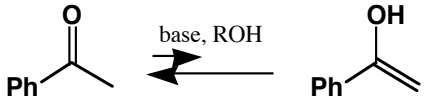
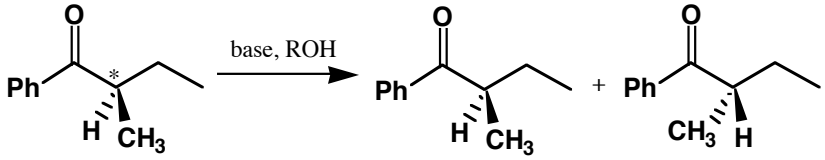
Chem 360-Jasperse **Chapter 22 (Enolate Chemistry) Reaction Summary**

PROTON as ELECTROPHILE

1. 

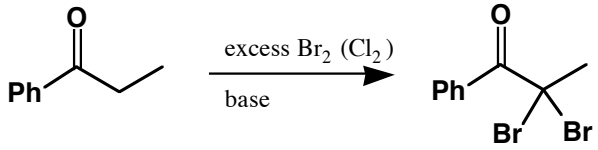
-Base-catalyzed keto-enol equilibrium
-know mech (either direction)
-know impact of substituents on enol concentration

2. 

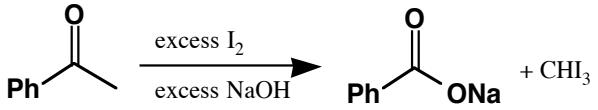
optically active racemic

-Racemization of α-chiral optically active carbonyls
-Mech

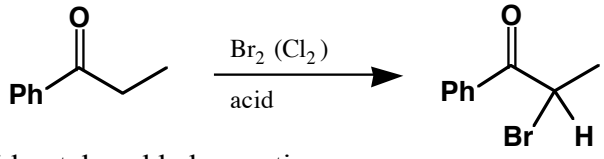
HALOGEN as ELECTROPHILE

3. 

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

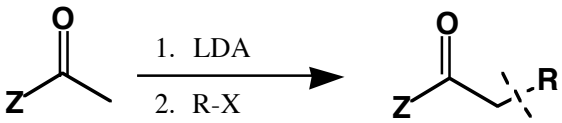
4. 

-Iodoform reaction.
-chemical test for methyl ketones

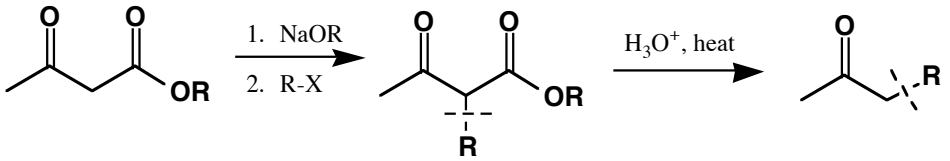
5. 

-Acid-catalyzed halogenation
-can achieve selective mono-halogenation

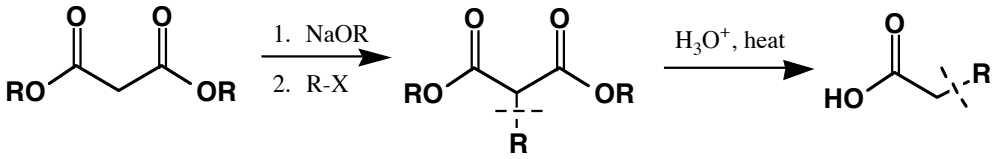
ALKYL HALIDE as ELECTROPHILE

6. 

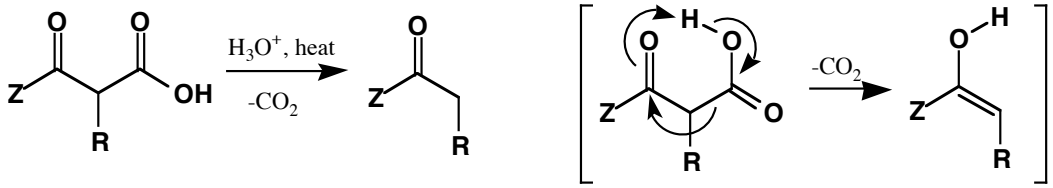
-Enolate alkylation
-strong LDA base required to completely deprotonate carbonyl
-Mech
-Ketones, Esters, Amides, Aldehydes: doesn't matter which kind of carbonyl
-unsymmetrical ketones give isomer problems
-S_N2 alkylation restricts R-X to active ones

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

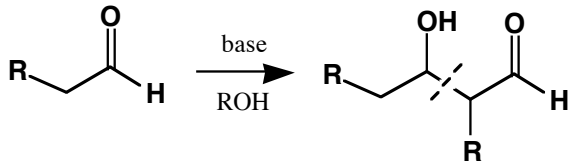
8. 

-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)

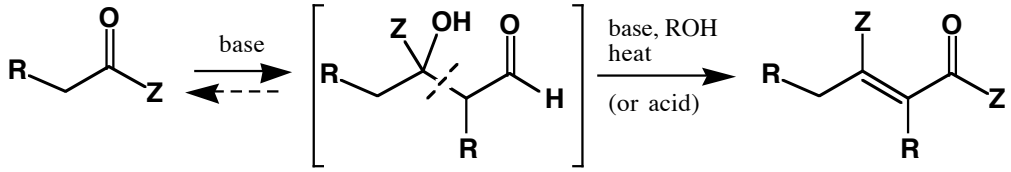
9. 

-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

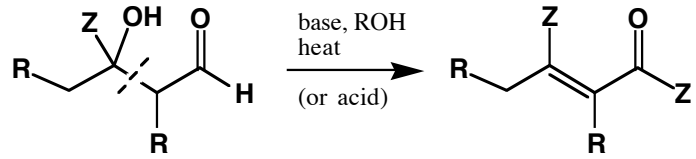
ALDEHYDE/KETONE as ELECTROPHILE

10. 

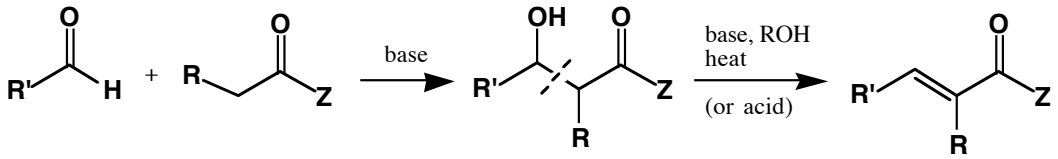
-Aldol Reaction
-Mech

11. 

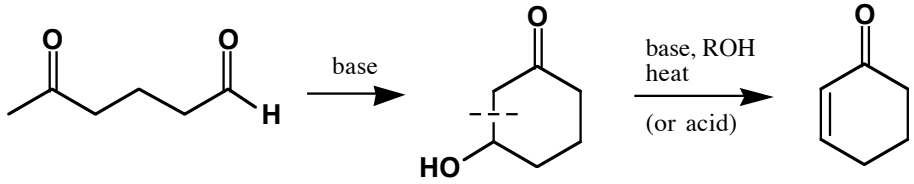
-Aldol Condensation
-Ketones as well as Aldehydes can be used
-In ketone case, unfavorable aldol equilibrium is still drawn off to enone
-In Aldehyde case, can stop at aldol if you don't heat
-Mech

12. 

-Aldol dehydration
-Mech under basic conditions

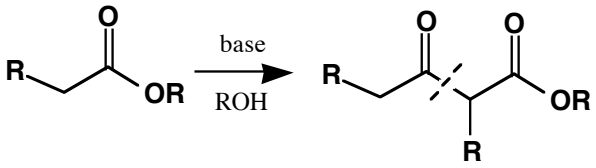
13. 

-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

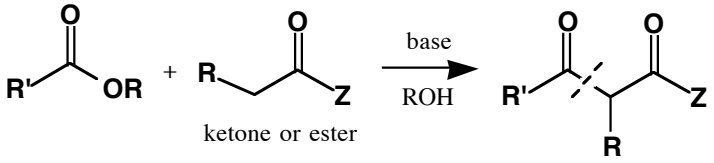
14. 

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

ESTER as ELECTROPHILE

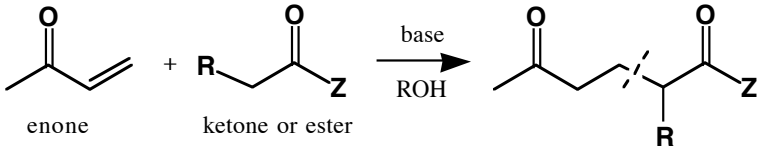
15. 

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

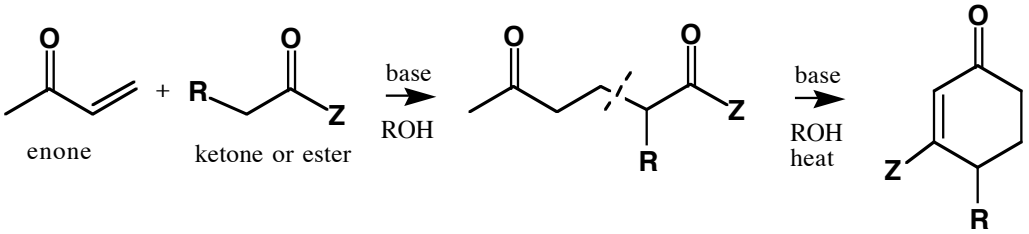
16. 

-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

ENONE as ELECTROPHILE

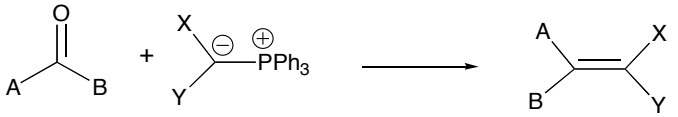
17. 

