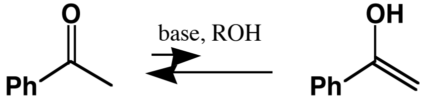
Chem 342-Jasperse **Chapter 22 (Enolate Chemistry) Reaction Summary**

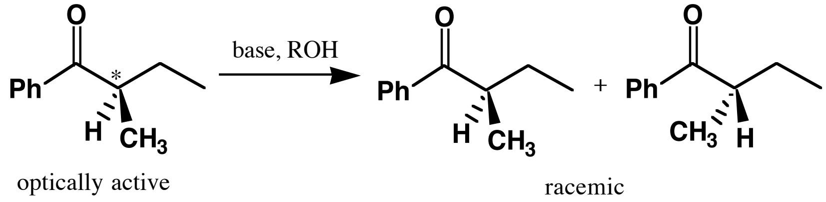
PROTON as ELECTROPHILE (22.1)

1.



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

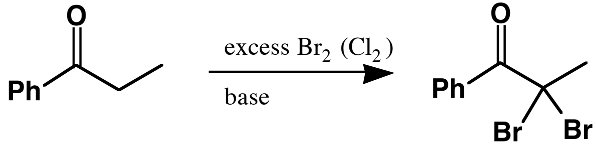
2.



-Racemization of α-chiral optically active carbonyls
-Mech

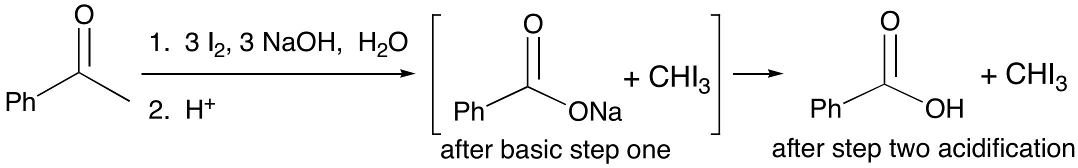
HALOGEN as ELECTROPHILE (22.3, 7)

3.



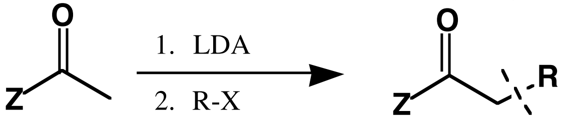
-Base catalyzed halogenation
-with excess halogen, all α-hydrogens get replaced
-Mech

4.

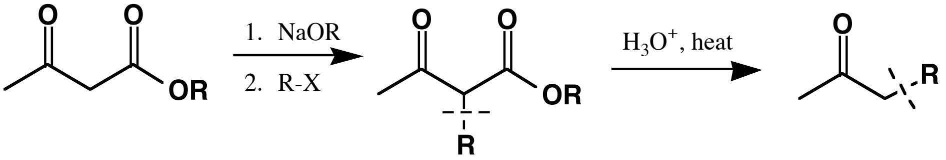


-Iodoform reaction.
-chemical test for methyl ketones

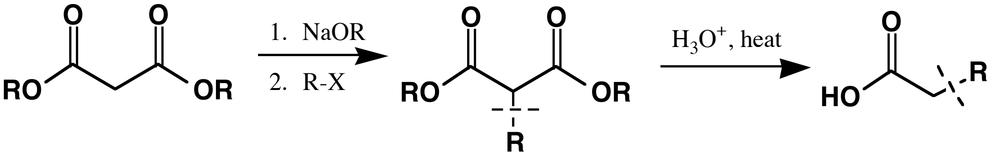
ALKYL HALIDE as ELECTROPHILE (22.7)

6.


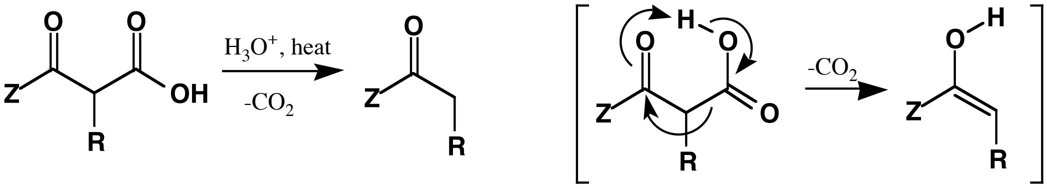
-Enolate alkylation
-strong LDA base required to completely deprotonate carbonyl
-Mech
-Ketones, Esters, Amides, Aldehydes: doesn't matter which kind of carbonyl
-unsymmetrical ketones give isomer problems
-S_N2 alkylation restricts R-X to active ones

7.


-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.


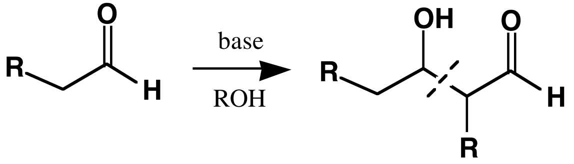
-Enolate alkylation of 1,3-diester
-alkoxide base strong enough to completely generate enolate
-Mech for alkylation
-S_N2 alkylation restricts R-X
-acid catalyzed hydrolysis/decarboxylation
-Final product is an ACID (Diester →Acid)

9.


-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

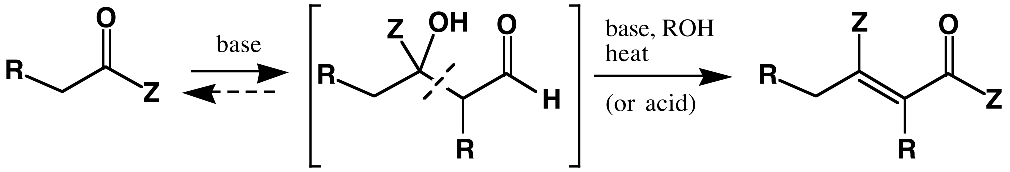
ALDEHYDE/KETONE as ELECTROPHILE (23.1-6)

10.



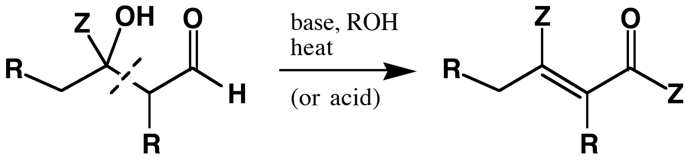
-Aldol Reaction
-Mech

11.



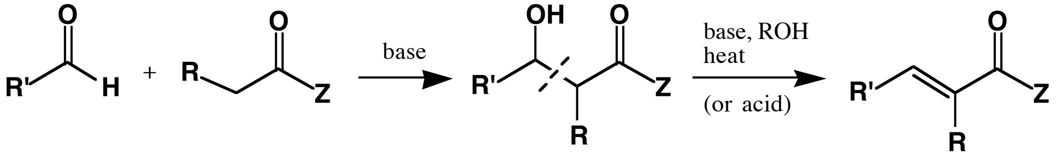
-Aldol Condensation
-Ketones as well as Aldehydes can be used
-In ketone case, unfavorable aldol equilibrium is still drawn off to enone
-In Aldehyde case, can stop at aldol if you don't heat
-Mech

12.



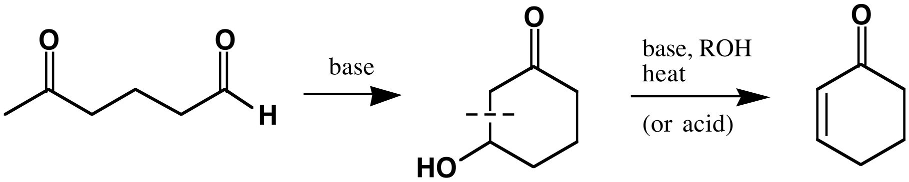
-Aldol dehydration
-Mech under basic conditions

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

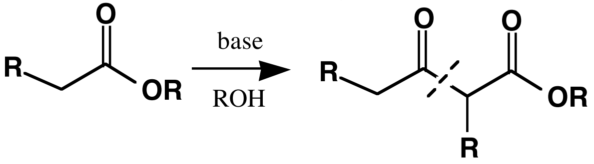
14.



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

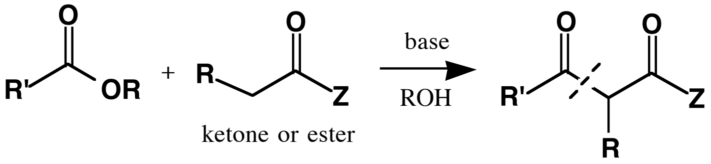
ESTER as ELECTROPHILE (23.7-9)

15.



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

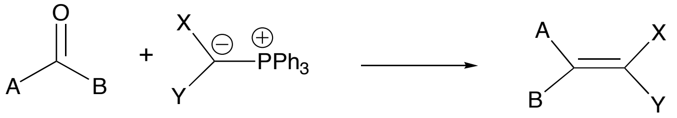
16.



-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 (19.11)

19.



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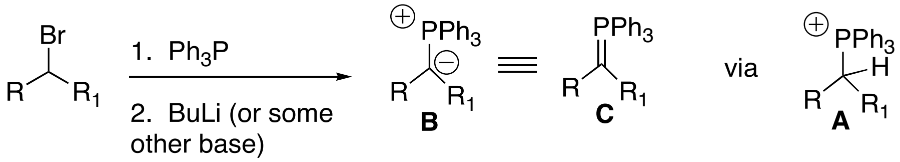


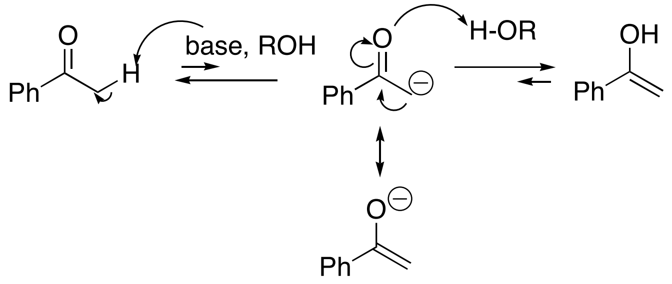
Chem 342-Jasperse **Chapter 22 (Enolate Chemistry) Reaction Mechanisms Summary**

- Note: in many of these reactions, I simply write in “base”. But for specific reactions, you need to recognize and specify the actual base that does the work.

