Lecture 5

Intramolecular Aldol Reactions for Ring Synthesis

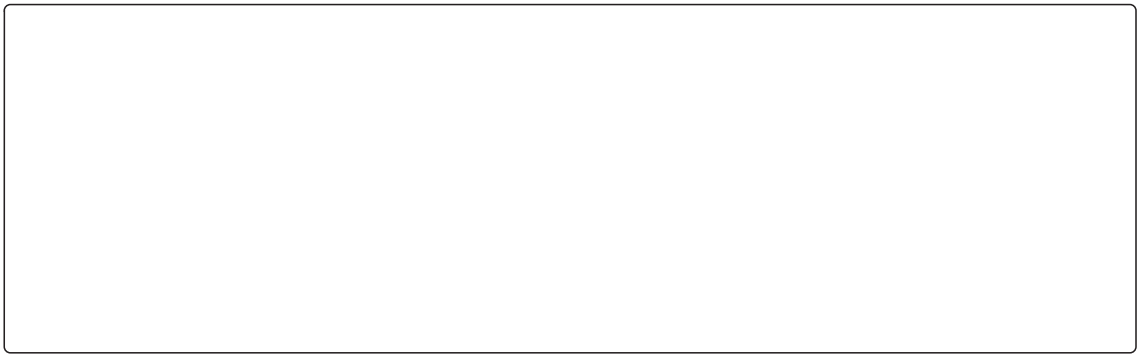
Objectives:

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

1. construct rings using intramolecular aldol reactions;
2. draw the mechanism for an E_1cb elimination;
3. prepare 1,5-dicarbonyl compounds by conjugate addition reactions.

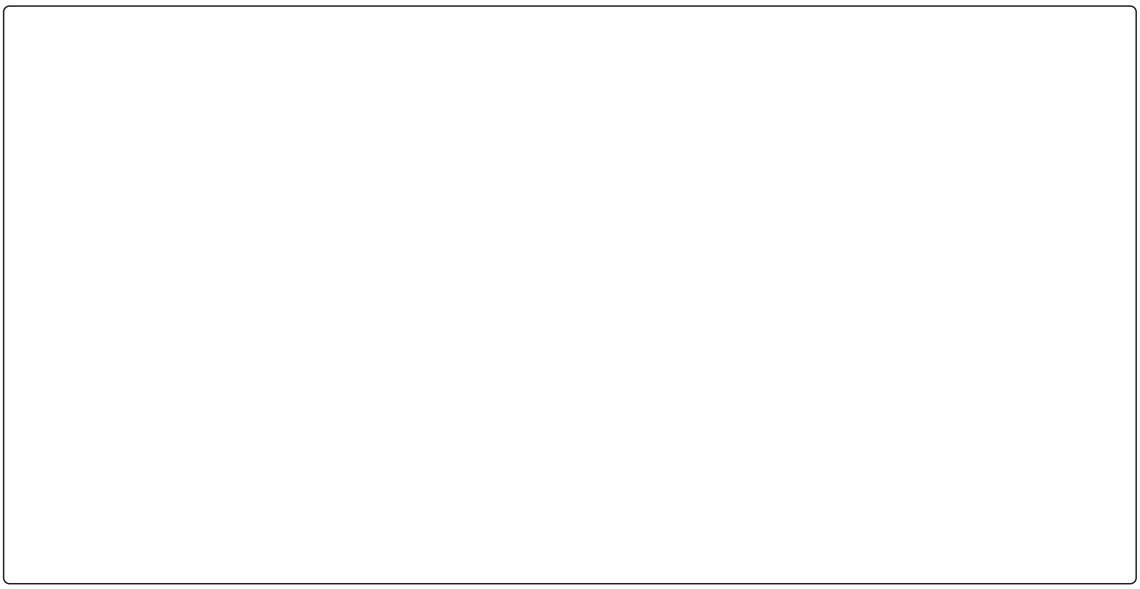
Enolates in Ring Formation

In previous lectures we have seen how the choice of base dictates whether we get partial or complete enolisation of a carbonyl compound. We highlighted a potential problem of self-condensation when we get partial enolisation *i.e.* if an enolate (or enol for that matter) is produced to any appreciable degree *in the presence* of the ketone electrophile.



