

File:Dream Team Basketball 1992 Olympic Games Barcelona.jpg

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Michael



Robinson

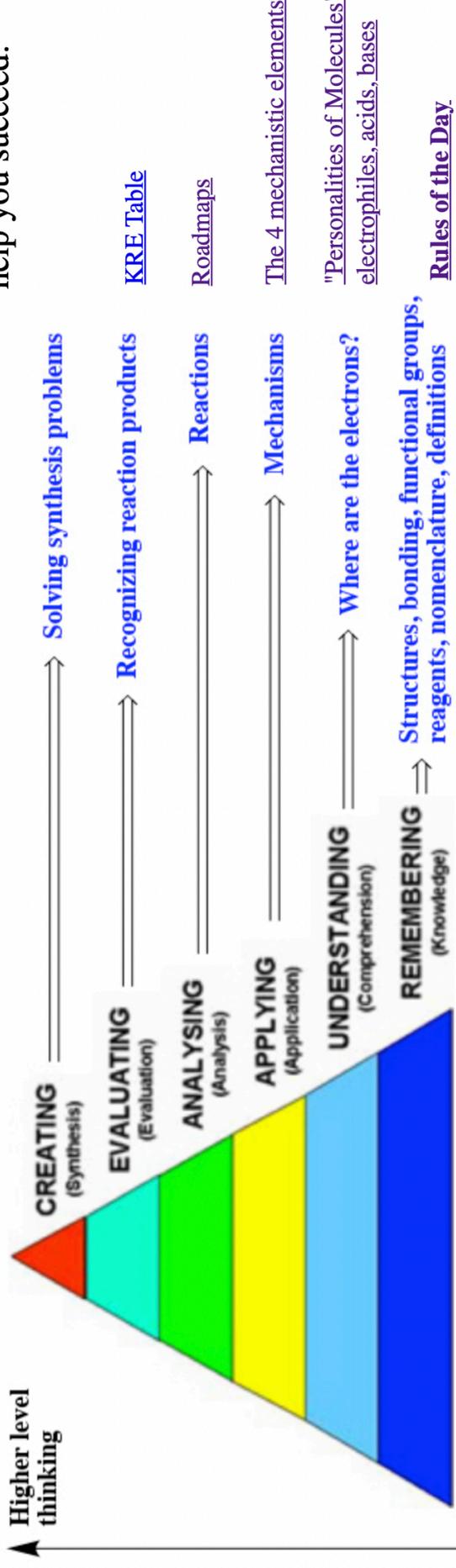
Iverson



Bloom's Taxonomy of Learning

Organic Chemistry Analog

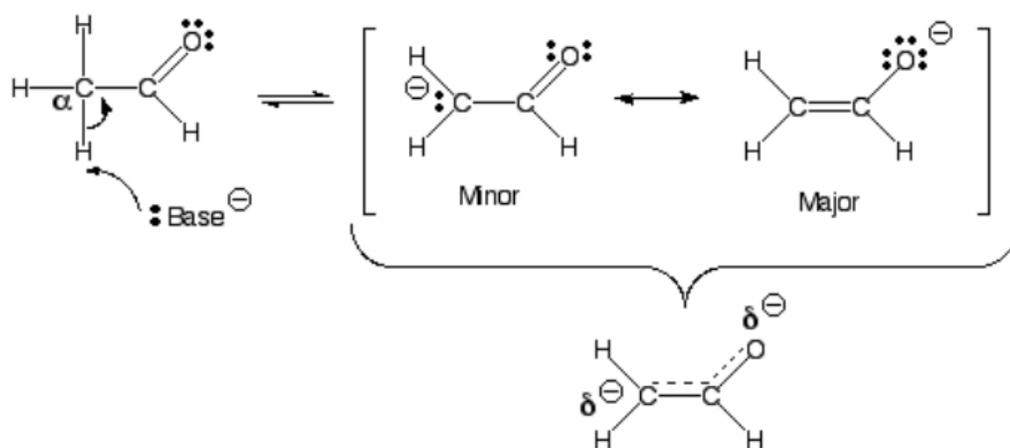
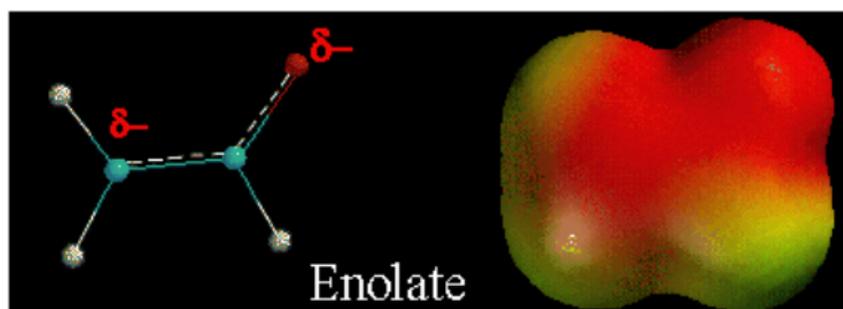
Tools we created to help you succeed:



Organic chemistry is difficult because it requires higher order thinking. According to Bloom's taxonomy of learning, the lowest level of learning involves pure memorization ("Remembering"). As one moves up the pyramid to higher learning, understanding, applying, analysing, evaluating and creating are reached. I believe there are Organic chemistry analogs of all of these, culminating in synthesis which involves creativity along with all of the other levels of thinking. It is likely that many of you have never been challenged all the way to the top of the Bloom's taxonomy of learning pyramid before, explaining why this feels different and disorienting. **DO NOT GIVE UP.** As shown on the right, we have created tools to help you master each step up the ladder. On the above diagram you can click on the tools listed to go directly to them. Also, if you have any questions about how to study, [click here to read about the way I learned to study.](#) I never earned a grade lower than an A after I started using this method during my own college career.

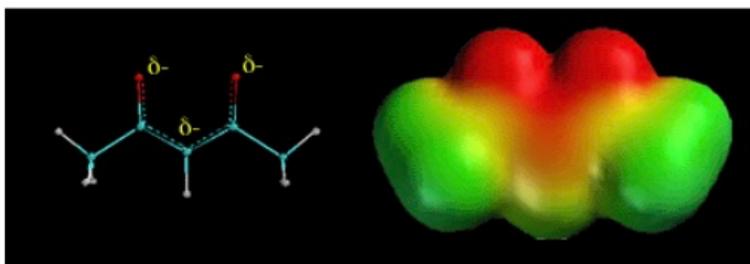
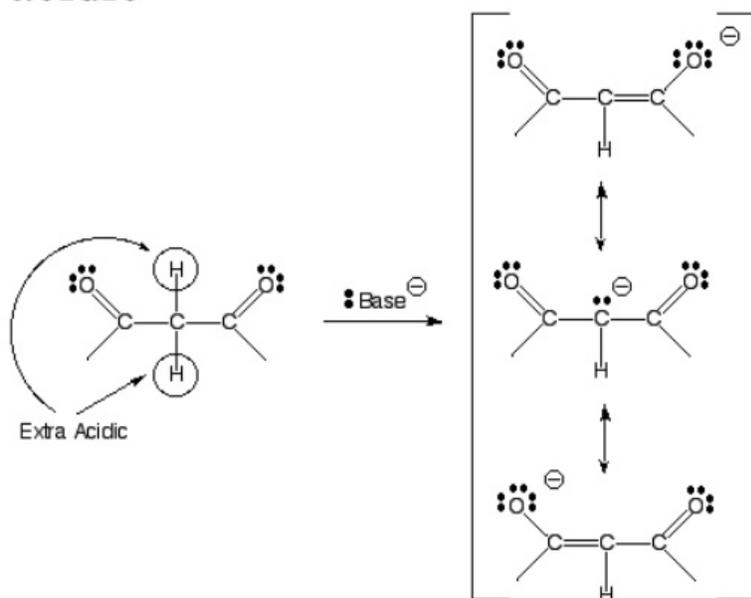
I understand that most of you are headed to the health professions, so you may be wondering if mastering synthesis problems will be important for you. I assert that it is. Solving a synthesis problem involves the detailed evaluation of a complex molecule while looking for KREs, then working backwards to the starting materials by analyzing possible reactions involved by thinking through your roadmaps, possibly applying your understanding of mechanism to make sure you predict the correct product for each reaction. This is the exact type of thinking you will need to diagnose a patient. A patient will present various complex combinations of symptoms, then you must evaluate which of these are important, then analyze, apply and understand how the patient got that way and how to get them back to their starting state (healthy) again. In other words, you will learn the "KREs of diagnosis" then work backwards to understand what happened to the originally healthy patient! Therefore, learning how to solve synthesis problems will teach you how to use higher level thinking skills, exactly the kind you will need to develop as a health care professional!

