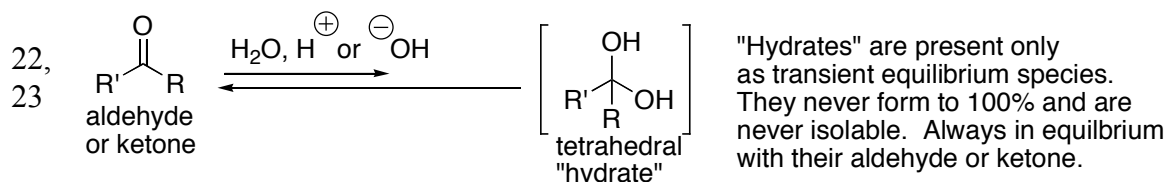
Draw products

a.   CH₃CH₂–C(=O)–CH₃   —KCN, HCN→

b.   Ph–C(=O)–H   —KCN, HCN→

c.
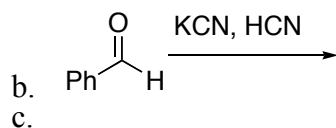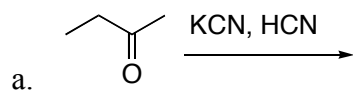
Key Application (not tested)

29   R'–C(OH)(CN)–R   —H⁺, H₂O→   R'–C(OH)(R)–C(=O)–OH

(for prep, see Rxn 21)   hydroxy-acid

• Unique access to 2-hydroxyacids..
• Indirect provides the equivalent ("Synthon") for a ⊖CO₂H anion

Draw Products

1.   Ph–C(=O)–H   —1. KCN, HCN / 2. H₂O, H⁺→
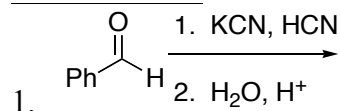
Reversible Addition of H₂O (H-OH) to Make Hydrates: Addition (and elimination) under Acidic or Basic Conditions (Section 17.6).
- Know mechanism under either base or acid
- Know mechanism for the reverse direction (hydrate to carbonyl) as well

22,
23

"Hydrates" are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilibrium with their aldehyde or ketone.

Anionic
Mech Forward: Addition-Protonation. Nucleophile, anionic mechanism. Reversible.
Mech Reverse: Deprotonation-Elimination. Anionic mechanism. Reversible.

Cationic
Mech Forward: Protonation-Addition-deprotonation. Weakly nucleophile, cationic mechanism. Reversible.
Mech Reverse: Protonation-Elimination-deprotonation.   Cationic   E1-type mechanism. Reversible.
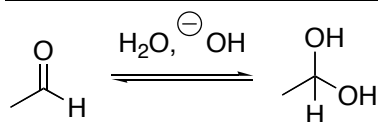
Notes:
1. True equilibrium.
2. Super unfavorable for ketones, moderately unfavorable for aldehydes
   - Ketone is stabilized more by the two alkyl donors
   - Ketone hydrate is destabilized more by sterics
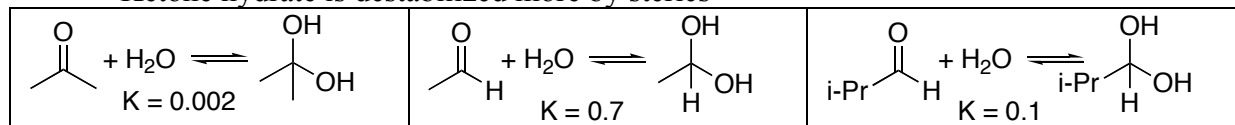
3. Hydrates can never be isolated, because as soon as you try to take them out of water, the drives back to the carbonyl side (LeChatelier's Principle)
4. While the hydrate is not present in high concentration, it is often a crucial intermediate in a variety of biological processes
   - We've also seen its importance in the oxidation of 1° alcohols to carboxylic acids using H_2CrO_4 in water.

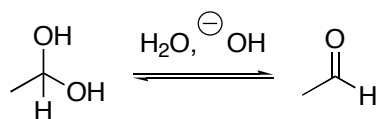Draw the **ANIONIC addition** mechanism   Draw the **CATIONIC addition** mechanism
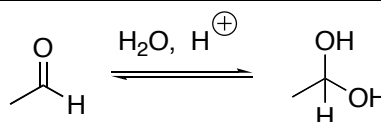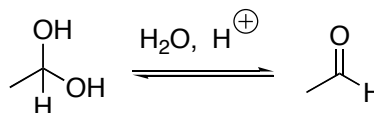
Hydrate Hydrolysis (Elimination of Water from Hydrate to Generate Carbonyl)

Draw the **ANIONIC elimination** mechanism
- Deprotonation precedes elimination
- E2-like

Draw the **CATIONIC elimination** mechanism
- Elimination precedes deprotonation
- E1-like

Reversible Reaction of ROH to Make Acetals via Hemiacetals. (Section 17.8,9). Addition/Substitution under Acidic Conditions.
Also know the reverses process, substitution/elimination under acid conditions
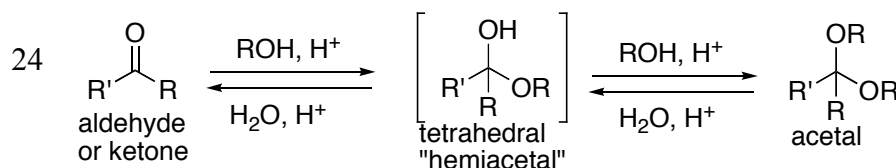
24

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. (It is stable in absence of water)
- 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

Notes:
1. While the acetal can be isolated, the hemiacetal cannot
2. Four reactions, each with their own mechanism:
   a. Carbonyl to hemiacetal = acid-catalyzed addition reaction.
   b. Hemiacetal to acetal = acid-catalyzed substitution reaction (S_N1-type)
   c. Acetal back to hemiacetal = acid-catalyzed substitution reaction (S_N1-type)
   d. Hemiacetal back to carbonyl = acid-catalyzed elimination (E1-type)

Draw the mechanism
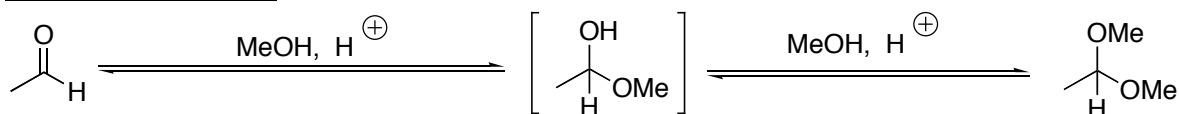
Draw the mechanism
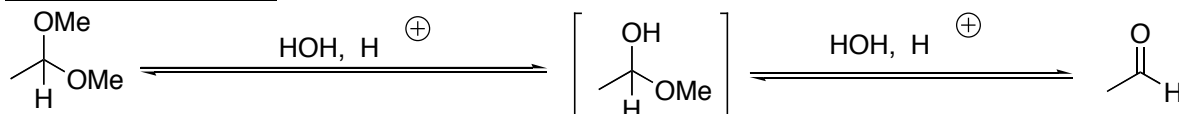
We have now seen three major acid-catalyzed reaction types in this chapter
1. Additions (protonate-**add**-deprotonate)
2. Eliminations (protonate-**eliminate**-deprotonate)
3. Substitutions (protonate-**eliminate-add**-deprotonate)
**Notice that a protonation/deprotonation sandwiches the key step(s) in each of them**

Draw the products for the following reactions

1   MeOH, H⊕
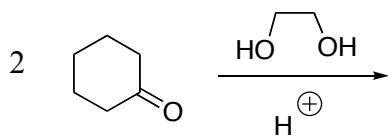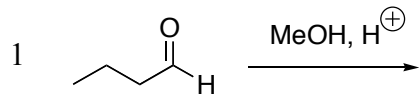
2   HO   OH   H⊕   "Cyclic Acetal"

Key Synthetic Notes:
1. **Ethylene glycol** works well for making acetals from aldehydes or ketones. Use **ethylene glycol for KETONES.**
   a. Once the first oxygen adds, the second oxygen is always close by and ready to add
   b. The cyclic acetal is more stable; even if one oxygen comes off, it can come right back on.
   c. The cyclic acetal formation is actually more favorable energetically (enthalpy)
   d. The cyclic acetal also has entropy advantages (entropy)
2. Methanol is simpler for making acetals from aldehydes, but often has problems for ketones. Use **methanol for ALDEHYDES**
3. **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.
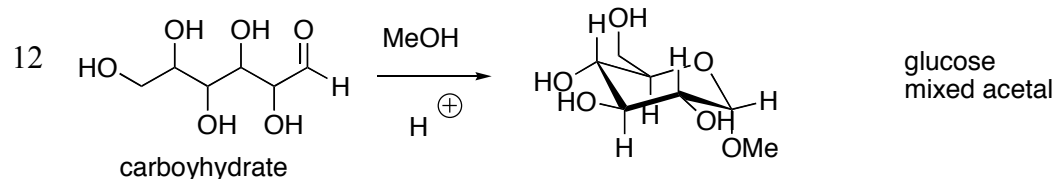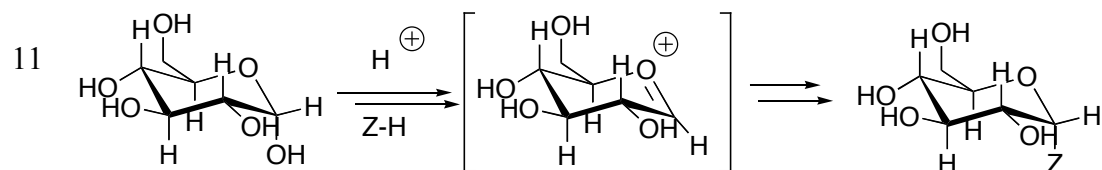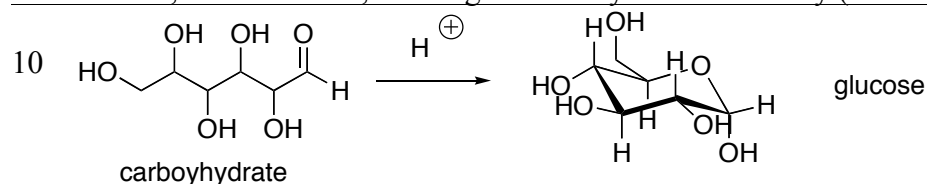
3   MeOH, H⊕

4   HO   OH   H⊕

5   H_2O, H⊕

6   H_2O, H⊕
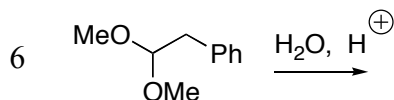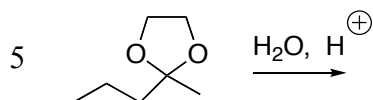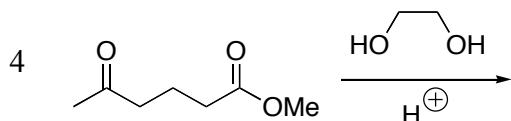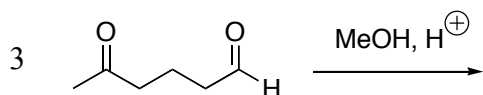
Equilibrium and Acetals
1. Normally favors the carbonyl, especially for ketones
2. Push to the acetal side by using excess alcohol
3. Push to carbonyl side by using excess water
4. **Equilibrium improves greatly for cyclic acetals.**

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.)

7   MeOH, H⊕ ⟶   "Mixed Acetal"

8   H⊕ ⟶   "Cyclic Acetal"

9   H₂O, H⊕ ⟶   Hydrolysis Of cyclic acetal

Hemiacetals, mixed acetals, and Sugar/Carbohydrate Chemistry (interest, not test)

10   H⊕ ⟶   glucose

carboyhydrate

11   H⊕, Z-H ⟶   ⟶

12   MeOH, H⊕ ⟶   glucose mixed acetal

carboyhydrate

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
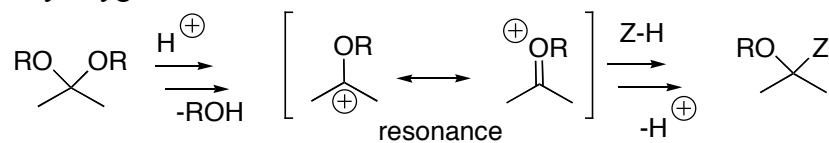
4. Carbohydrates exist as hemiacetals or acetals
5. Carbohydrates can polymerize or make complex derivatives via substitution at their acetal carbons
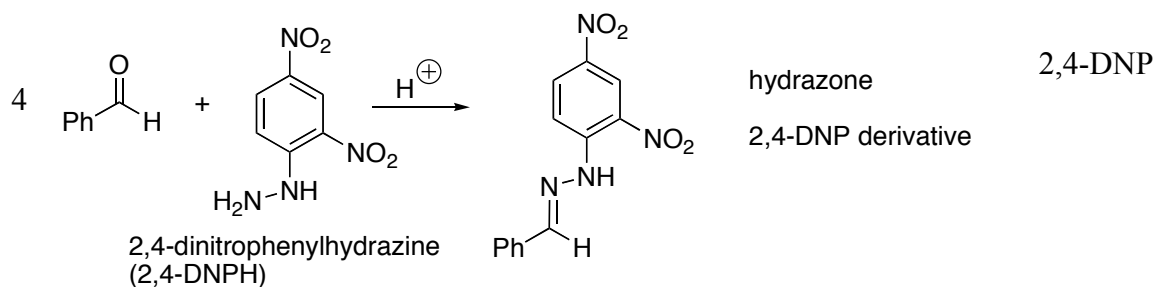
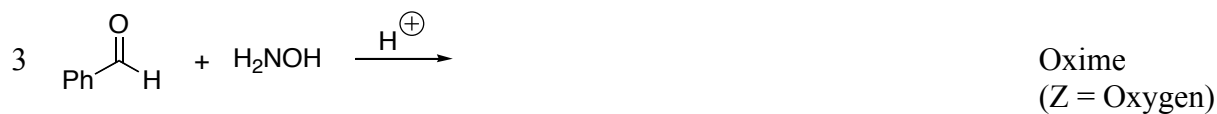**Acetals as Protecting Groups in Synthesis (Section 17.9)**
1. Reactivity: Aldehydes > Ketones >> Esters
    a. Aldehydes versus Ketones Why:
        •   Sterics, ketones are more cluttered and additions make things worse
        •   Electronics, ketones are more stable with two electron-donating groups
    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.

