Lecture 7

The Claisen Condensation, and Control of Relative Stereochemistry in Aldol Reactions

Objectives:

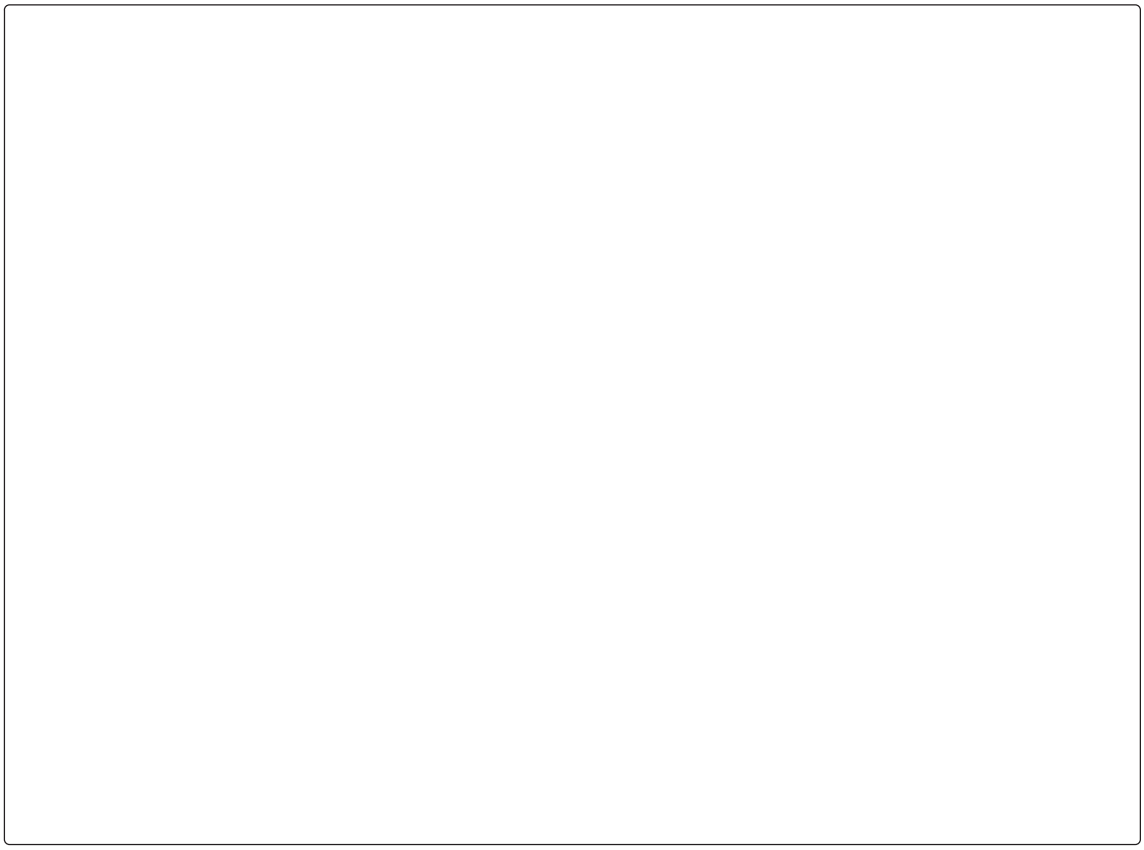
By the end of this lecture you will be able to:

1. Prepare 1,3-dicarbonyl compounds using Claisen and related condensation reactions;
2. Draw the mechanism for the formation of 1,3-dicarbonyl compounds;
3. Understand the limitations of the traditional Claisen condensation reaction conditions (alkoxide base) and be able to provide some solutions to the problem;
4. Recognise the issues of stereoselectivity involved in an aldol reaction;
5. Draw and assign the configuration of the two possible enolate stereoisomers that can be formed from ethyl ketones;
6. Use lithium enolates to control the relative stereochemistry in aldol reactions;
7. Draw transition state diagrams that rationalise the stereochemistry of this stereospecific process.

