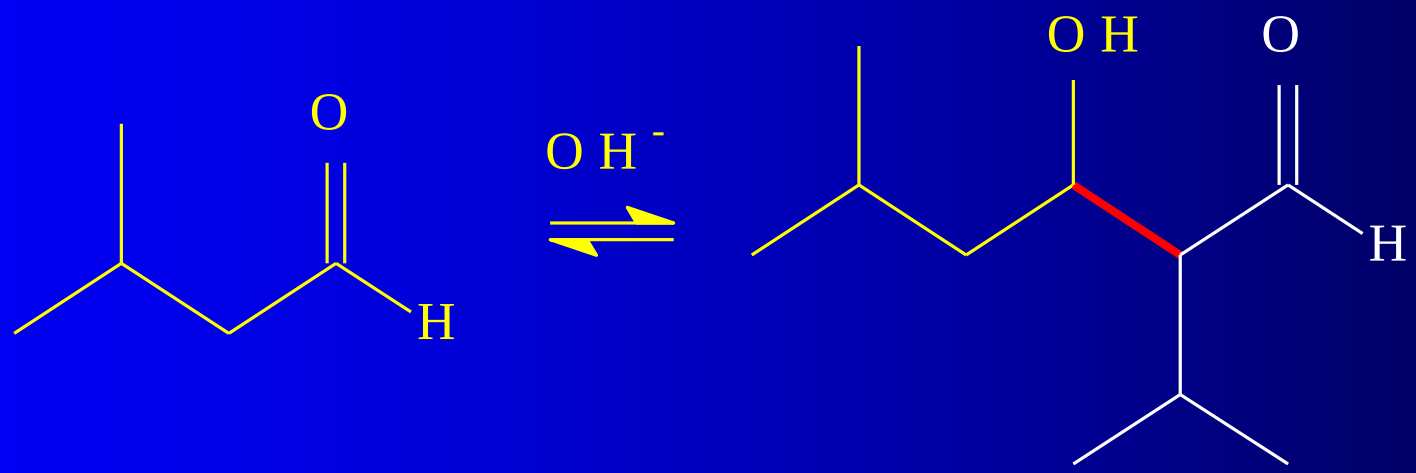
Lecture 21

The Aldol Revisited



- and some other interesting enolate anion chemistry…

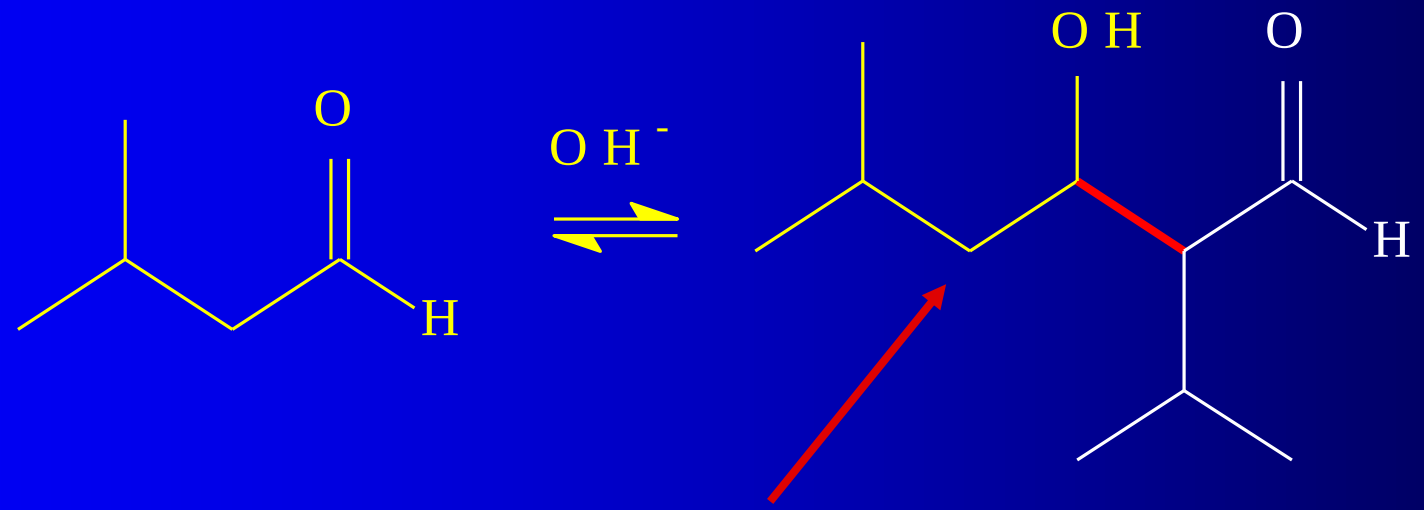
The Aldol Reaction

- An important reaction of enolate anions is nucleophilic addition to the carbonyl group of another molecule of the same or different compound…Claisen Condensation is but one example. The Aldol is another.

- Actually, the Aldol reaction may be catalyzed by either acid or base, but base catalysis is more common

The Aldol Condensation

- The product of an aldol condensation is
  - a β-hydroxyaldehyde…



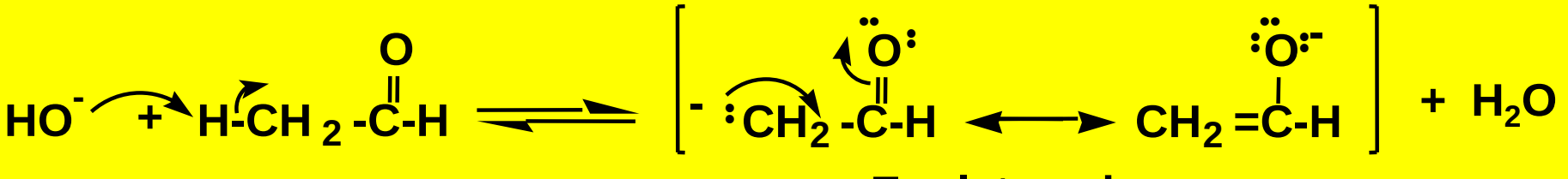
an Aldol!

{Aldehyde / Alcohol}

Base Catalyzed Aldol Reaction

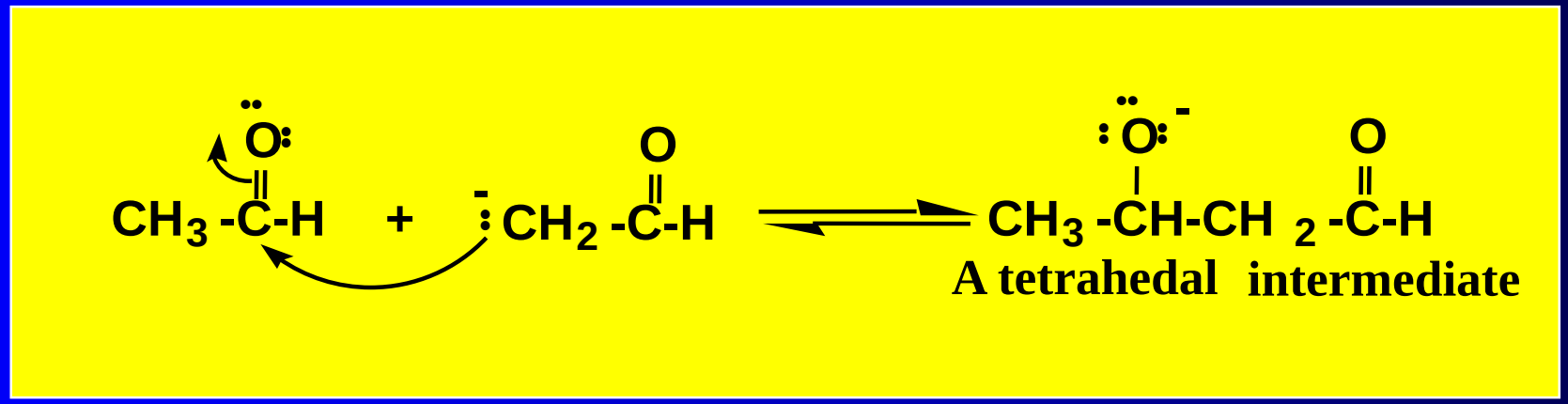
- The mechanism of the base-catalyzed aldol reaction can be divided into three steps

Step 1: formation of a resonance-stabilized enolate anion



The Aldol Reaction

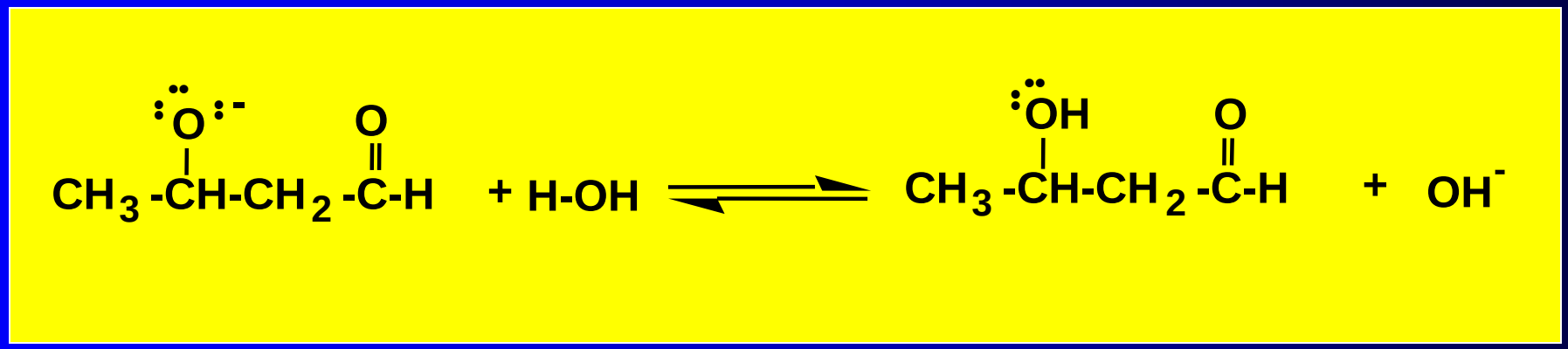
Step 2: addition of the enolate anion to the carbonyl group of another carbonyl-containing molecule to form a "Tetrahedral intermediate" [sp^3 hybridized carbon]



Nucleophilic acyl substitution does NOT occur….why??

