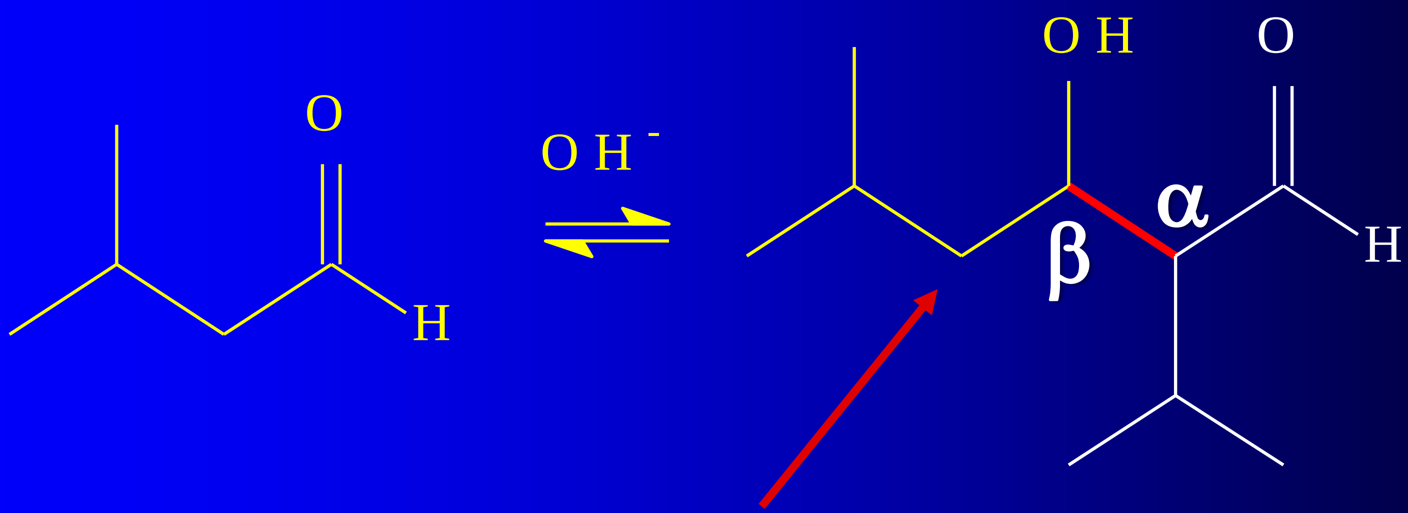
Lecture 22

The Aldol Condensation

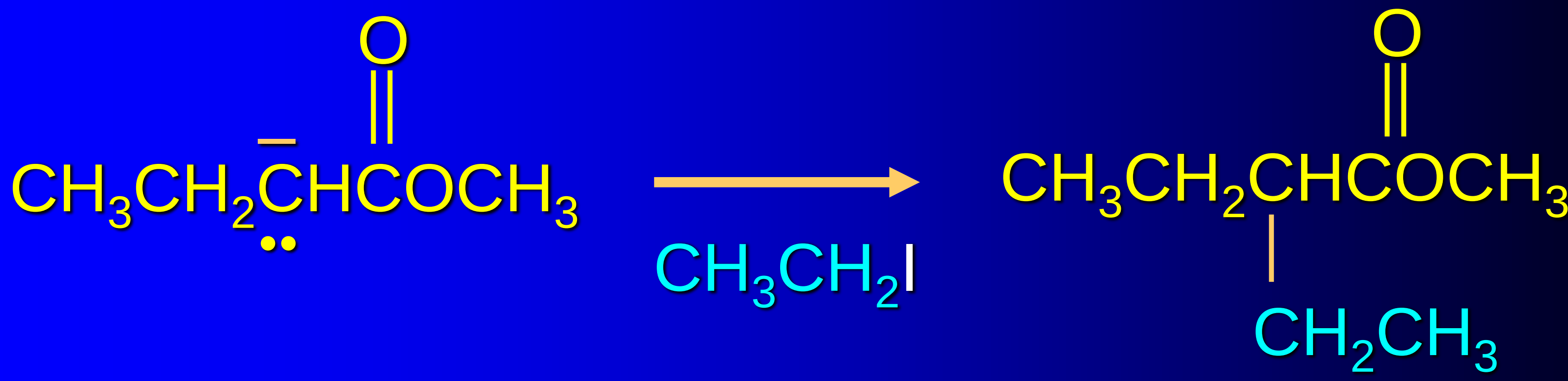


an Aldol!

A Quick Review from Tuesday

Lithium diisopropylamide (LDA)

- Enolates generated from esters and LDA can be alkylated.



(92%)

