PROBLEM 22-23

When propionaldehyde is warmed with sodium hydroxide, one of the products is 2-methylpent-2-enal. Propose a mechanism for this reaction.

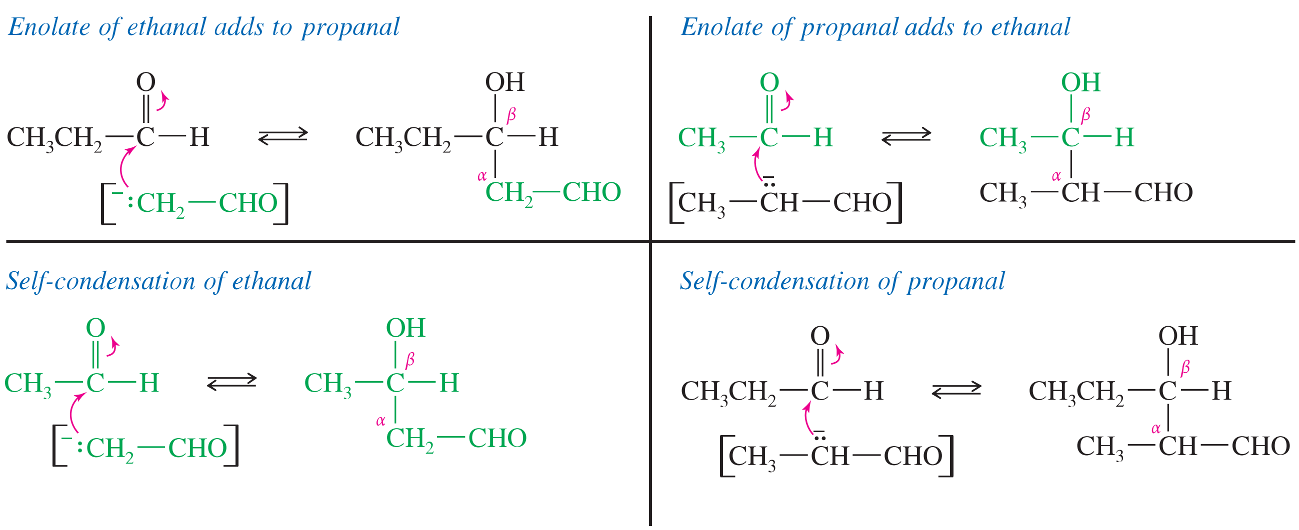
PROBLEM 22-24

Predict the products of aldol condensation, followed by dehydration, of the following ketones and aldehydes.
(a) butyraldehyde **(b)** acetophenone **(c)** cyclohexanone

22-9 Crossed Aldol Condensations

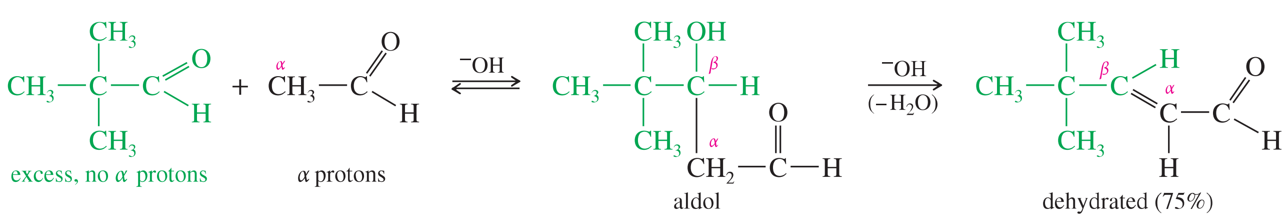
When the enolate of one aldehyde (or ketone) adds to the carbonyl group of a different aldehyde or ketone, the result is called a **crossed aldol condensation.** The compounds used in the reaction must be selected carefully, or a mixture of several products will be formed.

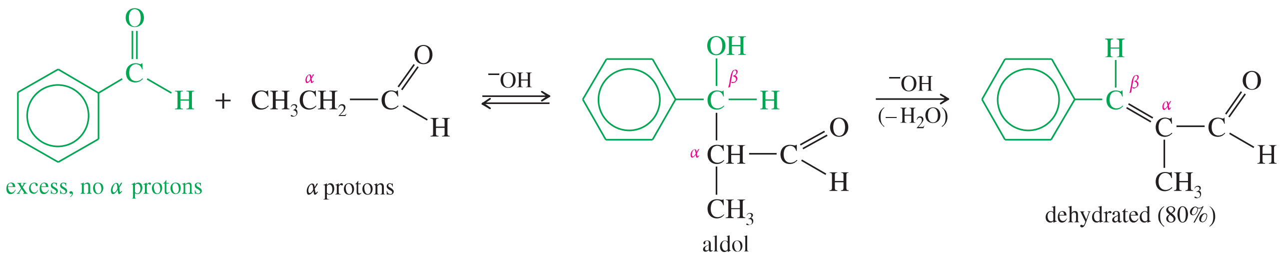
Consider the aldol condensation between ethanal (acetaldehyde) and propanal shown below. Either of these reagents can form an enolate ion. Attack by the enolate of ethanal on propanal gives a product different from the one formed by attack of the enolate of propanal on ethanal. Also, self-condensations of ethanal and propanal continue to take place. Depending on the reaction conditions, various proportions of the four possible products result.



