Alkylation of enolates

26

Connections

Building on:

- Enols and enolates ch21
- Electrophilic addition to alkenes ch20
- Nucleophilic substitution reactions ch17

Arriving at:

- How to make new C–C bonds using carbonyl compounds as nucleophiles
- How to prevent carbonyl compounds reacting with themselves

Looking forward to:

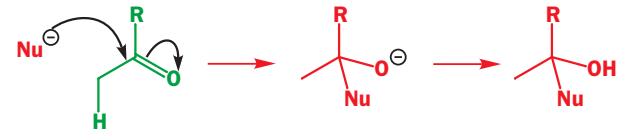
- Forming C–C bonds by reacting nucleophilic enolates with electrophilic carbonyl compounds ch27
- Forming C–C bonds by reacting nucleophilic enolates with electrophilic carboxylic acid derivatives ch28
- Forming C–C bonds by reacting nucleophilic enolates with electrophilic alkenes ch29
- Retrosynthetic analysis ch30

Chapters 26–29 continue the theme of synthesis that started with Chapter 24 and will end with Chapter 30. This group of four chapters introduces the main C–C bond-forming reactions of enols and enolates. We develop the chemistry of Chapter 21 with a discussion of enols and enolates attacking to alkylating agents (Chapter 26), aldehydes and ketones (Chapter 27), acylating agents (Chapter 28), and electrophilic alkenes (Chapter 29).

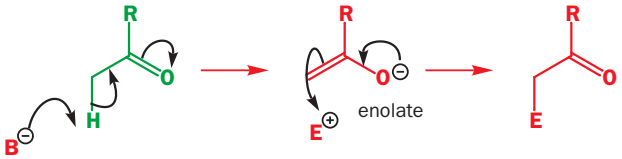
Carbonyl groups show diverse reactivity

In earlier chapters we discussed the two types of reactivity displayed by the carbonyl group. We first described reactions that involve **nucleophilic attack** on the carbon of the carbonyl, and in Chapter 9 we showed you that these are among the best ways of making new C–C bonds. In this chapter we shall again be making new C–C bonds, but using **electrophilic attack** on carbonyl compounds: in other words, the carbonyl compound will be reacting as the nucleophile in the reaction. We introduced the nucleophilic forms of carbonyl compounds—enols, and enolates—in Chapter 21. There you saw them reacting with heteroatomic electrophiles, but they will also react well with carbon electrophiles provided the reaction is thoughtfully devised. Much of this chapter will concern that phrase, 'thoughtfully devised'.

carbonyl compound acts as an electrophile

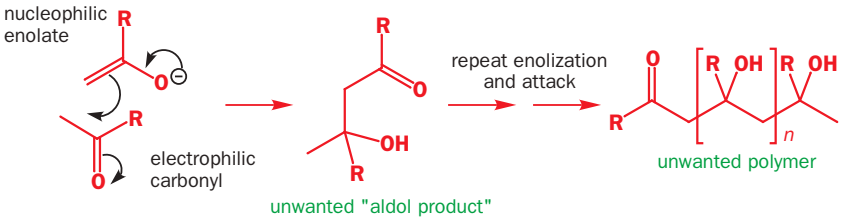


enolate acts as a nucleophile



Thought is needed to ensure that the carbonyl compound exhibits the right sort of reactivity. In particular, the carbonyl compound must not act as an electrophile when it is intended to be a nucleophile. If it does, it may react with itself to give some sort of dimer—or even a polymer—rather than neatly attacking the desired electrophile. This chapter is devoted to ways of avoiding this: in Chapter 27 we shall talk about how to promote and control the dimerization, known as the **aldol reaction**.

aim to avoid an unwanted dimerization: the aldol reaction



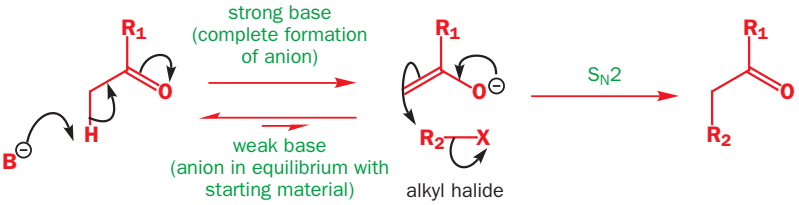
Fortunately, over the last three decades lots of thought has *already* gone into the problem of controlling the reactions of enolates with carbon electrophiles. This means that there are many excellent solutions to the problem: our task in this chapter is to help you understand which to use, and when to use them, in order to design useful reactions.

Some important considerations that affect all alkylations

These reactions consist of two steps. The first is the formation of a stabilized anion—usually (but not always) an enolate—by deprotonation with base. The second is a substitution reaction: attack of the nucleophilic anion on an electrophilic alkyl halide. All the factors controlling S_N1 and S_N2 reactions, which we discussed at length in Chapter 17, are applicable here.

step 1: formation of enolate anion

step 2: alkylation (S_N2 reaction with alkyl halide)



In each case, we shall take one of two approaches to the choice of base.

- A strong base can be chosen to deprotonate the starting material completely. There is complete conversion of the starting material to the anion before addition of the electrophile, which is added in a subsequent step
- Alternatively, a weaker base may be used *in the presence of the electrophile*. The weaker base will not deprotonate the starting material completely: only a small amount of anion will be formed, but that small amount will react with the electrophile. More anion is formed as alkylation uses it up

The second approach is easier practically (just mix the starting material, base, and electrophile), but works only if the base and the electrophile are compatible and don't react together. With the first approach, which is practically more demanding, the electrophile and base never meet each other, so their compatibility is not a concern. We shall start with some compounds that avoid the problem of competing aldol reactions completely, because they are not electrophilic enough to react with their own nucleophilic derivatives.

Nitriles and nitroalkanes can be alkylated

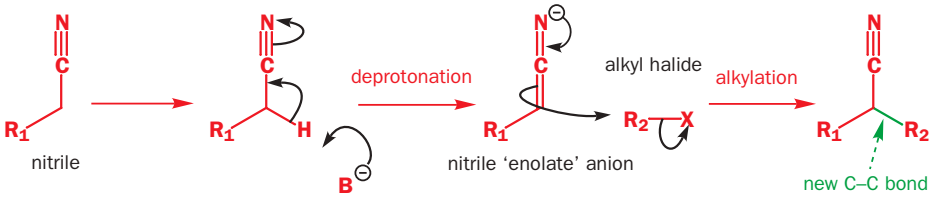
Problems that arise from the electrophilicity of the carbonyl group can be avoided by replacing C=O by functional groups that are much less electrophilic but are still able to stabilize an adjacent anion. We shall consider two examples, both of which you met in Chapter 21.

Alkylation of nitriles

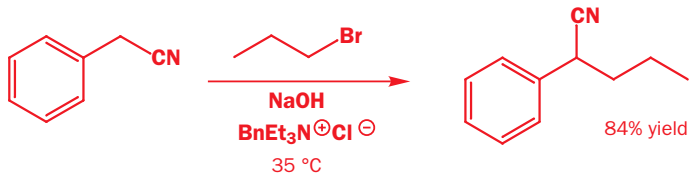
■ You met nitrile hydrolysis and addition reactions, for example, in Chapter 12.

Firstly, the nitrile group, which mirrors the carbonyl group in general reactivity but is much less easily attacked by nucleophiles (N is less electronegative than O).

The anion formed by deprotonating a nitrile using strong base will not react with other molecules of nitrile but will react very efficiently with alkyl halides. The slim, linear structure of the anions makes them good nucleophiles for S_N2 reactions.



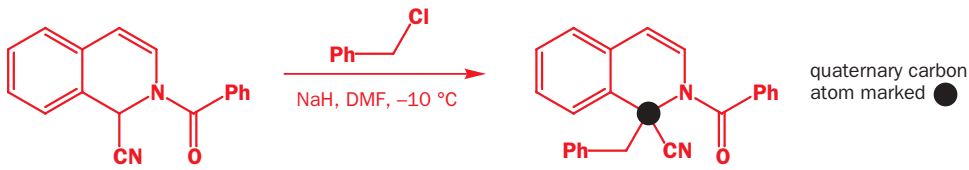
The nitrile does not have to be deprotonated completely for alkylation: with sodium hydroxide only a small amount of anion is formed. In the example below, such an anion reacts with propyl bromide to give 2-phenylpentanenitrile.



This reaction is carried out in a two-phase mixture (water + an immiscible organic solvent) to prevent the hydroxide and propyl bromide merely reacting together in an S_N2 reaction to give propanol. The hydroxide stays in the aqueous layer, and the other reagents stay in the organic layer. A tetraalkylammonium chloride (benzyltriethylammonium chloride $BnEt_3N^+Cl^-$) is needed as a **phase transfer catalyst** to allow sufficient hydroxide to enter the organic layer to deprotonate the nitrile.

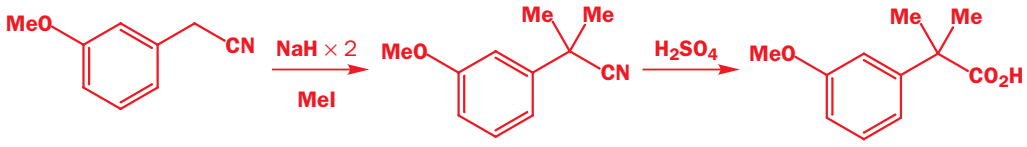
■ You met phase transfer catalysis in Chapter 23, p. 000.

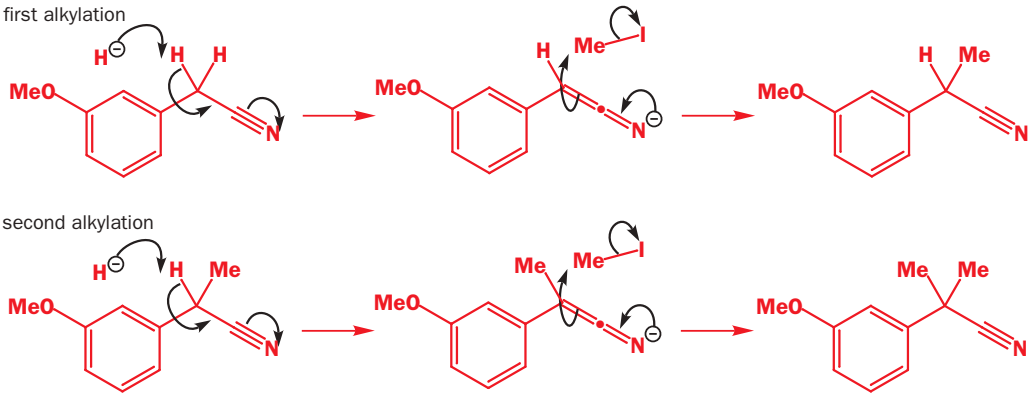
Nitrile-stabilized anions are so nucleophilic that they will react with alkyl halides rather well even when a crowded quaternary centre (a carbon bearing no H atoms) is being formed. In this example the strong base, sodium hydride, was used to deprotonate the branched nitrile completely and benzyl chloride was the electrophile. The greater reactivity of benzylic electrophiles compensates for the poorer leaving group. In DMF, the anion is particularly reactive because it is not solvated (DMF solvates only the Na^+ cation).



▶ Remember our discussion about the lack of nucleophilicity of hydride (H^-) in Chapter 6? Here is hydride acting as a base even in the presence of the electrophile: there was no need to do this reaction in two steps because the base and electrophile cannot react together.

The compatibility of sodium hydride with electrophiles means that, by adding two equivalents of base, alkylation can be encouraged to occur more than once. This dimethylated acid was required in the synthesis of a potential drug, and it was made in two steps from a nitrile. Double alkylation with two equivalents of NaH in the presence of excess methyl iodide gave the methylated nitrile which was hydrolysed to the acid. The monoalkylated product is not isolated—it goes on directly to be deprotonated and react with a second molecule of MeI.



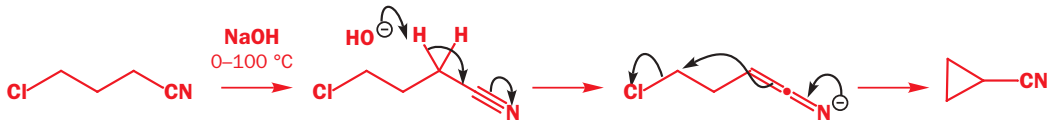


▶

Multiple alkylation is not always desirable, and one of the side-reactions in alkylations that are intended to go only once is the formation of doubly, or in special cases triply, alkylated products. These arise when the first alkylation product still has acidic protons and can be deprotonated to form another anion. This may in turn react further. Clearly, this is more likely to be a problem if the base is present in excess and can usually be restricted by using only one equivalent of the electrophile.

With two nitrile groups, the delocalized anion is so stable that even a weak, neutral amine (triethylamine) is sufficiently basic to deprotonate the starting material. Here double alkylation again takes place: note that the electrophile is good at S_N2, and the solvent is dipolar and aprotic (DMSO and DMF have similar properties). The doubly alkylated quaternary product was formed in 100% yield.

If the electrophile and the nitrile are in the same molecule and the spacing between them is appropriate, then intramolecular alkylation will lead to cyclization to form rings that can have anything from three to six members. The preparation of a cyclopropane is shown using sodium hydroxide as the base and chloride as a leaving group. With an intramolecular alkylation, the base and the electrophile have to be present together, but the cyclization is so fast that competing S_N2 with HO^- is not a problem.

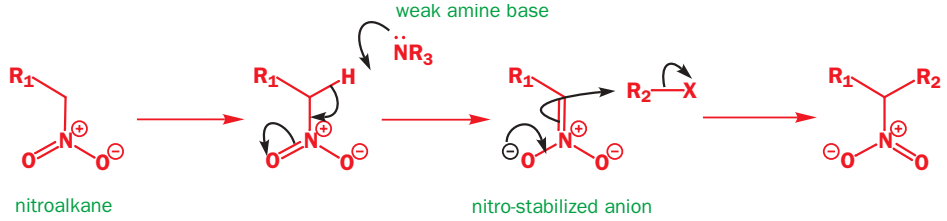


Alkylation of nitroalkanes

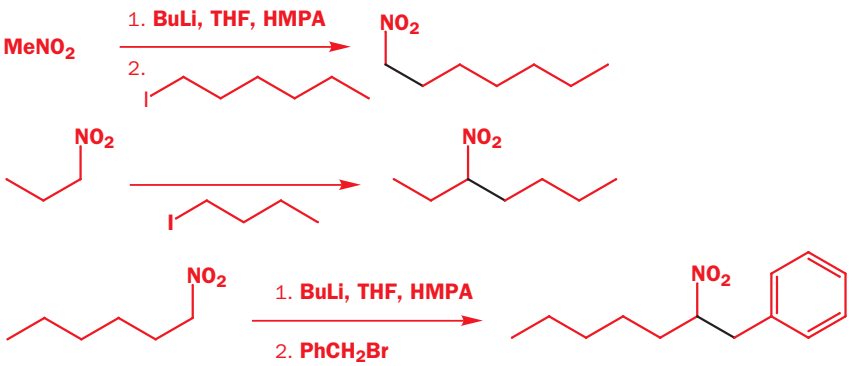
The powerful electron-withdrawing nature of the nitro group means that deprotonation is possible even with very mild bases (the pK_a of $MeNO_2$ is 10). The anions react with carbon electrophiles and a wide variety of nitro-containing products can be produced. The anions are not, of course, enolates, but replacing the nitrogen with a carbon should help you to recognize the close similarity of these alkylations with the enolate alkylations described later.

■

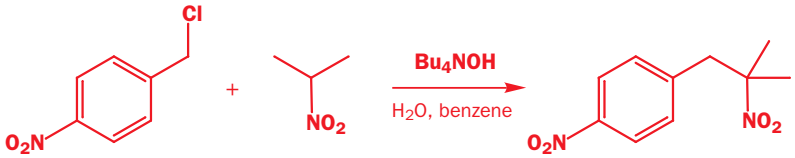
Nitro-stabilized anions also undergo additions to aldehydes, ketones, and electrophilic alkenes: these reactions appear in Chapters 27 and 29.



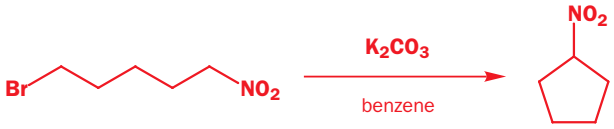
Surprisingly few simple nitroalkanes are commercially available but more complex examples can be prepared readily by alkylation of the anions derived from nitromethane, nitroethane, and 2-nitropropane. Deprotonation of nitroalkanes with butyllithium followed by the addition of alkyl halides gives the alkylated nitroalkanes in good yield. Some examples of this general method are shown below. These reactions really do have to be done in two steps: BuLi is not compatible with alkyl halides!



Nitroalkanes can be alkylated in a single step with hydroxide as a base: phase transfer conditions keep the HO^- and the electrophile apart, preventing alcohol formation. This compound forms despite its quaternary carbon atom.

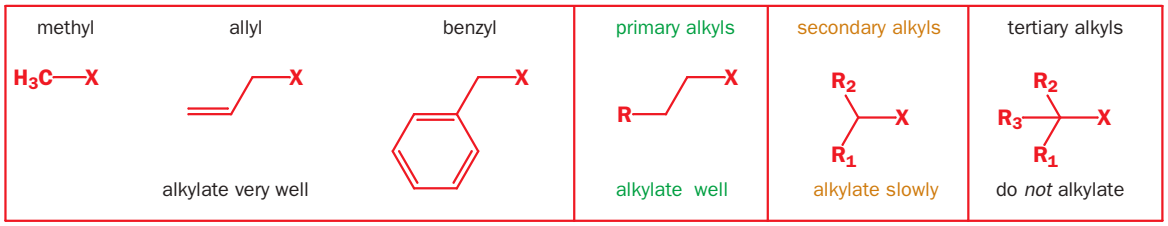


Cyclic nitroalkanes can be prepared by intramolecular alkylation provided that the ring size is appropriate (3–7 members). Now there really is no alternative: the base and electrophile must cohabit in the reaction mixture, so a weaker base such as potassium carbonate must be used—amines are no good here because they undergo substitution reactions with the halide.



Choice of electrophile for alkylation

Enolate alkylations are S_N2 reactions (polar solvents, good charged nucleophile) so the electrophile needs to be S_N2-reactive if the alkylation is to succeed: primary and benzylic alkyl halides are among the best alkylating agents. More branched halides tend to prefer to undergo unwanted E2 elimination reactions (Chapter 19), because the anions themselves are rather basic. As a result, tertiary halides are useless for enolate alkylation. We shall see a way round this problem later in the chapter.

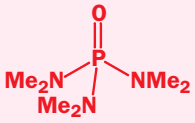


Lithium enolates of carbonyl compounds

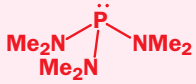
The problem of self-condensation of carbonyl compounds (that is, enolate reacting with unenolized carbonyl) under basic conditions does not exist if there is absolutely no unenolized carbonyl compound present. One way to achieve this is to use a base sufficiently strong (pK_a at least 3 or 4 units higher than pK_a of the carbonyl compound) to ensure that all of the starting carbonyl is converted into the corresponding enolate. This will work only if the resulting enolate is sufficiently stable to survive until the alkylation is complete. As you saw in Chapter 21, lithium enolates are stable, and are among the best enolate equivalents for use in alkylation reactions.

▶Hexamethylphosphoramide (HMPA)

HMPA has the structure shown below, and the basic oxygen atom coordinates to lithium extremely powerfully. The cation is solvated, leaving the anion unsolvated and more reactive. HMPA is known to cause cancer, and should not be confused with its less common cousin HMPT (hexamethylphosphorous triamide).



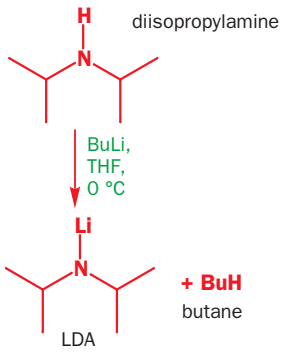
HMPA



HMPT

■
LDA is described on p. 000.

a reminder: how to make LDA

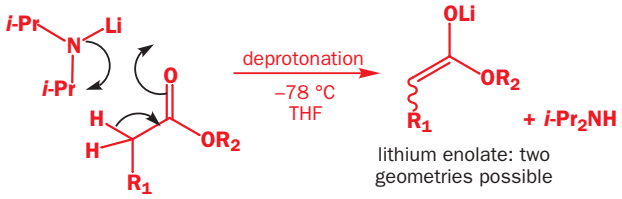


▶
Enolates are a type of alkene, and there are two possible geometries of the enolate of an ester. The importance of enolate geometry is discussed in Chapter 34 and will not concern us here. More important is the question of regioselectivity when unsymmetrical ketones are deprotonated. We shall discuss this aspect later in the chapter.

The best base for making lithium enolates is usually LDA, made from diisopropylamine (*i*-Pr2NH) and BuLi. LDA will deprotonate virtually all ketones and esters that have an acidic proton to form the corresponding lithium enolates rapidly, completely, and irreversibly even at the low temperatures (about –78°C) required for some of these reactive species to survive.

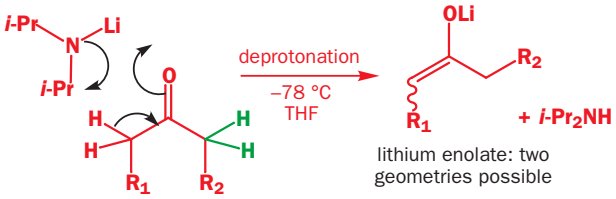
Deprotonation occurs through a cyclic mechanism illustrated below for ketones and esters. The basic nitrogen anion removes the proton as the lithium is delivered to the forming oxyanion.

deprotonation of an ester



lithium enolate: two geometries possible

deprotonation of a ketone

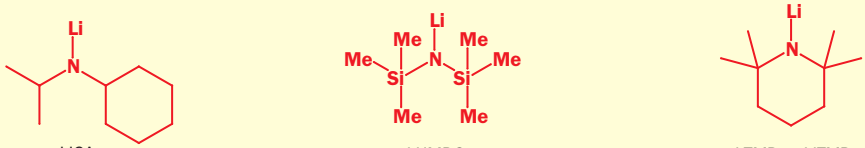


lithium enolate: two geometries possible

if $R^1 \neq R^2$, removal of the green protons gives a different enolate

Variations on a theme

LDA came into general use in the 1970s, and you may meet more modern variants derived from butyllithium and isopropylcyclohexylamine (lithium isopropylcyclohexylamide, LICA) or 2,2,6,6-tetramethylpiperidine (lithium tetramethylpiperidide, LTMP) or hexamethyldisilazane (lithium hexamethyldisilazide, LHMDS), which are even more hindered and are even less nucleophilic as a result.

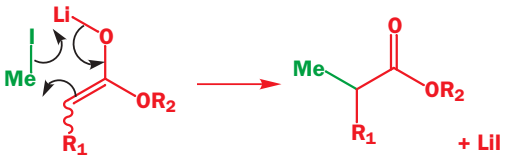


LICA LHMDS LTMP or LiTMP

Alkylations of lithium enolates

The reaction of these lithium enolates with alkyl halides is one of the most important C–C bond-forming reactions in chemistry. Alkylation of lithium enolates works with both acyclic and cyclic ketones as well as with acyclic and cyclic esters (lactones). The general mechanism is shown below.

alkylation of an ester enolate

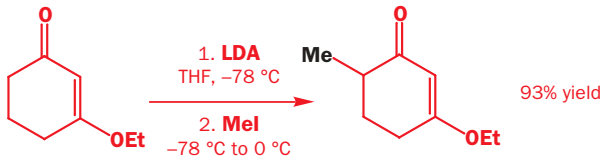


alkylation of a ketone enolate

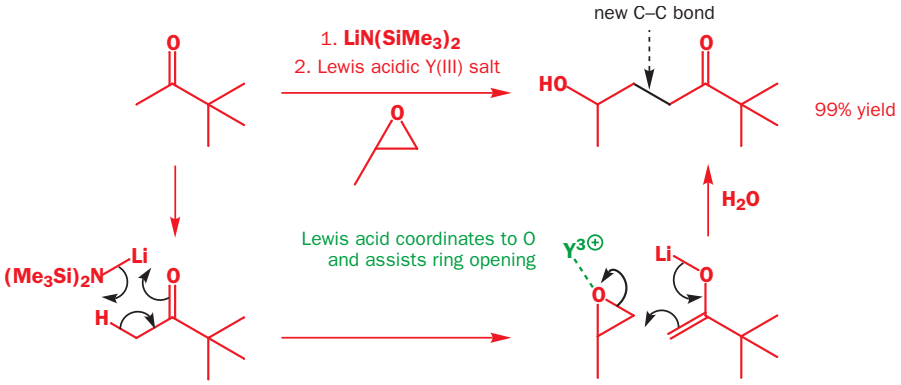
Typical experimental conditions for reactions of kinetic enolates involve formation of the enolate at very low temperature (–78°C) in THF. Remember, the strong base LDA is used to avoid self-condensation of the carbonyl compound but, while the enolate is forming, there is always a chance that self-condensation will occur. The lower the temperature, the slower the self-condensation reaction, and the fewer by-products there are. Once enolate formation is complete, the electrophile is added (still at –78°C: the lithium enolates may not be stable at higher temperatures). The reaction mixture is then usually allowed to warm up to room temperature to speed up the rate of the S_N2 alkylation.

Alkylation of ketones

Precisely this sequence was used to methylate the ketone below with LDA acting as base followed by methyl iodide as electrophile.

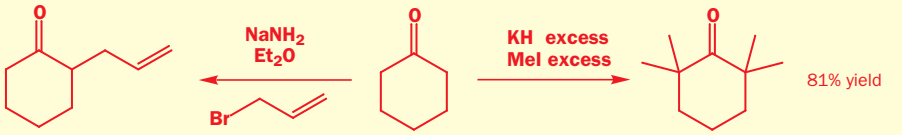


In Chapter 17 you saw epoxides acting as electrophiles in S_N2 reactions. They can be used to alkylate enolates providing epoxide opening is assisted by coordination to a Lewis acidic metal ion: in this case the lanthanide yttrium(III). The new C–C bond in the product is coloured black. Note that the ketone starting material is unsymmetrical, but has protons only to one side of the carbonyl group, so there is no question over which enolate will form. The base is one of the LDA variants we showed you on p. 000—LHMDS.



Sodium and potassium also give reactive enolates

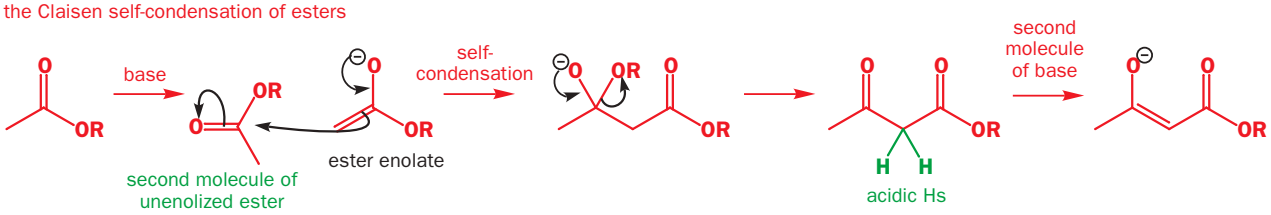
Their stability at low temperature means that lithium enolates are usually preferred, but sodium and potassium enolates can also be formed by abstraction of a proton by strong bases. The increased separation of the metal cation from the enolate anion with the larger alkali metals leads to more reactive but less stable enolates. Typical very strong Na and K bases include the hydrides (NaH, KH) or amide anions derived from ammonia ($NaNH_2$, KNH_2) or hexamethyldisilazane (NaHMDS, KHMDS). The instability of the enolates means that they are usually made and reacted in a single step, so the base and electrophile need to be compatible. Here are two examples of cyclohexanone alkylation: the high reactivity of the potassium enolate is demonstrated by the efficient tetramethylation with excess potassium hydride and methyl iodide.



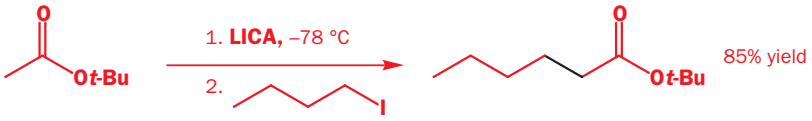
Alkylation of esters

In Chapter 28 you will meet the reaction of an ester with its own enolate: the **Claisen condensation**. This reaction can be an irritating side-reaction in the chemistry of lithium ester enolates when alkylation is desired, and again it can be avoided only if the ester is converted entirely to its enolate under conditions where the Claisen condensation is slow. A good way of stopping this happening is to add the ester *to the solution of LDA* (and not the LDA to the ester) so that there is never excess ester for the enolate to react with.

the Claisen self-condensation of esters



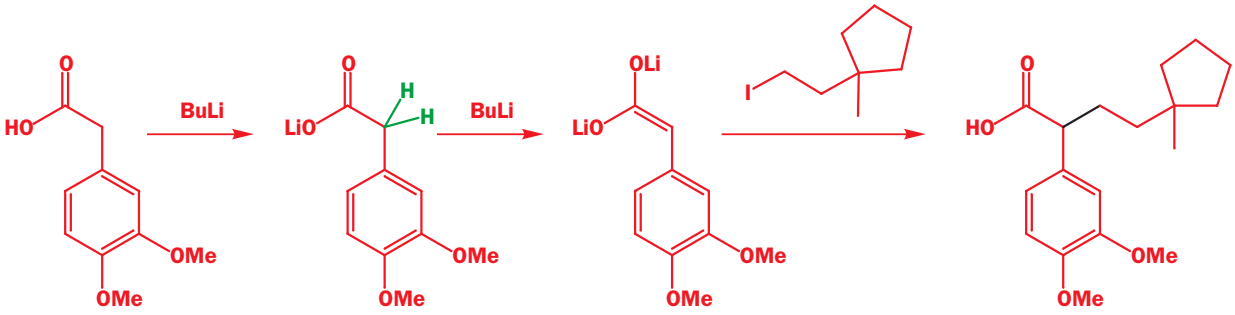
Another successful tactic is to make the group R as large as possible to discourage attack at the carbonyl group. Tertiary butyl esters are particularly useful in this regard, because they are readily made, *t*-butyl is extremely bulky, and yet they can can still be hydrolysed in aqueous acid under mild conditions by the method discussed on p. 000. In this example, deprotonation of *t*-butyl acetate with LICA (lithium isopropylcyclohexylamide) gives a lithium enolate that reacts with butyl iodide as the reaction mixture is warmed to room temperature.



Alkylation of carboxylic acids

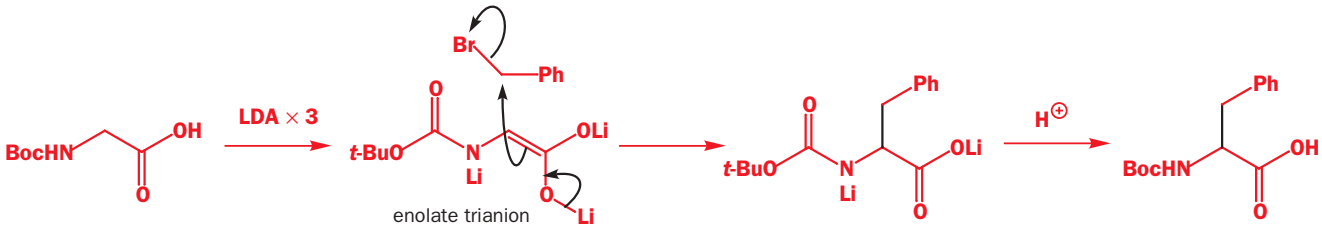
The lithium enolates of carboxylic acids can be formed if two equivalents of base are used. Carboxylic acids are very acidic so it is not necessary to use a strong base to remove the first proton but, since the second deprotonation requires a strong base such as LDA, it is often convenient to use two equivalents of LDA to form the dianion. With carboxylic acids, even BuLi can be used on occasion because the intermediate lithium carboxylate is much less electrophilic than an aldehyde or a ketone.

■ Why doesn't BuLi add to the carboxylate as you saw in Chapter 12 to form the ketone? Presumably in this case the aromatic ring helps acidify the benzylic protons to tip the balance towards deprotonation. Even with carboxylic acids, LDA would be the first base you would try.



▶ You saw this sort of reactivity with dianions in Chapter 24: the last anion to form will be the most reactive.

The next alkylation of an acid enolate is of a carbamate-protected amino acid, glycine. As you saw in Chapter 25, carbamates are stable to basic reaction conditions. Three acidic protons are removed by LDA, but alkylation takes place only at carbon—the site of the last proton to be removed. Alkylation gets rid of one of the negative charges, so that, if the molecule gets a choice, it alkylates to get rid of the least stable anion, keeping the two more stabilized charges. A good alternative to using the dianion is to alkylate the ester or nitrile and then hydrolyse to the acid.



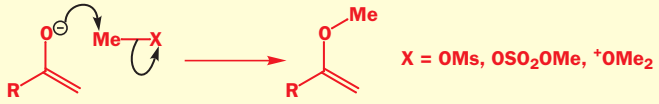
● **Alkylation of ketones, esters, and carboxylic acids is best carried out using the lithium enolates.**

Why do enolates alkylate on carbon?

Enolates have two nucleophilic sites: the carbon and the oxygen atoms: on p. 000 we showed that:

- Carbon has the greater coefficient in the HOMO, and is the softer nucleophilic site
- Oxygen carries the greater total charge and is the harder nucleophilic site

hard electrophiles react at O

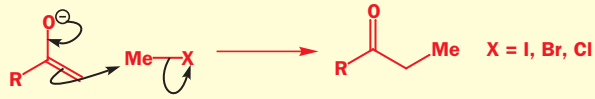


In general:

- Hard electrophiles, particularly sulfates and sulfonates (mesylates, tosylates), tend to react at oxygen
- Soft nucleophiles, particularly halides (I > Br > Cl), react at carbon
- Polar aprotic solvents (HMPA, DMF) promote *O*-alkylation by separating the enolate anions from each other and the counterion (making the bond more polar and increasing the charge at O) while ethereal solvents (THF, DME) promote *C*-alkylation
- Larger alkali metals (Cs > K > Na > Li) give more separated ion pairs (more polar bonds) which are harder and react more at oxygen

In Chapter 21 you saw that hard electrophiles prefer to react at oxygen—that is why it is possible to make silyl enol ethers, for example. Some carbon electrophiles with very good leaving groups also tend to react on carbon, but soft electrophiles such as alkyl halides react at carbon, and you will see only this type of electrophile in this chapter.

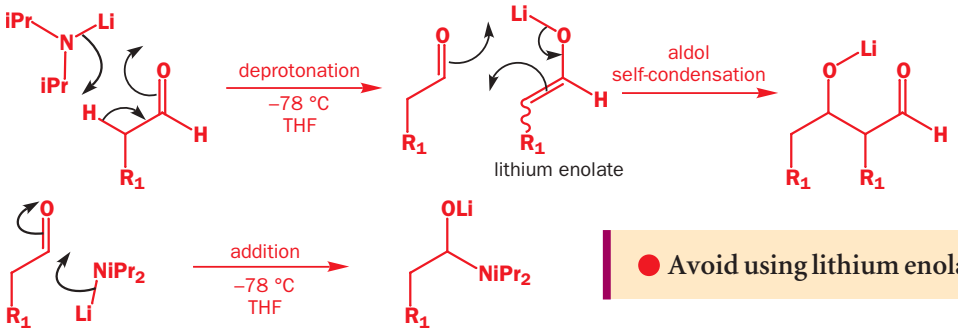
soft electrophiles react at C



Alkylation of aldehydes

Aldehydes are so electrophilic that, even with LDA at –78°C, the rate at which the deprotonation takes place is not fast enough to outpace reactions between the forming lithium enolate and still-to-be-deprotonated aldehyde remaining in the mixture. Direct addition of the base to the carbonyl group of electrophilic aldehydes can also pose a problem.

reactions which compete with aldehyde enolate formation



● Avoid using lithium enolates of aldehydes.

Using specific enol equivalents to alkylate aldehydes and ketones

These side-reactions mean that aldehyde enolates are not generally useful reactive intermediates. Instead, there are a number of aldehyde enol and enolate equivalents in which the aldehyde is present only in masked form during the enolization and alkylation step. The three most important of these **specific enol equivalents** are:

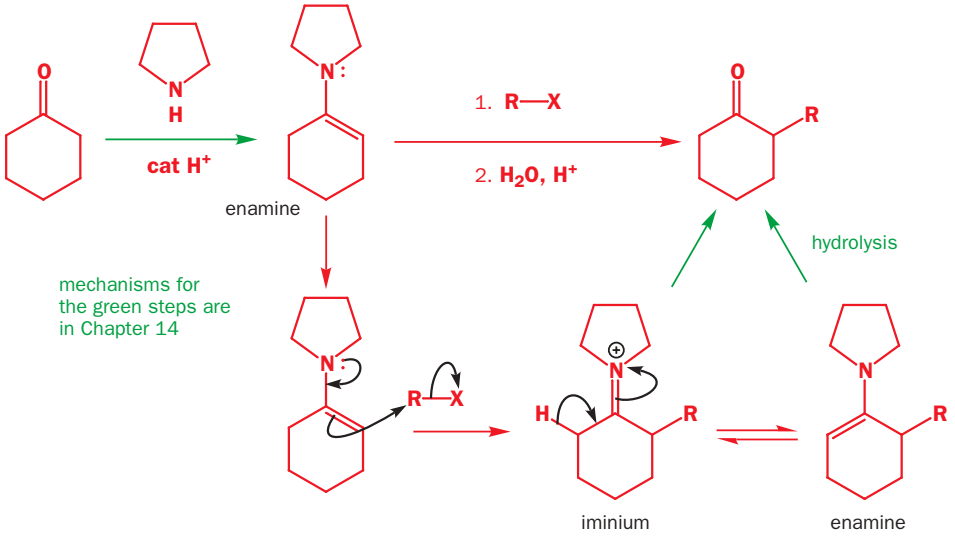
- enamines
- silyl enol ethers
- aza-enolates derived from imines

You met all of these briefly in Chapter 21, and we shall discuss how to use them to alkylate aldehydes shortly. All three types of specific enol equivalent are useful not just with aldehydes, but with ketones as well, and we shall introduce each class with examples for both types of carbonyl compound.

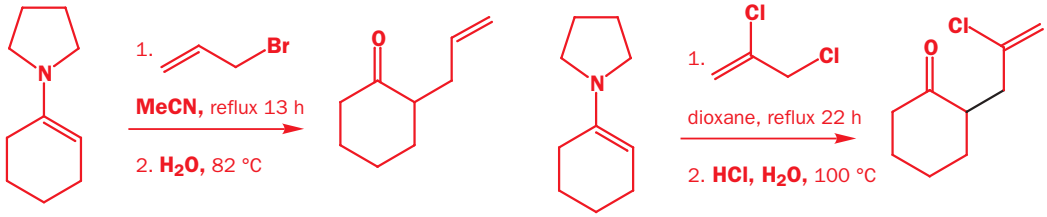
Enamines are alkylated by reactive electrophiles

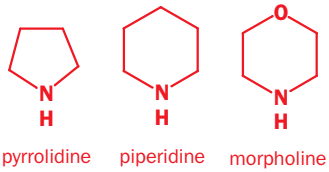
Enamines are formed when aldehydes or ketones react with secondary amines. The mechanism is given in Chapter 14. The mechanism below shows how they react with alkylating agents to form new

carbon–carbon bonds: the enamine here is the one derived from cyclohexanone and pyrrolidine. The product is at first not a carbonyl compound: it's an iminium ion or an enamine (depending on whether an appropriate proton can be lost). But a mild acidic hydrolysis converts the iminium ion or enamine into the corresponding alkylated carbonyl compound.



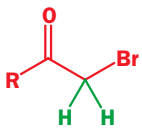
The overall process, from carbonyl compound to carbonyl compound, amounts to an enolate alkylation, but no strong base or enolates are involved so there is no danger of self-condensation. The example below shows two specific examples of cyclohexanone alkylation using enamines. Note the relatively high temperatures and long reaction times: enamines are among the most reactive of neutral nucleophiles, but they are still a lot less nucleophilic than enolates.

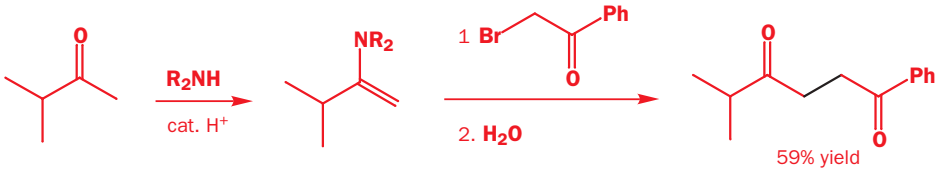




The choice of the secondary amine for formation of the enamine is not completely arbitrary even though it does not end up in the final alkylated product. Simple dialkyl amines can be used but cyclic amines such as pyrrolidine, piperidine, and morpholine are popular choices as the ring structure makes both the starting amine and the enamine more nucleophilic (the alkyl groups are 'tied back' and can't get in the way). The higher boiling points of these amines allow the enamine to be formed by heating.

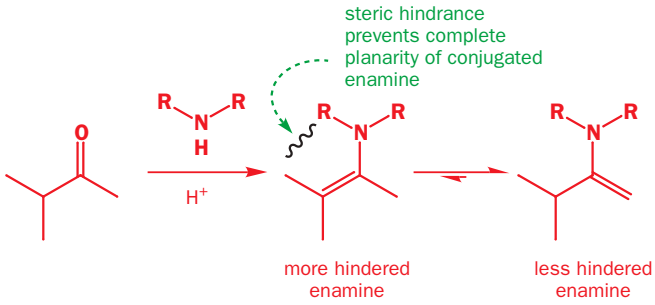
α-Bromo carbonyl compounds are excellent electrophiles for S_N2 reactions because of the rate-enhancing effect of the carbonyl group (Chapter 17). The protons between the halogen and the carbonyl are significantly more acidic than those adjacent to just a carbonyl group and there is a serious risk of an enolate nucleophile acting as a base. Enamines are only very weakly basic, but react well as a nucleophile with a-bromo carbonyl compounds, and so are a good choice.



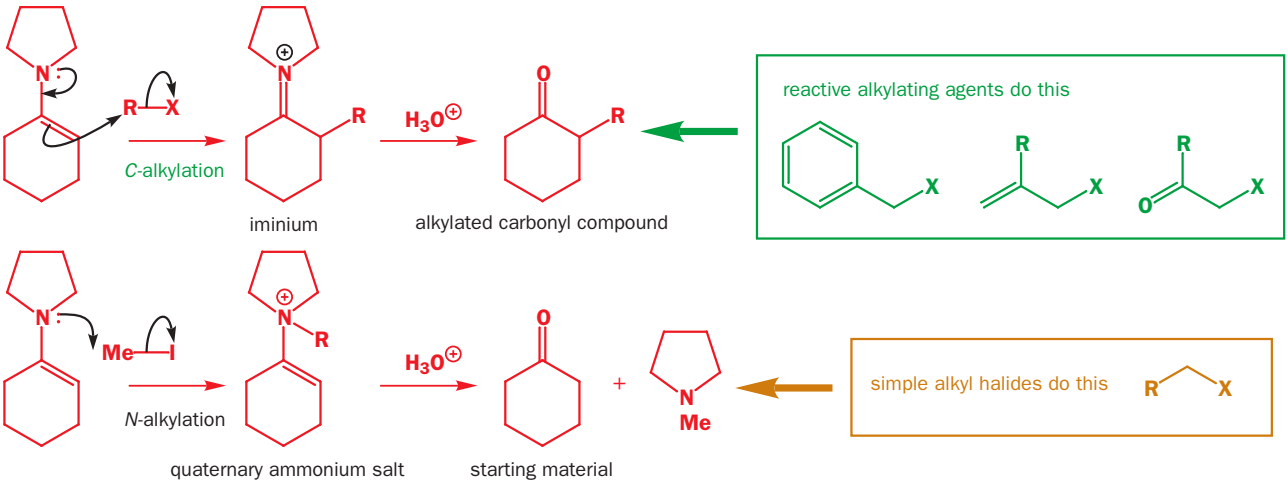


The original ketone here is unsymmetrical, so two enamines are possible. However, the formation of solely the *less* substituted enamine is typical. The outcome may be explained as the result of thermodynamic control: enamine formation is reversible so the less hindered enamine predominates.

For the more substituted enamine, steric hindrance forces the enamine to lose planarity, and destabilizes it. The less substituted enamine, on the other hand, is rather more stable. Note how the preference for the less substituted enamine is opposite to the preference for a *more* substituted enol.

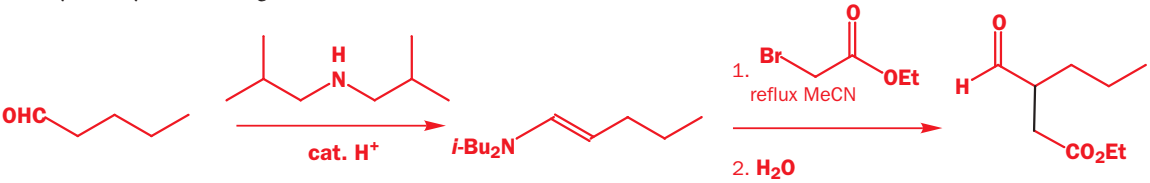


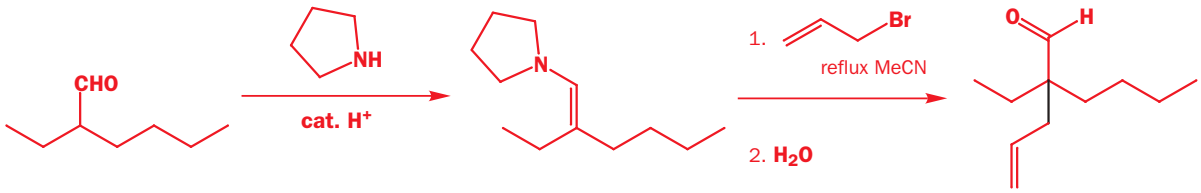
There is, however, a major problem with enamines: reaction at nitrogen. Less reactive alkylating agents—simple alkyl halides such as methyl iodide, for example—react to a significant degree at N rather than at C. The product is a quaternary ammonium salt, which hydrolyses back to the starting material and leads to low yields.



- **Enamines can be used only with reactive alkylating agents.**
  - allylic halides
  - benzyl halides
  - α-halo carbonyl compounds

That said, enamines are a good solution to the aldehyde enolate problem. Aldehydes form enamines very easily (one of the advantages of the electrophilic aldehyde) and these are immune to attack by nucleophiles—including most importantly the enamines themselves. Below are two examples of aldehyde alkylation using the enamine method.



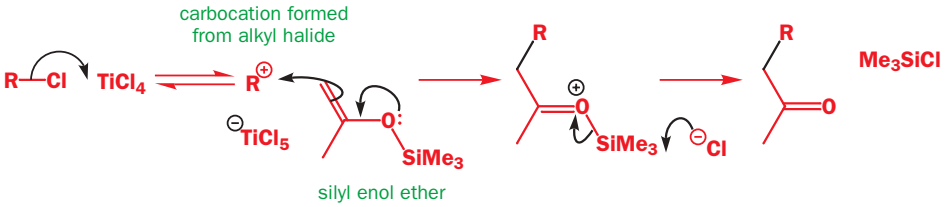


Both again use highly S_N2-reactive electrophiles, and this is the main drawback of enamines. In the next section we consider a complementary class of enol equivalents that react only with highly S_N1-reactive electrophiles.

Silyl enol ethers are alkylated by S_N1-reactive electrophiles in the presence of Lewis acid

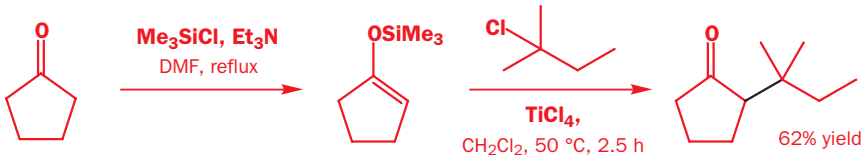
■ You saw the quantitative formation of carbocations by this method in Chapter 17.

Enamines are among the most powerful neutral nucleophiles and react spontaneously with alkyl halides. Silyl enol ethers are less reactive and so require a more potent electrophile to initiate reaction. Carbocations will do, and they can be generated *in situ* by abstraction of a halide or other leaving group from a saturated carbon centre by a Lewis acid.



The best alkylating agents for silyl enol ethers are tertiary alkyl halides: they form stable carbocations in the presence of Lewis acids such as TiCl4 or SnCl4. Most fortunately, this is just the type of compounds that is unsuitable for reaction with lithium enolates or enamines, as elimination results rather than alkylation: a nice piece of complementary selectivity.

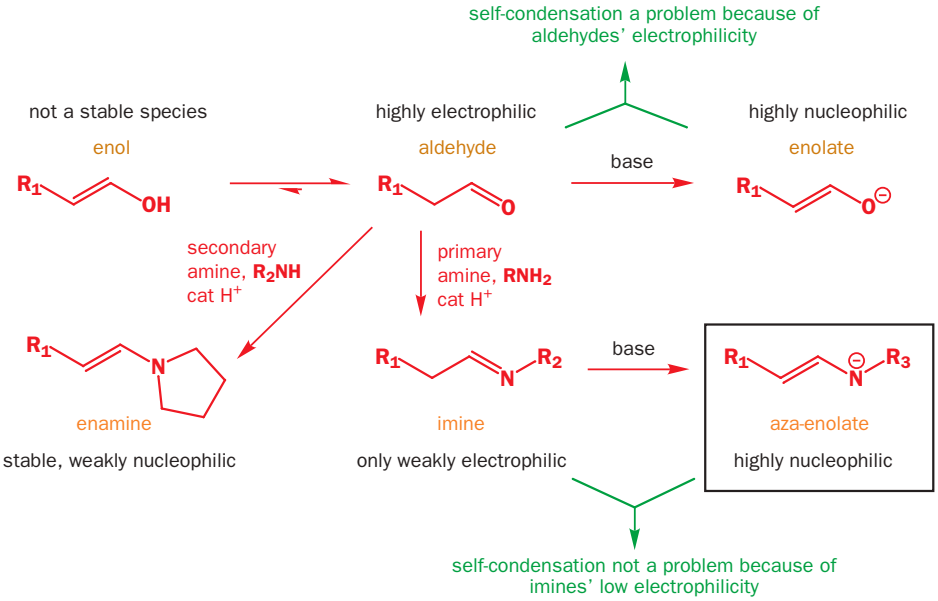
Below is an example: the alkylation of cyclopentanone with 2-chloro-2-methylbutane. The ketone was converted to the trimethylsilyl enol ether with triethylamine and trimethylsilylchloride: we discussed this step on p. 000 (Chapter 21). Titanium tetrachloride in dry dichloromethane promotes the alkylation step.



Aza-enolates react with S_N2-reactive electrophiles

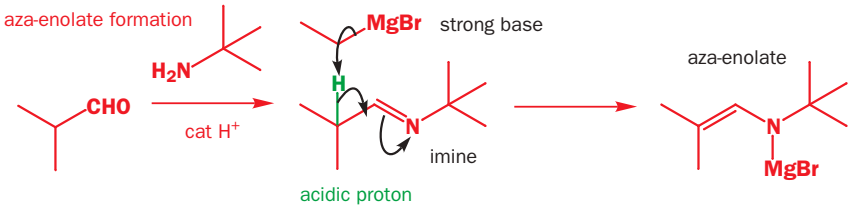
Enamines are the nitrogen analogues of enols and provide one solution to the aldehyde enolate problem when the electrophile is reactive. Imines are the corresponding nitrogen analogues of aldehydes and ketones: a little lateral thinking should therefore lead you to expect some useful reactivity from the nitrogen equivalents of enolates, known as aza-enolates. Aza-enolates are formed when imines are treated with LDA or other strong bases.

In basic or neutral solution, imines are less electrophilic than aldehydes: they react with organolithiums, but not with many weaker nucleophiles (they are more electrophilic in acid when they are protonated). So, as the aza-enolate forms, there is no danger at all of self-condensation.

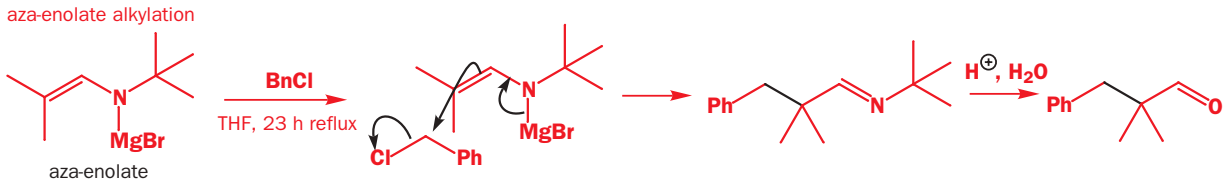


The overall sequence involves formation of the imine from the aldehyde that is to be alkylated—usually with a bulky primary amine such as t-butyl- or cyclohexylamine to discourage even further nucleophilic attack at the imine carbon. The imine is not usually isolated, but is deprotonated directly with LDA or a Grignard reagent (these do not add to imines, but they will deprotonate them to give magnesium aza-enolates).

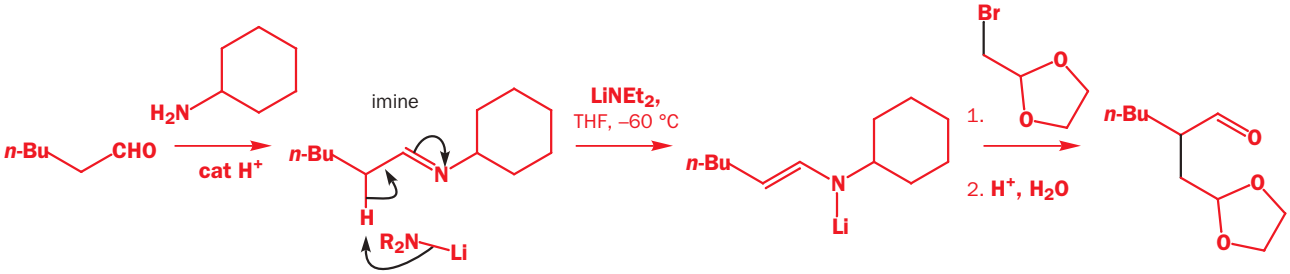
Note. Aza-enolates are formed from imines, which can be made only from *primary* amines. Enamines are made from aldehydes or ketones with *secondary* amines.



The resulting aza-enolate reacts like a ketone enolate with SN2-reactive alkylating agents—here, benzyl chloride—to form the new carbon–carbon bond and to re-form the imine. The alkylated imine is usually hydrolysed by the mild acidic work-up to give the alkylated aldehyde.



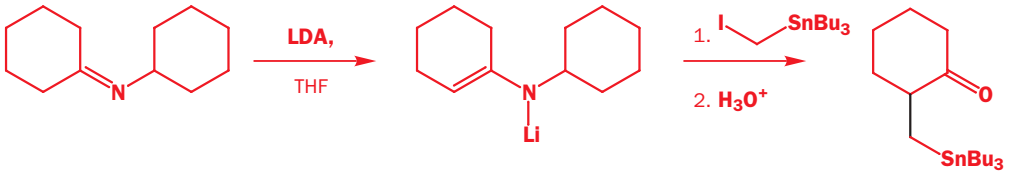
In the next example, a lithium base (lithium diethylamide) is used to form the aza-enolate. The ease of imine cleavage in acid is demonstrated by the selective hydrolysis to the aldehyde without any effect on the acetal introduced by the alkylation step. The product is a mono-protected dialdehyde—difficult to prepare by other methods.



● Aldehyde alkylation

Aza-enolates are the best general solution for alkylating aldehydes with most electrophiles. With very S_N2-reactive alkylating agents, enamines can be used, and with very S_N1-reactive alkylating agents, silyl enol ethers must be used

Aza-enolate alkylation is so successful that it has been extended from aldehydes, where it is essential, to ketones where it can be a useful option. Cyclohexanones are among the most electrophilic simple ketones and can suffer from undesirable side-reactions. The imine from cyclohexanone and cyclohexylamine can be deprotonated with LDA to give a lithium aza-enolate. In this example, iodomethylstannane was the alkylating agent, giving the tin-containing ketone after hydrolysis.



● Specific enol equivalents for aldehydes and ketones

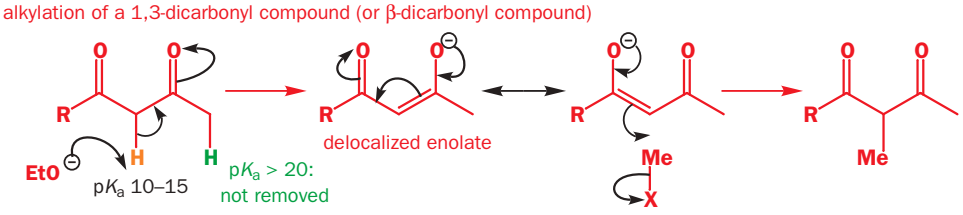
To summarize:

- **Lithium enolates can be used with S_N2-reactive electrophiles, but cannot be made from aldehydes**
- **Aza-enolates of aldehydes or ketones can be used with the same S_N2-reactive electrophiles, but *can* be made from aldehydes**
- **Enamines of aldehydes or ketones can be used with allylic, benzylic, or α-halocarbonyl compounds**
- **Silyl enol ethers of aldehydes or ketones can be used with S_N1-reactive (tertiary, allylic or benzylic) alkyl halides**

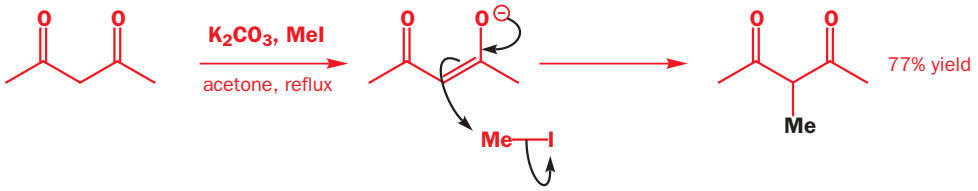
Alkylation of β-dicarbonyl compounds

▶ Typical electron-withdrawing groups include COR, CO_2R, CN, $CONR_2$, SO_2R, $P{=}O(OR)_2$.

The presence of two, or even three, electron-withdrawing groups on a single carbon atom makes the remaining proton(s) appreciably acidic (pK_a 10–15), which means that even mild bases can lead to complete enolate formation. With bases of the strength of alkoxides or weaker, only the multiply stabilized anions form: protons adjacent to just one carbonyl group generally have a $pK_a > 20$. The most important enolates of this type are those of 1,3-dicarbonyl (or β-dicarbonyl) compounds.

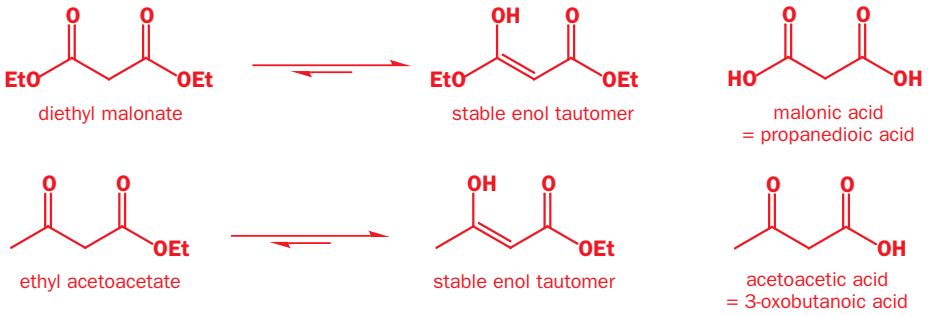


The resulting anions are alkylated very efficiently. This diketone is enolized even by potassium carbonate, and reacts with methyl iodide in good yield. Carbonate is such a bad nucleophile that the base and the electrophile can be added in a single step.



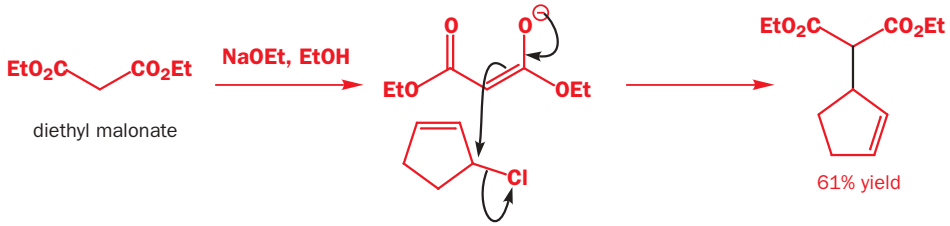
Among the β-dicarbonyls, two compounds stand out in importance—diethyl (or dimethyl) malonate and ethyl acetoacetate. You should make sure you remember their structures and trivial names.

■ You met these compounds, and their stable enols, in Chapter 21.

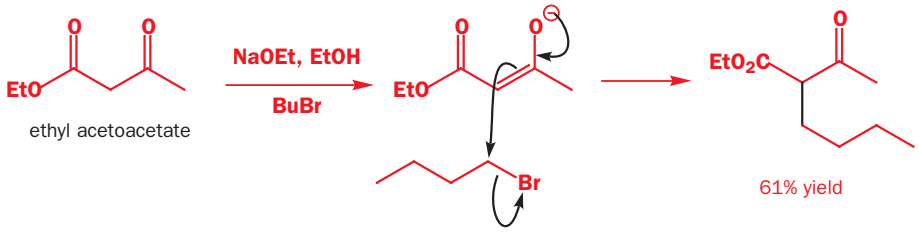


With these two esters, the choice of base is important: nucleophilic addition can occur at the ester carbonyl, which could lead to transesterification (with alkoxides), hydrolysis (with hydroxide), or amide formation (with amide anions). The best choice is usually an alkoxide identical with the alkoxide component of the ester (that is, ethoxide for diethy lmalonate; methoxide for dimethyl malonate). Alkoxides (pK_a 16) are basic enough to deprotonate between two carbonyl groups but, should substitution occur at C=O, there is no overall reaction.

In this example the electrophile is the allylic cyclopentenyl chloride, and the base is ethoxide in ethanol—most conveniently made by adding one equivalent of sodium metal to dry ethanol.



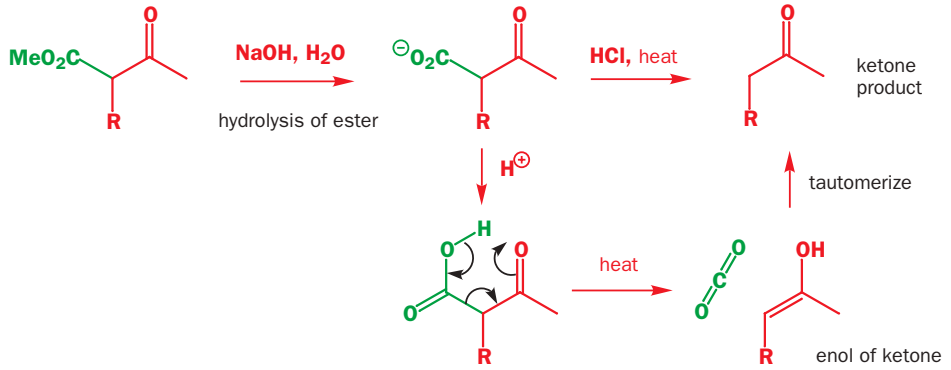
The same base is used in the alkylation of ethyl acetoacetate with butyl bromide.



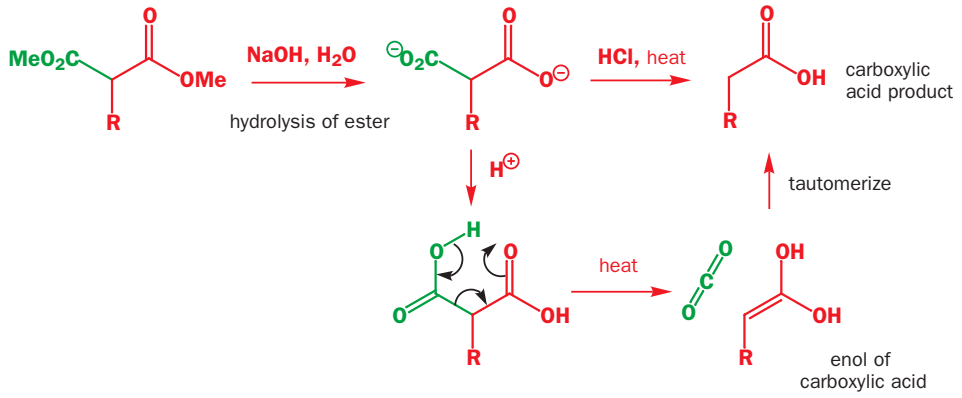
Various electron-withdrawing groups can be used in almost any combination with good results. In this example an ester and a nitrile cooperate to stabilize an anion. Nitriles are not quite as anion-stabilizing as carbonyl groups so this enolate requires a stronger base (sodium hydride) in an aprotic solvent (DMF) for success. The primary alkyl tosylate serves as the electrophile.

These doubly stabilized anions are alkylated so well that it is common to carry out an alkylation between two carbonyl groups, only to remove one of them at a later stage. This is made possible by the fact that carboxylic acids with a b-carbonyl group **decarboxylate** (lose carbon dioxide) on heating. The mechanism below shows how. After alkylation of the dicarbonyl compound the unwanted ester is first hydrolysed in base. Acidification and heating lead to decarboxylation via a six-membered cyclic transition state in which the acid proton is transferred to the carbonyl group as the key bond breaks, liberating a molecule of carbon dioxide. The initial product is the enol form of a carbonyl compound that rapidly tautomerizes to the more stable keto form—now with only one carbonyl group. Using this technique, β-keto-esters give ketones while malonate esters give simple carboxylic acids (both ester groups hydrolyse but only one can be lost by decarboxylation). Decarboxylation can occur only with a second carbonyl group appropriately placed β to the acid, because the decarboxylated product must be formed as an enol.

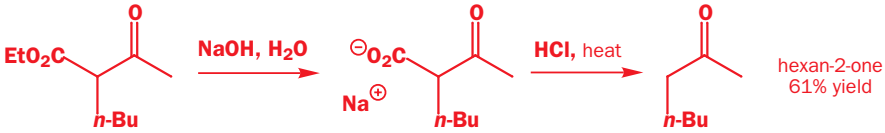
decarboxylation of acetoacetate derivatives to give ketones



decarboxylation of malonate derivatives to give carboxylic acids

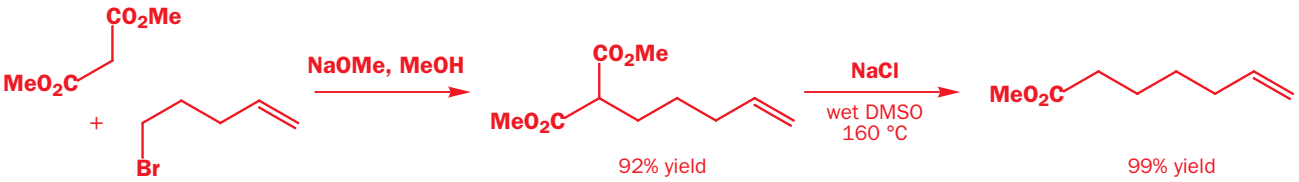


The alkylation of ethyl acetoacetate with butyl bromide on p. 000 was done with the expressed intention of decarboxylating the product to give hexan-2-one. Here are the conditions for this decarboxylation: the heating step drives off the CO_2 by increasing the gearing on the entropy term ($TDS^{\ddagger}$) of the activation energy (two molecules are made from one).

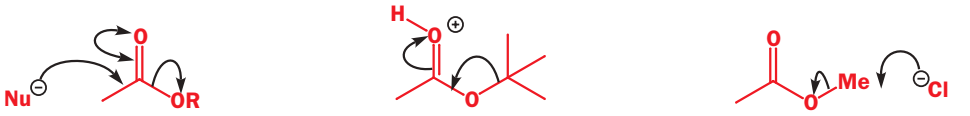


Esters are much easier to work with than carboxylic acids, and a useful alternative procedure removes one ester group without having to hydrolyse the other. The malonate ester is heated in a

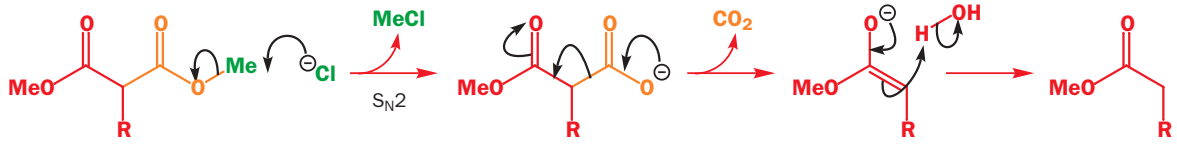
polar aprotic solvent—usually DMSO—in the presence of sodium chloride and a little water. No acid or base is required and, apart from the high temperature, the conditions are fairly mild. The scheme below shows a dimethyl malonate alkylation (note that NaOMe is used with the dimethyl ester) and removal of the methyl ester.



