Reactions of enolates with aldehydes and ketones: the aldol reaction

27

Introduction: the aldol reaction

The simplest enolizable aldehyde is acetaldehyde (ethanal, CH_3CHO). What happens if we add a small amount of base, say NaOH, to this aldehyde? Some of it will form the enolate ion.
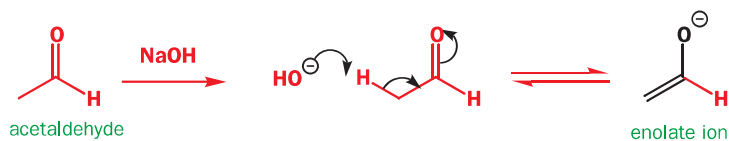
Only a small amount of the nucleophilic enolate ion is formed: hydroxide is not basic enough to enolize an aldehyde completely. Each molecule of enolate is surrounded by molecules of the aldehyde that are not enolized and so still have the electrophilic carbonyl group intact. Each enolate ion will attack one of these aldehydes to form an alkoxide ion, which will be protonated by the water molecule formed in the first step.
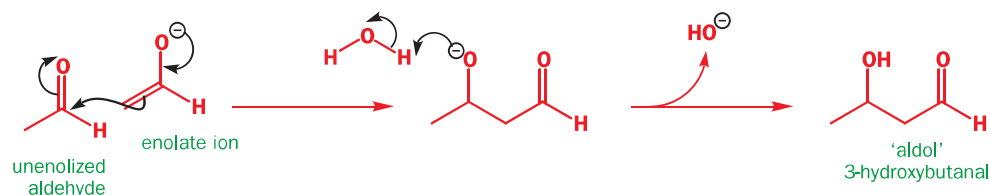
The product is an aldehyde with a hydroxy (ol) group whose trivial name is **aldol**. The name aldol is given to the whole class of reactions between enolates (or enols) and carbonyl compounds even if in most cases the product is not a hydroxy-aldehyde at all. Notice that the base catalyst (hydroxide ion) is regenerated in the last step, so it is truly a catalyst.

This reaction is so important because of the carbon–carbon bond formed when the nucleophilic

enolate attacks the electrophilic aldehyde. This bond is shown as a black bond in this version of the key step.

carbon–carbon bond formation

electrophilic   nucleophilic
aldehyde   enolate

newly formed
carbon–carbon bond
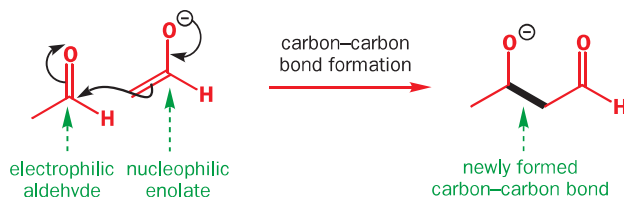
The rate equation for the aldol reaction

Not only is this step the most important; it is usually the rate-determining step. The rate expression for the aldol reaction at *low concentrations* of hydroxide is found experimentally to be

$$rate = k_2[CH_3CHO] \times [HO^-]$$

showing that the formation of the enolate ion is rate-determining. Though this is a proton transfer, which we normally expect to be fast, the proton is being removed from a carbon atom. Proton transfers to and from carbon atoms can be slow.

At higher hydroxide ion concentration, the rate expression becomes termolecular (k_3 expresses this) with the aldehyde concentration being squared.

$$rate = k_3[CH_3CHO]^2 \times [HO^-]$$

The mechanism does not, of course, involve three molecules colliding together. The rate-determining step has changed, and is now the second step.

But this does not obviously give a termolecular rate expression. The rate expression for this step is

$$rate = k_2[CH_3CHO] \times [enolate\ ion]$$

We cannot easily measure the concentration of the enolate, but we can work it out because we know that the enolate and the aldehyde are in equilibrium.
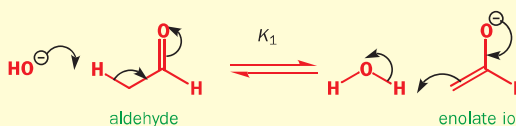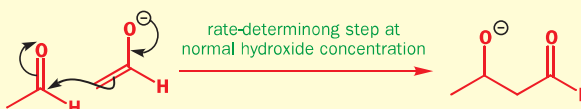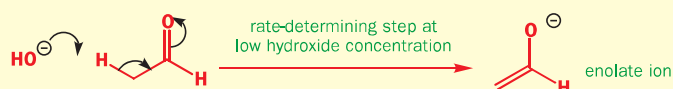
So we can express the enolate concentration using K_1 as the equilibrium constant and omitting the water concentration. We can write

$$K_1 = \frac{[enolate\ ion]}{[MeCHO][HO^-]}$$

Or, rearranging this to get the enolate ion concentration,

$$[enolate\ ion] = K_1[CH_3CHO] \times [HO^-]$$

And, substituting this in the rate expression,

rate-determining step at
low hydroxide concentration

enolate ion

rate-determinong step at
normal hydroxide concentration

aldehyde   enolate ion

$$rate = k_2[CH_3CHO] \times [enolate\ ion]$$
$$= k_2[CH_3CHO] \times K_1[CH_3CHO] \times [HO^-] = k_2K_1[CH_3CHO]^2 \times [HO^-]$$

This is what is observed, if we can remind you:

$$rate = k_3[CH_3CHO]^2 \times [HO^-]$$

It just turns out that the 'termolecular rate constant' k_3 is actually the product of an equilibrium constant K_1 and a genuine bimolecular rate constant k_2 such that $k_3 = K_1 \times k_2$. You saw a similar thing in the rate expressions for amide hydrolysis (Chapter 13) and E1cB elimination (Chapter 19, p. 000)

The reaction occurs with ketones as well. Acetone is a good example for us to use at the start of this chapter because it gives an important product and, as it is a symmetrical ketone, there can be no argument over which way it enolizes.

the enolization step

acetone

enolate ion
of acetone
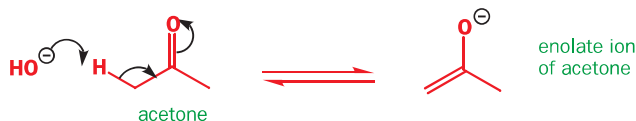
the carbon–carbon bond-forming step

second molecule
of acetone

'aldol' product from acetone
4-hydroxy-4-methylpentan-2-one
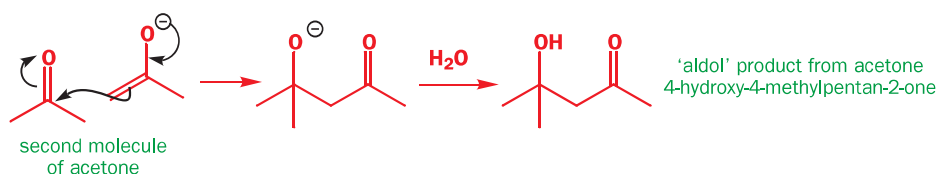
Each step is the same as the aldol sequence with acetaldehyde, and the product is again a hydroxy-carbonyl compound, but this time a hydroxy-ketone.

The acetaldehyde reaction works well when one drop of dilute sodium hydroxide is added to acetaldehyde. The acetone reaction is best done with insoluble barium hydroxide, $Ba(OH)_2$. Both approaches keep the base concentration low. Without this precaution, the aldol products are not the compounds isolated from the reaction. 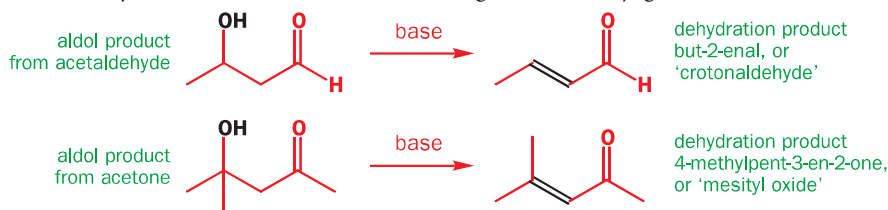With more base, further reactions occur, because the aldol products dehydrate rather easily under the reaction conditions to give stable conjugated unsaturated carbonyl compounds.


These are elimination reactions, and you met them in Chapter 19. You cannot normally eliminate water from an alcohol in basic solution and it is the carbonyl group that allows it to happen here. A second enolization reaction starts things off, and these are E1cB reactions.
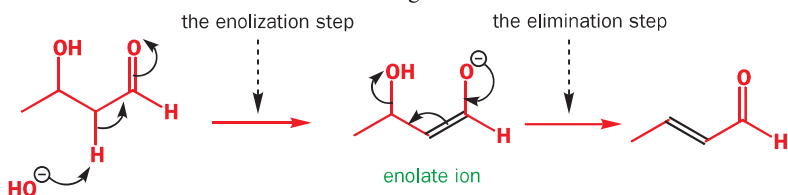
In the examples that follow in the rest of the chapter you will see that base-catalysed aldol reactions sometimes give the aldol and sometimes the elimination product. The choice is partly based on conditions—the more vigorous conditions (stronger base, higher temperatures, longer reaction time) tend to give the elimination product—and partly on the structure of the reagents: some combinations are easy to stop at the aldol stage, while some almost always give the elimination reaction as well. You do not, of course, need to learn the results: if you ever need to do an aldol reaction you can consult the massive review in the 1968 volume of *Organic Reactions* to find the best conditions for getting the result you want.

The elimination is even easier in acid solution and acid-catalysed aldol reactions commonly give unsaturated products instead of aldols. In this simple example with a symmetrical cyclic ketone, the enone is formed in good yield in acid or base. We shall use the acid-catalysed reaction to illustrate the mechanism. First the ketone is enolized under acid catalysis as you saw in Chapter 21.
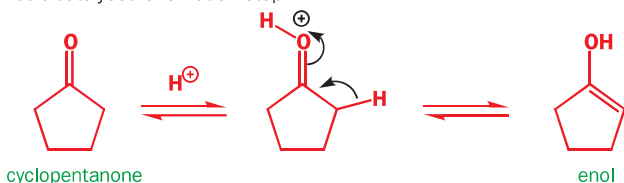
Then the aldol reaction takes place. Enols are less nucleophilic than enolates, and the reaction occurs because the electrophilic carbonyl component is protonated: the addition is acid-catalysed. An acid-catalysed aldol reaction takes place.
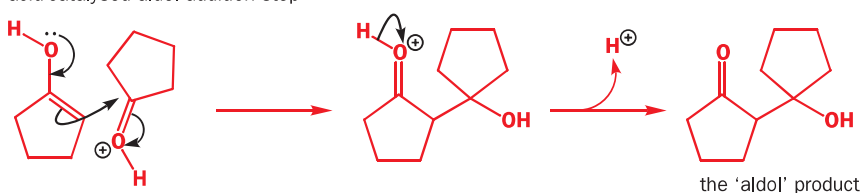
The aldol is a tertiary alcohol and would be likely to eliminate by an E1 mechanism in acid even without the carbonyl group. But the carbonyl ensures that only the stable conjugated enone is formed. Notice that the dehydration too is genuinely acid-catalysed as the acid reappears in the very last step.

the acid-catalysed dehydration step (E1 elimination)

None of these intermediates is detected or isolated in practice—simple treatment of the ketone with acid gives the enone in good yield. A base-catalysed reaction gives the same product via the aldol–E1cB elimination mechanism.
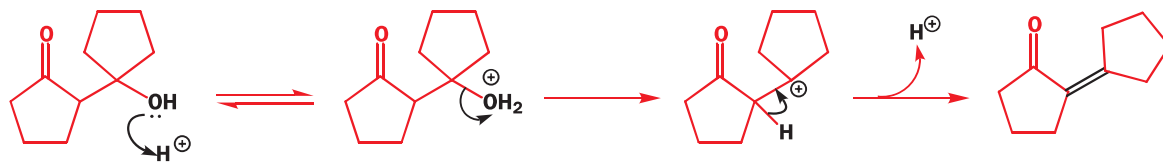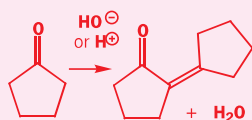
> - **Base-catalysed aldol reactions may give the aldol product, or may give the dehydrated enone or enal by an E1cB mechanism**
> - **Acid-catalysed aldol reactionsmay give the aldol product, but usually give the dehydrated enone or enal by an E1 mechanism**
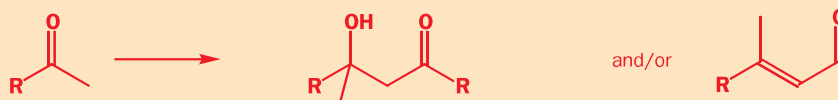

► Condensation reactions

condensation of cyclopentanone

The term condensation is often used of reactions like this. Condensations are reactions where two molecules combine with the loss of another small molecule—usually water. In this case, two ketones combine with the loss of water. This reaction is called an **aldol condensation** and chemists may say 'two molecules of cyclopentanone condense together to give a conjugated enone'. You will also find the term 'condensation' used for all aldol reactions whether they occur with dehydration or not. The distinction is no longer important.

Aldol reactions of unsymmetrical ketones

If the ketone is blocked on one side so that it cannot enolize—in other words it has no α protons on that side—only one aldol reaction is possible. Ketones of this type might bear a tertiary alkyl or an aryl substituent. *t*-Butyl methyl ketone (3,3-dimethylbutan-2-one), for example, gives aldol reactions with various bases in 60–70% yield. Enolization cannot occur towards the *t*-butyl group and must occur towards the methyl group instead.

ketones which can enolize only one way:
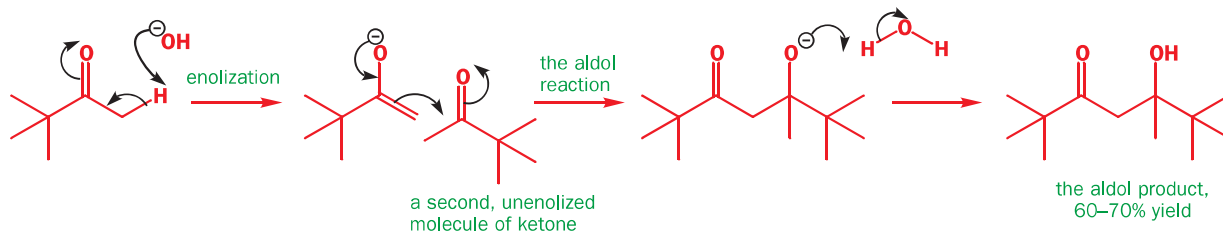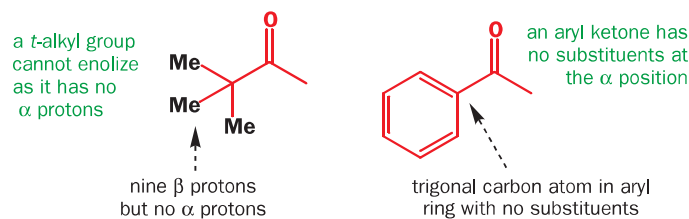
A specially interesting case of the blocked carbonyl compound is the lactone or cyclic ester. Open-chain esters do not give aldol reactions: they prefer a different reaction that is the subject of the next chapter. But lactones are in some ways quite like ketones and give unsaturated carbonyl products under basic catalysis. Enolization is unambiguous because the ester oxygen atom blocks enolization on one side.

enolate formation from a lactone (cyclic ester)

no α protons
on this side - - - ->
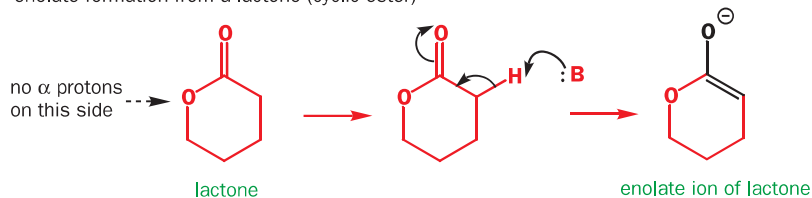
lactone   enolate ion of lactone

The enolate then attacks the carbonyl group of an unenolized lactone just as we have seen with aldehydes and ketones.

