

Lecture 4

Enolates in Synthesis

Objectives:

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

- 1) explain why enolates are ambident nucleophiles;
- 2) understand why enolates provide the O-alkylation product preferentially with silyl electrophiles;
- 3) recognise some of the problems associated with using enolates in synthesis;
- 4) use enolates derived from 1,3-dicarbonyl compounds to circumvent some of these problems. Specifically you will be able to use this class of enolates:
 - in alkylation reactions with primary alkyl halides;
 - for regioselective enolisation;
 - as masked ketone enolates;
 - in conjugate addition reactions;
- 5) use silyl enol ethers to circumvent some of the problems associated with the basicity of lithium enolates. Specifically you will be able to use silyl enol ethers:
 - in alkylation reactions with tertiary alkyl halides;
 - in conjugate addition reactions.

Enolates are Ambident Nucleophiles

Enolates are ambident nucleophiles in that electrophiles can react at *two* sites on the enolate, namely at the oxygen, or at the terminal carbon.



Whether O-alkylation or C-alkylation occurs depends on the reagents and reaction conditions, in particular the associated counteraction, and the electrophile.

In general:

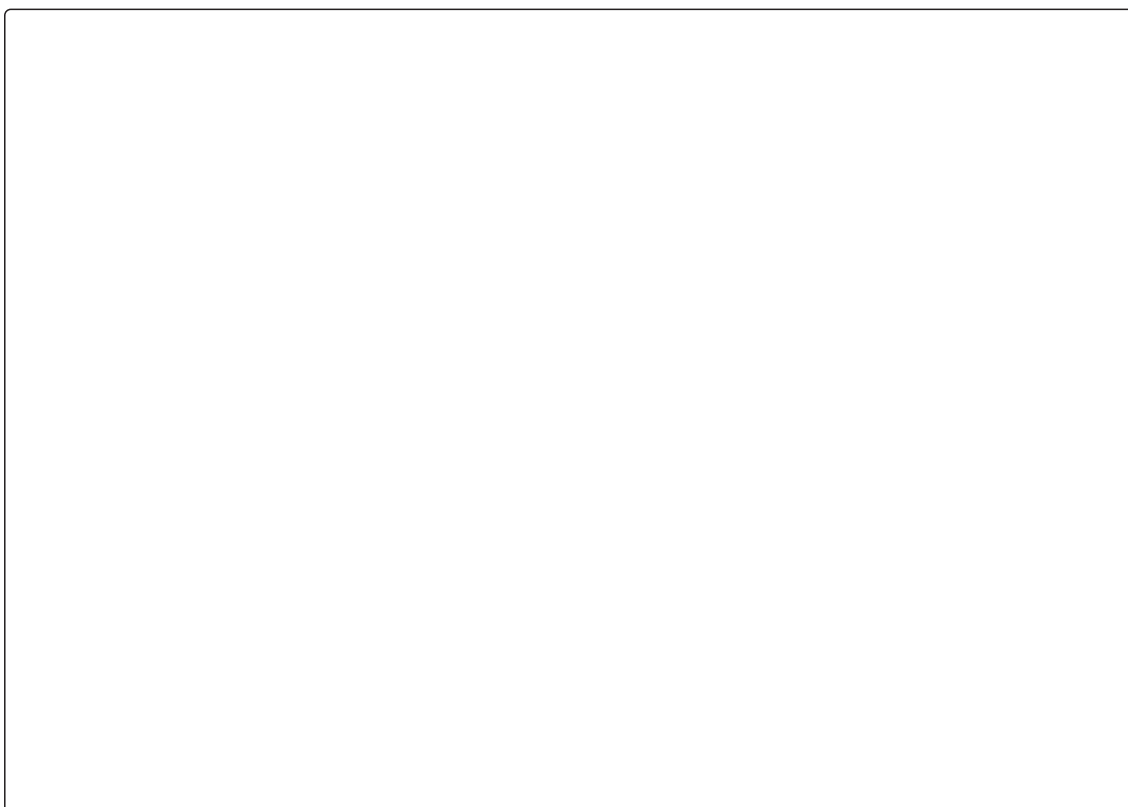
C-alkylation is far more common than O-alkylation; indeed with most carbon electrophiles, including aldehydes, C-alkylation is usually the exclusive reaction pathway. The re-formation of a strong C=O bond provides a good thermodynamic driving force for this alkylation pathway.