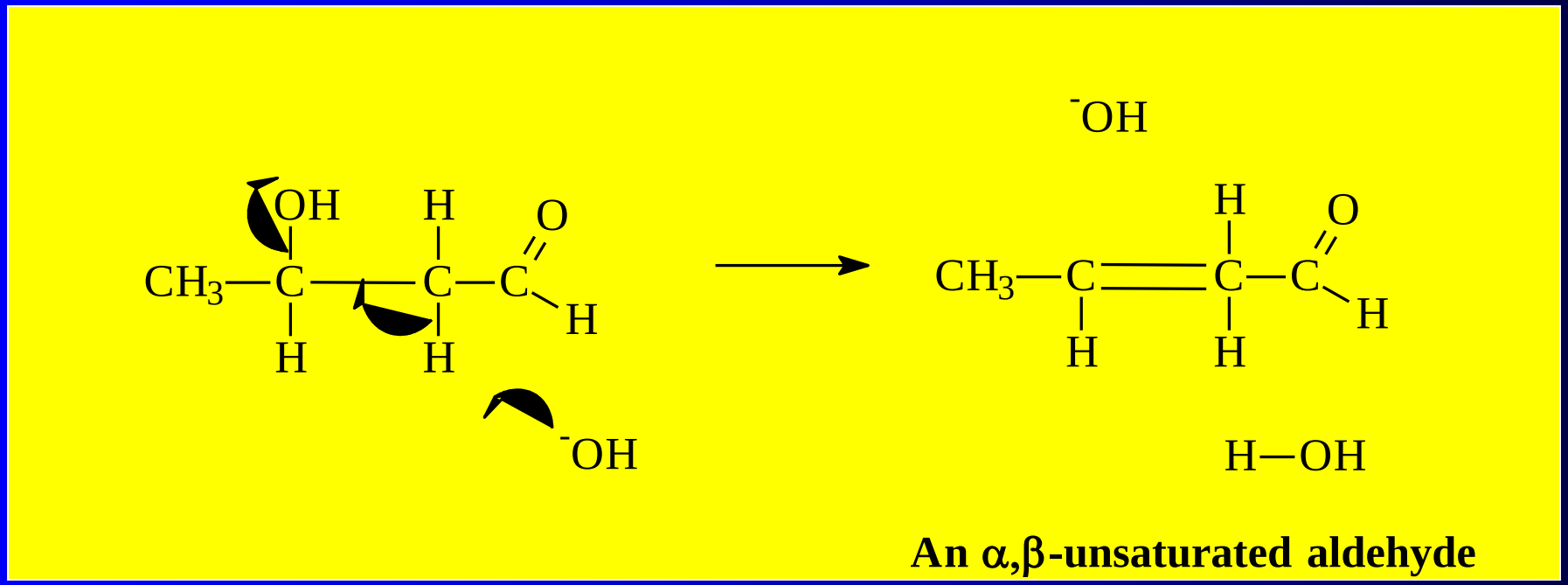
The Aldol Reaction

Step 3: Reaction of the tetrahedral intermediate with a proton donor gives the aldol product



Loss of water!

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

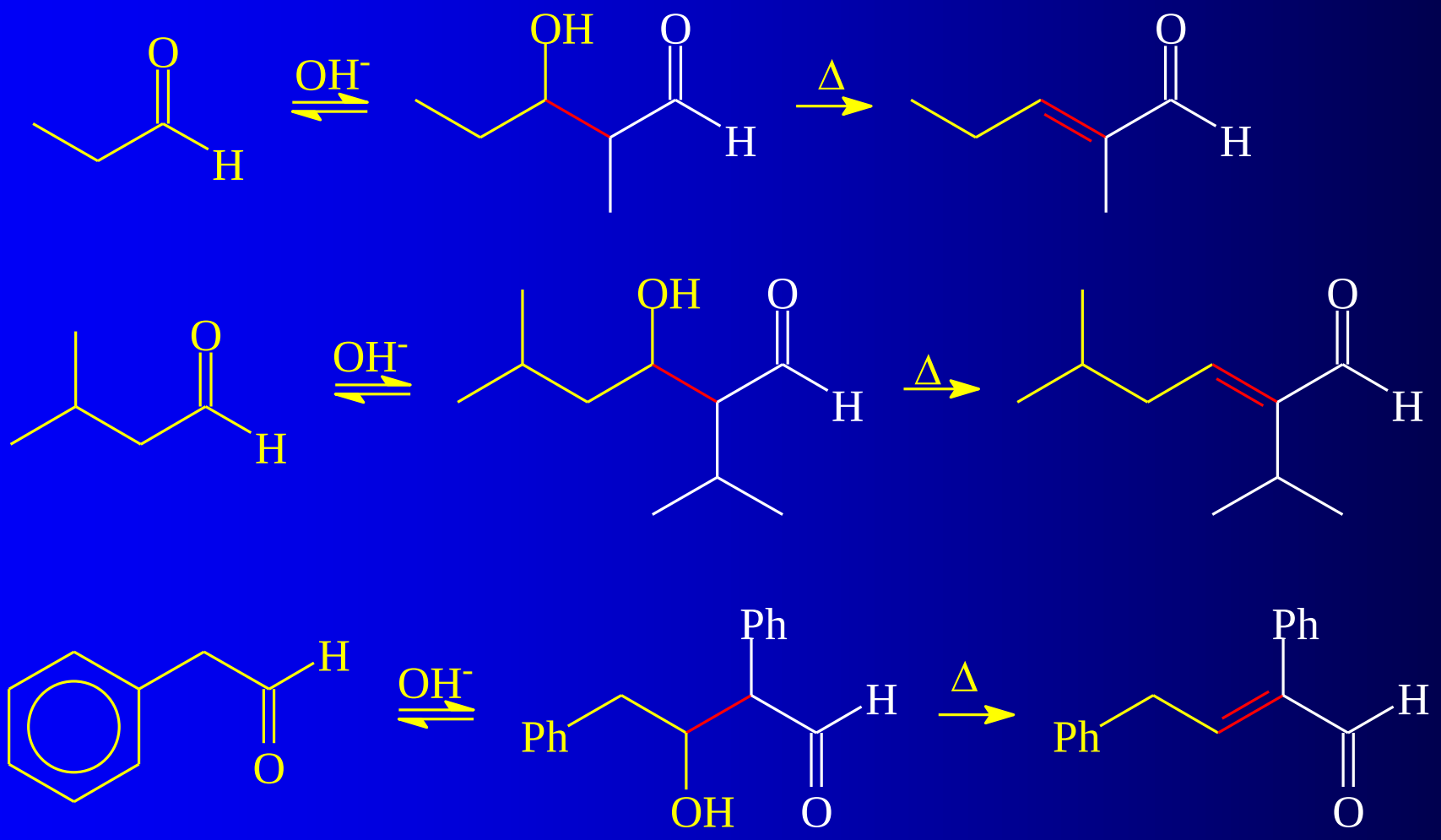


A Note about Aldol Reactions

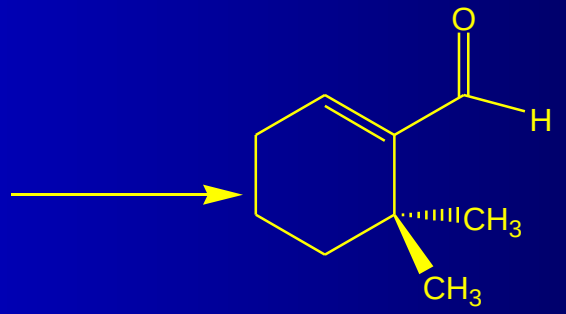
aldol reactions are reversible and, particularly for ketones, there is often little aldol present at equilibrium. K_{eq} for dehydration is generally large and, if reaction conditions bring about dehydration, good yields of product can be obtained

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

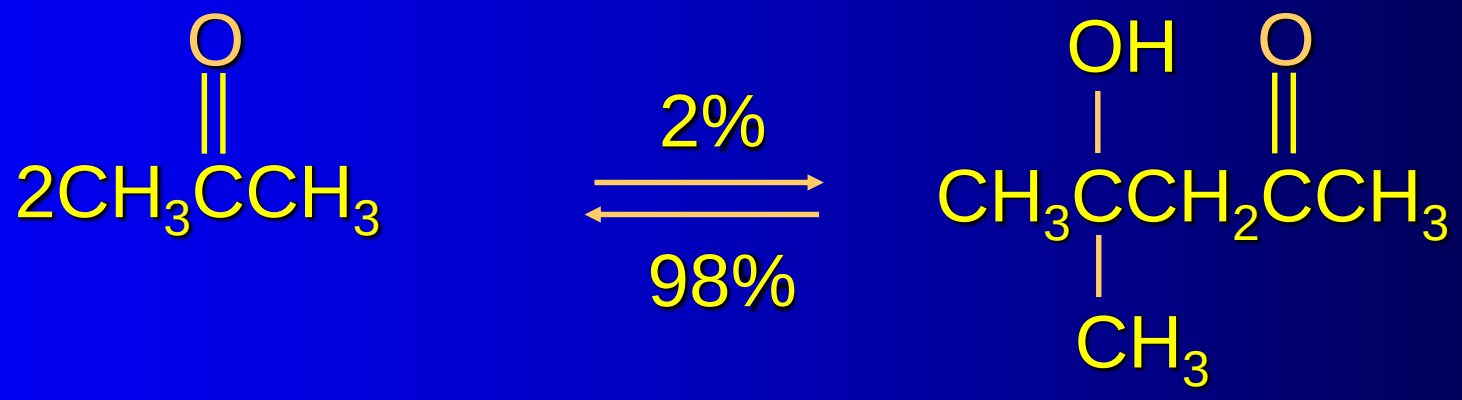
Aldol condensation



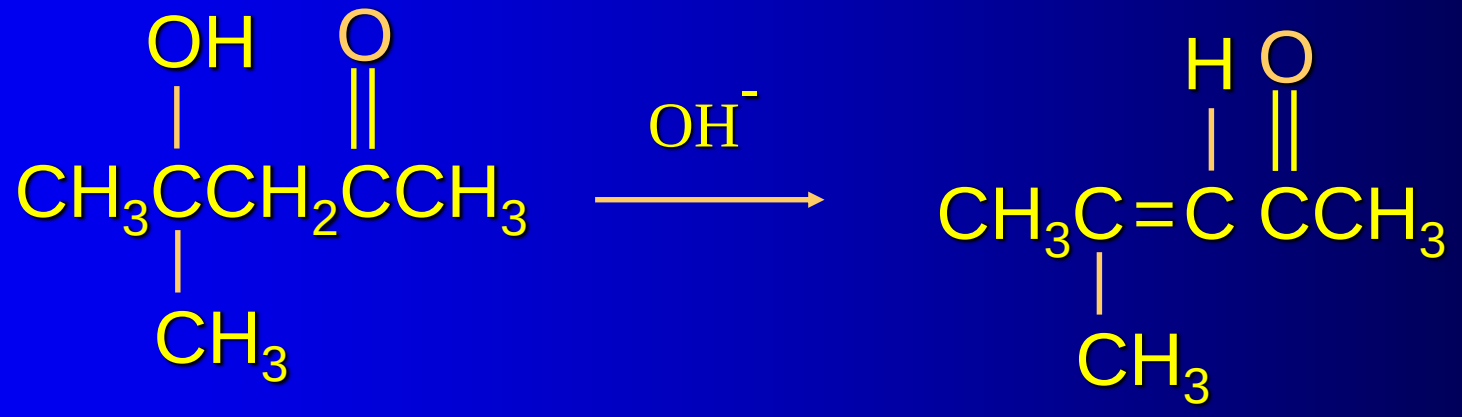
From what??