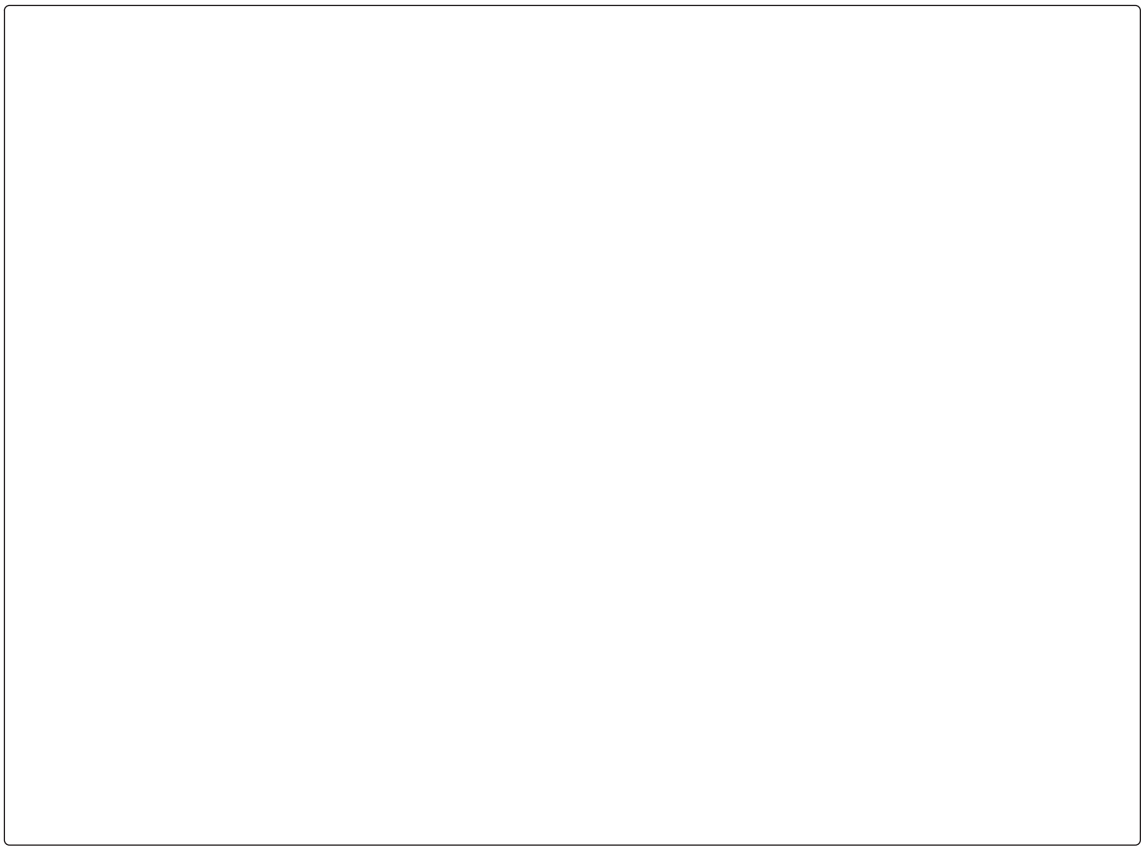
Claisen, Dieckmann and Related Condensation Reactions

An aldol-like reaction between two esters is known as the *Claisen condensation*. The product is a β-keto ester, which we have already seen is an important class of carbonyl compound on account of its ability to behave as a *latent ketone enolate*.

Traditionally, to effect condensation, a mixture of the two esters is treated with a metal alkoxide. If both esters have enolisable α-C–Hs, a mixture of the four possible products will usually be obtained. This clearly limits its synthetic utililty.



Mechanism of the Claisen Condensation



- Since the pK_a of the internal protons in a β-keto ester is low (pK_a ~ 11) compared with the pK_a of EtOH (pK_a ~ 16), the final product from the reaction will be the enolate conjugate base.
- The neutral product is only isolated after an acidic work-up.
- The relatively high stability of the final enolate product provides a thermodynamic driving force for the reaction (all steps are reversible).
- Since one equivalent of base is required to form the product enolate, the alkoxide base must be used in stoichiometric quantities. Compare this to the base-mediated aldol reaction where the base can be used in sub-stoichiometric amounts.
- The mechanism for the Claisen condensation is very similar to that for an aldol process, the only difference being that the tetrahedral intermediate can collapse by expelling an alkoxy group, to regenerate the carbonyl group of the electrophile.