Enolates as nucleophiles



- A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.
- B) Enolates are nucleophiles, so they could react at either the carbon atom or oxygen atom. The partial negative charges give them the **opportunity** to react at either the carbon or oxygen.
- C) Reaction at the carbon atom gives the final product a C=O bond, while reaction at the oxygen atom gives the final product a C=C bond. However, C=O bonds are stronger than C=C bonds, **so the motive is to react at the carbon atom with most electrophiles.**

Beta-dicarbonyls have alpha-hydrogens that are extra acidic



The C-H hydrogen atoms between two carbonyl groups are even more acidic than normal alpha hydrogens because the resulting anion is double resonance stabilized. The above electrostatic potential surface shows how the negative charge (red color) is spread over all three atoms as predicted by the three resonance contributing structures.

Weaker bases are favored at equilibrium

Compound	pK _a	Strongest Acid (Weakest conjugate base)	
H-Cl	-7	←	
Carboxylic acids* R-CO-H	3-5		
β-Dicarbonyls* R ¹ C(=O)-CH ₂ -C(=O)-R ²	10		
β-Ketoesters* R ¹ C(=O)-CH ₂ -C(=O)-OR ²	11		
β-Diesters* R ¹ O-C(=O)-CH ₂ -C(=O)-OR ²	13		
Water HOH	15.7		
Alcohols RCH ₂ OH	15-19		
Acid chlorides* RCH ₂ -COCl	16		
Aldehydes* RCH ₂ -CHO	18-20		
Ketones* RCH ₂ -C(=O)-R ¹	18-20		
Esters* RCH ₂ -C(=O)-OR ¹	23-25		
Terminal alkynes RC≡C-H	25		
LDA H-N(i-C ₃ H ₇) ₂	40		
Terminal alkenes R ₂ C=C-H	44		
Alkanes CH ₃ CH ₂ -H	51		Weakest Acid (Strongest conjugate base)

A) Reactions are favored (i.e. have a motive) if they lead to formation of a weaker acid and/or weaker base.

B) Checking pK_a values can predict if a reaction has a motive even if there are other steps besides a proton transfer.

C) Recall that the conjugate base of a stronger acid (lower pK_a) is a weaker base.

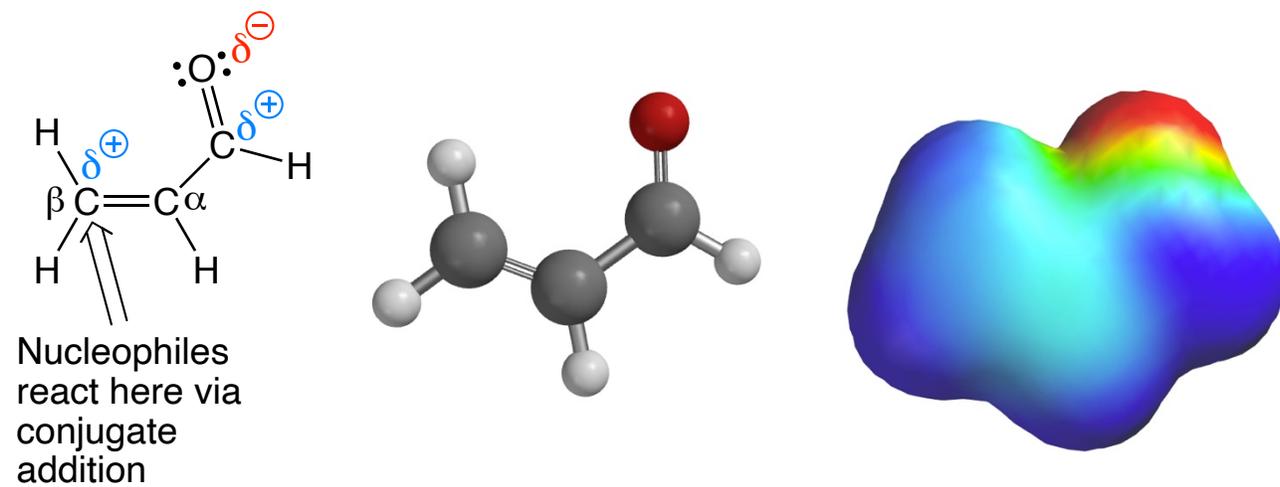
D) Check the pK's of the conjugate acid of the bases on either side of the equation. Lower pK_a value corresponds to stronger acid of the conjugate acid, and thus weaker conjugate base. The base with a stronger conjugate acid (lower pK_a value) will be the weaker base and will be favored at equilibrium.

E) Another way to look at it is that the base that is favored at equilibrium is the one that has the more stabilized anion, i.e. the one with the charge spread around more (electronegative) atoms.

F) Above is a pK_a table that we will refer to often.

*These have resonance stabilized anions

Conjugate Addition



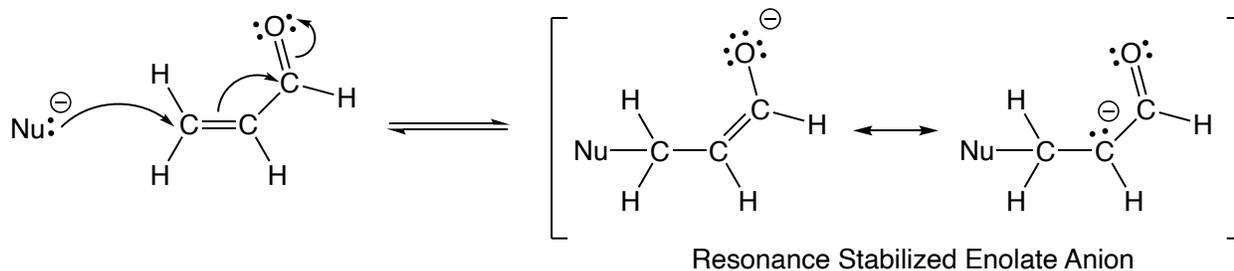
A) Alkenes adjacent to a carbonyl are conjugated and are therefore electrophilic.

B) These species are called α,β unsaturated carbonyl compounds.

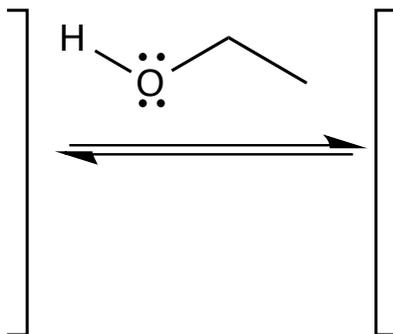
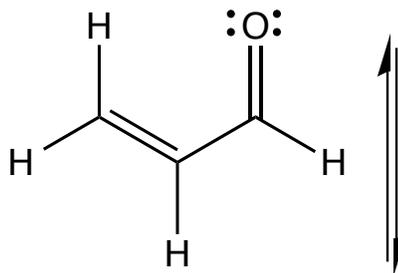
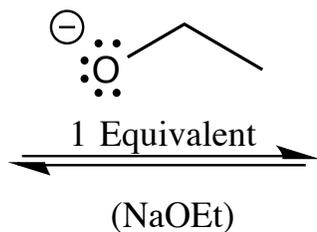
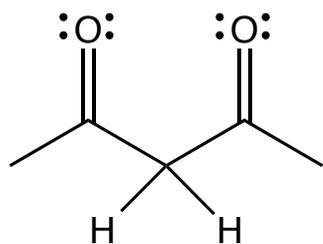
C) α,β unsaturated carbonyl compounds are conjugated, in that the pi electrons of the C=C and C=O bonds can delocalize over all four atoms. This lends some degree of extra stabilization to these species, because [pi electrons prefer to delocalize](#).

D) Nucleophiles can, however, react at the β carbon atom in a process called conjugate addition.