PROTON as ELECTROPHILE

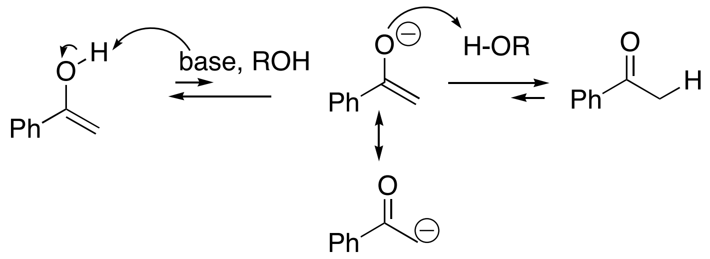
Ketone to Enol

1.



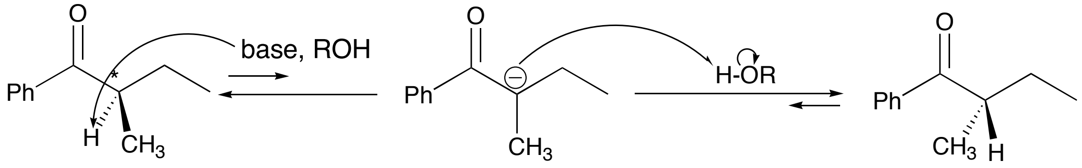
Enol Back to Ketone:

1.-reverse



Deprotonation/Reprotonation to Racemize an optically active α-chiral center

2.



optically active

racemic

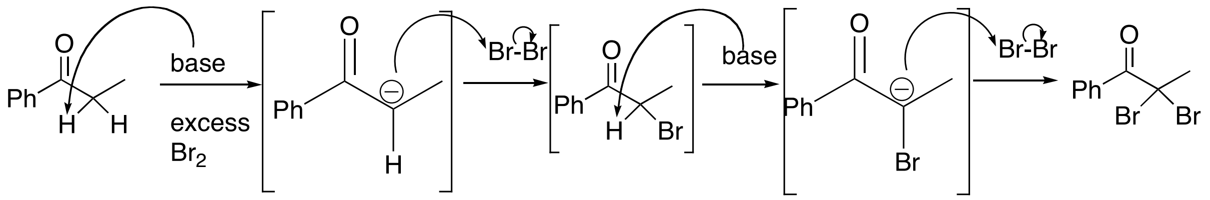
enantiomer or original. Protonation from the front gives enantiomer, from the back gives the original. The result is a 50/50 racemic mixture.

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.)

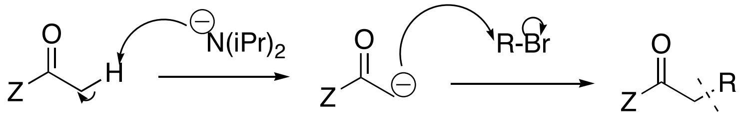
3.



ALKYL HALIDE as ELECTROPHILE

With Strong LDA as Base, using a Monocarbonyl

6.

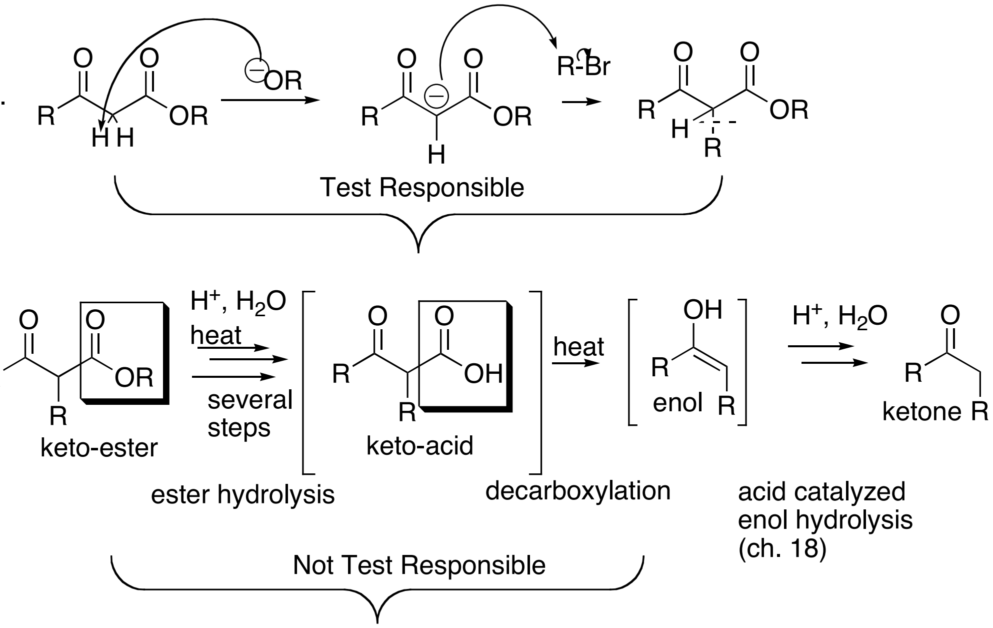


1. Z can be anything: works for ketones, esters, aldehydes, esters,…
2. "LDA" is lithium diisopropylamine, provides the nitrogen anion shown
3. strong LDA base required to completely deprotonate carbonyl. The base strength enables the enolate to form completely, no equilibrium or reversibility issues.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



-alkoxide base strong enough to completely generate enolate

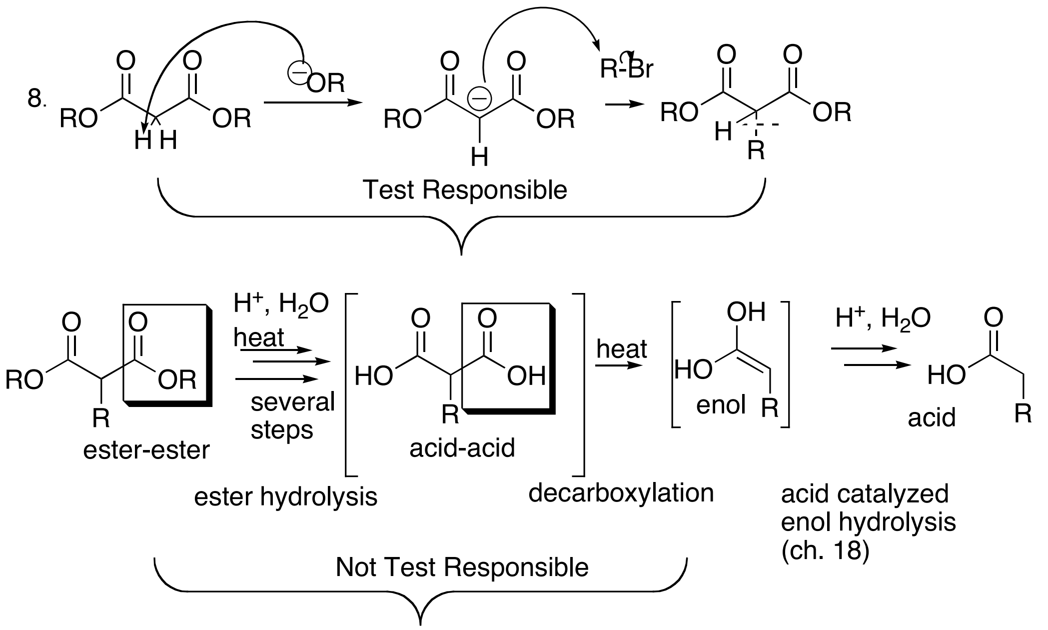
-S_N2 alkylation restricts R-X

-acid-catalyzed hydrolysis/decarboxylation

-not test responsible for the acid/catalyzed ester hydrolysis or the keto-acid decarboxylation mechanisms

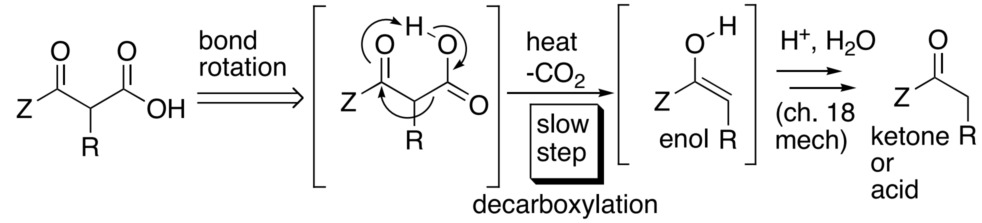
-you are responsible for the acid-catalysis enol hydrolysis (not detailed here, but was in Ch. 18)

8.



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

9.