This reaction between the nucleophilic form of a ketone (enol or enolate) with its electrophilic form (the ketone) is called a SELF-CONDENSATION **ALDOL** reaction. It is not a very useful reaction when used in an intermolecular sense. However we can exploit this reaction in a profitable synthesis of rings by using an INTRAmolecular version of this aldol reaction process.

Suppose we need to develop a synthesis of the cyclohexene below. Let's perform a retrosynthetic analysis (*i.e.* work backwards) of the molecule to see if we can arrive at suitable starting molecules which can then be used in the forward sense to prepare the product.



We know that dehydration is a good method for installing double bonds. So let's convert the enone into a β-hydroxy ketone. At this point you should recognise that a β-hydroxy ketone. This is the first product from the reaction between a ketone and an enolate. If we therefore perform this reaction (an aldol reaction) in reverse *i.e.* a *retroaldol* transform, we end up with an acyclic bis-ketone. Since acyclic molecules are generally much easier to prepare than cyclic systems, we have now deconstructed a relatively complicated molecule into a simple acyclic species from which the cyclohexane ring can be readily constructed.

We can discuss the synthesis of the bis-ketone starting material later, but let's assume that we have it to hand. We need to think about appropriate reaction conditions that will allow us to generate an enolate in the presence of a ketone. From earlier lectures, if we use a base (B^-) which has a conjugate acid (B–H) that has a similar pK_a value to the α-C–Hs of the ketone, then we can have the partial enolisation that we desire. Metal alkoxides *e.g.* KO^tBu, NaOEt or NaOMe would all be suitable for this purpose, as would NaOH.

You should recognise that the bis-ketone is symmetrical (internal mirror plane). There are however still two different sites at which enolisation can occur. Although the outer hydrogens on the methyl substituents are slightly more acidic than the internal α-C–Hs (pK_a ~ 19 for the methyl group compared with a pK_a ~ 20 for the internal α-C–Hs), the alkoxide base will generate small quantities of both types of enolate (**A** (kinetic enolate) and **B** (thermodynamic enolate)):

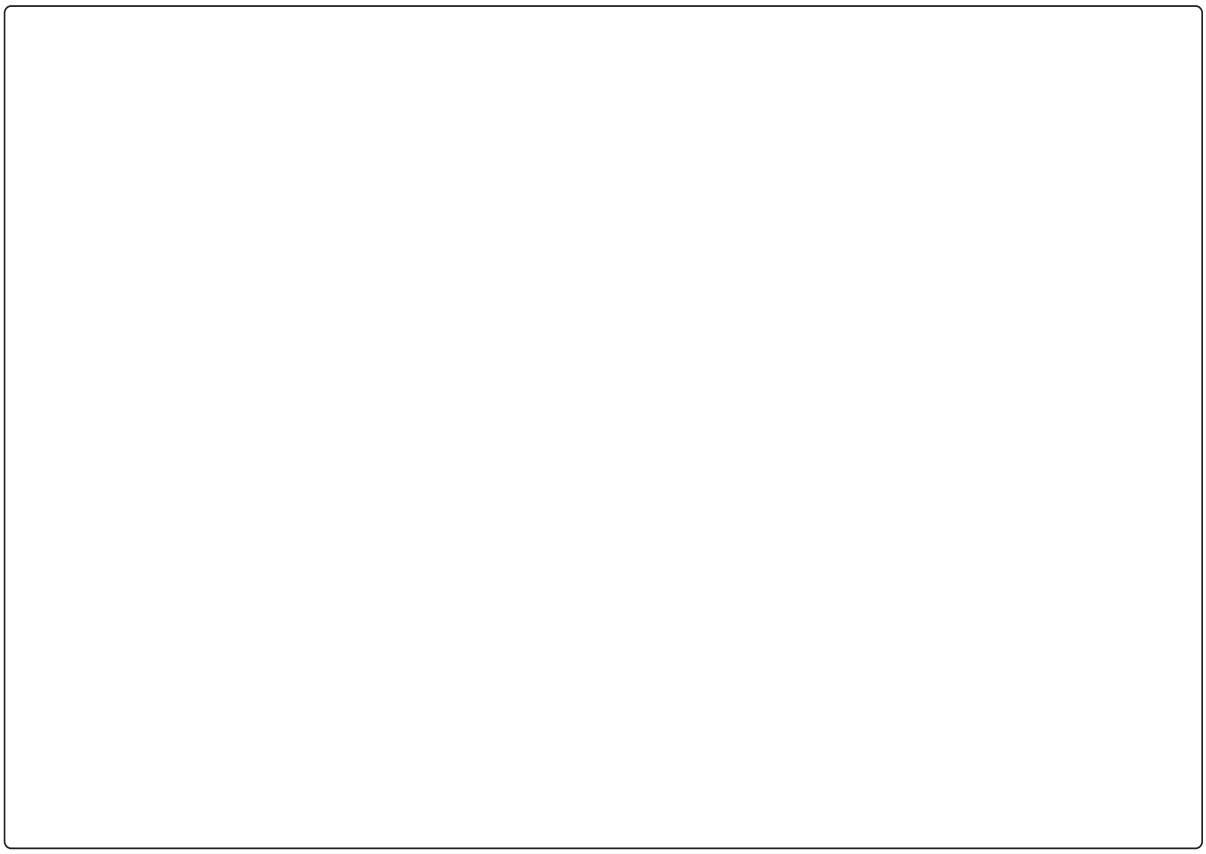
Intramolecular processes are more rapid than their corresponding intermolecular reactions providing the reacting species are relatively close to one another and there are no geometrical constraints to prevent the intramolecular reaction.