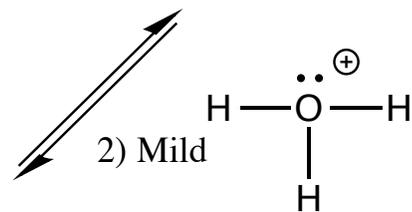
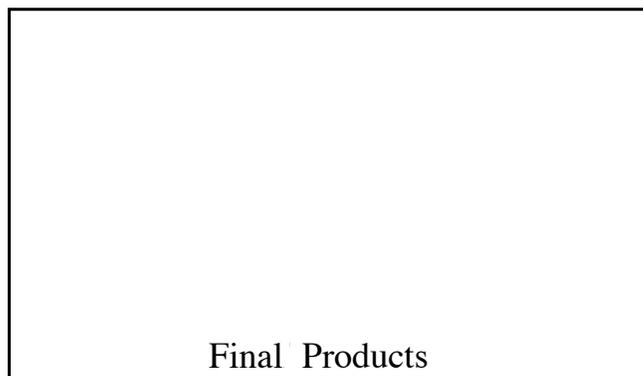
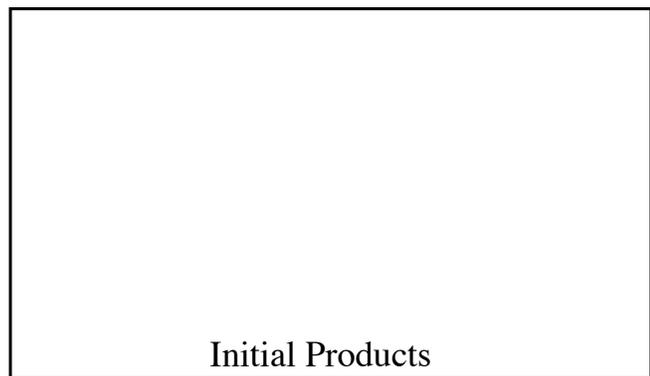
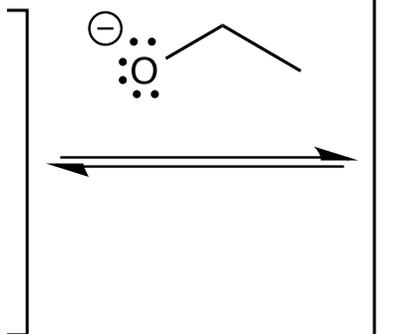
E) Conjugate addition is favorable because the intermediate formed is a resonance stabilized enolate, thus relatively low energy.



Michael Reaction



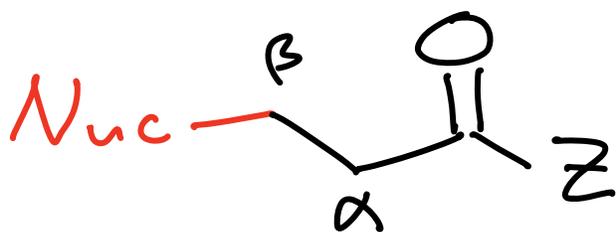
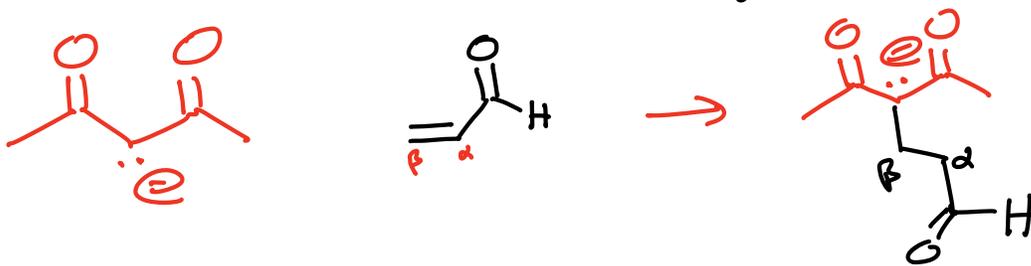
tautomerization



2) Mild

(Chemist opens flask and adds a mild acid)

Overall Balanced Equation



KRE →

Nucleophiles →

"Michael
Acceptor"

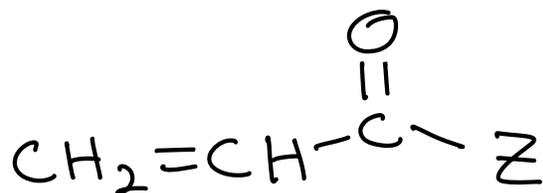
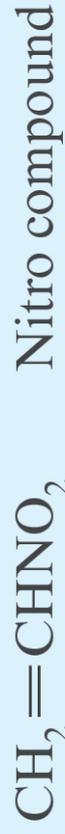
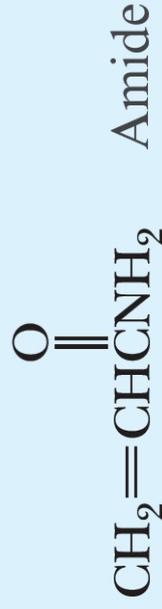
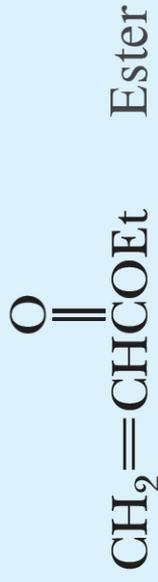
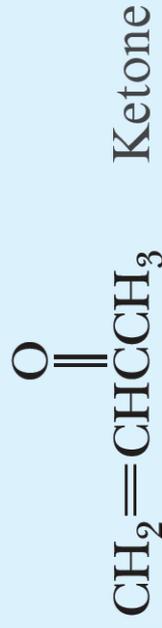
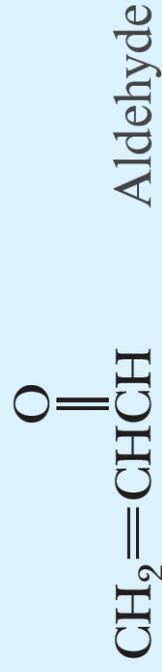
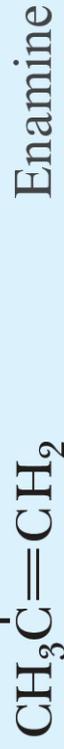
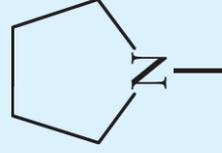
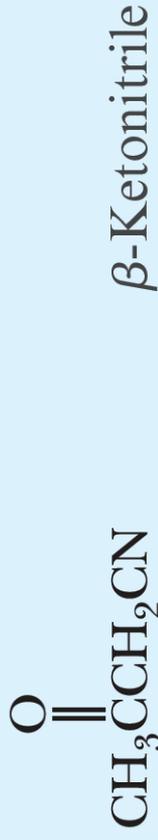


Table 19.1 Combinations of Reagents for Effective Michael Reactions

These Types of α,β -Unsaturated Compounds Are Nucleophile Acceptors in Michael Reactions

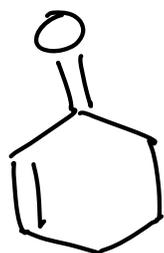


These Types of Compounds Provide Effective Nucleophiles for Michael Reactions



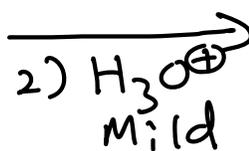
Example

Nucleophile



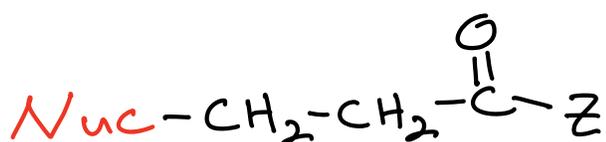
Michael
Acceptor

1) 1.0 equivalent
NaOEt



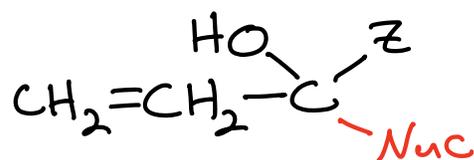
Why is conjugate addition
(reaction at $C=C$) favored
over reaction at the
carbonyl carbon?

Motive - Products



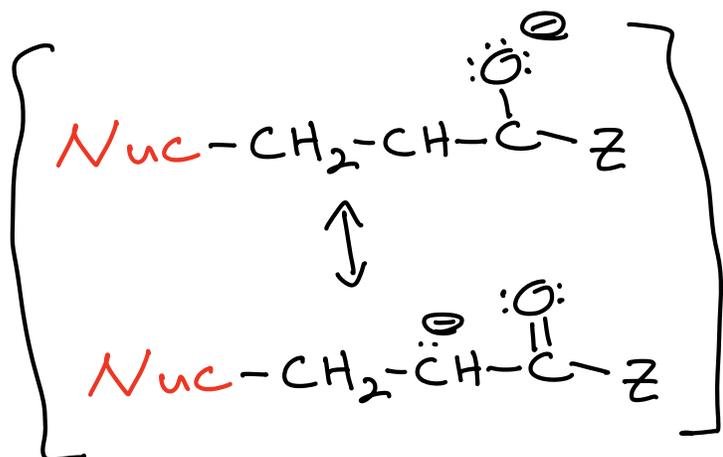
(A)

vs.