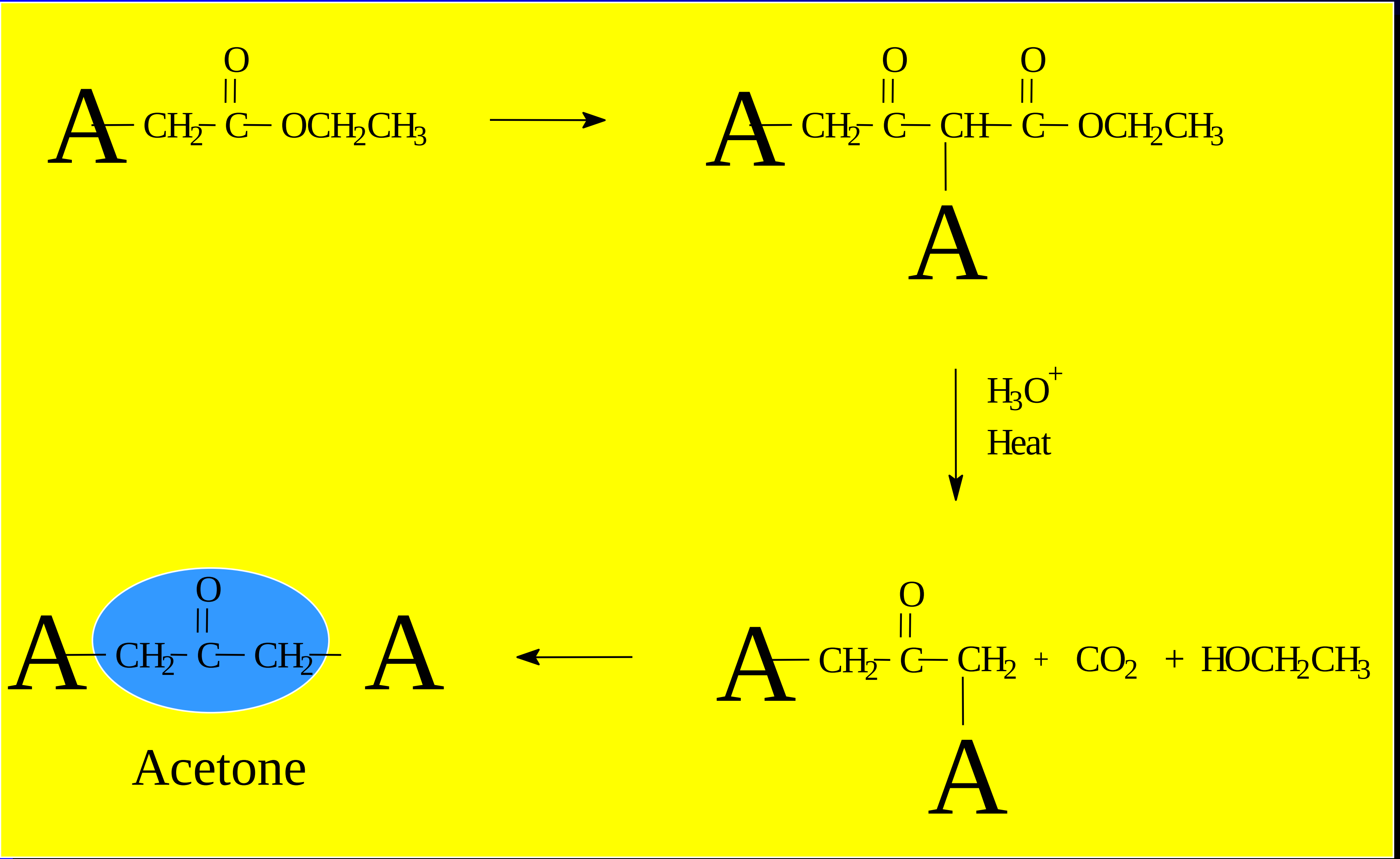
Classical Claisen Condensation

An excellent path to β-keto esters

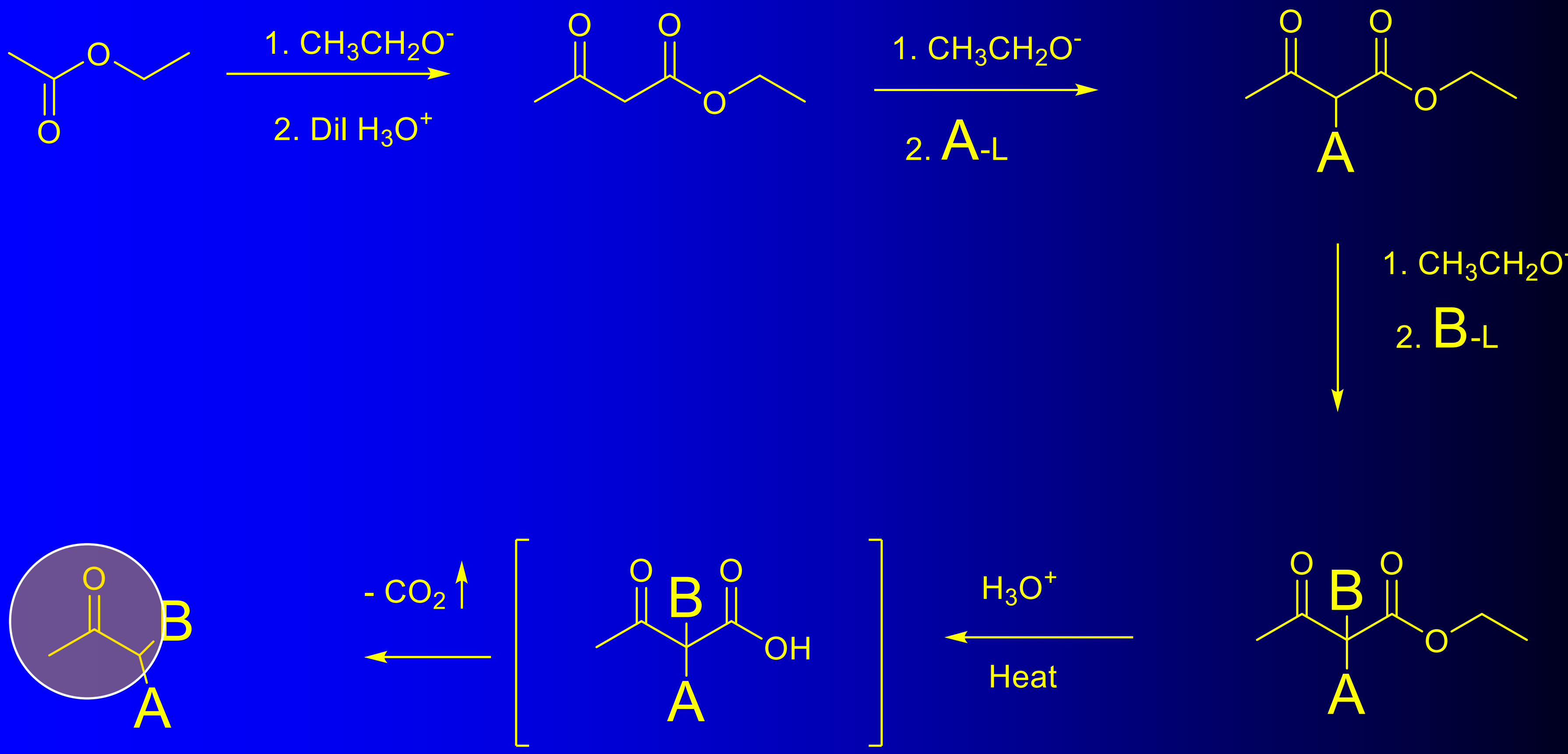
$$2CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaOCH_2CH_3} CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3$$

- Two moles of ethyl acetate condense to give ethyl 3-oxobutanoate or … *ethyl acetoacetate aka acetoacetic ester*

A versatile synthesis of β-ketoesters and *symmetrically* substituted acetones

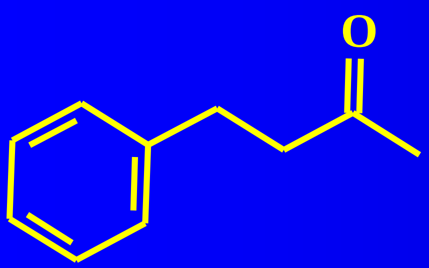


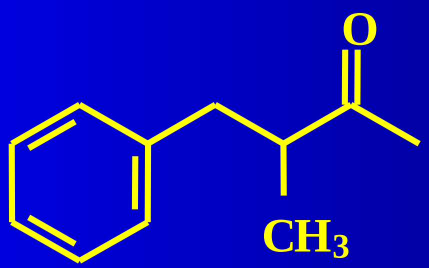
Alkylation of Acetoacetic Ester gives *unsymmetrically* substituted acetone