Aldol reactions of ketones

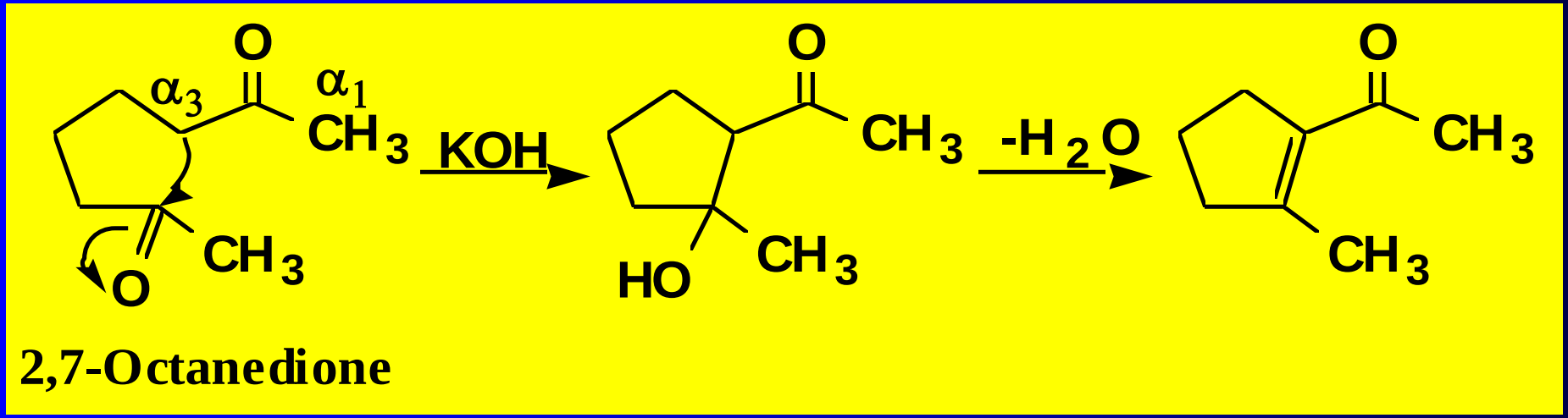


- the equilibrium constant for aldol addition reactions of ketones is usually unfavorable but can be driven by dehydration



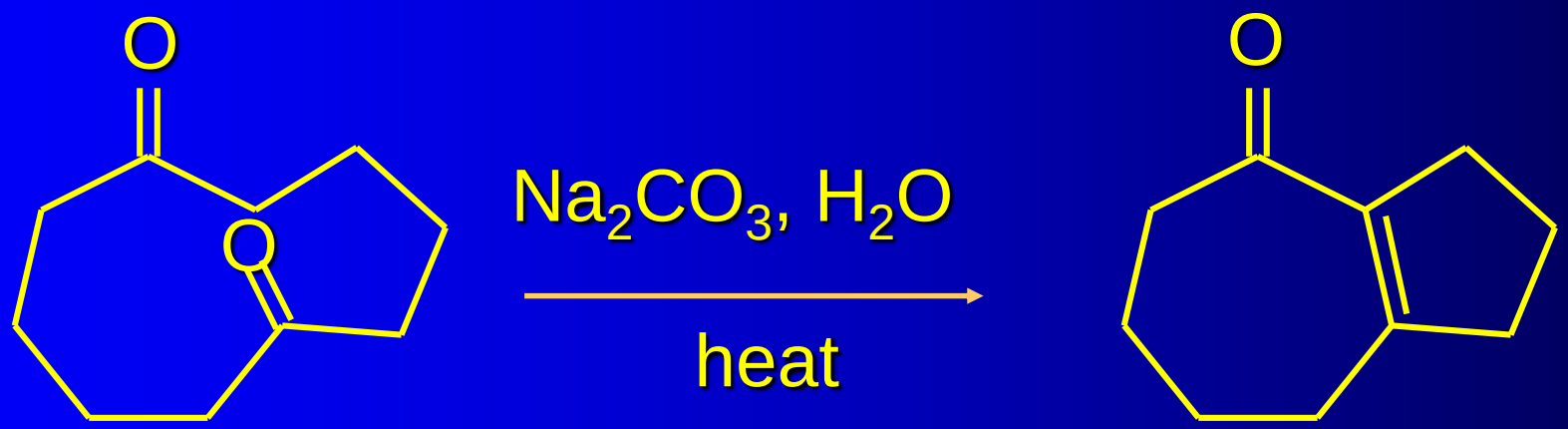
Aldol Reactions

- 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



(96%)

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

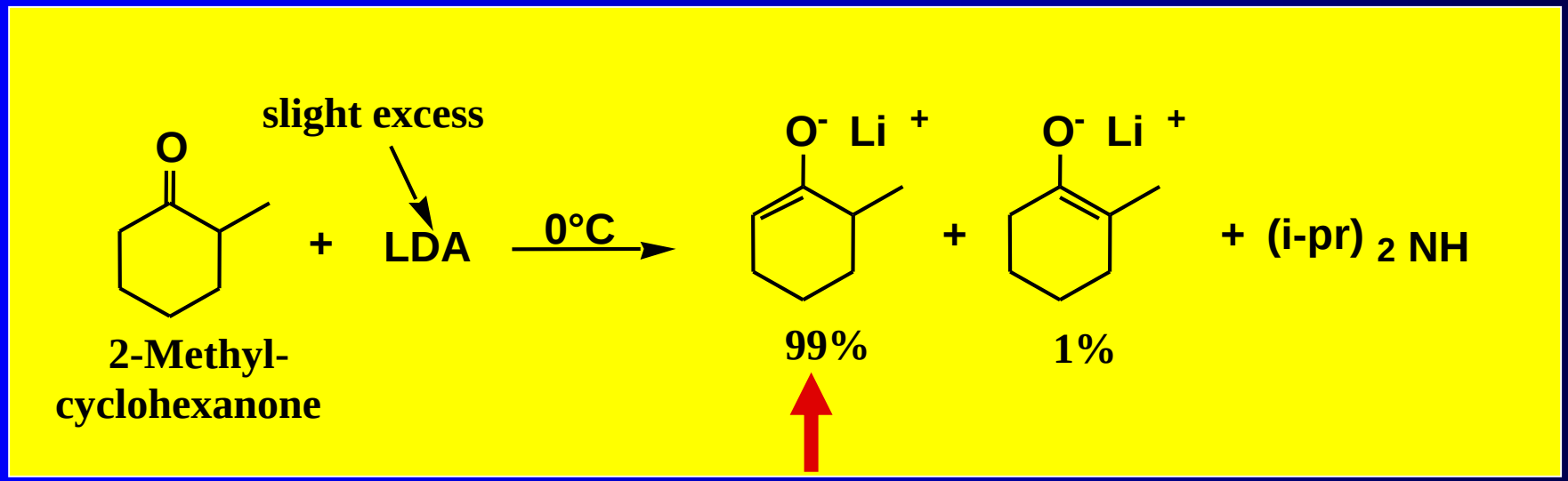
Enolate Anions

- When a ketone has two different α-hydrogens, is formation of the enolate anion regio-selective?

- The answer depends on experimental conditions
  - when a slight excess of LDA, a ketone is converted to its lithium enolate anion, which consists almost entirely of the less substituted enolate anion
  - this reaction is said to be under **kinetic control**

Kinetic Control

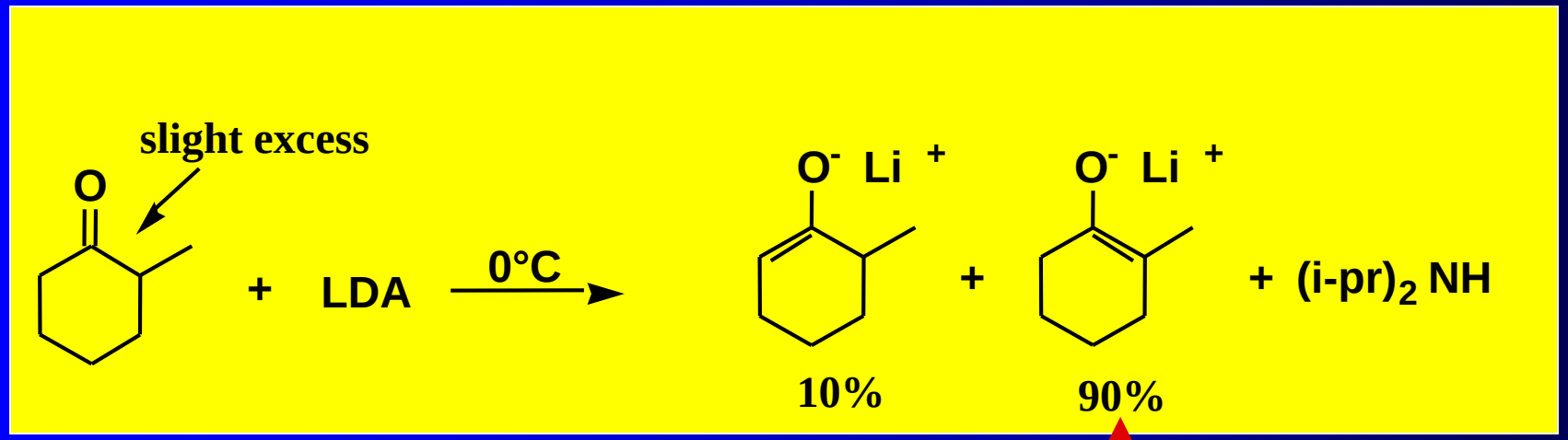
– with slight excess of LDA



"fastest" but least stable

Thermodynamic Control

– With slight excess of ketone



Slow but most Stable

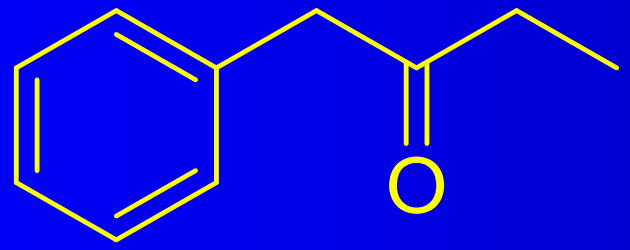
Kinetic Control

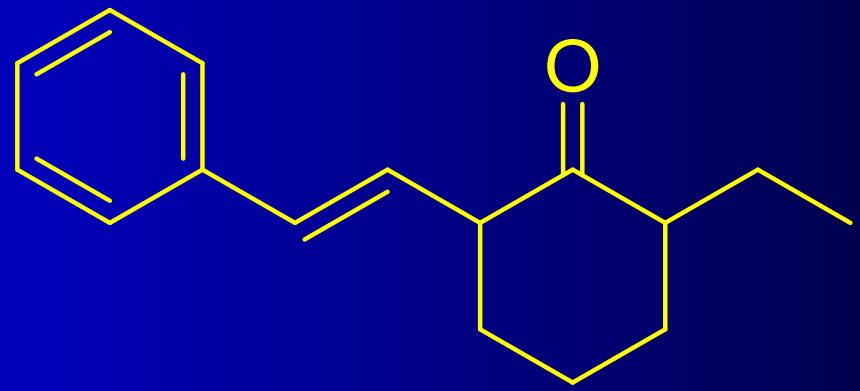
- When a reaction is under kinetic control, the composition of the product mixture is determined by the relative rates of formation of each product

