Principles of Organic Synthesis
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Lecture 1
Base-Catalyzed Carbon-Carbon Bond Formation

Welcome you all to principles of organic synthesis. This is our first lecture. We will start with the base-catalyzed carbon-carbon bond formation.

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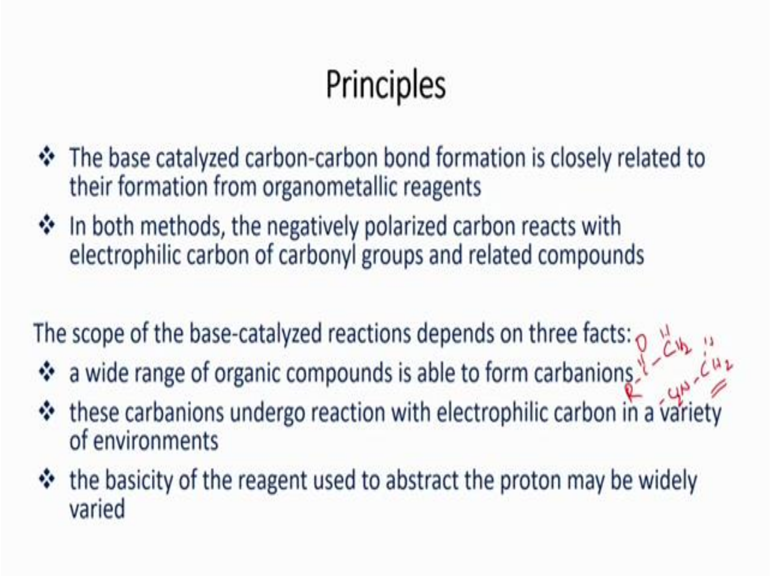

Principles

- The base catalyzed carbon-carbon bond formation is closely related to their formation from organometallic reagents
- In both methods, the negatively polarized carbon reacts with electrophilic carbon of carbonyl groups and related compounds

The scope of the base-catalyzed reactions depends on three facts:

- a wide range of organic compounds is able to form carbanions
- these carbanions undergo reaction with electrophilic carbon in a variety of environments
- the basicity of the reagent used to abstract the proton may be widely varied

The base-catalyzed carbon-carbon bond formation is closely related to their formation using organometallic reagents. In both approaches, the negatively polarized carbon reacts as nucleophiles with electrophilic carbon of carbonyl group and related compounds like alkyl halides. The scope of the reaction depends on three facts. Wide range of organic compounds are able to form carbanions. For example, if the C-H is bonded with an electron withdrawing group like carbonyl or nitro group, it can be deprotonated to generate the carbanion. These carbanions can undergo reaction with the electrophilic carbon in a variety of environments. For example, they can undergo addition reaction with carbonyl compounds. Similarly, they can lead to substitution reaction with alkyl halides.

The basicity of the reagent used to the deprotonation may be widely varied. For example, if you look at these two substrates, the acidity of these hydrogens is different. Therefore, you have to choose the base depends on the acidity of the hydrogen.

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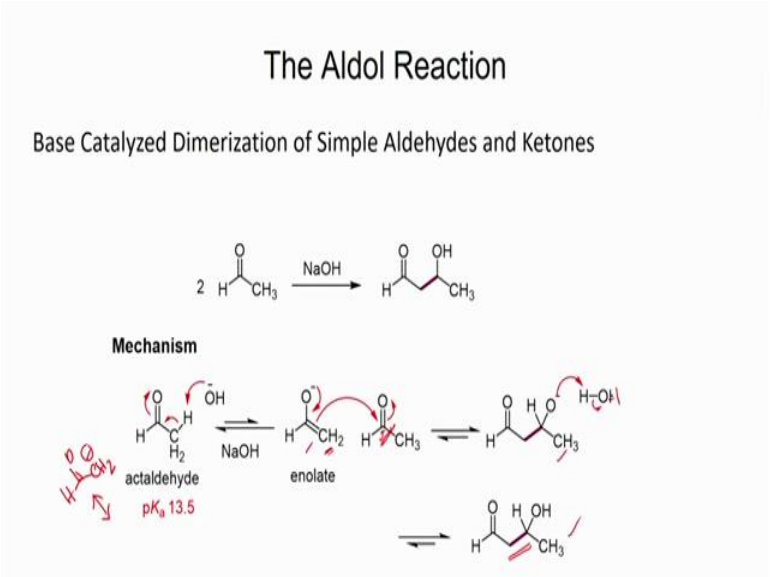

