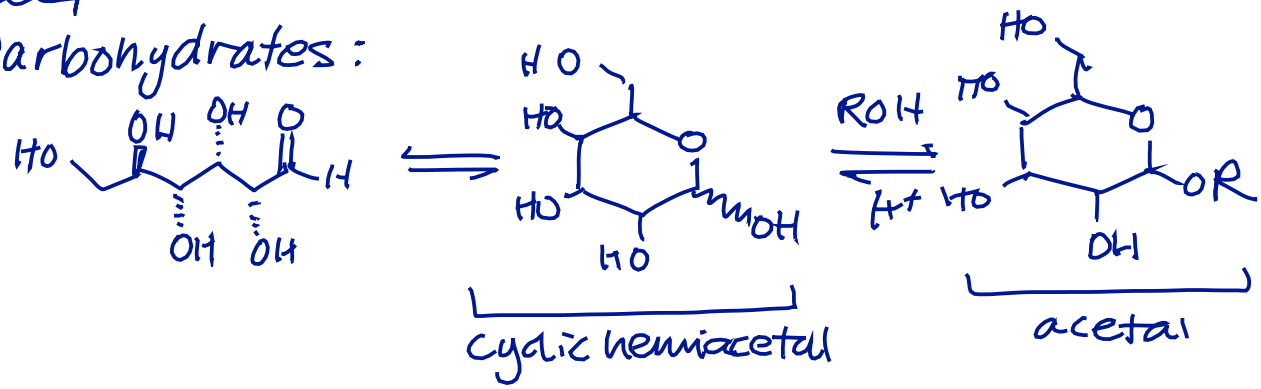
Exam 4: 2013 mean: 65
2014 mean: 70 media: 72

## Recap:

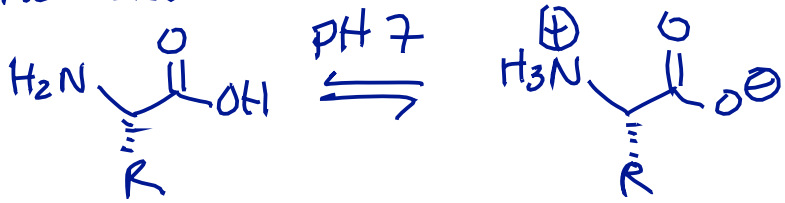
- Carbohydrates:



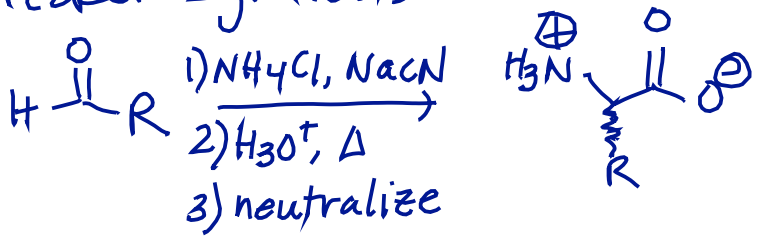

anomers:

anomeric effect ($lp \rightarrow \sigma^*$)

- Amino acids

1) 


2) Strecker synthesis



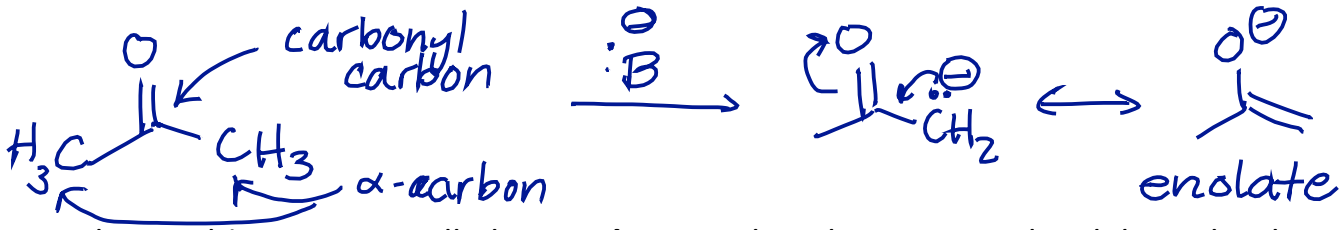

3) Peptide synthesis
- solution phase
- solid-phase
- protecting groups

Reagents: DCC, $Cs_2CO_3$, $Boc_2O$, TFA, HF

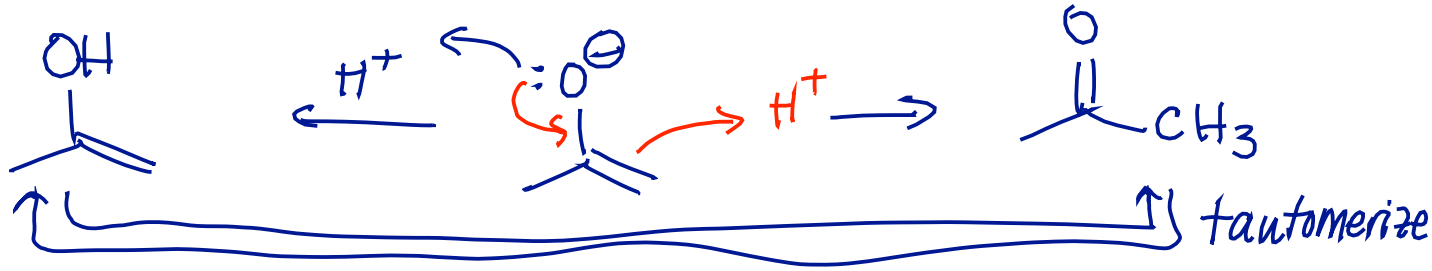
Week 5 July 22, 2014

# Enols & Enolates:
## Carbonyl Compounds as Nucleophiles(?!)

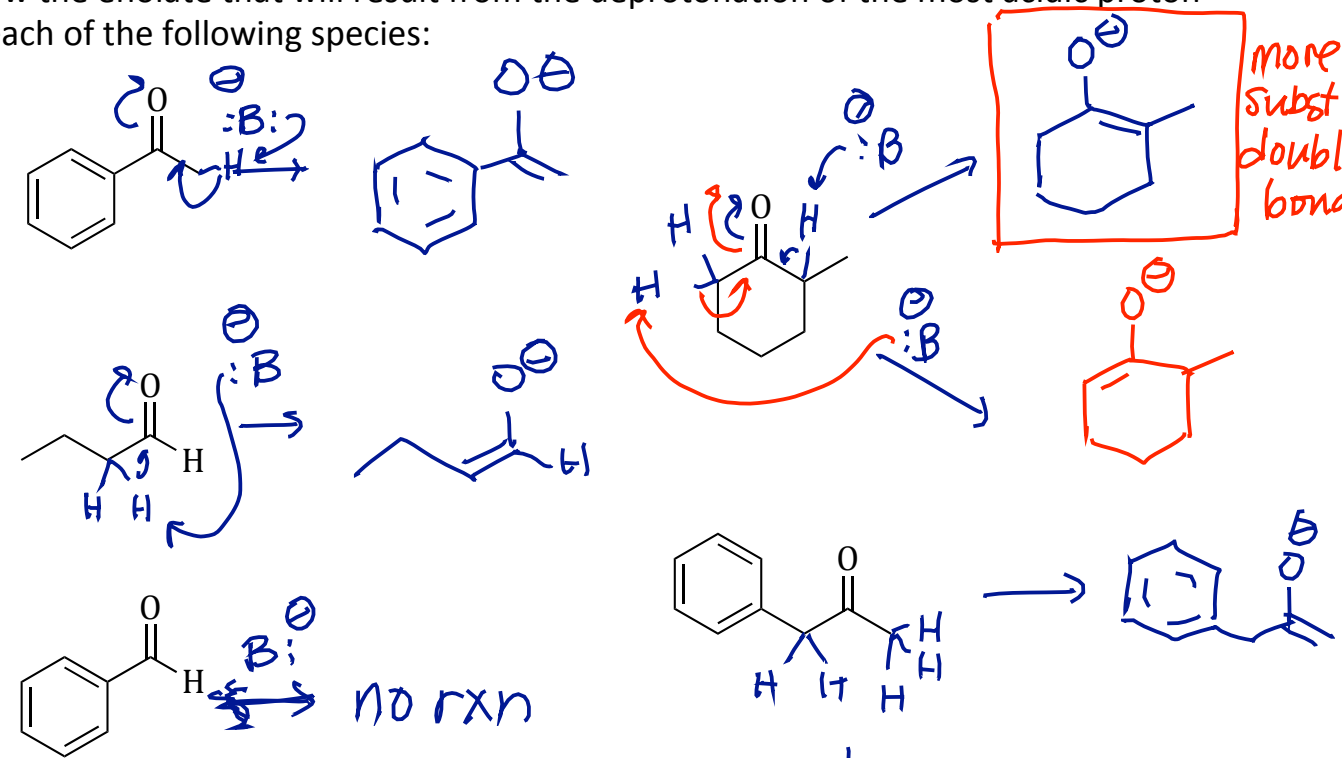
What will happen if you treat **acetone** with 1 equivalent of a very strong base?




The resulting species, called an **enolate**, can be a *base* or a *nucleophile*, and is therefore known as an ***ambident nucleophile***. Show the *two* products that can result from the protonation of this enolate. Do you recognize these products?




Show the enolate that will result from the deprotonation of the most acidic proton in each of the following species:



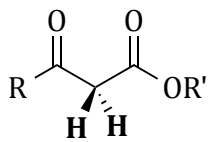
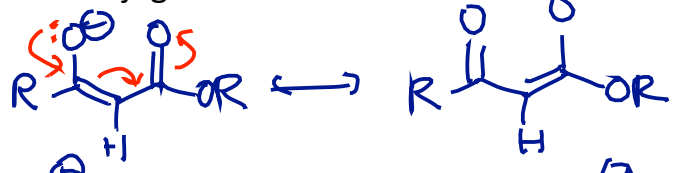
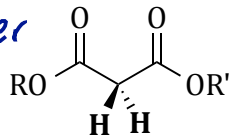
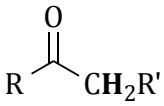
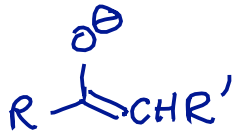
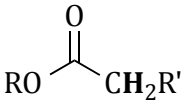
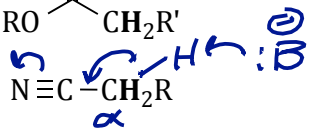

*Reading*: Section 22.1

#s to KNOW!

Week 5 July 22, 2014

# Enols & Enolates:
## p$K_a$s of Carbonyl Compounds

Explain the trends in p$K_a$ values for the following carbonyl compounds.