aldol reaction of a lactone (cyclic ester)

H_2O
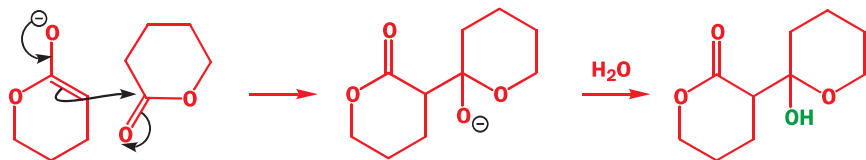
The last step is the familiar dehydration. As this reaction is being carried out in base we had better use the E1cB mechanism via the enolate of the aldol product.

the dehydration step

base-catalysed
enolization

elimination
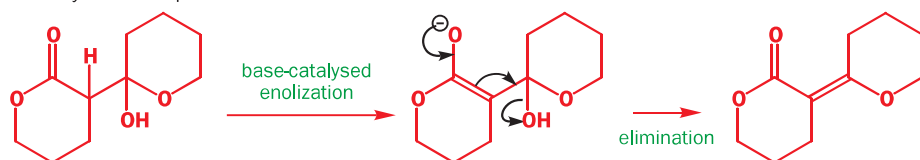
You might have been surprised that the intermediate in the aldol step of this reaction did not decompose. This intermediate could be described as a tetrahedral intermediate in a nucleophilic substitution at a carbonyl group (Chapter 12). Why then does it not break down in the usual way?

possible breakdown of a tetrahedral intermediate in a lactone aldol reaction
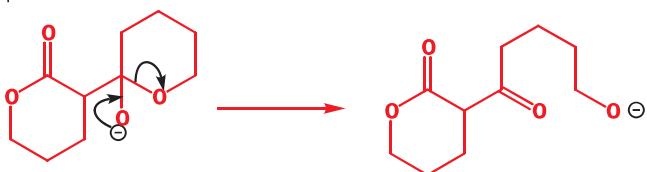
The best leaving group is the alkoxide and the product is quite reasonable. But what is it to do now? The only reasonable next step is for it to close back up again. Because the lactone is a *cyclic* ester, the leaving group cannot really leave—it must stay attached to the molecule. This reaction is reversible, but dehydration is effectively irreversible because it gives a stable conjugated product. This is the true situation.
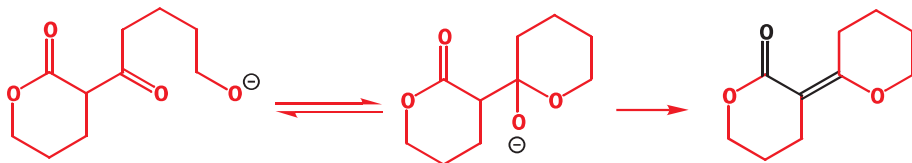
The equilibrium on the left does not affect the eventual product; it simply withdraws some of the material out of the productive reaction. We call this sort of equilibrium a **parasitic equilibrium** as it has no real life of its own—it just sucks the blood of the reaction.

Cross-condensations

So far we have considered only 'self-condensations'—dimerization reactions of a single carbonyl compound. These form only a tiny fraction of known aldol reactions. Those that occur between two different carbonyl compounds, one acting as a nucleophile in its enol or enolate form, and the other as an electrophile, are called **cross-condensations**. They are more interesting than self-condensations, but working out what happens needs more thought.

We shall start with an example that works well. The ketone PhCOMe reacts with 4-nitrobenzaldehyde in aqueous ethanol under NaOH catalysis to give a quantitative yield of an enone.
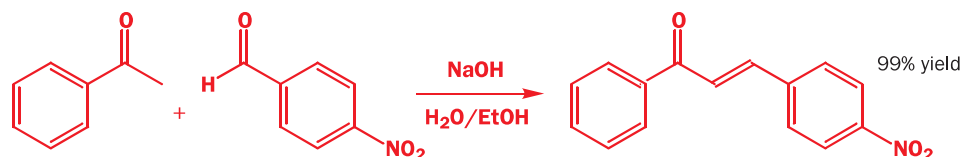
The first step must be the formation of an enolate anion using NaOH as a base. Though both carbonyl compounds are unsymmetrical, there is only one site for enolization as there is only one set of α protons, on the methyl group of the ketone. The aldehyde has no α protons at all.
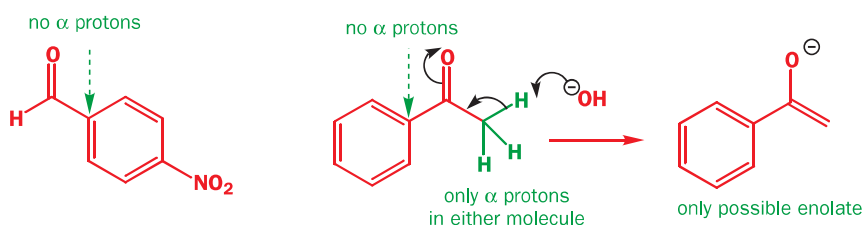
To get the observed product, the enolate obviously attacks the aldehyde to give an aldol, which then dehydrates by the E1cB mechanism.
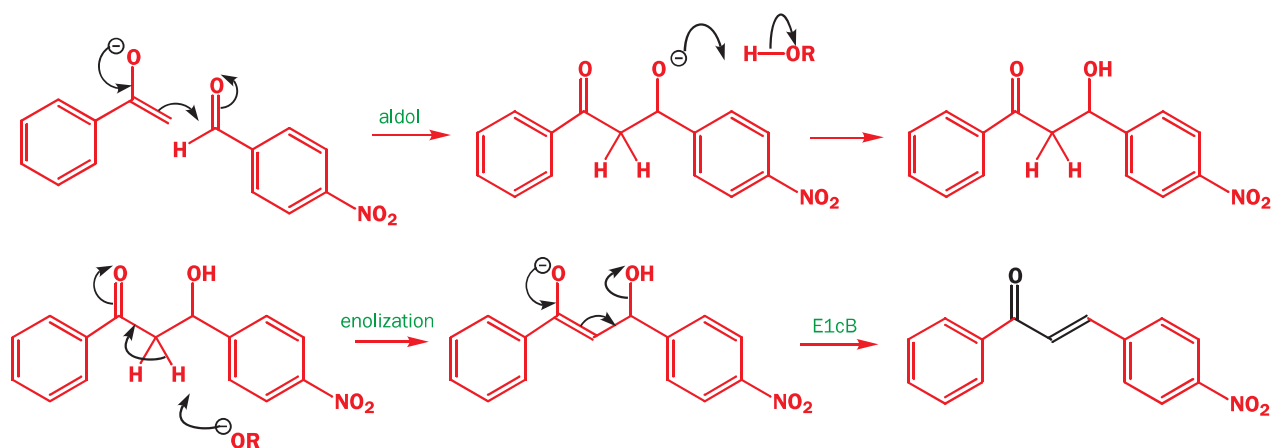
Now, in this step there was a choice. The enolate could have attacked another molecule of unenolized ketone. It didn't, because ketones are less reactive than aldehydes (Chapter 6). In this case the aldehyde has an electron-withdrawing nitro substituent too, making it even more reactive. The enolate selects the better electrophile, that is, the aldehyde.

In other cases the balance may shift towards self-condensation. You might think that a crossed aldol reaction between acetaldehyde and benzophenone (diphenylketone $Ph_2C=O$) should work well.

After all, only the aldehyde can enolize and the enolate could attack the ketone.
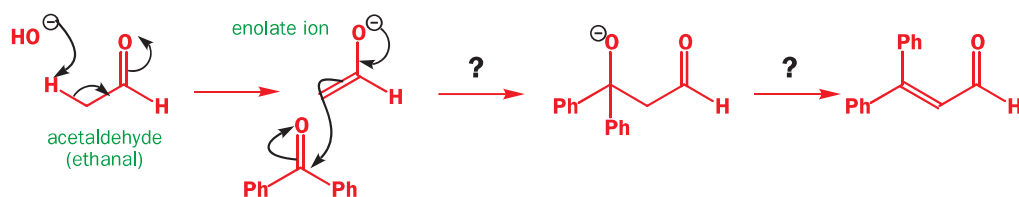
But it won't work. The ketone is very hindered and very conjugated. It is less electrophilic than a normal ketone and normal ketones are less reactive than aldehydes. Given a choice between attacking this ketone and attacking another (but unenolized) molecule of acetaldehyde, the enolate will choose the aldehyde every time. The reaction at the start of the chapter occurs and the ketone is just a spectator.

> ● **Successful crossed aldol reactions**
>
> For this kind of crossed aldol reaction to work well we must have two conditions.
> - One partner only must be capable of enolization
> - The other partner must be incapable of enolization and be *more electrophilic than the enolizable partner.*
>
> Everyone remembers the first of these conditions, but it is easy to forget the second.

Here follows a list of carbonyl substituents that prevent enolization. They are arranged roughly in order of reactivity with the most reactive towards nucleophilic attack by an enolate at the top. You do, of course, need two substituents to block enolization so typical compounds also appear in the list.

Carbonyl substituents that block enolization

	Substituent	Typical compounds
most reactive[a]	H	(HCHO) [b]
	CF_3, CCl_3	(Cl_3C—CO—CCl_3) (F_3C—CO—CF_3)
	t-alkyl	(*t*-Bu—CHO)
	alkenyl	(Ph—CH=CH—CHO)
	aryl	(Ph—CHO)
least reactive[a]	NR_2	(Me_2N—CHO)
	OR	(γ-butyrolactone)

[a] Reactivity towards nucleophilic attack by an enolate.
[b] This compound needs special methods, discussed in the section on the Mannich reaction, p. 000.

nitromethane

'enolization'   'enolate' ion
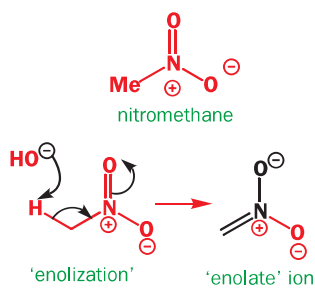
Compounds that can enolize but that are not electrophilic

We can complement this type of selectivity with the opposite type. Are there any compounds that can enolize but that cannot function as electrophiles? No carbonyl compound can fill this role, but in Chapter 21 we met some 'enolizable' compounds that lacked carbonyl groups altogether. Most notable among these were the nitroalkanes. Deprotonation of nitroalkanes is not enolization nor is the product an enolate ion, but the whole thing is so similar to enolization that it makes sense to consider them together. The anions, sometimes called **nitronates**, react well with aldehydes and ketones.

anion of nitromethane
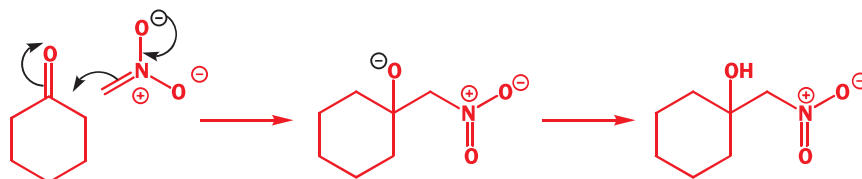
This particular example, using cyclohexanone as the electrophile and nitromethane itself as the source of the 'enolate', works quite well with NaOH as the base in methanol solution to give the 'aldol' in reasonable yield. Once again this reaction involves choice. Either compound could enolize, and, indeed, cyclohexanone reacts well with itself under essentially the same conditions.

70% yield

Although cyclohexanone forms an enolate in the absence of nitromethane, when both ketone and nitroalkane are present the base prefers to remove a proton from nitromethane. This is simply a question of pK_a values. The pK_a of a typical ke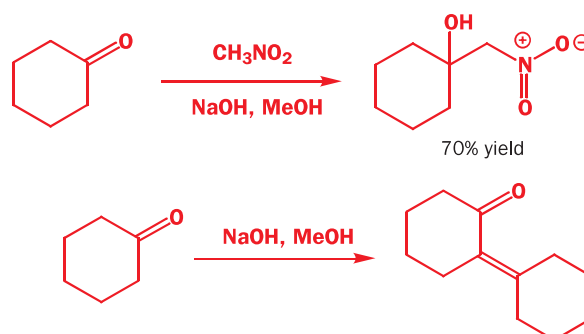tone is about 20 but that of nitromethane is 10. It is not even necessary to use as strong a base as NaOH ($pK_{aH} = 15.7$) to deprotonate nitromethane: an amine will do (pK_{aH} about 10) and secondary amines are often used.

The elimination step also occurs easily with nitro compounds and is difficult to prevent in reactions with aromatic aldehydes. Now you can see how the useful nitroalkene Michael acceptors in Chapter 23 were made.

85% yield
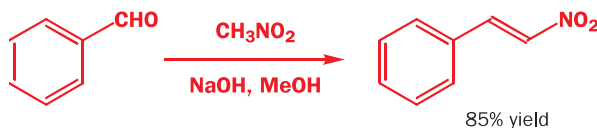
Nitroalkenes as termite defence compounds

Termites are social insects, and every species has its own 'soldier' termites that defend the nest. Soldier termites of the species *Prorhinotermes simplex* have huge heads from which they spray a toxic nitroalkene on their enemies.

defensive nitroalkene from termite soldiers

R = *n*-dodecyl

Though this compound kills other insects and even other species of termites, it has no effect on the workers of the same species. To find out why this was so, Prestwich made some radioactive compound using the aldol reaction. First, the right aldehyde was made using an S_N2 reaction with radioactive (^{14}C) cyanide ion on a tosylate followed by DIBAL reduction (Chapter 24) of the nitrile. The position of the ^{14}C atom in each compound is shown in black.

Then the aldol reaction was carried out with nitromethane and sodium methoxide to give the nitro aldol. Elimination using acetic anhydride in pyridine gave the defence compound (*E*-1-nitropentadec-1-ene) in 37% yield over the four steps.

It was found that, if the worker termites were sprayed with the labelled compound, they were able to make it harmless by using an enzyme to reduce the nitroalkene to a nitroalkane. The labelled nitroalkane could only be re-isolated from workers of the same species: other insects do not have the enzyme.

If an aldol reaction can be done with

- only one enolizable component
- only one set of enolizable protons
- a carbonyl electrophile more reactive than the compound being enolized

then you are lucky and the crossed aldol method will work. But most aldol reactions aren't like this: they are cross-condensations of aldehydes and ketones of various reactivities with several different enolizable protons. Crossed aldols on most pairs of carbonyl compounds lead to hopeless mixtures of products. In all cases that fail to meet these three criteria, a specific enol equivalent will be required: one component must be turned quantitatively into an enol equivalent, which will be reacted in a separate step with an electrophile. That is what the next section is about—and you will find that some of the methods have a lot in common with those we used for alkylating enolates in Chapter 26.

Controlling aldol reactions with specific enol equivalents

In Chapter 26 we saw that the alkylation of enolates was most simply controlled by preparing a specific enol equivalent from the carbonyl compound. The same approach is the most powerful of all the ways to control the aldol reaction. The table is a reminder of some of the most useful of these specific enol equivalents.

Specific enol equivalents are intermediates that still have the reactivity of enols or enolates but are stable enough to be prepared in good yield from the carbonyl compound. That was all we needed to know in Chapter 26. Now we know that

Important specific enol equivalents
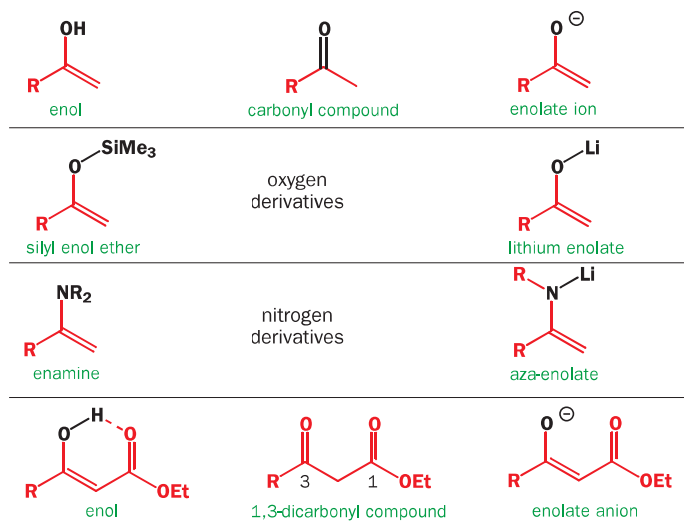
a further threat is the reaction of the partly formed enol derivative with its unenolized parent and we should add that 'no aldol reaction should occur during the preparation of the specific enol equivalent'.