Thermodynamic Control

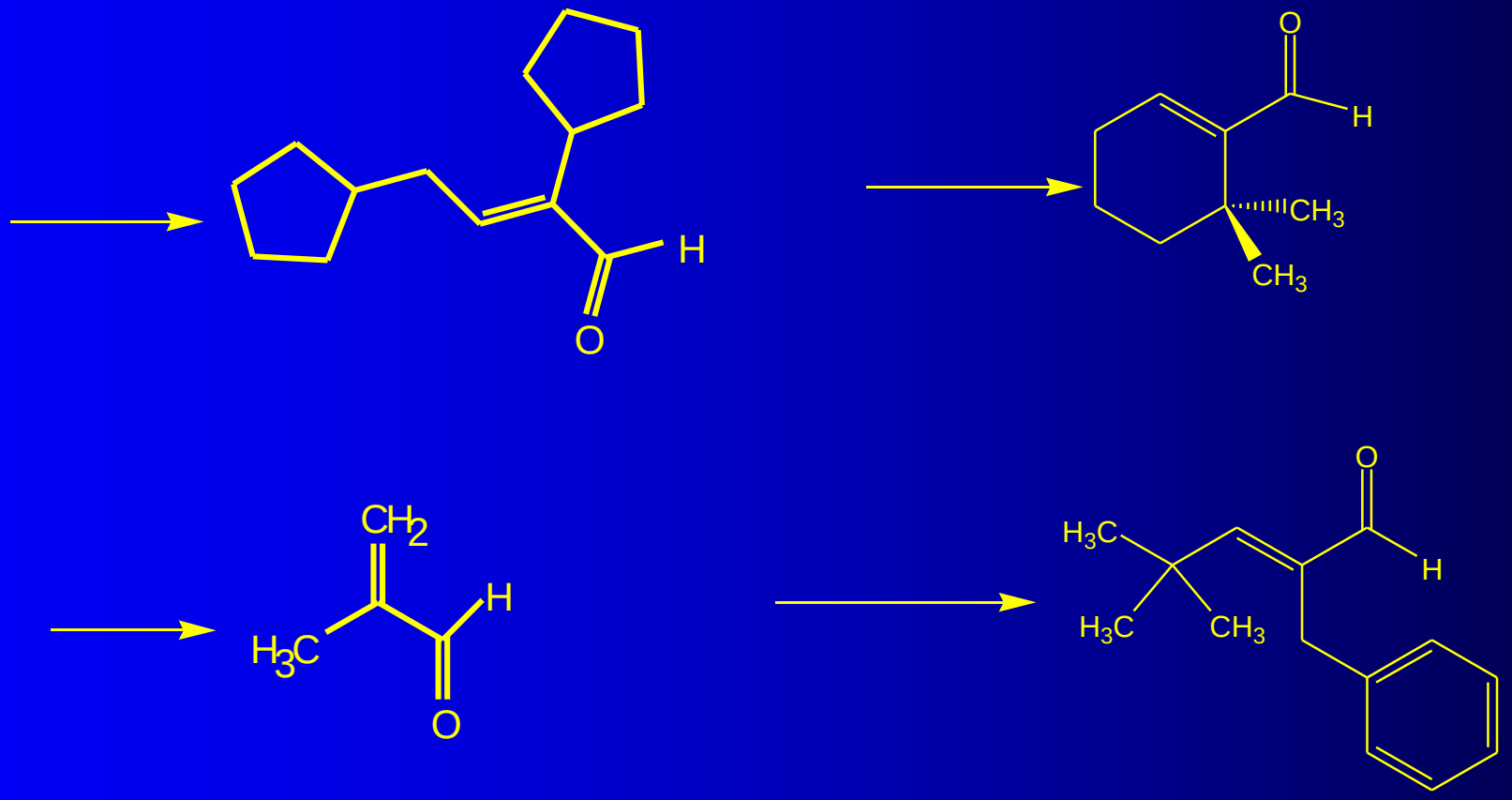
- When a reaction is under thermodynamic control, the composition of the product mixture is determined by the relative stabilities of each product

Which is which??? Why??



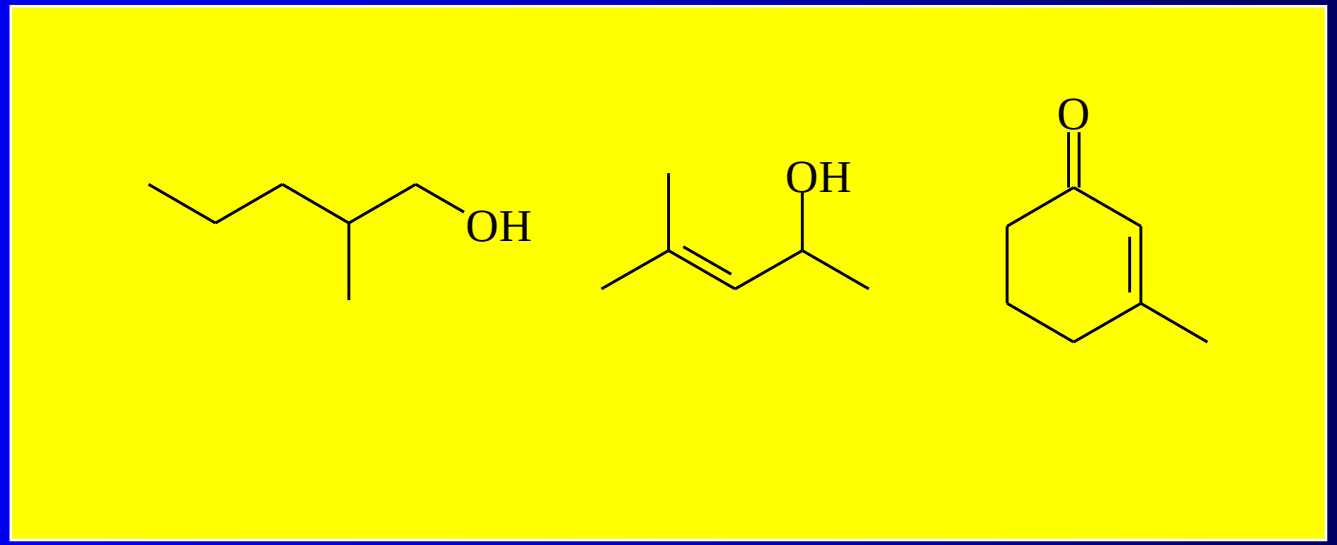


From what??



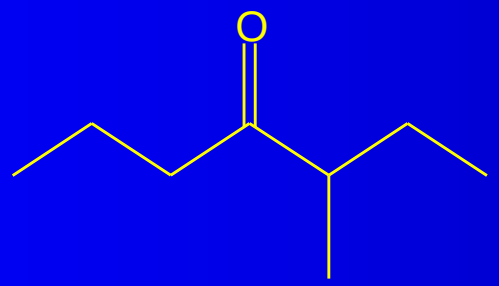
Practice Exercises

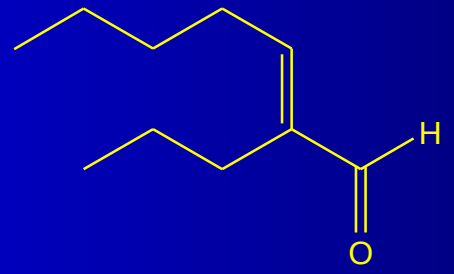
show how the following compounds could be synthesized by a path that Includes an aldol or mixed aldol condensation,

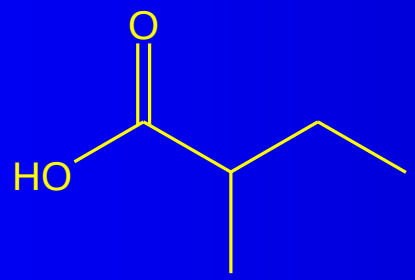


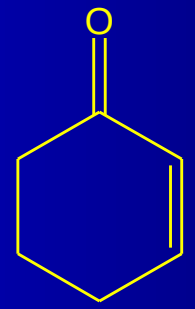
Don’t let disguises fool you!