The Aldol Reaction

Base Catalyzed Dimerization of Simple Aldehydes and Ketones

This slide shows the reaction of acetaldehydes in the presence of sodium hydroxide to give aldol. One of the aldehydes undergoes reaction with sodium hydroxide and the deprotonation take place to generate carbanion, which exists as an enolate. This enolate can undergo addition reaction with the carbonyl group of another aldehyde to give the aldol. In this process, you make a carbon-carbon bond between the carbanion and carbonyl carbon of another aldehyde. During the process, you generate chiral center. If you happen to see a multistep synthesis, in general, you will be able to find the application of the aldol reaction.

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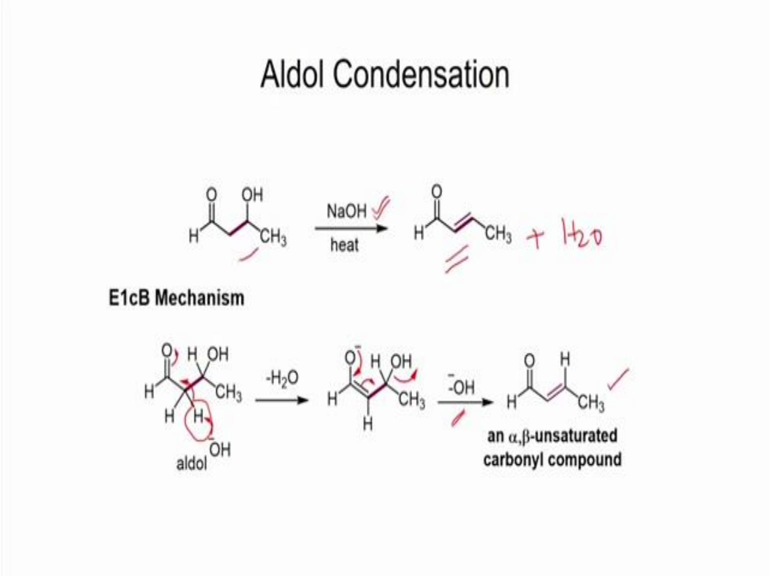

Aldol Condensation

E1cB Mechanism

an α,β-unsaturated carbonyl compound

When you heat the aldol in the presence of base, it can undergo dehydration to give alpha beta unsaturated carbonyl compound. The whole process is known as aldol condensation. The mechanism is shown here. Base can deprotonate the acidic hydrogen to generate the enolate that can convert into the alpha beta unsaturated carbonyl compound by elimination of hydroxide ion. The reaction can be carried out the presence of catalytic amount of base.

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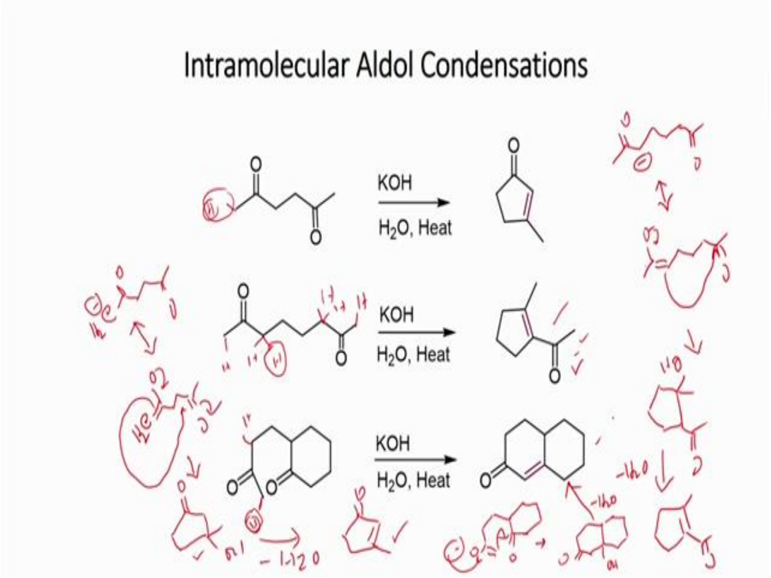