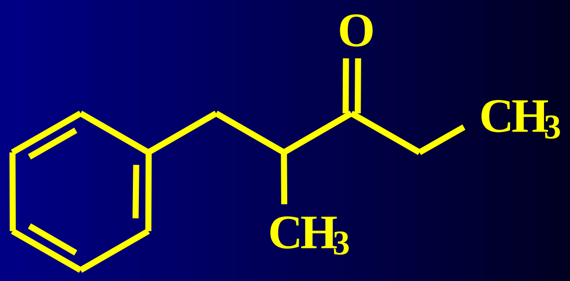


Ketone Synthesis

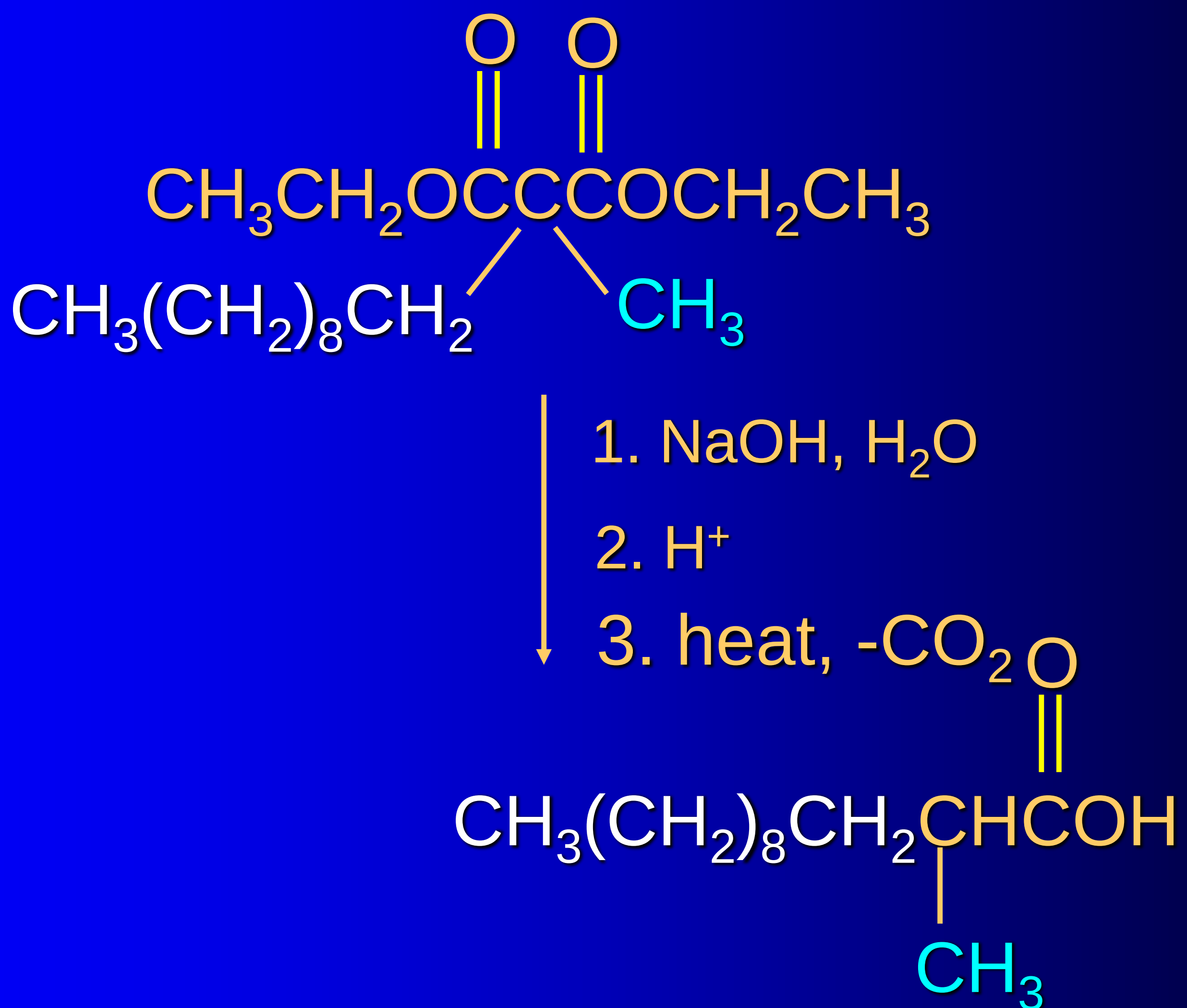
Let’s work another example together







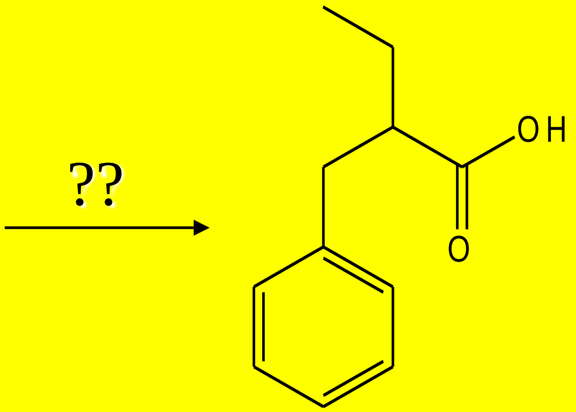
Malonic Ester Synthesis



Versatile Synthesis of Carboxylic acids

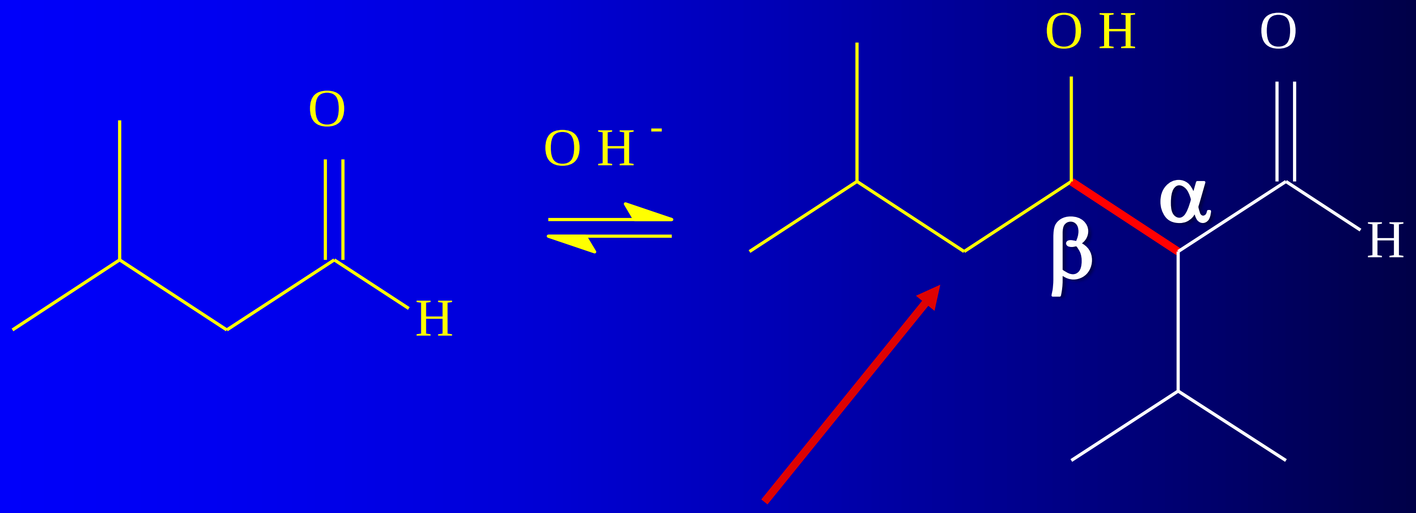
Apply Malonic Ester Synthesis

Write the structure of the malonic ester derivative which would yield this acid and the conditions required to run the reaction



The Aldol Condensation

- The product of an aldol condensation is
  - a β-hydroxyaldehyde…nucleophilic acyl substitution is not possibe here….why??

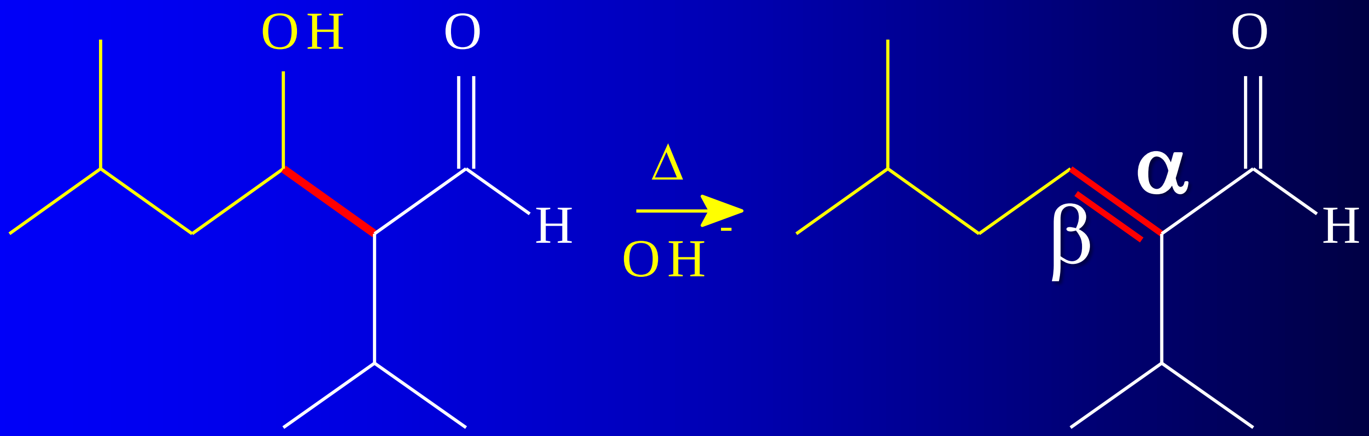


an Aldol!

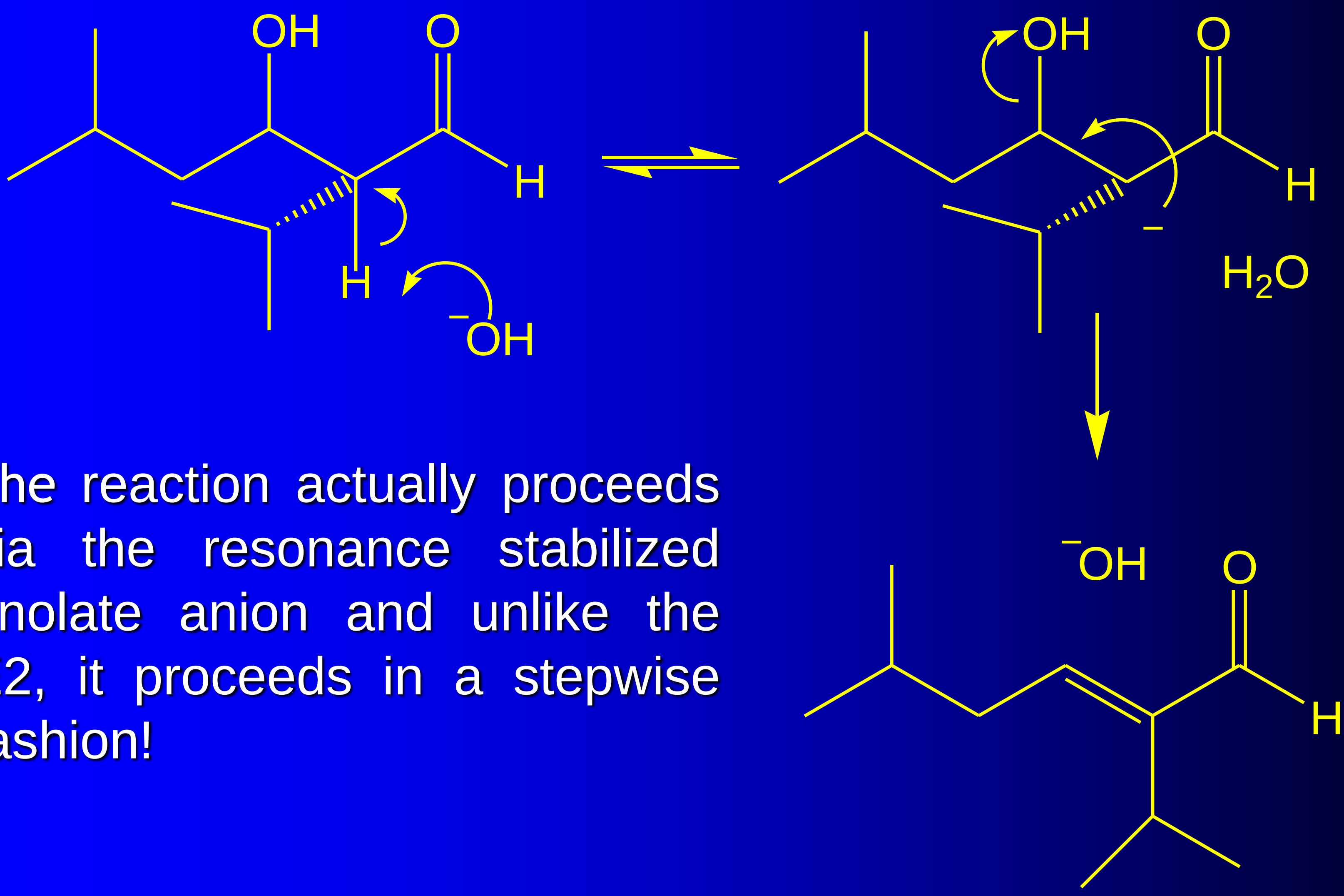
{Aldehyde / Alcohol}

Loss of water!

- Aldol products are easily dehydrated so the major product is an α,β-unsaturated aldehyde or ketone



“E_2 like” Elimination



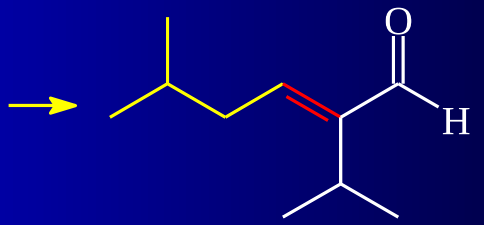
The reaction actually proceeds via the resonance stabilized enolate anion and unlike the E2, it proceeds in a stepwise fashion!