An important exception is the reaction of enolates with silyl electrophiles. In this case the strength of the O–Si bond leads to preferential O-alkylation. The resulting *silyl enol ethers* are very important nucleophiles.

Some Problems Associated with Using Enolates as Nucleophiles

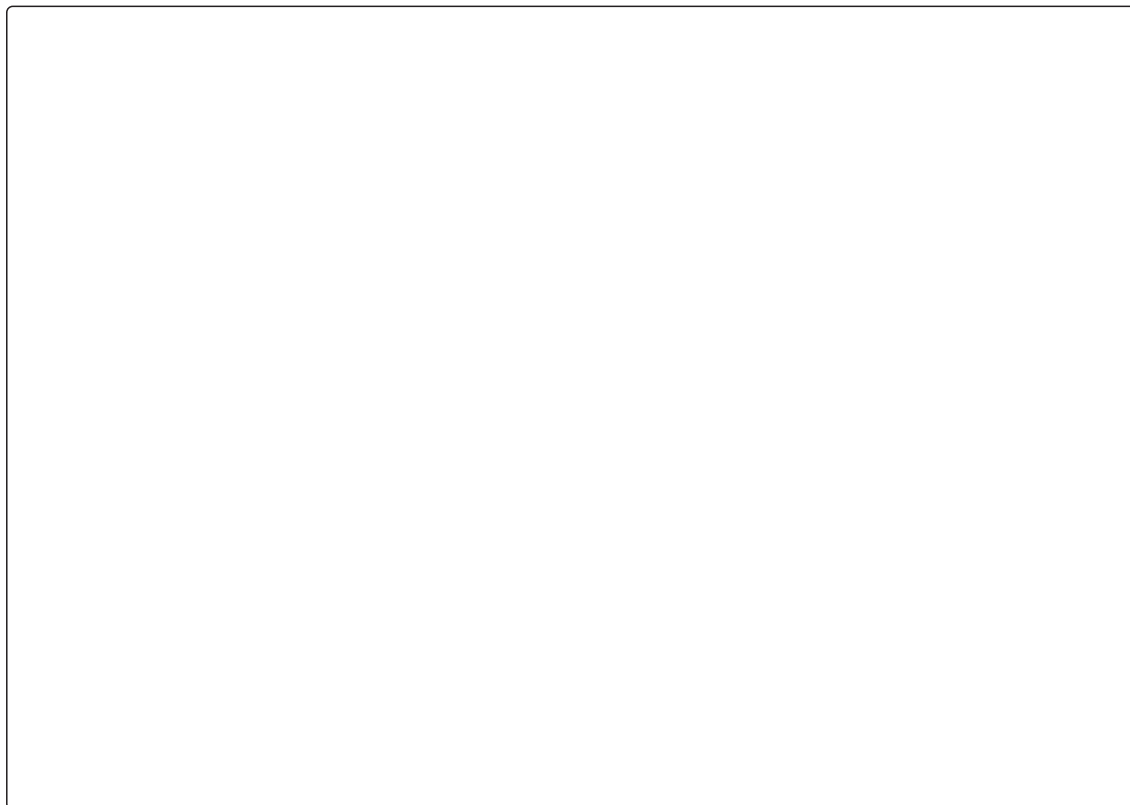
All nucleophiles are capable of behaving as bases (Brønsted and Lewis). Although lithium enolates are easy to form they need to be used with care in synthesis. Admittedly they are very good nucleophiles; however they are also very good bases. Their ability to act as a base and their very high reactivity as a nucleophile often leads to the enolate being consumed in deleterious side-reactions. These include:

1. **self condensation** aldol reactions. This can be a particular problem with enolates generated from aldehydes. If at all possible you should avoid using enolates derived from aldehydes in synthesis - they are very difficult to handle.

