Formation and reactions of enols and enolates

21

Connections

Building on:

- Carbonyl chemistry ch6, ch9–ch10, ch12, & ch14
- Electrophilic additions to alkenes ch20

Arriving at:

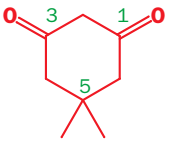
- How carbonyl compounds exist in equilibrium with isomers called enols
- How acid or base promotes the formation of enols and their conjugate bases, enolates
- How enols and enolates have inherent nucleophilic reactivity
- How this reactivity can be exploited to allow the introduction of functional groups next to carbonyl groups
- How silyl enol ethers and lithium enolates can be used as stable enolate equivalents

Looking forward to:

- Aromatic compounds as nucleophiles ch22
- The use of enolates in the construction of C–C bonds ch26–ch29
- The central position of enolate chemistry in the chemist's methods of making molecules ch30

We make no apologies for the number of pages we have devoted to carbonyl chemistry. The first reactions you met, in Chapter 6, involved carbonyl compounds. Then in Chapters 9, 10, 12, and 14 we considered different aspects of nucleophilic attack on electrophilic carbonyl compounds. But carbonyl compounds have two opposed sides to their characters. They can be nucleophilic as well: *electrophilic* attack on aldehydes, ketones, and acid derivatives is a useful reaction too. How can the same class of compound be subject both to nucleophilic and to electrophilic attack? The resolution of this paradox is the subject of this chapter where we shall see that most carbonyl compounds exist in two forms—one electrophilic and one nucleophilic. The electrophilic form is the carbonyl compound itself and the nucleophilic form is called the **enol**.

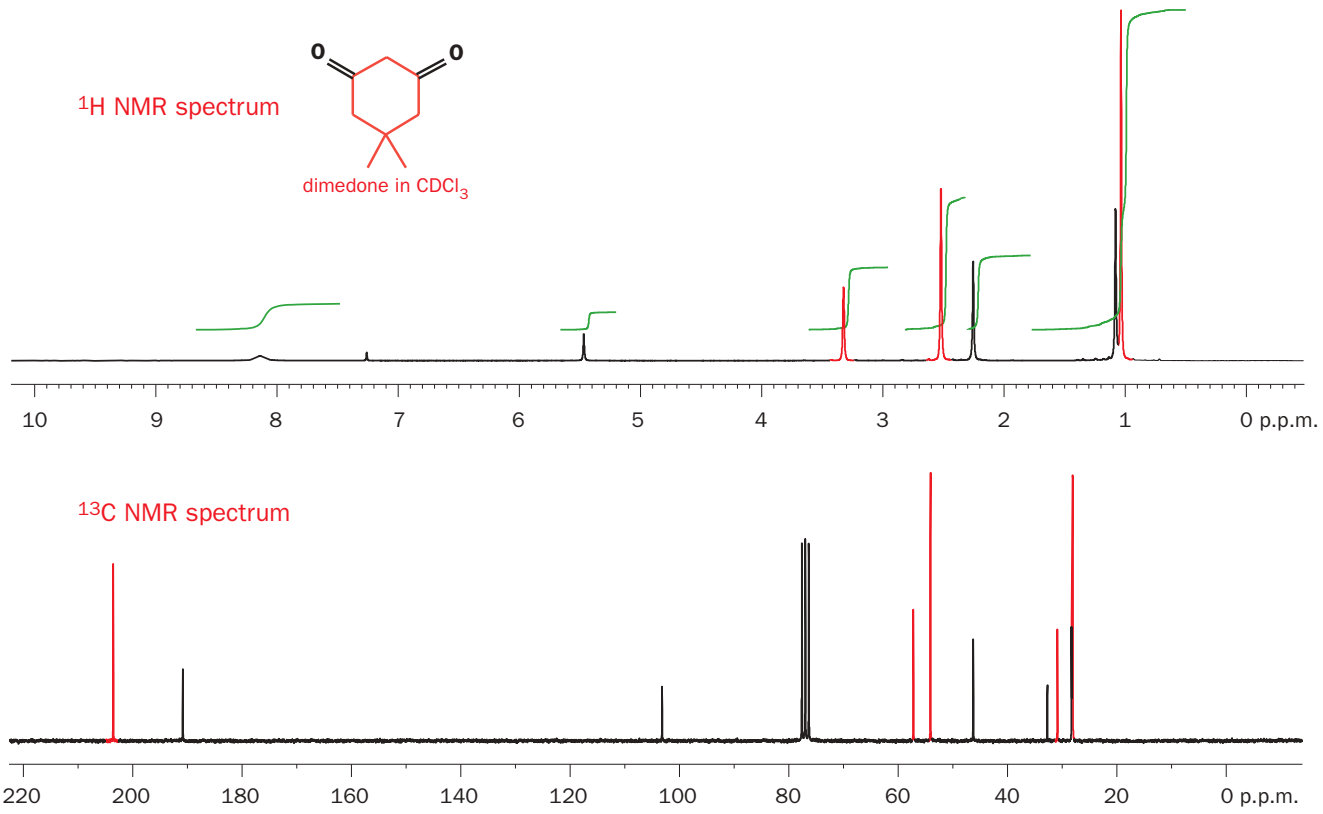
Would you accept a mixture of compounds as a pure substance?



"dimedone"
5,5-dimethylcyclohexane-1,3-dione

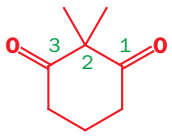
You can buy dimedone (5,5-dimethylcyclohexane-1,3-dione) from chemical suppliers. If, as is wise when you buy any compound, you run an NMR spectrum of the compound to check on its purity, you might be inclined to send the compound back. In $CDCl_3$ solution it is clearly a mixture of two compounds. Overleaf you can see ^{1}H and ^{13}C NMR spectra of the mixture with the peaks of the dione in red.

The majority of the sample is indeed 5,5-dimethylcyclohexane-1,3-dione. What is the rest? The other component has a similar spectrum and is clearly a similar compound: it has the 6H singlet for the CMe_2 group and the two CH_2 groups at the side of the ring; it also has five signals in its ^{13}C NMR spectrum. But it has a broad signal at δ_H 8.15, which looks like an OH group, and a sharp signal at δ_H 5.5 in the double-bond region. It also has *two different* sp^2 carbon atoms. All this fits the *enol* structure.



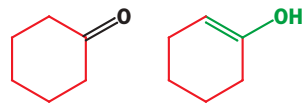
The NMR spectra of the enol are still symmetrical because the proton very rapidly hops from one oxygen to the other, making the two halves of the ring, and the two sp^2 C atoms bearing oxygen, the same.

These forms are in equilibrium and cannot be separated at room temperature. The equilibrium is nothing to do with the two methyl groups at C5. And yet the 2,2-dimethyl compound is a perfectly normal diketone with all the expected peaks in the NMR. You will see later that it is only the relative position (1,3) of the carbonyl groups and the presence of at least one hydrogen at C2 that matter.



2,2-dimethylcyclohexane-1,3-dione

Tautomerism: formation of enols by proton transfer

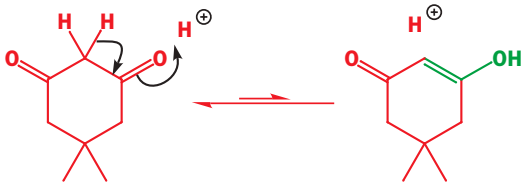


keto form of cyclohexanone

enol form of cyclohexanone

An enol is exactly what the name implies: an ene-ol. It has a C=C double bond and an OH group joined directly to it. Simple carbonyl compounds have enols too—in the margin is the enol of cyclohexanone (just dimedone without the extras).

In the case of dimedone, the enol must be formed by a transfer of a proton from the central CH_2 group of the keto form to one of the OH groups.

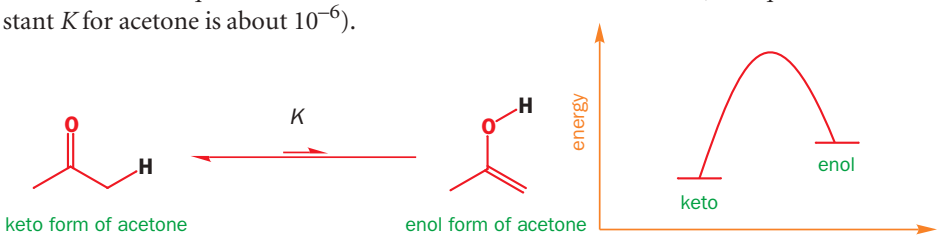


Notice that there is no change in pH—a proton is lost from carbon and gained on oxygen. The reaction is known as **enolization** as it is the conversion of a carbonyl compound into its enol. It is a strange reaction in which little happens. The product is almost the same as the starting

material since the only change is the transfer of one proton and the shift of the double bond. Reactions like this are given the name **tautomerism**.

Why don't simple aldehydes and ketones exist as enols?

When we were looking at spectra of carbonyl compounds in Chapter 15 we saw no signs of enols in IR or NMR spectra. Dimedone is exceptional—although any carbonyl compound with protons adjacent to the carbonyl group can enolize, simpler carbonyl compounds like cyclohexanone or acetone have only a trace of enol present under ordinary conditions. The equilibrium lies well over towards the keto form (the equilibrium constant K for acetone is about 10^{-6}).



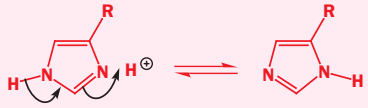
keto form of acetone — enol form of acetone

This is because the combination of a C=C double bond and an O–H single bond is (slightly) less stable than the combination of a C=O double bond and a C–H single bond. The balance between the bond energies is quite fine. On the one hand, the O–H bond in the enol is a stronger bond than the C–H bond in the ketone but, on the other hand, the C=O bond of the ketone is much more stable than the C=C bond of the enol. Here are some average values for these bonds.

Typical amounts of enols in solution are about one part in 10^5 for normal ketones. So why do we think they are important? *Because enolization is just a proton transfer, it is occurring all the time even though we cannot detect the minute proportion of the enol.* Let us look at the evidence for this statement.

▶ Any reaction that simply involves the intramolecular transfer of a proton is called a tautomerism. Here are two other examples.

tautomerism of a carboxylic acid. The mixture must be exactly 50:50 as the two forms (tautomers) are identical



tautomerism of an imidazole. The mixture need not be exactly 50:50 as the two forms are not identical

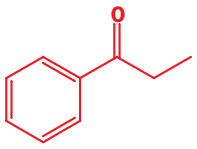
This sort of chemistry was discussed in Chapter 8 where the acidity and the basicity of atoms were the prime considerations. In the first case the two tautomers are the same and so the equilibrium constant must be exactly 1 or, if you prefer, the mixture must be exactly 50:50. In the second case the equilibrium will lie on one side or the other depending on the nature of R.

Typical bond strengths (kJ mol^{-1}) in keto and enol forms

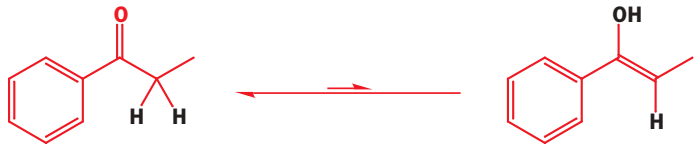
	Bond to H	π bond	Sum
keto form	(C–H) 440	(C=O) 720	1160
enol form	(O–H) 500	(C=C) 620	1120

Evidence for equilibration of carbonyl compounds with enols

If you run the NMR spectrum of a simple carbonyl compound (for example, 1-phenyl-propan-1-one, 'propiophenone') in D_2O, the signal for protons next to the carbonyl group very slowly disappears. If the compound is isolated from the solution afterwards, the mass spectrum shows that those hydrogen atoms have been replaced by deuterium atoms: there is a peak at $(M + 1)^+$ or $(M + 2)^+$ instead of at M^+. To start with, the same keto–enol equilibrium is set up.



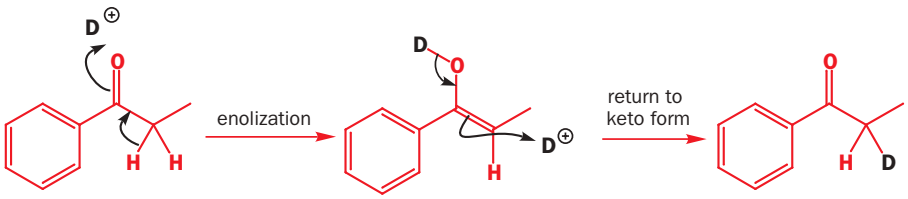
1-phenylpropan-1-one



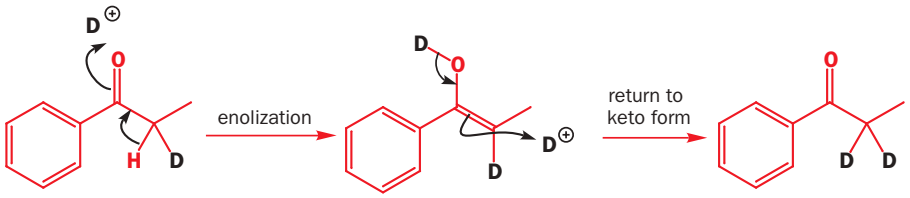
keto form of 1-phenylpropan-1-one — enol form of 1-phenylpropan-1-one

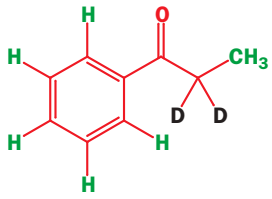
▶ Notice that the double bond in this enol could be either *E* or *Z*. It is drawn as *Z* here, but in reality is probably a mixture of both—though this is irelevant to the reaction. We shall not be concerned with the geometry of enols in this chapter, but there are some reactions that you will meet in later chapters where it is important, and you need to appreciate that the issue exists.

But, when the enol form reverts to the keto form, it picks up a deuteron instead of a proton because the solution consists almost entirely of D_2O and contains only a tiny amount of DOH (and no H_2O at all).



The process can now be repeated with the other hydrogen atom on the same carbon atom.





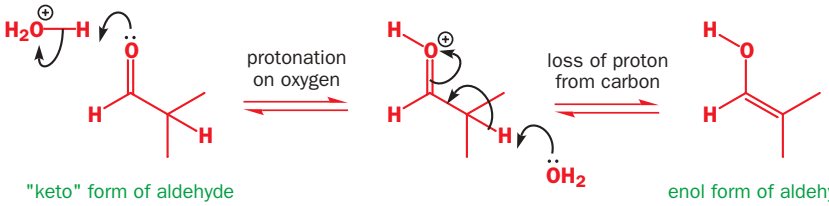
There are, of course, eight other hydrogens in the molecule but they are not affected. In the NMR spectrum we see the slow disappearance of the 2H signal for the protons on C2 next to the carbonyl group.

■ Something else will happen to the proton NMR spectrum. The signal for the CH_3 group was a triplet in the original ketone, but when those two Hs are replaced by Ds, it becomes a singlet. In the carbon spectrum, coupling to deuterium appears: remember the shape of the $CDCl_3$ peak (Chapter 3)?

Enolization is catalysed by acids and bases

Enolization is, in fact, quite a slow process in neutral solution, even in D_2O, and we would catalyse it with acid or base if we really wanted it to happen. In the acid-catalysed reaction, the molecule is first protonated on oxygen and then loses the C–H proton in a second step. We shall use a different example here to show that aldehydes form enols too.

acid-catalysed enolization of an aldehyde

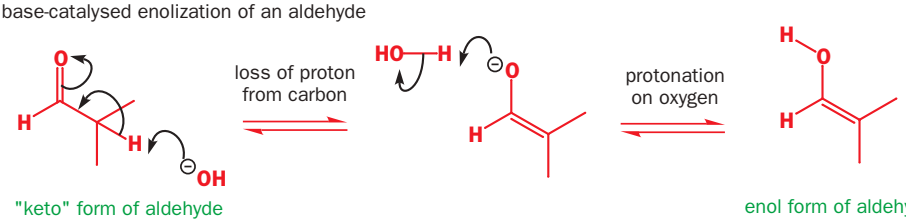


■ In Chapter 19 (p. 000) we discussed the equivalence of mechanisms showing protons just 'falling off' with those in which basic solvent molecules are involved to remove a proton. In this chapter, and in the rest of the book, you will see both variants in use according to the context. They mean exactly the same thing.

This is a better mechanism for enolization than those we have been drawing because it shows that something (here a water molecule) must actually be removing the proton from carbon. Though this reaction will occur faster than the uncatalysed enolization, the equilibrium is not changed and we still cannot detect the enol spectroscopically.

In the base-catalysed reaction the C–H proton is removed first by the base, say, a hydroxide ion, and the proton added to the oxygen atom in a second step.

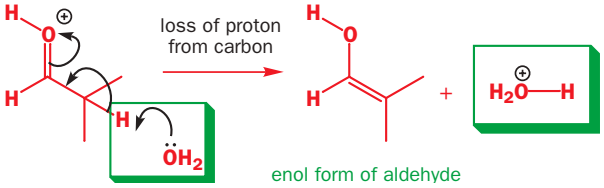
base-catalysed enolization of an aldehyde



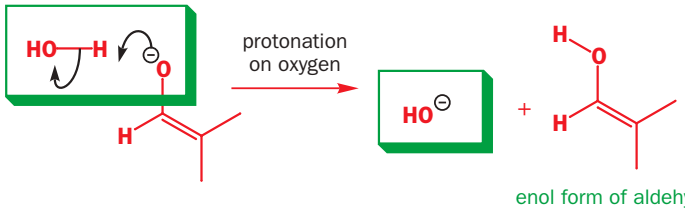
This is a good mechanism too because it shows that something must remove the proton from carbon and something (here a water molecule—we can't, of course, have protons in basic solution) must put the proton on the oxygen atom. The concentration of free protons in water is vanishingly small (Chapter 8).

Notice that both of these reactions are genuinely catalytic.

You get the proton back again at the end of the acid-catalysed mechanism.

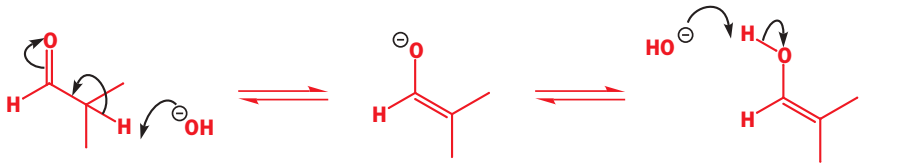


And you get the hydroxide ion back again at the end of the base-catalysed mechanism.



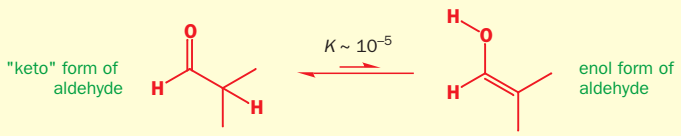
The intermediate in the base-catalysed reaction is the enolate ion

There are more insights to be gained from the base-catalysed reaction. The intermediate anion is called the **enolate ion**. It is the conjugate base of the enol and can be formed either directly from the carbonyl compound by the loss of a C–H proton or from the enol by loss of the O–H proton.



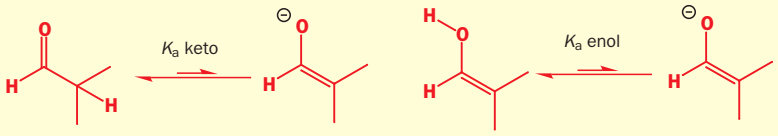
The enol form is more acidic than the keto form

The enol is less stable than the aldehyde and both lose a proton to give the same enolate ion. It follows that the enol is the more acidic. Make sure you understand this. Think of it this way: the keto/enol equilibrium constant is small.



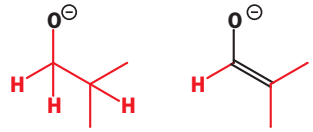
The acidity equilibrium constants for each form (with the enolate ion) are both small, but they are not the same.

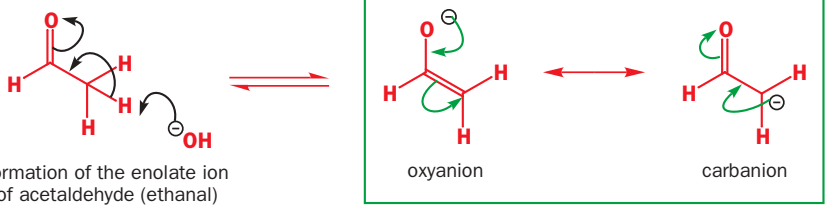
If the keto form is more stable than the enol form, then K_a (keto) must be smaller than K_a(enol): the enol form gives *more* of the enolate ion. The acidity of each form is measured by pK_a which is just $-\log_{10} K_a$ so if K_a(keto) < K_a(enol) then pK_a(keto) > pK_a(enol) and the keto form is less acidic.



The enolate ion is an alkoxide ion as we have drawn it, but it is more stable than the corresponding saturated structure because it is conjugated.

The enolate ion is one of those three-atom four-electron systems related to the allyl anion that we met in Chapter 7. The negative charge is mainly on oxygen, the most electronegative atom. We can show this with curly arrows using the simplest enolate possible (from MeCHO).

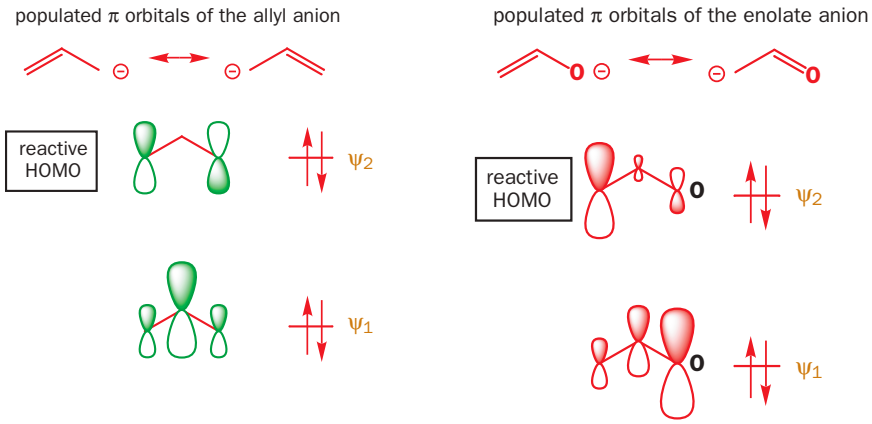




▶

It is important that you appreciate one key difference between the enolate and enol forms: the enolate is a delocalized system, with negative charge carried on both C and O—we use a double-headed conjugation arrow to connect these two representations. But for the proton to move from C to O in the enol form requires σ bonds to break and form, and this is a real equilibrium, which must be represented by equilibrium arrows.

Remember that the oxyanion and carbanion structures are just two different ways to represent the same thing. We shall usually prefer the oxyanion structure as it is more realistic. You can say the same thing in orbitals.