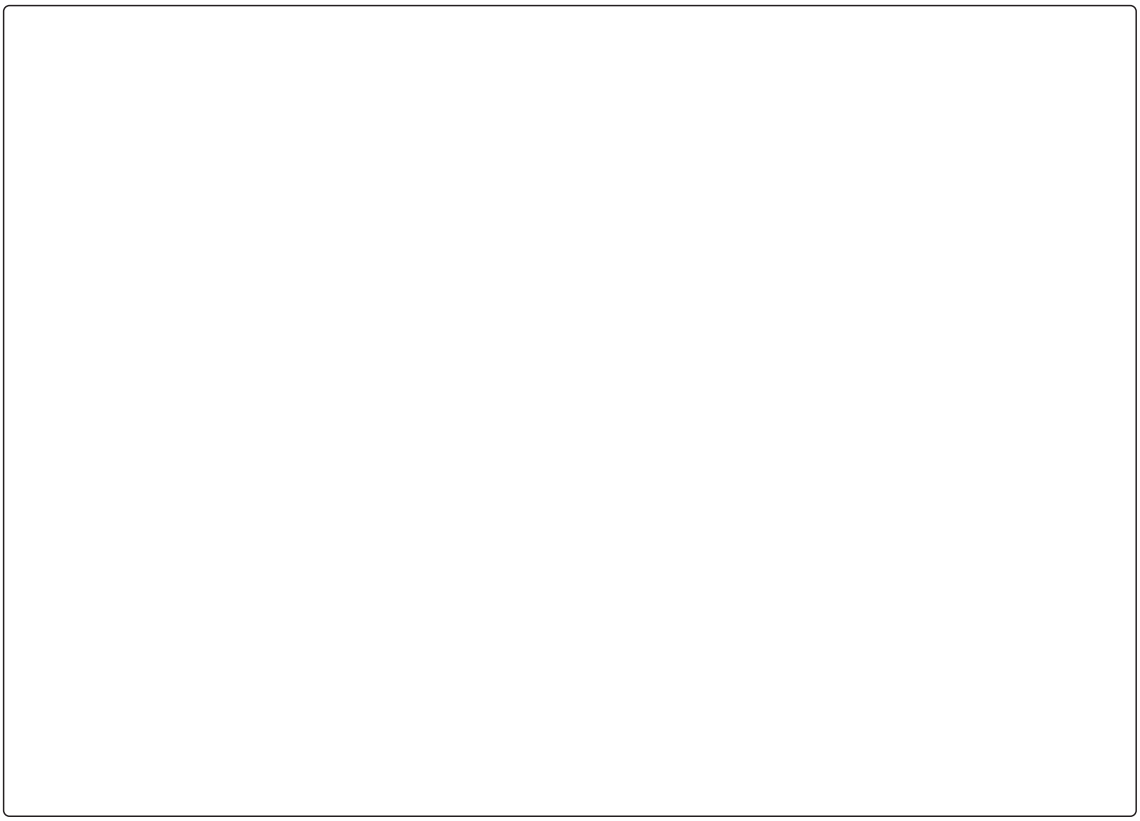
Synthetically Useful Claisen Condensations

If only one ester has an acidic α-C–H then the Claisen condensation becomes more synthetically useful since there is only one possible cross-condensation product and one possible self-condensation product.

Furthermore if the ester lacking any acidic α-C–Hs - *i.e.* that which is going to act as the electrophile - is used in excess, the cross-condensation product will also be the major product.

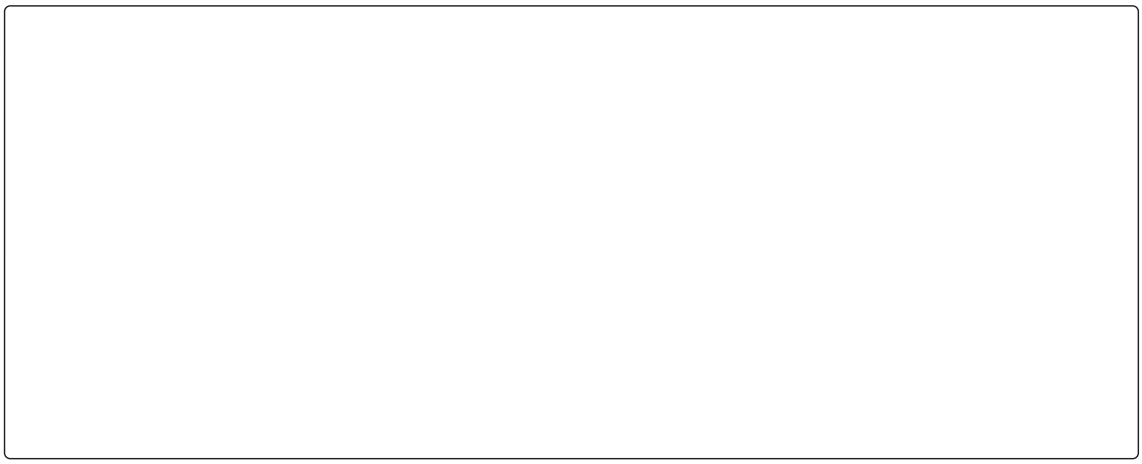
Commonly used esters that lack acidic α-C–Hs include those derived from aromatic carboxylic acids.

The *intramolecular* version of the Claisen Condensation is called the **Dieckmann condensation**. It provides a very useful method for forming rings especially 5-, 6- and 7-membered rings.