A crossed aldol condensation can be effective if it is planned so that only one of the reactants can form an enolate ion and so that the other compound is more likely to react with the enolate. If only one of the reactants has an α hydrogen, only one enolate will be present in the solution. If the other reactant is present in excess or contains a particularly electrophilic carbonyl group, it is more likely to be attacked by the enolate ion.

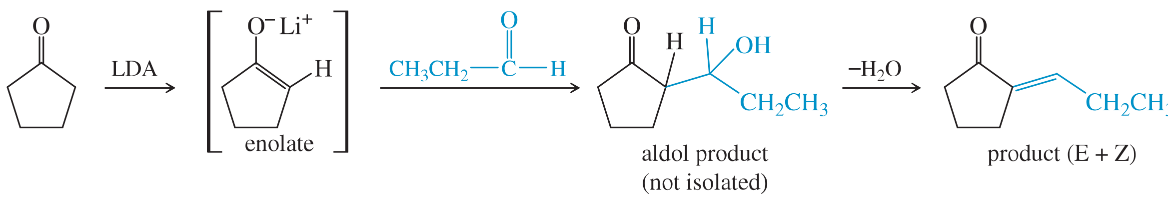
The following two reactions are successful crossed aldol condensations. The aldol products may or may not undergo dehydration, depending on the reaction conditions and the structure of the products.





To carry out these reactions, slowly add the compound with α protons to a basic solution of the compound with no α protons. This way, the enolate ion is formed in the presence of a large excess of the other component, and the desired reaction is favored.

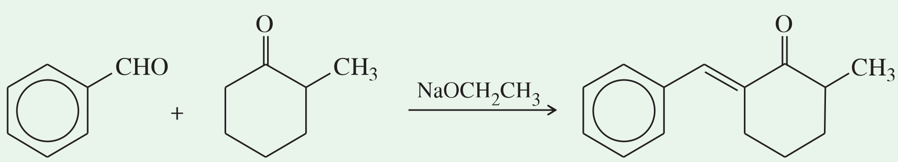
Lithium enolates formed using LDA (Section 22-2B) can react with other ketones and aldehydes to give crossed aldol products that could not be formed by standard base-catalyzed aldols. We can use LDA to make just the desired enolate ion, then add the compound we want to react as the electrophile. In this way, we control which enolate adds to which carbonyl group.



PROBLEM-SOLVING STRATEGY Proposing Reaction Mechanisms

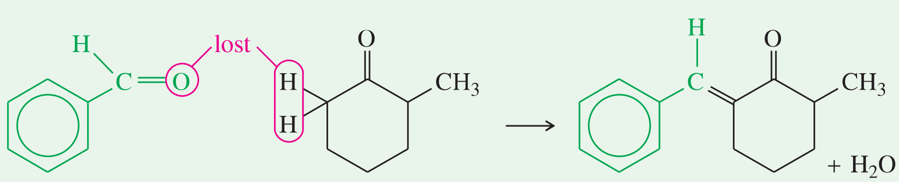
The general principles for proposing reaction mechanisms, first introduced in Chapter 4 and summarized in Appendix 3A, are applied here to a crossed aldol condensation. This example emphasizes a base-catalyzed reaction involving strong nucleophiles. In drawing mechanisms, be careful to draw all the bonds and substituents of each carbon atom involved. Show each step separately, and draw curved arrows to show the movement of electrons from the nucleophile to the electrophile.

Our problem is to propose a mechanism for the base-catalyzed reaction of methylcyclohexanone with benzaldehyde:

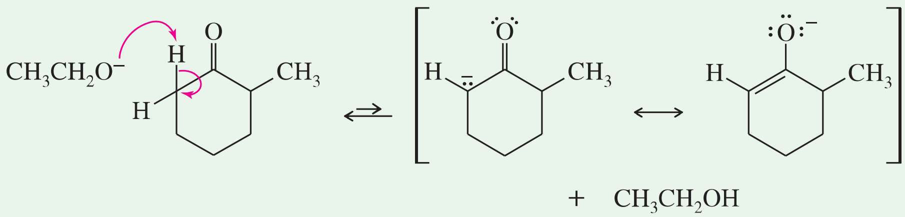


First, we must determine the type of mechanism. Sodium ethoxide, a strong base and a strong nucleophile, implies the reaction involves strong nucleophiles as intermediates. We expect to see strong nucleophiles and anionic intermediates (possibly stabilized carbanions), but no strong electrophiles or strong acids, and certainly no carbocations or free radicals.