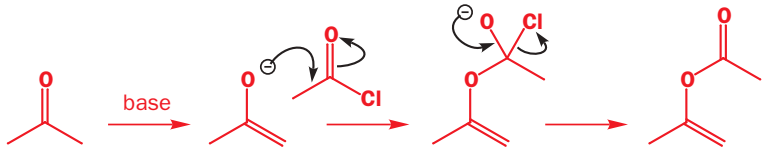


■ Refer to Chapter 7 if you fail to see where these orbitals come from.

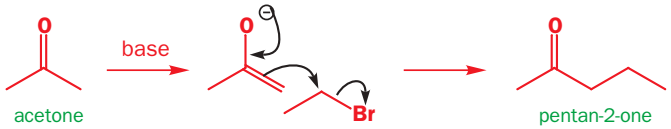
On the left you see the populated orbitals of the allyl anion and on the right the corresponding orbitals of the enolate ion. The allyl anion is, of course, symmetrical. Two changes happen when we replace one carbon by an oxygen atom. Because oxygen is more electronegative, both orbitals go down in energy. The orbitals are also distorted. The lower-energy atomic orbital of the more electronegative oxygen contributes more to the lower-energy orbital (ψ_1) and correspondingly less to ψ_2. The charge distribution comes from both populated orbitals so the negative charge is spread over all three atoms, but is mostly on the ends. The important reactive orbital is the HOMO (ψ_2) which has the larger orbital on the terminal carbon atom.

▶ In other words, the oxygen is a *hard* nucleophilic centre and the carbon is a *soft* nucleophilic centre. For related discussions, see Chapters 10 and 17.

In the enolate, the oxygen atom has more of the negative charge, but the carbon atom has more of the HOMO. One important consequence is that we can expect reactions dominated by charges and electrostatic interactions to occur on oxygen and reactions dominated by orbital interactions to occur on carbon. Thus acyl chlorides tend to react at oxygen to give enol esters, while alkyl halides tend to react at carbon.



▶ Notice that in drawing this mechanism it is *not* necessary to locate the negative charge on the carbon atom. You should always draw enolate mechanisms using the better oxyanion structure.

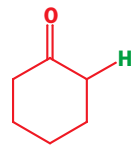


We shall be looking at these reactions in Chapter 26. For the rest of this chapter we are going to look at some simpler consequences of enolization and some reactions of enolates with heteroatom nucleophiles.

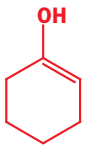
Summary of types of enol and enolate

In this section, the hydrogen atom lost in the enolization is shown in green. First let us summarize the various kinds of enol and enolate we can have from carbonyl compounds. We have seen such

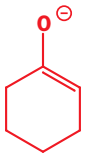
compounds from aldehydes and ketones already, but here are some variants. Cyclic ketones form enols and enolates just like open-chain compounds.



cyclohexanone



enol

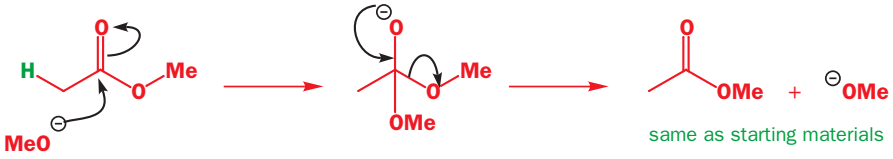


enolate ion

You can have a cyclic aldehyde only if the carbonyl group is outside the ring and cyclic aldehydes too form enols and enolates.

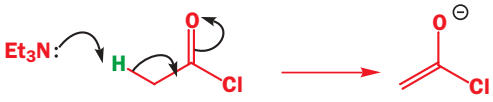
All the acid derivatives can form enols of some kind. Those of esters are particularly important and either enols or enolates are easily made. It is obviously necessary to avoid water in the presence of acid or base, as esters hydrolyse under these conditions. One solution is to use the alkoxide belonging to the ester (MeO^- with a methyl ester, EtO^- with an ethyl ester, and so on) to make enolate ions.

Then, if the alkoxide does act as a nucleophile, no harm can be done as the ester is simply regenerated.

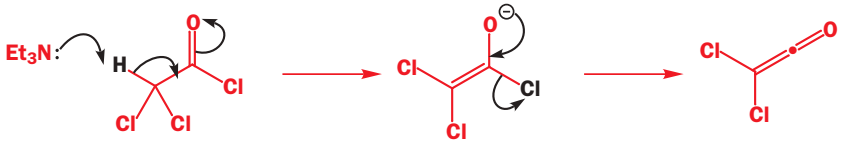


same as starting materials

The carbonyl group is accepting electrons both in the enolization step and in the nucleophilic attack. The same compounds that are the most electrophilic are also the most easily enolizable. This makes acyl chlorides very enolizable. To avoid nucleophilic attack, we cannot use chloride ion as base since chloride is not basic, so we must use a nonnucleophilic base such as a tertiary amine.



The resulting enolate is not stable as it can eliminate chloride ion, a good leaving group, to form a ketene. This works particularly well in making dichloroketene from dichloroacetyl chloride as the proton to be removed is very acidic.



unstable enolate

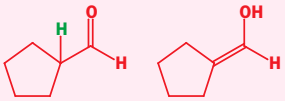
dichloroketene

Carboxylic acids do not form enolate anions easily as the base first removes the acidic OH proton. The same thing protects acids from attack by nucleophiles.

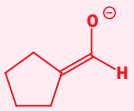
stable carboxylate anion

In acid solution, there are no such problems and 'ene-diols' are formed. The original OH group of the carboxylic acid and the new OH group of the enol are equivalent.

▶ Note that the aldehyde proton itself (C*H*O) is *never* enolized. Try to draw the curly arrows and you will see that they don't work.

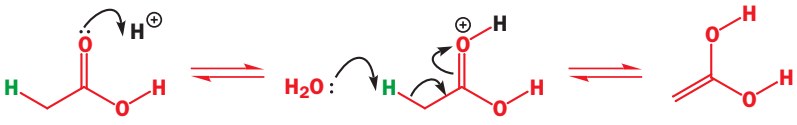


cyclopentane aldehyde enol

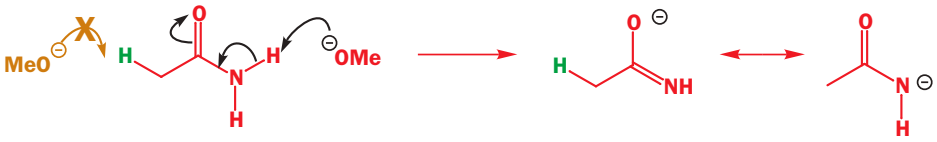


enolate ion

■ This is an E1cB elimination, and you saw this sort of chemistry in Chapter 19.

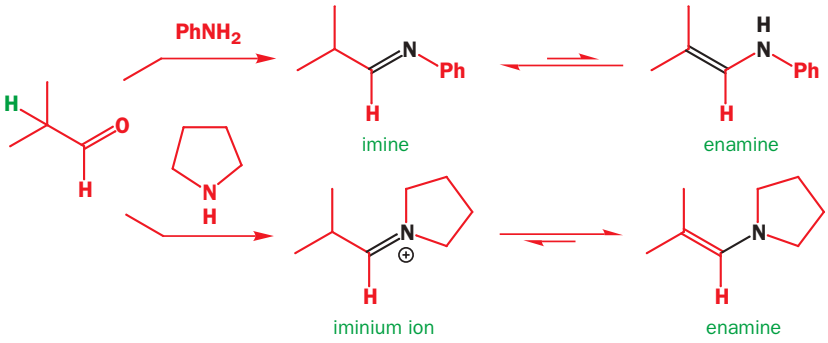


Amides also have rather acidic protons, though not, of course, as acidic as those of carboxylic acids. Attempted enolate ion formation in base removes an N–H proton rather than a C–H proton. Amides are also the least reactive and the least enolizable of all acid derivatives, and their enols and enolates are rarely used in reactions.



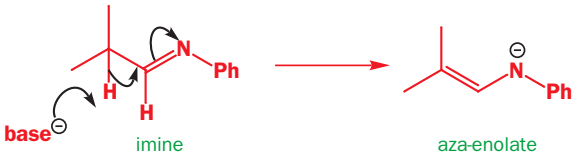
It is not even necessary to have a carbonyl group to observe very similar reactions. Imines and enamines are related by the same kind of tautomeric equilibria.

■ You should make sure you can write mechanisms for these reactions: we discussed them in Chapter 14.



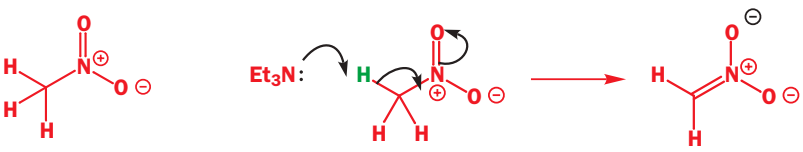
With a primary amine (here $PhNH_2$) a reasonably stable imine is formed, but with a secondary amine (here a simple cyclic amine) the imine itself cannot be formed and the iminium salt is less stable than the enamine.

Just as enamines are the nitrogen analogues of enols, **aza-enolates** are the nitrogen analogues of enolates. They are made by deprotonating enamines with strong base. You will see both enamines and aza-enolates in action in Chapters 26 and 27.

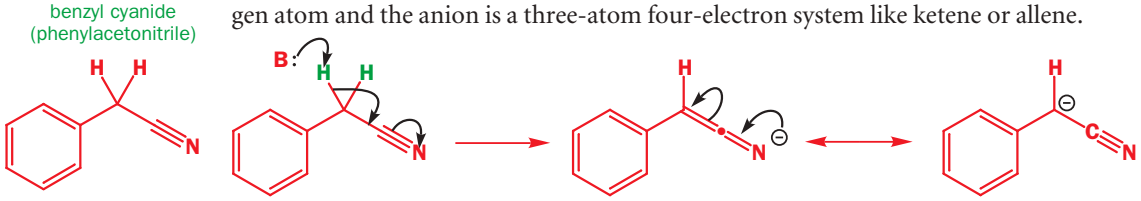


■ Deprotonation of nitroalkanes is discussed in detail in Chapter 8.

Nitroalkanes form enolate-like anions in quite weak base. As in base-catalysed enolization, a proton is removed from a carbon atom and a stable oxyanion is formed.



Nitriles (cyanides) also form anions but require stronger base as the negative charge is delocalized on to a single nitrogen atom rather than on to two oxygens. The negative charge is mostly on a nitrogen atom and the anion is a three-atom four-electron system like ketene or allene.



Requirement for enolization

In summary, any organic compound with an electron-withdrawing functional group, with at least one π bond joined to a saturated carbon atom having at least one hydrogen atom, may form an enol in neutral or acid solution. Many also form enolates in basic solution (exceptions are carboxylic acids and primary and secondary amides).

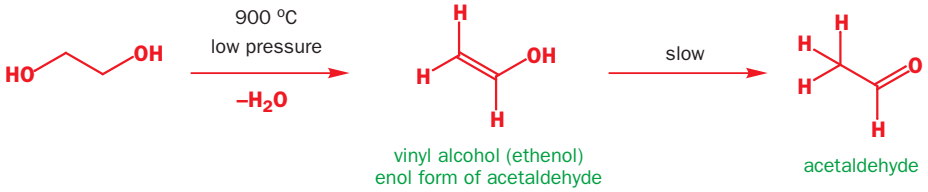
The enols will probably not be detectable in solution (only about one part in 10^4–10^6 is enol for most compounds). Some compounds by contrast form stable enols.

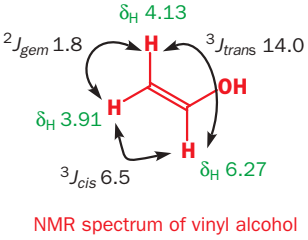
Stable enols

Kinetically stable enols

We have established that enols are, in general, less stable than the keto form of the molecule. We might hope to see stable enols if we changed that situation by adding some feature to the molecule that stabilized the enol thermodynamically. Or we might try to create an enol that would revert only slowly to the keto form—in other words, it would be *kinetically* stable. We shall look at this type first.

We have established that the formation of enols is catalysed by acids and bases. The reverse of this reaction—the formation of ketone from enol—must therefore also be catalysed by the same acids and bases. If you prepare simple enols in the strict absence of acid or base they have a reasonable lifetime. A famous example is the preparation of the simplest enol, vinyl alcohol, by heating ethane-1,2-diol (glycol—antifreeze) to very high temperatures (900 °C) at low pressure. Water is lost and the enol of acetaldehyde is formed. It survives long enough for its proton NMR spectrum to be run, but gives acetaldehyde slowly.

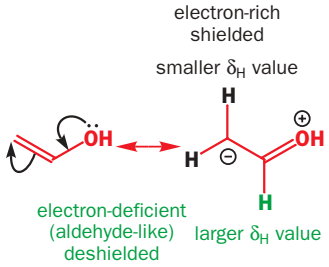




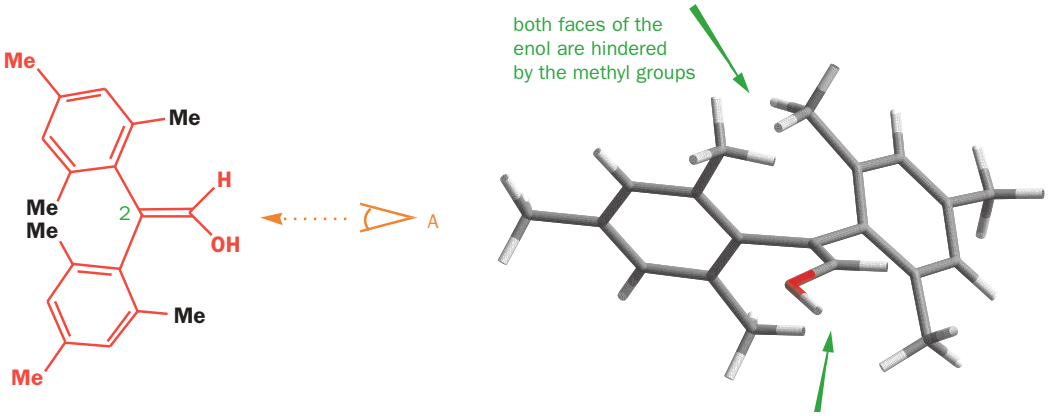
NMR spectrum of vinyl alcohol

The spectrum fits the enol perfectly. The alkene proton next to OH is deshielded and the two alkene protons on the other carbon atom shielded as we should expect from the feeding of electrons into the double bond by the OH group.

The coupling constants across the double bond are as expected too. The *trans* coupling is large (14.0 Hz) and the *cis* coupling smaller (6.5 Hz). The geminal coupling is very small as is usually the case for a CH_2 group on a double bond.



Other enols can be made that are stable because it is very difficult for the carbon atom to be protonated. This example is very crowded by two substituted benzene rings.



The enol would have to be protonated at the C2 to form the aldehyde but this is not possible because the two benzene rings are twisted out of the plane of the double bond by the interference of the *ortho* methyl groups. The view down the double bond shows that both faces are blocked by one of the *ortho* methyl groups and an acid cannot approach close enough to deliver its proton.

Enols of 1,3-dicarbonyl compounds: thermodynamically stable enols

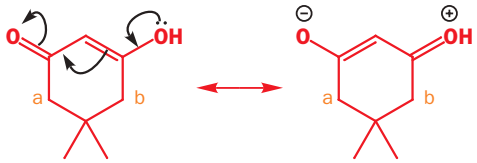
We started this chapter by looking at a molecule that contained about 33% enol in solution—dimedone. In fact, this is just one example of the class of 1,3-dicarbonyl compounds (also called β-dicarbonyls) all of which contain substantial amounts of enol and may even be completely enolized in polar solvents.

keto form of dimedone (67% in $CDCl_3$)

enol form of dimedone (33% in $CDCl_3$)

We need now to examine why these enols are so stable. The main reason is that this unique (1,3) arrangement of the two functional groups leads to enols that are conjugated rather like a carboxylic acid.

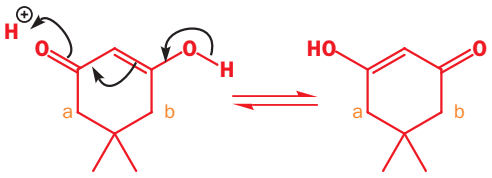
delocalization in the enol form of dimedone



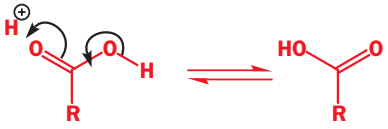
delocalization in a carboxylic acid

Did you notice when we were looking at the NMR spectrum of dimedone (p. 000) that the two CH_2 groups in the ring seemed to be the same, though they are different (a and b) and the delocalization we have just looked at does not make them the same? This must mean that the enol is in *rapid* equilibrium with another identical enol. This is *not* delocalization—a proton is moving—so it is **tautomerism**.

equilibration of the enol form of dimedone

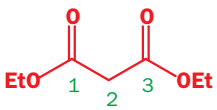


equilibration of a carboxylic acid



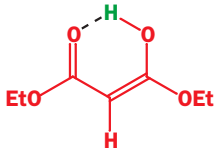
Once again, this is very like the situation in a carboxylic acid. Thus the two enols equilibrate fast with each other in $CDCl_3$ solution but equilibrate slowly enough with the keto form for the two spectra to be recorded at the same time. If equilibration with the keto form were fast, we should see a time-averaged spectrum of the two. In CD_3OD solution the ^1H and ^{13}C NMR spectra show that only the enol form exists, presumably stabilized by hydrogen bonding.

Other 1,3-dicarbonyl compounds also exist largely in the enol form. In some examples there is an additional stabilizing factor, intramolecular hydrogen bonding. Diethyl malonate (diethyl propanedioate) has a symmetrical enol stabilized by conjugation. The enol form is also stabilized by a very favourable intramolecular hydrogen bond in a six-membered ring.



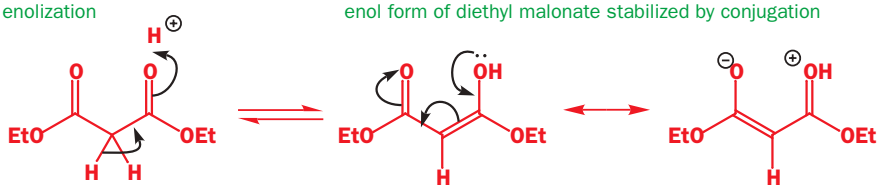
diethyl malonate

■ This hydrogen bond was not possible in dimedone.



enol form of diethyl malonate stabilized by an intramolecular hydrogen bond

enolization



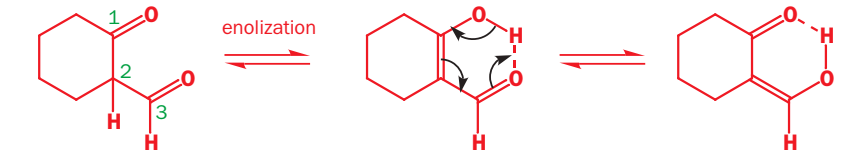
enol form of diethyl malonate stabilized by conjugation

This allows interconversion of the two identical enol structures by proton transfer, that is, by tautomerism.

tautomerism in the enol form of diethyl malonate

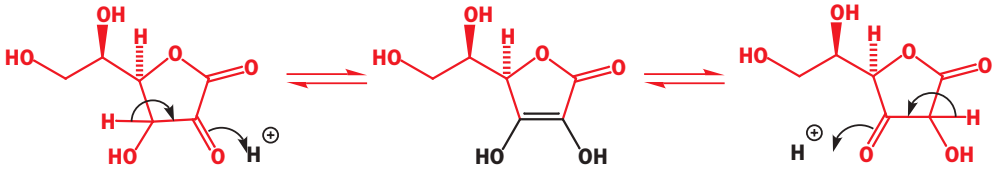
The 1,3-dicarbonyl compound need not be symmetrical and if it is not two different enol forms will interconvert by proton transfer. Here is a cyclic keto-aldehyde as an example. It exists as the rapidly equilibrating enol. The proportions of the three species can be measured by NMR: there is 0% keto-aldehyde, 76% of the first enol, and 24% of the second.

1,3-dicarbonyl (keto-aldehyde) two different stable enols rapidly interconverting by tautomerism

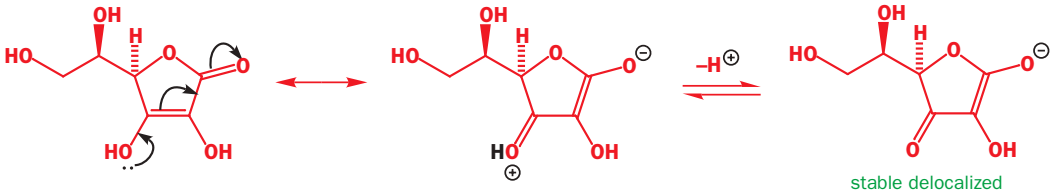


Enols occur in nature too. Vitamin C has a five-membered ring containing two carbonyl groups but normally exists as a very conjugated ene-diol.

one unstable keto form stable ene-diol form of vitamin C another unstable keto form

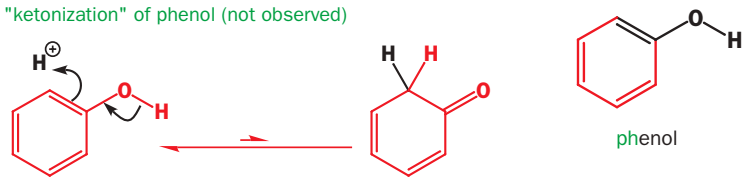


The enol is stable; it is delocalized. We can show the delocalization and explain why vitamin C is called ascorbic *acid* at the same time. The black enol proton is acidic because the anion is delocalized over the 1,3-dicarbonyl system.



The ultimate in stable enols has to be the Ph-enol, the aromatic alcohols or phenols, which prefer the substantial advantage of aromaticity to the slight advantage of a C=O over a C=C double bond. They exist entirely in the phenol form.

"ketonization" of phenol (not observed)

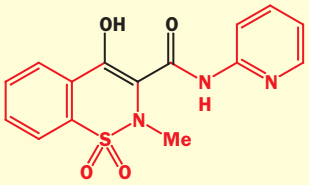


Even so, you will see in Chapter 22 that intermediates with this 'keto' structure are formed in reactions on the benzene ring of phenols. Like ascorbic acid, phenol is also quite acidic (pK_a 10) and used to be called carbolic acid.

▶ Again, note carefully the difference between this **tautomerism** in which a proton is moved around the molecule and the structures are linked by *equilibrium* arrows and the **delocalization** (conjugation) where only electrons are 'moved' (no actual movement occurs, of course) and the two structures are linked by one *double-headed* arrow as they are just two ways of drawing the same thing.

Stable enols

Pfizer's antiinflammatory drug 'Feldene' (used to treat arthritis) is a stable enol based on a 1,3-dicarbonyl compound. It also has amide and sulfonamide groups in its structure but you should be able to pick out the enol part.

