Alpha Carbon Chemistry
2 – Aldol and Claisen Reactions

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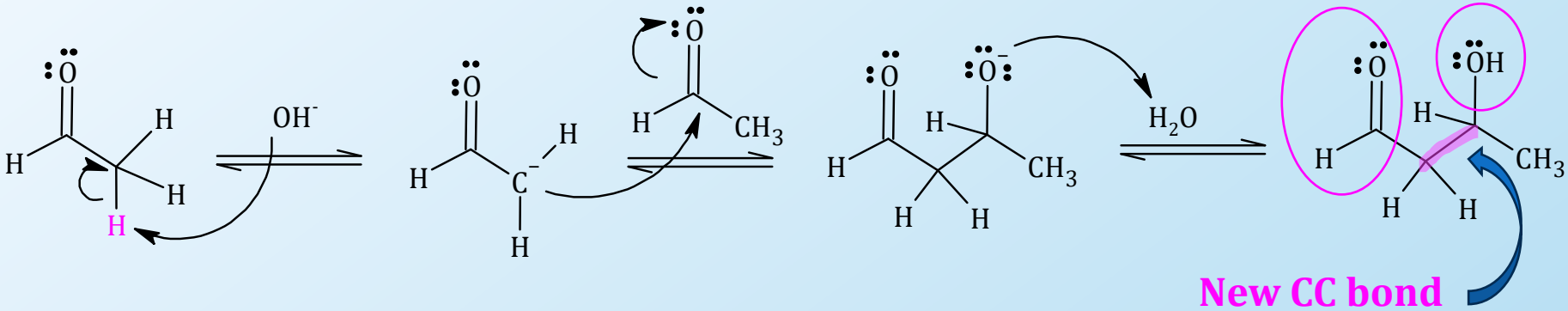
Reactions: Aldol Reaction/Condensation

Aldol reactions occur when an aldehyde reacts with another aldehyde in presence of a strong base. One aldehyde forms the nucleophile from the base which then reacts with the second aldehyde (substrate).

Some key points of this reaction:

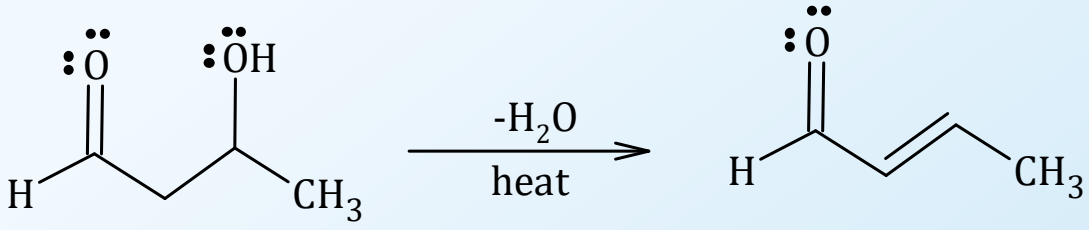
- Water is formed as a result – hence called condensation reaction.
- Product has the **ald**ehyde and alcoh**ol** – hence called aldol.
- The reaction is in equilibrium therefore reversible.

Mechanism:

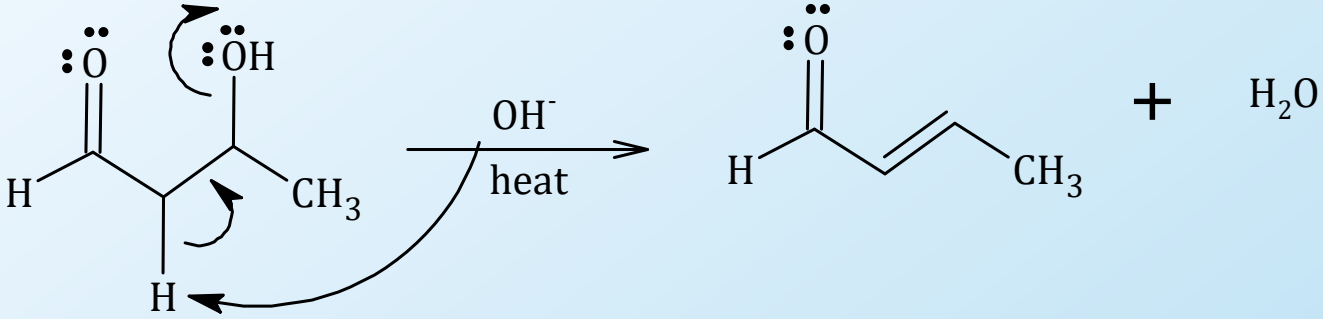


Dehydration of the Aldol Product

If the aldol product is heated it will dehydrate to give an alkene. The alkene is more stable due to conjugation with the carbonyl.