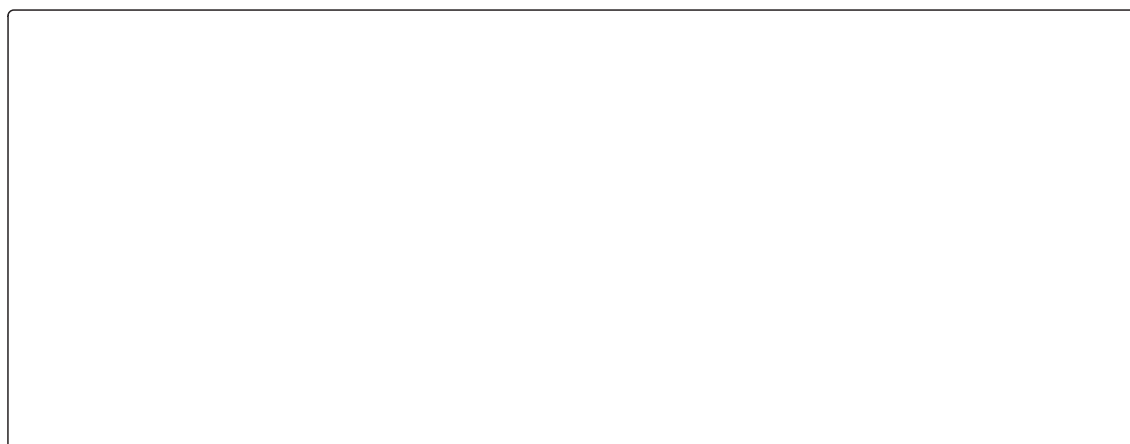


Since the aldol reaction between the enolate and another carbonyl group regenerates the original carbonyl group, further condensation reactions can occur, rapidly leading to polymers.

2. **polyalkylation** - this can be a problem if there is more than one acidic proton present α - to the carbonyl group.



3. If the alkyl halide is tertiary or hindered, the enolate can behave preferentially as a base and cause **elimination** of H-X in the alkyl halide rather than providing the alkylation product.



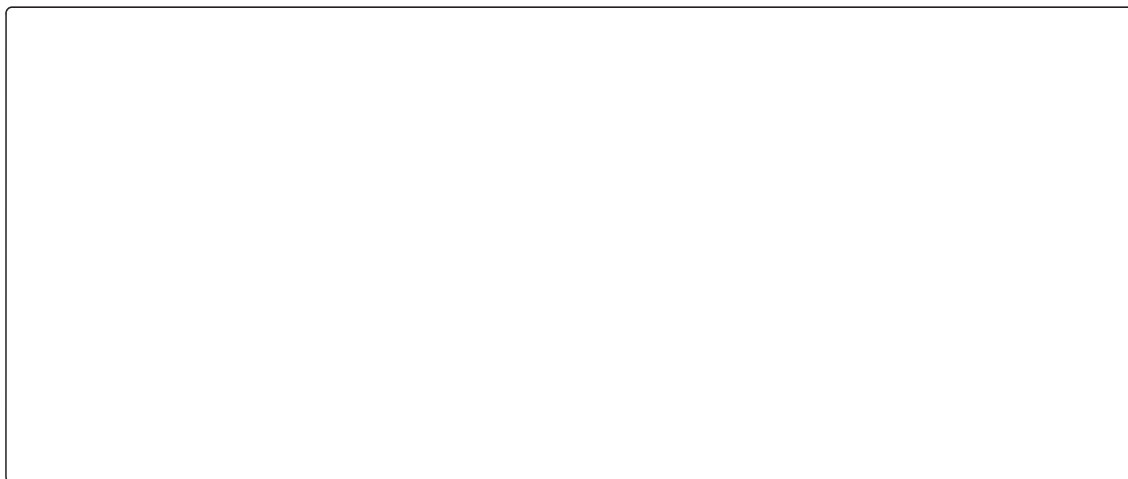
4. **Regioselective enolisation** especially of unsymmetrical ketones can be difficult - we have already discussed this in lecture 3 and provided some solutions to this problem.

A variety of methods can be employed to reduce the reactivity and basicity of enolates allowing more control in reactions.