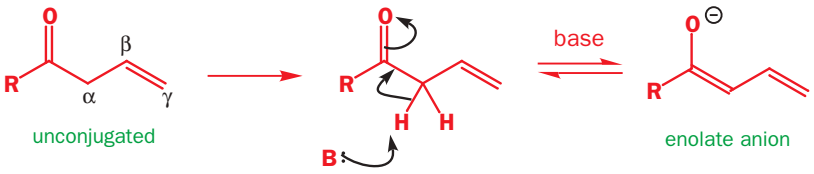


Pfizer's piroxicam or Feldene once-a-day treatment for arthritis

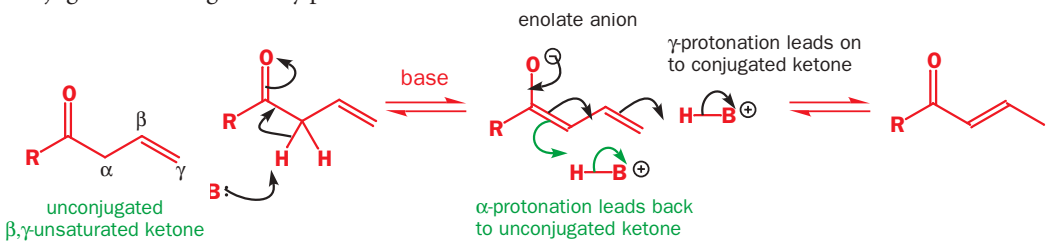
Consequences of enolization

Unsaturated carbonyl compounds prefer to be conjugated

It is difficult to keep a β,γ-unsaturated carbonyl compound because the double bond tends to move into conjugation with the carbonyl group in the presence of traces of acid or base. The intermediate is, of course, an enol in acid solution but an enolate ion in base.

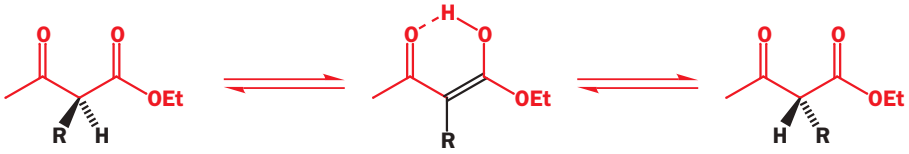


Protonation at the α position takes the molecule back to the unconjugated ketone, but protonation in the γ position gives the more stable conjugated isomer. All the reactions are equilibria so the conjugated isomer gradually predominates.



Racemization

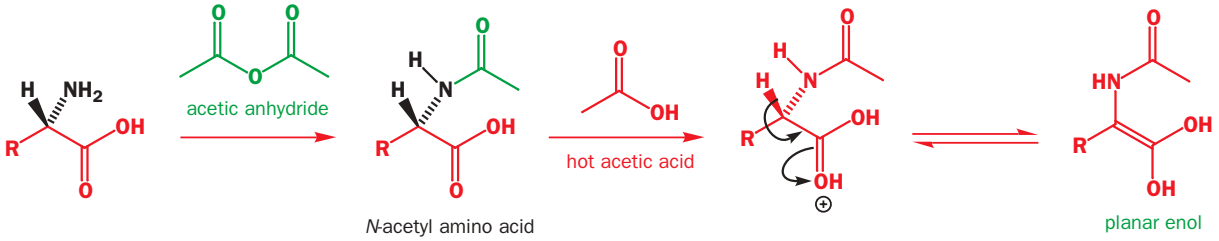
Any stereogenic centre next to a carbonyl group is precarious because enolization will destroy it. It would be foolish to try and make optically active β-dicarbonyl compounds whose only stereogenic centre was between the two carbonyl groups.



Though the keto-ester is chiral, the enol is flat and cannot be chiral. The two forms are in rapid equilibrium so all optical activity would quickly be lost.

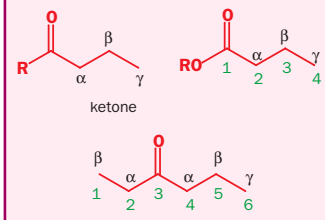
Compounds with one carbonyl group next to the stereogenic centre can be made but care still needs to be taken. The α amino acids, the component parts of proteins, are like this. They are perfectly stable and do not racemize in aqueous acid or base. In base they exist as carboxylate anions that do not enolize, as explained above. Enolization in acid is prevented by the NH_3^+ group, which inhibits the second protonation necessary for enol formation.

Amino acids can be converted into their *N*-acetyl derivatives with acetic anhydride. These *N*-acetyl amides can be racemized on recrystallization from hot acetic acid, no doubt by enolization. The amino group is no longer basic, is not protonated in acid, and so protonation on the carbonyl group and hence enolization is now possible.



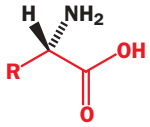
▶ When speaking generally of carbonyl compounds, the Greek letters α, β, γ, and so on are used to designate the positions along the chain from the carbonyl group. Of course, if the compound is an aldehyde or an acid derivative, we can use the normal numbers instead as the carbonyl group will normally be C1, but this will not usually be the case for ketones. It is useful to have a general method of describing the positions where enolization may take place and so they are called the α positions.

labelling carbon atoms in carbonyl compounds



An enolizable position is always α, even if there are two of them as in an unsymmetrical alkyl ketone, while enolizable carbons may happen to have any number in simple IUPAC nomenclature such as C2 and C4 in the example above.

▶ A planar molecule *must* have a plane of symmetry.



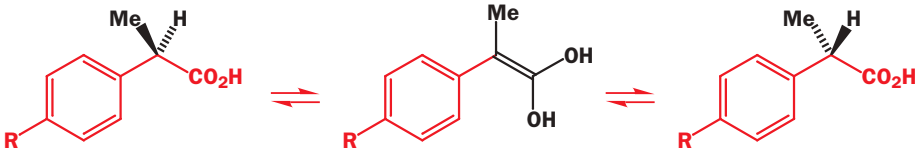
a natural (*S*) amino acid

■ Note the use of α: the amino group is on the α position with respect to the carboxylic acid.

You may think it a crazy idea to *want* to racemize an amino acid. Supposing, however, that you are preparing pure (*S*)-amino acid by resolution. Half your material ends up as the wrong (*R*)-enantiomer and you don't want just to throw it away. If you racemize it you can put it back into the next resolution and convert half of it into the (*S*)-acid. Then you can racemize what remains and so on.

Some compounds may be racemized inside the human body. Bacterial cell walls are built partly from 'unnatural' (*R*)-amino-acids and we can't digest these. Instead, we use enzymes designed to racemize them. These also work by enolization, though it is the imine–enamine type from p. 000.

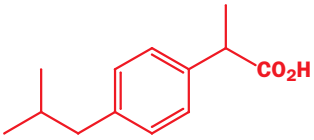
There is an important group of analgesic (pain-killing) drugs such as ibuprofen based on the aryl-propionic acid structure. Ibuprofen is given to arthritis sufferers as 'Brufen' and can be bought over the counter in chemists' shops as the headache remedy 'Nurofen'. Only one enantiomer actually cures pain but the compound is administered as the racemate. The body does the rest, racemizing the compound by enolizing it.



the biologically inactive enantiomer of ibuprofen — flat achiral enol — the biologically active enantiomer of ibuprofen

■ We discussed **resolution**, the separation of enantiomers by the formation of diastereoisomers with an optically active resolving agent, in Chapter 16.

■ There are details of this reaction in Chapter 50.



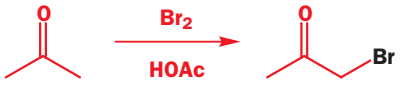
ibuprofen

Reaction with enols or enolates as intermediates

We have already seen that exchange of hydrogen for deuterium, movement of double bonds into conjugation, and racemization can occur with enols or enolates as intermediates. These are chemical reactions of a sort, but it is time to look at some reactions that make significant changes to the carbonyl compound.

Halogenation

Carbonyl compounds can be halogenated in the α position by halogens (such as bromine, Br_2) in acidic or basic solutions. We shall look at the acid-catalysed reaction first because it is simpler. Ketones can usually be cleanly brominated in acetic acid as solvent.

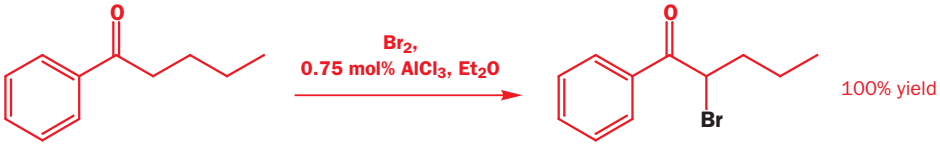


acetone — bromoacetone

The first step is acid-catalysed enolization and the electrophilic bromine molecule then attacks the nucleophilic carbon of the enol. The arrows show why this particular carbon is the one attacked.

enol

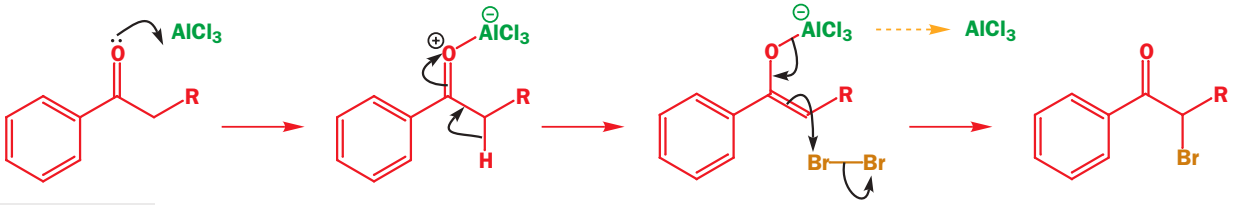
Notice that the acid catalyst is regenerated at the end of the reaction. The reaction need not be carried out in an acidic solvent, or even with a protic acid at all. Lewis acids make excellent catalysts for the bromination of ketones. This example with an unsymmetrical ketone gives 100% yield of the bromoketone with catalytic $AlCl_3$ in ether as solvent.



100% yield

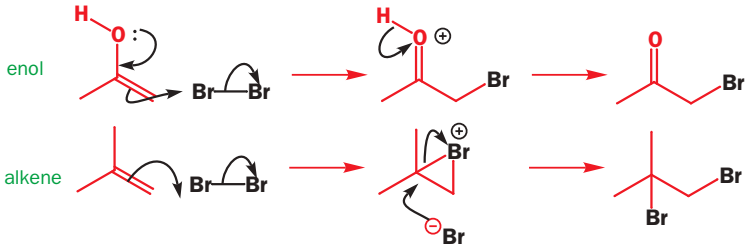
Bromination occurs nowhere else in the molecule—not on the benzene ring (which, as you will see in the next chapter, it easily might under these conditions), nor on any other atom of the

aliphatic side chain. This is because only one position can form an enol and the enol is more reactive towards bromine than the aromatic ring.



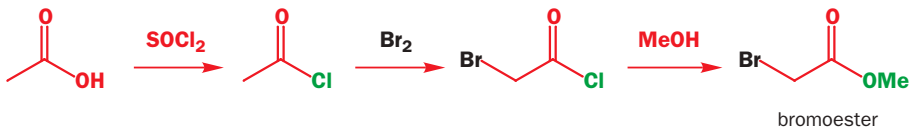
■ We have introduced a slight but unimportant variation into this mechanism. In the previous mechanism, we used the lone pairs on oxygen to assist attack on Br_2 and then lost the acid catalyst in a separate step. Here, we have written $AlCl_3$ leaving as the Br_2 is attacked. The difference is not significant, and you will see mechanisms written in both ways. The second way saves a step, of course.

These mechanisms should remind you of the mechanism of alkene bromination (p. 000)—except that here the attack on the bromine is assisted by an electron pair on oxygen. The product, instead of being a bromonium ion (which would undergo further reactions), loses a proton (or the Lewis acid) to give a ketone.

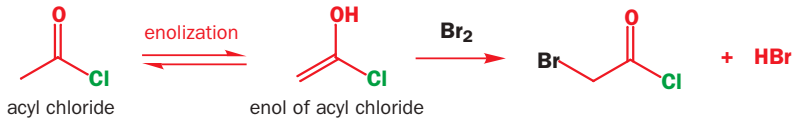


Enols are more nucleophilic than simple alkenes—the HOMO is raised by the interaction with the oxygen's lone pairs and looks not unlike the HOMO of the enolate anion we discussed on p. 000.

Bromination of acid derivatives is usually carried out not on the acid itself but by converting it to an acyl bromide or chloride, which is not isolated but gives the α-bromoacyl halide via the enol. This used to be done in one step with red phosphorus and bromine, but a two-step process is usually preferred now, and the bromoester is usually made directly without isolating any of the intermediates. We can summarize the overall process like this.

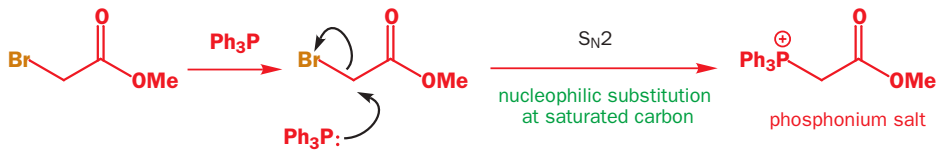


The formation of the acyl chloride with $SOCl_2$ and the conversion of the α-bromoacyl chloride into the bromoester with MeOH are simple nucleophilic substitutions at the carbonyl group, just like the synthesis of esters from acyl chlorides in Chapter 12. The intermediate stage, the bromination of the very easily enolized acyl chloride, is a typical enol bromination.



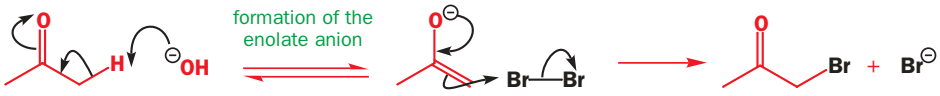
■ Hard and soft nucleophiles in substitution reactions are discussed in Chapter 17.

In the reaction of the bromoacyl chloride with methanol, attack occurs at the carbonyl group with an alcohol because oxygen nucleophiles are 'hard' nucleophiles (controlled by charge interactions). If we want to displace the α-bromo group we can use any 'soft' (orbital-dominated) nucleophile. Triphenylphosphine Ph_3P is particularly important—the product is a phosphonium salt, employed in Wittig reactions and discussed in Chapter 31.



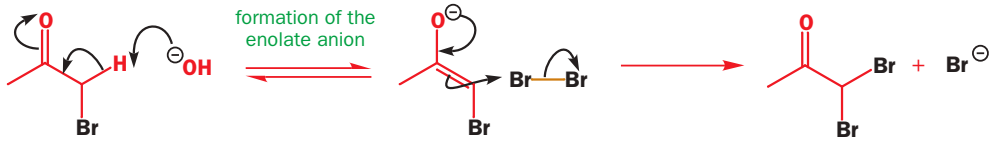
Base-catalysed halogenation

This is different and more complicated because it usually won't stop at the introduction of one halogen atom. If we go back to the bromination of acetone, the first step will now be a base-catalysed enolization to give the enolate ion instead of the enol. The enolate ion can attack a bromine molecule in a very similar way to the attack of the enol on bromine. The enolate will, of course, be even more reactive than the enol was (the enolate carries a negative charge).

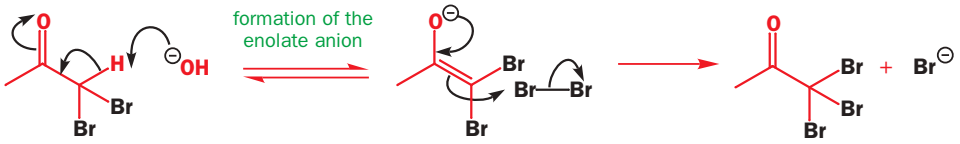


▶ Notice that the hydroxide ion is *not* regenerated in this reaction—bromide ion is not basic and does not react with water to regenerate hydroxide ion (Chapter 8). So we need to add a whole equivalent of hydroxide.

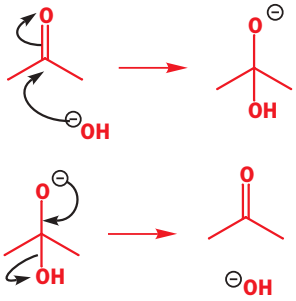
The problem is that the reaction does not stop at this point. The first step was the removal of a proton and the protons between the carbonyl group and the bromine atom in the product are *more* acidic than those in the original acetone because of the electron-withdrawing bromine atom. Bromoacetone forms an enolate faster than acetone does.



Dibromoacetone is formed. Now we have one remaining proton in between the carbonyl group and two bromine atoms. It is even more acidic and so forms a new enolate ion even more quickly. The first product we can see in any amount is tribromoacetone.

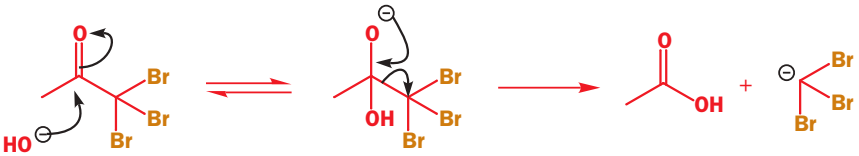


But even this is not the end of the story. To see why, we need to backtrack a bit. You may already have asked yourself, 'Why doesn't the hydroxide ion, being a nucleophile, attack the carbonyl group?' This is a general question you might ask about all base-catalysed enolizations. The answer is that it does. The reaction is shown in the margin. A tetrahedral intermediate forms.



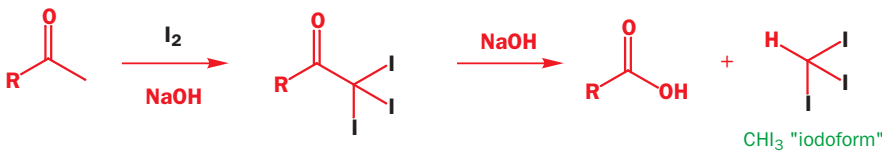
What can happen now? This tetrahedral intermediate will revert to a carbonyl compound by expelling the best leaving group—and in Chapter 12 we saw that this is usually the group with the lowest pK_{aH}. But Me^- can never act as a leaving group ($pK_{aH} > 50$). Indeed the only possible leaving group is the hydroxide ion ($pK_{aH} = 15.7$), so it just drops out again.

This state of affairs continues until we reach the tribromoketone. In Chapter 8, you saw that the pK_a of $CHBr_3$ is only 9: the CBr_3^- group is a better leaving group than hydroxide since the carbanion is stabilized by three bromine atoms. So now a real reaction occurs.



These initial products exchange a proton to reveal the true products of the reaction—the anion of a carboxylic acid and tribromomethane ($CHBr_3$).

The same thing happens with iodine, and we can summarize the whole process with iodine using a general structure for a carbonyl compound bearing a methyl group. It must be a methyl group because three halogens are necessary to make the carbanion into a leaving group.



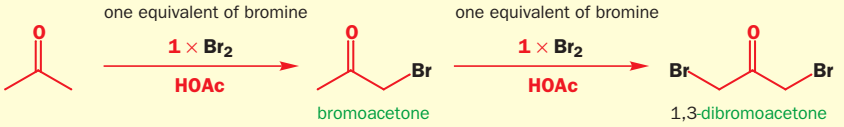
This reaction is often called the 'iodoform' reaction. Iodoform was an old name for triiodomethane, just as chloroform is still used for trichloromethane. It is one of the rare cases where nucleophilic substitution at a carbonyl group results in the cleavage of a C–C single bond.

Acid mediated halogenation is best

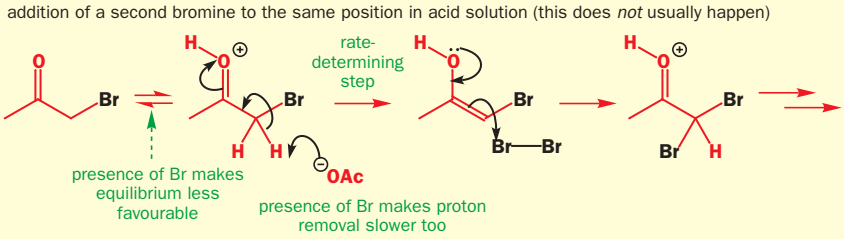
Halogenation of carbonyl compounds should be carried out in acid solution. Attempts in basic solution lead to multiple substitutions and C–C bond cleavage.

Why does acid-catalysed halogenation work better?

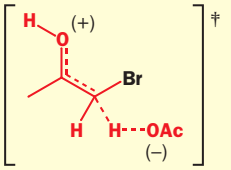
The reason why halogenation in base continues until all the hydrogens have been replaced is clear: each successive halide makes the remaining proton(s) more acidic and the next enolization easier. But why does acid-catalysed halogenation stop after the introduction of one halogen? It would be more accurate to say that it *can be made to stop* after one halogen is introduced if only one equivalent of halogen is used. Acid-catalysed halogenation *will* continue if there is more halogen available.



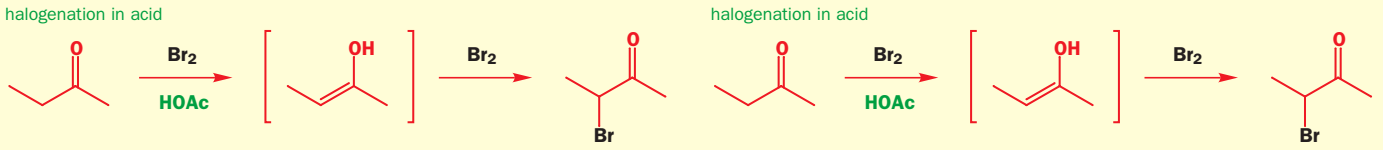
However, the second halogen goes on the other side of the carbonyl group, if it can. It is evidently the case that the second halogenation is slower than the first. This is firstly because most of the intermediates are positively charged and hence destabilized by the presence of a halogen. The bromoketone is less basic than acetone so less of the reactive protonated form is present. This slows down any further electrophilic attack.



The second step is the rate-determining step, and the presence of a bromine atom at the α position slows this step down still further: if a proton can be lost from a different α position—one without a Br atom—it will be lost. The transition state for proton removal illustrates why bromine slows this step down. The part of the structure close to the bromine atom is positively charged.



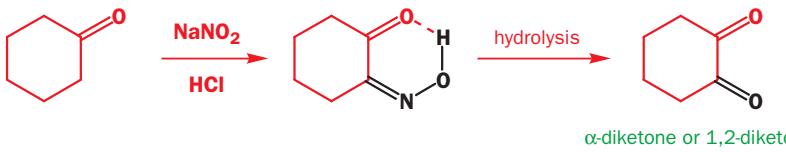
We can add a useful piece of evidence to this weak-sounding explanation. The halogenation of an unsymmetrical dialkyl ketone gives different results in acid and in base. In base halogenation occurs preferentially on a methyl group, that is, on the less highly substituted side. In acid solution by contrast, halogenation occurs on the more substituted side of the carbonyl group. Alkyl groups have the opposite effect to bromine atoms—they stabilize positive charges. So the reactions of an enol, with a positively charged transition state, are faster at more highly substituted positions. Enolates react through negatively charged transition states, and are faster at less highly substituted carbon atoms.