13

14

15   1. ethylene glycol, H^+
     2. Mg

     3, benzaldehyde
     4. H_2O, H^+
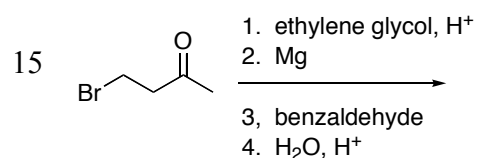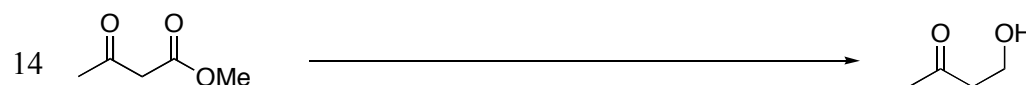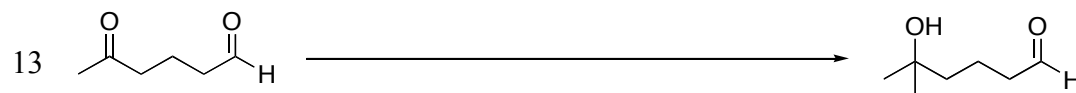
Addition of H$_2$N-Z Reagents (Sections 17.10)
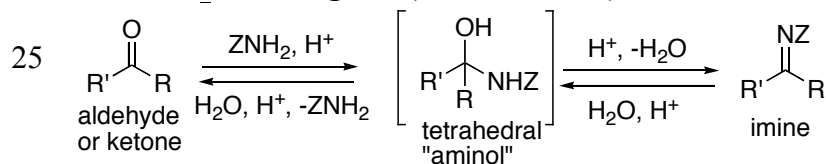
25

aldehyde H_2O, H^+, -ZNH$_2$ tetrahedral   imine
or ketone   "aminol"

   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-
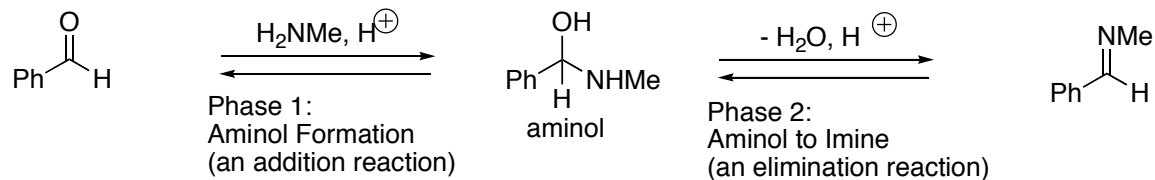   elimination- deprotonation (aldehyde or ketone). Reversible.

   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.
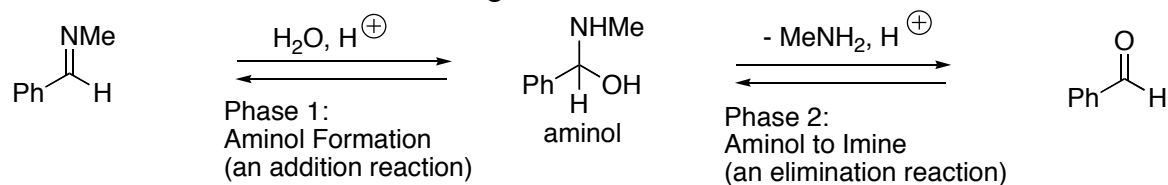
1

$$Ph\overset{O}{\underset{H}{\bigg\|}}\quad + \quad MeNH_2 \quad \xrightarrow{\ H^{\oplus}\ }$$

"Imine"
(Z = alkyl)

2

$$Ph\overset{O}{\underset{H}{\bigg\|}}\quad + \quad H_2NNH_2 \quad \xrightarrow{\ H^{\oplus}\ }$$

Hydrazone
(Z   =
Nitrogen)

3

$$Ph\overset{O}{\underset{H}{\bigg\|}}\quad + \quad H_2NOH \quad \xrightarrow{\ H^{\oplus}\ }$$

Oxime
(Z = Oxygen)

4

$$Ph\overset{O}{\underset{H}{\bigg\|}}\quad + \quad$$

2,4-dinitrophenylhydrazine
(2,4-DNPH)

$$\xrightarrow{\ H^{\oplus}\ }$$

hydrazone

2,4-DNP derivative

2,4-DNP

Notes:
1. C=N species can sometimes be hydrolyzed back to carbonyls by H_2O/H^+
2. "Imines" are frequent biology intermediates
3. 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

5

$$\xrightarrow{\quad\quad}$$

6

$$\xrightarrow{\quad\quad}$$

Draw the mechanism for the following:

O
‖
Ph   H   H₂NMe, H⊕   OH   - H₂O, H ⊕   NMe
                 ⇌   Ph   │   NHMe   ⇌   Ph   H
                 Phase 1:   H   Phase 2:
                 Aminol Formation   aminol   Aminol to Imine
                 (an addition reaction)   (an elimination reaction)

Draw the mechanism for the following:

NMe   H₂O, H⊕   NHMe   - MeNH₂, H ⊕   O
‖   ‖
Ph   H   ⇌   Ph   │   OH   ⇌   Ph   H
                 Phase 1:   H   Phase 2:
                 Aminol Formation   aminol   Aminol to Imine
                 (an addition reaction)   (an elimination reaction)

Notes:
1. All steps are reversible, under equilibrium control
2. I'm writing these as cationic, acid-catalyzed steps
   a. Conditions are actually buffered;
   b. $1 \text{ RNH}_2 + 0.5 \text{ H}^+ \rightarrow 0.5 \text{ RNH}_2 + 0.5 \text{ RNH}_3^+ \rightarrow$ a buffer system.
   c. In some cases, nucleophilic addition addition by the neutral but reactive amines (to give oxyanions) may actually precede protonation

Oxidation of Aldehydes (Section 17.15)
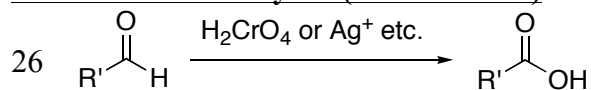
26

$$\underset{R'\overset{O}{\underset{}{\parallel}}H}{} \xrightarrow{\text{H}_2\text{CrO}_4 \text{ or Ag}^+ \text{ etc.}} \underset{R'\overset{O}{\underset{}{\parallel}}OH}{}$$

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".
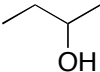
Review: Chromic Acid Oxidation proceeds in water via hydrate

$$\underset{Ph \quad H}{\overset{O}{\parallel}} \underset{\text{H}^+, \text{H}_2\text{O}}{\overset{\text{H}_2\text{CrO}_4,}{\rightleftharpoons}} \underset{Ph \overset{OH}{\underset{H}{\mid}} OH}{} \xrightarrow{\text{H}_2\text{CrO}_4,} \underset{Ph \quad OH}{\overset{O}{\parallel}}$$
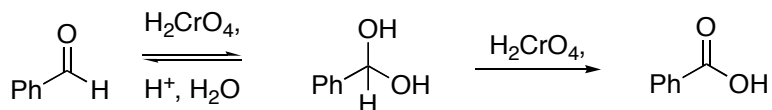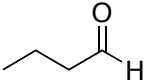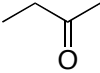
New: Ag$^+$ salts oxidize aldehydes in presence of alcohols, ketones

Tollens reagent: Ag(NH$_3$)$_2^+$ Chemical test for **aldehydes**

* A silver mirror forms
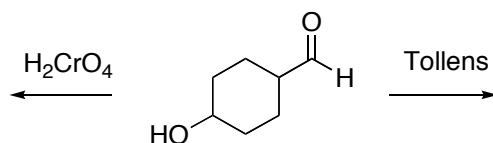
$$\xleftarrow{\text{H}_2\text{CrO}_4} \qquad \xrightarrow{\text{Tollens}}$$

Chemical Tests

Class		DNP	Tollens	H$_2$CrO$_4$
Aldehydes				
Ketones				
Alcohols				

Chem 360-Jasperse   **Chapter 20 (Enolate Chemistry) Reaction Summary**

PROTON as ELECTROPHILE
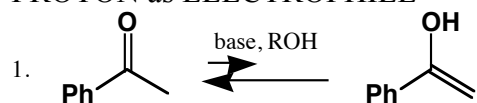
1.

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

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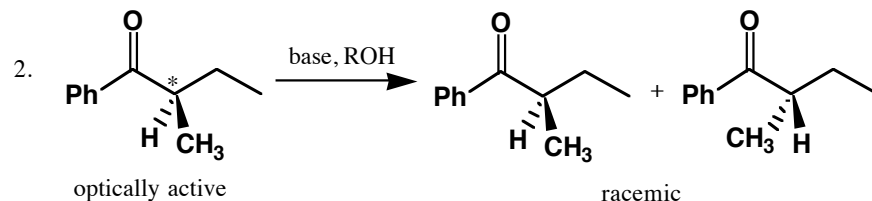
optically active   racemic
-Racemization of α-chiral optically active carbonyls
-Mech

HALOGEN as ELECTROPHILE

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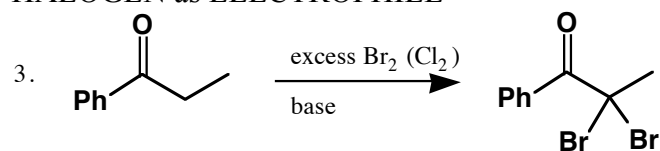
-Base catalyzed halogenation
-with excess halogen, all α-hydrogens get replaced
-Mech

4.

after basic step one   after step two acidification
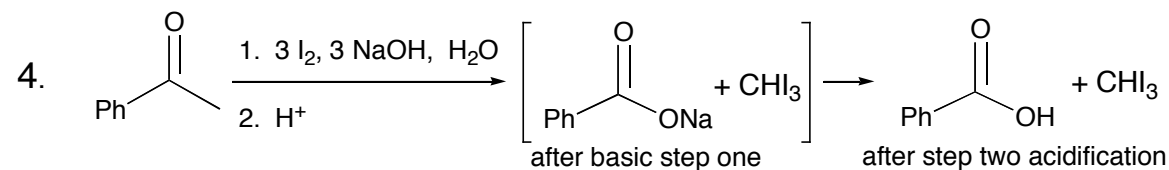
-Iodoform reaction.
-**chemical test for methyl ketones**

ALKYL HALIDE as ELECTROPHILE

6.

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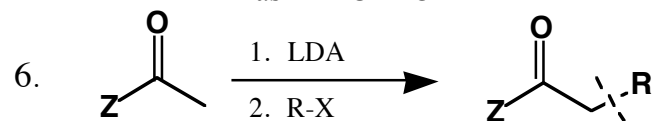
-Enolate alkylation
-strong LDA base required to completely deprotonate carbonyl
-Mech
-Ketones, Esters, Amides, Aldehydes: doesn't matter which kind of carbonyl
-unsymmetrical ketones give isomer problems
-S_N2 alkylation restricts R-X to active ones

7.

$$\xrightarrow[\text{2. R-X}]{\text{1. NaOR}} \qquad \xrightarrow{H_3O^+, \text{ heat}}$$
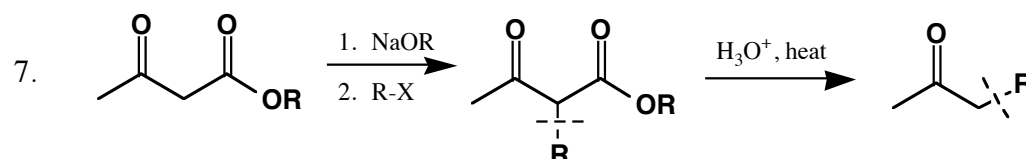
-Enolate alkylation of 1,3-ketoester
-alkoxide base strong enough to completely generate enolate
-Mech for alkylation
-S_N2 alkylation restricts R-X
-position of alkylation is unambiguous
-acid-catalyzed hydrolysis/decarboxylation

8.

$$\xrightarrow[\text{2. R-X}]{\text{1. NaOR}} \qquad \xrightarrow{H_3O^+, \text{ heat}}$$
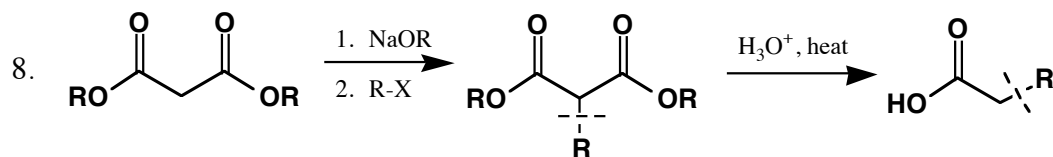
-Enolate alkylation of 1,3-diester
-alkoxide base strong enough to completely generate enolate
-Mech for alkylation
-S_N2 alkylation restricts R-X
-acid catalyzed hydrolysis/decarboxylation
-Final product is an ACID (Diester →Acid)
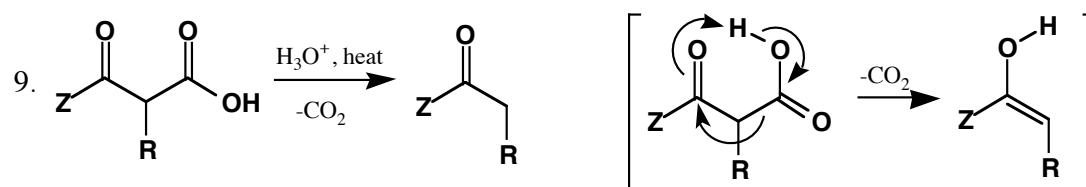
9.

$$\xrightarrow[-CO_2]{H_3O^+, \text{ heat}} \qquad \xrightarrow{-CO_2}$$

-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.
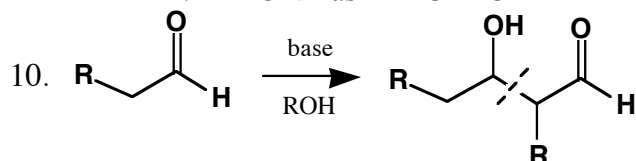
-Aldol Reaction
-Mech

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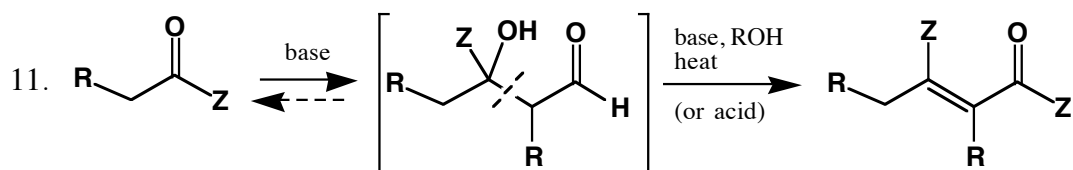
-Aldol Condensation
-Ketones as well as Aldehydes can be used
-In ketone case, unfavorable aldol equilibrium is still drawn off to enone
-In Aldehyde case, can stop at aldol if you don't heat
-Mech
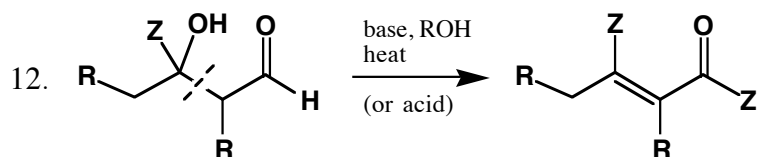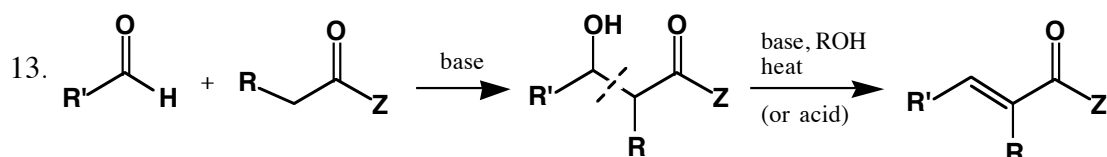
12.