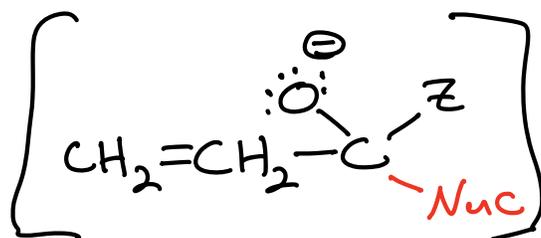


(B)

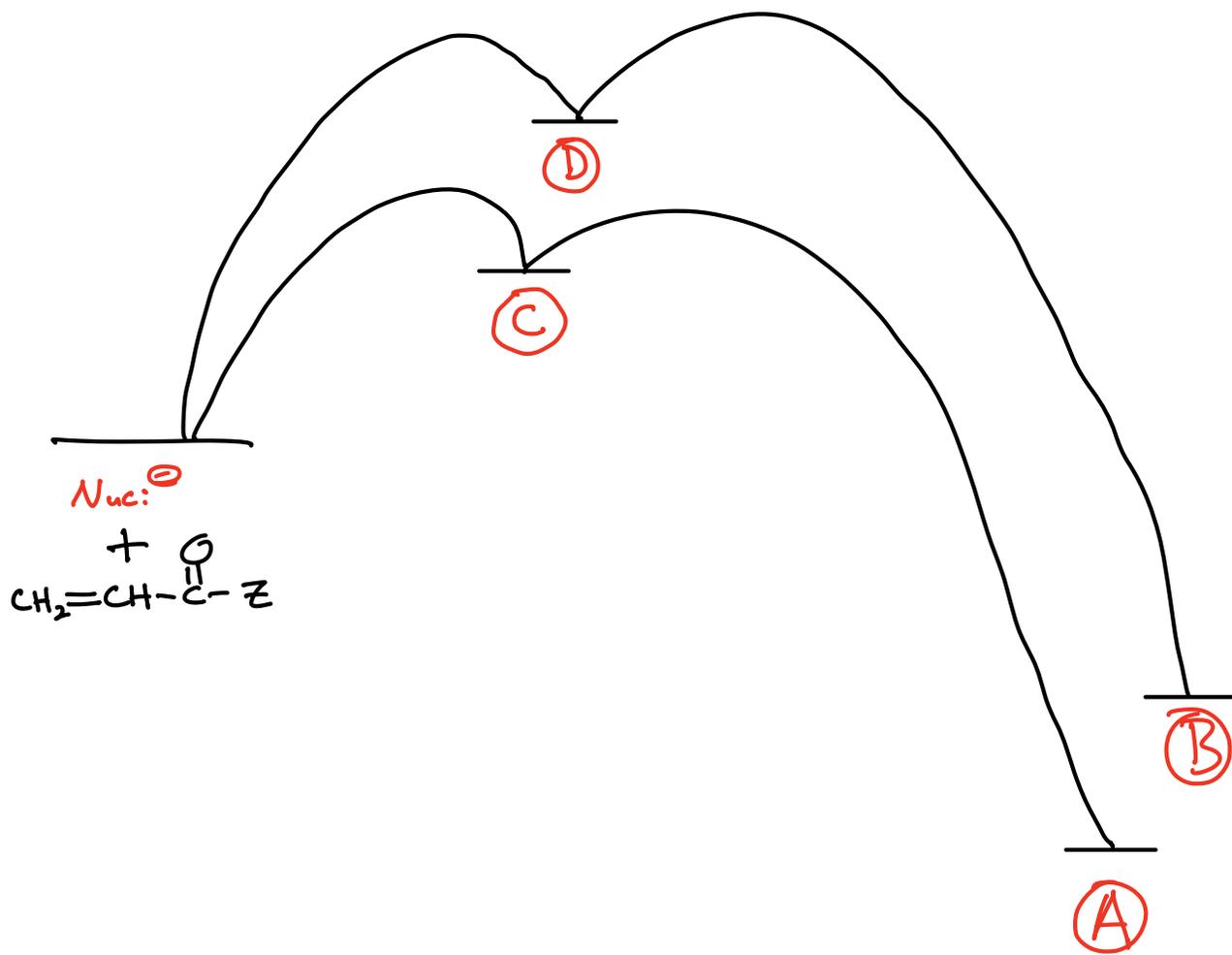
Opportunity - Intermediates



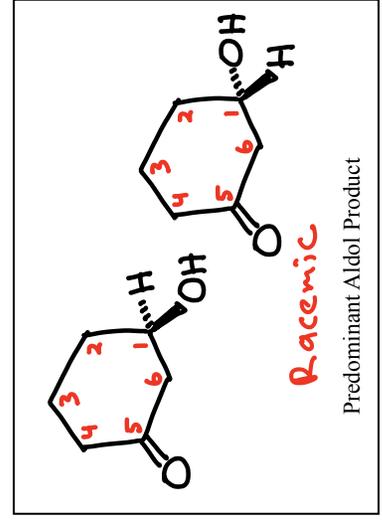
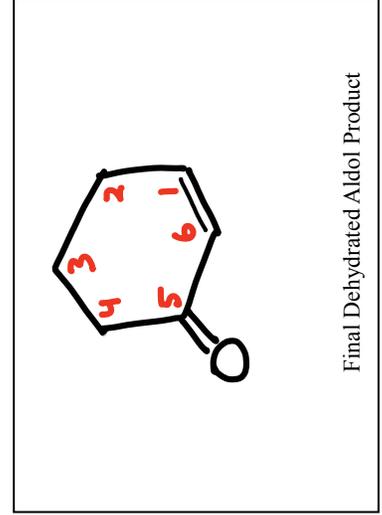
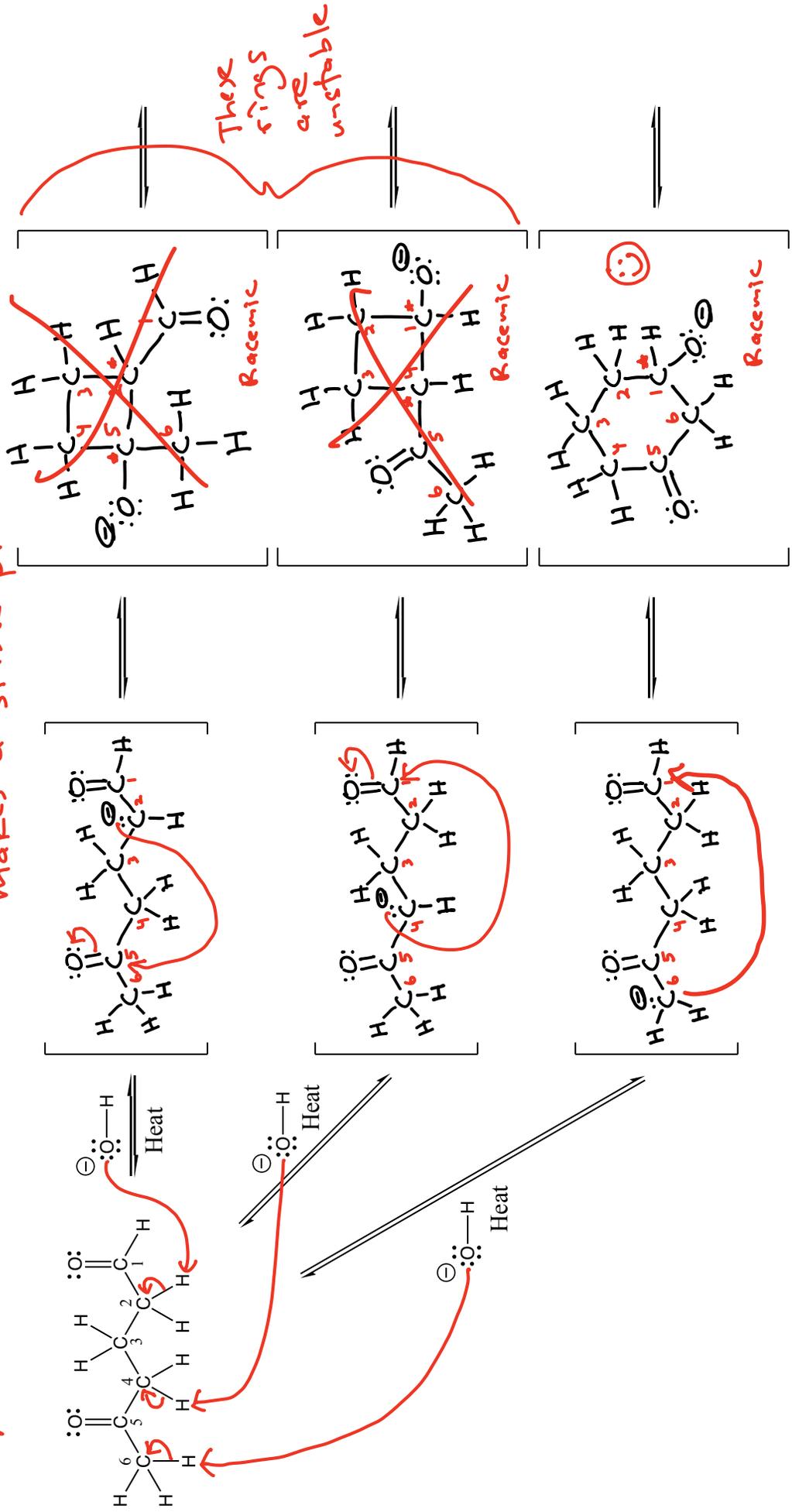
(C)