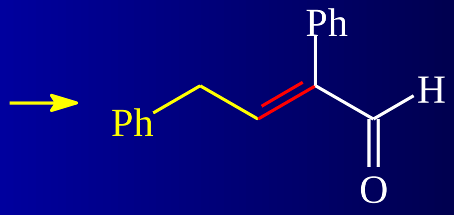
A Note about Aldol Reactions

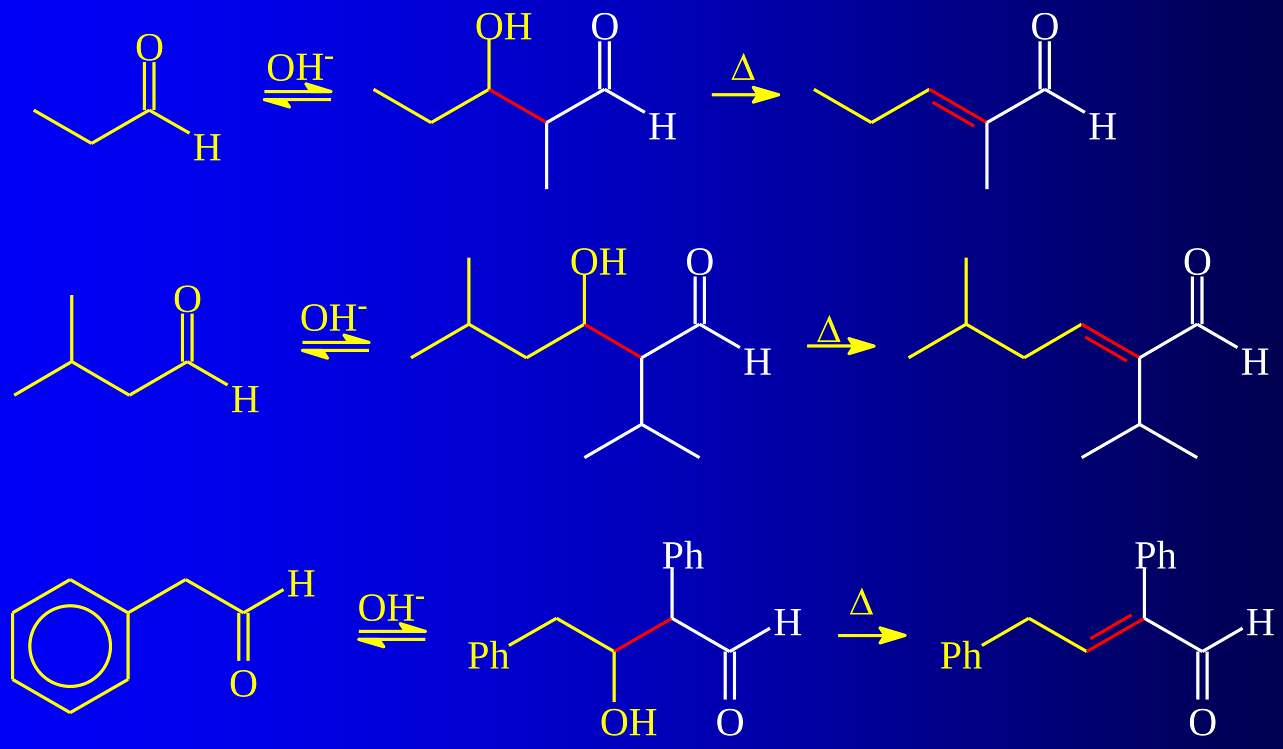
aldol reactions are reversible and, particularly for ketones, there is often little aldol present at equilibrium. K_{eq} for dehydration is generally large and, if reaction conditions bring about dehydration, good yields of product can be obtained

It takes special efforts to isolate an Aldol…the product is generally the a,b -unsaturated aldehyde or ketone

What are the starting materials that lead to these producs via the Aldol condensation

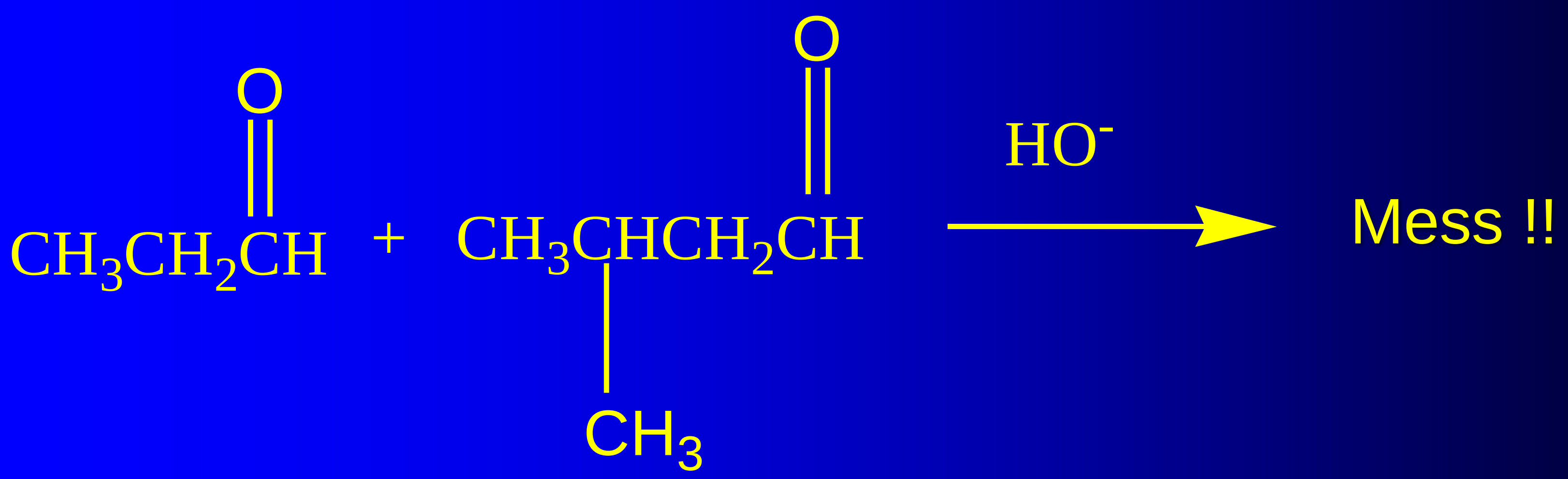





O
H
OH-
OH
O
H
Δ
O
H
O
H
OH-
OH
O
H
Δ
O
H
H
O
OH-
Ph
Ph
H
OH
O
Δ
Ph
Ph
H
O

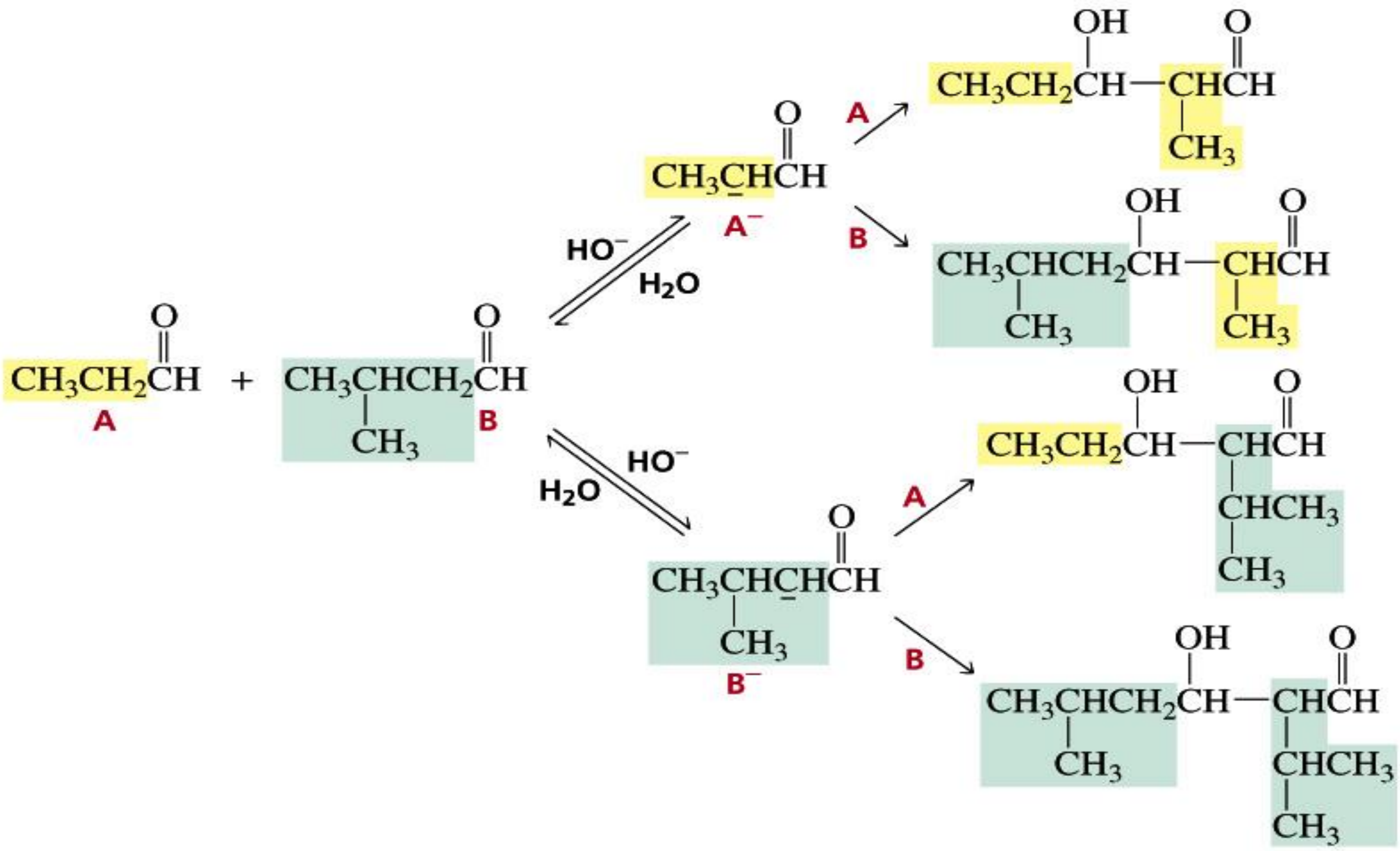
Crossed Aldol Reactions

- In a “crossed aldol” reaction, one kind of molecule provides the enolate anion and another kind provides the carbonyl group



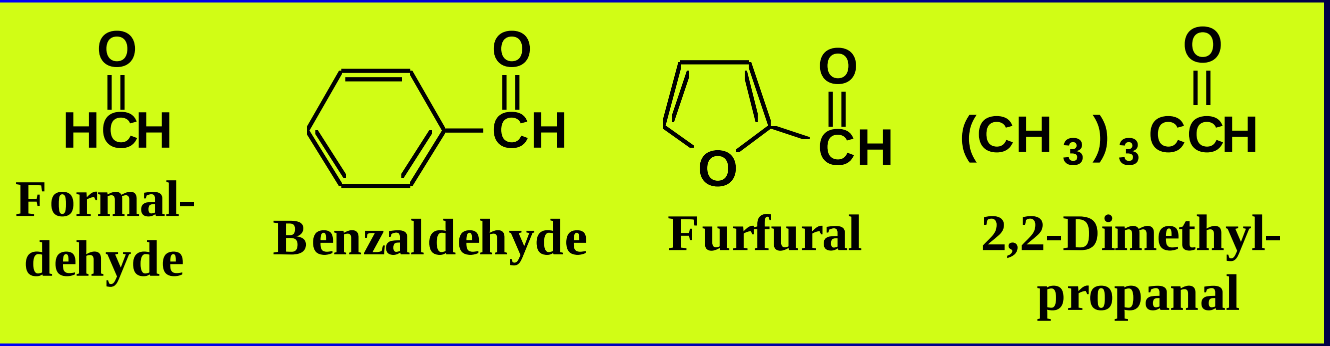
In most cases, this makes a big fat mess!!