-Mech
-"Michael Addition"

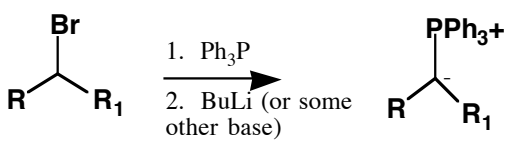
18. 

-"Robinson Annulation"
-Mech
-Michael addition gives 1,5-dicarbonyl, then intramolecular aldol reaction-dehydration

WITTIG REACTION

19. 

-Mech

20. 

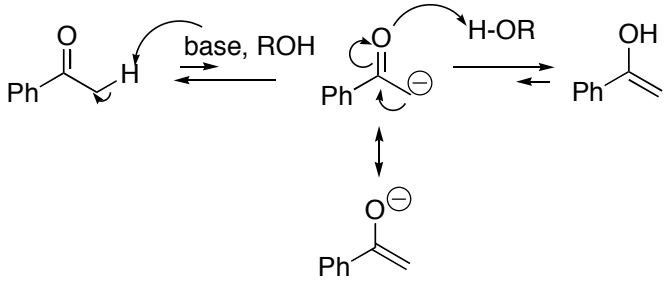
-Mech

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

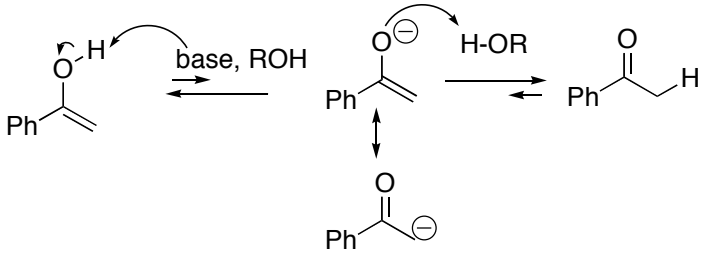
- Note: in many of these reactions, I simply write in "base". But for specific reactions, you need to recognize and specify the actual base that does the work.

PROTON as ELECTROPHILE

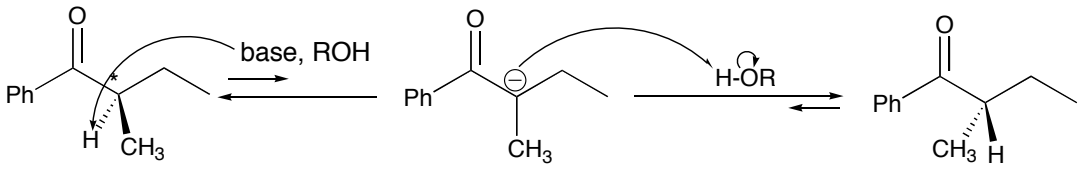
Ketone to Enol

1. 

Enol Back to Ketone:

1.-reverse 

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

2. 

optically active

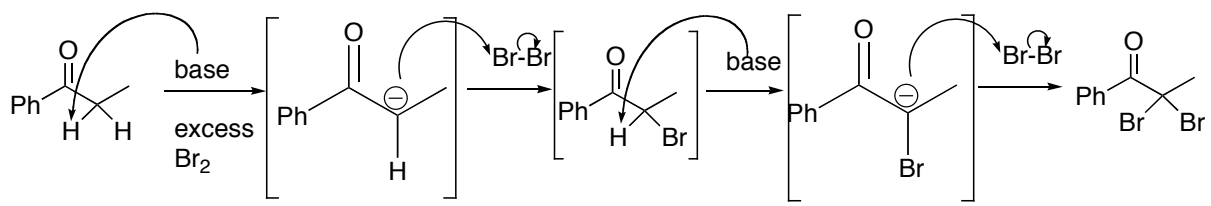
racemic

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

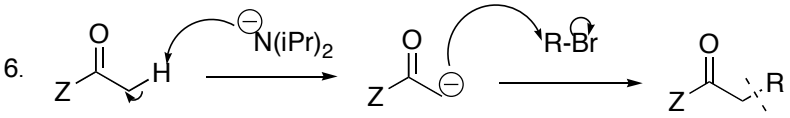
HALOGEN as ELECTROPHILE

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.)

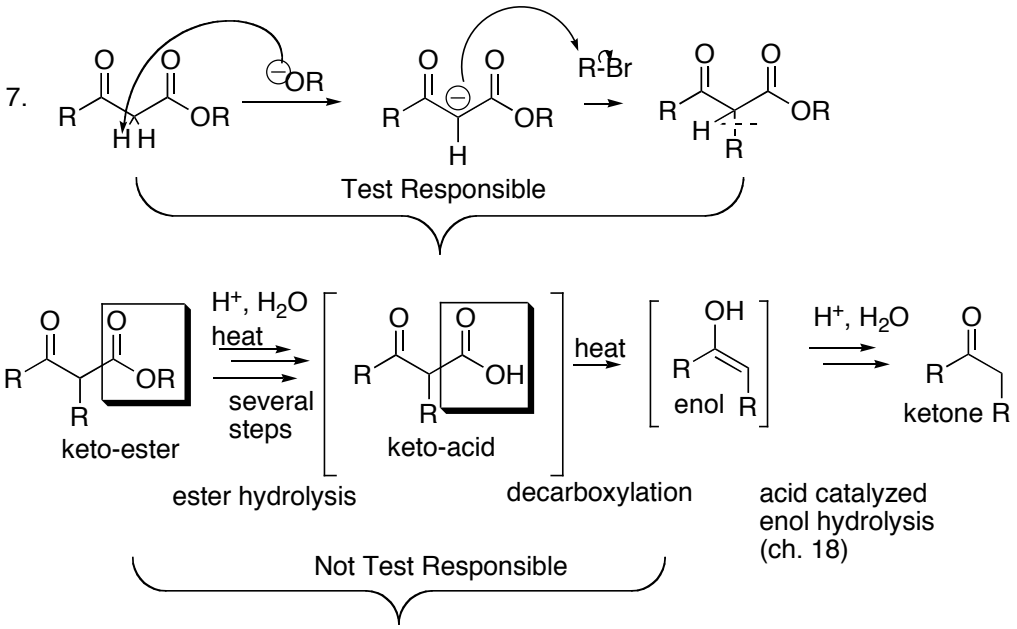
3. 

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

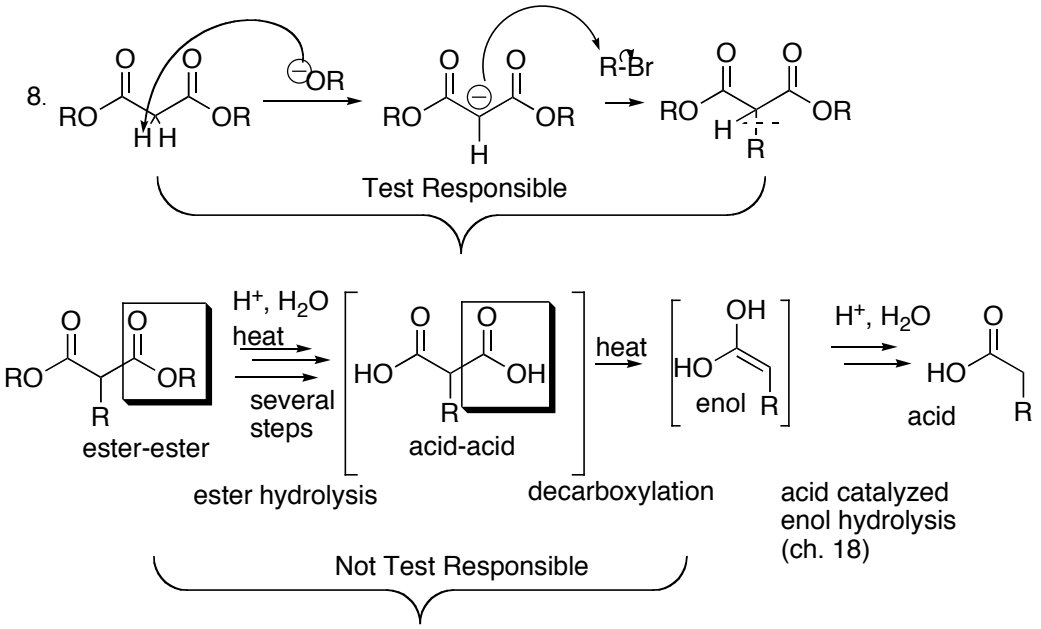
6. 