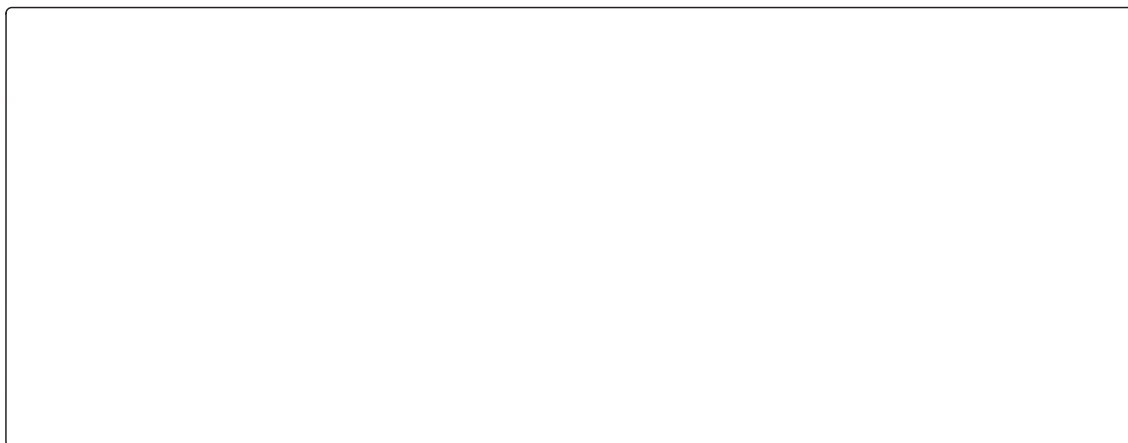
β -Dicarbonyl Compounds

1,3-Diketones, 1,3-diesters (malonates) and 1,3-keto-esters are very useful reagents for a variety of reasons:

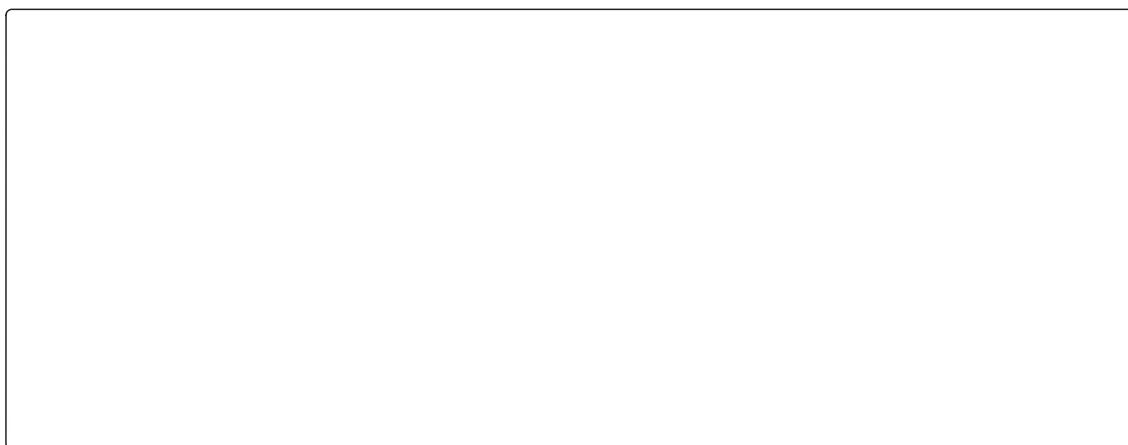
1. Regioselective enolisation is straightforward since the difference in pK_a between the adjacent α -C-Hs is very large. Careful choice of a relatively mild base such as a metal alkoxide ensures the formation of one enolate regioisomer with a high level of predictability and selectivity.



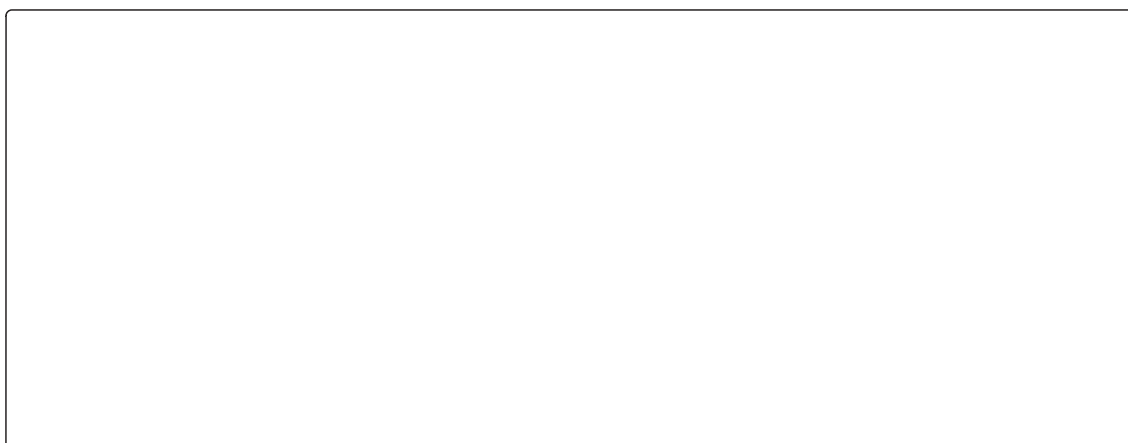
2. Self-condensation is not a problem (*Compare the pK_a of an alcohol with the internal C-H of a 1,3-dicarbonyl compound to explain why addition of the enolate to a carbonyl group is readily reversible*).