The Crossed Aldol Reaction



Crossed Aldol Reactions

- Crossed aldol reactions only work if:
  - one of the reactants has no α-hydrogen and, therefore, cannot form an enolate anion and
  - the other reactant has a very reactive carbonyl group, namely an aldehyde



Look…no a-hydrogens…. so no enolate anions!!

Let’s discuss a plan for actually running a crossed aldol reaction

Does the addition sequence matter??

What goes into the pot first, second and third?

The Signature Page

Claisen Condensation: β-ketoesters

Dieckmann: Cyclic β-ketoesters

Acetoacetic ester synthesis: decorated acetones

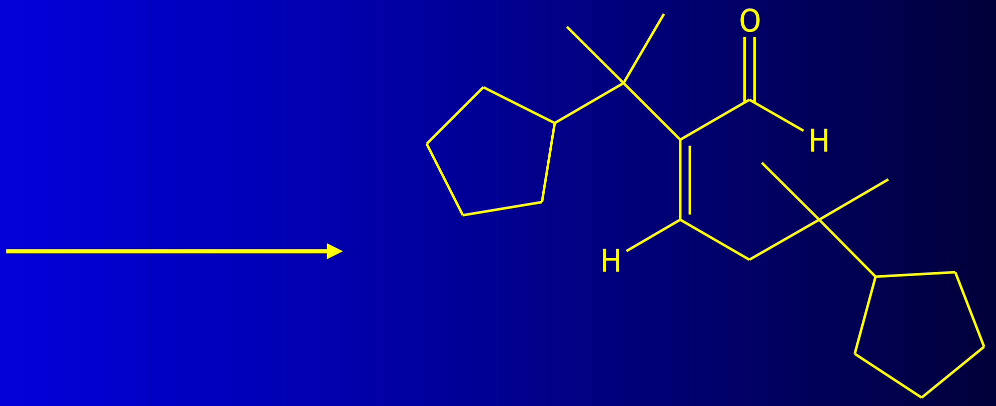
Malonic ester synthesis: decorated acetic acids

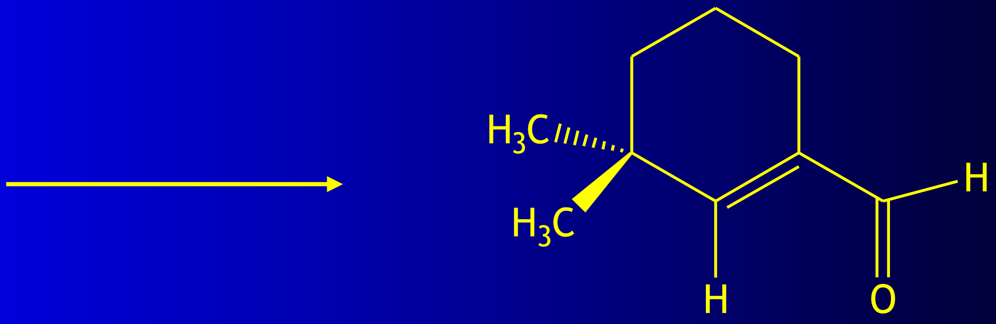
Aldol: α, β-unsaturated aldehydes and ketones

Grignard Reaction: Alcohols…, etc.

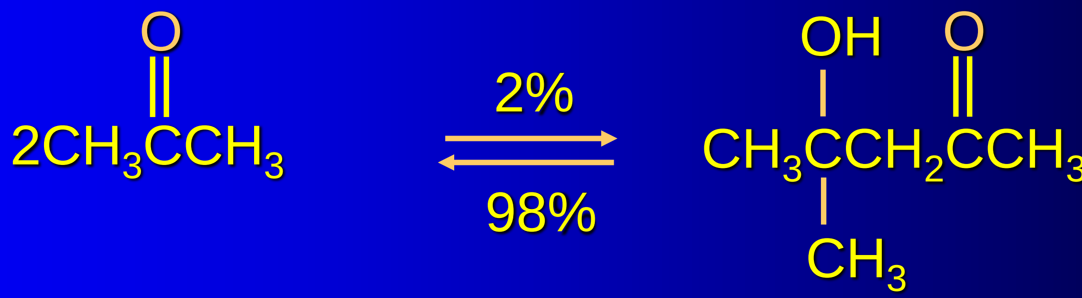
Wittig:

From what??

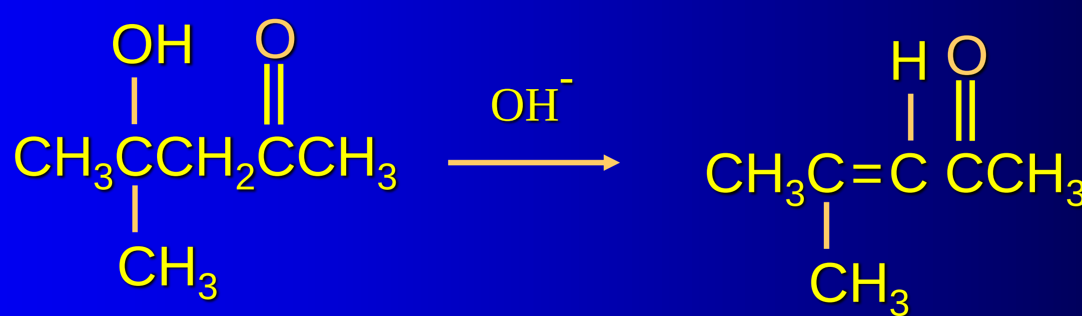




Aldol reactions of ketones

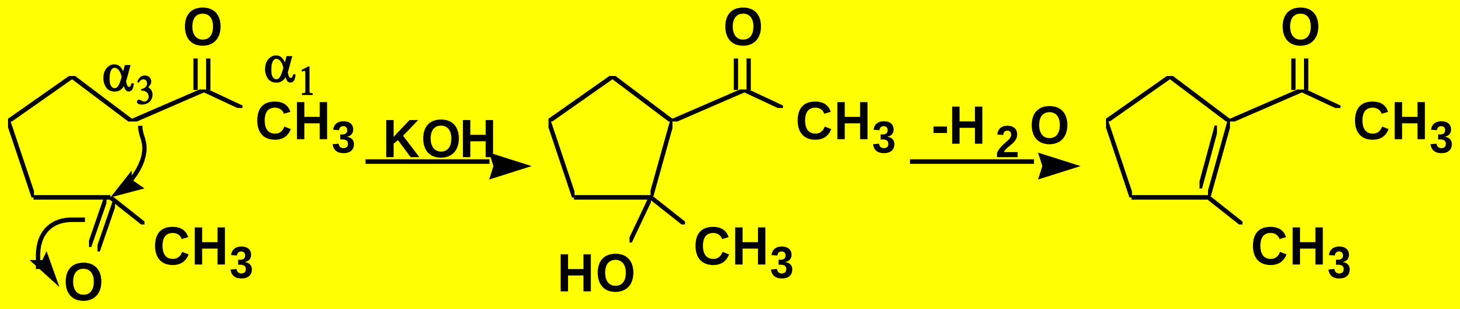


- the equilibrium constant for aldol addition reactions of ketones is usually unfavorable but can be driven by dehydration



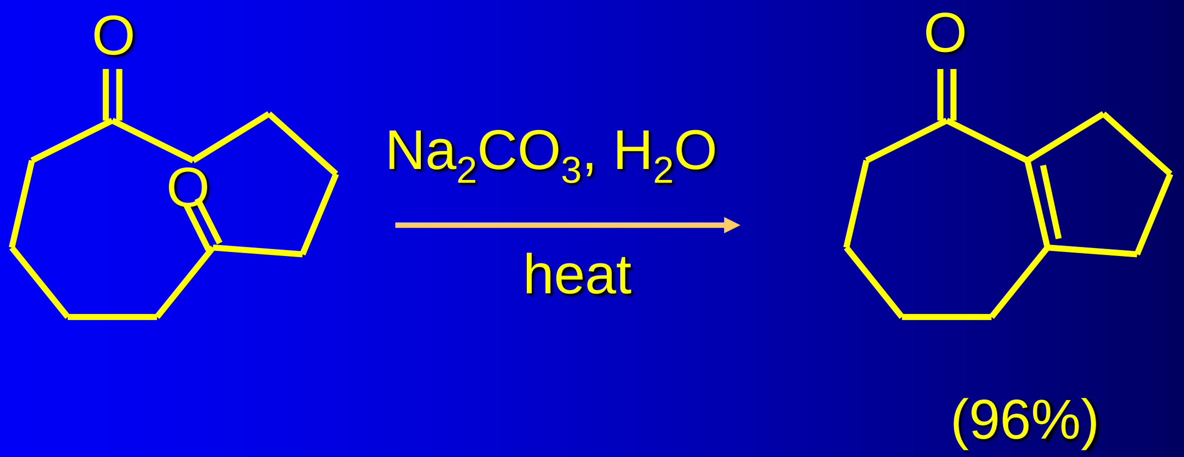
Aldol Reactions

- Intramolecular aldol reactions (when the enolate anion and the carbonyl acceptor are in the same molecule) are most successful for formation of five- and six-membered rings