> ● Specific enol equivalents are intermediates that still have the reactivity of enols or enolates but are stable enough to be prepared in good yield from the carbonyl compound *without any aldol reaction.*

Sensible choice of an appropriate specific enol equivalent will allow almost any aldol reaction to be performed successfully. T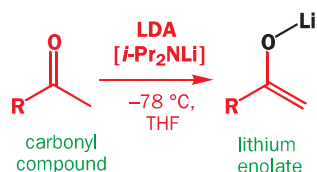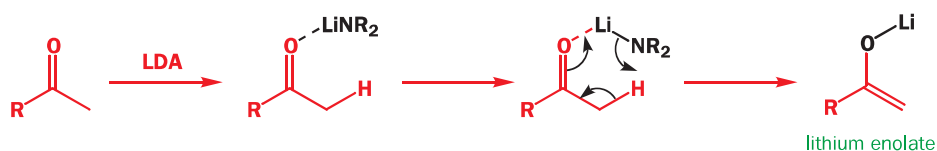he first two compounds in our list, the silyl enol ethers and the lithium enolates, have a specially wide application and we should look first at the way these work. As the table suggests, silyl enol ethers are more like enols: they are nonbasic and not very reactive. Lithium enolates are more like enolate anions: they are basic and reactive. Each is appropriate in different circumstances.
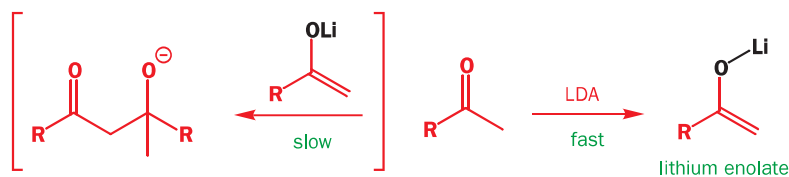
Lithium enolates in aldol reactions

Lithium enolates are usually made at low temperature in THF with a hindered lithium amide base (often LDA) and are stable under those conditions because of the strong O–Li bond. The formation of the enolate begins with Li–O bond formation before the removal of the proton from the α position by the basic nitrogen atom.
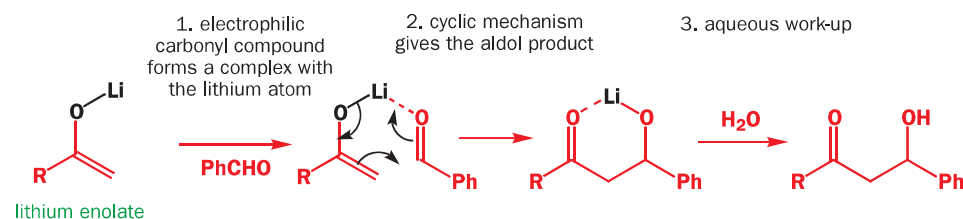
This reaction happens very quickly—so quickly that the partly formed enolate does not have a chance to react with unenolized carbonyl compound before proton removal is complete.

Now, if a second carbonyl compound is added, it too complexes with the same lithium atom. This allows the aldol reaction to take place by a cyclic mechanism in the coordination sphere of the lithium atom.

aldol reaction with a lithium enolate

1. electrophilic carbonyl compound forms a complex with the lithium atom
2. cyclic mechanism gives the aldol product
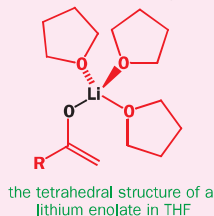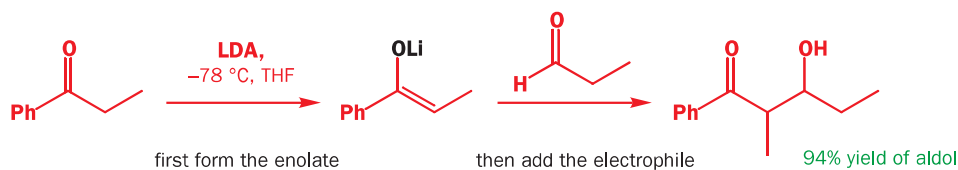3. aqueous work-up

The aldol step itself is now a very favourable intramolecular reaction with a six-membered cyclic transition state. The product is initially the lithium alkoxide of the aldol, which gives the aldol on work-up.

This reaction works well even if the electrophilic partner is an enolizable aldehyde. In this example, an unsymmetrical ketone (blocked on one side by an aromatic ring) as the enol partner reacts in excellent yield with a very enolizable aldehyde. This is the first complete aldol reaction we have shown you using a specific enol equivalent: notice the important point that it is done in two steps—first, form the specific enol equivalent (here, the lithium enolate); *then* add the electrophile. Contrast the crossed aldols earlier in the chapter, where enolizable component, base, and electrophile were all mixed together in one step.

LDA [*i*-Pr₂NLi]
−78 °C, THF

carbonyl compound → lithium enolate

■ The formation of lithium enolates was discussed in Chapter 26.

▶ Aldehydes are an exception. You can make lithium enolates from some aldehydes such as *i*-PrCHO, but generally self-condensation is too fast, so unwanted aldol self-condensation products are produced during the formation of the lithium enolate. To make specific enolates of aldehydes we need to use another type of derivative: see later.

▶ There are four coordination sites on the lithium atom—those we do not show are occupied by THF molecules. Before the aldol reaction can take place, one of the THFs must be displaced by the electrophilic carbonyl partner.

the tetrahedral structure of a lithium enolate in THF

first form the enolate   then add the electrophile   94% yield of aldol

The next example is particularly impressive. The enol partner is a symmetrical ketone that is very hindered—there is only one α hydrogen on either side. The electrophilic partner is a conjugated enal that is not enolizable but that might accept the nucleophile in a conjugate manner. In spite of these potential problems, the reaction goes in excellent yield.

> Because of the six-membered ring mechanism for the addition, lithium enolates don't usually do conjugate additions. For enol equivalents that do, see Chapter 29.

first form the enolate   then add the electrophile   82% yield of aldol

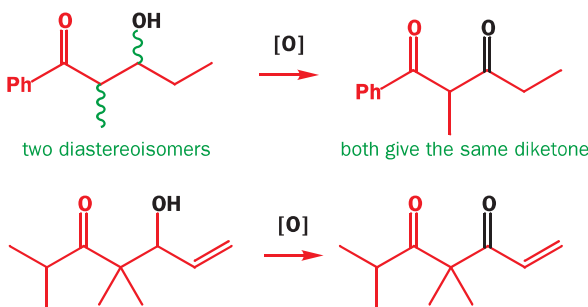You may wonder why we did not mention the stereochemistry of the first of these two products. Two new stereogenic centres are formed and the product is a mixture of diastereoisomers. In fact, both of these products were wanted for oxidation to the 1,3-diketone so the stereochemistry is irrelevant. This sequence shows that the aldol reaction can be used to make diketones too.


two diastereoisomers   both give the same diketone

> The symbol [O] denotes oxidation by one of the very general but ill-defined oxidizing agents from the laboratory of the famous Welsh chemist Owen Bracketts. Here the or Swern reagents were the best (see Chapter 24).

## Silyl enol ethers in aldol reactions

The silyl enol ether can be prepared from its parent carbonyl compound by forming a small equilibrium concentration of enolate ion with weak base such as a tertiary amine and trapping the enolate with the very efficient oxygen electrophile Me$_3$SiCl. The silyl enol ether is stable enough to be isolated but is usually used immediately without storing.

You should look upon silyl enol ethers as rather reactive alkenes that combine with things like protons or bromine (Chapter 21) but do not react with aldehydes and ketones without catalysis: they are much less reactive than lithium enolates. As with alkylation (p. 000), a Lewis acid catalyst is needed to get the aldol reaction to work, and a Ti(IV) compound such as TiCl$_4$ is the most popular.

carbonyl compound   silyl enol ether

silyl ether of aldol   aldol
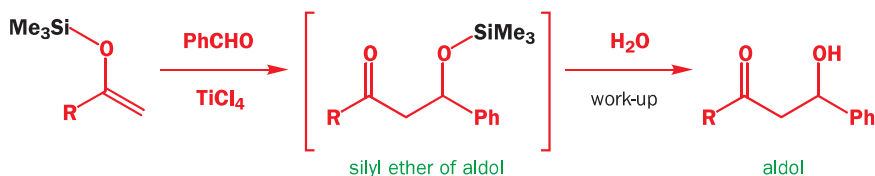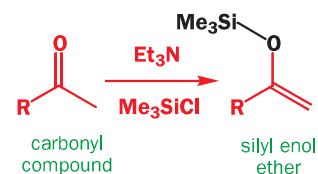
The immediate product is actually the silyl ether of the aldol but this is hydrolysed during work-up and the aldol is formed in good yield. The Lewis acid presumably bonds to the carbonyl oxygen atom of the electrophile.

Now the aldol reaction can occur: the positive charge on the titanium-complexed carbonyl oxygen atom makes the aldehyde reactive enough to be attacked even by the not very nucleophilic silyl enol ether. Chloride ion removes the silyl group and the titanium alkoxide captures it again. This last step should not surprise you as any alkoxide (MeOLi for example) will react with Me$_3$SiCl to form a silyl ether.

Lewis acid binds to the carbonyl oxygen atom
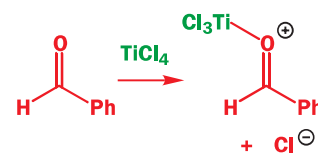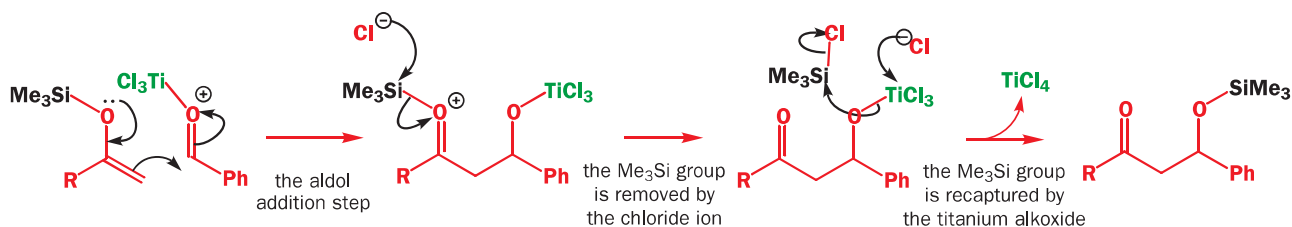
This mechanism looks complicated, and it is. It is, in fact, not clear that the details of what we have written here are right: the titanium may well coordinate to *both* oxygens through the reaction, and some of the steps that we have represented separately probably happen simultaneously. However, all reasonable mechanisms will agree on two important points, which you must understand:

- Lewis acid is needed to get silyl enol ethers to react
- The key step is an aldol attack of the silyl enol ether with the Lewis-acid complexed electrophile

The use of silyl enol ethers can be illustrated in a synthesis of manicone, a conjugated enone that ants use to leave a trail to a food source. It can be made by an aldol reaction between the pentan-3-one (as the enol component) and 2-methylbutanal (as the electrophile). Both partners are enolizable so we shall need to form a specific enol equivalent from the ketone. The silyl enol ether works well.


92% yield of aldol   83% yield of manicone
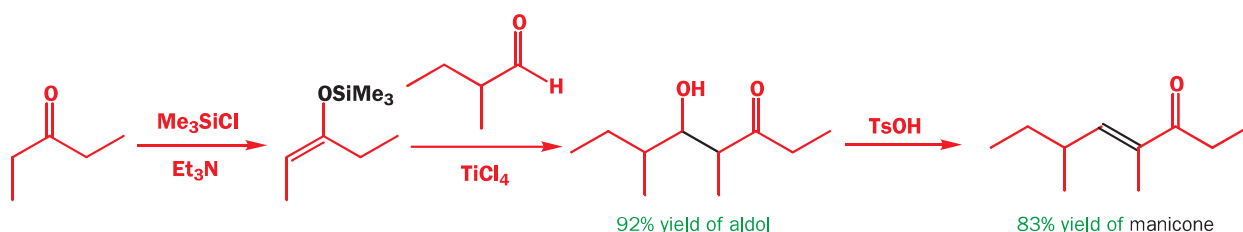
The silyl enol ether is not isolated but reacted immediately with the aldehyde to give an excellent yield of the aldol. Dehydration in acid solution with toluene sulfonic acid (TsOH) gives the enone. You can see by the high yield in the aldol reaction that there is no significant self-condensation of either partner in the aldol reaction.

Conjugated Wittig reagents as specific enol equivalents

When the Wittig reaction was introduced (Chapter 14) we saw it simply as an alkene synthesis. Now if we look at one group of Wittig reagents, those derived from α-halo-carbonyl compounds, we can see that they behave as specific enol equivalents in making unsaturated carbonyl compounds.

α-halo carbonyl   phosphonium salt   ylid, or enolate
compound
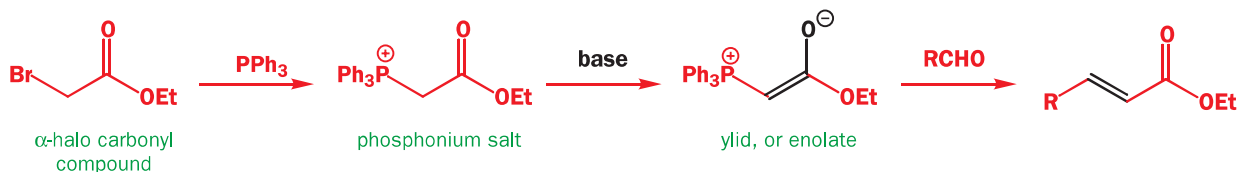
You notice that we have drawn the intermediate ylid as an enolate just to emphasize that it is an enolate derivative: it can also be represented either as the ylid or as a C=P 'phosphorane' structure. If we look at the details of this sort of Wittig reaction, we shall see that ylid formation is like enolate anion formation (indeed it *is* enolate anion formation). Only a weak base is needed as the enolate is stabilized by the Ph_3P^+ group as well.

ylid drawn as enolate   conventional ylid   phosphorane structure
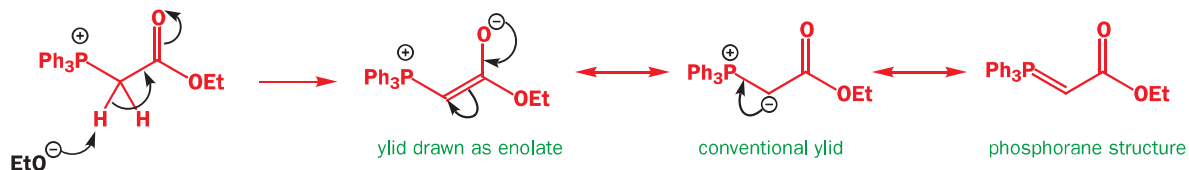
The first step of the Wittig reaction proper is just like an aldol reaction as it consists of an enolate attacking an electrophilic carbonyl compound. But, instead of forming an 'aldol' product, this adduct goes on to form an unsaturated carbonyl compound directly.
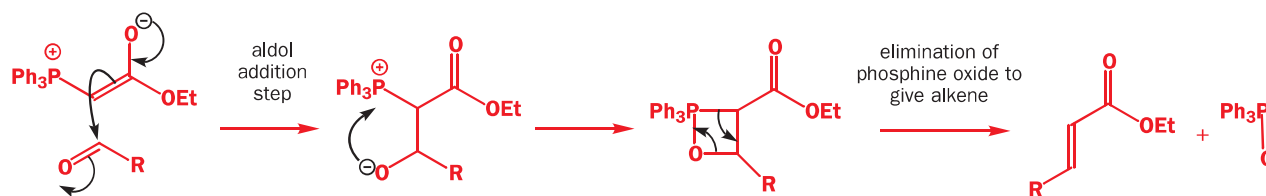
The final stages follow the mechanism of the Wittig reaction you met in Chapter 14: you see them as a special case of dehydration made favourable by the formation of a phosphine oxide as well as an unsaturated carbonyl compound.

