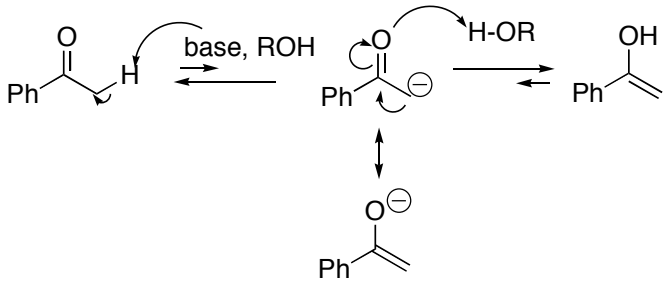
Chem 360-Jasperse **Chapter 22 (Enolate Chemistry) Reaction Mechanisms Summary**

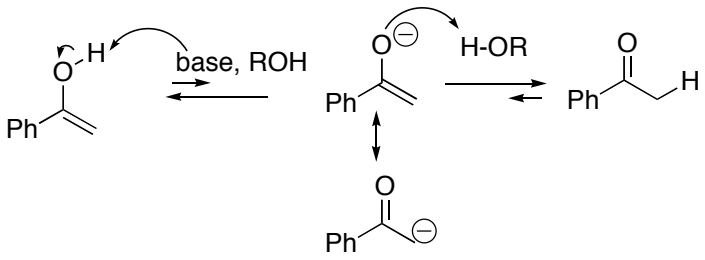
- Note: in many of these reactions, I simply write in "base". But for specific reactions, you need to recognize and specify the actual base that does the work.

PROTON as ELECTROPHILE

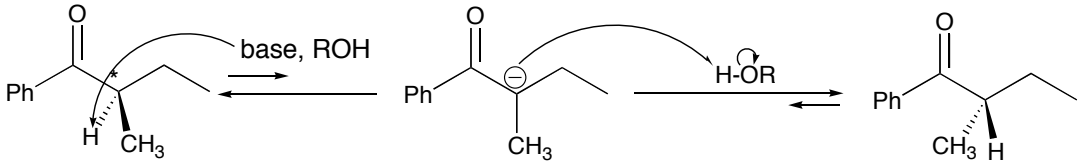
Ketone to Enol

1. 

Enol Back to Ketone:

1.-reverse 

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

2. 

optically active

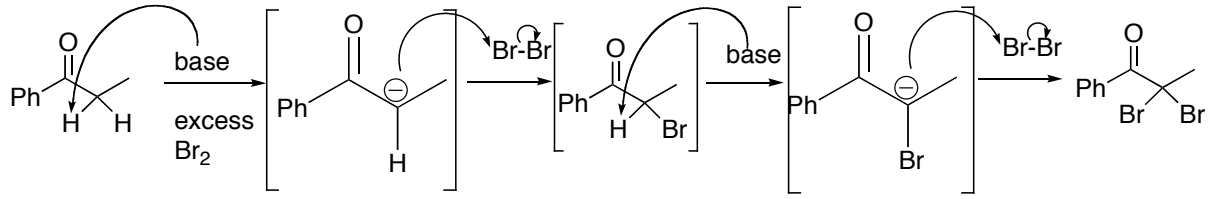
racemic

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

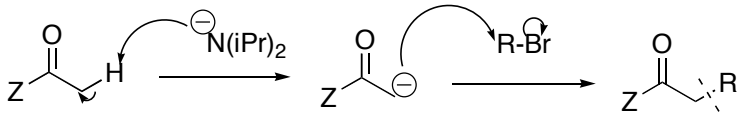
HALOGEN as ELECTROPHILE

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.)