2,7-Octanedione

Intramolecular Aldol Condensation



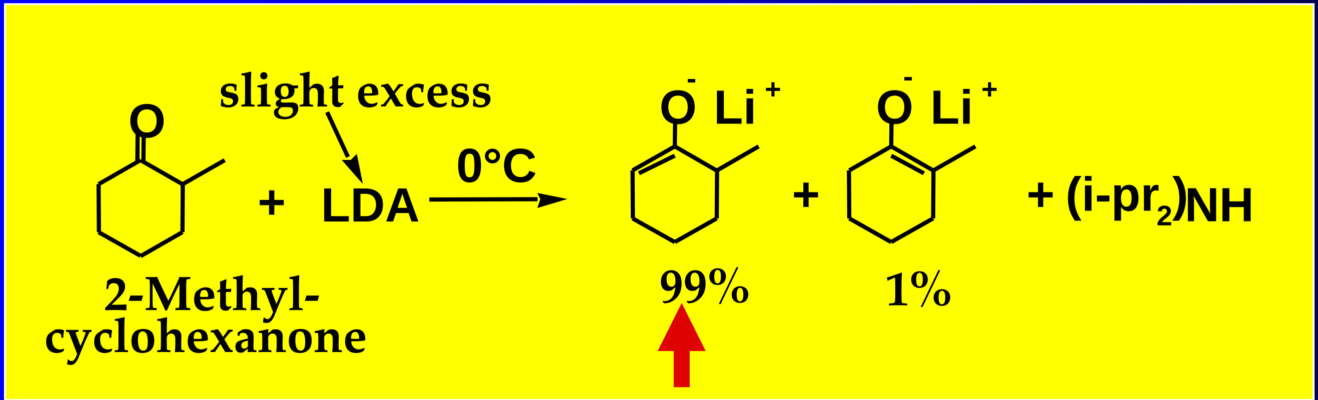
- ketones give very good yields of aldol condensation products when the reaction is intramolecular and driven by dehydration

Enolate Anions

- When a ketone has two different α-hydrogens, is formation of the enolate anion regio-selective?
- The answer depends on experimental conditions

Kinetic Control

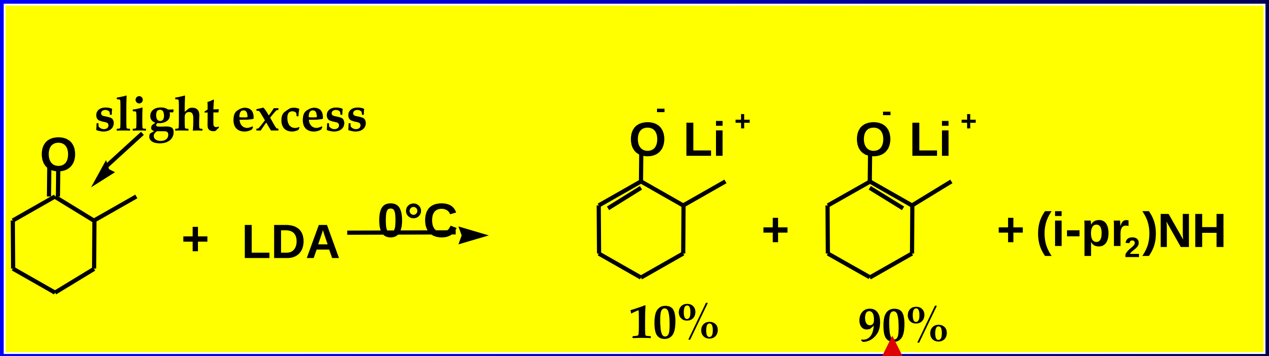
– with slight excess of LDA



"fastest" but least stable

Thermodynamic Control

– **With slight excess of ketone**



Slow but most Stable

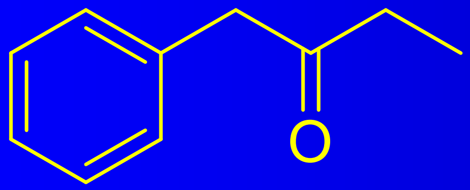
Kinetic Control

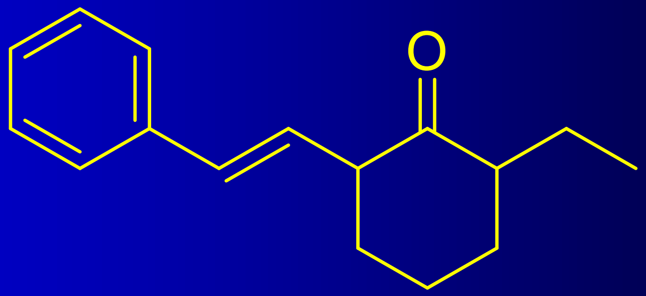
- **When a reaction is under kinetic control, the composition of the product mixture is determined by the <u>relative rates</u> of formation of each product**

Thermodynamic Control

- **When a reaction is under thermodynamic control, the composition of the product mixture is determined by the <u>relative stabilities</u> of each product**

Which position is “thermodynamic” ???
Why??



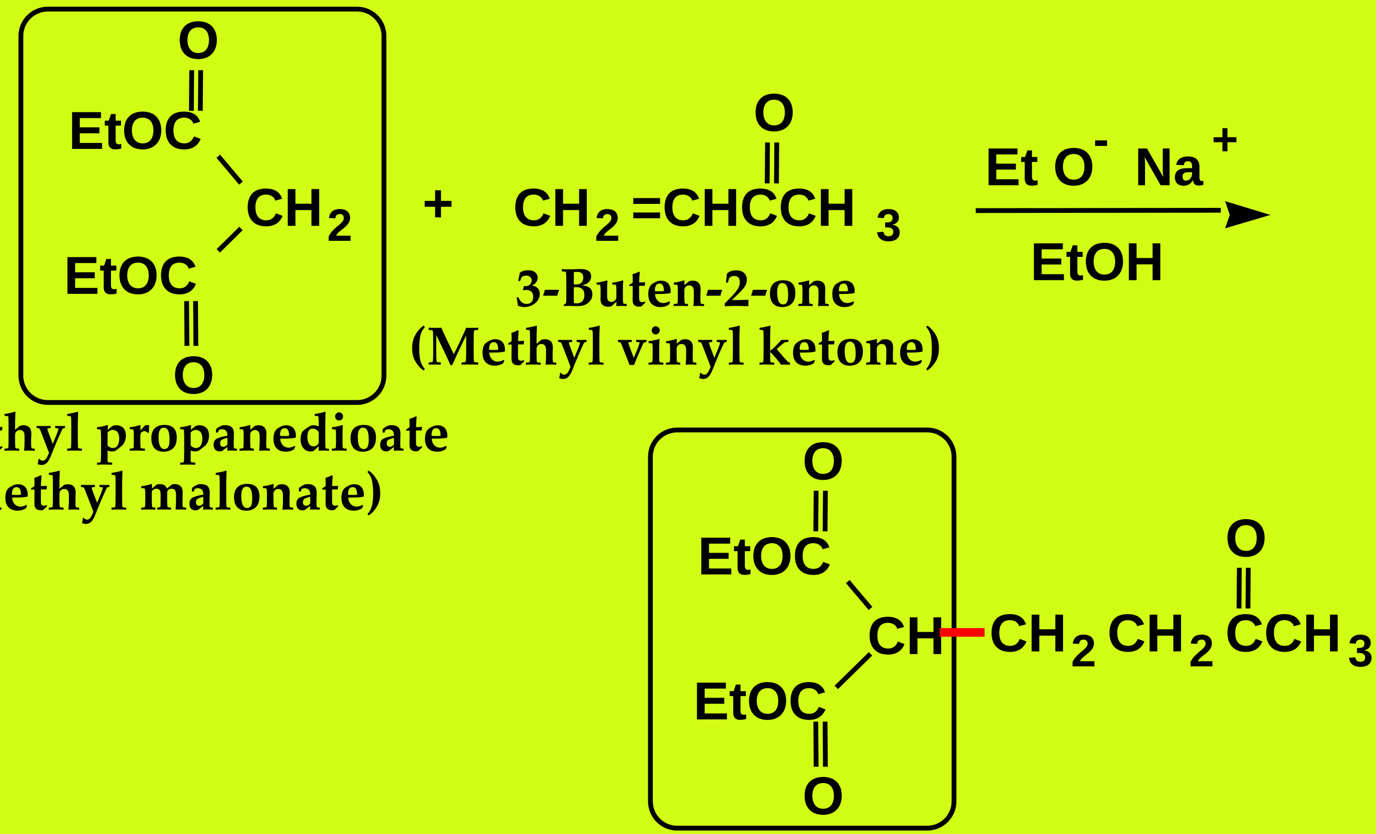


Michael Reaction

- Michael reaction: conjugate addition of an enolate anion to an [...]nyl compound!!
- Following a[...]
  - in the first[...]on of malonic ester
  - in the seco[...] of acetoacetic ester
- An excellen[...]yl compounds