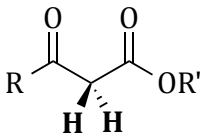
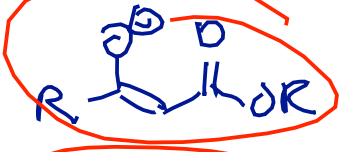
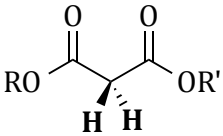
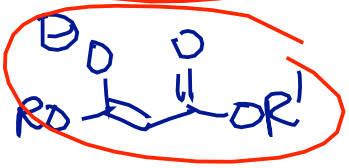
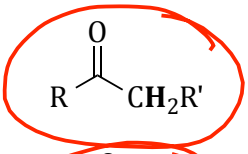
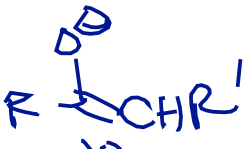
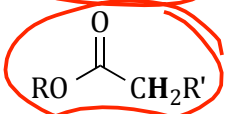
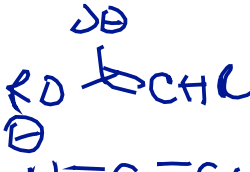
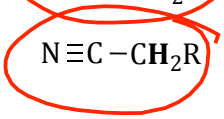
| | | p$K_a$ | Conjugate base |
|---|---|---|---|
| β-keto ester |  | 11 |  |
| β-diester |  | 13 | |
| ketone |  | 20 |  |
| ester |  | 25 | |
| nitrile |  | 31 |  |

res. deloccl. bases, stable

nitrile enolate

N less e⁻neg

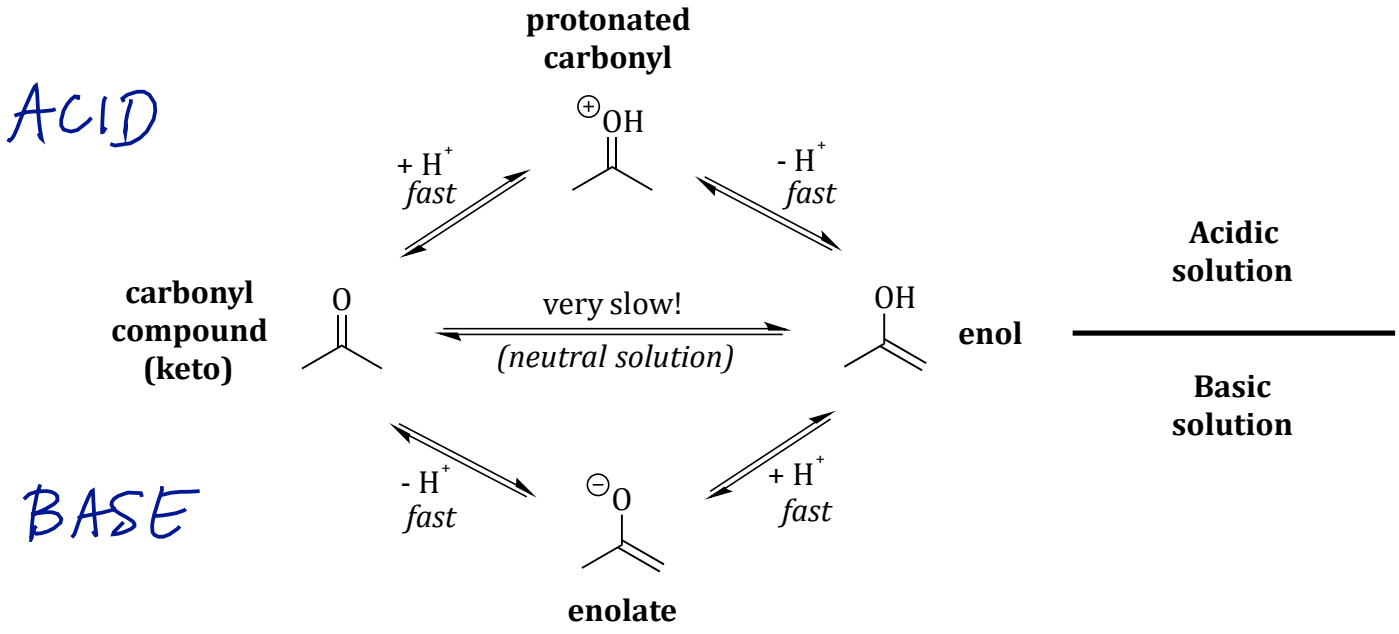
Each of these compounds is treated with the base *sodium ethoxide*. What will the *predominant* species be at equilibrium in each case?

| pKa | | | | |
|---|---|---|---|---|
| 11 |  | $\rightleftharpoons$ |  + EtOH | β-dicarbonyl favor products |
| 13 |  | $\rightleftharpoons$ |  + EtOH | |
| 20 |  | $\rightleftharpoons$ |  + EtOH | SM favored |
| 25 |  | $\rightleftharpoons$ |  + EtOH | |
| 31 |  | $\underbrace{\rightleftharpoons}_{16}$ | + EtOH | |

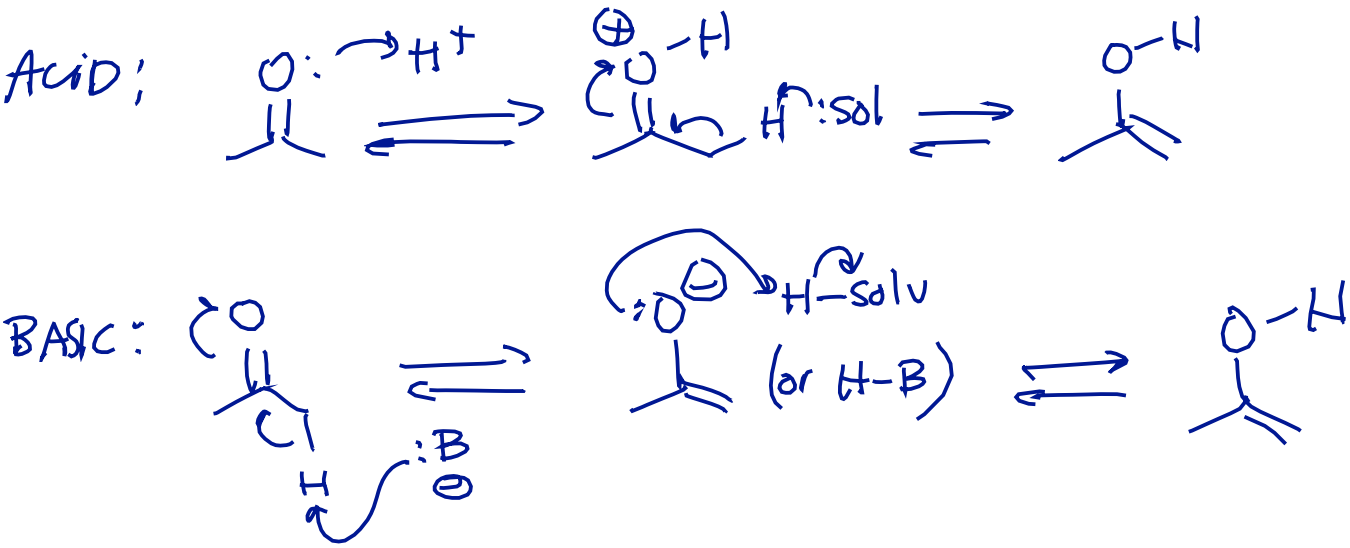
*Reading*: Section 22.1

# Enols & Enolates:
## Keto/Enol(ate) Equilibria

All carbonyl compounds are in equilibrium with their *enol* forms; in addition, depending on the pH, they may be in equilibrium with their protonated or deprotonated forms:



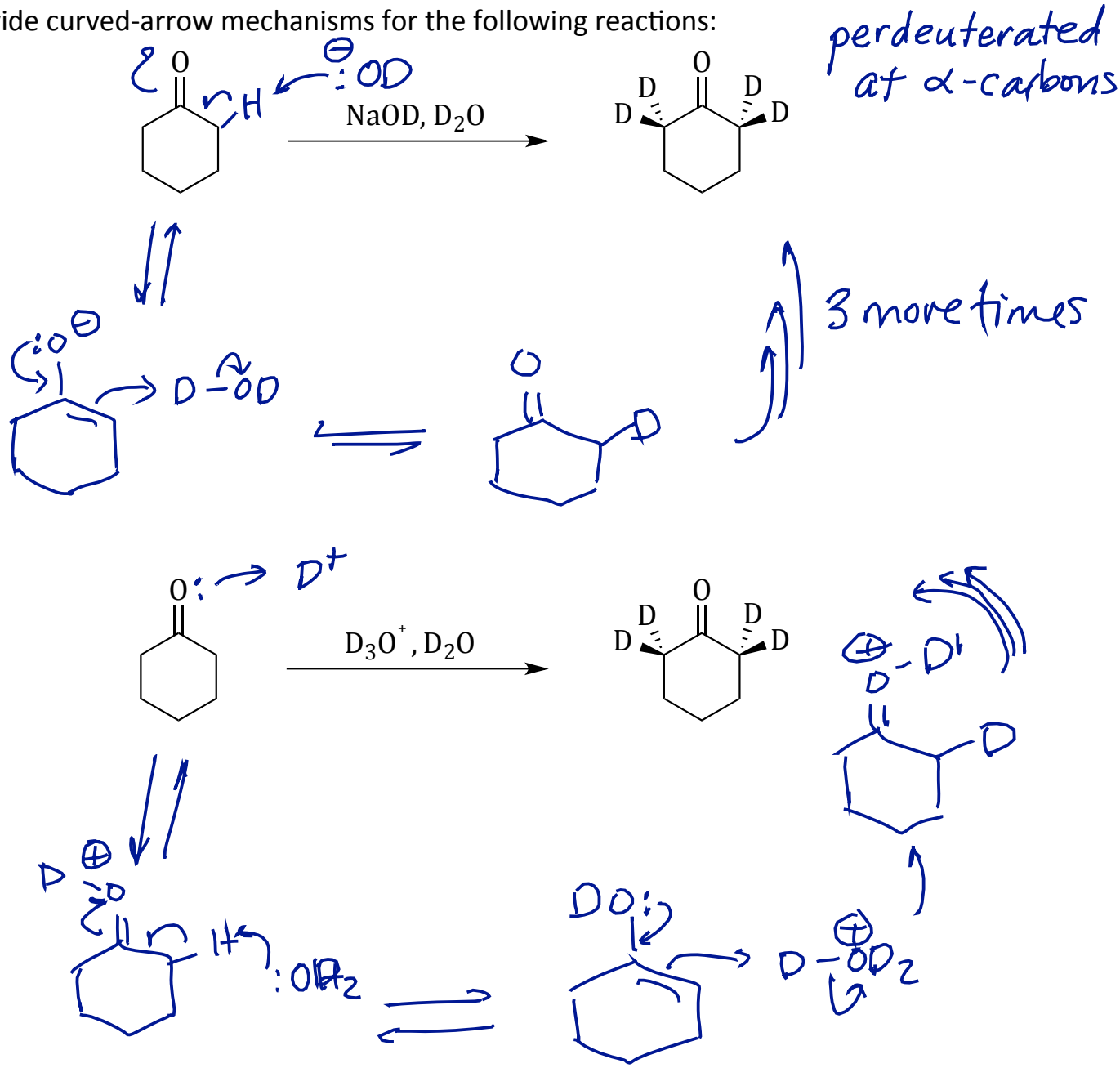

Show the mechanisms for *base*- and *acid-catalyzed* conversion from keto to enol.




*Reading*: Section 22.2

# Enols & Enolates:
## Deuteration

Provide curved-arrow mechanisms for the following reactions:



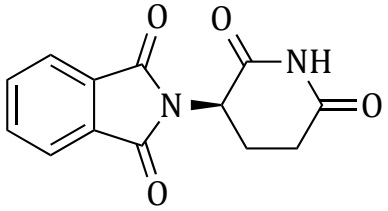

*Reading*: Section 22.2

Week 5 July 22, 2014

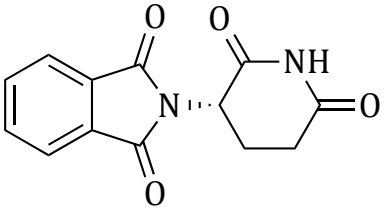
(R) convert to (S)

# Enols & Enolates:
## Racemization of α-Carbons

The thalidomide story:

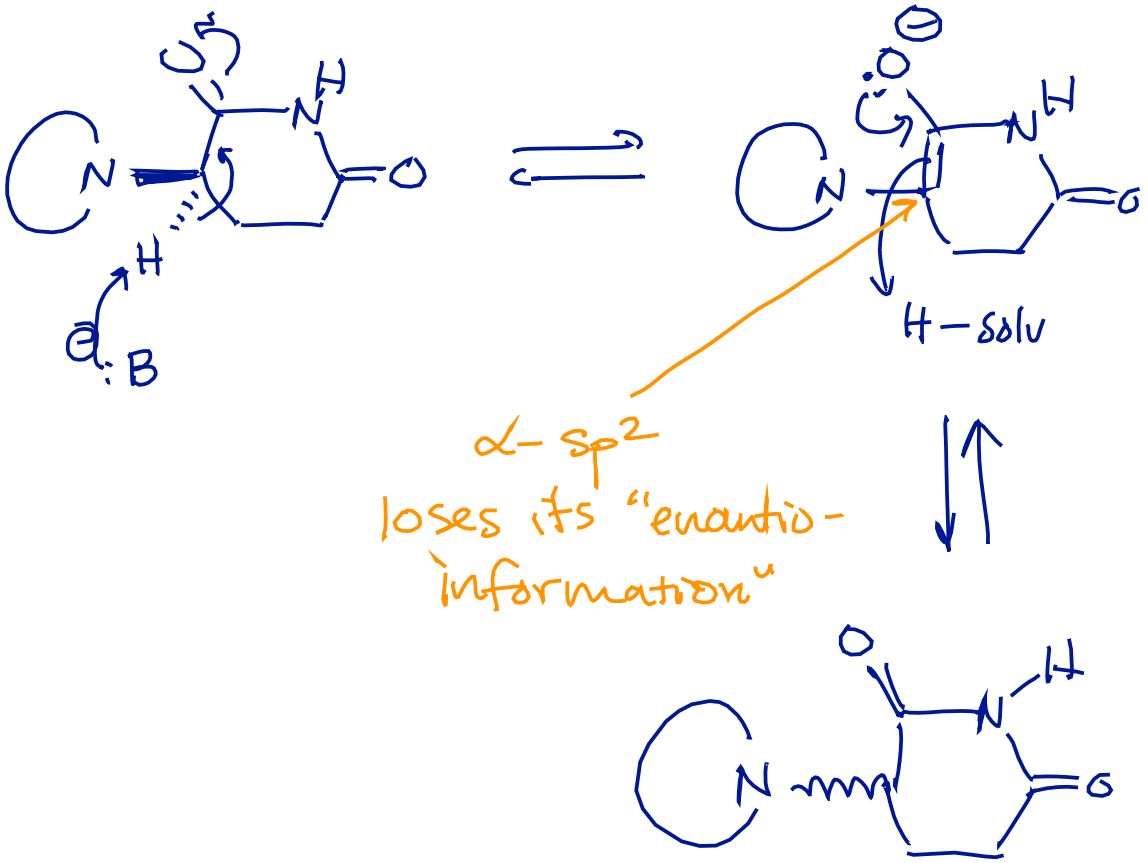


*(R)-thalidomide*
**sedative**



*(S)-thalidomide*
**teratogen**

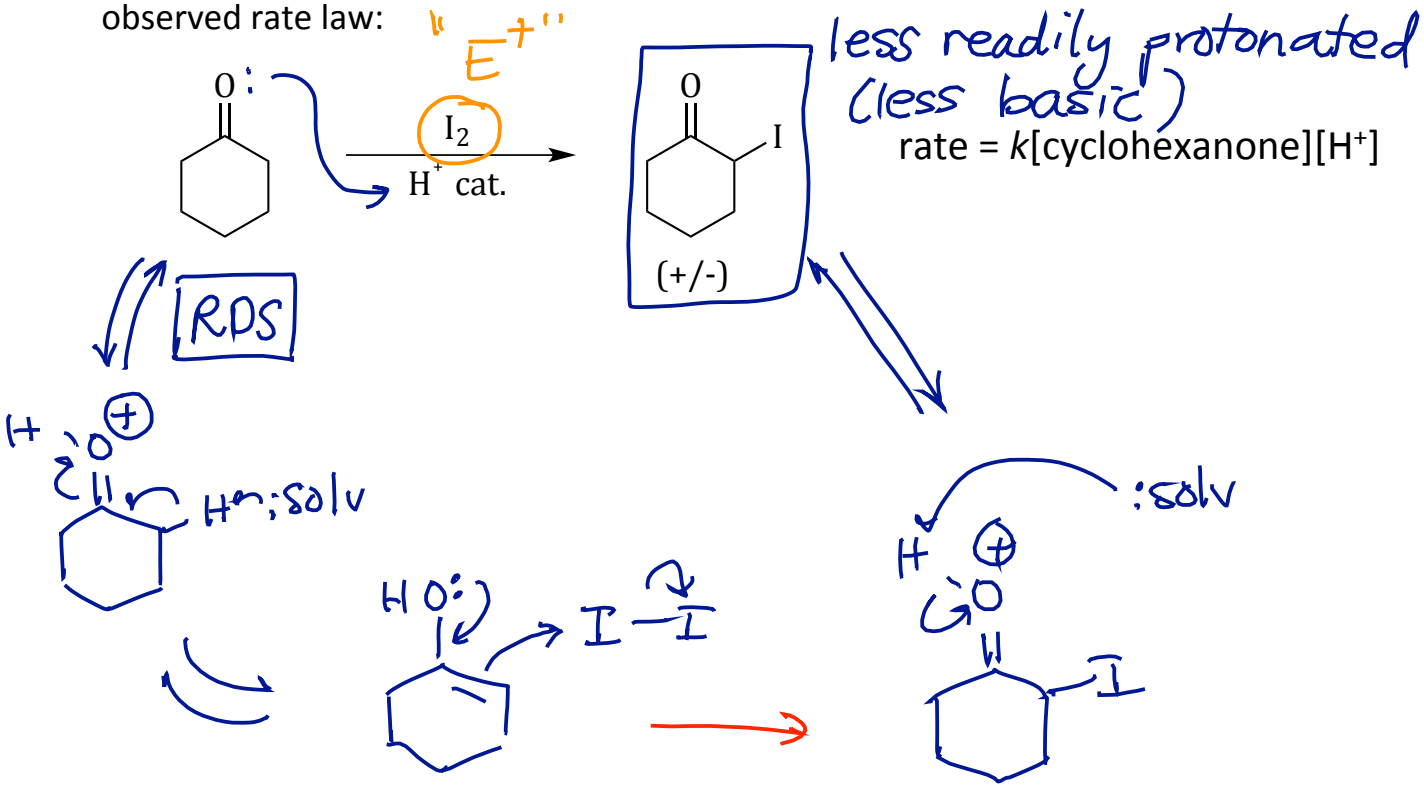
Why can't we safely administer *only* the *R* enantiomer of thalidomide?




*Reading*: Section 22.2

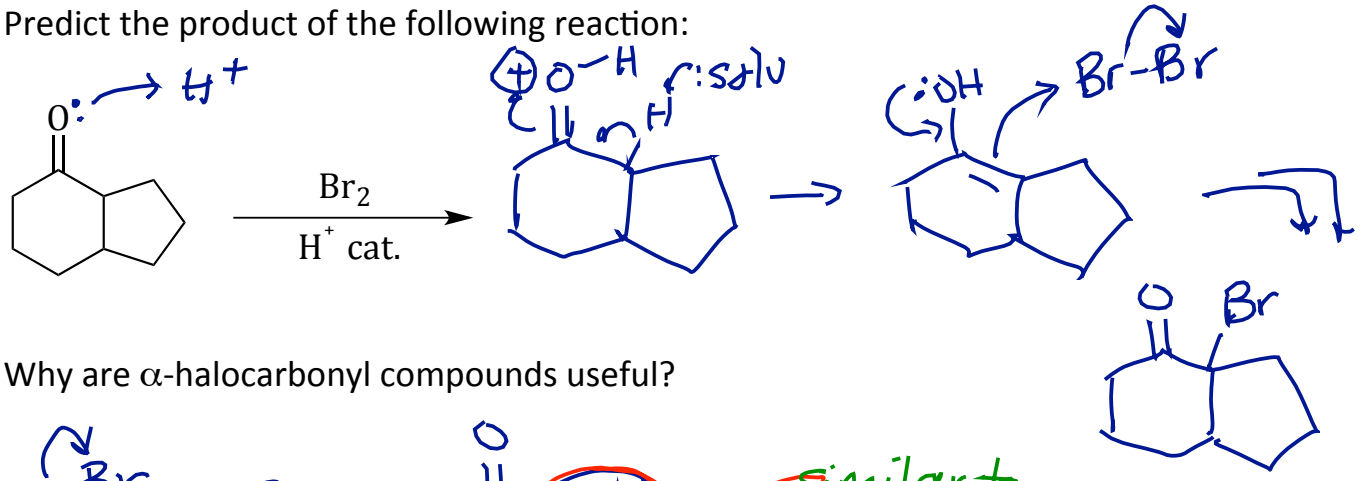
# Enols & Enolates:
## α-Halogenation, Acidic Conditions

Provide a curved-arrow mechanism for the following reaction **and** explain the observed rate law:

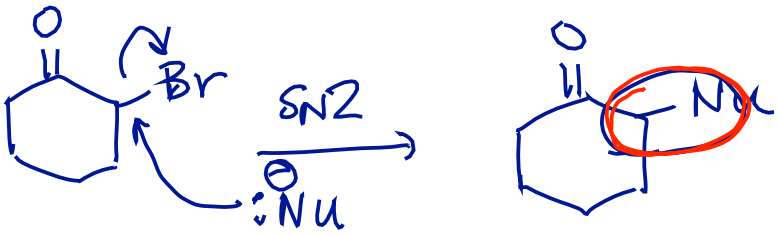



rate = $k$[cyclohexanone][$H^+$]

Predict the product of the following reaction:




Why are α-halocarbonyl compounds useful?




similar to allylic SN2

*Reading*: Section 22.3

α-C—H
α-C—D
α-C—X (halogen)
α-C—Nu (SN2)

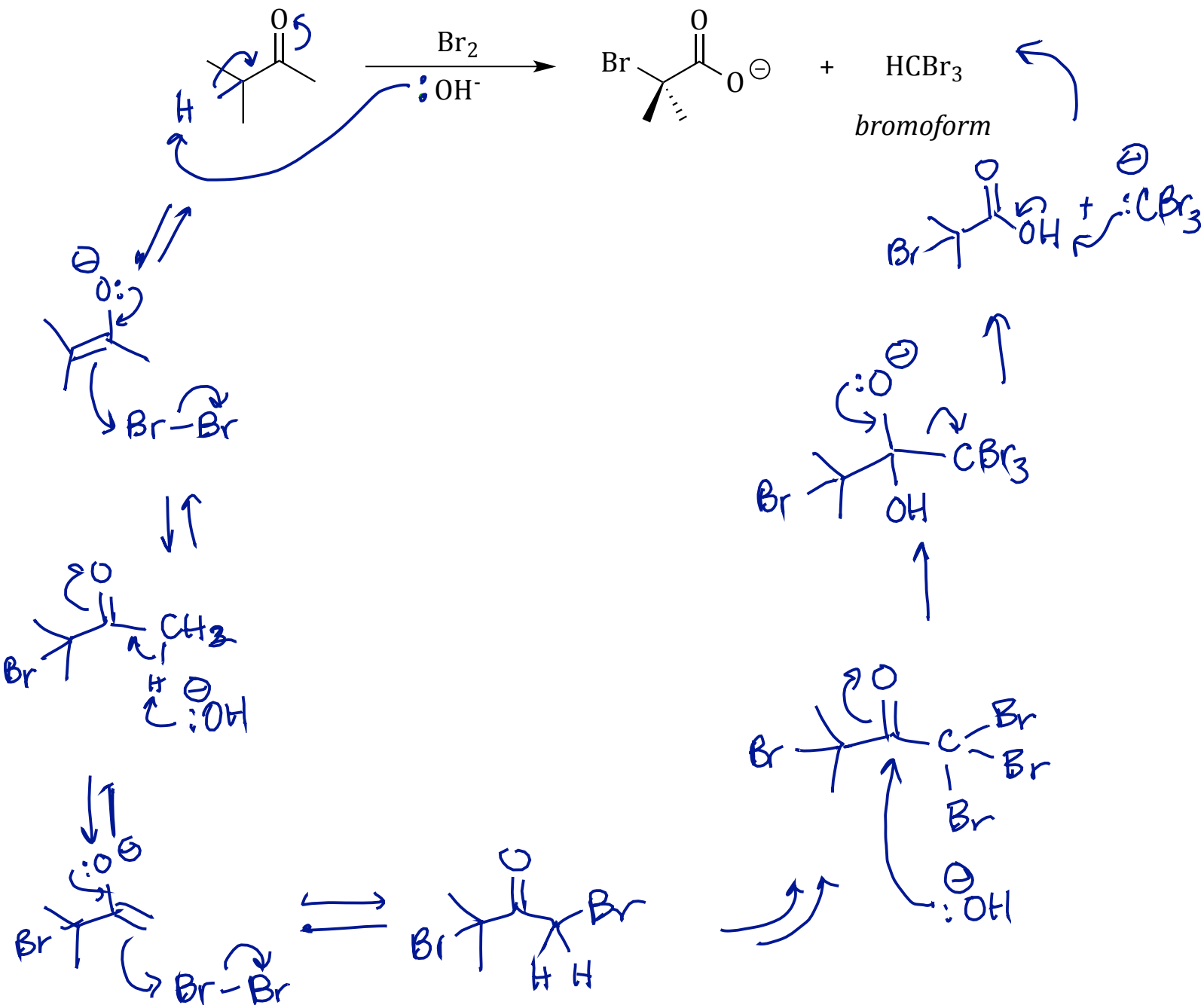
methyl ketone ⟶ carboxylate

Week 5 also - brominated all α-C July 22, 2014

# The Haloform Reaction:

## α-Halogenation, Basic Conditions

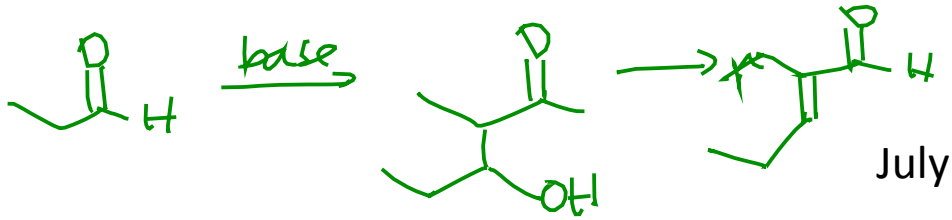
Provide a curved-arrow mechanism for the following:




*Reading*: Section 22.3



Most generally: ketone $\xrightarrow[\text{base}]{X_2}$ completely α-halogenated ketone



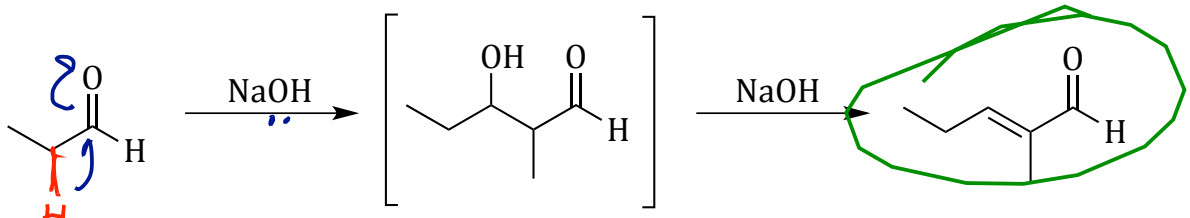

Week 5 July 22, 2014

# The Most Interesting Reaction in the World:
## The Aldol Reaction

*"Nature, it seems, is an organic chemist having some predilection for the aldol condensation."*

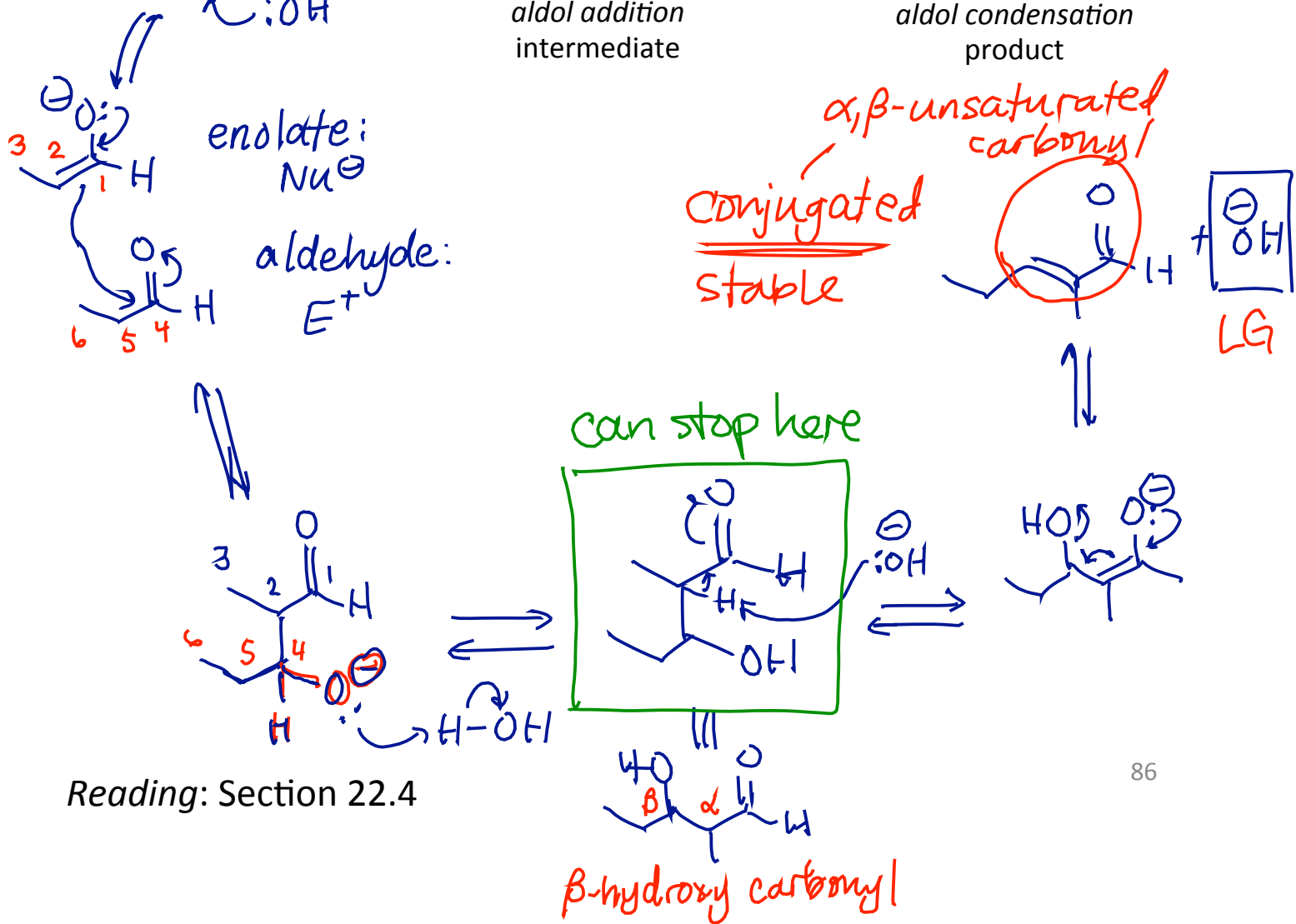
John W. Cornforth
Nobel Prize in Chemistry, 1975

Provide a complete curved-arrow mechanism for the following reaction:




*aldol addition* intermediate

*aldol condensation* product




*Reading*: Section 22.4

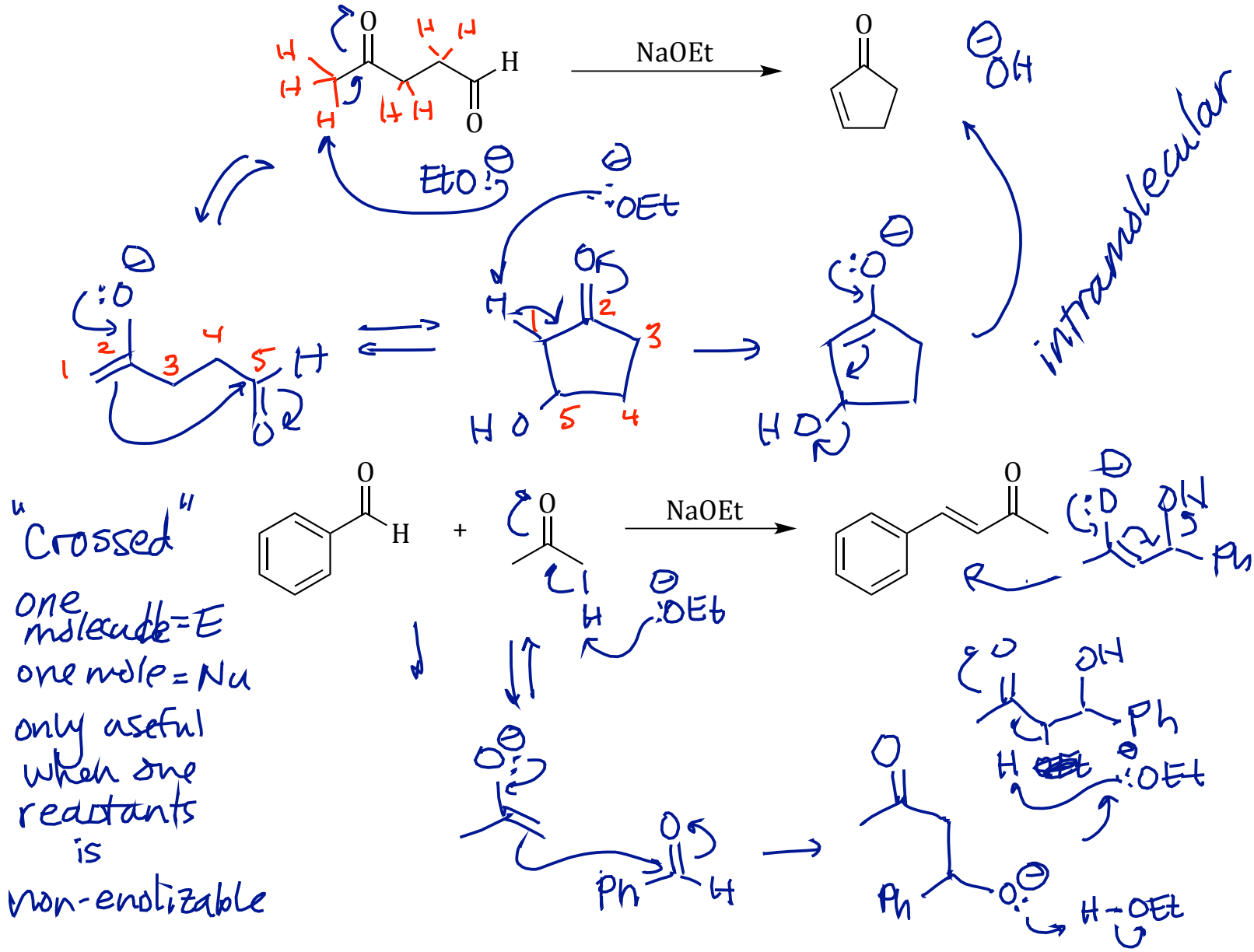
Self-aldol: 2 same molecule

Week 5 July 22, 2014

# The Aldol Reaction:
## Intramolecular & "Crossed" Aldols

5- or 6-membered

Provide complete curved-arrow mechanisms for the following reactions:




Why can "crossed" aldol condensations be used only in limited cases?