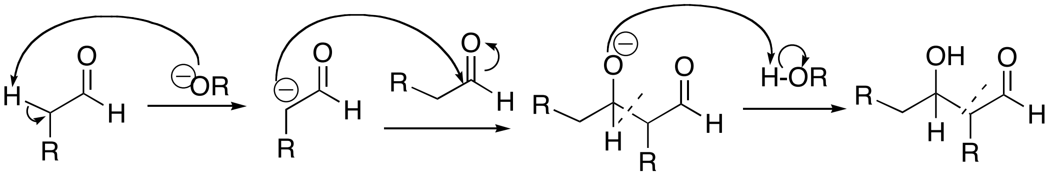
Not Fully Test Responsible. But must know that ENOL is key intermediate that forms in the slow step.
What is good for the enol (and it's alkene) accelerates the decarboxylation

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

ALDEHYDE/KETONE as ELECTROPHILE

Simple Aldol Reaction, giving a β-hydroxy-carbonyl. In which the same carbonyl functions as both enolate precursor and electrophile.

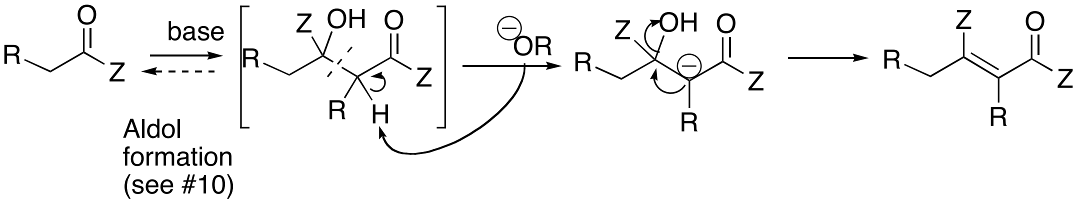
10.



-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.

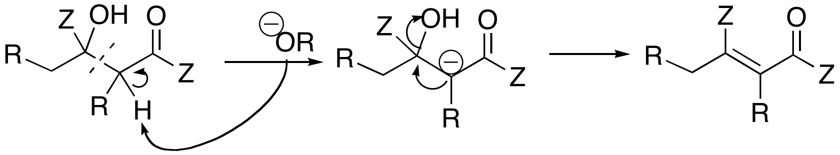
11.



-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

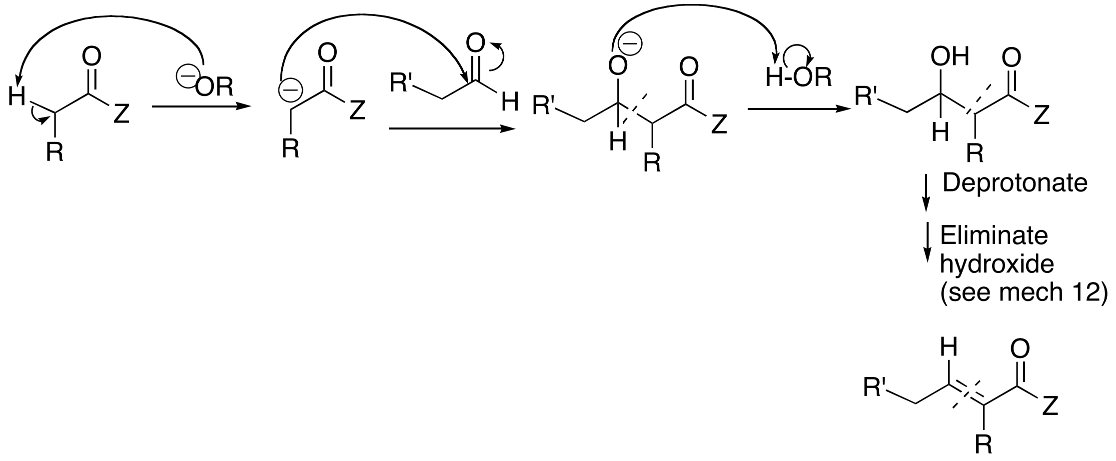
12.



-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

13.



-Crossed Aldol (2 different carbonyls)

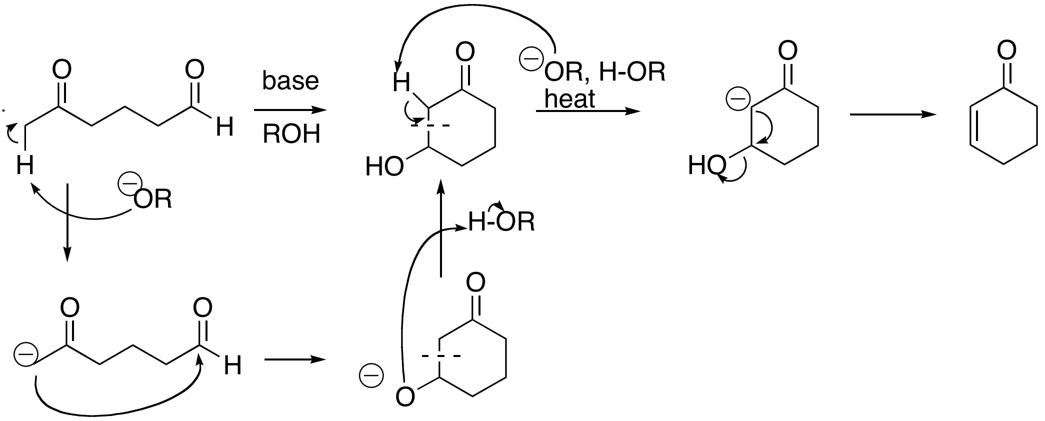
-Many variations, but there must be some differentiation so that one acts selectively as the enolate and the other as the electrophile

-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

14.



-Intramolecular aldol

-many variations

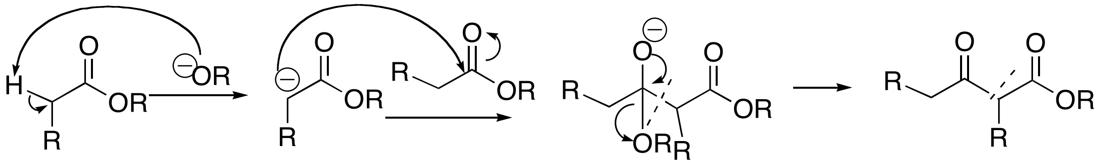
-Normally only good for 5, 6-membered rings

-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

Simple Claisen Reaction, giving a β-ketoester. In which the same ester functions as both enolate precursor and electrophile.

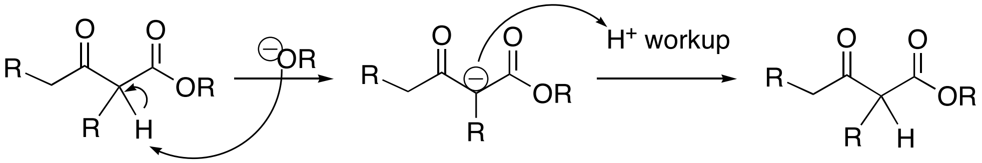
15.


-Produces 1,3-ketoester

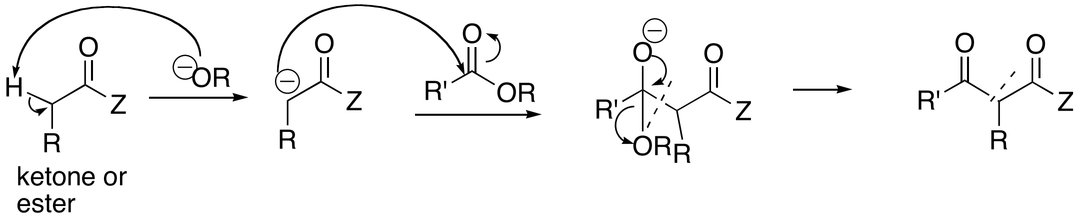
-The alkoxide used as base should match the R-group found in the ester. For example, if the ester OR group is OMe, then the base should be NaOMe/MeOH. If the ester OR group is OEt, then NaOEt/EtOH should be used, etc.

-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.



Crossed Claisen Reaction, 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.


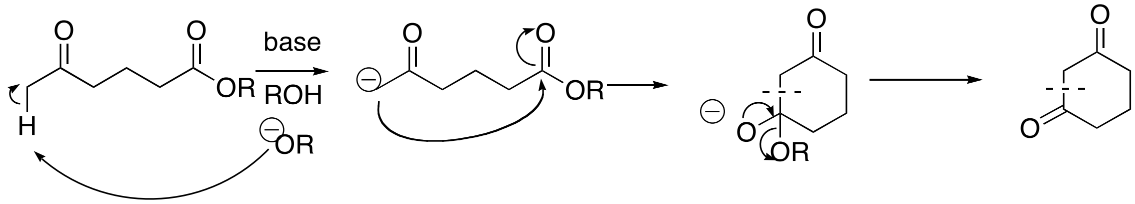
-Crossed Claisen

-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

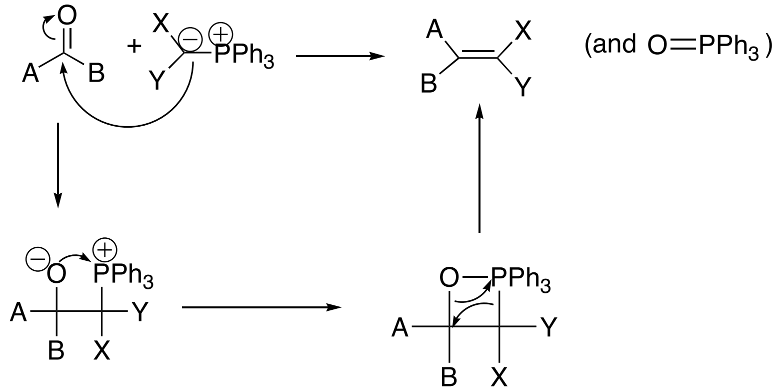
-If the “enolate” carbonyl is an ester, get a 1,3-ketoester. These work best if only one of the esters has α-hydrogens, so that you have just one enolate available.