Now let us look at some examples for the intramolecular reactions. In the first example, the base deprotonates to generate the carbanion, which undergoes the intramolecular addition reaction with the carbon group. Since you carry out the reaction under heating, it can undergo dehydration to give cyclopentenone derivative.

The second example also has two methyl groups. Deprotonation this acidic hydrogen can produce carbanion, which can undergo intramolecular cyclization followed dehydration to form the favored five membered cyclic compound.

In third example, there are four acidic hydrogens. Selectively this hydrogen is deprotonated to give the target compound. On the other hand, if you deprotonate this hydrogen, you will end up with seven membered ring. Five and six membered rings are more favored therefore the deprotonation of this hydrogen leads to this product.

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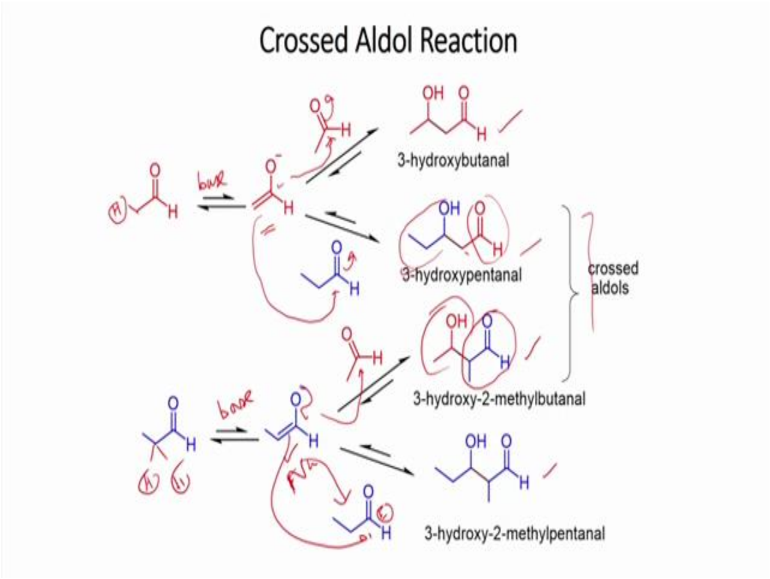

Now let us look at the reaction of two different aldehydes or ketones. The reaction of acetaldehyde with propionaldehyde is here given that can lead to the formation of four aldols. As we have seen earlier, acetaldehyde can undergo dimerization to give this aldol product. Alternatively, the enolate of acetaldehyde can undergo addition reaction with the carbonyl group of propionaldehyde to give the cross aldol product. Similarly, the enolate derived from propionaldehyde can react with the carbonyl group of acetaldehyde to give the another cross aldol. Further, the dimerization of propionaldehyde can produce another aldol.

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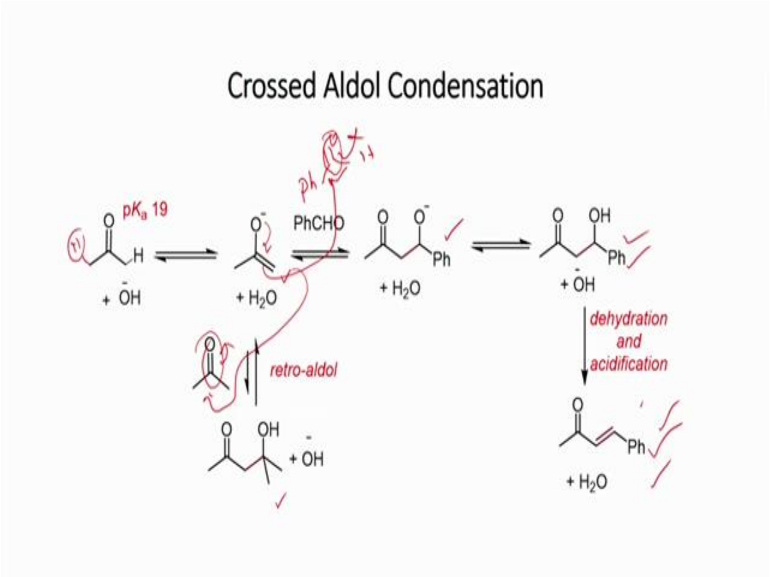