Arthur Michael

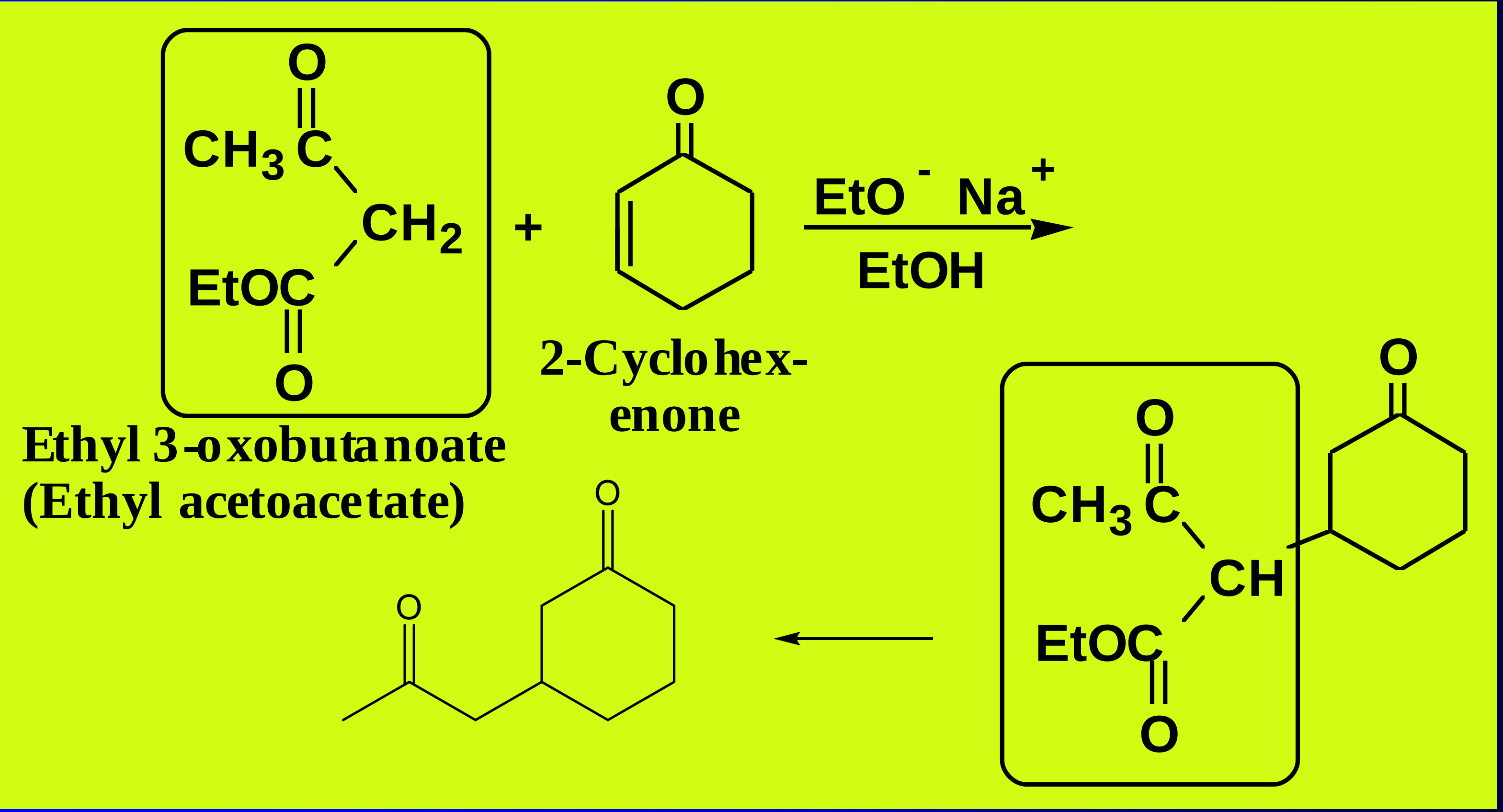
Michael Reaction



Diethyl propanedioate
(Diethyl malonate)

3-Buten-2-one
(Methyl vinyl ketone)

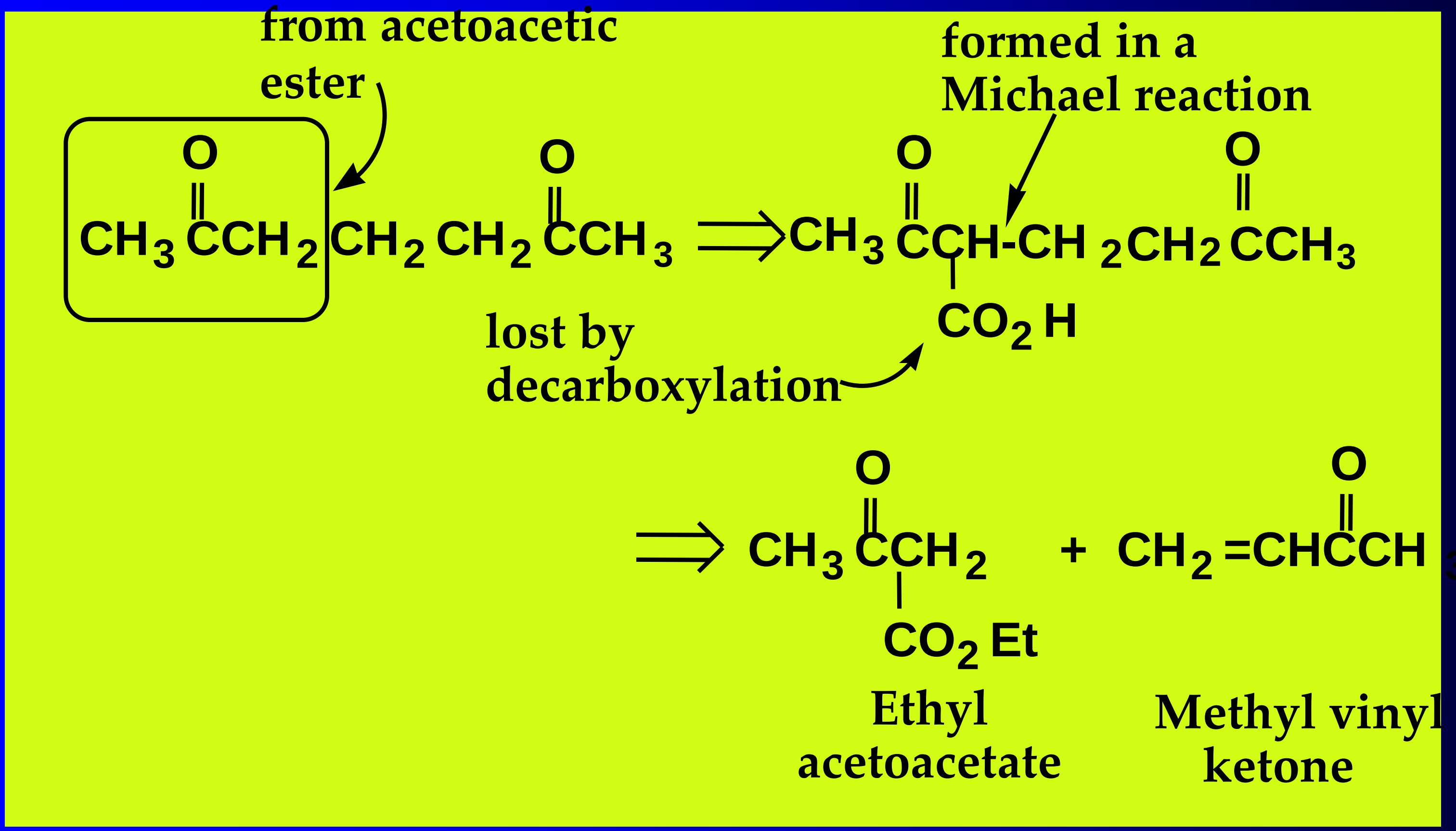
Michael Reaction



Ethyl 3-oxobutanoate
(Ethyl acetoacetate)