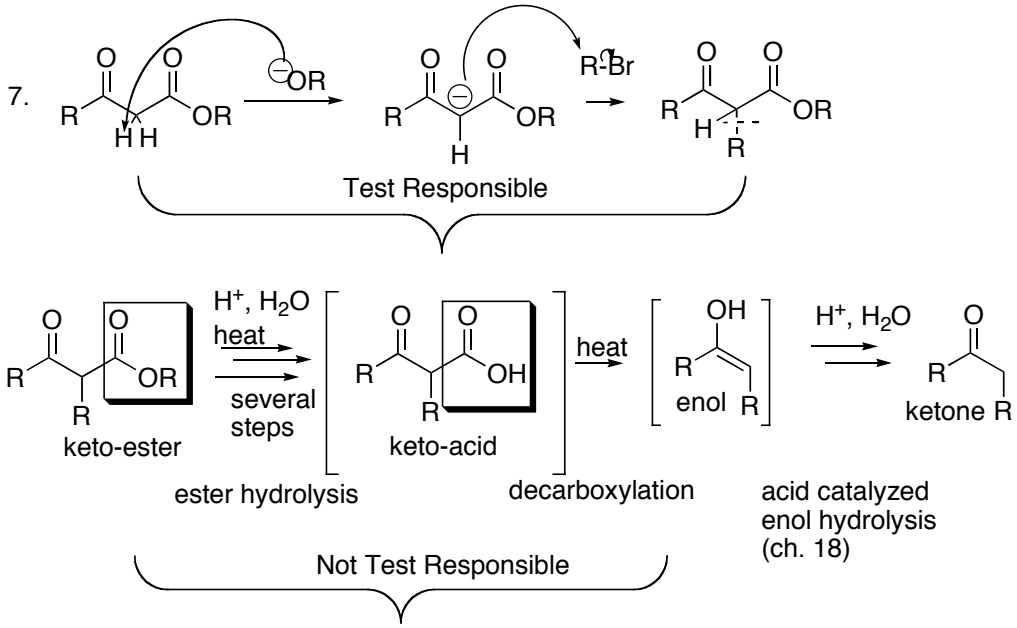
3. 

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

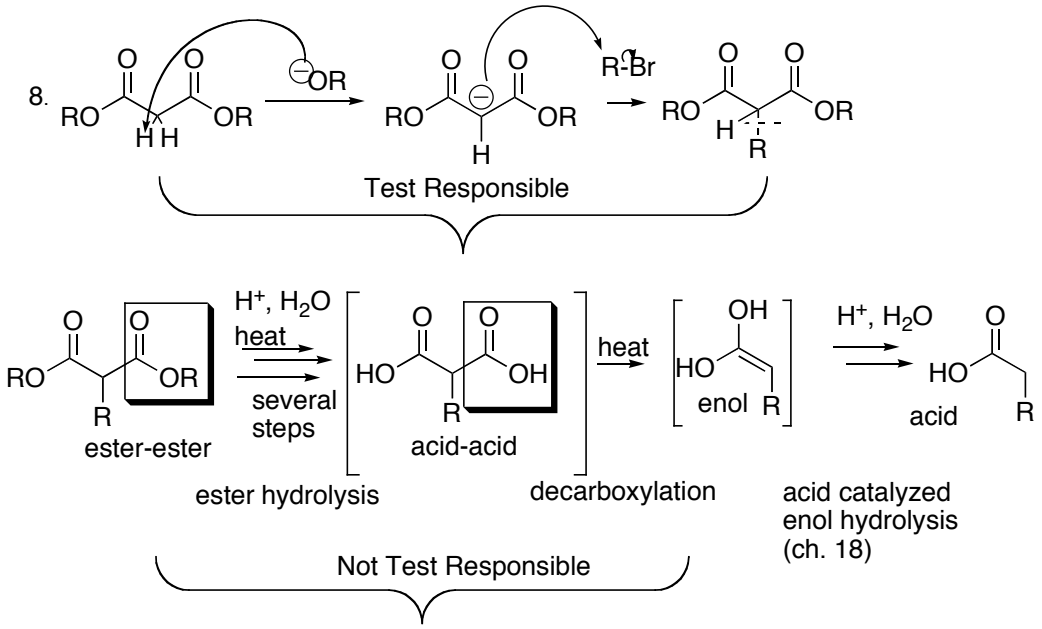
6. 