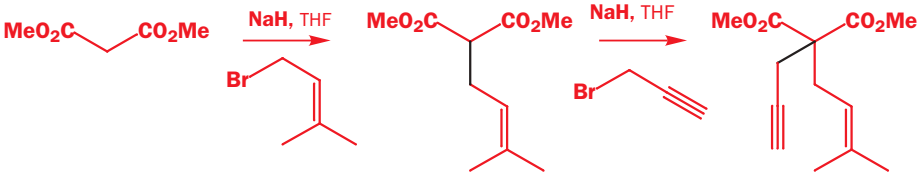
The mechanism is a rather unusual type of ester cleavage reaction. You met, in Chapter 17 and again in Chapter 25, the cleavage of *t*-butyl esters in acid solution via an S_N1 mechanism. In the reaction we are now considering, the same bond breaks (O–alkyl)—but not, of course, via an S_N1 mechanism because the alkyl group is Me. Instead the reaction is an S_N2 substitution of carboxylate by Cl^-.



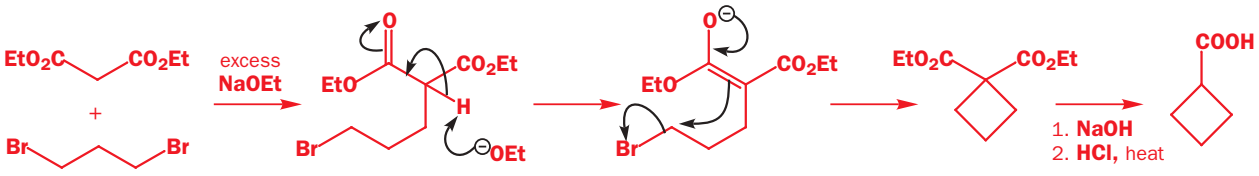
Chloride is a poor nucleophile, but it is more reactive in DMSO by which it cannot be solvated. And, as soon as the carboxylate is substituted, the high temperature encourages (entropy again) irreversible decarboxylation, and the other by-product, MeCl, is also lost as a gas. The 'decarboxylation' (in fact, removal of a CO_2Me group, not CO_2) is known as the **Krapcho decarboxylation**. Because of the S_N2 step, it works best with *methyl* malonate esters.



We have only looked at single alkylations of dicarbonyl compounds, but there are two acidic protons between the carbonyl groups and a second alkylation is usually possible. Excess of base and alkyl halide gives two alkylations in one step. More usefully, it is possible to introduce two different alkyl groups by using just one equivalent of base and alkyl halide in the first step.

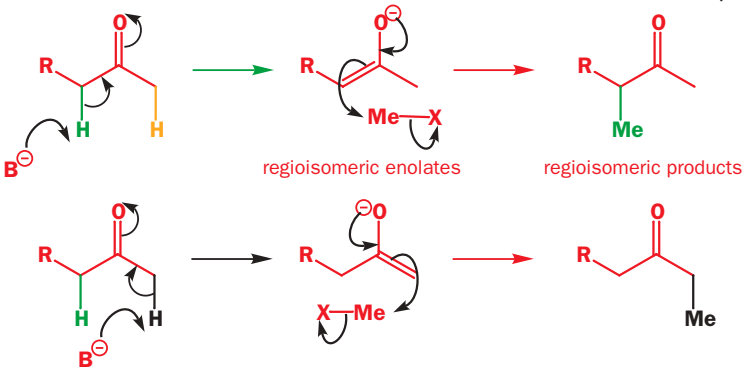


With a dihaloalkane, rings can be formed by two sequential alkylation reactions: this is an important way of making cycloalkanecarboxylic acids. Even the usually more difficult (see Chapter 42) four-membered rings can be made in this way.



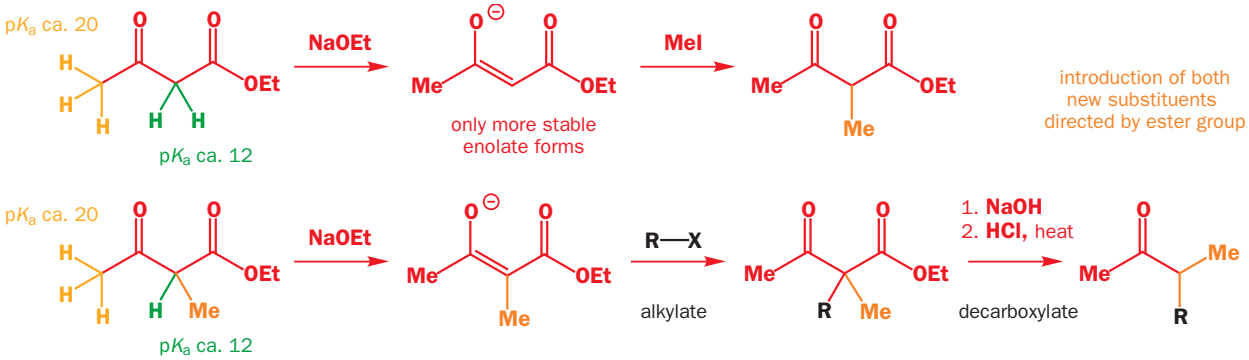
Ketone alkylation poses a problem in regioselectivity

Ketones are unique because they can have enolizable protons on both sides of the carbonyl group. Unless the ketone is symmetrical, or unless one side of the ketone happens to have no enolizable protons, two regioisomers of the enolate are possible and alkylation can occur on either side to give regioisomeric products. We need to be able to control which enolate is formed if ketone alkylations are to be useful.

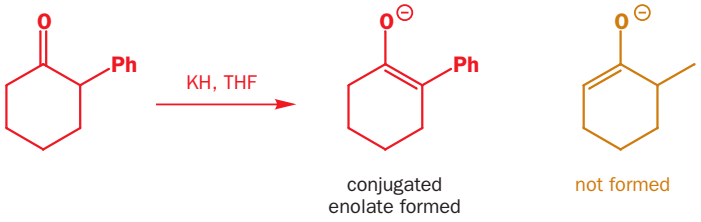


Thermodynamically controlled enolate formation

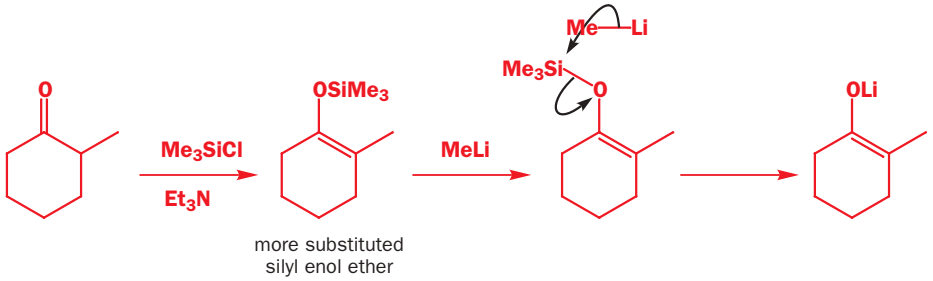
Selective enolate formation is straightforward if the protons on one side of the ketone are significantly more acidic than those on the other. This is what you have just seen with ethyl acetoacetate: it is a ketone, but with weak bases ($pK_aH < 18$) it only ever enolizes on the side where the protons are acidified by the second electron-withdrawing group. If two new substituents are introduced, in the manner you have just seen, they will always both be joined to the same carbon atom. This is an example of thermodynamic control: only the more stable of the two possible enolates is formed.



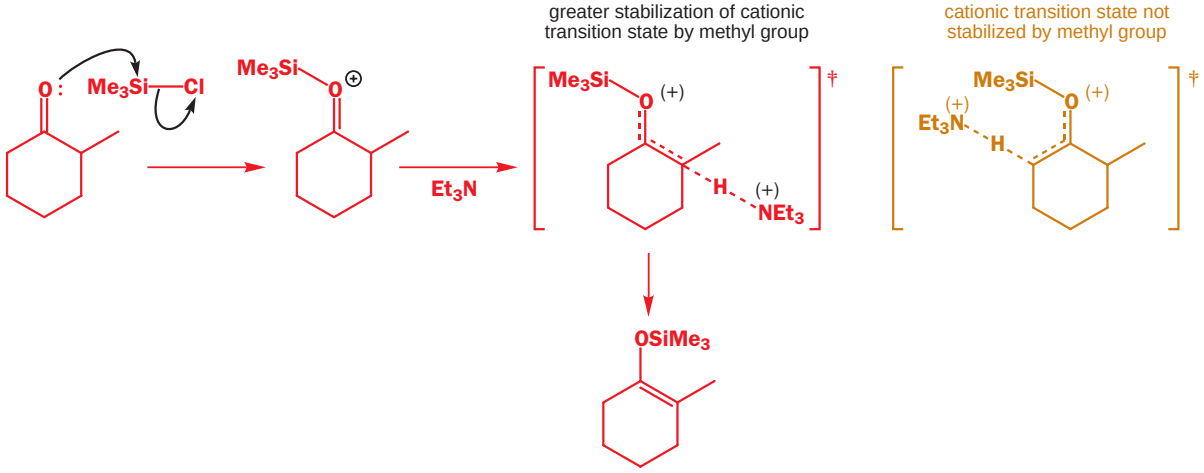
This principle can be extended to ketones whose enolates have less dramatic differences in stability. We said in Chapter 21 that, since enols and enolates are alkenes, the more substituents they carry the more stable they are. So, in principle, even additional alkyl groups can control enolate formation under thermodynamic control. Formation of the more stable enolate requires a mechanism for equilibration between the two enolates, and this must be proton transfer. If a proton source is available—and this can even be just excess ketone—an equilibrium mixture of the two enolates will form. The composition of this equilibium mixture depends very much on the ketone but, with 2-phenylcyclohexanone, conjugation ensures that only one enolate forms. The base is potassium hydride: it's strong, but small, and can be used under conditions that permit enolate equilibration.



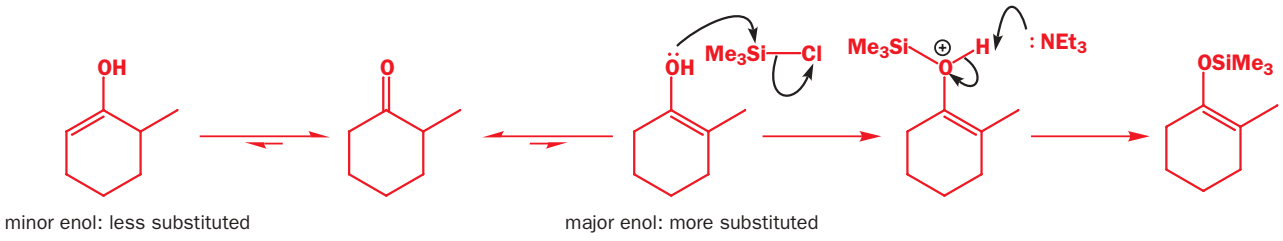
The more substituted lithium enolates can also be formed from the more substituted silyl enol ethers by substitution at silicon—a reaction you met in Chapter 21. The value of this reaction now becomes clear, because the usual way of making silyl enol ethers (Me_3SiCl, Et_3N) typically produces, from unsymmetrical ketones, the more substituted of the two possible ethers.



One possible explanation for the thermodynamic regioselectivity in the enol ether-forming step is related to our rationalization of the regioselectivity of bromination of ketones in acid on p. 000. Triethylamine (pK_{aH} 10) is too weak a base to deprotonate the starting carbonyl compound (pK_a ca. 20), and the first stage of the reaction is probably an oxygen–silicon interaction. Loss of a proton now takes place through a cationic transition state, and this is stabilized rather more if the proton being lost is next to the methyl group: methyl groups stabilize partial cations just as they stabilize cations.



An alternative view is that reaction takes place through the enol: the Si–O bond is so strong that even neutral enols react with Me_3SiCl, on oxygen, of course. The predominant enol is the more substituted, leading to the more substituted silyl enol ether.



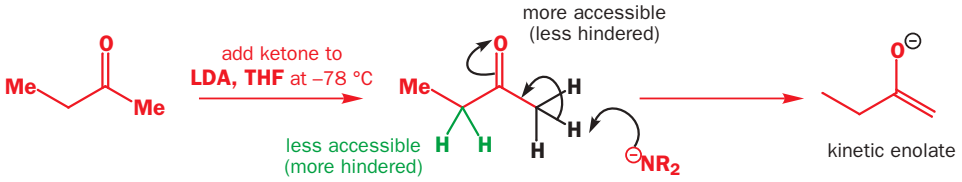
Kinetically controlled enolate formation

LDA is too hindered to attack C=O, so it attacks C–H instead. And, if there is a choice of C–H bonds, it will attack the least hindered possible. It will also prefer to attack more acidic C–H bonds, and C–H bonds on less substituted carbons are indeed more acidic. Furthermore, statistics helps, since a less substituted C atom has more protons to be removed (three versus two in this example) so, even if the rates were the same, the less substituted enolate would predominate.

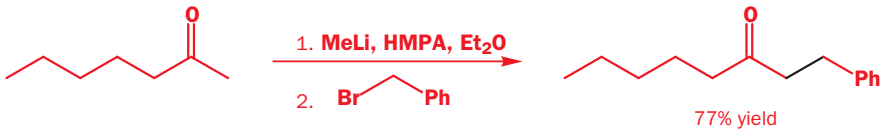
▶ Think of base strengths: MeLi is a weaker base than *t*-BuLi, so the conjugate acid must be a stronger acid.

▶ There must never be more ketone in the mixture than base, or exchange of protons between ketone and enolate will lead to equilibration. Kinetic enolate formations with LDA must be done by adding the ketone *to* the LDA so that there is excess LDA present throughout the reaction.

These factors multiply to ensure that the enolate that forms will be the one with the fewer substituents—provided we now prevent equilibration of the enolate to the more stable, more substituted one. This means keeping the temperature low, typically –78 °C, keeping the reaction time short, and using an excess of strong base to deprotonate irreversibly and ensure that there is no remaining ketone to act as a proton source. The enolate that we then get is the one that formed faster—the kinetic enolate—and not necessarily the one that is more stable.

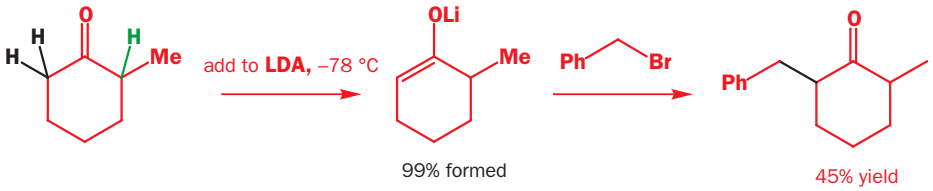


In general, this effect is sufficient to allow selective kinetic deprotonation of methyl ketones, that is, where the distinction is between Me and alkyl. In this example, unusually, MeLi is used as a base: LDA was probably tried but perhaps gave poorer selectivity. The first choice for getting kinetic enolate formation should always be LDA.

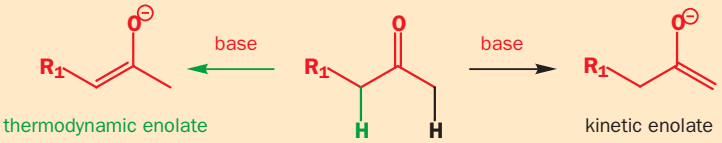


The same method works very well for 2-substituted cyclohexanones: the less substituted enolate forms. Even with 2-phenylcyclohexanone, which, as you have just seen, has a strong thermodynamic preference for the conjugated enolate, only the less substituted enolate forms.

2-Methylcyclohexanone can be regioselectively alkylated using LDA and benzyl bromide by this method.



● Regioselective formation of enolates from ketones

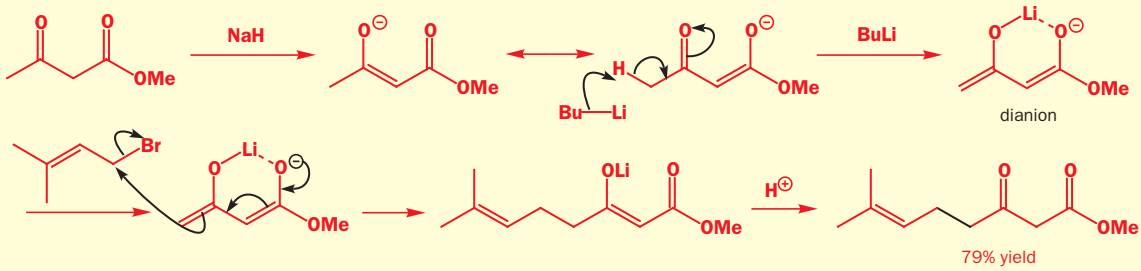


Thermodynamic enolates are:
- more substituted
- more stable
- favoured by excess ketone, high temperature, long reaction time

Kinetic enolates are:
- less substituted
- less stable
- favoured by strong, hindered base, low temperature, short reaction time

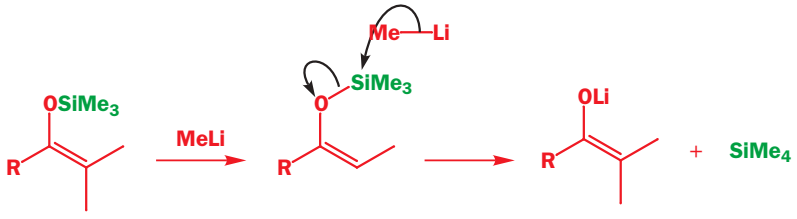
Dianions allow unusual regioselectivity in alkylations of methyl acetoacetate

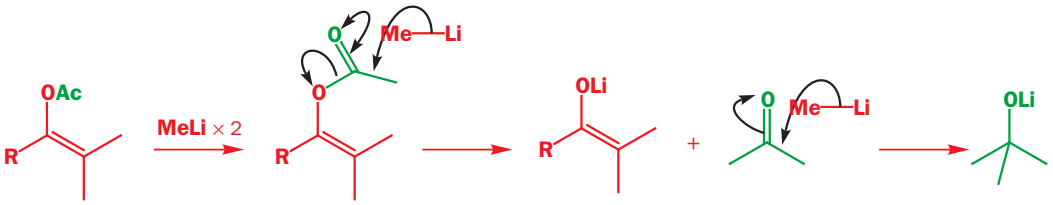
In Chapter 24, we introduced the idea that the last-formed anion in a dianion or trianion is the most reactive. Methyl acetoacetate is usually alkylated on the central carbon atom because that is the site of the most stable enolate. But methyl acetoacetate dianion—formed by removing a second proton from the usual enolate with a very strong base (usually butyllithium)—reacts first on the less stable anion: the terminal methyl group. Protonation of the more stable enolate then leads to the product. Butyllithium can be used as a base because the anionic enolate intermediate is not electrophilic.



Enones provide a solution to regioselectivity problems

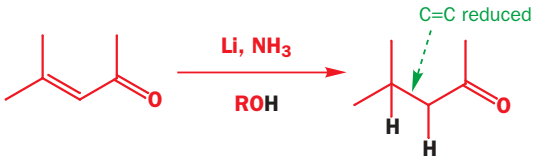
Enolates can be made regiospecifically from, for example, silyl enol ethers or enol acetates just by treating them with an alkyllithium. These are both substitution reactions in which RLi displaces the enolate: one is S_N2(Si) and the other is attack at C=O. Provided there is no proton source, the enolate products have the same regiochemistry as their stable precursors, and single enolate regioisomers are formed. But there is a problem: forming enol ethers or enol esters will usually itself require a regioselective enolization! There are two situations in which this method is nonetheless useful: when the *more* substituted lithium enolate (which is hard to make selectively otherwise) is required, and when a silyl enol ether can be formed by a method not involving deprotonation. These methods are what we shall now consider.



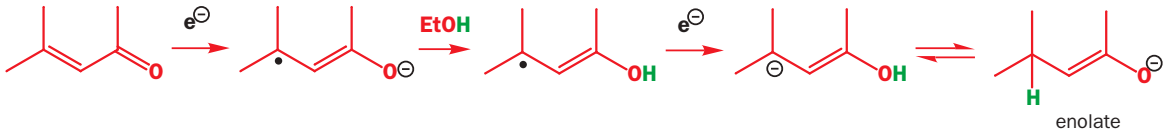


Dissolving metal reduction of enones gives enolates regiospecifically

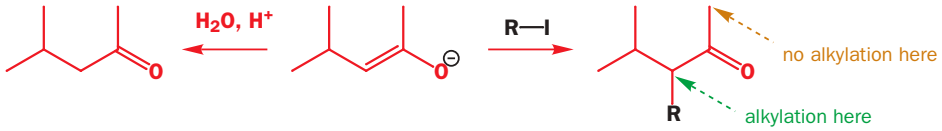
In Chapter 24 you met the **Birch reduction**: the use of dissolving metals (K, Na, or Li in liquid ammonia, for example) to reduce aromatic rings and alkynes. The dissolving metal reduction of enones by lithium metal in liquid ammonia is similar to these reactions—the C=C bond of the enone is reduced, with the C=O bond remaining untouched. An alcohol is required as a proton source and, in total, two electrons and two protons are added in a stepwise manner giving net addition of a molecule of hydrogen to the double bond.



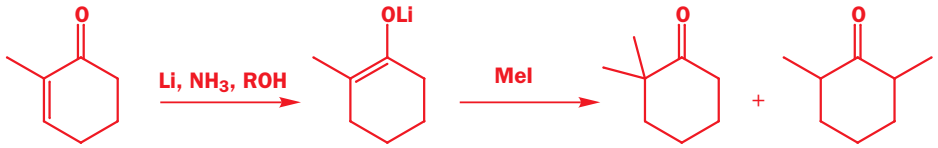
The mechanism follows that described on p. 000: transfer of an electron forms a radical anion that is protonated by the alcohol to form a radical. A second electron transfer forms an anion that can undergo tautomerization to an enolate.



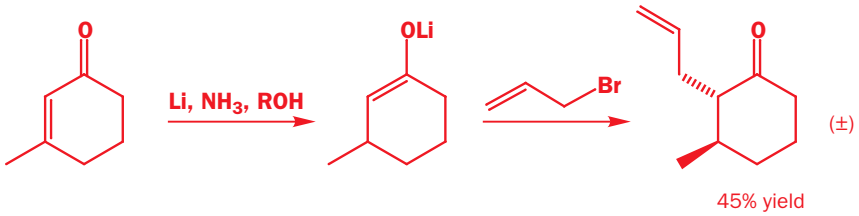
The enolate is stable to further reduction, and protonation during the work-up will give a ketone. But reaction with an alkyl halide is more fruitful: because the enolate forms only where the double bond of the enone was, regioselective alkylation becomes possible.



You saw above that an equilibrium mixture of the enolates of 2-methylcyclohexanone contains only about a 4:1 ratio of regioisomers. By reducing an enone to an enolate, only 2% of the unwanted regioisomer is formed.

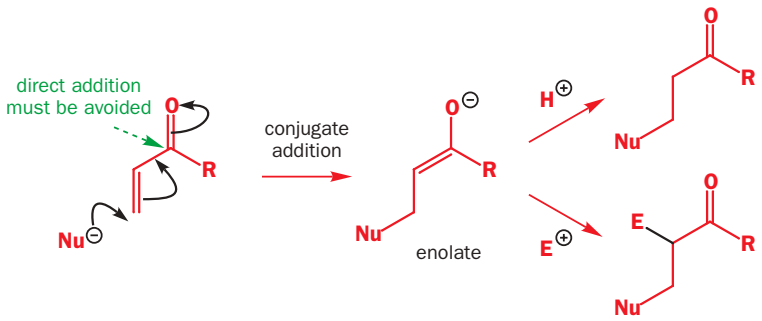


The transfer of electrons is not susceptible to steric hindrance so substituted alkenes pose no problem. In the next example, the enolate reacts with allyl bromide to give a single stereoisomer of the product (the allyl bromide attacks from the face opposite the methyl group). Naturally, only one regioisomer is formed as well, and it would be a tall order to expect formation of this single enolate regioisomer by any form of deprotonation method.



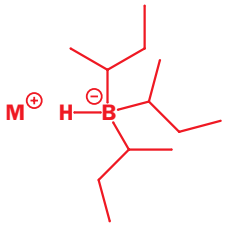
Conjugate addition to enones gives enolates regiospecifically

Although we did not talk in detail about them at that time, you will recall from Chapter 10 that conjugate addition to enones generates first an enolate, which is usually protonated in the work-up. But, again, more fruitful things can be done with the enolate under the right conditions.



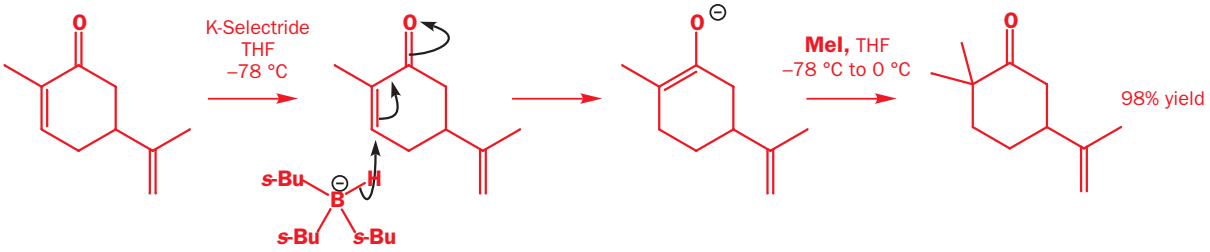
The simplest products are formed when Nu = H, but this poses a problem of regioselectivity in the nucleophilic attack step: a nucleophilic hydride equivalent that selectively undergoes conjugate addition to the enone is required. This is usually achieved with extremely bulky hydride reagents such as lithium or potassium tri(sec-butyl)borohydride (often known by the trade names of L- or K-Selectride, respectively). In this example, K-Selectride reduces the enone to an enolate that is alkylated by methyl iodide to give a single regioisomer. The reaction also illustrates the difference in reactivity between conjugated and isolated double bonds.

bulky reducing agents

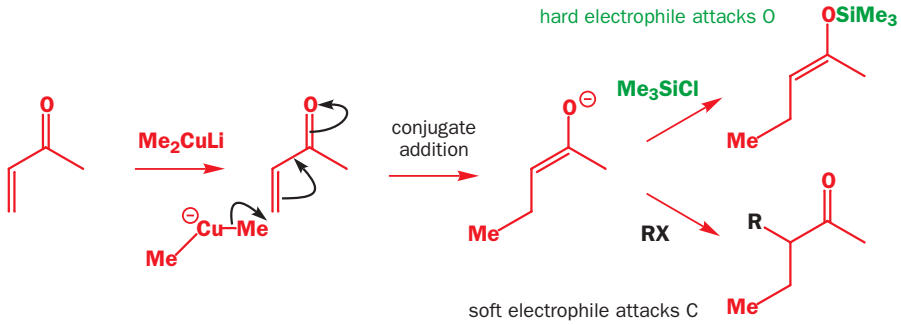


M = Li: lithium tri-*sec*-butylborohydride (L-Selectride)

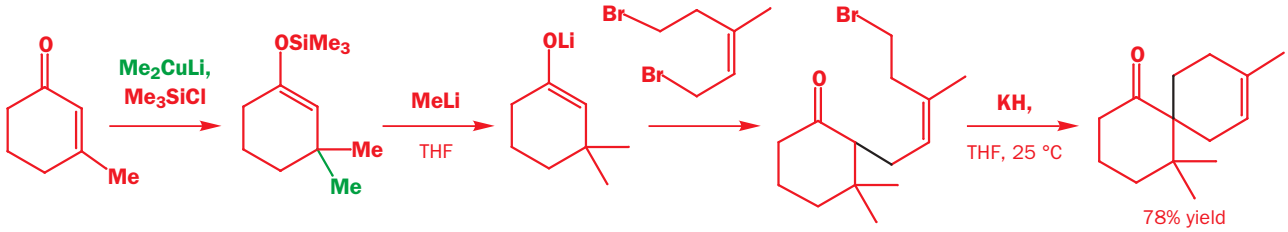
M = K: potassium tri-*sec*-butylborohydride (K-Selectride)



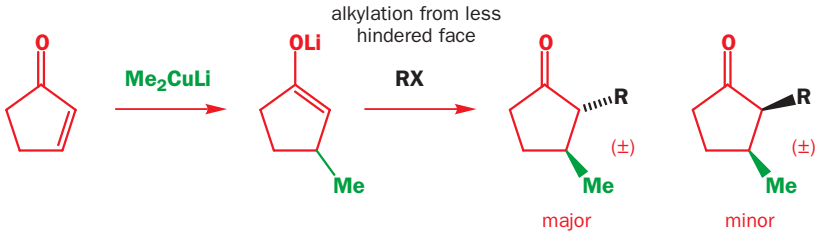
With organocopper reagents, conjugate addition introduces a new alkyl group and, if the resulting enolates are themselves alkylated, two new C–C bonds can be formed in a single step (a **tandem reaction**: one C–C bond-formation rides behind another). In Chapter 10 we explained that the best organocuprate additions are those carried out in the presence of Me_3SiCl: the product of these reactions is a silyl enol ether, formed regioselectively (the 'enol' double bond is always on the side where the enone used to be).



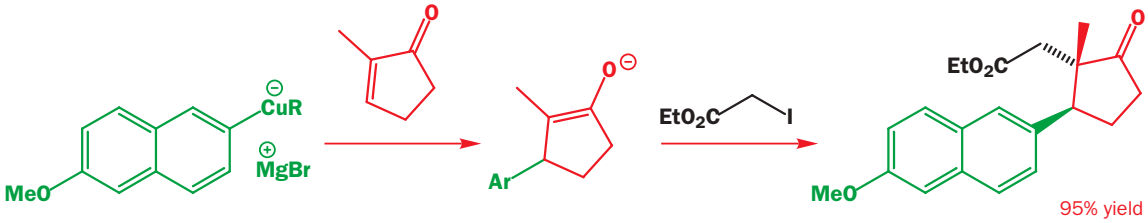
The silyl enol ethers are too unreactive for direct alkylation by an alkyl halide, but by converting them to lithium enolates all the usual alkylation chemistry becomes possible. This type of reaction forms the key step in a synthesis of the natural product α-chamigrene. Conjugate addition of Me_2CuLi gives an enolate that is trapped with trimethylsilyl chloride. Methyllithium converts the resulting silyl enol ether into a lithium enolate (by S_N2 at Si). The natural product has a *spiro* six-membered ring attached at the site of the enolate, and this was made by alkylating with a dibromide (you saw this done on p. 000). The first substitution is at the more reactive allylic bromide. A second enolization is needed to make the ring, but this can be done under equilibrating conditions because the required six-membered ring forms much faster than the unwanted eight-membered ring that would arise by attack on the other side of the ketone.



Among the most important of these tandem conjugate addition–alkylation reactions are those of cyclopentenones. With cyclopentenone itself, the *trans* diastereoisomer usually results because the alkylating agent approaches from the less hindered face of the enolate.



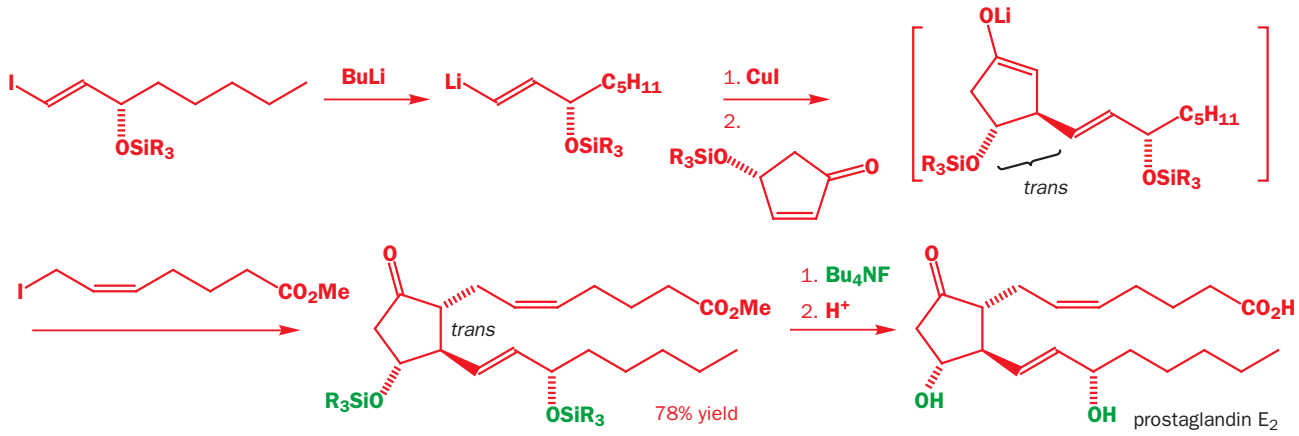
This is the sort of selectivity evident in the next example, which looks more complicated but is really just addition of an arylcopper reagent followed by alkylation (*trans* to the bulky Ar group) with an iodoester.



■

Ryoji Noyori works at the University of Nagoya in Japan. He has introduced many methods for making molecules, the most important of which allow the formation of single enantiomers using chiral catalysts. You will meet some more of his chemistry in Chapter 45.

One of the most dramatic illustrations of the power of conjugate addition followed by alkylation is the short synthesis of the important biological molecule prostaglandin E_2 by Ryoji Noyori in Japan. The organocopper reagent and the alkylating agent contain all the functionality required for both side chains of the target in protected form. The required *trans* stereochemistry is assembled in the key step, which gives a 78% yield of a product requiring only removal of the silyl ether and ester protecting groups. The organometallic nucleophile was prepared from a vinyl iodide by halogen–metal exchange (Chapter 9). In the presence of copper iodide this vinyllithium adds to the cyclopentenone in a conjugate sense to give an intermediate enolate. Because in this case the starting enone already has a stereogenic centre, this step is also stereoselective: attack on the less hindered face (opposite the silyl ether) gives the *trans* product. The resulting enolate was alkylated with the allylic iodide containing the terminal ester: once again the *trans* product was formed. It is particularly vital that enolate equilibration is avoided in this reaction to prevent the inevitable E1cB elimination of the silyloxy group that would occur from the other enolate.



To conclude...

We have considered the reactions of enolates and their equivalents with alkyl halides. In the next chapter we move on to consider the reactions of the same types of enolate equivalents with a different class of electrophiles: carbonyl compounds themselves.

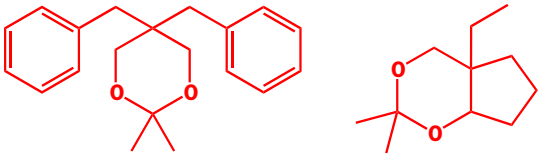
Summary of methods for alkylating enolates

Specific enol equivalent	Notes
To alkylate esters	
• LDA → lithium enolate	
• use diethyl- or dimethylmalonate and decarboxylate	gives acid (NaOH, HCl) or ester (NaCl, DMSO)
To alkylate aldehydes	
• use enamine	with reactive alkylating agents
• use silyl enol ether	with S_N1-reactive alkylating agents
• use aza-enolate	with S_N2-reactive alkylating agents
To alkylate symmetrical ketones	
• LDA → lithium enolate	
• use acetoacetate and decarboxylate	equivalent to alkylating acetone
• use enamine	with reactive alkylating agents
• use silyl enol ether	with S_N1-reactive alkylating agents
• use aza-enolate	with S_N2-reactive alkylating agents
To alkylate unsymmetrical ketones on more substituted side	
• Me_3SiCl, Et_3N → silyl enol ether	with S_N1-reactive alkylating agents
• Me_3SiCl, Et_3N → silyl enol ether → lithium enolate with MeLi	with S_N2-reactive alkylating agents
• alkylate acetoacetate twice and decarboxylate	two successive alkylations of ethyl acetoacetate
• addition or reduction of enone to give specific lithium enolate or silyl enol ether	
To alkylate unsymmetrical ketones on less substituted side	
• LDA → kinetic lithium enolate	with S_N2-reactive electrophiles
• LDA then Me_3SiCl → silyl enol ether	with S_N1-reactive electrophiles
• use dianion of alkylated acetoacetate and decarboxylate	two successive alkylations of ethyl acetoacetate
• use enamine	with reactive electrophiles

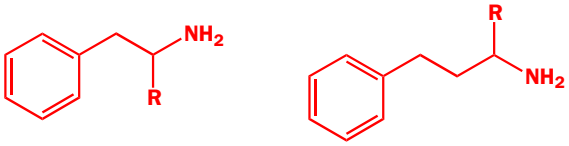
Problems

1. Suggest how the following compounds might be made by the alkylation of an enol or enolate.

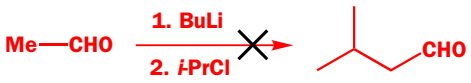
2. And how might these compounds be made using alkylation of an enol or enolate as one step in the synthesis?



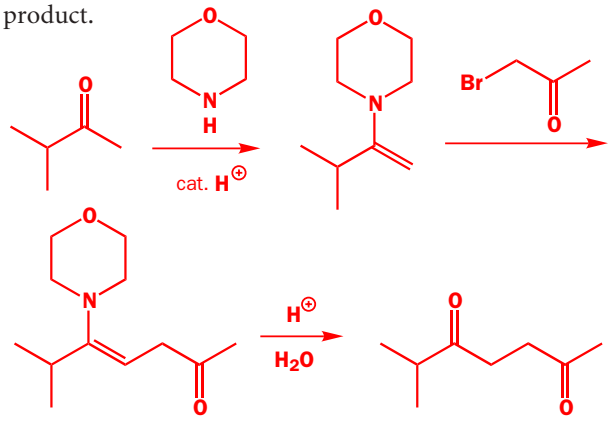
3. And, further, how might these amines by synthesized using alkylation reactions of the enolate style as part of the synthesis?



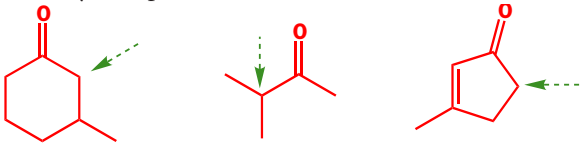
4. This attempted enolate alkylation does not give the required product. What goes wrong? What products would be expected from the reaction?



5. Draw mechanisms for the formation of this enamine, its reaction with the alkyl halide shown, and the hydrolysis of the product.

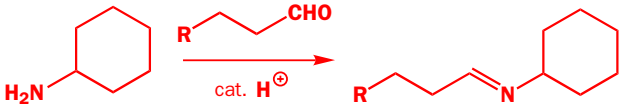


6. How would you produce specific enol equivalents at the points marked with the arrows (not necessarily starting from the simple carbonyl compound shown)?

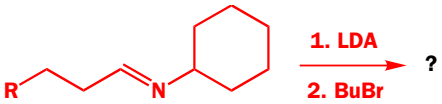


7. How would the reagents you have suggested in Problem 6 react with: (a) Br_2; (b) a primary alkyl halide RCH_2Br?

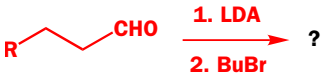
8. Draw a mechanism for the formation of the imine from cyclohexylamine and the following aldehyde.



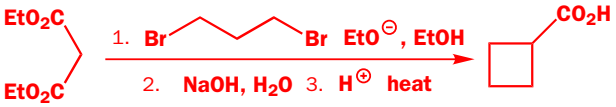
9. How would the imine from Problem 8 react with LDA followed by *n*-BuBr? Draw mechanisms for each step: reaction with LDA, reaction of the product with *n*-BuBr, and the work-up.



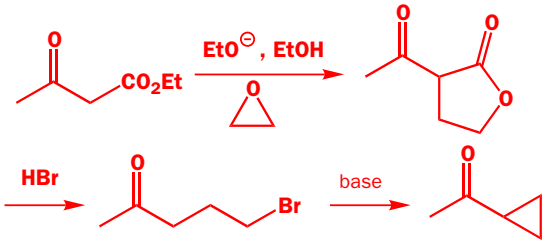
10. What would happen if this short cut for the reaction in Problems 8 and 9 were tried?



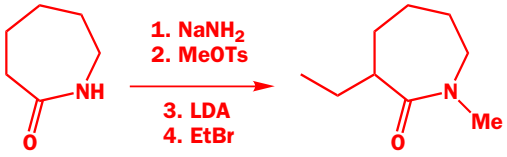
11. Suggest mechanisms for these reactions.



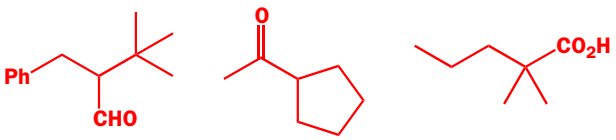
12. How does this method of making cyclopropyl ketones work? Give mechanisms for all the reactions.



13. Give the structures of the intermediates in the following reaction sequence and mechanisms for the reactions. Comment on the formation of this particular product.



14. Suggest how the following products might be made using enol or enolate alkylation as at least one step. Explain your choice of specific enol equivalents.



Reactions of enolates with aldehydes and ketones: the aldol reaction

27

Connections

Building on:

- Carbonyl compounds reacting with cyanide, borohydride, and bisulfite nucleophiles ch6
- Carbonyl compounds reacting with organometallic nucleophiles ch9
- Carbonyl compounds taking part in nucleophilic substitution reactions ch12 & ch14
- How enols and enolates react with heteroatomic electrophiles such as Br_2 and NO^+ ch21
- How enolates and their equivalents react with alkylating agents ch26

Arriving at:

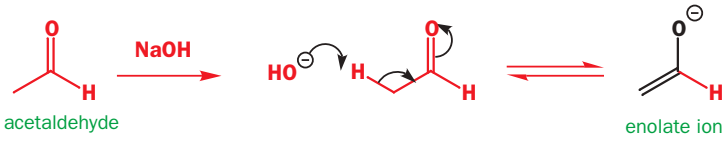
- Reactions with carbonyl compounds as both nucleophile and electrophile
- How to make hydroxy-carbonyl compounds or enones by the aldol reaction
- How to be sure that you get the product you want from an aldol reaction
- The different methods available for doing aldol reactions with enolates of aldehydes, ketones, and esters
- How to use formaldehyde as an electrophile
- How to predict the outcome of intramolecular aldol reactions

Looking forward to:

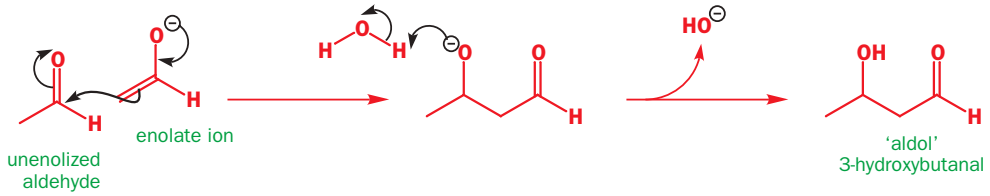
- Enolates taking part in a substitution at C=O ch28
- Enolates undergoing conjugate addition ch29
- Synthesis of aromatic heterocycles ch44
- Asymmetric synthesis ch45
- Biological organic chemistry ch49–ch51

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.



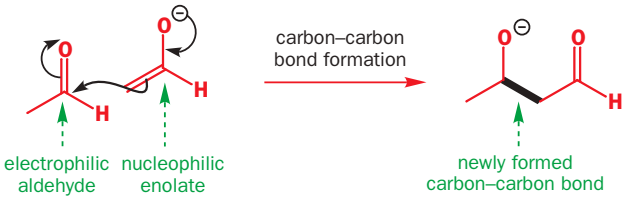
Only a small amount of the nucleophilic enolate ion is formed: hydroxide is not basic enough to enolize an aldehyde completely. Each molecule of enolate is surrounded by molecules of the aldehyde that are not enolized and so still have the electrophilic carbonyl group intact. Each enolate ion will attack 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.

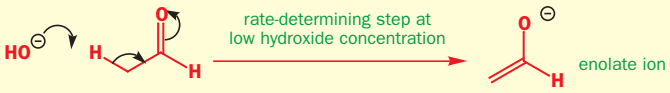
This reaction is so important because of the carbon–carbon bond formed when the nucleophilic

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



The rate equation for the aldol reaction

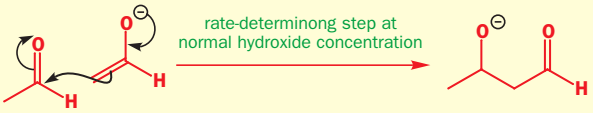
Not only is this step the most important; it is usually the rate-determining step. The rate expression for the aldol reaction at *low concentrations* of hydroxide is found experimentally to be



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

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.

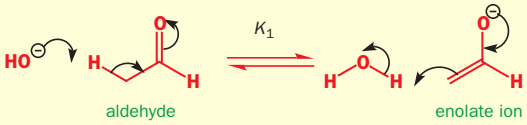
At higher hydroxide ion concentration, the rate expression becomes termolecular (k_3 expresses this) with the aldehyde concentration being squared.



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

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



$$\text{rate} = k_2[CH_3CHO] \times [\text{enolate ion}]$$

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

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

Or, rearranging this to get the enolate ion concentration,

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

And, substituting this in the rate expression,

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

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

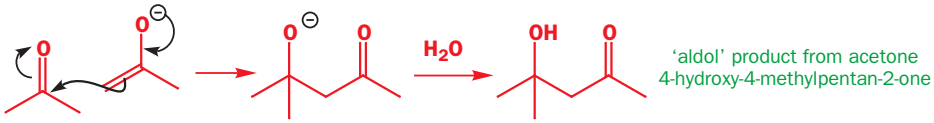
$$\text{rate} = k_3[CH_3CHO]^2 \times [HO^-]$$

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.

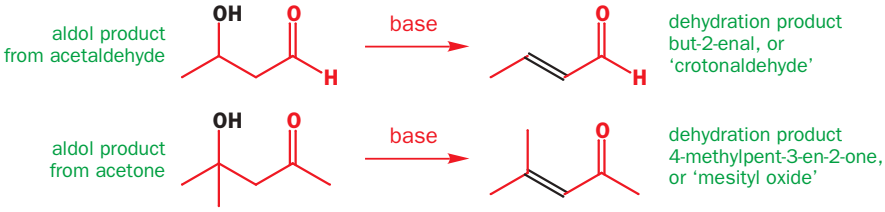
the enolization step

the carbon–carbon bond-forming step

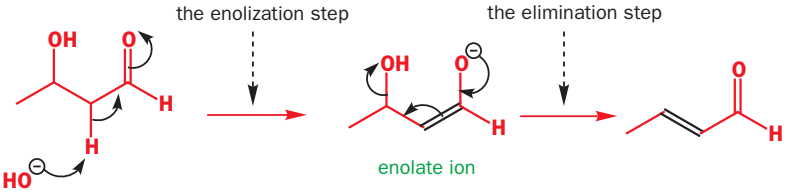


Each step is the same as the aldol sequence with acetaldehyde, and the product is again a hydroxy-carbonyl compound, but this time a hydroxy-ketone.

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.

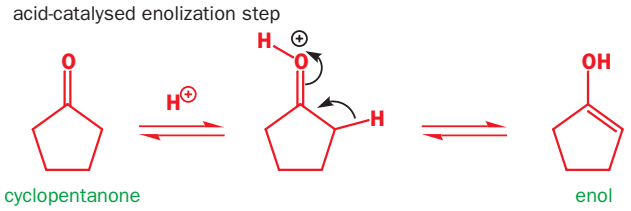


These are elimination reactions, and you met them in Chapter 19. You cannot normally eliminate water from an alcohol in basic solution and it is the carbonyl group that allows it to happen here. A second enolization reaction starts things off, and these are E1cB reactions.

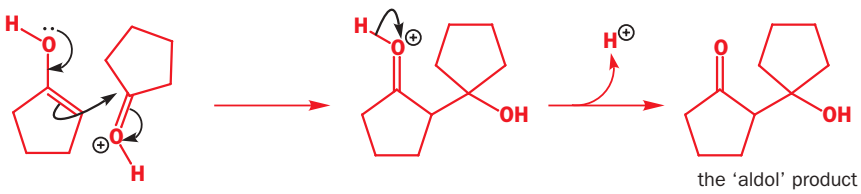


In the examples that follow in the rest of the chapter you will see that base-catalysed aldol reactions sometimes give the aldol and sometimes the elimination product. The choice is partly based on conditions—the more vigorous conditions (stronger base, higher temperatures, longer reaction time) tend 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.

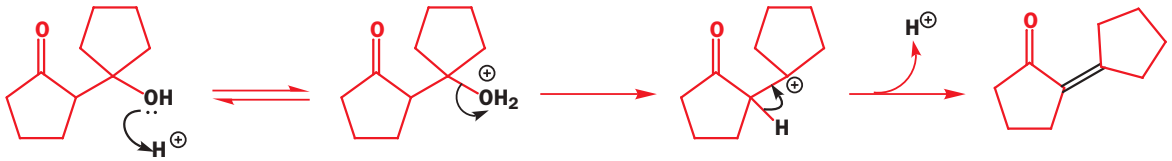


With the acetone reaction a further trick is required to ensure that the aldol product does not meet the base. The apparatus is arranged so that, on heating, the volatile acetone is condensed into a vessel containing the insoluble base. The less volatile aldol product is kept away from it.

See p. 000 for a discussion of the E1cB mechanism.

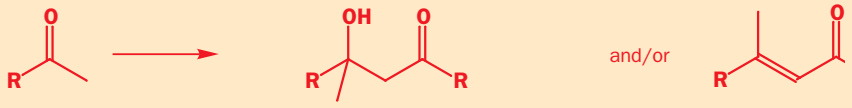
The aldol is a tertiary alcohol and would be likely to eliminate by an E1 mechanism in acid even without the carbonyl group. But the carbonyl ensures that only the stable conjugated enone is formed. Notice that the dehydration too is genuinely acid-catalysed as the acid reappears in the very last step.

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.

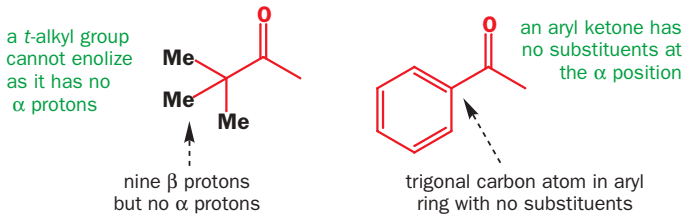
- **Base-catalysed aldol reactions may give the aldol product, or may give the dehydrated enone or enal by an E1cB mechanism**
- **Acid-catalysed aldol reactionsmay give the aldol product, but usually give the dehydrated enone or enal by an E1 mechanism**

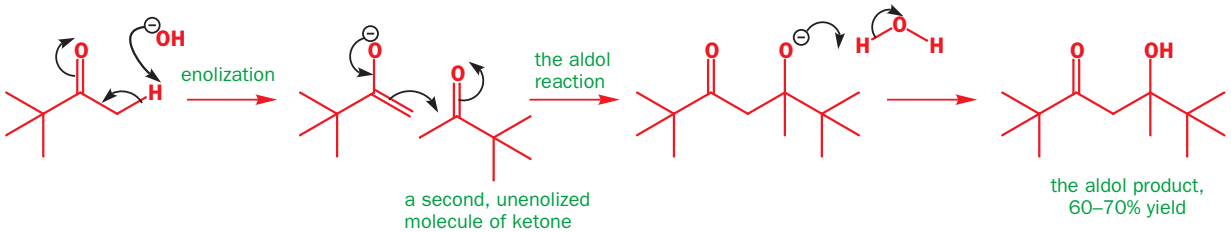


Aldol reactions of unsymmetrical ketones

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:

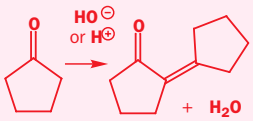




A specially interesting case of the blocked carbonyl compound is the lactone or cyclic ester. Open-chain esters do not give aldol reactions: they prefer a different reaction that is the subject of the next chapter. But lactones are in some ways quite like ketones and give unsaturated carbonyl products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

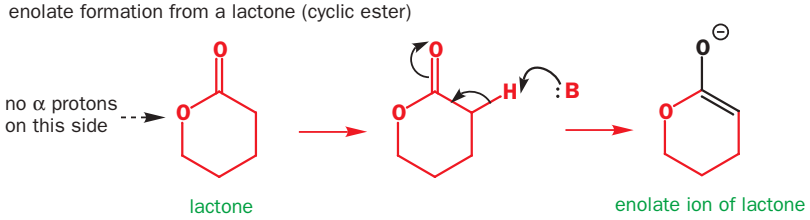
▶Condensation reactions

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.

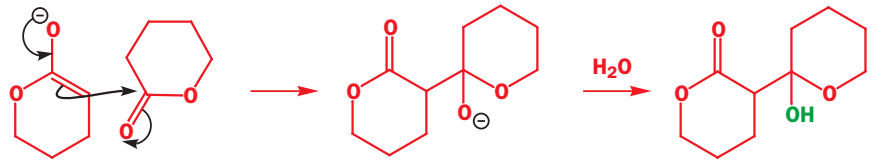
enolate formation from a lactone (cyclic ester)



▶ B in this scheme means 'base'.

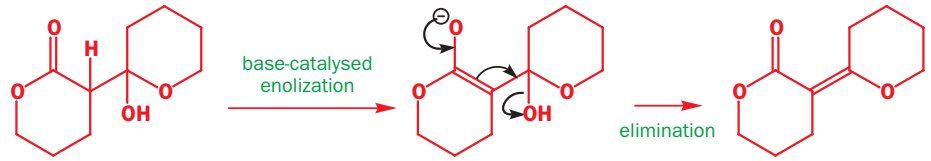
The enolate then attacks the carbonyl group of an unenolized lactone just as we have seen with aldehydes and ketones.

aldol reaction of a lactone (cyclic ester)



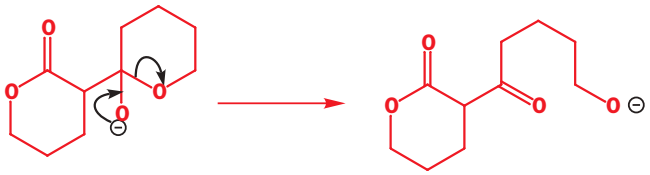
The last step is the familiar dehydration. As this reaction is being carried out in base we had better use the E1cB mechanism via the enolate of the aldol product.

the dehydration step

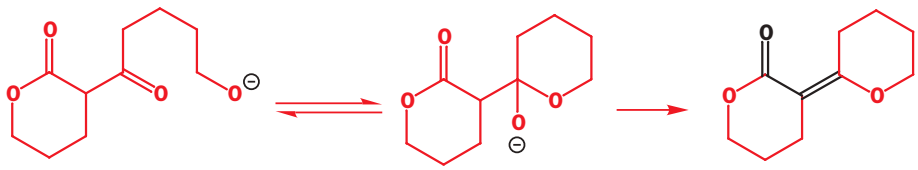


You might have been surprised that the intermediate in the aldol step of this reaction did not decompose. This intermediate could be described as a tetrahedral intermediate in a nucleophilic substitution at a carbonyl group (Chapter 12). Why then does it not break down in the usual way?

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.



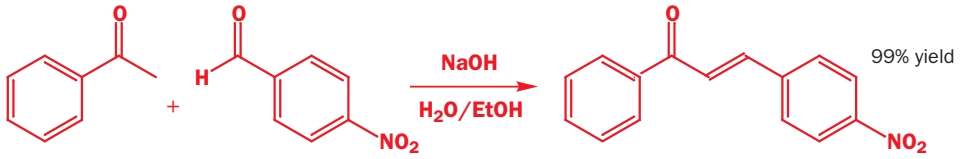
The equilibrium on the left does not affect the eventual product; it simply withdraws some of the material out of the productive reaction. We call this sort of equilibrium a **parasitic equilibrium** as it has no real life of its own—it just sucks the blood of the reaction.

▶ Normal, acyclic esters are different: their alkoxide leaving groups *can* leave, and the result is a different sort of reaction, which you will meet in the next chapter.

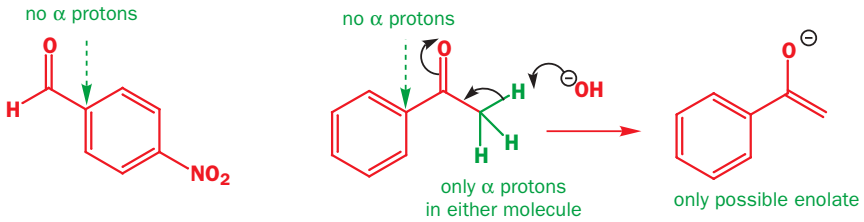
Cross-condensations

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.

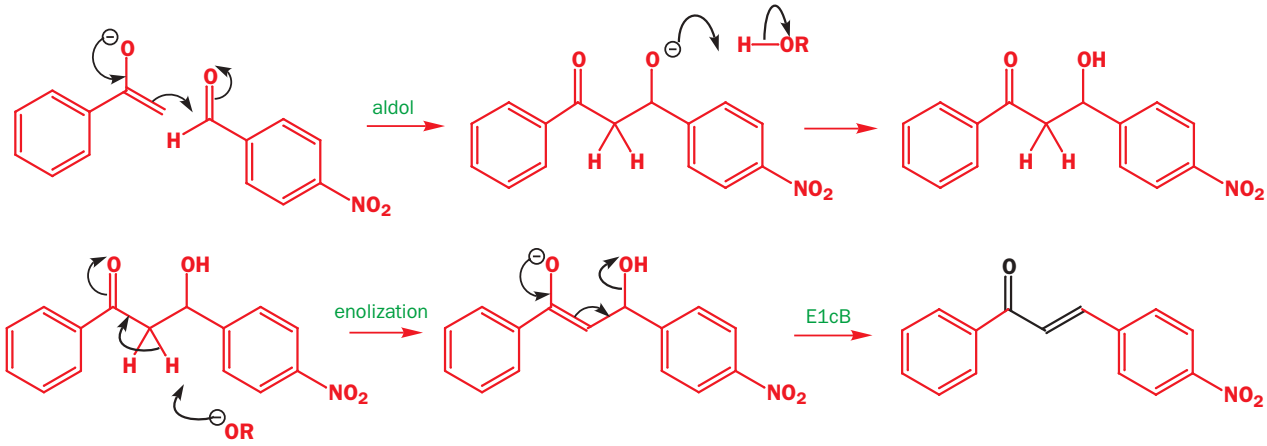
We shall start with an example that works well. The ketone PhCOMe reacts with 4-nitrobenzaldehyde in aqueous ethanol under NaOH catalysis to give a quantitative yield of an enone.



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.



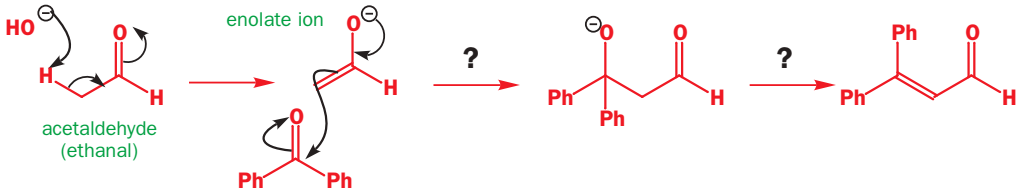
To get the observed product, the enolate obviously attacks the aldehyde to give an aldol, which then dehydrates by the E1cB mechanism.



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

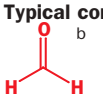
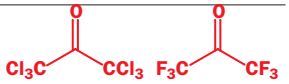
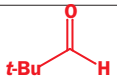
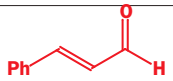
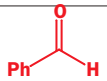
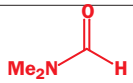
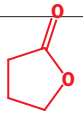
For this kind of crossed aldol reaction to work well we must have two conditions.

- **One partner only must be capable of enolization**
- **The other partner must be incapable of enolization and be *more electrophilic than the enolizable partner.***

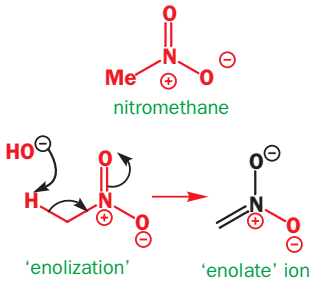
Everyone remembers the first of these conditions, but it is easy to forget the second.

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

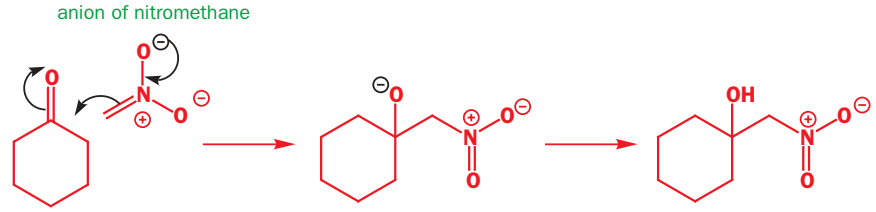
	Substituent	Typical compounds
most reactive[a]	H	 [b]
	CF_3, CCl_3	
	t-alkyl	
	alkenyl	
	aryl	
least reactive[a]	NR_2	
	OR	

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

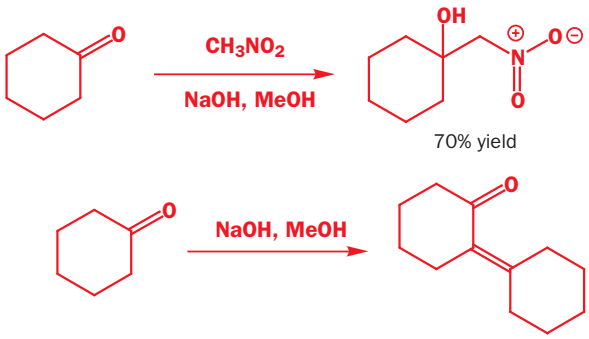


Compounds that can enolize but that are not electrophilic

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.

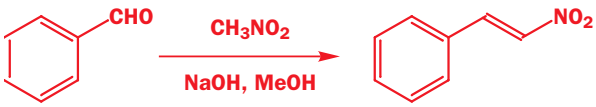


This particular example, using cyclohexanone as the electrophile and nitromethane itself as the source of the 'enolate', works quite well with NaOH as the base in methanol solution to give the 'aldol' in reasonable yield. Once again this reaction involves choice. Either compound could enolize, and, indeed,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



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 ketone 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.

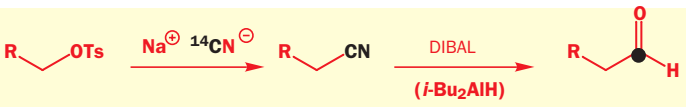


Nitroalkenes as termite defence compounds

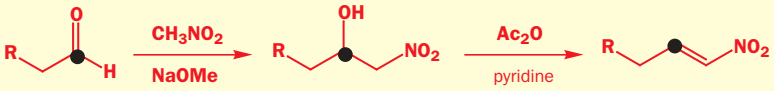
Termites are social insects, and every species has its own 'soldier' termites that defend the nest. Soldier termites of the species *Prorhinotermes simplex* have huge heads from which they spray a toxic nitroalkene on their enemies.

defensive nitroalkene from termite soldiers

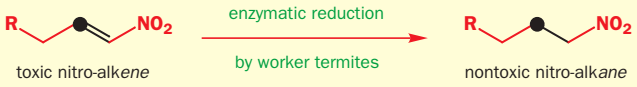
Though this compound kills other insects and even other species of termites, it has no effect on the workers of the same species. To find out why this was so, Prestwich made some radioactive compound using the aldol reaction. First, the right aldehyde was made using an S_N2 reaction with radioactive (^{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

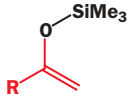
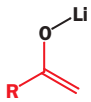
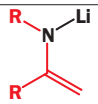
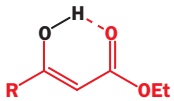
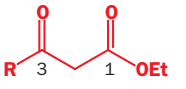
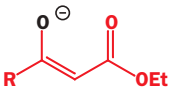
- only one enolizable component
- only one set of enolizable protons
- a carbonyl electrophile more reactive than the compound being enolized

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.

Important specific enol equivalents

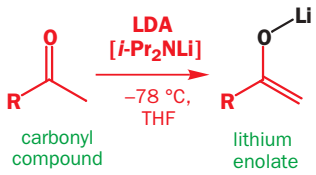
 enol	 carbonyl compound	 enolate ion
 silyl enol ether	oxygen derivatives	 lithium enolate
 enamine	nitrogen derivatives	 aza-enolate
 enol	 1,3-dicarbonyl compound	 enolate anion

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 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. The 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.

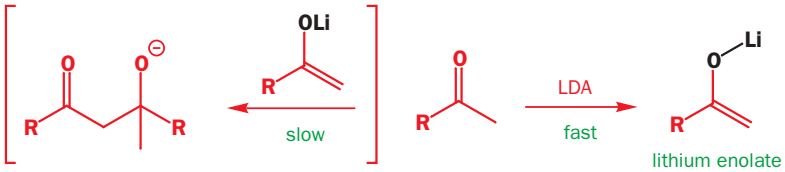
Lithium enolates in aldol reactions



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.

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

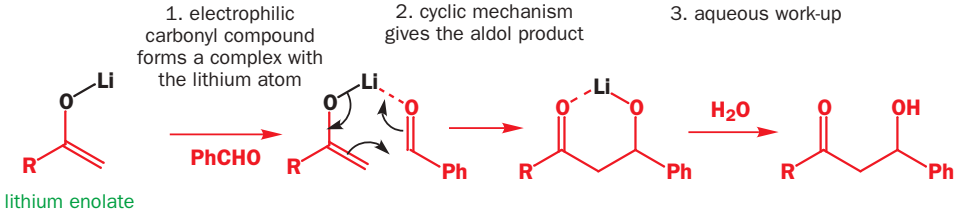
This reaction happens very quickly—so quickly that the partly formed enolate does not have a chance to react with unenolized carbonyl compound before proton removal is complete.



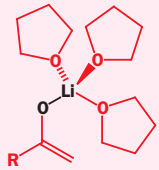
▶ Aldehydes are an exception. You can make lithium enolates from some aldehydes such as *i*-PrCHO, but generally self-condensation is too fast, so unwanted aldol self-condensation products are produced during the formation of the lithium enolate. To make specific enolates of aldehydes we need to use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

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



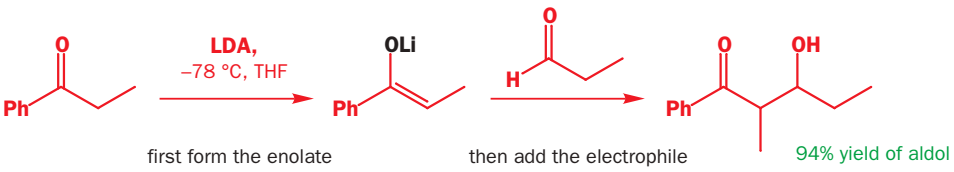
▶ There are four coordination sites on the lithium atom—those we do not show are occupied by THF molecules. Before the aldol reaction can take place, one of the THFs must be displaced by the electrophilic carbonyl partner.



the tetrahedral structure of a lithium enolate in THF

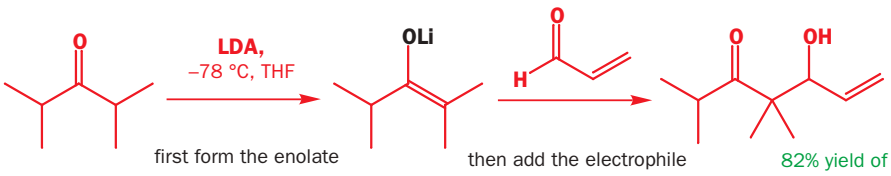
The aldol step itself is now a very favourable intramolecular reaction with a six-membered cyclic transition state. The product is initially the lithium alkoxide of the aldol, which gives the aldol on work-up.

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.

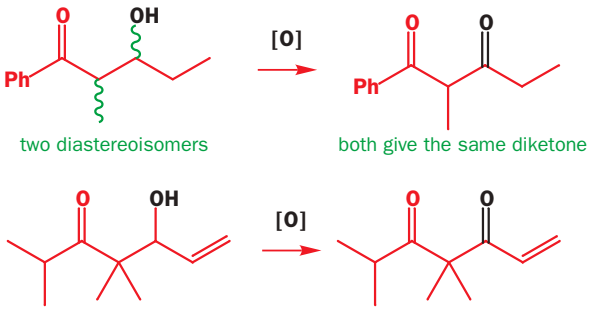


The next example is particularly impressive. The enol partner is a symmetrical ketone that is very hindered—there is only one α hydrogen on either side. The electrophilic partner is a conjugated enal that is not enolizable but that might accept the nucleophile in a conjugate manner. In spite of these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



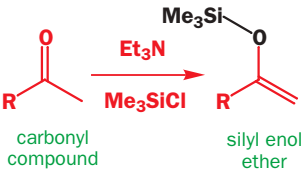
You may wonder why we did not mention the stereochemistry of the first of these two products. Two new stereogenic centres are formed and the product is a mixture of diastereoisomers. In fact, both of these products were wanted for oxidation to the 1,3-diketone so the stereochemistry is irrelevant. This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



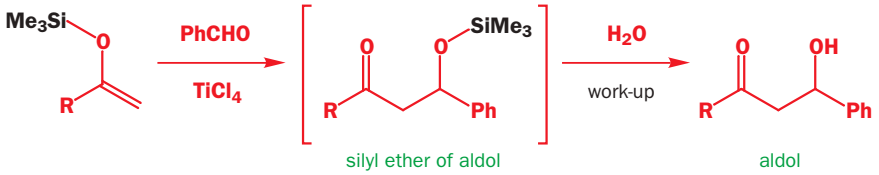
▶ The symbol [O] denotes oxidation by one of the very general but ill-defined oxidizing agents from the laboratory of the famous Welsh chemist Owen Bracketts. Here the or Swern reagents were the best (see Chapter 24).