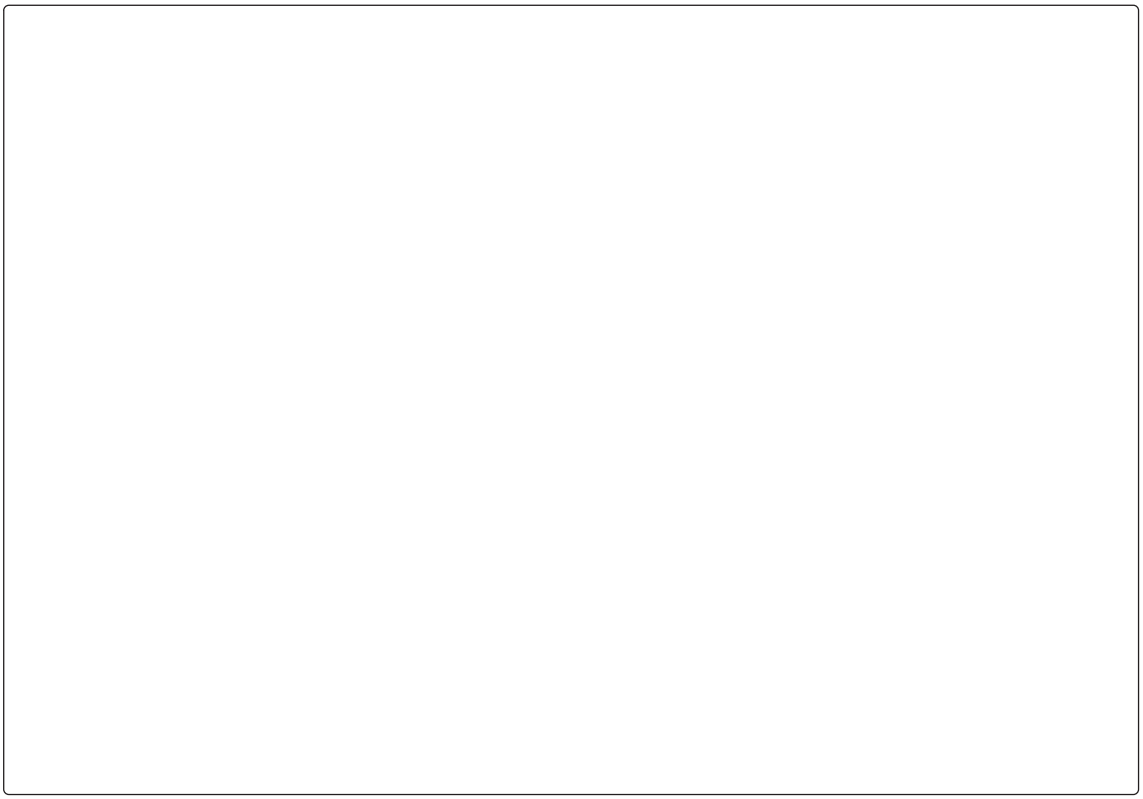


Stereoselectivity Issues in the Aldol Reaction

The aldol reaction between an enolate derived from a methyl ketone and an aldehyde generates a molecule (a β-hydroxy ketone) containing one new stereogenic centre. In the example below, we therefore produce two *enantiomeric* aldol products. We need to be able to control the *absolute stereochemistry* of this reaction.

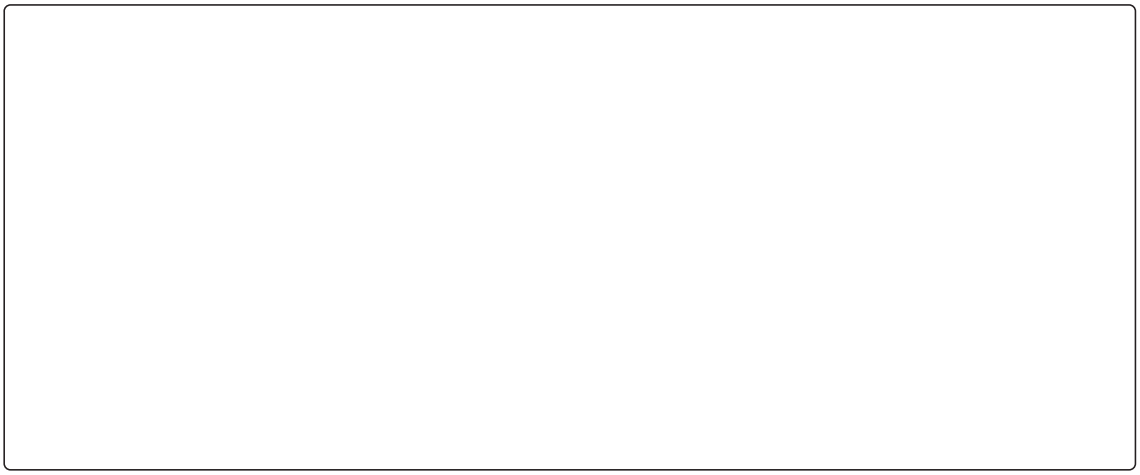


When a *substituted* enolate is used as the nucleophile, *two* new stereogenic centres are formed. We now need to be able to control both the *relative* stereochemistry (*i.e.* diastereoselectivity) and the *absolute* stereochemistry (*i.e.* enantioselectivity) of the aldol product.