The conjugated ylides derived from aldehydes, ketones, and esters are all sufficiently stable to be commercially available as the ylids—one of the few examples of specific enol equivalents that you can actually buy. The ylid corresponding to the enolate of acetaldehyde is a solid, m.p. 185–188 °C that reacts well with other aldehydes, even if they are enolizable.

solid, m.p. 185–188 °C
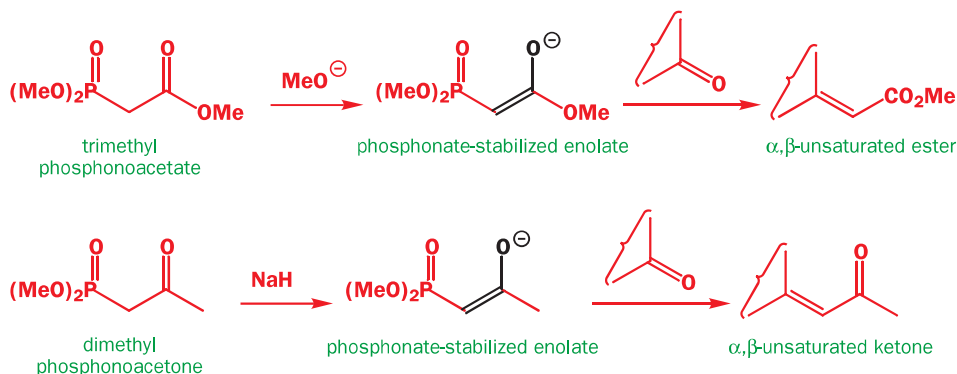commercially available

enolizable aldehyde
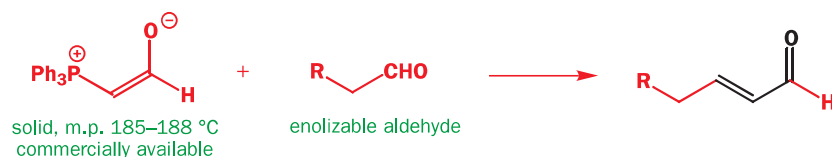
The Wittig equivalent of an aldol reaction with a ketone enolate can be illustrated by the synthesis of a compound in juniper berries, junionone, with a four-membered ring.

junionone
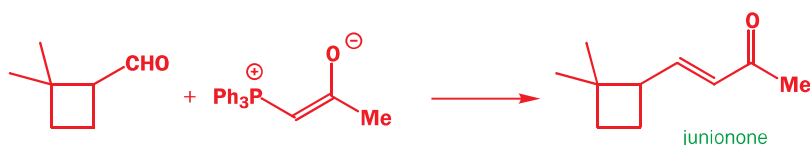
No base was needed in either of the last two examples: the stable ylid itself was used as a reagent. The stability of the enolate ylid means that the Wittig reagent must act as the enol partner and the other compound as the electrophile.

The stability of the phosphonium-stabilized enolates also means that, although they react well with aldehydes, their reactions with ketones are often poor, and it is better in these cases to use phosphonate-stabilized enolates. Being anionic, rather than neutral, these are more reactive. If an ester enolate equivalent is being used, the best base is the alkoxide ion belonging to the ester; with a ketone enolate equivalent, use sodium hydride or an alkoxide.

trimethyl
phosphonoacetate

phosphonate-stabilized enolate

α,β-unsaturated ester

dimethyl
phosphonoacetone

phosphonate-stabilized enolate

α,β-unsaturated ketone

These last reagents, where the anion is stabilized both by the adjacent carbonyl group (as an enolate) and by the adjacent P=O group, are just one of many examples of enolate anions stabilized by

We haven't yet considered in detail the geometry of the double bonds arising from aldol condensations. Those that are E1 or E1cB eliminations give mainly the more stable *E*-alkene products for the reasons described in Chapter 19. These Wittig variants are usually highly *E*-selective: we shall consider why in Chapter 31, where we deal with the question of how to control double bond geometry.
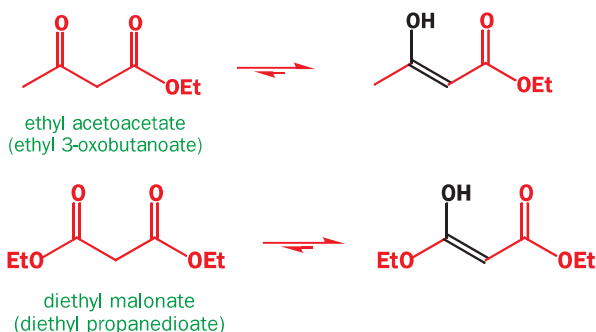
The 'brace' device here is commonly used rather like 'R'—it means that the rest of the molecule is unimportant to the reaction in question and could be anything.
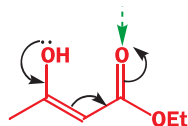
two electron-withdrawing groups. The most important members of this class, enolates of 1,3-dicarbonyl compounds, are the subject of the next section.

Specific enol equivalents from 1,3-dicarbonyl compounds

Though these are the oldest of the specific enol equivalents, they are still widely used because they need no special conditions—no low temperatures or strictly anhydrous solvents. The two most important are derived from malonic acid and ethyl acetoacetate.
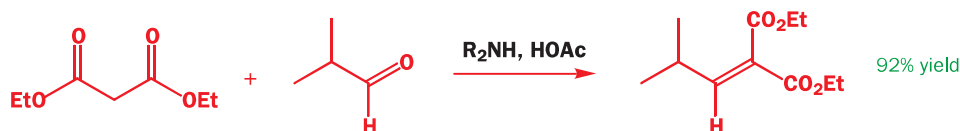
These compounds are largely enolized under normal conditions. So, you might ask, why don't they immediately react with themselves by the aldol reaction? There are two aspects to the answer. First, the enols are very stable (see Chapter 21 for a full discussion) and, secondly, the carbonyl groups in the unenolized fraction of the sample are poorly electrophilic ester and ketone groups. The second carbonyl group of the enol is not electrophilic because of conjugation.

When a normal carbonyl compound is treated with catalytic acid or base, we have a small proportion of reactive enol or enolate in the presence of large amounts of unenolized electrophile. Aldol reaction (self-condensation) occurs. With 1,3-dicarbonyl compounds we have a small proportion of not particularly reactive unenolized compound in the presence of large amounts of stable (and hence unreactive) enol. No aldol occurs.

If we want a **crossed aldol reaction**, we simply add a second, electrophilic carbonyl compound such as an aldehyde, along with a weak acid or base. Often a mixture of a secondary amine and a carboxylic acid is used.

electrons are fed into this carbonyl group making it less electrophilic

▶

Tautomers are isomers related to one another by tautomerism: see Chapter 21, p. 000.

Reaction no doubt occurs via the enolate ion generated by the amine while the carboxylic acid buffers the solution, neutralizing the product, and preventing enolization of the aldehyde. The amine (pK_{aH} about 10) is a strong enough base to form a significant concentration of enolate from the 1,3-dicarbonyl compound (pK_a about 13) but not strong enough to form the enolate from the aldehyde (pK_a about 20). The formation of the enolate can be drawn from either tautomer of the malonate.
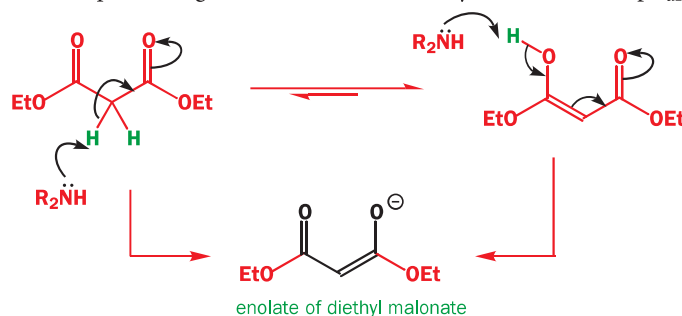
Now the enolate ion can attack the aldehyde in the usual way, and the buffer action of the acid produces the aldol in the reaction mixture.

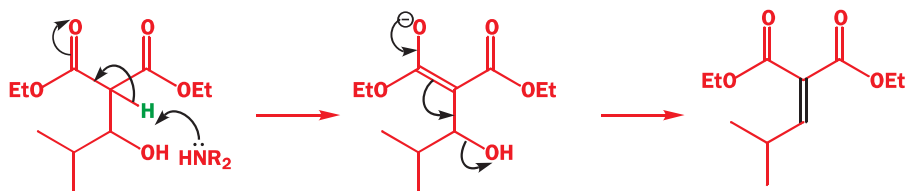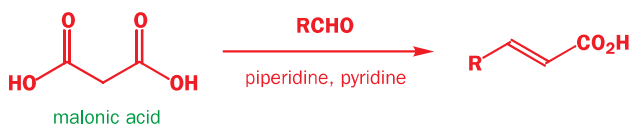There is still one proton between the two carbonyl groups so enolate anion formation is again easy and dehydration follows to give the unsaturated product.


You may not want a product with both ester groups present, and we discussed in Chapter 26 how one of two 1,3-related ester groups may be removed by hydrolysis and decarboxylation. There is a simpler route with the aldol reaction. If, instead of the malonate diester, malonic *acid* is used, the decarboxylation occurs spontaneously during the reaction. The catalysts this time are usually a more basic mixture of piperidine and pyridine.
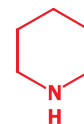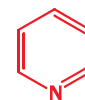
The reaction under these conditions is sometimes called the **Knoevenagel reaction** after its nineteenth century inventor, and presumably uses the enolate anion of the monocarboxylate of the malonic acid. Though this enolate is a dianion, its extensive delocalization and the intramolecular hydrogen bond make it really quite stable.
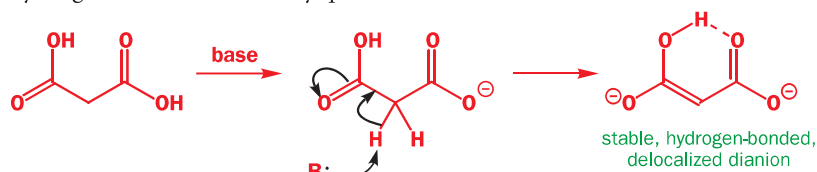
Next comes the aldol step. The dianion attacks the aldehyde, and after proton exchange the aldol is formed (still as the monocarboxylate in this basic solution).
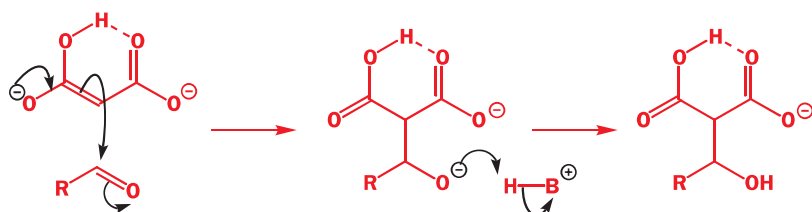
Finally comes the decarboxylation step, which can occur though a cyclic mechanism (compare the decarboxylation mechanisms in Chapter 26). The decarboxylation could give either *E* or *Z* double bond depending on which acid group is lost as CO_2, but the transition state leading to the more stable *E* product must be lower in energy since the product has *E* geometry.
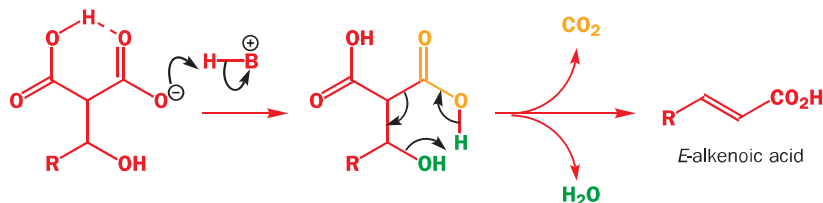
● We have now completed our survey of the most important types of aldol reaction and of the varieties of specific enol equivalents available. We shall now move on to look at carbonyl compounds type by type, and consider the best options for making specific enol equivalents of each.

Specific enol equivalents for carboxylic acid derivatives

electrophilic reactivity for X =
Cl > OCOR > OR > NR$_2$
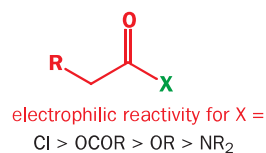
We established in Chapter 12 a hierarchy for the electrophilic reactivity of acid derivatives that should by now be very familiar to you—acyl chlorides at the top to amides at the bottom. But what about the reactivity of these same derivatives towards enolization at the α position, that is, the CH$_2$ group between R and the carbonyl group in the various structures? You might by now be able to work this out. The principle is based on the mechanisms for the two processes.

mechanism of nucleophilic attack

mechanism of enolate formation

See how similar these two mechanisms are. In particular, they are the same at the carbonyl group itself. Electrons move into the C=O π* orbital: the C=O bond becomes a C–O single bond as a negative charge develops on the oxygen atom. It should come as no surprise that *the order of reactivity for enolization is the same as the order of reactivity towards nucleophilic attack.*

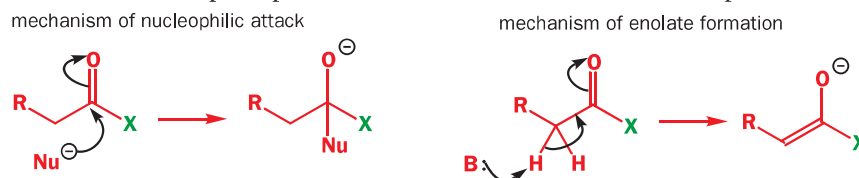**Enolate formation and electrophilic reactivity of acid derivatives**

Electrophilic reactivity	Derivative	Structure	Reactivity towards *enolate* formation
very high	acid chloride		very high
high	anhydride		high
low	ester		low
very low	amide		very low

In Chapter 21 we established that enolates can be formed from acid chlorides, but that they decompose to ketenes. Enolates can be formed from amides with difficulty, but with primary or secondary amides one of the NH protons is likely to be removed instead.

For the remainder of this section we shall look at how to make specific enol equivalents of the remaining carboxylic acid derivatives.

Enols and enolates from acid anhydrides

Enols or enolates from anhydrides are not used very often in aldol reactions other than in one important application, usually known as the **Perkin reaction**. An acid anhydride, such as acetic anhydride, is combined with a non-enolizable aldehyde and a weak base, usually the salt of the acid. This base is used so that nucleophilic attack on the anhydride does no harm, simply regenerating the anhydride.
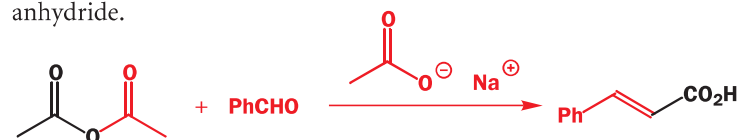
■
The fact that the anhydride is enolized by such a weak base lends weight to our argument that acid chlorides and anhydrides are the most enolizable of acid derivatives.