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)



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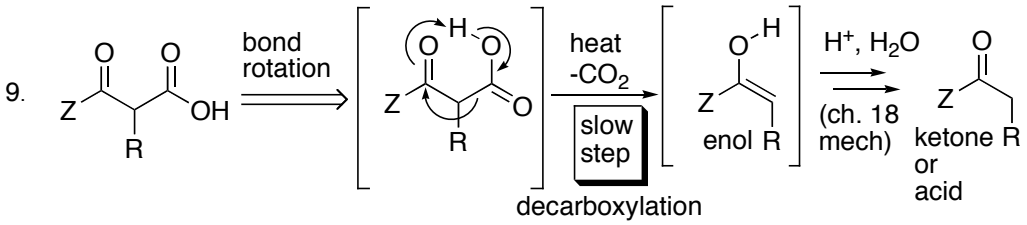
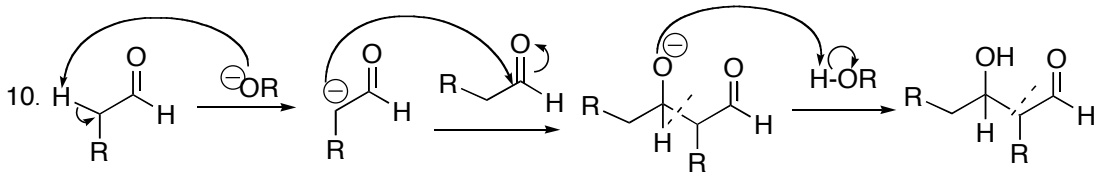


Not Fully Test Responsible. But must know that ENOL is key intermediate that forms in the slow step.
What is good for the enol (and it's alkene) accelerates the decarboxylation

-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

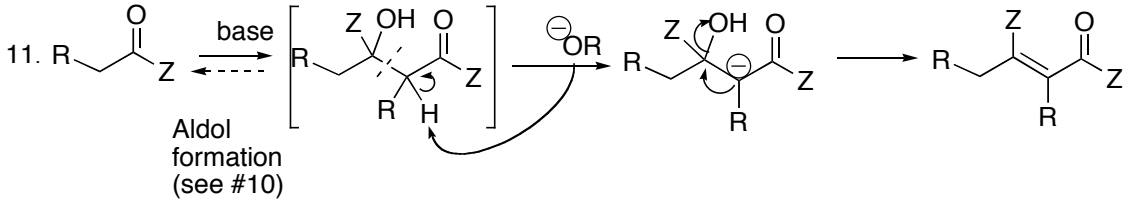
ALDEHYDE/KETONE as ELECTROPHILE

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



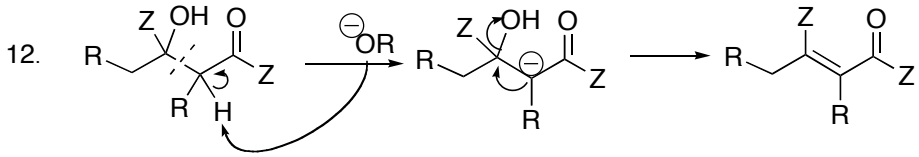
-Deprotonate-react-protonate
-Notice in this case that it's the same carbonyl that functions as both the enolate precursor but also as the electrophile.