Only useful if one partner is non-enolizable

(unambiguous E+, unambiguous Nu)

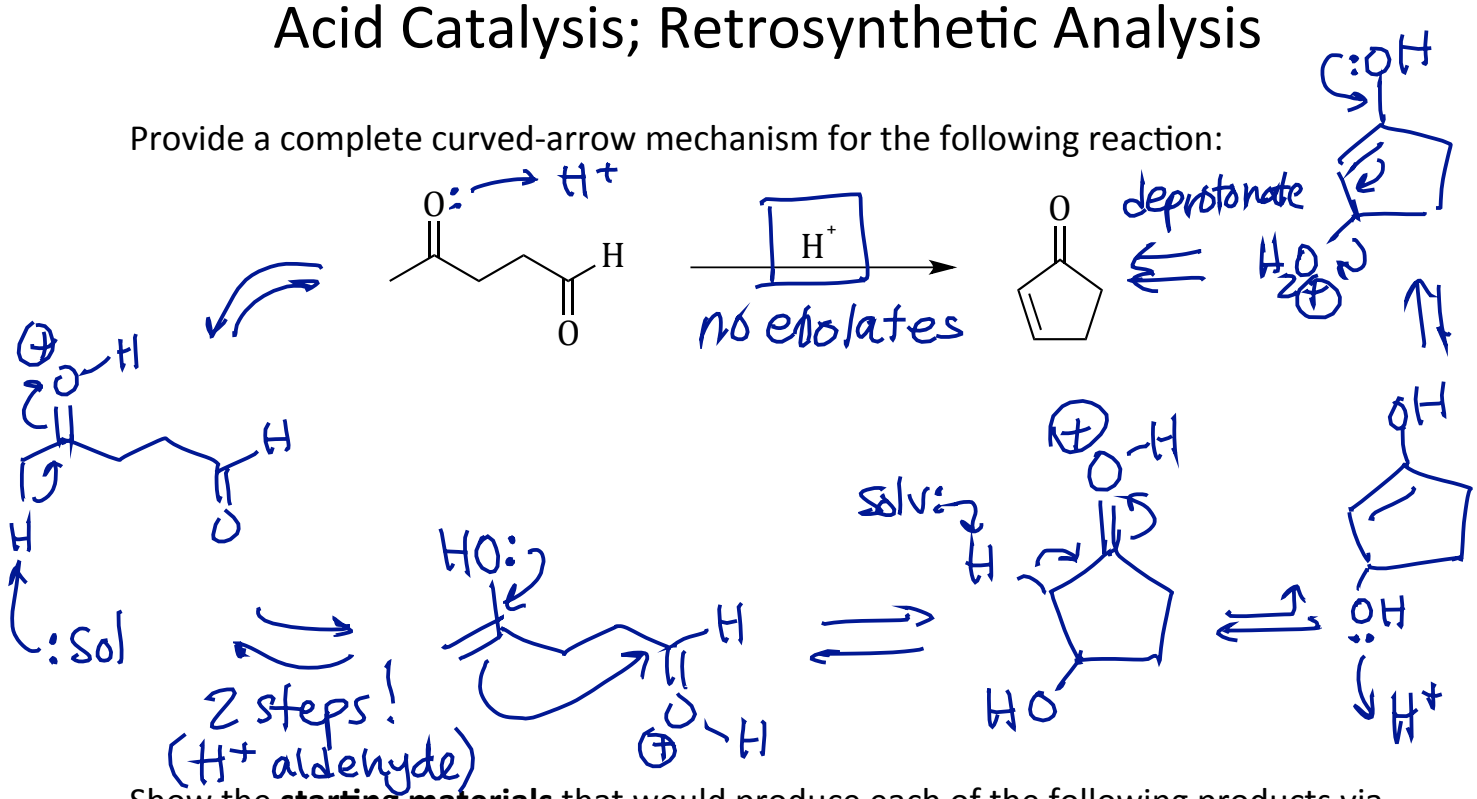
*Reading*: Section 22.4

β-hydroxy carbonyl  α,β-unsaturated carbonyl

Week 5  July 22, 2014

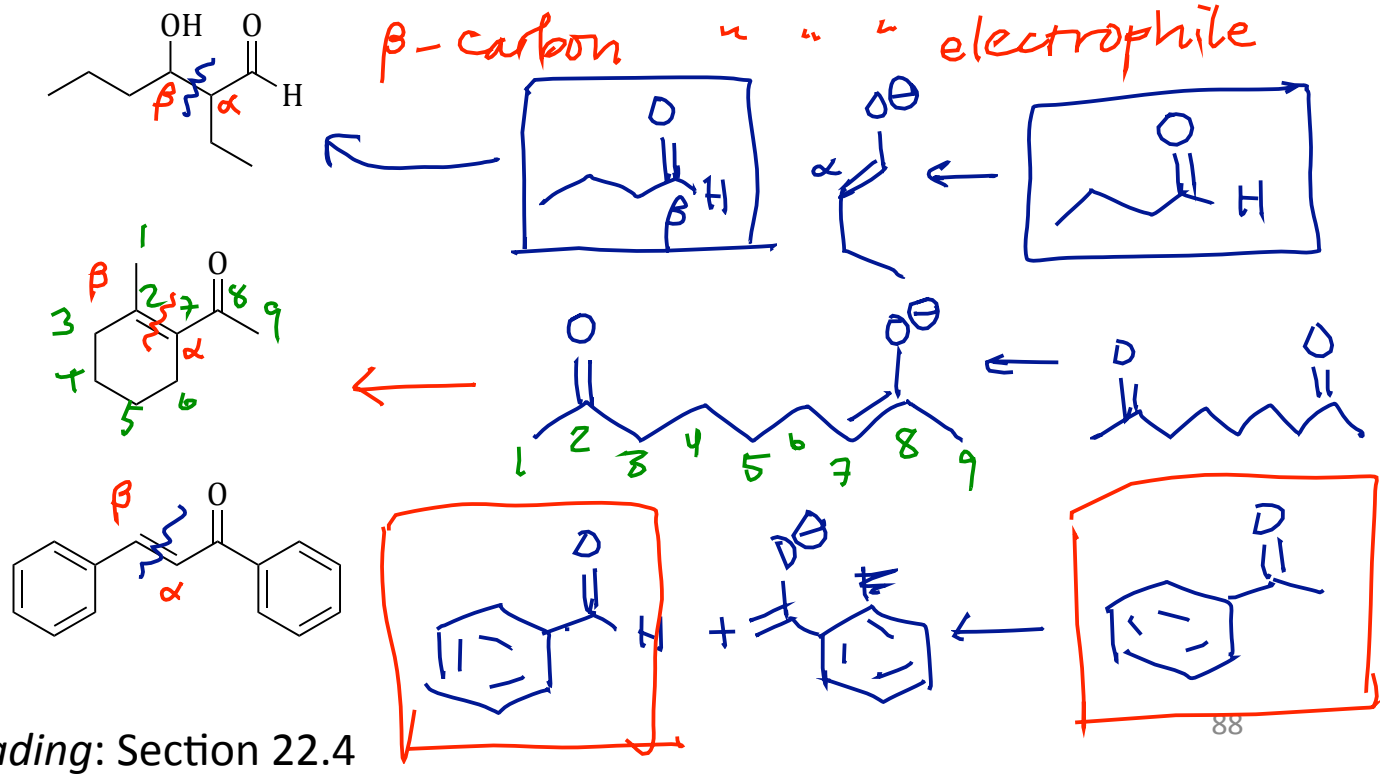
# The Aldol Reaction:
## Acid Catalysis; Retrosynthetic Analysis

Provide a complete curved-arrow mechanism for the following reaction:




Show the **starting materials** that would produce each of the following products via an aldol reaction:

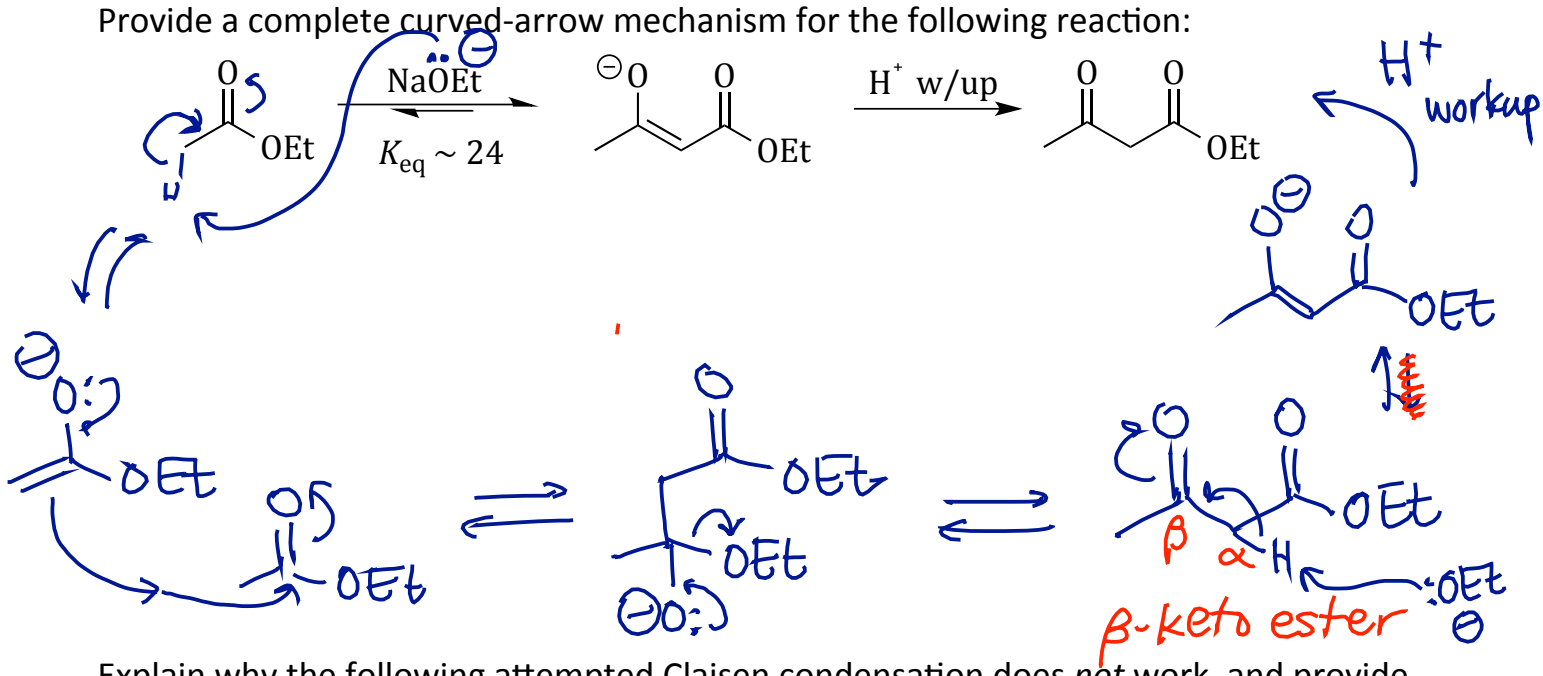
α - carbon used to be enolate (Nu)
β - carbon " " " electrophile



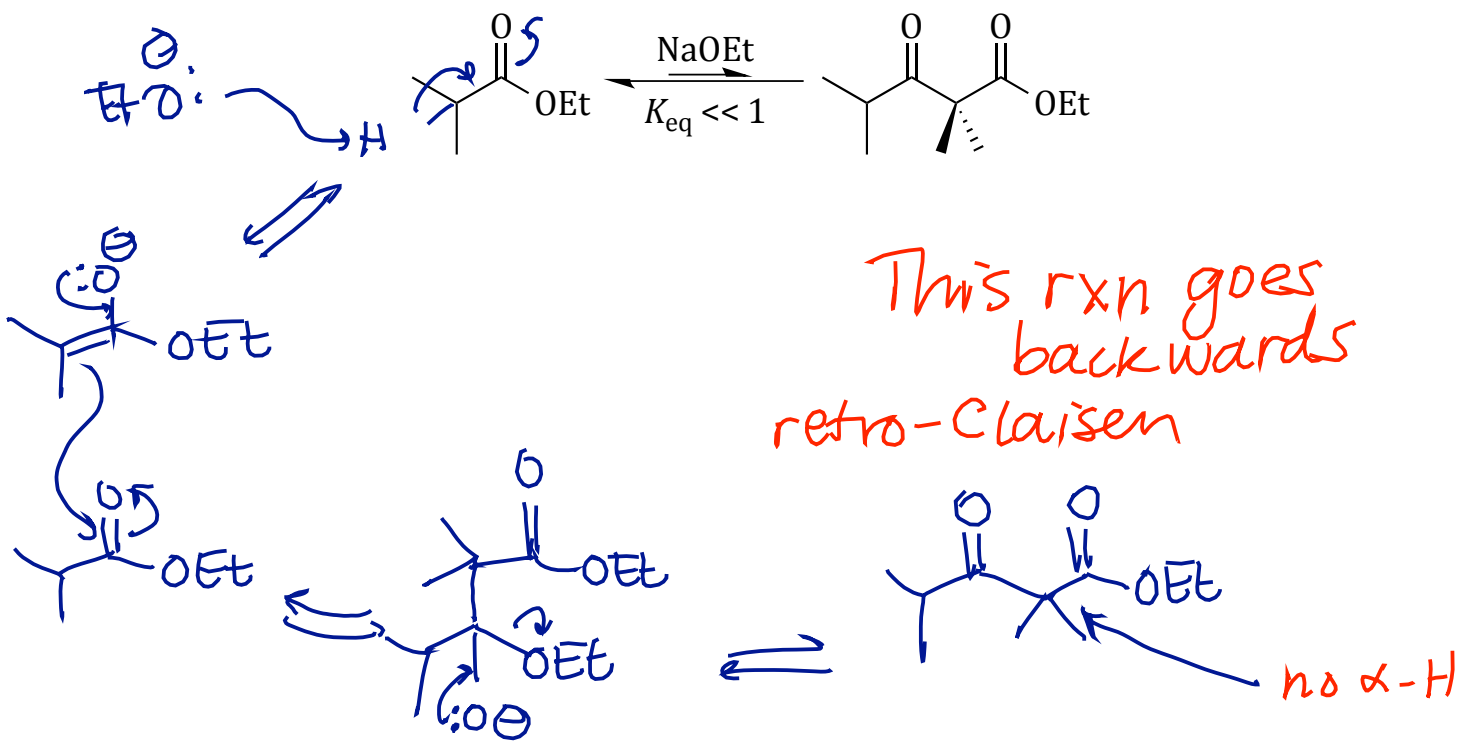
*Reading*: Section 22.4

# The Claisen Condensation:
## Another Cool Reaction

Provide a complete curved-arrow mechanism for the following reaction:




Explain why the following attempted Claisen condensation does *not* work, and provide a curved-arrow mechanism for the *reverse* reaction:



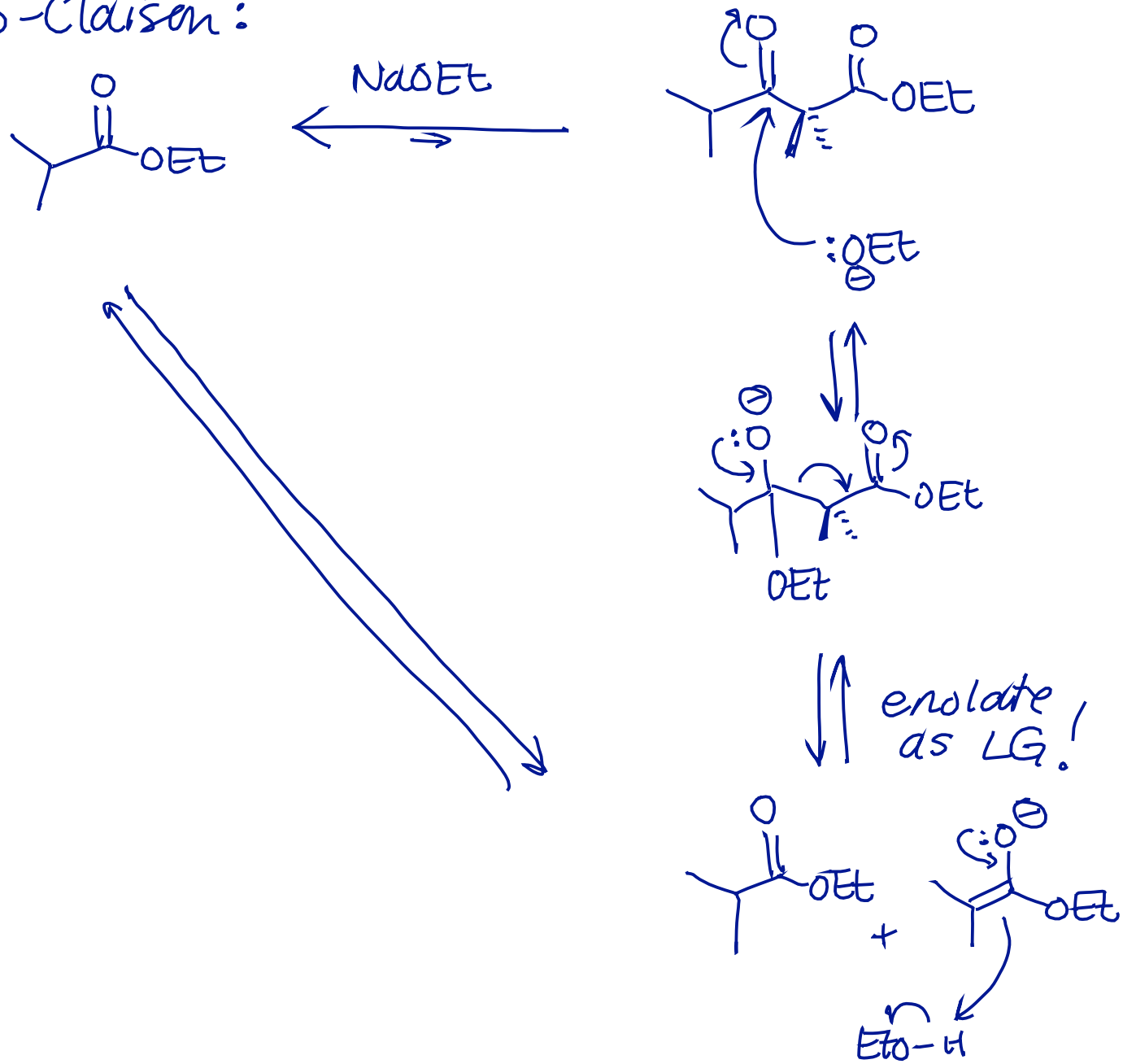



*Reading*: Section 22.5

no acidic proton in β-keto ester

ADD PAGE

Retro-Claisen:




Equibrium favors starting materials...

MUST have α-H in product, which can be IRREVERSIBLY deprotonated...

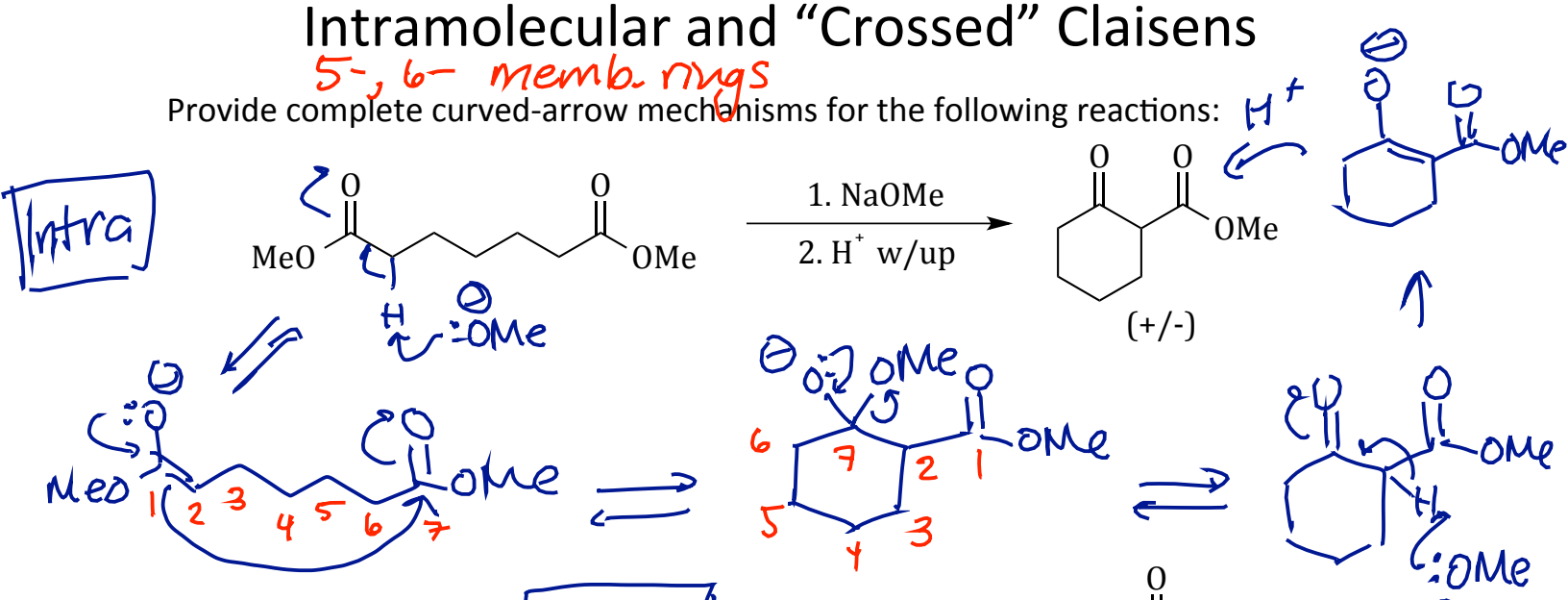
# The Claisen Condensation:

## Intramolecular and "Crossed" Claisens

5-, 6- memb. rings

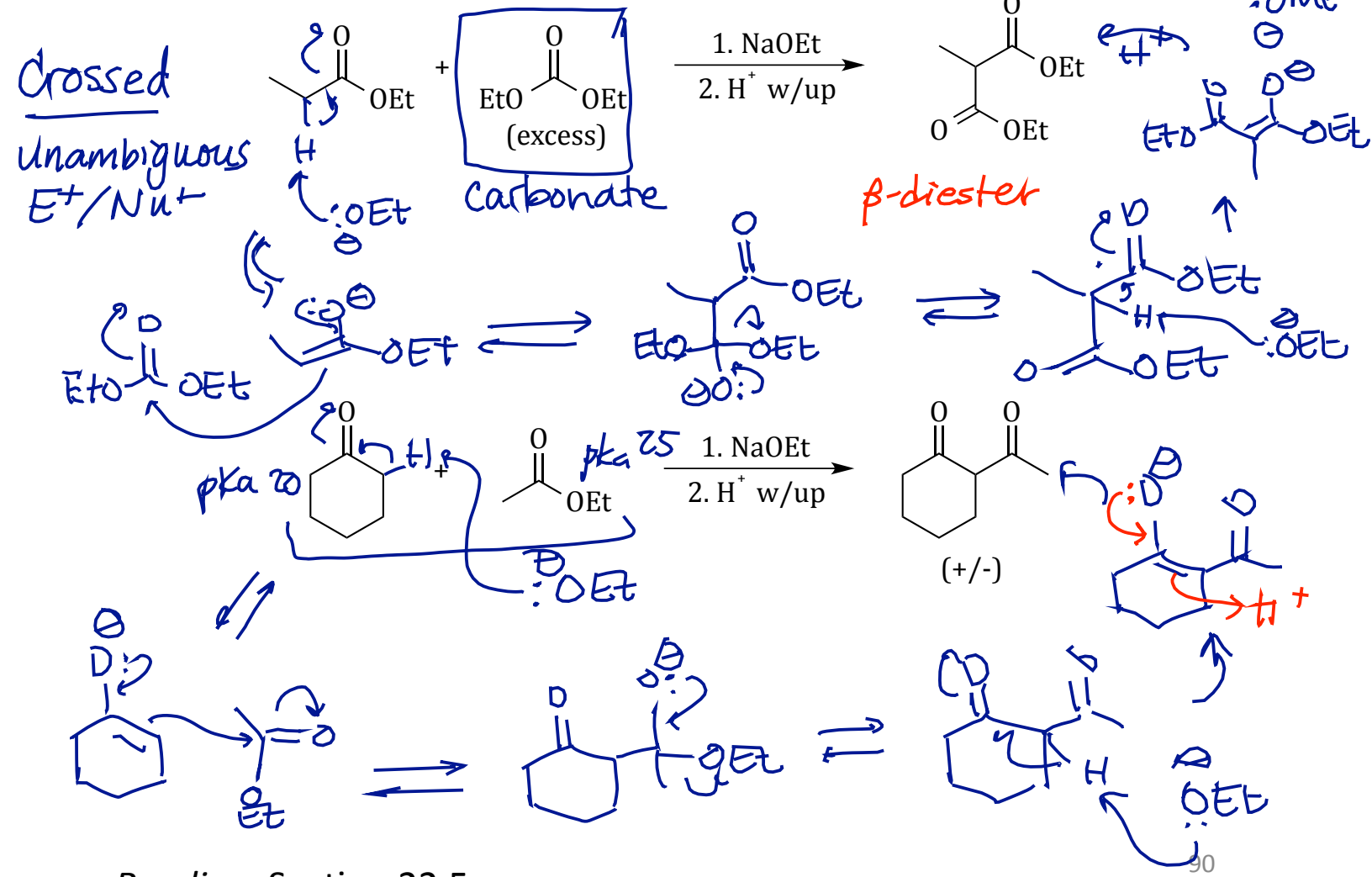
Provide complete curved-arrow mechanisms for the following reactions:

Intra

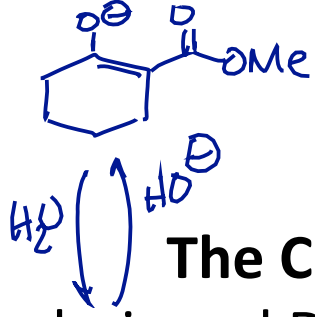



Crossed

Unambiguous E+/Nu+



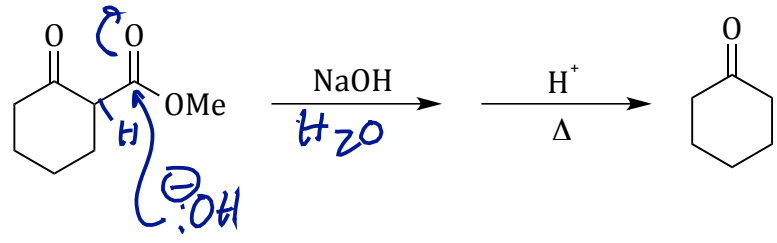

*Reading*: Section 22.5

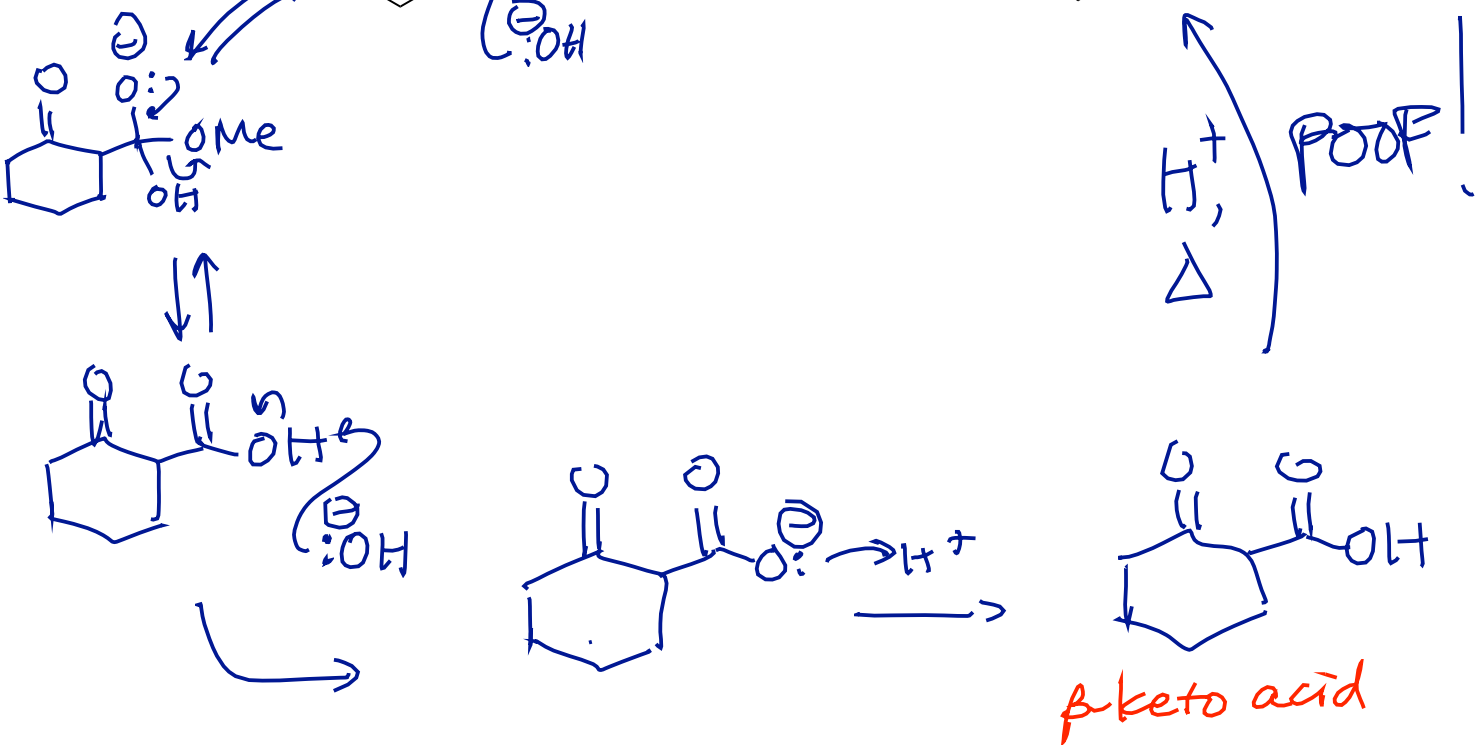


Week 5 July 22, 2014

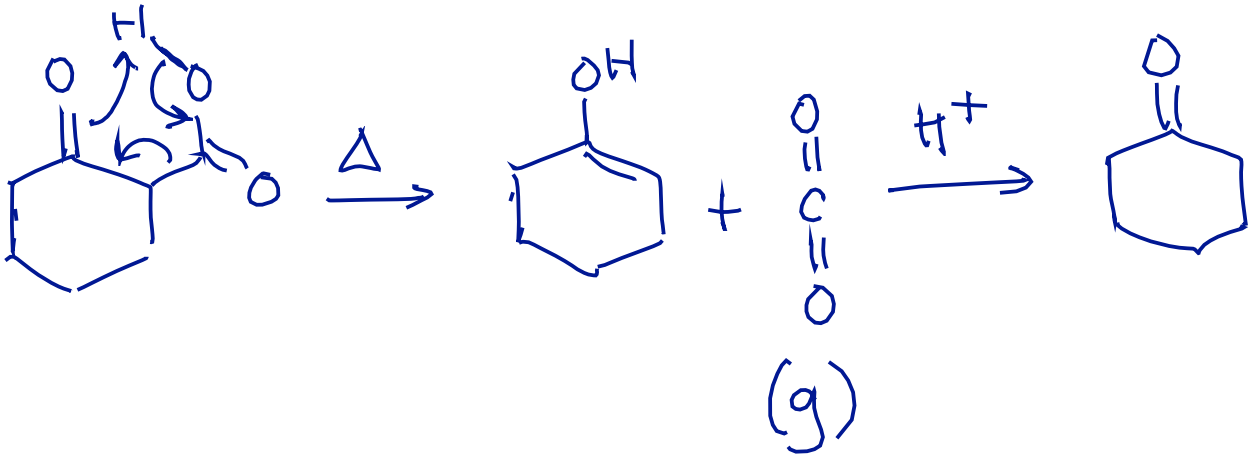
# The Claisen Condensation:
## Hydrolysis and Decarboxylation of β-Keto Esters

Provide a complete curved-arrow mechanism for the following reaction:

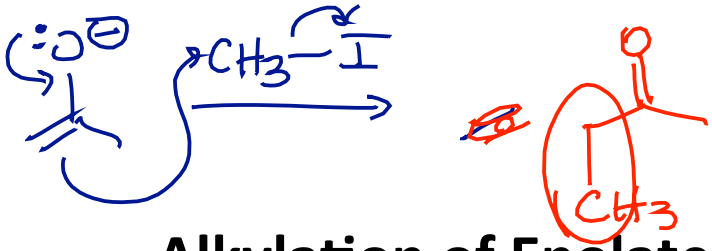



Why is the β-carbonyl *essential* for this reaction?



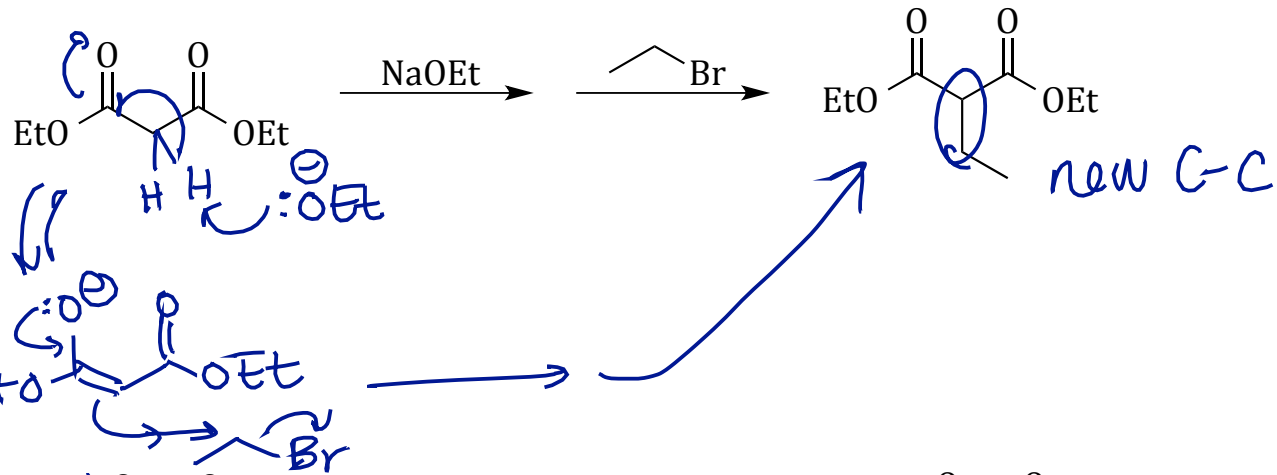

*Reading*: Section 20.11 (not a typo!)

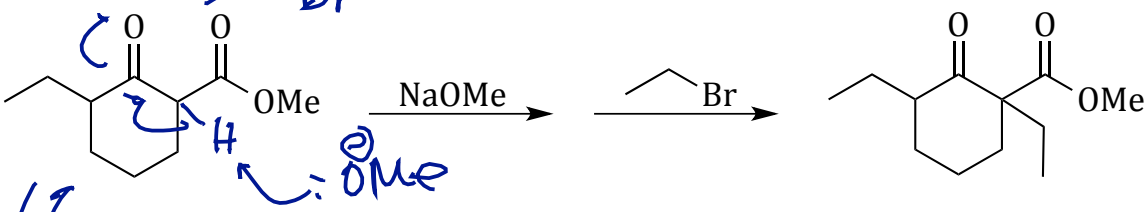


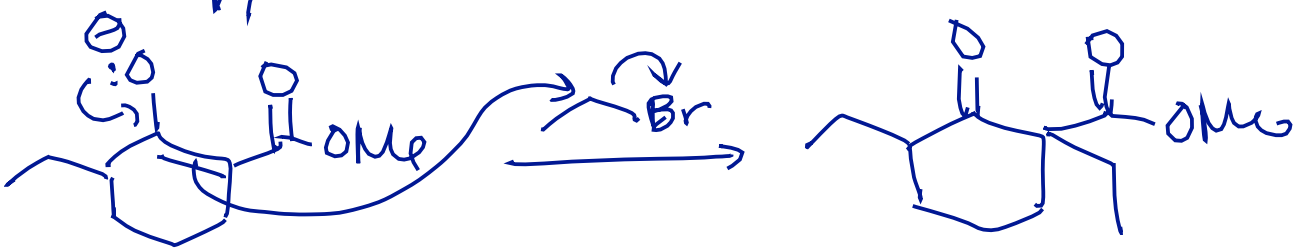
# Alkylation of Enolates

Enolate ions can be good SN2 nucleophiles, but *not* under equilibrium conditions: you need a carbonyl compound to be *completely* deprotonated under the reaction conditions!