2-Cyclohex-
enone

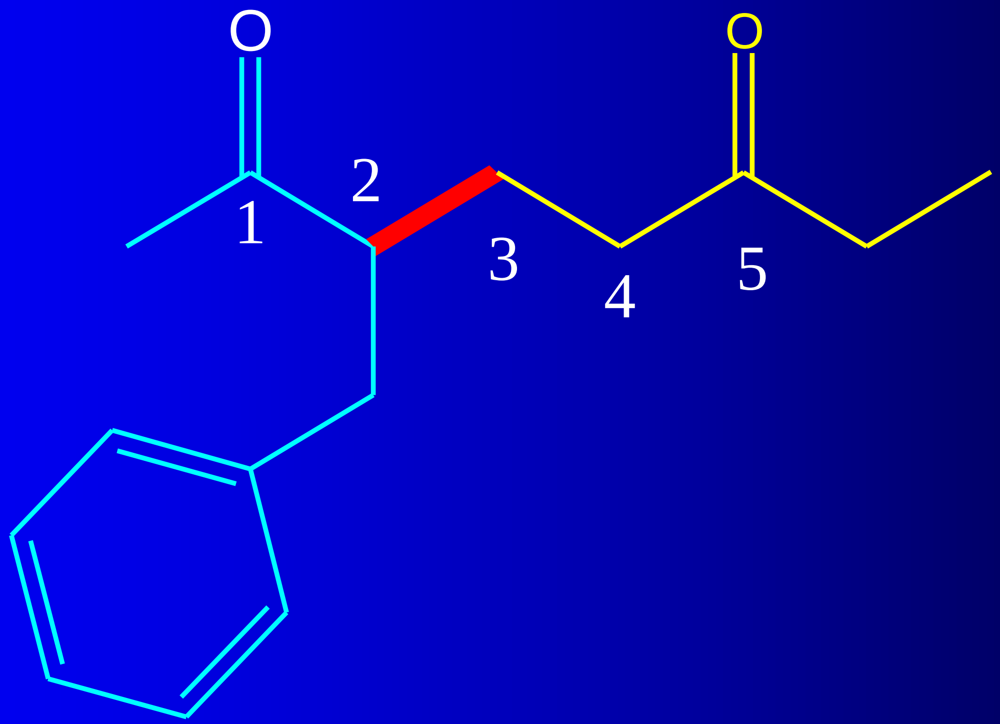
Retro-synthesis of 2,6-Heptadione



Always gives a 1,5-dicarbonyl product

Michael Addition

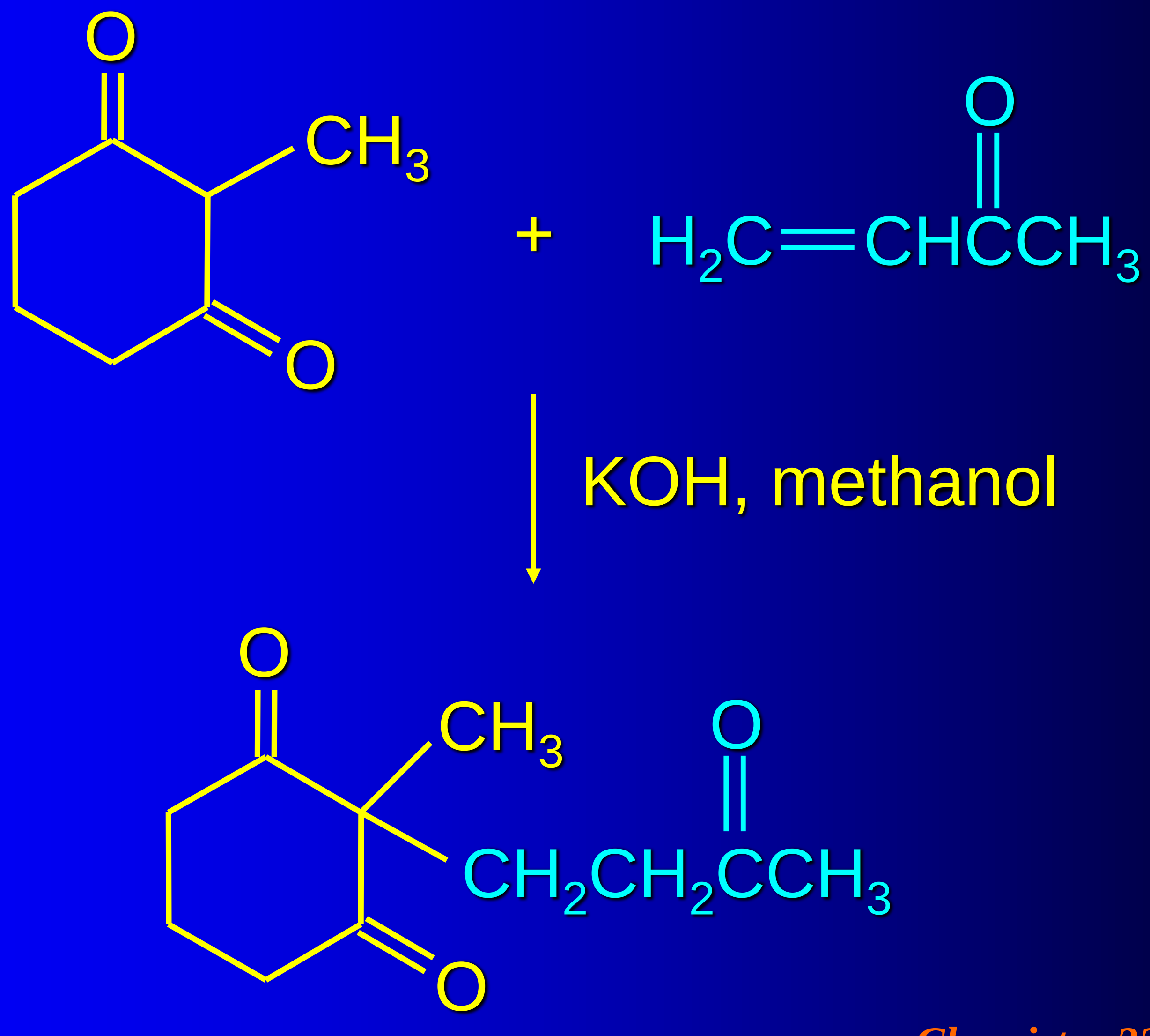
- The Michael reaction is a useful method for forming carbon-carbon bonds….1,5 dicarbonyls



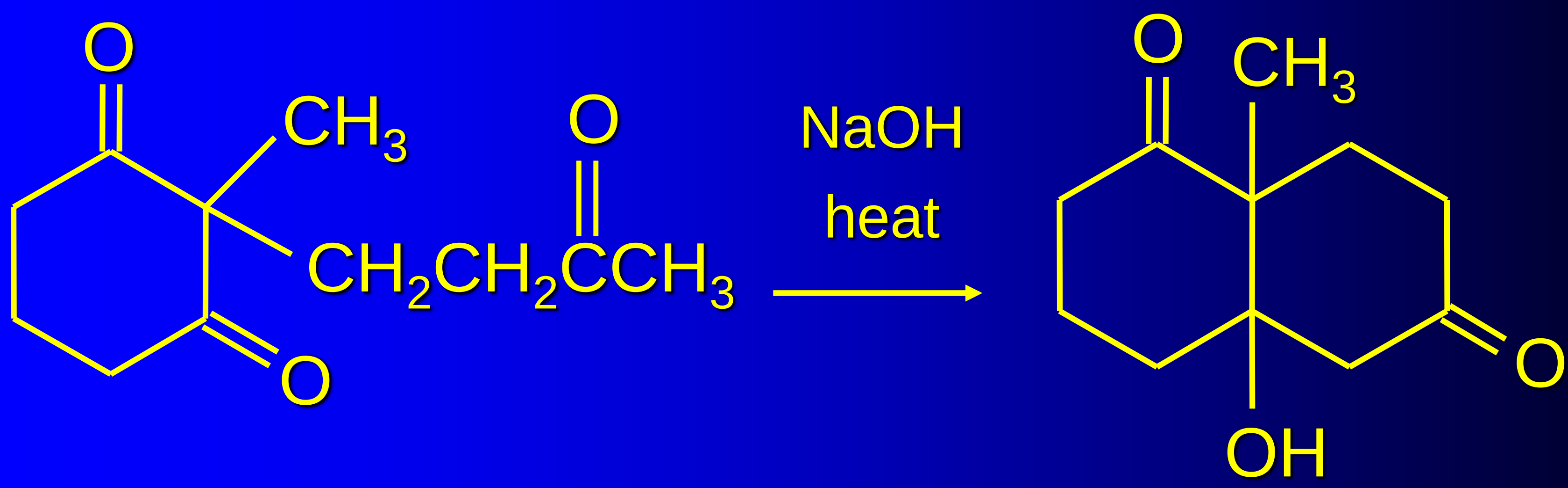
Michael Addition

- It is also useful in that the product of the reaction can undergo an intramolecular aldol condensation to form a six-membered ring. One such application is called the Robinson annulation.
- This reaction enabled the first synthesis of steroids

The Robinson Annelation: 1. Michael addition

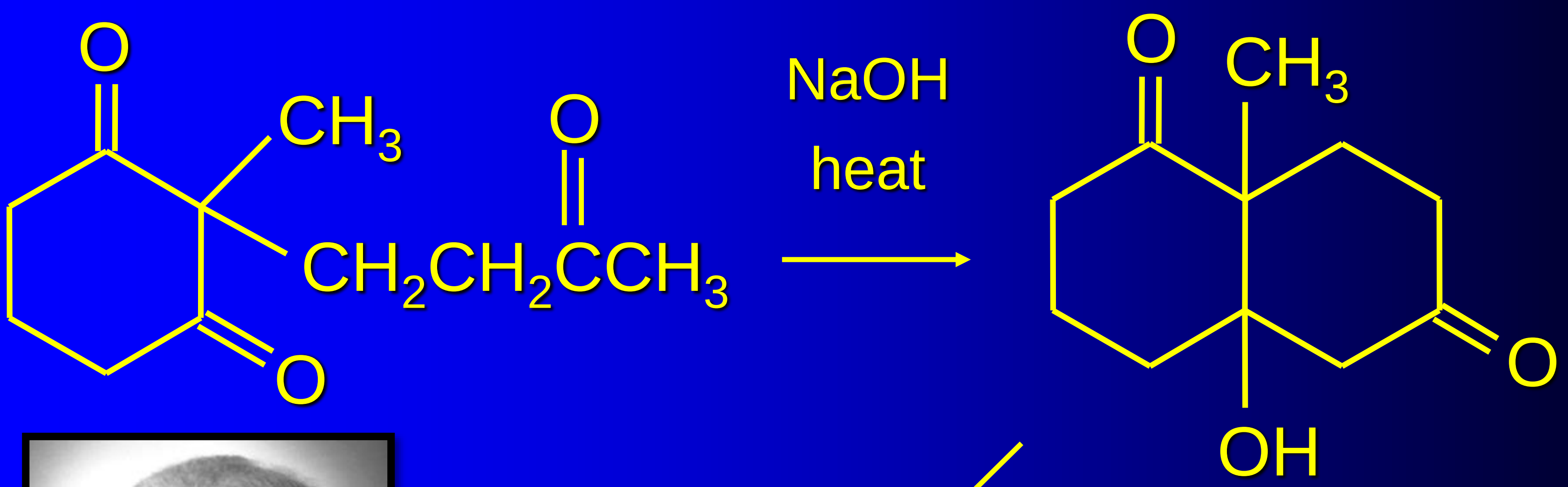


<u>Robinson annelation:</u> *2. aldol condensation*



not isolated;
dehydrates under
reaction conditions

Robinson annelation: 3. elimination



Robert Robinson
Nobel 1947