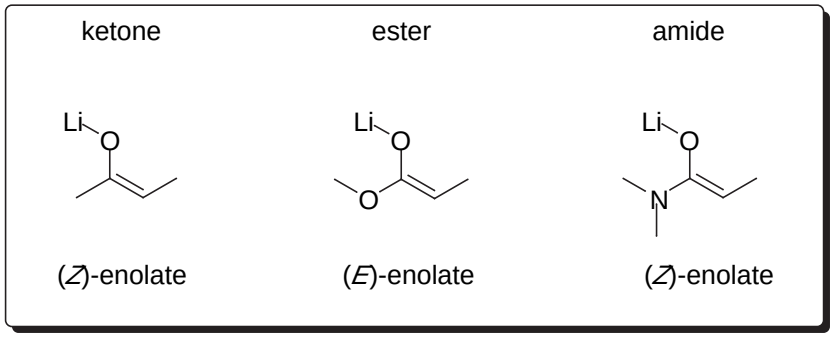
Stereoselective Enolate Formation

Treatment of pentan-3-one with base affords two possible stereoisomeric enolates, the so-called *cis*-enolate and the *trans*-enolate.

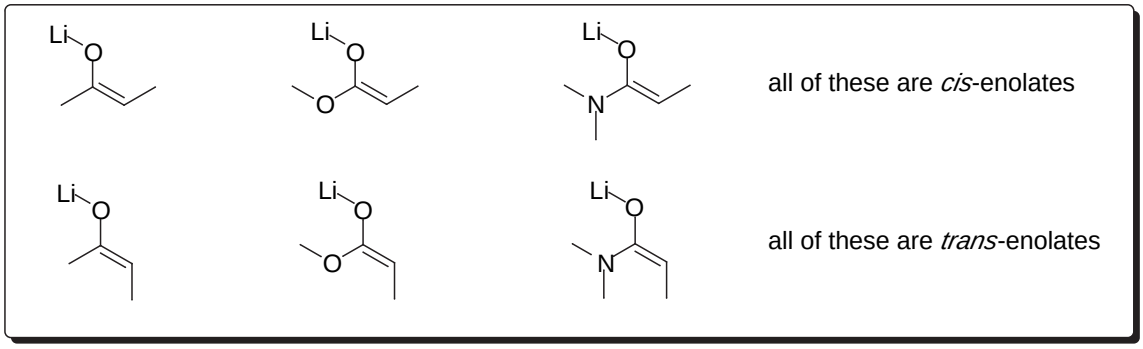


A note on stereochemical nomenclature:

The configuration of olefins is normally assigned using (*Z*)- and (*E*)-descriptors, and under normal circumstances this is more desirable than using the *cis* / *trans* nomenclature. However confusion can arise when assigning the configuration of enolates. Some examples will illustrate the point:



Therefore to avoid confusion when going from one functional group to another, we will use the *cis* / *trans* nomenclature and always *assume the* O–*metal bond of the enolate takes priority on that end of the olefin*:



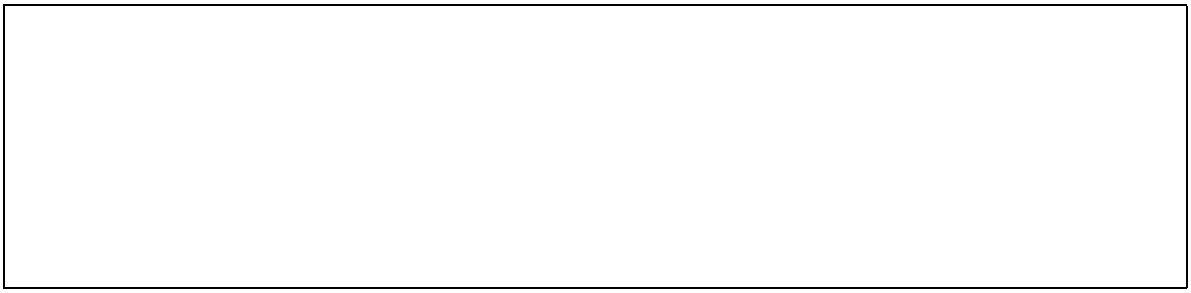
The geometry of a substituted enolate (*i.e.* whether it is *cis* or *trans*) can be very important in determining the stereochemical outcome of aldol reactions. In some cases the aldol reaction is *stereospecific i.e.* stereochemical information in the starting material is transferred *in a predictable fashion* to the strereochemistry found in the final product. In these cases, if we can access either enolate geometry at will, it should be possible to control the stereochemistry in the aldol products. This will be crucial for preparing polypropionate natural products.

We have already used a variety of enolates (silyl enol ethers, zinc enolates, and lithium enolates) in the aldol reaction. Although the same C–C bond is formed in every case, the precise reaction mechanism is strongly dependent on the metal enolate employed in the reaction. We can divide enolates into two classes, those that react with aldehydes through CLOSED transition states, and those that react through OPEN transition states. For this course we will only consider those enolates that react through closed T.S.s.