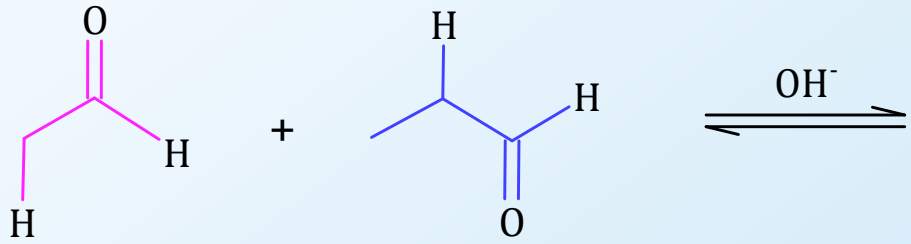


Mechanism:



Reactions: Cross Aldol Reaction with two Aldehydes

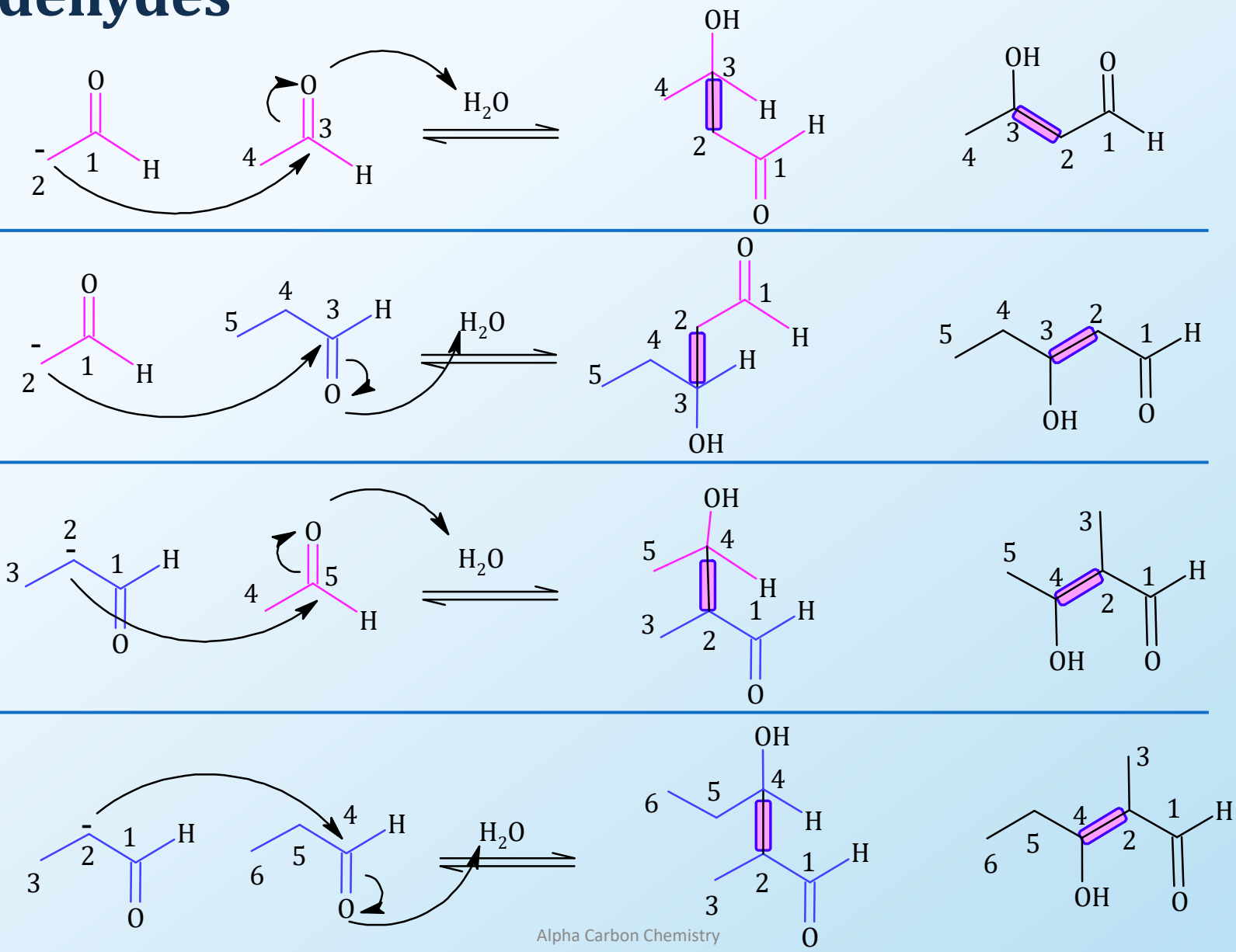
Cross aldol reactions occur with two different aldehydes. In the example on the right, ethanal is reacting with propanal.



See the next slide for all the products formed.