Five- and six-membered rings form particularly readily. The relative rate of ring formation follows the order:

5 > 6 > 3 > 7 > 4 > 8

This is a *kinetic* observation. Three-membered rings form so readily because the reacting species are in such close proximity (separated by only one atom); they are not necessarily thermodynamically very stable (a six-membered ring is usually the most thermodynamically stable ring size).

Assuming intermolecular reactions are not operating, enolate **A** can cyclise on to the remaining ketone to form a six-membered ring. Enolate **B**, which will be formed to a slightly greater extent than **A**, can cyclise on to the remaining ketone to form an eight-membered ring. Eight-membered rings are generally very difficult to form by this type of cyclisation mode, and will not compete with the reaction that forms a cyclohexane ring system. Eight-membered rings are also thermodynamically not very stable. Since this aldol cyclisation reaction is a reversible process, the reverse (retro-aldol) reaction will tend to further disfavour the formation of the eight-membered ring product.

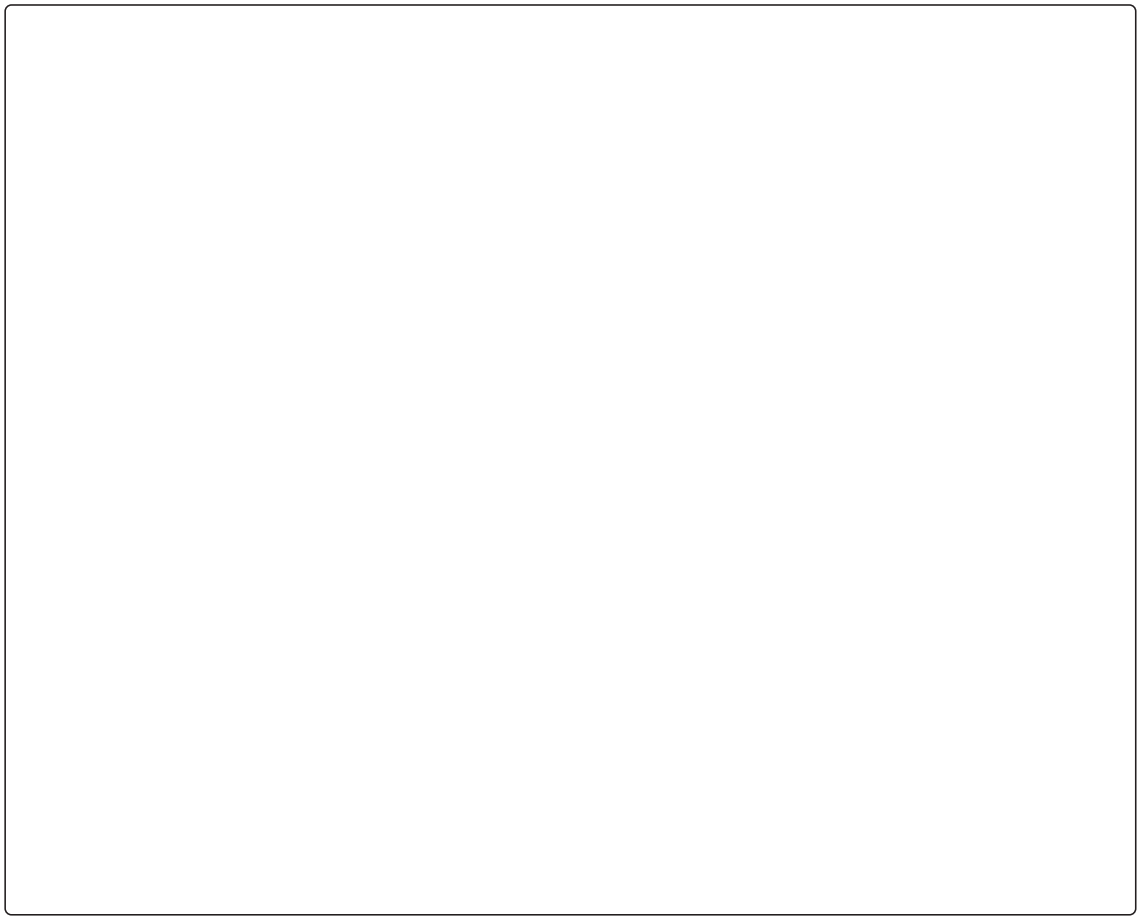


Since forming an eight-membered ring is both kinetically and thermodynamically disfavoured, there is essentially only one pathway that will be followed, namely formation of the six-membered ring.

E_1cb-Dehydration

Under the reaction conditions it is difficult to stop the reaction at the β-hydroxy ketone stage; a further dehydration step tends to follow rapidly. The mechanism of this elimination is possibly new to you. So far you should have seen two types of elimination mechanism, namely E_1 and E_2 (you should revise these mechanisms if they are unfamiliar to you; see: Chapter 6, pp 247-266 of Maitland Jones 2nd Edition). The dehydration of the β-hydroxy ketone proceeds *via* an **E_1cb pathway**.

The rate-determining elimination step is a unimolecular process and proceeds on the conjugate base, which in our case is just another enolate.