Silyl enol ethers in aldol reactions

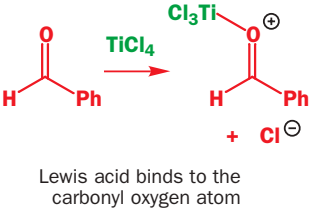
The silyl enol ether can be prepared from its parent carbonyl compound by forming a small equilibrium concentration of enolate ion with weak base such as a tertiary amine and trapping the enolate with the very efficient oxygen electrophile Me_3SiCl. The silyl enol ether is stable enough to be isolated but is usually used immediately without storing.



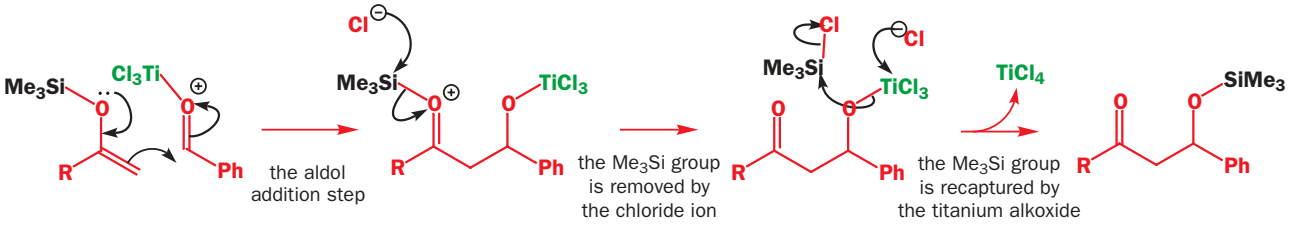
You should look upon silyl enol ethers as rather reactive alkenes that combine with things like protons or bromine (Chapter 21) but do not react with aldehydes and ketones without catalysis: they are much less reactive than lithium enolates. As with alkylation (p. 000), a Lewis acid catalyst is needed to get the aldol reaction to work, and a Ti(IV) compound such as $TiCl_4$ is the most popular.



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.



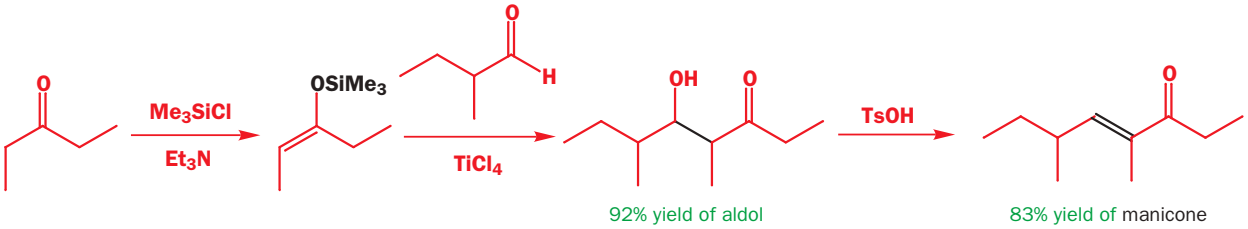
Now the aldol reaction can occur: the positive charge on the titanium-complexed carbonyl oxygen atom makes the aldehyde reactive enough to be attacked even by the not very nucleophilic silyl enol ether. Chloride ion removes the silyl group and the titanium alkoxide captures it again. This last step should not surprise you as any alkoxide (MeOLi for example) will react with Me_3SiCl to form a silyl ether.



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

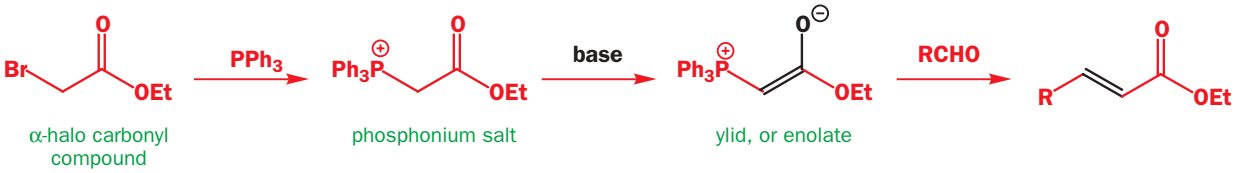
The use of silyl enol ethers can be illustrated in a synthesis of manicone, a conjugated enone that ants use to leave a trail to a food source. It can be made by an aldol reaction between the pentan-3-one (as the enol component) and 2-methylbutanal (as the electrophile). Both partners are enolizable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



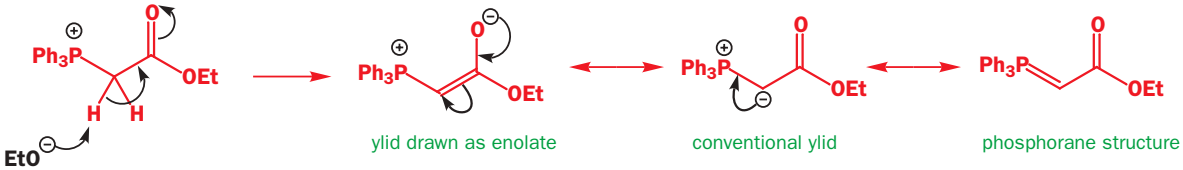
The silyl enol ether is not isolated but reacted immediately with the aldehyde to give an excellent yield of the aldol. Dehydration in acid solution with toluene sulfonic acid (TsOH) gives the enone. You can see by the high yield in the aldol reaction that there is no significant self-condensation of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

Conjugated Wittig reagents as specific enol equivalents

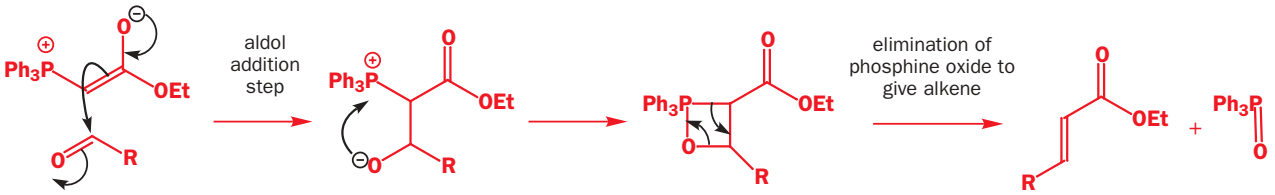
When the Wittig reaction was introduced (Chapter 14) we saw it simply as an alkene synthesis. Now if we look at one group of Wittig reagents, those derived from α-halo-carbonyl compounds, we can see that they behave as specific enol equivalents in making unsaturated carbonyl compounds.



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.

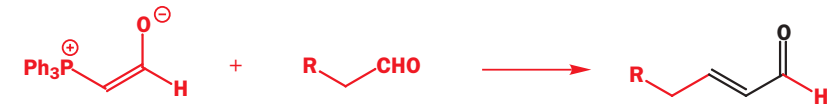


The first step of the Wittig reaction proper is just like an aldol reaction as it consists of an enolate attacking an electrophilic carbonyl compound. But, instead of forming an 'aldol' product, this adduct goes on to form an unsaturated carbonyl compound directly.



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.



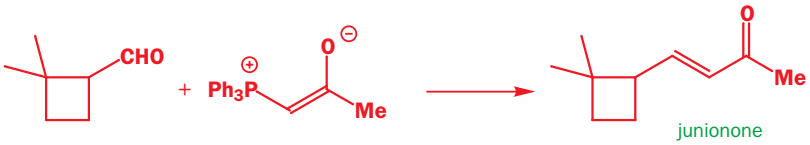
solid, m.p. 185–188 °C
commercially available

enolizable aldehyde

■

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.

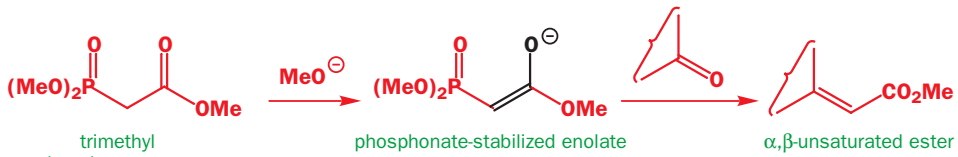
The Wittig equivalent of an aldol reaction with a ketone enolate can be illustrated by the synthesis of a compound in juniper berries, junionone, with a four-membered ring.



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.

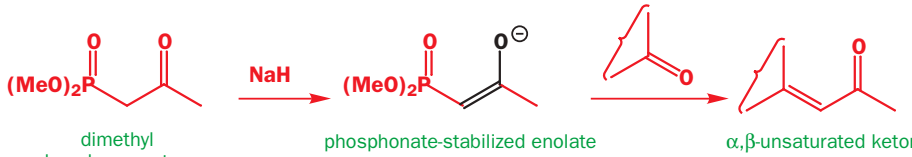
The stability of the phosphonium-stabilized enolates also means that, although they react well with aldehydes, their reactions with ketones are often poor, and it is better in these cases to use phosphonate-stabilized enolates. Being anionic, rather than neutral, these are more reactive. If an ester 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

▶

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.

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

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

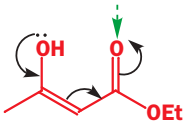
Though these are the oldest of the specific enol equivalents, they are still widely used because they need no special conditions—no low temperatures or strictly anhydrous solvents. The two most important are derived from malonic acid and ethyl acetoacetate.

ethyl acetoacetate
(ethyl 3-oxobutanoate)

diethyl malonate
(diethyl propanedioate)

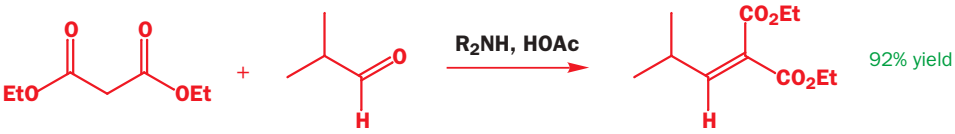
These compounds are largely enolized under normal conditions. So, you might ask, why don't they immediately react with themselves by the aldol reaction? There are two aspects to the answer. First, the enols are very stable (see Chapter 21 for a full discussion) and, secondly, the carbonyl groups in the 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.

electrons are fed into this carbonyl group making it less electrophilic

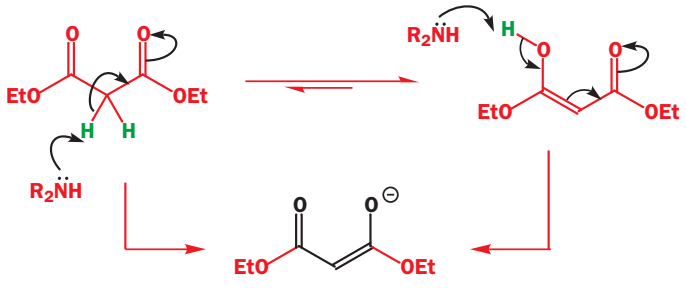


When a normal carbonyl compound is treated with catalytic acid or base, we have a small proportion of reactive enol or enolate in the presence of large amounts of unenolized electrophile. Aldol reaction (self-condensation) occurs. With 1,3-dicarbonyl compounds we have a small proportion of not particularly 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.



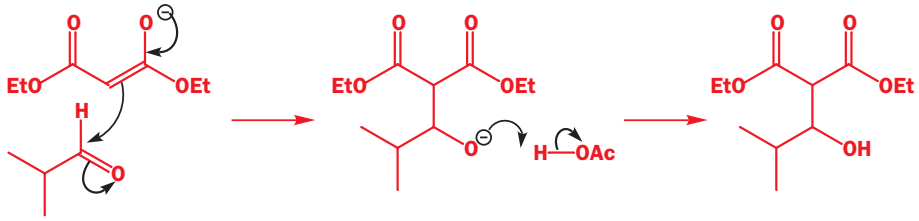
Reaction no doubt occurs via the enolate ion generated by the amine while the carboxylic acid buffers the solution, neutralizing the product, and preventing enolization of the aldehyde. The amine (pK_{aH} about 10) is a strong enough base to form a significant concentration of enolate from the 1,3-dicarbonyl 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.



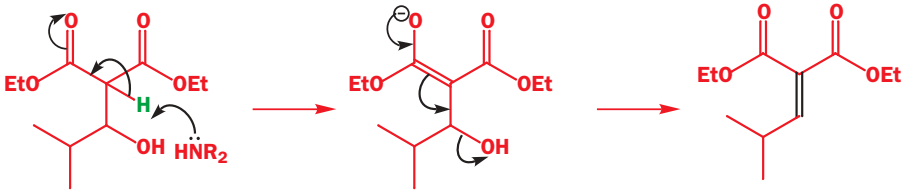
enolate of diethyl malonate

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

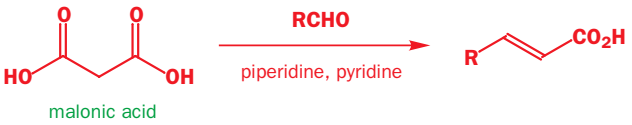
Now the enolate ion can attack the aldehyde in the usual way, and the buffer action of the acid produces the aldol in the reaction mixture.

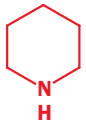


There is still one proton between the two carbonyl groups so enolate anion formation is again easy and dehydration follows to give the unsaturated product.

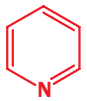


You may not want a product with both ester groups present, and we discussed in Chapter 26 how one of two 1,3-related ester groups may be removed by hydrolysis and decarboxylation. There is a simpler route with the aldol reaction. If, instead of the malonate diester, malonic *acid* is used, the decarboxylation occurs spontaneously during the reaction. The catalysts this time are usually a more basic mixture of piperidine and pyridine.



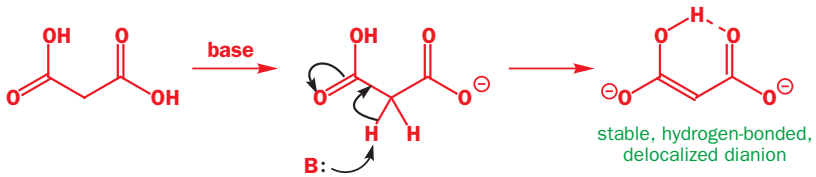


piperidine
pK_{aH} 11

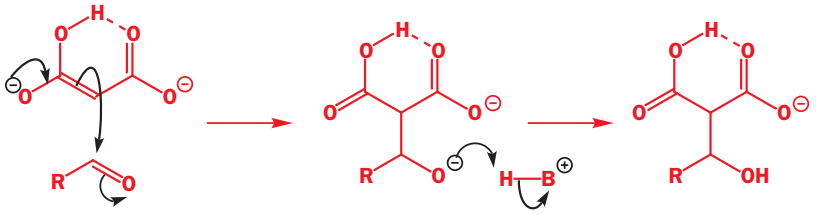


pyridine
pK_{aH} 5.5

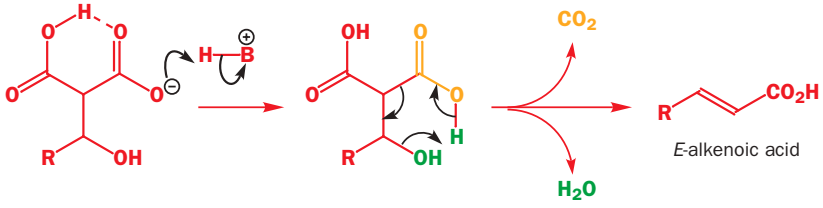
The reaction under these conditions is sometimes called the **Knoevenagel reaction** after its nineteenth century inventor, and presumably uses the enolate anion of the monocarboxylate of the malonic acid. Though this enolate is a dianion, its extensive delocalization and the intramolecular hydrogen 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).



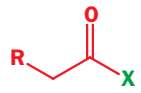
Finally comes the decarboxylation step, which can occur though a cyclic mechanism (compare the decarboxylation mechanisms in Chapter 26). The decarboxylation could give either *E* or *Z* double bond depending on which acid group is lost as CO_2, but the transition state leading to the more stable *E* product must be lower in energy since the product has *E* geometry.



E-alkenoic acid

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.

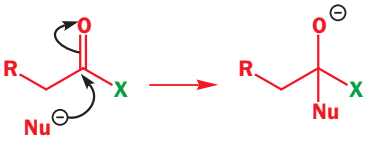
Specific enol equivalents for carboxylic acid derivatives



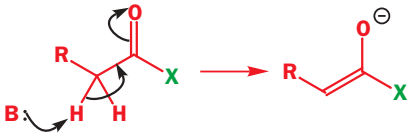
electrophilic reactivity for X =
Cl > OCOR > OR > NR_2

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

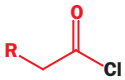
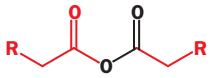
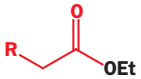
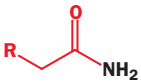


mechanism of enolate formation

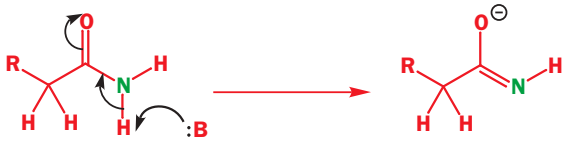


See how similar these two mechanisms are. In particular, they are the same at the carbonyl group itself. Electrons move into the C=O π* orbital: the C=O bond becomes a C–O single bond as a negative charge develops on the oxygen atom. It should come as no surprise that *the order of reactivity for enolization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

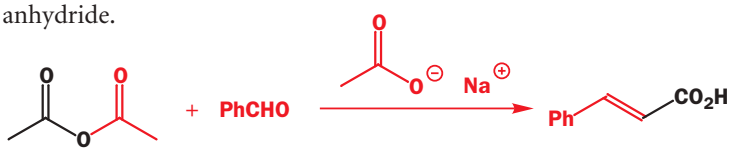


For the remainder of this section we shall look at how to make specific enol equivalents of the remaining carboxylic acid derivatives.

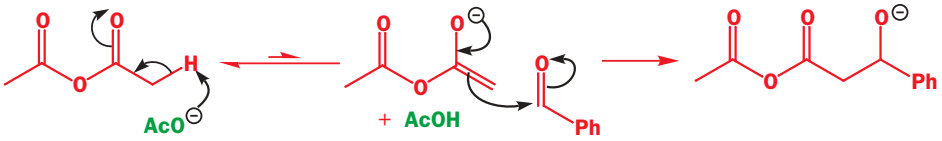
Enols and enolates from acid anhydrides

■ 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.

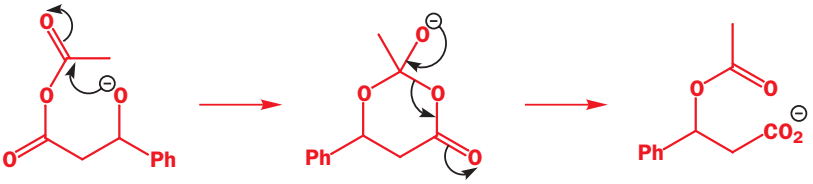
Enols or enolates from anhydrides are not used very often in aldol reactions other than in one important application, usually known as the **Perkin reaction**. An acid anhydride, such as acetic anhydride, is combined with a non-enolizable aldehyde and a weak base, usually the salt of the acid. This base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



The low equilibrium concentration of the enolate attacks the aldehyde.

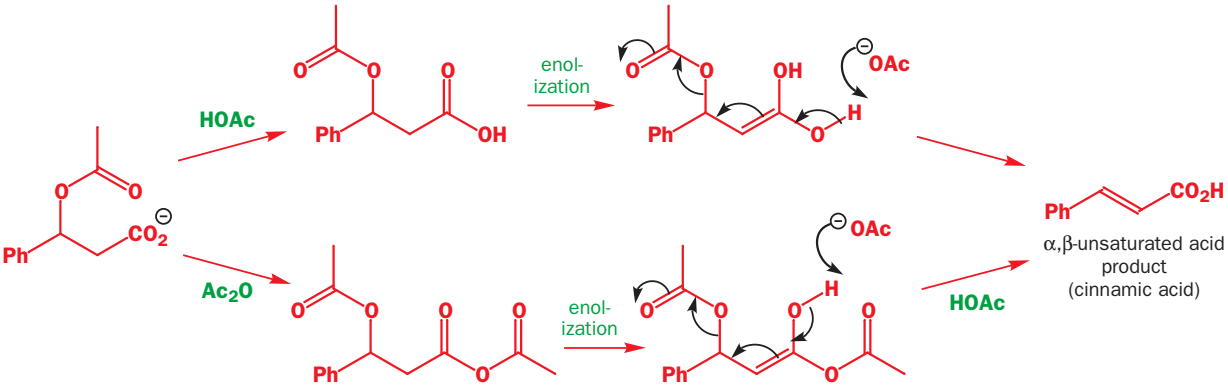


Thus far the reaction is a normal aldol reaction, but now something quite different happens. Six atoms along the molecule from the alkoxide ion is the carbonyl group of an anhydride. An intramolecular acylation is inevitable, given that anhydrides acylate alcohols even if the two groups are in different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

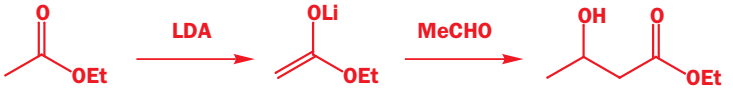


Enols and enolates from esters

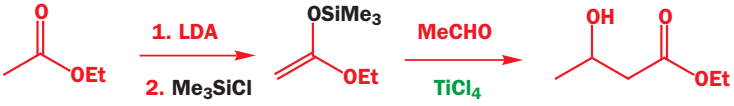
Among the enolates of carboxylic acid derivatives, esters are the most widely used. Ester enolates cannot be used in crossed aldols with aldehydes because the aldehyde is both more enolizable and more electrophilic than the ester. It will just condense with itself and ignore the ester. The same is true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

■ We have already discussed the special examples of malonate and phosphonoacetate esters. Now we need to consider ester enolates more generally.

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.

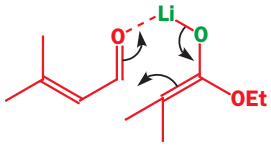


lithium enolate of ester



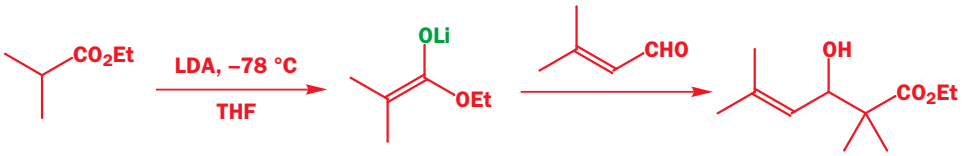
silyl enol ether of ester

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



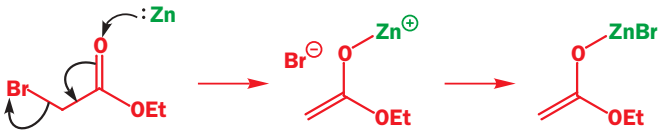
cyclic mechanism for ester aldol reaction

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.



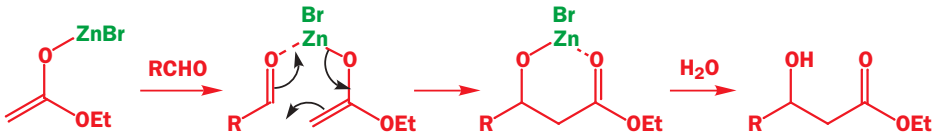
lithium enolate — 72% yield

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.

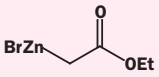


zinc enolate

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.



▶ 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.



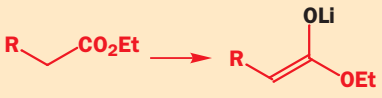
bad structure

▶ 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

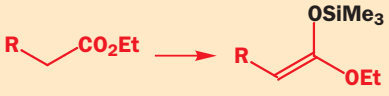
For aldol reactions with an ester enolate equivalent, use

- lithium enolates *or*



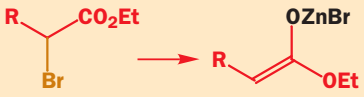
lithium enolate

- silyl enol ethers *or*



silyl enol ether

- zinc enolates

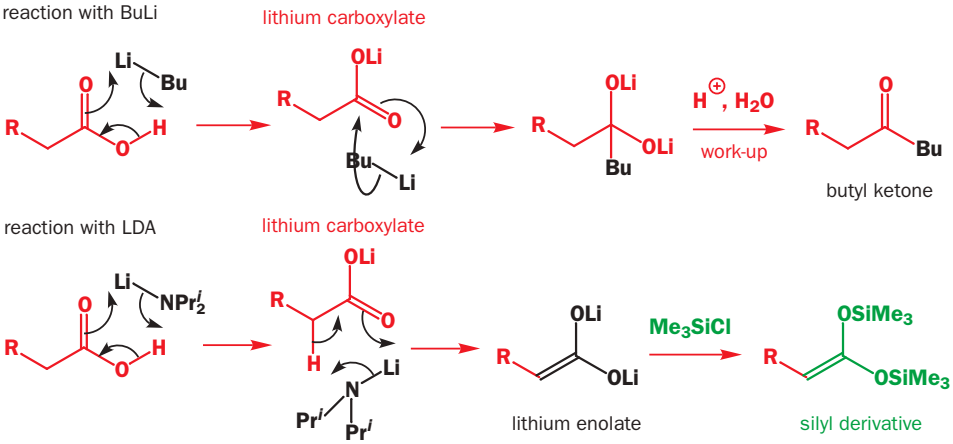


zinc enolate

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

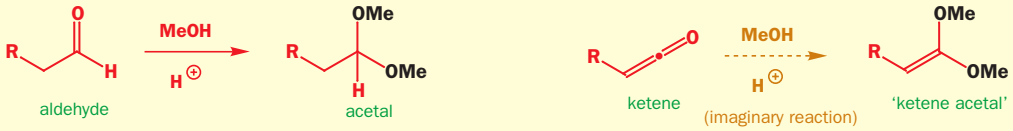
immediately results in the removal of the acidic proton and the formation of the lithium salt of the carboxylic acid. If BuLi is used, the next step is addition of BuLi to the carbonyl group and the eventual formation of a ketone (see Chapter 12, p. 000). But, if LDA is used, it is possible to form the 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.

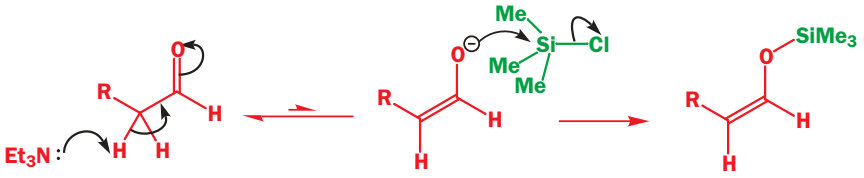
Ketene acetals

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.

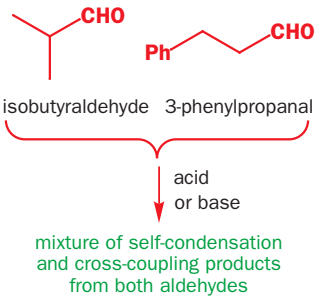


Specific enol equivalents for aldehydes

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.

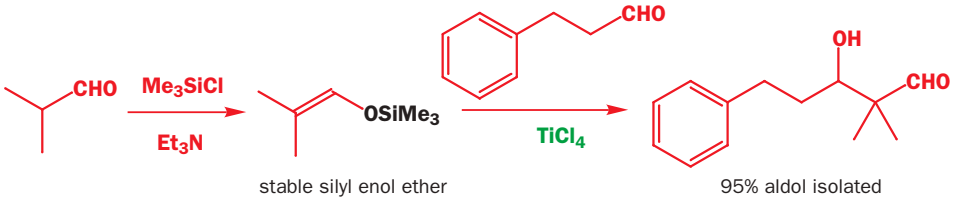


These silyl enol ethers are probably the best way of carrying out crossed aldol reactions with an aldehyde as the enol partner. An example is the reaction of the enol of the not very enolizable isobutyraldehyde with the very enolizable 3-phenylpropanal. Mixing the two aldehydes and adding base would 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 Me_3SiCl captures the enolate faster than self-condensation occurs. Here we

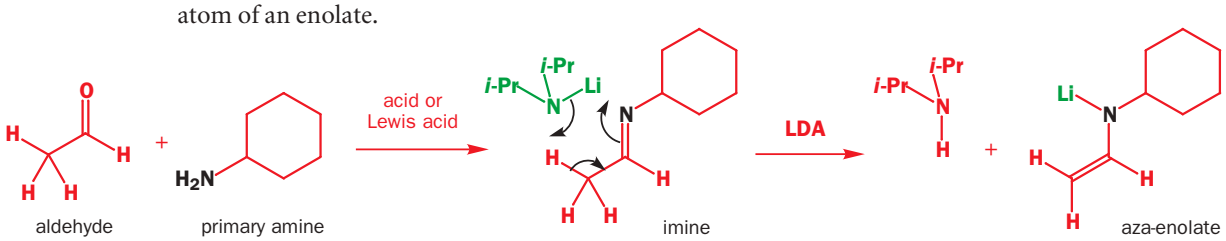
need the silyl enol ether from isobutyraldehyde. The other aldehyde is now added along with the necessary Lewis acid, here $TiCl_4$. The mechanism described on p. 000 gives the aldol after work-up in an excellent 95% yield. No more than 5% of other reactions can have occurred.



stable silyl enol ether — 95% aldol isolated

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.

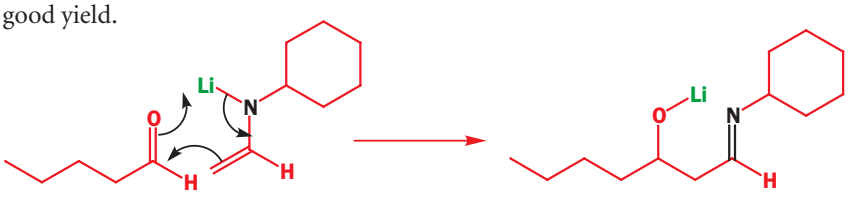
Cyclohexylamine gives a reasonably stable imine even with acetaldehyde and this can be isolated and lithiated with LDA to give the aza-enolate. The mechanism is similar to the formation of lithium enolates and the lithium atom binds the nitrogen atom of the aza-enolate, just as it binds the oxygen atom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



aldehyde — primary amine — imine — aza-enolate

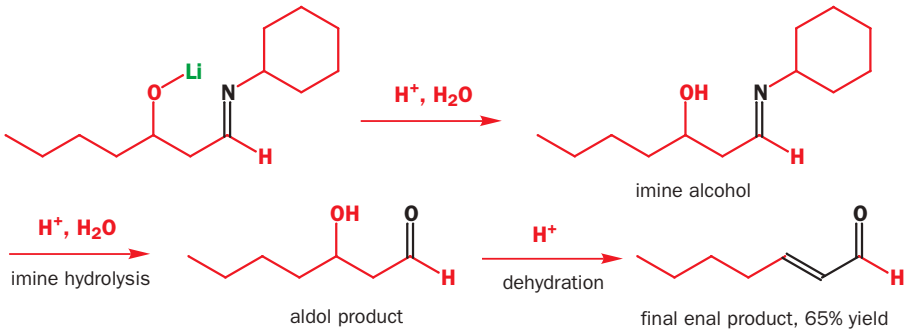
▶ Imines are susceptible to hydrolysis and they are best not stored but used at once. To understand fully these reactions you should ensure you are familiar with the mechanisms of imine formation and hydrolysis from Chapter 14.

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.



electrophilic and enolizable aldehyde — first formed product contains imine and lithium alkoxide

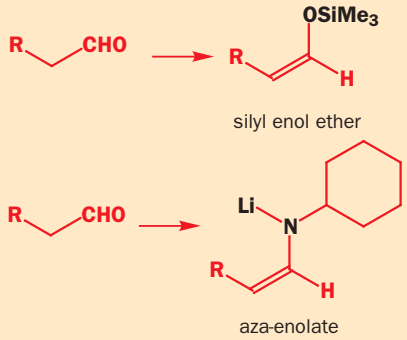
The initial product is a new imine, which is easily hydrolysed during acidic aqueous work-up. The alkoxide is protonated, the imine hydrolysed, and finally the aldol is dehydrated to give the enal—65% overall yield in this case.



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*
  - aza-enolates



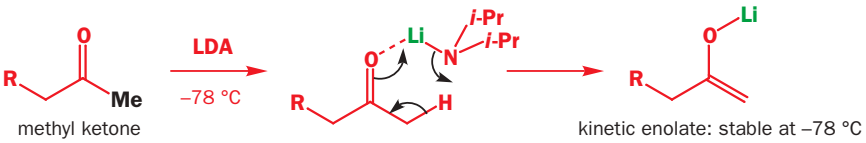
Specific enol equivalents for ketones

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.

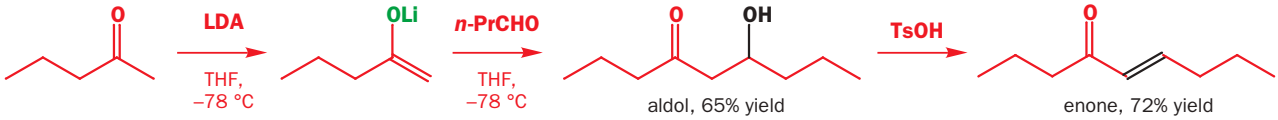
Making the less substituted enolate equivalent: kinetic enolates

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*:

- 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



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.

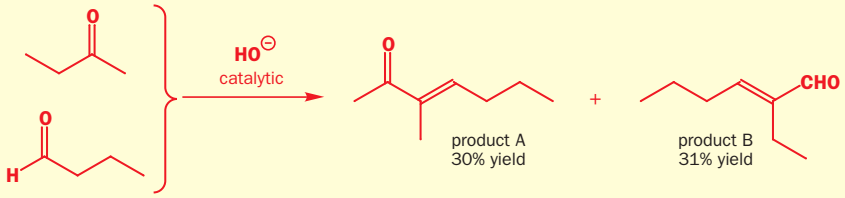


■ Kinetic and thermodynamic enolates were introduced in Chapter 26, p. 000.

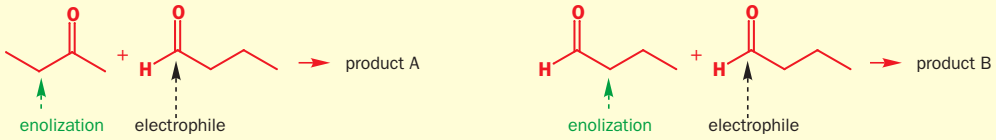
■ Gilbert Stork was born in Brussels and became an assistant professor of chemistry at Harvard in 1948. Since 1953, Stork has been at Columbia University in New York. Since the 1950s, he has pioneered new synthetic methods, among them many involving enolates and enamines.

An uncontrolled ketone aldol

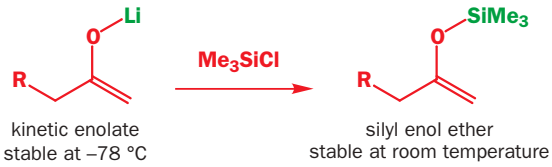
A more typical result from the days before specific enol equivalents had been invented is this attempted crossed condensation between butanone and butanal with catalytic base. Two products were isolated in low yield.



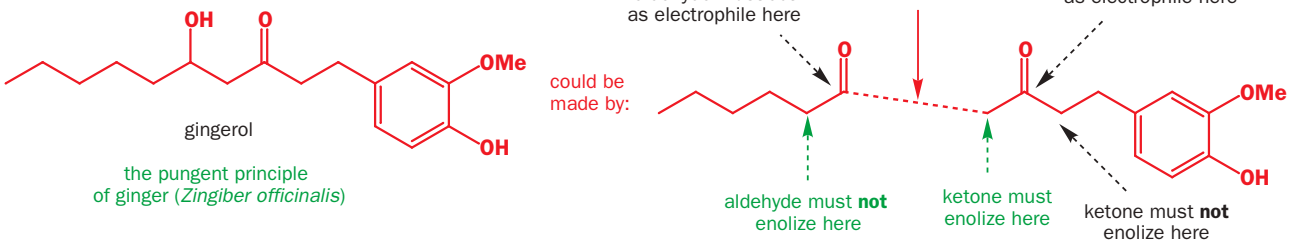
Product A is from the enolate of the more substituted side of the ketone reacting with the aldehyde, and product B is just the self-condensation product from the aldehyde.



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.

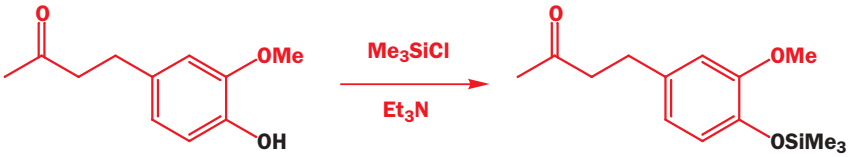


Aldol reactions can be carried out with either the lithium enolate or the silyl enol ether. As an example we shall use the synthesis of a component of the flavour of ginger. The hotness of ginger comes from 'gingerol'—the 'pungent principle' of ginger. Gingerol is a 3-hydroxyketone, so we might consider 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.

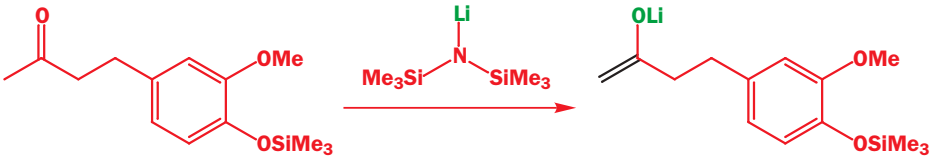


We might consider using the lithium enolate or the silyl enol ether. As we need the kinetic enolate (the enolate formed on the less substituted side of the ketone), we shall be using the lithium enolate to make the silyl enol ether, so it would make sense to try that first.

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 Me_3Si groups on the nitrogen atom.



kinetic lithium enolate

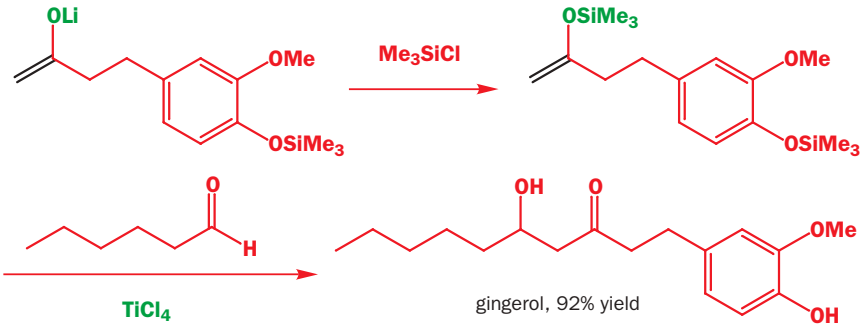
Lithium hexamethyldisilazide

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.

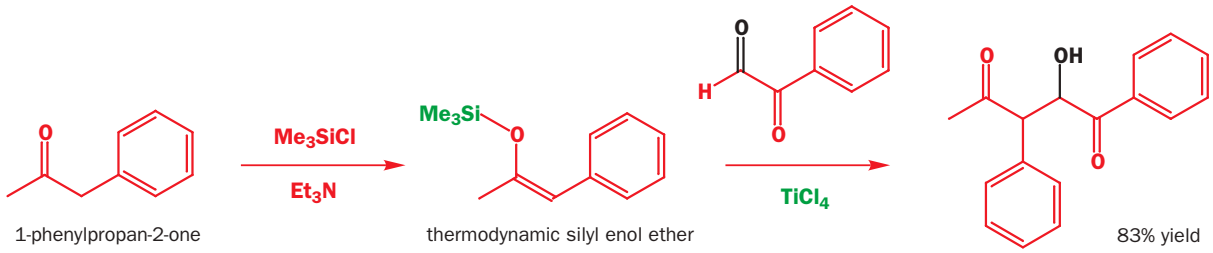
■ Teruaki Mukaiyama, of the Science University of Tokyo (and formerly of the Tokyo Institute of Technology and the University of Tokyo) is one of the foremost Japanese chemists, whose work has had a significant impact on the development of the aldol reaction and on other areas of organic synthesis.



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	×	×	✓	×

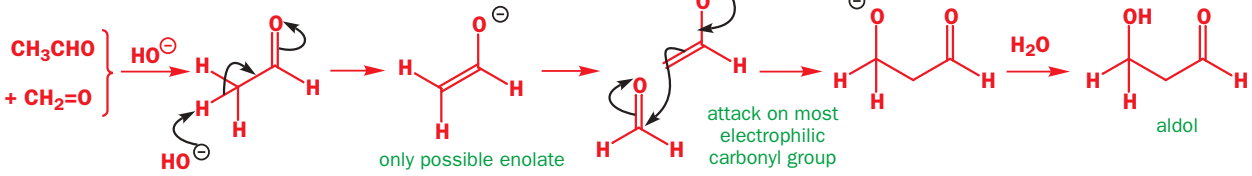
This concludes our general survey of the aldol reaction. Two special topics remain, both important, one dealing with an awkward and difficult reagent and one with a collection of aldol reactions that are particularly easy to do.

The Mannich reaction

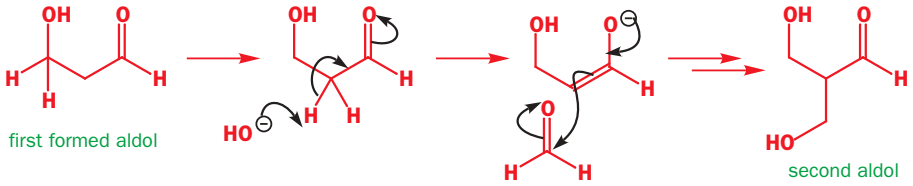
At first sight formaldehyde (methanal, $CH_2{=}O$) seems the ideal electrophilic partner in a mixed aldol reaction. It cannot enolize. (Usually we are concerned with α hydrogen atoms in an aldehyde. Formaldehyde does not even have α carbon atoms.) And it is a super aldehyde. Aldehydes are more electrophilic 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.

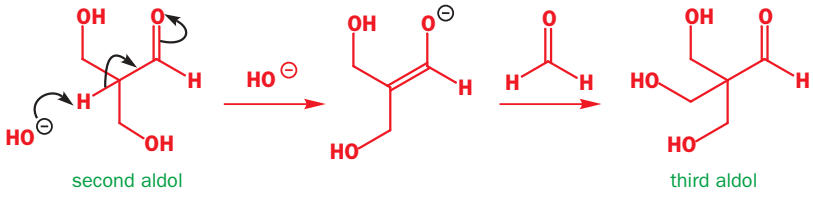
crossed aldol reaction between acetaldehyde and formaldehyde



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.

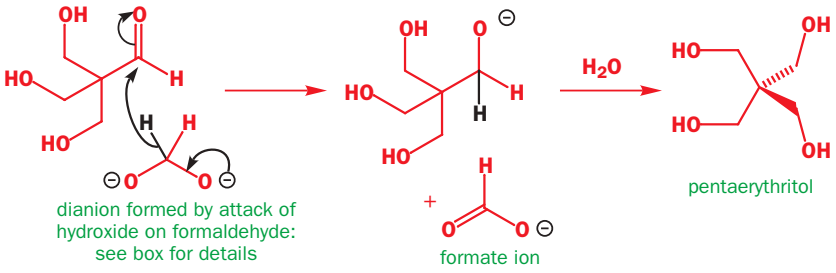


In each reaction the only possible enolate attacks another molecule of formaldehyde. By now you have got the idea so we simply draw the next enolate and the structure of the third aldol.



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

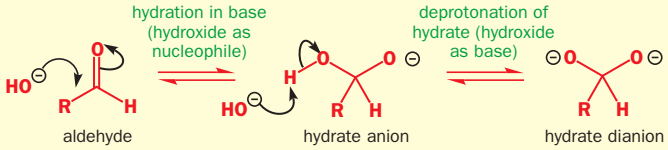


■ Pentaerythritol is a useful industrial product in, for example, the cross-linking of polymers: see Chapter 52.

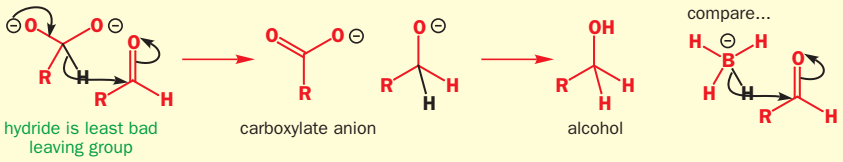
The overall reaction uses four molecules of formaldehyde and can give a high yield (typically 80% with NaOH but as much as 90% with MgO) of the product.

The Cannizzaro reaction

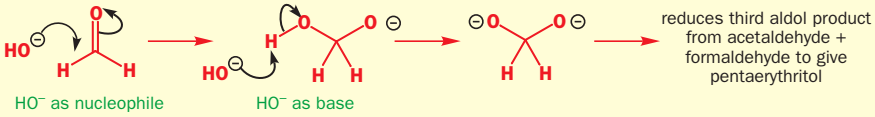
As you know, aldehydes are generally at least partly hydrated in water. Hydration is catalysed by base, and we can represent the hydration step in base like this. The hydration product is an anion but, if the base is sufficiently strong (or concentrated) and as long as the aldehyde cannot be enolized,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



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.

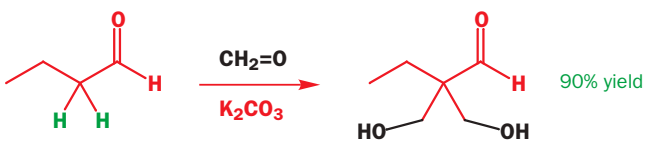


The dianion becomes a much more stable carboxylate monoanion, and a second molecule of aldehyde has been reduced to an alcohol. This is the Cannizzaro reaction: in this case it takes the form of a disproportionation of two molecules of aldehyde to one of carboxylate and one of alcohol.



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**.

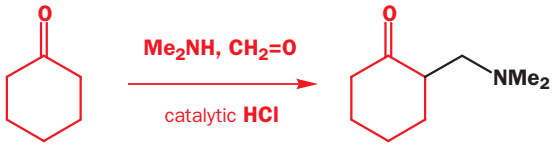
If you want a more controlled reaction with addition of formaldehyde to an aldehyde or ketone without the reduction step, you can sometimes succeed with a weaker base such as potassium carbonate. Typically in these reactions *all* the enolizable hydrogen atoms (green) are replaced by molecules of formaldehyde (black).



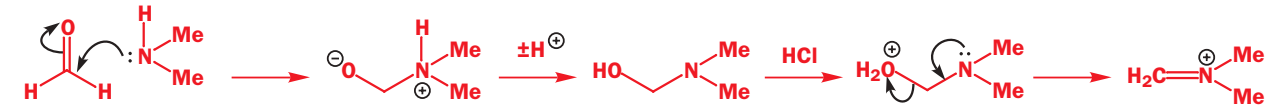
▶ Formaldehyde is not available as a pure monomer because it forms trimers and tetramers in the pure state (Chapter 52). The aqueous solution 'formalin' used to preserve biological specimens is available—it is 37% formaldehyde and mostly consists of the hydrate $CH_2(OH)_2$; see Chapter 6. A pure dry 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.

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



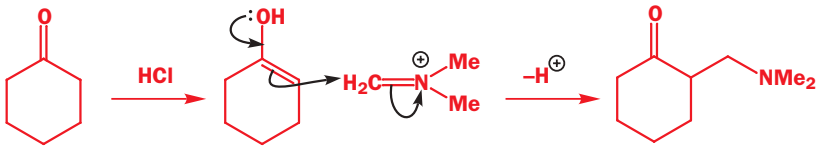
The mechanism involves the preliminary formation of an imine salt from the amine and formaldehyde. The amine is nucleophilic and attacks the more electrophilic of the two carbonyl compounds available. That is, of course, formaldehyde. No acid is needed for this addition step, but acid-catalysed dehydration 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

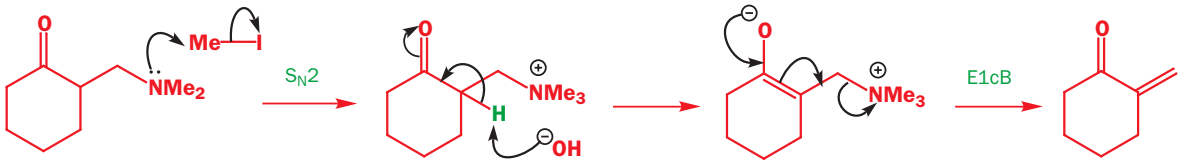
imine salt

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.

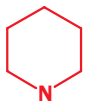
The most reliable method for making the enone is to alkylate the Mannich base with MeI and then treat the ammonium salt with base. Enolate ion formation leads to an E1cB reaction rather like the dehydration of aldols, but with a better leaving group.



1. alkylate amine to give ammonium salt 2. treat with base: E1cB elimination gives enone

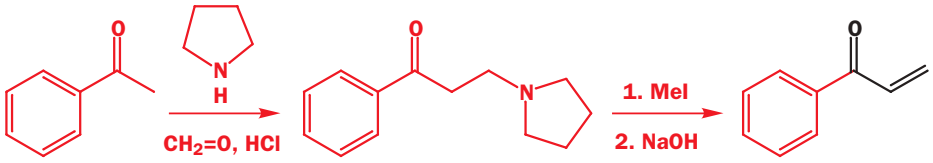
Enones like this, with two hydrogen atoms at the end of the double bond, are called **exo-methylene compounds**; they are very reactive, and cannot easily be made or stored. They certainly cannot be made by aldol reactions with formaldehyde alone as we have seen. The solution is to make the Mannich base, 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.

pyrrolidine



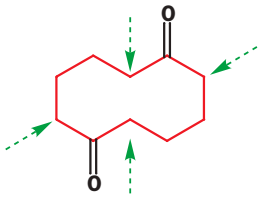
piperidine

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.



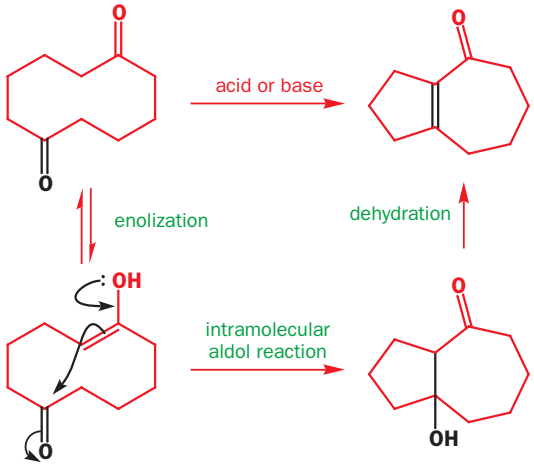
Intramolecular aldol reactions

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.



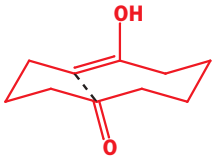
cyclodeca-1,6-dione: four identical positions for enolization (⇢)

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.

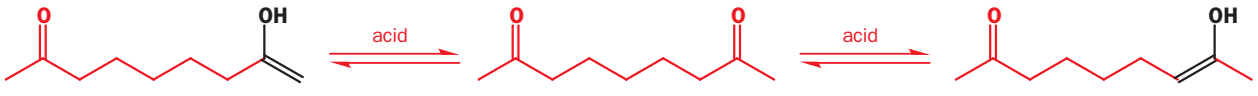
This may look like a long stretch for the enol to reach across the ten-membered ring to reach the other ketone, but the conformational drawing in the margin shows just how close they can be. You should compare this conformation with that of a decalin (Chapter 18).



The key point to remember with intramolecular aldols is this.

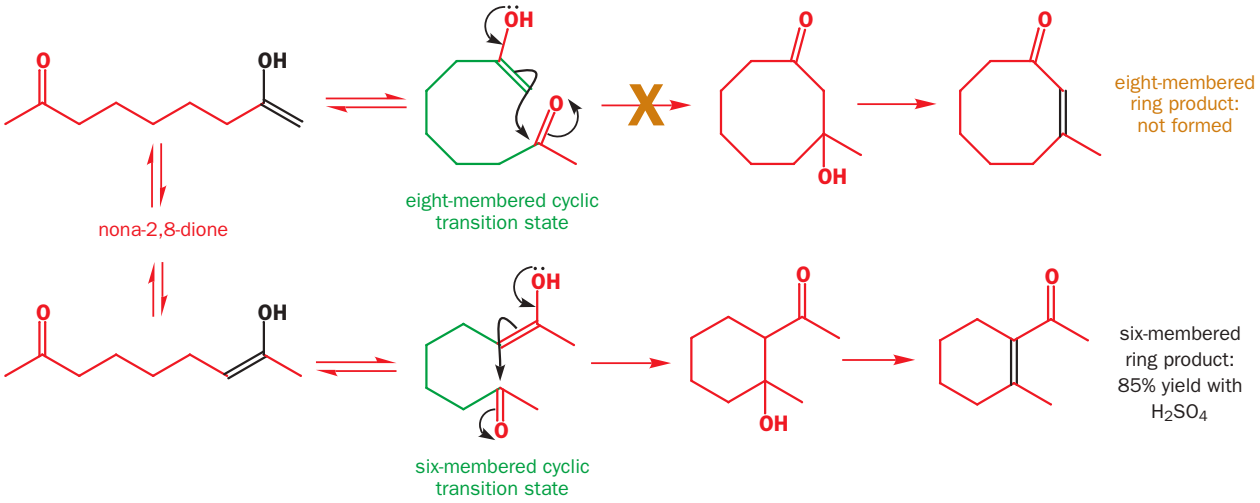
● **Intramolecular reactions giving five- or six-membered rings are preferred to those giving strained three- or four-membered rings on the one hand or medium rings (eight- to thirteen-membered) on the other.**

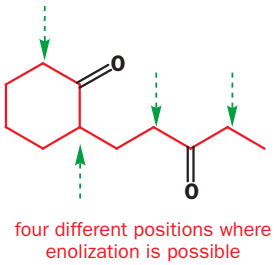
Acid-catalysed cyclization of the symmetrical diketone nona-2,8-dione could give two enols.



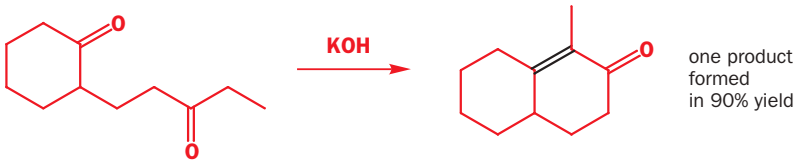
nona-2,8-dione

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.

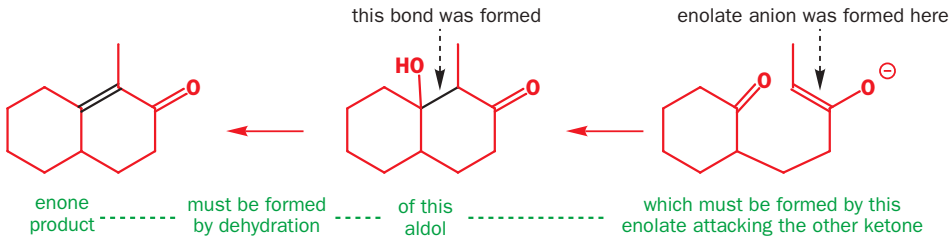




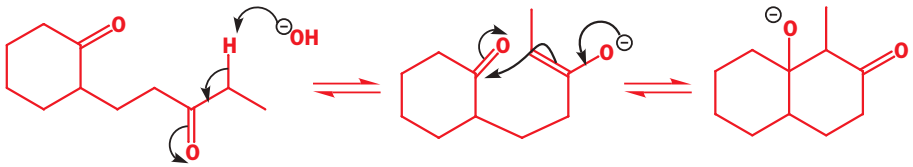
Most diketones lack symmetry, and will potentially have four different sites for enolization. Consider what might happen when this diketone is treated with KOH. There are four different places where an enolate anion might be formed as there are four different α carbon atoms. There are also two different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



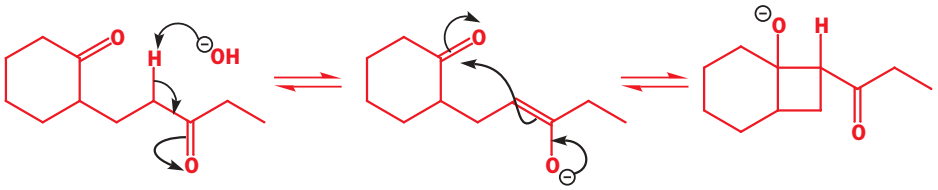
We can deduce the mechanism of the reaction simply from the structure of the product by working backwards. The double bond is formed from an aldol whose structure we can predict and hence we can see which enolate anion was formed and which ketone acted as the electrophilic partner.



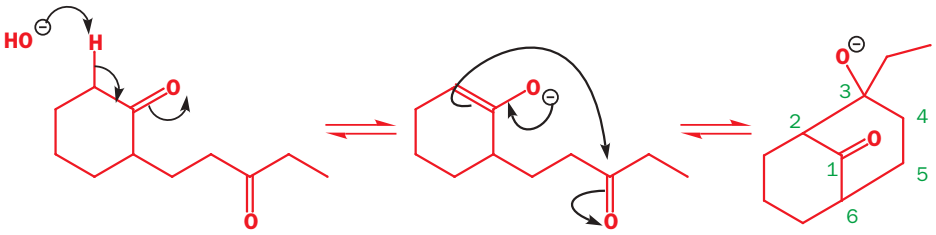
Must we argue that this one enolate is more easily formed than the other three? No, of course not. There is little difference between all four enolates and almost no difference between the three enolates from CH_2 groups. We *can* argue that this is the only aldol reaction that leads to a stable conjugated enone in a stable six-membered ring. This must be the mechanism; protonation and dehydration follow as usual.



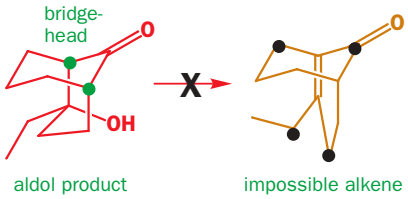
Now try one of the alternatives in which the same ketone forms an enolate on the other side.



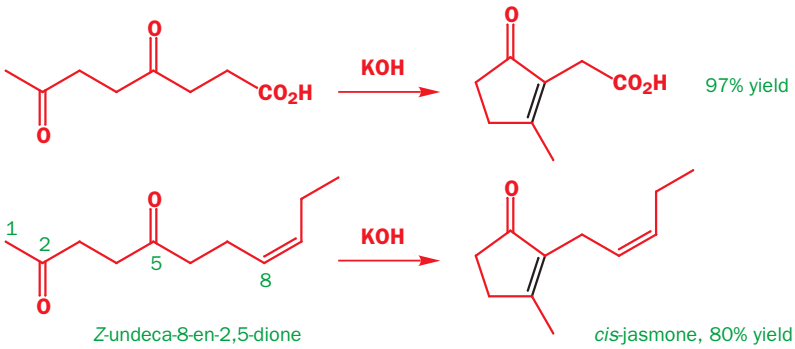
This reaction gives an unstable four-membered ring that would revert to the enolate. Providing the reaction is done under equilibrating conditions, the whole process would go into reverse back to the original diketone and the observed (six-membered ring) cyclization would eventually predominate. There 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.

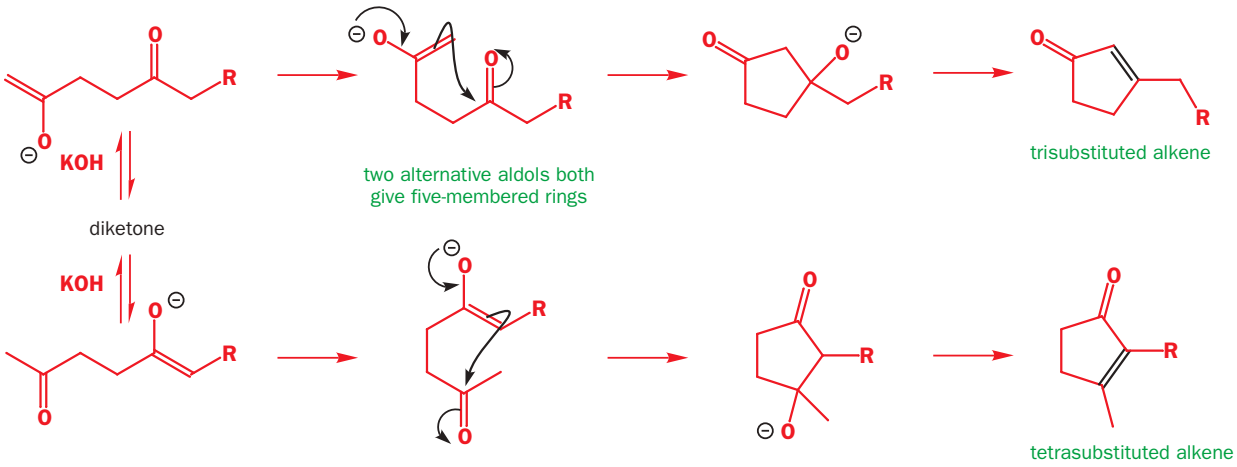


Even without the constraint of avoiding a bridgehead alkene, some completely unsymmetrical diketones give single products in high yield. Here are two related examples with similar structures.



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.



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

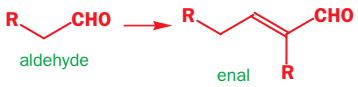
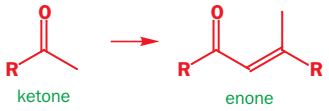
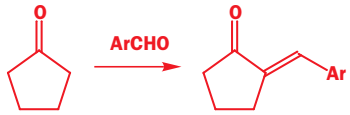
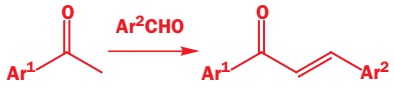
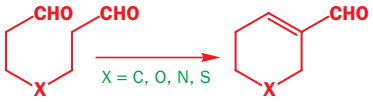
As we leave this chapter, it is important to make sure that you understand the two different approaches to controlled aldol reactions that we have been considering. The two methods ensure in their different ways that only one carbonyl group gives only one enol or enolate as the nucleophilic partner in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

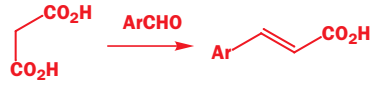
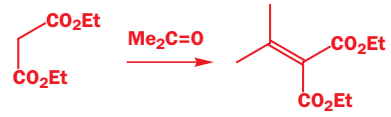
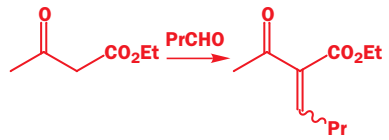
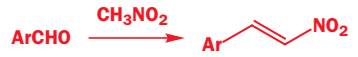
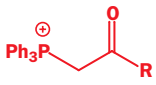
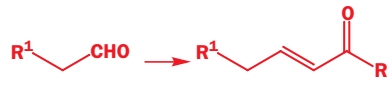
In the equilibrium method, 'weak' acid or base means too weak to ensure complete conversion to enol or enolate. The method works only if enol and carbonyl compound are in equilibrium. Typical examples are shown in the table.

Types of aldol reaction under thermodynamic control

Type of reaction	Typical conditions	Example
self-condensation of aldehydes	2% NaOH aqueous ethanol	
self-condensation of ketones	HCl, $Al(OR)_3$, NaOH, or KOH	
cross-condensations of an enolizable ketone and a non-enolizable aldehyde	NaOH, KOH, Na_2CO_3, HCl, or H_2SO_4	
cross-condensations of aryl methyl ketones and non-enolizable aldehydes	dilute HCl or NaOH	
cyclization reactions	2% NaOH aqueous ethanol, or HCl, or H_2SO_4	

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 $CH_2(CO_2H)_2$	piperidine, DMSO	
malonic esters $CH_2(CO_2Et)_2$	$NH_4^+AcO^-$	
acetoacetates $CH_3CO{\cdot}CH_2CO_2Et$	piperidine, EtOH, room temperature	
nitro compounds[a] RCH_2NO_2	NaOH, H_2O	
Wittig reagents[a] 	NaOMe, MeOH	

[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

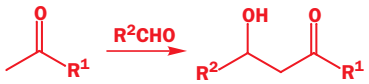
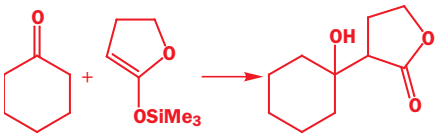
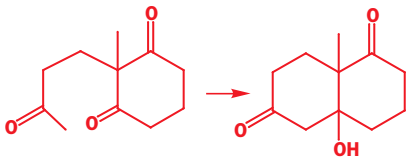
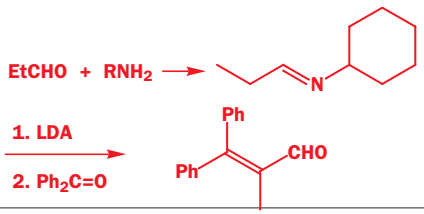
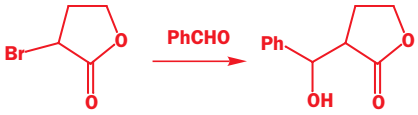
In the directed aldol reaction, one component is first converted into a specific enol equivalent and *only then* combined with the electrophilic partner.

▶ 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-Pr_2NH) 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.

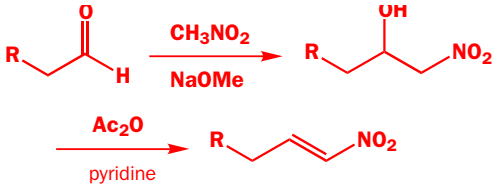
The table gives some details of the conditions used for directed aldol reactions. You should refer to the table on p. 000 to see which specific enol equivalents are appropriate to which types of carbonyl compounds.

Specific enol equivalent	Conditions	Example
lithium enolate	1. LDA, THF, –78 °C, 2. aldehyde, 3. NH_4Cl, H_2O	
silyl enol ether	$TiCl_4$, CH_2Cl_2, –78 °C, 1 hour, under argon	
enamine	 heat	
aza-enolate	1. RNH_2, 2. LDA, 3. ketone, 4. dilute H_2SO_4	
zinc enolate (Reformatsky)	1. Zn, 2. aldehyde or ketone	

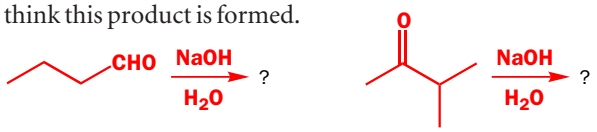
We have spent some considerable time and effort in understanding the aldol reaction simply because it is one of the most important reactions in organic chemistry. In the next chapter you will see how these ideas can be extended with almost no addition of principles to the acylation of enolates—the reaction 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.

Problems

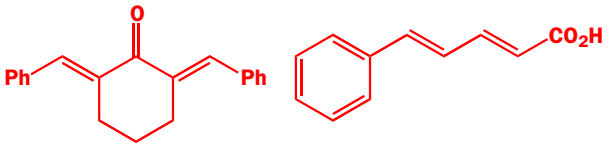
1. Propose mechanisms for the 'aldol' and dehydration steps in the termite defence compound synthesis presented in the chapter.



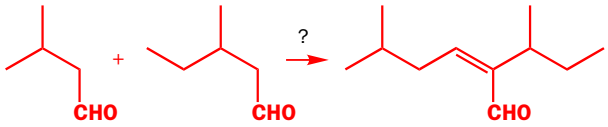
2. The aldehyde and ketone below are self-condensed with aqueous NaOH so that an unsaturated carbonyl compound is the product. Give a structure for each product and explain why you think this product is formed.



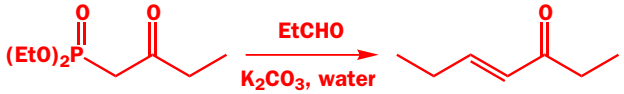
3. How would you synthesize the following compounds?



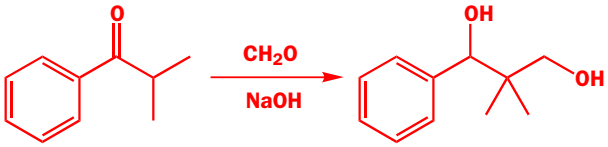
4. How would you use a silyl enol ether to make this aldol product? Why is it necessary to use this particular intermediate? What would the products be if the two carbonyl compounds were simply mixed and treated with base?



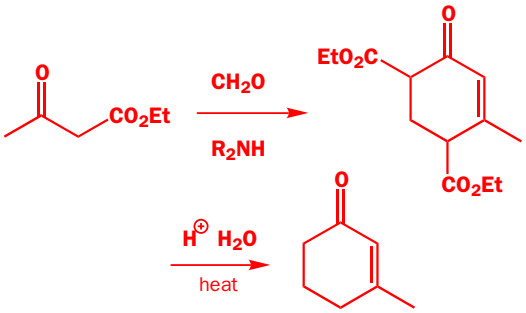
5. In what way does this reaction resemble an aldol reaction? How could the same product be made without using phosphorus chemistry? Comment on the choice of base.



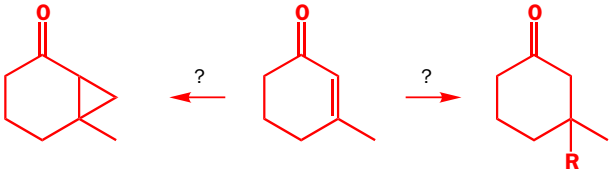
6. Suggest a mechanism for this attempted aldol reaction. How could the aldol product actually be made?