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)



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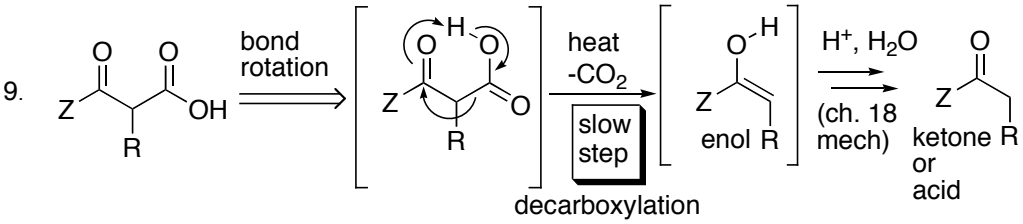
-you are responsible for the acid-catalysis enol hydrolysis (not detailed here, but was in Ch. 18)

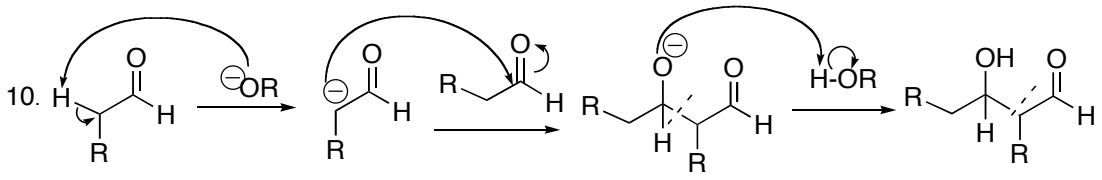


Not Fully Test Responsible. But must know that ENOL is key intermediate that forms in the slow step.
What is good for the enol (and it's alkene) accelerates the decarboxylation

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

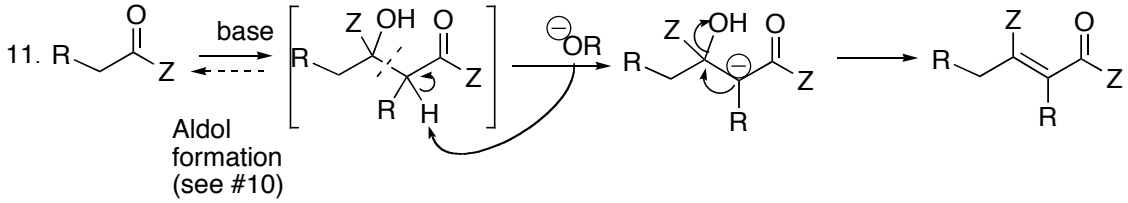
ALDEHYDE/KETONE as ELECTROPHILE

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



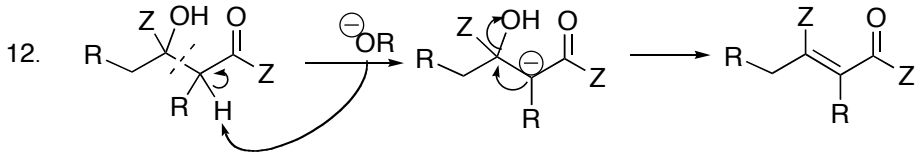
-Deprotonate-react-protonate
-Notice in this case that it's the same carbonyl that functions as both the enolate precursor but also as the electrophile.

Aldol Condensation, giving an enone. In which the initial aldol product undergoes dehydration.



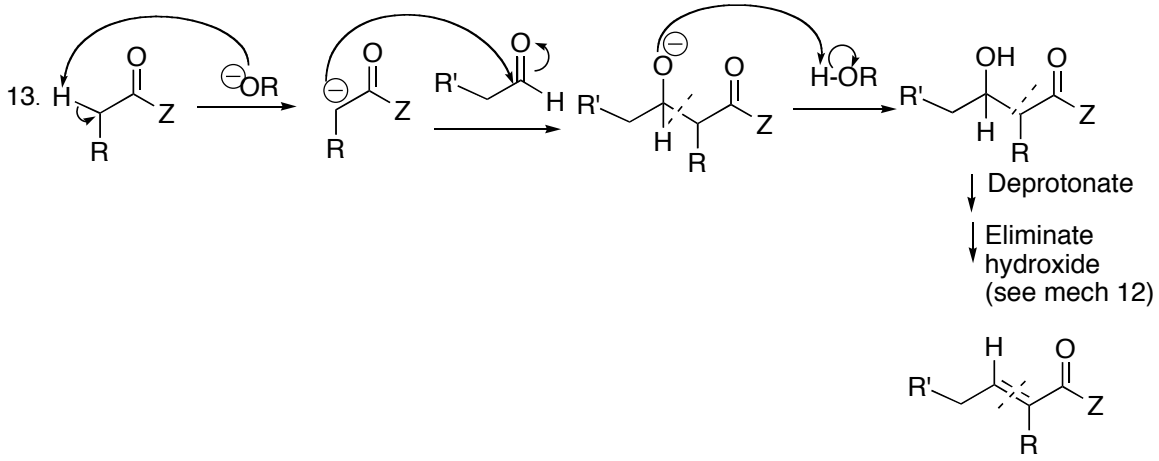
-The aldol product is formed as shown in mechanism 10. But under extended opportunity or heat, the product β-hydroxy group is eliminated to give the enone.
-The elimination mechanism involves deprotonation to enolate, followed by hydroxide extrusion
-Ketones as well as Aldehydes can be used
-In ketone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

General Dehydration of β-hydroxy Carbonyls to Give α,β-unsaturated carbonyls



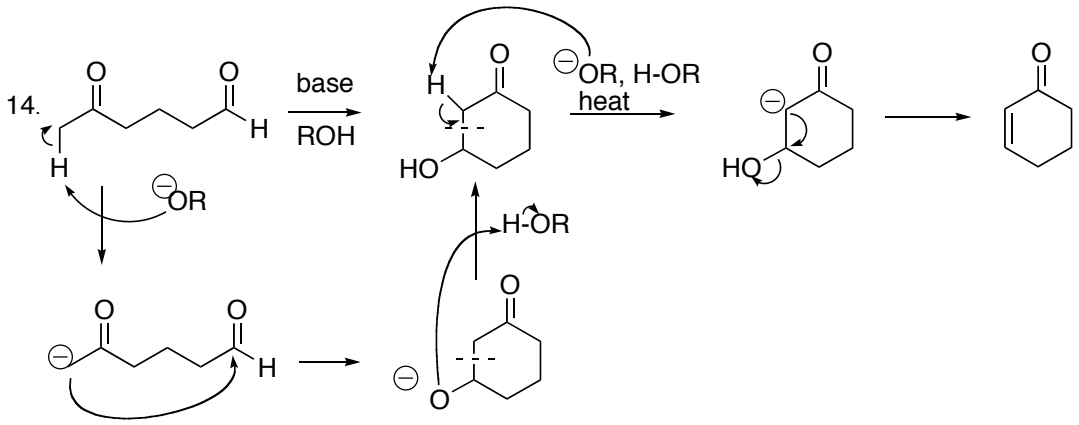
-Aldol dehydration
-Mech under basic conditions
- β-hydroxy Carbonyls can also eliminate water to give enones under acid conditions, via a different mechanism.

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



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

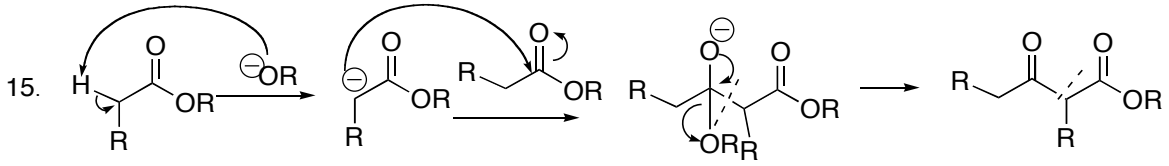
Aldol Cyclization: Basically a crossed aldol reaction in which both carbonyls are tied together, and in which aldol reaction results in formation of a cyclic rather than an acylic β-hydroxy carbonyl



-Intramolecular aldol
-many variations
-Normally only good for 5, 6-membered rings
-There are often multiple α-hydrogens that can give multiple different enolates. But since enolate formation is reversible, reaction proceeds via the enolate that can:
react with the best electrophile. (Aldehyde rather than a ketone), and react to give the best ring size (5 or 6 membered rings >>> 7-membered rings >> 3-, 4-, or ≥8-membered rings)

ESTER as ELECTROPHILE

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

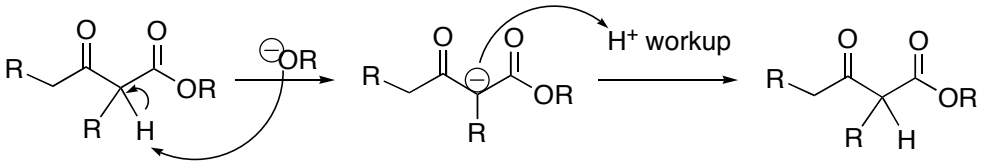
15. 

-Produces 1,3-ketoester

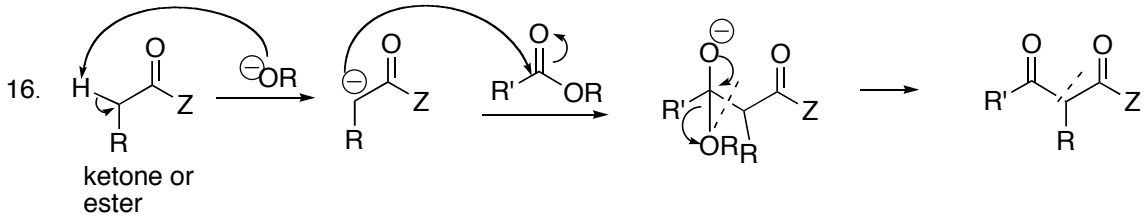
-The alkoxide used as base should match the R-group found in the ester. For example, if the ester OR group is OMe, then the base should be NaOMe/MeOH. If the ester OR group is OEt, then NaOEt/EtOH should be used, etc.

-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. 