Make these starting with ethyl acetate or diethyl malonate and anything else

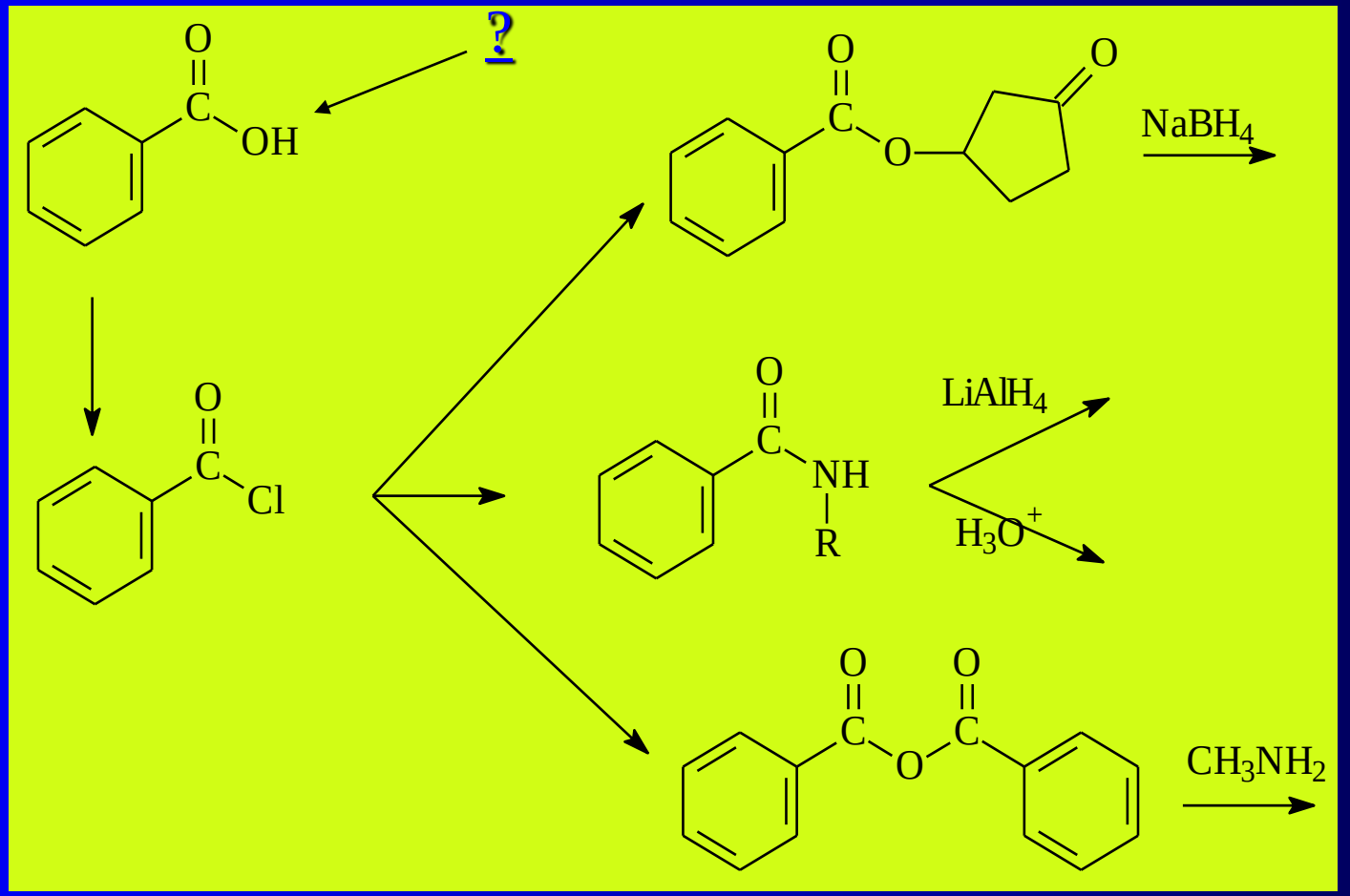






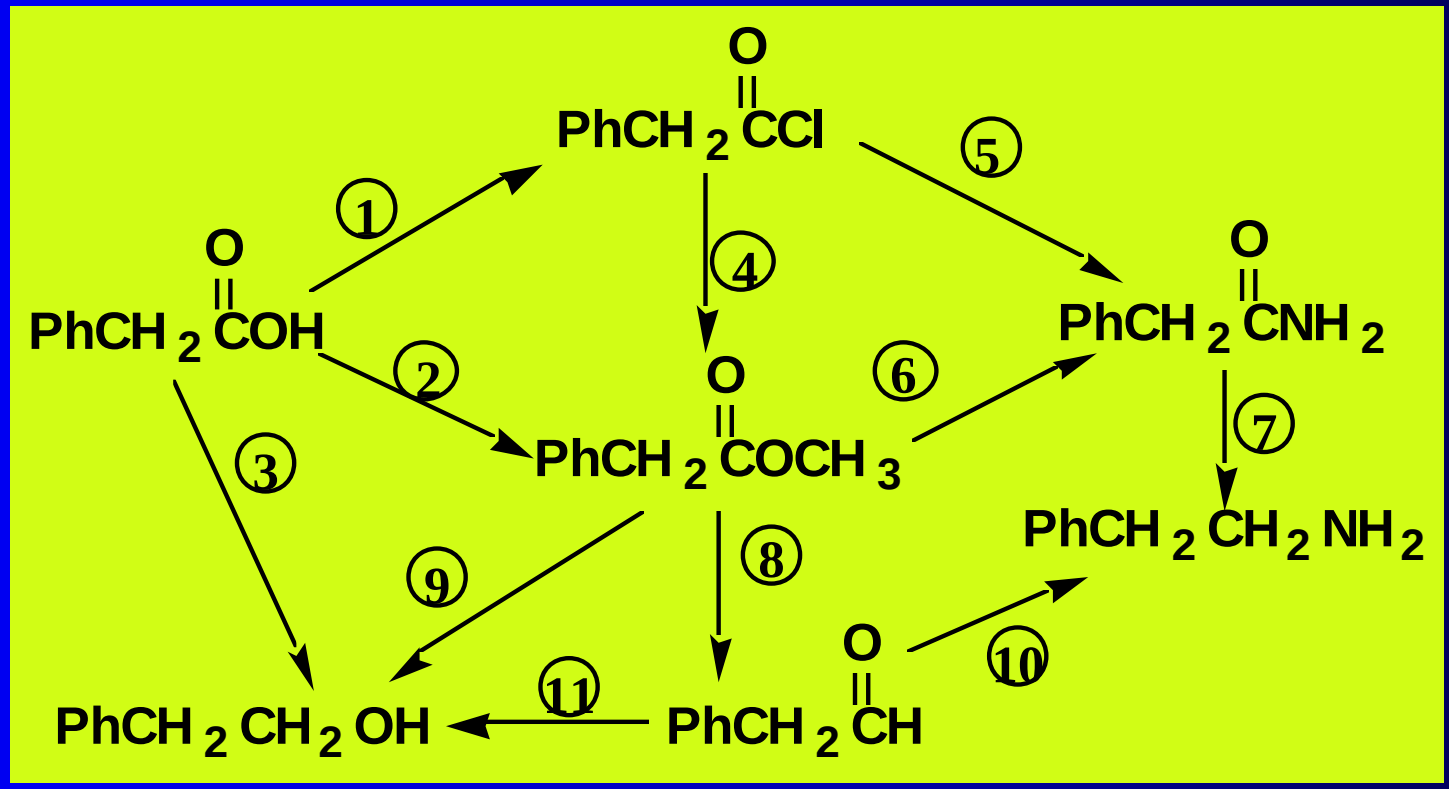


How far can you expand this web?

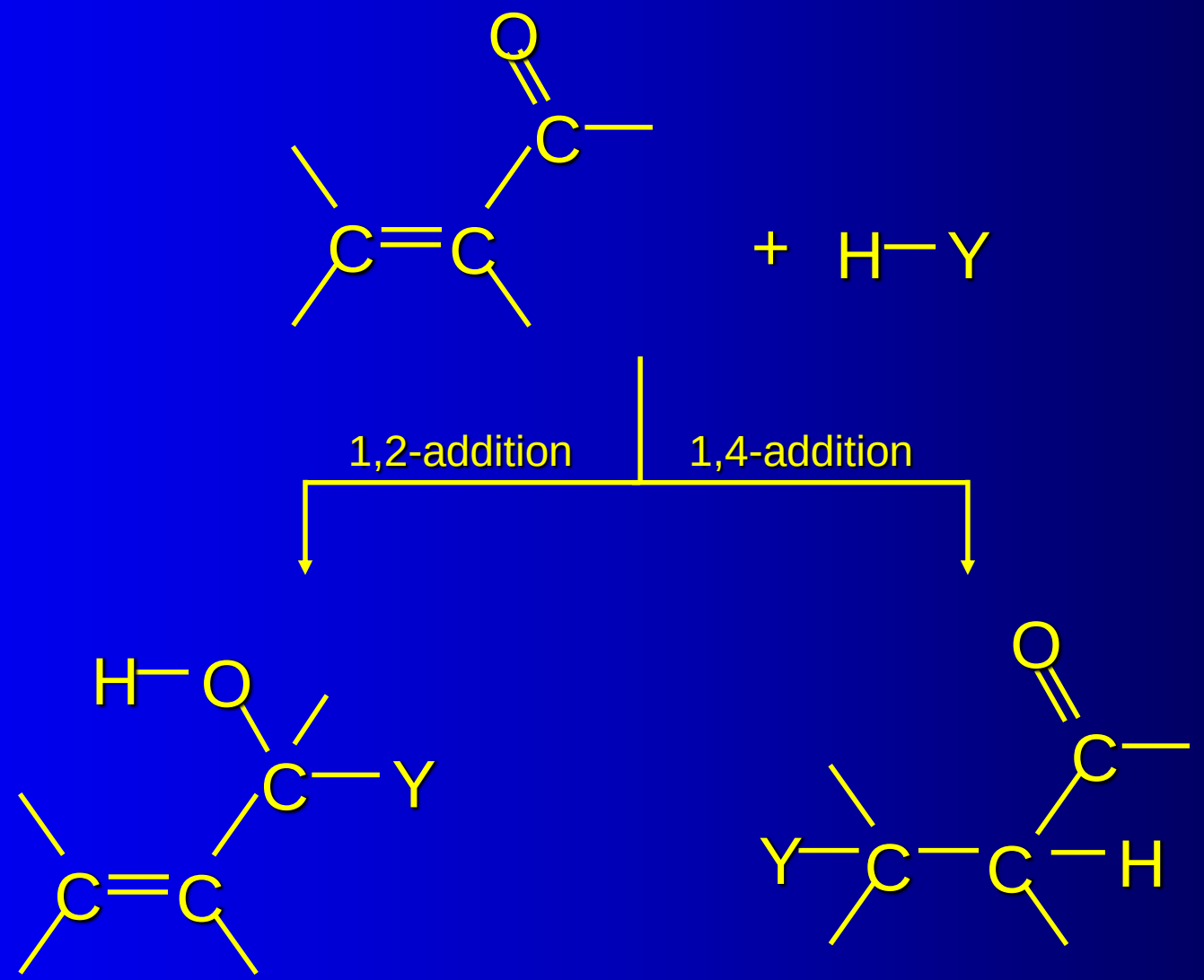


Interconversions

- Problem: show reagents and experimental conditions to bring about each reaction

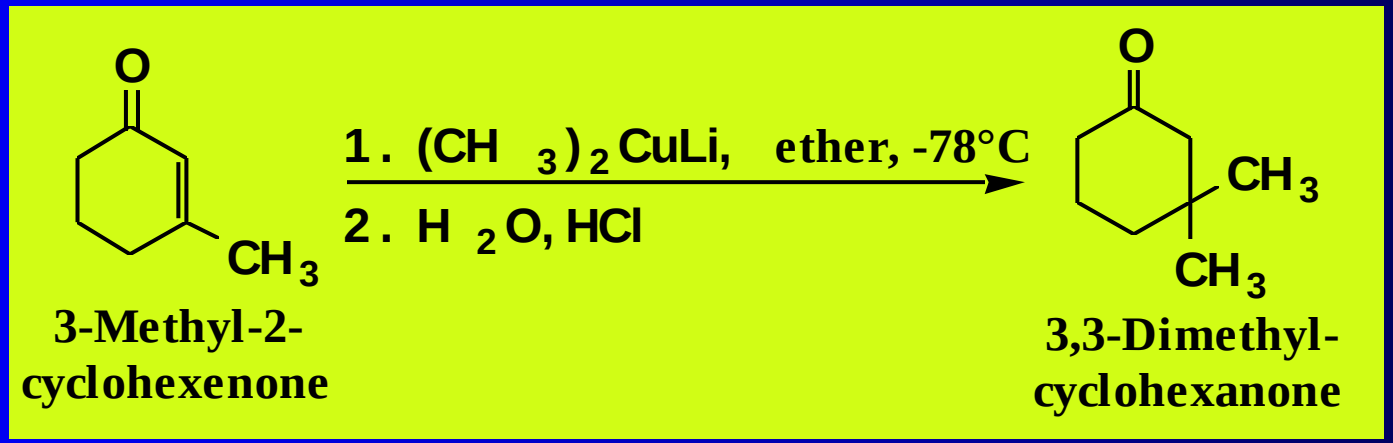


Addition to α,β-unsaturated carbonyls



Gilman Reagents

- Surprisingly, Gilman reagents undergo conjugate addition to α, β-unsaturated aldehydes and ketone