Nitrosation of enols

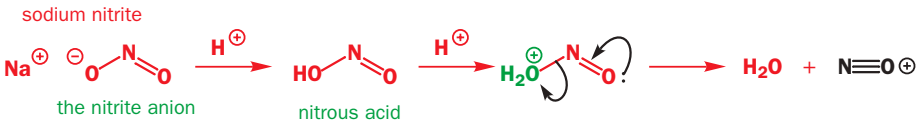
Now for a reaction with nitrogen as an electrophile that illustrates enol reactivity and reminds us that tautomerism applies to functional groups other than the carbonyl. Let us suppose you have a

carbonyl compound and wish to introduce another carbonyl group next to the first. One way you might go about it is this.



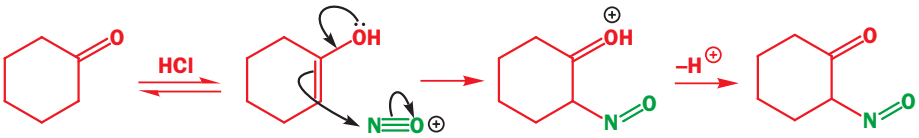
α-diketone or 1,2-diketone

The first step involves the formation of the weak acid nitrous acid (HNO_2 or, more helpfully, HONO) from the sodium salt and the strong acid HCl. Nitrous acid is itself protonated and then loss of water creates the reactive electrophile NO^+.



This diatomic cation, isoelectronic with carbon monoxide, is electrophilic at nitrogen and attacks the enol of the ketone to form an unstable nitroso compound.

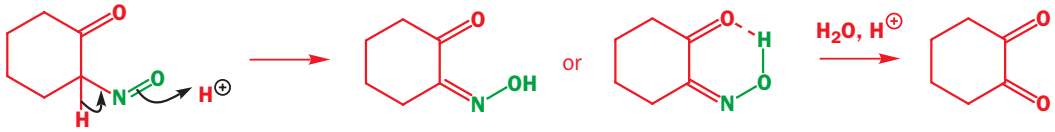
■ The nitroso functional group, –N=O, may be new to you.



nitroso-ketone

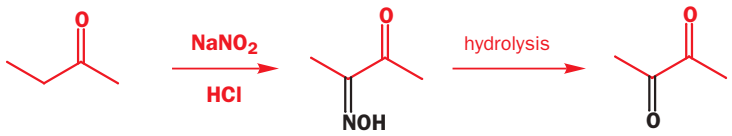
The nitroso compound is unstable because it can tautomerize with the transfer of a proton from carbon to the oxygen of the nitroso group. This process is exactly like enolization but uses an N=O instead of a C=O group. It gives a more familiar functional group from Chapter 14, the oxime, as the stable 'enol'. The second structure shows how the oxime's O–H can form an intramolecular hydrogen bond with the ketone carbonyl group. Hydrolysis of the oxime reveals the second ketone.

■ Imine (and therefore oxime) hydrolysis was discussed in Chapter 14, p. 000.



oximino-ketone hydrogen-bonded oxime

If the ketone is unsymmetrical, this reaction will occur on the more substituted side, for the same reason that acid-catalysed enol bromination gives the more substituted α-bromocarbonyl compound (see the box on p. 000).

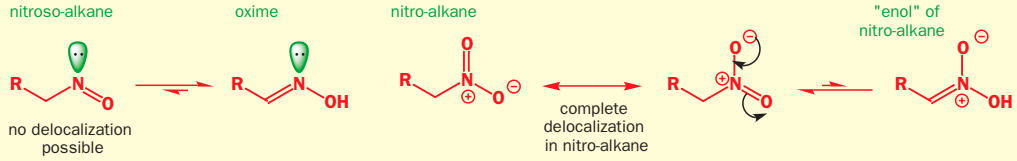


Before we move on to any more reactions, we want you to take away this message from the reactions of enols and enolates with Br_2 and with NO^+.

● **Enols and enolates generally react with electrophiles at *carbon*.**

The nitroso group

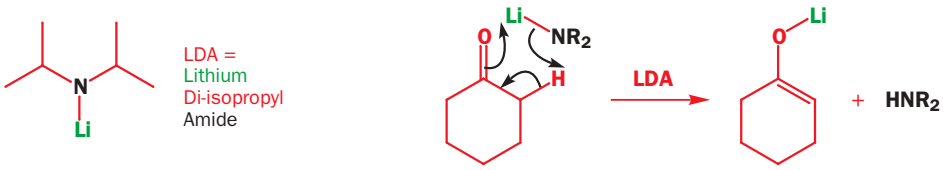
The difference between the nitro and nitroso groups is one of oxidation state and conjugation. The nitroso group contains trigonal trivalent nitrogen with a lone pair in the plane and is not delocalized. The much more stable nitro group has trigonal N^+ with no lone pair and is delocalized. Both can form 'enols' but the equilibria are biased in different directions.



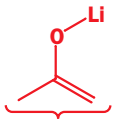
Stable enolate equivalents

Even with fairly strong bases such as hydroxides or alkoxides, most carbonyl compounds are converted to their enolates only to a very small extent. A typical pK_a for the protons next to a carbonyl group is 20–25, while the pK_a of methoxide is around 16, so we can only hope for about 1 part enolate in 10^4 parts carbonyl compound. With a much stronger base, this all changes, and the enolate is formed quantitatively from the carbonyl compound. This is a very important result which we shall capitalize on in Chapters 26 and 27. The base usually used is LDA (Lithium Di-isopropyl Amide), and it works like this.

■ You have already met LDA in Chapter 19 promoting elimination reactions, but no other use of this base compares in importance with what we are telling you now. By far the most important use of LDA is for making lithium enolates.



▶ Never try to use BuLi to deprotonate a carbonyl compound! BuLi almost invariably adds to carbonyl groups as a *nucleophile*.


lithium enolate

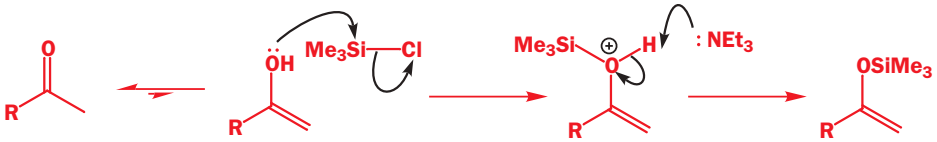

silyl enol ether

■ The TriMethyl Silyl group is sometimes abbreviated to TMS. As this is not much shorter than Me_3Si, we shall use the real thing instead of the abbreviation.

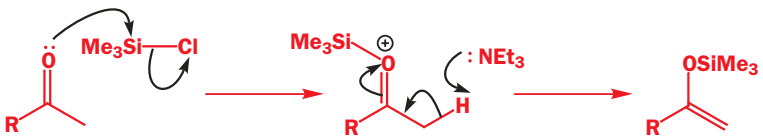
LDA is bulky, so it does not undergo nucleophilic attack on the carbonyl group, and it is basic—the pK_a of diisopropylamine is about 35—plenty basic enough to deprotonate next to any carbonyl group. The lithium enolate is stable at low temperature (–78 °C) but reactive enough to be useful. Lithium enolates are the most commonly used stable enolate equivalents in chemistry.

Second only to lithium enolates in usefulness are silyl enol ethers. Silicon is less electropositive than lithium, and silyl enol ethers are more stable, but less reactive, than lithium enolates. They are made by treating an enolate with a silicon electrophile. Silicon electrophiles invariably react with enolates at the oxygen atom firstly because they are hard (see p. 000) and secondly because of the very strong Si–O single bond. The most common silicon electrophile is trimethylsilyl chloride (Me_3SiCl), an intermediate made industrially in bulk and used to make the NMR standard tetramethyl silane (Me_4Si).

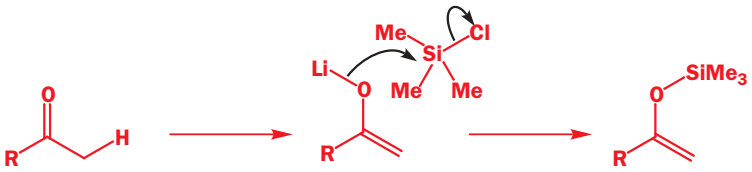
Silicon–oxygen bonds are so strong that silicon reacts with carbonyl compounds on oxygen even without a strong base to form the enolate: the reaction probably goes through the small amount of enol present in neutral solution, and just needs a weak base (Et_3N) to remove the proton from the product. An alternative view is that the silicon reacts with oxygen first, and the base just converts to oxonium ion to the silyl enol ether. Both mechanisms are given below—either might be correct. This is one of the two best ways to make a stable enol derivative from virtually any enolizable carbonyl compound.



another possible mechanism:

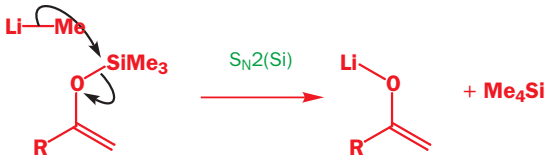


Silyl enol ethers can also be made from lithium enolates just by treating them with trimethylsilyl chloride.



lithium enolate silyl enol ether

Occasionally, it can be useful to run this reaction in reverse, generating the lithium enolate from the silyl enol ether. This can be done with methyllithium, which undergoes nucleophilic substitution at silicon to generate the lithium enolate plus tetramethylsilane. The reason why you might want to carry out this seemingly rather pointless transformation will become clear in Chapters 26 and 27.

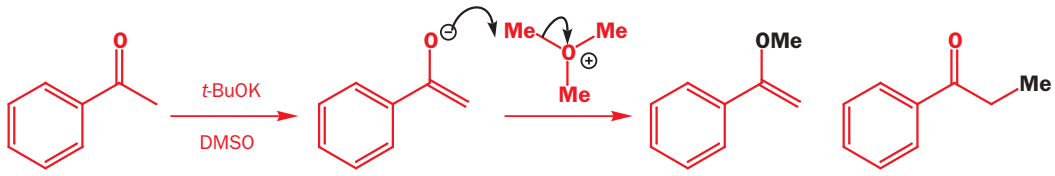


silyl enol ether lithium enolate

We shall be returning to silyl enol ethers and lithium enolates later in the book, but for the moment you should view them simply as enol derivatives that are stable enough to be isolated. This is important because it means that we do not have to content ourselves simply with small, equilibrium concentrations of enol or enolate for our reactions: we can actually prepare enolate derivatives like these in quantitative yield, and use them in a separate step.

Enol and enolate reactions at oxygen: preparation of enol ethers

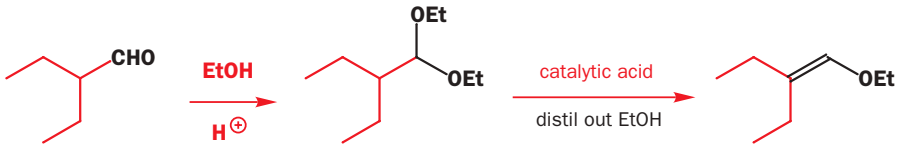
You have just seen that silyl enol ethers are easy to make. But, if enolate ions have most of their negative charge on the oxygen atom, it ought to be possible to make ordinary enol ethers from them. It is—but only under strange conditions. Normally, enols and enolate ions prefer to react with alkyl electrophiles at carbon, as we shall see in Chapter 27. If enolate ions are prepared with potassium bases in dipolar aprotic solvents (such as dimethyl sulfoxide, DMSO) that cannot solvate the oxygen anion, and are reacted with dimethyl sulfate or trimethyloxonium ion—powerful methylating agents that react best with charged atoms—some at least of the enol ether is formed. The Me_3O^+ ion is found in the stable (though reactive) compound trimethyloxonium tetrafluoroborate, or 'Meerwein's salt', $Me_3O^+BF_4^-$. This compound and dimethylsulfate, Me_2SO_4, are hard electrophiles with highly polarized C–O bonds and therefore react at hard O rather than soft C.



free enolate not bound by potassium not solvated by DMSO enol ether C-alkylated by-product

The yield in this reaction is about 60–70% of enol ether, the rest being mainly C-alkylated product. A more reliable method is the acid-catalysed decomposition of an acetal in the strict absence of water. Here is an example.

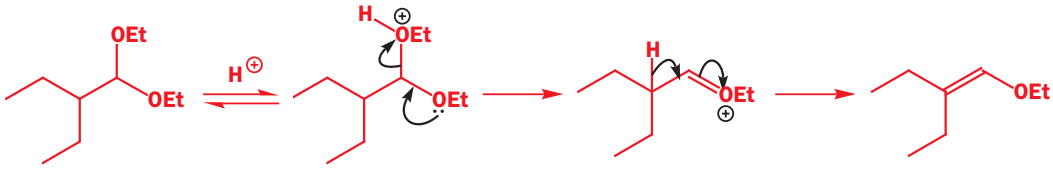
■ Although we didn't discuss the details at that stage, you first met silyl enol ethers in Chapter 10, where you saw that adding Me_3SiCl is a good way of ensuring high yields in the addition of cuprates to unsaturated carbonyl compounds.



aldehyde acetal enol ether

■ Acetal hydrolysis is discussed in Chapter 14.

The reaction starts as though the acetal were being hydrolysed, but there is no water to continue the hydrolysis, so a proton is lost instead. In other words, with no suitable nucleophile for S_N1 substitution, E1 elimination takes place.



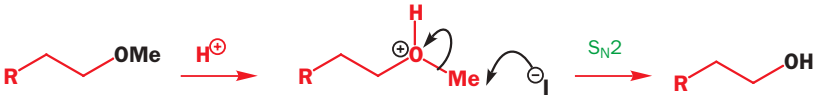
These enol ethers are rather unstable, particularly towards acid-catalysed hydrolysis (next section) and are not as useful as the silyl enol ethers. We shall next look at the enol-like reactions of both groups of enol ethers.

Reactions of enol ethers

Hydrolysis of enol ethers

Enols have an OH group and are alcohols of a sort. Normal alcohols form stable ethers that are difficult to convert back to the alcohol. Powerful reagents such as HI or BBr_3 are required and these reactions were discussed in Chapter 17. The reaction with HI is an S_N2 attack on the methyl group of the protonated ether and that is why a good nucleophile for saturated carbon, such as iodide or bromide, is needed for the reaction.

conversion of normal ether to alcohol with HI



Enol ethers, by contrast, are relatively unstable compounds that are hydrolysed back to the carbonyl compound simply with aqueous acid.

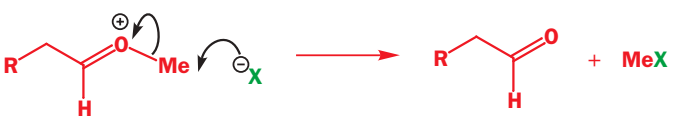
hydrolysis of enol ether with aqueous acid

enol ether enol

Why the big difference? The reason is that the enol ether can be protonated at carbon using the delocalization of the oxygen lone pair in the enol derivative to produce a reactive oxonium ion.

enol ether oxonium ion

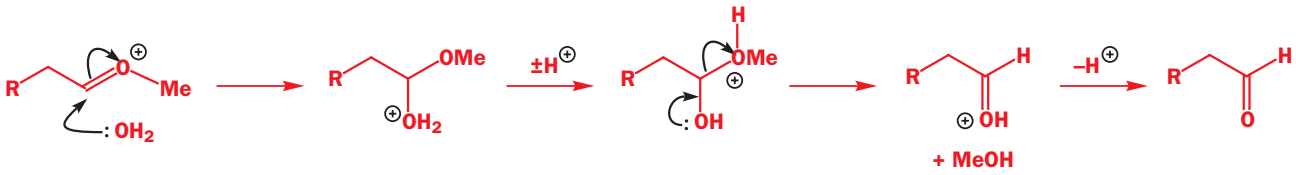
This oxonium ion could be attacked on the methyl group in the same way that the ordinary ether was attacked.



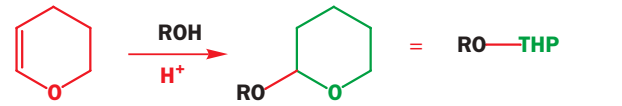
We wouldn't really expect this reaction to happen much faster than the same reaction on an ordinary ether. So there must be another better and faster mechanism. It is attack on the π bond instead of on the σ bond.

▶ Attacks on π bonds are inherently faster than attacks on σ bonds as the more weakly held π electrons are more polarized by the difference in electronegativity between C and O.

In aqueous acid the nucleophile X^- is just water and we find ourselves in the middle of the mechanism of hydrolysis of acetals (Chapter 14). The oxonium ion is a common intermediate to both mechanisms.



A similar reaction occurs when enol ethers react with alcohols in acid solution and in the absence of water, but now we are starting in the middle of the acetal hydrolysis mechanism and going the other way, in the direction of the acetal A useful example is the formation of THP (= TetraHydroPyranyl) derivatives of alcohols from the enol ether dihydropyran. You will see THP derivatives of alcohols being used as 'protecting groups' in Chapter 24.

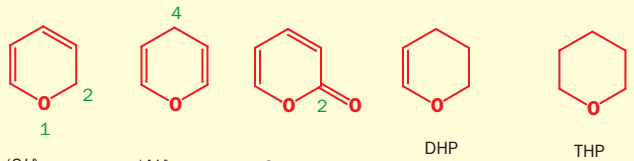


DHP
DiHydroPyran

the TetraHydroPyranyl derivative of the alcohol

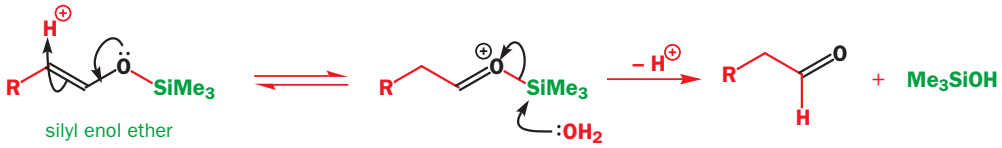
Pyrans

The naming of these compounds is a bit odd. Pyran refers to the six-membered oxygen-containing heterocyclic ring system with two double bonds. It is not aromatic though compounds like pyrones are. The compound with only one double bond is therefore dihydropyran, and the saturated ring system is tetrahydropyran.



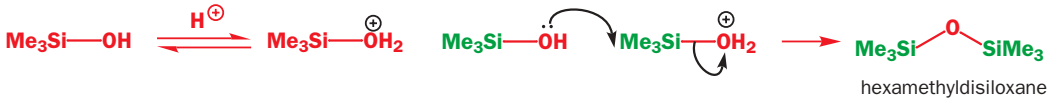
(2*H*)-pyran (4*H*)-pyran 2-pyrone DHP DiHydroPyran THP TetraHydroPyran

Silyl enol ethers hydrolyse by a slightly different mechanism, though the first step is the same—protonation at carbon using the lone pair on oxygen. We have already seen how easy it is to attack silicon with nucleophiles, especially those with oxygen or a halogen as the nucleophilic atom. This tips the balance towards attack by water at silicon for the next step.



silyl enol ether

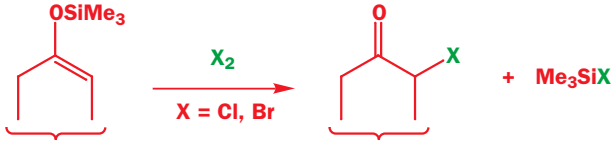
The aldehyde is formed immediately. What happens to the other product illustrates again just how easy nucleophilic substitution at silicon can be. Two of these compounds combine together to give a disilyl ether, called a disiloxane. This wouldn't have happened with *t*-butanol!



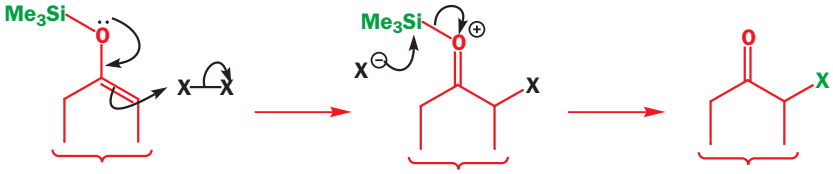
hexamethyldisiloxane

Reactions of enol ethers with halogen and sulfur electrophiles

In comparison with other ethers, enol ethers of all kinds are rather unstable. As alkenes they are also more reactive than normal alkenes because of the lone pair of electrons on the oxygen atom. They react with electrophiles like bromine or chlorine on the α carbon atom, behaving like enol derivatives and not like alkenes.



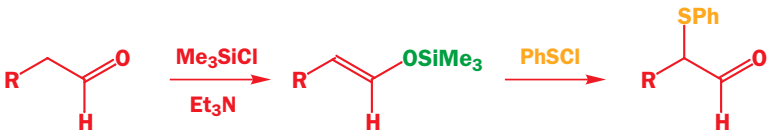
Electrophilic attack occurs at the α carbon atom and the halide ion released in this step then attacks the silicon atom to release the product and a molecule of Me_3SiX, which will be hydrolysed during the work-up.



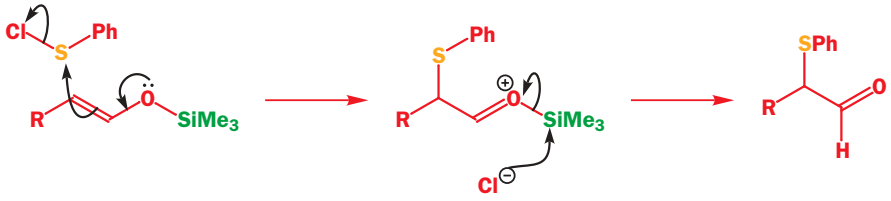
This procedure avoids the difficulties we outlined earlier in the direct halogenation of aldehydes and ketones. It allows the preparation of haloketones on the less substituted side of the carbonyl group, for instance.

LDA removes the least hindered proton

A similar method with the good soft electrophiles RSCl allows sulfenylation next to the carbonyl group.



The mechanism is very similar: the electrophilic sulfur atom attacks the α carbon atom of the silyl enol ether releasing a chloride ion that removes the Me_3Si group from the intermediate.

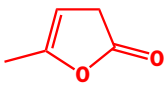


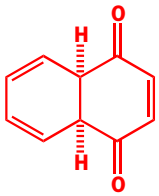
To conclude...

You have now seen how enols and enolates react with electrophiles based on hydrogen (deuterium), carbon, halogens, silicon, sulfur, and nitrogen. What remains to be seen is how new carbon–carbon bonds can be formed with alkyl halides and carbonyl compounds in their normal electrophilic mode. These reactions are the subject of Chapters 26–29. We must first look at the ways aromatic compounds react with electrophiles. You will see similarities with the behaviour of enols.

