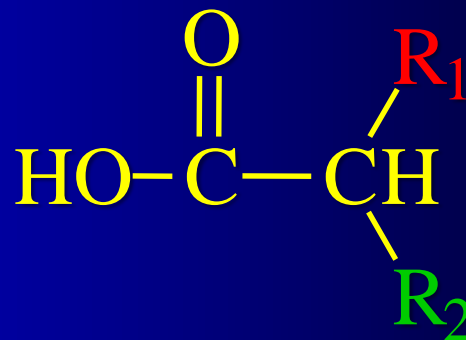
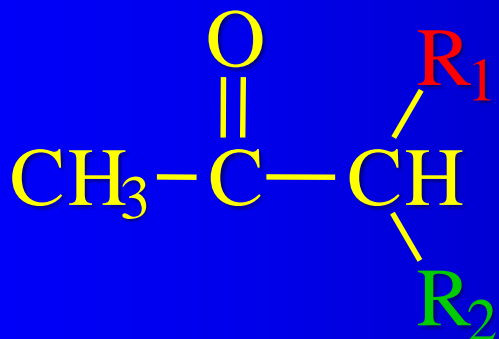


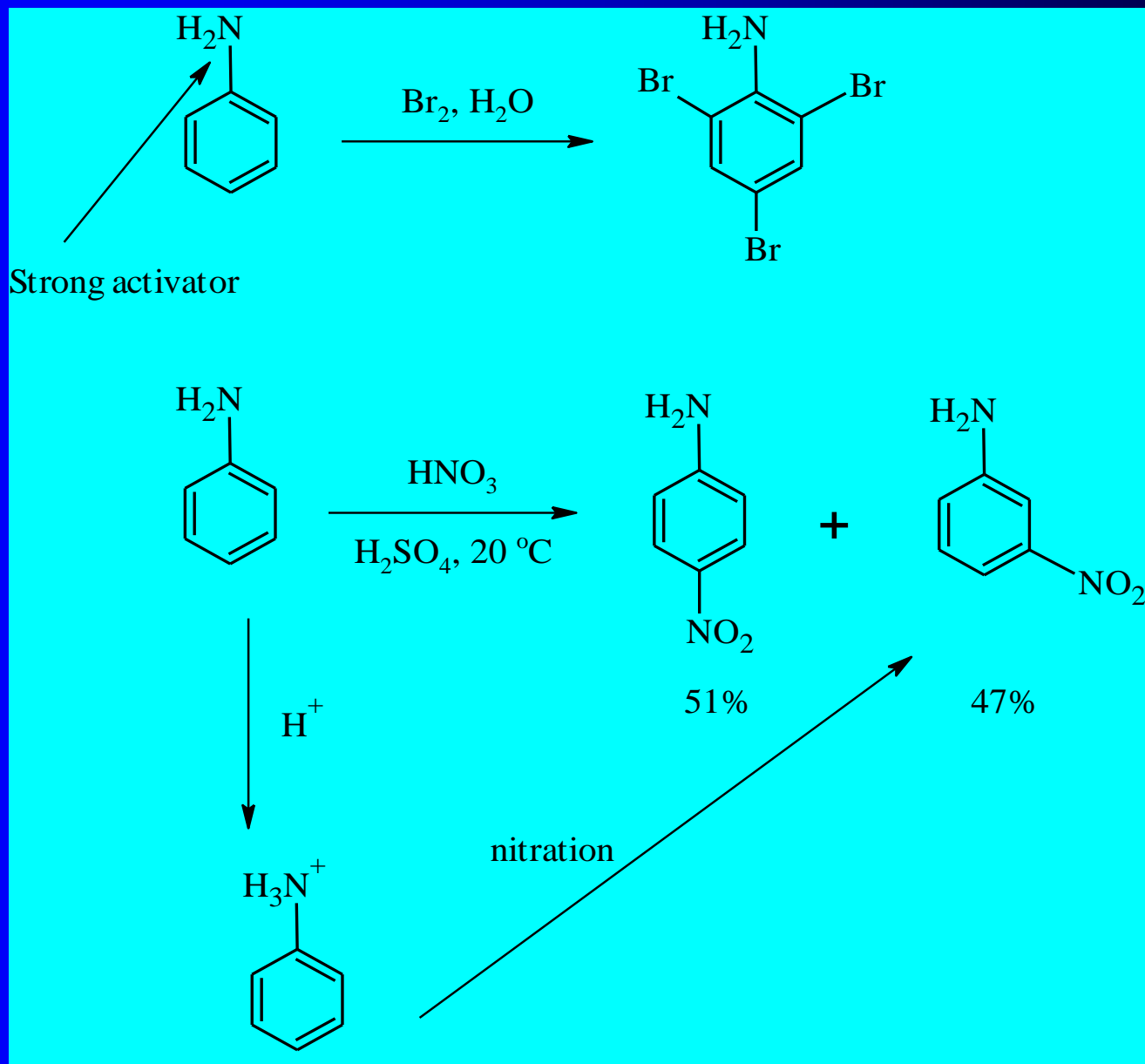
Lecture 20

Acetoacetic ester synthesis & Malonic ester synthesis

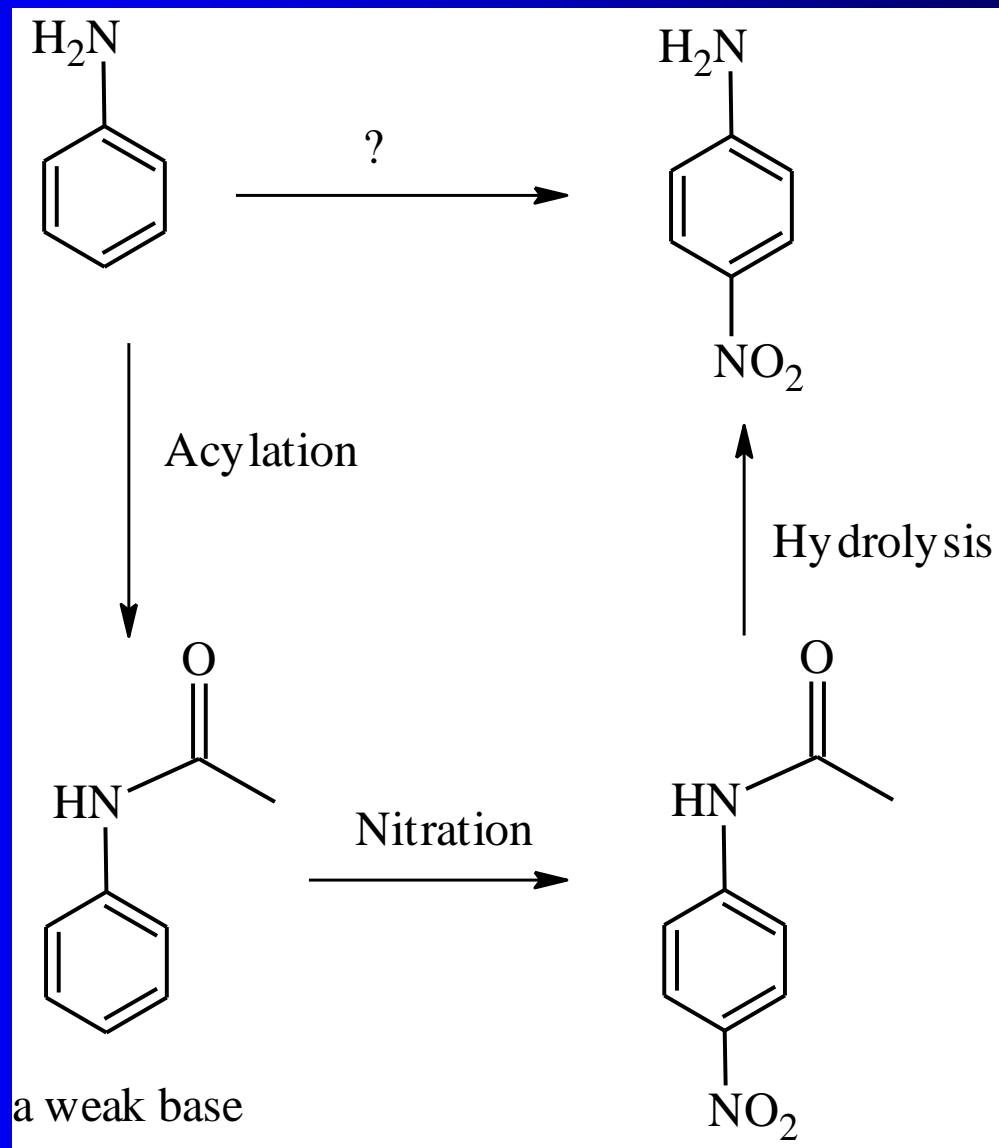