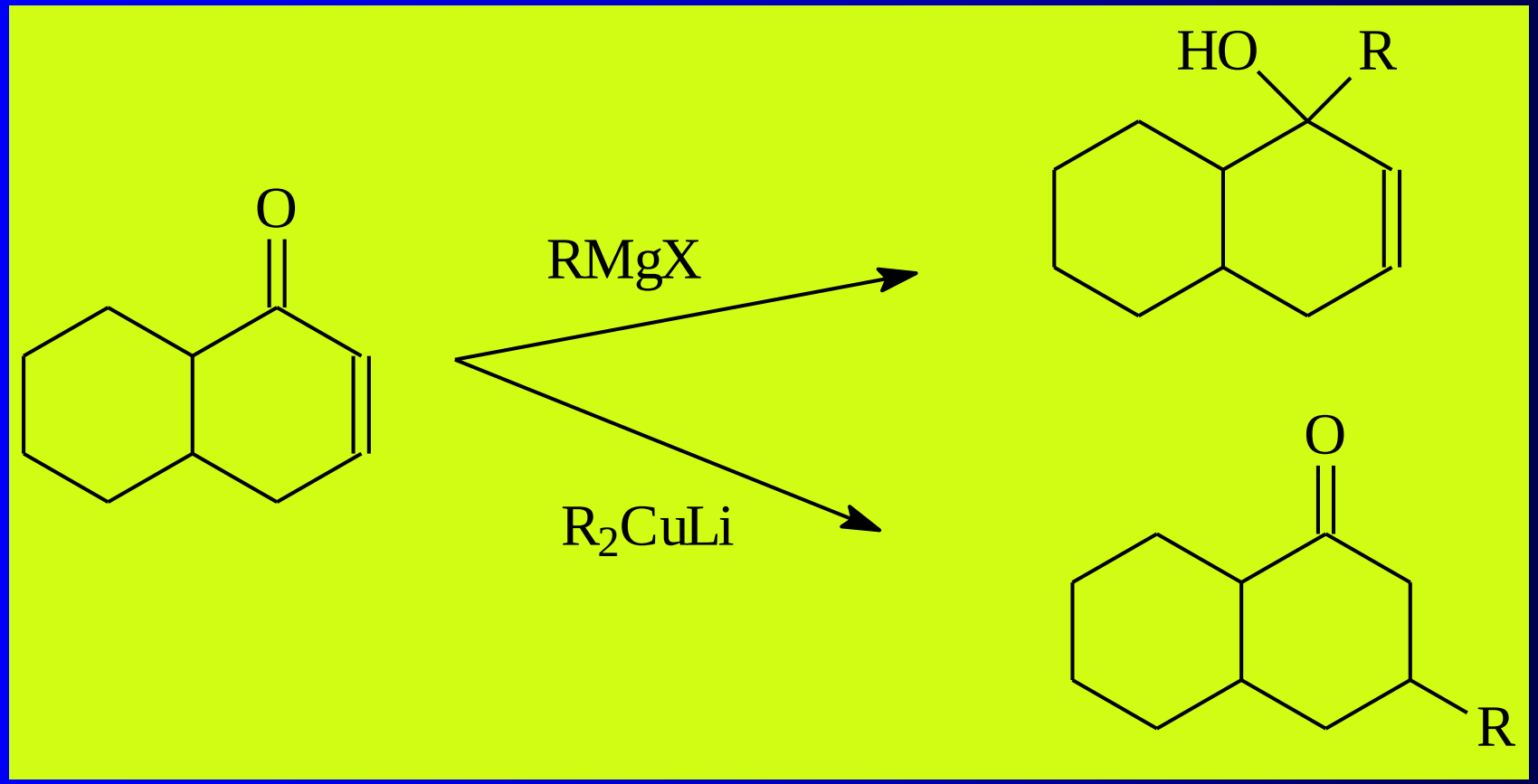
3-Methyl-2-cyclohexenone

3,3-Dimethyl-cyclohexanone

Gilman Reagents

- Gilman reagents are unique among organometallic compounds in that they give almost exclusively 1,4- addition
- Other organometallic compounds, including Grignard reagents, add to the carbonyl carbon by 1,2-addition
- The mechanism of conjugate addition of Gilman reagents is not fully understood

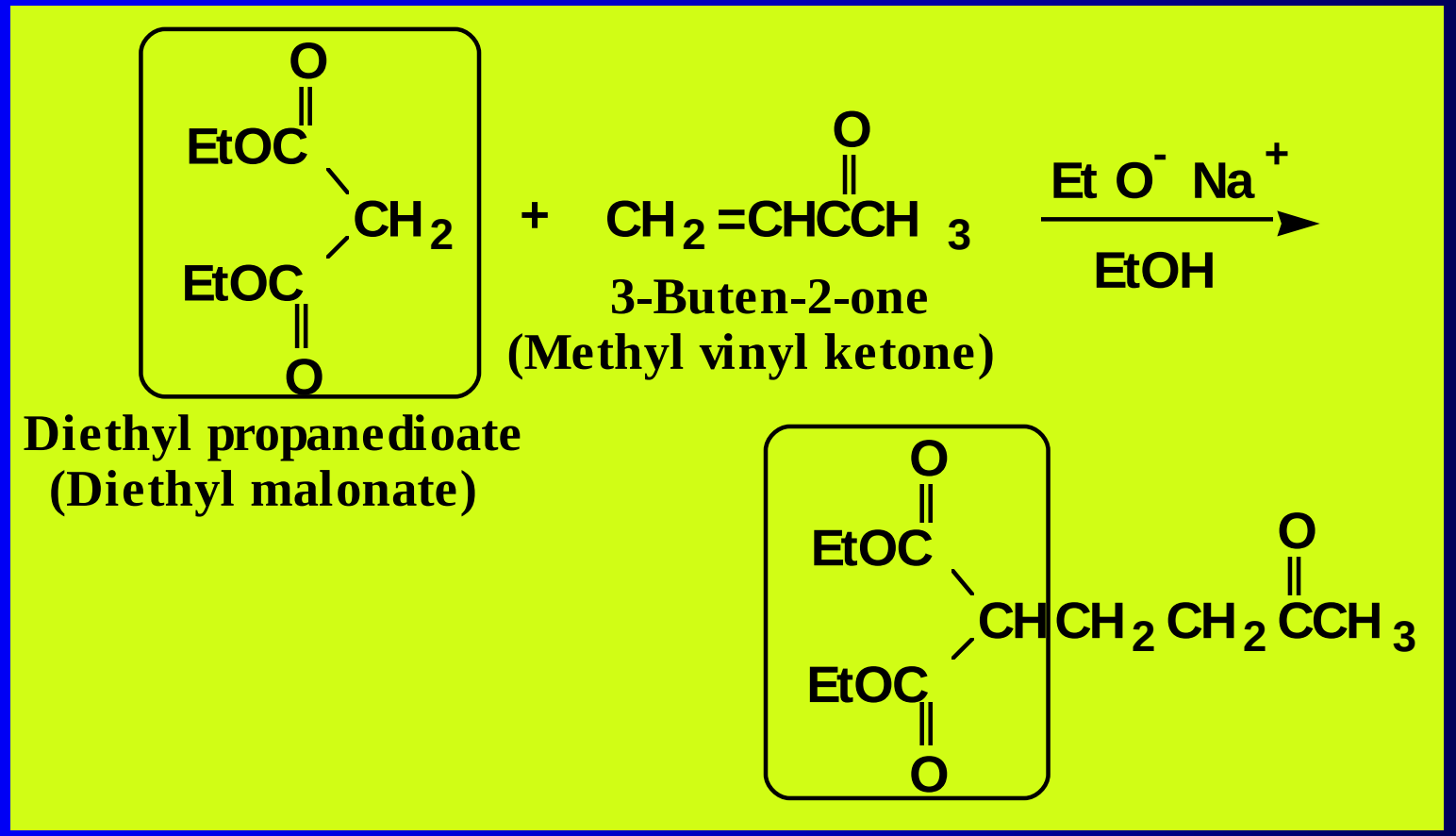
Selectivity!!



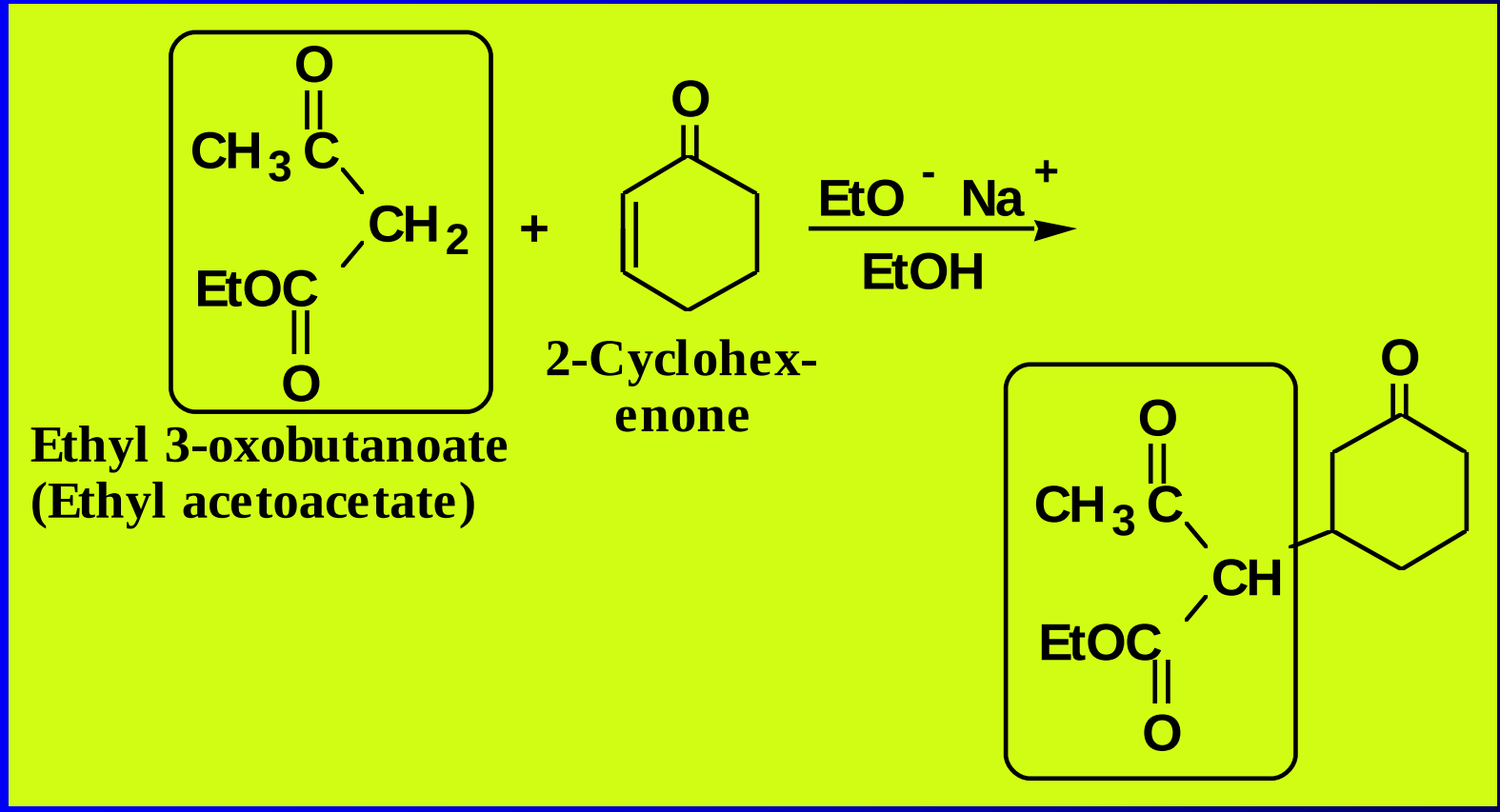
Michael Reaction

- Michael reaction: the 1,4-addition of an enolate anion to an α,β-unsaturated carbonyl compound!!
- Following are two examples
  - in the first, the nucleophile is the enolate anion of malonic ester
  - in the second, it is the enolate anion of acetoacetic ester