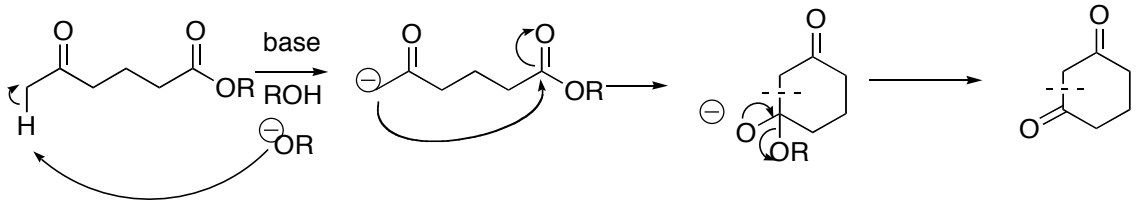
-Crossed Claisen

-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

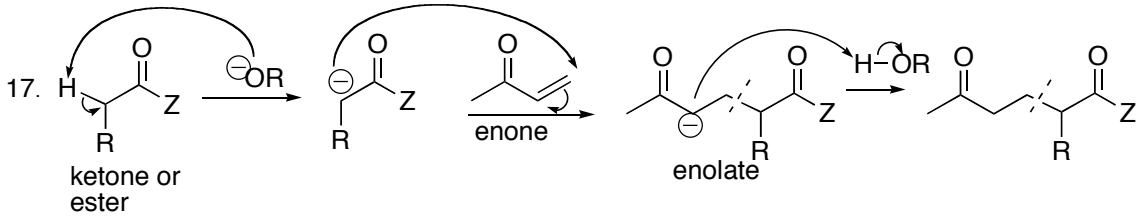
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester. These work best if only one of the esters has α-hydrogens, so that you have just one enolate available.

-May include cyclic Claisen reactions (see example below)



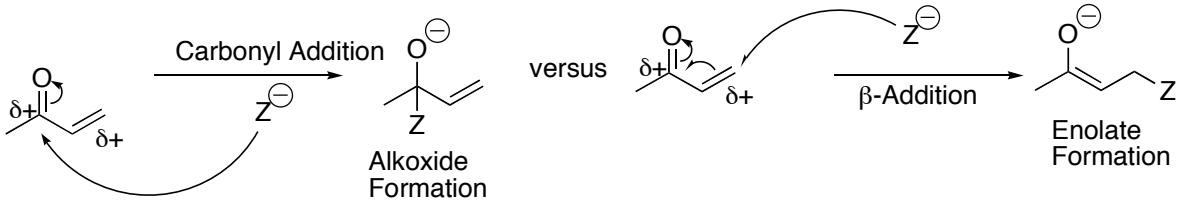
ENONE as ELECTROPHILE

"Michael Addition": in which an enolate adds to the β-carbon on an enone to give a new enolate, and ultimated resulting in a 1,5-dicarbonyl compound.

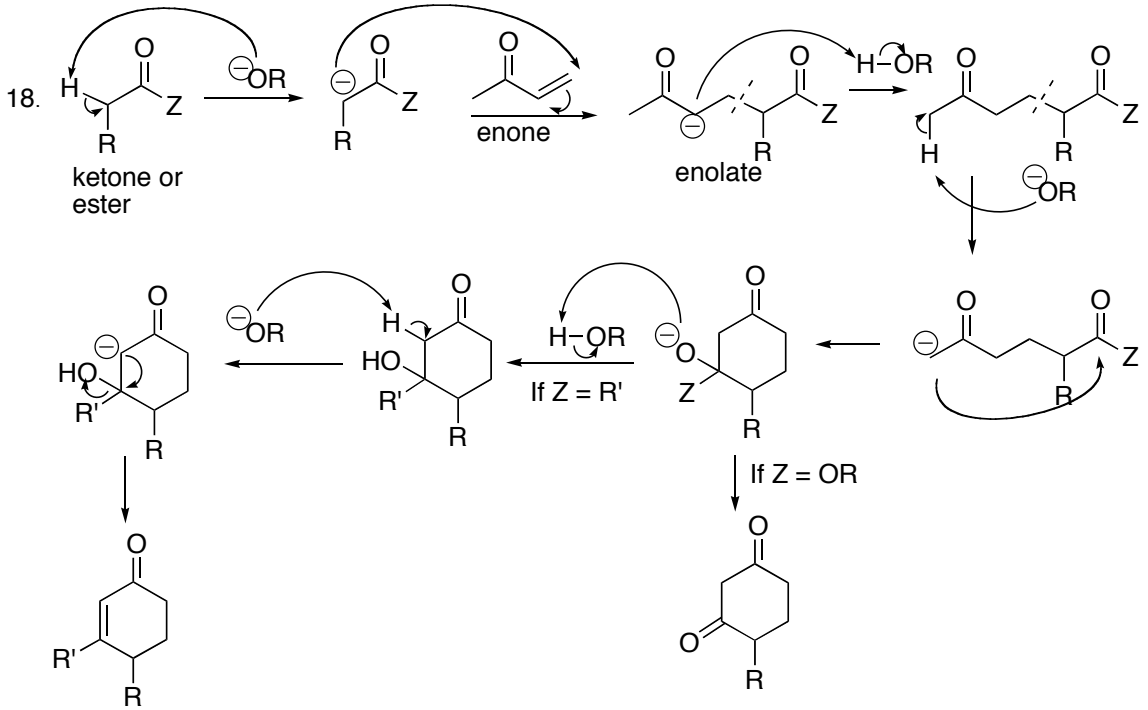


-Enolate addition to the enone's β−carbon results in formation of a new enolate, which is subsequently protonate.

-When nucleophiles attack enones, there is often a competition between carbonyl addition (resulting in alkoxide formatin) versus β−addition (resulting in enolate formation). Which process happens depends on the nucleophile.



"Robinson Annulation": in which Michael addition is followed by a cyclization reaction (either an aldol or a claisen reaction).



-Steps 1-3 = Michael addition.

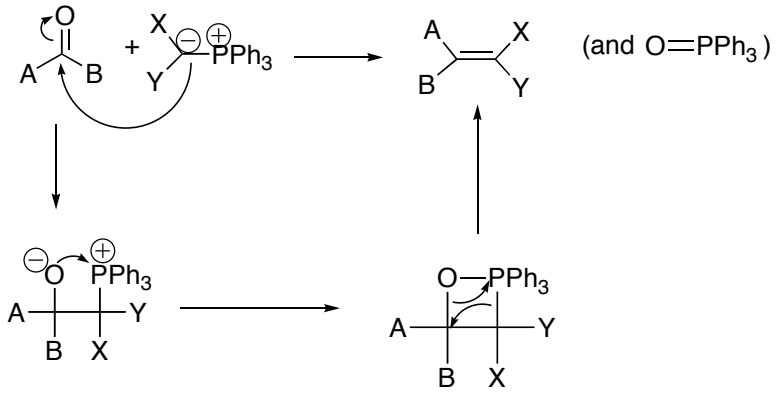
-Steps 4-6 = Aldol reaction (or Claisen reaction, if using an ester)

-Steps 7-8 = Dehydration reaction.

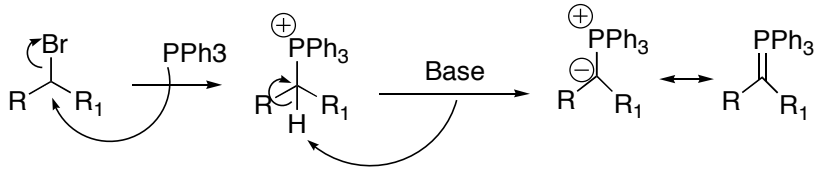
-Enolate chemistry is central to each of these stages!

WITTIG REACTION

19.

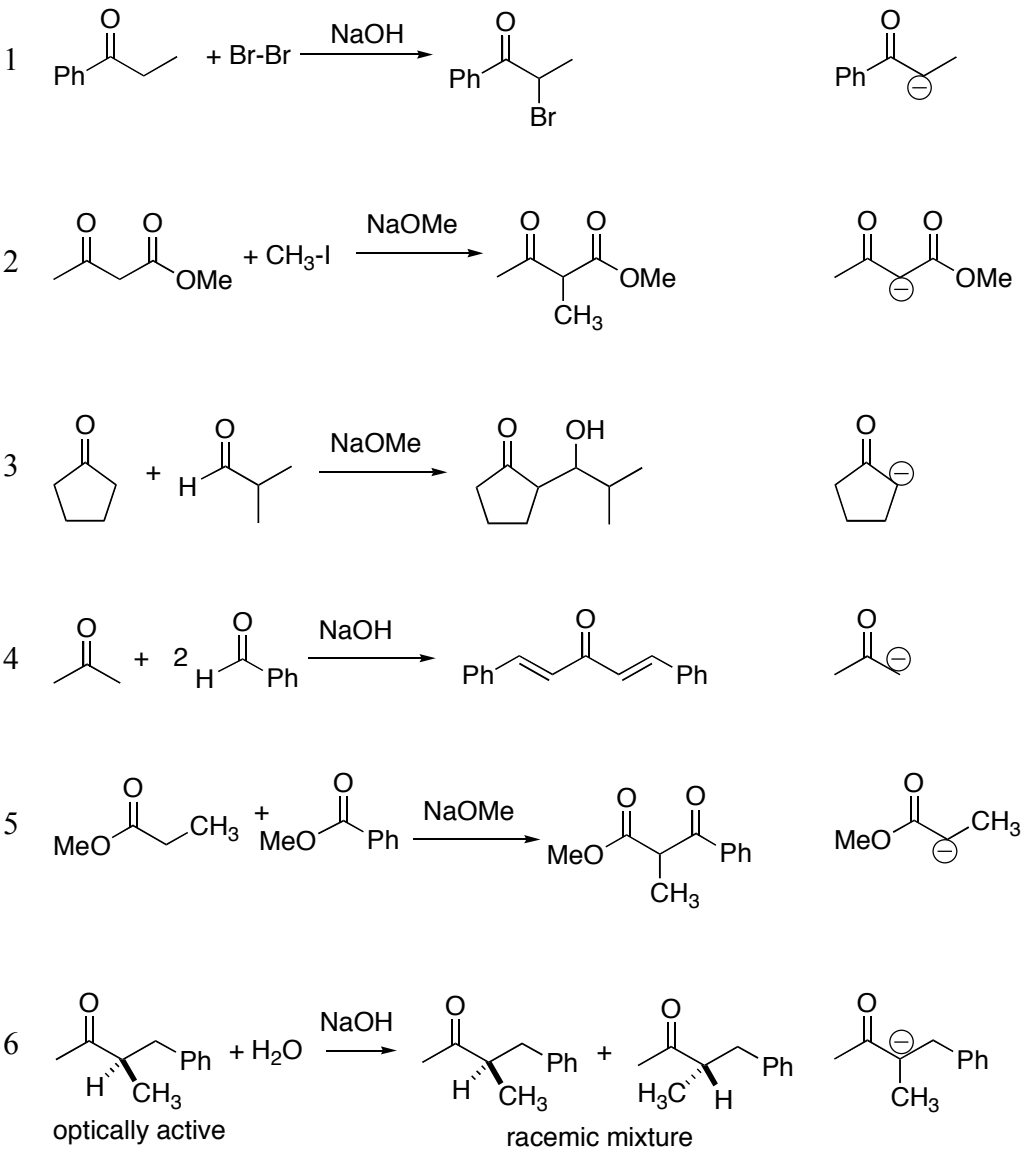


20.