Crossed Aldol Condensation

Here is the reaction of acetone with benzaldehyde, which produces alpha beta unsaturated ketone as a sole product. Acetone can undergo deprotonation to give the enolate, which can react with another molecule of acetone to give the aldol, however, it undergoes retro-aldol to furnish the enolate back. Alternatively, the enolate can react with carbonyl of benzaldehyde to produce the aldol that can undergo dehydration to give the alpha beta unsaturated carbonyl compound. Thus, the reaction of acetone with benzaldehyde produces a single product.

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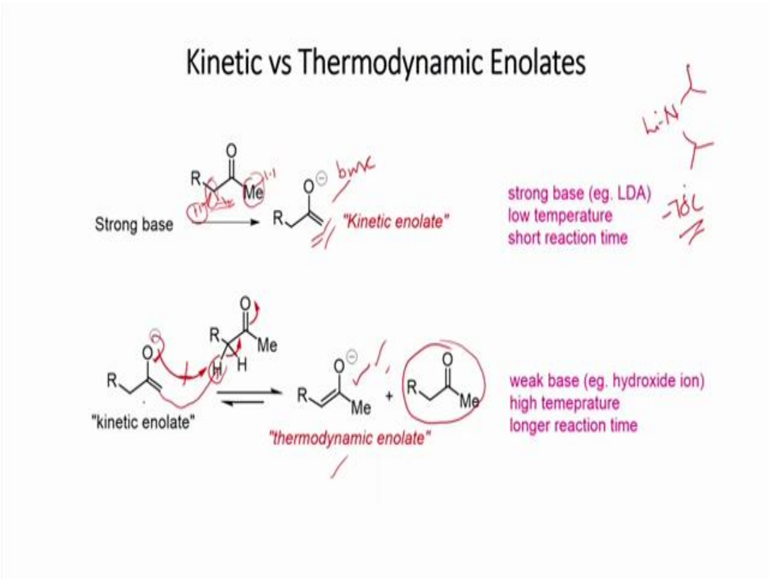

Kinetic vs Thermodynamic Enolates

Strong base

"Kinetic enolate"

strong base (eg. LDA)
low temperature
short reaction time

"kinetic enolate"

"thermodynamic enolate"

weak base (eg. hydroxide ion)
high temeprature
longer reaction time

Now, let us look at the formation of the enolate. For example, let us look at this ketone, both alpha C-H can deprotonate, which can be controlled by the reaction conditions. If we carry out the reaction at low temperature using strong base like LDA with short reaction time, the deprotonation occurs at the less sterically hindered C-H to give the less substituted enolate in aprotic THF. This is known as kinetically controlled enolate. So, depends upon the reaction condition, you can generate the kinetic or thermodynamic enolate as major intermediate that can react with aldehyde to give the aldol accordingly. The formation of thermodynamic enolate can also be favored when you use protic solvent like tertiary butanol in the presence of sodium or potassium tert-butoxide.