- I have highlighted the new bonds formed in the adducts.
- What is the problem? Some mixed products also form. (*How can you control that?*)

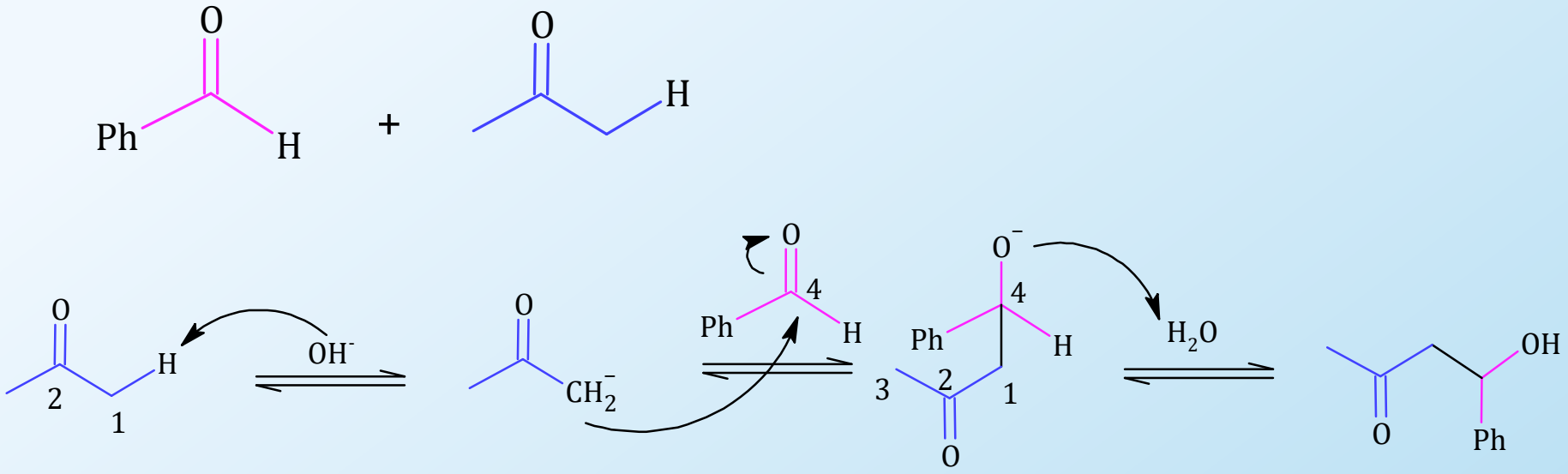
Reactions: Cross Aldol Reaction with two Aldehydes



Reactions: Cross Aldol Reaction with a Ketone and an Aldehyde

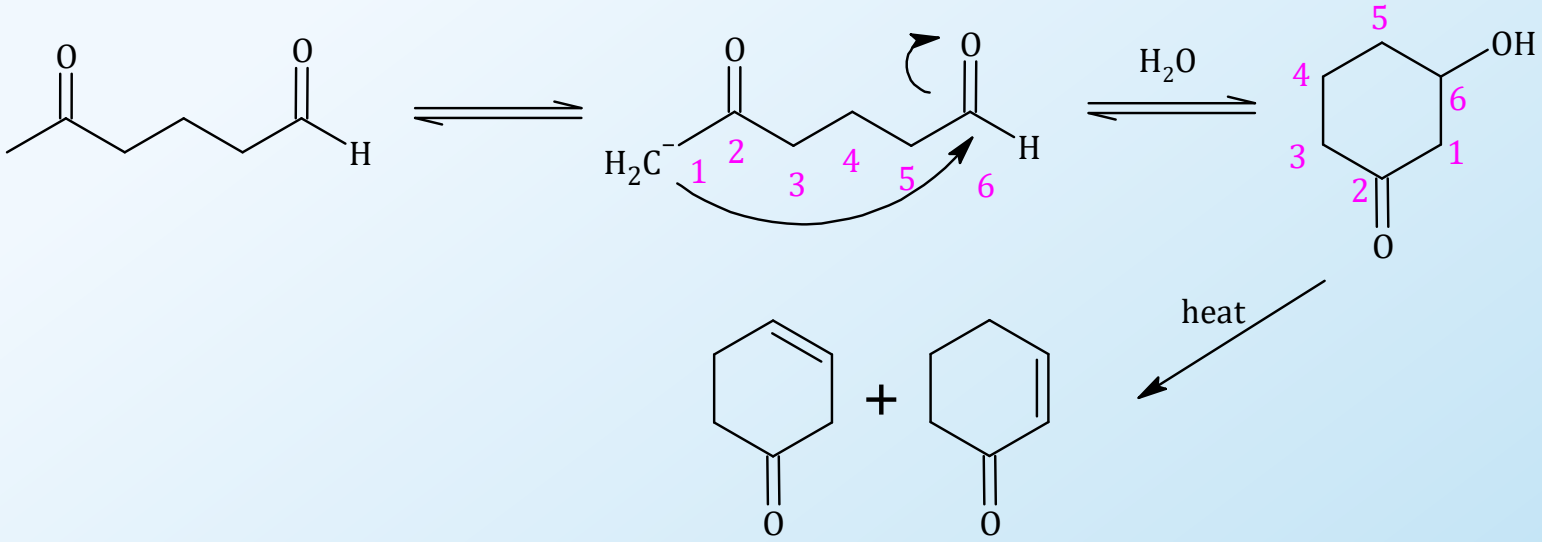
In Claisen-Schmidt reaction an aldehyde and ketone in presence of a strong base.