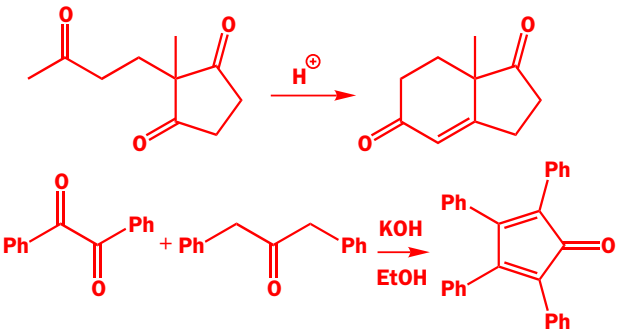
7. What are the structures of the intermediates and the mechanisms of the reactions leading to this simple cyclohexenone?



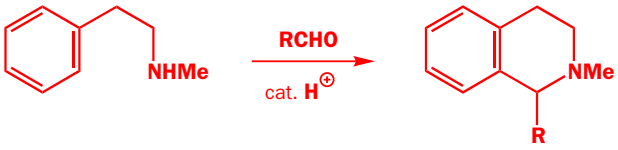
8. How would you convert the product of that last reaction into these two products?



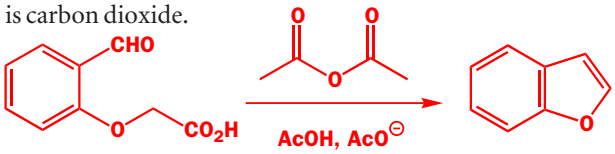
9. Comment on the selectivity shown in these two cyclizations.



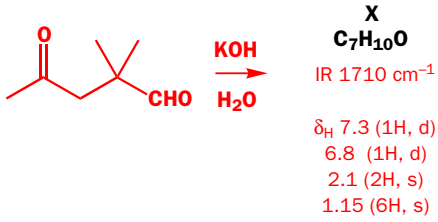
10. Using the Mannich reaction as a guide, suggest a mechanism for this reaction.



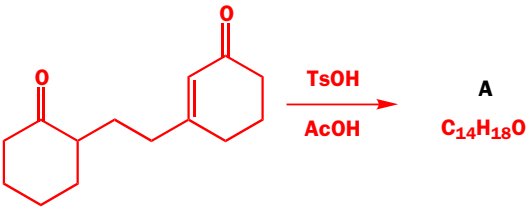
11. Suggest mechanisms for this reaction. One of the by-products is carbon dioxide.



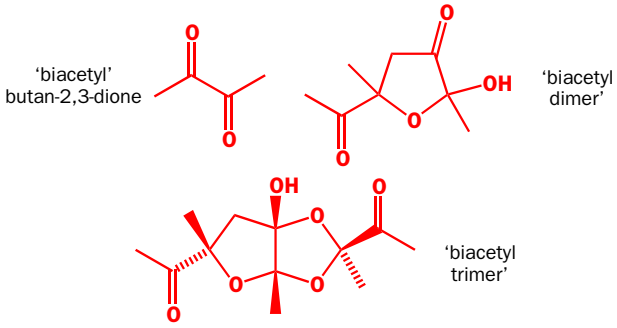
12. Treatment of this keto-aldehyde with KOH gives a compound $C_7H_{10}O$ with the spectroscopic data shown. What is its structure and how is it formed? You should, of course, assign the NMR spectrum and give a mechanism for the reaction.



13. Predict which enone product would be formed in this intramolecular aldol reaction.



14. The unstable liquid diketone 'biacetyl' deposits crystals of a dimer slowly on standing or more quickly with traces of base. On longer standing the solution deposits crystals of a trimer. Suggest mechanisms for the formation of the dimer and the trimer. Why are they more stable than the monomer?



Acylation at carbon

28

Connections

Building on:

- Enols and enolates ch21
- Alkylation of enolates ch26
- The aldol reaction ch27
- Nucleophilic substitution at C=O ch12

Arriving at:

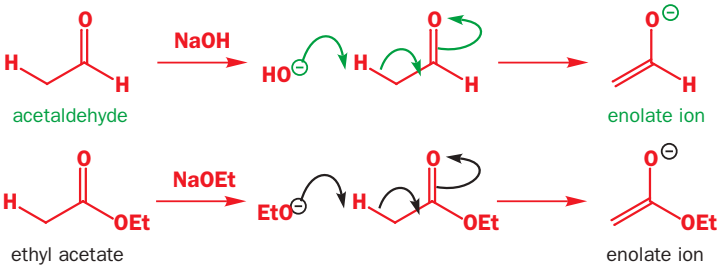
- How esters react with enolates: the Claisen condensation
- How to acylate the enolates of esters and ketones
- How to get *C*-acylation and avoid *O*-acylation
- How to make cyclic ketones by intramolecular acylation
- Enamines in acylation reactions
- Modelling acylation on nature

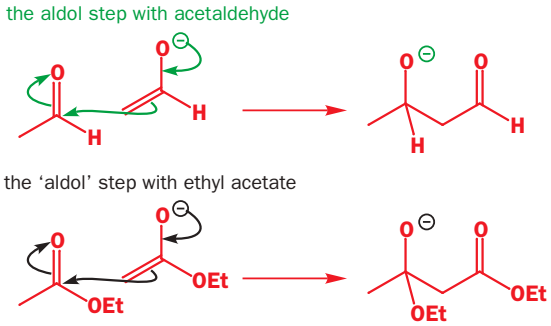
Looking forward to:

- Michael additions of enolates ch29
- Retrosynthetic analysis ch30
- Biological chemistry ch49–ch51

Introduction: the Claisen ester condensation compared to the aldol reaction

We began the last chapter with the treatment of acetaldehyde with base. This led initially to the formation of an enolate anion and then to the aldol reaction. We are going to start this chapter with the treatment of ethyl acetate with base. To start with, there is hardly any difference. We shall use ethoxide as base rather than hydroxide as hydroxide would hydrolyse the ester, but otherwise the first steps are very similar. Here they are, one above the other.

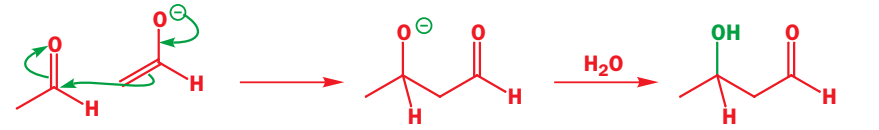




The next step in both cases is nucleophilic attack by the enolate ion on unenolized carbonyl compound. The concentration of enolate is low and each enolate ion is surrounded by unenolized aldehyde or ester molecules, so this reaction is to be expected. Here is that step, again shown for both aldehyde and ester.

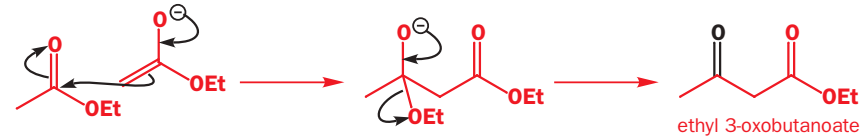
Only now does something different happen. The aldehyde dimer simply captures a proton from the solvent to give an aldol product. The 'aldol' from the ester (not, in fact, an aldol at all) has a leaving group, EtO^-, instead of a hydrogen atom and is actually the tetrahedral intermediate in a nucleophilic substitution at the carbonyl group. Compare the two different steps again.

completion of the aldol with acetaldehyde



3-hydroxybutanal ('aldol')

the Claisen condensation with ethyl acetate



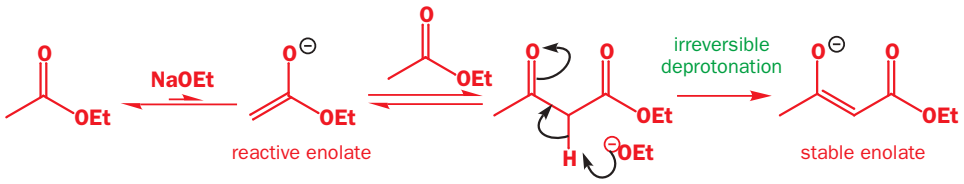
ethyl 3-oxobutanoate
(ethyl acetoacetate)

Even though the last step is different, the two products are quite similar. Both are dimers of the original two-carbon chain and both have carbonyl groups at the end of the chain and oxygen substituents at position three. The two reactions obviously belong to the same family but are usually given different names. The ester reaction is sometimes known as the **Claisen ester condensation** and sometimes as the **Claisen–Schmidt reaction**. More important than remembering the name is being familiar with the reaction and its mechanism. Here is a summary.

ethyl acetate

ethyl 3-oxobutanoate
(ethyl acetoacetate)

This is another of those reactions where the base is not strong enough to transform the ester entirely into the enolate. Only a small equilibrium concentration is produced, which reacts with the ester electrophile. The by-product from the reaction is ethoxide ion and so it looks at first sight as though we get our catalyst back again—the aldol, if you remember, is catalytic in base. But not the Claisen reaction. The second step of the reaction is also really an equilibrium, and the reaction works only because the product can be irreversibly deprotonated by the ethoxide by-product, consuming ethoxide in the process. You recall that the aldol reaction often works best when there is an extra driving force to push it across—dehydration to an enone, for example. Similarly, the ester dimerization works best when the product reacts with the ethoxide ion to give a stable enolate ion.

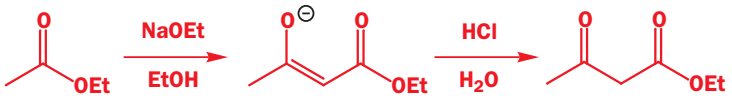


reactive enolate

stable enolate

The point is that the base used, ethoxide ion EtO^-, is too weak (EtOH has a pK_a of about 16) to remove the proton completely from ethyl acetate (pK_a about 25), but is strong enough to remove a proton from the acetoacetate product (pK_a about 10). Under the conditions of the reaction, a small amount of the enolate of ethyl acetate is produced—just enough to let the reaction happen—but the product is completely converted into its enolate. The neutral product, ethyl acetoacetate itself, is formed on acidic work-up.

the complete Claisen ester condensation

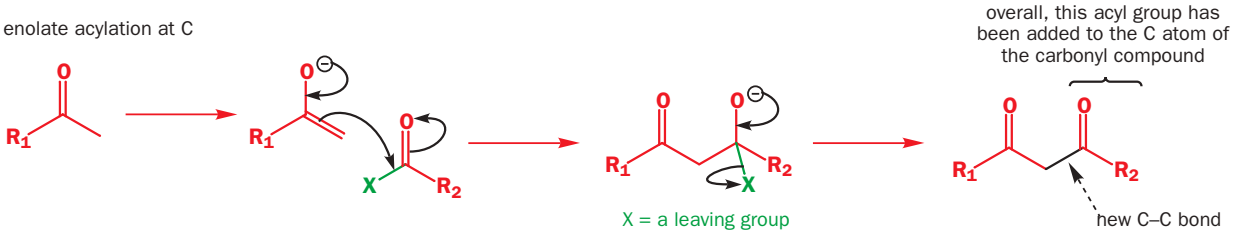


stable enolate

ethyl acetoacetate

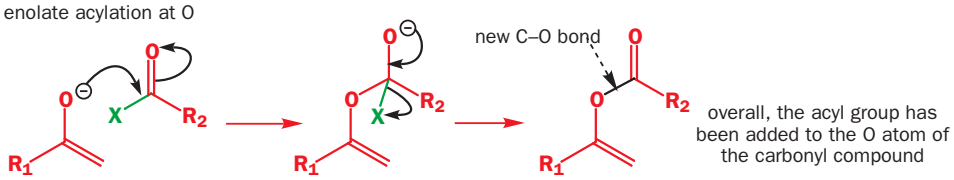
The final product has been formed by the acylation at carbon of the enolate of an ester. This general process—acylation at carbon—is the subject of this chapter. It so happened in this case that the

acylating agent was another molecule of the same ester, but the general process we shall consider is the acylation of enolates at carbon. We shall use a variety of enols, enolates, and specific enol equivalents and a variety of acylating agents, but the basic idea is this.

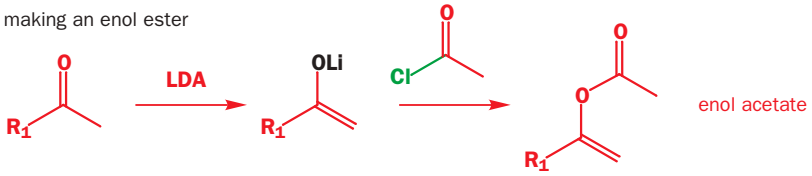


Problems with acylation at carbon

The main problem with the acylation of enolates is that reaction tends to occur at oxygen rather than at carbon.



The product of acylation on oxygen is an **enol ester**. The tendency to attack through oxygen is most marked with reactive enolates and reactive acylating agents. The combination of a lithium enolate and an acid chloride, for example, is pretty certain to give an enol ester.



If we want acylation at carbon we must use *either*

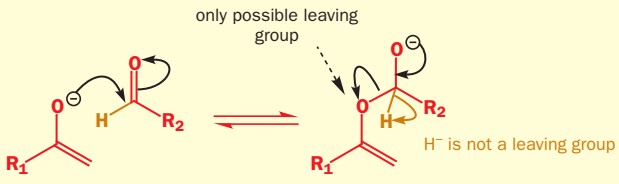
- less reactive specific enol equivalents, such as enamines or silyl enol ethers, with reactive acylating agents such as acid chlorides *or*
- reactive enols, such as the enolate anions themselves, with less reactive acylating agents such as esters

We introduced this chapter with an example of the second type of reaction, and we shall continue with a more detailed consideration of the Claisen ester condensation and related reactions.

▶ You have seen reaction at oxygen before. Enolates react on oxygen with silicon electrophiles and we found the products, silyl enol ethers, useful in further reactions. Enol esters also have their uses—as precursors of lithium enolates, for example. You saw one being used like this on p. 000.

Reaction at oxygen

In Chapter 27, we mentioned no trouble with reaction at oxygen in the aldol reaction. This may now seem surprising, in view of what we have said about esters, as the electrophiles were aldehydes and ketones—not so very different from esters. We can resolve this by looking at what would happen if an aldehyde did attack an enolate on the oxygen atom.

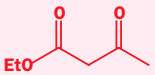


The only plausible leaving group from the intermediate is the enolate anion itself: the reaction just reverses. It may well be that aldol reactions *do* involve attack through oxygen. But no products can be formed from this reversible pathway: only when the electrophile has a leaving group is reaction at oxygen productive.

Acylation of enolates by esters

The Claisen ester condensation and other self-condensations

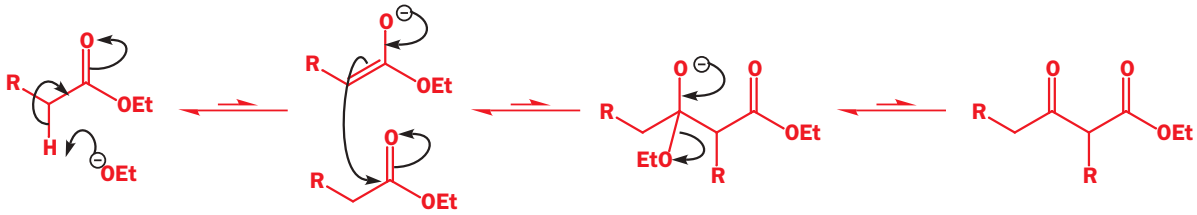
▶ We spent some time in Chapters 26 and 27 considering the reactions of ethyl acetoacetate: now you see how it is made.



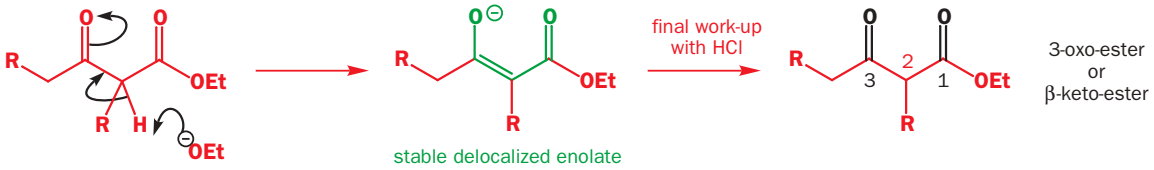
ethyl acetoacetate

The self-condensation of ethyl acetate, with which we opened this chapter, is the most famous example of the Claisen ester condensation and it works in good yield under convenient conditions. The product (ethyl acetoacetate) is commercially available—and cheap too—so you are unlikely to want to do this particular example.

A more generally useful reaction is the self-condensation of simple substituted acetates RCH_2CO_2Et. These work well under the same conditions (EtO^- in EtOH). The enolate anion is formed first in low concentration and in equilibrium with the ester. It then carries out a nucleophilic attack on the more abundant unenolized ester molecules.



These steps are all unfavourable equilibria and, on their own, would give very little product. However, as we mentioned before, the reaction works because the equilibrium is driven over by the essentially irreversible formation of a stable, delocalized enolate from the product.

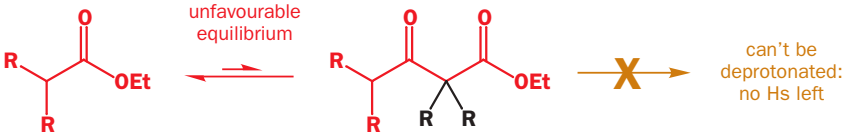


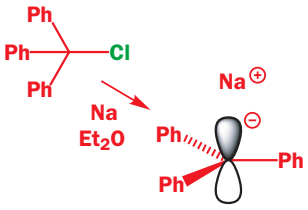
■ We shall discuss the significance of the 1,3-relationship in Chapter 30.

Finally, the reaction is worked up in acid and the β keto-ester product is formed. Notice that all products of Claisen ester condensations have a 1,3-dicarbonyl relationship. These compounds are useful in the preparation of specific enol equivalents and you have seen them in action in Chapters 21, 26, and 27.

How do we know that deprotonation drives the reaction?

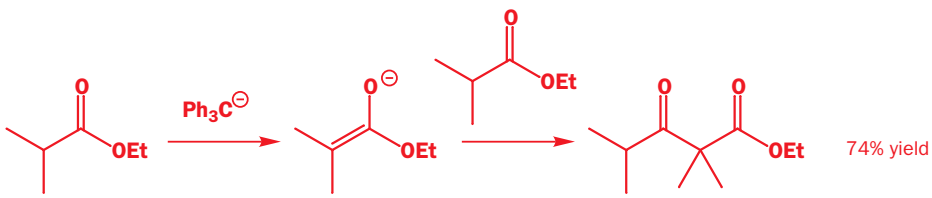
If the original ester has two substituents on the α carbon atom (C2 of the ester), the formation of the stable enolate of the product is no longer possible as there are no hydrogen atoms left to remove.



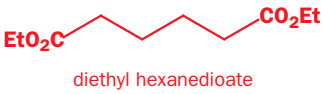


As you might expect, all the equilibria are now unfavourable, and this reaction does not go well under the normal equilibrating conditions (EtO^- in EtOH). It can be made to go in reasonable yield if a stronger base is used. Traditionally, triphenylmethyl sodium is chosen. This is made from Ph_3CCl and sodium metal and is a very conjugated carbanion.

Triphenylmethyl carbanion is a strong enough base to convert an ester entirely into its enolate. Reaction of the enolate with a second molecule of ester then gives the keto-ester in good yield.



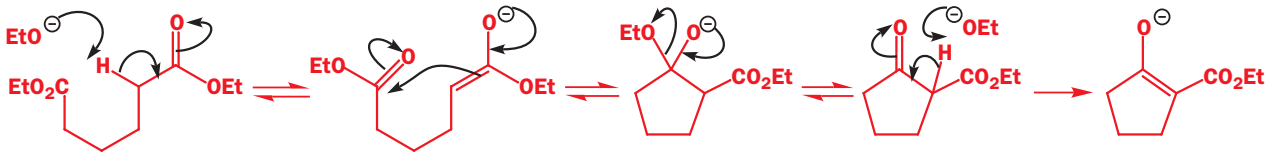
Intramolecular acylation: the Dieckmann reaction



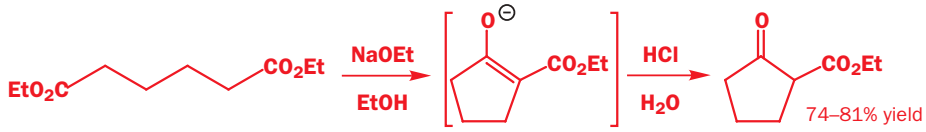
diethyl hexanedioate

Intramolecular acylations often go very well indeed when a five- or a six-membered ring is being formed. A classic case is the cyclization of the diethyl ester of adipic acid (diethyl hexanedioate), a component in nylon manufacture.

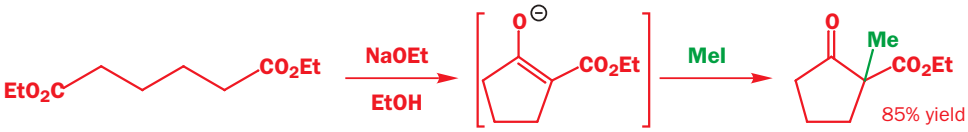
It doesn't matter which ester group forms the enolate anion as they are the same. The cyclization has to give a five-membered ring.



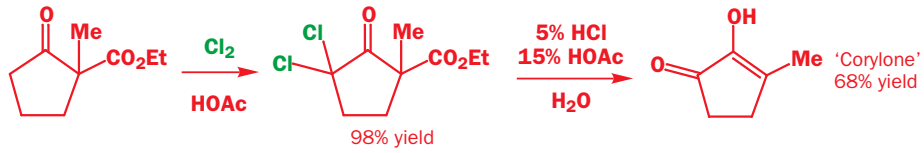
As in the intermolecular version, the product under the reaction conditions is the stable enolate but work-up in acid forms the keto-ester as final product.



We can simultaneously prove that the enolate really is formed under the reaction conditions and demonstrate the usefulness of the process by trapping the enolate with an alkyl halide before work-up.

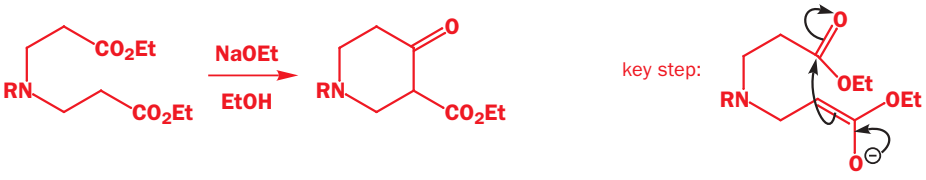


This sequence was used to prepare the important flavouring compound 'Corylone' which has, it is claimed, a 'sweet and powerful spicy–coffee–caramel odour'. You may imagine how popular it is with food-additive chemists and this sequence provides a short process for its manufacture.

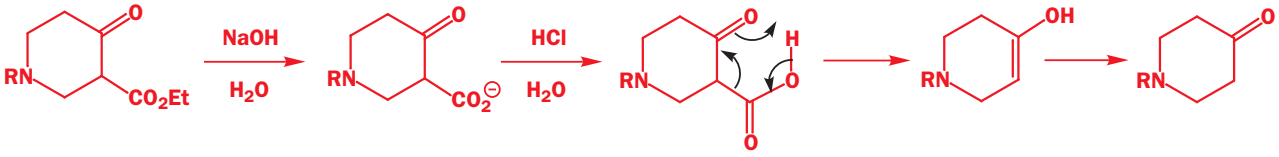


The intramolecular version of the Claisen ester condensation is sometimes known as the **Dieckmann reaction**. It provides an excellent route to heterocyclic ketones (cyclic ketones with heteroatoms in the ring: very important in drug manufacture). The starting diester can be made by two Michael additions to conjugated esters (see Chapter 10).

Treatment with base under the usual equilibrating conditions allows an efficient intramolecular condensation by the usual mechanism. Both ester groups are again identical and, since you should by now be accustomed to this mechanism, we just show the key step.



The β keto-esters can be easily hydrolysed and decarboxylated by the methods of Chapter 26 to give the symmetrical cyclic ketone. The carboxylate anion is reasonably stable, but the free acid cannot usually be isolated as it loses carbon dioxide easily and gives the enol of the final product.

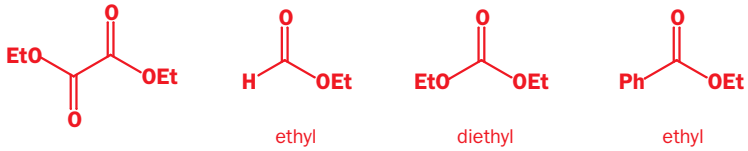


Crossed ester condensations

Much the same type of arguments applies here as applied in the crossed aldol reaction (Chapter 27). We must be quite sure that we know which compound is going to act as the enol partner and which as the acylation partner.

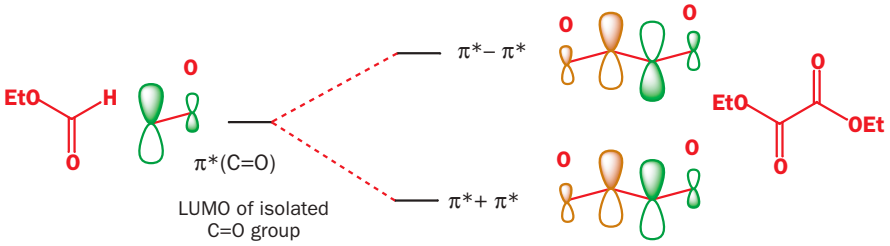
Reactive esters that cannot enolize

There are several useful esters of this kind, of which these four are the most important. They cannot act as the enol partner, and the first three are more electrophilic than most esters, so they should acylate an ester enolate faster than the ester being enolized can.



diethyl oxalate | ethyl formate | diethyl carbonate | ethyl benzoate

These four are arranged in order of reactivity towards nuclophiles, the most electrophilic first and the least electrophilic last. Oxalates are very reactive because each carbonyl group makes the other more electrophilic. The molecular LUMO is the *sum* of the two π* orbitals and is lower in energy than either.



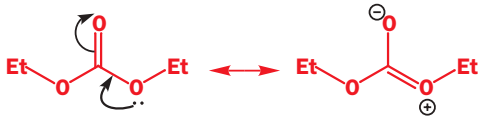
▶ σ conjugation from adjacent C–H bonds raises the LUMO of most esters, just as an adjacent nitrogen lone pair raises the LUMO of an amide, but to a lesser extent.

Formate esters look a bit like aldehydes but their ester character dominates. The hydrogen atom just makes them very electrophilic as they lack the σ conjugation (and steric hindrance) of simple esters.

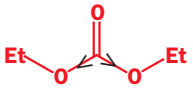
Carbonates are particularly useful as they introduce a CO_2R group on to an enolate. It is not immediately obvious why they are more electrophilic than simple esters. Normal esters are (slightly) less electrophilic than ketones bcause the deactivating lone pair donation by the oxygen atom is more important than the inductive effect of the electronegative oxygen atom.

conjugation reduces electrophilic reactivity | inductive effect increases electrophilic reactivity

The result is a small difference between two large effects. In carbonate esters there are two oxygen atoms on the same carbonyl group. Both can exert their full inductive effect but the lone pairs are trying to overlap with the same π^* orbital. The balance is changed—the summed inductive effects win out—and carbonates are more electrophilic than ordinary esters.

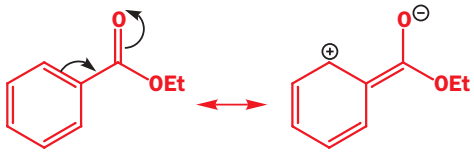


conjugation reduces electrophilic reactivity



two inductive effects increase electrophilic reactivity a lot

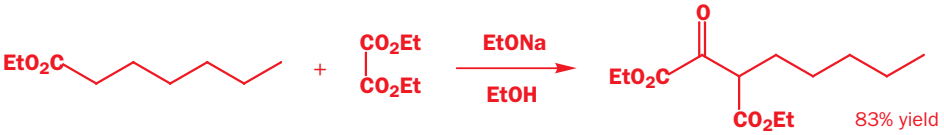
Finally, esters of aromatic acids cannot enolize but are less reactive than ordinary esters because of conjugation from the aromatic ring. These compounds may still be useful as we shall see.



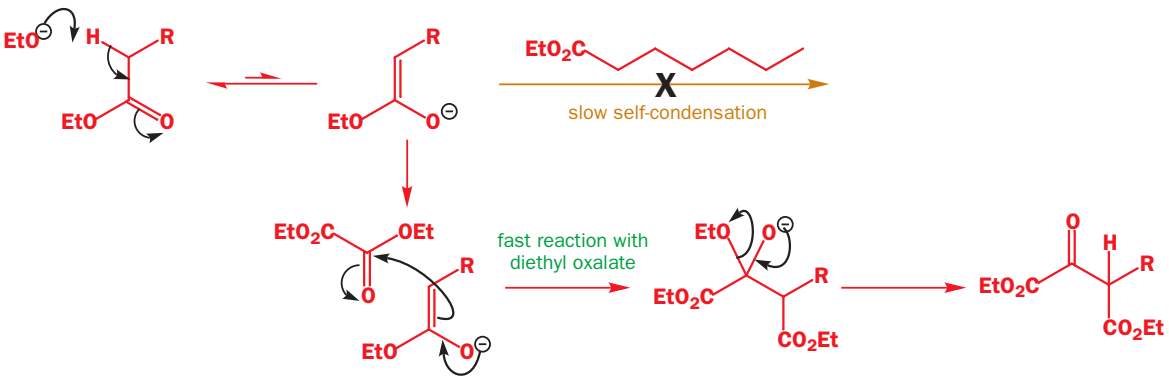
conjugation reduces the electrophilic reactivity of aromatic esters

Crossed Claisen ester condensations between two different esters

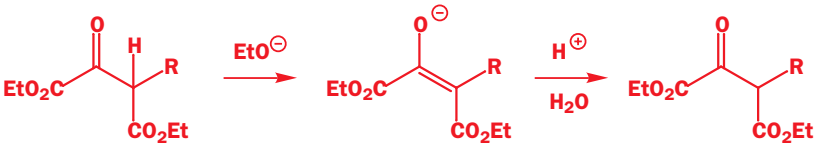
We shall now give a few examples of crossed Claisen ester condensations between ordinary esters and the compounds we have just discussed. First, a reaction between a simple linear ester and diethyl oxalate performed under equilibrating conditions with ethoxide as the base.



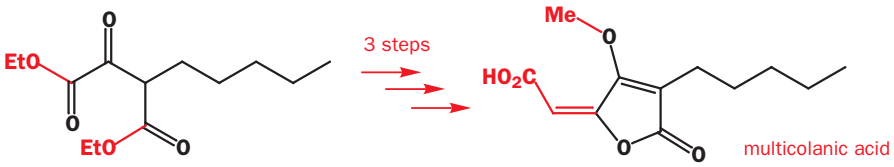
Only the simple ester can give an enolate, and the low concentration of this enolate reacts preferentially with the more electrophilic diethyl oxalate in a typical acylation at carbon.

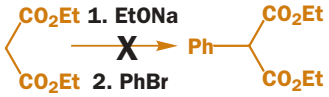


The product has an acidic hydrogen atom so it is immediately converted into a stable enolate, which is protonated on work-up in aqueous acid to give the tricarbonyl compound back again.



This compound was made because it was needed in a synthesis of multicolanic acid, a metabolite of a penicillium mould. It is easy to see which atoms of the natural product were provided by the compound we have just made in a single easy step.



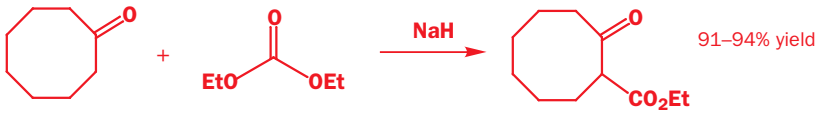


Another important example leads to the preparation of diethyl phenylmalonate. This compound cannot be made by 'alkylation' of diethyl malonate as aryl halides do not undergo nucleophilic substitution (Chapter 23).

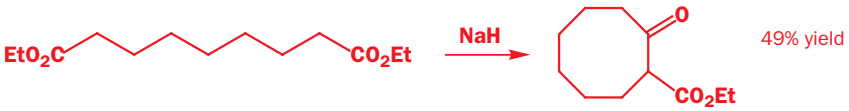
A crossed Claisen ester condensation between very enolizable ethyl phenylacetate and unenolizable but electrophilic diethyl carbonate works very well indeed under equilibrating conditions.

Claisen condensations between ketones and esters

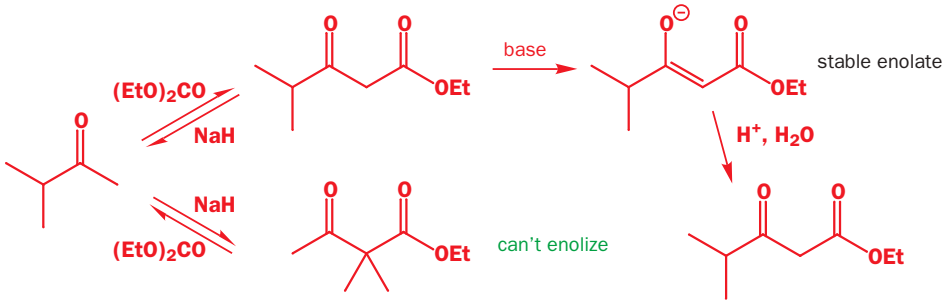
Claisen condensations always involve esters as the electrophilic partner, but enolates of other carbonyl compounds—ketones, for example—may work equally well as the enol partner. In a reaction with a carbonate, only the ketone can enolize and the reactive carbonate ester is more electrophilic than another molecule of the ketone. A good example is this reaction of cyclooctanone. It does not matter which side of the carbonyl group enolizes—they are both the same.



The alternative route to this cyclic dicarbonyl—Dieckmann condensation—would be a bad choice in this case. Dieckmann condensation works well for five- and six-membered rings, reasonably well for seven-membered rings, but not very well at all for eight-membered rings. The yield is almost exactly half what the ketone–carbonate reaction gives.

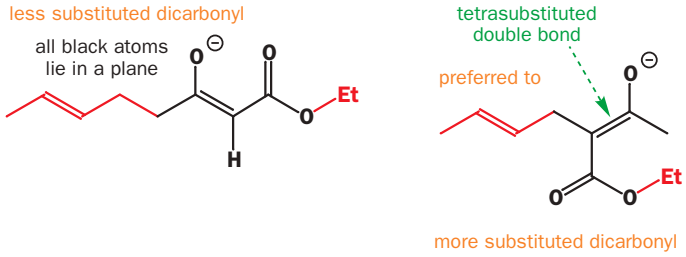


Unsymmetrical ketones often give a single product, even without the use of a specific enol equivalent, as reaction usually occurs on the less substituted side. This is another consequence of the final enolization being the irreversible step. In this example, both possible products may form, but only one of them can enolize. Under the equilibrating conditions of the reaction, only the enolate is stable, and all the material ends up as the isomer shown.

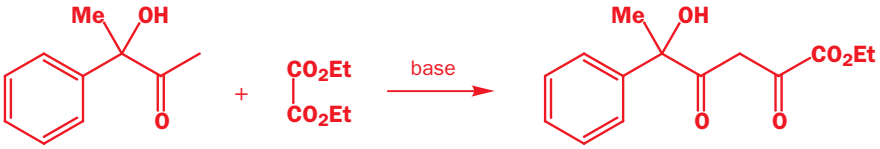


Unsymmetrical ketones work well even when one side is a methyl group and the other a primary alkyl chain. This example gives an impressive yield and shows that, as expected, a remote alkene does not affect the reaction.

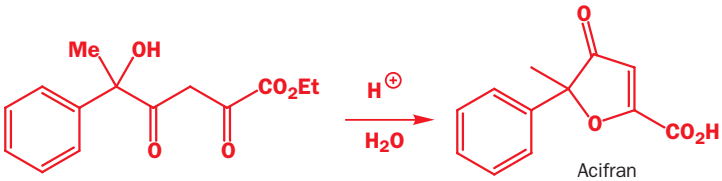
Even when both enolates can form, the less substituted dicarbonyl enolate is preferred because it constrains fewer groups to lie in the hindered plane of the tetrasubstituted enolate double bond.



Diethyl oxalate also gives well-controlled condensations with ketones and we shall take the synthesis of a new drug as an example. One way to try and prevent heart disease is to reduce the amount of 'bad' lipoproteins in the blood. The drug Acifran does this, and a key step in its synthesis is the base-catalysed reaction between diethyl oxalate and a methyl ketone.

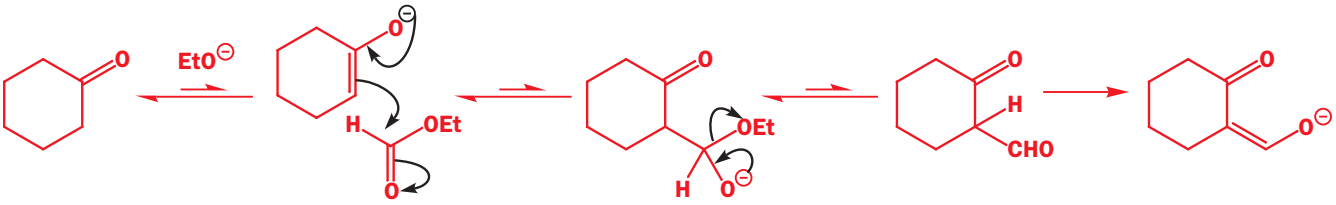


Notice that the hydroxyl group on the ketone does not interfere with the reaction. No doubt the first molecule of base removes the OH proton and the second molecule forms the enolate (the only possible enolate in either molecule). Fast condensation with highly electrophilic diethyl oxalate follows. The drug itself results from simple acid treatment of this product.

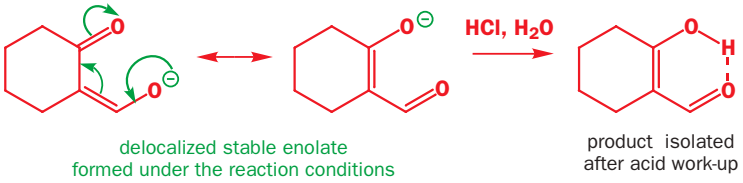


■ Try to write a mechanism for the cyclization step.

The other two unenolizable esters we mentioned on p. 000 undergo cross-condensations with ketones. Unlike formaldehyde, formate esters are well behaved—no special method is necessary to correspond with the Mannich reaction in aldol chemistry. Here is what happens with cyclohexanone.

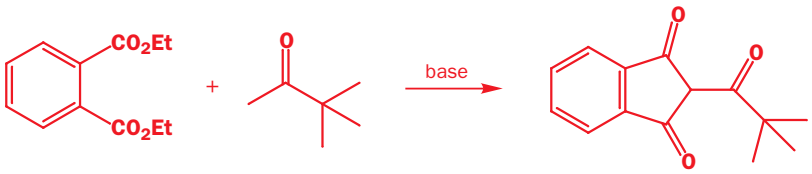


The product aldehyde is not at risk from nucleophilic attack, as it appears to be, because it immediately enolizes in base. The product is formed as a stable enol with an intramolecular hydrogen bond.

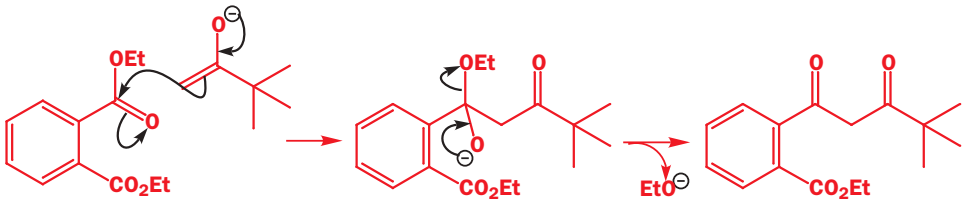


Esters of aromatic acids are used rather less frequently in this manner because they are considerably less reactive than carbonates or formates. This simple example works quite well—admittedly the ketone is very enolizable.

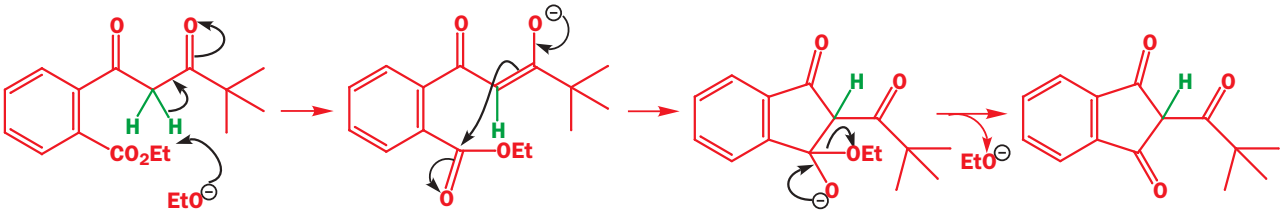
A more important example is the synthesis of the rat poison 'Pival'. An enolizable ketone that is blocked on one side by a tertiary butyl group reacts with diethyl phthalate to give a five-membered cyclic diketone in one reaction by two Claisen ester condensations.



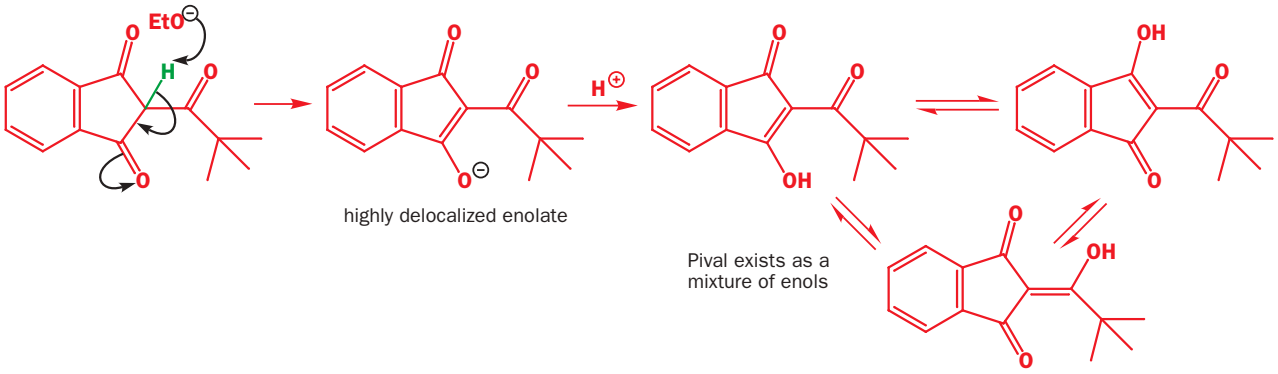
Only one enolate can be formed and this attacks either of the two aromatic ester groups to give a 1,3-diketone by a crossed Claisen condensation.



The ethoxide ion released in this first reaction will, as usual, form a stable enolate from the 1,3-diketone but this now cyclizes in a second Claisen condensation on to the second ester group.



The product has an exceptionally acidic hydrogen atom, shown in green, on a carbon atom between three carbonyl groups. Under the reaction conditions this will of course be lost to form an enolate, and after protonation Pival itself exists as a mixture of enol forms.

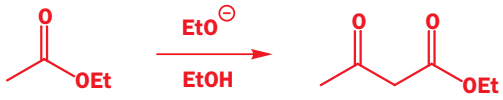


Summary of preparation of keto-esters by the Claisen reaction

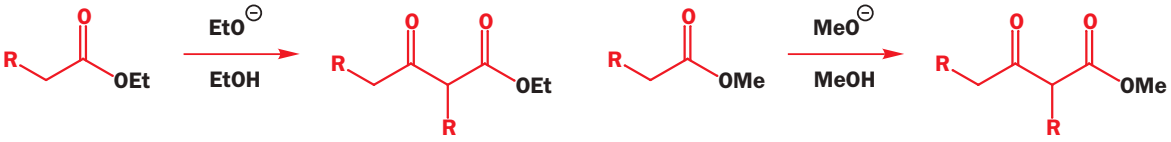
It is worth pausing at this moment to summarize which keto-esters can be made easily by the two methods we have discussed, namely

- Claisen ester condensation
- acylation of ketones with enolates

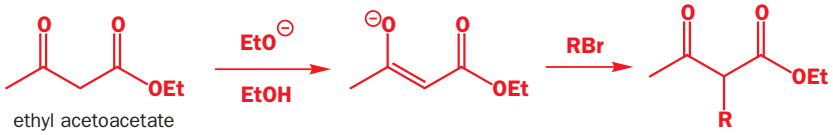
Ethyl acetoacetate (ethyl 3-oxobutyrate) can of course be made by the self-condensation of ethyl acetate.



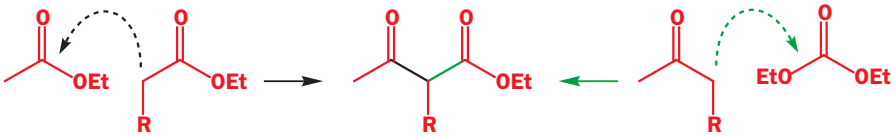
This ester is cheap to buy but homologues, available by the self-condensation of other esters, are usually made in the laboratory. Which esterifying group is used (OEt, OMe, etc.) is not important so long as the same alkoxide is used as the base.



Compounds with only one of the 'R' substituents in this structure are also easy to make. If the 'R' substituent is at C2, it is best introduced by alkylation of the unsubstituted ester.



Attempts to make this compound by the Claisen ester condensation would require one of the approaches in the diagram below. The dashed curly arrows suggest the general direction of the condensation required and the coloured bonds are those that would be formed *if* the reaction worked.



Unfortunately neither reaction willwork! The black route requires a controlled condensation between two different enolizable esters—a recipe for a mixture of products. The simple alkylation route above removes the need for control. The green route requires a condensation between an unsymmetrical ketone and diethyl carbonate. This condensation will work all right, but not to give this product. As you saw on p. 000, Claisen condensations prefer to give the less substituted dicarbonyl compound, and condensation would occur at the methyl group of the ketone on the right to give the other unsymmetrical keto-ester.

■ We shall see later in this chapter how such reactions *can* be controlled.

● Making β keto-esters: a check-list

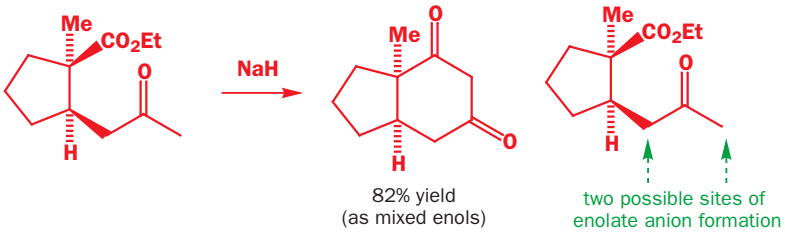
A combination of self-condensation, condensation with diethyl carbonate, and alkylation of keto-esters prepared by one of these means will allow us to make most β keto-esters that we are likely to want. Look out for all the usual problems of enolate chemistry.

- **Will the right carbonyl compound enolize?**
- **If it is a ketone, will it enolize in the right way?**
- **Will the enolate react with the right acylation partner?**

If any of these poses problems, try using an alkylation step.

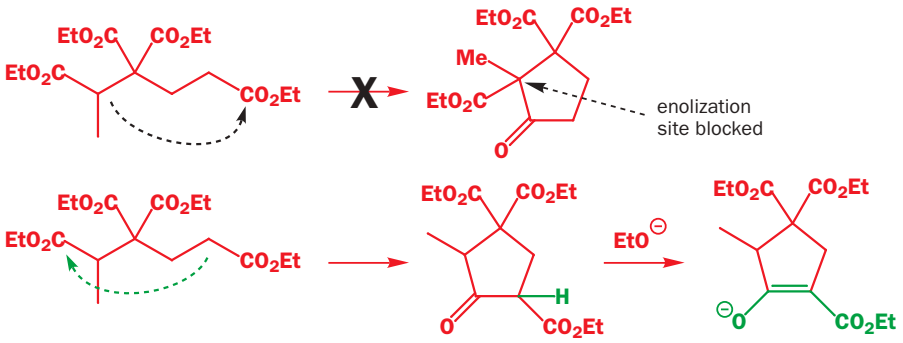
Intramolecular crossed Claisen ester condensations

As usual with intramolecular condensations, we do not have to worry so much about controlling where enolization occurs providing that one product is more stable than the others—for example, it might have a five- or a six-membered ring (rather than a four- or eight-membered one)—and we carry out the reaction under equilibrating conditions. A couple of examples should show what we mean.

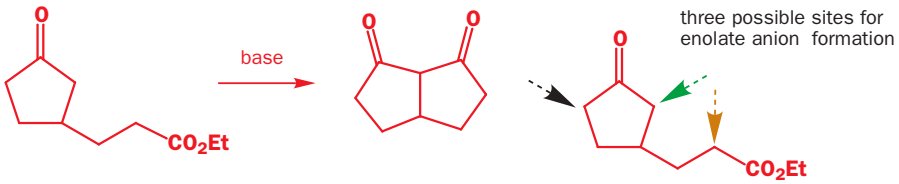


Though there are two sites for enolate anion formation, one would give a four-membered ring and can be ignored. Only enolization of the methyl group leads to a stable six-membered ring.

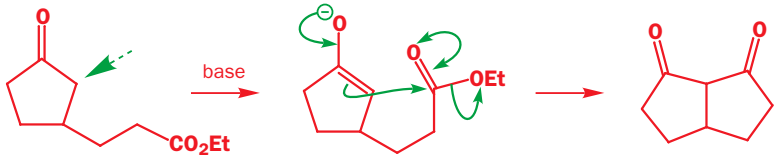
This time the two possible sites for enolate anion formation would both lead to stable five-membered rings, but one product cannot form a stable enolate anion under the reaction conditions so the other is preferred.



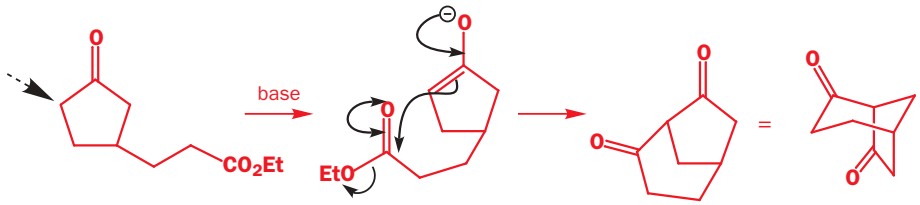
In the next example, there are three possible sites for enolate anion formation, but only one product is formed and in good yield too.



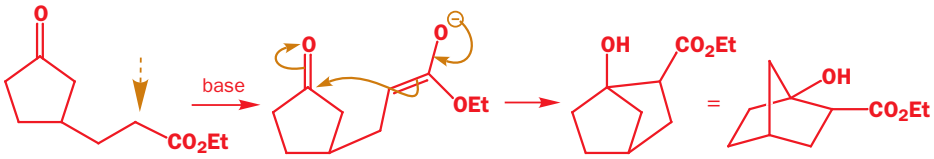
If we consider all three possible enolate anions, the choice is more easily made. First, the reaction that *does* happen. An enolate anion is formed from the ketone at the green site and acylation at carbon follows.



We could form the enolate anion on the other side of the ketone and attack the ester in the same way using the black arrows. The product is an attractive bicyclic diketone, but it is not formed.

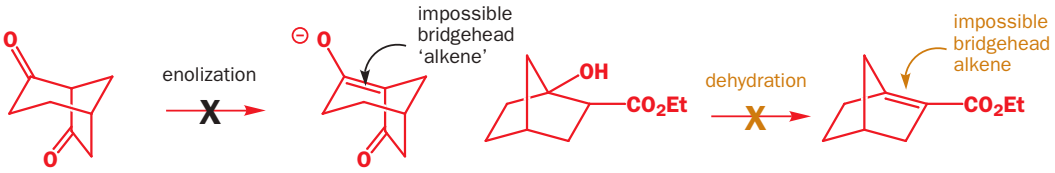


The third cyclization mode (brown arrows) would be to form an enolate from the ester and attack the ketone. This would be an aldol rather than a Claisen reaction.

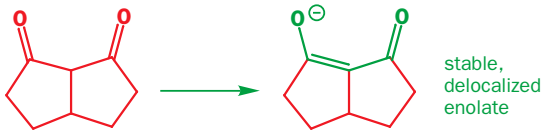


This is another bicyclic compound but again it is not formed. The choice is made by considering what can happen to the three products under the reaction conditions. The aldol product cannot dehydrate nor can the black Claisen product form a stable enolate because both would have an impossible double bond at a bridgehead position.

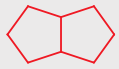
■ We discussed bicyclic compounds and bridgehead double bonds in Chapter 19.



The product from the green Claisen reaction is, on the other hand, a fused rather than a bridged bicyclic structure. It can easily form a stable enolate anion.



■ Remind yourself (p. 000) of the difference between fused compounds (one bond in common), *spiro* compounds (one atom in common), and bridged compounds (rings joined at two non-adjacent atoms). Each of these three examples has two five-membered rings

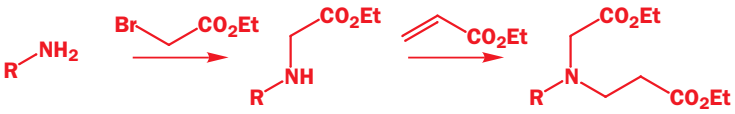

fused bicyclic


spiro-cyclic

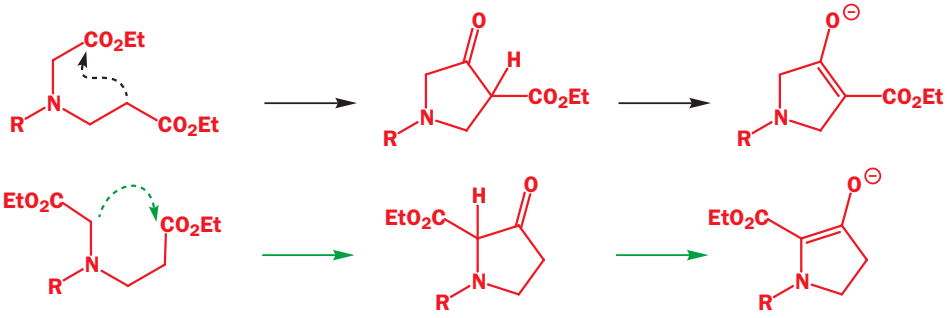

bridged bicyclic

Symmetry in intramolecular crossed Claisen condensations

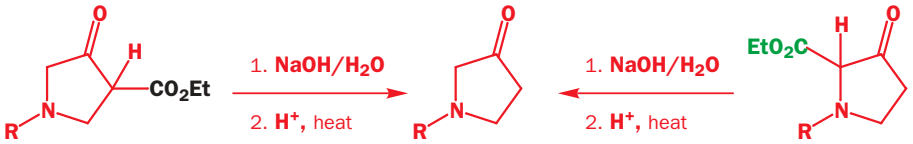
If cyclization is to be followed by decarboxylation, a cunning plan can be set in motion. Addition of an amine by an S_N2 reaction to an α halo-ester followed by conjugate addition to an unsaturated ester gives a substrate for Claisen ester cyclization.



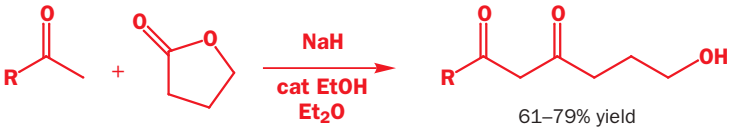
This diester is unsymmetrical so cyclization is likely to lead to two different keto-esters. Either can form a stable enolate so both are indeed formed. This sounds like very bad news since it gives a mixture of products.



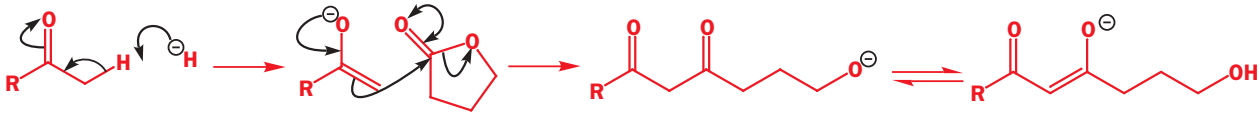
The cunning plan is that the relative positions of the ketone and the nitrogen atom in the five-membered ring are the same in both products. All that differs is the position of the CO_2Et group. When the two different products are hydrolysed and decarboxylated they give the same amino-ketone!



Just occasionally it is possible to carry out cross-condensations between two different enolizable molecules under equilibrating conditions. A notable example is the base-catalysed reaction between methyl ketones and lactones. With sodium hydride—a strong base that can convert either starting material entirely into its enolate anion—good yields of products from the attack of the enolate of the ketone on the electrophilic lactone can be obtained.



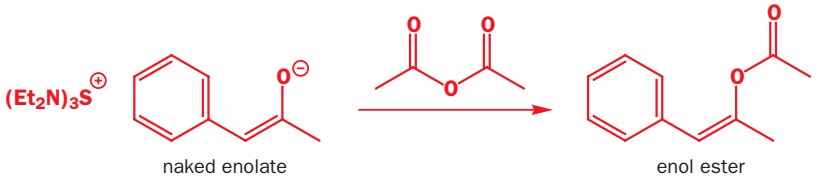
Kinetic enolate formation must occur at the methyl group of the ketone followed by acylation with the lactone. Lactones are rather more electrophilic than noncyclic esters, but the control in this sequence is still remarkable. Notice how a stable enolate is formed by proton transfer within the first-formed product.



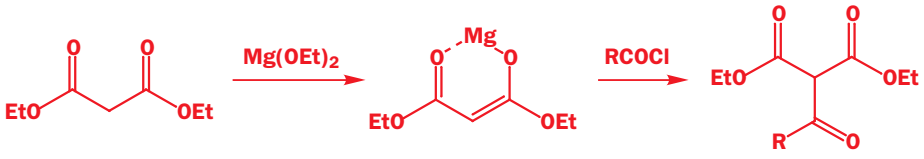
All these reactions have depended for their selectivity on the spontaneous behaviour of the molecules. It is time now to look at some reactions that cannot be controlled in that way—reactions where we must impose our will on the molecules by using specific enol equivalents.

Directed *C*-acylation of enols and enolates

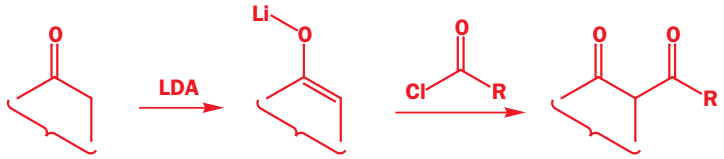
The danger we have to face is that acylation is inclined to occur on oxygen rather than on carbon. In the extreme case, naked enolates (those with completely non-coordinating cations) acylate cleanly on oxygen with anhydrides or acid chlorides.



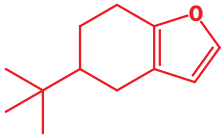
Alkali metal enolates (Li, Na, or K) tend to acylate on oxygen with acid chlorides too and it is often necessary to use magnesium enolates, particularly those of 1,3-dicarbonyl compounds, if reliable *C*-acylation is wanted. The magnesium atom bonds strongly to both oxygens, lessening their effective negative charge.



Hydrolysis and decarboxylation in the usual way lead to keto-esters or keto-acids. Of the more common metals used to form enolates, lithium is the most likely to give good *C*-acylation as it, like magnesium, forms a strong O–Li bond. It is possible to acylate simple lithium enolates with enolizable acid chlorides.

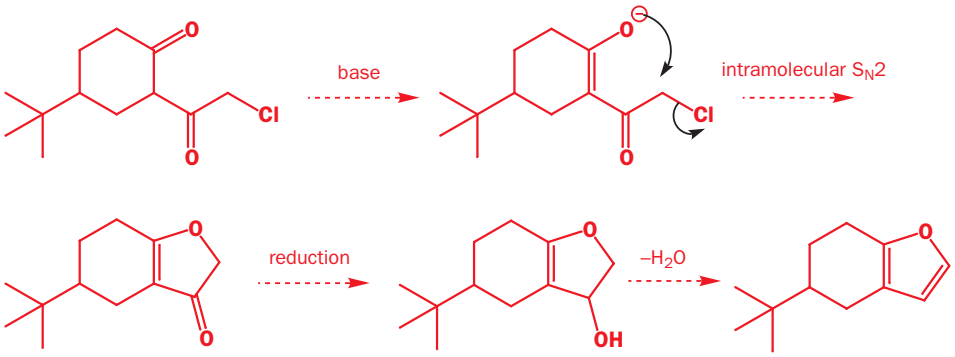


We shall describe two examples of this reaction being used as part of the synthesis of natural products. The first is pallescensin A, a metabolite of a sponge.

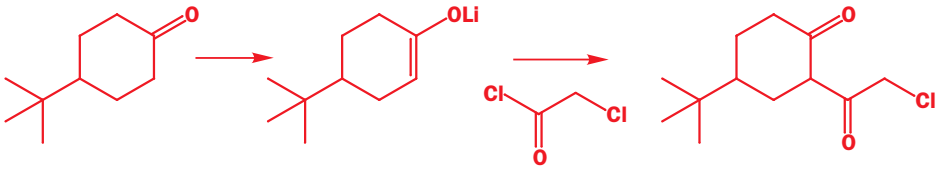


pallescensin A

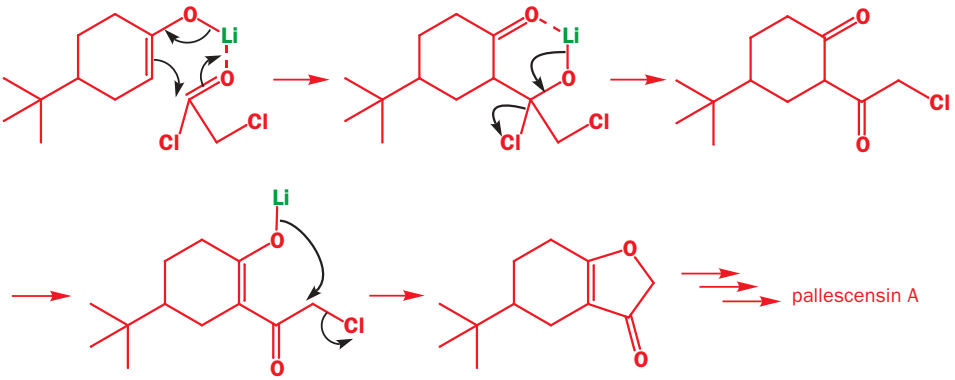
It is quite a simple compound and some chemists in Milan conceived that it might be made from the chloro-diketone shown below by alkylation of the enolate and subsequent reduction and dehydration of the remaining ketone.

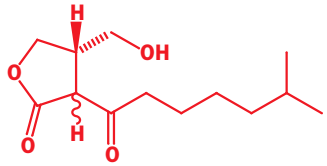


To test this idea, the chloro-diketone must be made and the route chosen was to react the lithium enolate of 4-*t*-butyl cyclohexanone with the correct acid chloride.



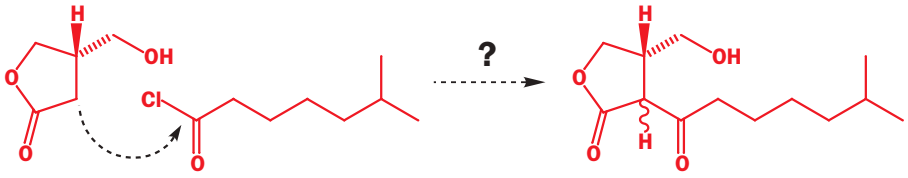
This reaction worked well, as did the rest of the synthesis of pallescensin A which was first made by this route. The key step, the acylation of the lithium enolate, is interesting because it could have alkylated instead. The acid chloride is more electrophilic than the alkyl chloride in this reaction, though alkylation does occur in the next step. Notice how the lithium atom holds the molecules together during the reaction.



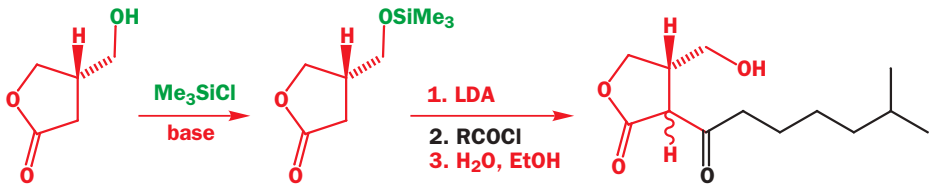

A-factor

Our second example is from the chemistry of microorganisms. The antibiotic streptomycin is produced rather erratically by the microorganism *Streptomyces griseus*. It has now been discovered that another compound, called 'A-factor', stimulates the microorganism into streptomycin production. Synthetic A-factor can be used to switch on antibiotic synthesis in the microorganism.

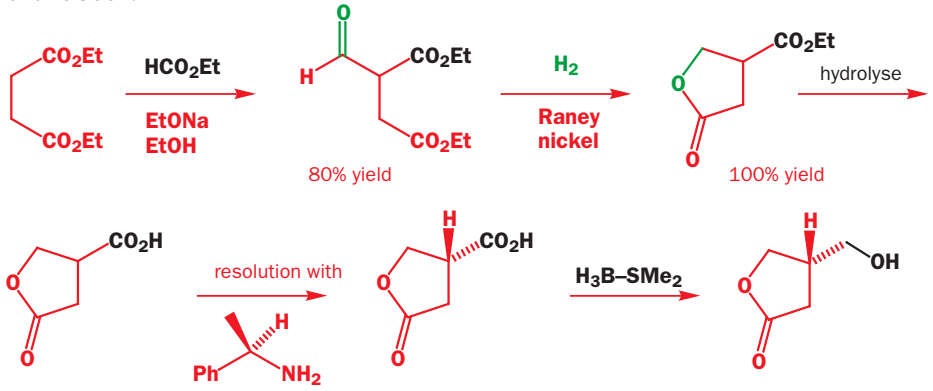
A-factor is an optically active compound, but notice that one stereogenic centre is not specified in the structure (H with a wavy line). This is because it is a 1,3-dicarbonyl compound and is therefore in equilibrium with its stable enol which has a trigonal centre at that point. The obvious way to complete the synthesis is to acylate an enolate of the lactone with an acid chloride.



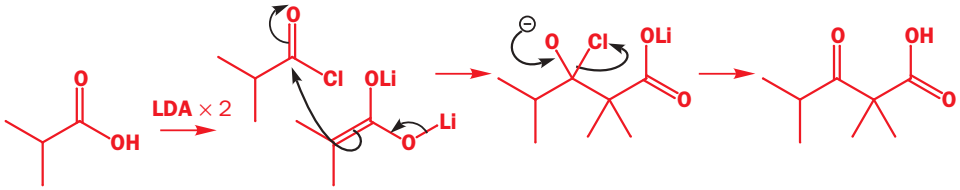
It will not be possible to have a free OH group on the lactone during this step as the acid chloride would, of course, react there too. In practice, protection as a silyl ether (Chapter 24) was enough and the lithium enolate was then used for the acylation reaction. Aqueous ethanol work-up removed the silyl protection.



The preparation of the starting material is worth a closer look because it too involved a cross-condensation between two esters. Here it is in full. You have met all of these reactions in earlier chapters of this book.

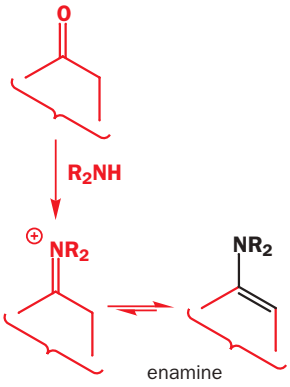


Even the dilithio derivatives of carboxylic acids, made by treating a carboxylic acid with two molecules of LDA, can give good reactions with acid chlorides. In these reactions it is not necessary to have a proton remaining between the two carbonyl groups of the product as the reaction is between a strong nucleophile and a strong electrophile and is under kinetic control.



It is rather more common to use enamines or silyl enol ethers in acylations with acid chlorides. These are more general methods—enamines work well for aldehydes and ketones while silyl enol

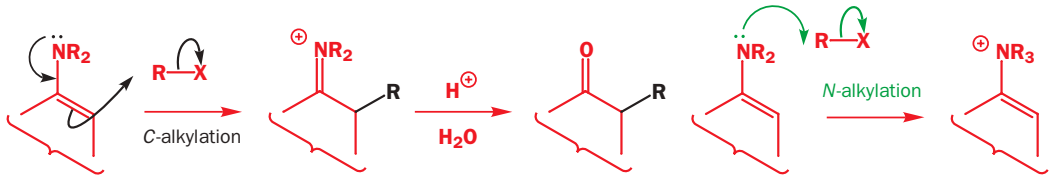
ethers work for all classes of carbonyl compounds. It is possible to combine two enolizable molecules quite specifically by these methods, and we shall consider them next.



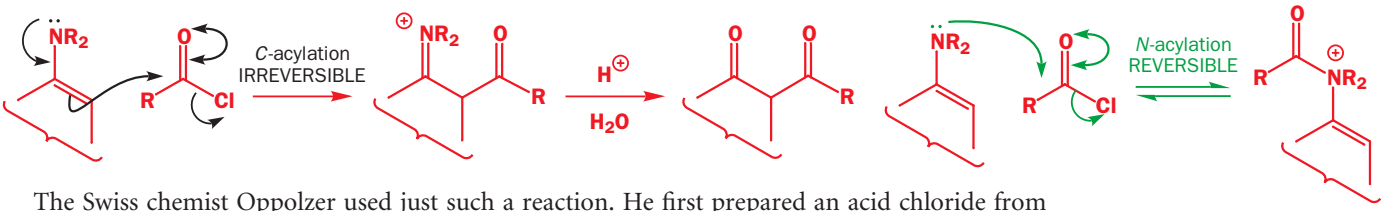
The acylation of enamines

Enamines are made from secondary amines and aldehydes or ketones via the iminium salt: you met them in Chapter 14 and have seen them in action in Chapters 21, 26, and 27.