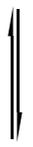
(D)



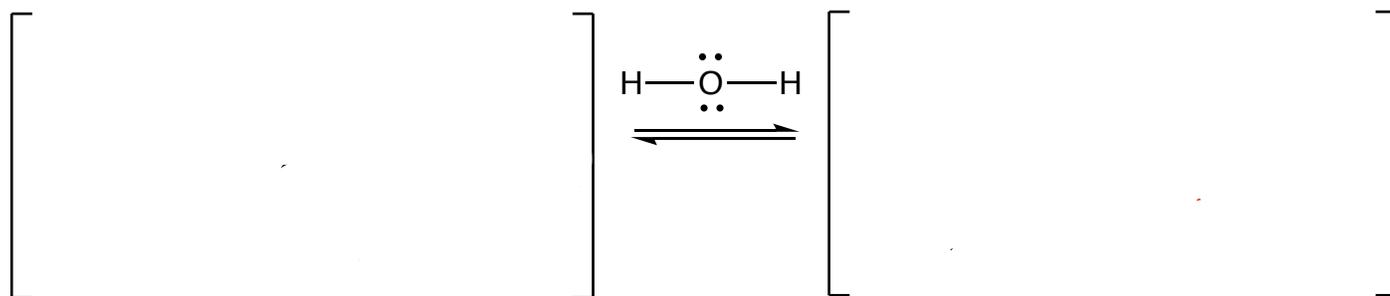
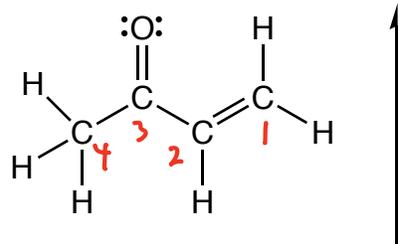
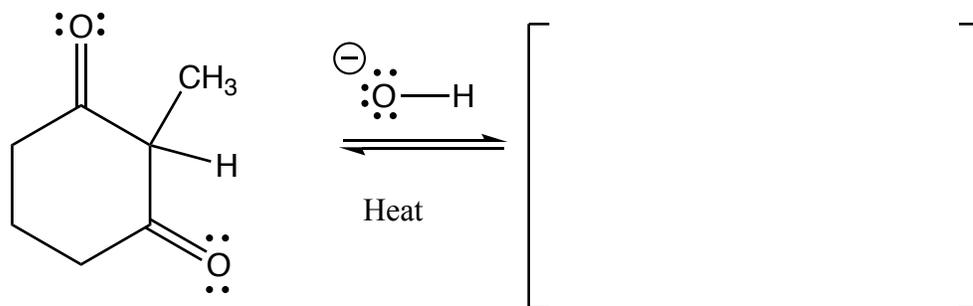
Cyclic Aldol Reaction \rightarrow 3 different enolates are possible, but only one makes a stable product



Dehydration



Robinson Annulation Part 1 - Michael Reaction Steps

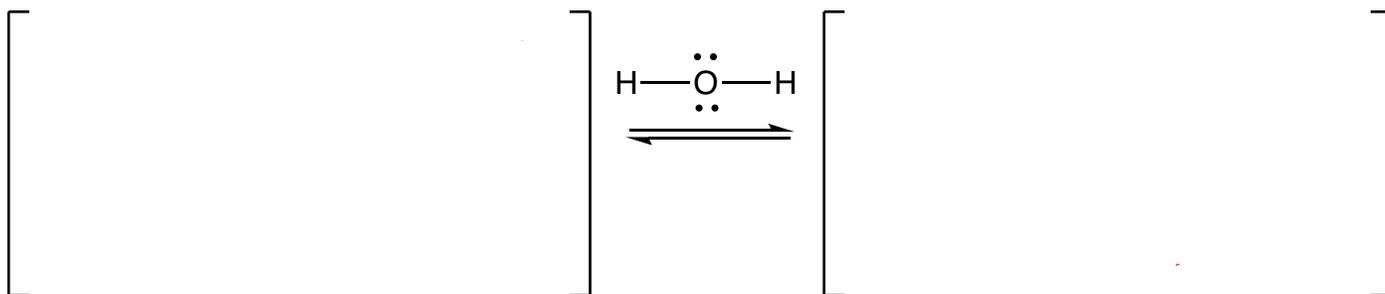
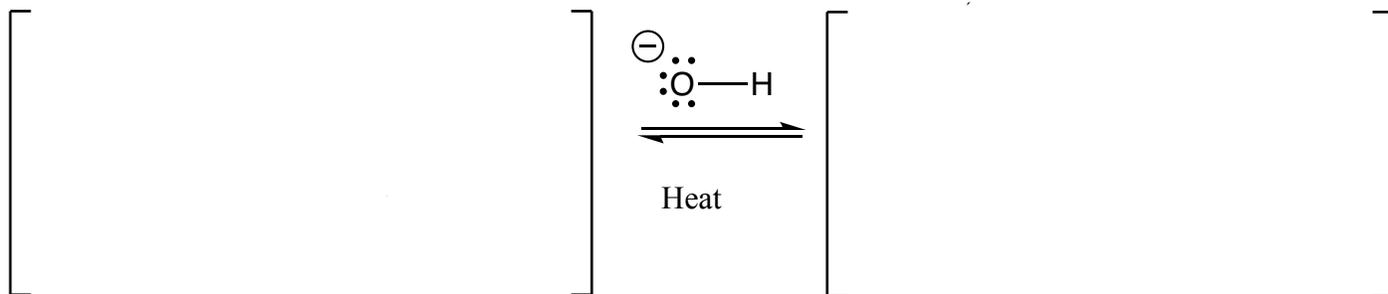


Tautomerization

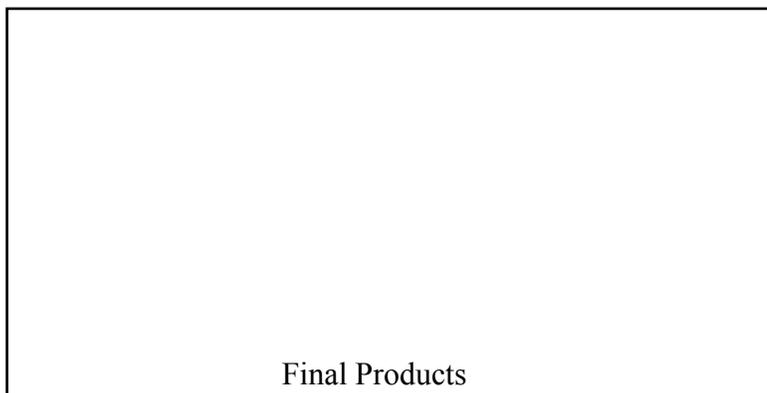


Michael Reaction Product

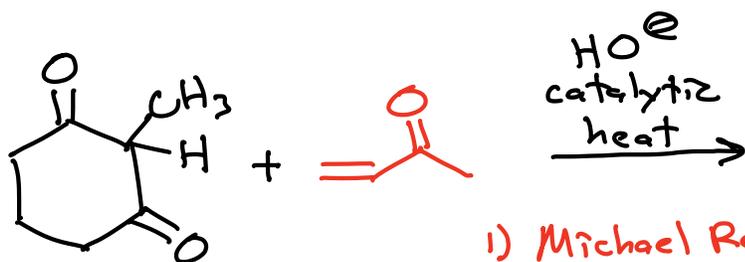
Robinson Annulation Part 2 - Aldol and Dehydration Steps



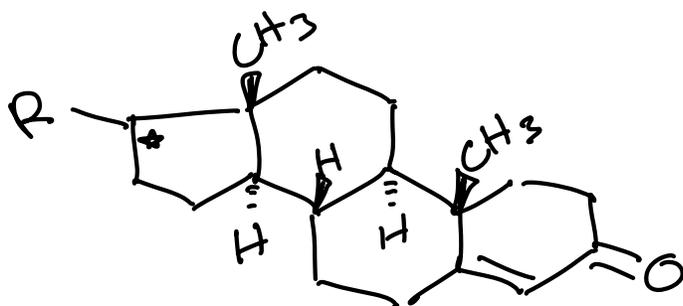
Spontaneous
dehydration - multiple steps
You are not responsible for
these