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…

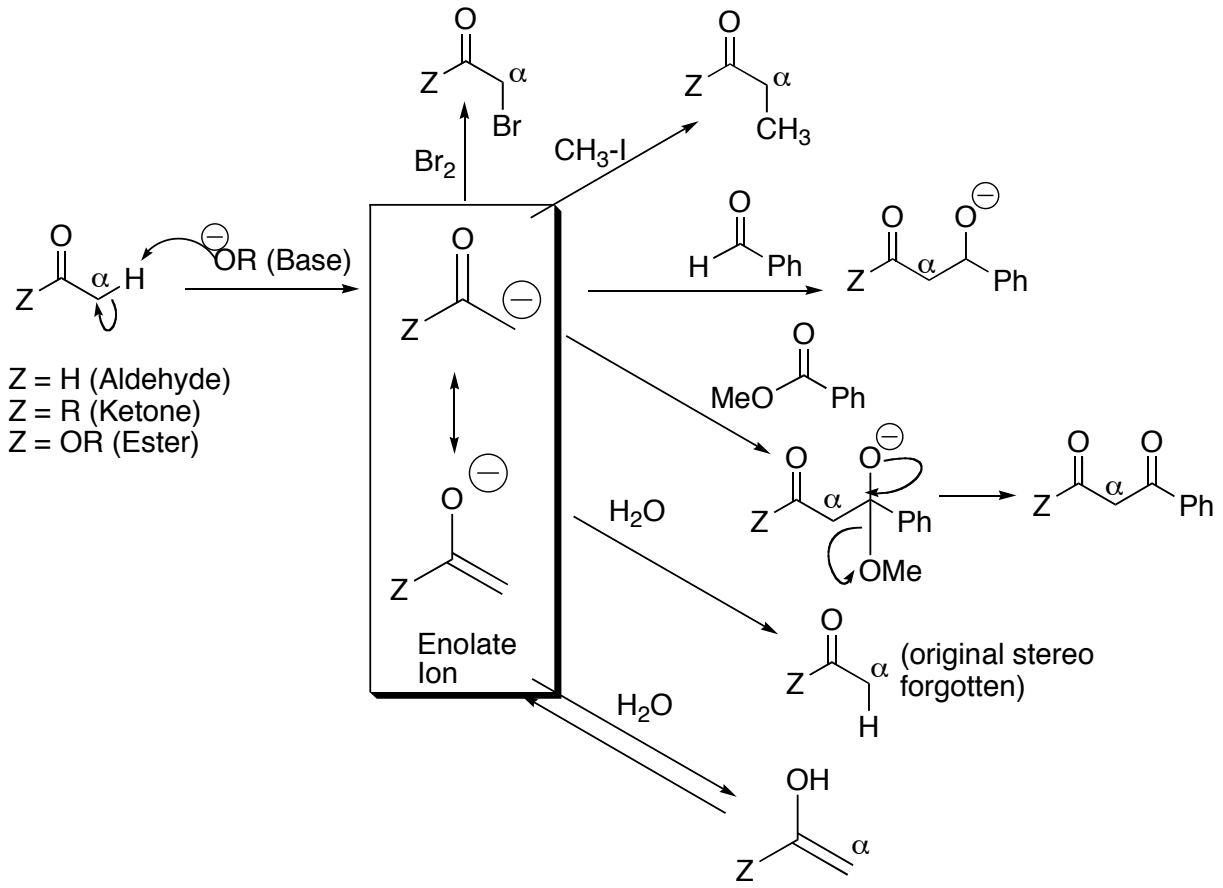


4 Things in Common

KEY: Deprotonation of an α-hydrogen generates ENOLATE anion, which is a good nucleophile

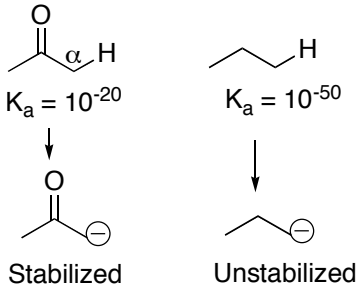
1. **Formation of a bond to the carbon α to a carbonyl**
2. **Basic/anionic reaction conditions**
3. **Involve an electrophile**
4. **At least one H α to a carbonyl is lost**

TYPICAL MECHANISM: Via ENOLATE Anion



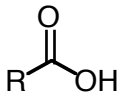
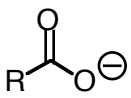
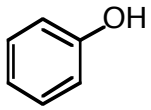
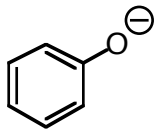
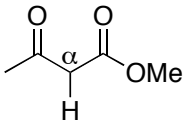
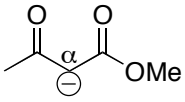
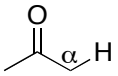
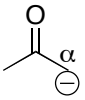
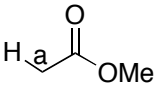
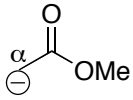
Under base conditions, a carbonyl compound with an α-hydrogen can be deprotonated to give a resonance-stablized, delocalized "enolate" anion, which is nucleophilic at the α-carbon.

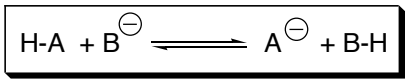
- Normal C-H bonds are very non-acidic. But C-H bonds α to a carbonyl are much more acidic because the resulting anion is resonance stabilized and is shared by the oxygen.



- 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

- **Acidity Table**

Class	Structure	Ka	Acid Strength	Anion	Base Strength
Strong Acids	H-Cl	10^{2}	Max on Top	$Cl^{\ominus}$	Max on Bottom
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}		$RCH_2^{\ominus}$	

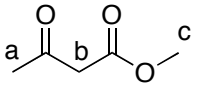


Relative stability of anions dictates equilibrium

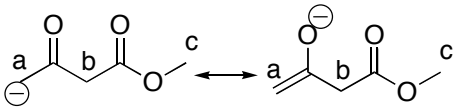
Notes to remember

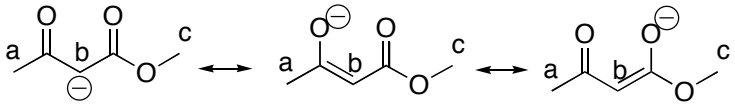
1. Carbonyls acidify α-H's (anion stabilized)
2. 1,3-Dicarbonyls are much more acidic than monocarbonyls (anion is more stabilized)
3. Ketones are more acidic than esters
4. A "lower" anion on the chart can favorably deprotonate any acid that's "higher" on chart. Because any acid-base equilibrium will 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.

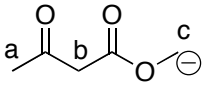
1. Rank the acidity of the hydrogens at the labeled positions, 1 being most acidic. Draw the three anions that would result from deprotionation at the three spots, and any pertinent resonance structures.



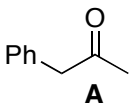
b > a > c

Site a:  Some resonance stabilization

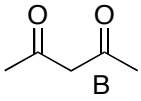
Site b:  Excellent resonance stabilization

Site c:  No resonance stabilization

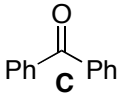
2. For the following compounds, record to what degree they would be deprotonated by $NaOCH_3$ or LDA [$LiN(iPr)_2$] respectively. The basic choices are "totally" (>98%), "zero" (no enolate whatsoever) or "slightly" (definitely some equilibrium amount, but <10%).



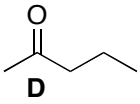
A



B



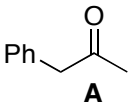
C



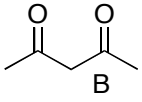
D

LDA:	totally	totally	none (no α-H)	totally
NaOMe:	slightly	totally	none (no α-H)	slightly

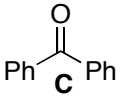
3. For the following compounds, rank them according to which would have the greatest amount of **enol isomer** present at equilibrium, 1 being most enol, 4 being least.