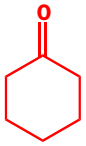
Problems

1. Draw all the possible enol forms of these carbonyl compounds and comment on the stability of the various enols.

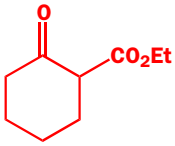




2. The proportions of enol in a neat sample of the two ketones below are shown. Why are they so different?

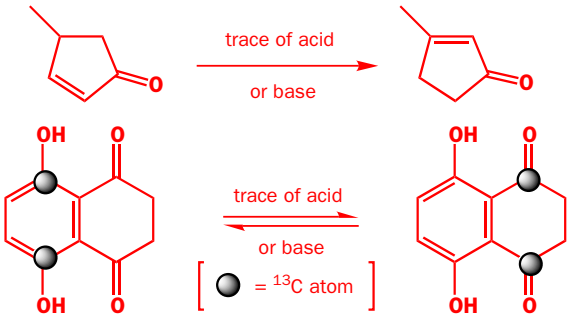


4×10^{-4}% enol

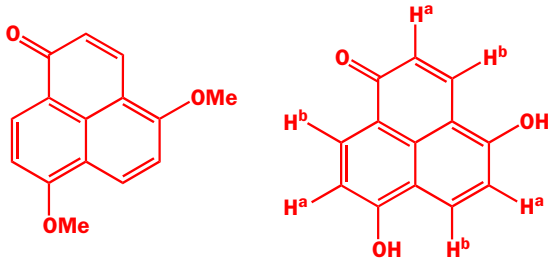


62% enol

3. Draw mechanisms for these reactions using just enolization and its reverse.



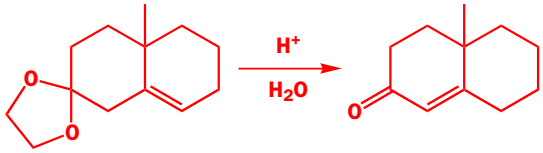
4. The NMR spectrum of this dimethyl ether is complicated—the two MeO groups are different as are all the hydrogen atoms on the rings. However, the diphenol has a very simple NMR—there are only two types of protons (marked a and b) on the rings. Explain.



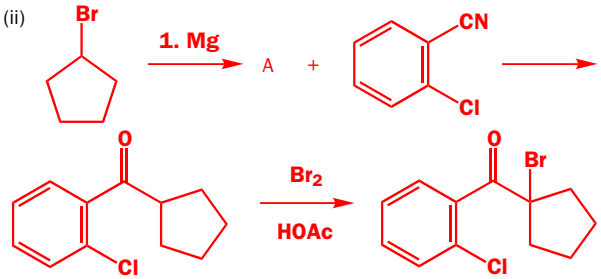
dimethyl ether diphenol

5. Suggest mechanisms for these reactions.

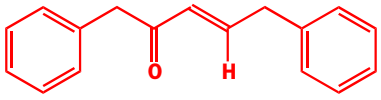
(i)



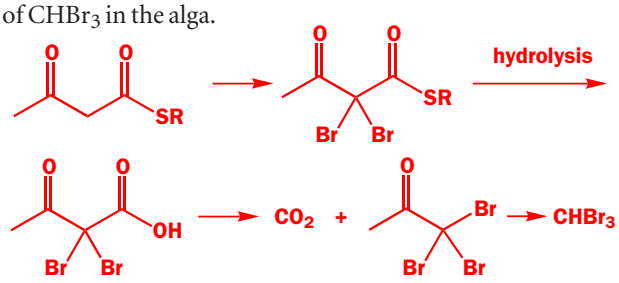
(ii)



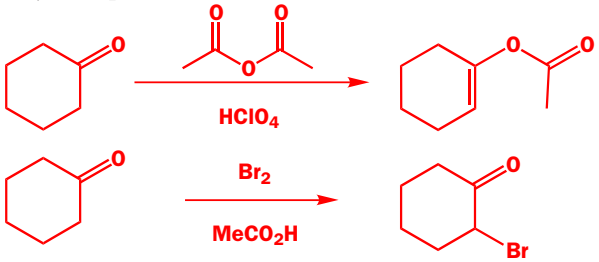
6. Treatment of this ketone with basic D_2O leads to rapid replacement of two hydrogen atoms by deuterium. Then, more slowly, all the other nonaromatic hydrogens *except* the one marked 'H' are replaced. How is this possible?



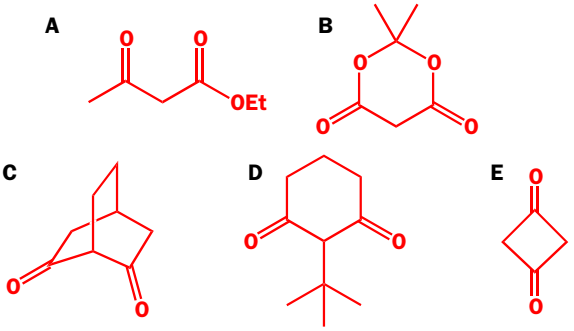
7. A red alga growing in sea water produces an array of bromine-containing compounds including $CHBr_3$, CBr_4, and $Br_2C{=}CHCO_2H$. The brominating agent is believed to be derived by the oxidation of bromide ion (Br^-) and can be represented as Br-OX. Suggest mechanistic details for the proposed biosynthesis of $CHBr_3$ in the alga.



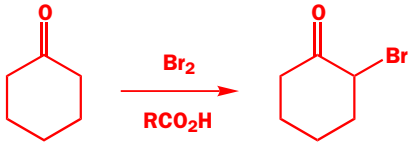
8. Suggest mechanisms for these reactions and explanations as to why these products are formed.



9. 1,3-Dicarbonyl compounds such as A are usually mostly enolized. Why is this? Draw the enols available to compounds B–E and explain why B is 100% enol but C, D, and E are 100% ketone.



10. Bromination of ketones can be carried out with molecular bromine in a carboxylic acid solution. Give a mechanism for the reaction.



The rate of the reaction is *not* proportional to the concentration of bromine [Br_2]. Suggest an explanation. Why is the bromination of ketones carried out in acidic and not in basic solution?

Electrophilic aromatic substitution 22

Connections

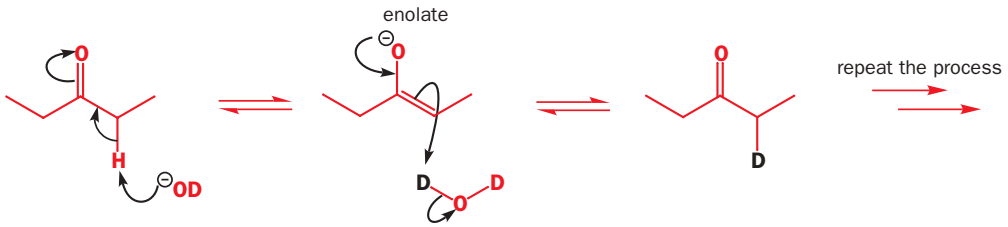
Building on:
- Structure of molecules ch4
- Conjugation ch7
- Mechanisms and catalysis ch13
- Electrophilic addition to alkenes ch20
- Enols and enolates ch21

Arriving at:
- Phenols as aromatic enols
- Benzene and alkenes compared
- Electrophilic attack on benzene
- Activation and deactivation
- Position of substitution
- Competition and cooperation
- Problems with some reactions

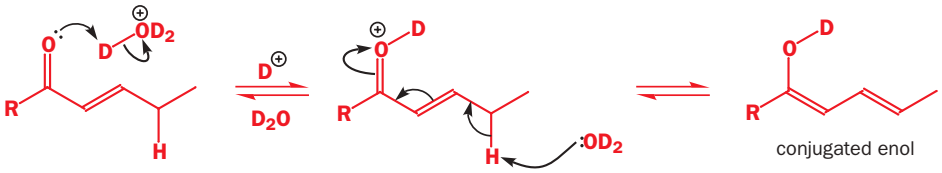
Looking forward to:
- Nucleophilic aromatic substitution ch23
- Oxidation and reduction ch24
- Synthesis in action ch25
- Retrosynthetic analysis ch30
- Aromatic heterocycles ch43–ch44
- Rearrangements ch37

Introduction: enols and phenols

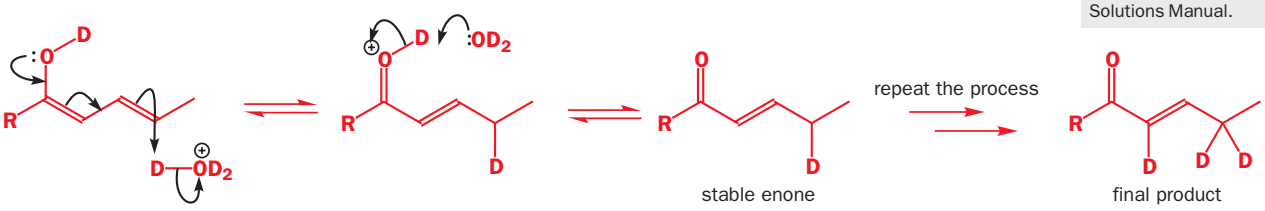
You have seen how, in acid or base, the protons in the α positions of ketones could be replaced by deuterium atoms (Chapter 21). In each case the reaction goes via the enol tautomer of the ketone (or enolate). For example, in base:



If you did Problem 6 in Chapter 21 (if you didn't, now would be a good time!), you also saw how conjugated ketones could be deuterated at positions other than the α positions; for example, in acid we now need to concentrate on the conjugated enol formed by loss of a more remote proton.



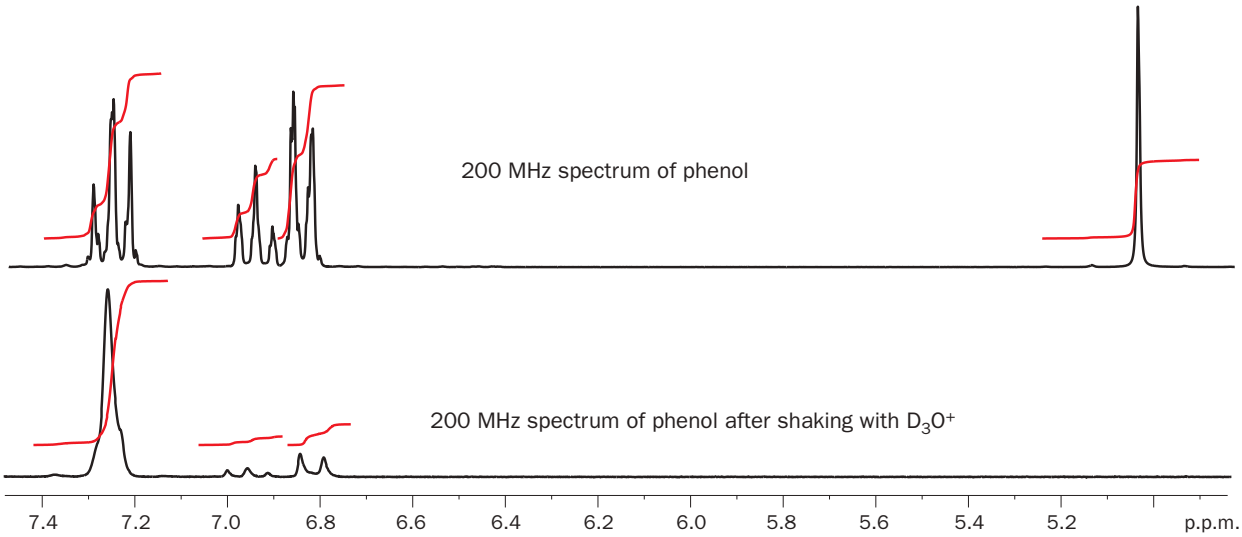
The conjugated enol could react with D_3O^+ at the normal α position, but it could also react at the more remote γ position, the position from which we have just removed a proton.



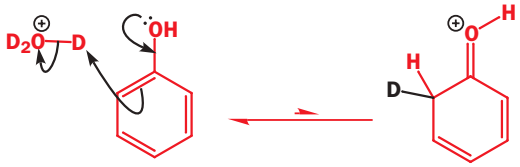
■ If you don't see how the third deuterium atom gets into the molecule, see the solution to Problem 21.6 in the Solutions Manual.

Here, as usual, the keto/enol equilibrium lies well over in favour of the ketone, but in this chapter we shall be discussing one very stable enol—phenol, PhOH. The proton NMR spectrum for phenol

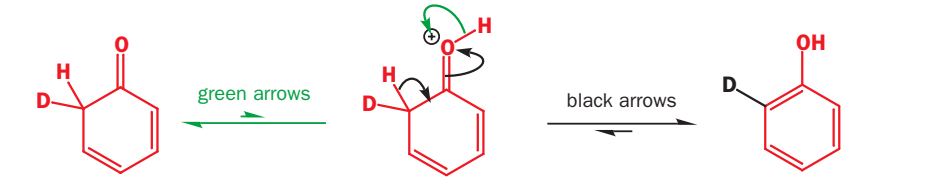
is shown below. Also shown below is the proton NMR after shaking phenol with acidic D_2O. Can you assign the spectra?



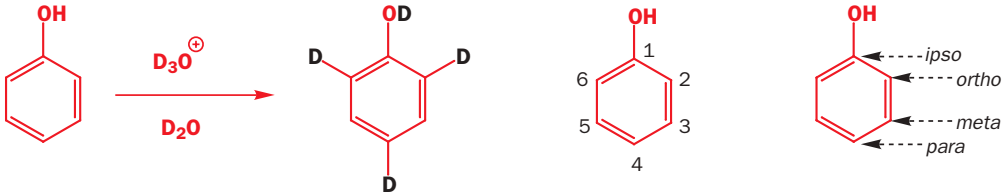
Phenol is deuterated in exactly the same way as any other conjugated enol except that the final product remains as the very stable enol form of phenol rather than the keto form. The enol form of phenol is so stable because of the aromaticity of the benzene ring. The first step is addition of D_3O^+ to the 'enol'.



Now the intermediate cation could lose the proton from oxygen to leave a ketone or it could lose the proton from carbon to leave the phenol, or it could lose the deuteron and go back to the starting material.



The end product on treating phenol with D_3O^+ simply has certain H atoms replaced by deuterium atoms. We say 'certain H atoms' but exactly which ones? The most acidic proton is the phenolic proton, the OH (pK_a about 10); this will rapidly be exchanged. The other protons that will be replaced will be the ones in the 2, 4, and 6 positions (that is, the *ortho* and *para* positions). Below is a reminder of the names we give to the positions around a benzene ring relative to any substituent.

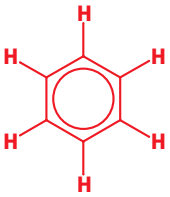


Phenol initially behaves like a conjugated enol in its reactions with electrophiles but, instead of giving a ketone product, the enol is formed because the very stable aromatic ring is regained. This

chapter is about the reactions of phenols and other aromatic compounds with electrophiles. You will see phenols reacting like enols, except that the final product is also an enol, and you will also see simple benzenes reacting like alkenes, except that the result is substitution rather than addition. We shall start with a discussion of the structure of benzene and of aromaticity.

■ The details of the orbitals of benzene appeared in Chapter 4 (p. 000).

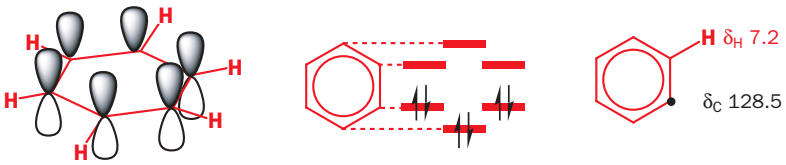
Benzene and its reaction with electrophiles



Benzene is a planar symmetrical hexagon with six trigonal (sp^2) carbon atoms, each having one hydrogen atom in the plane of the ring. All the bond lengths are 1.39 Å (compare C–C 1.47 Å and C=C 1.33 Å). All the ^{13}C shifts are the same (δ_C 128.5 p.p.m.).

The special stability of benzene (aromaticity) comes from the six π electrons in three molecular orbitals made up by the overlap of the six atomic p orbitals on the carbon atoms. The energy levels of these orbitals are arranged so that there is exceptional stability in the molecule (a notional 140 kJ mol^{-1} over a molecule with three conjugated double bonds), and the shift of the six identical hydrogen atoms in the NMR spectrum (δ_H 7.2 p.p.m.) is evidence of a ring current in the delocalized π system.

■ This section revises material from Chapters 4, 8, and 11 where more details can be found.



Drawing benzene rings

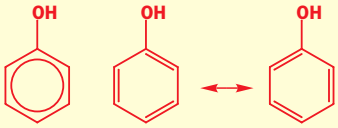
Benzene is symmetrical and the circle in the middle best represents this. However, it is impossible to draw mechanisms on that representation so we shall usually use the **Kekulé** form with three double bonds. This does not mean that we think the double bonds are localized but just that we need to draw curly arrows. It makes no difference which Kekulé structure you draw—the mechanism can be equally well drawn on either.

this circle structure best represents the six delocalized π electrons

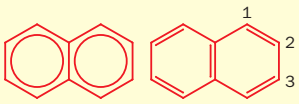
these Kekulé structures are best for drawing curly arrows. They are equivalent

When we move away from benzene itself to discuss molecules such as phenol, the bond lengths are no longer exactly the same. However, it is still all right to use either representation, depending on the purpose of the drawing. With some aromatic compounds, such as naphthalene, it does matter as there is some bond alternation. Either representation is still all right, but only one Kekulé representation shows that the central bond is the strongest and shortest in the molecule and that the C1–C2 bond is shorter that the C2–C3 bond.

three acceptable drawings of phenol. The Kekulé drawings are equivalent



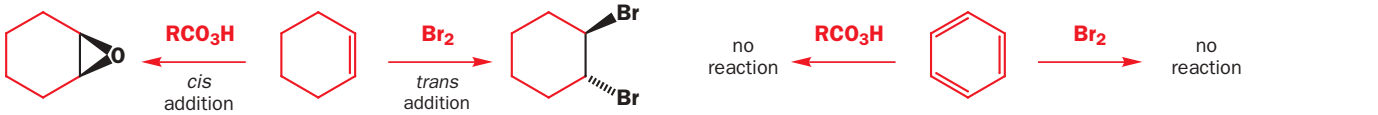
two acceptable drawings of naphthalene. Only one Kekulé drawing is satisfactory



▶ Not everyone agrees that the two circles are all right for naphthalene. If each circle represents six electrons, this representation is wrong as there are only ten electrons altogether. If you don't interpret the circles quite so strictly they're all right.

Electrophilic attack on benzene and on cyclohexene

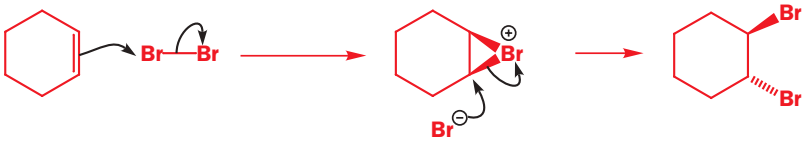
Simple alkenes, including cyclohexene, react rapidly with electrophiles such as bromine or peroxy-acids (Chapter 20). Bromine gives a product of *trans* addition, peracids give epoxides by *cis* addition. Under the same conditions benzene does not react with either reagent.



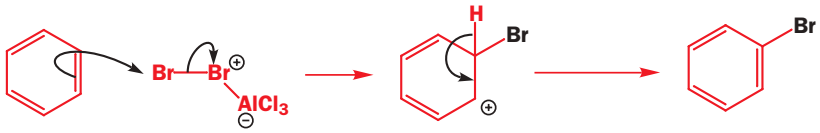
Benzene can be persuaded to react with bromine if a Lewis acid catalyst such as $AlCl_3$ is added. The product contains bromine but is not from either *cis* or *trans* addition.

The bromine atom has replaced an atom of hydrogen and so this is a substitution reaction. The reagent is electrophilic bromine and the molecule is aromatic so the reaction is **electrophilic aromatic substitution** and that is the subject of this chapter. We can compare the bromination of cyclohexene and of benzene directly.

electrophilic addition to an alkene



electrophilic substitution on benzene

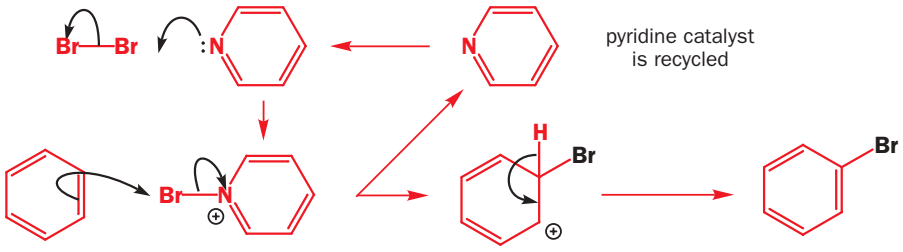


The intermediate in both reactions is a cation but the first (from cyclohexene) adds an anion while the second (from benzene) loses a proton so that the aromatic system can be restored. Notice also that neutral bromine reacts with the alkene but the cationic $AlCl_3$ complex is needed for benzene. Another way to produce a more electrophilic source of bromine is to use a pyridine catalyst. Pyridine attacks the bromine molecule producing a cationic bromine compound.

formation of reactive brominating agent

pyridine catalyst is recycled

electrophilic substitution on benzene



Bromine itself is a very reactive electrophile. It is indeed a dangerous compound and should be handled only with special precautions. Even so it does not react with benzene. It is very difficult to get benzene to react with anything.

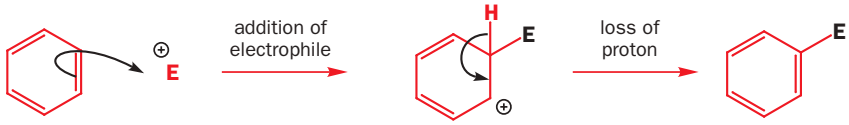
Benzene is very unreactive

- **It combines only with very reactive (usually cationic) electrophiles**
- **It gives substitution and not addition products**

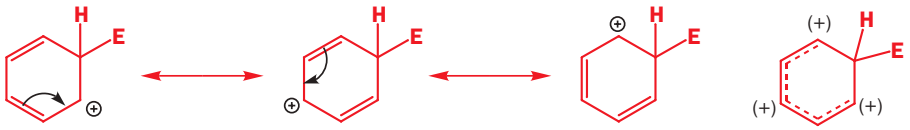
The intermediate in electrophilic aromatic substitution is a delocalized cation

These two brominations are examples of the mechanism of electrophilic aromatic substitution, which, in many different guises, will return again and again during this chapter. In its most general form the mechanism has two stages: attack by an electrophile to give an intermediate cation and loss of a proton from the cation to restore the aromaticity.

mechanism for electrophilic aromatic substitution

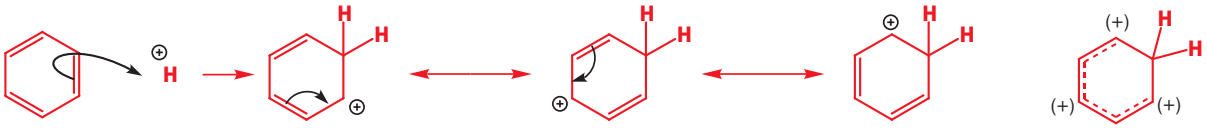


The cationic intermediate is, of course, less stable than the starting materials or the product but as a cation it is reasonably stable because of delocalization around the six-membered ring. The charge can be delocalized to the two *ortho* positions and to the *para* position or can be drawn as a delocalized structure with dotted bonds and about one-third of a plus charge (+) at three atoms.