Electrophilic reactions of aniline ...the true story

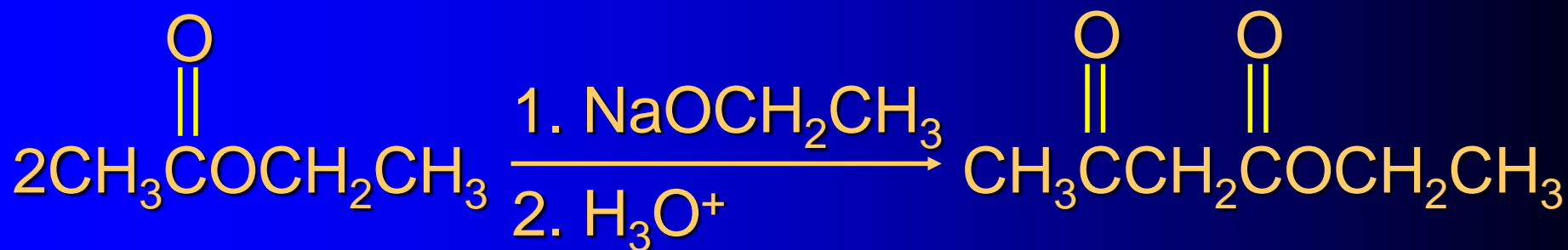


Protection-deprotection allows us to synthesize p-nitroaniline in a high yield



Classical Claisen Condensation

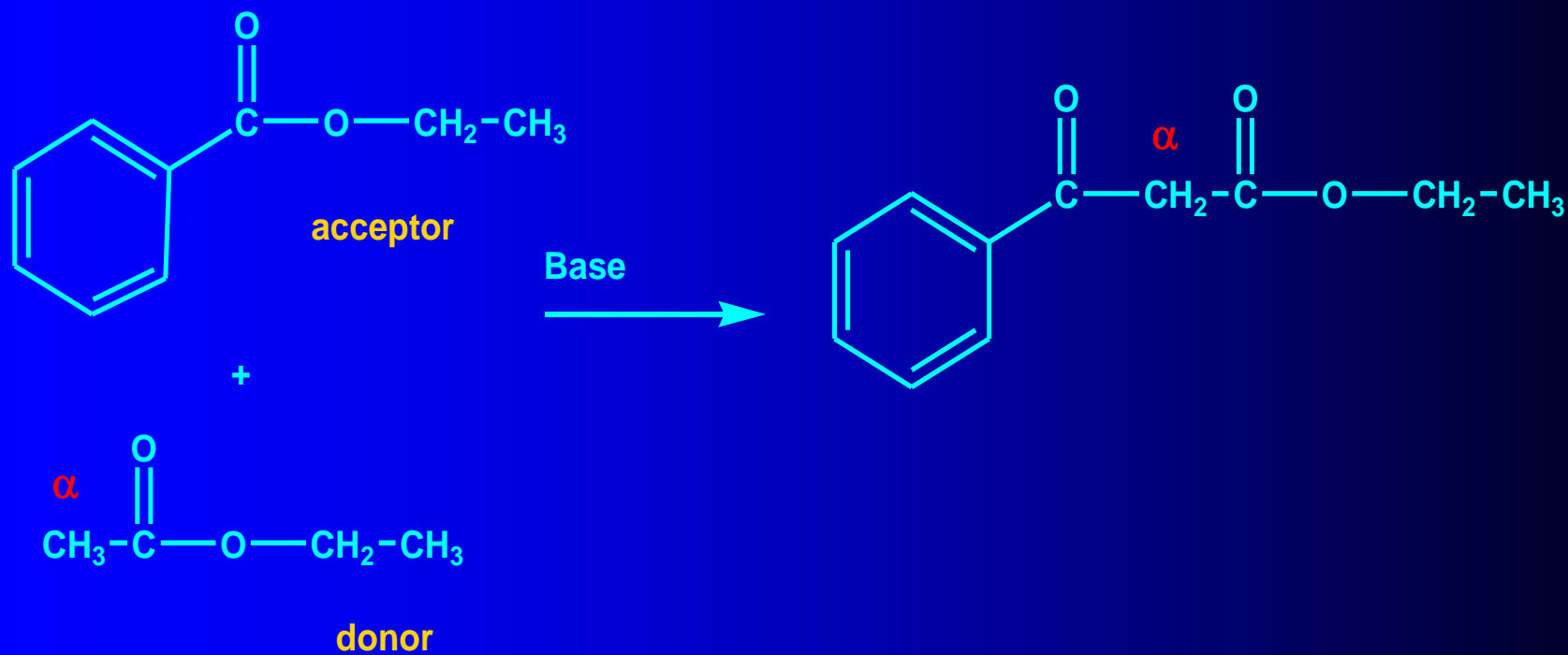