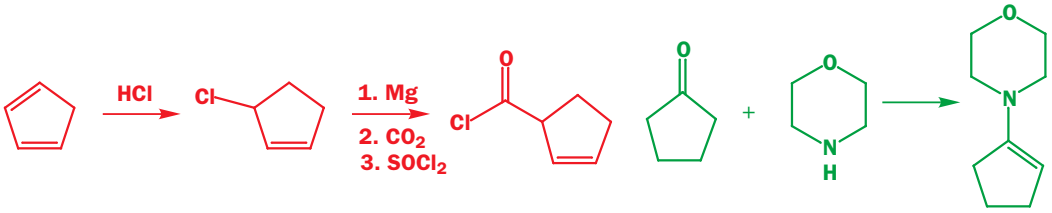
In Chapter 26 we saw that reliable *C*-alkylation occurs with reactive allyl halides and α halocarbonyl compounds, but that unwanted *N*-alkylation often competes with simple alkyl halides.



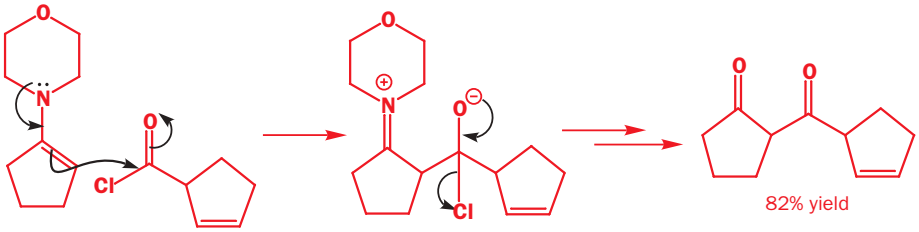
Acylation with acid chlorides could follow the same two pathways, but with one big difference. The products of *N*-acylation are unstable salts and *N*-acylation is reversible. Acylation on carbon, on the other hand, is irreversible. For this reason enamines end up acylated reliably on carbon.



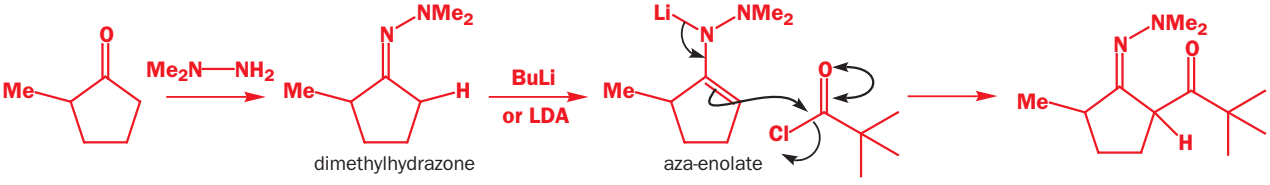
The Swiss chemist Oppolzer used just such a reaction. He first prepared an acid chloride from cyclopentadiene, and the enamine from cyclopentanone and the secondary amine morpholine.



Combining the enamine with the acid chloride led to a clean acylation at carbon in 82% yield and eventually to a successful synthesis of the natural product longifolene.



Aza-enolates also react cleanly at carbon with acid chlorides. Good examples come from dimethylhydrazones of ketones. When the ketone is unsymmetrical, the aza-enolate forms on the less substituted side, even when the distinction is between primary and secondary carbons. The best of our previous regioselective acylations have distinguished only methyl from more highly substituted carbon atoms.

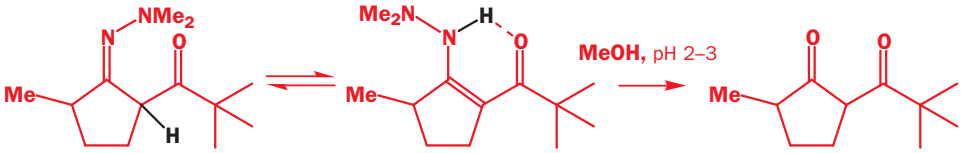


▶ Morpholine is frequently used in the preparation of enamines—see p. 000.

■ We shall revisit this synthesis in Chapter 35 when we discuss [2 + 2] cycloadditions.

▶ Hydrazones, as we explained on p. 000 of Chapter 14, are much less electrophilic than ketones. Even BuLi can be used as a base: it does not attack the C=N bond.

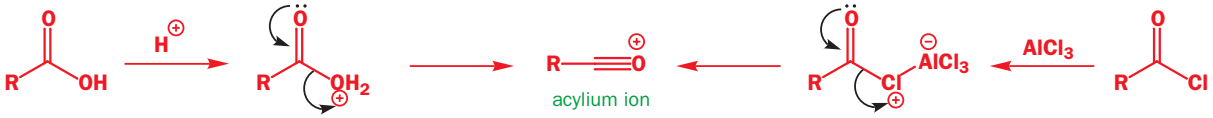
You will not be surprised to find that the immediate product tautomerizes to an acyl-enamine further stabilized by an internal hydrogen bond. Mild acidic work-up releases the diketone product. The overall procedure may sound complicated—Me_2NNH_2 then base then acyl chloride then acidic methanol—but it is performed in a single flask and the products, the 1,3-diketones, are formed in excellent yield—in this case 83% overall.



83% yield from starting ketone

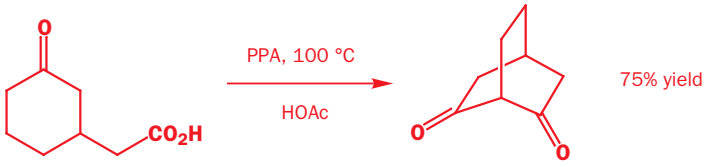
Acylation of enols under acidic conditions

Under strongly acidic anhydrous conditions, carboxylic acids dehydrate to give the acylium ions, which you met as intermediates in the Friedel–Crafts reaction (Chapter 22).



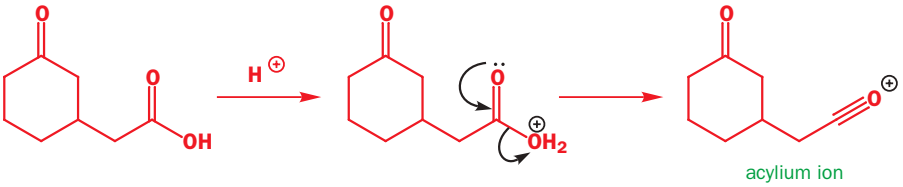
(polyphosphoric acid)

With another enolizable carbonyl group in the molecule, cyclization may occur to give a new 1,3-dicarbonyl compound. Popular conditions for this reaction are polyphosphoric acid (PPA—partly dehydrated and polymerized H_3PO_4) in acetic acid as solvent.

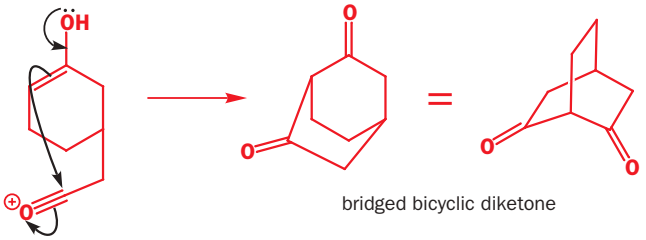


75% yield

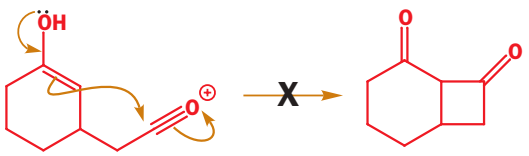
The first step is the formation of the acylium ion, which cyclizes on to one of the two possible enols of the ketone.



Though the cyclization looks awkward—the product is a bridged bicyclic diketone—the alternative would give a strained four-membered ring and does not occur.

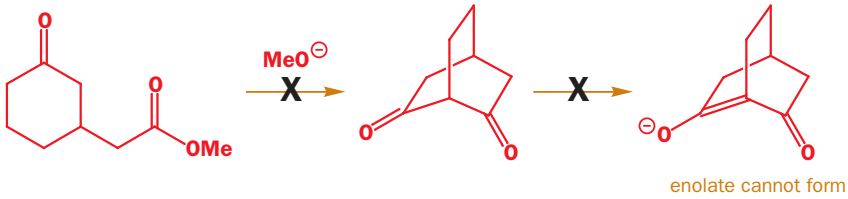


bridged bicyclic diketone

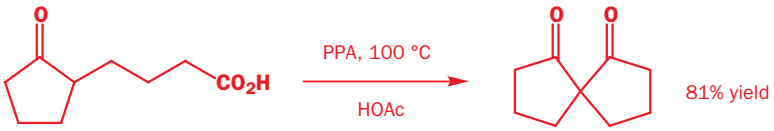


four-membered ring
—not formed

This cyclization is particularly impressive as the corresponding base-catalysed reaction on the keto-ester does not occur because a stable enolate cannot be formed—it would have an impossible bridgehead double bond.



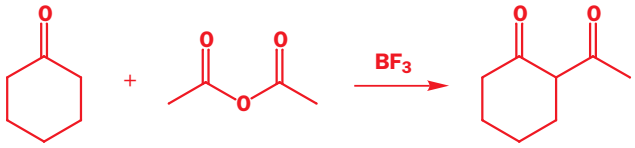
Evidently it is not necessary to form a stable conjugated enol in this acid-catalysed cyclization of keto-acids, and the reaction can even be used to make 1,3-diketones with no hydrogen atoms between the two carbonyl groups.



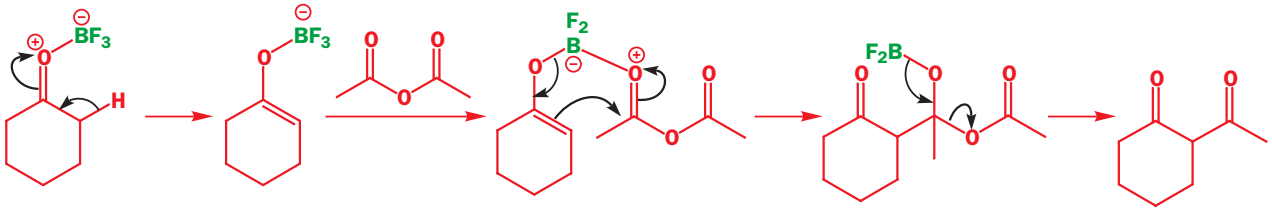
This time the *spiro*-bicyclic diketone (one C atom common to both rings) is preferred to the alternative bridged bicyclic compound because both rings are five-membered.

Lewis acid-catalysed acylation of enols

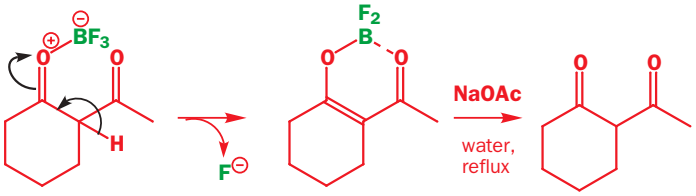
Acylations of ketone enols with anhydrides are catalysed by Lewis acids such as BF_3. This process will remind you of Friedel–Crafts acylation but a better analogy is perhaps the aldol reaction where metals such as lithium hold the reagents together so that reaction can occur around a six-membered ring.



The mechanism obviously involves attack by the enol (or 'boron enolate') of the ketone on the anhydride, catalysed by the Lewis acid. Probably BF_3 or BF_2 groups (fluoride can come and go from boron easily) hold the reagent together at all times, much like lithium in the aldol reaction (p. 000).

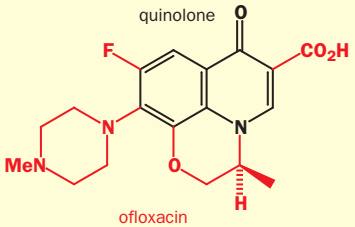


Under the conditions of the reaction, the product forms a stable boron enolate, which needs to be decomposed to the diketone with refluxing aqueous sodium acetate.



Preparation of a modern antibiotic—ofloxacin

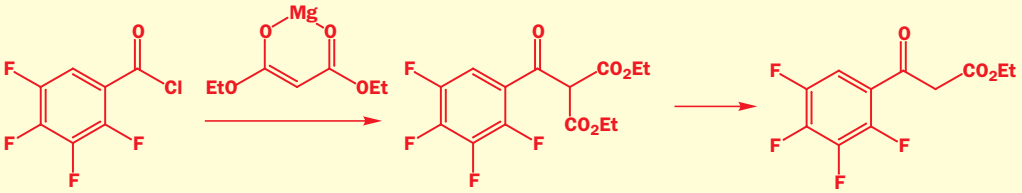
As resistance to familiar antibiotics such as penicillin grows, it becomes even more important to discover not only new antibiotics but new classes of antibiotics having totally new structures. Ofloxacin is a member of one such class—the quinolone antibiotics.



ofloxacin

Members of this class usually have an amine and a fluorine atom on the benzene ring as well as other embellishments as in ofloxacin, a recent example. The preparation of ofloxacin starts with two enolate acylations.

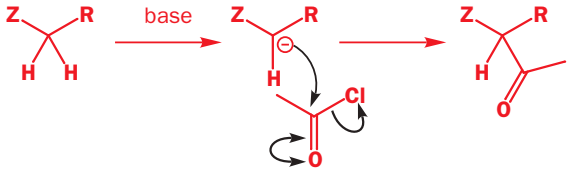
The first is the acylation of the magnesium derivative of diethyl malonate. The magnesium atom prevents *O*-acylation with acid chlorides, and decarboxylation (p. 000) removes the redundant ester group.



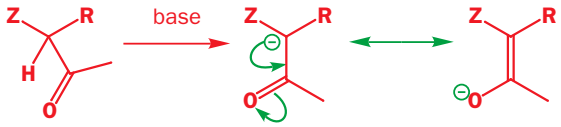
Later steps in the synthesis of ofloxacin were discussed in Chapter 23.

Acylation at nucleophilic carbon (other than enols and enolates)

We should not leave the subject of acylation at carbon without considering a problem that affects all such reactions to some degree. It can be understood most easily if we imagine some functional group Z that is able to stabilize a carbanion, and the acylation of that carbanion with an acid chloride—something like this.

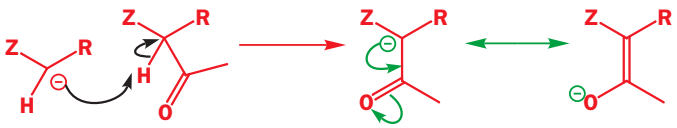


All looks well until we consider what might happen to the product under the reaction conditions. It too can form an anion, and a very stable one at that, because, not only is it stabilized by Z, but it is also an enolate.



stabilized enolate anion

Since this anion is *more stable* (less basic) than the original anion, if there is an equilibrium between the two carbanions in the reaction mixture, the original carbanion will be sufficiently basic to act as the base that removes the proton from the product.

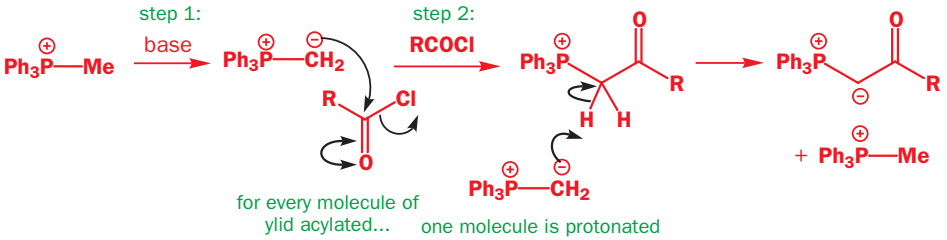


stabilized enolate anion

So, instead of being acylated, the starting anion is protonated. This side-reaction could reduce the maximum possible yield in the acylation reaction to 50%: half the starting material forms the product by acylation, while the other half simply *deprotonates* the product. How is this to be avoided?

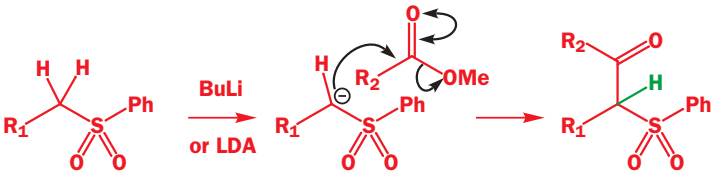
In most of this chapter, we used enolates as our nucleophiles and worked under equilibrating conditions with alkoxide bases. There was alkoxide base present throughout the reaction, so the enolate didn't get used up deprotonating the product or, if it did, it could be re-deprotonated by the

alkoxide. But the problem does arise in reactions such as the acylation of simple phosphorus ylids. Here two equivalents of ylid must be used to give a good yield of product. This does not matter in this case, because the ylid is cheap and disposable.

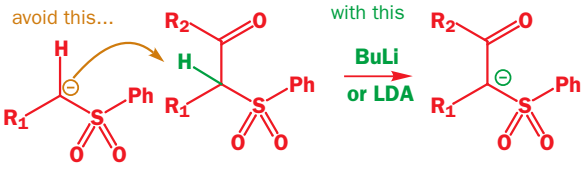


■ This is a good way of making stabilized ylides for the Wittig reaction: see pp. 000 and 000.

If the reagent is too precious to waste, another device is to use two molecules of base for every one of the compound. In this way there is always a molecule of strong base waiting to remove a proton from the product. The acylation of sulfones with esters is a good example.



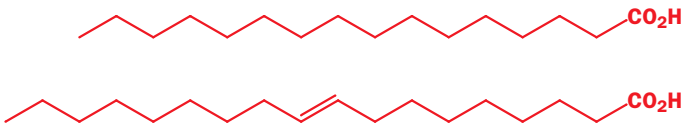
The product has a more acidic hydrogen atom (green) than any in the starting material so it could protonate the original anion. Using two equivalents of base avoids this.



By this device good yields of keto-sulfone can be formed even when both partners are aliphatic compounds with acidic protons.

How Nature makes fatty acids

Fatty acids are big news, whether saturated or unsaturated. Too much saturated fatty acid seems to be bad for us, clogging arteries, while some unsaturated fatty acids seem to protect us against that fatal condition. There are hundreds of fatty acids in living things but most have one special characteristic—they have an even number of carbon atoms. Here are two of the most frequently found fatty acids.



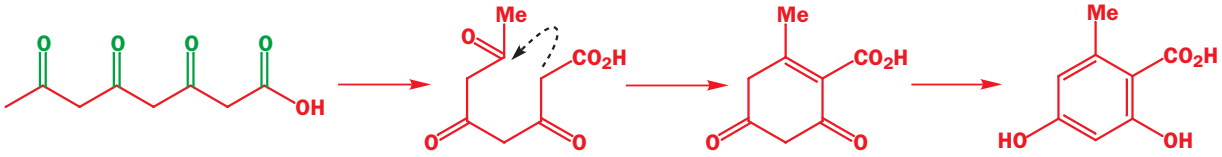
palmitic acid
(saturated fatty acid)

elaidic acid
'monounsaturate'

They have an even number of carbon atoms because they are made in living things by Claisen ester style condensations of acetic acid derivatives. In fact, at some stage in the biosynthesis of palmitic acid, there was a carbonyl group at each atom marked with a green blob here.

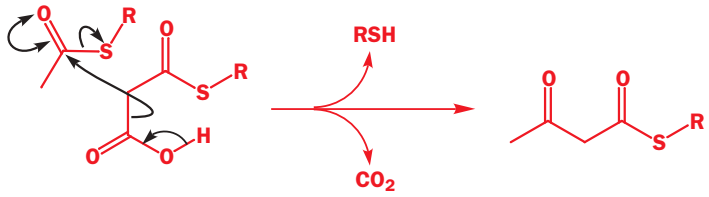
Nature takes the trouble to remove all these carbonyl groups. So why were they put there in the first place? It is because these long chains are much easier to assemble by the Claisen ester

conjugation than by alternatives such as alkylation. Other natural products in this group show more obvious traces of carbonyl groups. Orsellinic acid, for example, is clearly formed directly by an aldol-style cyclization of this tetracarbonyl precursor.

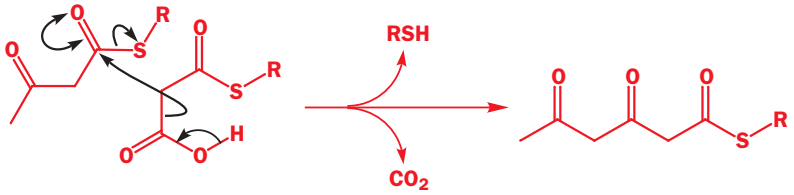


The straight-chain triketo-acid wraps itself round and cyclizes by a simple aldol reaction. Enolization of the two remaining ketones gives a benzene ring. So how does Nature assemble these chains in the first place?

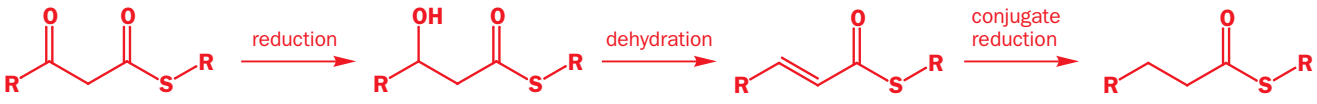
The reactions use thiol esters rather than ordinary esters. The esterifying group is a thiol called coenzyme A, and we shall just represent this molecule as R (you can find its full structure on p. 000). The first reaction is between a malonate half-hioester and an acetate thioester of coenzyme A. Look at the mechanism and you will see how similar it is to the Claisen ester condensation.



The main difference is that no discrete enol or enolate is actually formed. Instead CO_2 is lost from the malonate as the acylation occurs. This is an improvement from Nature's point of view—it is much easier to lose a proton from a carboxylic acid than from a CH_2 group. This reaction joins two C_2 units together and the whole process can be repeated as many times as necessary.



Because of the ketone group on every other carbon atom in the growing chain, these compounds are known collectively as **polyketides**. To make a saturated fatty acid, the ketone needs to be selectively reduced to an alcohol, water needs to be eliminated, and the conjugated double bond reduced. All these steps have simple chemical analogies.



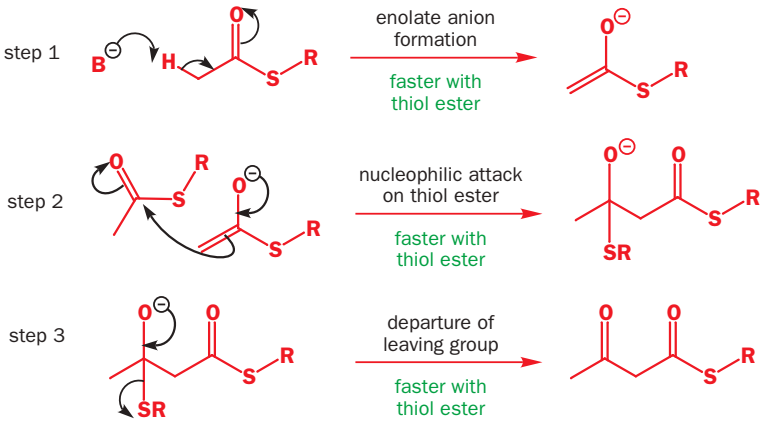
Polyketides of enormous variety are known with all these groups present in the chain at the various stages of reduction. But all are made by Nature's version of the Claisen ester condensation.

Learning from Nature

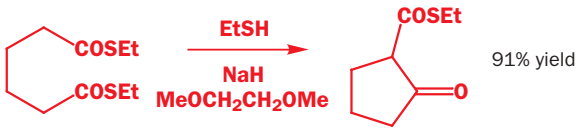
So what is so special about thiol esters? The main difference from ordinary esters is that the lone pairs on the sulfur atom are in 3p orbitals instead of 2p orbitals. These orbitals are too large to overlap efficiently with the 2p orbital on the carbon atom of the carbonyl group, so thiol esters have less conjugation than ordinary esters.

This difference affects each stage of the Claisen ester condensation in the same way. Thiol esters are more easily converted to enolate anions, they are more easily attacked by nucleophiles, and RS^- is a better leaving group than RO^-. In each case the reaction is better (faster or equilibrium further towards product).

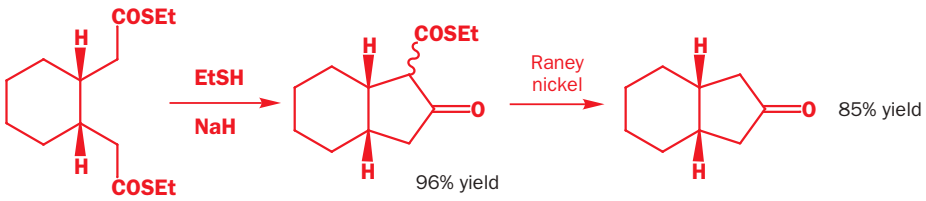
the Claisen thiol ester condensation



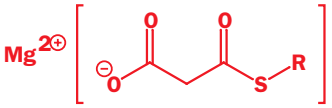
We can learn from Nature by using thiol esters in simple Claisen condensations. Cyclization of this COSEt diester rather than the CO_2Et diester needs milder conditions (2 hours at room temperature in dimethoxyethane) and gives better yields.



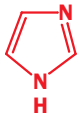
The thiol ester group can be removed, if necessary, by using Raney nickel, a good reducing agent for C–S bonds (see Chapter 46). Decarboxylation follows.



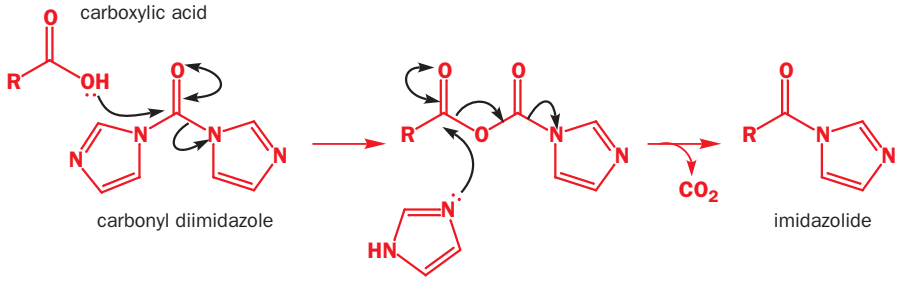
If we copy Nature rather more exactly, the Claisen ester condensation can be carried out under neutral conditions. This requires rather different reagents. The enol component is the magnesium salt of a malonate mono-thiol-ester, while the electrophilic component is an **imidazolide**—an amide derived from the heterocycle imidazole. This amine has a pK_a of about 7. Imidazolides are therefore very reactive amides, of about the same electrophilic reactivity as thiol esters. They are prepared from carboxylic acids with 'carbonyl diimidazole' (CDI).



malonate mono-thiol ester magnesium salt

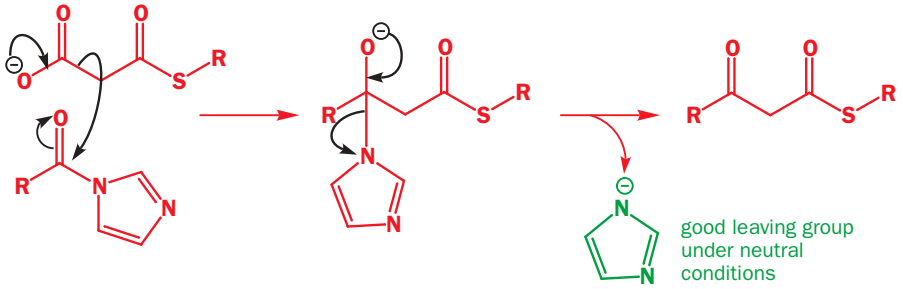


imidazole



▶ Reactions like these are said to be **bio-mimetic** because they draw their inspiration from Nature even if the imitation is not exact. We shall be discussing other important reactions carried out in Nature at various points of the book and collecting these ideas together in Chapters 49–51.

Combining the two reagents at neutral pH gives clean specific acylation at carbon. This is very like the biological reaction as CO_2 is lost *during* acylation.



To conclude . . .

You have now met enols and enolates doing nearly all of the things that other nucleophiles do:

- taking part in nucleophilic substitution reactions at saturated C (Chapter 26)
- adding to C=O groups (the aldol reaction, Chapter 27)
- substituting at C=O groups (Chapter 28)

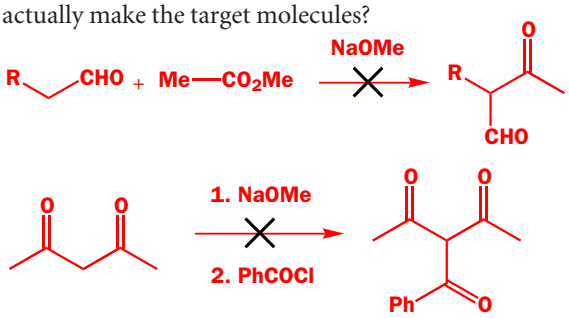
There is one more aspect of enolate chemistry left to discuss:

- conjugate addition

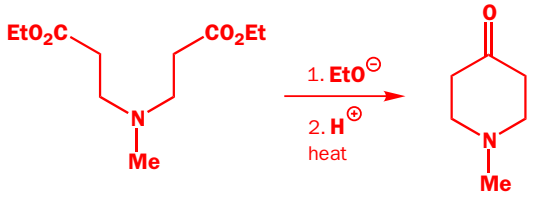
It follows in the next chapter.

Problems

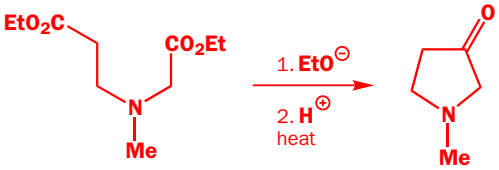
1. Attempted acylation at carbon often fails. What would be the true products of these attempted acylations, and how would you actually make the target molecules?



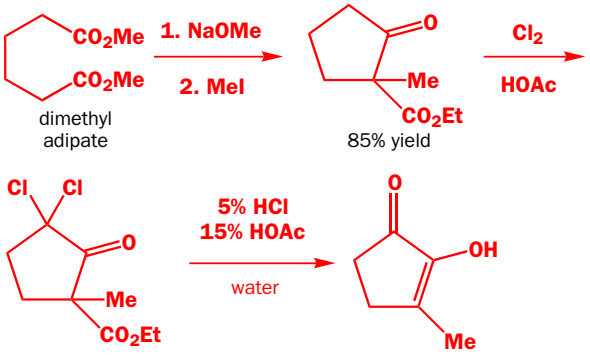
2. The synthesis of six-membered heterocyclic ketones by intramolecular Claisen condensation was described in the chapter and we pointed out that it doesn't matter which way round the cyclization happens as the product is the same. For example:



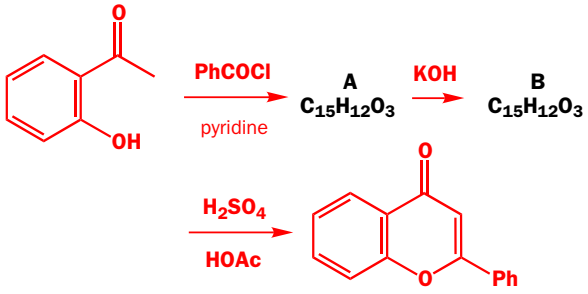
Strangely enough, five-membered heterocyclic ketones can be made by a similar process. The starting material is not symmetrical and two possible cyclized products can be formed. Draw structures for these two products and explain why it is unimportant which is formed.



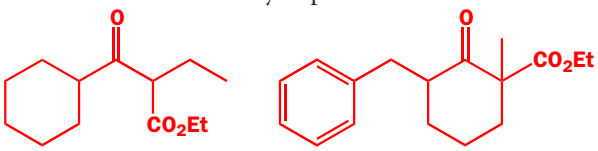
3. The synthesis of corylone was outlined in the chapter but no mechanistic details were given. Suggest mechanisms for the first two steps. The last step is a very unusual type of reaction and you have not met anything quite like it before. However, organic chemists should be able to draw mechanisms for new reactions and you might like to try your hand at this one. There are several steps.



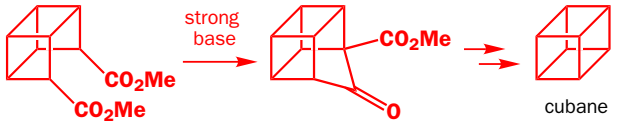
4. Acylation of the phenolic ketone gives a compound A, which is converted into an isomeric compound B in base. Cyclization of B in acid gives the product shown. Suggest mechanisms for the reactions and structures for A and B.



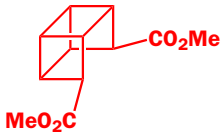
5. How could these compounds be made using the acylation of an enol or enolate as a key step?



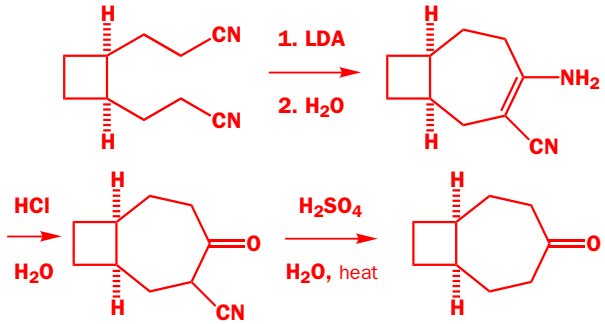
6. In a synthesis of cubane, a key step was the intramolecular acylation of this symmetrical diester. Explain why a strong base (the anion of DMSO, $MeSO.CH_2^-$, was actually used) is necessary for this cyclization.



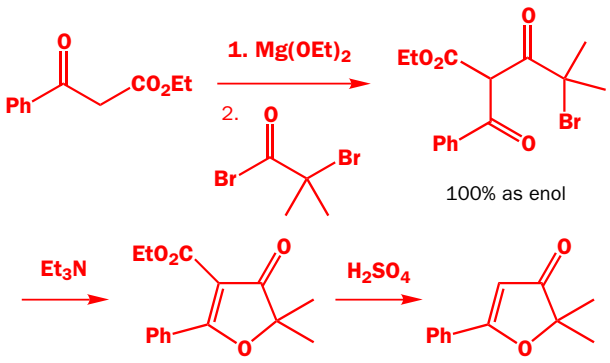
The starting material had both of the ester groups on the outside of the molecule so that cyclization is impossible. What preliminary step must first occur for it to become possible?



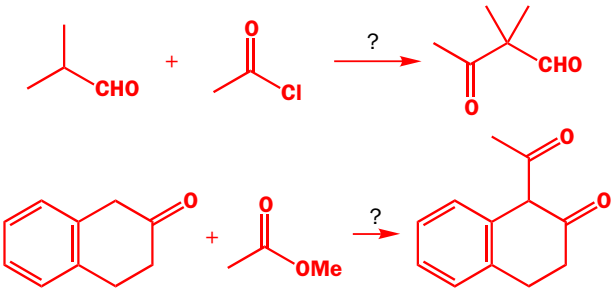
7. Suggest mechanisms for this sequence leading to a bicyclic compound with four- and seven-membered rings *cis*-fused to each other.



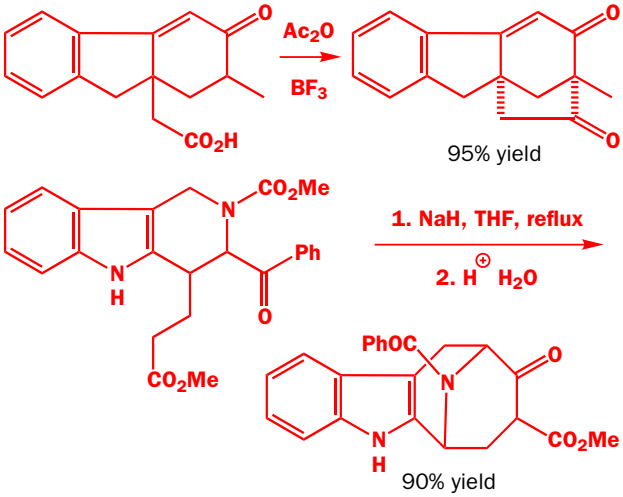
8. Give mechanisms for the steps used in this synthesis of the natural product bullatenone. Comment on the reagents used for the acylation step, on the existence of the first intermediate as 100% enol, on the mechanism of the cyclization, and on how the decarboxylation is possible.



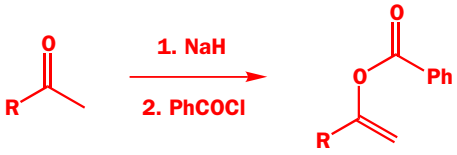
9. Suggest how the following reactions might be made to work. You will probably have to select a specific enol equivalent.



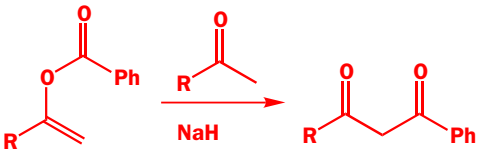
10. Suggest mechanisms for these reactions, explaining why these particular products are formed.



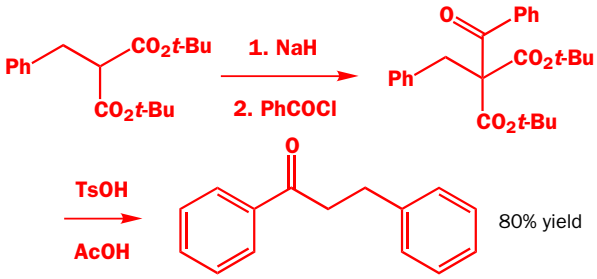
11. Sodium enolates generally react with acid chlorides to give enol esters. Give a mechanism for this reaction and explain the selectivity.



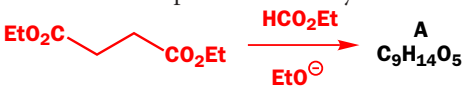
If the enol ester is treated with an excess of the sodium enolate, *C*-acylation occurs. Give a mechanism for this reaction. Why does the *C*-acylated product predominate?



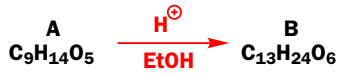
12. This is a *C*-acylation route to a simple ketone. Why was NaH chosen as the base? Why did *O*-acylation not occur? Why were *t*-butyl esters used? What would probably have happened if the more obvious Friedel–Crafts (Chapter 22) route were tried instead?



13. Base-catalysed reaction between these two esters allows the isolation of one product in 82% yield. Predict its structure.



The NMR spectrum of the product shows that two species are present. Both show two 3H triplets at about δ_H = 1 p.p.m. and two 2H quartets at about δ_H = 3 p.p.m. One has a very low field proton and an ABX system at 2.1–2.9 p.p.m. with J_{AB} 16 Hz, J_{AX} 8 Hz, and J_{BX} 4 Hz. The other has a 2H singlet at 2.28 p.p.m. and two protons at 5.44 and 8.86 p.p.m. coupled with J 13 Hz. One of these protons exchanges with D_2O. Any attempt to separate the mixture (for example, by distillation or chromatography) gives the same mixture. Both compounds, or the mixture, on treatment with ethanol in acid solution give the same product. What are these compounds?



Compound B has IR 1740 cm^{-1}, δ_H 1.15–1.25 p.p.m. (four t, each 3H), 3.45 p.p.m. (2H, q), 3.62 p.p.m. (2H, q), 4.1 p.p.m. (two 2, each 2H), 2.52 p.p.m. (2H, ABX system, J_{AB} 16 Hz), 3.04 p.p.m. (1H, X of ABX split into a further doublet by J 5 Hz), and 4.6 p.p.m. (1H, d, J 5 Hz). The couplings between A and X and between B and X are not quoted in the paper. Nevertheless, you should be able to work out a structure for compound B.

Conjugate addition of enolates

29

Connections

Building on:

- Carbonyl chemistry ch6, ch12, & ch14
- Conjugate addition ch10
- Enols and enolates ch21
- Nucleophilic attack on electrophilic alkenes ch23
- Synthesis in action ch25
- Chemistry of enol(ate)s ch26–ch29

Arriving at:

- Convergent plans for synthesis
- Thermodynamic control
- Selection of reagents for enol(ate) conjugate addition
- Tandem reactions and Robinson annelation
- Substitution may be elimination–conjugate addition in disguise
- Nitriles and nitro compounds

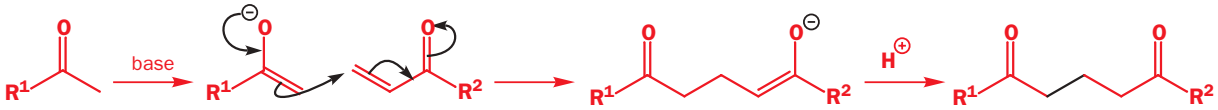
Looking forward to:

- Synthesis and retrosynthesis ch30
- Diastereoselectivity ch33–ch34
- Saturated and unsaturated heterocycles ch42 & ch44
- Main group chemistry ch46–ch47
- Asymmetric synthesis ch45
- Natural products ch51

Introduction: conjugate addition of enolates is a powerful synthetic transformation

■ Conjugate addition is also called Michael addition and is described in Chapters 10 and 23.

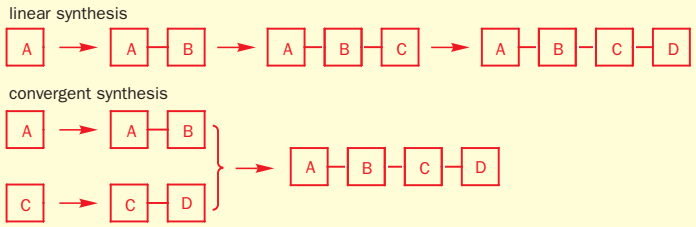
The product of a conjugate addition of an enolate or enol equivalent to an α,β-unsaturated carbonyl compound will necessarily be a dicarbonyl compound or an equivalent derivative. As the carbonyl group occupies such a central position in synthesis it will come as no surprise that these intermediates, with two carbonyl groups, are very widely used.



The other important feature of this conjugate addition reaction is that the two carbonyl groups in the product are reasonably far apart while the newly formed bond is in the middle of the molecule. This means that Michael addition can be a *convergent* route to the product—a feature that usually maximizes synthetic efficiency.

Linear vs. convergent syntheses

A **convergent synthesis** joins large fragments that have been assembled beforehand rather than adding together many small fragments in a linear fashion. The overall yield will generally be higher.

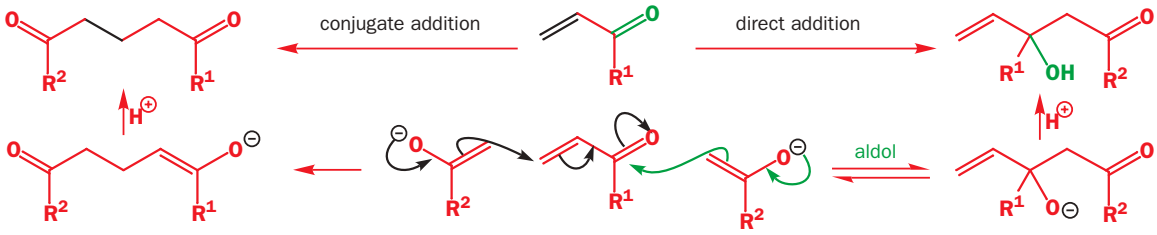


Conjugate addition of enolates is the result of thermodynamic control

Enolate nucleophiles have exactly the same opportunity to attack the carbonyl group directly as do the simple nucleophiles discussed in Chapter 10 and the same factors govern the eventual outcome

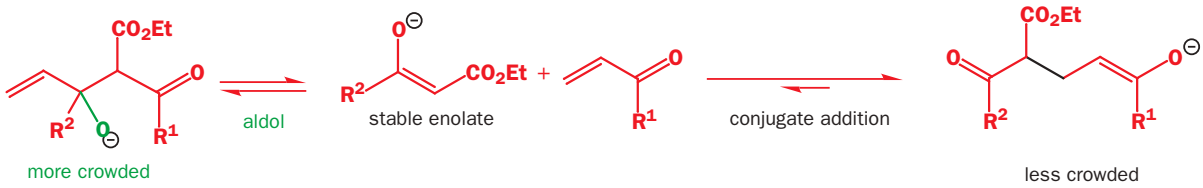
■ We discussed the reason for this in Chapters 10 and 23. The main reason that the conjugate addition product is more stable is that it has a C=O group while the direct addition product has a C=C group

of the reaction. Thermodynamic control leads to conjugate addition but kinetic control leads to direct addition. The key to successful conjugate addition is to ensure that direct addition to the carbonyl (an aldol reaction, Chapter 28) is reversible. This enables the conjugate addition to compete and, as its product is more stable, it eventually becomes the sole product. This is thermodynamic control at its best!



▶ A **retro-aldol reaction** is just an aldol reaction in the reverse direction. You will meet other 'retro' reactions later in the book, such as the important retro-Diels–Alder reaction in Chapter 35.

The aldol product is more sterically hindered than the conjugate addition product so increased branching on the nucleophile tends to accelerate the retro-aldol process, which releases steric strain and favours equilibration to the thermodynamic product. Perhaps more important is the stability of the enolate: the more stable the starting enolate, the easier it is to reverse both reactions and this favours the more stable conjugate addition product. One of the most important ways of stabilizing an enolate—using another electron-withdrawing group such as CO_2Et—achieves both of these enhancements at the same time as branching inevitably accompanies the extra anion stabilization.

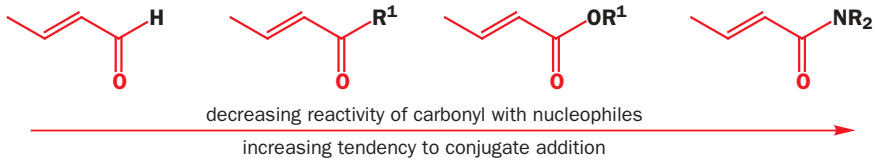


There is also a frontier orbital effect that assists conjugate addition over the aldol reaction. You will recall that the carbonyl carbon is a relatively hard centre, whereas the β carbon of an enone is soft. As the nucleophilic enolate becomes more stabilized with extra electron-withdrawing groups, it becomes increasingly soft and hence more likely to attack the β carbon.

The unsaturated component plays an important role

■ These factors are discussed in Chapters 10 and 23.

The nature of the carbonyl group in the α,β-unsaturated electrophile is also important as the more electrophilic carbonyl groups give more direct addition and the less electrophilic carbonyl groups (esters, amides) give more conjugate addition. Aldehydes are unhindered and very reactive and thus very prone to direct addition but, if the enolate equivalent is carefully chosen, conjugate addition works well. Ketones are borderline and can be pushed towards either the aldol or conjugate addition pathways by choice of enolate equivalent as we shall see. Esters and amides are much less electrophilic at the carbonyl carbon and so are good substrates for conjugate addition.



Conjugate addition is *thermodynamically* controlled; direct addition is *kinetically* controlled

Stable enolates promote conjugate addition by:

- making the aldol reaction more reversible
- making the enolate anion softer

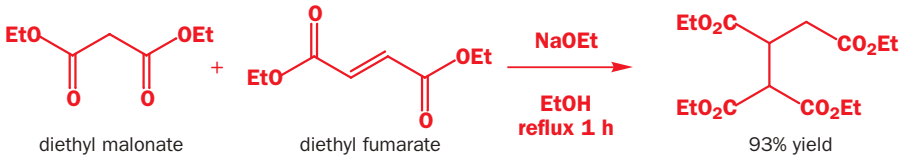
Less reactive Michael acceptors promote conjugate addition by:

- making the aldol reaction more reversible
- making the carbonyl group less electrophilic

Esters are excellent anion-stabilizing groups on enolate or Michael acceptors

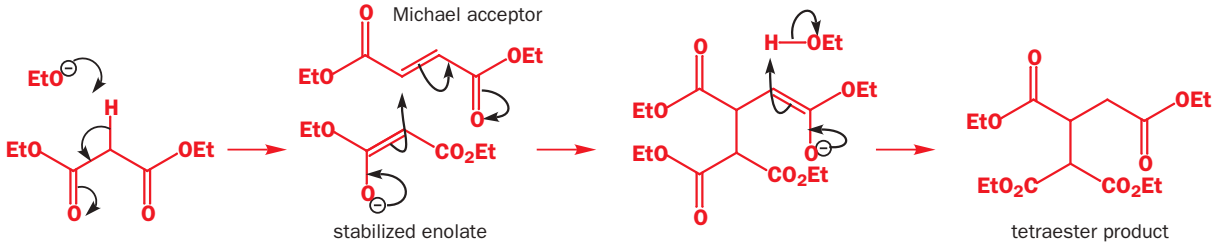
β-Diesters (malonates and substituted derivatives) combine three useful features in conjugate addition reactions: they form stable enolate anions that undergo clean conjugate addition; if required, one of the ester groups can be removed by hydrolysis and decarboxylation; and, finally, the remaining acid or ester is ideal for conversion into other functional groups.

■ Hydrolysis and decarboxylation and the choice of base were discussed in Chapter 26.



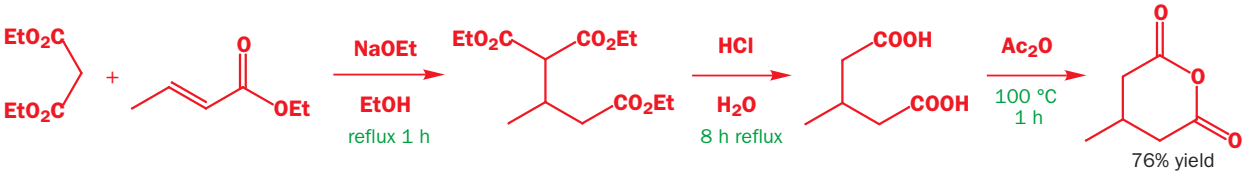
diethyl malonate diethyl fumarate 93% yield

Diethyl malonate adds to diethyl fumarate in a conjugate addition reaction promoted by sodium ethoxide in dry ethanol to give a tetraester. Diethyl fumarate is an excellent Michael acceptor because two ester groups withdraw electrons from the alkene. The mechanism involves deprotonation of the malonate, conjugate addition, and reprotonation of the product enolate by ethanol solvent. In this reaction two ester groups stabilize the enolate and two more promote conjugate addition.



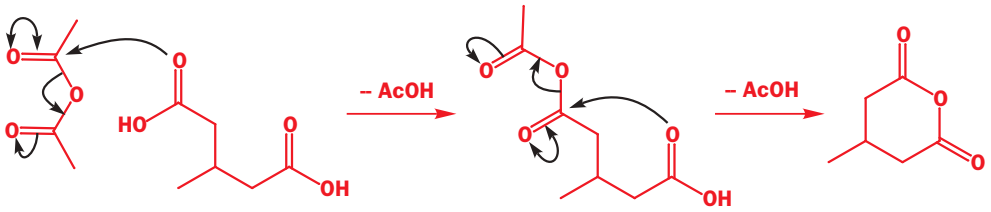
stabilized enolate tetraester product

The value of malonate esters is illustrated in this synthesis of a substituted cyclic anhydride by conjugate addition to ethyl crotonate, hydrolysis, and decarboxylation, followed by dehydration with acetic anhydride. This route is very general and could be used to make a range of anhydrides with different substituents simply by choosing an appropriate unsaturated ester.



76% yield

The mechanism of the conjugate addition is the same as that in the previous example and the mechanism for ester hydrolysis was covered in Chapter 12. The key step in the dehydration reaction is the formation and cyclization of the mixed anhydride formed from the diacid and acetic anhydride. Both steps have the same mechanism, attack of an acid on an anhydride, but the second step is intramolecular. Like most cyclizations the reaction is entropically favoured as two molecules react to give three—the cyclic anhydride and two molecules of acetic acid.



Use of electron-withdrawing groups to favour conjugate addition

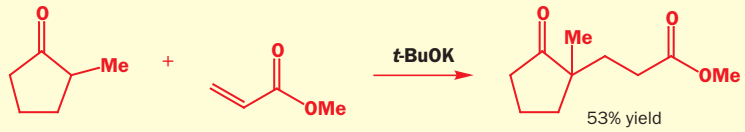
Conjugate addition of enolates is promoted by electron-withdrawing groups (for example, CO_2Et), especially by:

- two electron-withdrawing groups stabilizing the enolate
- two electron-withdrawing groups conjugated with the alkene

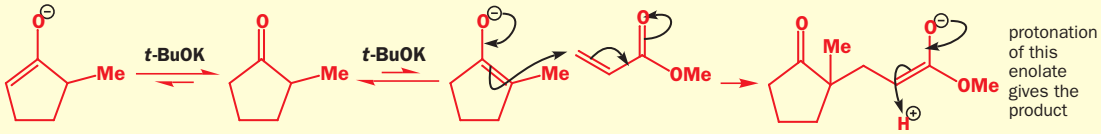
It is not necessary to have both features in the same reaction.

Alkali metal (Li, Na, K) enolates can undergo kinetic conjugate addition

It is not essential to have two anion-stabilizing groups for successful conjugate addition and it is even possible with simple alkali metal (Li, Na, and K) enolates. Lithium enolates are not ideal nucleophiles for thermodynamically controlled conjugate addition. Better results are often observed with sodium or potassium enolates, which are more dissociated and thus more likely to revert. Lithium binds strongly to oxygen and so tends to prevent reversible aldol addition, which leads to loss of conjugate addition product. Potassium *t*-butoxide is the ideal base for this example as it is hindered and so will not attack the ester but is basic enough to deprotonate the ketone to a certain extent.



Two enolates are possible but, under the equilibrating conditions, the more stable and more reactive enolate is the important intermediate leading to the more interesting product with a quaternary carbon atom.



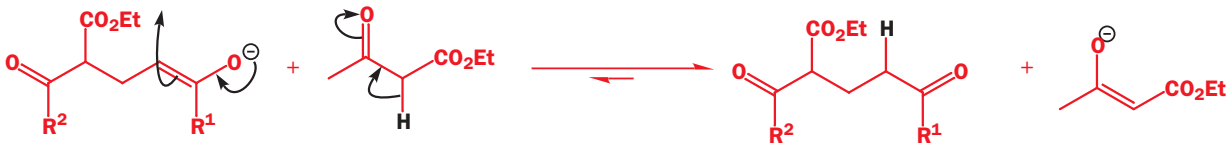
If the conditions are right, good yields are sometimes observed from *kinetically* controlled conjugate addition even with lithium enolates. This unlikely outcome is favoured by hindered nucleophiles and conjugated or hindered carbonyls. In these cases the lack of reversibility is not an issue as the aldol product is never formed. In this example the enolate of the *t*-butyl ketone is the hindered nucleophile and the conjugated ketone is rather unreactive.

90% yield: conjugate addition only

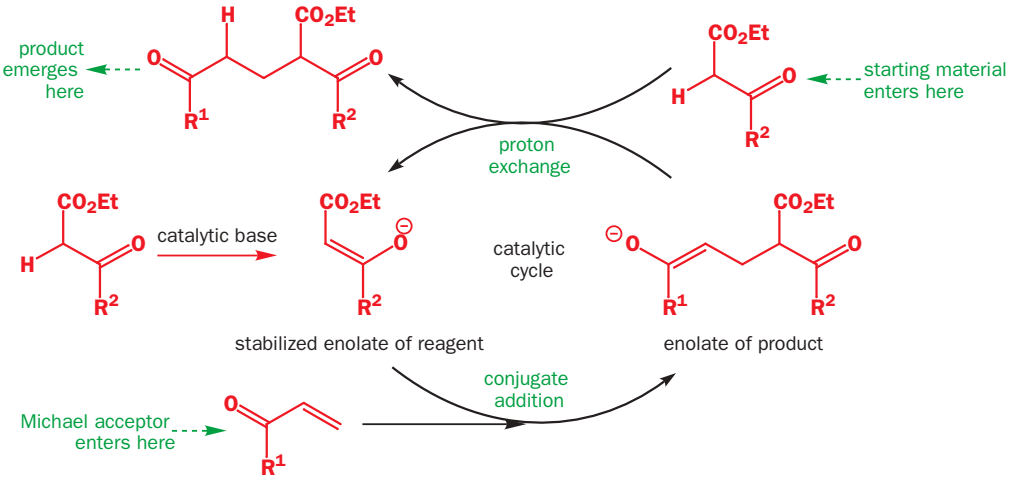
However, most successful conjugate additions use stable enol or enolate equivalents and we shall continue to discuss them in the next section.

Conjugate addition can be catalytic in base

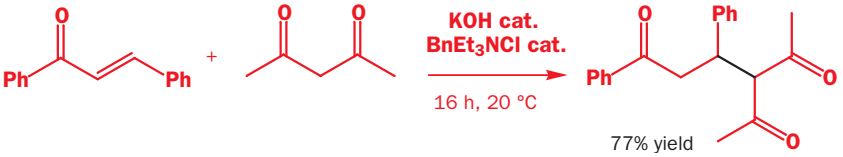
As the penultimate product in a conjugate addition is an enolate anion, if the pK_a of the nucleophile is appropriate, only a catalytic quantity of base is required to initiate the reaction. The enolate anion of the product is protonated by a molecule of starting material to give the neutral final product and another enolate anion of starting material. The reversible reaction sequence, including the unwanted aldol equilibrium, can be forced over towards the conjugate addition product. The balance of pK_as is likely to be right for nucleophiles with two electron-withdrawing groups when adding to a double bond conjugated to a single carbonyl group.



This proton exchange sets up a catalytic cycle. The cycle is started by an external base removing a proton from the most acidic species present in the reaction mixture at the start which is the nucleophile. This is an important condition for success of the catalytic method and the reason that all the reactants can be mixed together at the start of the reaction with no adverse effects. There is no need to form the nucleophilic enolate quantitatively; more is formed as the reaction proceeds. The advantages of this way of running a conjugate addition are that strongly basic conditions are avoided so that mild bases such as tertiary amines (for example, Et_3N) or fluorides (for example, Bu_4NF) can be employed successfully.

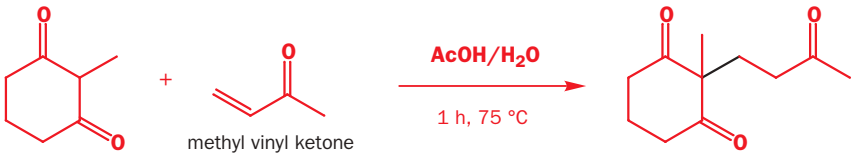


The catalytic approach to conjugate addition is illustrated by the addition of a β-diketone to an aromatic enone catalysed by potassium hydroxide and benzyltriethylammonium chloride, which is a phase transfer catalyst. Once again, the catalytic cycle is initiated by deprotonation of the most acidic component in the reaction mixture, acetyl acetone, which is followed by a cycle of conjugate addition and proton exchange leading inexorably to the product.



Enols are more likely than enolates to undergo direct conjugate addition

Base catalysis is not required for conjugate addition. If the nucleophile is sufficiently enolized under the reaction conditions then the enol form is perfectly able to attack the unsaturated carbonyl compound. Enols are neutral and thus soft nucleophiles favouring conjugate attack, and β-dicarbonyl compounds are enolized to a significant extent (Chapter 21). Under acidic conditions there can be absolutely no base present but conjugate addition proceeds very efficiently. In this way methyl vinyl ketone (butenone) reacts with the cyclic β-diketone promoted by acetic acid to form a quaternary centre. The yield is excellent and the triketone product is an important intermediate in steroid synthesis as you will see later in this chapter.



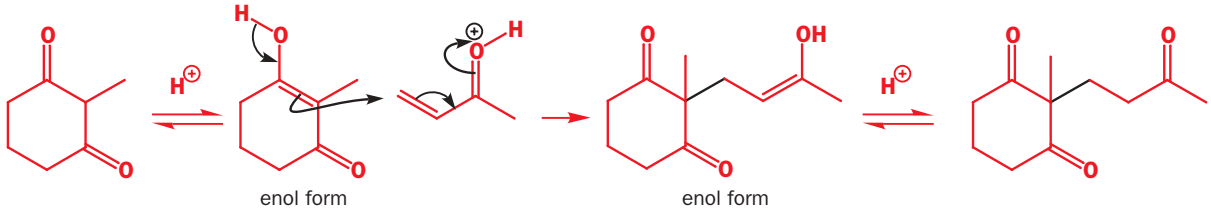
The mechanism involves acid-catalysed conversion of the keto form of the cyclic β-diketone into the enol form, which is able to attack the protonated enone. The mechanistic detail is precisely analogous to the attack of an enolate shown above; the only difference is that both reactants are

▶ Hydrogen fluoride is a weak acid in aqueous solution, $pK_a = 3.45$, due to the strength of the H–F bond. This bond strength also accounts for the basicity of thefluoride ion.

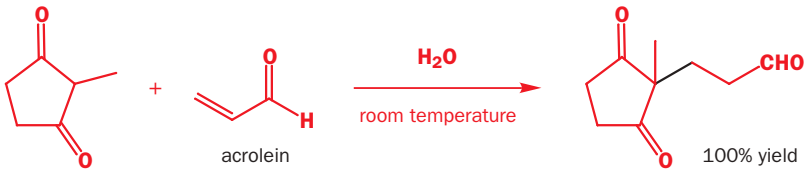
▶ Diagrams of catalytic cycles are not always easy to understand. The main cycle rotates anticlockwise round the centre of the diagram with the starting materials entering top right and bottom left with the product emerging top left. The first molecules of enolate enter middle left. It would be helpful if you were to follow the formation of one molecule of product on the diagram and see how it sets off the next cycle. It is very important that you do not allow catalytic cycles to replace mechanisms in your understanding of chemical reactions.

■ The origins of the benefits of phase transfer catalysis (PTC) were presented in Chapters 23 and 26.

protonated. The product is the enol form of the triketone, which rapidly tautomerizes to the more stable keto form.

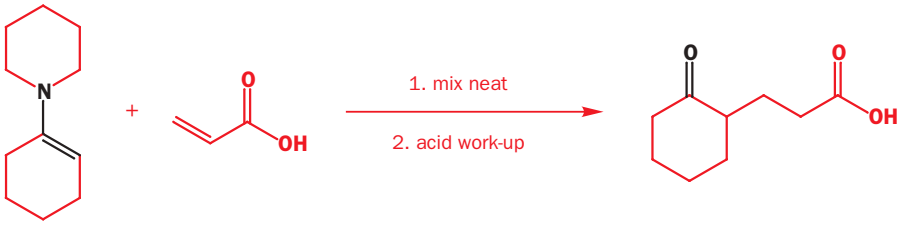


The thermodynamic control of conjugate addition allows even enals that are very electrophilic at the carbonyl carbon to participate successfully. Any aldol reaction, which must surely occur, is reversible and 1,4-addition eventually wins out. Acrolein combines with this five-membered diketone under very mild conditions to give a quantitative yield of product. The mechanism is analogous to that shown above.

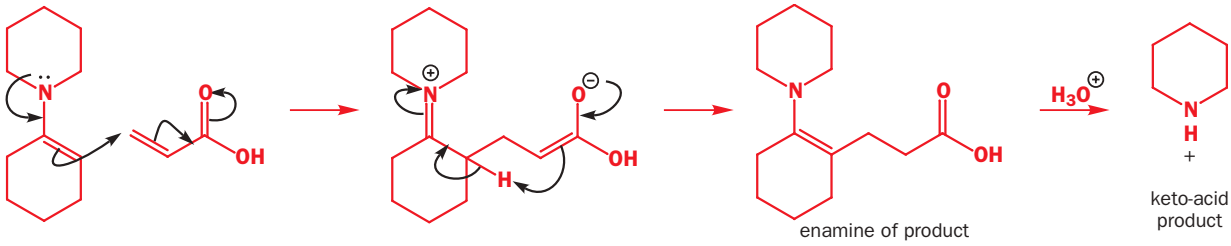


Enamines are convenient stable enol equivalents for conjugate addition

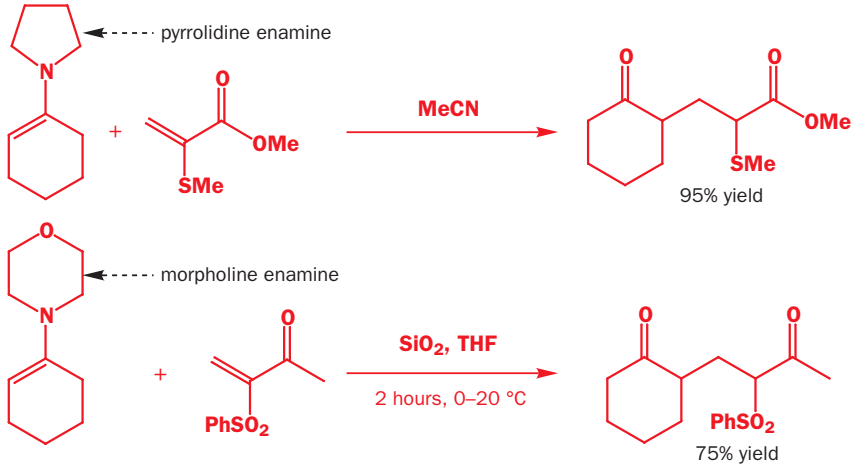
If you want to do a conjugate addition of a carbonyl compound without having a second anion-stabilizing group, you need some stable and relatively unreactive enol equivalent. In Chapters 27 and 28 you saw how enamines are useful in alkylation reactions. These neutral species are also perfect for conjugate addition as they are soft nucleophiles but are more reactive than enols and can be prepared quantitatively in advance. The reactivity of enamines is such that heating the reactants together, sometimes neat, is all that is required. Protic or Lewis acid catalysis can also be used to catalyse the reaction at lower temperature.



The mechanism is rather like enol addition. The differences are that the enamine is more nucleophilic because of the nitrogen atom and that the product is an enamine, which can be converted into the corresponding carbonyl by mild acidic hydrolysis. This is usually performed during the work-up and so does not really constitute an extra step. The amine is washed out as the hydrochloride salt so isolation is straightforward. After conjugate addition the resulting enolate-iminium ion undergoes proton transfer rapidly to produce the more stable carbonyl-enamine tautomer. This is shown as an intramolecular process but it could just as easily be drawn with an external base and source of protons. The resulting enamine is then stable until aqueous acid is added at the end of the reaction. Hydrolysis occurs via the iminium ion to reveal the second carbonyl group and release the secondary amine.

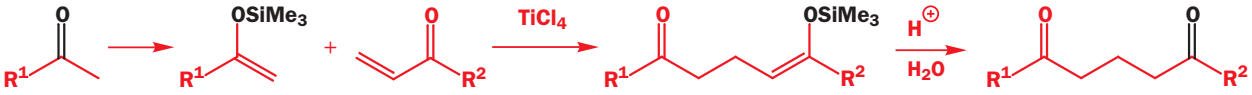


A range of secondary amines can be used to form the enamines but those formed from piperidine, pyrrolidine, and morpholine combine reduced steric demands at the reactive double bond with good availability of the nitrogen lone pair. The electronic nature of the other substituents on the key double bond can vary without affecting the success of the conjugate addition. In these two examples enamines from cyclohexanone formed with pyrrolidine and morpholine add in good yield to an α,β-unsaturated carbonyl compound with an extra electron-withdrawing methylthio or phenylsulfonyl group.

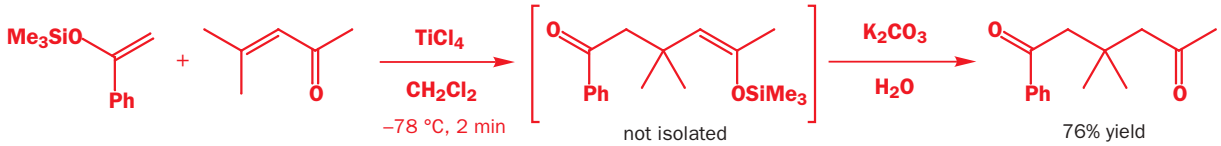


Conjugate addition of silyl enol ethers leads to the silyl enol ether of the product

The best alternatives to enamines for conjugate addition of aldehyde, ketone, and acid derivative enols are silyl enol ethers. Their formation and some uses were discussed in Chapters 21 and 26–28, but these stable neutral nucleophiles also react very well with Michael acceptors either spontaneously or with Lewis acid catalysis at low temperature.

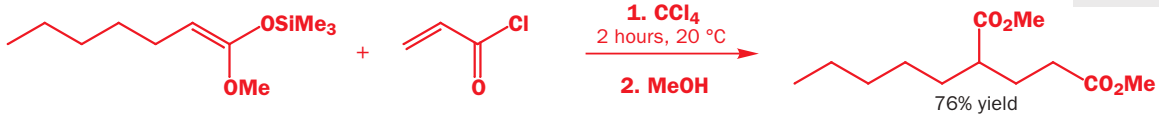


If the 1,5-dicarbonyl compound is required, then an aqueous work-up with either acid or base cleaves the silicon–oxygen bond in the product but the value of silyl enol ethers is that they can undergo synthetically useful reactions other than just hydrolysis. Addition of the silyl enol ether derived from acetophenone (PhCOMe) to a disubstituted enone promoted by titanium tetrachloride is very rapid and gives the diketone product in good yield even though a quaternary carbon atom is created in the conjugate addition. This is a typical example of this very powerful class of conjugate addition reactions.