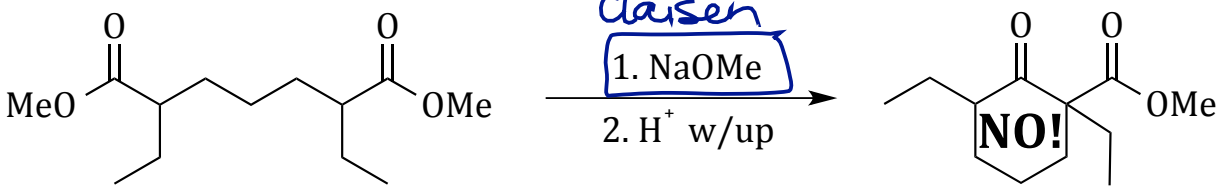
Provide complete curved-arrow mechanisms for the following reactions:



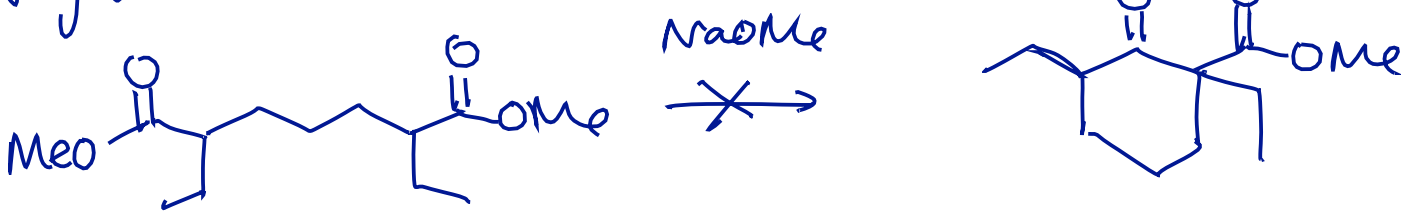



Why can't we use the following Claisen condensation to form the product above?

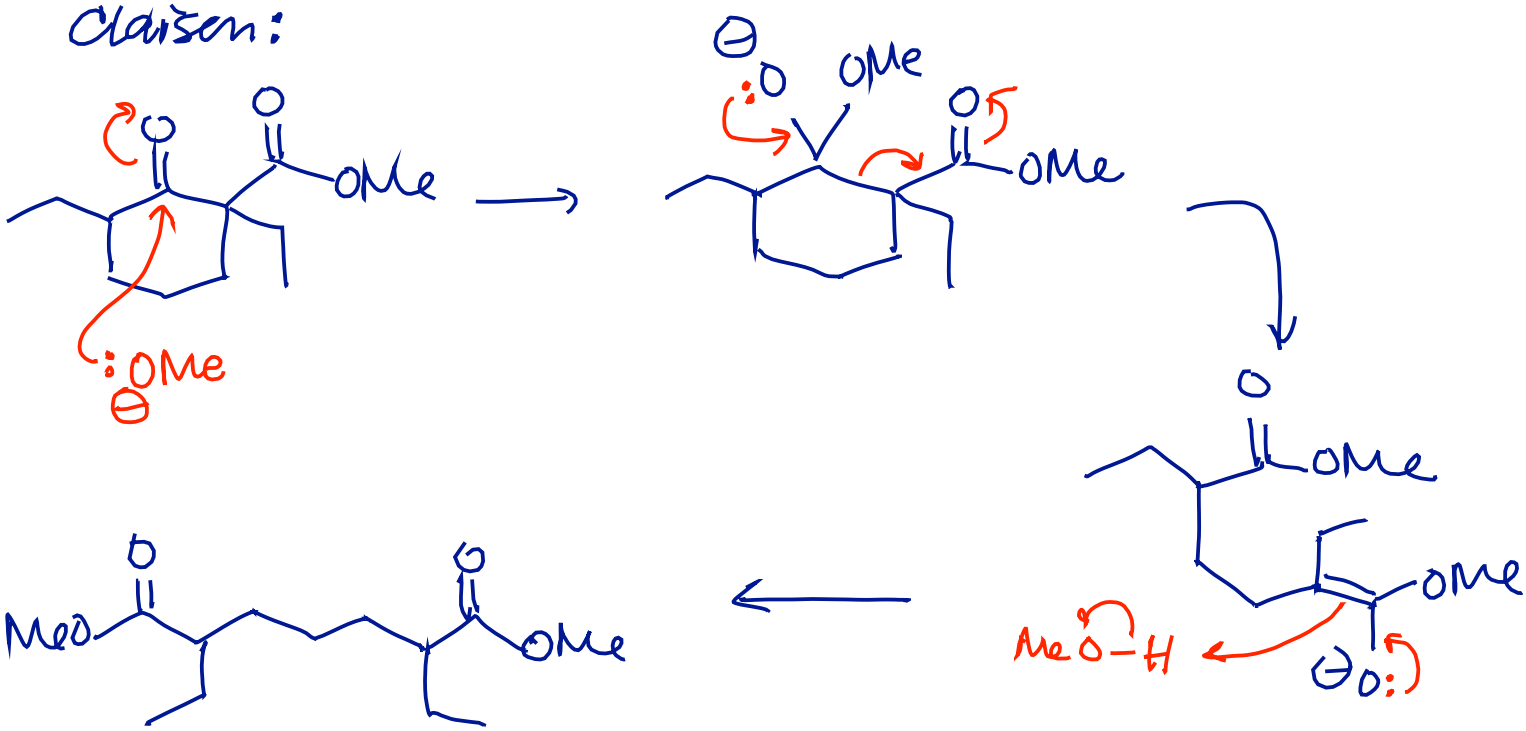



*Reading*: Section 22.7

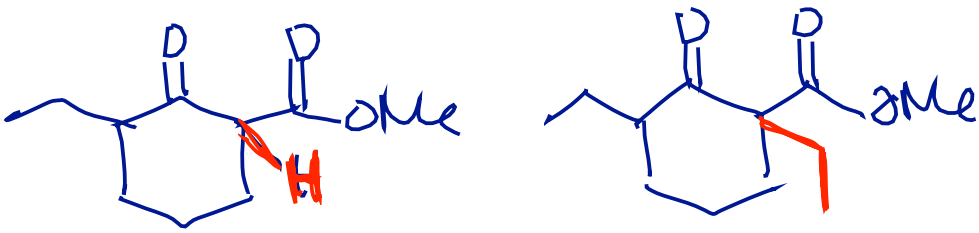
Why?




Because the supposed product undergoes the "retro-Claisen":



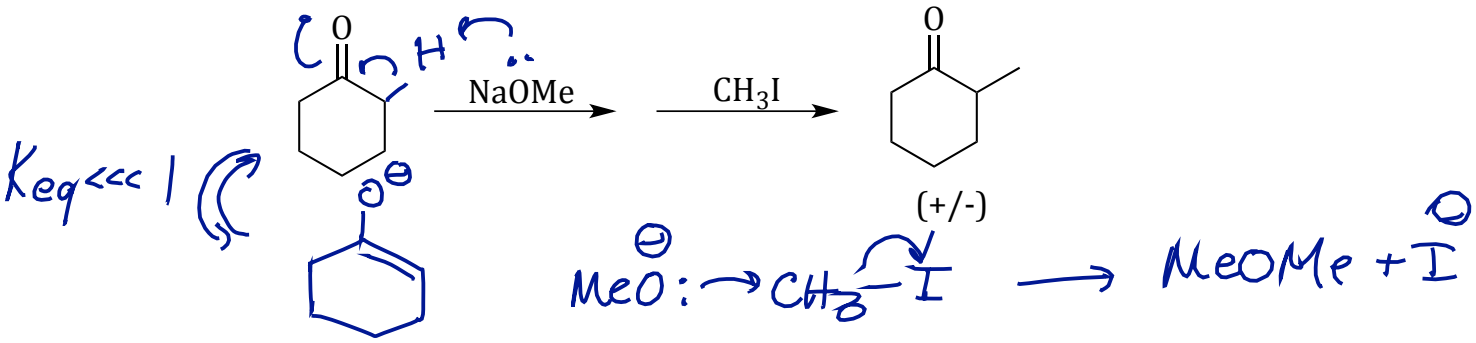

If we had been able to deprotonate the product (the β-keto ester), this reaction WOULD have worked...



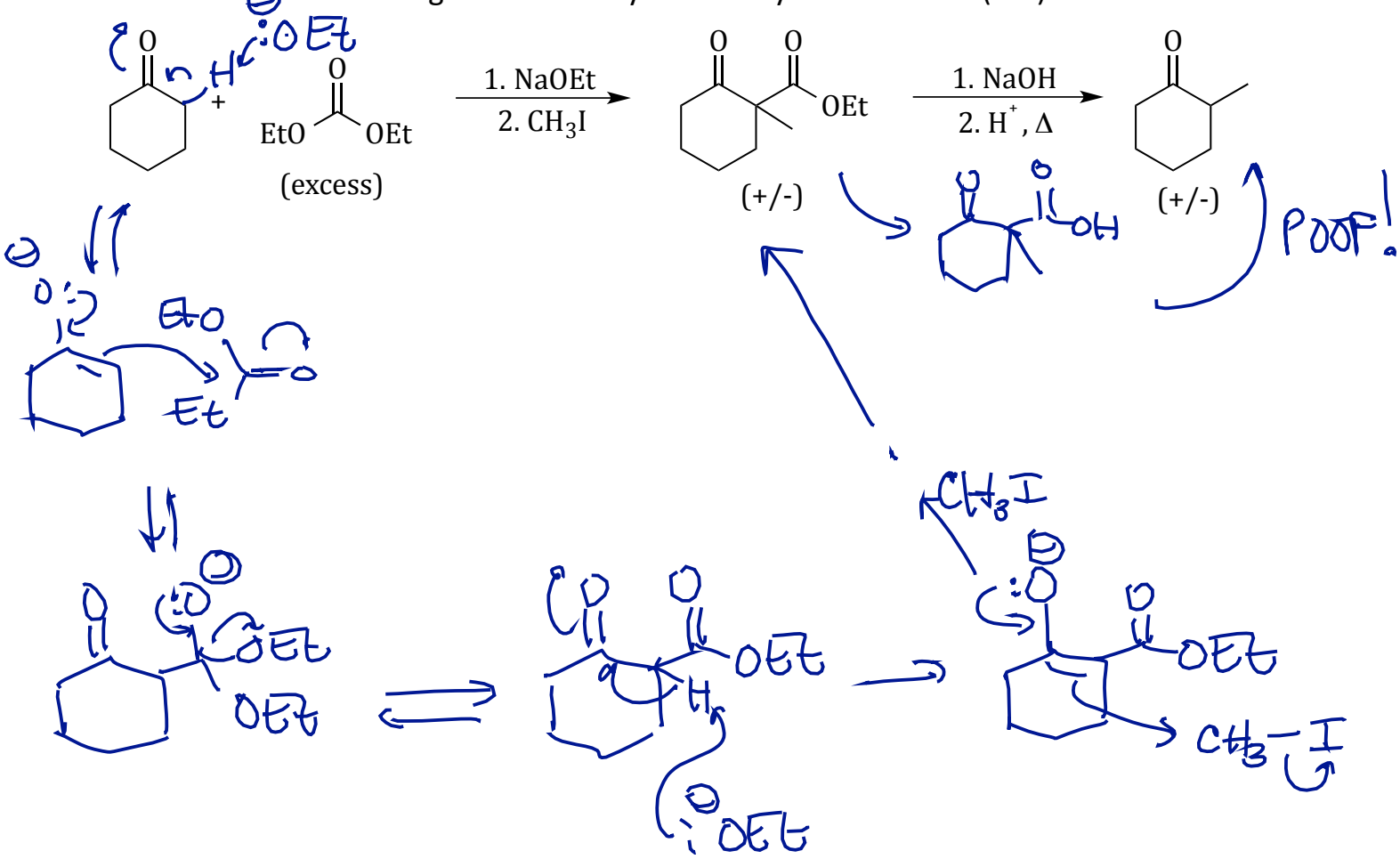

YES. NO.

# Alkylation of Enolates:
## Sequential Alkylation/Decarboxylation

Why can't you carry out the following transformation as written?




Show how the following route allows you to carry out the same (net) transformation.




*Reading*: Section 22.7