Michael Reaction



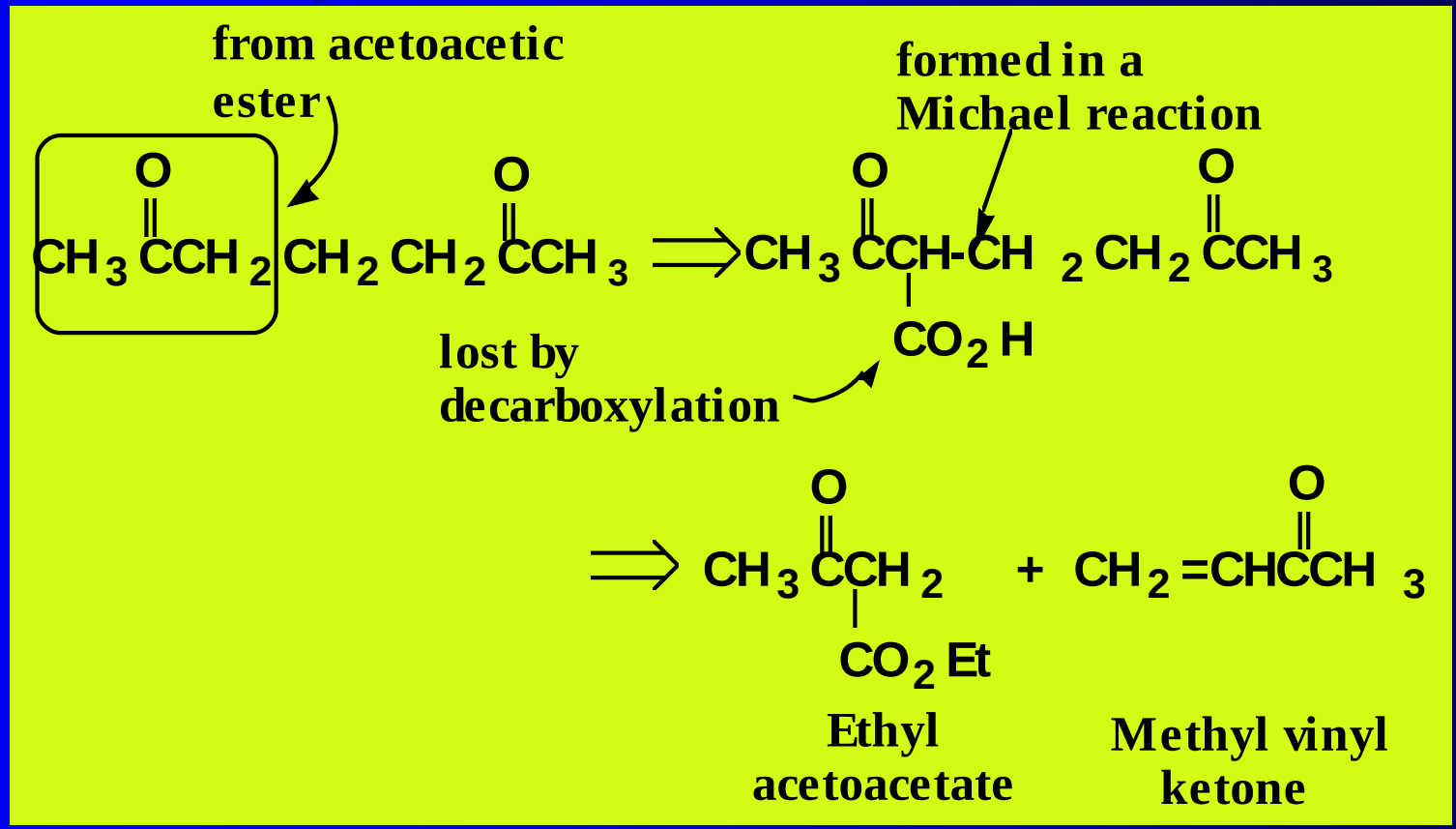
Michael Reaction



Ethyl 3-oxobutanoate (Ethyl acetoacetate)