An excellent path to β -keto esters



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

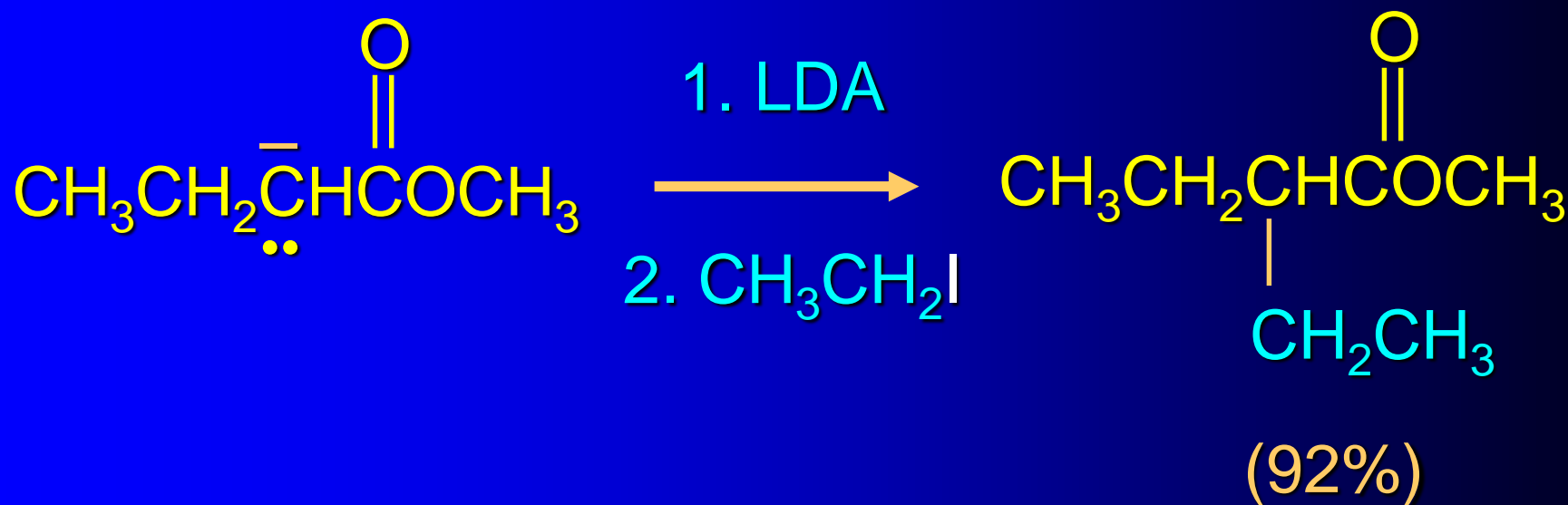


Crossed Claisen Condensation -- An Example

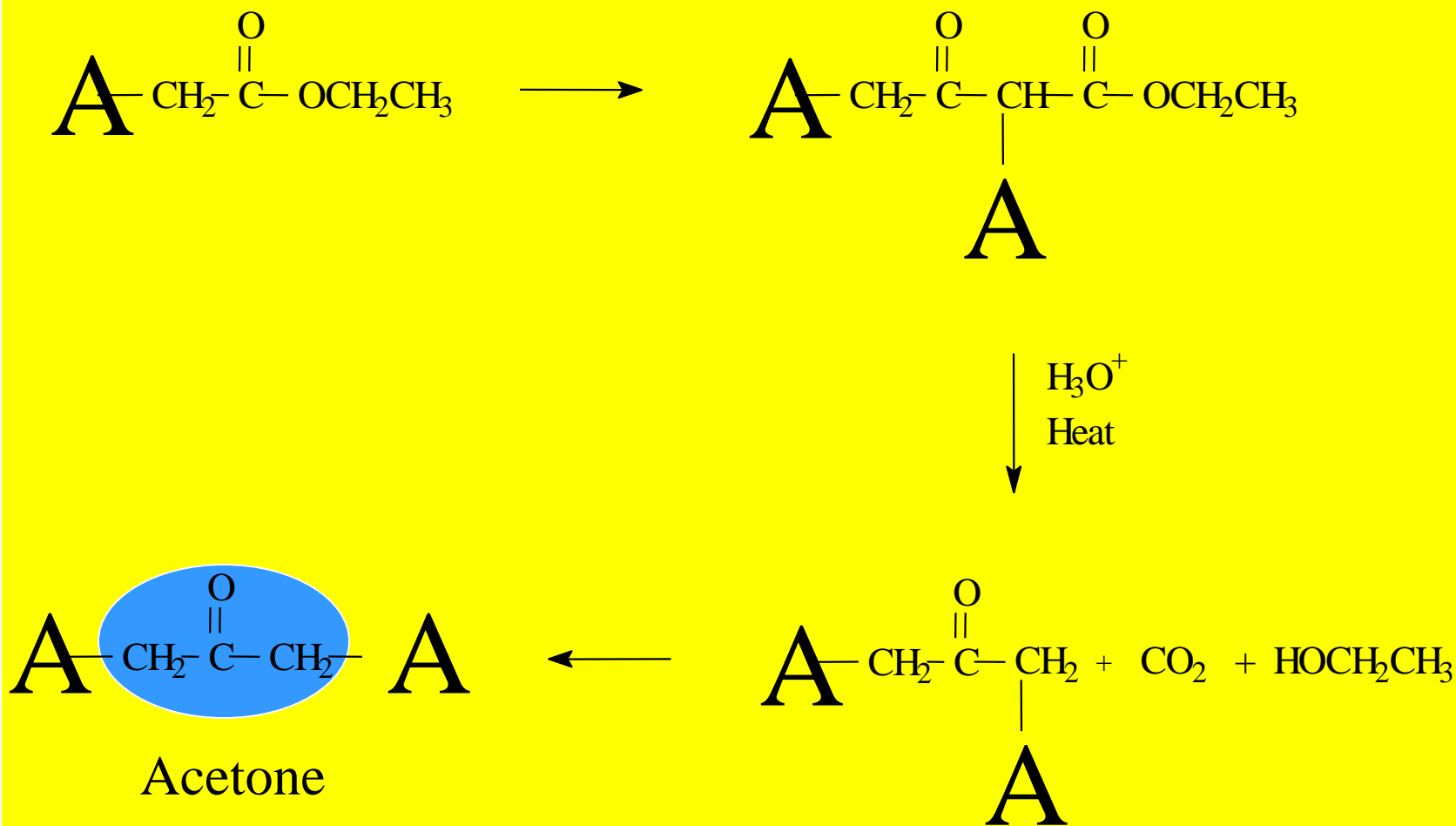


Lithium diisopropylamide (LDA)