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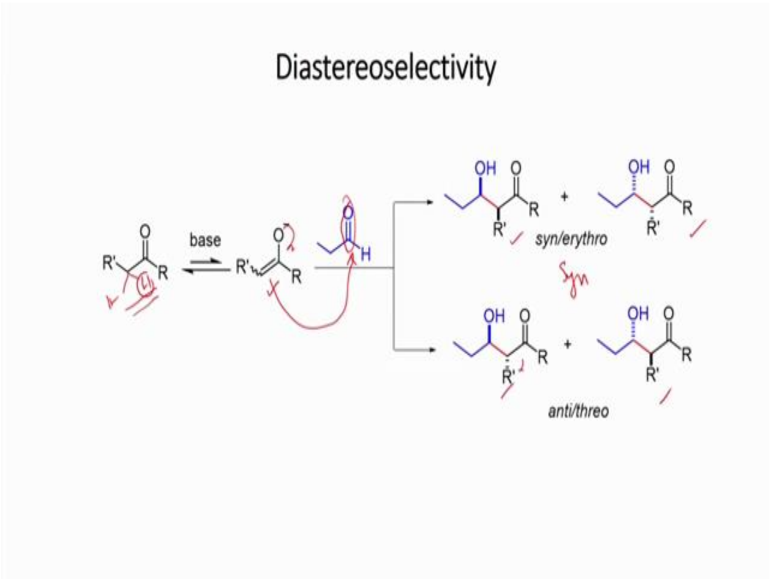

Diastereoselectivity

base

syn/erythro

anti/threo

Now, let us look at the diastereoselectivity. Depends on the substrates, there is a possibility of the formation of diastereomers. For example, this substrate can undergo dimerization to produce four stereoisomers.

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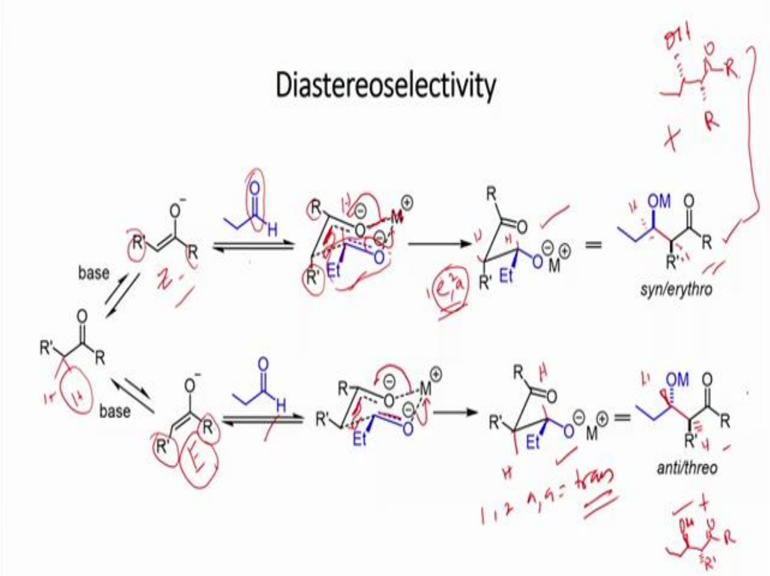

Diastereoselectivity

The formation of diastereomers can be explained through the six membered transition state. The base can deprotonate the alpha C-H to form the *Z* or *E* enolate, whose concentration depends on the size of the R substituent. The reaction of *Z* enolate produces *syn* compound, whereas the reaction of *E* leads the formation of *anti* compound.

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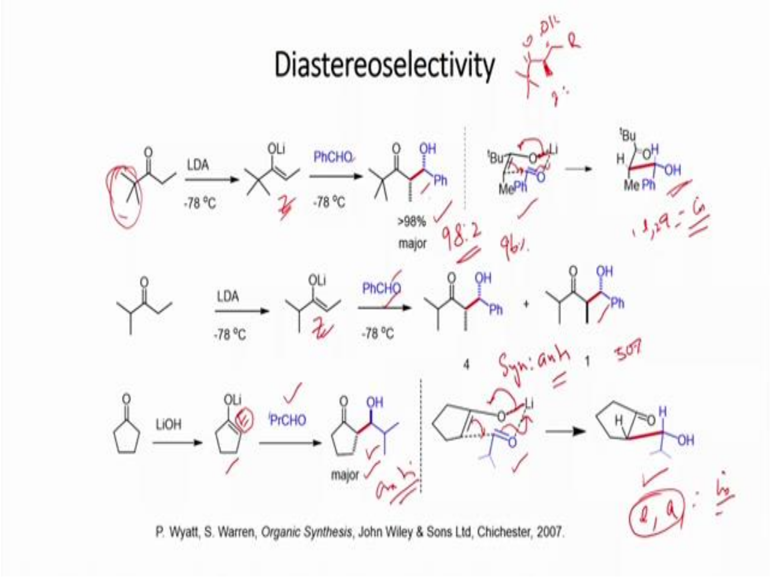