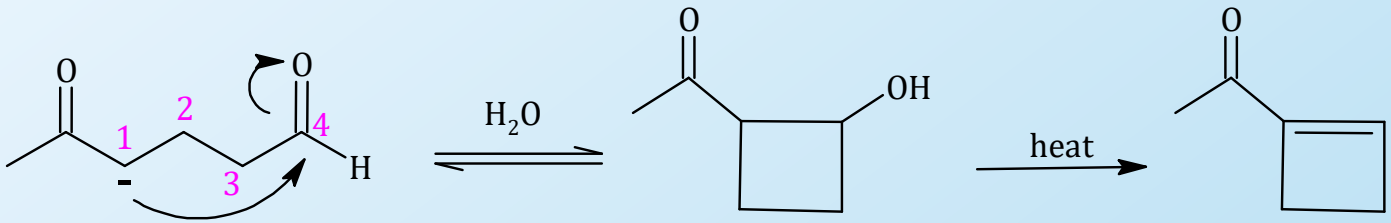
To prevent a mixture of products, this reaction works better if one of the compounds has no α hydrogen. Below is the reaction between acetone and benzaldehyde (no α H).



Reactions: Cyclization with Aldol Reaction

Intramolecular aldol condensation can occur when a molecule has two aldehyde groups. Reaction occurs preferentially at the **less sterically** hindered carbonyl. Keep in mind that the ring formed will be the more stable size. I have numbered the carbons to show the α hydrogen preferentially abstracted to form the more stable ring.