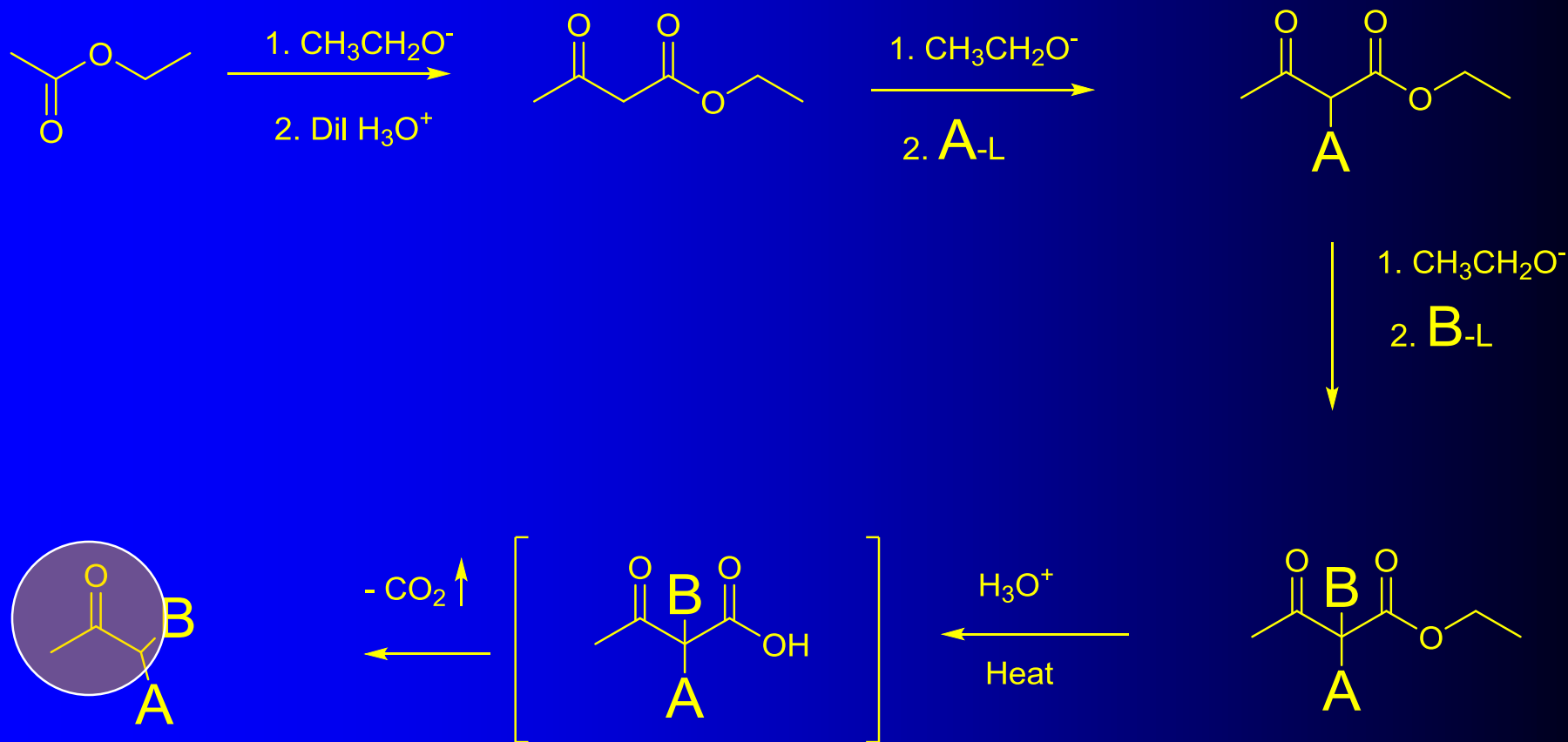
- Enolates generated from esters and LDA can be alkylated.



A versatile synthesis of β -ketoesters and symmetrically substituted acetones

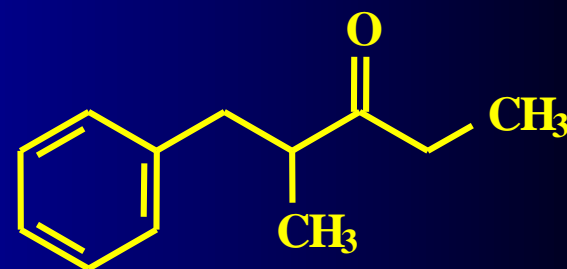
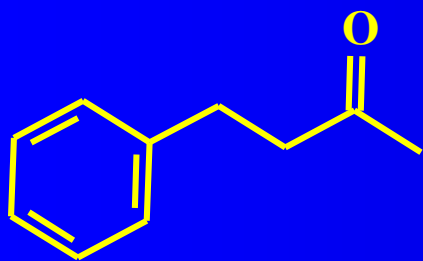