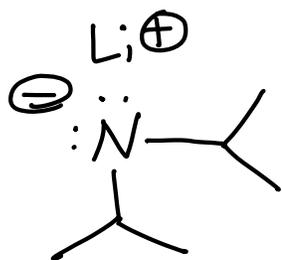
This is the only Robinson annulation reaction you will see on exams



- 1) Michael Reaction
- 2) Aldol Reaction
- 3) Dehydration



The wicked strong base that changes things

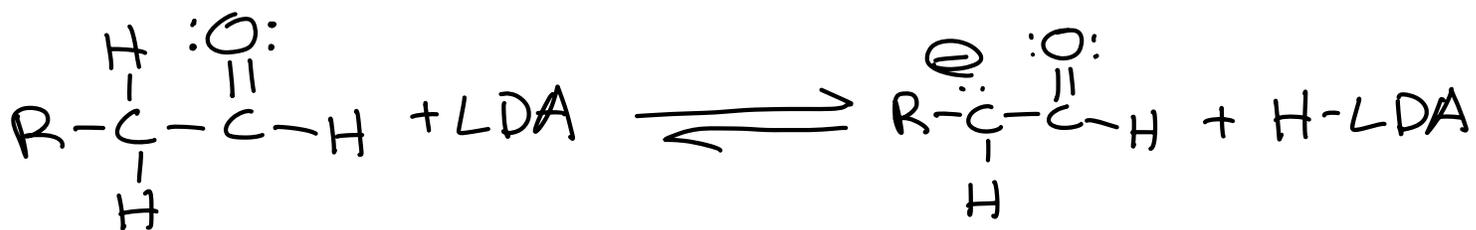


Lithium Diisopropylamide
"LDA"

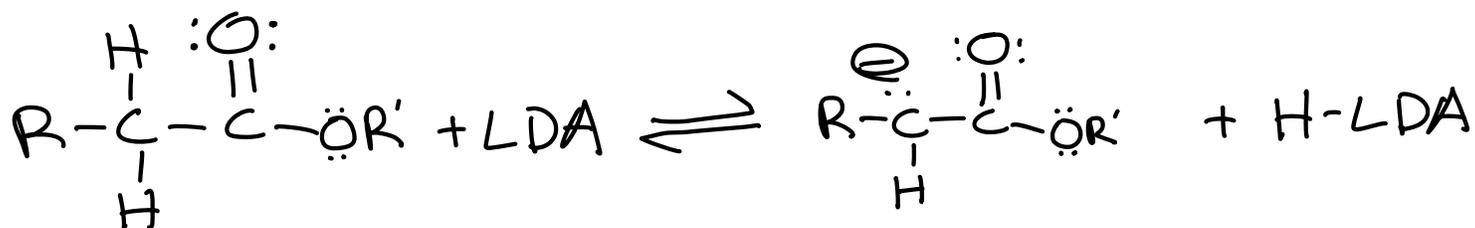


$pK_a \approx 40$
"H-LDA"

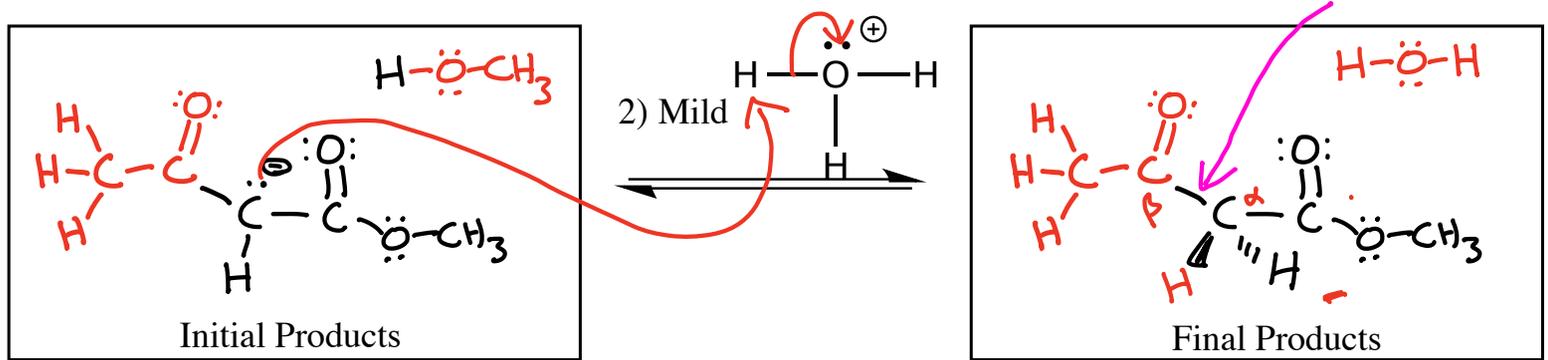
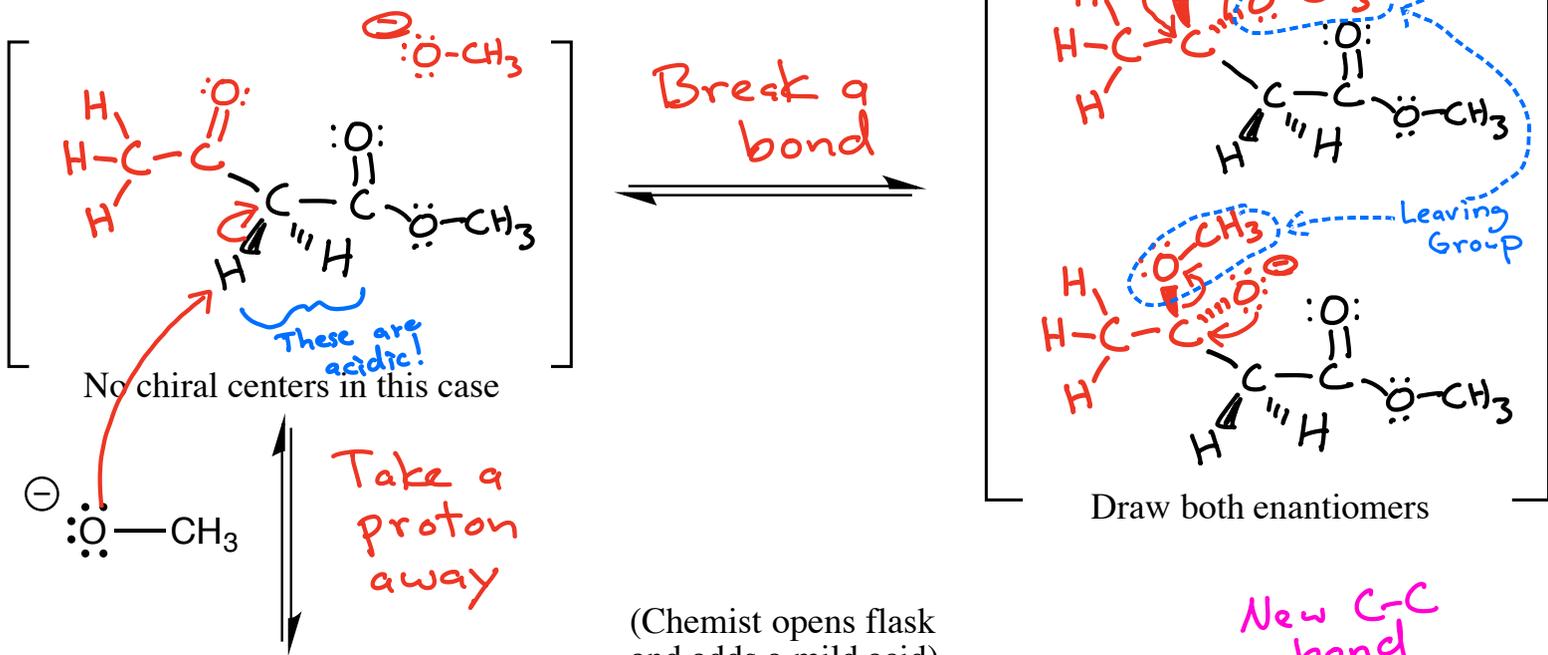
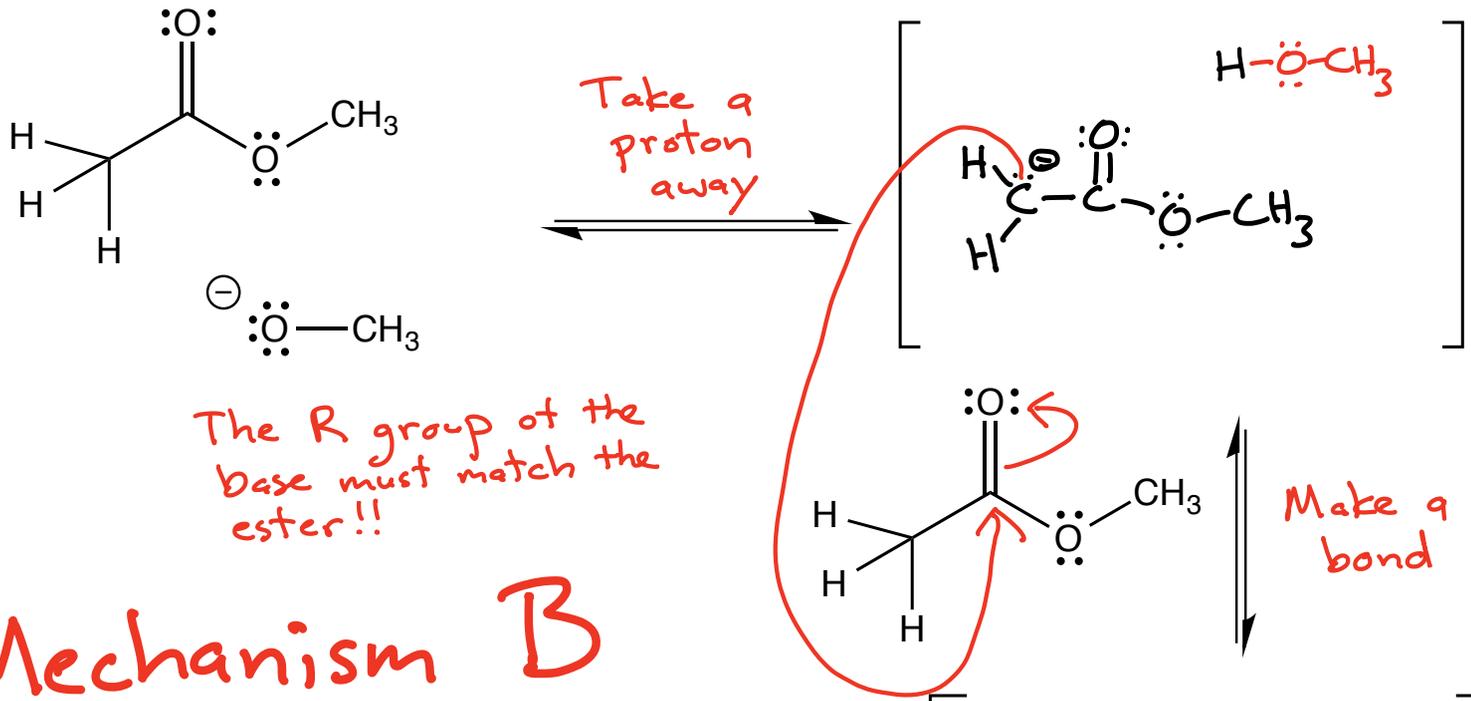
Aldehydes