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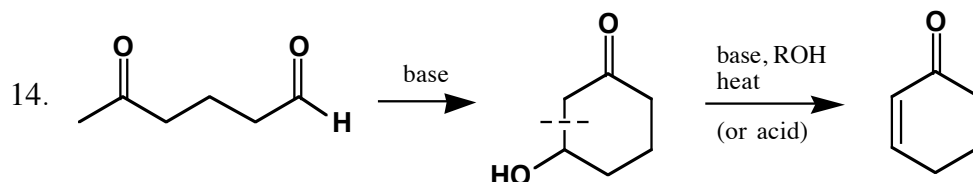
-Intramolecular aldol
-Mech
-many variations
-Normally only good for 5, 6-membered rings

ESTER as ELECTROPHILE
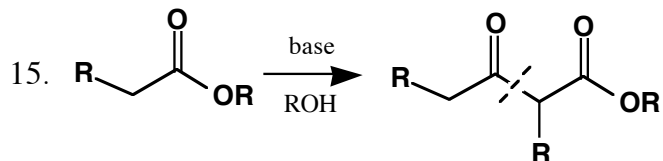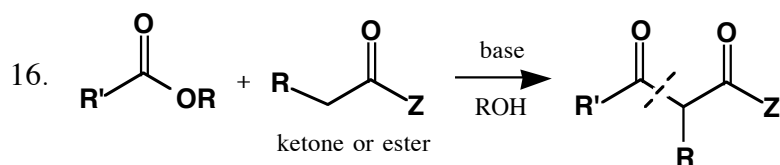
15.

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

16.

-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.
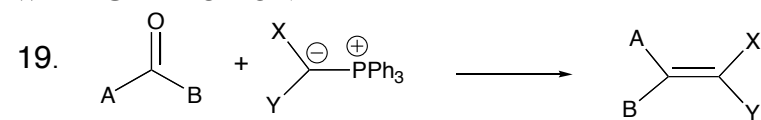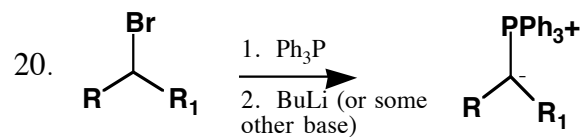
-Mech

Chem 342-Jasperse   **Chapter 20 (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
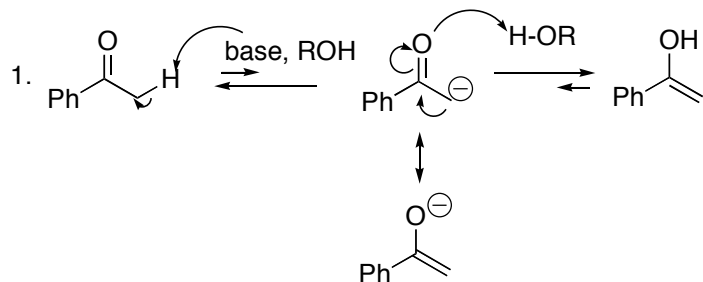
Enol Back to Ketone:
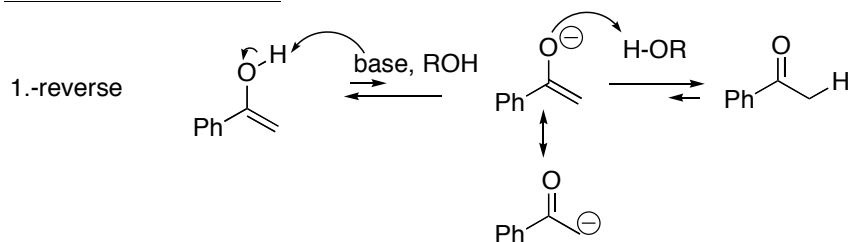
Deprotonation/Reprotonation to Racemize an optically active α-chiral center

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.
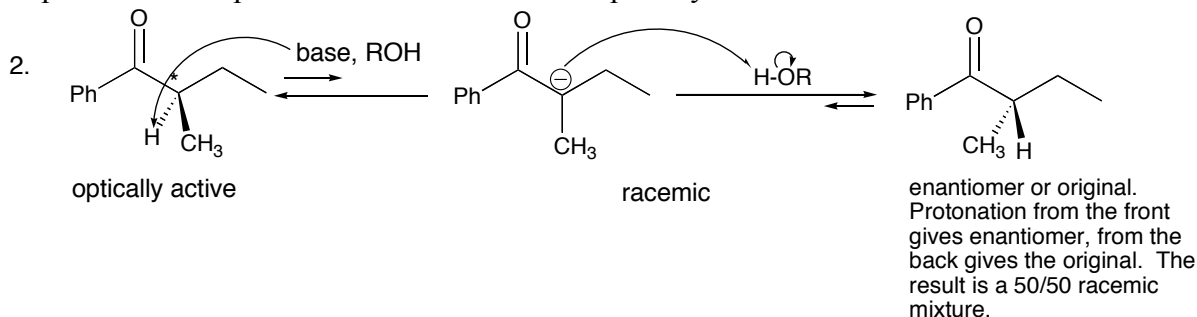
HALOGEN as ELECTROPHILE

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.)
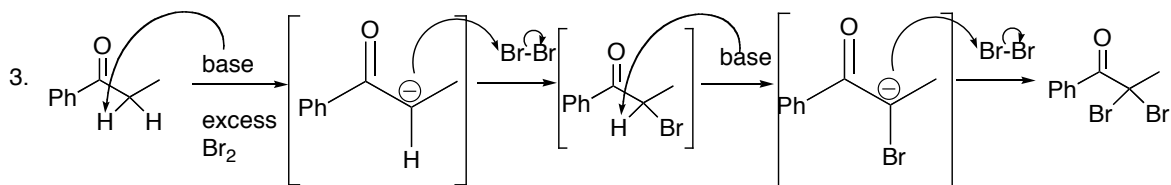
ALKYL HALIDE as ELECTROPHILE
With Strong LDA as Base, using a Monocarbonyl

6.
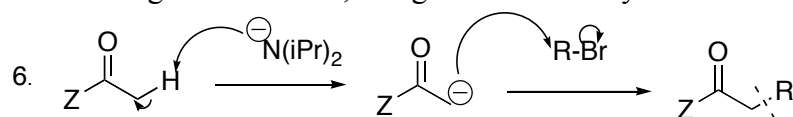
1. Z can be anything: works for ketones, esters, aldehydes, esters,…
2. "LDA" is lithium diisopropylamine, provides the nitrogen anion shown
3. strong LDA base required to completely deprotonate carbonyl. The base strength enables the enolate to form completely, no equilibrium or reversibility issues.
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

keto-ester
ester hydrolysis

keto-acid
decarboxylation

enol
acid catalyzed
enol hydrolysis
(ch. 18)

ketone

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)

8.

Test Responsible

H⁺, H₂O
heat

several
steps

ester-ester

ester hydrolysis

acid-acid

decarboxylation

heat

enol R

acid catalyzed
enol hydrolysis
(ch. 18)

H⁺, H₂O

acid R

Not Test Responsible

-alkoxide base strong enough to completely generate enolate
-S$_N$2 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.

bond
rotation

heat
-CO₂

slow
step

decarboxylation

enol R

H⁺, H₂O

(ch. 18
mech)

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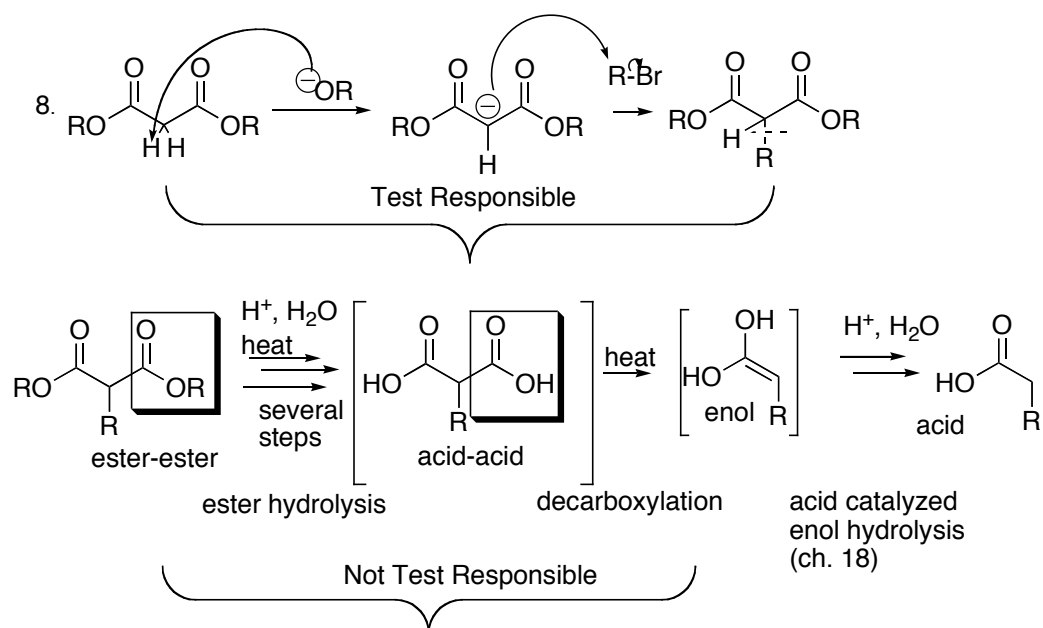
Not Fully Test Responsible. But must know that ENOL is key intermediate
that forms in the slow step.
What is good for the enol (and it's alkene) accelerates the decarboxylation

-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.
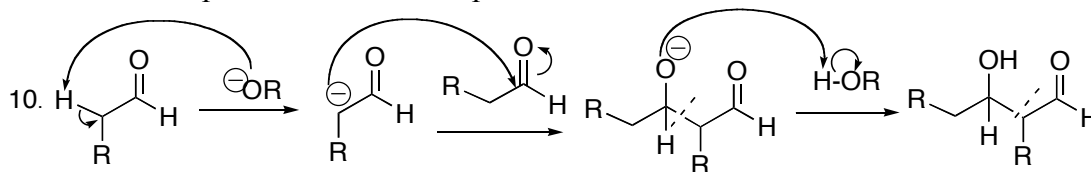
-Deprotonate-react-protonate
-Notice in this case that it's the same carbonyl that functions as both the enolate precursor but also as the electrophile.

Aldol Condensation, giving an enone.   In which the initial aldol product undergoes dehydration.
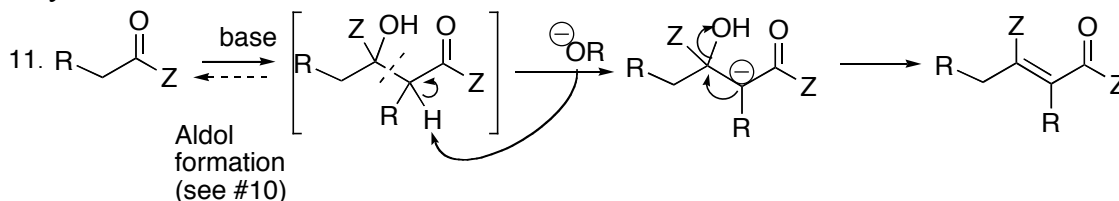
-The aldol product is formed as shown in mechanism 10. But under extended opportunity or heat, the product β-hydroxy group is eliminated to give the enone.
-The elimination mechanism involves deprotonation to enolate, followed by hydroxide extrusion
-Ketones as well as Aldehydes can be used
-In ketone 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
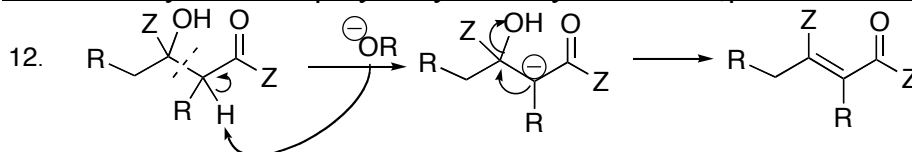
-Aldol dehydration
-Mech under basic conditions
- β-hydroxy Carbonyls can also eliminate water to give enones under acid conditions, via a different mechanism.