-May include cyclic Claisen reactions (see example below)

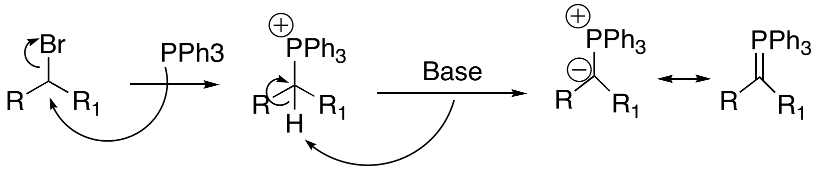


WITTIG REACTION

19.



20.

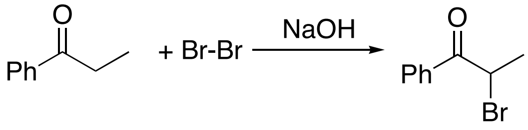


Ch. 22 Additions and Condensations of Enols and Enolate Ions

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…**

Key Intermediate

1


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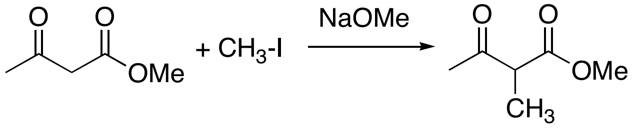

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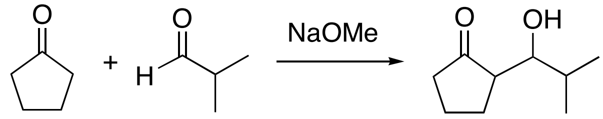

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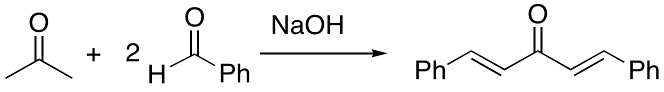
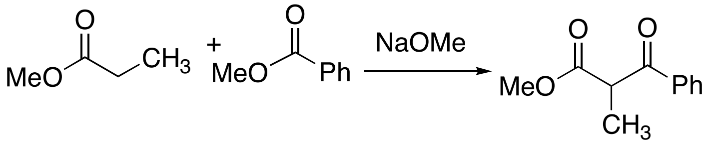
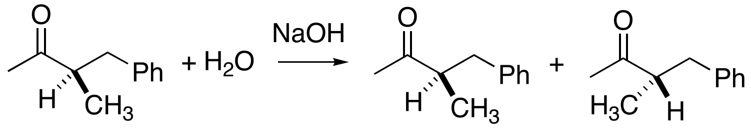


5


6


optically active

racemic mixture

__Things in Common__

KEY:

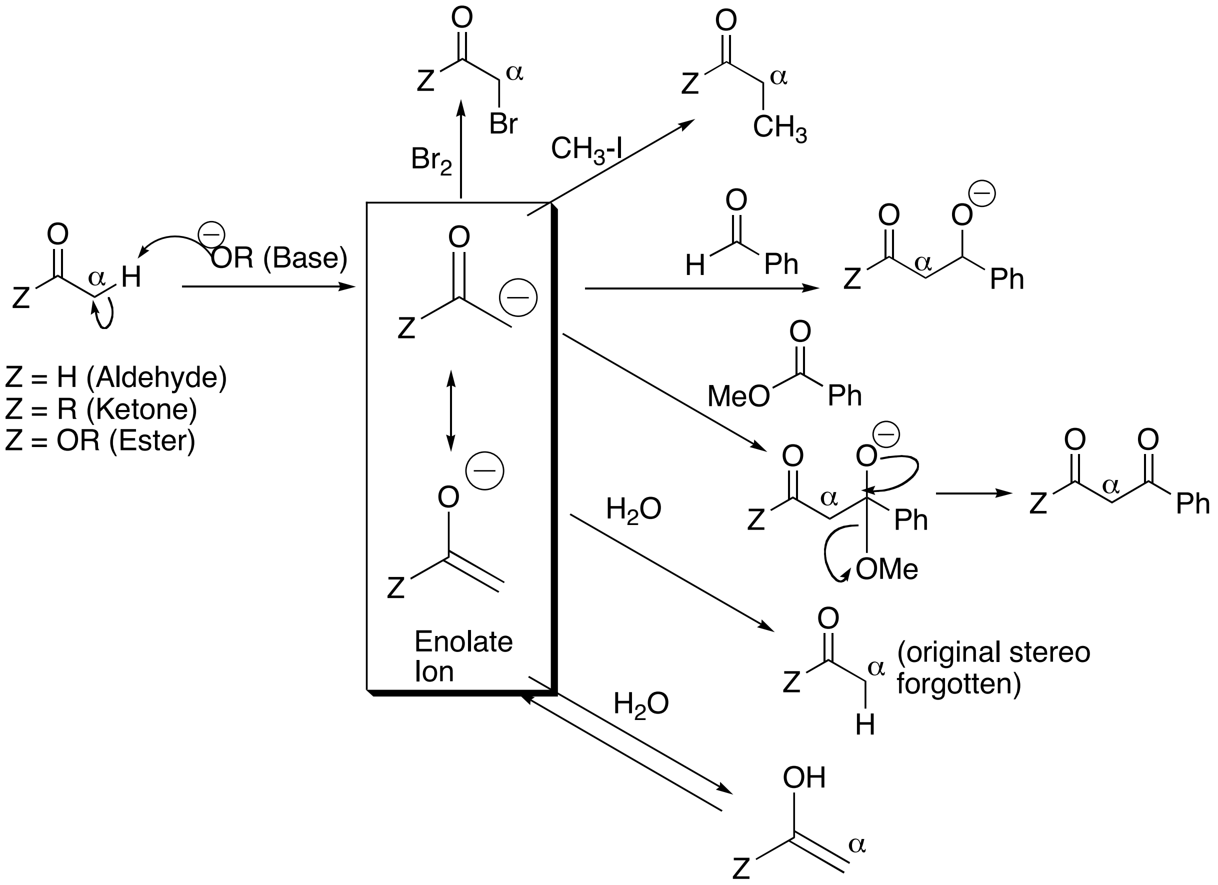
1.

2.

3.

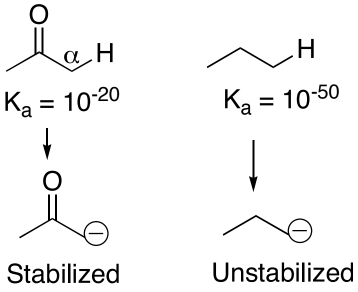
4.

TYPICAL MECHANISM: Via ENOLATE Anion



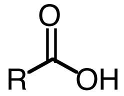
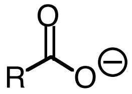
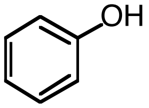
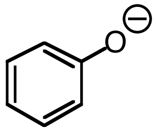
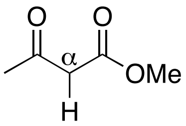
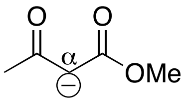
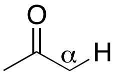
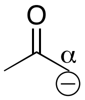
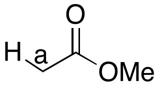
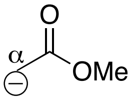
Under base conditions, a carbonyl compound with an α-hydrogen can be deprotonated to give a resonance-stablized, delocalized "enolate" anion, which is nucleophilic at the α-carbon.

- 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.



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

- **B: Acid/Base Considerations (Sections 22.5) Acidity Table**

Class	Structure	Ka	Acid Strength	Anion	Base Strength
Strong Acids	H-Cl	10^{2}		$Cl^{\ominus}$	
Carboxylic Acid		10^{-5}			
Phenol		10^{-10}			
1,3-Dicarbonyl		10^{-12}			
Water	HOH	10^{-16}		$HO^{\ominus}$	
Alcohol	ROH	10^{-17}		$RO^{\ominus}$	
Ketones and Aldehydes		10^{-20}			
Ester		10^{-24}			
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$ "LDA"	
Alkane (C-H)	RCH_3	10^{-50}		$^{\ominus}RCH_2$	

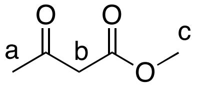
$$\boxed{\text{H-A} + \text{B}^{\ominus} \rightleftharpoons \text{A}^{\ominus} + \text{B-H}}$$

Relative stability of anions dictates equilibrium

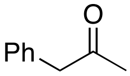
Notes to remember

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 **completely** deprotonate **ketones**, **esters**, or 1,3-dicarbonyls
6. NaOH, NaOR can **completely** deprotonate a 1,3-dicarbonyl (but not ketones or esters)
7. NaOH, NaOR do **not** completely deprotonate ketones or esters, but do provide a usable equilibrium supply of the enolate that can procede to product in some reactions.

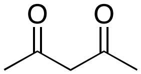
1. Rank the acidity of the hydrogens at the labeled positions, 1 being most acidic. Draw the three anions that would result from deprotonation at the three spots, and any pertinent resonance structures.



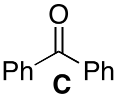
2. For the following compounds, record to what degree they would be deprotonated by $NaOCH_3$ or LDA [$LiN(iPr)_2$] respectively. The basic choices are "totally" (>98%), "zero" (no enolate whatsoever) or "slightly" (definitely some equilibrium amount, but <10%).