The low equilibrium concentration of the enolate attacks the aldehyde.
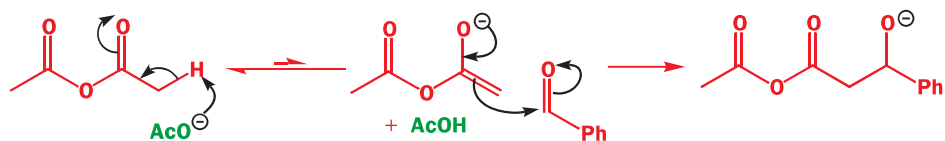
Thus far the reaction is a normal aldol reaction, but now something quite different happens. Six atoms along the molecule from the alkoxide ion is the carbonyl group of an anhydride. An intramolecular acylation is inevitable, given that anhydrides acylate alcohols even if the two groups are in different molecules.

carboxylate is the best leaving group
from this tetrahedral intermediate

Next, acetic acid is lost. Just as acetate is a better leaving group than hydroxide, this step is much more favourable than the usual dehydration at the end of an aldol condensation. Elimination of acetic acid may occur either from the carboxylic acid itself or from the mixed anhydride formed from one more molecule of the acetic anhydride. Whichever route is followed, the unsaturated acid is formed in a single step with the anhydride assisting both the aldol and the dehydration steps.
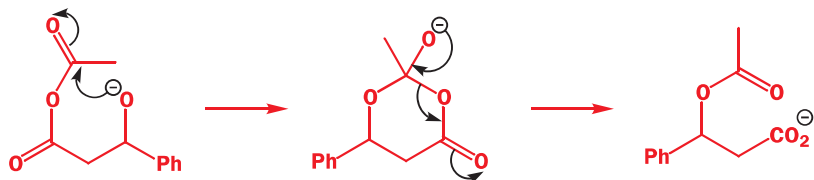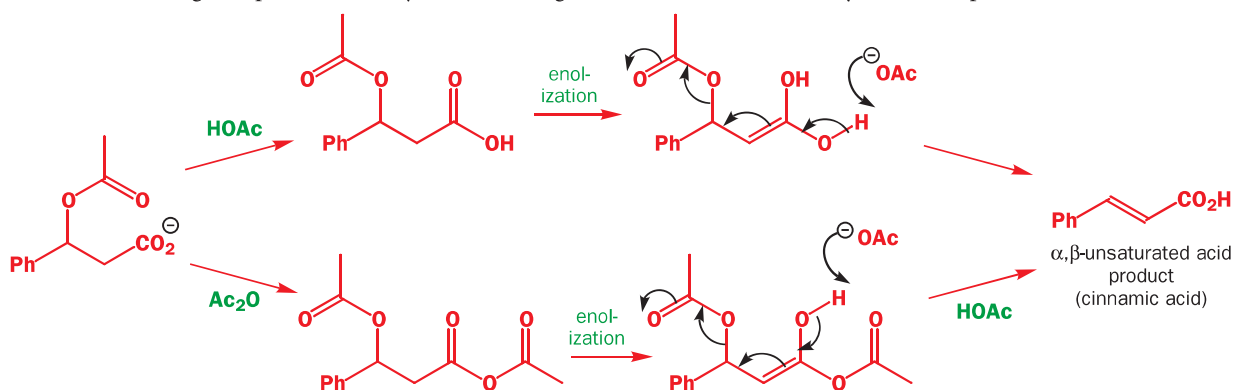

α,β-unsaturated acid
product
(cinnamic acid)

Enols and enolates from esters

Among the enolates of carboxylic acid derivatives, esters are the most widely used. Ester enolates cannot be used in crossed aldols with aldehydes because the aldehyde is both more enolizable and more electrophilic than the ester. It will just condense with itself and ignore the ester. The same is true for ketones. A specific enol equivalent for the ester will therefore be needed for a successful ester aldol reaction.

Fortunately, because this is a classic problem, many solutions are available. You can use the lithium enolate, or the silyl enol ether, usually made best via the lithium enolate.
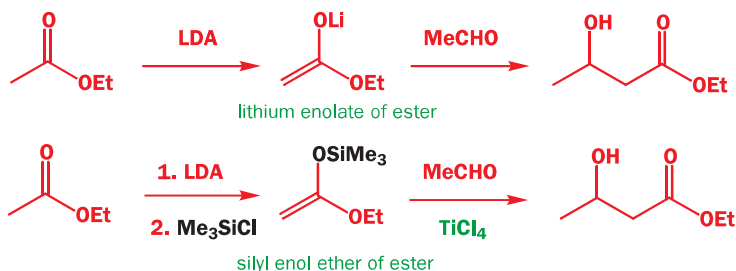
■ We have already discussed the special examples of malonate and phosphonoacetate esters. Now we need to consider ester enolates more generally.

▶ Forgive the reminder that a Lewis acid is necessary with silyl enol ethers.

lithium enolate of ester

silyl enol ether of ester

cyclic mechanism for ester
aldol reaction

A good example is the first step in a synthesis of the natural product himalchene by Oppolzer and Snowden. Even though the ester and the aldehyde are both crowded with substituents, the aldol reaction works well with the lithium enolate of the ester. The cyclic mechanism ensures that the enolate adds directly to the carbonyl group of the aldehyde and not in a conjugate (Michael) fashion.

Zinc enolates, made from the bromoesters, are a good alternative to lithium enolates of esters. The mechanism for zinc enolate formation should remind you of the formation of a Grignard reagent.

► Zinc, like magnesium, is a two-electron donor and likes to be oxidized from Zn(0) to Zn(II). This enolate is often called the **Reformatsky reagent** after its inventor, which is fine, and often drawn as a C–Zn compound, which is not fine because it isn't one.

bad structure

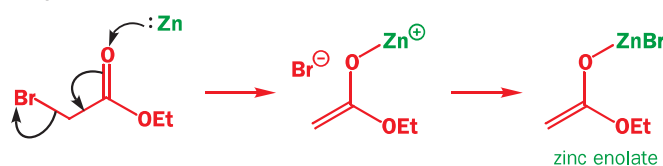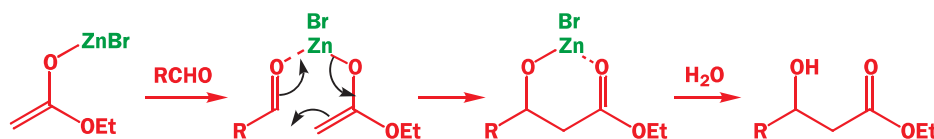There is no danger of self-condensation with zinc enolates as they do not react with esters. But they do react cleanly with aldehydes and ketones to give aldols on work-up. You will appreciate that the use of zinc enolates is therefore special to esters: you cannot make a zinc enolate from a 2-bromoaldehyde or an α-bromoketone as then you *would* get self-condensation.

► The dehydration product from this aldol product is best made directly by one of the Wittig variants we discussed earlier. The same bromoester is of course the starting material for the ylid synthesis.

● **Ester enolate equivalents**

For aldol reactions with an ester enolate equivalent, use
- lithium enolates *or*
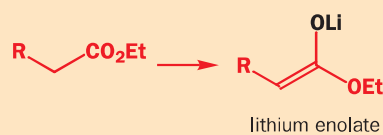
- silyl enol ethers *or*
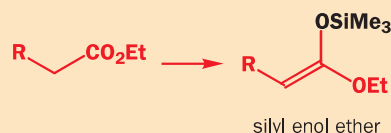
- zinc enolates
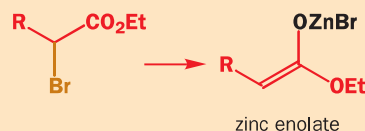
Enols and enolates from free carboxylic acids

You might think that the presence of the acidic proton in a carboxylic acid would present an insuperable barrier to the formation and use of any enol derivatives. In fact, this is not a problem with either the lithium enolates or the silyl enol ethers. Addition of BuLi or LDA to a carboxylic acid

immediately results in the removal of the acidic proton and the formation of the lithium salt of the carboxylic acid. If BuLi is used, the next step is addition of BuLi to the carbonyl group and the eventual formation of a ketone (see Chapter 12, p. 000). But, if LDA is used, it is possible to form the lithium enolate of the lithium derivative of the carboxylic acid.
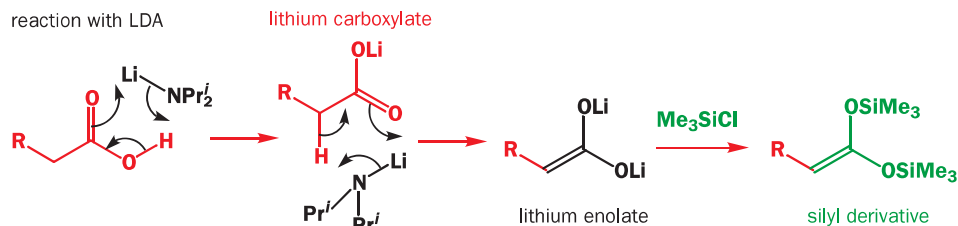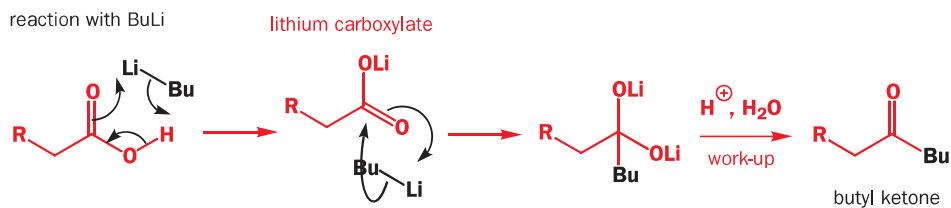
The enolate derivative is rather strange as it has two OLi groups on the same double bond, but it can be cleanly converted to the corresponding silyl enol ether. Both lithium enolates and silyl enol ethers from acids can be used in aldol reactions.

Ketene acetals

Because these compounds have two identical OR groups joined to the same end of the same double bond, you will see them called 'ketene acetals' or, here, 'silyl ketene acetals'. This is a reasonable description as you can

imagine the carbonyl group of a ketene forming an acetal in the same way as an aldehyde. In fact, they cannot be made this way.
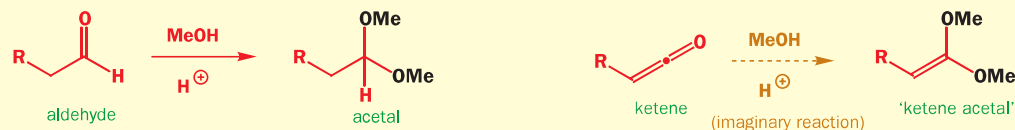
Specific enol equivalents for aldehydes

Aldehydes enolize very readily but also self-condense rather easily. Lithium enolates can't be made cleanly, because the self-condensation reaction happens even at −78 °C and is as fast as the enolization by LDA. Silyl enol ethers are a much better choice. They clearly must not be made via the lithium enolate, and amine bases are usually used. As each molecule of enolate is produced in the equilibrium, it is efficiently trapped by the silylating agent.

weak base used with aldehyde · low concentration of enolate · efficient trapping by oxygen-loving silicon electrophile
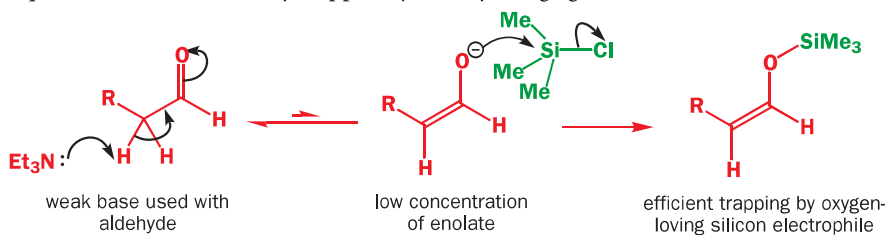
These silyl enol ethers are probably the best way of carrying out crossed aldol reactions with an aldehyde as the enol partner. An example is the reaction of the enol of the not very enolizable isobutyraldehyde with the very enolizable 3-phenylpropanal. Mixing the two aldehydes and adding base would of course lead to an orgy of self-condensation and cross-couplings.

Preliminary formation of the silyl enol ether from either aldehyde, *in the absence of the other*, would be trouble-free as Me₃SiCl captures the enolate faster than self-condensation occurs. Here we

isobutyraldehyde   3-phenylpropanal

acid or base

mixture of self-condensation and cross-coupling products from both aldehydes
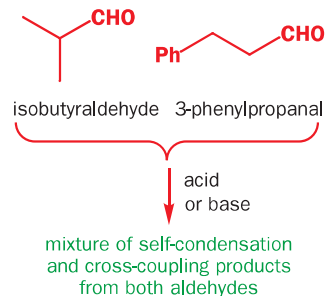
need the silyl enol ether from isobutyraldehyde. The other aldehyde is now added along with the necessary Lewis acid, here TiCl$_4$. The mechanism described on p. 000 gives the aldol after work-up in an excellent 95% yield. No more than 5% of other reactions can have occurred.
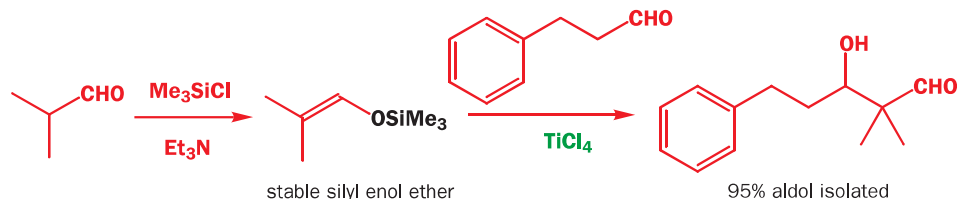
Other useful specific enol equivalents of aldehydes and ketones are enamines and aza-enolates, which you saw in use in alkylation reactions in Chapter 26. Aza-enolates—the lithium enolates of imines—derived from aldehydes are useful too in aldol reactions.

Cyclohexylamine gives a reasonably stable imine even with acetaldehyde and this can be isolated and lithiated with LDA to give the aza-enolate. The mechanism is similar to the formation of lithium enolates and the lithium atom binds the nitrogen atom of the aza-enolate, just as it binds the oxygen atom of an enolate.

▶
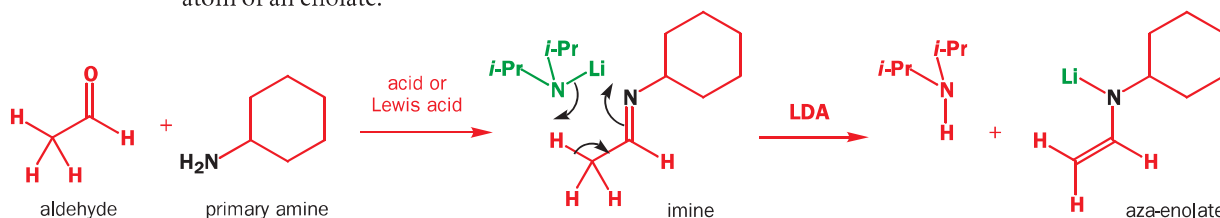
Imines are susceptible to hydrolysis and they are best not stored but used at once. To understand fully these reactions you should ensure you are familiar with the mechanisms of imine formation and hydrolysis from Chapter 14.

The aza-enolate reacts cleanly with other aldehydes or ketones to give aldol products. Even the most challenging of cross-couplings—attack on another similar enolizable aldehyde—occurs in good yield.
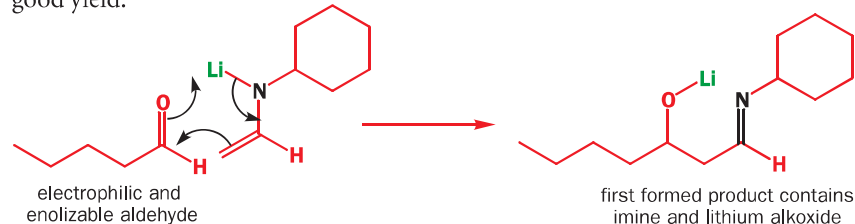
The initial product is a new imine, which is easily hydrolysed during acidic aqueous work-up. The alkoxide is protonated, the imine hydrolysed, and finally the aldol is dehydrated to give the enal—65% overall yield in this case.
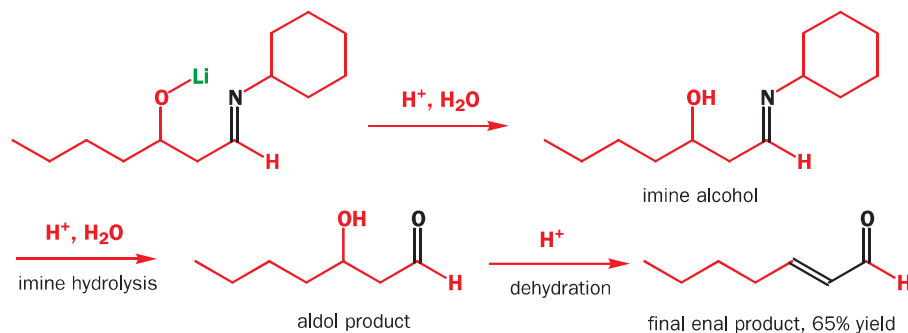
The key to the success of the aza-enolates is that the imine is first formed from the aldehyde with the primary amine, a relatively weak base, and under these conditions imine formation is faster than self-condensation. Only after the imine is formed is LDA added when self-condensation cannot occur simply because no aldehyde is left.