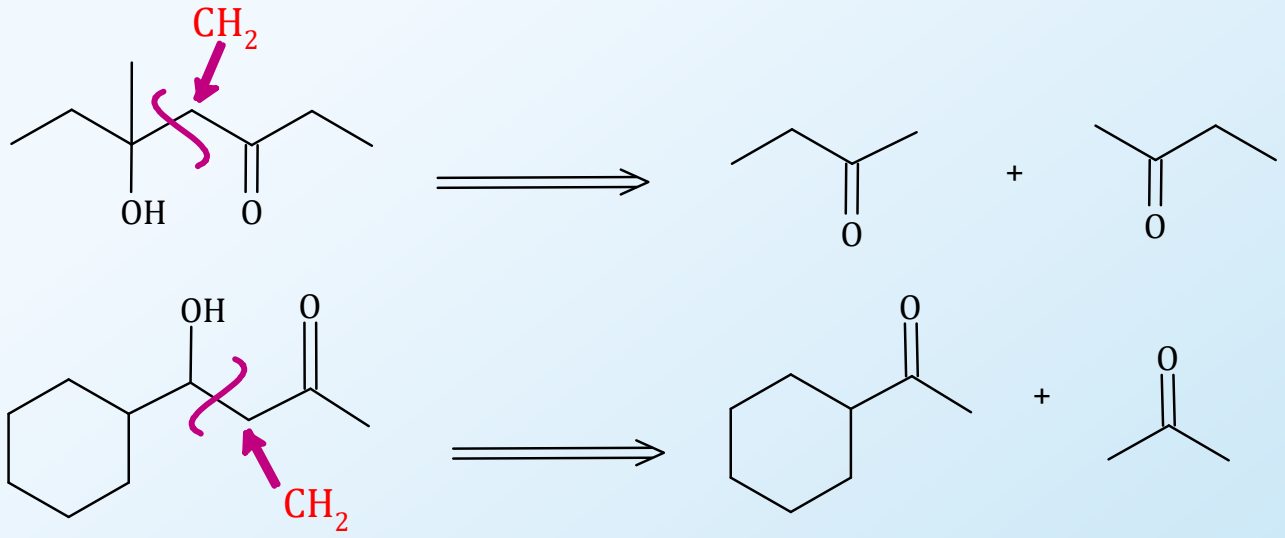




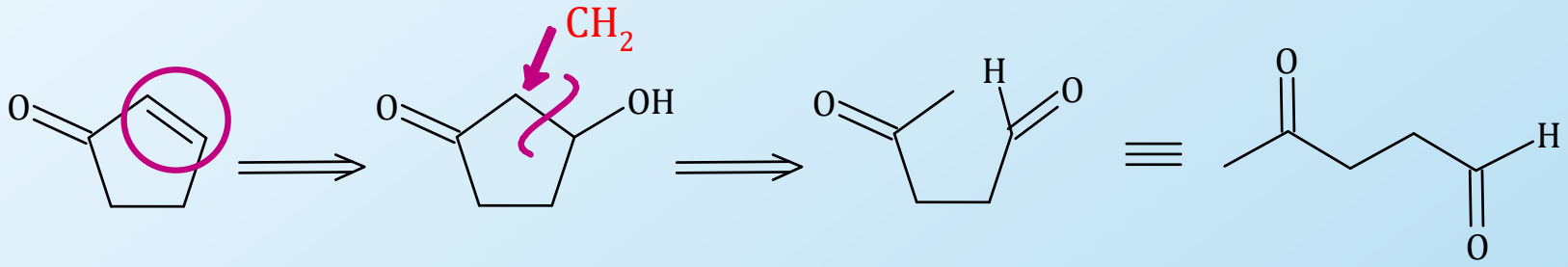
Not likely to form

Retrosynthesis of Aldol Products

Look for the carbonyl and alcohol separated by one carbon (CH_2) – that is the new bond formed from aldol reaction or condensation.



In case of condensation products, look for the double bond conjugated with carbonyl. That is where the alcohol group dehydrated.

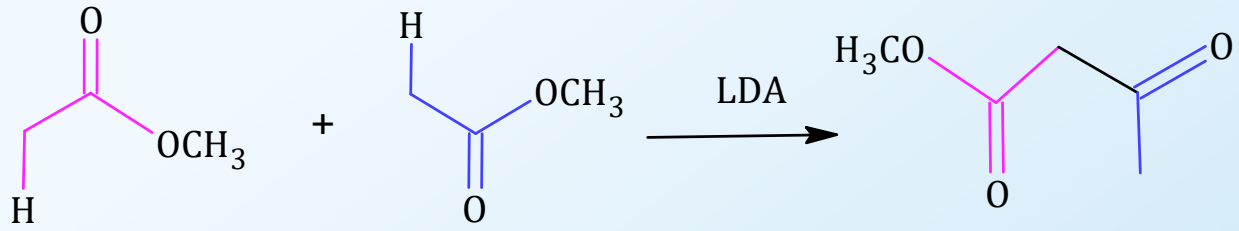


Aldol Products

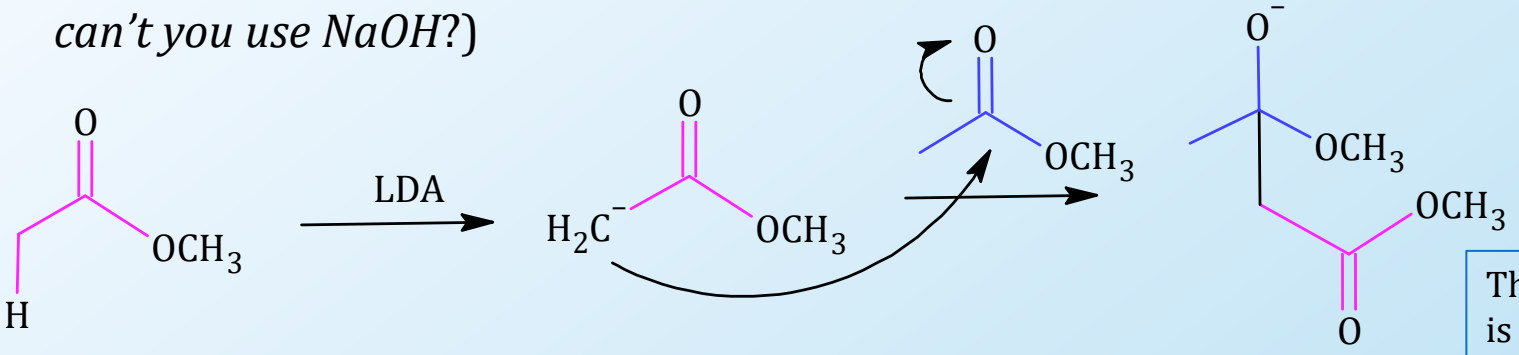
- Aldol products can be used as such, or reactions can be continued on with the new functional group created.
- One of the biggest advantage of Aldol reaction is a new C-C bond formation. It can thus be used to join two molecules to make a macromolecule.
- Dehydration gives another advantage that an alkene is formed; so in addition to alcohol chemistry, alkene chemistry can also be carried out.