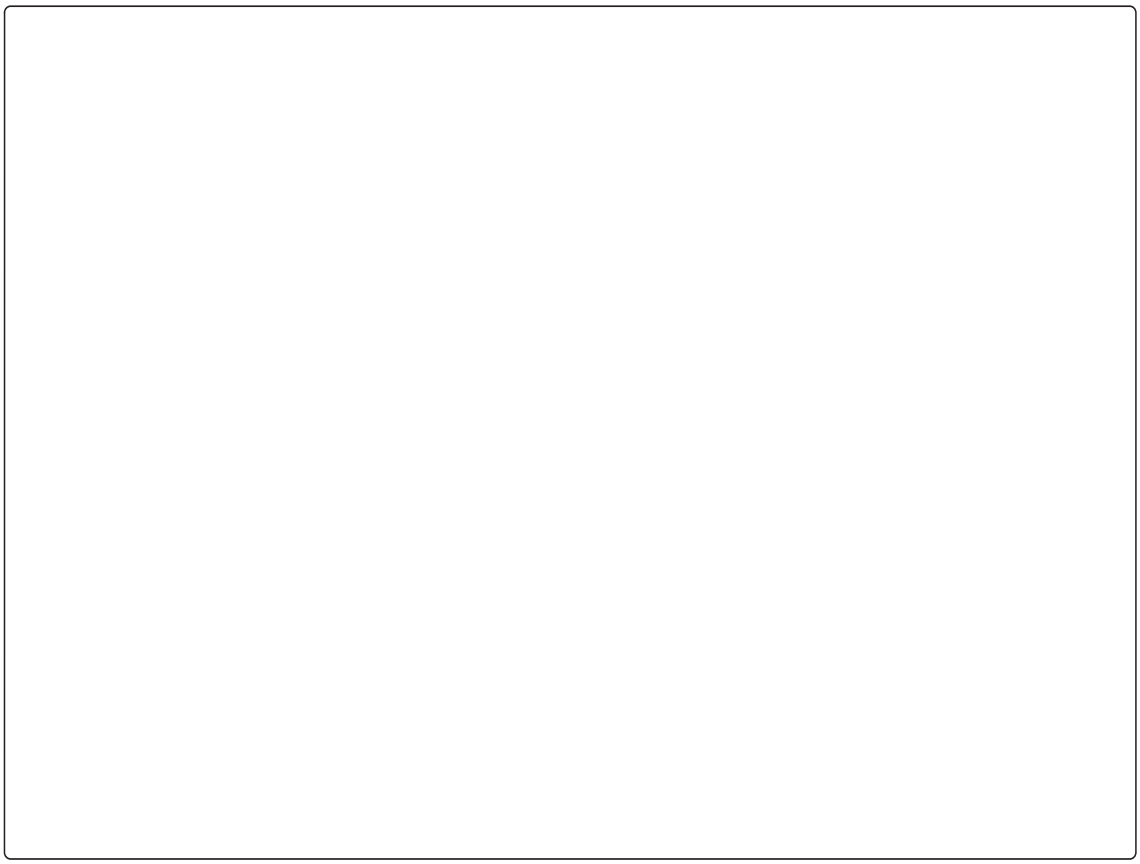
The elimination reaction is essentially an irreversible process as hydroxide and water are both relatively poor nucleophiles for conjugate addition reactions (see below). The α,β-unsaturated enone therefore represents the **THERMODYNAMIC** product from the reaction. In reactions that proceed under equilibrating conditions, as in this case, the product that is isolated represents a *thermodynamic sink* for the reaction system; it is not easy to form anything else.