Diastereoselectivity

P. Wyatt, S. Warren, *Organic Synthesis*, John Wiley & Sons Ltd, Chichester, 2007.

Now let us look at some examples. Here the reaction between *tert*-butyl ketone and benzaldehyde is shown. When you treat the ketone with LDA at negative temperature, you would form Z enolate, which can react with benzaldehyde to give *syn* compound as the major product (98:2). Formation of the compound can be explained through the six membered transition state.

If you look at the second example, where tert-butyl group is replaced with isopropyl. Which on deprotonation using LDA at low temperature forms Z enolate that undergoes reaction with benzaldehyde. Here the ratio of the products is reduced to 4:1. This is because the less bulkiness of isopropyl group compared to tert-butyl that can lead a mixture of Z and E enolates for the reaction.

Now, let us look at the reaction of cyclopentenone with a lithium hydroxide. It forms the E enolate that reacts with isopropyl aldehyde to give anti-stereoisomer. The stereochemistry of the product can be explained through the six membered transition state.

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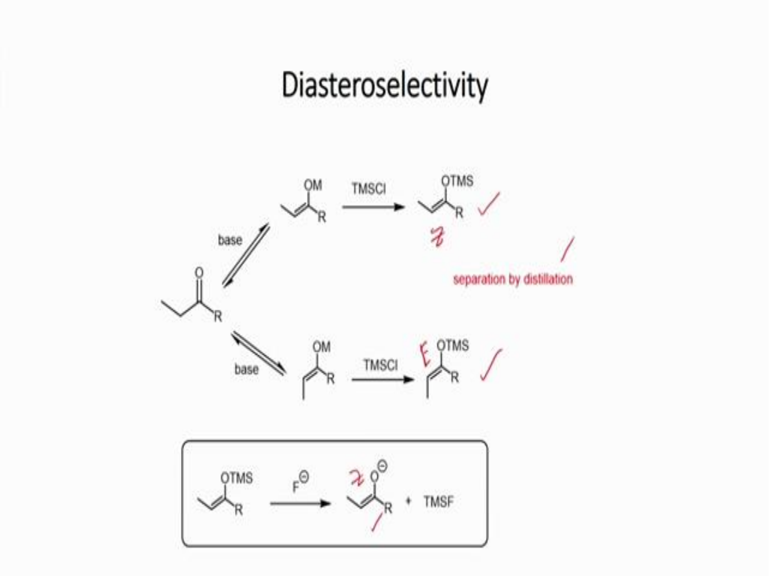

This slide shows the formation of both the E and Z enolates, which can be reacted with a TMS chloride to give the respective TMS ethers. They have different boiling points and can separated by distillation. After separation, silyl ethers can be reacted with a fluoride ion to get selectively the Z or E enolate that can be further react with aldehyde to get selectively the syn or the stereoisomer.

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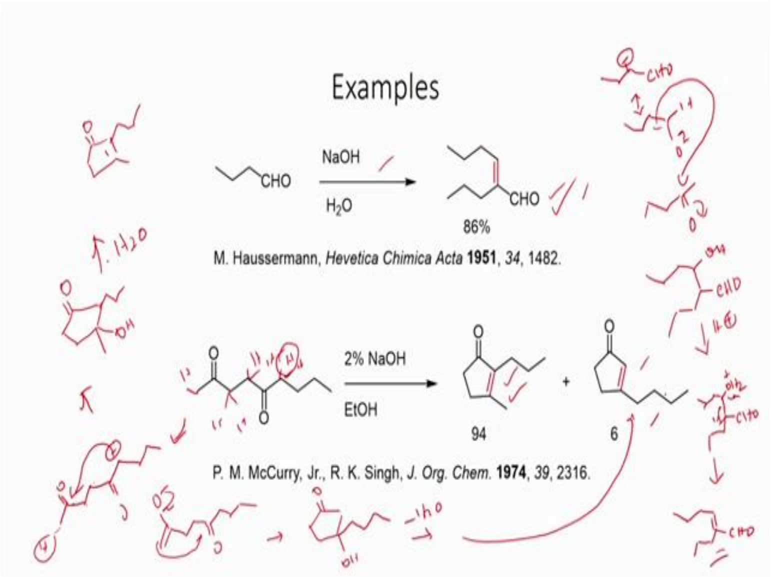