Claisen Condensation

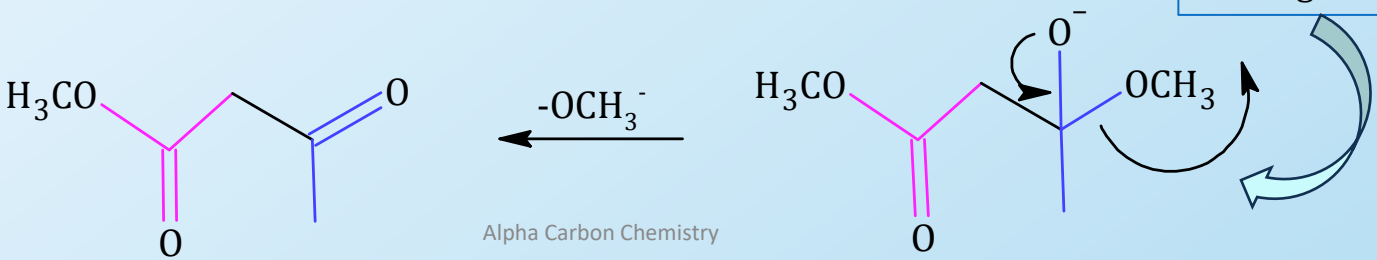
These reactions are similar to aldol but done using carboxylic esters as starting materials. The product is a keto ester.



Mechanism: Only LDA or methoxide or ethoxide can be used as bases. (*Why can't you use NaOH*?)



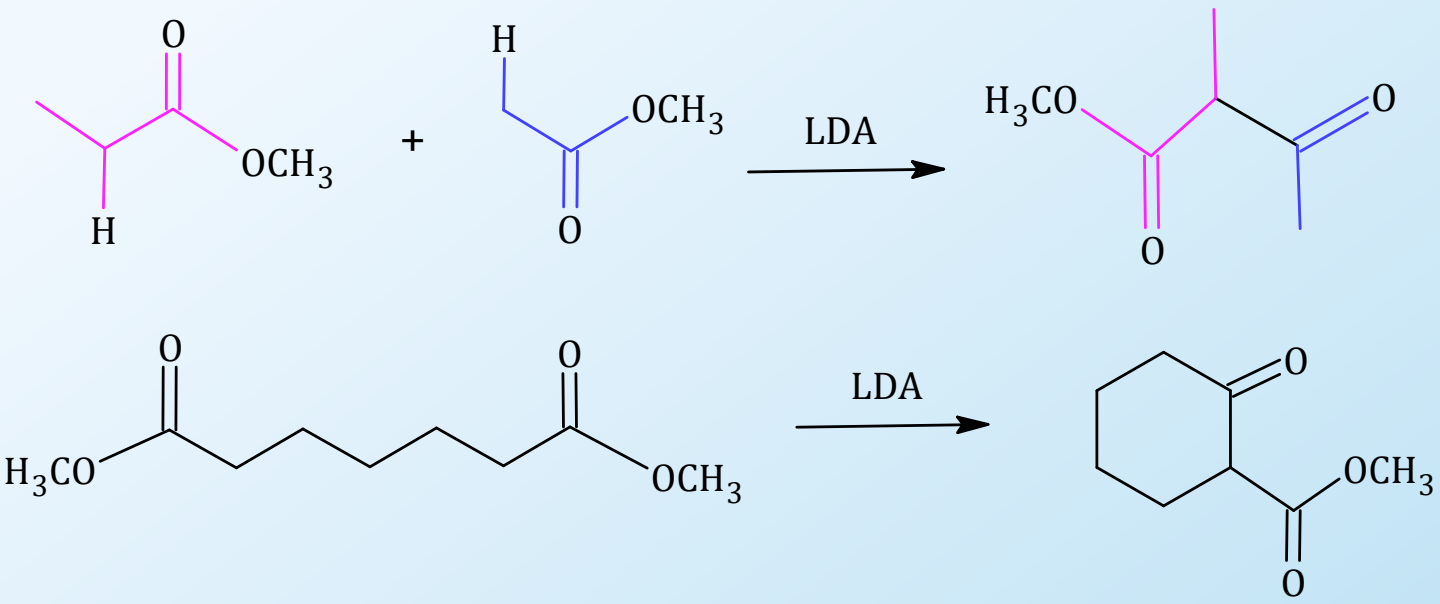
The structure below is rearranged to give a straight structure.