Aldol Reactions that Proceed through Closed Transition States

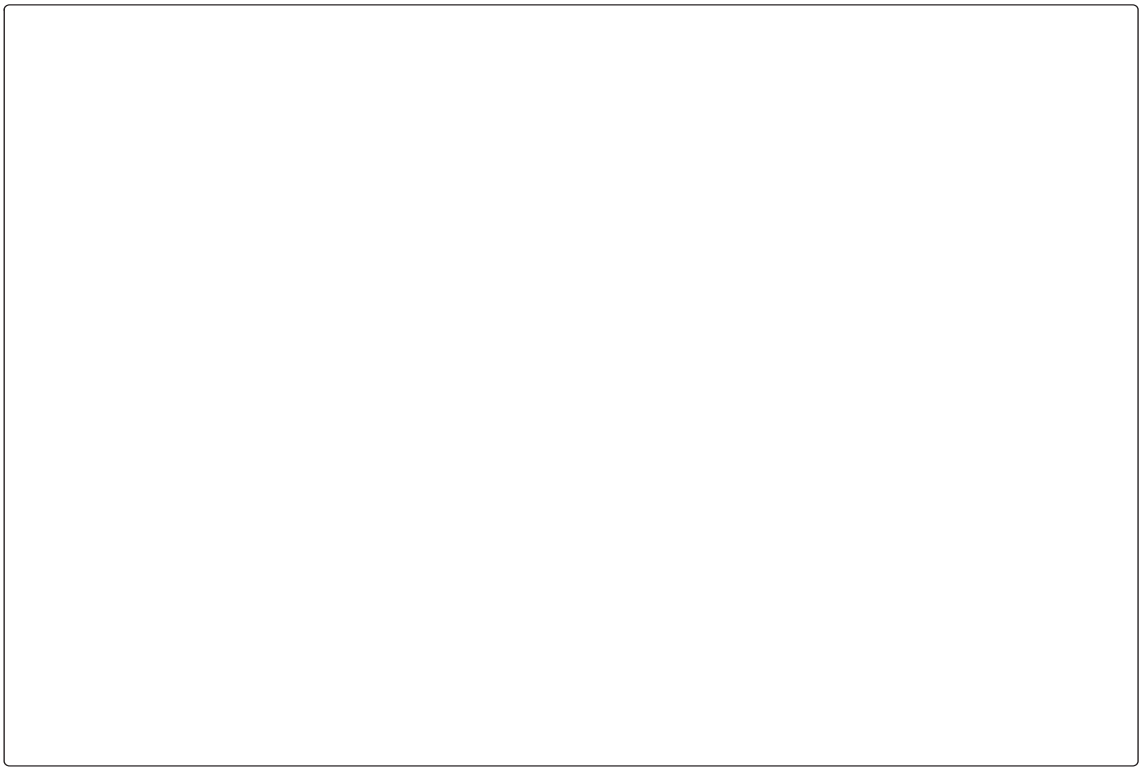
Some metals have vacant coordination sites, which means they can behave as Lewis acids. Thus a reacting aldehyde in an aldol reaction can behave as a Lewis base and coordinate to the metal centre in the enolate. This associative process brings together the reacting nucleophile (enolate) and electrophile (aldehyde) rendering the aldol condensation an intramolecular process.

Aldol reactions that proceed through this type of mechanism react through a *closed, cyclic chair-like transition state*, the so-called *Zimmerman-Traxler transition state*. This transition state is well defined so we can readily predict the stereochemical outcome of the product providing we know the stereochemistry of the starting enolate.