Enamines are not generally used in aldol condensations, partly because they are not reactive enough, but mainly because they are too much in equilibrium with the carbonyl compound itself and exchange would lead to self-condensation and the wrong cross-couplings. You will see in the next chapter that enamines come into their own when we want to acylate enols with the much more reactive acid chlorides.

> ● **For crossed aldol reactions with an aldehyde as the enol partner, use**
>
> - **silyl enol ethers** *or*
>
>
> silyl enol ether
>
> - **aza-enolates**
>
>
> aza-enolate

Specific enol equivalents for ketones

The enolization of ketones, unless they are symmetrical, poses a special problem. Not only do we need to prevent them self-condensing (though this is less of a problem than with aldehydes), but we also need to control which side of the carbonyl group the ketone enolizes. In this section we shall introduce aldol reactions with unsymmetrical ketones where one of two possible enols or enolates must be made.

Making the less substituted enolate equivalent: kinetic enolates
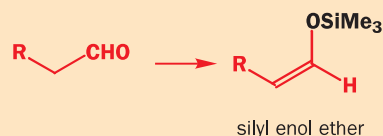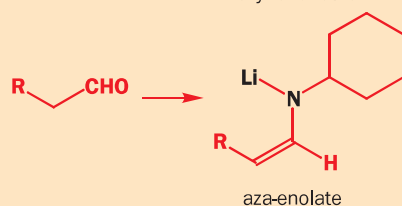
Treatment of methyl ketones with LDA usually gives only the lithium enolate on the methyl side. This is the enolate that forms the fastest, and is therefore known as the **kinetic enolate**. It is formed faster *because*:

■ Kinetic and thermodynamic enolates were introduced in Chapter 26, p. 000.

- the protons on the methyl group are more acidic
- there are three of them as against two on the other side, and
- there is steric hindrance to attack by LDA on the other side of the carbonyl group

methyl ketone   kinetic enolate: stable at −78 °C

A simple example from the first report of this reaction by Gilbert Stork and his group in 1974 is the condensation of pentan-2-one with butanal to give the aldol and then the enone oct-4-en-3-one by acid-catalysed dehydration. The yields may seem disappointing, but this was the first time anyone had carried out a crossed aldol reaction like this with an unsymmetrical ketone and an enolizable aldehyde and got just one aldol product in any reasonable yield at all.

■ Gilbert Stork was born in Brussels and became an assistant professor of chemistry at Harvard in 1948. Since 1953, Stork has been at Columbia University in New York. Since the 1950s, he has pioneered new synthetic methods, among them many involving enolates and enamines.

aldol, 65% yield   enone, 72% yield

An uncontrolled ketone aldol

A more typical result from the days before specific enol equivalents had been invented is this attempted crossed condensation between butanone and butanal with catalytic base. Two products were isolated in low yield.
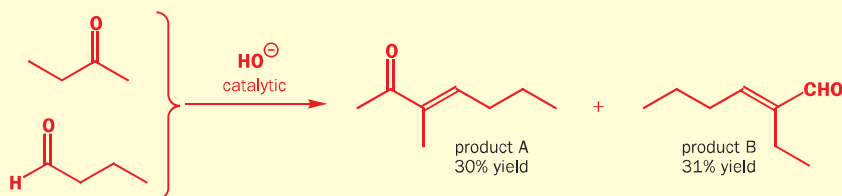
Product A is from the enolate of the more substituted side of the ketone reacting with the aldehyde, and product B is just the self-condensation product from the aldehyde.
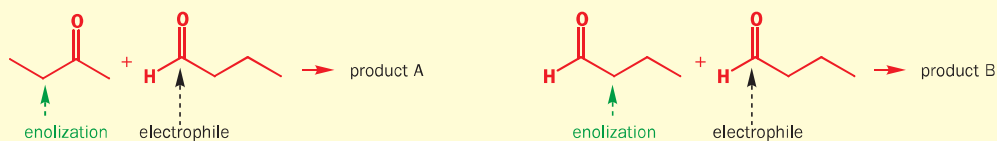
These kinetic lithium enolates are stable in THF at −78 °C for a short time but can be preserved at room temperature in the form of their silyl ethers.
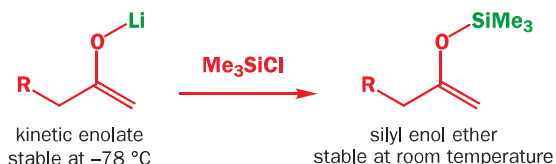
Aldol reactions can be carried out with either the lithium enolate or the silyl enol ether. As an example we shall use the synthesis of a component of the flavour of ginger. The hotness of ginger comes from 'gingerol'—the 'pungent principle' of ginger. Gingerol is a 3-hydroxyketone, so we might consider using an aldol reaction to make it. We shall need the enol (or enolate) on the methyl side of an unsymmetrical ketone to react with a simple aldehyde (pentanal) as the electrophilic partner in the aldol reaction. Pentanal is an enolizable aldehyde, so we must stop it enolizing. The diagram summarizes the proposed aldol reaction.
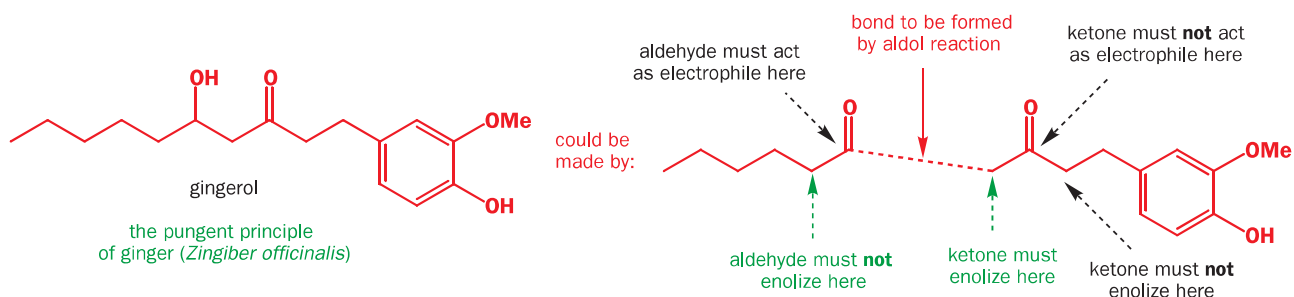
We might consider using the lithium enolate or the silyl enol ether. As we need the kinetic enolate (the enolate formed on the less substituted side of the ketone), we shall be using the lithium enolate to make the silyl enol ether, so it would make sense to try that first.

There is another problem too. The ketone has a free OH group on the far side of the ring that will interfere with the reaction. We must protect that first as an ordinary silyl ether (not a silyl *enol* ether).
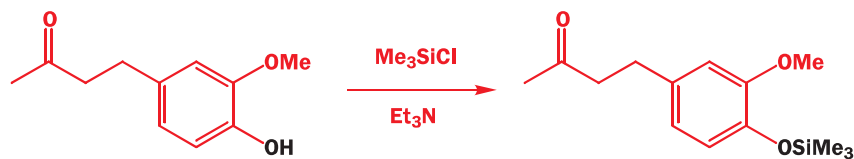
Now we can make the kinetic lithium enolate with a hindered lithium amide base. In fact, the one chosen here was even more hindered than LDA as it has two Me₃Si groups on the nitrogen atom.

kinetic lithium enolate
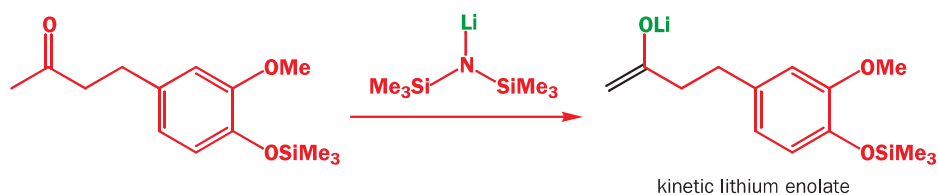
Lithium hexamethyldisilazide

Lithium hexamethyldisilazide (LiHMDS) is a little more hindered than LDA and a little less basic. It is made by deprotonating hexamethyldisilazane with BuLi.

hexamethyldisilazane

lithium hexamethyldisilazide (LiHMDS)
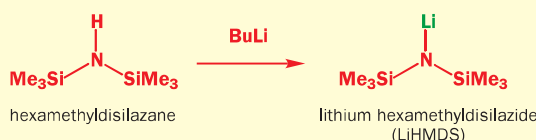
An aldol reaction with this lithium enolate on pentanal was successful and the protecting group (the silyl ether) conveniently fell off during work-up to give gingerol itself. However, the yield was only 57%. When the silyl enol ether was used with $TiCl_4$ as the Lewis acid catalyst, the yield jumped to 92%. This is one of the many successful uses of this style of aldol reaction by Mukaiyama, the inventor of the method.
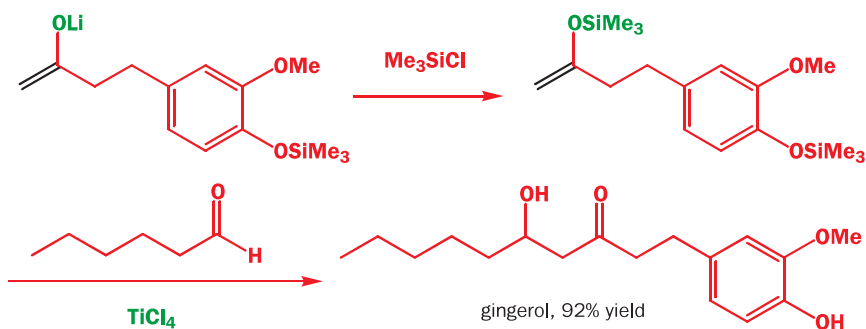
■ Teruaki Mukaiyama, of the Science University of Tokyo (and formerly of the Tokyo Institute of Technology and the University of Tokyo) is one of the foremost Japanese chemists, whose work has had a significant impact on the development of the aldol reaction and on other areas of organic synthesis.

gingerol, 92% yield

Making the more substituted enolate equivalent: thermodynamic enolates

Being an alkene, an enol or enolate is more stable if it has more substituents. So the way to make the more substituted enolate equivalent is to make it under conditions where the two enolates can interconvert: equilibration will give the more stable. You have seen in Chapter 26 (p. 000) how the silyl enol ether on the more substituted side of a ketone can be made by treating the ketone with Me_3SiCl and a weak base, but these thermodynamic silyl enol ethers have been little used in aldol reactions. One successful example is the thermodynamic silyl enol ether of 1-phenylpropan-2-one: enolization on the conjugated side is overwhelmingly favoured thermodynamically. The aldol reaction with a 2-keto-aldehyde goes exclusively for the more reactive aldehyde group.

1-phenylpropan-2-one

thermodynamic silyl enol ether

83% yield
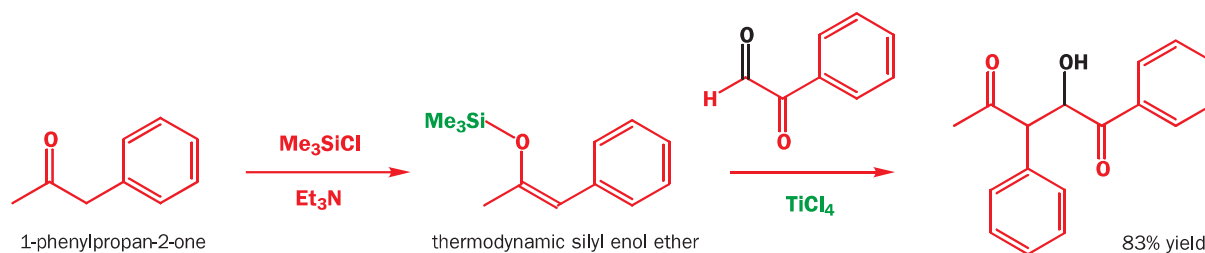
● Summary of the last four sections on specific enol equivalents.

Useful enolates for the aldol reaction

Enolate type	Aldehyde	Ketone	Ester	Acid
lithium enolate	×	✓	✓	✓
silyl enol ether	✓	✓	✓	✓
enamine	✓	✓	×	×
aza-enolate	✓	✓	×	×
zinc enolate	×	×	✓	×

This concludes our general survey of the aldol reaction. Two special topics remain, both important, one dealing with an awkward and difficult reagent and one with a collection of aldol reactions that are particularly easy to do.

The Mannich reaction

At first sight formaldehyde (methanal, $CH_2=O$) seems the ideal electrophilic partner in a mixed aldol reaction. It cannot enolize. (Usually we are concerned with α hydrogen atoms in an aldehyde. Formaldehyde does not even have α carbon atoms.) And it is a super aldehyde. Aldehydes are more electrophilic than ketones because a hydrogen atom replaces one of the alkyl groups. Formaldehyde has two hydrogen atoms.

The trouble is that it is too reactive. It tends to react more than once and to give extra unwanted reactions as well. You might think that condensation between acetaldehyde and formaldehyde in base would be quite simple. The acetaldehyde alone can form an enolate, and this enolate will attack the more electrophilic carbonyl group, which is formaldehyde, like this.

crossed aldol reaction between acetaldehyde and formaldehyde
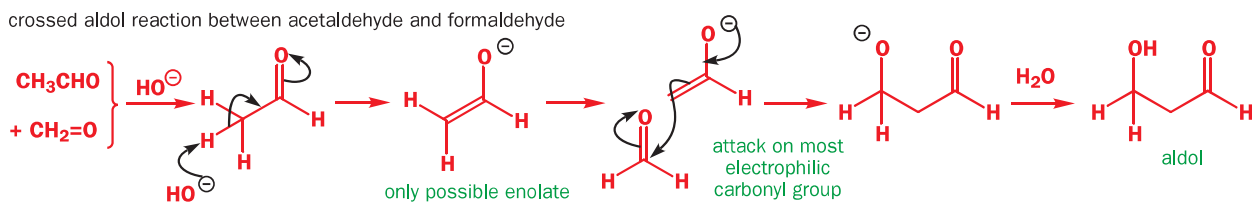
This aldol is formed all right but it is not the final product of the reaction because, with an electrophile as powerful as formaldehyde, a second and a third aldol follow swiftly on the heels of the first. Here is the mechanism of the second aldol.
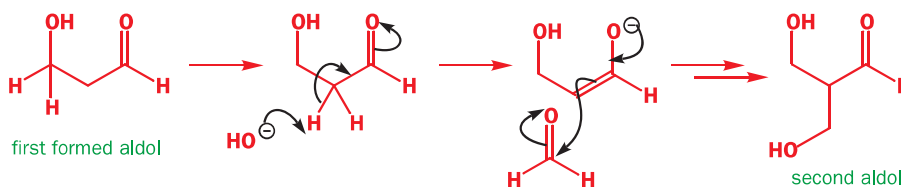
In each reaction the only possible enolate attacks another molecule of formaldehyde. By now you have got the idea so we simply draw the next enolate and the structure of the third aldol.
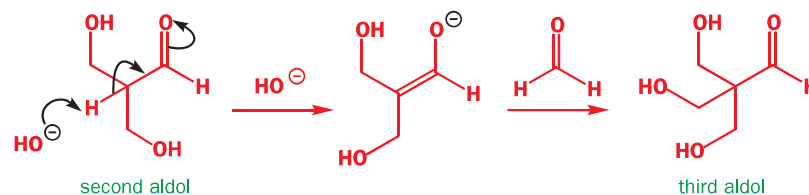
Even this is not all. A fourth molecule of formaldehyde reacts with hydroxide ion and then reduces the third aldol. This reduction is known as the **Cannizzaro reaction**, and is described in the box. The final product is the highly symmetrical 'pentaerythritol', $C(CH_2OH)_4$, with four CH_2OH groups joined in a tetrahedral array about the same carbon atom.

reduction by the Cannizzaro reaction

dianion formed by attack of hydroxide on formaldehyde: see box for details

formate ion
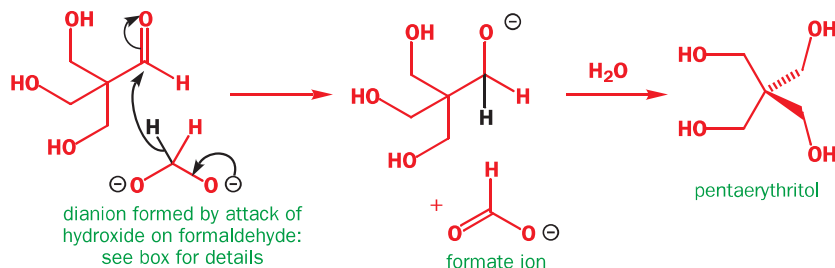
pentaerythritol

■ Pentaerythritol is a useful industrial product in, for example, the cross-linking of polymers: see Chapter 52.