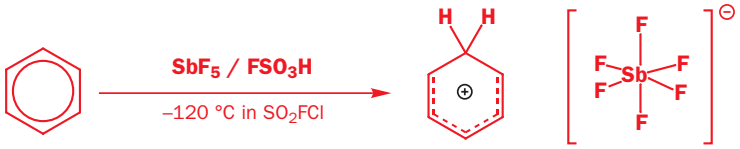
the intermediate in electrophilic aromatic substitution

In strong acid, the electrophile would be a proton and the reaction would be the exchange of the protons in the benzene ring in the style of the proton exchange on phenol with which we started this chapter. In D_3O^+, this would ultimately lead to C_6D_6 which is a useful solvent in NMR. As with the bromination reaction, the first step in the mechanism is the formation of a cationic intermediate.

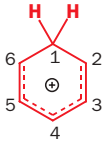
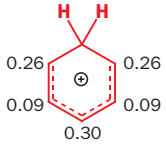


It is actually possible to observe this cationic intermediate. The trick is to pick a nonnucleophilic and nonbasic counterion X^-, such as antimony hexafluoride SbF_6^-. In this octahedral anion, the central antimony atom is surrounded by the fluorine atoms and the negative charge is spread over all seven atoms. The protonation is carried out using FSO_3H and SbF_5 at –120 °C.

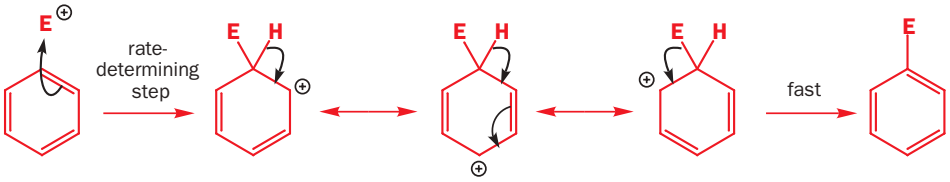
■ This trick was used to show the existence of simple carbocations as intermediates in the S_N1 mechanism in Chapter 17.



Under these conditions it is possible to record the ^1H and ^{13}C NMR spectra of the cation. The shifts show that the positive charge is spread over the ring but is greatest (or the electron density is least) in the *ortho* and *para* positions. Using the data for the ^1H and ^{13}C NMR shifts (δ_H and δ_C, respectively), a charge distribution can be calculated.

Compound	Position	δ_H, p.p.m.	δ_C, p.p.m.	Calculated charge distribution
	1	5.6	52.2	
	2, 6	9.7	186.6	
	3, 5	8.6	136.9	
	4	9.3	178.1	
benzene		7.33	129.7	

Curly arrows also predict the same electron distribution for all these intermediates, whether the electrophile is a proton or any of the other reagents we will meet in this chapter. The cation can be represented as three different delocalized structures that show clearly the electron-deficient atoms, or by a structure with partial bonds that shows the delocalization but is of no use for drawing mechanisms.

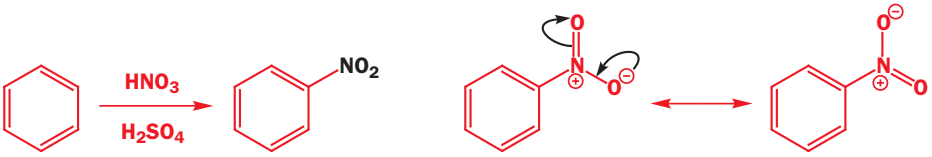


It is not surprising that the formation of the cationic intermediate is the rate-determining step, as aromaticity is temporarily lost in this step. The mechanism of the fast proton loss from the intermediate is shown in three ways just to prove that it doesn't matter which of the delocalized structures you choose. A useful piece of advice is that, when you draw the intermediate in any electrophilic aromatic substitution, you should always draw in the hydrogen atom at the point of substitution, just as we have been doing.

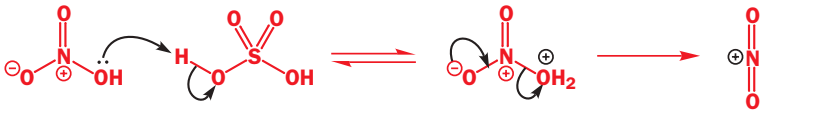
Nitration of benzene

■ In Chapter 2 the structure of the nitro group was discussed. It has a delocalized structure with two charges as nitrogen cannot have five bonds as it would then have to have ten electrons.

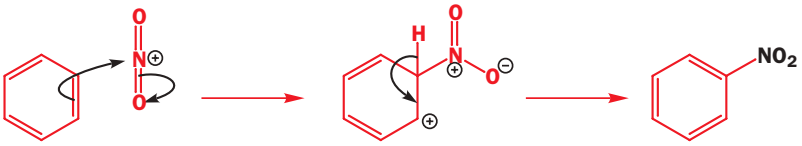
Perhaps the most important of all the reactions in this chapter is nitration, the introduction of a nitro (NO_2) group, into an aromatic system, as it provides a general entry into aromatic nitrogen compounds. This reaction is not available for aliphatic nitrogen compounds, which are usually made with nucleophilic nitrogen reagents. Aromatic nitration requires very powerful reagents, the most typical being a mixture of concentrated nitric and sulfuric acids.



The first steps are the formation of a very powerful electrophile, none other than NO_2^+, by the interaction of the two strong acids. Sulfuric acid is the stronger and it protonates the nitric acid on the OH group so that a molecule of water can leave.



Notice that the nitronium ion (NO_2^+) is linear with an sp hybridized nitrogen at the centre. It is isoelectronic with CO_2. It is also very reactive and combines with benzene in the way we have just described. Benzene attacks the positively charged nitrogen atom but one of the N=O bonds must be broken at the same time to avoid five-valent nitrogen.

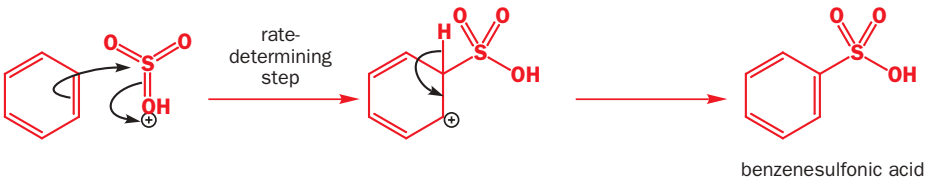


● **Nitration converts aromatic compounds (ArH) into nitrobenzenes ($ArNO_2$) using NO_2^+ from $HNO_3 + H_2SO_4$.**

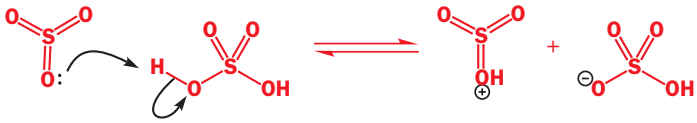
Sulfonation of benzene

Benzene reacts slowly with sulfuric acid alone to give benzenesulfonic acid. The reaction starts with the protonation of one molecule of sulfuric acid by another and the loss of a molecule of water. This is very similar to the first steps in nitration.

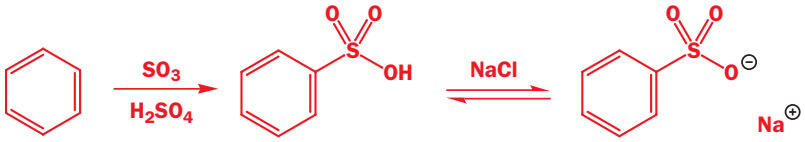
The cation produced is very reactive and combines with benzene by the same mechanisms we have seen for bromination and nitration: slow addition to the aromatic π system followed by rapid loss of a proton to regenerate the aromaticity. The product contains the sulfonic acid functional group $–SO_2OH$.



The cationic intermediate can also be formed by the protonation of sulfur trioxide, SO_3, and another way to do sulfonations is to use concentrated sulfuric acid with SO_3 added. These solutions have the industrial name **oleum**. It is possible that the sulfonating agent in all these reactions is not protonated SO_3 but SO_3 itself.



Sulfonic acids are strong acids, about as strong as sulfuric acid itself. They are stronger than HCl, for example, and can be isolated from the reaction mixture as their crystalline sodium salts if an excess of NaCl is added. Not many compounds react with NaCl.



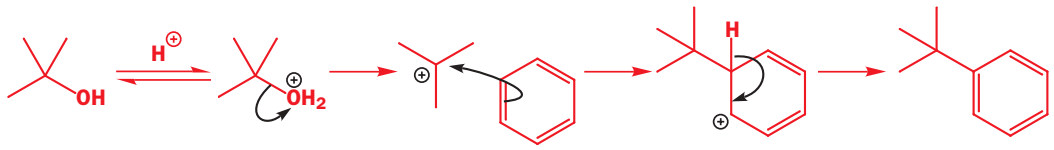
benzenesulfonic acid

crystalline sodium benzene sulfonate

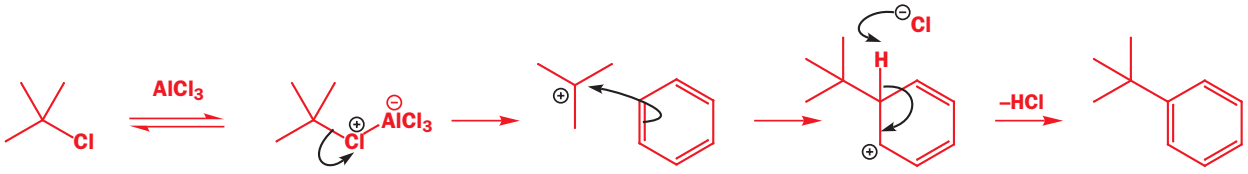
Sulfonation with H_2SO_4 or SO_3 in H_2SO_4 converts aromatic compounds (ArH) into aromatic sulfonic acids ($ArSO_2OH$). The electrophile is SO_3 or SO_3H^+.

Alkyl and acyl substituents can be added to a benzene ring by the Friedel–Crafts reaction

So far we have added heteroatoms only—bromine, nitrogen, or sulfur. Adding carbon electrophiles requires reactive carbon electrophiles and that means carbocations. In Chapter 17 you learned that any nucleophile, however weak, will react with a carbocation in the S_N1 reaction and even benzene rings will do this. The classic S_N1 electrophile is the *t*-butyl cation generated from *t*-butanol with acid.



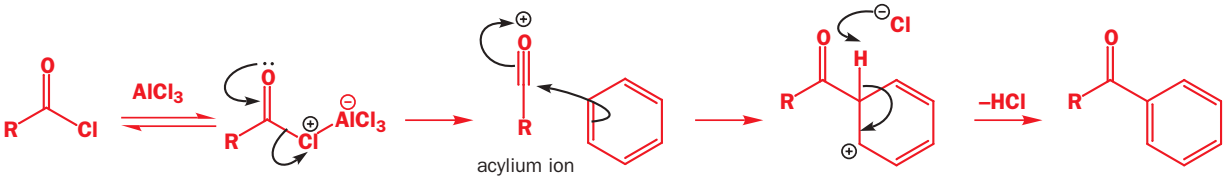
This is, in fact, an unusual way to carry out such reactions. The **Friedel–Crafts alkylation**, as this is known, usually involves treating benzene with a *t*-alkyl chloride and the Lewis acid $AlCl_3$. Rather in the manner of the reaction with bromine, $AlCl_3$ removes the chlorine atom from *t*-BuCl and releases the *t*-Bu cation for the alkylation reaction.



We have not usually bothered with the base that removes the proton from the intermediate. Here it is chloride ion as the by-product is HCl, so you can see that even a very weak base will do. Here is the second reaction in a few pages that is carried out by chloride ion. Anything, such as water, chloride, or other counterions of strong acids, will do this job well enough and you need not in general be concerned with the exact agent.

Charles Friedel (1832–99), a French chemist, and James Crafts (1839–1917), an American mining engineer, both studied with Wurtz and then worked together in Paris where in 1877 they discovered the Friedel–Crafts reaction.

A more important variation is the Friedel–Crafts acylation with acid chlorides and $AlCl_3$. As you saw in Chapter 13, acid chlorides can give the rather stable acylium ions even in hydrolytic reactions and they do so readily with Lewis acid catalysis. Attack on a benzene ring then gives an aromatic ketone. The benzene ring has been acylated.



The acylation is better than the alkylation because it does not require any particular structural feature in the acyl chloride—R can be almost anything. In the alkylation step it is essential that the alkyl group can form a cation; otherwise the reaction does not work very well. In addition, for reasons we are about to explore, the acylation stops cleanly after one reaction whereas the alkylation often gives mixtures of products.

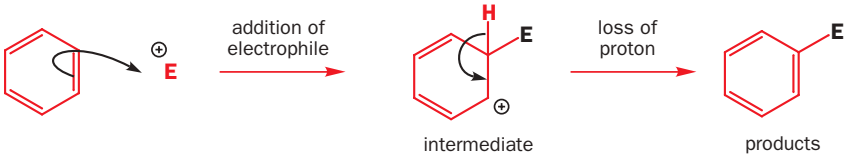
● Friedel–Crafts reactions

Friedel–Crafts alkylation with *t*-alkyl chlorides and Lewis acids (usually $AlCl_3$) gives *t*-alkyl benzenes. The more reliable Friedel–Crafts acylation with acid chlorides and Lewis acids (usually $AlCl_3$) gives aryl ketones.

Summary of electrophilic substitution on benzene

This completes our preliminary survey of the most important reactions in aromatic electrophilic substitution. We shall switch our attention to the benzene ring itself now and see what effects various types of substituent have on these reactions. During this discussion we will return to each of the main reactions and discuss them in more detail. Meanwhile, we leave the introduction with an energy profile diagram in the style of Chapter 13 for a typical substitution.

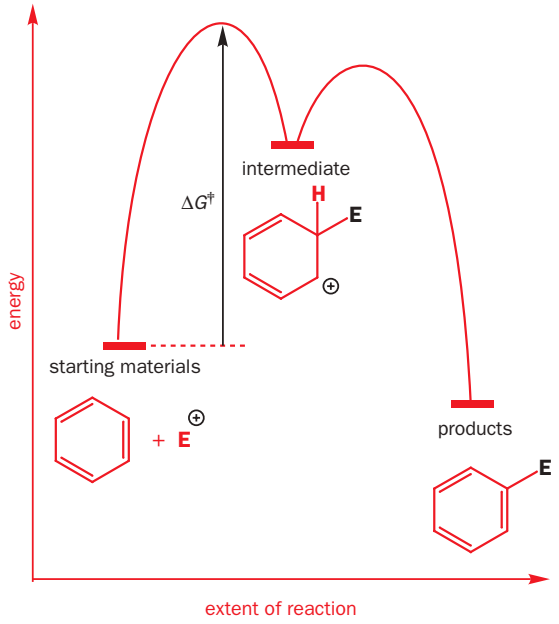
mechanism for electrophilic aromatic substitution



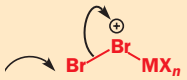
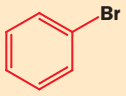
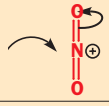
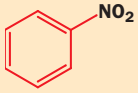
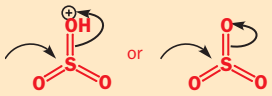
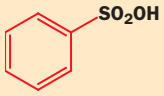
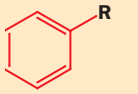
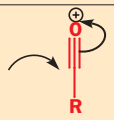
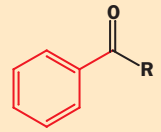
▶ This argument is based on the **Hammond postulate,** which suggests that structures close in energy that transform directly into each other are also similar in structure.

Since the first step involves the temporary disruption of the aromatic π system, and is therefore rate-determining, it must have the higher-energy transition state. The intermediate is unstable and has a much higher energy that either the starting material or the products, close to that of the transition states. The two transition states will be similar in structure to the intermediate and we shall use the intermediate as a model for the important first transition state.

The reaction is so slow and the transition state so high because the only HOMO available is a pair of very low-energy bonding electrons in the benzene ring and because the uniquely stable aromatic π system is already disrupted in the transition state.



Summary of the main electrophilic substitutions on benzene

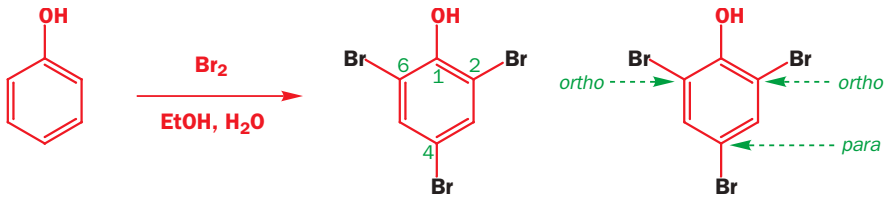
Reaction	Reagents	Electrophile	Products
bromination	Br_2 and Lewis acid, e.g. $AlCl_3$, $FeBr_3$, Fe powder		
nitration	$HNO_3 + H_2SO_4$		
sulfonation	concentrated H_2SO_4 or $H_2SO_4 + SO_3$ (oleum)		
Friedel–Crafts alkylation	RX + Lewis acid usually $AlCl_3$		
Friedel–Crafts acylation	RCOCl + Lewis acid usually $AlCl_3$		

Electrophilic substitution on phenols

We started this chapter by comparing phenols with enols (Ph-enol is the phenyl enol) and now we return to them and look at electrophilic substitution in full detail. You will find that the reaction is much easier than it was with benzene itself because phenols are like enols and the same reactions (bromination, nitration, sulfonations, and Friedel–Crafts reactions) occur more easily. There is a new question too: the positions round the phenol ring are no longer equivalent—where does substitution take place?

Phenols react rapidly with bromine

Benzene does not react with bromine except with Lewis acid catalysis. Phenols react in a very different manner: no Lewis acid is needed, the reaction occurs very rapidly, and the product contains three atoms of bromine in specific positions. All that needs to be done is to add bromine dropwise to a solution of phenol in ethanol. Initially, the yellow colour of the bromine disappears but, if, when the colour just remains, water is added, a white precipitate of 2,4,6-tribromophenol is formed.

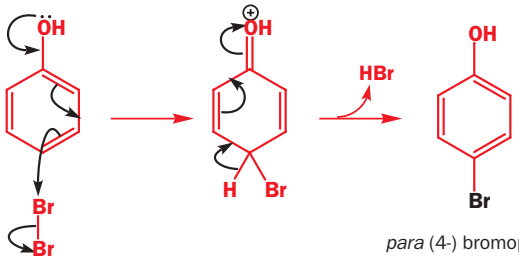


The product shows that bromination has occurred at the *para* position and at both *ortho* positions. What a contrast to benzene! Phenol reacts three times as rapidly without catalysis at room temperature. Benzene reacts once and needs a Lewis acid to make the reaction go at all. The difference is, of course, the enol nature of phenol. The highest-energy electrons in phenol are no longer those in the benzene ring but the lone pairs on oxygen. These nonbonding electrons contribute to a much higher-energy HOMO than the very low-energy bonding electrons in the aromatic ring. We should let our mechanism show this. Starting in the *para* position:

▶ This is not strictly *catalysis* as a stoichiometric amount of Lewis acid is needed and cannot be recovered.

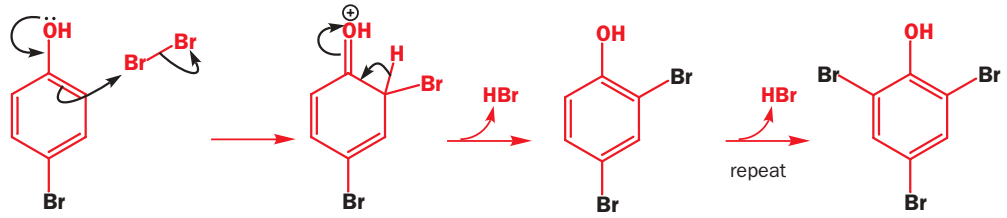
■ This should remind you of the bromination of enols in Chapter 21.

Notice that we start the chain of arrows with the lone pair electrons on the OH group and push them through the ring so that they emerge at the *para* position to attack the bromine molecule. The benzene ring is acting as a conductor allowing electrons to flow from the OH group to the bromine molecule.



para (4-) bromophenol

Now repeating the reaction but this time at one of the two equivalent *ortho* positions:

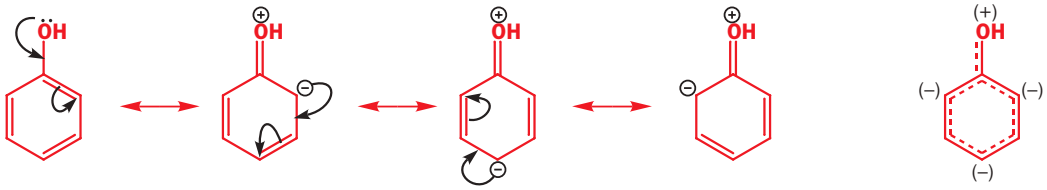


para (4-) bromophenol — 2,4-dibromophenol — 2,4,6-tribromophenol

▶ Why do we use numbers for some descriptions such as 2,4-dibromophenol but also use *ortho* and *para* in others? The numbers are best in naming compounds but we need *ortho* and *para* to describe the relationship between substituents. Phenol brominates in both *ortho* positions. In this molecule they happen to be positions 2 and 6 but in other molecules, where the OH group is not on C1, they will have other numbers, but they will still be *ortho* to the OH group. Use whichever description suits the point you are making.

Again the lone pair electrons on the OH group are the HOMO and these electrons are fed through the benzene ring to emerge at the *ortho* position. A third bromination in the remaining *ortho* position—you could draw the mechanisms for this as practice—gives the final product 2,4,6-tribromophenol.

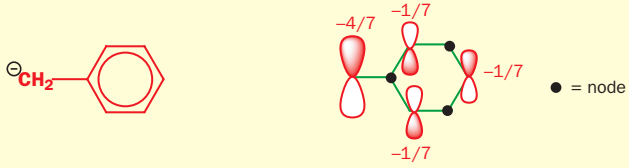
The OH group is said to be ***ortho, para*-directing** towards electrophiles. No substitution occurs in either *meta* position. We can understand this by looking at the curly arrow mechanisms or by looking at the molecular orbitals. In Chapter 21 (p. 000) we looked at the π system of an enolate and saw how the electron density is located mainly on the end atoms (the oxygen and the carbon). In phenol it is the *ortho* and *para* positions that are electron-rich (and, of course, the oxygen itself). We could show this using curly arrows.



The curly arrows actually give an indication of the electron distribution in the HOMO of the molecule. The reason is that the HOMO has large coefficients at *every other* atom, just as the allyl anion had large coefficients at its ends but not in the middle (Chapter 7).

Benzyl anion HOMO – a model for phenol

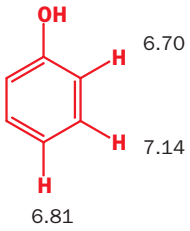
A better analogy for phenol is the benzyl anion. The benzyl anion is simpler because we do not have the added complication of the differences in electronegativities between the oxygen and carbon atoms. According to simple calculations, the highest occupied molecular orbital (HOMO) for the benzyl anion is a nonbonding molecular orbital (MO) with the distribution like this.



the benzyl anion — the charge distribution in the HOMO for the benzyl anion

In this MO there are no bonding interactions between adjacent atoms so the HOMO for the benzyl anion is actually a nonbonding MO. Most of the electron density is on the benzylic carbon atom not in the ring, but there is also significant electron density on the ring carbon atoms in the *ortho* and *para* positions. The distribution for phenol will be different because it is not an anion and the oxygen atom is more electronegative than carbon but the overall distribution will be as predicted by the curly arrows—most on the oxygen and on the *ortho* and *para* carbon atoms.

