Lecture 6

The Crossed Aldol Reaction and its Many Variants

Objectives:

By the end of this lecture you will be able to:

1. make an appropriate choice of base to completely enolise carbonyl compounds;
2. use enolates in a crossed aldol reaction;
3. recognise the aldol functional group motif, and its variants, in complex molecules;
4. use the aldol disconnection to simplify a retrosynthetic analysis;
5. use the Reformatski and Mukaiyama aldol reactions in synthesis;
6. draw arrow-pushing mechanisms for all the aldol reactions discussed in this lecture.

Introduction

We have seen how choosing a base (B$^-$) whose conjugate acid (B–H) is a much poorer acid – *i.e.* has a much higher pK_a – than the proton we wish to abstract, ensures effectively complete deprotonation of the α-C–H of a carbonyl compound to provide the corresponding enolate.

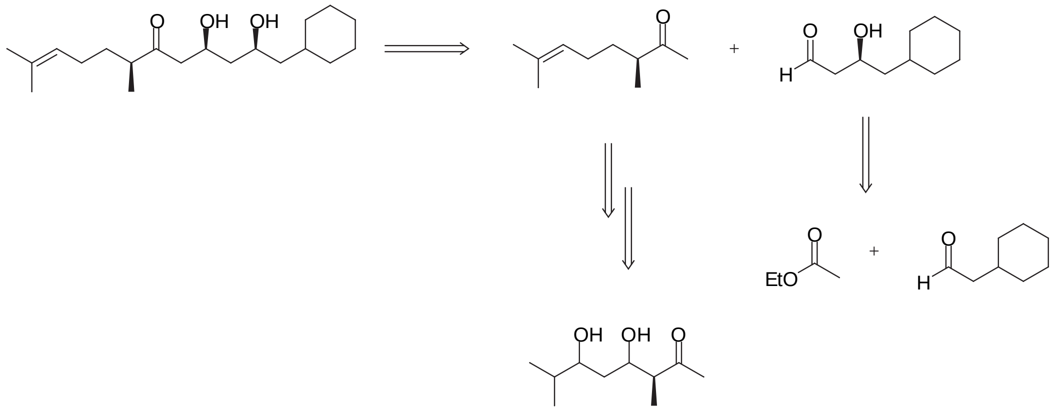
By completely enolising the carbonyl group, we can suppress self-condensation aldol processes, and instead use a different electrophile such as an aldehyde to form a β-hydroxy carbonyl compound.

This reaction sequence is identical in basic mechanism to the intramolecular aldol processes that we discussed in previous lectures. It is now described as a ***crossed* aldol condensation** because the electrophile is a different carbonyl compound to the one that was used to form the nucleophilic enolate. This reaction, and its many variants, provides one of the most important methods for preparing C–C bonds.

Pattern Recognition

The aldol reaction and its many variants are very useful reactions in synthesis. You need to be able to identify the patterns or functional group motifs where this type of bond-forming process can be used. Let's consider some of the products that can be prepared from the initial aldol product from a ketone enolate and an aldehyde *i.e.* a β-hydroxy ketone.

We could use an aldol reaction to prepare any of the functional group motifs outlined in the scheme above (there are also many others); it is clearly a very useful synthetic transformation. In a retrosynthetic sense the aldol bond disconnection is often *strategic* in providing a rapid simplification of the synthetic problem. Consider the molecule in the scheme below. We can recognise a number of bonds that could be formed from aldol reactions.



The first aldol disconnection is one of the best bonds to break as it divides the molecule into two of roughly equal size and with similar levels of complexity. By performing functional group interconversions (FGIs) we can see that the first two disconnection products can also be prepared by sequential aldol reactions.

You need to be able to recognise the patterns of functional groups in a complex molecule that lead to aldol and aldol-like disconnections.

The Crossed Aldol Reaction

- Use of LDA, a polar aprotic solvent, such as THF, and low temperature, ensures the formation of the kinetic enolate:

- The use of a strong lithium amide base ensures complete enolisation thereby avoiding self condensation aldol reactions.
- Lithium enolates are very reactive; they are therefore formed at low temperature. They also react at low temperature especially with reactive electrophiles such as aldehydes.
- A potential side-reaction is subsequent dehydration of the aldol product. This is normally not a major problem; until the work-up the product exists as the β-alkoxy ketone and oxide is not a good leaving group. However, the presence of adventitious water (or any other proton source for that matter) in the reaction mixture can generate small amounts of β-hydroxy ketone that can then undergo dehydration (E_1cb mechanism remember!).