The overall reaction uses four molecules of formaldehyde and can give a high yield (typically 80% with NaOH but as much as 90% with MgO) of the product.

The Cannizzaro reaction

As you know, aldehydes are generally at least partly hydrated in water. Hydration is catalysed by base, and we can represent the hydration step in base like this. The hydration product is an anion but, if the base is sufficiently strong (or concentrated) and as long as the aldehyde cannot be enolized, at least some will be present as a dianion.

hydration in base (hydroxide as nucleophile)

deprotonation of hydrate (hydroxide as base)

aldehyde   hydrate anion   hydrate dianion

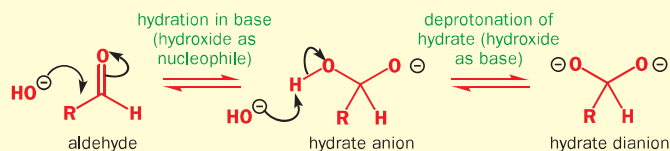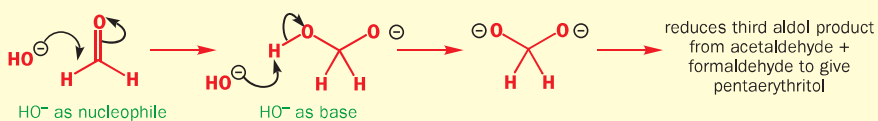The dianion is very unstable, and one way in which it can become much more stable is by behaving like a tetrahedral intermediate. Which is the best leaving group? Out of a choice of O^{2-}, R^-, and H^-, it's H^- that (if reluctantly) has to go. Hydride is, of course, too unstable to be released into solution but, if there is a suitable electrophile at hand (another molecule of aldehyde, for example), it is transferred to the electrophilic centre in a mechanism that bears some resemblance to a borohydride reduction.

hydride is least bad leaving group   carboxylate anion   alcohol   compare...
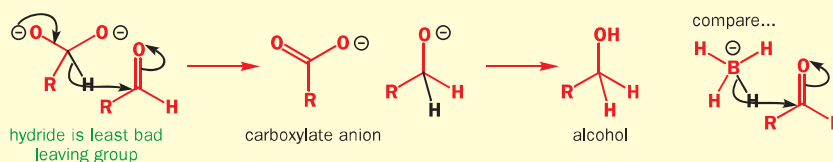
The dianion becomes a much more stable carboxylate monoanion, and a second molecule of aldehyde has been reduced to an alcohol. This is the Cannizzaro reaction: in this case it takes the form of a disproportionation of two molecules of aldehyde to one of carboxylate and one of alcohol.

HO^- as nucleophile HO^- as base   reduces third aldol product from acetaldehyde + formaldehyde to give pentaerythritol

In the pentaerythritol case, the dianion reducing agent is formed from formaldehyde: first hydroxide attacks it as a nucleophile, then as a base. The dianion transfers 'hydride' to a different aldehyde, the third aldol product, to

make pentaerythritol. The Cannizzaro reaction waits till this point because only after the third aldol does the aldehyde lose its ability to enolize, and the reaction works **only with unenolizable aldehydes.**

If you want a more controlled reaction with addition of formaldehyde to an aldehyde or ketone without the reduction step, you can sometimes succeed with a weaker base such as potassium carbonate. Typically in these reactions *all* the enolizable hydrogen atoms (green) are replaced by molecules of formaldehyde (black).
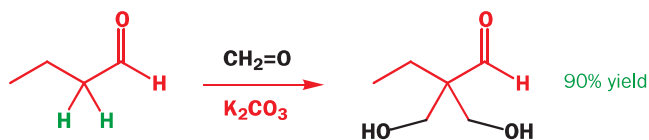
▶ Formaldehyde is not available as a pure monomer because it forms trimers and tetramers in the pure state (Chapter 52). The aqueous solution 'formalin' used to preserve biological specimens is available—it is 37% formaldehyde and mostly consists of the hydrate $CH_2(OH)_2$; see Chapter 6. A pure dry polymer 'paraformaldehyde' is also available and was mentioned in Chapter 9. Neither of these is particularly useful in aldol reactions. The aqueous solution is used in the Mannich reaction that we describe shortly. It is possible to make the short-lived monomer and capture it with a lithium enolate, but this is not trivial experimentally.

$CH_2=O$

K_2CO_3

90% yield

But a more general solution is to use the **Mannich reaction**. A typical example is shown here: the reaction involves an enolizable aldehyde or ketone (here we use cyclohexanone), a secondary amine (here dimethylamine), formaldehyde as its aqueous solution, and catalytic HCl. The product is an amino-ketone from the addition of one molecule each of formaldehyde and the amine to the ketone.

the Mannich reaction
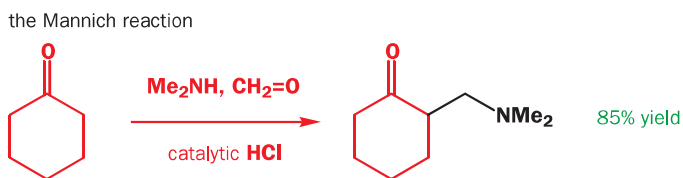
The mechanism involves the preliminary formation of an imine salt from the amine and formaldehyde. The amine is nucleophilic and attacks the more electrophilic of the two carbonyl compounds available. That is, of course, formaldehyde. No acid is needed for this addition step, but acid-catalysed dehydration of the addition product gives the imine salt. In the normal Mannich reaction, this is just an intermediate but it is quite stable and the corresponding iodide is sold as 'Eschenmoser's salt' for use in Mannich reactions.

nucleophilic attack on more
electrophilic C=O group

imine salt
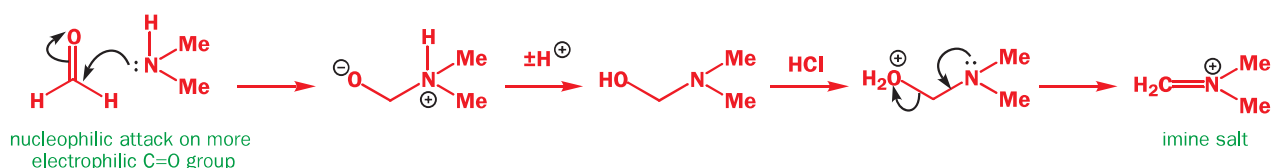
The electrophilic salt can now add to the enol (we are in acid solution) of the ketone to give the product of the reaction, an amine sometimes called a **Mannich base**.

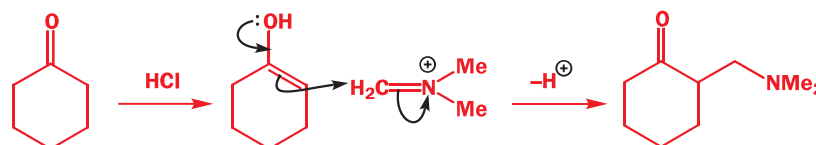By using this reaction, you can add one molecule of formaldehyde—one only—to carbonyl compounds. You might, of course, reasonably object that the product is not actually an aldol product at all—indeed, if you wanted the aldol product, the Mannich reaction would be of little use to you. It nevertheless remains a very important reaction. First of all, it is a simple way to make amino-ketones and many drug molecules belong to this class. Secondly, the Mannich products can be converted to enones. We will discuss this reaction next.

The most reliable method for making the enone is to alkylate the Mannich base with MeI and then treat the ammonium salt with base. Enolate ion formation leads to an E1cB reaction rather like the dehydration of aldols, but with a better leaving group.

1. alkylate amine to give ammonium salt   2. treat with base: E1cB elimination gives enone
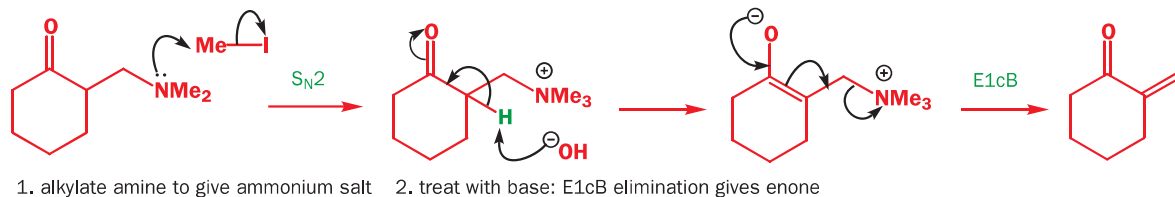
Enones like this, with two hydrogen atoms at the end of the double bond, are called **exo-methylene compounds**; they are very reactive, and cannot easily be made or stored. They certainly cannot be made by aldol reactions with formaldehyde alone as we have seen. The solution is to make the Mannich base, store that, and then to alkylate and eliminate only when the enone is needed. We shall see how useful this is in the Michael reaction in Chapter 29.
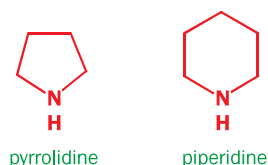
If the enone is wanted, the secondary amine does not end up in the molecule so the more convenient (less volatile and less smelly) cyclic amines, pyrrolidine and piperidine, are often used. Enones with monosubstituted double bonds can be made in this way.

pyrrolidine   piperidine
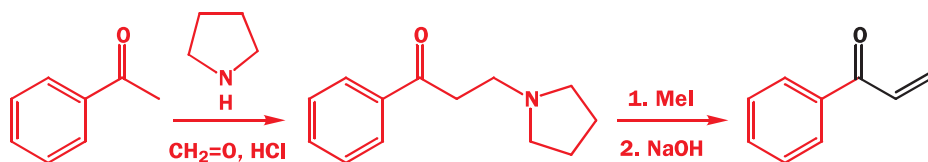
Intramolecular aldol reactions

Now for something easy. When an aldol reaction can form a five- or six-membered ring, you need no longer worry about specific enols or anything like that. Equilibrium methods with weak acids or bases are quite enough to give the cyclic product by an intramolecular aldol reaction because intramolecular reactions are faster than intermolecular ones. We shall illustrate intramolecular reactions by looking at the cyclization of a series of diketones of increasing complexity starting with one that can form four equivalent enols: cyclodeca-1,6-dione.

cyclodeca-1,6-dione:
four identical positions
for enolization (----▶)

It doesn't matter where enolization occurs, because the same enol is formed. And once the enol is formed, there is only one thing it can reasonably do: attack the other ketone to form a stable five-membered ring. It also gives a reasonably stable seven-membered ring, but that is by the way. In weak acid or base, only a small proportion of carbonyl groups will be enolized, so the chance of two being in the same molecule is very low. No intermolecular condensation is found and the yield of the bicyclic enone from the intramolecular reaction is almost 100% (96% with Na_2CO_3).
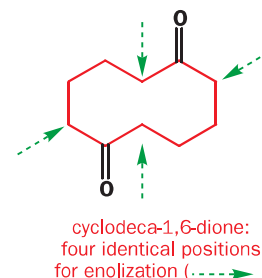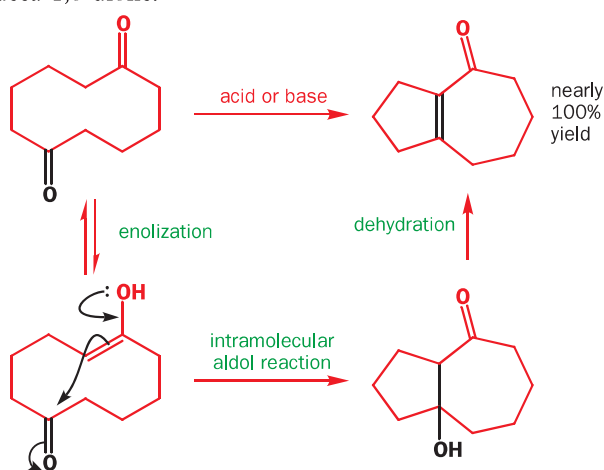
■ Ring size and stability were discussed in Chapter 18.

This may look like a long stretch for the enol to reach across the ten-membered ring to reach the other ketone, but the conformational drawing in the margin shows just how close they can be. You should compare this conformation with that of a decalin (Chapter 18).
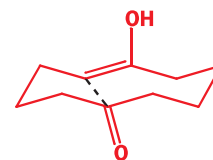
The key point to remember with intramolecular aldols is this.

● **Intramolecular reactions giving five- or six-membered rings are preferred to those giving strained three- or four-membered rings on the one hand or medium rings (eight- to thirteen-membered) on the other.**

Acid-catalysed cyclization of the symmetrical diketone nona-2,8-dione could give two enols.

nona-2,8-dione
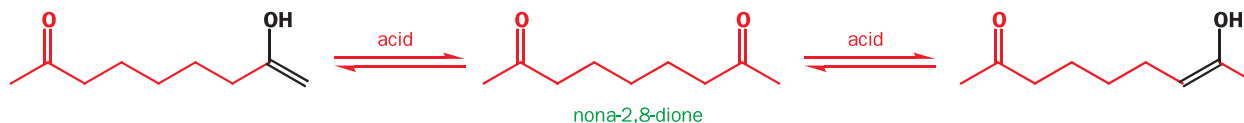
One enol can cyclize through an eight-membered cyclic transition state and the other through a six-membered ring. In each case the product would first be formed as an aldol but would dehydrate to the cyclic enone having the same ring size as the transition state. In practice, only the less strained six-membered ring is formed and the enone can be isolated in 85% yield.

eight-membered cyclic transition state

nona-2,8-dione

eight-membered ring product: not formed

six-membered cyclic transition state

six-membered ring product: 85% yield with H_2SO_4

four different positions where enolization is possible
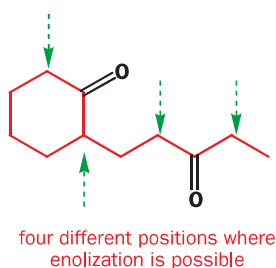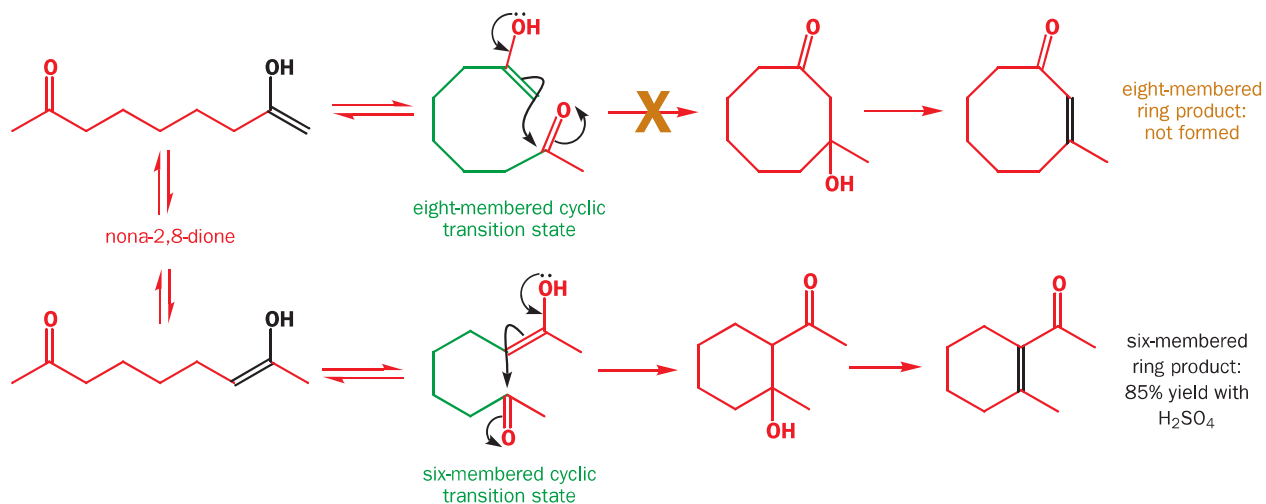
Most diketones lack symmetry, and will potentially have four different sites for enolization. Consider what might happen when this diketone is treated with KOH. There are four different places where an enolate anion might be formed as there are four different α carbon atoms. There are also two different electrophilic carbonyl groups so that there are many possibilities for inter- and intramolecular condensation. Yet only one product is formed, in 90% yield.