Crossed Aldol Reaction, in Which One carbonyl compound serves selectively as the Enolate Precursor and a different one (usually aldehyde) as the electrophile
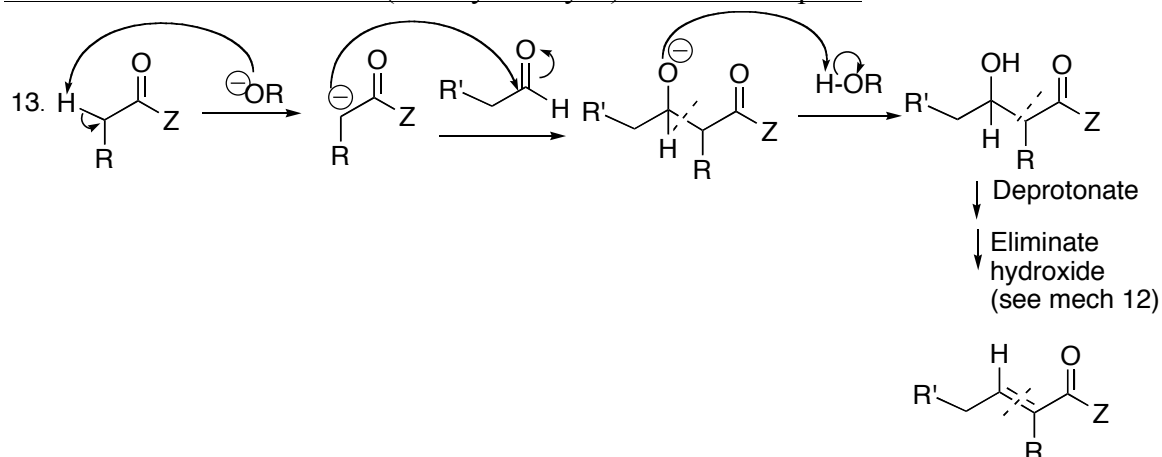
Deprotonate

Eliminate hydroxide (see mech 12)

-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
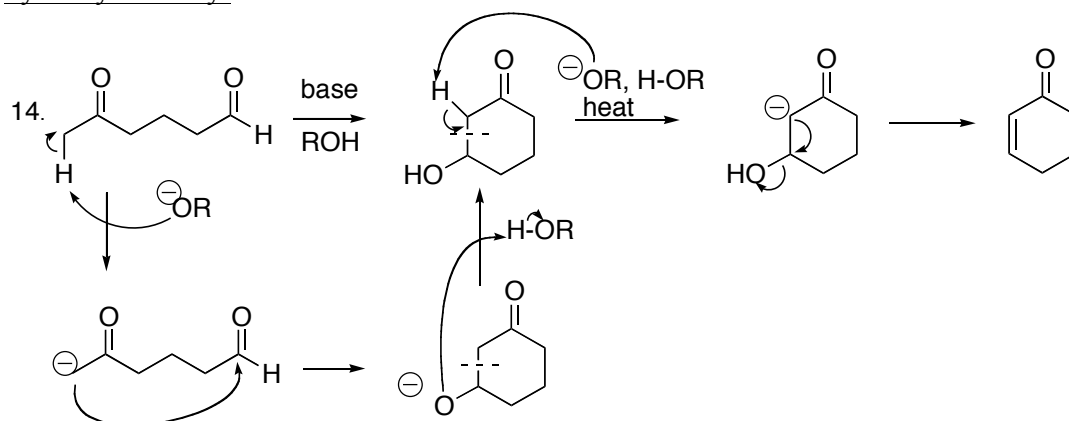
-Intramolecular aldol
-many variations
-Normally only good for 5, 6-membered rings
-There are often multiple α-hydrogens that can give multiple different enolates. But since enolate formation is reversible, reaction proceeds via the enolate that can:
react with the best electrophile. (Aldehyde rather 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.
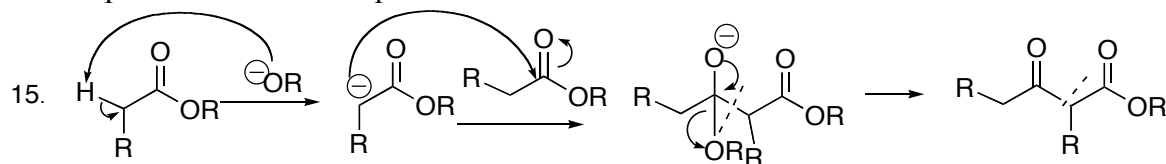
-Produces 1,3-ketoester
-The alkoxide used as base should match the R-group found in the ester. For example, if the ester OR group is OMe, then the base should be NaOMe/MeOH. If the ester OR group is OEt, then NaOEt/EtOH should be used, etc.
-Following enolate addition, the tetrahedral intermediate is *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.
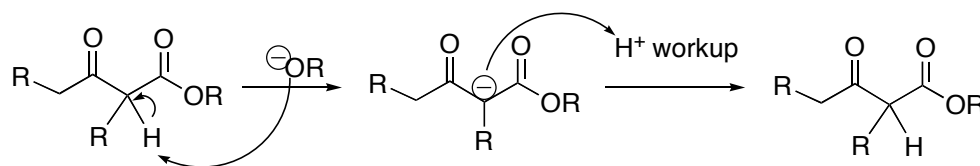
<u>Crossed Claisen Reaction</u>, giving either a β-ketoester or a 1,3-diketone. In which either a ketone or an ester functions as the enolated precursor, and a different ester functions as electrophile.

16.
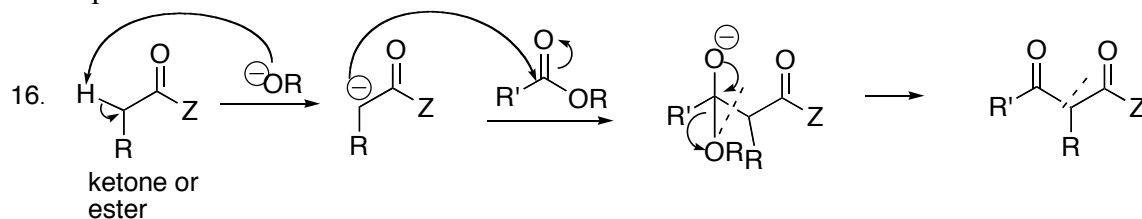
ketone or
ester

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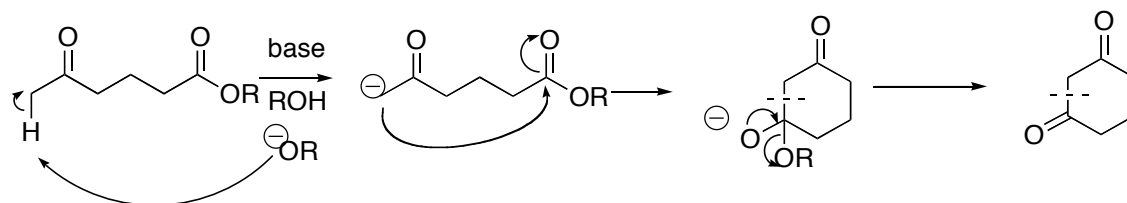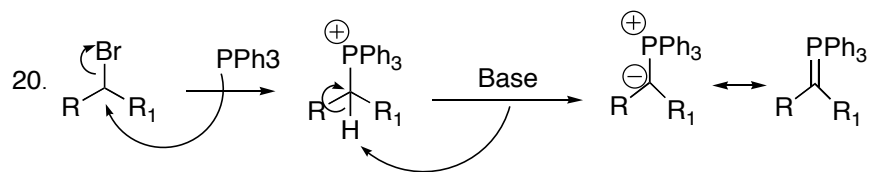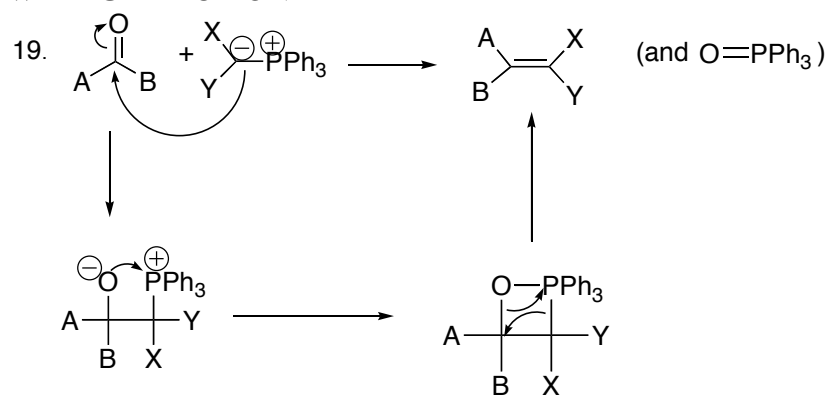
Ch. 20 Additions and Condensations of Enols and Enolate Ions

A. Intro: What is in Common for the Following Reactions, and How Do They Work?
*   **You should eventually be able to draw the mechanism for these (and other) reactions…**

<u>Key Intermediate</u>

1   Ph + Br-Br → (NaOH) → Ph ... Br

2   + CH₃-I → (NaOMe) → OMe CH₃

3   + H → (NaOMe) → OH

4   + 2 H Ph → (NaOH) → Ph ... Ph

5   MeO CH₃ + MeO Ph → (NaOMe) → MeO Ph CH₃

6   Ph + H₂O → (NaOH) → Ph + Ph
H CH₃   H CH₃   H₃C H
optically active   racemic mixture
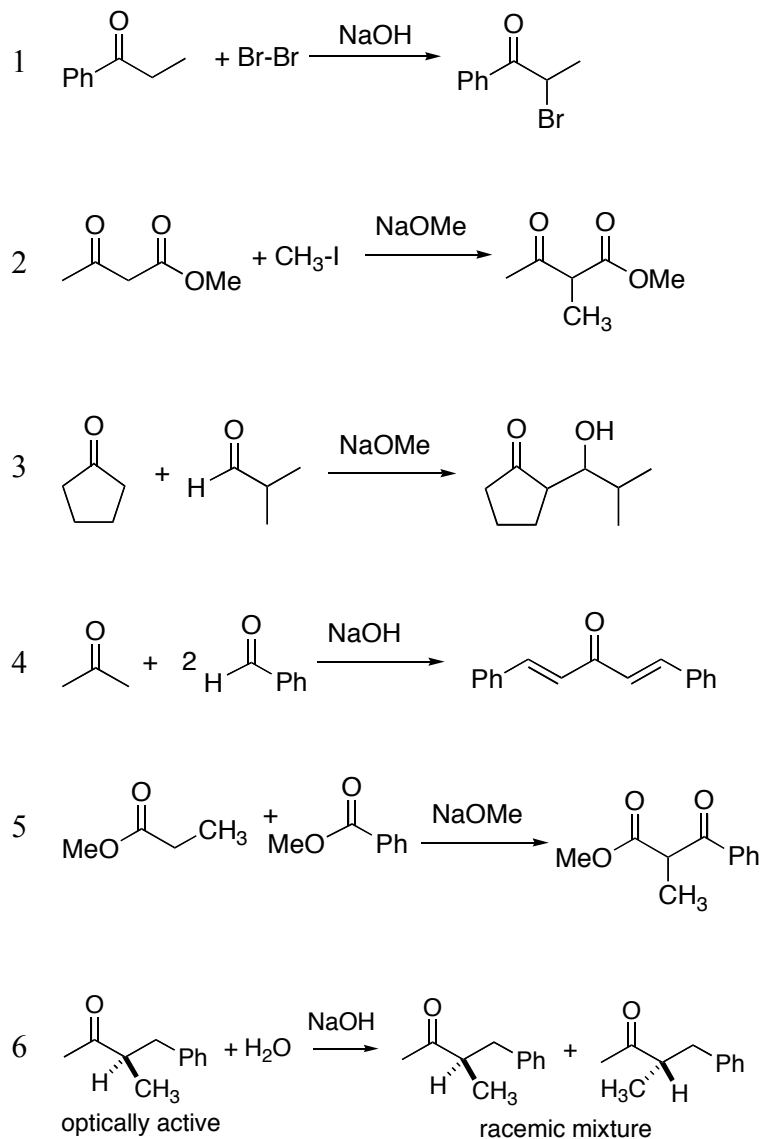
Things in Common   KEY:

1.

2.

3.

4.