Claisen Condensation - Continued

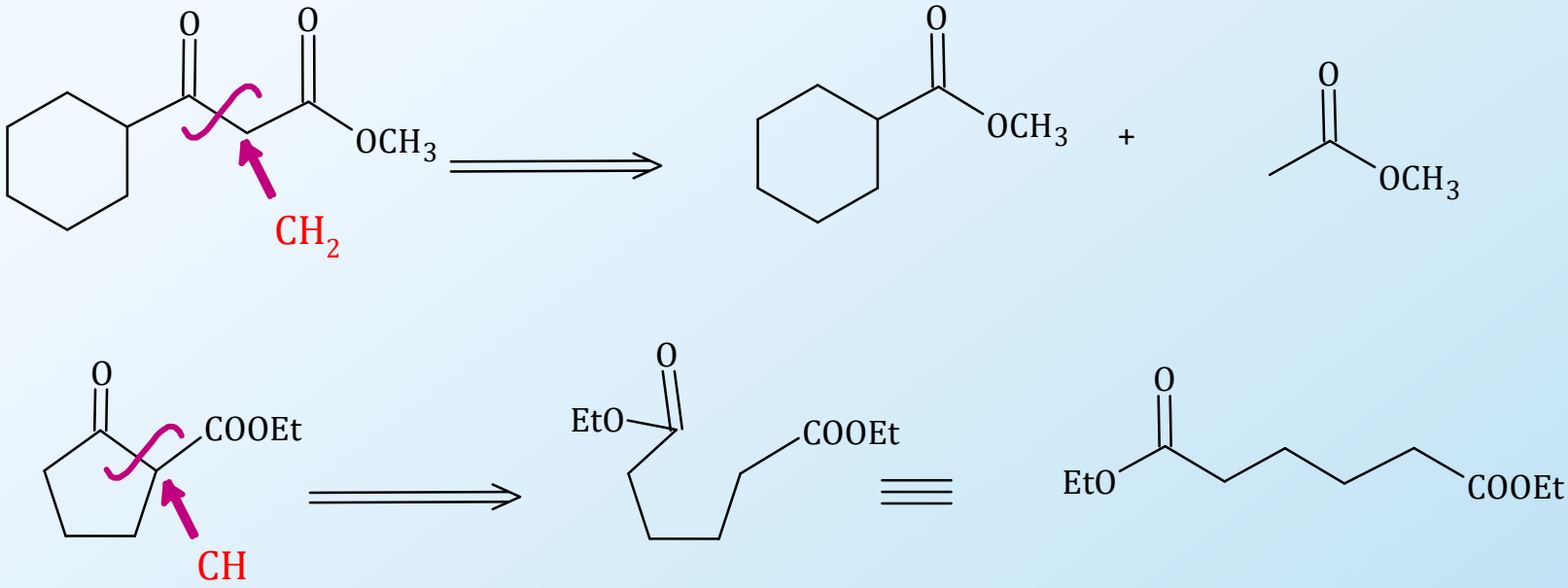
As with cross aldols, one can use different esters to form keto esters to make cyclized keto esters using intramolecular cyclization.

(*Write the mechanism on your own*)

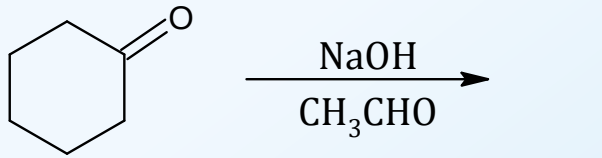


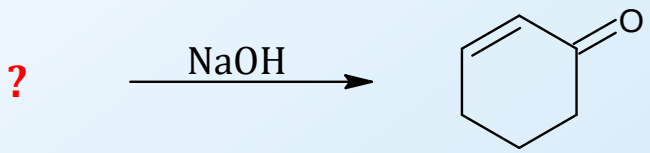
Claisen Condensation - Retrosynthesis

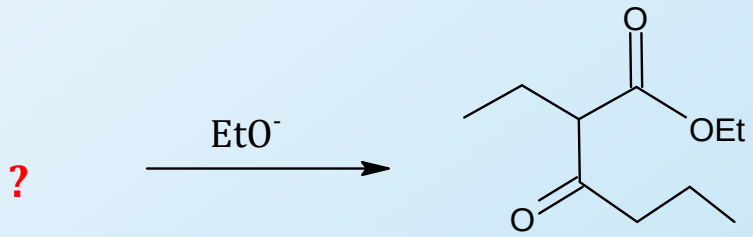
In case of determining the starting materials for the keto esters, look for the keto group and the ester, it should be separated by a CH (in cyclized products) or CH_2, that is where the cleavage will occur for retrosynthesis.



Worked Example: Complete the following reactions with the appropriate product or substrate.