Alkylation of Acetoacetic Ester gives unsymmetrically substituted acetone



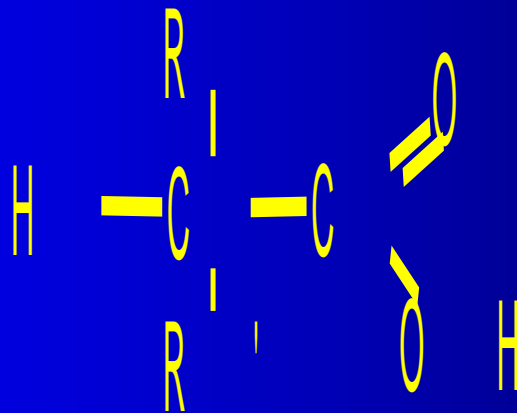
Ketone Synthesis

Let's work some examples together

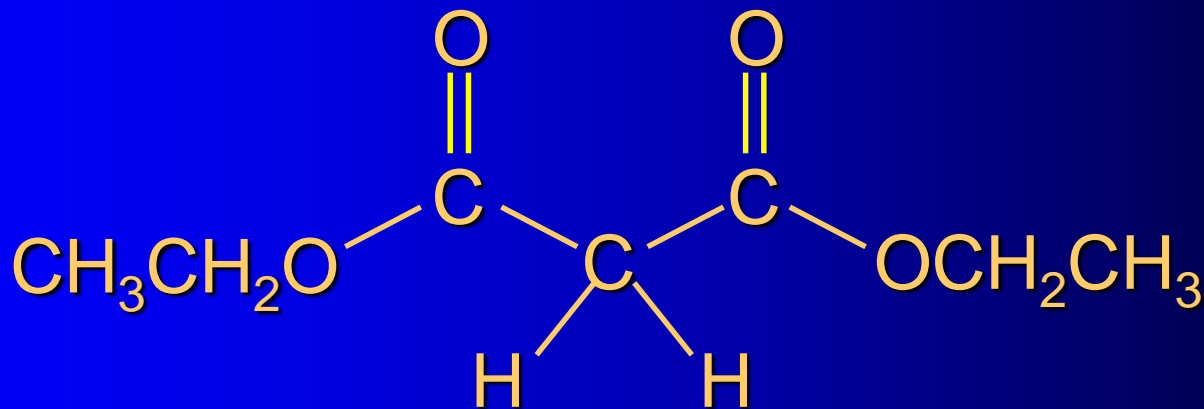


The Malonic Ester Synthesis

Versatile Synthesis of Carboxylic acids



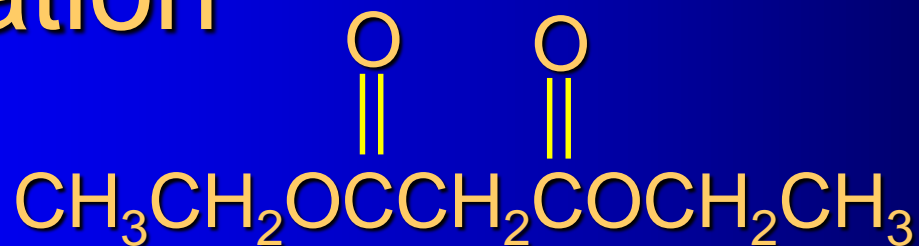
Malonic Ester



- *Malonic ester* is another name for *diethyl malonate*.
- The "malonic ester synthesis" uses diethyl malonate as a reactant for the preparation of carboxylic acids.