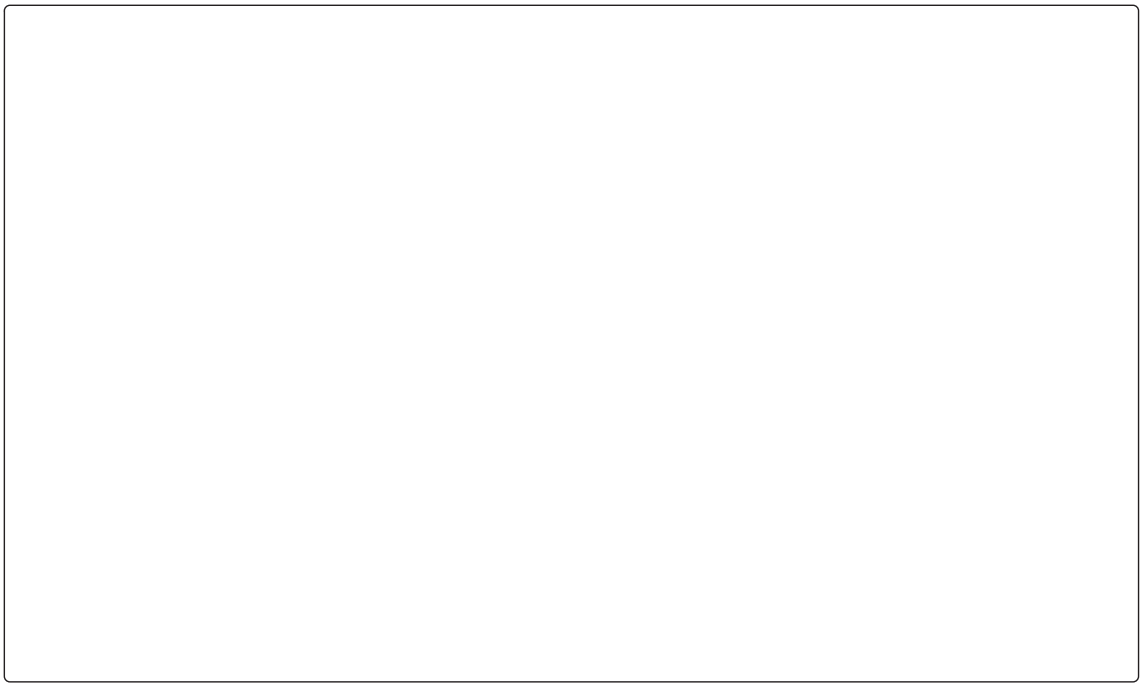


Since the stereochemistry in the starting materials is transcribed in a very predictable sense to the products, this reaction is a good example of a *stereospecific* process.

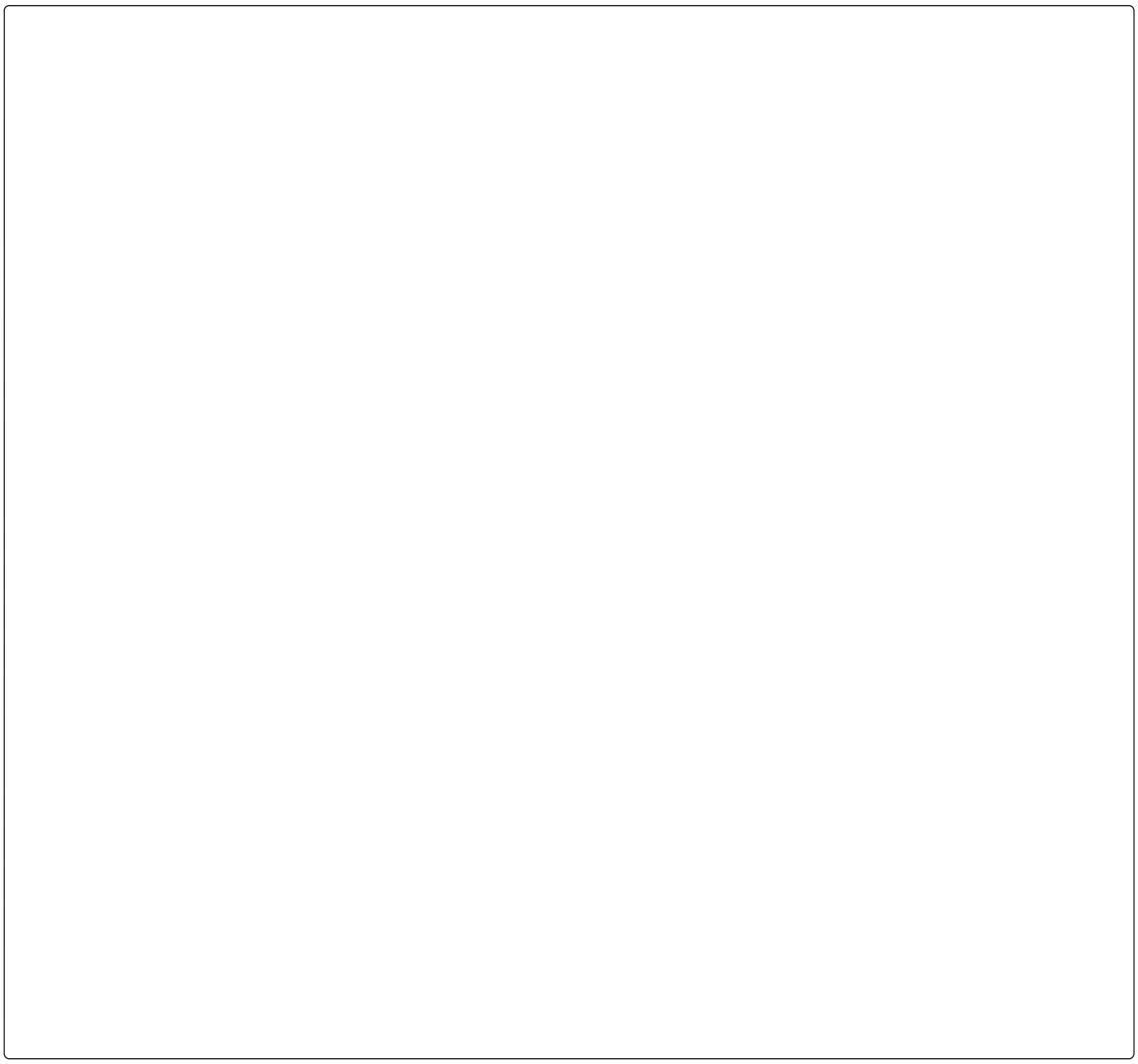
Of the metal enolates we have encountered so far, lithium enolates are capable of reacting in this fashion. Let's consider the reaction between the *cis*-lithium enolate of pentan-3-one and benzaldehyde:



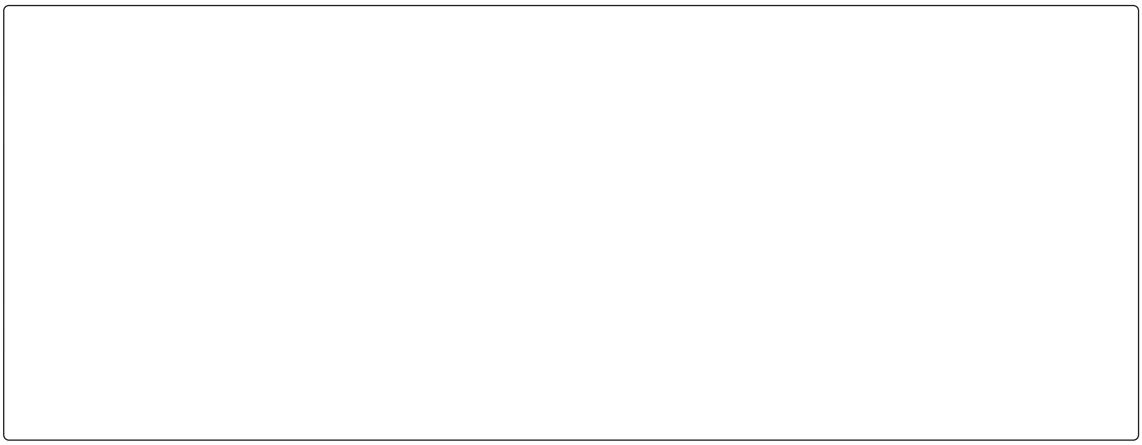
We need to examine the T.S. in more detail to see if we can understand why the *syn* aldol product is obtained. Six atoms are involved in the cyclic T.S. Whenever you see this, an accurate representation of the T.S. can usually be made by arranging these six atoms into a chair conformation (the most stable arrangement for six atoms in a ring). When we do this we need to consider two possible chair transition states **A** and **B**.



In both cases we have no choice but to put the methyl substituent off the lithium enolate into a pseudoaxial position - we are reacting a *cis*-enolate and we must preserve its geometry. However we can present the aldehyde to the enolate in two ways. In T.S. **A**, the aldehyde reacts in such a way that the substituent (in our example the Ph group) is in a pseudoequatorial position. In T.S. **B**, the aldehyde substituent occupies a pseudoaxial position. The lower energy T.S. is that in which steric interactions are minimised. In this case we can do this by positioning the aldehyde substituent in the pseudoequatorial position to minimise *1,3-diaxial interactions*. From this analysis we would therefore predict the reaction to proceed through T.S. **A**. If the aldol reaction proceeds through transition state **A**, the *syn*-aldol product is produced:



If we had used the *trans*-lithium-enolate, we would have obtained the diastereoisomeric *anti* aldol product.



We now have a very useful method for controlling the *relative* stereochemical outcome of an aldol reaction *providing* we can stereoselectively prepare the metal enolate.

Summary

This lecture has been divided into two sections.

In the first section we saw how ester enolates react with esters to provide β-keto esters. The intermolecular reaction is known as the Claisen condensation. If the two reacting esters are in the same molecule, the reaction is intramolecular and known as the Dieckmann condensation.

Since β-keto esters can be used as latent ketone enolates, these reactions are important synthetic transformations.

The traditional reaction conditions for this type of condensation reaction are to generate the enolate using an alkoxide base. If both esters have acidic α-C–Hs, four compounds can be produced, two resulting from self-condensation processes, the other two from cross-condensation processes. The situation can be improved in a number of ways:

i) If only one ester has an α-C–H, then only this can be enolised and behave as the nucleophile. The other ester can only behave as the electrophile, and if used in excess, will ensure that the major product is that resulting from the only cross-condensation reaction available.

ii) Carry out the reaction intramolecularly (Dieckmann condensation). As the steps in this reaction mechanism are reversible only the thermodynamic product is produced - this is normally the most stable ring.

In the second part of the lecture we discussed the issue of stereoselective enolate formation. Enolates derived from ketones and esters (except for methyl ketones and esters) can exist in two stereoisomeric forms. The ratio of *cis*- and *trans*-enolates depends not only on the carbonyl compound but also on the base used (as well as many other factors).

The aldol reaction between a substituted enolate and an aldehyde generates a product containing two new stereogenic centres. We therefore need to be able to control both absolute and relative stereochemistry. In this lecture we have concentrated on a method for controlling the relative stereochemistry in this reaction. Lithium enolates can react with aldehydes through a *closed Zimmerman-Traxler* chair T.S. This T.S. is well defined and allows us to predict the stereochemical outcome of the aldol reaction providing we know the stereochemistry of the reacting enolate. *Cis*-enolates generate *syn* aldol products; *trans*-enolates generate *anti* aldol products.