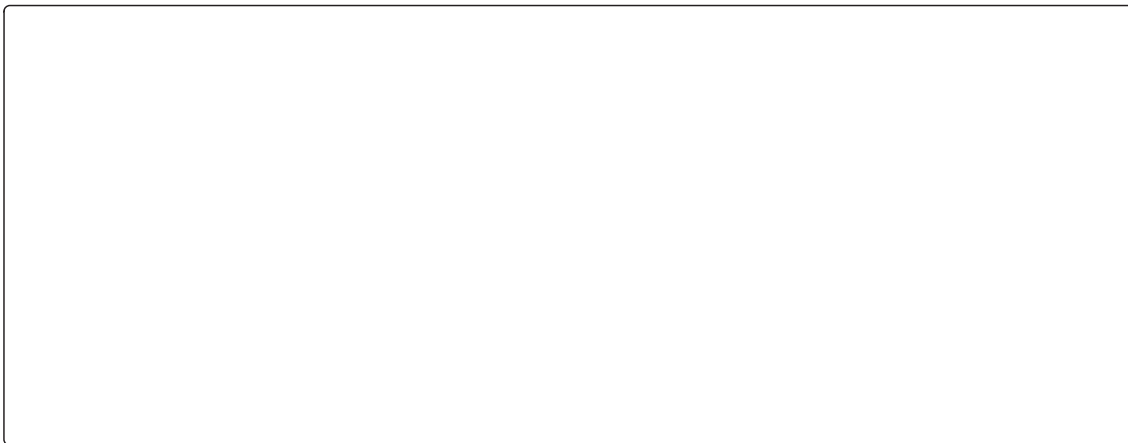
3. The enolates are good nucleophiles but relatively poor bases. Nevertheless fairly powerful electrophiles are still required for alkylation reactions to proceed with good efficiency: primary alkyl halides are good electrophiles, secondary alkyl halides react sluggishly and tertiary alkyl halides not at all.