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



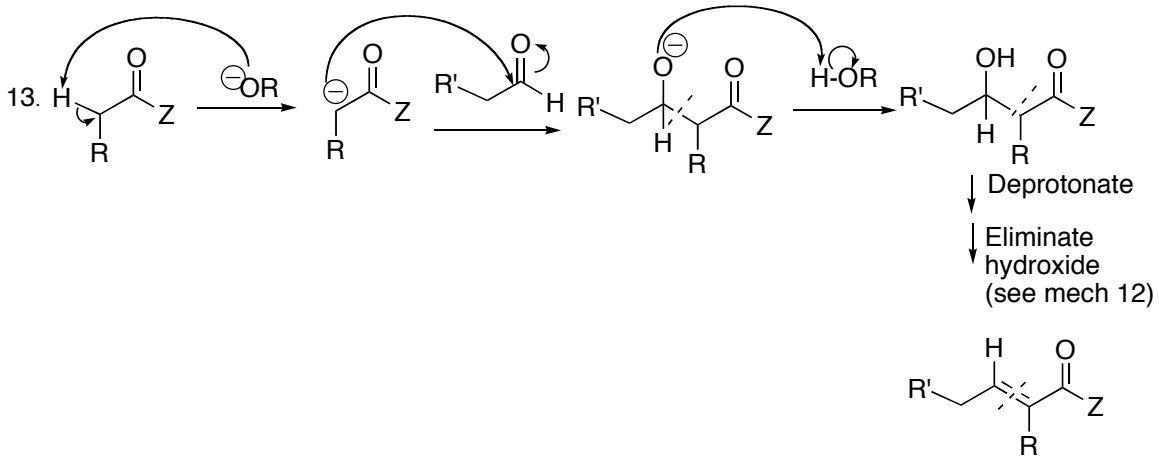
-The aldol product is formed as shown in mechanism 10. But under extended opportunity or heat, the product β-hydroxy group is eliminated to give the enone.
-The elimination mechanism involves deprotonation to enolate, followed by hydroxide extrusion
-Ketones as well as Aldehydes can be used
-In ketone 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



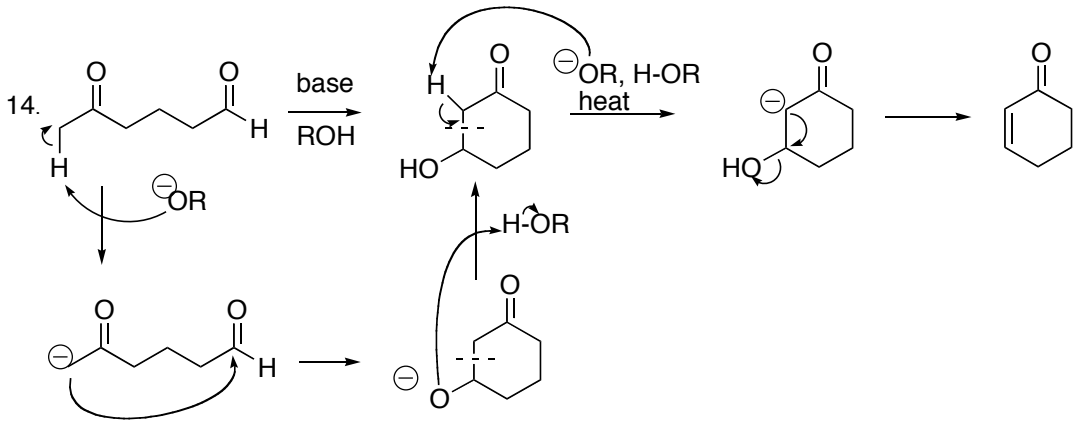
-Aldol dehydration
-Mech under basic conditions
- β-hydroxy Carbonyls can also eliminate water to give enones under acid conditions, via a different mechanism.

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.

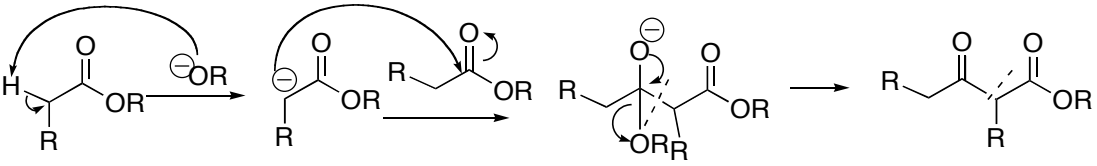
Aldol Cyclization: Basically a crossed aldol reaction in which both carbonyls are tied together, and in which aldol reaction results in formation of a cyclic rather than an acylic β-hydroxy carbonyl



-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.