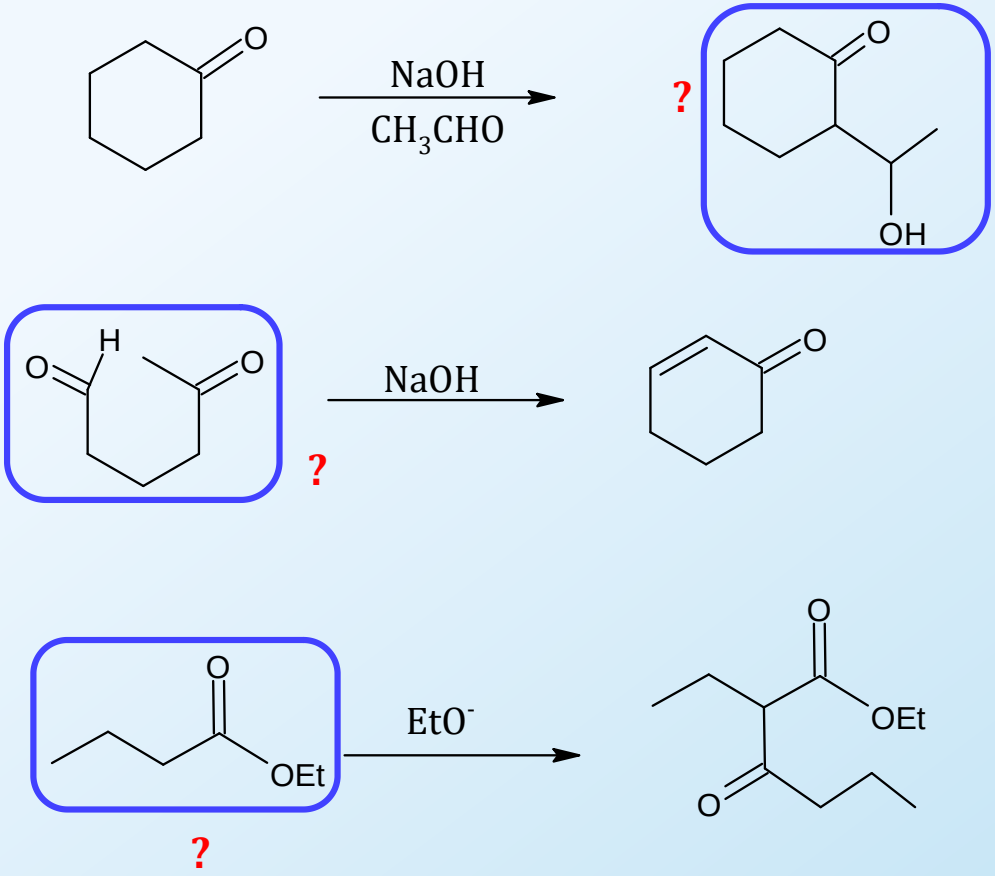






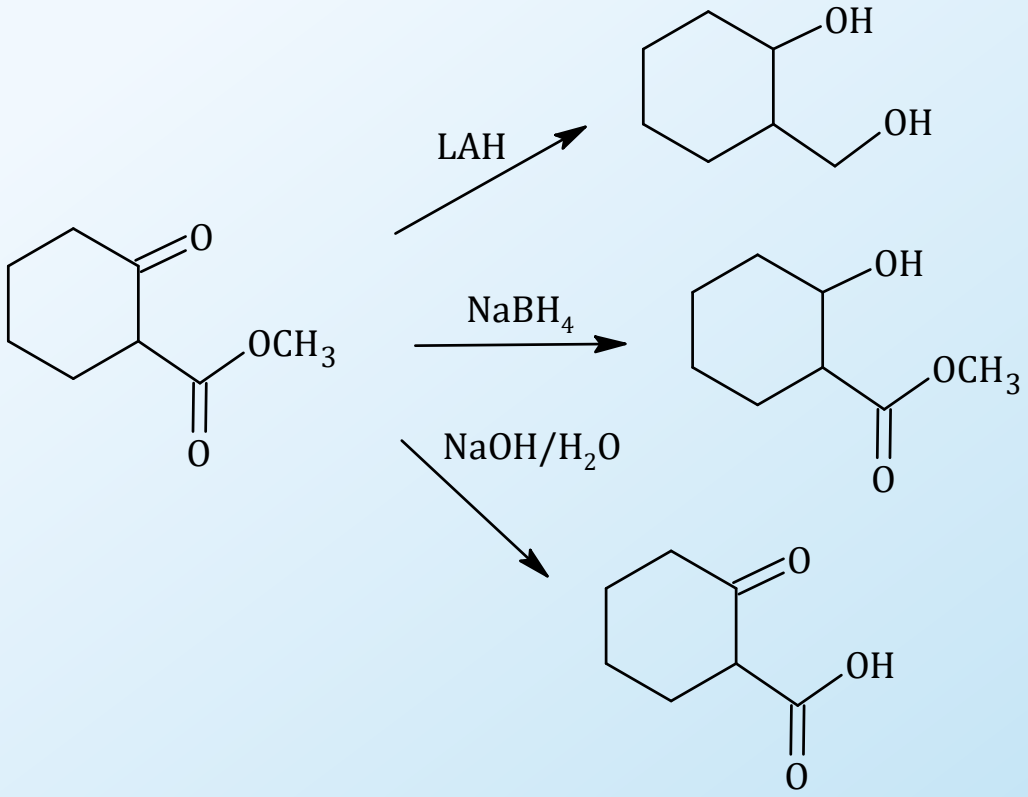
Worked Example: Complete the following reactions with the appropriate product or substrate.

Answers



Claisen Condensation More

Just like any other functional groups, the keto esters can be used as substrates for further reactions. Below are a few given as example.



Key Concepts

- α protons
- Aldol condensation
- Claisen-Schmidt reaction
- Intramolecular cyclization
- Claisen condensation