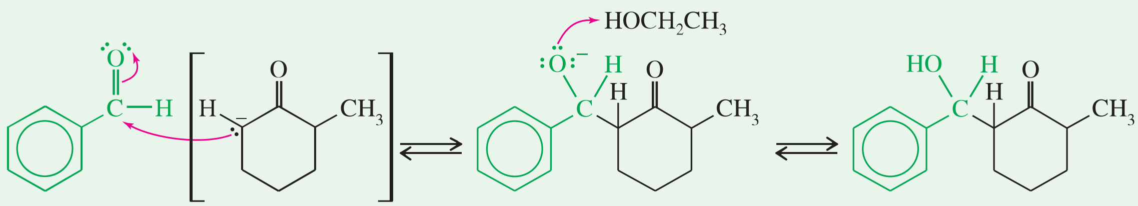
1. **Consider the carbon skeletons of the reactants and products, and decide which carbon atoms in the products are likely derived from which carbon atoms in the reactants.**
   Because one of the rings is aromatic, it is clear which ring in the product is derived from which ring in the reactants. The carbon atom that bridges the two rings in the products must be derived from the carbonyl group of benzaldehyde. The two α protons from methylcyclohexanone and the carbonyl oxygen are lost as water.



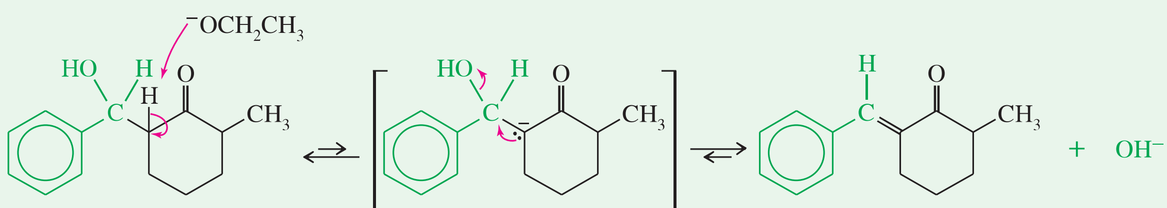
2. Consider whether any of the reactants is a strong enough nucleophile to react without being activated. If not, consider how one of the reactants might be converted to a strong nucleophile by deprotonation of an acidic site or by attack on an electrophilic site.
Neither of these reactants is a strong enough nucleophile to attack the other. If ethoxide removes an α proton from methylcyclohexanone, however, a strongly nucleophilic enolate ion results.



3. Consider how an electrophilic site on another reactant (or, in a cyclization, another part of the same molecule) can undergo attack by the strong nucleophile to form a bond needed in the product. Draw the product of this bond formation.
Attack at the electrophilic carbonyl group of benzaldehyde, followed by protonation, gives a β-hydroxy ketone (an aldol).



4. Consider how the product of nucleophilic attack might be converted to the final product (if it has the right carbon skeleton) or reactivated to form another bond needed in the product.
The β-hydroxy ketone must be dehydrated to give the final product. Under these basic conditions, the usual alcohol dehydration mechanism (protonation of hydroxy, followed by loss of water) cannot occur. Removal of another proton gives an enolate ion that can lose hydroxide in a strongly exothermic step to give the final product.



5. Draw out all the steps using curved arrows to show the movement of electrons. Be careful to show only one step at a time.
The complete mechanism is given by combining the equations shown above. We suggest you write out the mechanism as a review of the steps involved.

As further practice in proposing mechanisms for base-catalyzed reactions, do Problem 22-25 using the steps just shown.

PROBLEM 22-25

Propose mechanisms for the following base-catalyzed condensations, with dehydration.
(a) 2,2-dimethylpropanal with acetaldehyde
(b) benzaldehyde with propionaldehyde

PROBLEM 22-26

When acetone is treated with excess benzaldehyde in the presence of base, the crossed condensation adds two equivalents of benzaldehyde and expels two equivalents of water. Propose a structure for the condensation product of acetone with two molecules of benzaldehyde.

PROBLEM-SOLVING HINT

The correct mechanism for the base-catalyzed dehydration of an aldol product requires two steps:

1. deprotonation to form an enolate ion.
2. expulsion of hydroxide ion.

Do not draw a concerted E2 reaction for the dehydration of an aldol product.