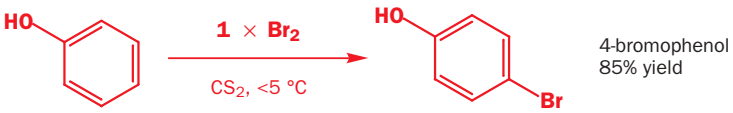
NMR can give us some confirmation of the electron distribution



proton NMR shifts in phenol (benzene, 7.26 p.p.m.)

The ^{1}H NMR shifts of phenol give us an indication of the electron distribution in the π system. The more electron density that surrounds a nucleus, the more shielded it is and so the smaller the shift (see p. 000). All the shifts for the ring protons in phenol are less than those for benzene (7.28 p.p.m.), which means that overall there is greater electron density in the ring. There is little difference between the *ortho* and the *para* positions: both are electron-rich.

The shifts are smallest in the *ortho* and *para* positions so these are where there is greatest electron density and hence these are the sites for electrophilic attack. The shifts in the *meta* positions are not significantly different from those in benzene. If you want to put just one bromine atom into a phenol, you must work at low temperature (< 5 °C) and use just one equivalent of bromine. The best solvent is the rather dangerously inflammable carbon disulfide (CS_2), the sulfur analogue of CO_2. Under these conditions, *para* bromophenol is formed in good yield as the main product, which is why we started the bromination of phenol in the *para* position. The minor product is *ortho* bromophenol.



4-bromophenol
85% yield

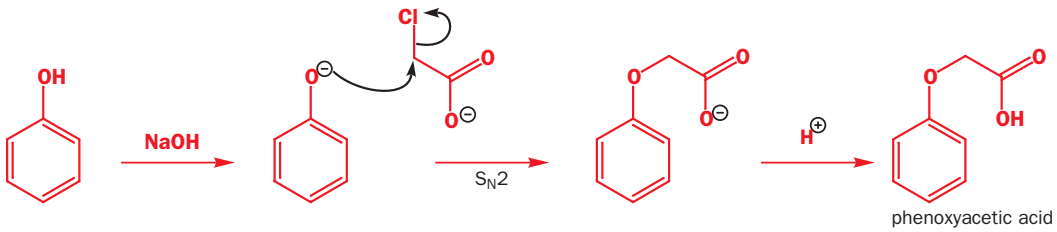
Electrophilic attack on phenols

- OH groups on benzene rings are *ortho, para*-directing and activating
- You will get the right product if you start your arrows at a lone pair on the OH group

Benzene is less reactive than phenol towards electrophiles

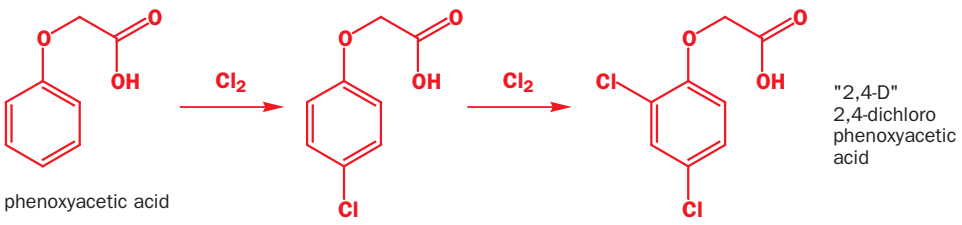
To brominate phenol, all we had to do was to mix bromine and phenol—if we do this with benzene itself, nothing happens. We therefore say that, relative to benzene, the OH group in phenol *activates* the ring towards electrophilic attack. The OH group is activating and *ortho, para*-directing. Benzene *will* undergo electrophilic aromatic substitution as we have seen in a variety of reactions with catalysis by strong protic acids or Lewis acids such as $AlCl_3$. It is the donation of electrons on the oxygen into the aromatic ring that makes phenol so much more reactive than benzene towards electrophiles. Other groups that can donate electrons also activate and direct *ortho, para*. Anisole (methoxybenzene) is the 'enol ether' equivalent of phenol. It reacts faster than benzene with electrophiles.

The multiple chlorination of another activated compound, phenoxyacetic acid, leads to a useful product. This compound is made industrially by an S_N2 reaction (Chapter 17) on chloroacetic acid (made by chlorination of acetic acid, Chapter 21) with phenol in alkaline solution. Reaction occurs at the oxygen atom rather than on the ring.



phenoxyacetic acid

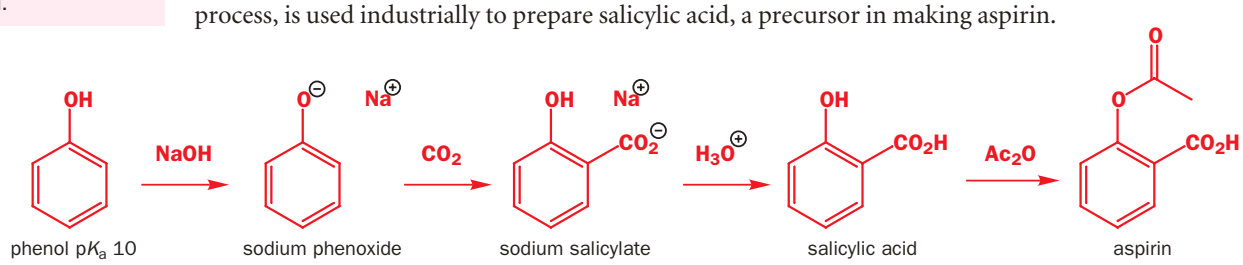
The herbicide '2,4-D' is 2,4-dichlorophenoxy acetic acid and is made, again industrially, by chlorination of the acid with two equivalents of chlorine. The first probably goes into the *para* position and the second into one of the equivalent *ortho* positions.



phenoxyacetic acid

▶ Salicylic acid is 2-hydroxybenzoic acid and is named after the willow trees (genus *Salix*) from which it was first isolated.

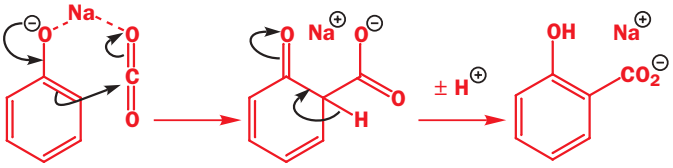
The phenoxide ion is even more reactive towards electrophilic attack than phenol. It will even react with such weak electrophiles as carbon dioxide. This reaction, known as the Kolbe–Schmitt process, is used industrially to prepare salicylic acid, a precursor in making aspirin.



phenol pK_a 10 | sodium phenoxide | sodium salicylate | salicylic acid | aspirin

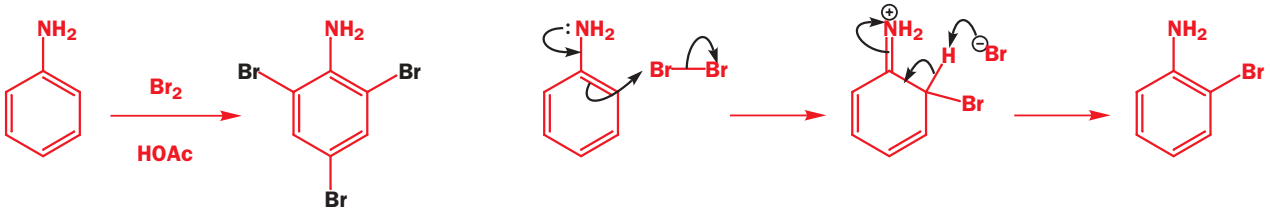
The O^- substituent is *ortho, para*-directing but the electrophilic substitution step with CO_2 gives mostly the *ortho* product so there must be some coordination between the sodium ion and two oxygen atoms, one from the phenoxide and one from CO_2. The electrophile is effectively delivered to the *ortho* position.

We shall return to reactions of phenols and phenyl ethers when we consider directing effects in electrophilic aromatic substitution in other reactions and in Friedel–Crafts reactions in particular.

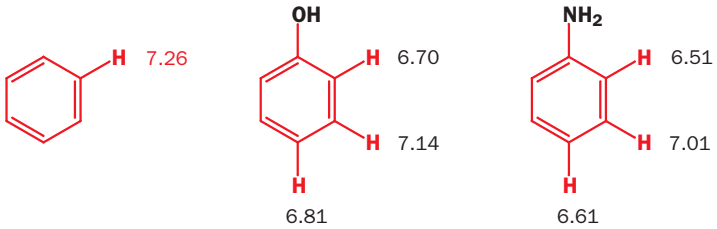


A nitrogen lone pair activates even more strongly

Aniline (phenylamine) is even more reactive towards electrophiles than phenols, phenyl ethers, or phenoxide ions. Because nitrogen is less electronegative than oxygen, the lone pair is higher in energy and so more available to interact with the π system than is the lone pair on oxygen (look back to p. 000 where we compare the reactivity of amides and esters). Reaction with bromine is very vigorous and rapidly gives 2,4,6-tribromoaniline. The mechanism is very similar to the bromination of phenol so we show only one *ortho* substitution.

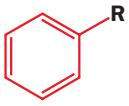


The ^{1}H NMR of aniline supports the increased electron density in the π system—the shifts for the aromatic protons are even smaller than those for phenol showing greater electron density in the *ortho* and *para* positions.



Just how good nitrogen is in donating electrons into the π system is shown by comparing the relative rates for the bromination of benzene, methoxybenzene (anisole), and *N,N*-dimethylaniline.

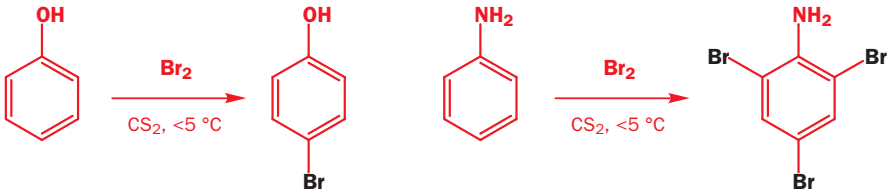
Compound	Rate of bromination relative to benzene
Benzene	1
Methoxybenzene (anisole)	10^9
N,N-dimethylaniline	10^{14}



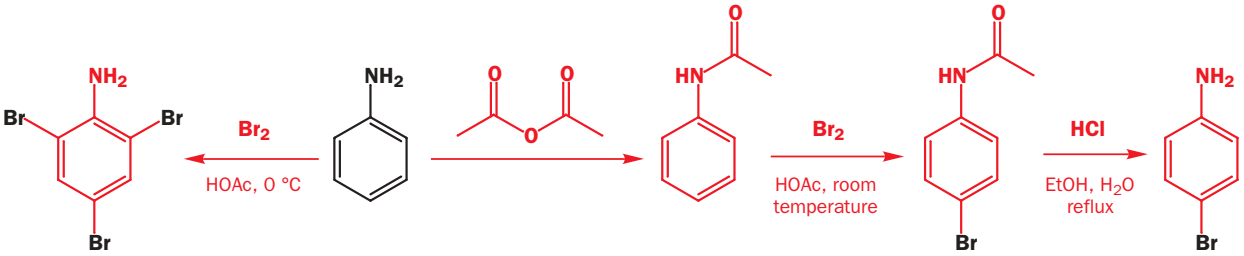
R = H; benzene
R = OMe; anisole
R = NMe_2; *N,N*-dimethylaniline

Making amines less reactive

The high reactivity of aniline can actually be a problem. Suppose we wanted to put just one bromine atom on to the ring. With phenol, this is possible (p. 000)—if bromine is added slowly to a solution of phenol in carbon disulfide and the temperature is kept below 5 °C, the main product is *para*-bromophenol. Not so if aniline is used—the main product is the triply substituted product.

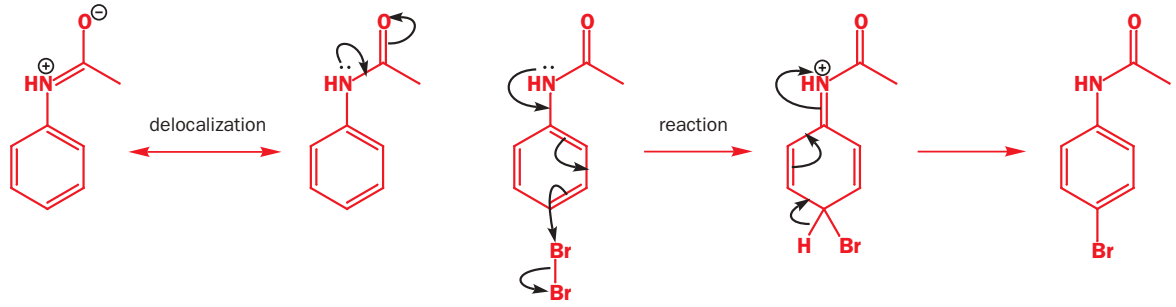


How then could we prevent oversubstitution from occurring? What we need is a way to make aniline less reactive by preventing the nitrogen lone pair from interacting so strongly with the π system of the ring. Fortunately, it is very simple to do this. In Chapter 8 (p. 000) we saw how the nitrogen atom in an amide is much less basic than a normal amine because it is conjugated with the carbonyl group. This is the strategy that we will use here—simply acylate the amine to form an amide. The amide nitrogen can still donate electrons into the ring, but much less efficiently than the amine and so the electrophilic aromatic substitution is more controlled. After the reaction, the amide can be hydrolysed back to the amine.



The lone pair electrons on the nitrogen atom of the amide are conjugated with the carbonyl group as usual but they are also delocalized into the benzene ring, though more weakly than in the amine. Reaction still occurs in the *ortho* and *para* positions (mainly *para*) but it occurs once only.

▶ Compounds formed by the acylation of ammonia are familiar to you as amides and those formed by the acylation of anilines are sometimes called *anilides*. If they are acetyl derivatives they are called *acetanilides*. We shall not use these names but you may see them in some books.

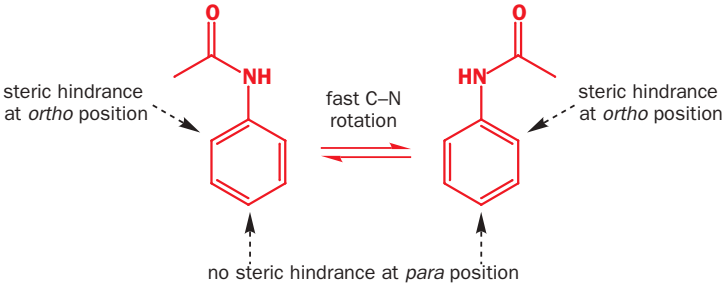


Selectivity between *ortho* and *para* positions is determined by steric hindrance

Phenols and anilines react in the *ortho* and/or *para* positions for electronic reasons. These are the most important effects in deciding where an electrophilic substitution will occur on a benzene ring.

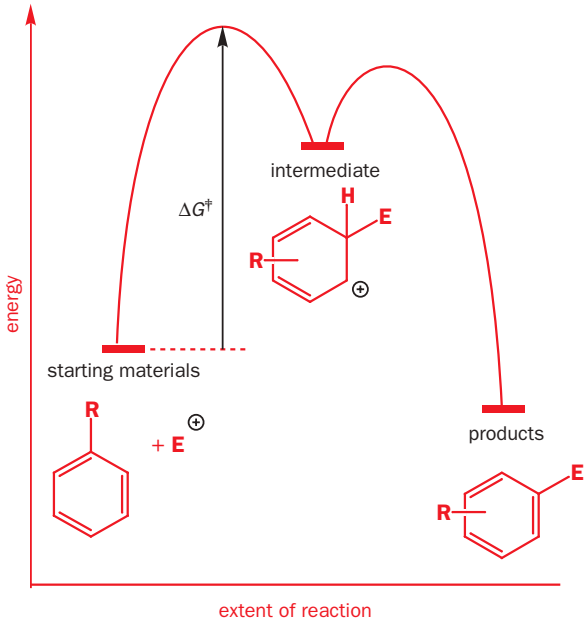
When it comes to choosing between *ortho* and *para* positions we need to consider steric effects as well. You will have noticed that we have seen one *ortho* selective reaction—the formation of salicylic acid from phenol—and several *para* selective reactions such as the bromination of an amide just discussed.

If the reactions occurred merely statistically, we should expect twice as much *ortho* as *para* product because there are two *ortho* positions. However, we should also expect more steric hindrance in *ortho* substitution since the new substituent must sit closely beside the one already there. With large substituents, such as the amide, steric hindrance will be significant and it is not surprising that we get more *para* product.



A closer look at the transition state

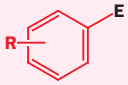
We haven't given the whole picture as to why groups with a lone pair that can conjugate into the ring make the ring so much more reactive towards electrophilic attack. What we have said so far is that the starting material is more reactive because of the increased electron density in the ring. This is true, but what we should really be concerned with is the activation energy for the reaction. The energy profile for an electrophilic substitution reaction with 'E^+' on a phenyl ether looks rather like the one we showed earlier for benzene.



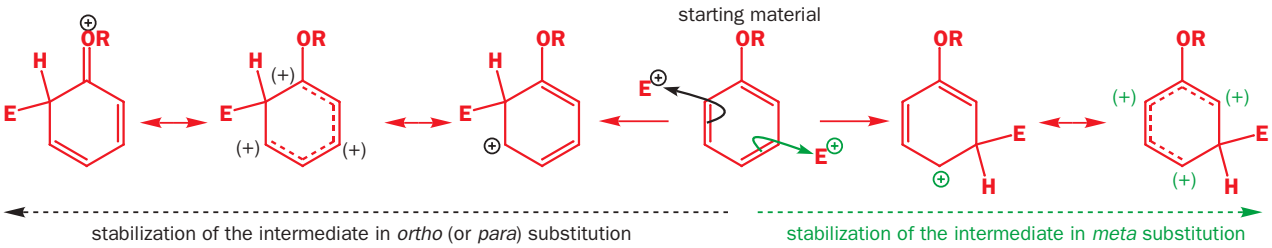
We need to understand how the activation energy, $\Delta G^{\ddagger}$, changes when R is an electron-donating substituent and so we really need to know the relative energy of the transition state. We do not know the energy of the transition state, or even exactly what it looks like (Chapter 13), but we can assume that the transition state looks more like the intermediate than like the starting material because it is close in energy to the unstable intermediate. It will help to look at the different intermediates that could be formed by attacking in the *ortho*, *meta*, and *para* positions and try to work out which of these, and hence which transition states, might be higher in energy.

For an electrophile attacking a benzene ring containing an electron-donating group (here OR), the following intermediates are possible, depending on whether the electrophile attacks *ortho*, *meta*, or *para* to the group already present. The intermediate in *para* substitution is not drawn since it has the same stabilization as the *ortho* intermediate.

▶ A diagram such as this shows a molecule with two substituents but either the relationship between them is not known or the compound is a mixture.



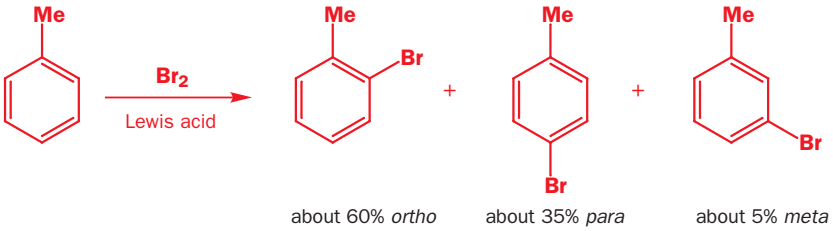
▶ This argument is based on the Hammond postulate, which suggests that structures close in energy that transform directly into each other are also similar in structure (Chapter 41).



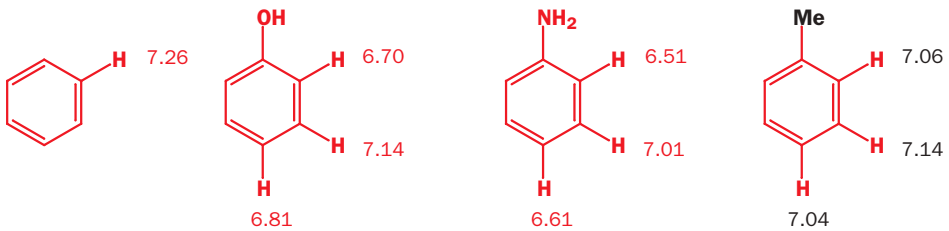
Each intermediate is stabilized by delocalization of the positive charge to three carbon atoms in the ring. If the electrophile attacks *ortho* (or *para*) to the electron-donating group, OR, the positive charge is further delocalized directly on to OR, but the intermediate in *meta* substitution does not enjoy this extra stabilization. We can assume that the extra stabilization in the intermediate in *ortho* (or *para*) substitution means that the transition state is similarly lower in energy than that in *meta* substitution. Not only is there more electron density in the *ortho* and *para* positions in the starting material (and hence a good interaction between these sites and the electrophile) but also the transition states resulting from *ortho* and *para* attack are lower in energy than the transition state for *meta* attack. These points both mean that $\Delta G^{\ddagger}$ is smaller for *ortho*/*para* attack and that the reaction is faster than *meta* attack.

Alkyl benzenes react at the *ortho* and *para* positions: σ donor substituents

The rate constant for the bromination of toluene (methylbenzene) is about 4000 times that for benzene (this may sound like a lot, but the rate constant for *N*,*N*-dimethylaniline is 10^{14} times greater). The methyl group also directs electrophiles mostly into the *ortho* and *para* positions. These two observations together suggest that alkyl groups may also increase the electron density in the π system of the benzene ring, specifically in the *ortho* and *para* positions, rather like a weakened version of an OR group.

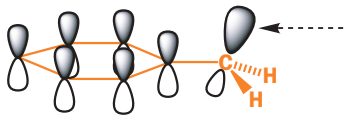


There is a small inductive effect between any sp^2 and sp^3 carbon atoms (Chapter 8) but, if this were the only effect, then the carbon to which the alkyl group is attached (the *ipso* carbon) should have the greatest electron density, followed by the *ortho* carbons, then the *meta* carbons, and finally the carbon atom furthest from the substituent, in the *para* position.



The ^{1}H NMR spectrum for toluene suggests that there is slightly more electron density in the *para* position than in the *meta* positions. All the shifts are smaller than those of benzene but not by much and the shielding is much less than it is in phenols or anilines. The methyl group donates electrons weakly by conjugation. In phenol, a lone pair on oxygen is conjugated into the π system. In

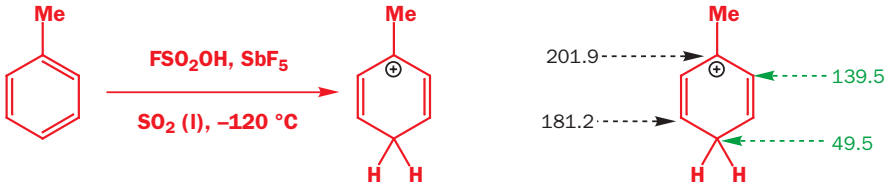
toluene there is no lone pair but one of the C–H σ bonds can interact with the π system in a similar way. This interaction, know as **σ conjugation**, is not as good as the full conjugation of the oxygen lone pair, but it is certainly better than no interaction at all.