Note that the enone product would also be formed if the reaction were carried out under acidic conditions. The mechanism would be similar only the enolates would be replaced by enols. Draw a mechanism for this reaction.

Conjugate Addition Reactions for Preparing 1,5-Dicarbonyl Compounds

Revision:

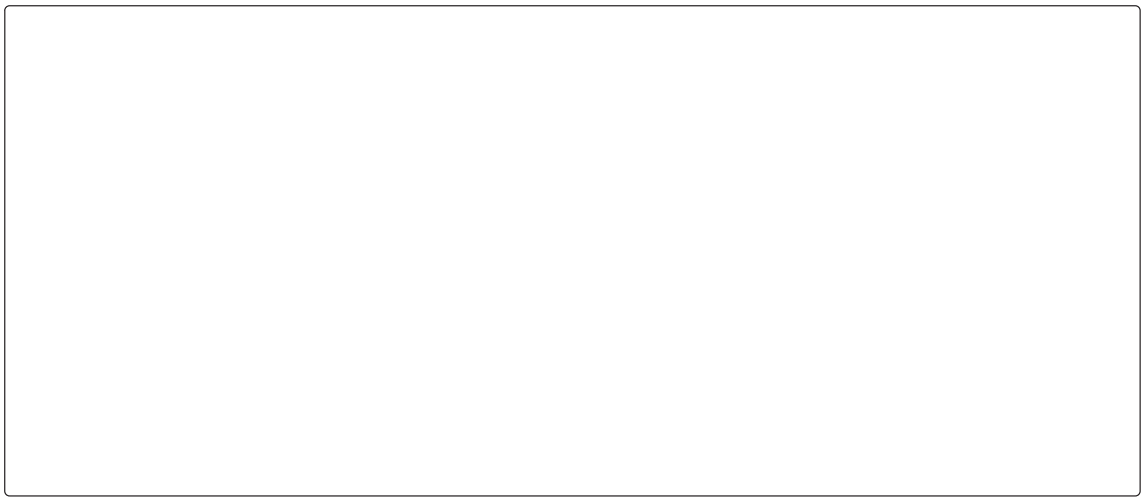
Enones and enoates (*i.e.* α,β-unsaturated ketones and esters respectively) are important functional groups in Organic Chemistry. They are *ambident* electrophiles in that there are two sites at which nucleophiles can attack this functional group:



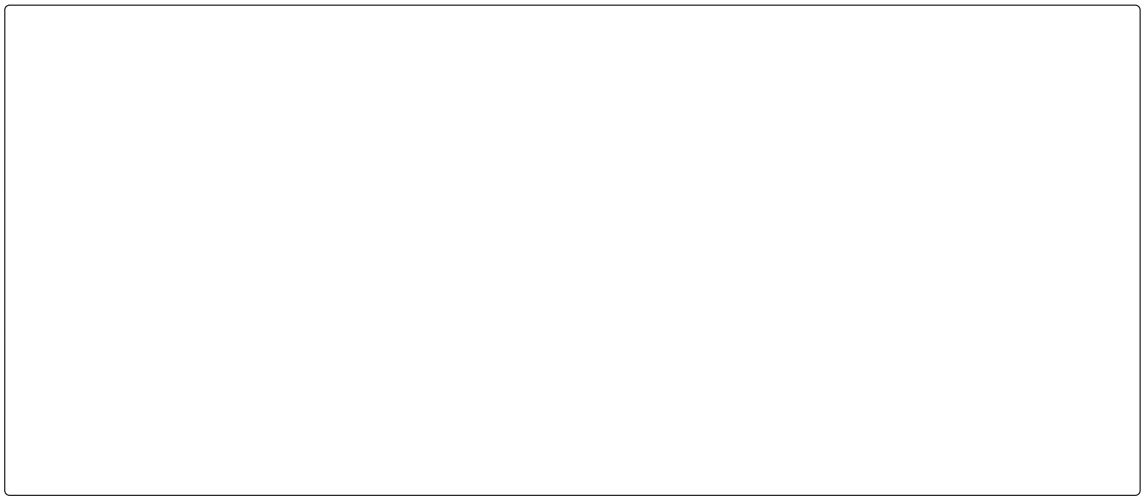
In the case of an enone, 1,2-addition of a nucleophile (Nu ≠ H^-) generates a tertiary alcohol. A more useful site of attack is for the nucleophile to attack at the end of the conjugated system, namely at the β-carbon. In this case the intermediate product is an enolate that can be used in further useful synthetic transformations.

The reaction of a nucleophile at the β-carbon of an α,β-unsaturated carbonyl group is best described as a **1,4-addition**, or as a **conjugate addition**; you will also see it described as a **Michael addition**, which strictly speaking refers only to the reaction of an enolate nucleophile with the α,β-unsaturated system. All three descriptors refer to the SAME type of reaction.