TYPICAL MECHANISM: Via ENOLATE Anion

Z = H (Aldehyde)
Z = R (Ketone)
Z = OR (Ester)

Enolate Ion

(original stereo forgotten)
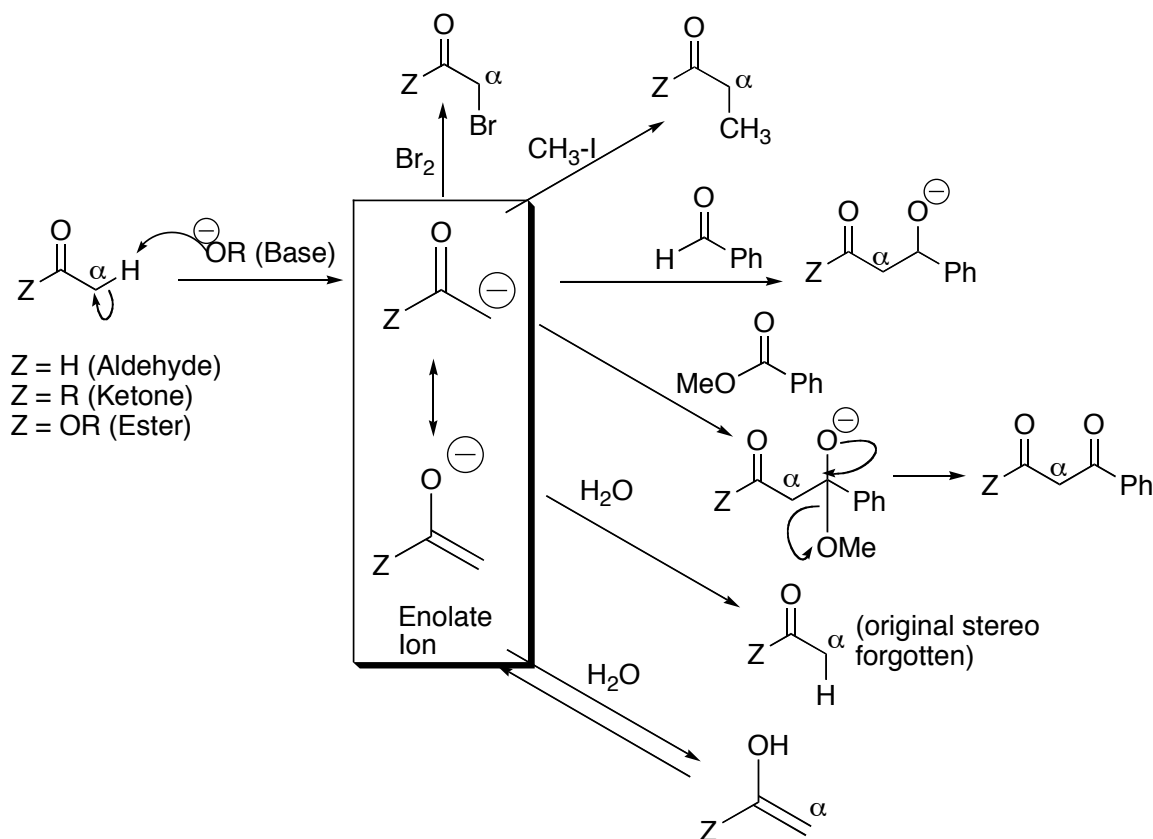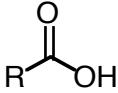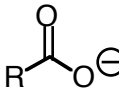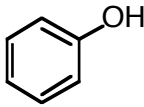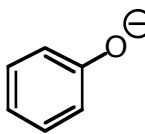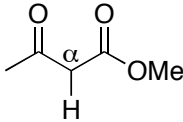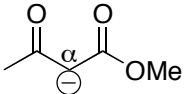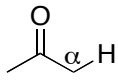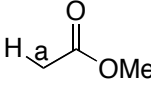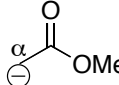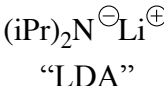
Under base conditions, a carbonyl compound with an α-hydrogen can be deprotonated to give a resonance-stablized, delocalized "enolate" anion, which is nucleophilic at the α-carbon.

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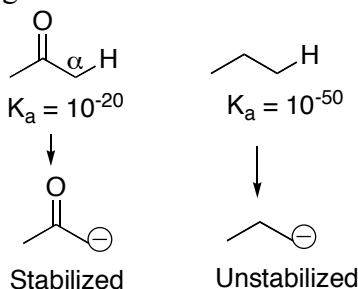
- The α-carbon has two other attachments in addition to the carbonyl and the H shown in this page. The other attachments will remain attached as spectators, and need to be accounted for in drawing products.
- α-Hydrogens are only slightly less acidic than is water or alcohol hydrogens

B: Acid/Base Considerations (Sections 20.1) Acidity Table

Class	Structure	Ka	Acid Strength	Anion	Base Strength
Strong Acids	H-Cl	10^2		Cl$^\ominus$	
Carboxylic Acid	R–C(=O)–OH	10^{-5}		R–C(=O)–O$^\ominus$	
Phenol	(phenol) OH	10^{-10}		(phenoxide) O$^\ominus$	
1,3-Dicarbonyl	(1,3-dicarbonyl) α H, OMe	10^{-12}		(anion) $\alpha^\ominus$ OMe	
Water	HOH	10^{-16}		HO$^\ominus$	
Alcohol	ROH	10^{-17}		RO$^\ominus$	
Ketones and Aldehydes	(ketone) α H	10^{-20}		(enolate) $\alpha^\ominus$	
Ester	H a –C(=O)–OMe	10^{-24}		$\alpha^\ominus$ –C(=O)–OMe	
Amine (N-H)	$(iPr)_2$N-H	10^{-33}		$(iPr)_2$N$^\ominus$Li$^\oplus$ "LDA"	
Alkane (C-H)	RCH$_3$	10^{-50}		RCH$_2{}^\ominus$	

$$\text{H-A } + \text{B}^\ominus \; \rightleftharpoons \; \text{A}^\ominus + \text{B-H}$$ 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 <u>completely</u> deprotonate ketones, esters, or 1,3-dicarbonyls**
6. NaOH, NaOR can **completely** deprotonate a <u>1,3-dicarbonyl (but not ketones or esters)</u>
7. NaOH, NaOR do **not** completely deprotonate <u>ketones or esters</u>, but do provide a usable equilibrium supply of the enolate that can procede to product in some reactions.

1. Rank the acidity of the hydrogens at the labeled positions, 1 being most acidic. Draw the three anions that would result from deprotionation at the three spots, and any pertinent resonance structures.
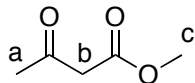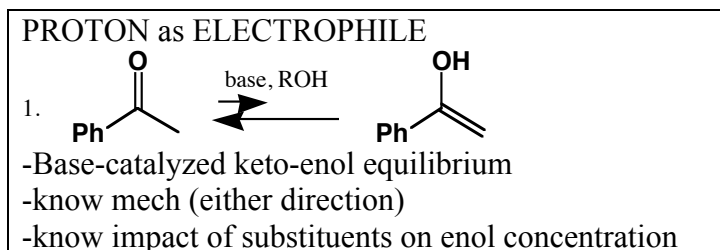
2. For the following compounds, record to what degree they would be deprotonated by NaOCH₃ or LDA [LiN(iPr)₂] respectively. The basic choices are "totally" (>98%), "zero" (no enolate whatsoever) or "slightly" (definitely some equilibrium amount, but <10%).
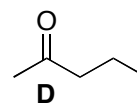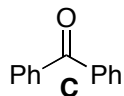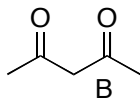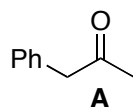
A **B** **C** **D**
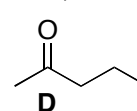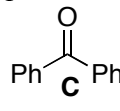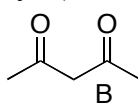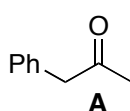
LDA:

NaOMe:

C. Enolates and Enols: Protons as Electrophile (22.13)

PROTON as ELECTROPHILE

1.

base, ROH

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

Notes:
1. Rapid equilibrium exists between the keto and the enol form
2. Both acid and base catalyze the equilibrium
3. All carbonyls with α-hydrogens can equilibrate with enols
   • But if there are no α-hydrogens, a carbonyl can **not** have any enol (or enolate!)
4. Ranking the population of enol:
   a. Normally, <5% enol will be present in solution, and >95% will be in the ketone form
   b. No α-hydrogens → no enol
   c. Two factors can stabilize enols and enrich the equilibrium enol population
      • Hydrogen bonding of the enol O-H to some other heteroatom (stabilizing)
      • Conjugation of the enol alkene (stabilizing)

1. For the following compounds, draw the best possible enol (if any) rank them according to which would have the greatest amount of **enol isomer** present at equilibrium, 1 being most.
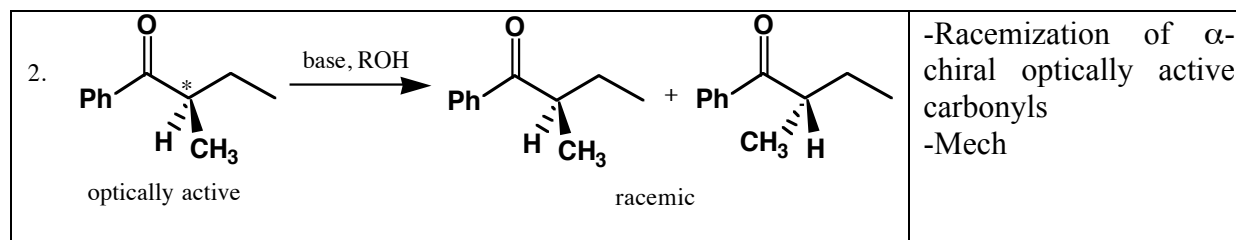
Ph — A (ketone structure)   B (1,3-diketone structure)   Ph—C—Ph (ketone structure)   D (ketone structure)

Mechanism for Base-Catalyzed Keto-Enol Equilibration:

2. Keto-Enol Mechanisms (use hydroxide as base, but many bases will do…)
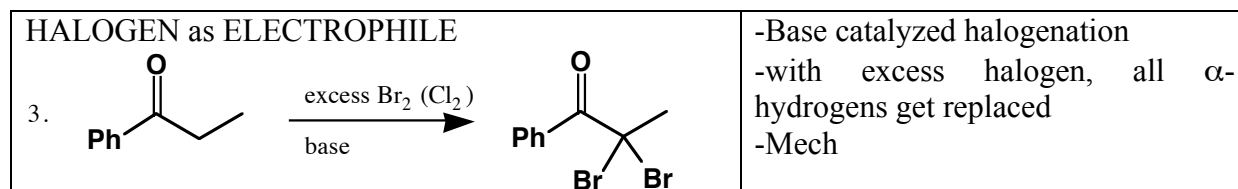
   a. Draw the mechanism for conversion of the keto form to the enol form
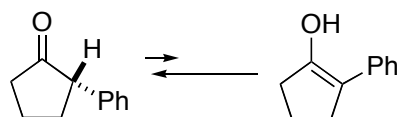
   b. Draw the mechanism for conversion of the enol form to the ketone

Racemization of α-chiral Compounds via Enolates

2. (structures: optically active ketone → base, ROH → racemic mixture of two enantiomers)	-Racemization of α-chiral optically active carbonyls -Mech
optically active racemic	

D. Halogen Electrophiles (20.14)

HALOGEN as ELECTROPHILE	-Base catalyzed halogenation
3. Ph (structure) $\xrightarrow[\text{base}]{\text{excess Br}_2 \ (\text{Cl}_2)}$ Ph (structure) Br Br	-with excess halogen, all α-hydrogens get replaced -Mech

1. Draw the product and mechanism for the following

Ph (structure) $\xrightarrow[\text{H}_2\text{O}]{\text{Br}_2, \text{NaOH}}$

2. Draw products for the following reactions

Ph (structure) $\xrightarrow[\text{H}_2\text{O}]{\text{2 Br}_2, \text{2NaOH}}$

(structure) $\xrightarrow[\text{H}_2\text{O}]{\text{3 Cl}_2, \text{2NaOH}}$
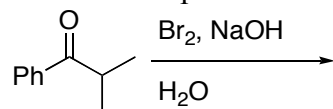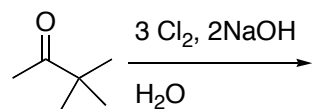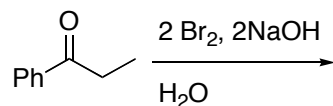
Polyhalogenation versus monohalogenation
*   Under base conditions, if you add only one equivalent of Br$_2$ (or Cl$_2$) when an α-carbon has more than one α-hydrogen, clean mono-halogenation (product **B**) does not occur
*   Instead messy mixtures result
*   The major product is polyhalogenated (**C**), combined with a bunch of unreacted starting material (**A**)
*   Why? Because the electron-withdrawing halogen makes product **B** more acidic (resulting in faster enolate formation) than the starting material **A**

1 Ph **A** (structure) $\xrightarrow[\text{H}_2\text{O}]{\text{1 Br}_2, \text{1 NaOH}}$ Ph (structure) H H **A**   +   Ph (structure) Br H **B**   +   Ph (structure) Br Br **C**

less reactive
toward enolate
formation

A
45%
less reactive
toward enolate
formation

B
10%
more reactive
toward enolate
formation

C
45%
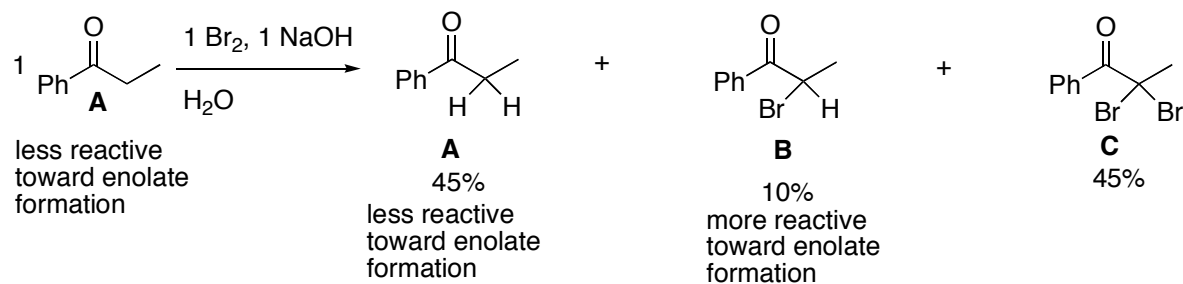
Acid-Catalyzed Monohalogenation (not for test)

5.	-Acid-catalyzed halogenation -can achieve selective mono-halogenation -No Mech required
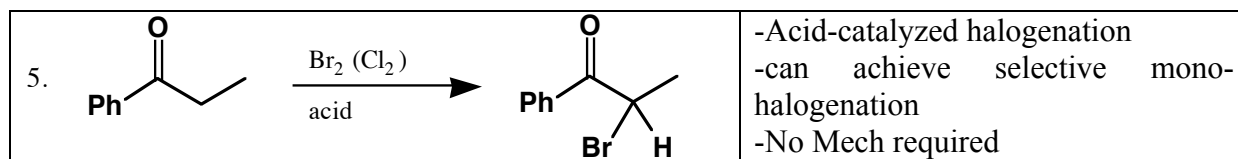
- Under acid conditions, a very different mechanism takes place which allows clean mono-halogenation to proceed
- Enol mechanism (not for test)
- Cationic mechanism
- An electron-withdrawing anion stabilizes and accelerates enolate formation, but destabilizes and decelerated enol formation
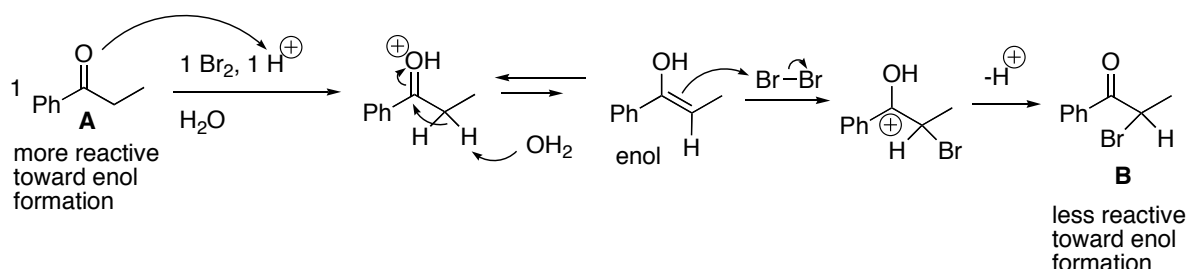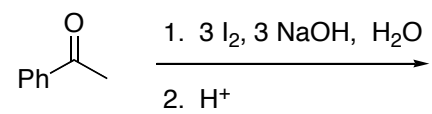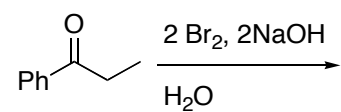