- Ketones also take part in the crossed aldol reaction. They are poorer electrophiles than aldehydes (*you should be able to explain why)* and often require slightly higher reaction temperatures.
- The product contains a tertiary alcohol that is much more prone to elimination. Dehydration is an important side-reaction when ketones are used as the electrophile.

Alternatives to Lithium Enolates

Lithium enolates are very reactive nucleophiles; they are also good bases. Their basicity can lead to undesirable side-reactions such as dehydration. There are many other types of enolate. We have already seen how enolates derived from β-keto-esters can be used as more nucleophilic and less basic ketone enolate equivalents.

One of the best methods for reducing the basicity of the enolate is to change the metal cation.

Zinc enolates - the Reformatski Reaction

We have already seen how α-bromo ketones can be used in regioselective enolisation. The corresponding zinc enolates are mild nucleophiles exhibiting relatively low basicity. They react readily with aldehydes to provide the corresponding aldol product. Again complete enolate formation ensures the isolation of just the *crossed* aldol product. The use of zinc enolates in aldol reactions is known as the Reformatski reaction.

- Zinc enolates can also be formed from α-halo esters.
- The lower basicity of zinc enolates ensures that side-reactions such as dehydration are less of a problem.

Silyl Enol Ethers - the Mukaiyama Aldol Reaction

Silyl enol ethers are not very nucleophilic and do not react with aldehydes without prior activation of the aldehyde. Lewis acids (LAs) (or Brønsted acids) can be used to activate carbonyl compounds and when they are added to the reaction, provide a strongly electrophilic species which is capable of reacting with silyl enol ethers. This reaction is named after the chemist who developed this process into a powerful variant of the aldol reaction: T. Mukaiyama.

- Many types of Lewis acids can be used in this reaction. Some of the most common include $BF_3 \cdot OEt_2$, $TiCl_4$, TMSOTf, and $SnCl_4$.
- In some cases the isolated product is the silyl ether in which the TMS group has transferred from the enol ether to the alcohol group. Whilst TMS ethers are not very stable to either acid or base they can sometimes be used as temporary protecting groups.

- The efficiency of this silyl transfer depends on the Lewis acid. However if the silyl group can be transferred from the incipient ketone to the alkoxide, you will note that the Lewis acid is released from the product. Under these circumstances it is then possible to use the Lewis acid as a catalyst in *sub-stoichiometric quantities*.
- An important variant of the Mukaiyama aldol reaction involves the use of acetals in place of aldehydes as *latent* electrophiles.

- Acetals are commonly employed as protecting groups for aldehydes and ketones. They are stable to basic conditions but react in the presence of Lewis or Brønsted acids. In the presence of a Lewis acid, the acetal breaks down to generate a highly electrophilic oxocarbenium cation with which silyl enol ethers readily react.

Summary

If we use a very strong base to abstract the α-C–H of a ketone, we can effect complete enolisation. The addition of another carbonyl group (*e.g.* aldehyde or ketone) results in a so-called crossed aldol reaction to provide a β-hydroxy ketone. This type of aldol reaction provides one of the most important methods for forming C–C bonds.

The initial product from an aldol reaction is a β-hydroxy ketone. It is important to be able to recognise this important functional group motif in complex molecules and be able to use an aldol disconnection for simplifying a retrosynthetic analysis (pattern recognition). The aldol product is often disguised; it is useful to be able to spot these masked aldol groups, as a functional group interconversion (FGI) followed by an aldol disconnection can often greatly simplify the retrosynthetic analysis.

Side-reactions can cause problems in crossed aldol reactions. Dehydration to provide an enone is one of the most common problems especially when basic enolates such as lithium enolates are used. To reduce these problems, less basic enolates have been introduced. Zinc enolates (Reformatski reaction) provide one solution.

Silyl enol ethers (Mukaiyama aldol reaction) are also good nucleophiles for an aldol reaction. Owing to their low nucleophilicity, Lewis acids are required to activate the carbonyl electrophile. Since acetals form highly electrophilic oxocarbenium cations in the presence of Lewis acids, these too can be used to form C–C bonds with silyl enol ethers. In some instances, silyl transfer in the intermediate aldolate provides the silyl-protected β-hydroxy ketone as the end-product. When this occurs efficiently, the Lewis acid activator can be used in sub-stoichiometric quantities making the reaction even more attractive.