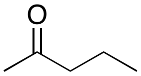
A



B



C



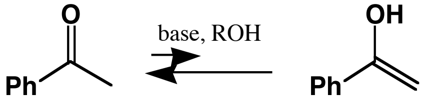
D

LDA:

NaOMe:

C. Enolates and Enols: Protons as Electrophile (22.1)

PROTON as ELECTROPHILE

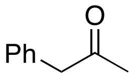
1.


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

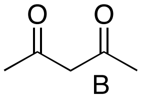
Notes:

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)

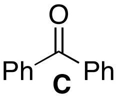
3. For the following compounds, draw the best possible enol (if any) rank them according to which would have the greatest amount of **<u>enol isomer</u>** present at equilibrium, 1 being most.



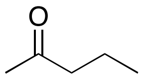
A



B



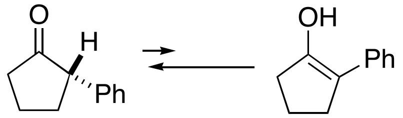
C



D

<u>Mechanism for Base-Catalyzed Keto-Enol Equilibration:</u>

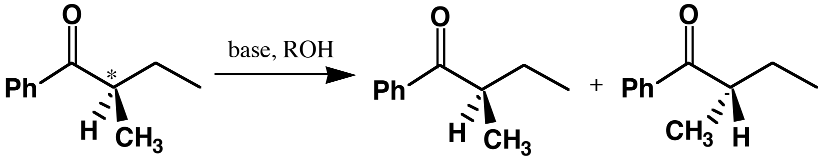
4. Keto-Enol Mechanisms (use hydroxide as base, but many bases will do…)
   a. Draw the mechanism for conversion of the keto form to the enol form



   b. Draw the mechanism for conversion of the enol form to the ketone

<u>Racemization of α-chiral Compounds via Enolates</u>

2.

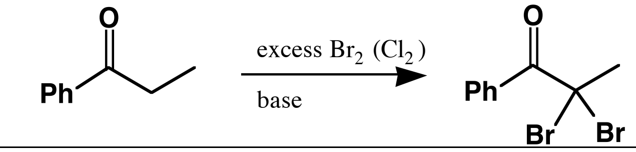


optically active

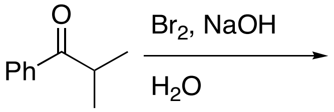
racemic

-Racemization of α-chiral optically active carbonyls
-Mech

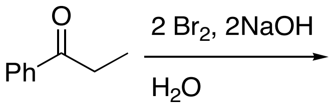
D. Halogen Electrophiles (22.3) (Skip 22.4)

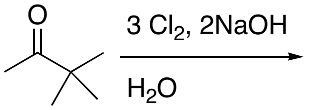
HALOGEN as ELECTROPHILE	-Base catalyzed halogenation -with excess halogen, all α-hydrogens get replaced -Mech
3. 	

5. Draw the product and mechanism for the following



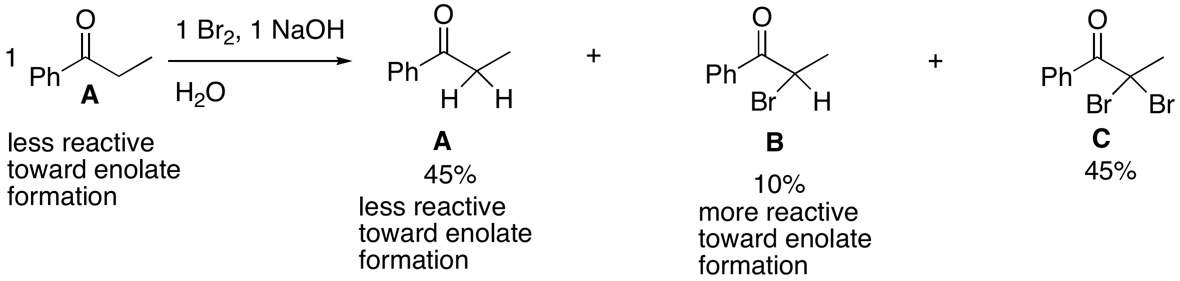
6. Draw products for the following reactions



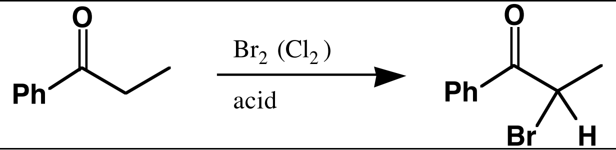


Polyhalogenation versus monohalogenation

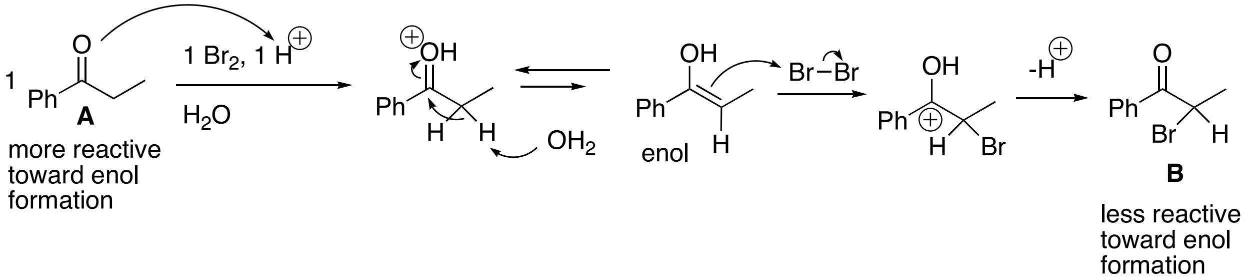
- Under base conditions, if you add only one equivalent of Br_2 (or Cl_2) when an α-carbon has more than one α-hydrogen, clean mono-halogenation (product **B**) does not occur
- Instead messy mixtures result
- The major product is polyhalogenated (**C**), combined with a bunch of unreacted starting material (**A**)
- Why? Because the electron-withdrawing halogen makes product **B** more acidic (resulting in faster enolate formation) than the starting material **A**



Acid-Catalyzed Monohalogenation (not for test)

5.		-Acid-catalyzed halogenation -can achieve selective mono-halogenation -No Mech required

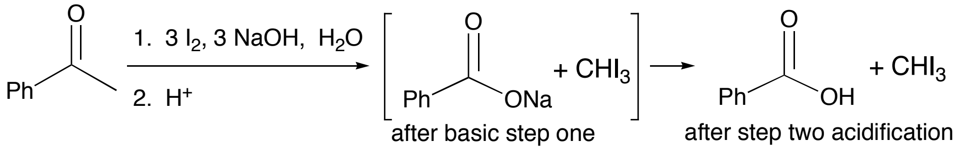
- Under acid conditions, a very different mechanism takes place which allows clean mono-halogenation to proceed
- Enol mechanism (not for test)
- Cationic mechanism
- An electron-withdrawing anion stabilizes and accelerates enolate formation, but destabilizes and decelerated enol formation



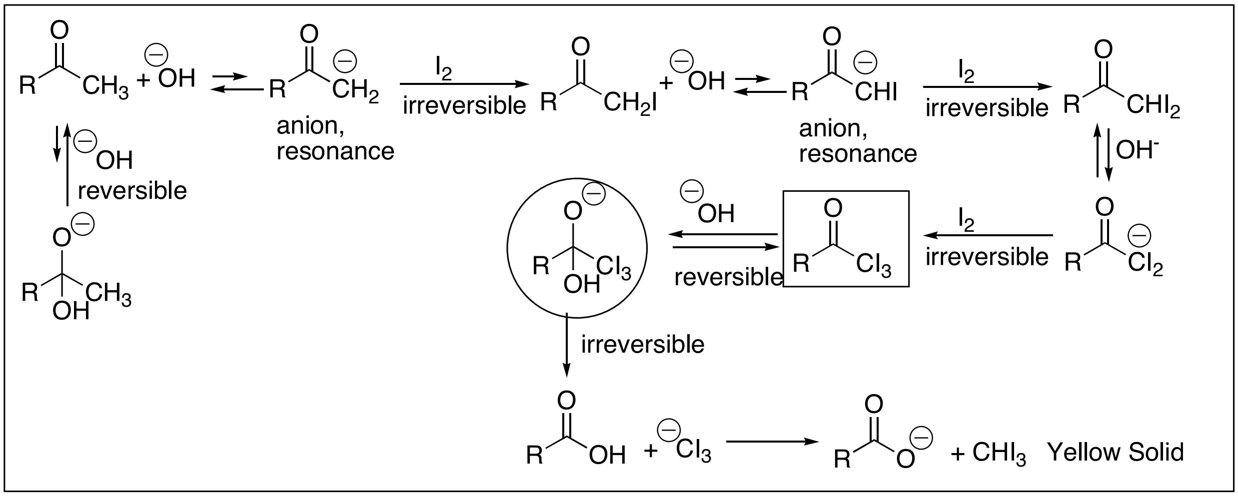
The Iodoform Reaction:

- A Chemical Test for methyl ketones (unknowns problems)
- A synthetic technique for converting methyl ketones to carboxylic acids

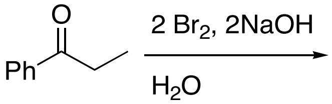
4.

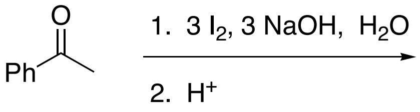


- You lose one carbon
- This only works for methyl ketones
- The chemical test involves formation of CHI_3 (iodoform), which is a yellow precipitate (and smelly)
- Mechanism (not for test):



7. Draw products for the following reactions

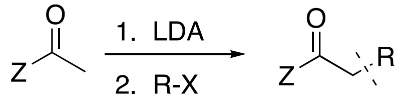




E. Enolate Alkylation: Alkyl Halides or Tosylates as Electrophiles (22.7)

Alkylation of Monocarbonyls: Use strong, bulky LDA [LiN(iPr)$_2$] as base

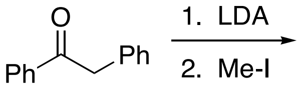
6.