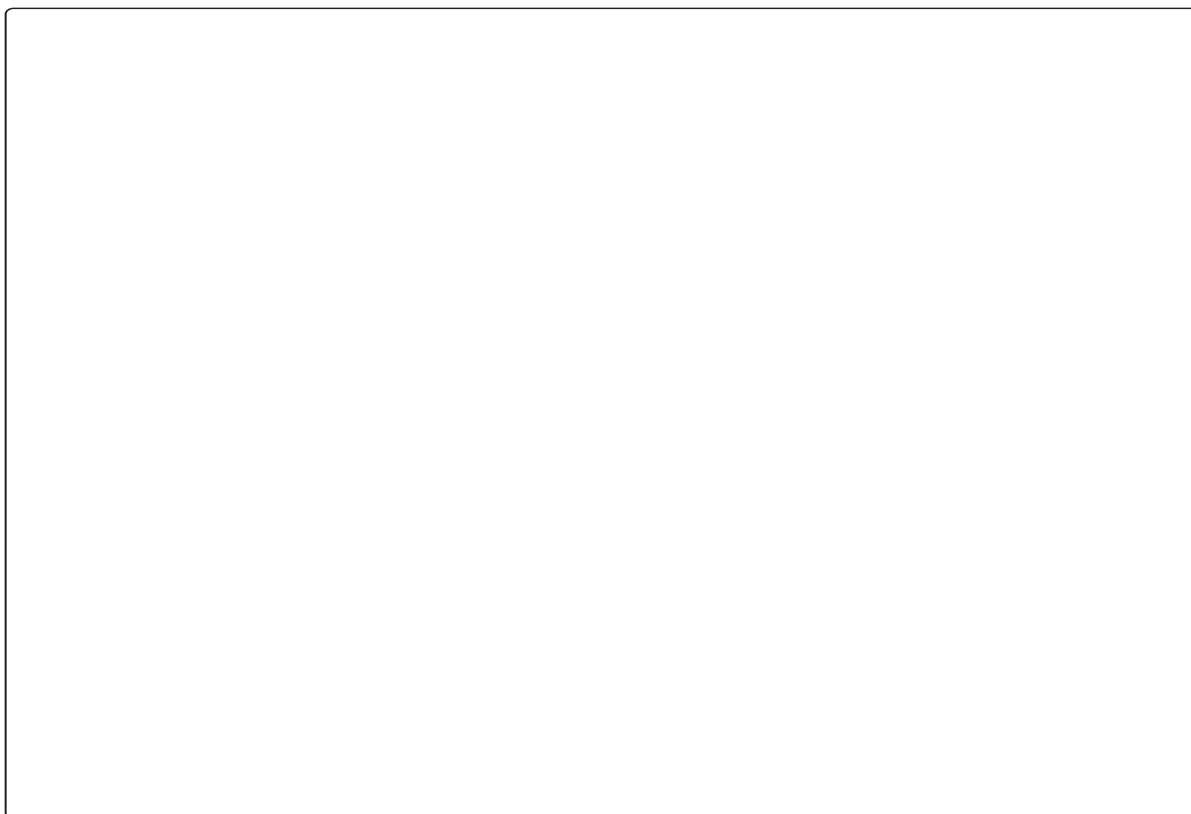
4. In the case of β -keto-esters the ester group can be readily removed *post* alkylation reaction using a saponification / decarboxylation procedure. This allows us to use enolates of β -keto-esters as *masked ketone enolates*.



The ester is generally removed in a two-step process. First, base-mediated hydrolysis converts the ester to the corresponding carboxylate salt (this process is known as saponification). *You should be able to draw the mechanism for this process.*



In the second step, protonation of the carboxylate generates the corresponding carboxylic acid. When this is heated decarboxylation (*i.e.* loss of CO_2) occurs. This reaction proceeds through a pericyclic mechanism:



Silyl Enol Ethers

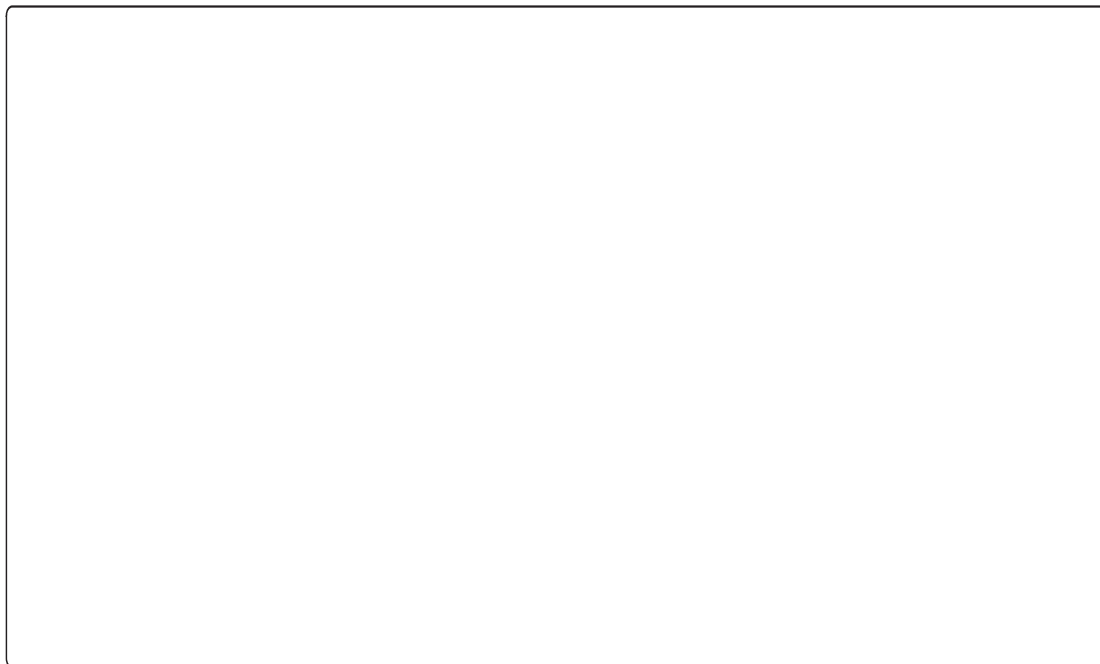
Silyl enol ethers are neutral molecules and therefore much less nucleophilic than metal enolates. They therefore tend to react only with strong electrophiles.