Examples

M. Haussermann, *Hevetica Chimica Acta* **1951**, *34*, 1482.

P. M. McCurry, Jr., R. K. Singh, *J. Org. Chem.* **1974**, *39*, 2316.

In this slide, the first example involves an intermolecular reaction using aq NaOH to give α,β-unsaturated aldehyde. Deprotonation of α C-H bond of the aldehyde can generate the carbanion, which can undergo reaction with another aldehyde carbonyl group to give the aldol product, which can undergo dehydration to give the α,β-unsaturated aldehyde.

In the next example diketone, the deprotonation takes place to give the more substituted enolate that can undergo intramolecular cyclization to yield the substituted cyclopentenone as the major product.

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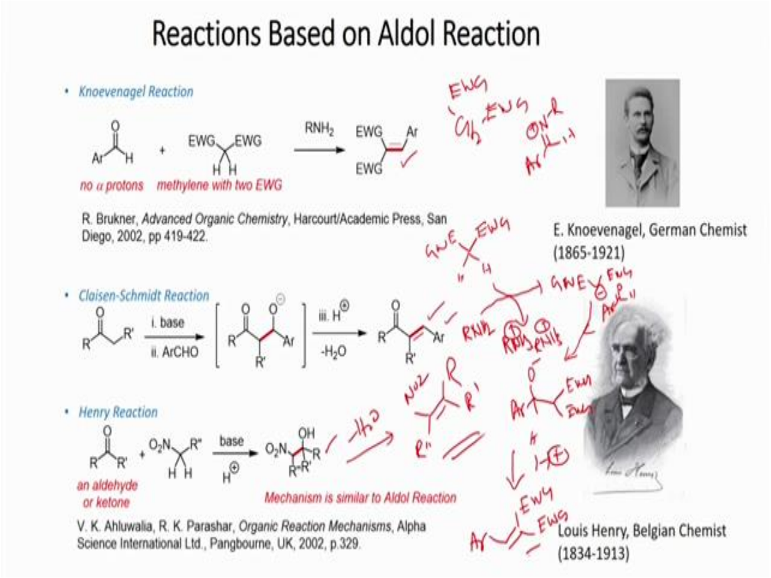