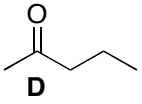
A



B



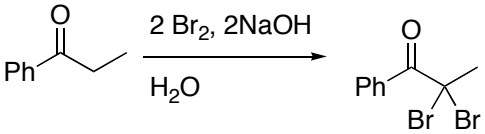
C

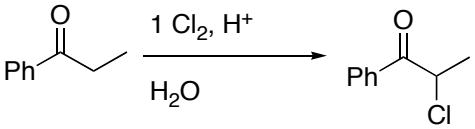


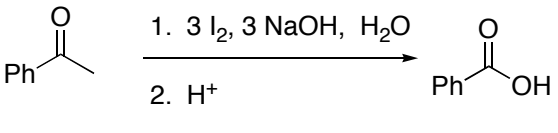
D

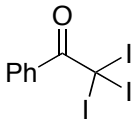
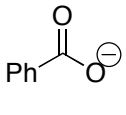
B (enol OH stabilized by H-bonding; enol alkene stabilized by conjugation) > A (enol alkene stabilized by conjugation) > D (no enol stabilization, but at least some enol is possible) > C no enol whatsoever, because no α-hydrogens

4. Draw products for the following reactions

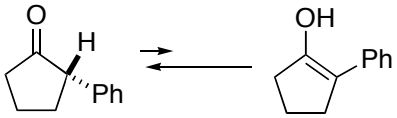






via  and 

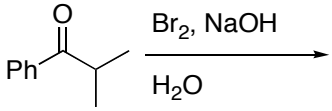
5. Keto-Enol Mechanisms



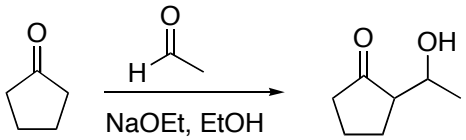
a. Draw the mechanism for conversion of the keto form to the enol form

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

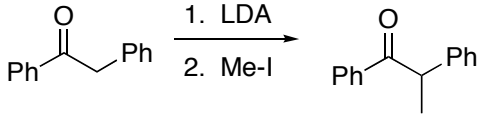
6. Draw the mechanism for the following

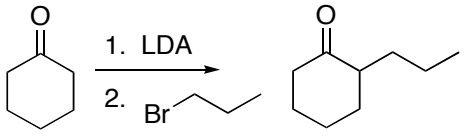


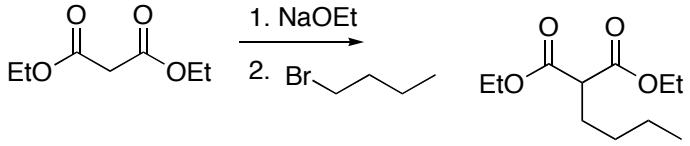
7. Try to draw the mechanism for the following.

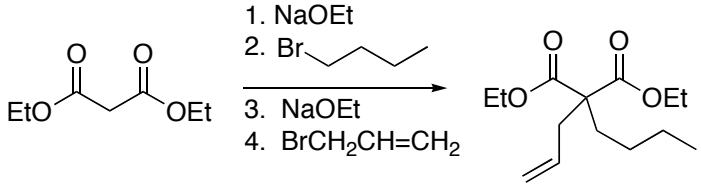


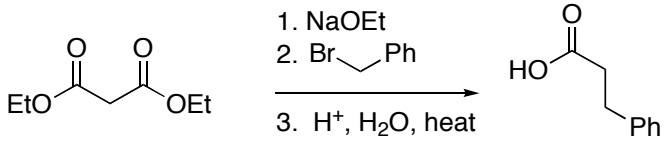
Draw products for the following alkylation reactions, often involving ester hydrolyses and thermal decarboxylations.

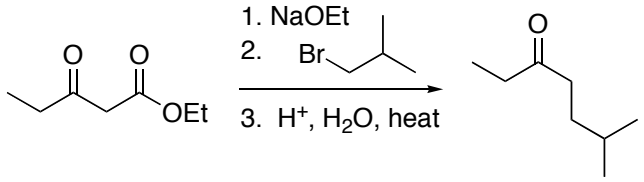
8. 

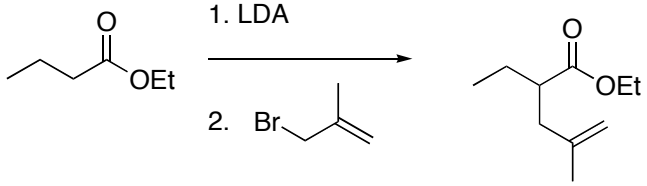
9. 

10. 

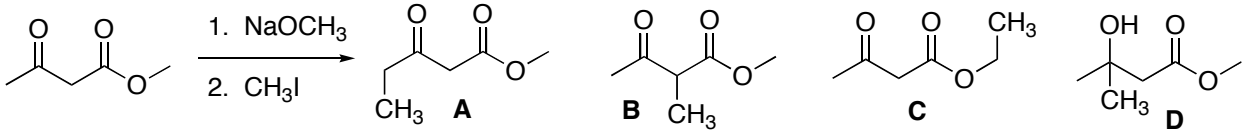
11. 

12. 

13. 

14. 

15. Which of **A, B, C, or D** is the correct product for the following reaction?



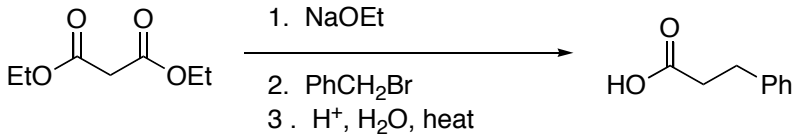
B, via the best enolate

Some Synthetic Strategy Tips

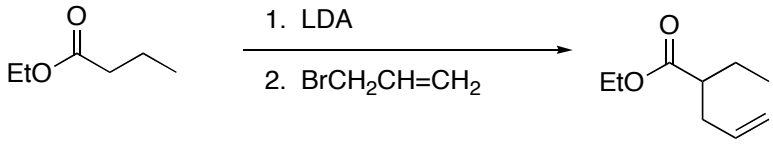
- Alkylation resulting eventually in an **acid**: from 1,3-diester, via NaOR, then subsequent ester hydrolysis/decarboxylation
- Alkylation resulting eventually in a **mono-ester**: from ester using LDA
- Alkylation resulting eventually in a **mono-ketone**, where unambiguous deprotonation was possible: 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:

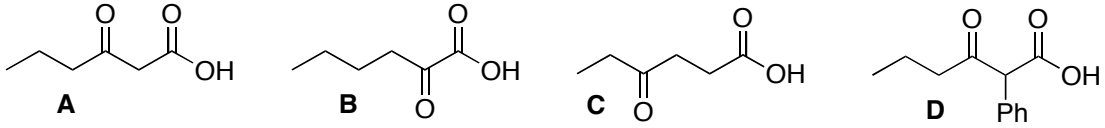
16.



17.

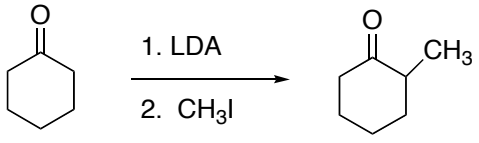


18. Which of the following would undergo decarboxylation? And which would go fastest?



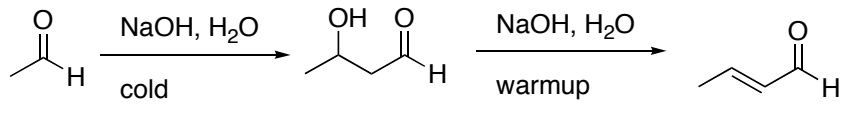
D > A (the 1,3-carbonyl acids that can proceed to enol) B and C won't, not 1,3
D > A because enol produced in rate-determining-step is stabilized by conjugation with the phenyl

19. Draw the mechanism for the following reaction.

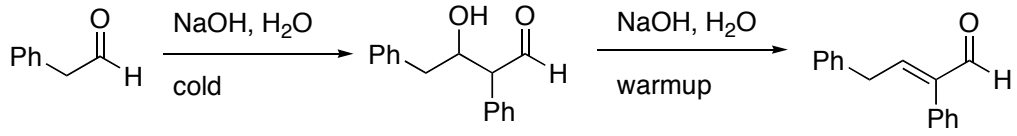


Aldol Examples: Aldehydes/Ketones as Electrophiles

1.

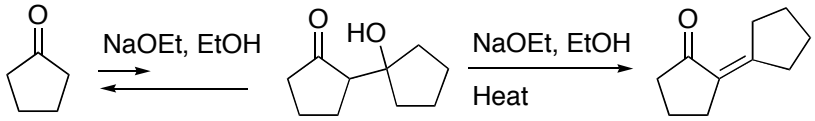


2.



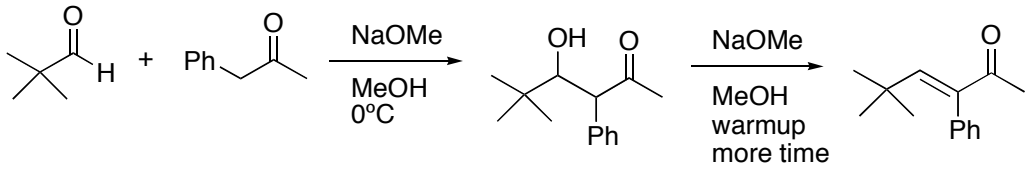
- With aldehydes, you can usually stop at the β-hydroxy carbonyl stage or proceed on to the α,β-unsaturated carbonyl, depending on time and temperature.

3.