The Iodoform Reaction:
- A Chemical Test for methyl ketones (unknowns problems)
- A synthetic technique for converting methyl ketones to carboxylic acids
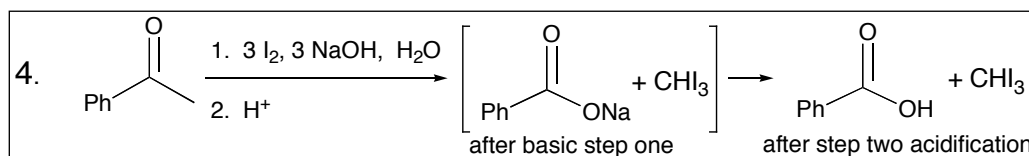
- You lose one carbon
- This only works for methyl ketones
- The chemical test involves formation of CHI_3 (iodoform), which is a yellow precipitate (and smelly)
- Mechanism (not for test):

1. Draw products for the following reactions

Ph—C(=O)—CH₃ $\xrightarrow[\text{H}_2\text{O}]{\text{2 Br}_2,\ \text{2NaOH}}$

Ph—C(=O)—CH₃ $\xrightarrow[\text{2. H}^+]{\text{1. 3 I}_2,\ \text{3 NaOH, H}_2\text{O}}$
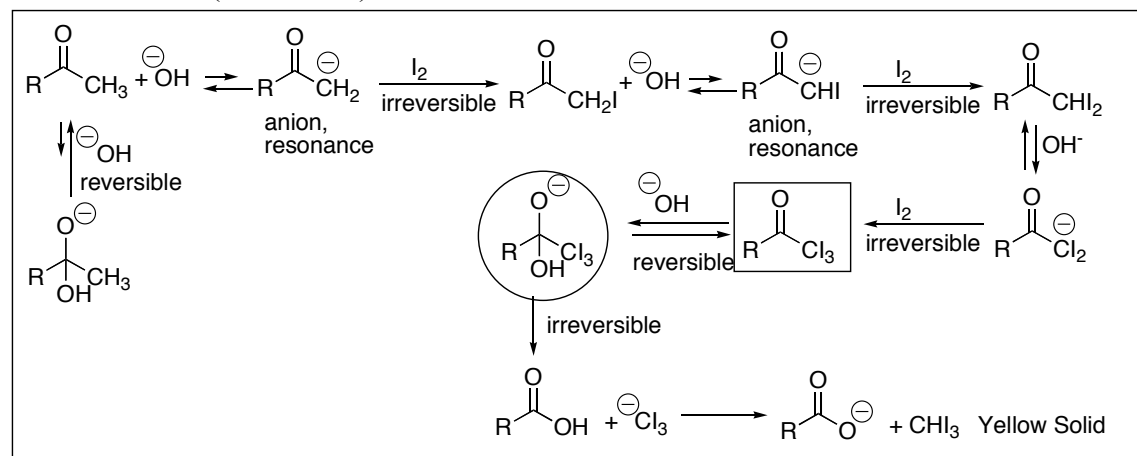
E. Enolate Alkylation: Alkyl Halides or Tosylates as Electrophiles (20.9)
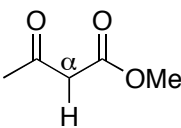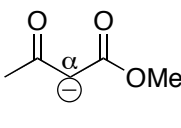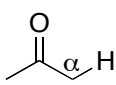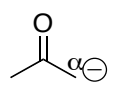
Alkylation of Monocarbonyls: Use strong, bulky LDA [LiN(iPr)$_2$] as base
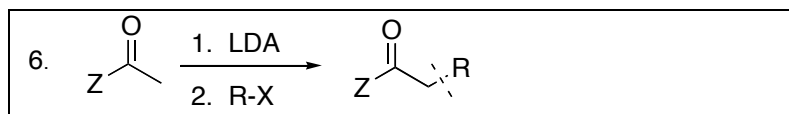
1. S$_N$2 alkylation reaction restricts R-X (or ROTs) to active, 1° electrophile
2. Ketones, Esters, Amides, Aldehydes all work, so long as they have an α-hydrogen that can be deprotonated
    • For unsymmetrical ketones, isomer problems can occur (which enolate forms?)
3. Predict the products: Attach 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$_2$

Practice: Draw products and mechanisms for the following alkylation reactions.

1.

2.

3.
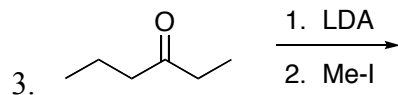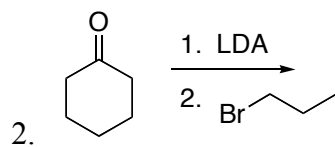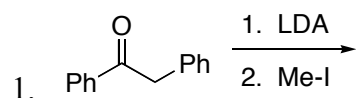
Class	Structure	Ka	Acid Strength	Anion	Base Strength
1,3-Dicarbonyl	(structure: CH₃-C(=O)-CHα(H)-C(=O)-OMe)	10^{-12}		(structure: CH₃-C(=O)-Cα(⊖)-C(=O)-OMe)	
Water	HOH	10^{-16}		HO⊖	
Alcohol	ROH	10^{-17}		RO⊖	
Ketones and Aldehydes	(structure: CH₃-C(=O)-α-H)	10^{-20}		(structure: CH₃-C(=O)-α⊖)	
Amine (N-H)	(iPr)₂N-H	10^{-33}		(iPr)₂N⊖Li⊕ "LDA"	

For Monocarbonyls, why must we use LDA as base, rather than a normal oxygen base (NaOH or NaOCH₃) or a simpler Nitrogen base (NaNH₂)?

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

For the following, which side would the equilibrium favor, and what product(s) would form?

Oxygen Base

(structure: CH₃-C(=O)-CH₂-H + ⊖OR) ⇌ (structure: CH₃-C(=O)-CH₂⊖ + HOR)
↓ R-X

Nitrogen Base

(structure: CH₃-C(=O)-CH₂-H + ⊖NR₂) ⇌ (structure: CH₃-C(=O)-CH₂⊖ + HNR₂)
↓ R-X
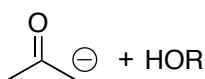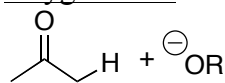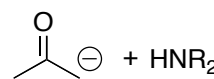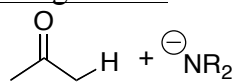
2. Base size: A bulky base favors deprotonation over nucleophilic attack
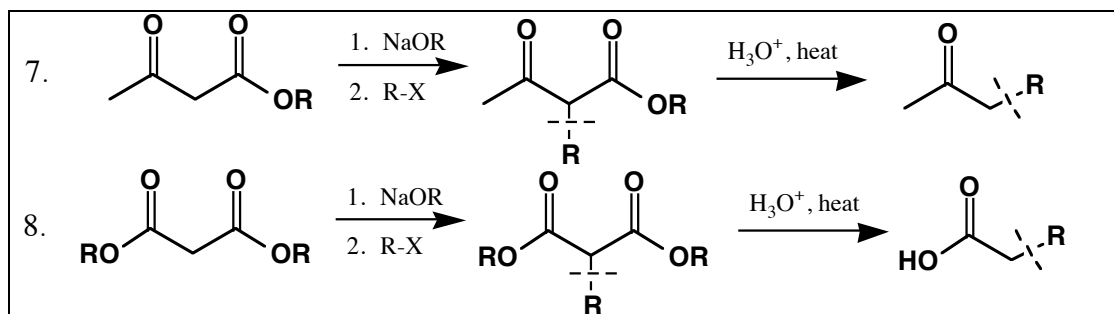- Comparable to E2 versus S_N2 competition

Bulky Base (LDA)

(structure: CH₃-C(=O)-CH₂-H + ⊖N(iPr)₂) →

LDA, bulky

Small Base

(structure: CH₃-C(=O)-CH₂-H + ⊖NH₂) →
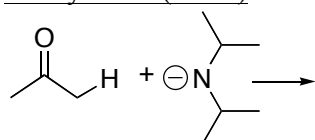
small
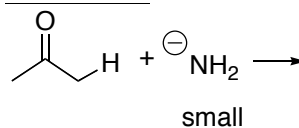
Alkylation of 1,3-dicarbonyls: Now oxygen bases are fine (20.10,11)
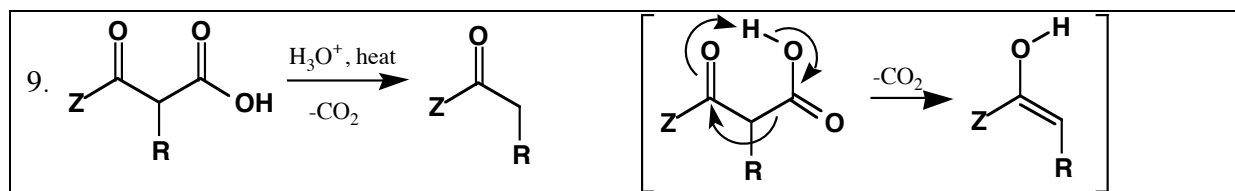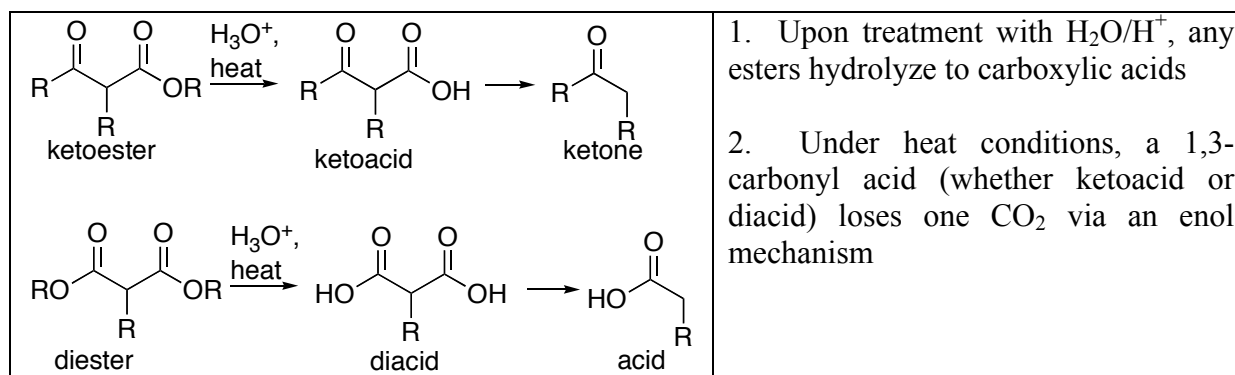

Stage One: Alkylation of a 1,3-Dicarbonyl
1. S_N2 alkylation reaction restricts R-X (or ROTs) to active, 1° electrophile
2. The dicarbonyl can be a 1,3-diketone, a 1,3 ketoester, or a 1,3-diester
3. Predict the products: Attach the electrophile R group to the α-carbon
4. Position of alkylation is unambiguous: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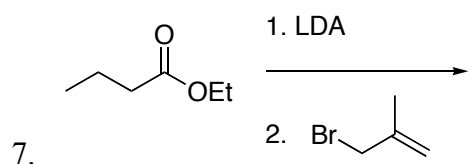

1. Decarboxylation of a 1,3-carbonyl acid
2. "Z" can be anything so that you end with a ketone, aldehyde, or acid at the end
3. Mechanism responsibility
   a. Be able to write the acid-catalyzed enol to carbonyl isomerization (see chapter 18)
   b. Know that an enol is involved in the rate-determining 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

1. Which of the following would undergo decarboxylation? And which would go fastest?

A   B   C   D   Ph
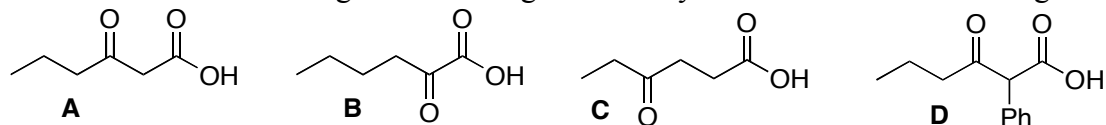
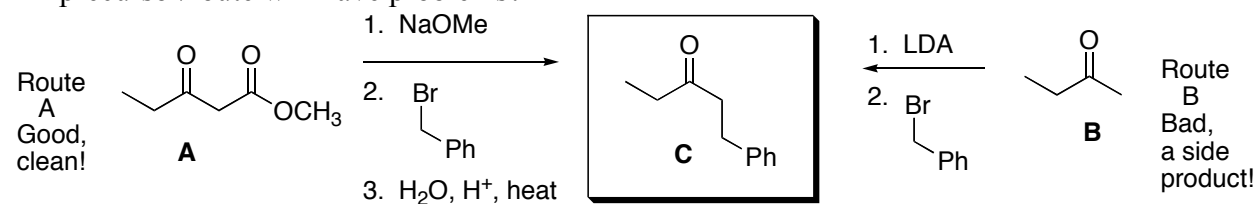Draw products for the following alkylation reactions, often involving ester hydrolyses and thermal decarboxylations.

2.

1. LDA

2. Br⁀⁀

3.

EtO   OEt

1. NaOEt

2. Br⁀⁀⁀

4.