Esters

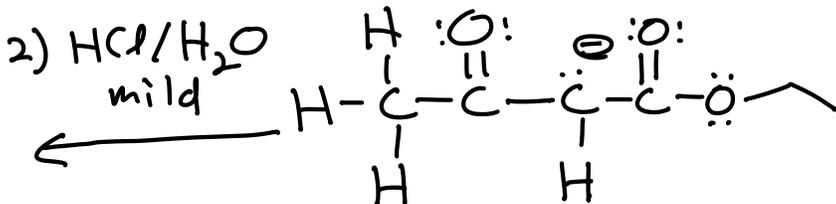
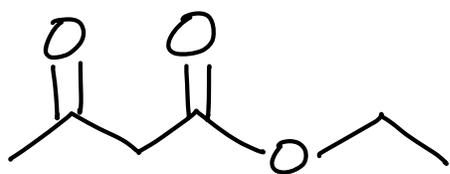
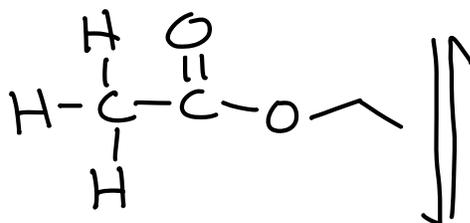
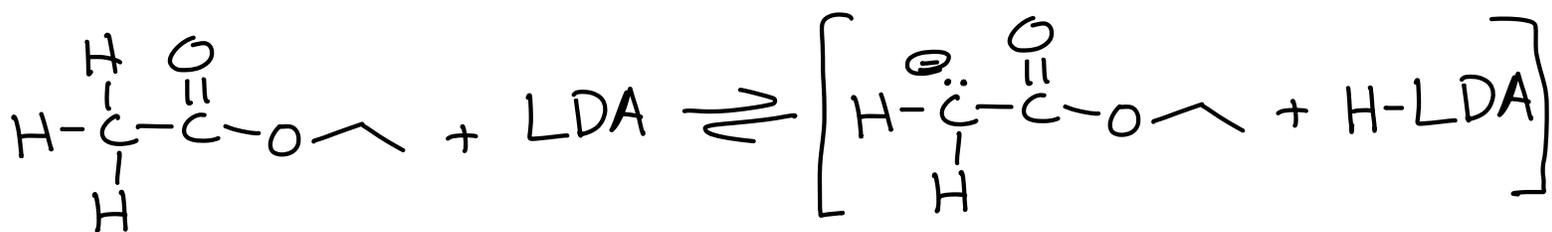


Claisen Condensation → "Aldol with Esters"

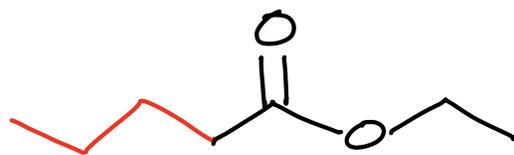
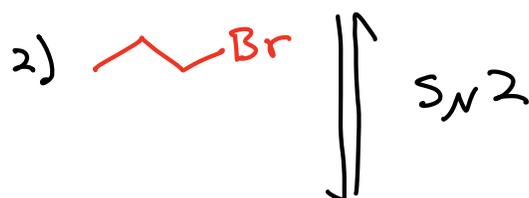
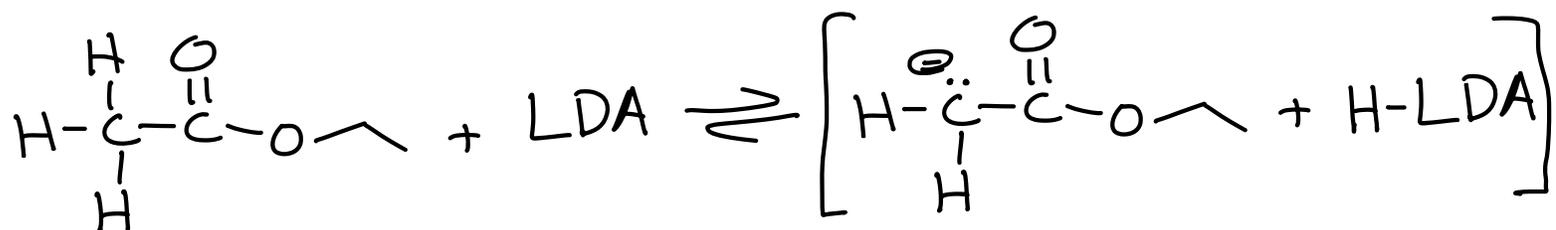


This is a much more stable anion compared to $\ominus\text{OCH}_3$, providing a strong driving force (motive) for the Claisen condensation reaction