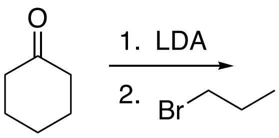
1. S_N2 alkylation reaction restricts R-X (or ROTs) to active, 1° electrophile
2. Ketones, Esters, Amides, Aldehydes all work, so long as they have an α-hydrogen that can be deprotonated
   - For unsymmetrical ketones, isomer problems can occur (which enolate forms?)
3. Predict the products: Attach the 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.

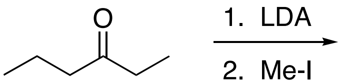
8.

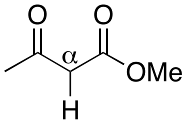
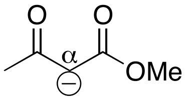
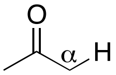
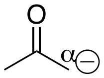


9.



10.



Class	Structure	Ka	Acid Strength	Anion	Base Strength
1,3-Dicarbonyl		10^{-12}			
Water	HOH	10^{-16}		$HO^{\ominus}$	
Alcohol	ROH	10^{-17}		$RO^{\ominus}$	
Ketones and Aldehydes		10^{-20}			
Amine (N-H)	$(iPr)_2N\text{-}H$	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$ “LDA”	

For Monocarbonyls, why must we use LDA as base, rather than a normal oxygen base ($NaOH$ or $NaOCH_3$) or a simpler Nitrogen base ($NaNH_2$)?

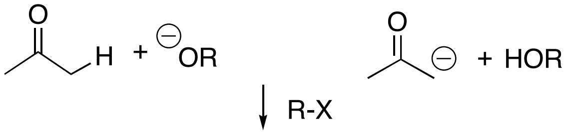
LDA is strong and bulky

1. Base Strength: the LDA base must be strong enough to **completely** deprotonate the carbonyl before the electrophile is added

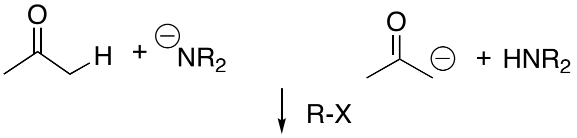
- With oxygen bases, the equilibrium favors the oxygen anion rather than the enolate, and it's just the oxygen anion which attacks the electrophile

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

Oxygen Base



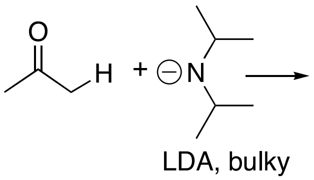
Nitrogen Base



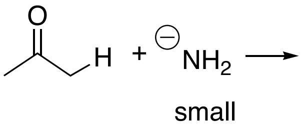
2. Base size: A bulky base favors deprotonation over nucleophilic attack

- Comparable to E2 versus S_N2 competition

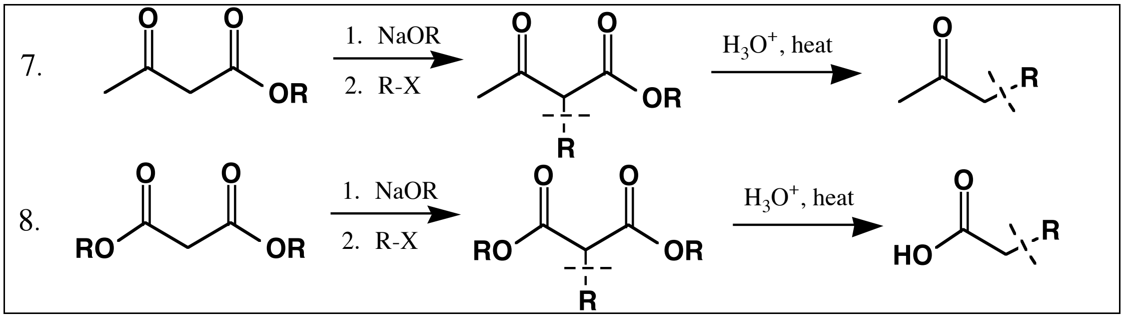
Bulky Base (LDA)



Small Base



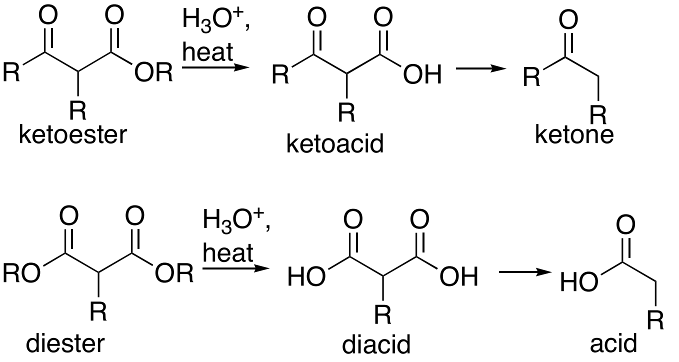
Alkylation of 1,3-dicarbonyls: Now oxygen bases are fine



Stage One: Alkylation of a 1,3-Dicarbonyl

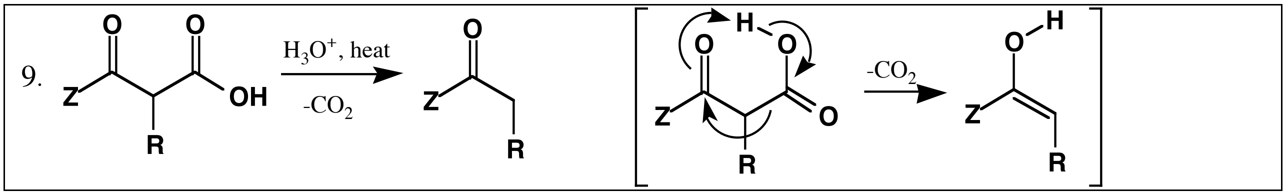
1. S_N2 alkylation reaction restricts R-X (or ROTs) to active, 1° electrophile
2. The dicarbonyl can be a 1,3-diketone, a 1,3 ketoester, or a 1,3-diester
3. Predict the products: Attach the electrophile R group to the α-carbon
4. Position of alkylation is unambiguous: in between the two carbonyls
5. Mechanism: Deprotonate first, add the electrophile second
    - $\ominus$ OR bases are fine, no need for LDA

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



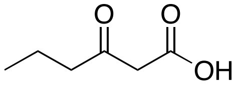
1. Upon treatment with H_2O/H^+, any esters hydrolyze to carboxylic acids

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

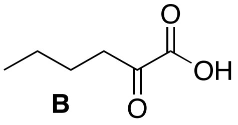


1. Decarboxylation of a 1,3-carbonyl acid
2. “Z” can be anything so that you end with a ketone, aldehyde, or acid at the end
3. Mechanism responsibility
    a. Be able to write the acid-catalyzed enol to carbonyl isomerization (see chapter 18)
    b. Know that an enol is involved in the rate-determining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

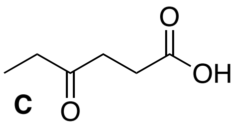
11. Which of the following would undergo decarboxylation? And which would go fastest?



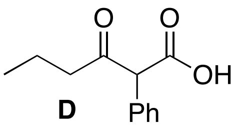
A



B



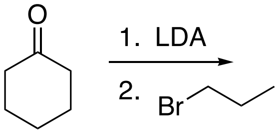
C



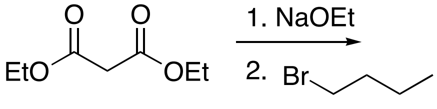
D

Draw products for the following alkylation reactions, often involving ester hydrolyses and thermal decarboxylations.

12.



13.



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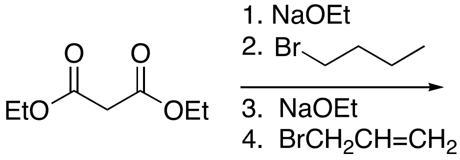

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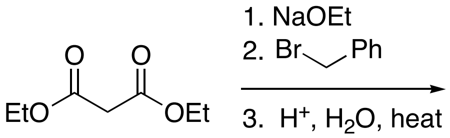

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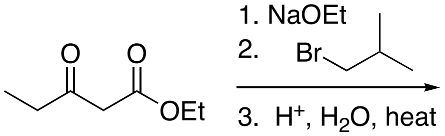

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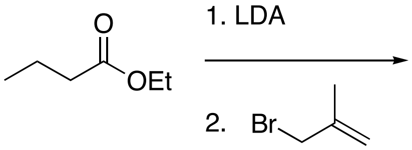
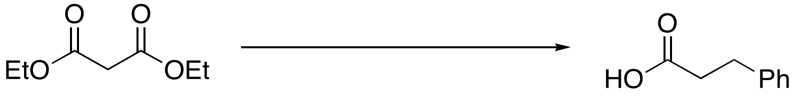


Some Synthetic Strategy Tips

- 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:

18.