We have seen that primary alkyl halides are good electrophiles for reactions with enolates derived from β -dicarbonyl compounds. Tertiary alkyl halides are particularly problematical since the enolate tends to behave preferentially as a base and provide elimination rather than alkylation products.

Silyl enol ethers are not very basic. They are also stable to strong Lewis acids. Remembering back to CHM1C3, you saw how to alkylate aromatic rings using a Friedel-Crafts reaction. This process was particularly useful when tertiary alkyl halides were used as the electrophiles since these provide a relatively stable tertiary carbocation.



We can use silyl enol ethers in a similar fashion if we want to alkylate a carbonyl group with a tertiary alkyl halide. As in the Friedel-Crafts reaction we need the presence of a strong Lewis acid to prepare *in situ* the very reactive cationic intermediate that functions as the active electrophile.



Secondary alkyl halides also react under these conditions although far less efficiently (secondary carbocations are far less stable than tertiary carbocations). Secondary alkyl halides are usually poor substrates for alkylation reactions irrespective of the type of enolate employed.

Silyl Enol Ethers in Conjugate Addition Reactions (Hosomi Sakurai Reaction)

Soft nucleophiles preferentially undergo 1,4-addition over 1,2-addition with α,β -unsaturated carbonyl groups. Silyl enol ethers are good soft nucleophiles and not surprisingly react well with these ambident electrophiles providing they are activated with a Lewis acid. This reaction provides a good route to 1,5-dicarbonyl groups.



Summary

Enolates are ambident nucleophiles. They react with electrophiles either at the terminal carbon to provide the C-alkylation product, or at the oxygen to provide the O-alkylation product. For most electrophiles the C-alkylation product predominates. Important exceptions are silyl electrophiles. In these cases the formation of a strong Si–O bond favours the formation of the O-alkylation product, namely the silyl enol ether.

In this lecture we have discussed some of the problems associated with using enolates in synthesis. These arise from a number of features of enolates including their inherent basicity and often high reactivity. Typical problems include self-condensation reactions leading to the formation of polymers, polyalkylation, and elimination processes. Regioselective enolisation can also be a problem with unsymmetrically substituted ketones. We have seen how two classes of enolates can be used to circumvent some of these problems.

1. Enolates derived from β -keto-esters and related 1,3-dicarbonyl systems.

- The low pK_a of the internal C–Hs means that enolates can be formed with high regioselectivity.
- The enolate products are not strongly basic, and react well with primary alkyl halides, far less so with secondary alkyl halides, and not at all with tertiary alkyl halides (suggests the alkylation reaction proceeds through an S_N2 reaction mechanism).
- They also react well in a conjugate addition reaction with α,β -unsaturated carbonyl groups.
- Self-condensation is not a problem.
- β -Keto-esters are invaluable as *masked* ketone enolates. The ester group can be removed after the reaction by a saponification-decarboxylation procedure.

2. Silyl enol ethers

- Silyl enol ethers are readily formed by trapping the corresponding lithium enolate with a silyl chloride.
- They are not strongly nucleophilic; more importantly they exhibit very low basicity.
- They are stable to most Lewis acids.
- Owing to their low nucleophilicity, they only react with the most reactive electrophiles. They are particularly useful if you want to alkylate a ketone with a tertiary alkyl halide. The low basicity of silyl enol ethers ensures that elimination does not compete and their stability to strong Lewis acids means that highly reactive carbocationic electrophiles can be used as alkylating agents - *c.f.* Friedel-Crafts alkylation of benzene derivatives.