KOH

one product formed in 90% yield
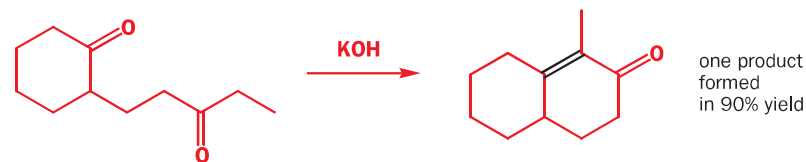
We can deduce the mechanism of the reaction simply from the structure of the product by working backwards. The double bond is formed from an aldol whose structure we can predict and hence we can see which enolate anion was formed and which ketone acted as the electrophilic partner.

this bond was formed

enolate anion was formed here

enone product ----- must be formed by dehydration ----- of this aldol ----- which must be formed by this enolate attacking the other ketone
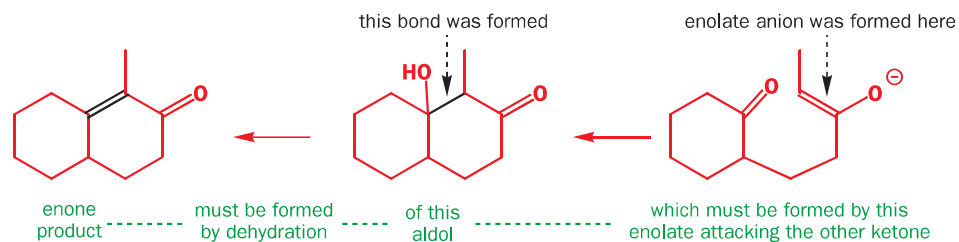
Must we argue that this one enolate is more easily formed than the other three? No, of course not. There is little difference between all four enolates and almost no difference between the three enolates from CH_2 groups. We *can* argue that this is the only aldol reaction that leads to a stable conjugated enone in a stable six-membered ring. This must be the mechanism; protonation and dehydration follow as usual.
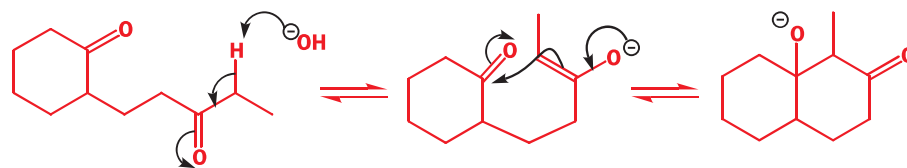
Now try one of the alternatives in which the same ketone forms an enolate on the other side.
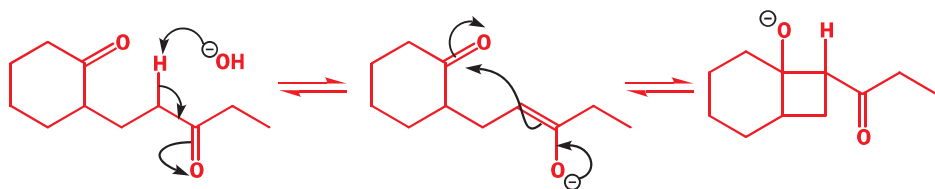
This reaction gives an unstable four-membered ring that would revert to the enolate. Providing the reaction is done under equilibrating conditions, the whole process would go into reverse back to the original diketone and the observed (six-membered ring) cyclization would eventually predominate. There is one alternative cyclization to give a six-membered ring and this does not occur for an interesting reason. Here is the reaction.
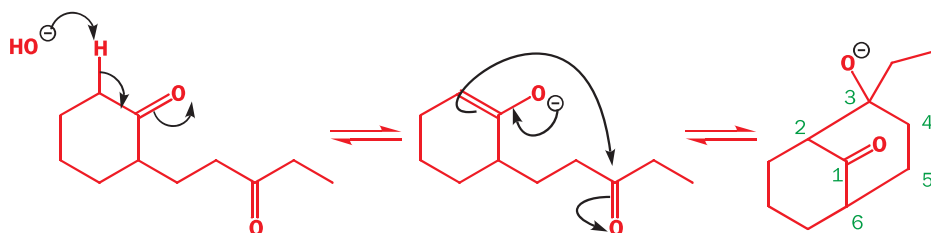
The new ring is a six-membered ring and we have numbered it to convince you. It is, of course, a rather strained bridged compound, but the key point is that dehydration is impossible. No enolate can form at the bridgehead, because bridgehead carbons cannot be planar (see Chapter 19) and the enone product cannot exist for the same reason: the carbons marked (•) in the brown structure would all have to lie in the same plane. The aldol has a perfectly acceptable conformation but that elimination is impossible. The aldol product remains in equilibrium with the alternative aldol products, but only one elimination is possible—and that is irreversible, so eventually all the material ends up as the one enone.

Even without the constraint of avoiding a bridgehead alkene, some completely unsymmetrical diketones give single products in high yield. Here are two related examples with similar structures.

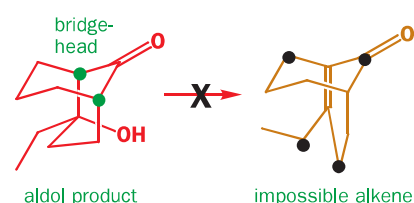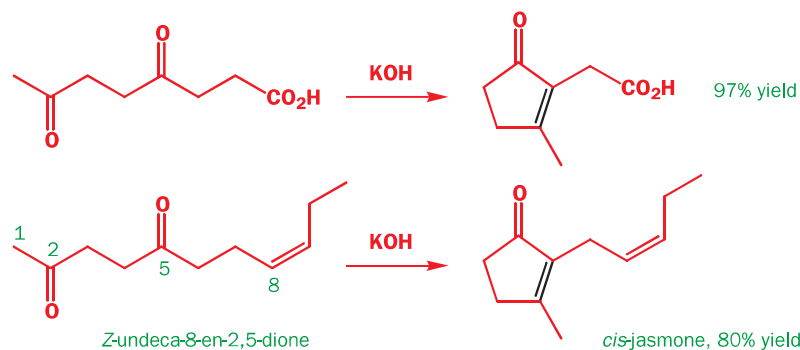The first of these is impressive for the high yield and the lack of interference by the carboxylic acid group. The second is important because the product is the perfumery compound *cis*-jasmone found naturally in jasmine flowers, and is formed in good yield with no change in the position or geometry of the *Z* double bond.

In these reactions there is some selectivity between two possible five-membered rings, both of which can easily dehydrate to give an enone. These are the alternatives, using a general structure where R might be CH_2CO_2H in the first or the unsaturated chain in the second example.

two alternative aldols both give five-membered rings

trisubstituted alkene

diketone

tetrasubstituted alkene
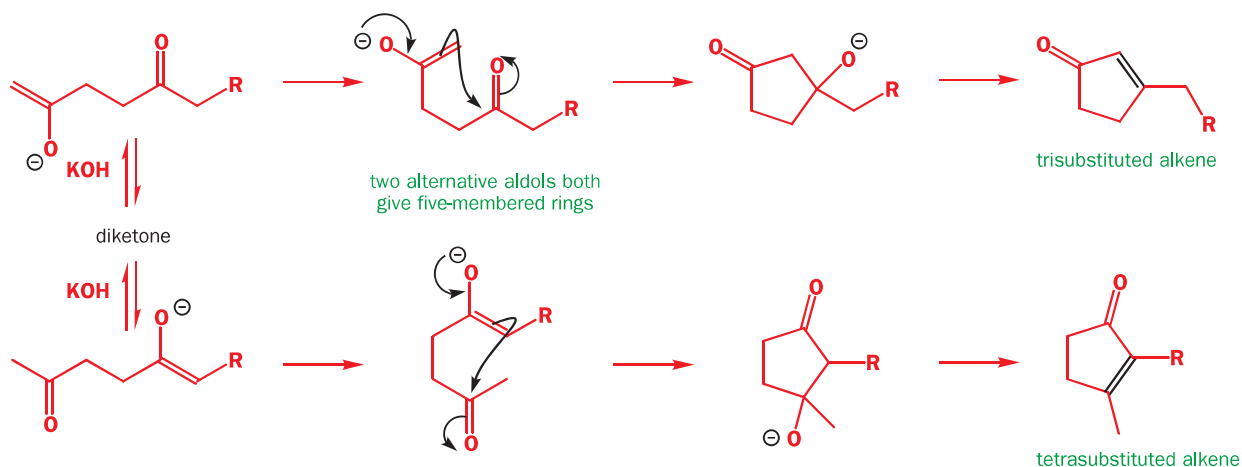
So far it is very difficult to see much difference between the two routes. Indeed, we might have argued that the upper route is better because enolization is faster at a methyl group. But this is wrong because the reaction is not under kinetic but rather under thermodynamic control. The two products differ by the number of substituents on the double bond, and the more substituents there are on a double bond, the more stable it is. This factor is discussed in Chapter 19. It is the only difference between these two products and it controls the reaction very effectively.

To conclude: a summary of equilibrium and directed aldol methods

As we leave this chapter, it is important to make sure that you understand the two different approaches to controlled aldol reactions that we have been considering. The two methods ensure in their different ways that only one carbonyl group gives only one enol or enolate as the nucleophilic partner in the aldol reaction while only one carbonyl compound acts as the electrophilic partner.

> ● **Equilibrium control**
>
> In the equilibrium method, the carbonyl compound(s) must be treated with weak, usually aqueous or alcoholic, acid or base and allowed to equilibrate with all possible enols or enolates. Either only one product is possible (due to symmetry or blocking of α positions) or some thermodynamic factor (such as the formation of a stable conjugated enone) ensures that the reaction goes down one preferred route.

In the equilibrium method, 'weak' acid or base means too weak to ensure complete conversion to enol or enolate. The method works only if enol and carbonyl compound are in equilibrium. Typical examples are shown in the table.

Types of aldol reaction under thermodynamic control

Type of reaction	Typical conditions	Example
self-condensation of aldehydes	2% NaOH aqueous ethanol	R–CHO (aldehyde) → R–CH=C(R)–CHO (enal)
self-condensation of ketones	HCl, Al(OR)$_3$, NaOH, or KOH	R–CO–CH$_3$ (ketone) → R–CO–CH=C(R)–CH$_3$ (enone)
cross-condensations of an enolizable ketone and a non-enolizable aldehyde	NaOH, KOH, Na$_2$CO$_3$, HCl, or H$_2$SO$_4$	cyclopentanone + ArCHO → 2-(arylmethylene)cyclopentanone (=CH–Ar)
cross-condensations of aryl methyl ketones and non-enolizable aldehydes	dilute HCl or NaOH	Ar^1–CO–CH$_3$ + Ar^{2}CHO → Ar^1–CO–CH=CH–Ar^2
cyclization reactions	2% NaOH aqueous ethanol, or HCl, or H$_2$SO$_4$	dialdehyde (CHO, CHO with X) → cyclohexene–CHO; X = C, O, N, S

Similar conditions are used for condensations where 1,3-dicarbonyl compounds provide the enol partner. The differences are that now the weak acid or base is strong enough to convert the 1,3-dicarbonyl compound essentially completely into enol or enolate, and that enolate (enolization between the two carbonyl groups) is highly favoured over all others. In a way these are intermediate between the two kinds of control, though they really belong to the directed aldol category.

Aldol reactions with highly enolizable compounds

1,3-Dicarbonyl compound	Conditions	Example
malonic acid CH$_2$(CO$_2$H)$_2$	piperidine, DMSO	CH$_2$(CO$_2$H)$_2$ + ArCHO → Ar–CH=CH–CO$_2$H
malonic esters CH$_2$(CO$_2$Et)$_2$	NH$_4^+$AcO$^-$	CH$_2$(CO$_2$Et)$_2$ + Me$_2$C=O → Me$_2$C=C(CO$_2$Et)$_2$
acetoacetates CH$_3$CO·CH$_2$CO$_2$Et	piperidine, EtOH, room temperature	CH$_3$CO·CH$_2$CO$_2$Et + PrCHO → CH$_3$CO–C(CO$_2$Et)=CH–Pr
nitro compounds[a] RCH$_2$NO$_2$	NaOH, H$_2$O	CH$_3$NO$_2$ + ArCHO → Ar–CH=CH–NO$_2$
Wittig reagents[a] Ph$_3$P$^\oplus$–CH$_2$–CO–R	NaOMe, MeOH	R^1–CH$_2$–CHO → R^1–CH=CH–CO–R

[a] These are not, of course, 1,3-dicarbonyl compounds but they have pK_as of about 10–12 and do form enolates with weak bases.

● **Directed aldol reactions**

In the directed aldol reaction, one component is first converted into a specific enol equivalent and *only then* combined with the electrophilic partner.

► If you don't think that this is too much of a problem, consider that, in order to make and use LDA, anhydrous di-isopropylamine (*i*-Pr₂NH) must be dissolved in anhydrous THF and treated with BuLi using a syringe technique in an inert anhydrous atmosphere (nitrogen or argon). The anhydrous carbonyl compound must be dissolved in anhydrous THF and both solutions cooled to −78 °C in a dry-ice/acetone bath before mixing, using a double-ended metal needle, under strictly anhydrous oxygen-free conditions. Then the electrophilic carbonyl compound must be added also… Do we need to go on? These are wonderful methods, but wouldn't you prefer to mix both compounds together in aqueous alcohol and add a little dilute aqueous NaOH and immediately isolate the product?

These are the most versatile methods and can be used to make essentially any aldol or any conjugated unsaturated carbonyl compound. The disadvantages are that an extra step is inevitably introduced (the making of the specific enol equivalent), that strong bases or powerful Lewis acids must be used, and that strictly anhydrous conditions in organic solvents are usually required.

The specific enol equivalents are used only when necessary. Check first whether you might be able to get away with an equilibrium method before planning a directed aldol reaction. Directed aldol reactions are among the greatest achievements of modern organic chemistry, but simpler methods still have their place.

The table gives some details of the conditions used for directed aldol reactions. You should refer to the table on p. 000 to see which specific enol equivalents are appropriate to which types of carbonyl compounds.

Specific enol equivalent	Conditions	Example
lithium enolate	1. LDA, THF, −78 °C, 2. aldehyde, 3. NH₄Cl, H₂O	
silyl enol ether	TiCl₄, CH₂Cl₂, −78 °C, 1 hour, under argon	
enamine	heat	
aza-enolate	1. RNH₂, 2. LDA, 3. ketone, 4. dilute H₂SO₄	
zinc enolate (Reformatsky)	1. Zn, 2. aldehyde or ketone	

We have spent some considerable time and effort in understanding the aldol reaction simply because it is one of the most important reactions in organic chemistry. In the next chapter you will see how these ideas can be extended with almost no addition of principles to the acylation of enolates—the reaction of enols, enolates, and specific enol equivalents with acid chlorides and esters. We hope that you will see that the ideas introduced in this chapter find immediate application in the next.