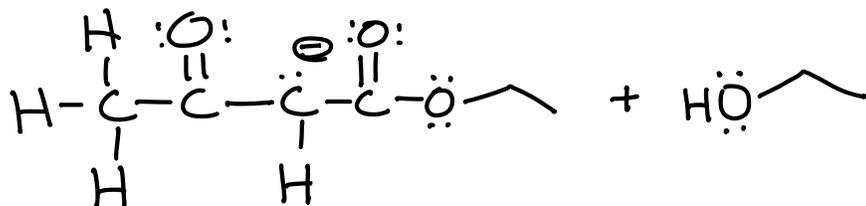
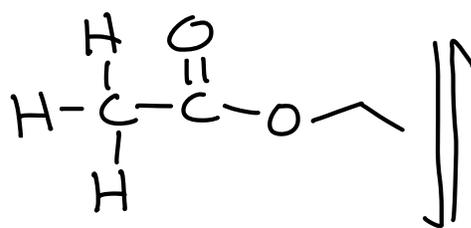
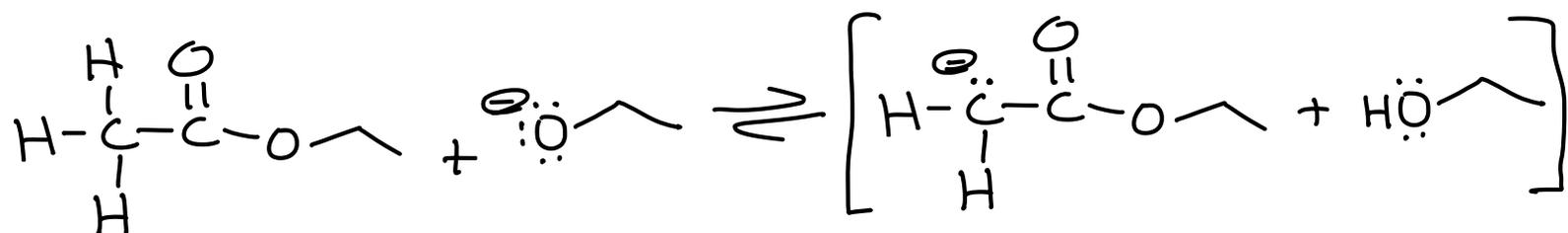
What if we use 0.5 equivalents of LDA with an ester?



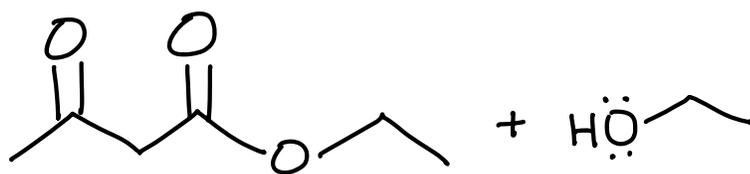
What if we use 1.0 equivalent of LDA with an ester?



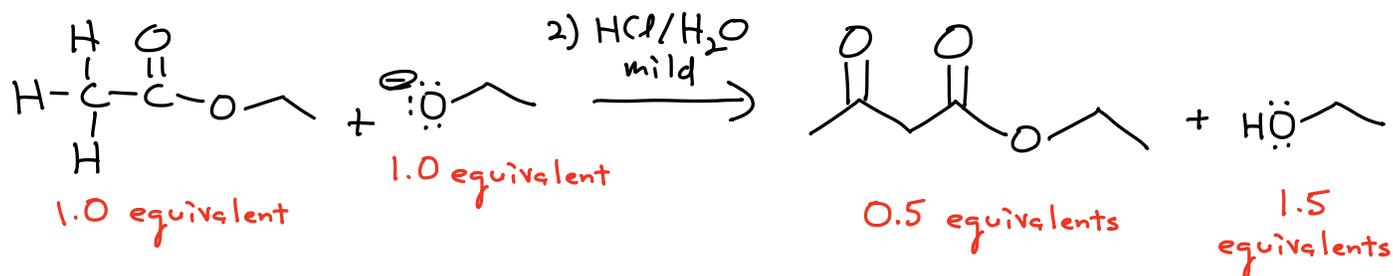
What if we use 1.0 equivalent of $\ominus \text{:}\ddot{\text{O}}\text{-CH}_2\text{-CH}_3$ with an ester?



2) $\text{HCl}/\text{H}_2\text{O}$
mild



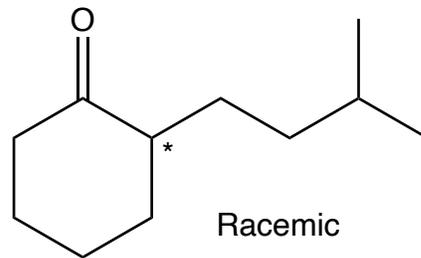
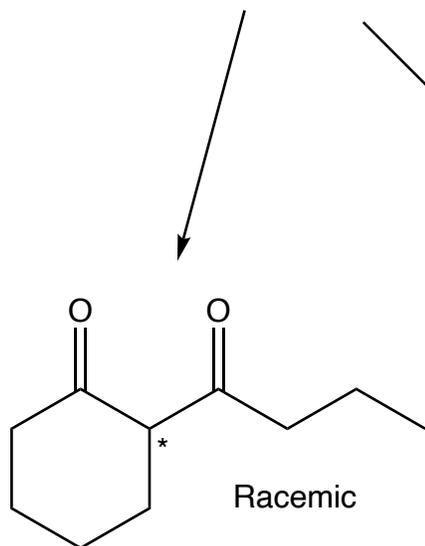
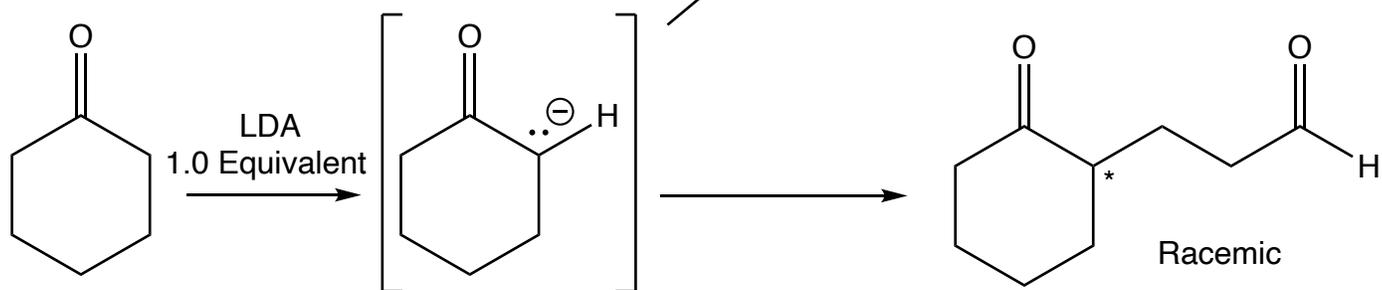
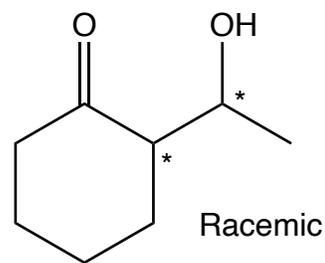
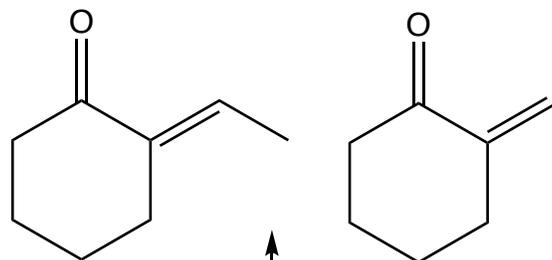
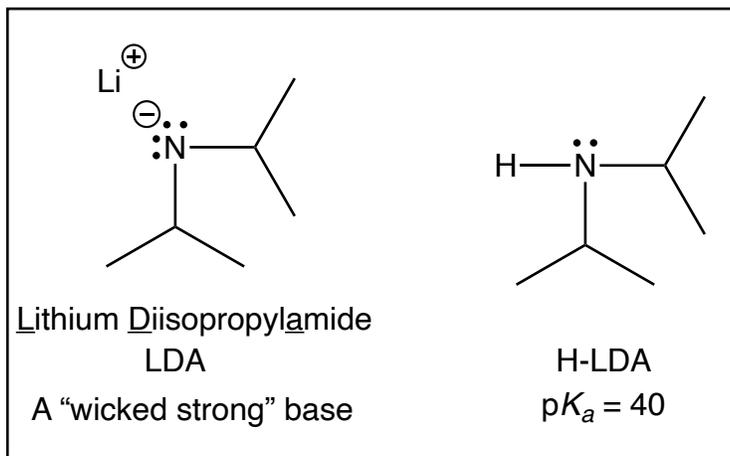
Overall Reaction



0.5 equivalents
comes from
first step,
formation
of the
enolate

0.5 equivalents
comes from
second step,
loss of $\text{CH}_3\text{CH}_2\text{O}^-$
leaving group
from ester
(see mechanism)

0.5 equivalents
is left over
from original
 $\text{CH}_3\text{CH}_2\text{O}^-$ that
was not
used



**β -Substituted
aldehydes,
nitriles, ketones,
or esters**

**α,β -Unsaturated, nitriles,
ketones, or esters**

β -Keto esters

α,β -Unsaturated aldehydes

Acid Chlorides

β -Hydroxy aldehydes

Aldehydes

Ketones

Carboxylic esters

β -Ketoaldehyde

β -Diketone

Carboxylic acids

Substituted aldehyde

Substituted ketone

β -Diester