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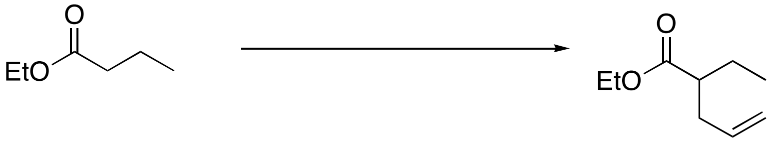
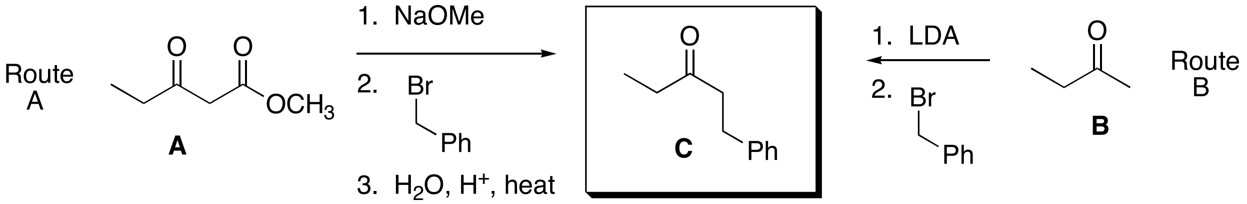
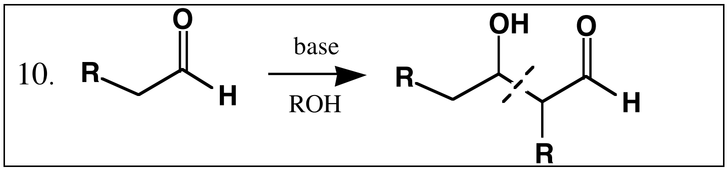


20. Shown below are two possible precursors **A** and **B** for making target ketone **C**. One works well, the other has a problem. Which is the good precursor, and which precursor/route will have problems?

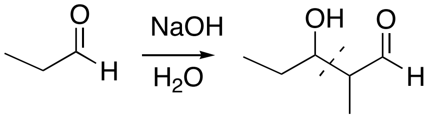


F. Aldehydes or Ketones as Electrophiles: The Aldol Reaction (23.1-6)

The basic aldol reaction: in which the same aldehyde functions as both enolate and electrophile, and in which a β-hydroxyaldehyde is produced. (23.1)

10.


21. Try to draw the mechanism for the following.

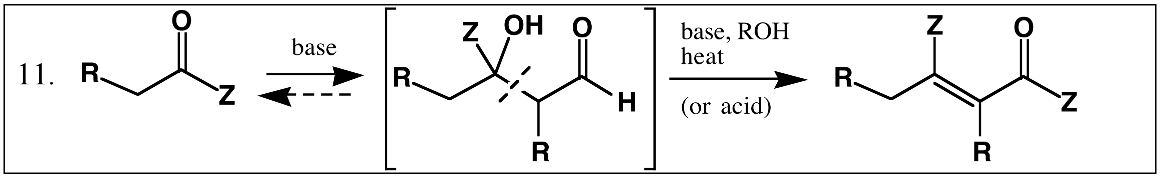


Notes:

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

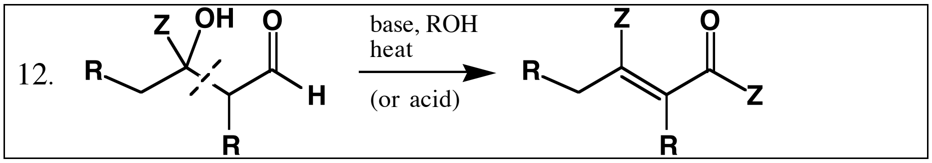
- With ketones, either you don't isolate β-hydroxycarbonyl. Either you proceed on to alkene (see below) or else you just recover starting ketone

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) (23.3)

11.


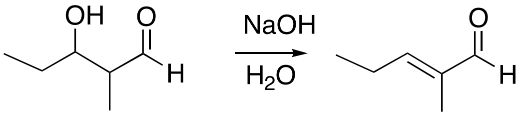
a. Elimination is irreversible
b. Ketones as well as Aldehydes can be used
  - In ketone case, unfavorable aldol equilibrium is still drawn off to enone
c. In Aldehyde case, can stop at aldol if you don't heat
  - To force toward the enone, give extra time or extra heat
d. Two a-hydrogens must be available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

General Process for Dehydration of β-Hydroxy Carbonyl Compounds (23.3)



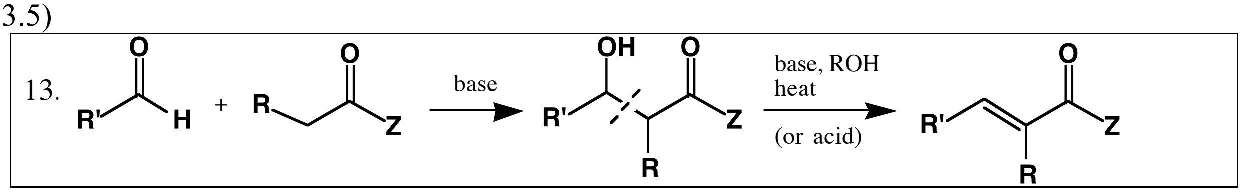
- We will focus on the base/enolate mechanism
- But this elimination is also possible using acid catalysis, via a different mechanism

22. Try to draw the mechanism for the following.



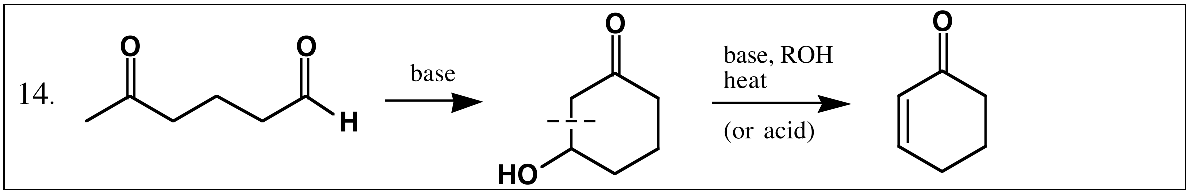
Crossed Aldol Reactions: Using 2 Different Carbonyls, One of Which Functions as Neutral Electrophile (normally an aldehyde) and the Other as the Nucleophilic Enolate

(23.5)



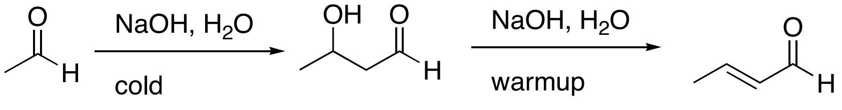
a. Mechanisms required
b. Many variations, but there must be some differentiation so that one carbonyl acts selectively as the enolate and the other as the electrophile
    1. If one carbonyl lacks any α-hydrogens, it can't be converted to nucleophile and can only function as electrophile
    2. Aldehydes 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

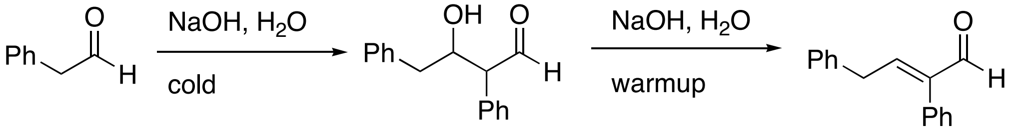
Ring-Forming Aldol Reactions (23.6)



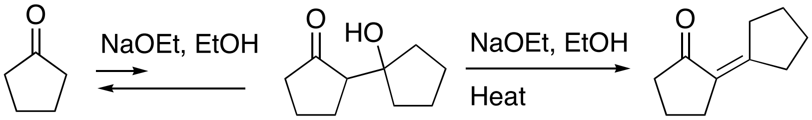
a. Intramolecular crossed aldol reactions
b. Electrophile: if one of the carbonyls is an aldehyde, it will function as the electrophile
c. Normally only good for 5, 6-membered rings
    - If more than one enolate can form, use the one that could produce a 5- or 6-ring

Aldol Examples: Aldehydes/Ketones as Electrophiles

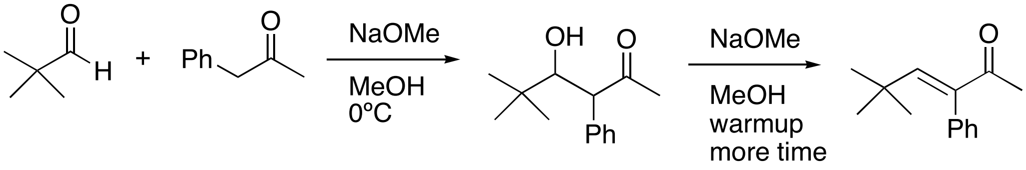
1.


2.


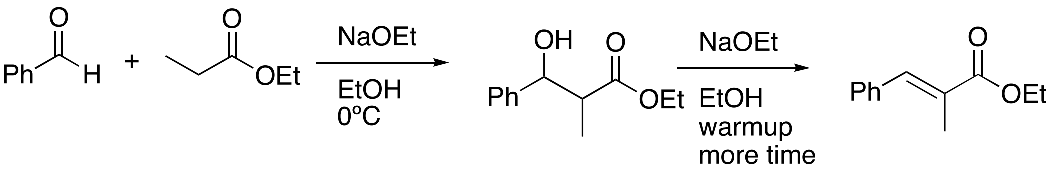
- With aldehydes, you can usually stop at the β-hydroxy carbonyl stage or proceed on to the α,β-unsaturated carbonyl, depending on time and temperature.

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 26he 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

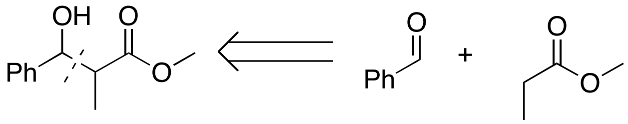
5.