Reactions Based on Aldol Reaction

- *Knoevenagel Reaction*

no α protons *methylene with two EWG*

R. Brukner, *Advanced Organic Chemistry*, Harcourt/Academic Press, San Diego, 2002, pp 419-422.

E. Knoevenagel, German Chemist (1865-1921)

- *Claisen-Schmidt Reaction*

- *Henry Reaction*

an aldehyde or ketone

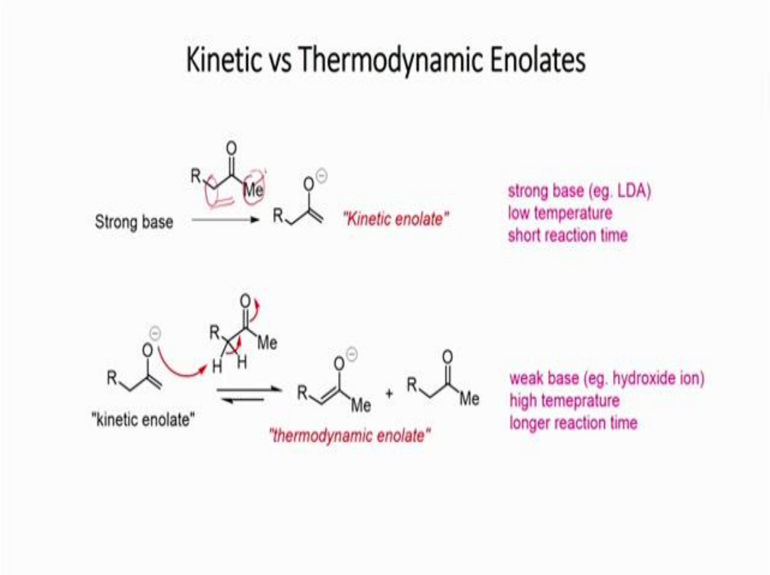
Mechanism is similar to Aldol Reaction

V. K. Ahluwalia, R. K. Parashar, *Organic Reaction Mechanisms*, Alpha Science International Ltd., Pangbourne, UK, 2002, p.329.

Louis Henry, Belgian Chemist (1834-1913)

This slide shows some of the reactions based on aldol reaction. The first one is Knoevenagel condensation, in which, the active methylene undergoes deprotonation and the carbanion leads to reaction with aromatic aldehyde to give the α,β-unsaturated carbonyl compound.

The another is Claisen-Schmidt reaction where the reaction of active methylene compound with aromatic aldehyde gives α,β-unsaturated carbonyl compound. The next one is Henry reaction where the reaction of aldehydes or ketones yields α,β-unsaturated nitro compounds. The mechanism of Henry reaction is similar to aldol reaction.



Kinetic vs Thermodynamic Enolates

strong base (eg. LDA)
low temperature
short reaction time

weak base (eg. hydroxide ion)
high temeprature
longer reaction time

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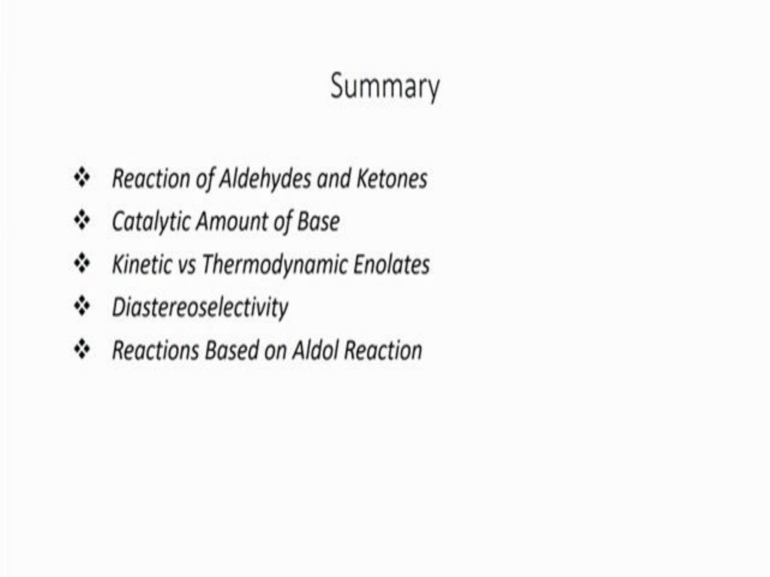

Summary

- *Reaction of Aldehydes and Ketones*
- *Catalytic Amount of Base*
- *Kinetic vs Thermodynamic Enolates*
- *Diastereoselectivity*
- *Reactions Based on Aldol Reaction*

In summary, today we have seen the aldol reaction, which is one of the important transformations in organic synthesis to make the carbon-carbon bond. Aldehydes as well as ketones serve as the substrates. The reaction can be carried out in the presence of a catalytic amount of base. One of the substrates undergoes deprotonation to give carbanion which acts as the nucleophiles and leads to addition to the carbonyl group of other substrate to give aldol product, which can be converted into α,β-unsaturated carbonyl compound.

Then, we have seen the formation of enolate depends on the nature of the substrate and reaction conditions. You can try to selectively form kinetic or thermodynamic enolate that can lead to the formation stereoselective product. For example, if you form thermodynamic enolate, which can react with aldehyde or ketone to get *syn* stereoisomer.

Then we have seen some reactions that are based on aldol reactions. With this let us conclude this lecture, thank you very much.