EtO   OEt

1. NaOEt
2. Br⁀⁀⁀
3. NaOEt
4. BrCH₂CH=CH₂

5.

EtO   OEt

1. NaOEt
2. Br⁀⁀Ph
3. H⁺, H₂O, heat

6.

OEt

1. NaOEt
2. Br⁀⁀⁀
3. H⁺, H₂O, heat

7.

1. LDA

2. Br
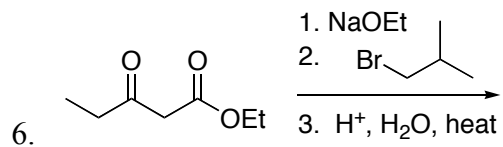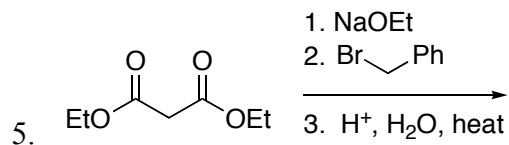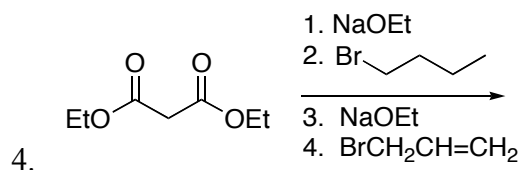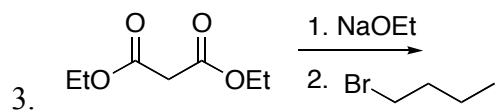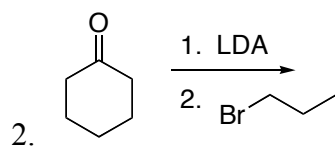
Some Synthetic Strategy Tips

- Alkylation resulting eventually in an **acid**: from 1,3-diester, via NaOR, then subsequent ester hydrolysis/decarboxylation
- Alkylation resulting eventually in a **mono-ester**: from ester using LDA
- Alkylation resulting eventually in a **mono-ketone**, where unambiguous deprotonation was possible: from ketone using LDA
- Alkylation resulting in a **mono-ketone**, where unambiguous LDA deprotonation would not have been possible: from keto-ester using NaOR, then subsequent ester hydrolysis/decarboxylation

Provide reagents for the following:

8.

9.
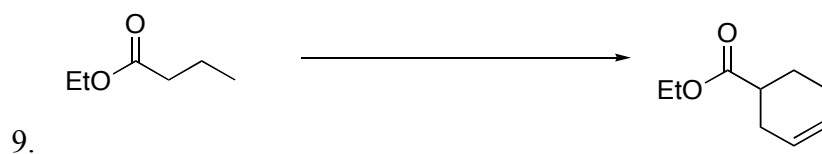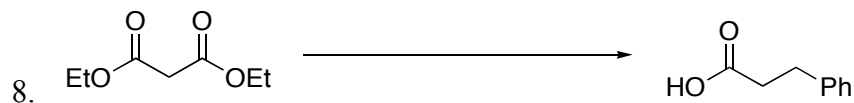
10. Shown below are two possible precursors **A** and **B** for making target ketone **C**. One works well, the other has a problem. Which is the good precursor, and which precursor/route will have problems?

Route
A
Good,
clean!

A

1. NaOMe

2. Br
    Ph

3. H₂O, H⁺, heat

C Ph

1. LDA

2. Br
   Ph

B

Route
B
Bad,
a side
product!

F. Aldehydes or Ketones as Electrophiles: The Aldol Reaction (20.3,4)
The basic aldol reaction: in which the same aldehyde functions as both enolate and electrophile, and in which a β-hydroxyaldehyde is produced.
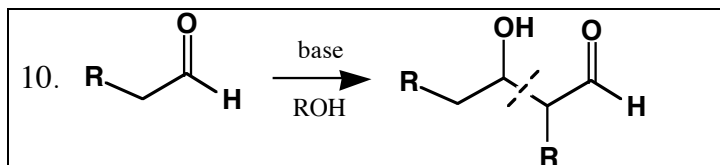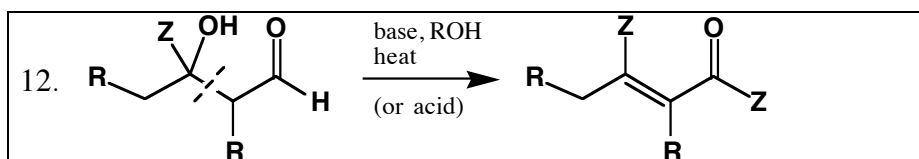

1. Try to draw the mechanism for the following.
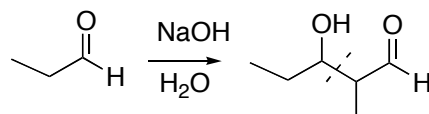
Notes:
a. Product: β-hydroxycarbonyl
b. One carbonyl converts to an enolate, another in its neutral form functions as electrophile
   • with oxygen anion as base, most carbonyl is in neutral form, only a small equilibrium population of enolate anion at any time.
c. Products and spectators: The α-carbon loses an H to make the enolate, but otherwise both the enolate and the electrophile retain all their spectator attachments
d. 3-step mechanism: deprotonate (to make enolate) – react (with electrophile) – protonate
   • the react-protonate steps are like normal Grignard addition-protonation
e. Aldol formation is reversible: favorable equilibrium for aldehydes, not for ketone
• With ketones, either you don't isolate β-hydroxycarbonyl. Either you proceed on to alkene (see below) or else you just recover starting ketone

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)
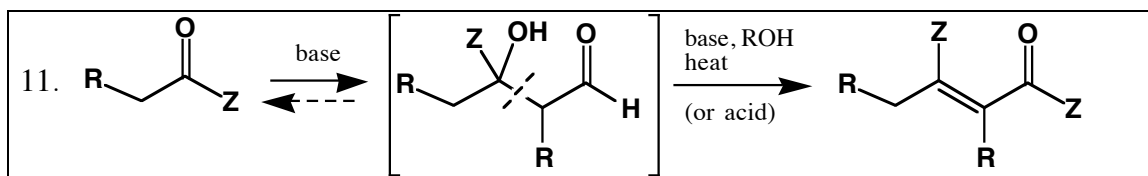

a. Elimination is irreversible
b. Ketones as well as Aldehydes can be used
   • In ketone case, unfavorable aldol equilibrium is still drawn off to enone
c. In Aldehyde case, can stop at aldol if you don't heat
   • To force toward the enone, give extra time or extra heat
d. Two a-hydrogens must be available for removal; otherwise product retains all spectators
e. Mechanism required

General Process for Dehydration of β-Hydroxy Carbonyl Compounds

12.

- We will focus on the base/enolate mechanism
- But this elimination is also possible using acid catalysis, via a different mechanism

1. Try to draw the mechanism for the following.
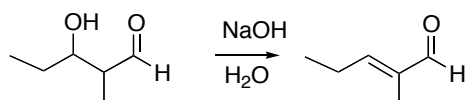
Crossed Aldol Reactions: Using 2 Different Carbonyls, One of Which Functions as Neutral Electrophile (normally an aldehyde) and the Other as the Nucleophilic Enolate

13.
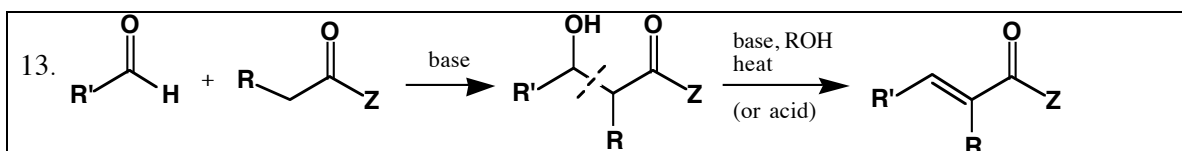
a. Mechanisms required
b. Many variations, but there must be some differentiation so that one carbonyl acts selectively as the enolate and the other as the electrophile
   1. If one carbonyl lacks any α-hydrogens, it can't be converted to nucleophile and can only function as electrophile
   2. Aldehydes are much better electrophiles than ketones
      - When ketones do function as electrophiles in aldol reactions, the reactions usually just reverses itself anyway
   3. Sometimes conjugation favors formation of one enolate over another

Ring-Forming Aldol Reactions

14.
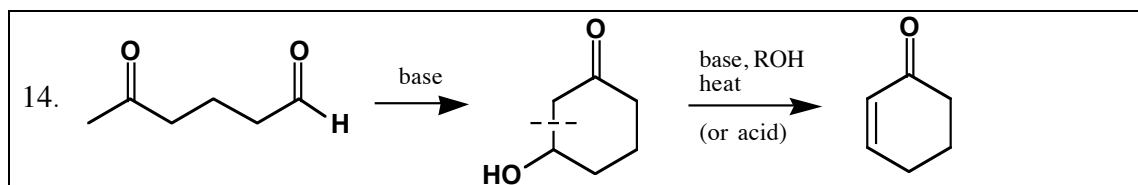
a. Intramolecular crossed aldol reactions
b. Electrophile: if one of the carbonyls is an aldehyde, it will function as the electrophile
c. Normally only good for 5, 6-membered rings
   - If more than one enolate can form, use the one that could produce a 5- or 6-ring

Aldol Examples: Aldehydes/Ketones as Electrophiles

1.

2.
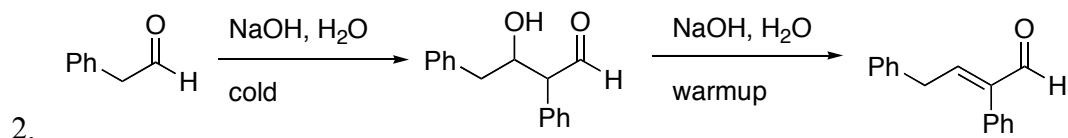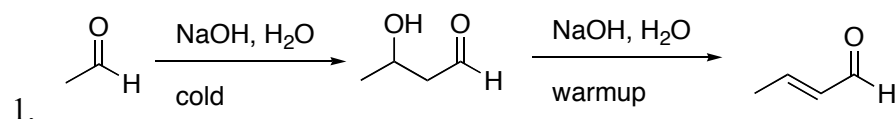
- With aldehydes, you can usually stop at the β-hydroxy carbonyl stage or proceed on to the α,β-unsaturated carbonyl, depending on time and temperature.

3.
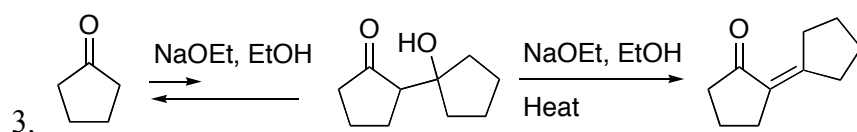
- With ketones as electrophiles, the aldol reaction to give the β-hydroxy carbonyl is normally reversible with an unfavorable equilibrium. However, while it is not possible to isolate high yields of the β-hydroxy ketone, further dehydration to give the enone is irreversible and can give good yields of the enone.

4.
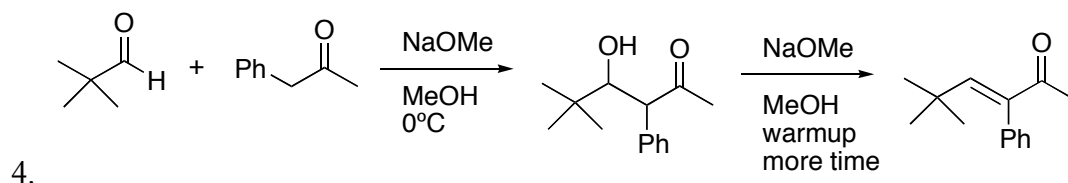
- With two different carbonyl compounds, one must function selectively as the enolate precursor, and the other as the electrophile.
- Since aldehydes are much more electrophilic, when mixed with a ketone **the aldehyde will always be the electrophile**
- If there are more than one site where an enolate might form, the most acidic site that would give a stabilized anion will form preferentially

5.
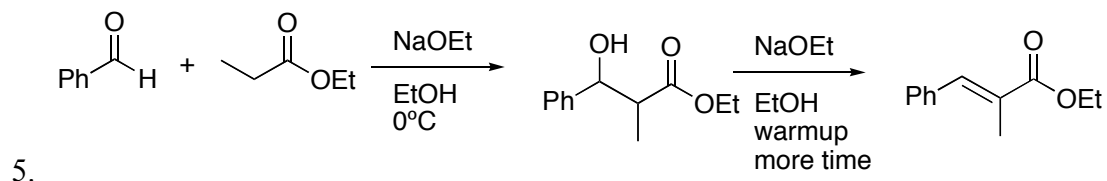
Comments
- Basic
- One carbonyl functions as the enolate nucleophile, a second carbonyl as the neutral electrophile. The enolate precursor and the electrophile carbonyl may be the same (examples 1-3) or different (examples 4 and 5)
- Loss of an α-H, replaced by an α,β C-C bond.