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.

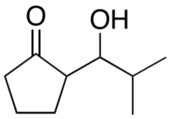
example:



Strategy: (23.5)

- 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!

23.



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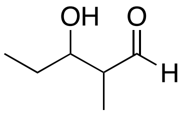
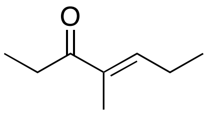
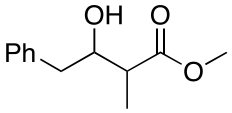


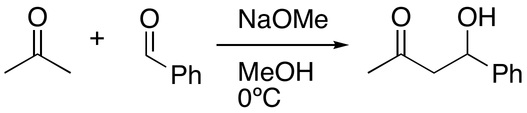
25.



26.

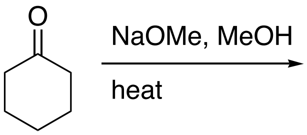


27. Draw the mechanism for the following reaction.



Provide products for the following aldol reactions.

28.


29.


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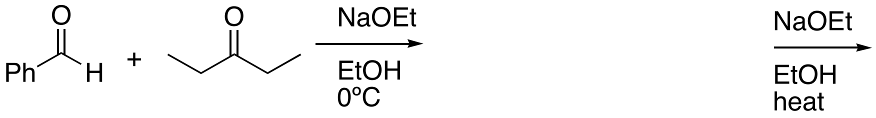
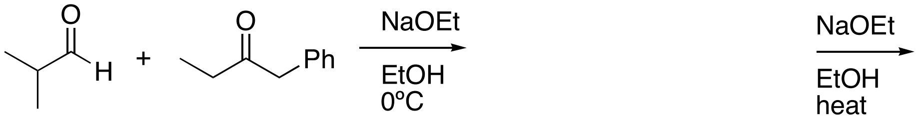
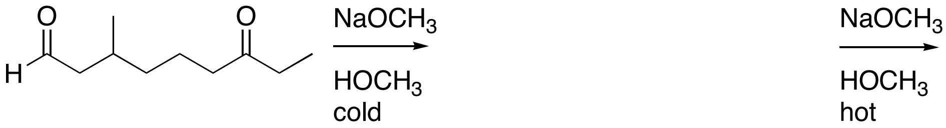


31.


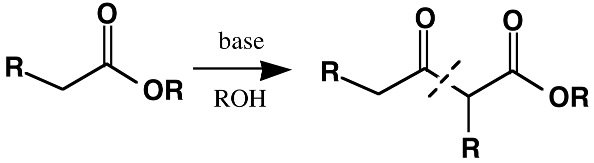
32.


33.


34. Draw the mechanism for phase one and then phase two of the reaction in problem 30.

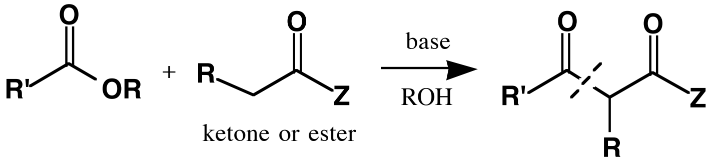
G. Esters as Electrophiles. The Claisen Reaction. (23.7-9)

15.



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

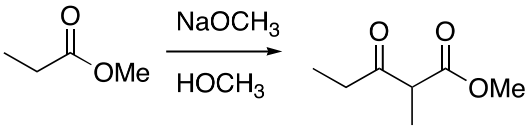
16.



-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

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

35. Draw the mechanism for the following reaction. (Claisen reaction).

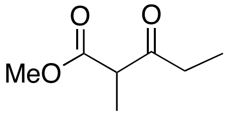


Notes

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.

36.



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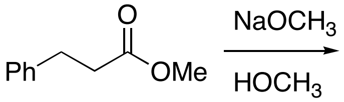

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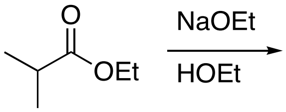

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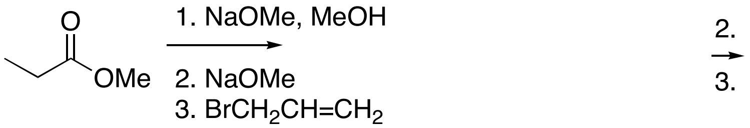

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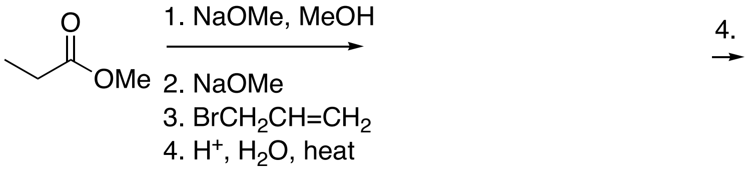

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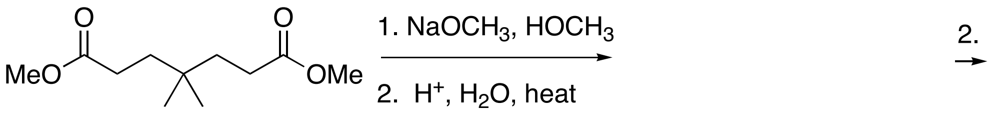

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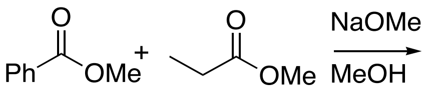

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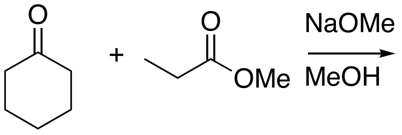
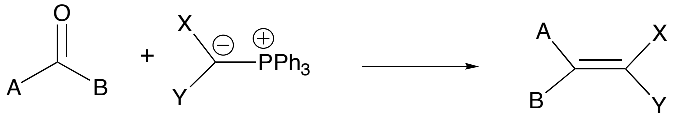


H. The WITTIG REACTION. A process involving carbonyls for coupling carbons to make alkenes. (19.11)

- No enolate chemistry is involved
- But this is process is complementary to the aldol condensation for making alkenes
- Very Powerful route to alkene synthesis

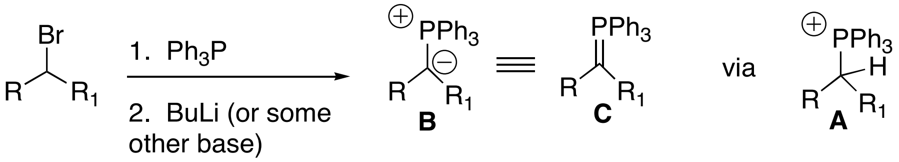
19.



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:

20.

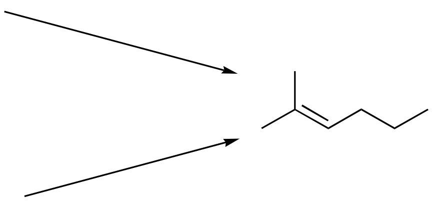


a. PPh_3 is a decent nucleophile, produces phosphonium salt (**A**)
b. Alkyl bromide is best 1° (S_N2 mechanism), but 2° can also work
c. The phosphonium salts **A** are weakly acidic and can be deprotonated by strong base (LDA also works) to produce Wittig reagent **B**
d. Wittig Reagent B is really 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_2CrO_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:

44. Combo 2:



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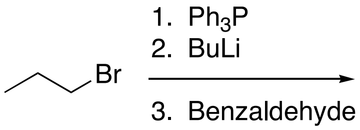

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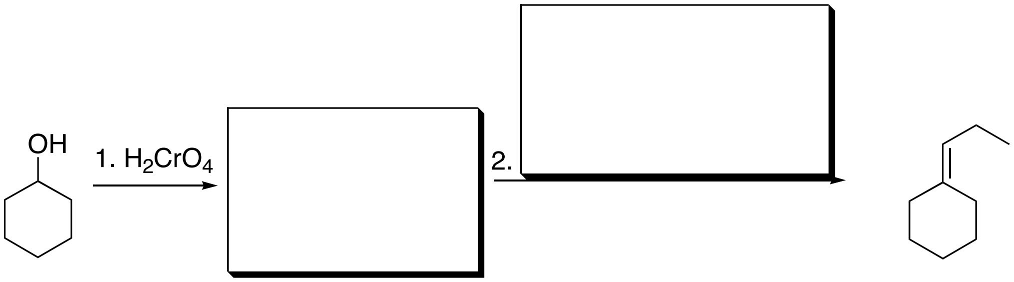
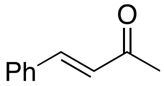


47.

General Routes to Make Alkenes

- **Wittig Reactions**.
  - Very general
  - Useful for making more elaborate organics, because two subcomponents can be coupled to make a larger product.
  - 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**.
  - Great for making enones (α,β-unsaturated carbonyls). But limited to making enones.
  - If you see an enone target, make via aldol condensation.
  - Useful for making more elaborate organics, because two subcomponents can be coupled to make a larger product.
- **Elimination reactions** (from either halides or alcohols).
  - Not useful for building up carbon chain lengths. Simply involves transforming one functional group into another.

48. For the following alkenes, which method should you use, and what would be the immediate precursors that would be suitable?



49. Synthesis design. Design syntheses of the following products, starting from **<u>alcohols of 4 carbons or less</u>**. Some key reminder reactions:
- PCC for oxidizing 1º alcohols to aldehydes
- H_2CrO_4 for oxidizing 2º alcohols to ketones
- PBr_3 for converting 1º or 2º alcohols to bromides needed for making Wittig reagents