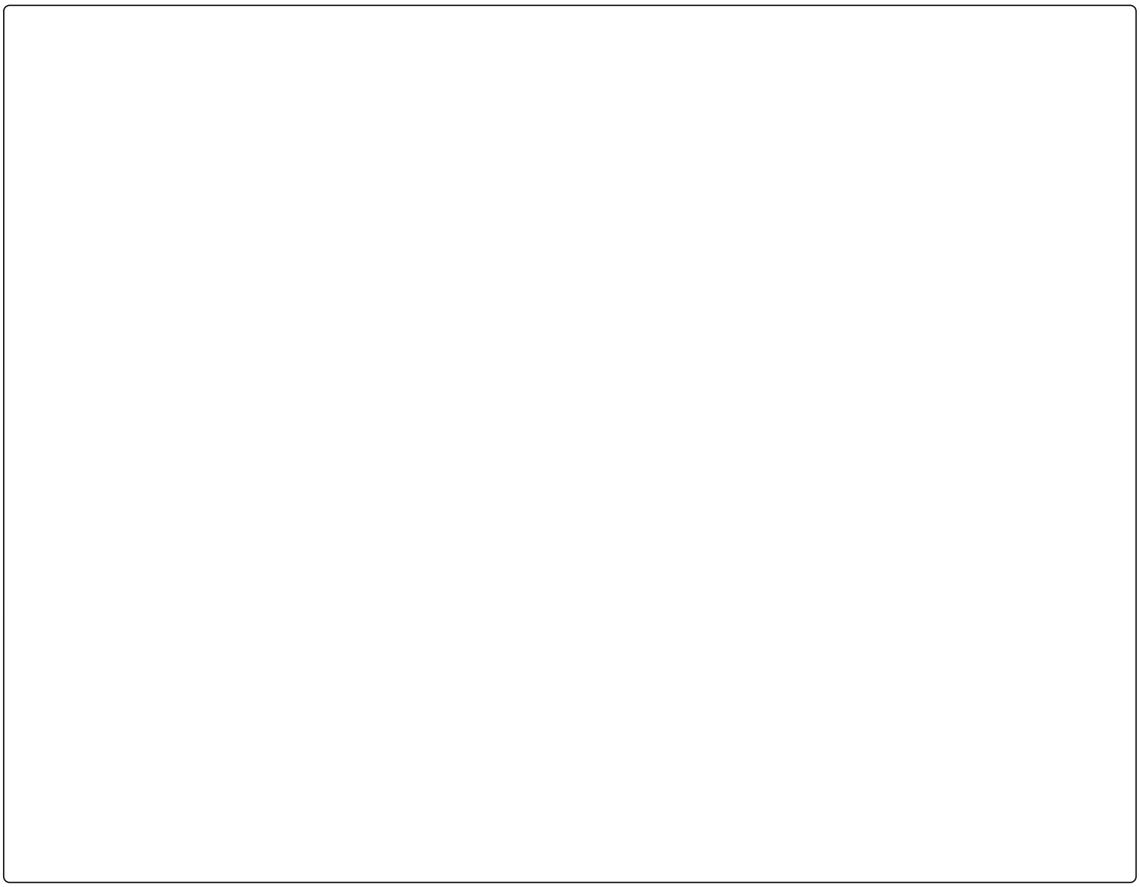
Mechanism:



Soft nucleophiles tend to react preferentially in a 1,4-sense. Some good examples of soft nucleophiles are sulfides and phosphines. The 'softness' of a simple carbon nucleophile (M–R) depends strongly on the metal, M. Organolithium and organomagnesium (Grignard) reagents are HARD nucleophiles, and react preferentially in a 1,2-fashion. To get 1,4-addition, use the corresponding copper or zinc reagent, both of which are much 'softer' in character.



Enolates, in particular silyl enol ethers and enolates derived from malonates (and related systems), are also good 'soft' nucleophiles.



The conjugate addition of enolates into α,β-unsaturated carbonyl groups provides one of the best methods for forming 1,5-dicarbonyl groups:

Summary

In this lecture we have used enolates in ring-forming reactions, specifically to form cyclic enones. In order to do this we needed to choose a base whose conjugate acid (*i.e.* B–H) has a similar pK_a to that of the α-C–H in the carbonyl compound. In this way, only small amounts of the nucleophilic enolate are produced at any one time. Cyclisation of this enolate on to another carbonyl group in the same molecule can then proceed. Cyclisation is particularly rapid and thermodynamically favourable when a five- or a six-membered ring is formed. The β-hydroxy ketone product is prone to further reaction, namely dehydration. This elimination process proceeds *via* an E_1cb pathway to provide an α,β-unsaturated system, namely an enone.

α-β-Unsaturated ketones and esters are very useful ambident electrophiles. Hard nucleophiles, such as organolithium reagents, tend to react in a 1,2-fashion, whereas soft nucleophiles preferentially react in a 1,4-fashion to provide an intermediate enolate that can be exploited in further useful transformations. Enolates, especially silyl enol ethers and malonate-derived enolates (and related molecules), are particularly good soft nucleophiles. Their reaction with α,β-unsaturated carbonyl groups provides a good route to 1,5-dicarbonyl compounds.