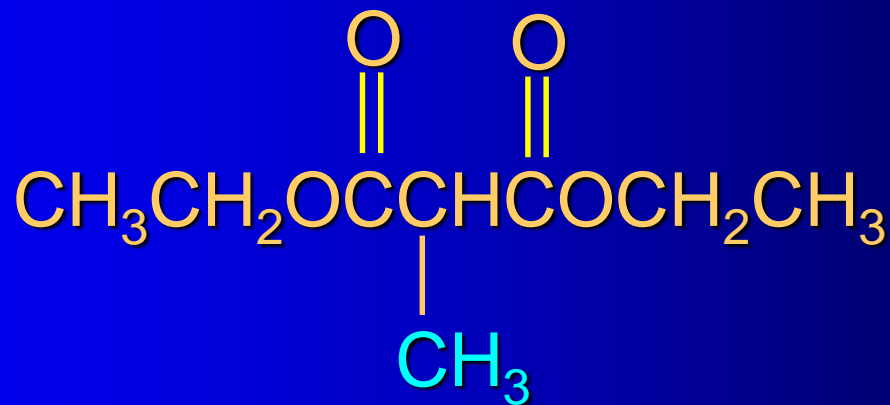


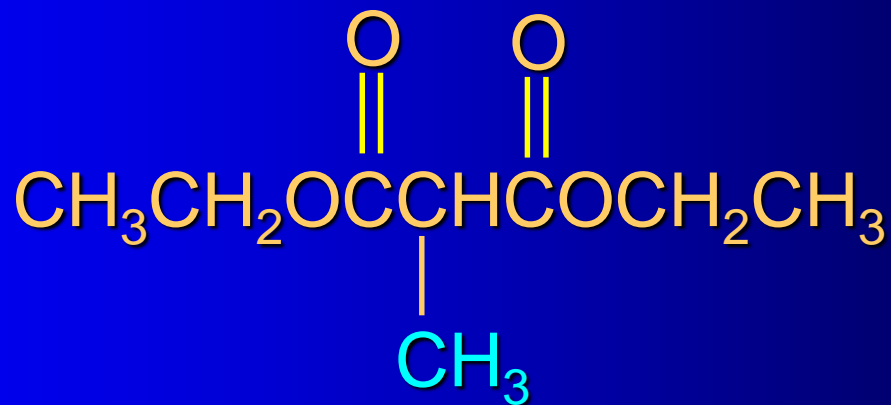
Dialkylation



1. $\text{NaOCH}_2\text{CH}_3$

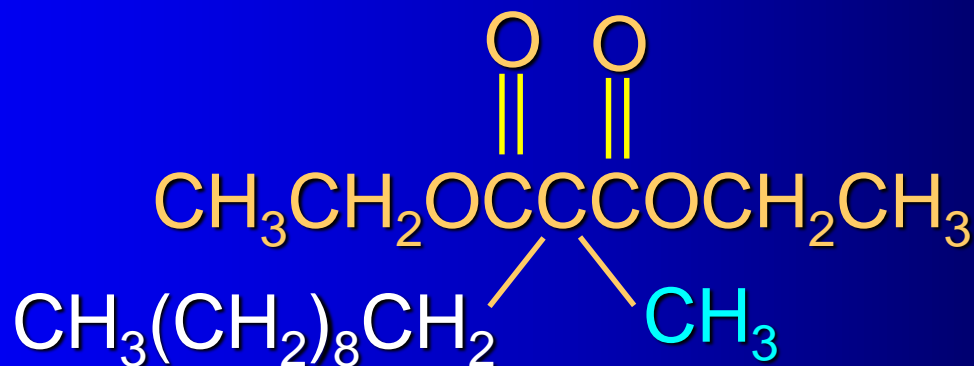
2. CH_3Br

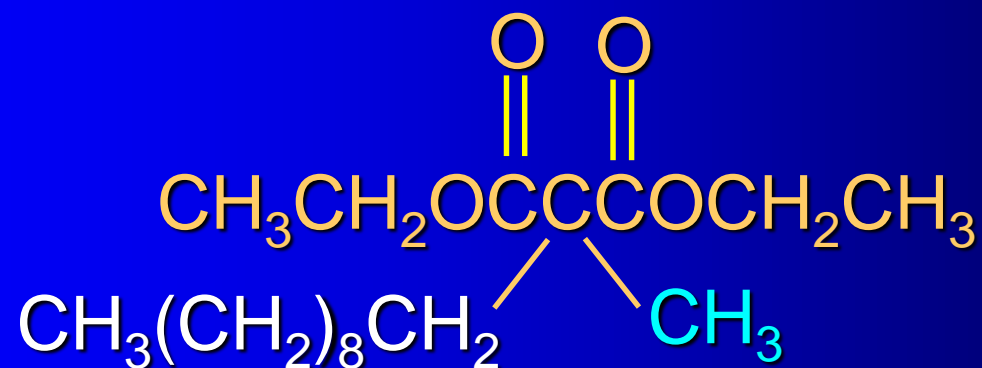




1. $\text{NaOCH}_2\text{CH}_3$

2. $\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{Br}$

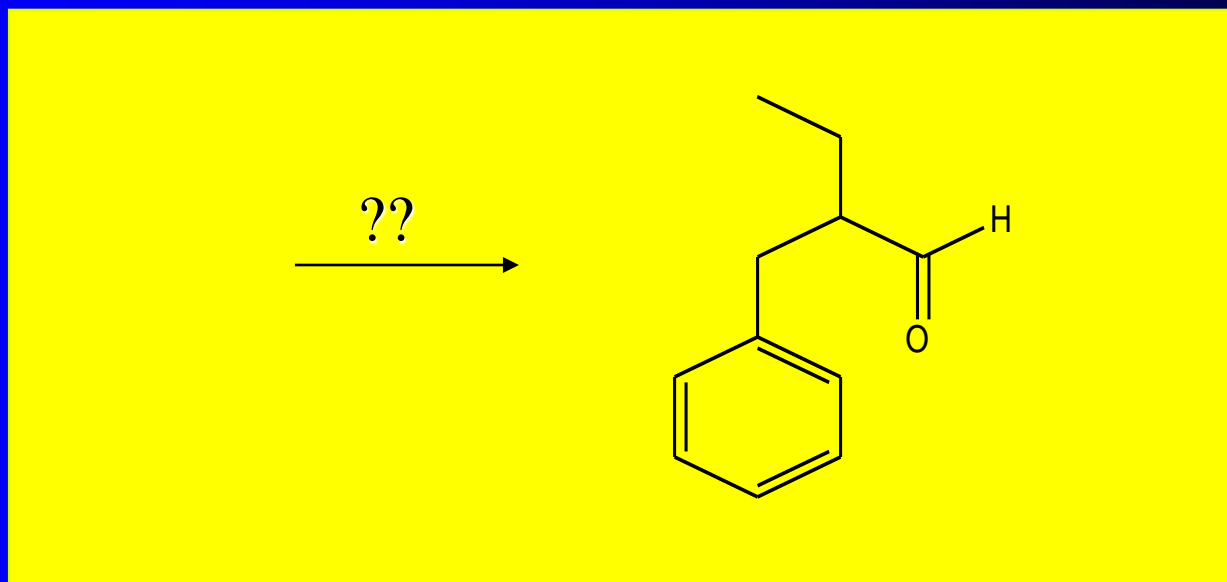




- ↓
1. NaOH, H₂O
 2. H⁺
 3. heat, -CO₂

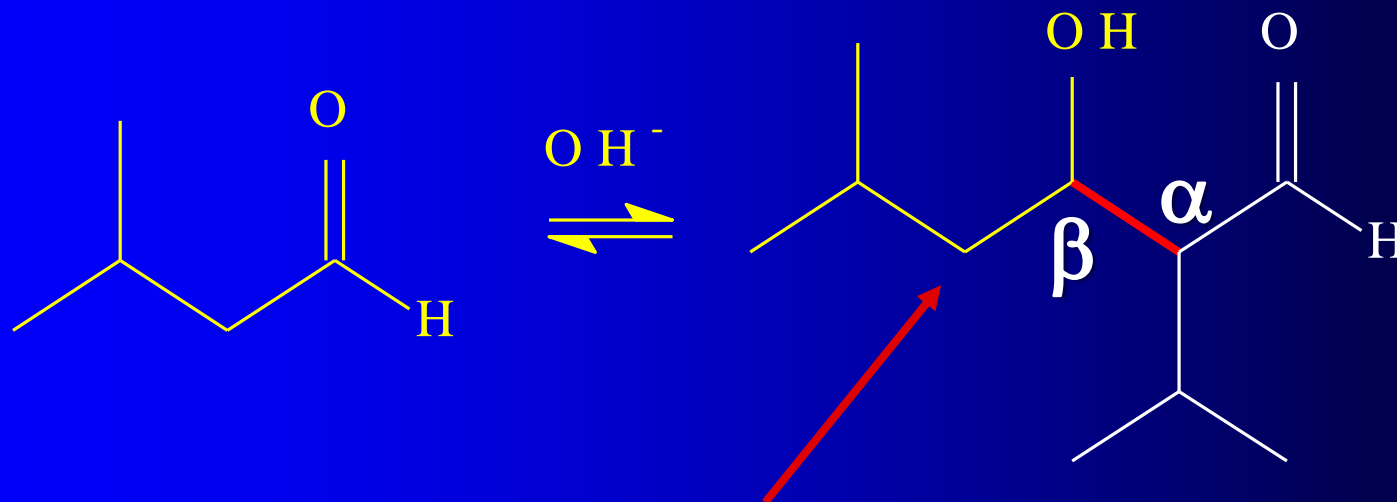


Malonic Ester Synthesis



The Aldol Condensation

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



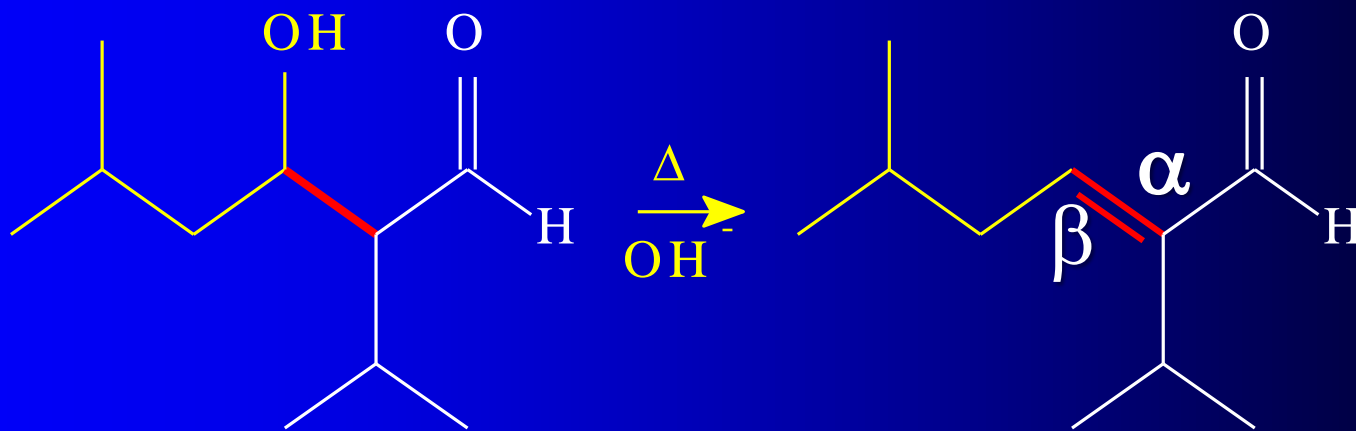
an Aldol!