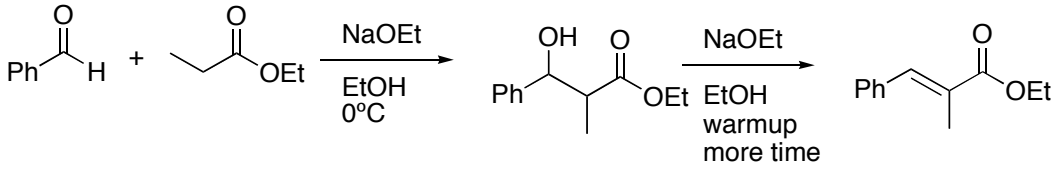
- With ketones as electrophiles, the aldol reaction to give the β-hydroxy carbonyl is normally reversible with an unfavorable equilibrium. However, while it is not possible to isolate high yields of the β-hydroxy ketone, further dehydration to give the enone is irreversible and can give good yields of 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 **<u>the aldehyde will always be the electrophile</u>**
- 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

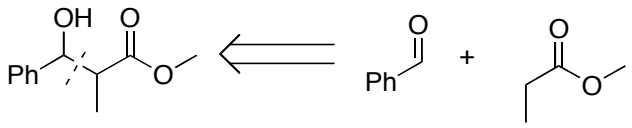
5.



<u>Comments</u>

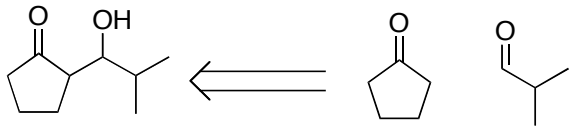
- Basic
- One carbonyl functions as the enolate nucleophile, a second carbonyl as the neutral electrophile. The enolate precursor and the electrophile carbonyl may be the same (examples 1-3) or different (examples 4 and 5)
- Loss of an α-H, replaced by an α,β C-C bond.

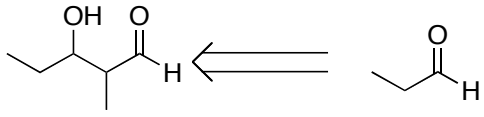
All of the following molecules can be made by an aldol-type reaction or an aldol-type condensation (aldol followed by loss of H_2O). Draw the carbonyl compound or compounds from which each is derived.

example: 

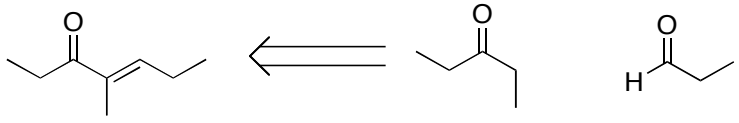
Strategy:

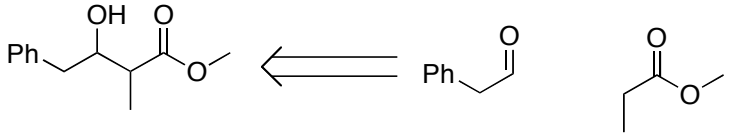
- Identify the carbonyl in the product, and mark off which are the α and β carbons. **The key bond connection will have been between the α and β carbons**.
- β was originally a carbonyl (the electrophile carbonyl)
- α originally had H's (it was the enolate carbanion)
- Note: **any attachments on the α and β carbons are spectators**. If they are there at the end, they must have been attached at the beinning!

20. 

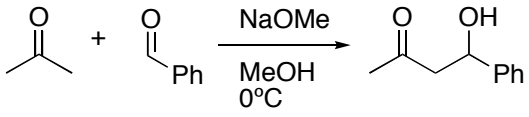
21. 

(both enolate precursor and electrophile)

22. 

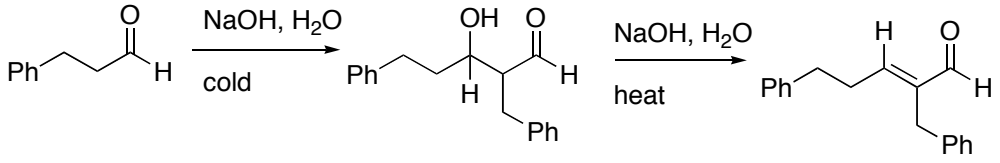
23. 

24. Draw the mechanism for the following reaction.

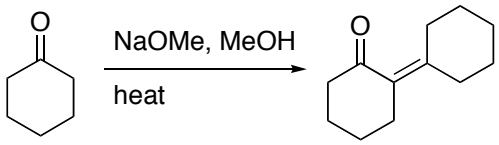


Provide products for the following aldol reactions.

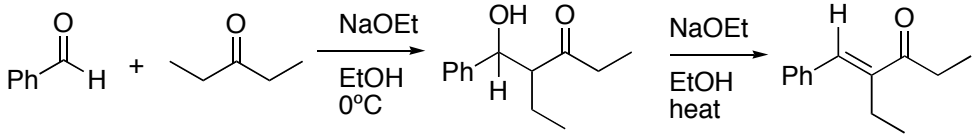
25.



26.



27.



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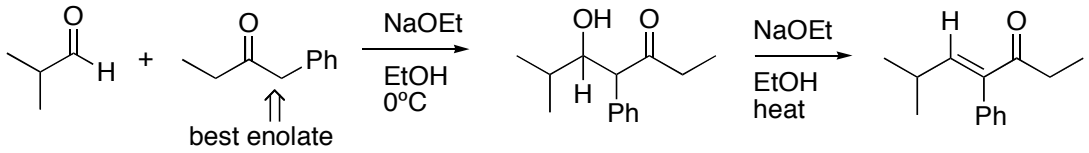
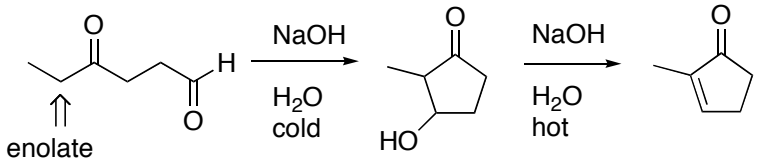


29.



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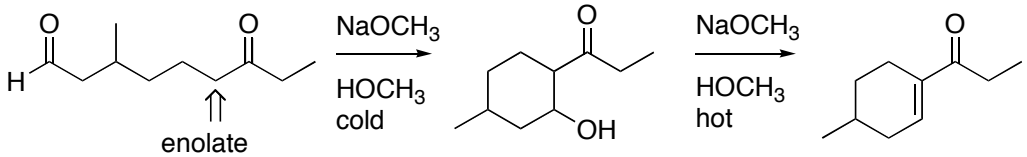
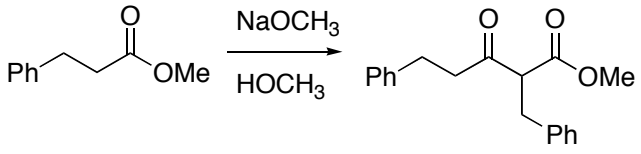
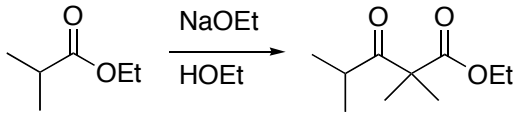
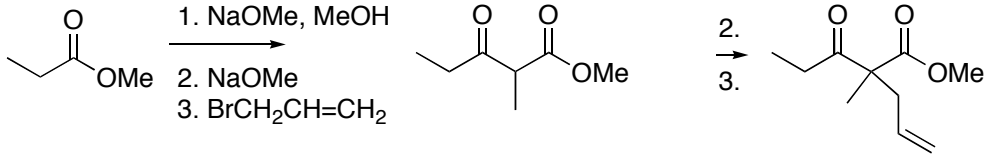


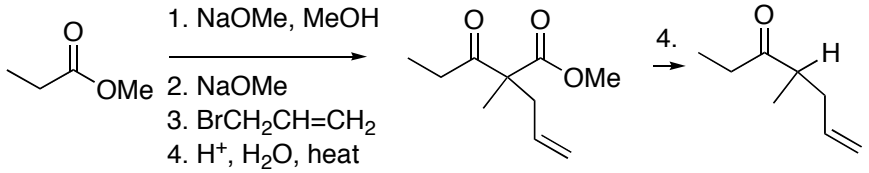
31. Draw the mechanism for phase one and then phase two of the reaction in problem 28.

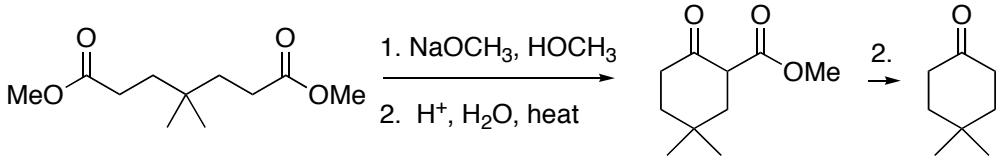
Provide products for the following Claisen reactions.

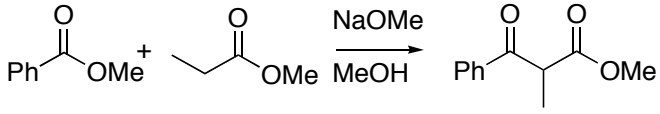
32. 

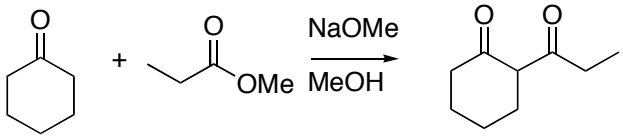
33. 

34. 

35. 

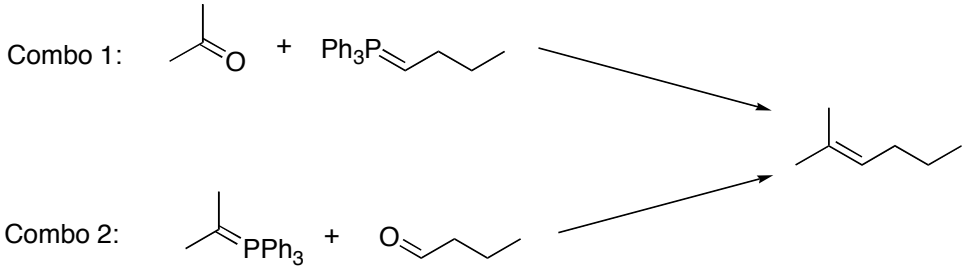
36. 