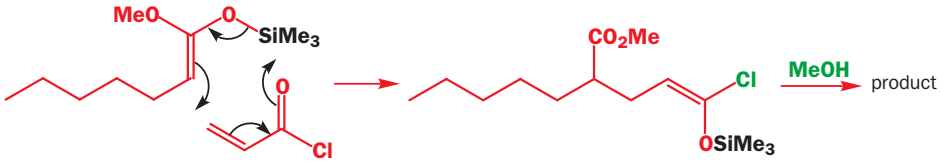
Silyl ketene acetals are even more nucleophilic than ordinary silyl enol ethers and react spontaneously with acyl chlorides. The intermediate enol ether of the acid chloride was not isolated but converted directly into a methyl ester with methanol.

■ The synthesis and reactivity of silyl ketene acetals are described in Chapters 21, 26, and 27.



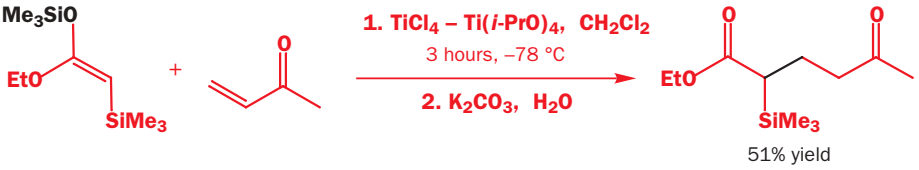
The mechanism, in the absence of a catalyst, can be written as a cyclic process involving direct transfer of silicon from the nucleophile to the electrophile but it might actually be stepwise. The soft

nature of the silyl enol ether is demonstrated by the choice of soft double bond over hard carbonyl carbon as the electrophilic partner even though the carbonyl compound is an acid chloride.



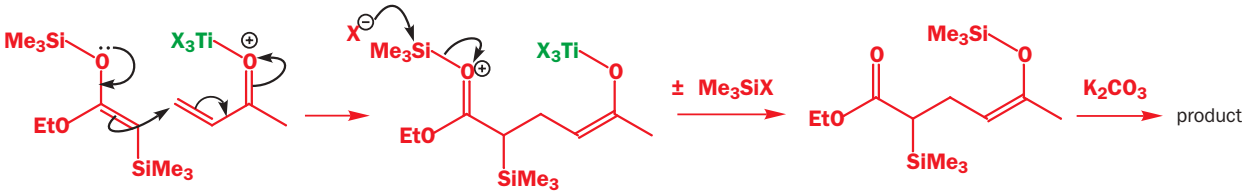
Lewis acid catalysis ($TiCl_4$) is normally required for silyl enol ether reactions

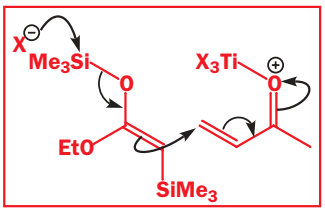
Conventional Lewis acid catalysis using a mixture of titanium tetrachloride and titanium isopropoxide is used to promote the addition of the silyl ketene acetal to methyl vinyl ketone. The key step in the mechanism is the conjugate addition of the silyl ketene acetal to the enone to form the bond shown in black in the product. The catalysis allows the reaction to proceed at much lower temperature, –78 °C. Do not be confused by the second $SiMe_3$ group. This is not an *O*-$SiMe_3$ group but a *C*-$SiMe_3$ group and plays no active part in the reaction.



51% yield

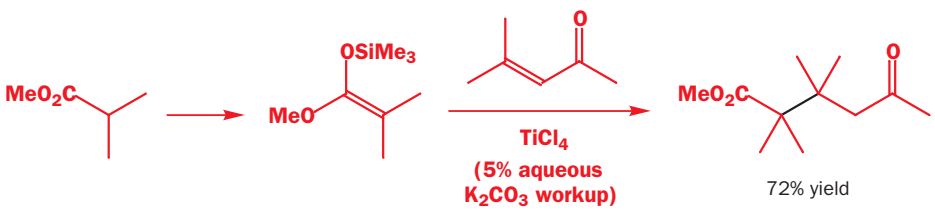
The electrophile coordinates to the Lewis acid first producing an activated enone that is attacked by the silylated nucleophile. It is difficult to determine at what stage the trimethylsilyl group moves from its original position and whether it is transferred intramolecularly to the product. In many cases the anion liberated from the Lewis acid (Cl^-, RO^-, Br^-) is a good nucleophile for silicon so it is reasonable to assume that there is a free trimethylsilyl species (Me_3SiX) that captures the titanium enolate (Chapter 28).





The mechanism can be drawn in a more concise form as shown in the frame. This gives the essence of the reaction but the details of the transfer of the TiX_3 and $SiMe_3$ groups are not shown and are in any case uncertain. The *C*-$SiMe_3$ group survived the mild basic treatment that cleaved the silyl enol ether formed by initial conjugate addition.

It is even possible to use a silyl enol ether to create a new C–C bond that joins two new quaternary centres. In this example the silyl ketene acetal does conjugate addition on an unsaturated ketone catalysed by the usual Lewis acid ($TiCl_4$) for such reactions.

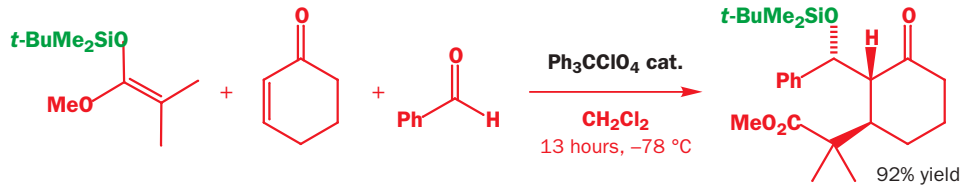


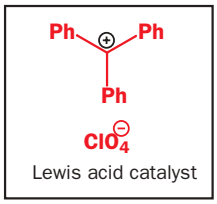
72% yield

Sequential (tandem) conjugate additions and aldol reactions build complex molecules in a few steps

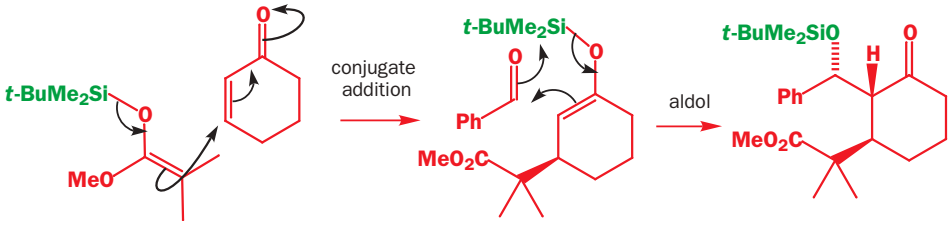
The silyl enol ether that is the initial product from conjugate addition of a silyl enol ether or silyl ketene acetal need not be hydrolysed but can also be used in aldol reactions. This example uses trityl perchlo-

rate (trityl = Ph_3C), which is a convenient source of the trityl cation, as catalyst rather than a metal-based Lewis acid. The very stable Ph_3C^+ cation carries a full positive charge and presumably functions in the same way as a Lewis acid. The combination of a silyl ketene acetal, cyclohexenone, and benzaldehyde gives a highly chemoselective and stereoselective conjugate addition–aldol sequence.



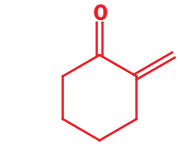


First, chemoselective (Chapter 24) conjugate addition of the silyl ketene acetal on the enone is preferred to direct aldol reaction with the aldehyde. Then an aldol reaction of the intermediate silyl enol ether on the benzaldehyde follows. The stereoselectivity results, firstly, from attack of benzaldehyde on the less hindered face of the intermediate silyl enol ether, which sets the two side chains *trans* on the cyclohexanone, and, secondly, from the intrinsic diastereoselectivity of the aldol reaction (this is treated in some detail in Chapter 34). This is a summary mechanism.

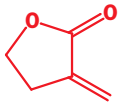


A variety of electrophilic alkenes will accept enol(ate) nucleophiles

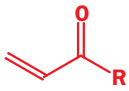
The simplest and best Michael acceptors are those α,β-unsaturated carbonyl compounds with exposed unsaturated β carbon atoms, such as *exo*-methylene ketones and lactones and vinyl ketones, and we shall see in the next section that these need to have their high reactivity moderated in most applications.



exo-methylene ketones

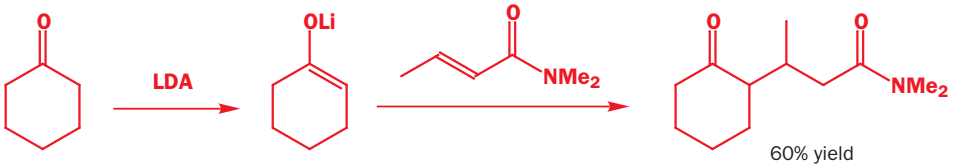


exo-methylene lactones



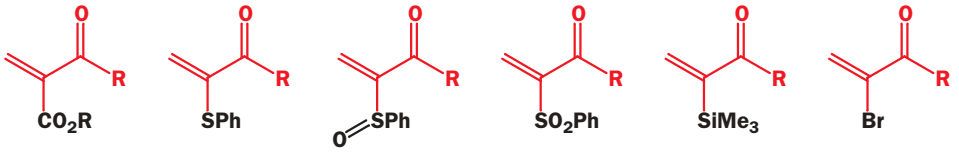
vinyl ketones

These Michael acceptors react with most enol equivalents to give good yields of conjugate addition products. Before discussing them we shall first briefly discuss other good Michael acceptors that are not so important but have their uses. Esters are good Michael acceptors because they are not very electrophilic. Unsaturated amides are even less electrophilic and will even give conjugate addition products with lithium enolates.



■ The fact that this is an *N,N*-dimethyl amide should remind you of the use of this kind of saturated amide in carbonyl substitution reactions with RLi in Chapter 12.

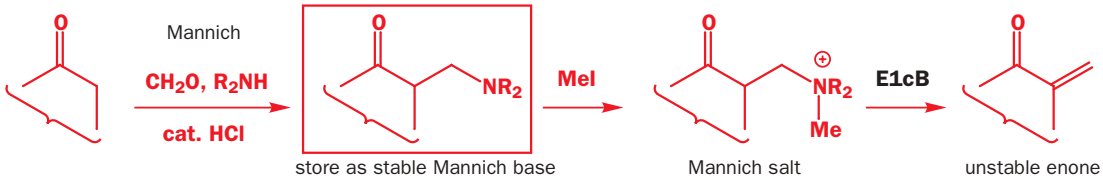
If all else fails, the trick to persuade a stubborn enolate to do conjugate rather than direct substitution is to add an extra anion-stabilizing substituent in the α position. Here is a selection of reagents that do this. In each case the extra group (CO_2Et, SPh, SOPh, SO_2Ph, $SiMe_3$, and Br) can be removed after the conjugate addition is complete.



However, most α,β-unsaturated *ketones* can be made to do conjugate addition by suitable choice of enol(ate) equivalent and conditions. Now we need to look at the best Michael acceptors, their reactions, and how to make them.

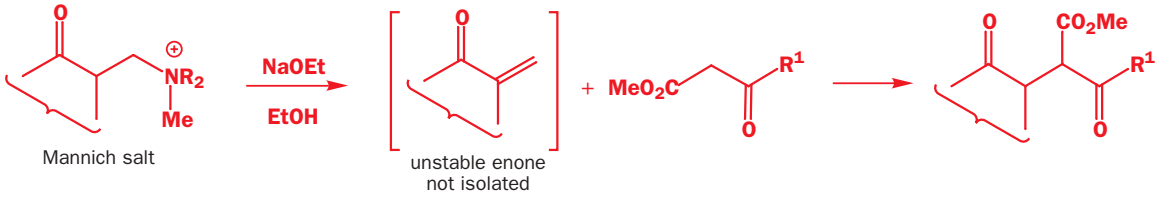
The Mannich reaction provides stable equivalents of *exo*-methylene ketones

The key substrates for conjugate addition are the α,β-unsaturated carbonyl compounds. When the double bond is inside a chain or ring these compounds are available via a wide variety of routes including the aldol reaction and are generally stable intermediates that can be stored for use at will. When the double bond is *exo* to the ring or chain (*exo*-methylene compounds), the unhindered nature of the double bond makes them especially susceptible to attack by nucleophiles (and radicals). This reactivity is needed for conjugate additions but the compounds are unstable and polymerize or decompose rather easily.



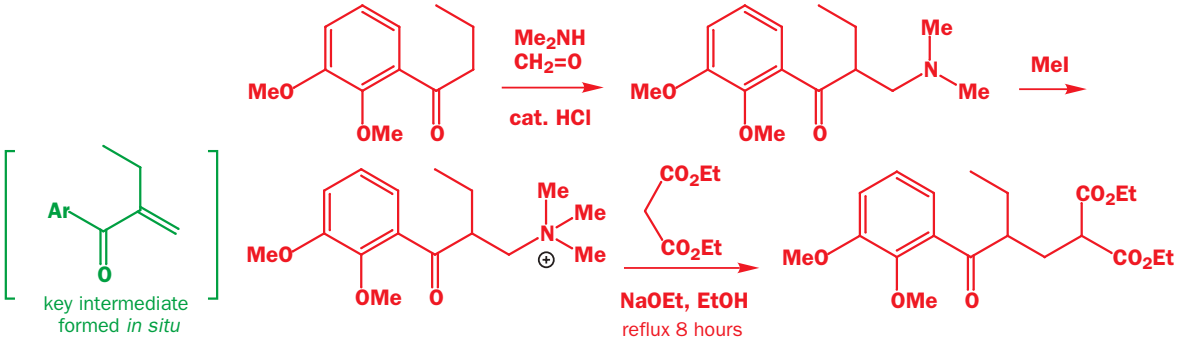
The preferred synthetic route to these important intermediates is the Mannich reaction (Chapter 27). The compound is stored as the stable Mannich base and the unstable enone released by elimination of a tertiary amine with mild base. The same conditions are right for this elimination and for conjugate addition. Thus the *exo*-methylene compounds can be formed in the flask for immediate reaction with the enol(ate) nucleophile. The overall reaction from β-amino carbonyl to 1,5-dicarbonyl appears to be a substitution but the actual mechanism involves elimination and conjugate addition.

■ The mechanism for the elimination is given in Chapter 27 and the mechanism for conjugate addition in Chapter 19 and earlier in this chapter.

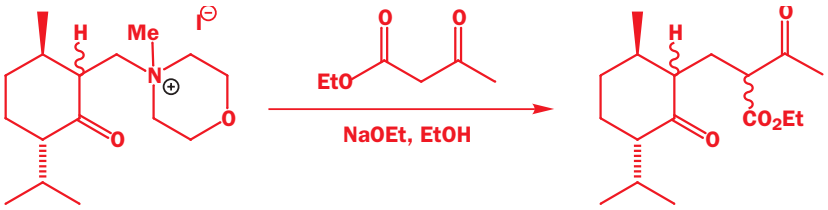


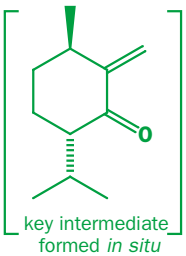
Using the Mannich reaction in conjugate addition

Either the tertiary amine or the quaternary ammonium salt can be stored as a stable equivalent of the *exo*-methylene compound. In our first example, the Mannich base with dimethylamine is first methylated with methyl iodide and then added to the conjugate addition reaction. Elimination of trimethylamine, which escapes from the refluxing ethanol as a gas, reveals the *exo*-methylene ketone in which the methylene group is *exo* to a chain. Fast conjugate addition of the stabilized enolate of diethyl malonate produces the product.



Cyclic ketones with *exo* cyclic methylenes can be prepared in just the same way and used *in situ*. Morpholine is often used as a convenient secondary amine for the Mannich reaction and the resulting amino-ketones can be methylated and undergo elimination–addition reactions with stabilized enolates such as that derived from ethyl acetoacetate. This starting material was prepared from natural menthone and the mixture of diastereoisomers produced is unimportant because the product is to be used in a Robinson annelation (see below).

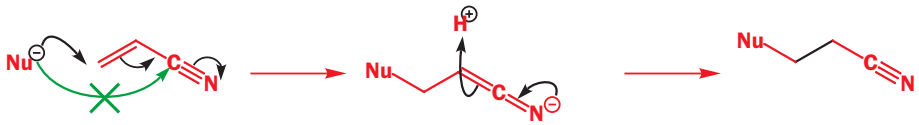




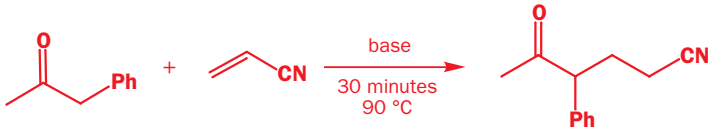
α,β-Unsaturated nitriles are ideal for conjugate addition

The nitrile group is not as reactive towards direct attack by nucleophiles as its carbonyl cousins but is equally able to stabilize an adjacent negative charge in the style of enolates. Alkenes conjugated with nitriles are thus activated towards nucleophilic attack without the complications of competing direct addition to the activating group.

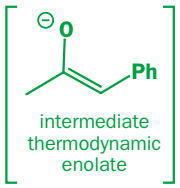
■ The selective activation achieved by a nitrile group was also exploited in enolate alkylation (Chapter 27).



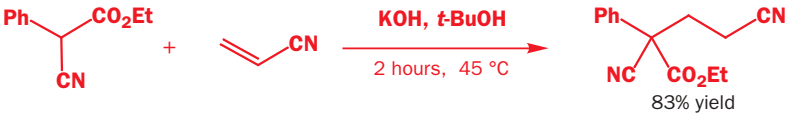
The regioselectivity of enolate formation is governed by the usual factors so that methyl benzyl ketone forms the more stable enolate with sodium metal. This undergoes smooth and rapid conjugate addition to acrylonitrile, which is unsubstituted at the β position and so very reactive.



80% yield



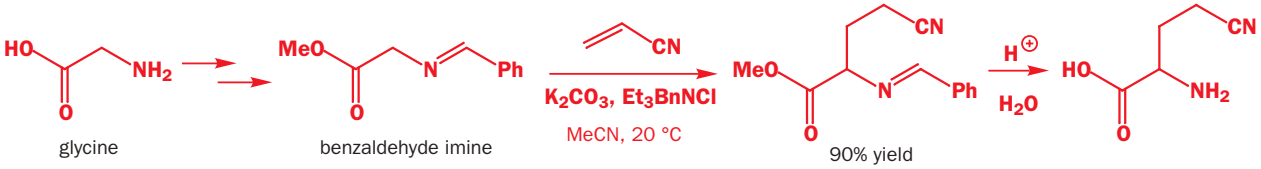
The cyanide group can also act as an anion-stabilizing group in the nucleophile. In combination with an ester group, the enolizable proton is acidified to such an extent that potassium hydroxide can be used as base.



83% yield

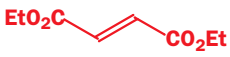
▶ Acrylonitrile CH_2=CHCN is one of the best Michael acceptors for enol(ate)s. The reaction is known as **cyanoethylation** as it adds a $-CH_2CH_2CN$ group to the enol(ate).

The simplest amino acid, glycine, would be an ideal starting material for the synthesis of more complicated amino acids but it does not easily form enols or enolates. The methyl ester of the benzaldehyde imine has two electron-withdrawing groups to help stabilization of the enolate and conjugate addition of acrylonitrile is now possible. The base used was solid potassium carbonate with a quaternary ammonium chloride as phase transfer catalyst. Simple hydrolysis of the alkylated product leads to the extended amino acid.



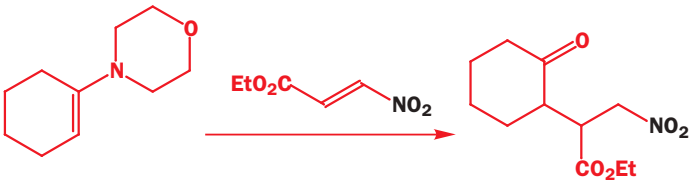
glycine benzaldehyde imine 90% yield

Nitro is more powerful than carbonyl in directing conjugate addition



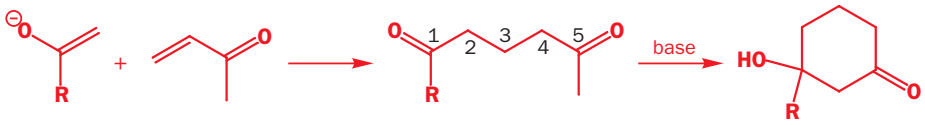
diethyl fumarate

We have seen how two ester groups in fumarate diesters encourage conjugate addition, but what if there are two *different* groups at the ends of the Michael acceptor? Then you must make a judgement as to which is more electron-withdrawing. One case is clear-cut. The nitro group is worth two carbonyl groups (p. 000) so that conjugate addition occurs β to the nitro group in this case.

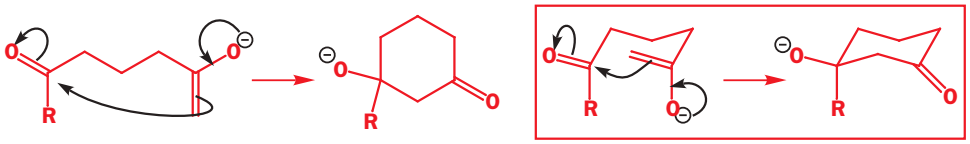


Conjugate addition followed by cyclization makes six-membered rings

The product of Michael addition of an enolate to an α,β-unsaturated carbonyl compound will normally be a 1,5-dicarbonyl compound. The two reactive carbonyl groups separated from one another by three carbon atoms present the opportunity for ring formation by intramolecular aldol condensation. If one of the carbonyls acts as an electrophile while the other forms a nucleophilic enolate, this cyclization gives a six-membered ring.

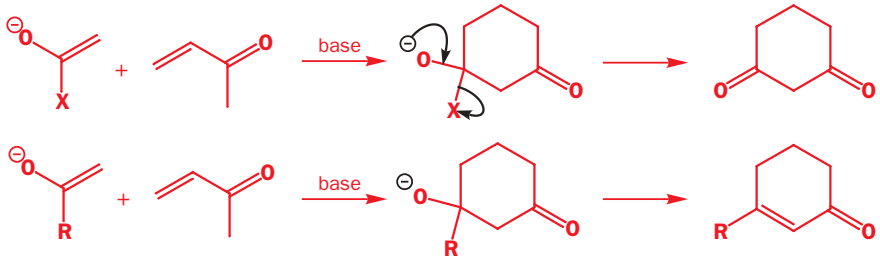


Drawing out the curly arrows for the formation is not easy as the chain has to fold back on itself which is hard to represent in two dimensions. However, remembering that the actual structure of a six-membered ring is a chair is extremely helpful. By using the structure of the product as a template for the transition state and reactive conformation of the starting material a clear representation is achieved.



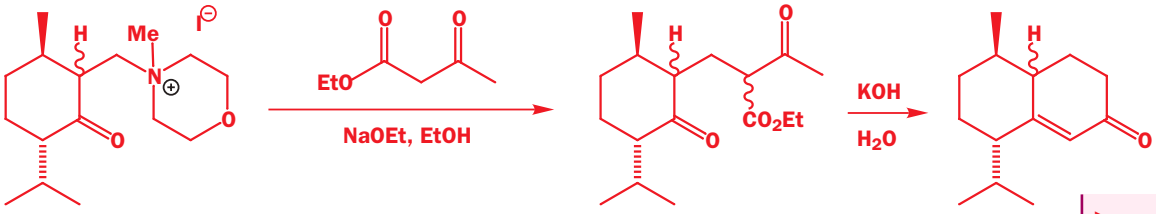
mechanism drawn on molecule in shape of product

The precise nature of the carbonyl groups determines what happens next. If R is a leaving group (OR, Cl, etc.), the tetrahedral intermediate collapses to form a ketone and the product is a 1,3-diketone. The synthesis of dimedone (later in this chapter) is an example of this process where an alkoxy group is the leaving group. Alternatively, if R is an alkyl or aryl group, loss of R is not an option and the cyclization is an intramolecular aldol reaction. Dehydration produces an α,β-unsaturated ketone, which is a stable final product.



The Robinson annelation is the result of conjugate addition followed by aldol cyclization

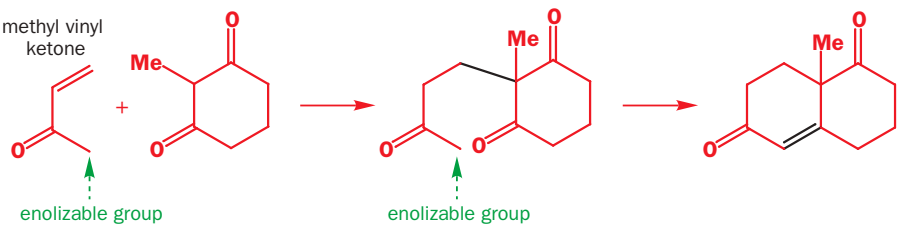
Conditions for aldol reactions are very similar to those required for conjugate addition so that it is not unusual for conjugate addition and cyclization to occur sequentially without isolation of any intermediates. When we described one Michael addition a few pages back, we were not telling you the whole truth. The product isolated from this reaction was actually the enone from cyclization.



This sequential process of Michael–aldol reaction leading to a new six-membered ring is known as the **Robinson annelation**. It was, in fact, Robinson who invented the idea of using a Mannich product in conjugate additions because he wanted to develop this important reaction. There are now thousands of examples used to make all kinds of compounds, especially steroids (Chapter 49).

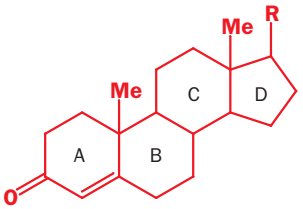
The essential requirement for a Robinson annelation is a Michael addition of an enolate to an enone that has a second enolizable group on the other side of the ketone. The classic enone is butenone (methyl vinyl ketone) and the classic Robinson annelation is the synthesis of rings A and B of the steroid nucleus.

the Robinson annelation



▶ **Annelation** describes the formation of a ring. You may also see the term spelt 'annulation'.

■ Sir Robert Robinson (1886–1975) carried out many famous syntheses at Liverpool and Oxford and has two reactions, this annelation and the tropinone synthesis (Chapter 51), named after him. He won the Nobel prize in 1947. He was brilliantly inventive and the first person to work out mechanistically how to do syntheses.

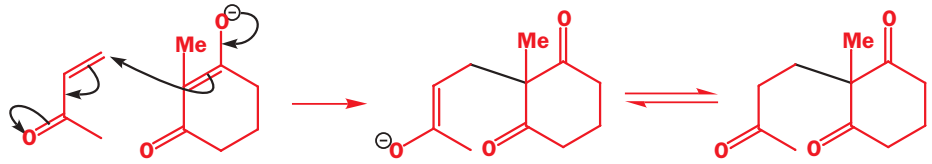


the steroid ring system

The Robinson annelation mechanism has three familiar stages

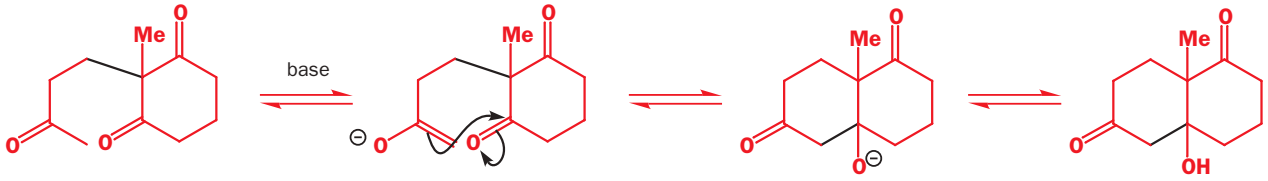
The mechanism combines two important reactions and we shall take it step by step. The first stage is the formation of the stable enolate, here of the 1,3-diketone, and the conjugate addition to the enone. The enolate of the product is in equilibrium with the triketone.

the Robinson annelation: mechanism—stage 1: the conjugate addition



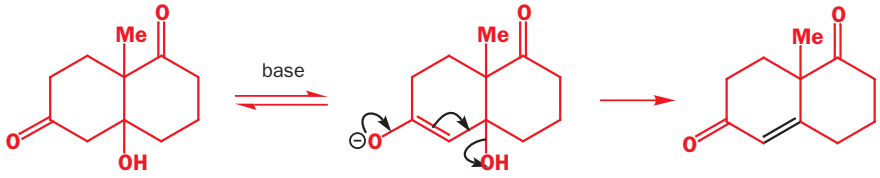
The second stage is the formation of a new enolate on the other side of the ketone from the first. Note that the original enolate, the intermediate in the conjugate addition, can cyclize to give only an unstable four-membered ring so this cyclization would be reversible. The next intermediate, the aldol product, is often isolated from Robinson annelations.

the Robinson annelation: mechanism—stage 2: the intramolecular aldol reaction



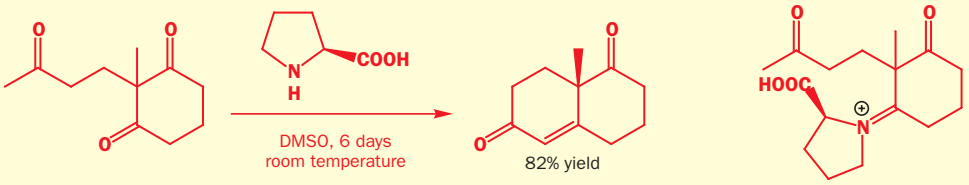
The final stage is dehydration of the aldol and an E1cB reaction that involves the carbonyl group as in a standard aldol reaction (Chapter 27). Another enolate must form in the same position as the last.

the Robinson annelation: mechanism—stage 3: the E1cB dehydration

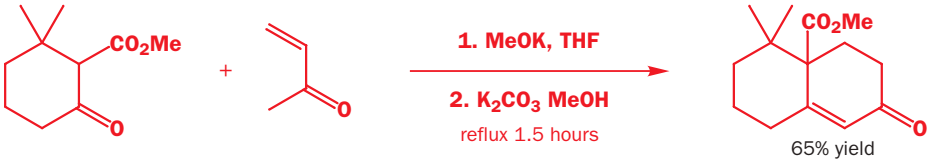


Enantioselective Robinson annelation

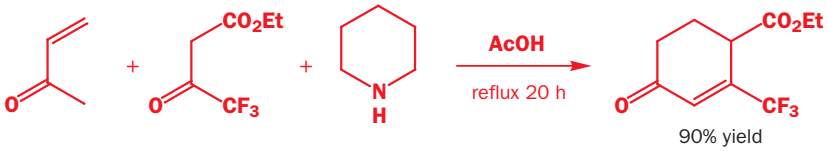
This particular product of the Robinson annelation is an important intermediate for the synthesis of natural products. The natural products exist as a single enantiomer so to be useful this material must also be a single enantiomer. A remarkably efficient preparation employs (*S*)-proline as the catalyst for the asymmetric aldol reaction that is the final stage. The product was isolated in high optical purity. Presumably, the proline forms an iminium ion that is the electrophile in the aldol reaction and the source of asymmetry. You will meet further examples of asymmetric synthesis in Chapter 45.



Each step in the Robinson annelation is controlled by the various devices you have already met. In the conjugate addition step, the α,β-unsaturated carbonyl compound is usually butenone or another ketone and they are suitable Michael acceptors. There is much more variation in the enol equivalent. Compounds with 1,3-dicarbonyl groups are popular so ester groups can be added to ketones and removed afterwards by hydrolysis and decarboxylation. Keto-esters react well in the Robinson annelation. The ester group stabilizes the enolate but is not very electrophilic. In this example MeOK is the base for the conjugate addition and a weaker base is used for the aldol.



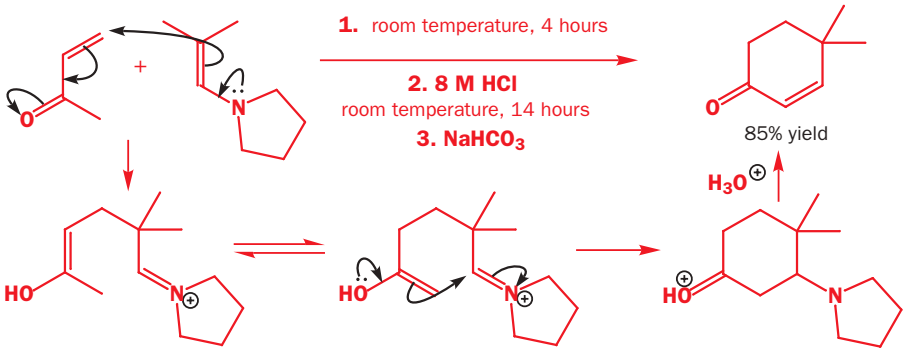
In fact, even very weak bases are enough for most 1,3-dicarbonyl compounds and piperidine and acetic acid combine to form a mild buffered system that facilitates both conjugate addition and aldol reactions via enol intermediates. The trifluoromethyl ketone is extremely electrophilic so the aldol reaction proceeds very smoothly.



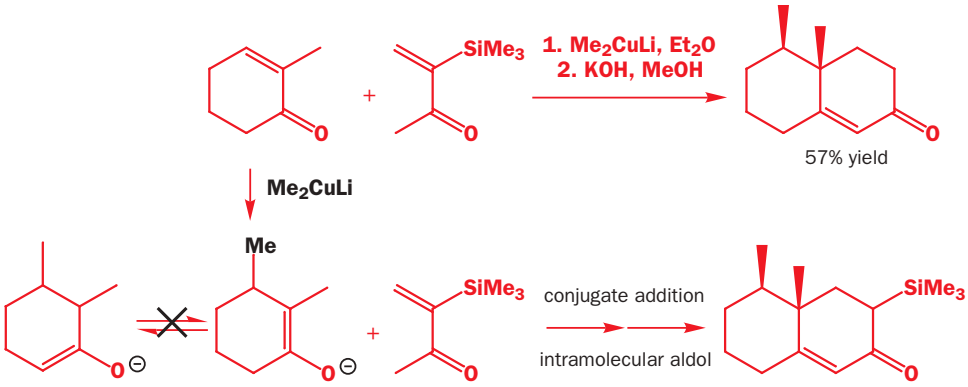
Enamines are good enol equivalents for Robinson annelation

If the enol component is an aldehyde, none of these methods will do and enamines or silyl enol ethers are the best choice. Enamines are excellent nucleophilic components and the iminium ion that is formed in the conjugate addition can provide the electrophilic component in a cyclization reaction. Acid-catalysed hydrolysis of the β amino-ketone liberates the amine that was used to form

the enamine at the start revealing the cyclohexenone product. In this example a quaternary centre is formed in the new ring.

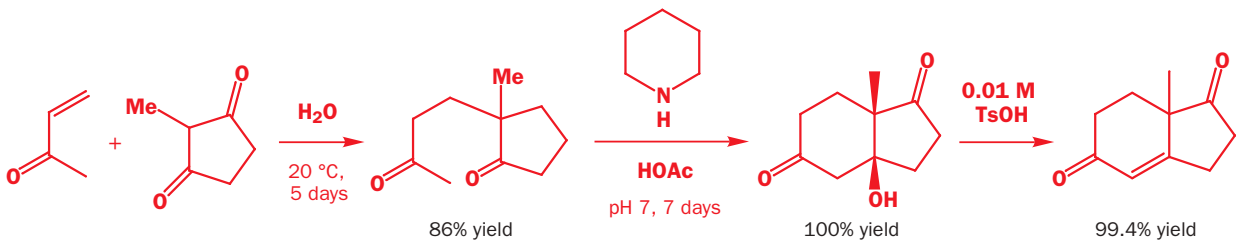


The addition of an anion-stabilizing group to the α,β-unsaturated component at the α carbon promotes conjugate addition and allows a wider range of enolate nucleophiles to be used. In particular, enolates that are prone to equilibration to regioisomers can be used because conjugate addition becomes essentially irreversible. Trimethylsilyl has proved very effective because it stabilizes the enolate intermediate in the conjugate addition and is easily removed during the later stages of the reaction. Conjugate addition of Me_2CuLi to the cyclohexenone in our next example produces a new carbon–carbon bond and a regiodefined enolate. The presence of a proton source would allow equilibration of the enolate to the less hindered position but the trimethylsilyl enone was used to trap the enolate without equilibration, creating the two adjacent stereocentres in the Robinson annelation.



A more common method of ensuring that the conjugate addition step is free from side-reactions is to use the method Robinson himself invented—replace the enone by the Mannich base or Mannich salt as we have discussed already in this chapter. This ensures that the enone need have only a very short lifetime in the reaction mixture.

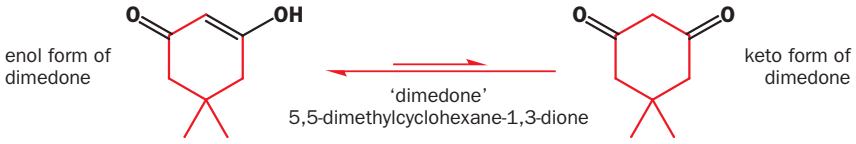
The aldol cyclization step and the dehydration are sometimes separated from the conjugate addition and from each other and sometimes not. It depends to some extent on the conditions. Very mild conditions in this example allowed each step to be performed separately and in good yield but notice the exceptionally mild conditions for the conjugate addition (just mix in water!) which are possible only because of the two carbonyl groups in the enol component.



We have devoted a lot of space to the Robinson annelation because it is so important. For a multi-stage reaction, it is easy to understand because each step is a well-known step in its own right. It is because the second step is an *intra*molecular aldol condensation that it occurs so easily.

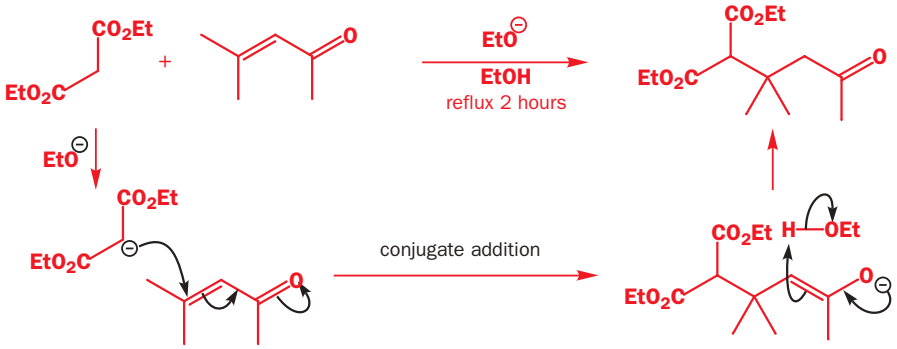
Conjugate addition followed by Claisen ester cyclization gives cyclic diketones

The first enol you saw at the start of Chapter 21 was the stable enol of 'dimedone', 5,5,-dimethyl-cyclohexa-1,3-dione. This six-membered ring is made by a close analogue of the Robinson annelation. The only difference is in the cyclization step, which is a Claisen ester condensation rather than an aldol reaction.

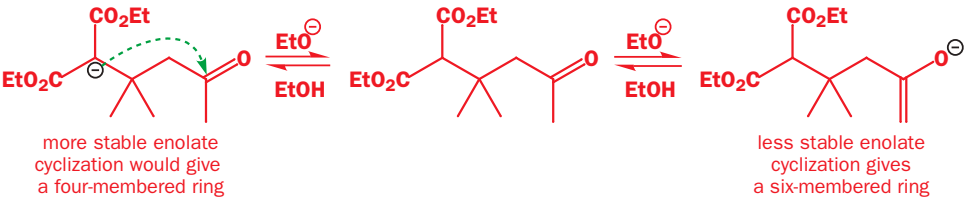


Dimedone has a trivial name because its preparation is so easy that it was discovered early in the history of organic chemistry. The first step is a conjugate addition of diethyl malonate to the unsaturated ketone 'mesityl oxide' (4-methylpent-3-en-2-one; given a trivial name for the same reason). Ethoxide ion is the base for the usual reason that nucleophilic substitution at the ester group simply regenerates starting material.

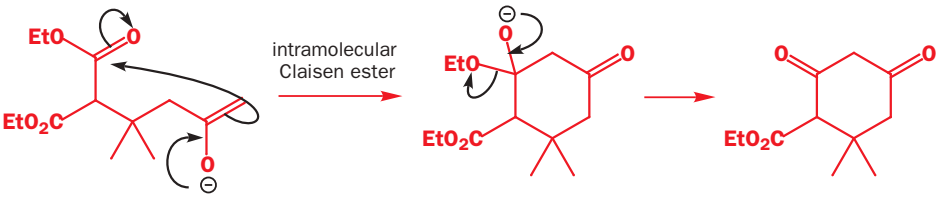
▶ Exceptionally we have drawn the enolate of diethyl malonate as a carbanion. This is not generally recommended but you will see it and in this case, with the negative charge delocalized over the two ester groups, it is relatively harmless.



Under the reaction conditions the product will exist as a stable enolate but cyclization of this enolate would lead to a four-membered ring so it is reversible. The alternative enolate on the methyl group at the other end of the chain leads to a six-membered ring so this is what happens.

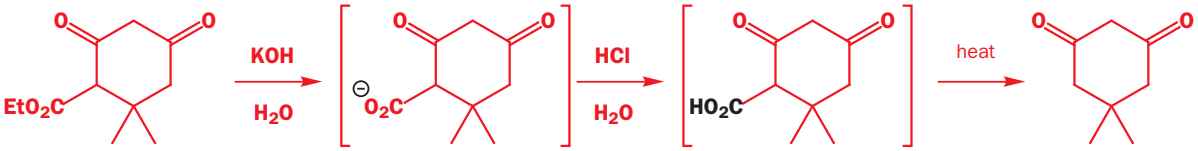


So far the mechanism is almost the same as that of the Robinson annelation but the cyclization is now the attack of a ketone enolate on an ester group (it doesn't matter which one as they are equivalent) and so it is an intramolecular Claisen ester condensation (Chapter 28). The intermediate must be redrawn to allow cyclization.



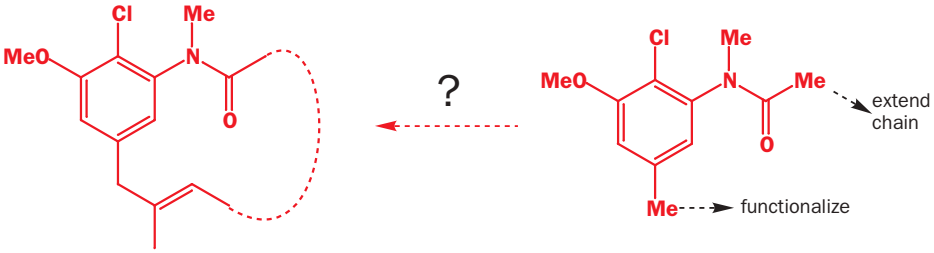
This intermediate will exist as a stable enolate under the reaction conditions. Now aqueous KOH is added to the reaction mixture, which is refluxed to hydrolyse the remaining ester. On acidification with HCl decarboxylation occurs and dimedone is released.

■ Decarboxylation of the free acid is faster than that of the anion (Chapter 26).

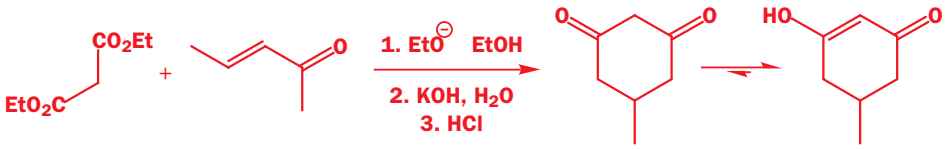


The whole operation is conducted in one flask, just as for the Robinson annelation, and dimedone is isolated as the crystalline enol in 84% yield. This reaction has not enjoyed such wide application as the Robinson annelation but it has been used to make an aromatic compound that is a starting material for the synthesis of maytensine, which we discussed at the end of Chapter 22.

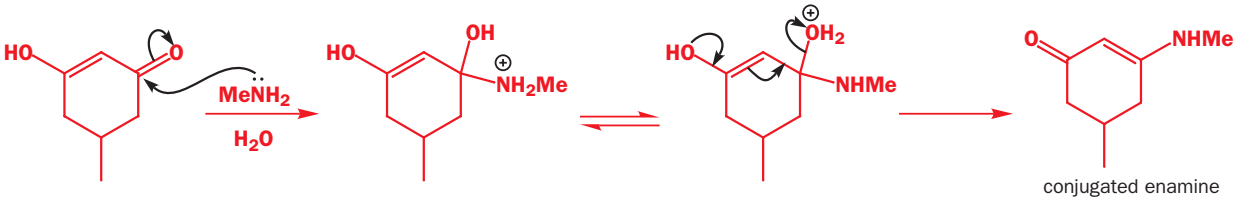
■ This aromatic compound is not the same as the one suggested at the end of Chapter 22: it resembles the natural product rather more and is an alternative starting material.



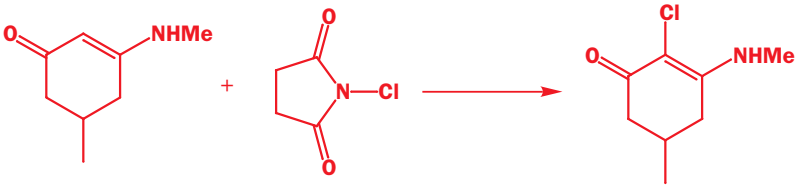
The clue to the synthesis of this compound using a dimedone-style condensation is the 1,3,5-relationship between OMe, N, and Me around the ring. If we carry out the conjugate addition on an enone with only one methyl group at the end of the double bond, this is what we will get.



Particularly in the enol form, this is beginning to look something like what is needed. The next step is to add $MeNH_2$. Even in aqueous solution ($MeNH_2$ is available as a 40% aqueous solution) the enamine forms very easily because it is conjugated, like the enol but more so. This is again a crystalline compound and formed in 70% yield.

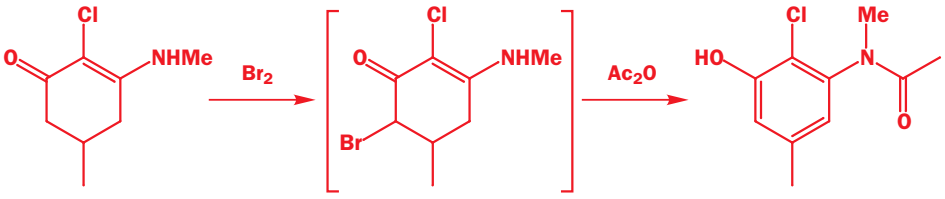


The chlorine atom can now be introduced by direct chlorination of the enamine with *N*-chlorosuccinimide. This electrophilic chlorine source reacts via the mechanism that enols follow when they react with halogens (Chapter 21).



Now it is time to aromatize the ring. If you imagine that the ketone in its enol form would already

be two double bonds in the ring, bromination and elimination of HBr would give the third. This can be done with bromine followed by acetic anhydride, which gives the benzene ring and acetylates the amine at one go.

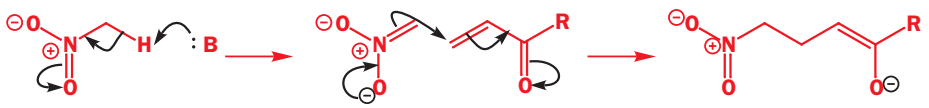


85–90% yield

Nitroalkanes are superb at conjugate addition

In this chapter so far we have concentrated on anions stabilized by carbonyl groups for use in conjugate addition. Anions that are well stabilized, such as those from β-dicarbonyl compounds, are the usual nucleophiles for this important class of reaction. The key to their success is the pK_a of the acidic proton, which allows initial enolate anion formation, helps to reverse the unwanted alternative aldol pathway, and facilitates proton transfer in the catalytic version of the reaction. The nitro group is so powerfully electron-withdrawing that just one is equivalent to two carbonyls in pK_a terms (Chapter 26). Thus if β-dicarbonyls are good for conjugate addition and our analysis of the reasons for this is correct, you might expect nitroalkanes to undergo conjugate addition in just the same way. The good news is that they do, very well. The first stage is a base-catalysed conjugate addition.

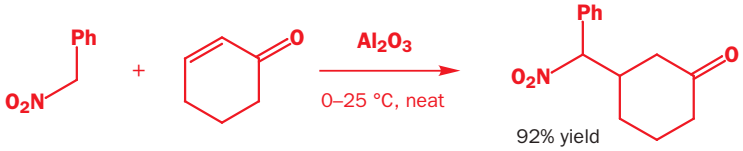
▶ Always draw out the nitro group in full when using it in mechanisms.



The enolate ion intermediate is now much more basic than the anion of the nitro compound so it removes a proton from the nitro compound and provides another molecule of anion for the second round of the reaction.

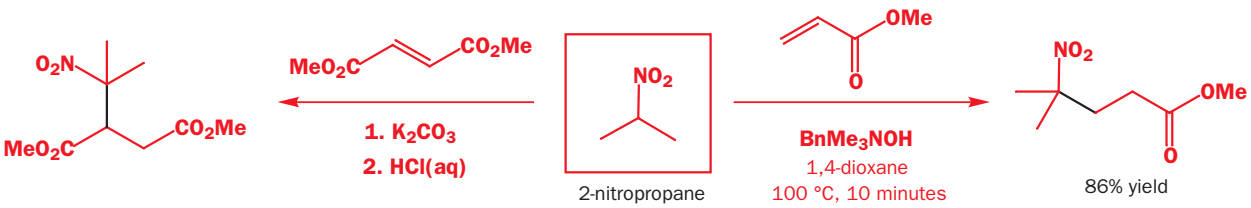
product

The acidifying effect of the nitro group is so profound that very mild bases can be used to catalyse the reaction. This enables selective removal of the proton next to the nitro group and helps to avoid side-reactions involving aldol condensations of the carbonyl component. Common examples include amines, quaternary ammonium hydroxides, and fluorides. Even basic alumina is sufficient to catalyse virtually quantitative addition of this benzylic nitroalkane to cyclohexenone at room temperature!

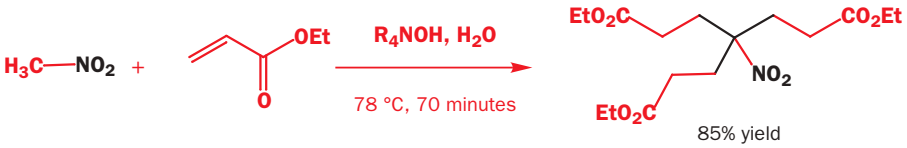


92% yield

Anions of nitro compounds form quaternary centres with ease in additions to α,β-unsaturated mono- and diesters. The difference between acidity of the protons next to a nitro group and those next to the esters in the products combined with the very mild basic conditions ensure that no unwanted Claisen condensations occur.

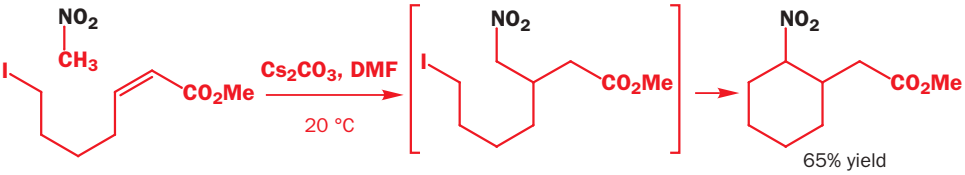


Nitromethane readily undergoes multiple conjugate additions under more forcing conditions with excess ester.



Nitroalkane conjugate addition can be combined with other reactions

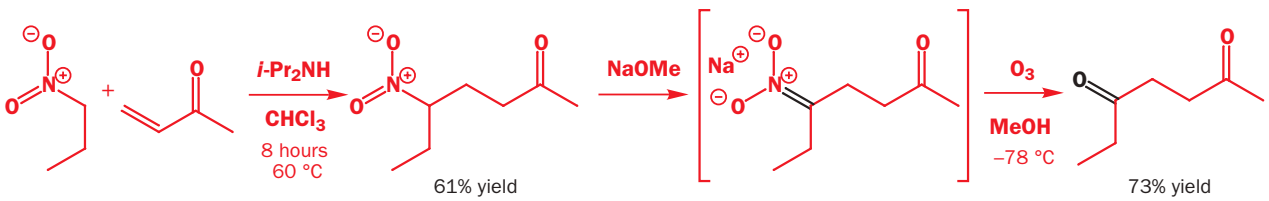
The effectiveness of nitro compound conjugate addition makes it ideal for use in combination with other reactions in making several bonds in one pot. The last example showed triple conjugate addition. The next example combines conjugate addition and intramolecular conjugate addition to make a six-membered ring. The base used for both steps is Cs_2CO_3. Caesium, the most electropositive of readily available metals, forms ionic compounds only so that the carbonate ion can exert its full basicity. Deprotonation of the conjugate addition product next to the nitro group produces a second anion, which does an intramolecular S_N2 displacement of iodide to form a six-membered ring.



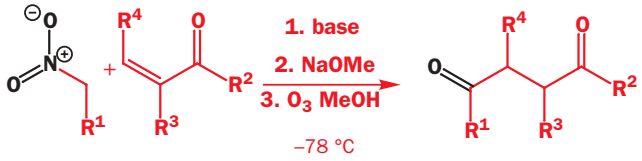
The nitro group can be converted into other useful functional groups following conjugate addition. Reduction gives primary amines while hydrolysis reveals ketones. The hydrolysis is known as the **Nef reaction** and used to be achieved by formation of the nitro-stabilized anion with a base such as sodium hydroxide followed by hydrolysis with sulfuric acid. These conditions are rather unforgiving for many substrates (and products) so milder methods have been developed. One of these involves ozonolysis of the nitro 'enolate' at low temperature rather than treatment with acid.

■ Ozonolysis is described in Chapter 35.

Base-catalysed conjugate addition of nitropropane to methyl vinyl ketone occurred smoothly to give the nitroketone. Formation of the salt with sodium methoxide was followed by oxidative cleavage of the C=N linkage with ozone. The product was a 1,4-diketone which was isolated without further aldol reaction by this route.



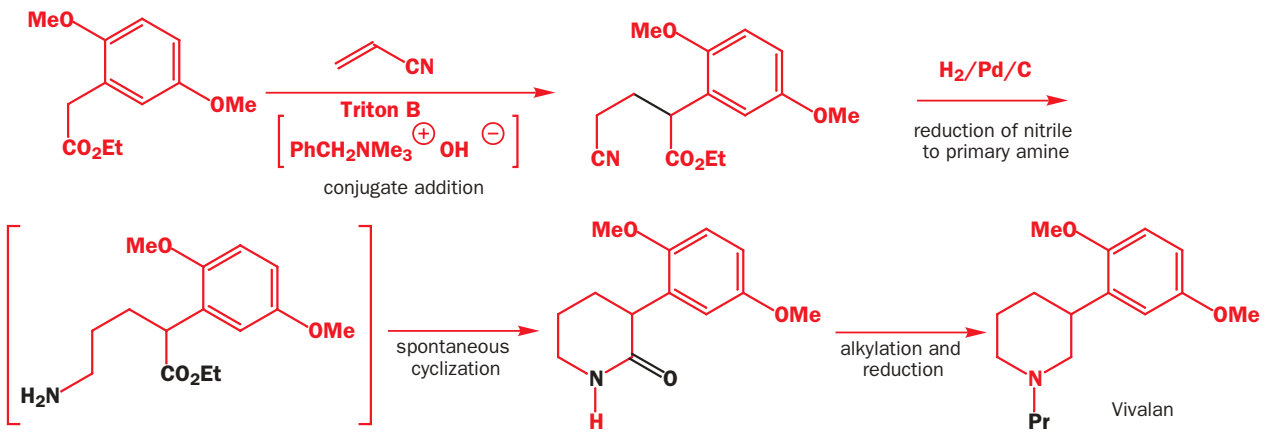
This is a good general method for the synthesis of 1,4-diketones, which can be otherwise difficult to make, and additional substituents are easily accommodated on the enone—a characteristic of conjugate addition.



The synthesis of Vivalan, a drug that acts on brain chemistry

We end this chapter with a simple commercial synthesis of a drug molecule. This is Vivalan, described as a dopaminergic antagonist. It uses four reactions that you have met: conjugate addition of an enolate to acrylonitrile; reduction of CN to a primary amine; alkylation; and reduction of the amide. There is another reaction involved—cyclization to an amide—but this occurs spontaneously. These reactions may be simple but they are important.

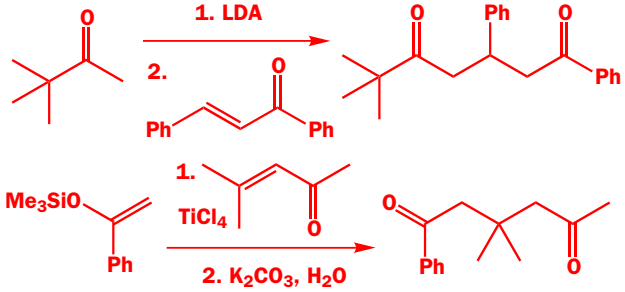
synthesis of Vivalan



This was the last chapter in our sequence (Chapters 26–28) devoted to the chemistry of enols and enolates and, in particular, to their use in making new C–C bonds. In the next chapter we shall be using these reactions when we introduce you to synthetic planning. We shall be answering questions such as, 'how was the synthesis of Vivalan planned?'

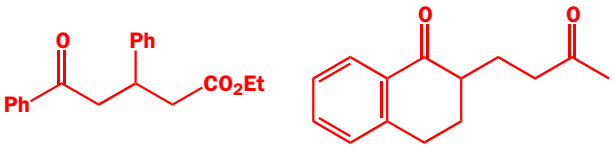
Problems

1. Write full mechanisms for these reactions mentioned earlier in the chapter.

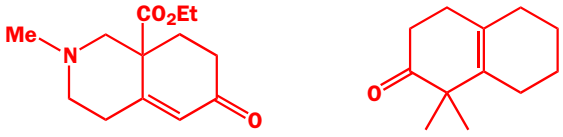


2. Suggest syntheses for these compounds.

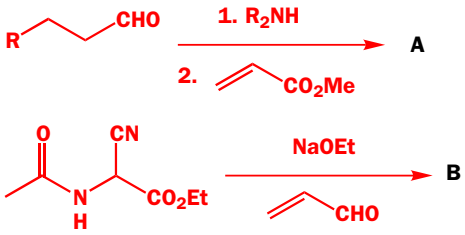
3. Suggest two different approaches to these compounds by conjugate addition of an enol(ate). Which do you prefer?



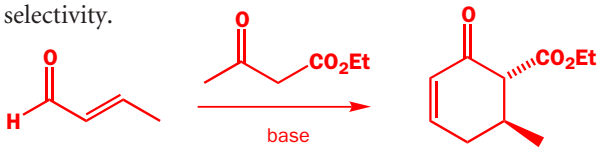
4. How could you use the Robinson annelation to make these compounds?



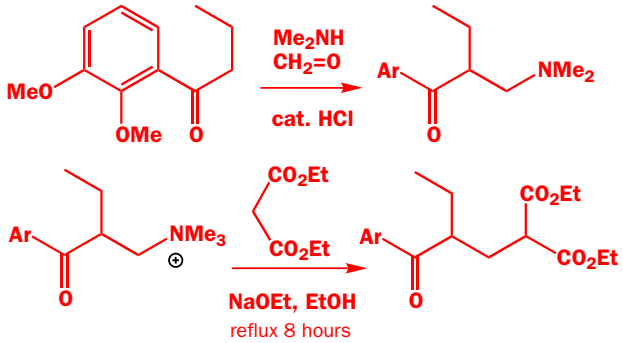
5. Predict the product that would be formed in these conjugate additions.



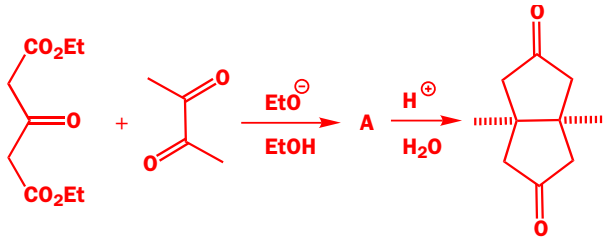
6. Suggest mechanisms for this reaction, commenting on any selectivity.



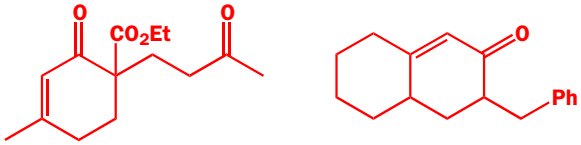
7. This example of the use of the Mannich reaction was given in the chapter. Draw detailed mechanisms for the two key steps shown here.



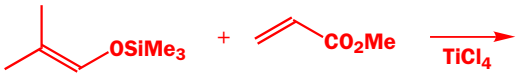
8. This symmetrical bicyclic ketone can easily be synthesized in two steps from simple precursors. What is the structure of the intermediate and what is the mechanism of the reactions?



9. Suggest ways to make these compounds using conjugate addition of enol(ate)s.

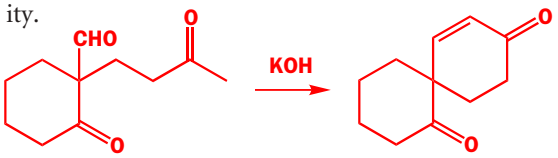


10. Identify the product of this reaction and propose a mechanism for its formation.

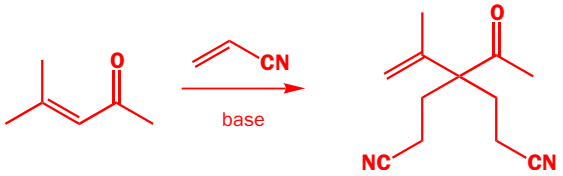


B, $C_8H_{14}O_3$
ν_{max}(cm^{-1}) 1745, 1730
δ_C(p.p.m.) 202, 176, 62, 48, 34, 22, 15
δ_H(p.p.m.) 1.21 (6H,s), 1.8 (2H, t, *J* 7 Hz), 2.24 (2H, t, *J* 7 Hz), 4.3 (3H, s), 10.01 (1H, s)

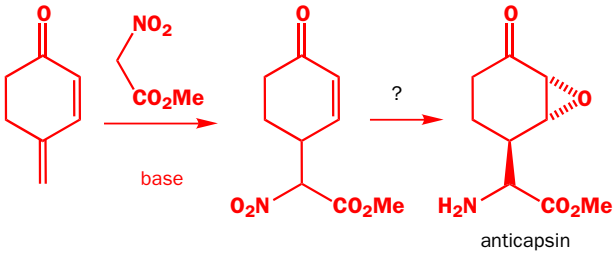
11. Suggest a synthesis for the starting material for this reaction, a mechanism for the reaction, and an explanation for the selectivity.



12. Suggest a mechanism for this reaction.



13. Suggest a mechanism for this reaction. How would you convert the product into the antibiotic anticapsin?



Retrosynthetic analysis

30

Connections

Building on:

- Carbonyl chemistry ch6, ch12, & ch14
- Conjugate addition ch10
- S_N1 and S_N2 reactions ch17
- Electrophilic aromatic substitution ch22

Arriving at:

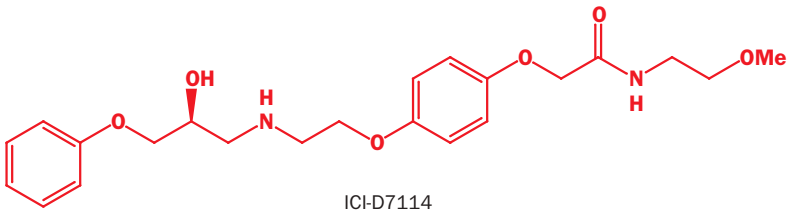
- Synthesis and retrosynthesis
- Thinking backwards
- How to make amines and ethers
- What are synthons?
- Choosing which C–C bonds to make
- Two-group disconnections are best
- Logical planning in enolate chemistry

Looking forward to:

- Diastereoselectivity ch33–ch34
- Pericyclic reactions ch35–ch36
- Synthesis of aromatic heterocycles ch44
- Asymmetric synthesis ch45
- Natural products ch51

Creative chemistry

Chemistry is above all a creative science. Nearly all that you have learned so far in this book has had one underlying aim: to teach you how to make molecules. This is after all what most chemists do, for whatever reason. Small amounts of many drugs can be isolated from plants or marine animals; much greater quantities are made by chemists in laboratories. A limited range of dyes can be extracted from plants; many more vivid and permanent ones are made by chemists in the laboratory. Synthetic polymers, created by chemists, have replaced more expensive and less durable alternatives like rubber. Despite the bad press it has received, the use of PVC as insulating material for electric wires has prevented numerous fires and saved many lives. Eating is cheap and people live longer because pesticides allow agriculture to supply copious quantities of food to the shelves of our shops, markets, and supermarkets. Most of the improvements in the quality of life over the last 50 to 100 years can be traced to new molecules created by chemists.

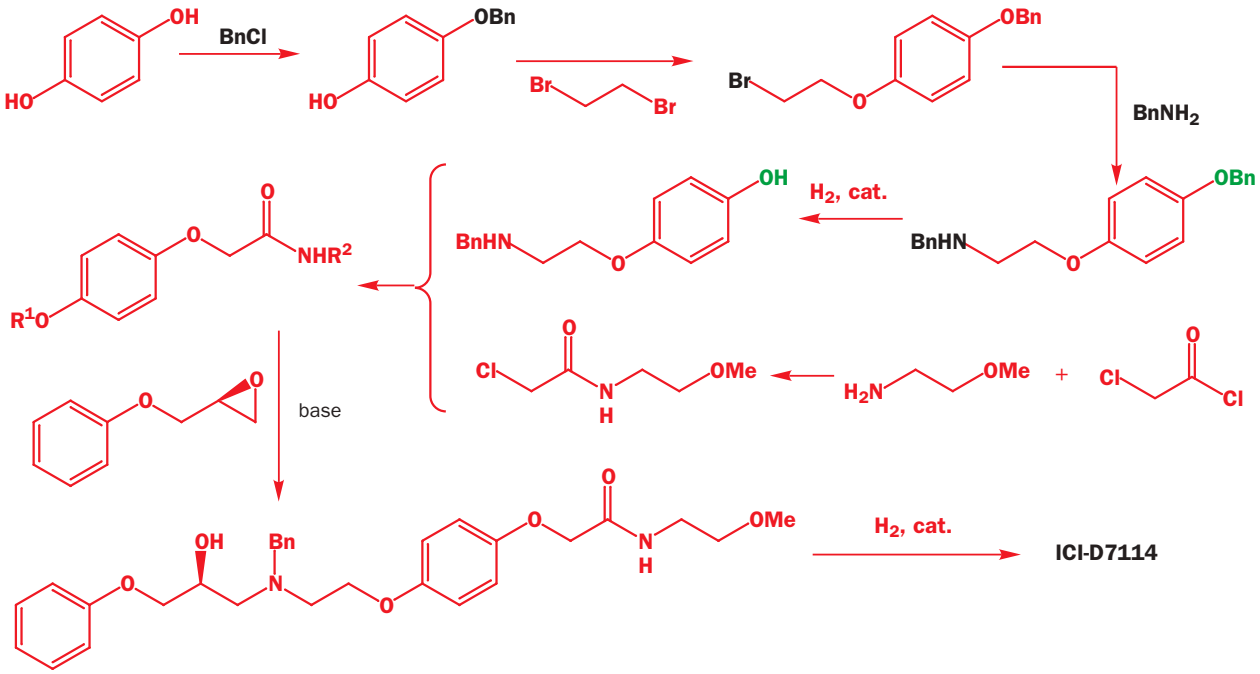


ICI-D7114

But, faced with the challenge of making a new compound, how do chemists go about deciding how to make it? This molecule is known as ICI-D7114, and was identified as a possible anti-obesity drug. To test its efficacy, several hundred grams of it had to be made, and overleaf is how it was done.

The chemists who made this molecule could have chosen any route—any starting materials and any sequence of reactions. All that mattered was the final product—what we will call the **target molecule**. Synthetic planning starts with the product, which is fixed and unchangeable, and works backwards towards the starting materials. This process is called **retrosynthesis**, and the art of planning the synthesis of a target molecule is called **retrosynthetic analysis**. The aim of this chapter is to introduce you to the principles of retrosynthetic analysis: once you have read and understood it you will be well on the way to designing your own organic syntheses.

■ Of course, in a general text like this we are limited in the amount of detail we can cover—if you want to know more then read a specialized text.



▶ You now know four types of reaction arrow: the simple reaction arrow → meaning 'reacts to give', the delocalization arrow ↔ meaning 'two different ways to draw the same delocalized structure', the equilibrium arrow ⇌ meaning 'these two structures are interconverting', and now the retrosynthesis arrow ⇒ meaning 'could be made from'.

▶ This chapter will rely heavily on the reactions you have met earlier in the book, and should therefore provide you with the opportunity to revise them and check you understand how they work. If you come across a reaction you aren't familiar with, look it up before carrying on to the next one.

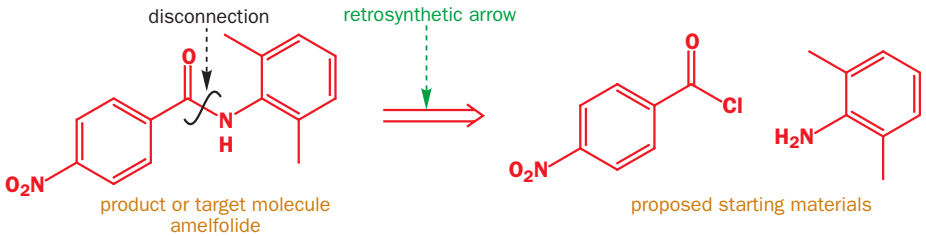
Retrosynthetic analysis: synthesis backwards

Most of the chemistry you have learned so far has concentrated on *reactions* (questions like 'what do you need to add to X to get Y?') or on *products* (questions like 'what will happen if X and Y react together?'). Now we're looking at **starting materials** (questions like 'what X and Y do you need to react together to make Z?'). We're looking at reactions in reverse, and we have a special symbol for a reverse reaction called a **retrosynthetic arrow** (the 'implies' arrow from logic).