{ Aldehyde / Alcohol }

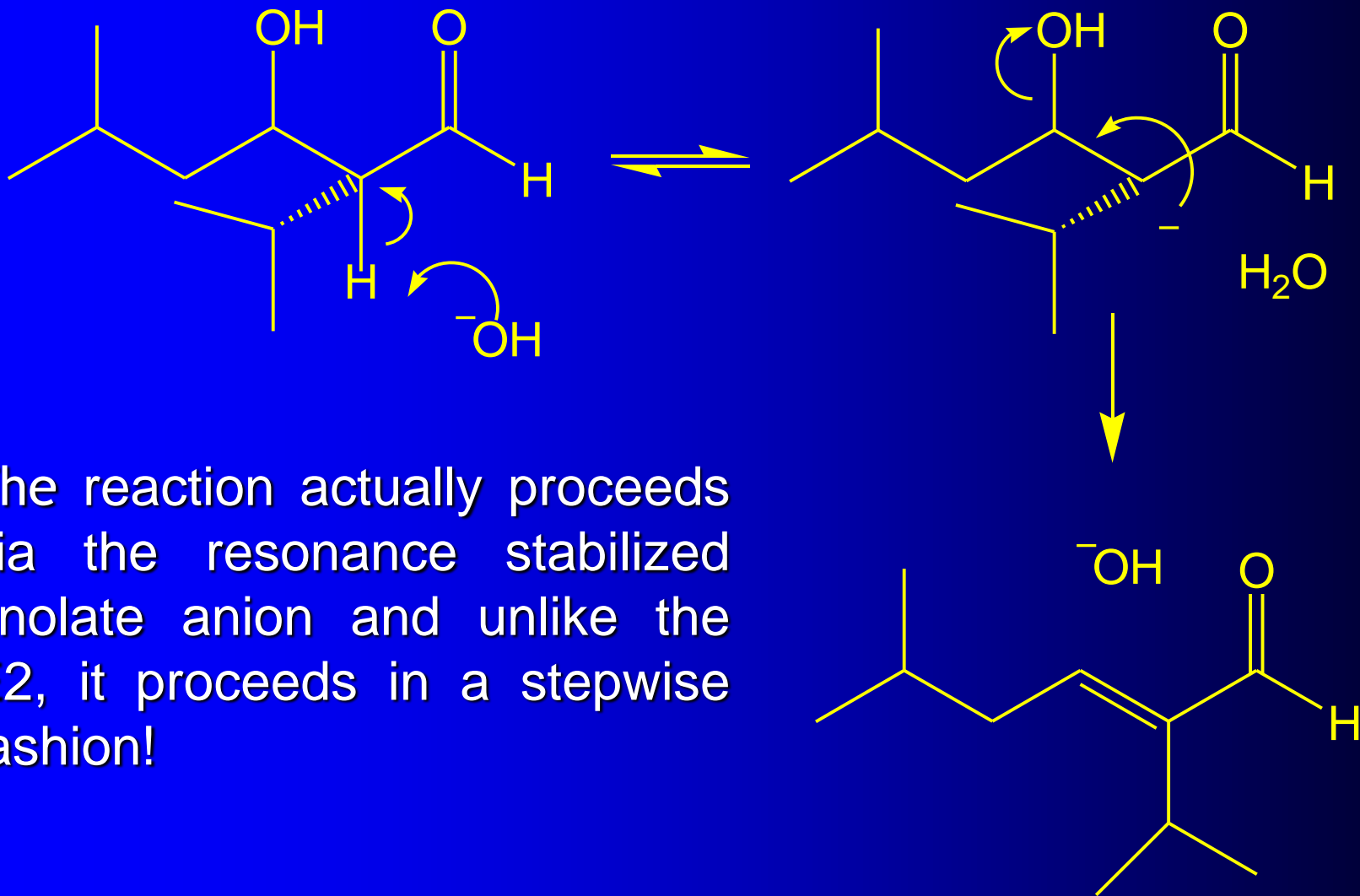


Loss of water!

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



"E₂ like" Elimination

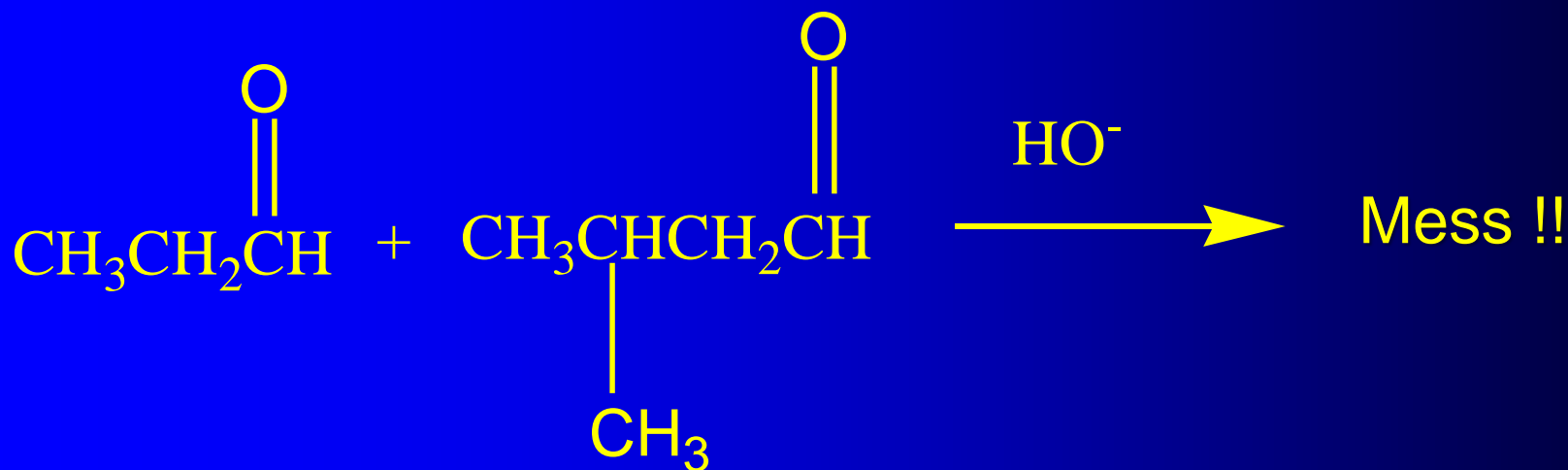


The reaction actually proceeds via the resonance stabilized enolate anion and unlike the E2, it proceeds in a stepwise fashion!