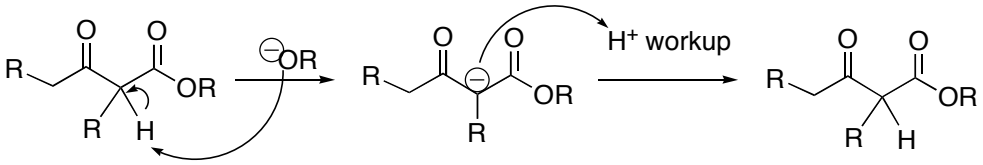
15. 

-Produces 1,3-ketoester

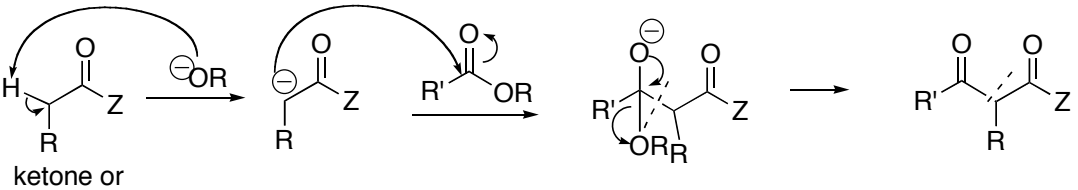
-The alkoxide used as base should match the R-group found in the ester. For example, if the ester OR group is OMe, then the base should be NaOMe/MeOH. If the ester OR group is OEt, then NaOEt/EtOH should be used, etc.

-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. 

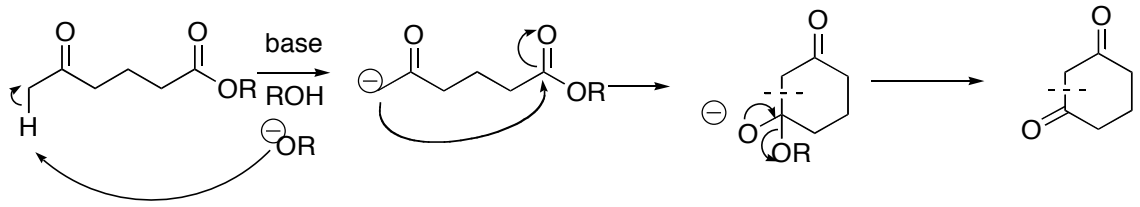
-Crossed Claisen

-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

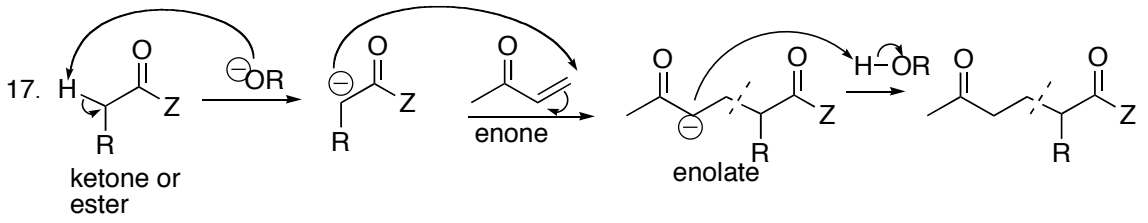
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester. These work best if only one of the esters has α-hydrogens, so that you have just one enolate available.

-May include cyclic Claisen reactions (see example below)



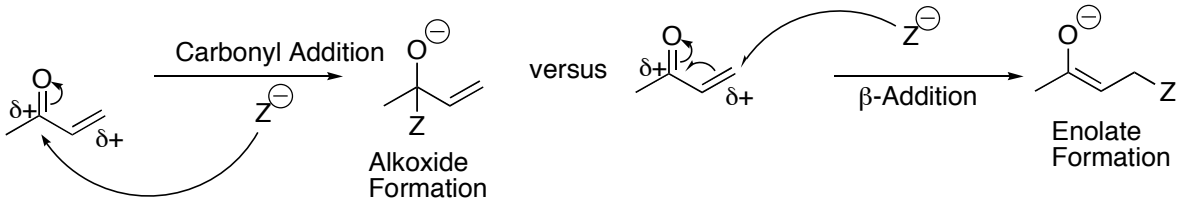
ENONE as ELECTROPHILE

"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.