A scheme with a retrosynthetic arrow $Z \Longrightarrow X + Y$ (a retrosynthetic arrow) means 'Z could be made from X plus Y'.

This compound is used as an insect repellent. As it's an ester, we know that it can be made from alcohol plus acyl chloride, and we can represent this using a retrosynthetic arrow.

The aromatic amide amelfolide is a cardiac antiarrhythmic agent. Because we see that it is an amide, we know that it can be made quite simply from *p*-nitrobenzoyl chloride and 2,6-dimethylaniline—again, we can represent this using a retrosynthetic arrow. Mentally breaking a molecule into its component parts like this is known as **disconnection**, and it's helpful to indicate the site of the disconnection with a wiggly line as we have here.

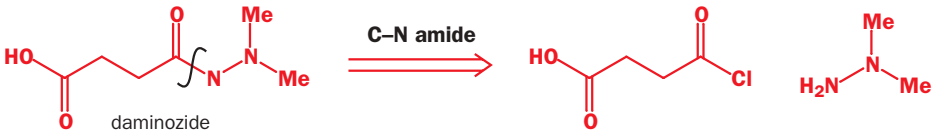


Disconnections must correspond to known, reliable reactions

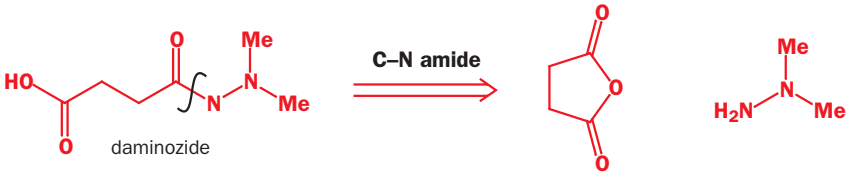
The chemists who first made amelfolide chose to make it from an amine and an acyl chloride because they knew that this reaction, the standard way of making an amide, had a very good chance of success. They chose to disconnect the C–N bond because this disconnection corresponds to a reliable reaction in a way that no other possible disconnection of this molecule does.

Now that you've seen the principle of retrosynthetic analysis at work, you should be able to suggest a reasonable disconnection of this compound, which is known as daminozide.

You probably spotted immediately that daminozide is again an amide, so the best disconnection is the C–N bond, which could take us back to acyl chloride and dimethylhydrazine. This time we've written 'C–N amide' above the retrosynthetic arrow as a reminder of why we've made the disconnection and we advise you to follow this practice.

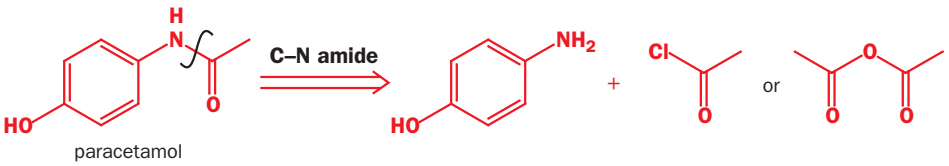


Now, in fact, there is a problem with this acyl chloride—it would be unstable as it can cyclize to an anhydride. But this poses no problem for the synthesis of daminozide—we could just use the anhydride instead, since the reaction should be just as reliable. A better retrosynthesis therefore gives the anhydride and indeed this is how daminozide is made.



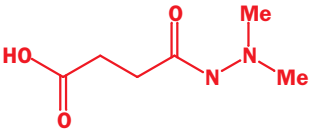
Synthons are idealized reagents

In the synthesis of daminozide an anhydride is used out of necessity rather than out of choice, but it often turns out that there are several alternative reagents all corresponding to the same disconnection. Paracetamol, for example, is an amide that can be disconnected either to amine + acyl chloride or to amine + anhydride.



Which reagent is best can often only be determined by experimentation—commercially, paracetamol is made from *para*-aminophenol and acetic anhydride largely because the by-product, acetic acid, is easier to handle than HCl. In a retrosynthetic analysis, we don't really want to be bothered by this sort of decision, which is best made later, so it's useful to have a single way of representing the key attributes of alternative reagents. We can depict both anhydride and acyl chloride in this scheme as an 'idealized reagent'—an electrophilic acetyl group $MeCO^+$.

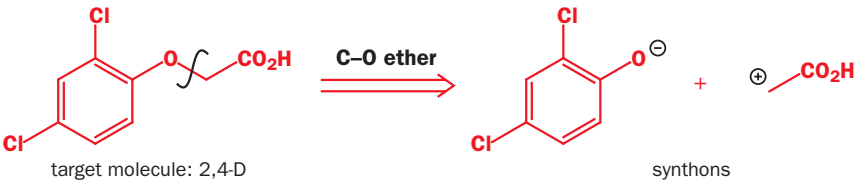
We call such idealized reagents **synthons**. Synthons are fragments of molecules with an associated polarity (represented by a '+' or '–') which stand for the reagents we are going to use in the forward synthesis. They are not themselves reagents, though they may occasionally turn out to be intermediates along the reaction pathway. By disconnecting bonds to synthons rather than to actual reagents we can indicate the polarity of the bond-forming reaction we are going to use without having to specify details of the reagents.



■ Daminozide is an agrochemical used to stunt the growth of chrysanthemums and dwarf fruit trees artificially.

▶ You will find that you learn much more and much faster if you try to do the retrosynthetic analyses in this chapter as you read it, before looking at the suggested solutions. Use a piece of paper to cover up the rest of the page as you read, and write some ideas down on another piece of paper. Don't just say 'oh I can do that' and move on—you'll miss out on the chance of teaching yourself a lot of chemistry. Don't waste the opportunity! Next time you read this chapter you'll have your memory as an aid—and retrosynthetic analysis isn't about remembering; it's about deducing. Another important thing about retrosynthetic analysis is that there is rarely one single 'right' answer, so even if your suggestions don't match up with ours, don't be discouraged. Aim to learn from the points where your attempts differ from our suggestions.

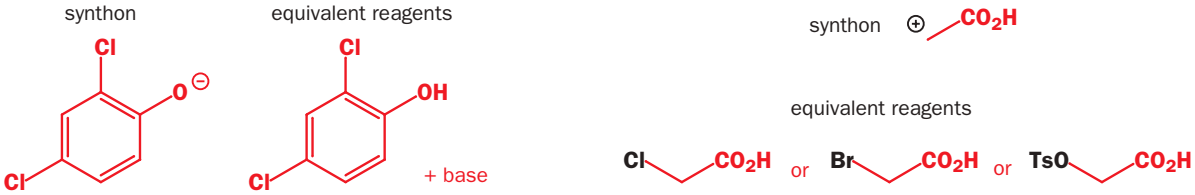
synthon



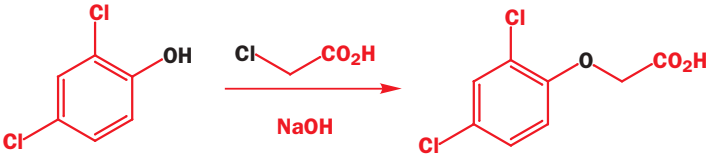
target molecule: 2,4-D synthons

We can apply these ideas to the synthesis of the herbicide 2,4-D (2,4-dichlorophenoxyacetic acid). The most reasonable disconnection of an ether is the C–O bond because we know that ethers can be made from alkyl halides by substitution with an alkoxide anion. We don't at this stage need to decide exactly which alkyl halide or alkoxide to use, so we just write the synthons.

Once the retrosynthetic analysis is done, we can go back and use our knowledge of chemistry to think of reagents corresponding to these synthons. Here, for example, we should certainly choose the anion of the phenol as the nucleophile and some functionalized acetic acid molecule with a leaving group in the α position.



We can then write out a suggested synthesis in full from start to finish. It isn't reasonable to try to predict exact conditions for a reaction: to do that you would need to conduct a thorough search of the chemical literature and do some experiments. However, all of the syntheses in this chapter are real examples and we shall often give full details of conditions to help you become familiar with them.



target molecule: 2,4-D

Some definitions of terms used in synthesis

• target molecule (or TM)	the molecule to be synthesized
• retrosynthetic analysis or retrosynthesis	the process of mentally breaking down a molecule into starting materials
• retrosynthetic arrow	an open-ended arrow, ⟹, used to indicate the reverse of a synthetic reaction
• disconnection	an imaginary bond cleavage, corresponding to the reverse of a real reaction
• synthon	idealized fragments resulting from a disconnection. *Synthons* need to be replaced by *reagents* in a suggested synthesis
• reagent	a real chemical compound used as the equivalent of a synthon

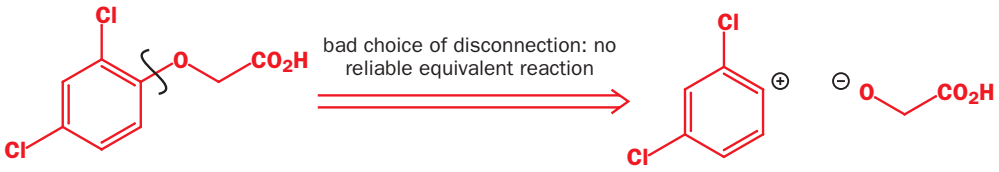
Choosing a disconnection

The hardest task in designing a retrosynthetic analysis is spotting where to make the disconnections. We shall offer some guidelines to help you, but the best way to learn is through experience and practice. The overall aim of retrosynthetic analysis is to get back to starting materials that are available from chemical suppliers, and to do this as efficiently as possible.

Guideline 1

Disconnections must correspond to known, reliable reactions

We have already mentioned that disconnections must correspond to known reliable reactions and it's the most important thing to bear in mind when working out a retrosynthesis. When we disconnected the ether 2,4-D we chose to disconnect next to the oxygen atom because we know about the synthesis of ethers. We chose *not* to disconnect on the aryl side of the oxygen atom because we know of no reliable reaction corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring.



■ We talked about cases where nucleophilic aromatic substitution *is* possible in Chapter 23.

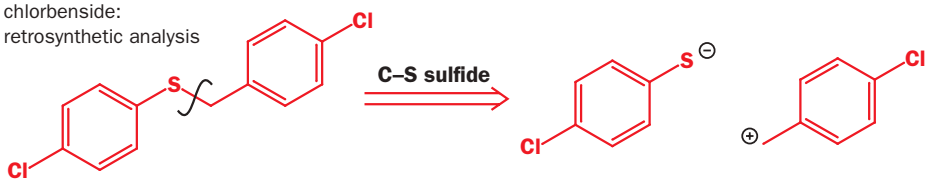
Guideline 2

For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom

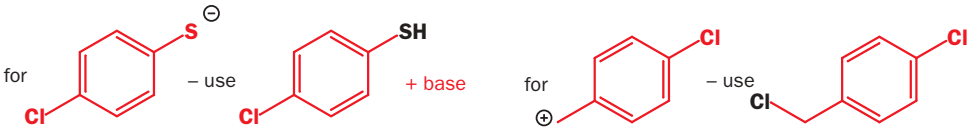
In all the retrosynthetic analyses you've seen so far there is a heteroatom (N or O) joining the rest of the molecule together, and in each case we made the disconnection next to that N or O. This guideline works for esters, amides, ethers, amines, acetals, sulfides, and so on, because these compounds are often made by a substitution reaction.

Chlorbenside is used to kill ticks and mites. Using Guideline 2 we can suggest a disconnection next to the sulfur atom; using Guideline 1 we know that we must disconnect on the alkyl and not on the aryl side.

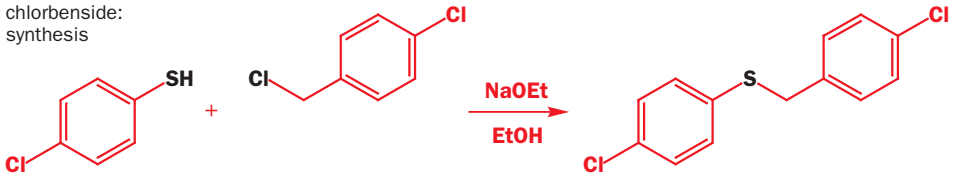
chlorbenside: retrosynthetic analysis



We can now suggest reagents corresponding to the synthons, and propose a synthetic scheme.



chlorbenside: synthesis

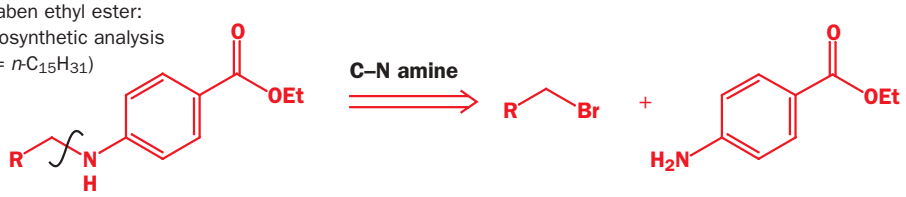


▶ You shouldn't have expected to predict that sodium ethoxide would be the base used for this reaction, but you should have been aware that a base is needed, and have had some idea of the base strength required to deprotonate a thiol.

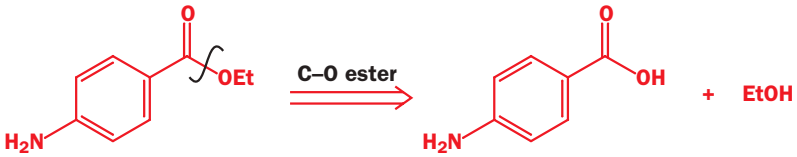
The next example is the ethyl ester of, and precursor to, cetaben, a drug that can be used to lower blood lipid levels. It is an amine, so we disconnect next to the nitrogen atom.

▶ You don't always need to write out the synthons first—here the reagents are simple so we just write those instead.

cetaben ethyl ester: retrosynthetic analysis (R = *n*-$C_{15}H_{31}$)

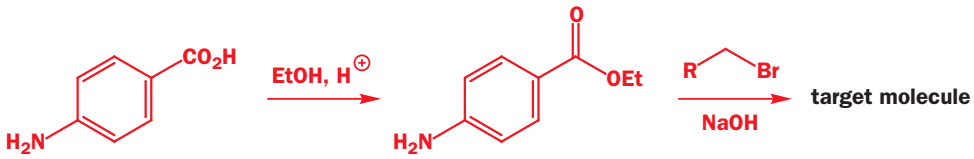


The alkyl bromide is available but we shall need to make the aromatic amino-ester and the best disconnection for an ester is the C–O bond between the carbonyl group and the esterifying group.



We have now designed a two-step synthesis of our target molecule, and this is how it was carried out.

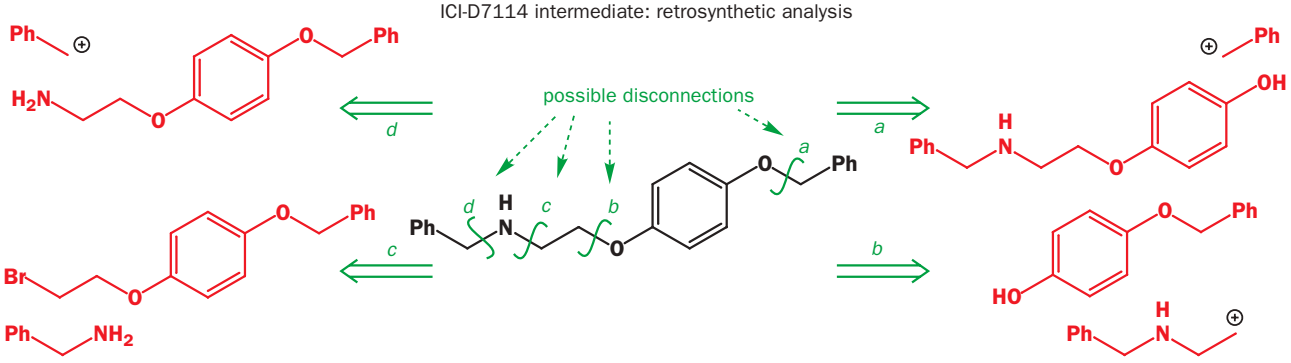
cetaben ethyl ester: synthesis (R = *n*-$C_{15}H_{31}$)



Multiple step syntheses: avoid chemoselectivity problems

This compound was an intermediate in the synthesis of the potential anti-obesity drug ICI-D7114 you met at the beginning of the chapter. You can spot that, with two ethers and an amine functional group, it requires several disconnections to take it back to simple compounds. The question is which do we do first? One way to solve the problem is to write down all the possibilities and see which looks best. Here there are four reasonable disconnections: one at each of the ether groups (*a* and *b*) or on either side of the amine (*c* and *d*).

ICI-D7114 intermediate: retrosynthetic analysis



Both (*a*) and (*b*) pose problems of chemoselectivity as it would be hard to alkylate the phenol in the presence of the basic nitrogen atom. Between (*c*) and (*d*), (*c*) appears to be the better choice because the next disconnection after (*d*) will have to be an alkylation of O in the presence of an NH_2 group. To avoid chemoselectivity problems like this, we want to try and *introduce reactive groups late in the synthesis*. In terms of retrosynthetic analysis, then, we can formulate another guideline.

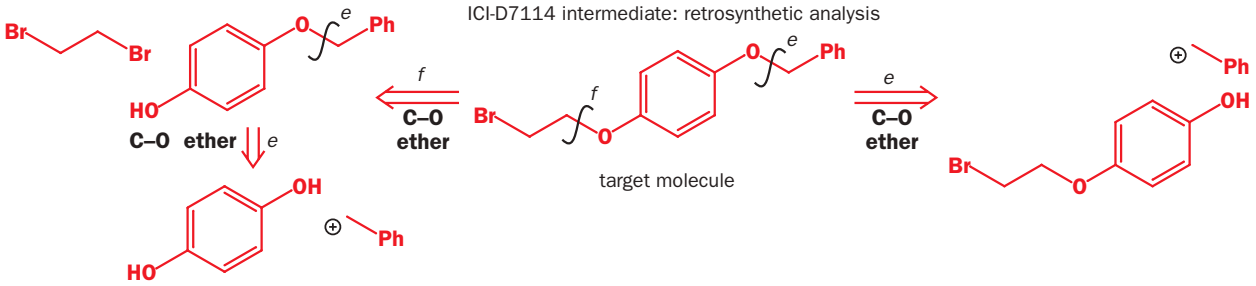
■ We talked about this type of thing in Chapter 24.

● Guideline 3

Consider alternative disconnections and choose routes that avoid chemoselectivity problems—often this means disconnecting reactive groups first

This guideline helps us in the next retrosynthetic step for the ICI-D7114 intermediate. Disconnection (*c*) gave us a compound with two ethers that might be disconnected further by disconnection (*e*) or (*f*).

ICI-D7114 intermediate: retrosynthetic analysis



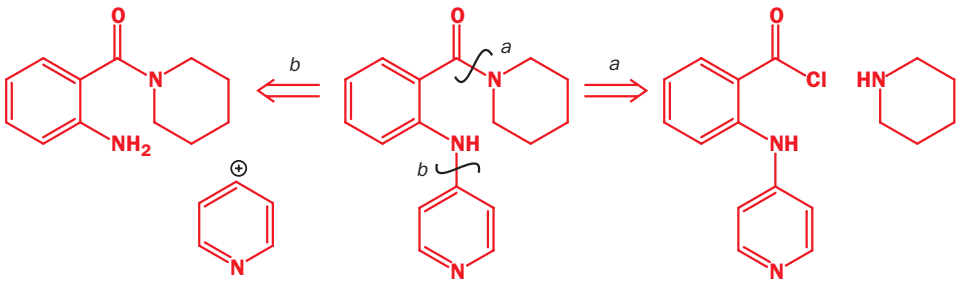
Disconnection (*e*) requires alkylation of a compound that is itself an alkylating agent. Disconnection (*f*) is much more satisfactory, and leads to a compound that is easily disconnected to 4-hydroxyphenol (*para*-cresol) and 1,2-dibromethane. Using Guideline 3, we can say that it's best to disconnect the bromoethyl group (*f*) before the benzyl group because the bromoethyl group is more reactive and more likely to cause problems of chemoselectivity.

ICI-D7114 intermediate: synthesis

Functional group interconversion

The antihypertensive drug ofornine contains an amide and an amine functional group, and we need to decide which to disconnect first. If we disconnect the secondary amine first (*b*), we will have chemoselectivity problems constructing the amide in the presence of the resulting NH_2 group.

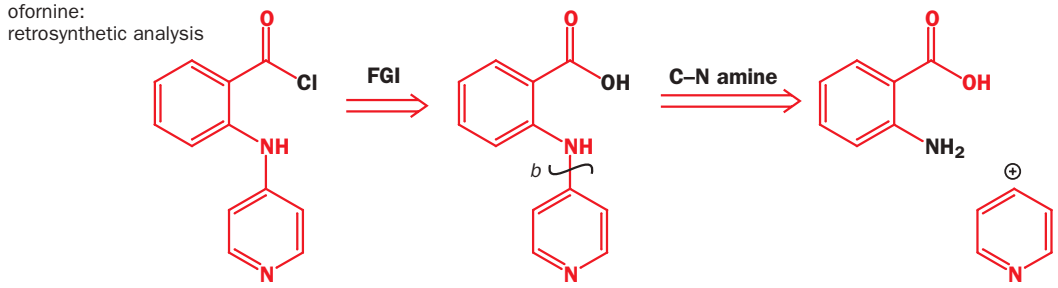
ofornine: retrosynthetic analysis



Yet disconnection (*a*), on the face of it, seems to pose an even greater problem because we now have to construct an amine in the presence of an acyl chloride! However, we shall want to make the acyl chloride from the carboxylic acid, which can then easily be disconnected to 2-aminobenzoic acid (anthranilic acid) and 4-chloropyridine.

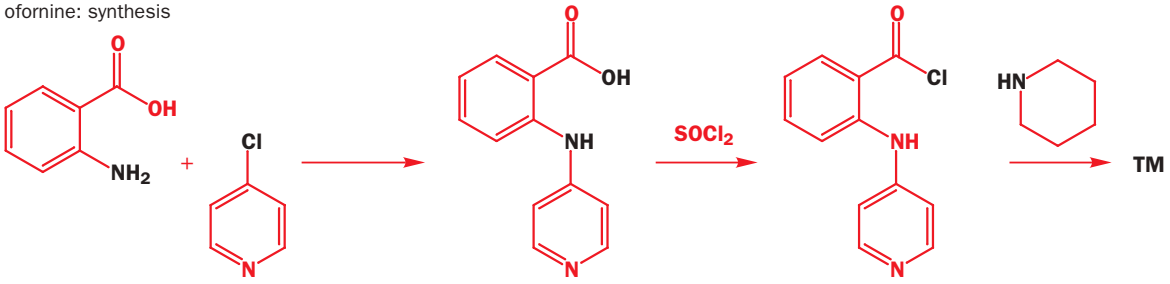
■ We discussed nucleophilic substitutions on electron-poor aromatic rings like this in Chapter 23 and there is more detail on chloropyridines in Chapter 43.

ofornine: retrosynthetic analysis



The retrosynthetic transformation of an acyl chloride to a carboxylic acid is not really a disconnection because nothing is being disconnected. We call it instead a **functional group interconversion**, or **FGI**, as written above the retrosynthetic arrow. Functional group interconversions often aid disconnections because the sort of reactive functional groups (acyl chlorides, alkyl halides) we want in starting materials are not desirable in compounds to be disconnected because they pose chemoselectivity problems. They are also useful if the target molecule contains functional groups that are not easily disconnected.

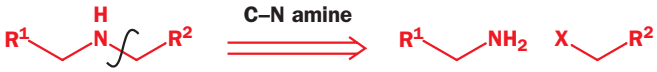
ofornine: synthesis



By using an appropriate reagent or series of reagents, almost any functional group can be converted into any other. You should already have a fair grasp of reasonable functional group interconversions. They mostly fall into the categories of oxidations, reductions, and substitutions (Chapters 12, 14, 17, and 24).

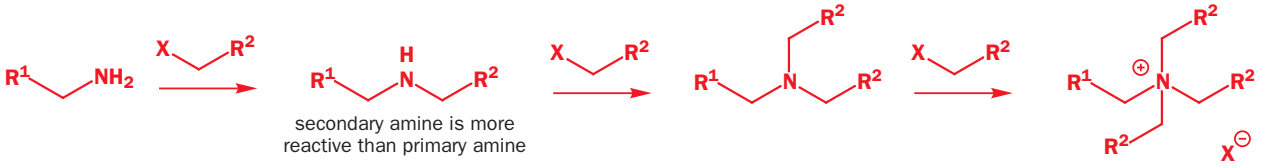
Amine synthesis using functional group interconversions

The synthesis of amines poses a special problem because only in certain cases is the obvious disconnection successful.

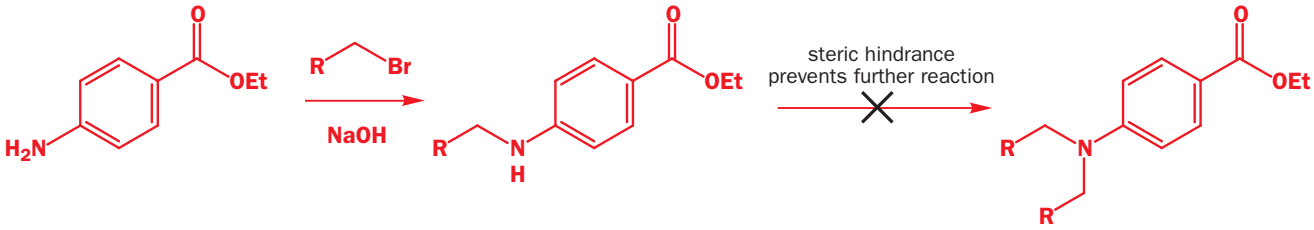


■ We discussed this in Chapters 14 and 24.

The problem is that the product is usually more reactive than the starting material and there is a danger that multiple alkylation will take place.



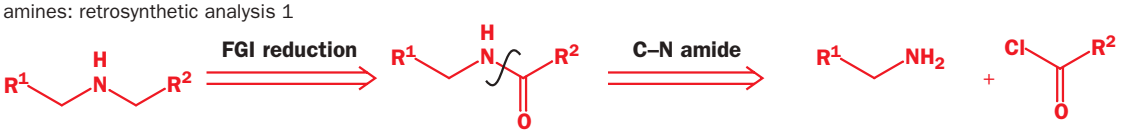
The few successful examples you have seen so far in this chapter have been exceptions, either for steric or electronic reasons, and from now on we advise you to avoid disconnecting an amine in this way. Sometimes further alkylation is made unfavourable by the increased steric hindrance that would result: this is probably the case for the cetaben ethyl ester we made by this reaction.



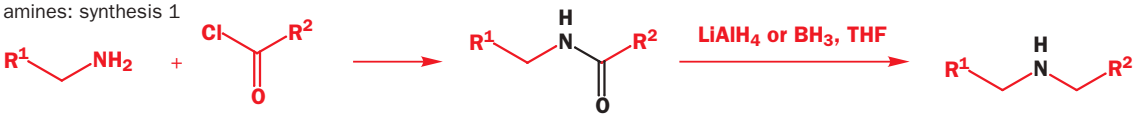
If the alkylating agent contains an inductive electron-withdrawing group, the product may be less reactive than the starting material—benzylamine was only alkylated once by the alkyl bromide in the synthesis of ICI-D7114 on p. 000 because of the electron-withdrawing effect of the aryloxy group.

What are the alternatives? There are two main ones, and both involve functional group interconversion, with the reactive amine being converted to a less reactive derivative before disconnection. The first solution is to convert the amine to an amide and then disconnect that. The reduction of amide to amine is quite reliable, so the FGI is a reasonable one.

amines: retrosynthetic analysis 1



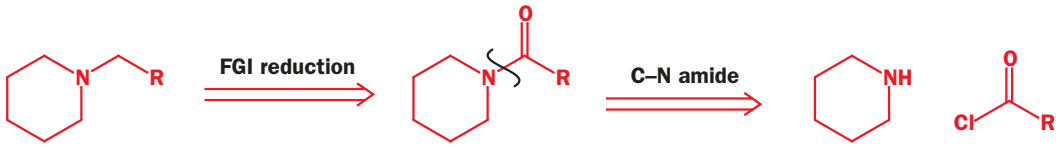
amines: synthesis 1



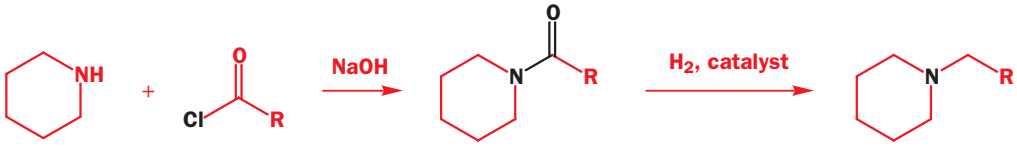
▶ Notice that we write 'FGI reduction' above the arrow because we are talking about the *forward* reaction we are going to do at this step.

This approach was used in a synthesis of this amine, though in this case catalytic hydrogenation was used to reduce the amide.

retrosynthetic analysis:
R = C_5H_{11}

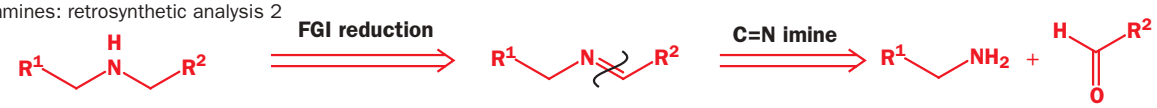


synthesis:

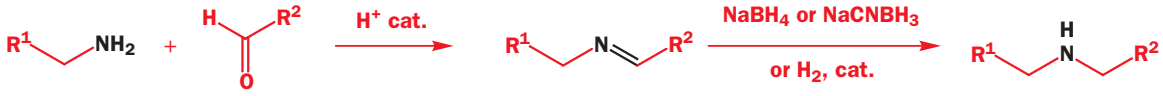


The second alternative is to convert to an imine, which can be disconnected to amine plus carbonyl compound. This approach is known as **reductive amination**, and we discussed it in detail in Chapter 14.

amines: retrosynthetic analysis 2

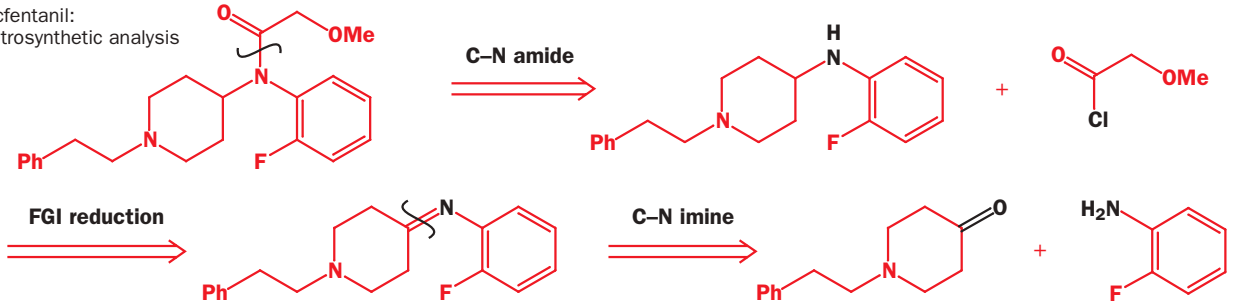


amines: synthesis 2 (reductive amination)

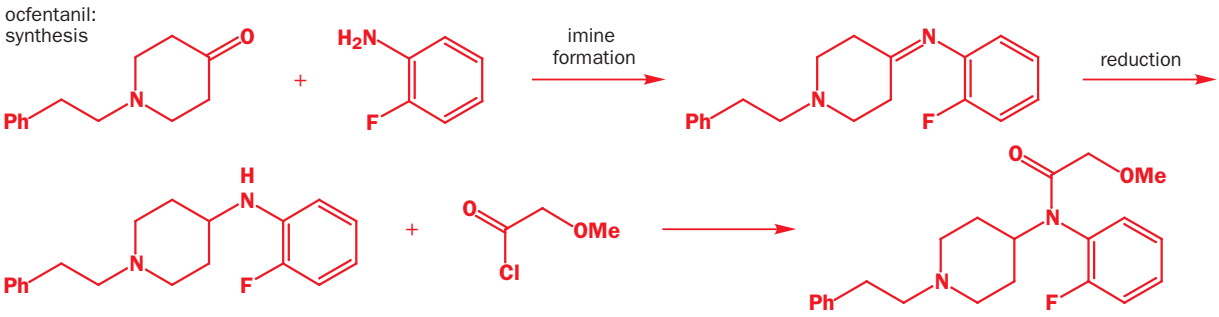


Ocfentanil is an opioid painkiller that lacks the addictive properties of morphine. Disconnection of the amide gives a secondary amine that we can convert to an imine for disconnection to a ketone plus 2-fluoro aniline.

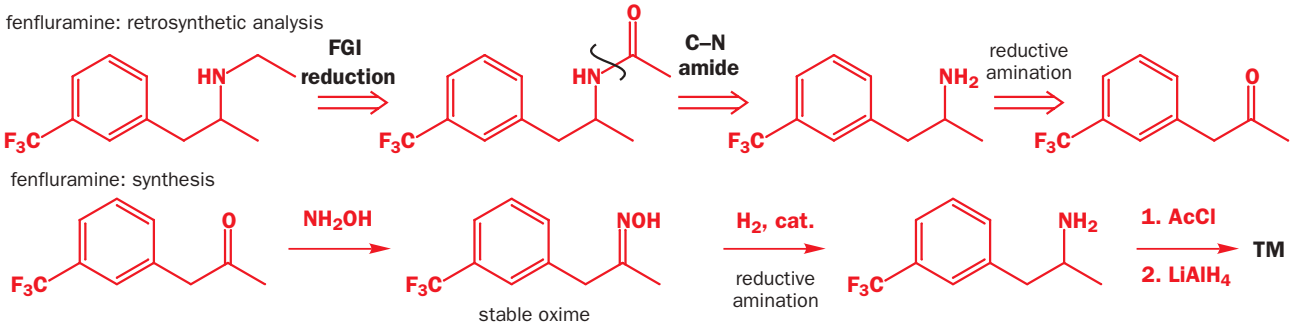
ocfentanil:
retrosynthetic analysis

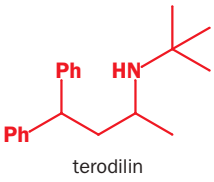


The synthesis is straightforward: a reductive amination followed by acylation of the only remaining NH group. The tertiary amine in the left-hand ring interferes with neither of these reactions.



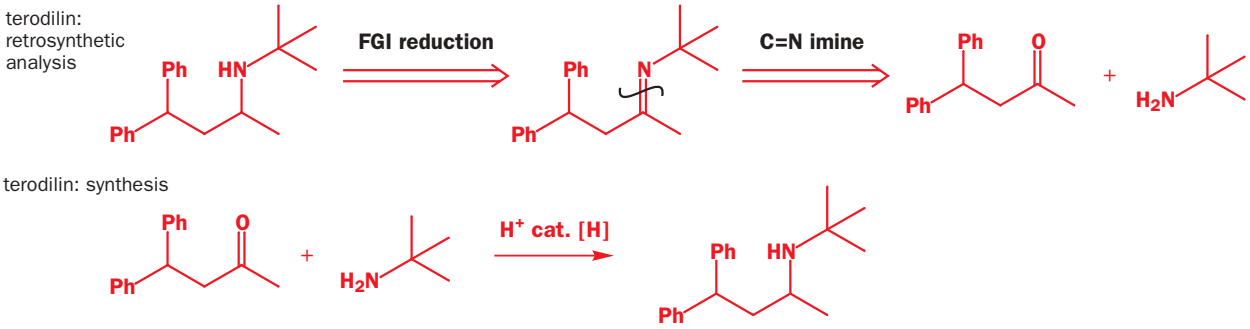
There are several conceivable routes to the neuroactive drug fenfluramine—one analysis, which uses both the amide and the imine FGI methods, is shown below and this was the route used to make the drug. Notice that the oxime was used instead of the imine. *N*-unsubstituted imines are very unstable, and the much more stable, indeed isolable oxime serves the same purpose. Oximes are generally reduced with $LiAlH_4$.




terodilin

You should now be able to suggest a plausible analysis of the secondary amine terodilin. This is the structure; write down a retrosynthetic analysis and suggested synthesis before looking at the actual synthesis below.

You should find yourself quite restricted in choice: the amide route clearly works only if there is a CH_2 group next to the nitrogen (this comes from the C=O reduction), so we have to use an imine.

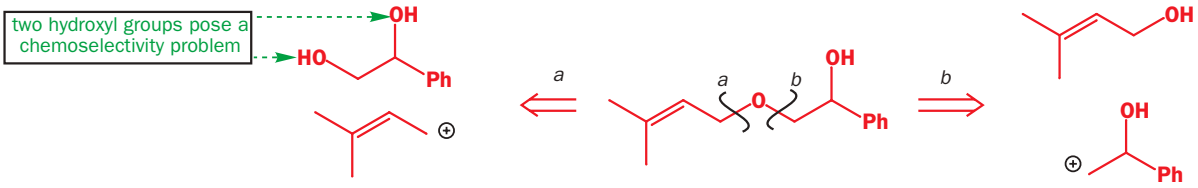


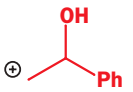
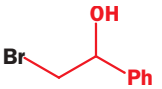
In the synthesis of terodilin, it was not necessary to isolate the imine—reduction of imines is faster than reduction of ketones, so formation of the imine in the presence of a mild reducing agent (usually $NaCNBH_3$ or catalytic hydrogenation) can give the amine directly.

■ See Chapter 24 for more on this.

Two-group disconnections are better than one

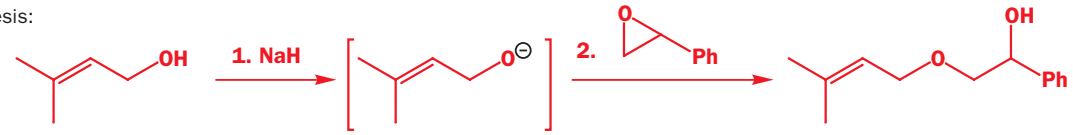
This compound was needed for some research into the mechanisms of rearrangements. We can disconnect on either side of the ether oxygen atom, but (*b*) is much better because (*a*) does not correspond to a reliable reaction: it might be hard to control selective alkylation of the primary hydroxyl group in the presence of the secondary one.



You might think that the best reagent to use as the equivalent of the synthon:  would be  Be more ingenious! A much better solution is to use an epoxide 

Nucleophile attack on the less hindered terminal carbon atom of the epoxide gives us the type of compound we want, and this was how the target molecule was made.

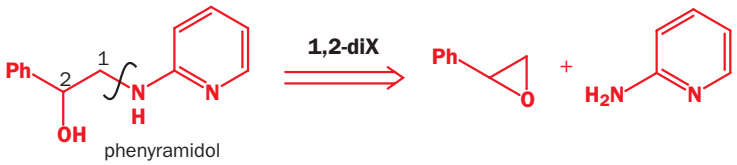
synthesis:



In using the epoxide we have gone one step beyond all the disconnections we have talked about so far, because we have *used one functional group to help disconnect another*—in other words, we noticed the alcohol adjacent to the ether we wanted to disconnect, and managed to involve them both in the disconnection. Such disconnections are known as **two-group disconnections**, and you should always be on the look-out for opportunities of using them because they are an efficient way of getting back to simple starting materials. We call this epoxide disconnection a 1,2-disconnection because the two functional groups in the two-group disconnection are in a 1,2-relationship.

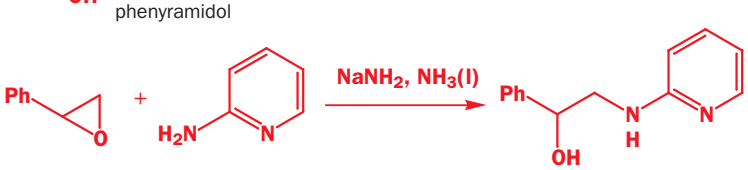
Drug molecules often have 1,2-related functional groups: 2-amino alcohols form one important class. Phenyramidol, for example, is a muscle relaxant. A simple two-group disconnection takes it straight back to 2-amino pyridine and styrene oxide.

phenyramidol: retrosynthetic analysis



phenyramidol

phenyramidol: synthesis



70% yield

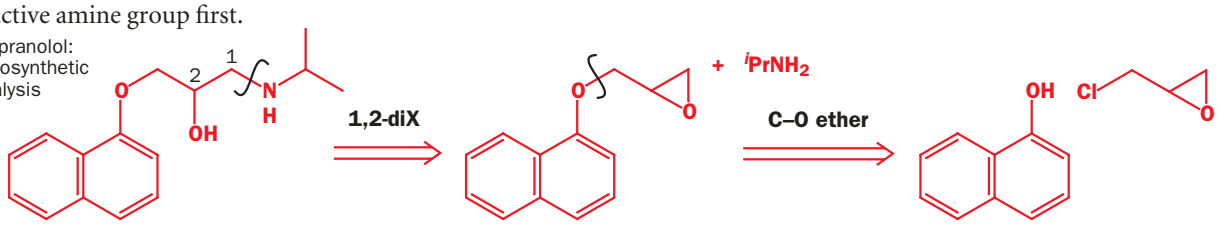
Notice that we have written '1,2-diX' above the arrow to show that it's a two-group ('diX') disconnection—we've also numbered the carbon atoms in the starting material to show the 1,2-relationship. It may seem trivial in such a simple example, but it's a useful part of the process of writing retrosynthetic analyses because it helps you to spot opportunities for making two-group disconnections.

▶ The observant among you may now be questioning why this synthesis is successful—after all, we have made a secondary amine by alkylating a primary one with an epoxide—exactly the sort of thing we advised against on p. 000. Alkylations with epoxides usually stop after the first step because the inductively electron-withdrawing hydroxyl group in the product makes it *less* nucleophilic than the starting material. In the synthesis of ICI-D7114 on p. 000, it's this same effect that prevents the amine being multiply alkylated.

Propranolol is one of the top heart drugs

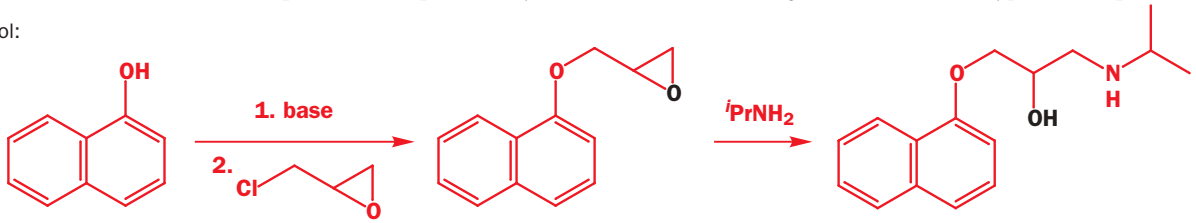
The Zeneca drug propranolol is a **beta-blocker** that reduces blood pressure and is one of the top drugs worldwide. It has two 1,2-relationships in its structure but it is best to disconnect the more reactive amine group first.

propranolol: retrosynthetic analysis



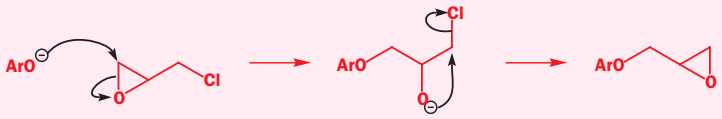
The second disconnection can't make use of an epoxide, but a simple ether disconnection takes us back to 1-naphthol and epichlorohydrin, a common starting material for this type of compound.

propranolol: synthesis



▶

Epichlorohydrin is a useful starting material for 1,2,3-substituted compounds. The epoxide is more electrophilic than the C–Cl bond, and the mechanism of the first step of the synthesis is surprising.

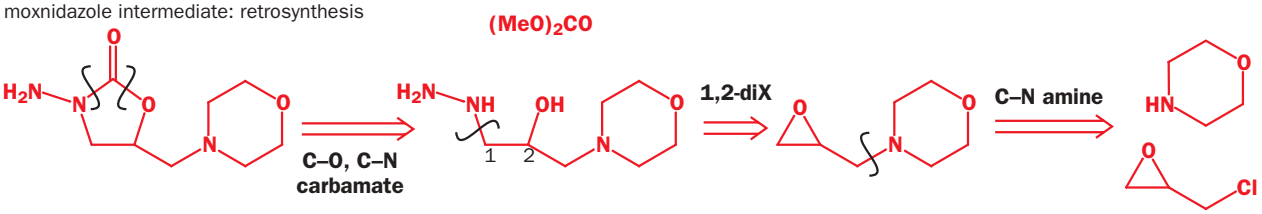


How would you verify this experimentally? Think about what would happen if the epichlorohydrin were enantiomerically pure.

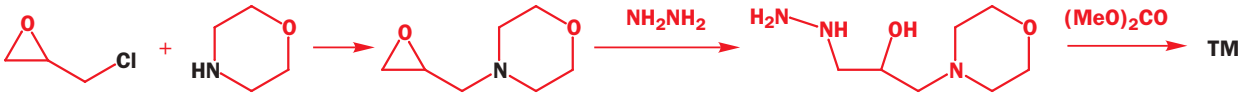
Moxnidazole can be made with epichlorohydrin

Moxnidazole is an antiparasitic drug, and our next target molecule is an important intermediate in its synthesis. The obvious first disconnection is of the carbamate group, revealing two 1,2 relationships. A 1,2-diX disconnection gives an epoxide that can be made by alkylation of morpholine with epichlorohydrin.

moxnidazole intermediate: retrosynthesis

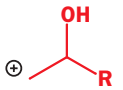


moxnidazole intermediate: synthesis

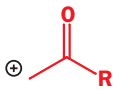


At the carbonyl oxidation level another synthon is needed for 1,2-diX disconnections

Just as epoxides are useful reagents for this synthon:



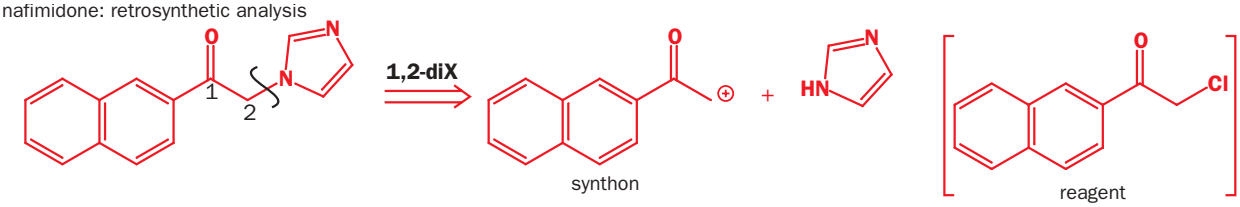
α halocarbonyl compounds are useful reagents for the carbonyl equivalent:



We can consider disconnection to this synthon to be a two-group disconnection because the α halocarbonyl equivalents are easily made by halogenation of a ketone, ester, or carboxylic acid (see Chapter 21) and the carbonyl group adjacent to the halide makes them extremely reactive electrophiles (Chapter 17).

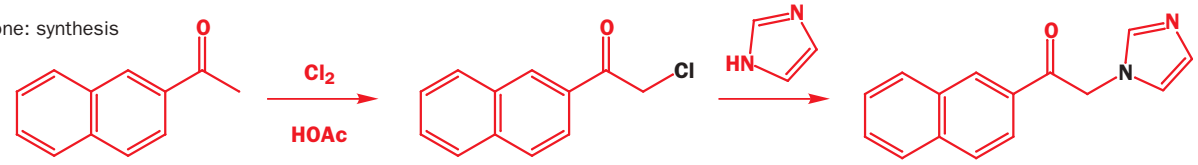
Nafimidone is an anticonvulsant drug with an obvious two-group disconnection of this type.

nafimidone: retrosynthetic analysis



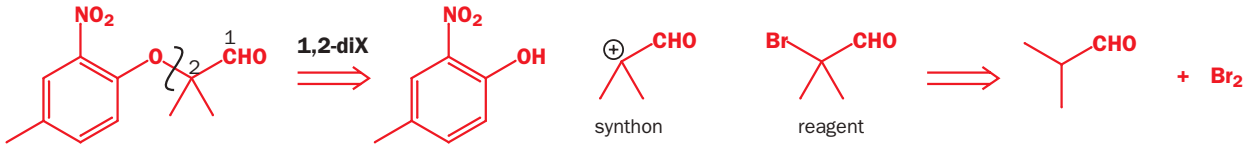
The α chloroketone is simply made by chlorination, and substitution is rapid and efficient even with the weakly basic (Chapter 8) heterocyclic amine.

nafimidone: synthesis



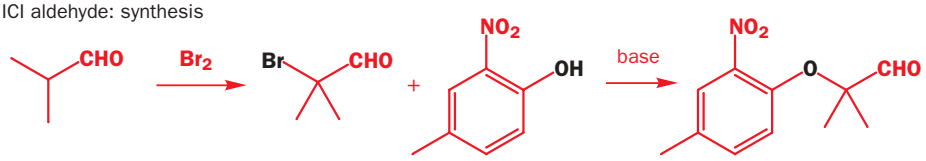
The aldehyde below was needed by ICI when they were developing a thromboxane antagonist. Two-group disconnection gives a 2-halo-aldehyde that can be made from isobutyraldehyde.

ICI aldehyde: retrosynthetic analysis



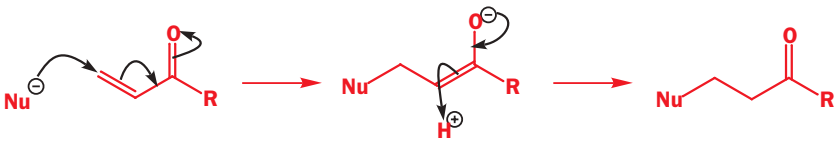
The synthesis requires a normal bromination of a carbonyl compound in acid solution but the next step is a most unusual S_N2 reaction at a *tertiary* centre. This happens because of the activation by the aldehyde group (Chapter 17) and is further evidence that the functional groups must be thought of as working together in this type of synthesis.

ICI aldehyde: synthesis

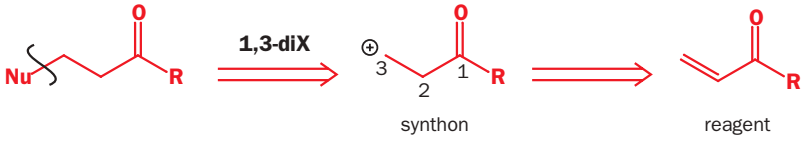


1,3-Disconnections

In Chapter 10 you saw how α,β-unsaturated carbonyl compounds undergo conjugate additions—reactions like this.

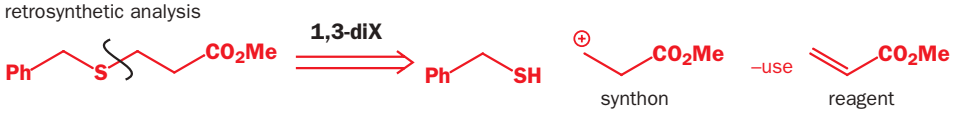


Two-group 1,3-disconnections are therefore possible because they correspond to this forward reaction. These **Michael acceptors** have an electrophilic site two atoms away from the carbonyl group, and are therefore the reagents corresponding to this synthon.



This type of reaction is available only when the alkene is conjugated to an electron-withdrawing group—usually carbonyl (Chapter 10) but it can be nitro, cyanide, etc. (Chapter 23). This disconnection is available only at this oxidation level unlike the last. We can do a two-group 1,3-disconnection on this sulfide, for example.

retrosynthetic analysis



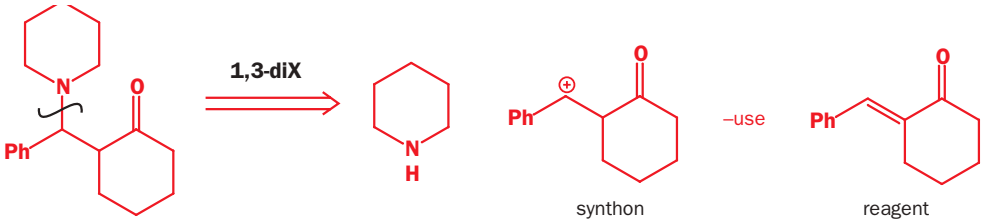
synthesis

Remember that not all nucleophiles will successfully undergo Michael additions—you must bear this in mind when making a 1,3-disconnection of this type. Most reliable are those based on nitrogen, sulfur, and oxygen (Chapter 10).

■ We shall discuss ways of disconnecting this starting material, and other α,β-unsaturated carbonyl compounds, later in the chapter.

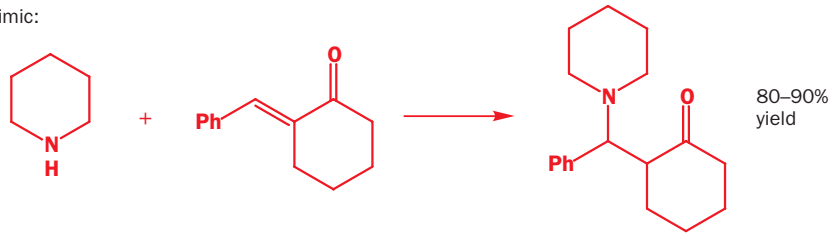
Our second example is an amine structurally similar to the 'deadly nightshade' drug, atropine, which has the ability to calm involuntary muscle movements. There is a 1,3-relationship between the amine and ketone functional groups, and 1,3-disconnection takes us back to piperidine and an unsaturated ketone.

atropine mimic: retrosynthetic analysis



▶ Don't be tempted to try using β haloketones as equivalents for this synthon! They are hard to make and highly unstable and they undergo rapid E1cB elimination (see Chapter 19).

atropine mimic: synthesis



To summarize...

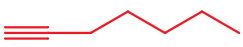
Before we leave C–X disconnections and go on to look at C–C disconnections we should just review some important points. We suggested three guidelines for choosing disconnections and now that you have met the principle of two-group disconnections, we can add a fourth:

● Guidelines for good disconnections

1. **Disconnections must correspond to known, reliable reactions**
2. **For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom**
3. **Consider alternative disconnections and choose routes that avoid chemoselectivity problems—often this means disconnecting reactive groups first**
4. **Use two-group disconnections wherever possible**

Two-group disconnections reduce the complexity of a target molecule more efficiently than one-group disconnections, and you should always be on the look-out for them. You will meet more two-group disconnections in the next section, which deals with how to disconnect C–C bonds.

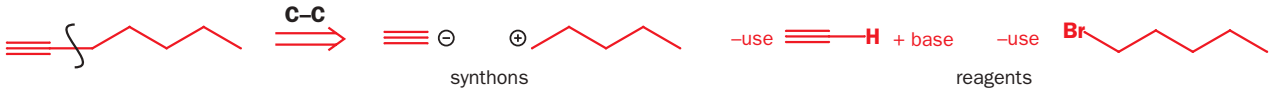
C–C disconnections



The disconnections we have made so far have all been of C–O, C–N, or C–S bonds, but, of course, the most important reactions in organic synthesis are those that form C–C bonds. We can analyse C–C disconnections in much the same way as we've analysed C–X disconnections. Consider, for example, how you might make this simple compound, which is an intermediate in the synthesis of a carnation perfume.

The only functional group is the triple bond, and we shall want to use the chemistry of alkynes to show us where to disconnect. You know that alkylation of alkynes is a reliable reaction, so a sensible disconnection is next to the triple bond.

carnation perfume intermediate: retrosynthetic analysis



carnation perfume intermediate: synthesis

Alkynes are particularly valuable as synthetic intermediates because they can be reduced either to *cis* or to *trans* double bonds.

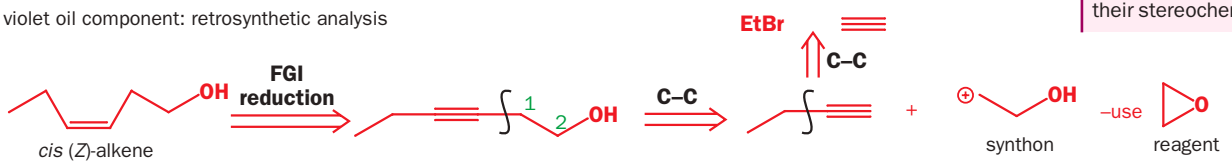
■ You met these reductions in Chapter 24, and we will talk about them again in the context of double bond synthesis in Chapter 31.

It's often a good idea to start retrosynthetic analysis of target molecules containing isolated double bonds by considering FGI to the alkyne because C–C disconnections can then become quite easy.

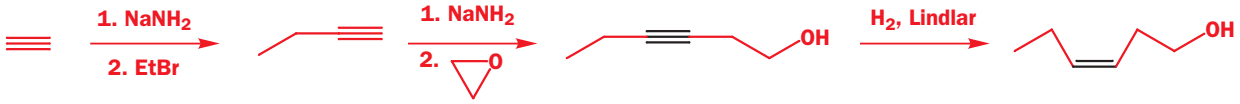
This *cis*-alkene is a component of violet oil, and is an intermediate in the synthesis of a violet oil component. FGI to the alkyne reveals two further disconnections that make use of alkyne alkylations. The reagent we need for the first of these is, of course, the epoxide as there is a 1,2-relationship between the OH group and the alkyne.

▶ There are, of course, many other ways of disconnecting double bonds: you are about to meet an important disconnection of double bonds conjugated with carbonyl groups. Chapter 31 is devoted to the alternative methods available for making double bonds and controlling their stereochemistry.

violet oil component: retrosynthetic analysis

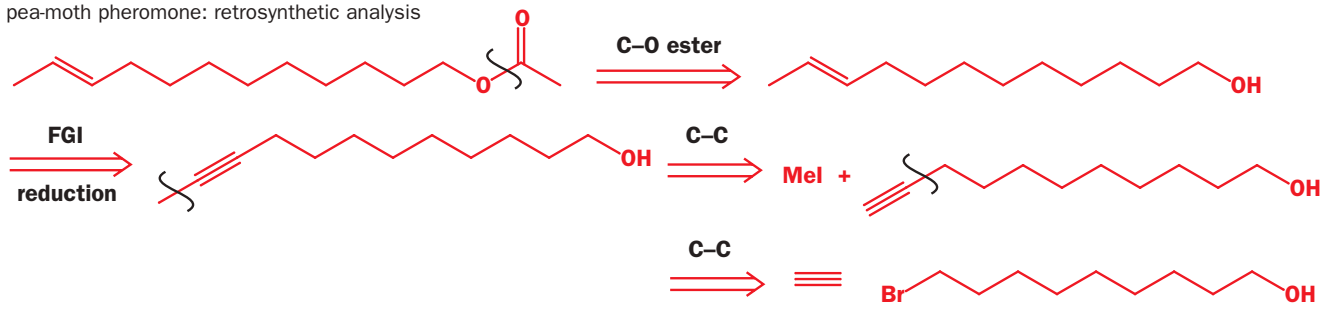


violet oil component: synthesis



The next example is the pheromone of the pea-moth, and can be used to trap the insects (see the introduction to Chapter 24). After disconnecting the ester, FGI on the *trans* double bond gives an alkyne.

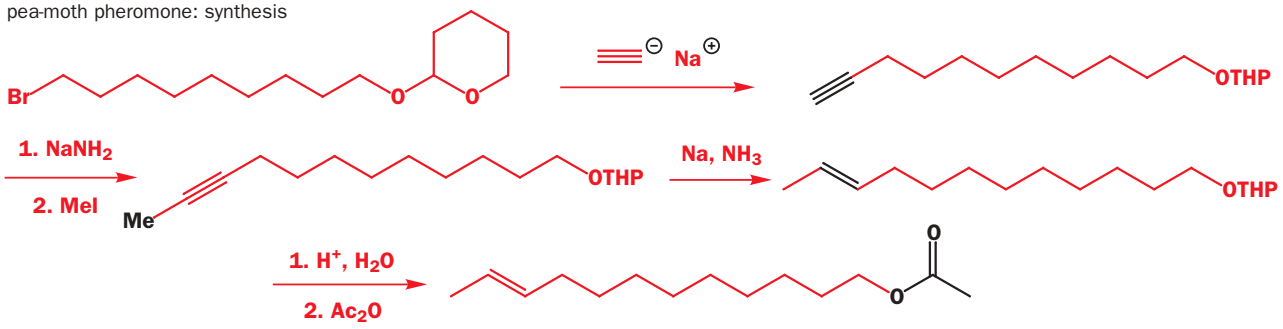
pea-moth pheromone: retrosynthetic analysis



Disconnection on either side of the alkyne leads us back to a bromo-alcohol alkylating agent. In the synthesis of the pheromone, it turned out to be best if the hydroxyl group was protected as its THP ether. You should be able to think of other alkylation-type reactions that you have met that proceed reliably and therefore provide a good basis for a disconnection—the alkylation of enolates of esters or ketones, for example (Chapter 26).

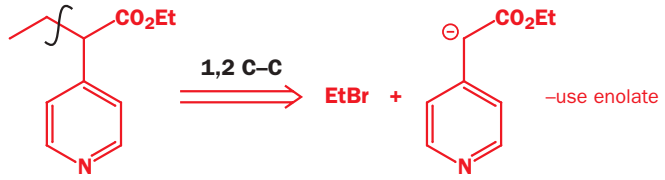
■ Protecting groups were discussed in detail in Chapter 24.

pea-moth pheromone: synthesis

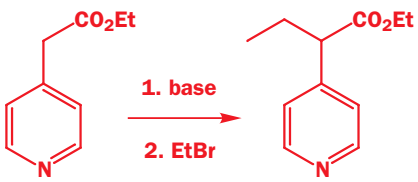


This next ester was needed for a synthesis of the sedative rogletimide (see later for the full synthesis). The ethyl group is disconnected because it can be readily introduced by alkylation of the ester enolate.

rogletimide intermediate: retrosynthetic analysis



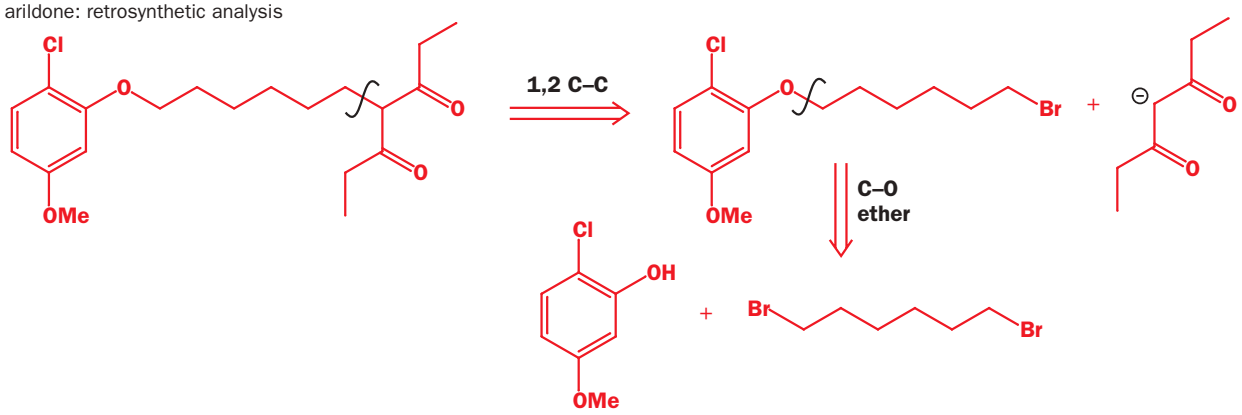
rogletimide intermediate: synthesis



We have labelled the disconnection '1,2 C–C' because the new C–C bond is forming two atoms away from the carbonyl group. To spot disconnections of this sort, you need to look for alkyl groups in this 2-position.

Arildone is a drug that prevents polio and herpes simplex viruses from 'unwrapping' their DNA, and renders them harmless. It has just the structural characteristic you should be looking for: a branch next to a carbonyl group.

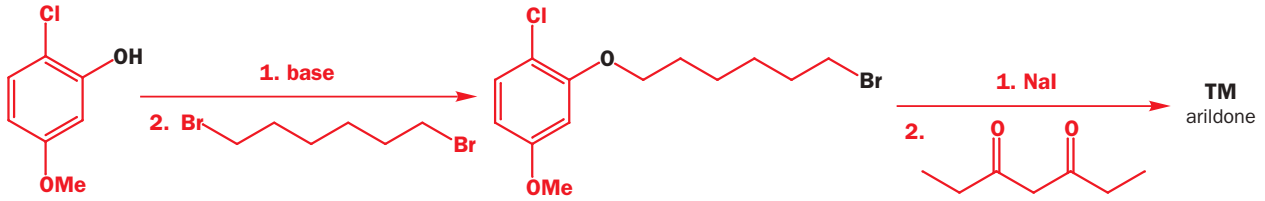
arildone: retrosynthetic analysis



■ Look back to Chapter 26 if you don't understand why.

With two carbonyl groups, the alkylation should be particularly straightforward since we can use a base like methoxide. The ether disconnection is then immediately obvious. In the synthesis of arildone the alkyl iodide was used for the alkylation.

arildone: synthesis

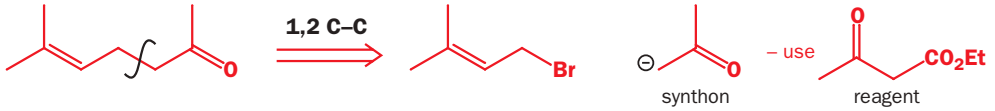


We introduced the chemistry of malonate esters in Chapters 21 and 26 as a useful way of controlling the enolization of carbonyl compounds. Alkylation followed by decarboxylation means that we can treat acetoacetate and malonate esters as equivalent for these synthons.

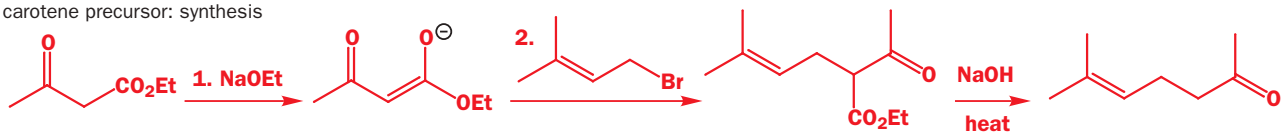
This unsaturated ketone is an important industrial precursor to β-carotene, vitamin A, and other similar molecules. Disconnection using the carbonyl group gives a synthon for which a good reagent will be acetoacetate.

▶ Having read Chapter 27, you should be able to suggest why the enolate of acetone itself would not be a good choice in this reaction.

carotene precursor: retrosynthetic analysis

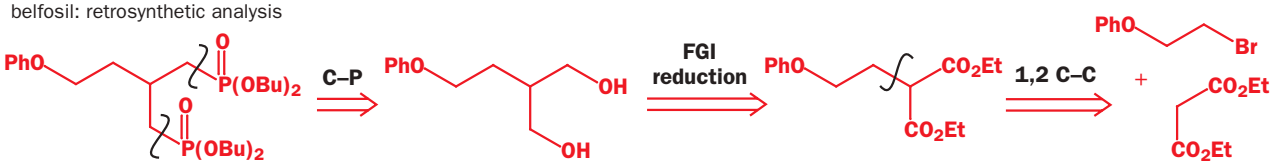


carotene precursor: synthesis



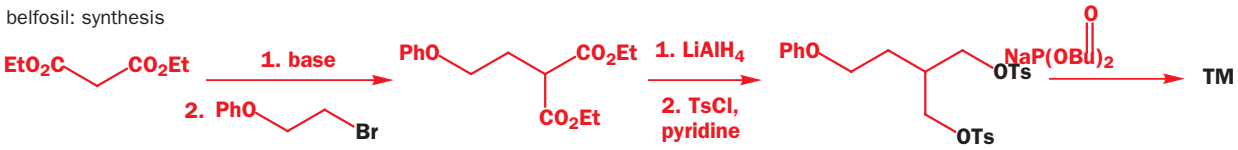
This organophosphorus compound, belfosil, is a Ca^{2+} channel blocker. You haven't met many phosphorus compounds yet, but you should be able to reason that a good disconnection will be the C–P bond by analogy with the sulfides you met earlier in the chapter. We could use bromide as a leaving group, but alkyl bromides are inconvenient to disconnect further, so we go back to the more versatile diol—in the forward synthesis we shall need a way of making the OH groups into good leaving groups. There is still no obvious disconnection of the diol, but FGI to the ester oxidation level reveals a malonate derivative.

belfosil: retrosynthetic analysis



In the synthesis, the diol was converted to the bis-tosylate (see Chapter 17 if you've forgotten about tosylates and mesylates) and reacted with a phosphorus nucleophile.

belfosil: synthesis



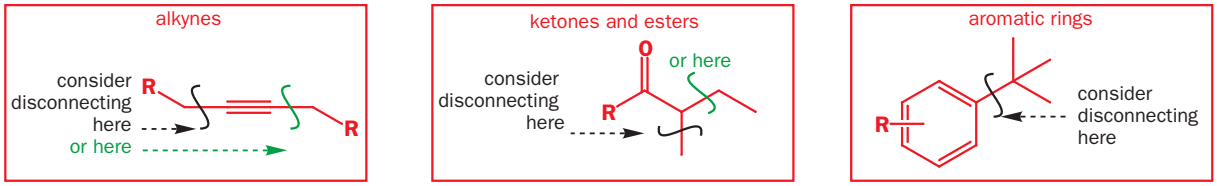
Notice how we disconnected the phosphorus-based functional groups straight back to alcohols in the retrosynthetic analysis, and not, say, to alkyl halides. Oxygen-based functional groups (alcohols, aldehydes, ketones, esters, and acids) have one important property in common—versatility. They are easily converted into each other by oxidation and reduction, and into other groups by substitution. What is more, many of the C–C disconnections you will meet correspond to reactions of oxygen-based groups, and particularly carbonyl groups. Faced with an unusual functional group in a target molecule the best thing to do is convert it to an oxygen-based group at the same oxidation level—it usually makes subsequent C–C disconnections simpler. So we add a new guideline.