All of the following molecules can be made by an aldol-type reaction or an aldol-type condensation (aldol followed by loss of H_2O). Draw the carbonyl compound or compounds from which each is derived.
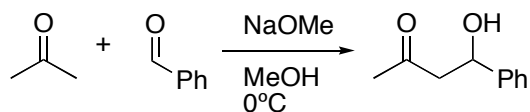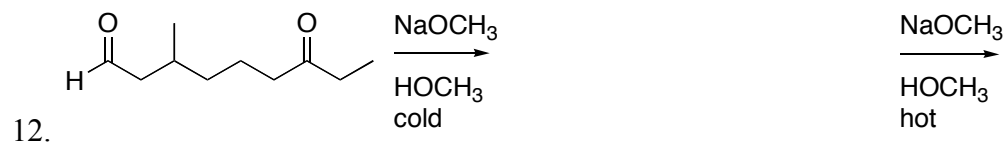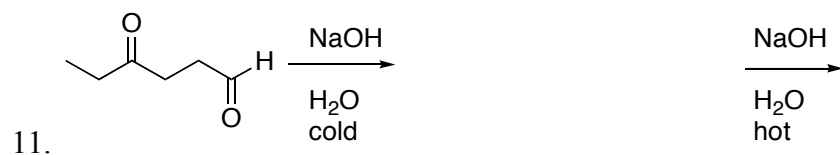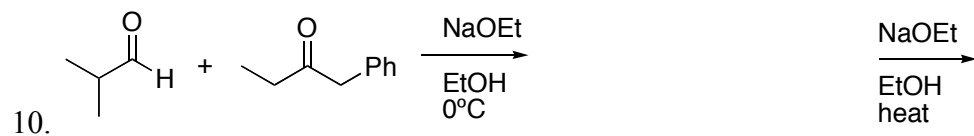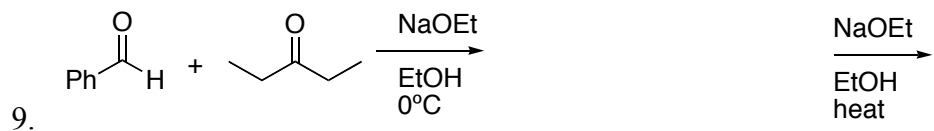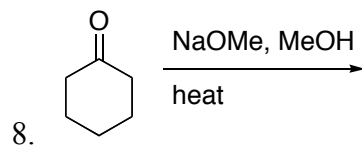
example:
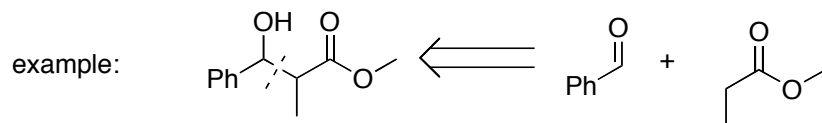
Strategy:
- Identify the carbonyl in the product, and mark off which are the α and β carbons. **The key bond connection will have been between the α and β carbons**.
- β was originally a carbonyl (the electrophile carbonyl)
- α originally had H's (it was the enolate carbanion)
- Note: **any attachments on the α and β carbons are spectators**. If they are there at the end, they must have been attached at the beinning!
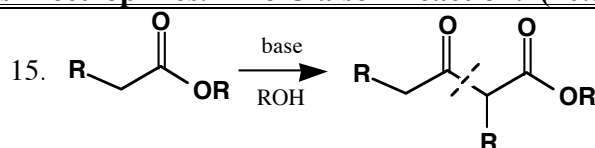
2.

3.

4.

5.
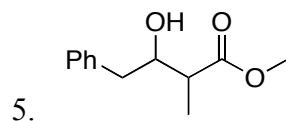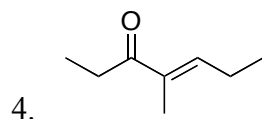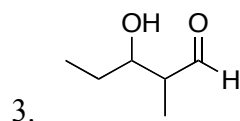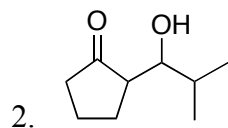
6. Draw the mechanism for the following reaction.

Provide products for the following aldol reactions.

7.
Ph ∼∼CHO   NaOH, H₂O / cold   NaOH, H₂O / heat

8.
cyclohexanone   NaOMe, MeOH / heat

9.
Ph—C(=O)—H + CH₃—C(=O)—CH₂CH₃   NaOEt / EtOH / 0°C   NaOEt / EtOH / heat

10.
(CH₃)₂CH—CHO + CH₃—C(=O)—CH₂—Ph   NaOEt / EtOH / 0°C   NaOEt / EtOH / heat

11.
    NaOH / H₂O / cold   NaOH / H₂O / hot

12.
    NaOCH₃ / HOCH₃ / cold   NaOCH₃ / HOCH₃ / hot

13. Draw the mechanism for phase one and then phase two of the reaction in problem 10.

## G. Esters as Electrophiles. The Claisen Reaction. (20.5-8)
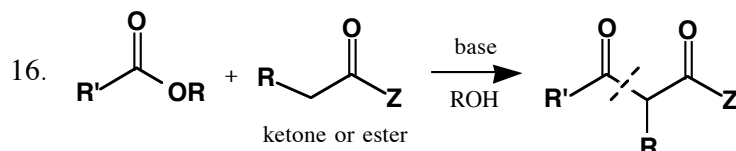
15.

-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

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

1. Draw the mechanism for the following reaction. (Claisen reaction).
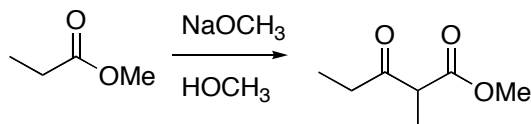
Notes
a. Product: β-keto ester (or ketone). The β-carbonyl was an ester, and the α-carbon was enolate
b. In actual laboratory, an acid workup is always required
   • The product, which has a 1,3-dicarbonyl, is actually more acidic than anything else, so it also gets deprotonated to the enolate; acid required to reprotonate it
   • The enolate of a 1,3-dicarbonyl is too stable to attack esters, so it doesn't compete as a nucleophile
c. Mechanism: does **not** involve direct S_N2 displacement on ester; addition to the carbonyl first to make a tetrahedral carbon (just like a Grignard addition) is followed by rapid fragmentation of the alkoxy group
d. In crossed Claisens that involve ketones, why does the ketone function as enolate nucleophile and the ester as the electrophile, even though ketones are normally better electrophiles?
   • Ketones are more acidic, so are more easily converted to enolates
   • While ketones are more reactive as electrophiles, addition to ketones is reversible and doesn't lead to product; whereas addition to esters leads irreversibly to product

Provide products or reactants for the following Claisen reactions.

1.

2.

3.

4.

2.
3.

5.

4.

6.

2.

7.

8.
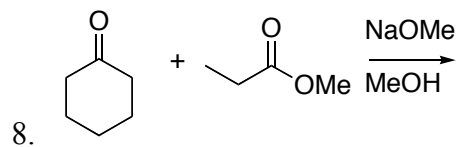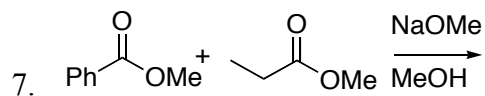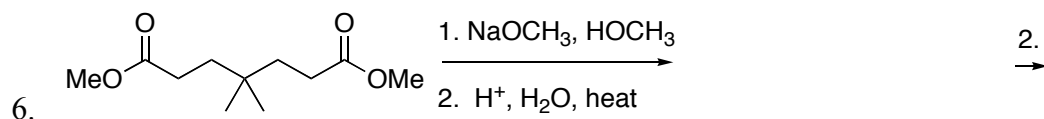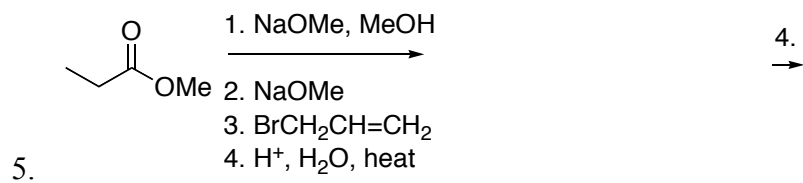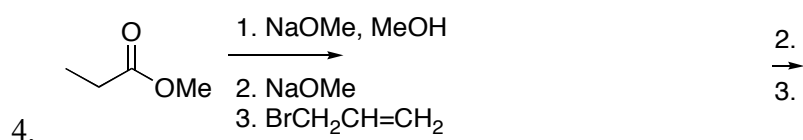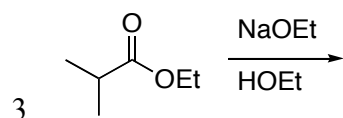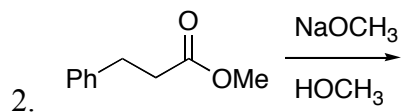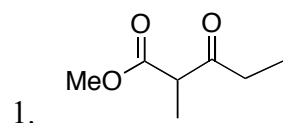
H. The WITTIG REACTION. A process involving carbonyls for coupling carbons to make alkenes. (17.12,13)
- No enolate chemistry is involved
- But this is process is complementary to the aldol condensation for making alkenes
- Very Powerful route to alkene synthesis

a. The carbonyl can be an aldehyde or a ketone
b. Phosphorus "ylide": a molecule with adjacent positive and negative charge, but overall neutral
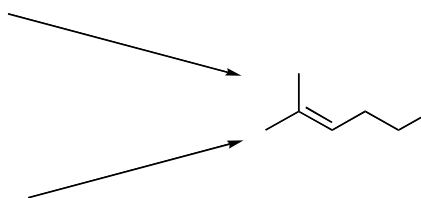c. The ylide carbon is strongly nucleophilic

Ylide Preparation:
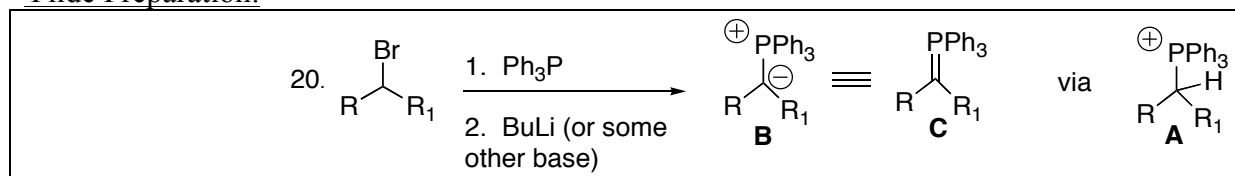
a. PPh$_3$ is a decent nucleophile, produces phosphonium salt (**A**)
b. Alkyl bromide is best 1° (S$_N$2 mechanism), but 2° can also work
c. The phosphonium salts **A** are weakly acidic and can be deprotonated by strong base (LDA also works) to produce Wittig reagent **B**
d. Wittig Reagent B is really in resonance with version C
   - **B** helps explain why the carbon is so nucleophilie
   - **C** is good for predicting alkene products
e. Bromide precursors for Wittig reagents are often available from alcohols, via PBr$_3$
   - PBr$_3$ – PPh$_3$ - BuLi is a common sequence for converting alcohols into Wittig reagents
   - PCC or H$_2$CrO$_4$ is a common conversion for alcohols into aldehydes or ketones (Wittig acceptors)

Draw the product, reagent, or starting material for the following Wittig reactions.

Combo 1:

Combo 2:

1.

1. Ph₃P
2. BuLi

3. Benzaldehyde

2.

OH   1. H₂CrO₄

2.

3.

1. PBr₃
2. PPh₃

3. BuLi
4. acetone
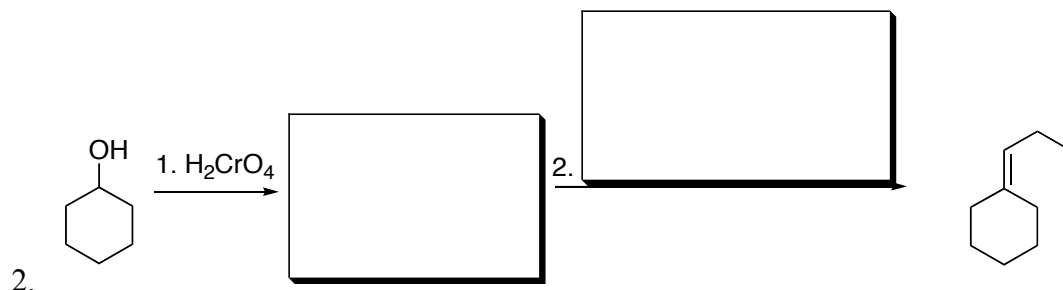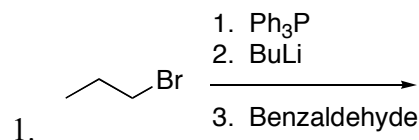
General Routes to Make Alkenes
* **Wittig Reactions**.
    * o Very general
    * o Useful for making more elaborate organics, because two subcomponents can be coupled to make a larger product.
    * o Technically longer and more difficult than an aldol condensation, so should not be used to make enones 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.

4. For the following alkenes, which method should you use, and what would be the
    immediate precursors that would be suitable?
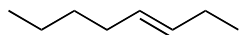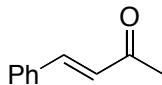
5. Synthesis design. Design syntheses of the following products, starting from **alcohols of 4
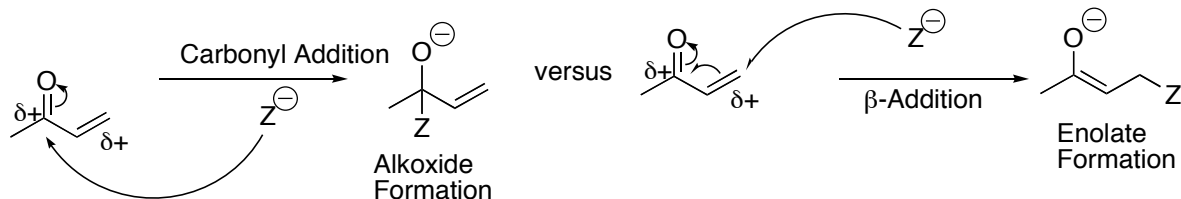   carbons or less**. Some key reminder reactions:
    - PCC for oxidizing 1° alcohols to aldehydes
    - H_2CrO_4 for oxidizing 2° alcohols to ketones
    - PBr_3 for converting 1° or 2° alcohols to bromides needed for making Wittig reagents
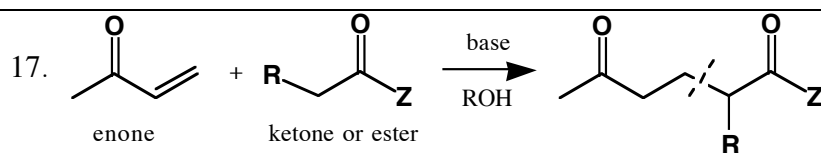
a.

b.
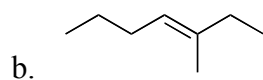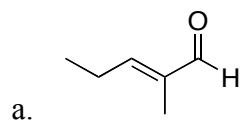
I. Enones as Electrophiles (20.17-20) Michael Reactions/β-Addition (Not for Test)

General: Enones as Electrophiles. Nucleophiles that attack enones must choose between:
- Carbonyl addition
- β-Addition
  - 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

17.
enone   ketone or ester

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

Draw the Products for the following Michael reactions

1.

2.