2-Cyclohex-enone

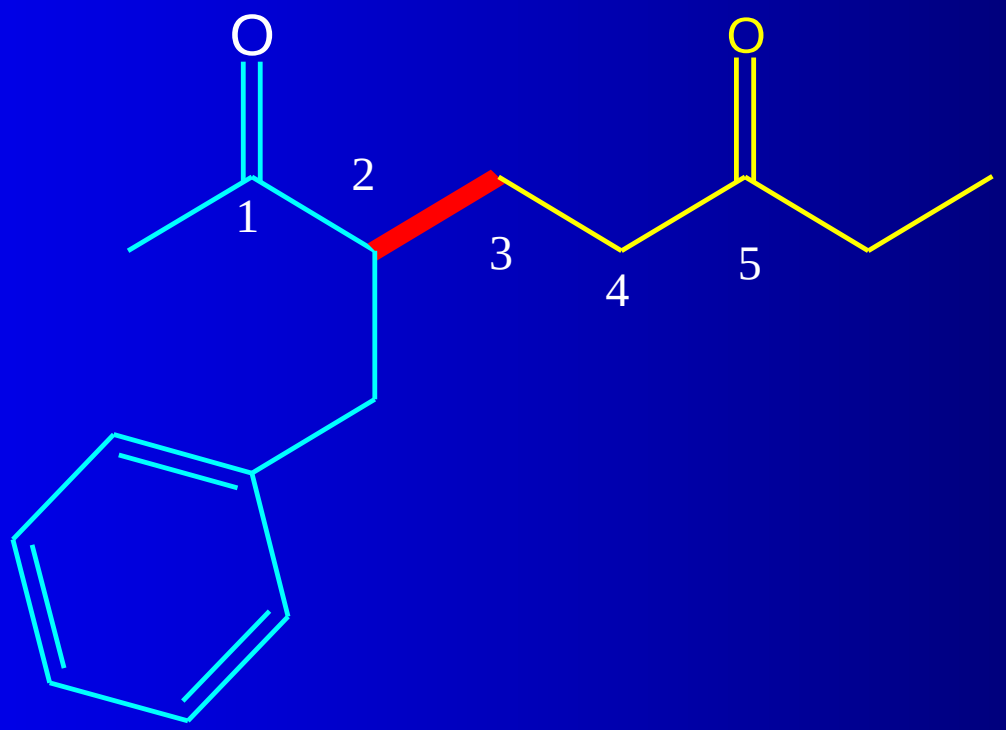
Retro-synthesis of 2,6-Heptadione



Always gives a 1,5-dicarbonyl product

Michael Addition

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

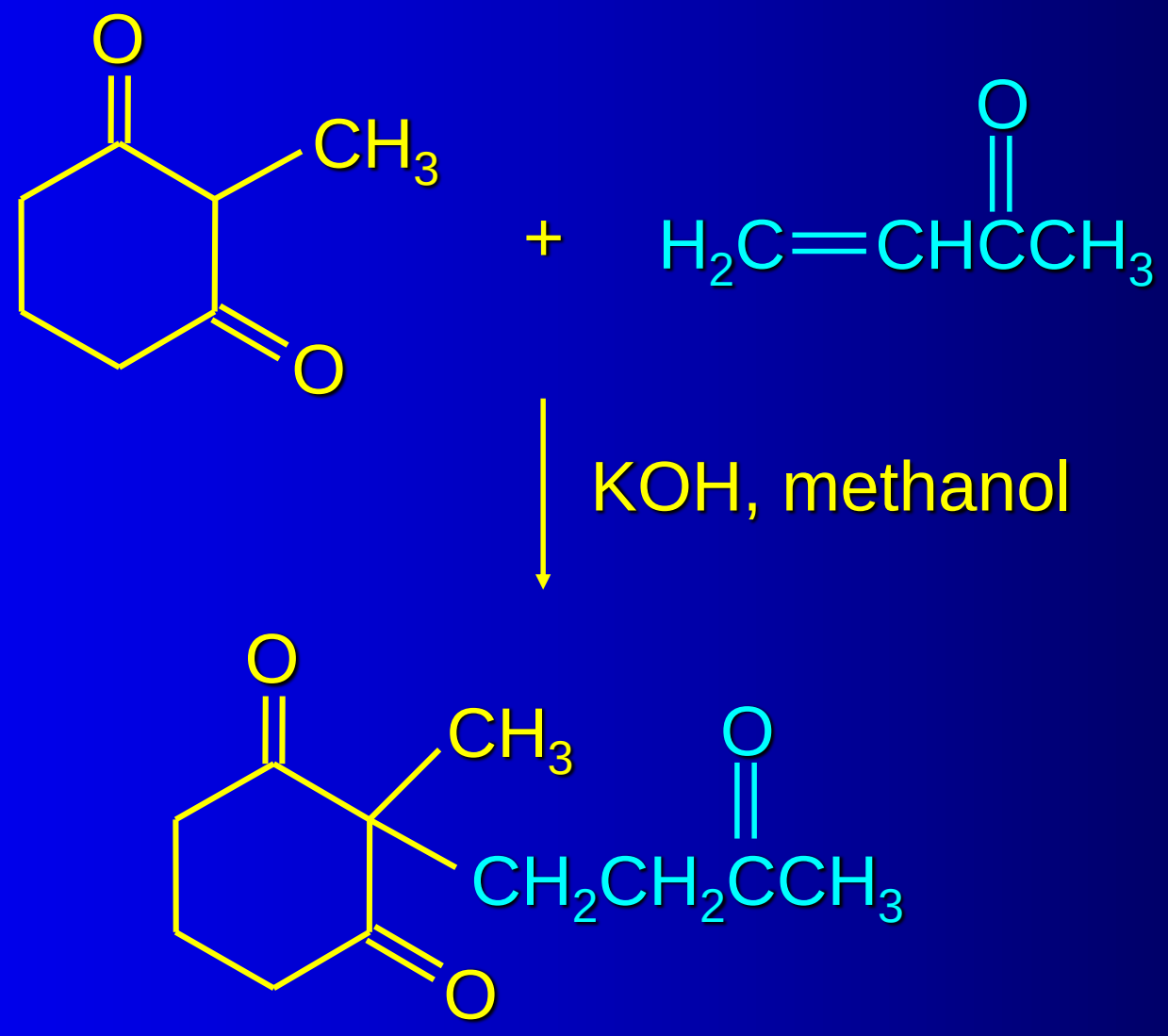


Michael Addition

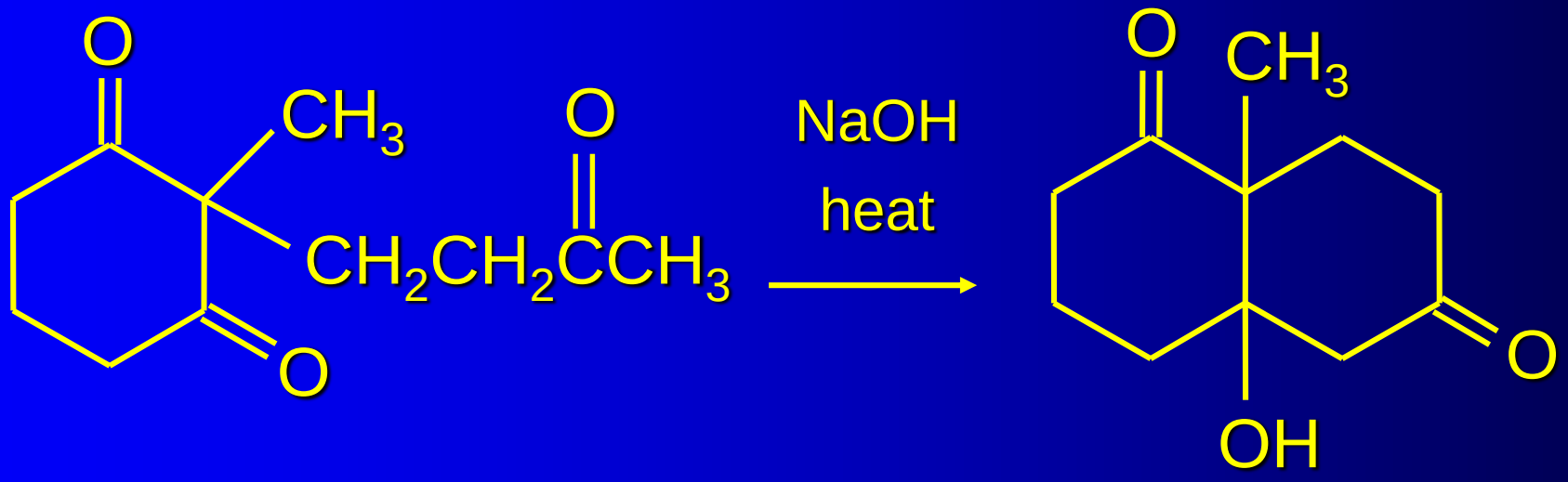
- It is also useful in that the product of the reaction can undergo an intramolecular aldol condensation to form a six-membered ring. One such application is called the Robinson annulation.

- This reaction enabled the first synthesis of steroids

The Robinson Annelation: 1. Michael addition

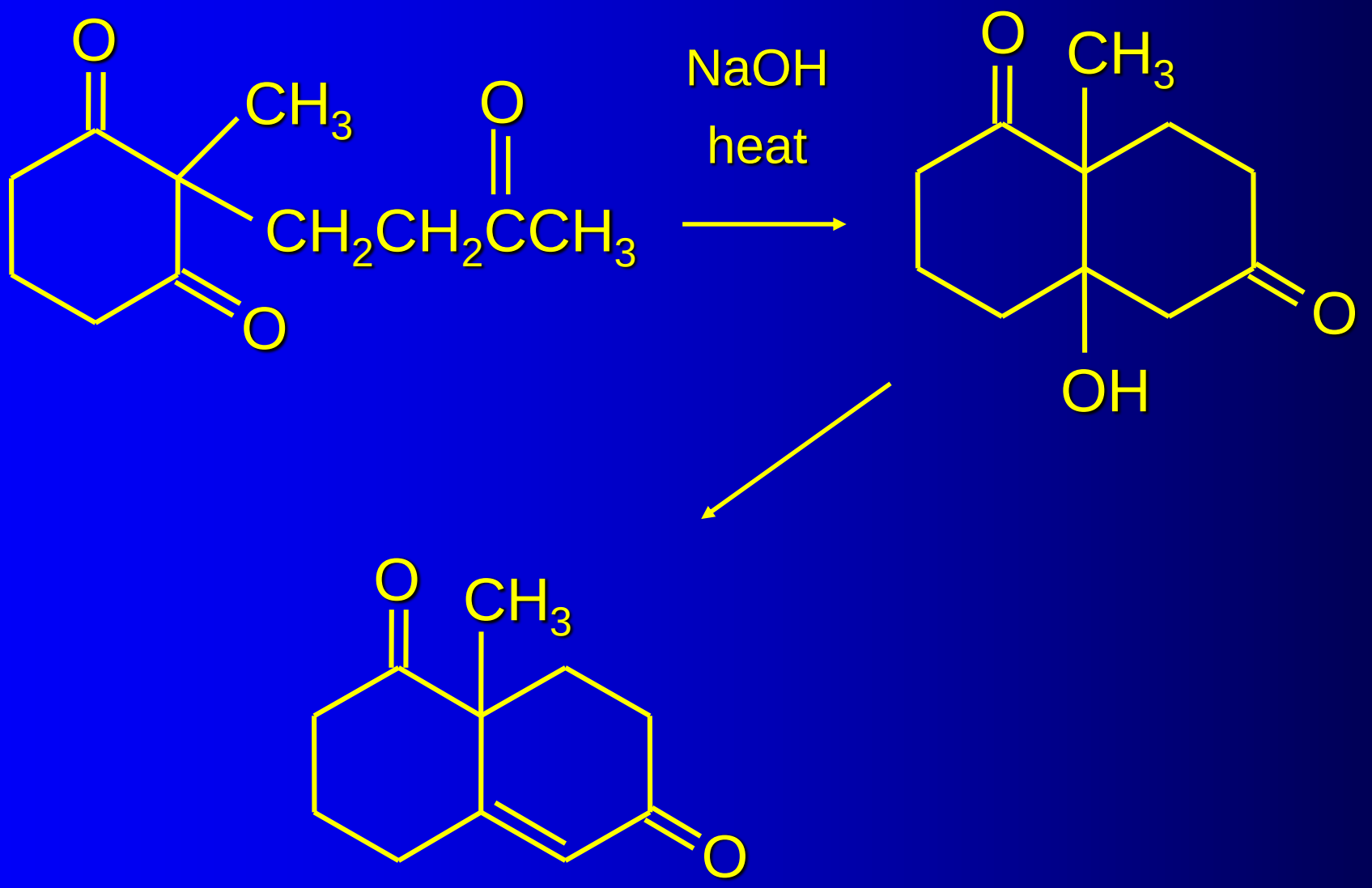


Robinson annelation: 2. aldol condensation

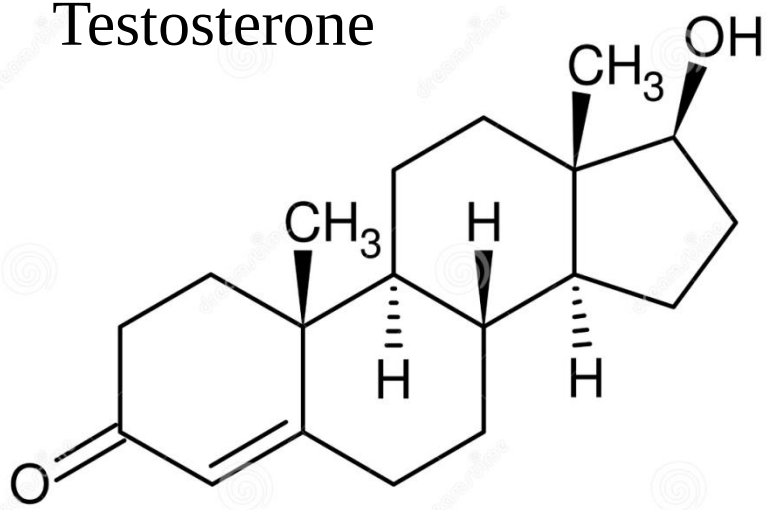


not isolated;
dehydrates under
reaction conditions

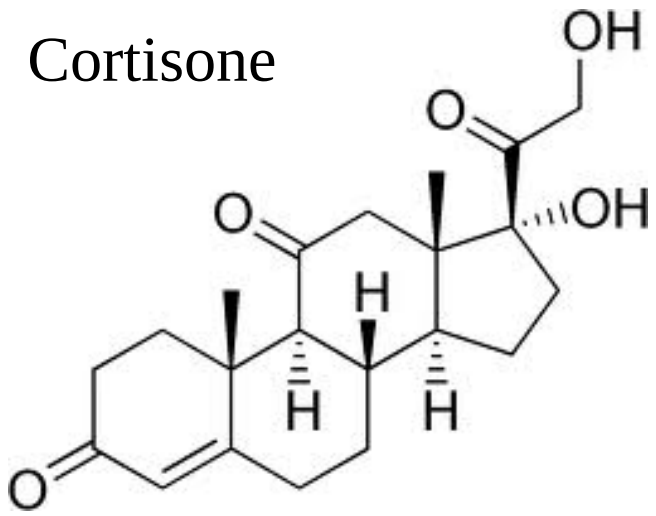
Robinson annelation: 3. elimination

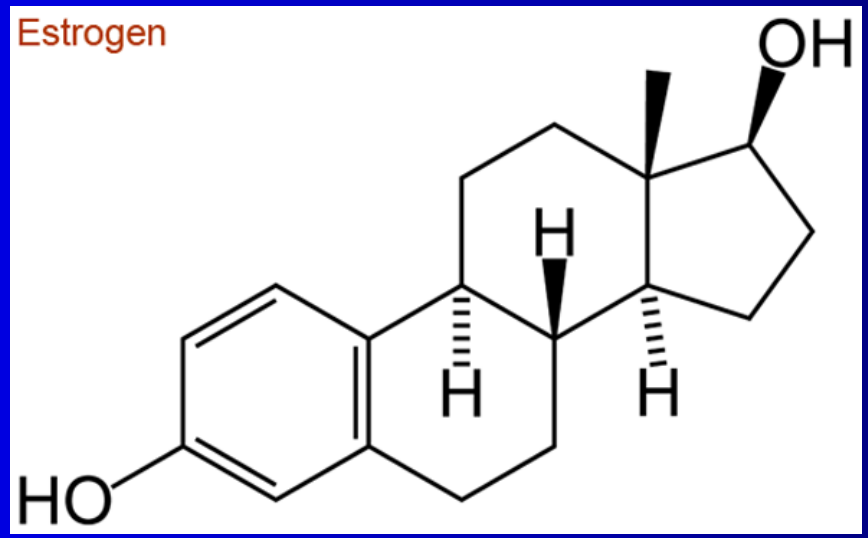


Testosterone



Cortisone





The Signature Page

Claisen Condensation: β-ketoesters

Dieckmann: Cyclic β-ketoesters

Aldol: α, β-unsaturated aldehydes and ketones

Acetoacetic ester synthesis: decorated acetones

Malonic ester synthesis: decorated acetic acids

Michael Reaction: 1-5 dicarbonyl compounds

Grignard Reaction: Alcohols…, etc.