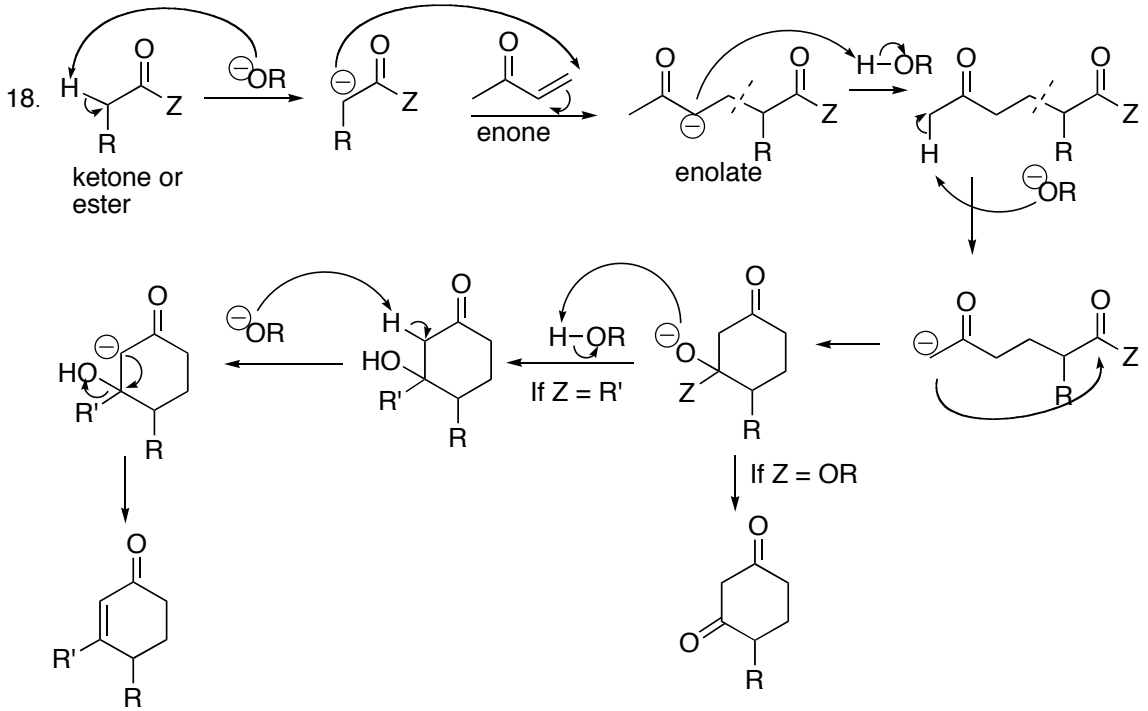


-Enolate addition to the enone's β–carbon results in formation of a new enolate, which is subsequently protonate.

-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.

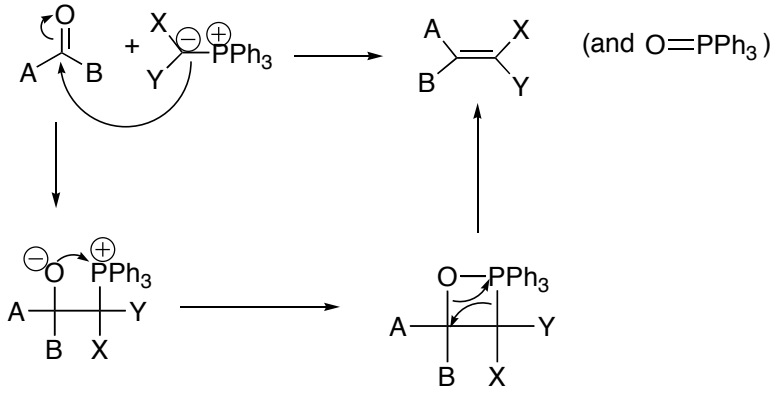
-Steps 4-6 = Aldol reaction (or Claisen reaction, if using an ester)

-Steps 7-8 = Dehydration reaction.

-Enolate chemistry is central to each of these stages!

WITTIG REACTION

19.



20.