37. 

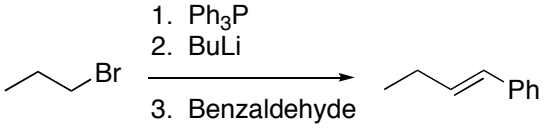
38. 

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

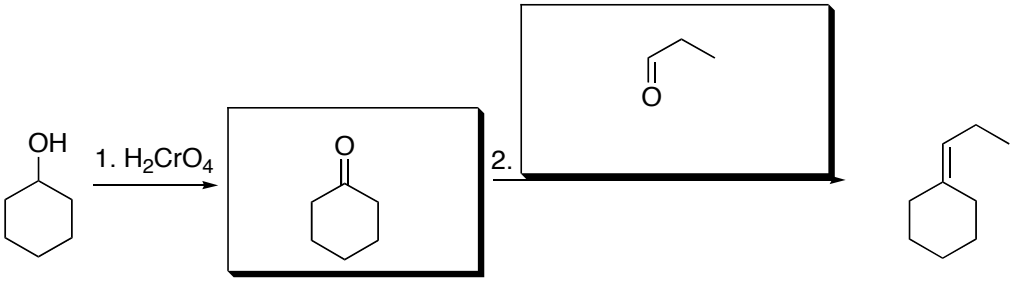
39.



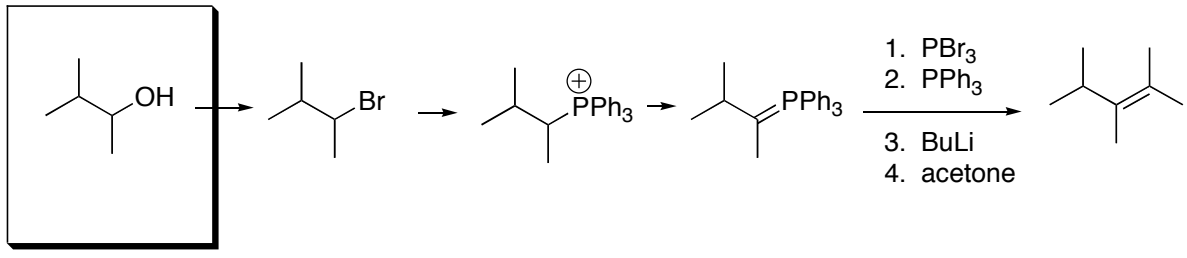
40.



41.



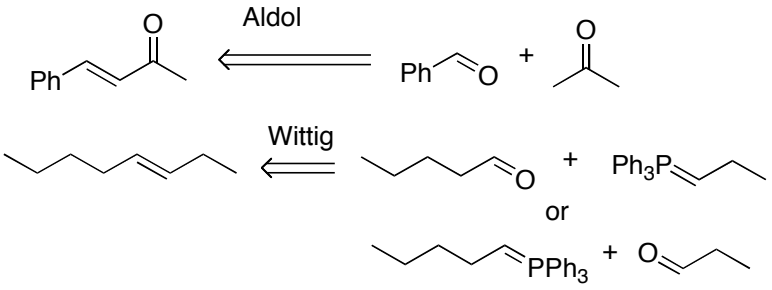
42.



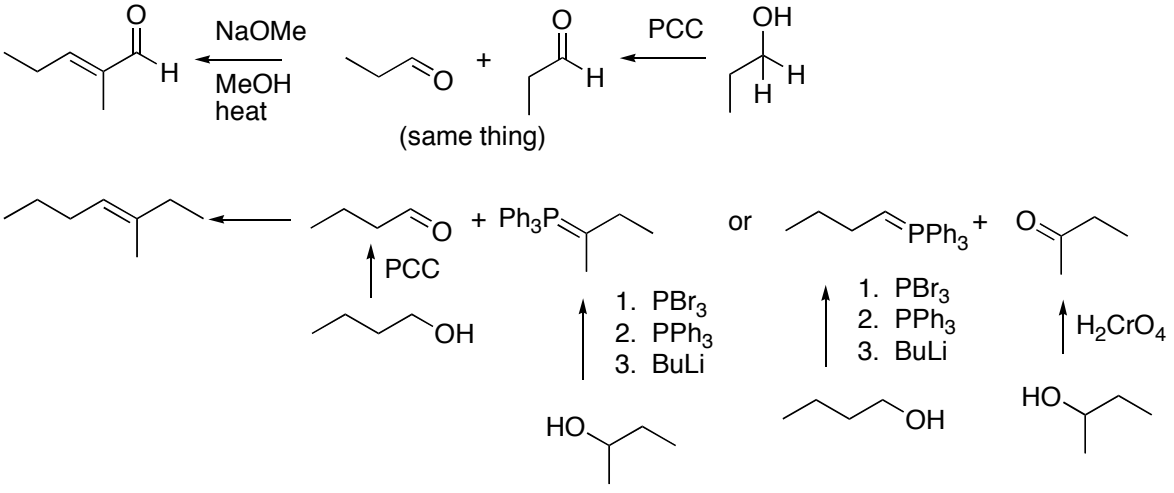
General Routes to Make Alkenes

- **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.

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

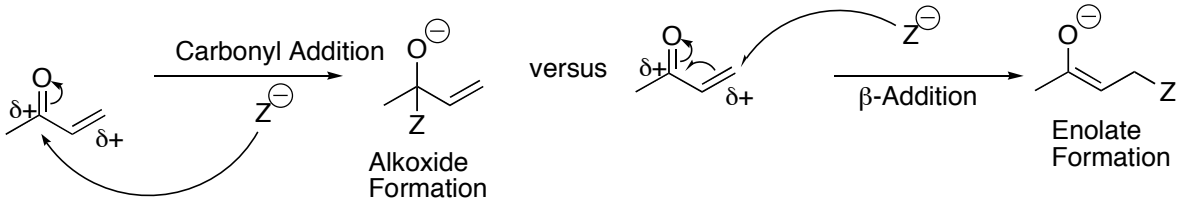


44. Synthesis design. Design syntheses of the following products, starting from **alcohols of 4 carbons or less**. Some key reminder reactions:
    - PCC for oxidizing 1° alcohols to aldehydes
    - H_2CrO_4 for oxidizing 2° alcohols to ketones
    - PBr_3 for converting 1° or 2° alcohols to bromides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



General: Enones as Electrophiles. Nucleophiles that attack enones must chooe between:

- Carbonyl addition
- β-Addition

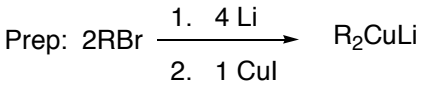


Carbonyl addition normally dominates with:

- RMgBr
- RLi
- $NaBH_4$
- $LiAlH_4$
- LiCCR

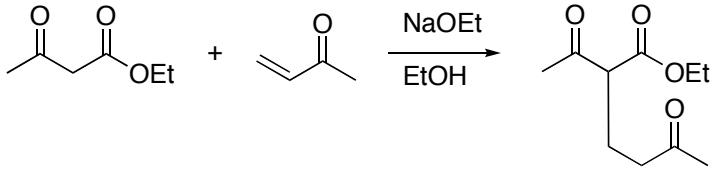
β- addition normally dominates with:

- enolates of dicarbonyls
- sometimes enolates of monocarbonyls (but not always)
- Cuprates (R_2CuLi)

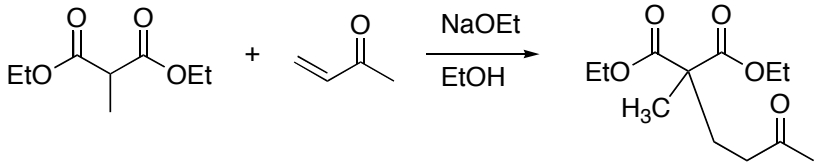


Draw the Products for the following Michael reactions

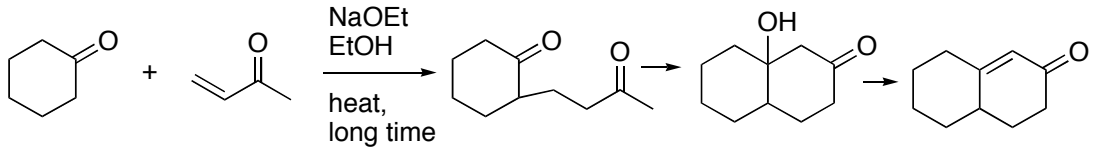
45.



46.

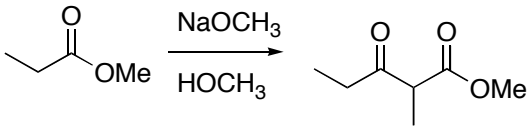


47.

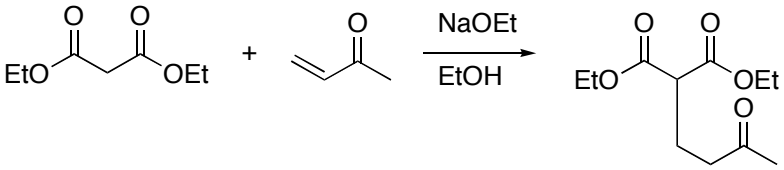


-draw in the initial product, second product, and third product

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



49. Draw the mechanism for the following reaction (Michael reaction).



50. Draw the mechanism for the following reaction. (Robinson cyclization, involving sequential Michael reaction, aldol reaction, β–hydroxyketone dehydration.)