● Guideline 5

Convert to oxygen-based functional groups to facilitate C–C disconnections

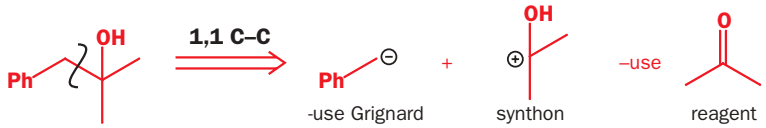
Looking for 1,2 C–C disconnections

In each of the cases you have met so far, we have used a functional group present in the molecule to help us to disconnect the C–C bond using a 1,2 C–C disconnection. You can look for 1,2 C–C disconnections in alkynes, carbonyl compounds, and alkylated aromatic rings. And, if the target isn't a carbonyl compound, consider what would be possible if functional groups such as hydroxyl groups were converted to carbonyl groups (just as we did with belfosdil).



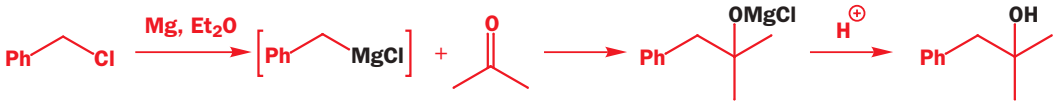
All of these disconnections relied on the reaction of a carbon electrophile with a nucleophilic functional group. The alternative, reaction of a carbon nucleophile (such as a Grignard reagent) with an electrophilic functional group, allows us to do C–C disconnections on alcohols. For example, this compound, which has a fragrance reminiscent of lilac, is a useful perfume for use in soap because (unlike many other perfumes that are aldehydes or ketones) it is stable to alkali.

lilac perfume: retrosynthetic analysis



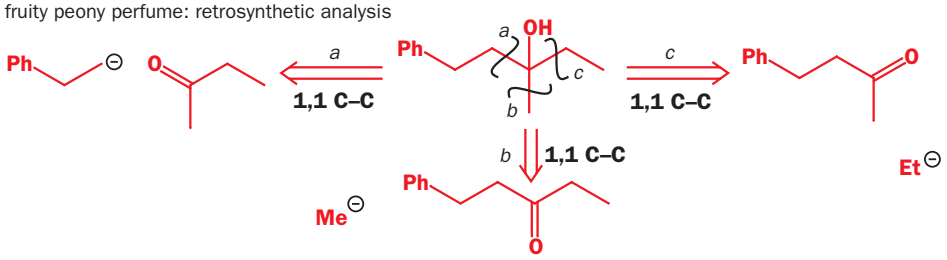
We look to the one functional group, the hydroxyl, to tell us where to disconnect, and disconnection next to the OH group gives two synthons for which sensible reagents are a Grignard reagent and acetone. The perfume is made from benzyl chloride and acetone in this way. Notice that we label these disconnections 1,1 C–C because the bond being disconnected is attached to the same carbon atom as the hydroxyl functional group.

lilac perfume: synthesis



This similar alcohol has a 'peony-like fruity odour' and could be disconnected in three ways.

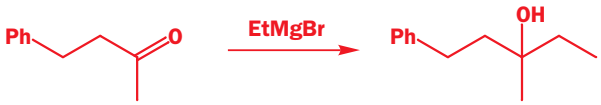
fruity peony perfume: retrosynthetic analysis



■ The synthesis of this starting material involves an aldol reaction between acetone and benzaldehyde of the sort discussed in Chapter 27 followed by hydrogenation of the double bond.

Disconnection (*c*) leads back to a ketone, which is cheaply made starting from acetone and benzaldehyde, and this was the route that was chosen for the synthesis.

fruity peony perfume: synthesis



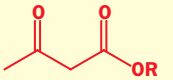
Available starting materials

Although any of the three routes to the fruity peony perfume would give an acceptable synthesis, the key factor in choosing route (*c*) was the ease of synthesis of the starting materials from available compounds. But how can you know which materials will be available? So far in this chapter we have avoided this question, and often our retrosynthetic analyses have been incomplete because the suggested starting materials must themselves be synthesized in the laboratory. From now on, though, we will take every analysis back to available starting materials to help you get a feel for what is, and is not, available.

The only way to be absolutely sure what you can buy is to look up a compound in a supplier's catalogue, and this is what a chemist would do when assessing possible alternative synthetic routes. A good rule of thumb is that **compounds with up to about six carbon atoms and with *one* functional group** (alcohol, aldehyde, ketone, acid, amine, double bond, or alkyl halide) **are usually available.** This is less true for heavily branched compounds, but most straight-chain compounds with these functional groups are available up to eight or more carbon atoms. Cyclic compounds with one functional group from five- to eight-membered are also available. Of course, many other compounds are available too, including some difunctional compounds. Here are a few of them.

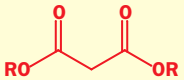
You will soon start to appreciate what is available as you see which compounds we use as starting materials. Supplier's catalogues are available free for the asking and make quite useful textbooks. You could consider getting one. In addition, on-line and CD catalogues are available in most chemistry departments and can be searched by structure.

acetoacetates



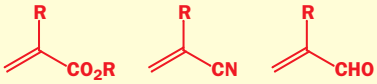
R = H, Me, Et

malonates

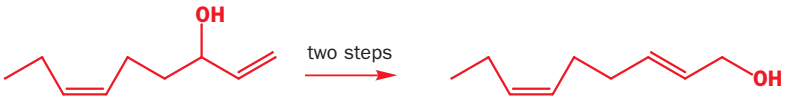


R = H, Me, Et

acrylates (R = H); methacrylates (R = Me)



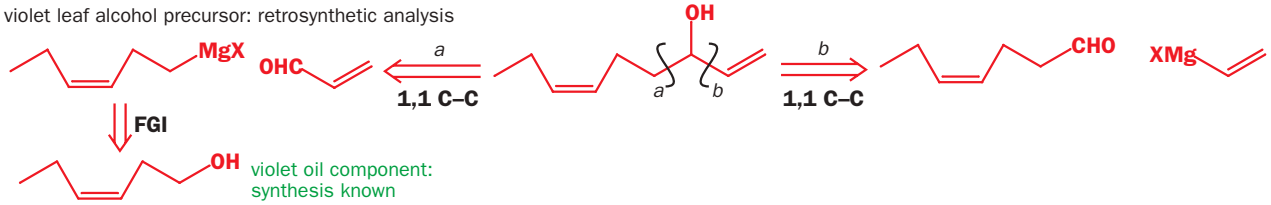
Some starting materials become available because other chemists have made them



violet leaf alcohol precursor — violet leaf alcohol

Our next target is an allylic alcohol that produces the perfumery compound 'violet leaf alcohol' by a rearrangement step . Two disconnections are possible, but one of them, (*a*), leads back to a Grignard reagent that can be made by FGI on the violet oil component whose synthesis we described on p. 000.

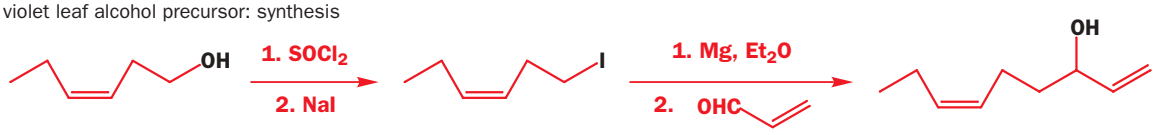
violet leaf alcohol precursor: retrosynthetic analysis



violet oil component: synthesis known

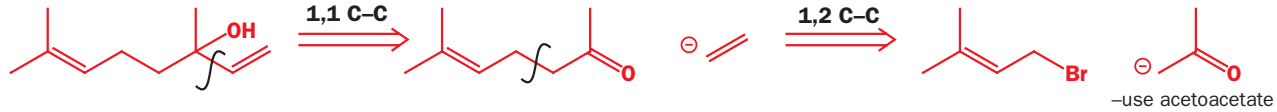
The synthesis was best carried out using the alkylmagnesium iodide and the iodide was made from the alcohol via the chloride.

violet leaf alcohol precursor: synthesis



Linalool is another perfumery compound. Disconnection of the vinyl group leads to the ketone you met on p. 000, best made by alkylation of acetoacetate, an acetone enolate equivalent.

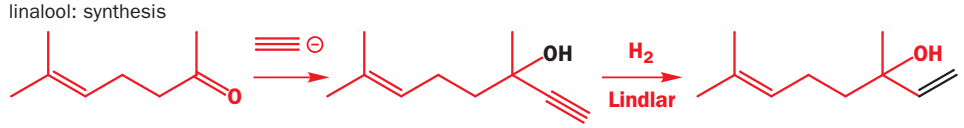
linalool: retrosynthetic analysis



–use acetoacetate

On an industrial scale it was best to introduce the vinyl anion synthon as acetylene and then hydrogenate the alkyne. The unsaturated ketone was chosen as the starting material because its synthesis was already known.

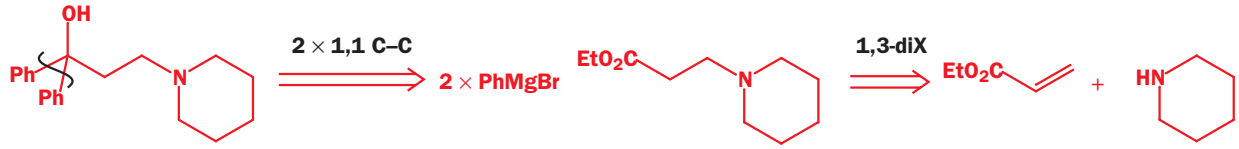
linalool: synthesis



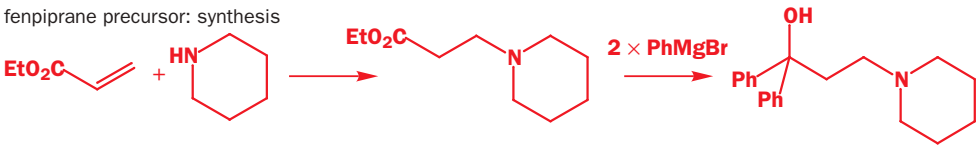
Double disconnections can be a short cut

Tertiary alcohols with two identical groups next to the hydroxyl group are often made by attack of two equivalents of a Grignard reagent on an ester. The synthesis of the antihistamine compound fenpiprane provides an example: the tertiary alcohol is a precursor to the drug and can be disconnected to ester + Grignard reagent because of the two Ph groups. The ester required has a 1,3 functional group relationship, and can be disconnected to amine plus Michael acceptor.

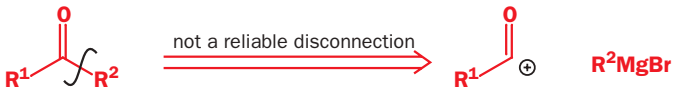
fenpiprane precursor: retrosynthetic analysis



fenpiprane precursor: synthesis

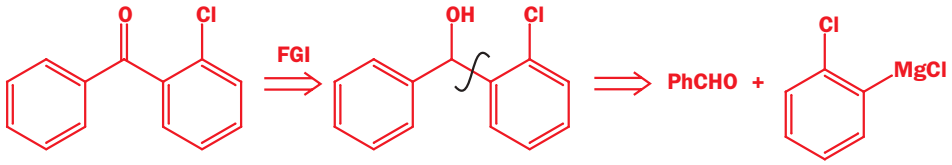


The fact that Grignard reagents add twice to esters means that disconnection of a *ketone* in this way is often not reliable. We talked about a few ways of doing this type of reaction in Chapter 12.

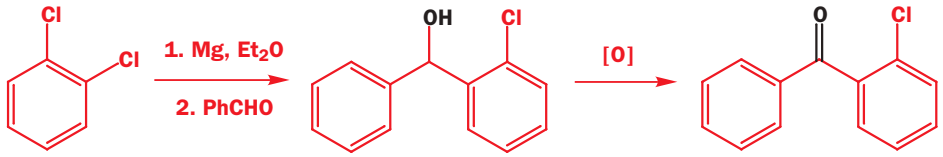


An alternative is to first convert to the alcohol oxidation level, then disconnect. This was the method chosen for this starting material for the synthesis of chlorphedianol.

chlorphedianol starting material: retrosynthetic analysis

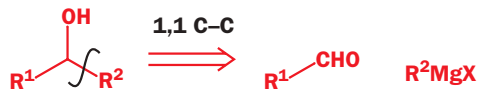


chlorphedianol starting material: synthesis

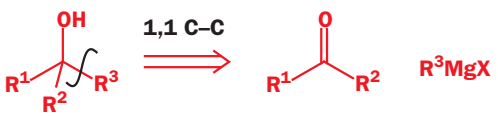


Summary: 1,1 disconnections using Grignard reagents

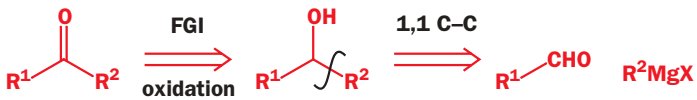
secondary alcohols



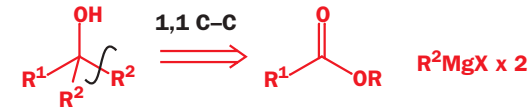
tertiary alcohols



ketones



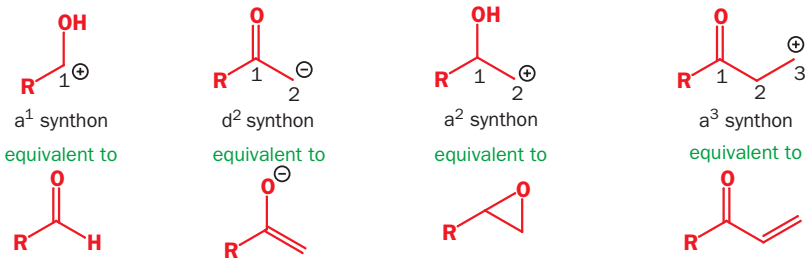
tertiary alcohols with $R^2 = R^3$



Donor and acceptor synthons

You've now met a variety of synthons and it's useful to be able to classify them as donor or acceptor synthons. We call a negatively polarized synthon a **donor synthon** and give it the symbol 'd'. Positively polarized synthons are called **acceptor synthons** and are given the symbol 'a'.

We can classify the synthons further according to where the functional group is in relation to the reactive site. The first synthon in the diagram below, which corresponds to an aldehyde, we call an **a^1 synthon**, because it is an acceptor that carries a functional group on the same carbon as its reactive centre. The second is a **d^2 synthon** because it is a donor whose reacting site is in the 2-position relative to the carbonyl group. Earlier you met two other types of synthon, corresponding to epoxide and Michael acceptor, and we can now classify these as **a^2** and **a^3 synthons**.



This terminology is useful because it reduces synthons to the bare essentials: what polarity they are and where the polarity is sited. The actual functional group they carry is, as you now appreciate, less important because FGI will usually allow us to turn one FG into another.

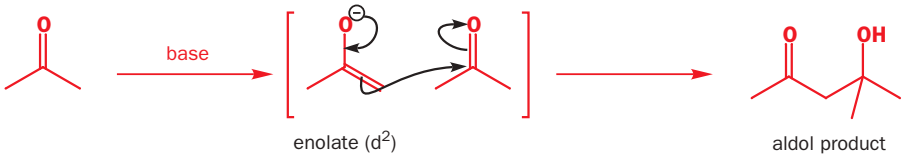
Synthons are classified as a (acceptor) or d (donor)

- A number shows the position of the acceptor or donor site relative to a functional group
- An a^1 synthon is a carbonyl compound and a d^2 synthon an enolate

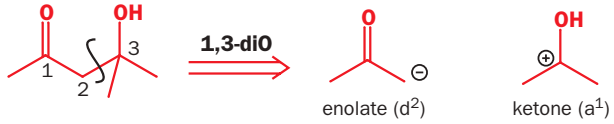
Two-group C–C disconnections

1,3-Difunctionalized compounds

It's not only Grignard reagents that will react with aldehydes or ketones to make alcohols: enolates will too—we spent Chapters 27 and 28 discussing this reaction, the aldol reaction, its variants, and ways to control it.

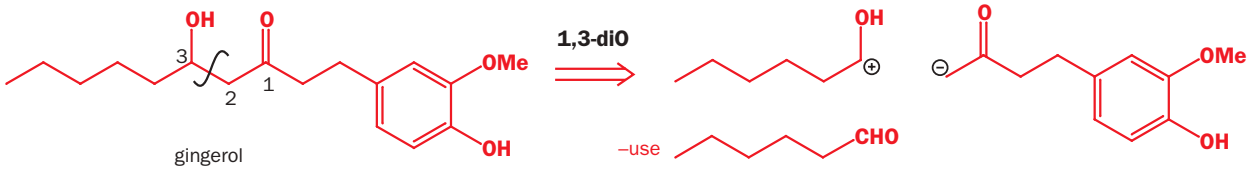


The aldol reaction is extremely important in organic synthesis because it makes compounds with two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule—think aldol! In disconnection terms we can represent it like this.



We call this disconnection a **two-group C–C disconnection**, because we are using the OH and the C=O groups together to guide our disconnection. The disconnection gives us a d^2 synthon for which we shall use an enolate equivalent, and an a^1 synthon, for which we shall use an aldehyde or a ketone.

Chapter 27 has many examples and perhaps gingerol is the best. As soon as you see the 1,3-relationship, the disconnection should be obvious.

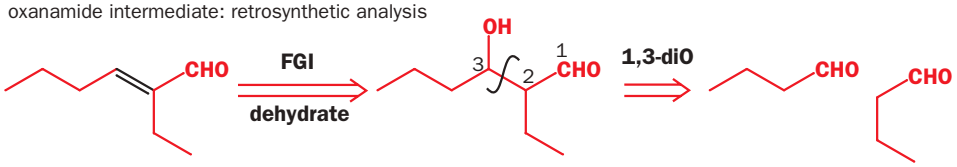


gingerol

■ The elimination is easy because it goes by an E1cB mechanism—see Chapter 18.

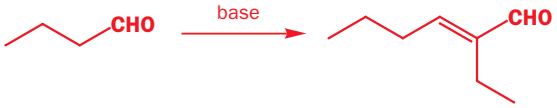
The β-hydroxy carbonyl products of aldol reactions are often very easily dehydrated to give α,β-unsaturated carbonyl compounds and, if you spot an α,β-unsaturated carbonyl group in the molecule, you should aim to make it by an aldol reaction. You will first need to do an FGI to the β-hydroxy carbonyl compound, then disconnect as before.

oxanamide intermediate: retrosynthetic analysis



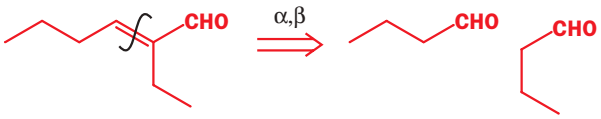
This aldehyde is an intermediate in the synthesis of the tranquillizer oxanamide. Because both components of the aldol reaction are the same, no special precautions need to be taken to prevent side-reactions occurring. In the synthesis, the dehydration happened spontaneously.

oxanamide intermediate: synthesis



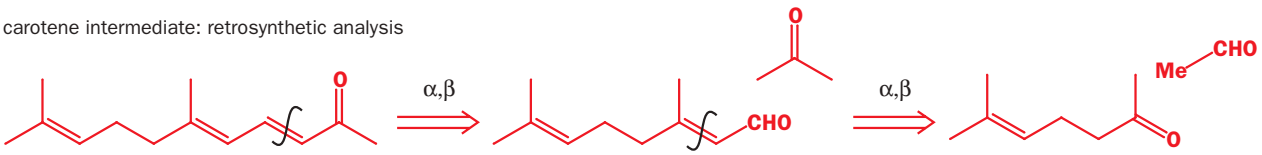
Because this disconnection of unsaturated carbonyl compounds is so common, it's often written using a shorthand expression.

oxanamide intermediate: retrosynthetic analysis



The next compound was needed for an early synthesis of carotene. Again, it's an α,β-unsaturated ketone so we can disconnect using the same 'α,β' disconnection.

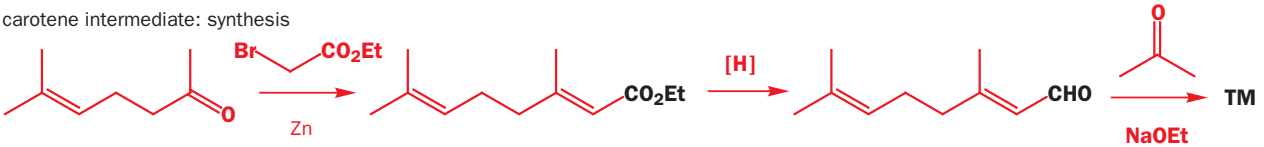
carotene intermediate: retrosynthetic analysis



The aldehyde generated by this first disconnection is also α,β-unsaturated, so we can do another α,β disconnection, back to a ketone whose synthesis we have already discussed (p. 000).

An aldol reaction using the enolate of acetaldehyde and requiring it to react with a ketone is doomed to failure: acetaldehyde itself is far too good an electrophile. In the forward synthesis, therefore, this first step was carried out at the ester oxidation level (using a Reformatsky reaction), and the ester was subsequently converted to the aldehyde by a reduction of the kind discussed in Chapter 24.

carotene intermediate: synthesis



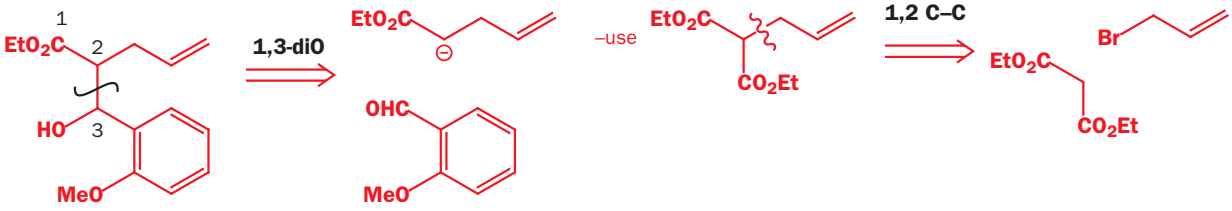
There was no problem with selectivity in the second aldol reaction because the aldehyde is not enolizable. The Reformatsky reaction in this sequence illustrates the fact that, of course, aldol-type

reactions happen at the ester oxidation level as well, and you should equally look to disconnect β-hydroxy or α,β-unsaturated esters, acids, or nitriles in this way. Just remember to look for 1,3-relationships, convert the functional groups to oxygen-based ones, and disconnect them to d^2 plus a^1 synthons.

■ If you don't understand what we are saying here, you must go back and read Chapter 27 on selectivity in the aldol reaction.

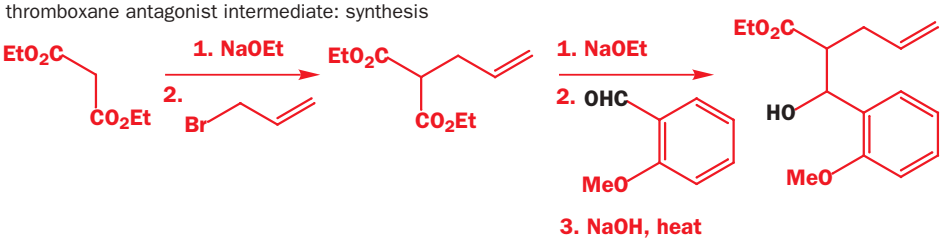
The next compound was needed by ICI when chemists there were developing a thromboxane antagonist to inhibit blood clot formation. You can immediately spot the 1,3-relationship between the ester and the hydroxyl group, so 1,3-diO disconnection is called for.

thromboxane antagonist intermediate: retrosynthetic analysis



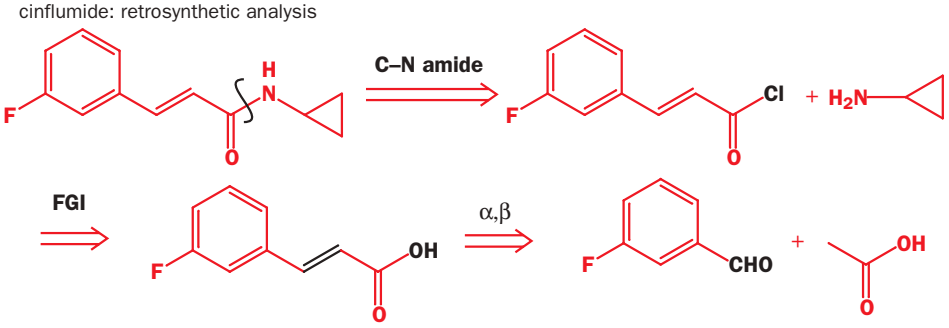
A good equivalent for the 'ester enolate' d^2 synthon is a β-dicarbonyl compound, because it can easily be disconnected to diethyl malonate and an alkylating agent.

thromboxane antagonist intermediate: synthesis



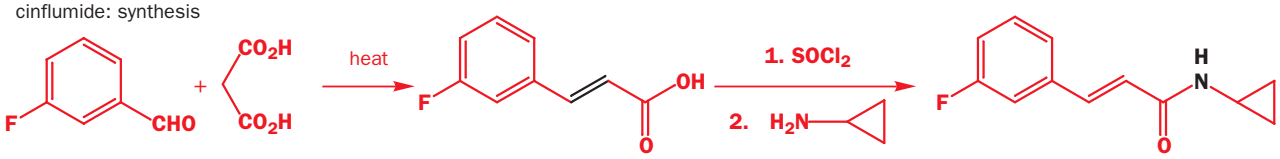
This unsaturated amide is known as cinflumide and is a muscle relaxant. Disconnection of the amide gives an acid chloride that we can make by FGI from the acid. You should then spot the α,β-unsaturated carbonyl disconnection, a masked 1,3-diO disconnection, back to *m*-fluorobenzaldehyde.

cinflumide: retrosynthetic analysis



Again, the forward reaction was best done using malonate chemistry but the variant with malonic acid was used. The cyclopropyl amine unit (here as an amide) is present in many biologically active compounds and the free amine is available.

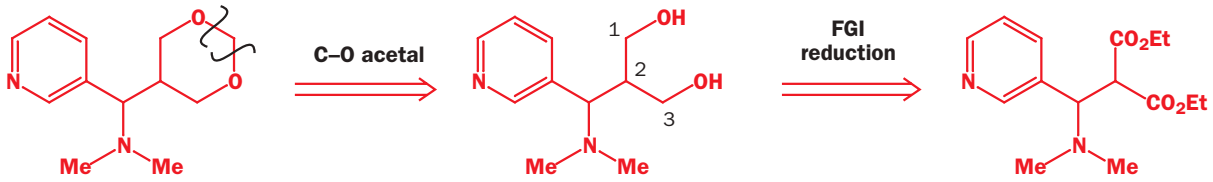
cinflumide: synthesis



Functional group relationships may be concealed by protection

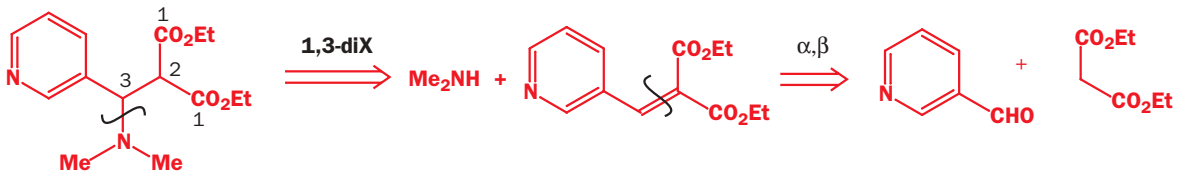
The analgesic doxpicomine is a more difficult problem than those you have seen so far. At first sight it has no useful disconnections especially as there are no carbonyl groups. However, removal of the acetal reveals a 1,3-diol that could be formed by reduction of a much more promising diester.

doxpicomine: retrosynthetic analysis I



The diester has a 1,3-diCO relationship and could be disconnected but we have in mind using malonate so we would rather disconnect the alternative 3-amino carbonyl compound (the Me_2N group has a 1,3-relationship with both ester groups) by a 1,3-diX disconnection giving an unsaturated ester. This α,β-unsaturated ester disconnects nicely to a heterocyclic aldehyde and diethyl malonate.

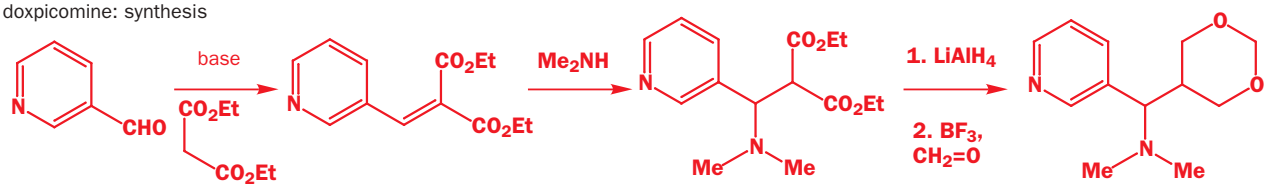
doxpicomine: retrosynthetic analysis II



▶ It is interesting to note that acetals, usually employed for protection, can be useful in their own right as in this drug.

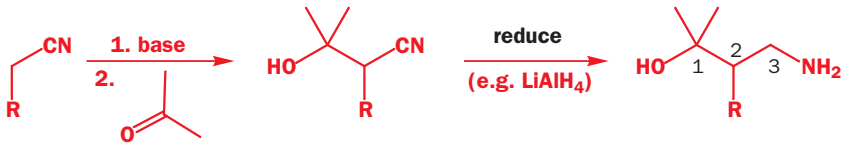
The synthesis is shorter than the retrosynthetic analysis and involves only three steps. Good retrosynthetic analysis, using two-group disconnections, should lead to short syntheses.

doxpicomine: synthesis

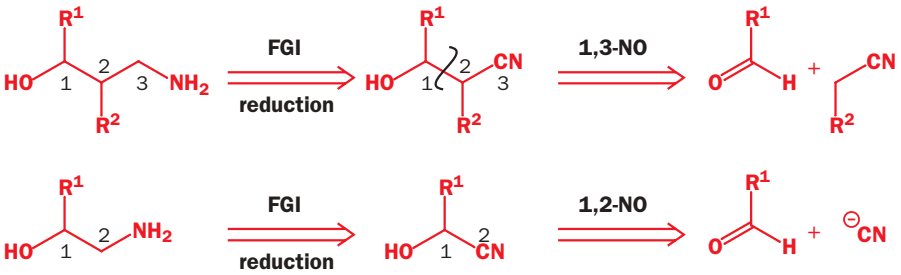


Aldol-style disconnections with N and O in a 1,3-relationship: I

Another important class of compounds that undergo aldol-type additions to aldehydes and ketones is nitriles. Because nitriles can be reduced to amines, this reaction provides another useful route to 3-amino-alcohols.



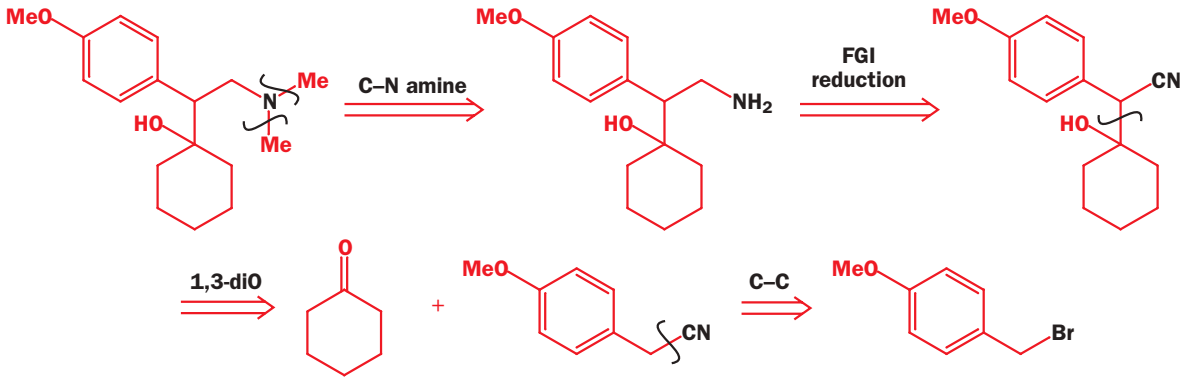
This reaction, coupled with the reduction of cyanohydrins (Chapter 6), means that compounds with either a 1,3- or a 1,2-relationship between N and O can be made from cyanides.



Venlafaxine is an antidepressant and, like many neuroactive agents, it is an amino-alcohol. In this case, the two functional groups are 1,3-related, so we aim to use a 1,3-diO disconnection. Usually,

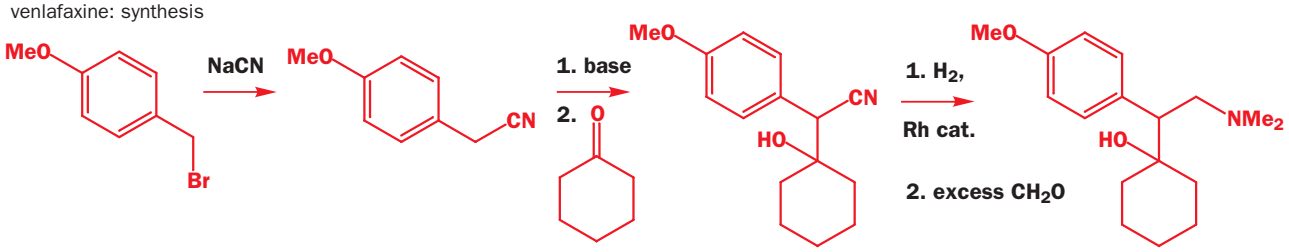
you would convert the amine to an alcohol to simplify the disconnection, but by spotting the opportunity for using a nitrile you can avoid the need for this extra step. A preliminary removal of the two *N*-Me groups is necessary.

venlafaxine: retrosynthetic analysis



In the forward synthesis, it turned out that the nitrile reduction was best done using hydrogen and a metal (Rh) catalyst. The final methylation of the primary amine had to be done via the imine and iminium ion (see Chapter 24) to prevent further unwanted alkylations. The reagent was an excess of formaldehyde (methanal CH_2=O). Problem xx offers a chance to try this mechanism.

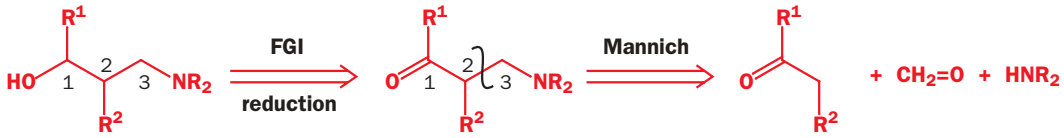
venlafaxine: synthesis



Aldol-style disconnections with N and O in a 1,3-relationship: II—the Mannich reaction

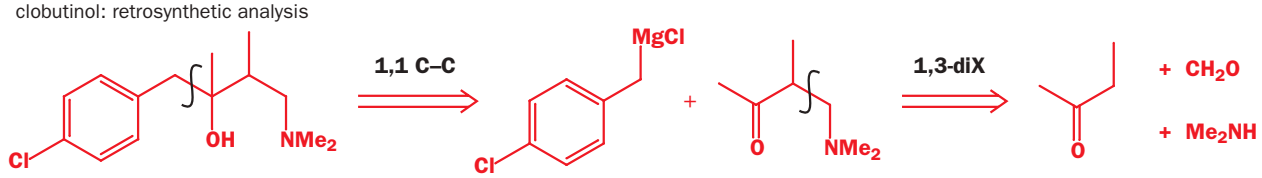
Another important reaction for making amines with a 1,3-relationship to a carbonyl group is the Mannich reaction. You met this in Chapter 27 as a way of doing otherwise unreliable aldol additions to formaldehyde. Because the amine is introduced directly and not by reduction of a nitrile, it can have two alkyl groups from the start. Compare this scheme with the one above using a nitrile group as the source of the amine.

the Mannich disconnection

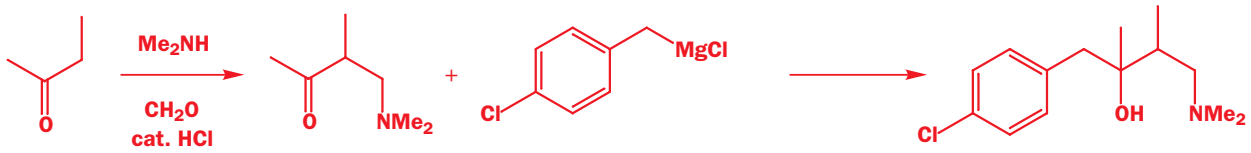


Our example is clobutinol—an antitussive (cough medicine). A preliminary 1,1 C–C disconnection of the tertiary alcohol is necessary to provide a 3-amino ketone that we can make by a Mannich reaction.

clobutinol: retrosynthetic analysis

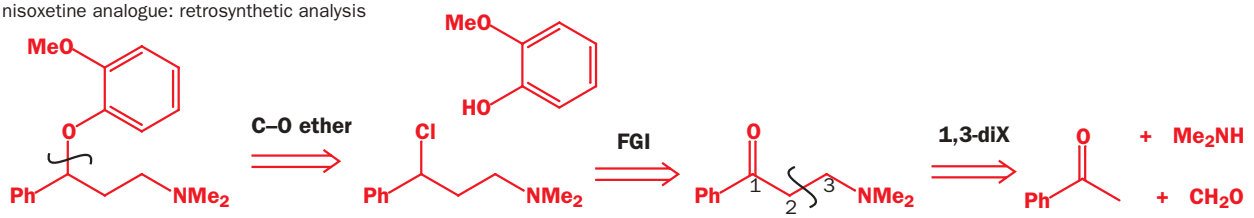


clobutinol: synthesis



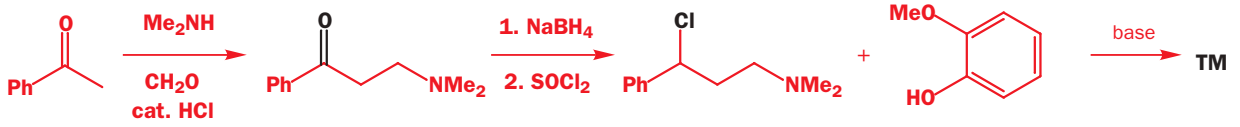
You can immediately spot the 1,3 relationship in this analogue of the antidepressant, nisoxetine, but, unfortunately, it can't be disconnected straight back to an amino-alcohol because that would require nucleophilic substitution on an electron-rich aromatic ring. We have to disconnect the ether on the other side, giving an alkyl chloride.

nisoxetine analogue: retrosynthetic analysis



Using guideline 5 (p. 000) we want to convert the halide to an oxygen-based group, and a sensible solution is to choose the ketone. 1,3-Disconnection of this compound corresponds to a Mannich reaction. This is another case where FGI of the amine to an alcohol is not desirable, because the Mannich reaction will produce the amine directly.

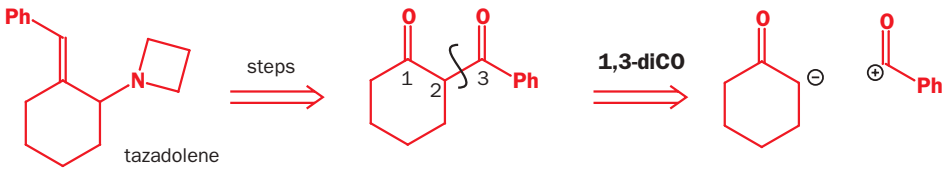
nisoxetine analogue: synthesis



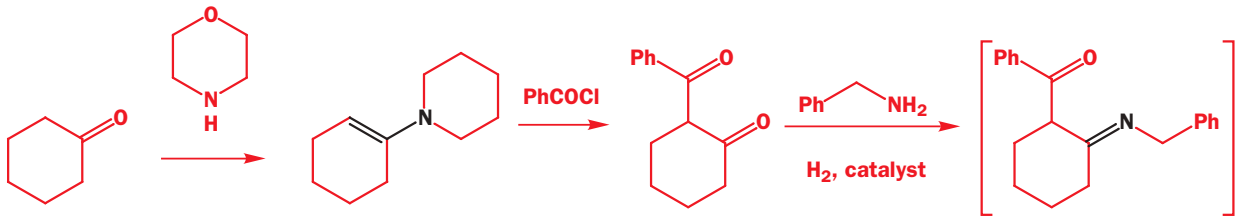
The Claisen ester disconnection: a 1,3-diO relationship needing two carbonyl groups

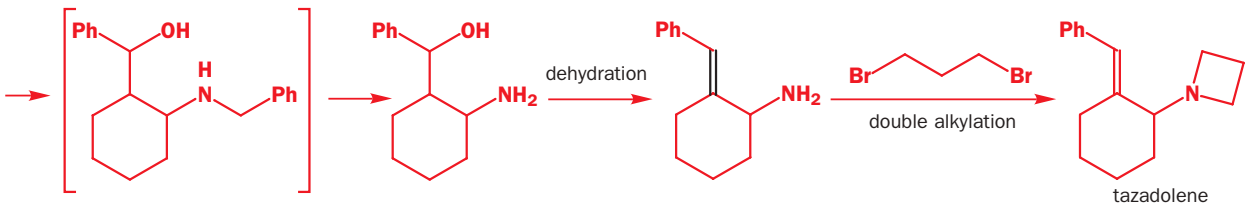
1,3-Diketones can be disconnected in a similar way: this time the disconnection corresponds to a Claisen condensation, but it's still 1,3-diO, and again you need to look out for the 1,3 relationship. The synthons are still d^2 plus a^1 but the a^1 synthon is used at the ester oxidation level. This diketone is the starting material for the synthesis of the antidepressant tazadolene. With 1,3-diketones, there's always a choice where to disconnect, and you should be guided by which disconnection (1) corresponds to the most reliable reaction and (2) gives the simplest starting materials. In this case, it's much better to disconnect back to cyclohexanone.

tazadolene starting material: retrosynthetic analysis



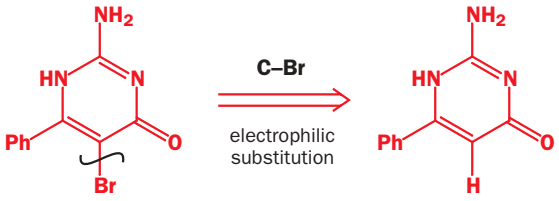
The synthesis is interesting because, after the acylation of the enamine, the amino group is introduced by a clever reductive amination with benzylamine ($PhCH_2NH_2$) that forms the C–N bond, reduces the ketone, and hydrogenolyses the N–benzyl bond (Chapter 24). Dehydration and double alkylation then give tazadolene.





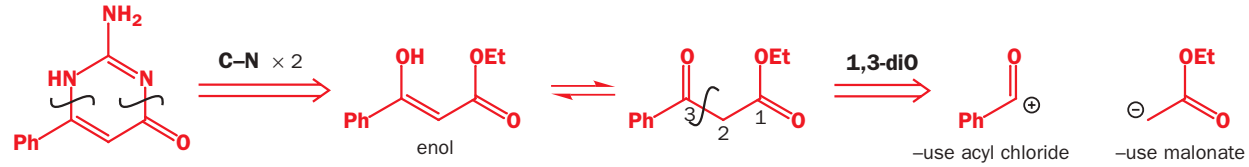
The 1,3-dicarbonyl relationship may not be revealed in the target molecule and C–heteroatom disconnections or FGIs may be needed before the 1,3-diO C–C disconnection. Bropirimine is a bromine-containing antiviral and anticancer drug. The bromine atom can be put in last of all by electrophilic bromination.

bropirimine: retrosynthetic analysis



Disconnection of two C–N bonds removes a molecule of guanidine and reveals a 1,3-dicarbonyl relationship with a straightforward disconnection.

bropirimine: retrosynthetic analysis

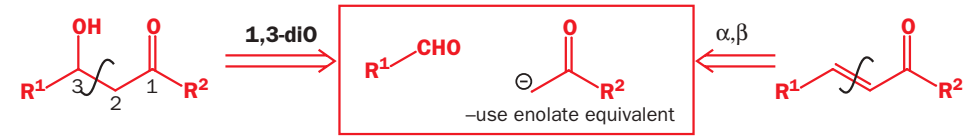


In the event, the 1,3-dicarbonyl was made using malonate chemistry with an unusual twist: the lithium derivative gave *C*-acylation in good yield. Simply refluxing the product with guanidine formed the heterocycle and bromination gave bropirimine.

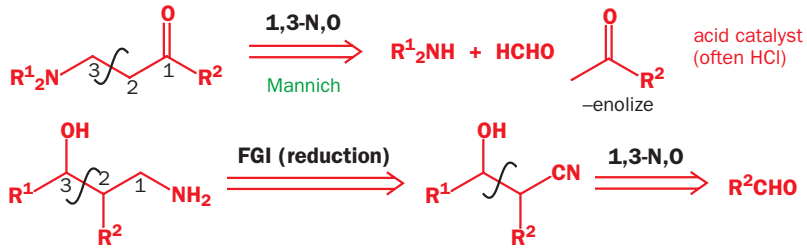
■ Guanidine is the strong delocalized organic base mentioned in Chapter 8.

Summary: 1,3-diO disconnections

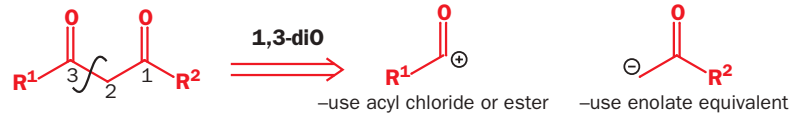
3-hydroxy carbonyls and α,β-unsaturated carbonyls: use the aldol reaction



3-amino ketones and alcohols: use Mannich or nitrile aldol



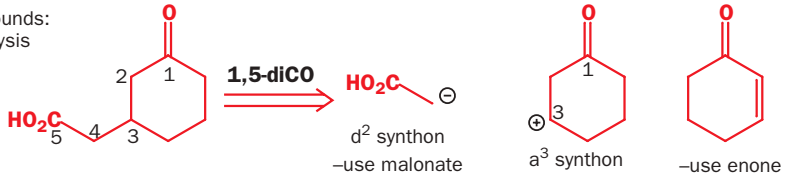
1,3-diketones: use the Claisen condensation



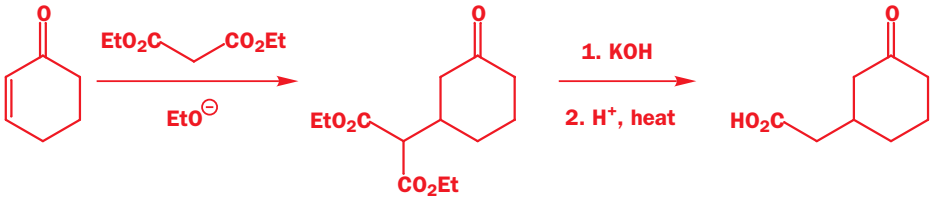
1,5-Related functional groups

This compound has a 1,5 rather than a 1,3 relationship between two carbonyl groups. Disconnection to give an enolate as one reagent therefore requires an a^3 rather than an a^1 synthon: in other words a **Michael acceptor**.

1,5-dicarbonyl compounds: retrosynthetic analysis

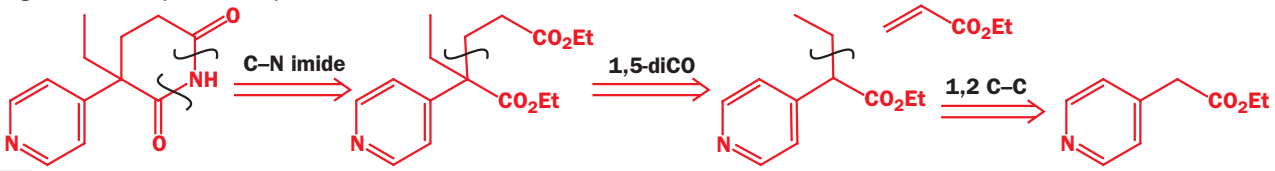


The synthesis will be successful only if (1) the right reagent enolizes and (2) the nucleophile undergoes conjugate (and not direct 1,2-) addition to the unsaturated carbonyl compound (Chapter 29). Malonate derivatives enolize easily *and* do Michael additions and are therefore a good choice for this type of reaction.



Michael addition of enolates to α,β-unsaturated compounds is a good way of making 1,5-difunctionalized compounds, and you should look for these 1,5-§relationships in target molecules with a view to making them in this way. Our example is rogletimide, a sedative that can be disconnected to a 1,5-diester. Further 1,5-diCO disconnection gives a compound we made earlier by ethylation of the ester enolate.

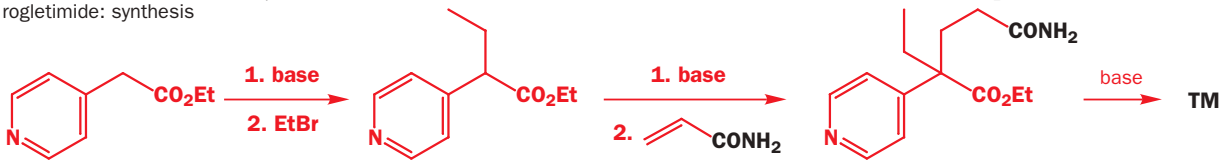
rogletimide: retrosynthetic analysis



■ There are many examples of conjugate addition of enolates in Chapter 29.

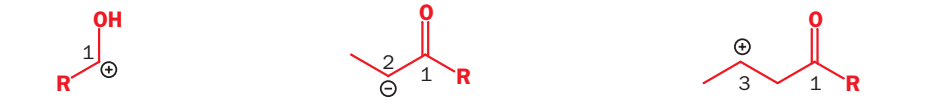
The synthesis was most efficient with an unsaturated amide as Michael acceptor.

rogletimide: synthesis



'Natural reactivity' and 'umpolung'

Cast your mind back over the synthons we have used in these two-group C–C disconnections.



a^1 (equivalent to aldehyde or ketone)

d^2 (equivalent to enolate of ester or ketone)

a^3 (equivalent to α,β-unsaturated carbonyl compounds)

Notice that the acceptor synthons have odd numbers; the donor synthon has an even number: donor and acceptor properties alternate along the chain as we move away from a carbonyl group. This 'natural reactivity' of carbonyl compounds explains why we find it easy to discuss ways of making 1,3- and 1,5-difunctionalized compounds, because they arise from $a^1 + d^2$ and from $a^3 + d^2$. Reagents corresponding to synthons like d^1 or a^2 are rarer, and therefore compounds with 1,2- or 1,4- related functional groups require special consideration retrosynthetically.

You have in fact met one example of each of the 'unnatural' synthons with a^2 and d^1 reactivity. Such synthons are given the German name *Umpolung*, meaning 'inverse polarity' because their natural reactivity is reversed, and **umpolung reagents** are the key to the synthesis of 1,2- and 1,4-difunctionalized compounds.

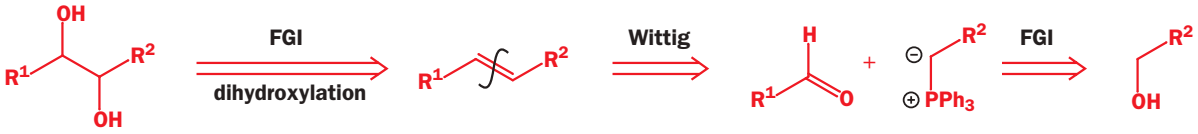
two umpolung reagents

d^1 synthon (cyanide anion) a^2 synthon (equivalent to epoxide)

We shall finish this chapter by looking at disconnections of 1,2- and 1,4-difunctionalized compounds because these require us to use reagents with umpolung equivalent to d^1, d^3, a^2, and a^4 synthons. There are very many reagents for these synthons—if you are interested to learn more, consult a specialized book.

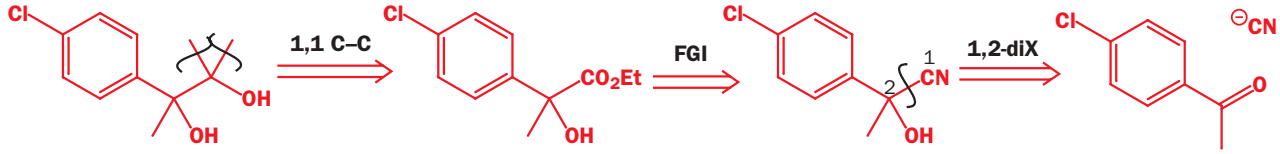
1,2-Difunctional compounds

You met ways of making 1,2-difunctionalized compounds when we first talked about two-group disconnections, and we used an epoxide as an a^2 synthon. Epoxides are, of course, also 1,2-functionalized, and in fact this is often the key to making 1,2-functionalized compounds: use something with the 1,2 relationship already in place. You saw lots of examples of this type of strategy earlier in this chapter. Perhaps the simplest approach is electrophilic addition to alkenes. If the alkene is made by a Wittig reaction, the disconnection is (eventually) between the two functionalized carbon atoms in the target molecule. This example shows dihydroxylation as the electrophilic addition but there is also epoxidation, bromination, and bromination in water to give Br and OH as the functional groups.



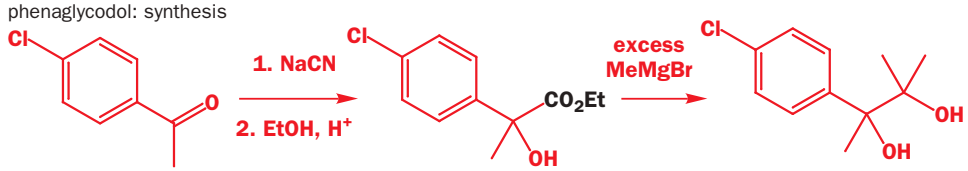
A normal C–C disconnection is also a possibility, but disconnection to the 'natural' a^1 synthon and the umpolung d^1 is necessary. One very useful umpolung reagent is cyanide, and you can see it in action in this synthesis of the tranquillizer phenaglycodol. The tertiary alcohol with two R groups the same should prompt you to think of doing a double Grignard addition to an ester. FGI then reveals the nitrile functional group necessary for a 1,2-diX disconnection to cyanide plus ketone.

phenaglycodol: retrosynthetic analysis



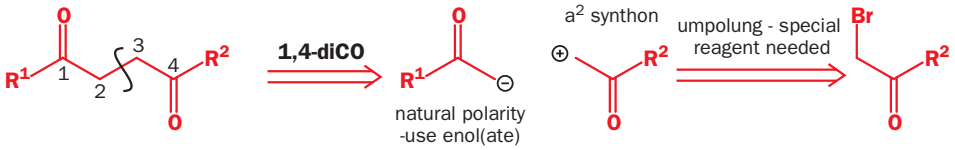
The starting material is obviously available by a Friedel–Crafts acylation of chlorobenzene and the rest of the synthesis follows. Note that the nitrile can be converted directly into the ester with acidic ethanol and that an excess of Grignard reagent is needed because the free OH group destroys some of it.

phenaglycodol: synthesis

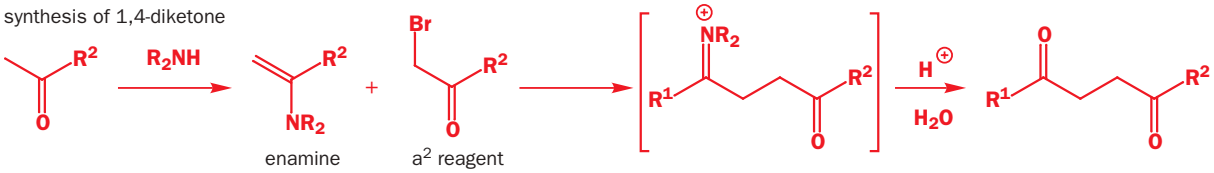


1,4-Difunctional compounds

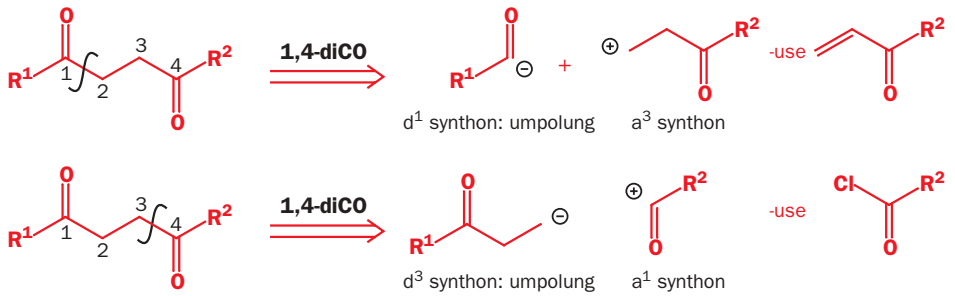
There are more possibilities here and we shall finish this chapter with a brief analysis of them to show you how much of this subject lies beyond what we can do in this book. If we start with a 1,4-dicarbonyl compound we might consider first disconnection of the central bond.



We can use an enolate for one reagent but the other will have to have umpolung. This is not a very serious kind of umpolung as an α-bromo carbonyl compound will do the job nicely if we select our enol(ate) equivalent carefully. In Chapter 26 we suggested enamines for this job. The synthesis becomes:

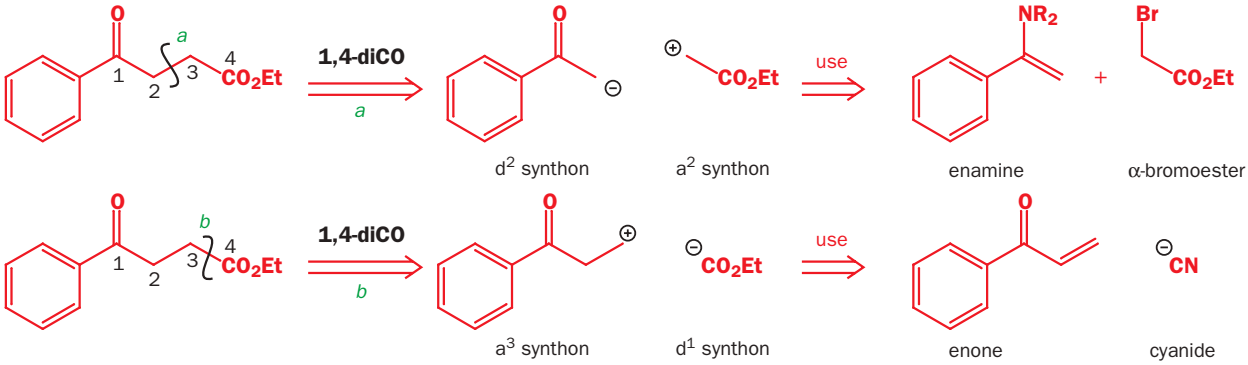


If we attempt the disconnection of one of the other bonds, two possibilities are available because the two fragments are different. We can use either a $d^1 + a^3$ strategy or an $a^1 + d^3$ strategy. In each case we have one natural synthon and one with umpolung.



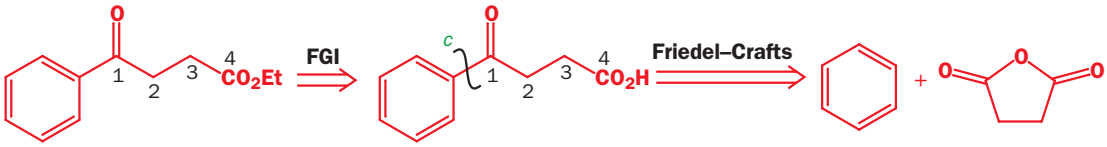
■ Another approach using the nitro group and the Nef reaction appears at the end of Chapter 29.

These strategies are more difficult to realize with the reagents you have met so far but conjugate addition of a cyanide to an unsaturated carbonyl compound would be an example of the $d^1 + a^3$ strategy. We have included these to try to convince you that there is no escape from umpolung in the synthesis of a 1,4-dicarbonyl compound. If you were making this keto-ester you would have to understand two of the three strategies.



There is one way to avoid umpolung and that is to make the disconnection outside the 1,4 relationship. As it happens, we have already seen this strategy in action (p. 000). It involves a Friedel–Crafts acylation of benzene (Chapter 22) with a cyclic anhydride and leads directly to this

product by quite a short route. This strategy is available only if there happens to be a starting material available to suit any particular case.

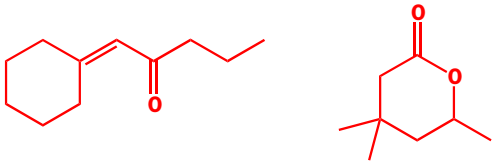


This chapter is meant to give you just the basic ideas of retrosynthetic analysis. They are important because they reinforce the concept that the combination of electrophile and nucleophile is the basis for the understanding of organic reactions. Synthesis and reactions are two sides of the same coin. From now on we shall use the methods introduced in this chapter when we think that they will help you to develop your understanding.

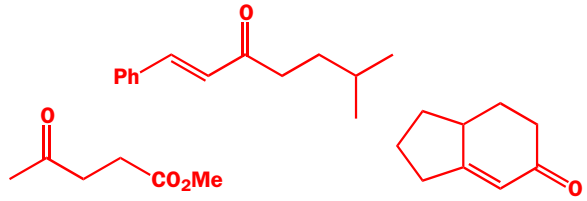
Problems

1. Suggest ways to make these two compounds. Show your disconnections and don't forget to number the relationships.

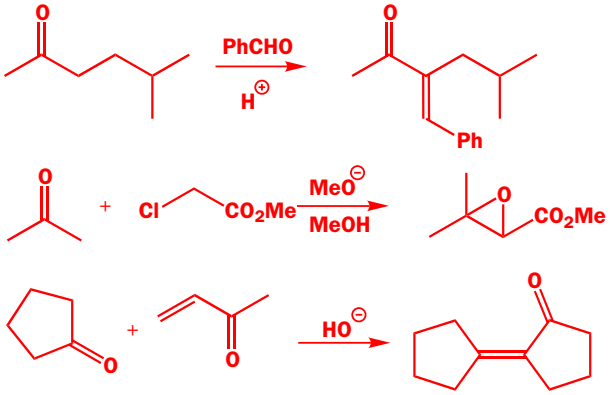
2. Propose syntheses of these two compounds, explaining your choice of reagents and how the necessary selectivity is achieved.



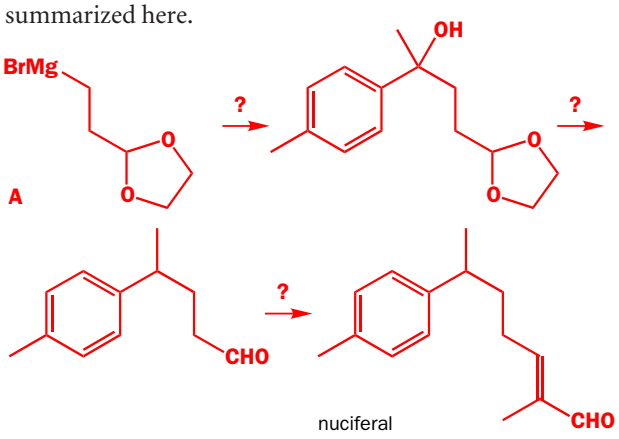
3. The reactions to be discussed in this problem were planned to give syntheses of these three target molecules.



In the event, each reaction gave a different product shown below. What went wrong? Suggest syntheses that would give the target molecules.



4. The natural product nuciferal was synthesized by the route summarized here.



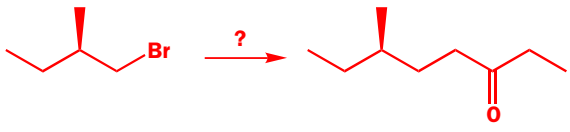
(**a**) Suggest a synthesis of the starting material A.

(**b**) Suggest reagents for each step.

(**c**) Draw out the retrosynthetic analysis giving the disconnections that you consider the planners had in mind and label them suitably.

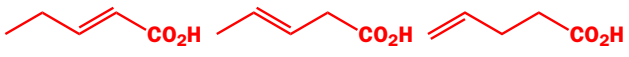
d) What synthon does the starting material A represent?

5. A synthesis of the enantiomerically pure ant pheromone is required. One suitable starting material might be the enantiomerically pure alkyl bromide shown. Suggest a synthesis of the pheromone based on this or another starting material.

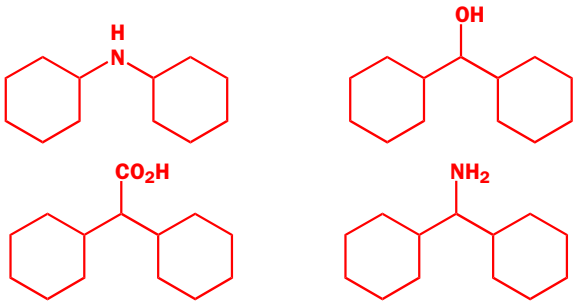


(*S*)-(–)-alkyl bromide (*S*)-(–)-ant pheromone

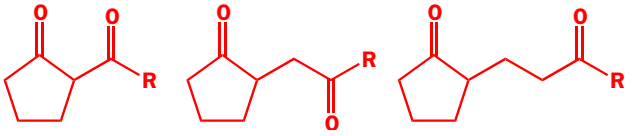
6. Show how the relationship between the alkene and the carboxylic acid influences your suggestions for a synthesis of these unsaturated acids.



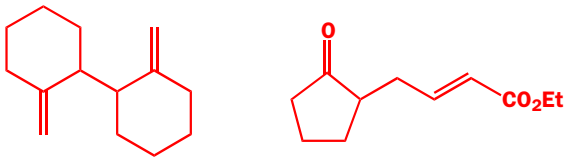
7. How would you make these compounds?



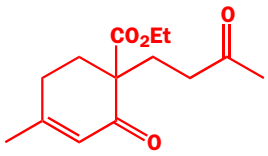
8. Show how the relationship between the two functional groups influences your suggestions for a synthesis of these diketones.



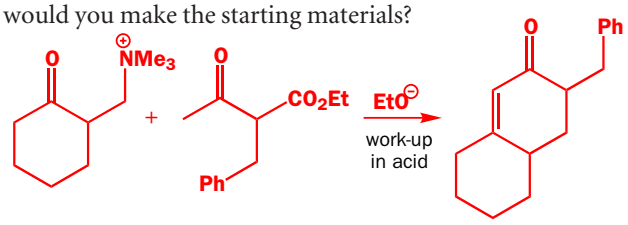
9. Suggest syntheses for these compounds. (*Hint.* Look out for a 1,4-dicarbonyl intermediate.)



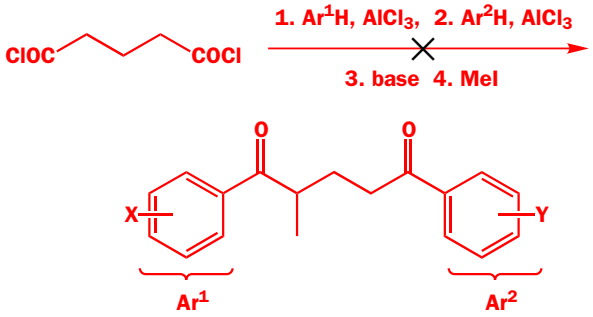
10. Suggest a synthesis of this diketo-ester from simple starting materials.



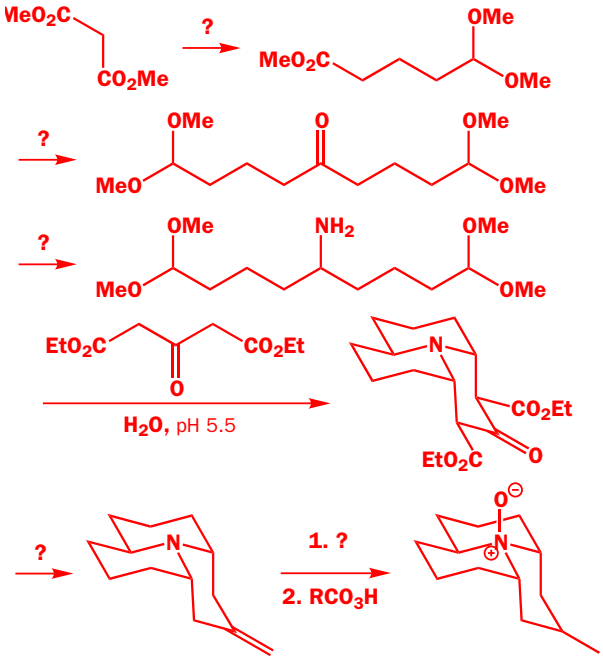
11. Explain what is happening in this reaction. Draw a scheme of retrosynthetic analysis corresponding to the synthesis. How would you make the starting materials?



12. These diketones with different aryl groups at the ends were needed for a photochemical experiment. The compounds could be prepared by successive Friedel–Crafts acylations with a diacid dichloride but the yields were poor. Why is this a bad method? Suggest a better synthesis.



13. This is a synthesis for the ladybird defence compound coccinelline.



Suggest reagents for the reactions marked '?' (several steps may be needed) and give mechanisms for those that are not.

14. Suggest syntheses for these compounds.