Crossed Aldol Reactions

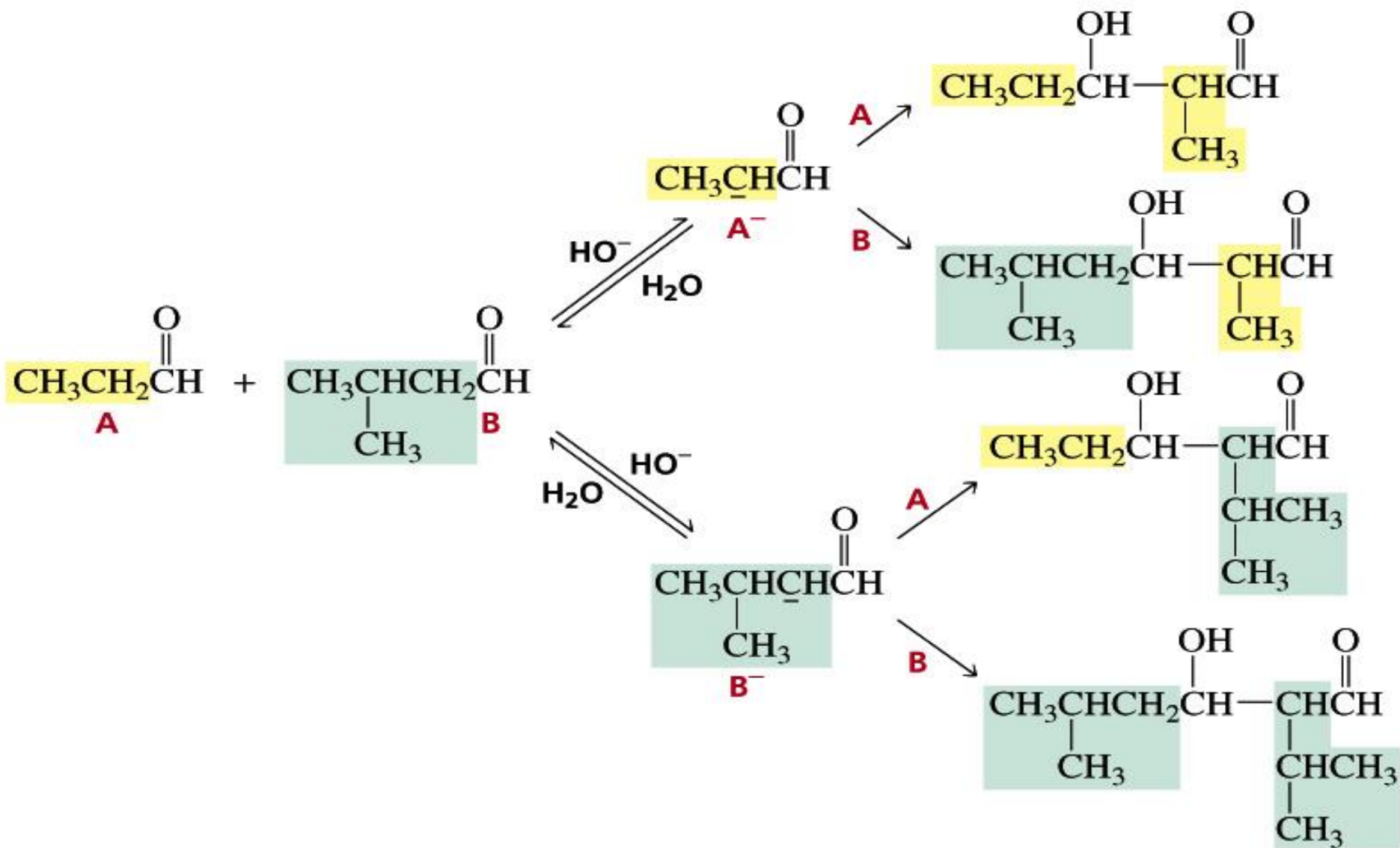
- In a “crossed aldol” reaction, one kind of molecule provides the enolate anion and another kind provides the carbonyl group



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

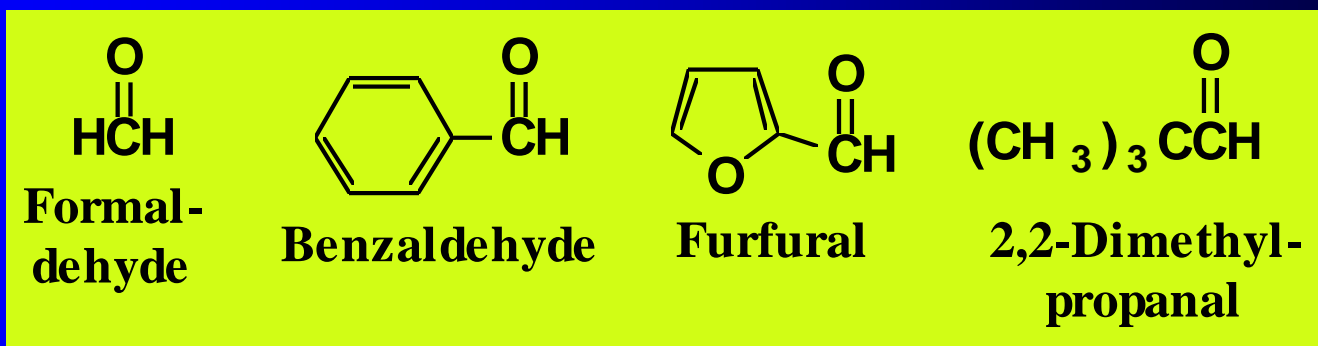


The Crossed Aldol Reaction



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 α -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.



From what??