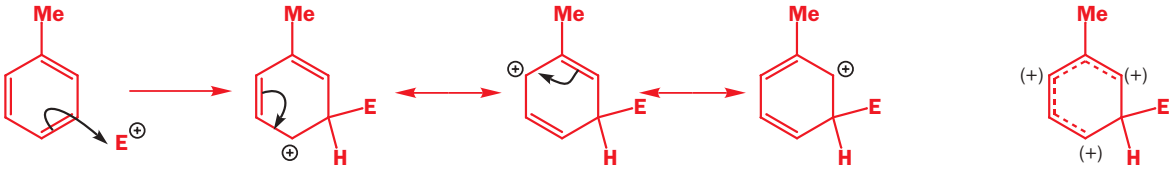
one of the C–H σ bonds can overlap with the π system of the ring

Just as the conjugation of the oxygen lone pair increases the electron density at the *ortho* and *para* positions, so too does σ conjugation, but more weakly. However, it does not provide another pair of electrons to act as the HOMO. Toluene uses π electrons, which are slightly higher in energy than those of benzene. It is best to regard alkyl benzenes as rather reactive benzenes. We have to draw the mechanism using the π electrons as the nucleophile.

The positive charge in the intermediate is delocalized over three carbons as usual and we can study the intermediate by protonation in superacid as we did with benzene. The result is more revealing because protonation actually occurs in the *para* position.



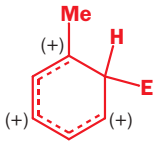
The *ortho* (to the Me group) carbon has a shift (139.5 p.p.m.) only 10 p.p.m. greater than that of benzene (129.7 p.p.m.) but the *ipso* and *meta* carbons have the very large shifts that we associate with cations. The charge is mainly delocalized to these carbons but the greatest charge is at the *ipso* carbon. Electrophilic attack occurs on alkyl benzenes so that the positive charge can be delocalized to the carbon bearing the alkyl group. This carbon is tertiary and so cations there are stable (Chapter 17) and they can enjoy the σ conjugation from the alkyl group. This condition is fulfilled if toluene is attacked at the *ortho* or *para* positions as you have seen but not if it is attacked at the *meta* position.



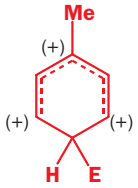
Now the charge is delocalized to the three carbon atoms that do not include the *ipso* carbon and no σ conjugation from the alkyl group is possible. The situation is no worse than that of benzene, but toluene reacts some 10^3 faster than benzene at the *ortho* and *para* positions. The stability of the transition states for electrophilic attack on toluene can again be modelled on these intermediates, so they follow the same pattern. The transition states for *ortho* and *para* attack have some positive charge at the *ipso* carbon but that for *meta* substitution does not.

favourable intermediates for

ortho substitution

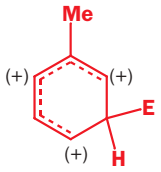


para substitution



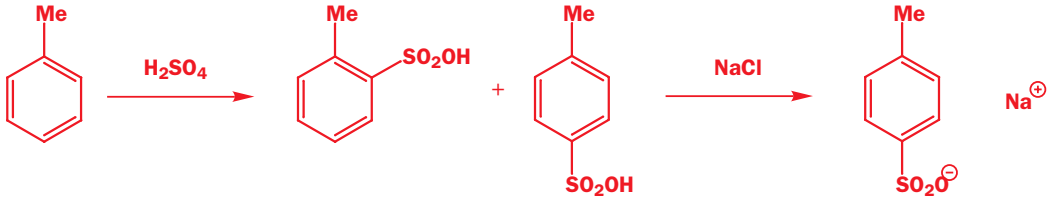
unfavourable intermediate for

meta substitution



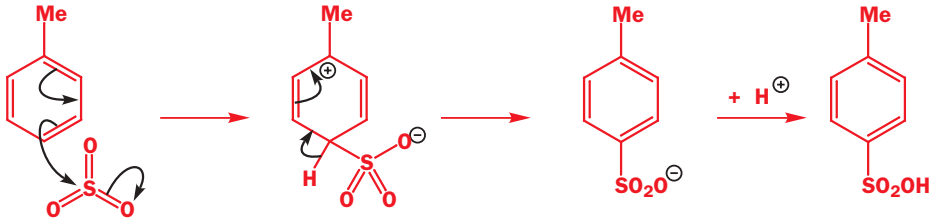
The sulfonation of toluene

Direct sulfonation of toluene with concentrated sulfuric acid gives a mixture of *ortho* and *para* sulfonic acids from which about 40% of toluene *para* sulfonic acid can be isolated as the sodium salt. The free acid is important as a convenient solid acid, useful when a strong acid is needed to catalyse a reaction. Being much more easily handled than oily and corrosive sulfuric acid or syrupy phosphoric acid, it is useful for acetal formation (Chapter 14) and eliminations by the E1 mechanism on alcohols (Chapter 19). It is usually called tosic acid, TsOH, or PTSA (*para* toluene sulfonic acid).

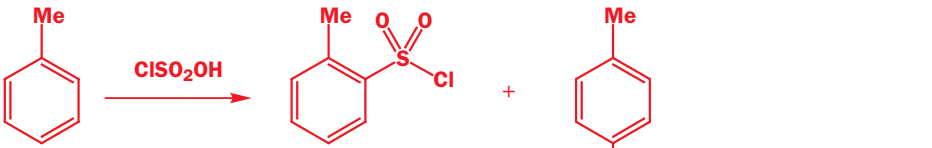


about 40% *para* isolated as sodium salt

We shall use SO_3 as the electrophile in this case and draw the intermediate with the charge at the *ipso* carbon to show the stabilization from the methyl group. We shall see later that these steps are reversible.



The toluene-*para*-sulfonate group (OTs) is important as a leaving group if you want to carry out an S_N2 reaction on an alcohol (Chapter 17) and the acid chloride (tosyl chloride, TsCl) can be made from the acid in the usual way with PCl_5. It can also be made directly from toluene by sulfonation with chlorosulfonic acid $ClSO_2OH$. This reaction favours the *ortho* sulfonyl chloride which is isolated by distillation.

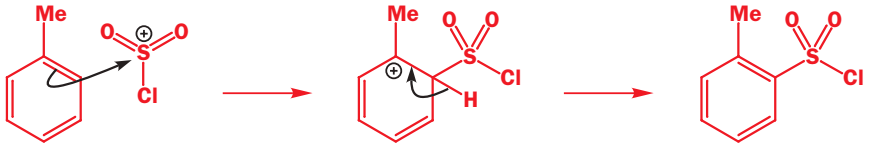


about 40% *ortho* isolated by distillation

about 15% *para* isolated by crystallization

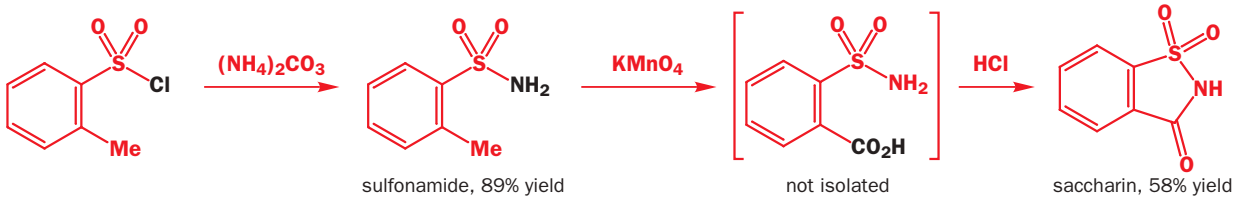
No Lewis acid is needed because chlorosulfonic acid is a very strong acid indeed and protonates itself to give the electrophile. This explains why OH is the leaving group rather than Cl and why chlorosulfonation rather than sulfonation is the result.

In drawing the mechanism, we again put the positive charge on the *ipso* atom. No treatment with NaCl is needed in this reaction as the major product (the *ortho* acid chloride) is isolated by distillation.



The preference for *para* product in the sulfonation and *ortho* product in the chlorosulfonation is the first hint that sulfonation is reversible and this point is discussed later. It is fortunate that the

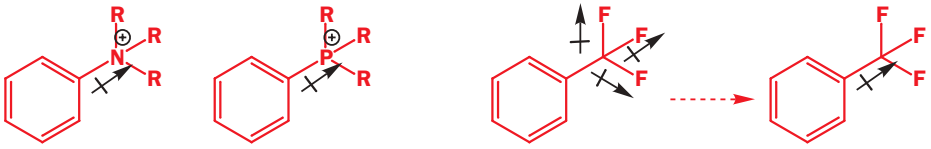
ortho acid chloride is the major product in the chlorosulfonation because it is needed in the synthesis of saccharin, the first and still one of the best of the non-fattening sweeteners.



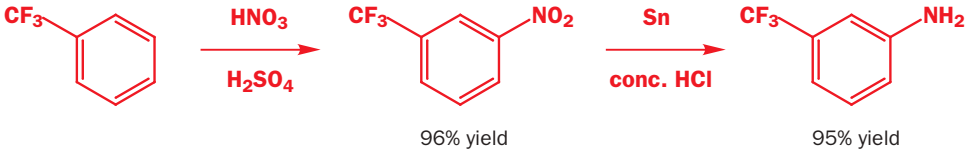
These are all reactions that you know, with the exception of the oxidation with $KMnO_4$ (Chapter 25) to carboxylic acids but the formation of sulfonamides is like that of ordinary amides. This synthesis is discussed in Chapter 25.

Electronegative substituents give *meta* products

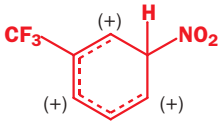
A few substituents (Z) exert an electronic effect on the benzene ring simply by polarization of the Ar–Z σ bond because of the electronegativity of Z. The most important is the CF_3 group, but ammonium (R_3N^+) and phosphonium (R_3P^+) fall into the same category. The Ar–N^+ and Ar–P^+ bonds are obviously polarized towards the positively charged heteroatom and the Ar–C bond in Ar–CF_3 is polarized towards the CF_3 group because of the three very electronegative fluorine atoms polarizing the C–F bonds so much that the Ar–C bond is polarized too.

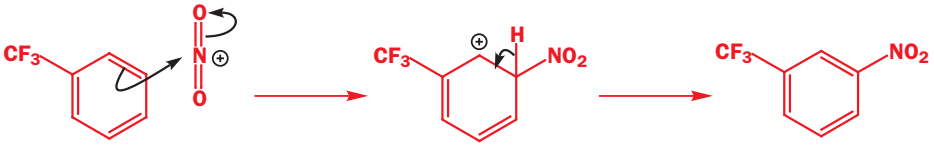


These groups direct electrophiles to the *meta* position and reduce reactivity. Nitration of trifluoromethyl benzene gives a nearly quantitative yield of *meta* nitro compound so there cannot be any significant *ortho* or *para* by-products. This reaction is important because reduction of the product (Chapter 24) gives the amine, also in very good yield.

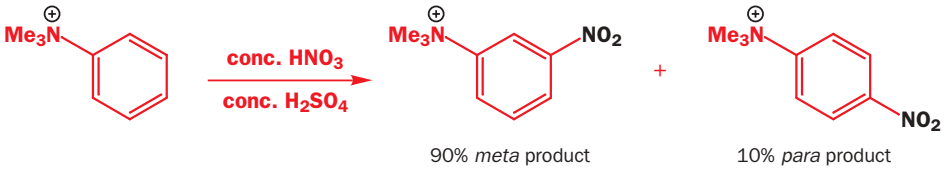


In drawing the mechanism we need to produce the intermediate in which the cation is not delocalized to the carbon atom bearing the electron-withdrawing group. In other words, the situation with electron-withdrawing CF_3 is the opposite to that with electron-donating CH_3. The CF_3 group is deactivating and *meta*-directing.



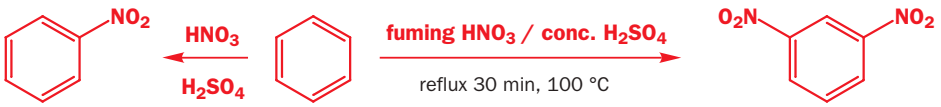


In the nitration of the phenyltrimethylammonium ion, 90% of the product is *meta*-substituted (with 10% *para*) and kinetic studies show that the nitration proceeds approximately 10^7 times more slowly than the nitration of benzene.



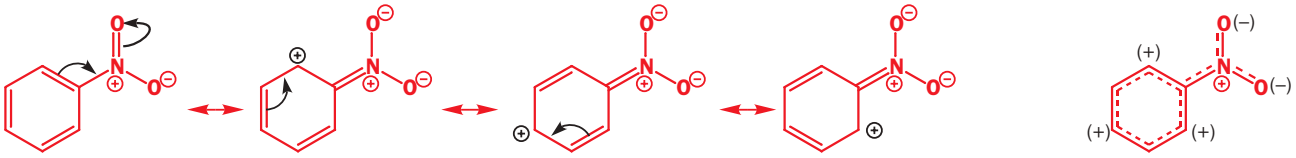
Some substituents withdraw electrons by conjugation

Aromatic nitration is important, because it is a convenient way of adding an amino group to the ring and because it stops cleanly after one nitro group has been added. Further nitration is possible but stronger conditions must be used—fuming nitric acid instead of normal concentrated nitric acid and the mixture refluxed at around 100 °C. The second nitro group is introduced *meta* to the first, that is, the nitro group is deactivating and *meta*-directing.



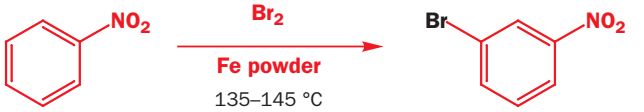
75% yield *meta*-dinitrobenzene

The nitro group is conjugated with the π system of the benzene ring and is strongly electron-*withdrawing*—and it withdraws electrons specifically from the *ortho* and *para* positions. We can use curly arrows to show this.



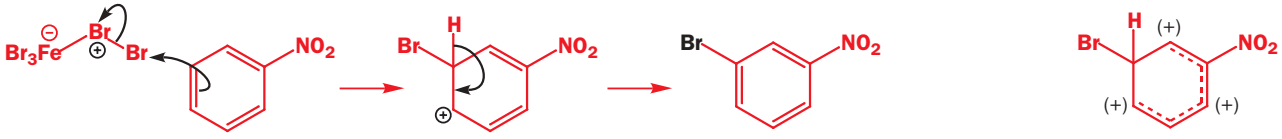
The nitro group withdraws electron density from the π system of the ring thereby making the ring less reactive towards something wanting electrons, an electrophile. Hence the nitro group is deactivating towards electrophilic attack. Since more electron density is removed from the *ortho* and *para* positions, the least electron-deficient position is the *meta* position. Hence the nitro group is *meta*-directing. In the nitration of benzene, it is much harder to nitrate a second time and, when we insist, the second nitro group goes in *meta* to the first.

Other reactions go the same way so that bromination of nitrobenzene gives *meta*-bromonitrobenzene in good yield. The combination of bromine and iron powder provides the necessary Lewis acid ($FeBr_3$) while the high temperature needed for this unfavourable reaction is easily achieved as the boiling point of nitrobenzene is over 200 °C.

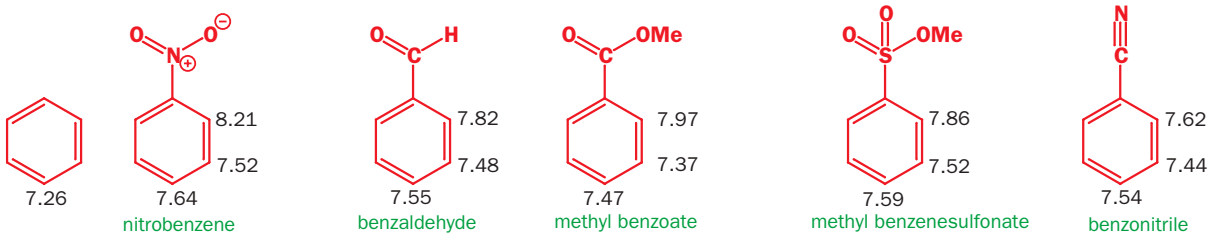


74% yield
meta-bromonitrobenzene

In drawing the mechanism it is best to draw the intermediate and to emphasize that the positive charge must not be delocalized to the carbon atom bearing the nitro group.



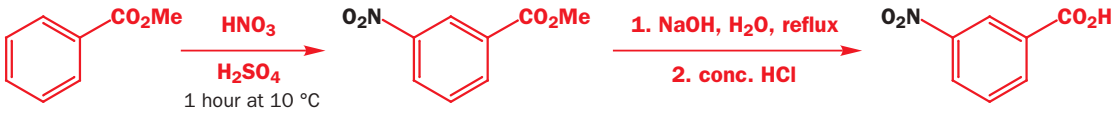
Nitro is just one of a number of groups that are also deactivating towards electrophiles and *meta*-directing because of electron withdrawal by conjugation. These include carbonyl groups (aldehydes, ketones, esters, etc.), cyanides, and sulfonates and their ^1H NMR shifts confirm that they remove electrons from the *ortho* and *para* positions.



Points to note:

- Each of the compounds contains the unit Ph–X=Y, where Y is an electronegative element, usually oxygen
- In each compound, all the protons resonate further downfield relative to benzene (that is, they have larger chemical shifts)
- The protons are less shielded than those of benzene because the electron density at carbon is less
- The protons in the *meta* position have the smallest shift and so the greatest electron density

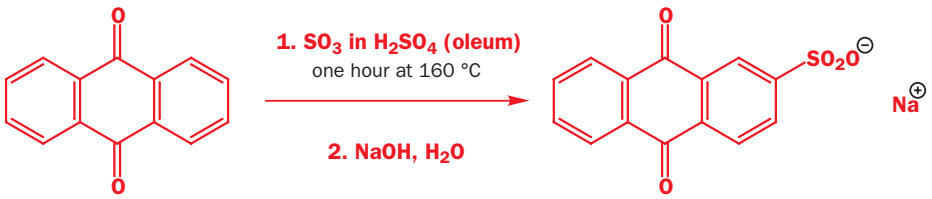
Nitro is the most electron-withdrawing of these groups and some of the other compounds are nearly as reactive (in the *meta* position, of course) as benzene itself. It is easy to nitrate methyl benzoate and the *m*-nitro ester can then be hydrolysed to *m*-nitrobenzoic acid very easily.



84% yield methyl *m*-nitrobenzoate

96% yield *m*-nitrobenzoic acid

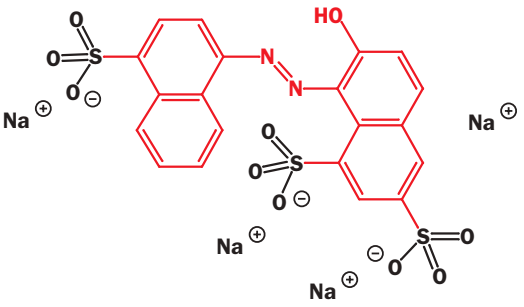
An interesting example of a reaction with a ketone is the sulfonation of anthraquinone. Many dyestuffs contain this unit and the sulfonate group makes them soluble in water. Oleum at 160 °C must be used for the sulfonation, which goes in one of the four equivalent positions on the two benzene rings, *meta* to one carbonyl group but *para* to the other.



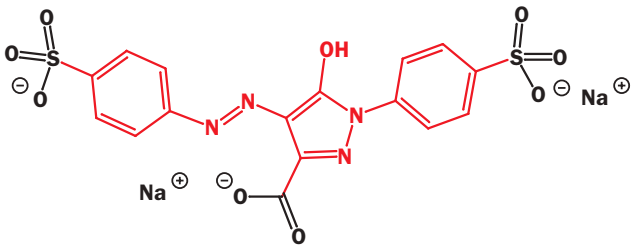
anthraquinone

60% yield sodium anthraquinone-2-sulfonate

The yield is not wonderful and the main by-product is unchanged anthraquinone showing how unreactive this compound is even under these forcing conditions. In Chapter 7 we saw how dyes are highly conjugated molecules, often containing aromatic rings. Here are two common water-soluble dyes containing sulfonate groups.



Brilliant scarlet 4R; E124



Tartrazine (yellow); E102

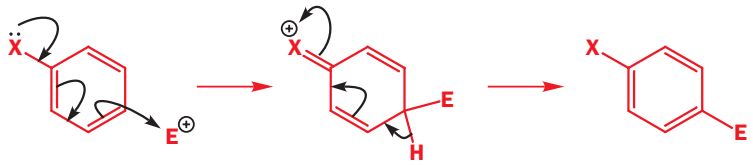
These dyes also contain the diazo group (–N=N–) and we shall return to that soon. One group of substituents remains and they are slightly odd. They are *ortho, para*-directing but they are also deactivating. These are the halogens.

Halogens (F, Cl, Br, and I) both withdraw and donate electrons

The halogens deactivate the ring towards electrophilic attack but direct *ortho* and *para*. The only way this makes sense is if there are two opposing effects—electron donation by conjugation and electron withdrawal by induction. The halogen has three lone pairs, one of which may conjugate with the ring

just like in phenol or aniline. However, there are two mismatching aspects to this conjugation: lone pair orbital size and electronegativity.

X = F, Cl, Br, or I

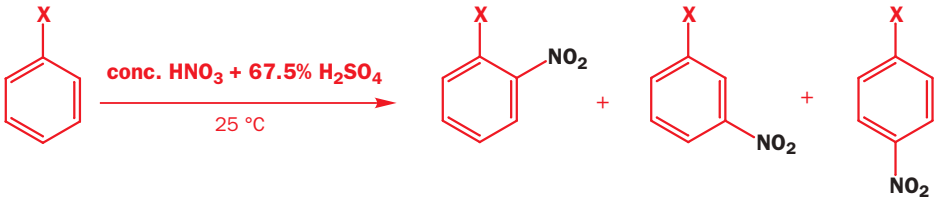


When Cl, Br, or I is the substituent, there is a size mismatch, and therefore a poor overlap, between the 2p orbitals from the carbon atoms and the p orbitals from the halogen (3p for chlorine, 4p for bromine, and 5p for iodine). This size mismatch is clearly illustrated by comparing the reactivities of aniline and chlorobenzene: chlorine and nitrogen have approximately the same electronegativity, but aniline is much more reactive than chlorobenzene because of the better overlap between the carbon and nitrogen 2p orbitals.

Fluorine 2p orbitals are the right size to overlap well with the carbon 2p orbitals, but the orbitals of fluorine are much lower in energy than the orbitals of carbon since fluorine is so electronegative. Also, the more electronegative a substituent, the better it is at withdrawing electrons by induction. When we looked at aniline and phenol, we didn't mention any electron withdrawal by induction, even though both oxygen and nitrogen are very electronegative. The conjugative electron donation was clearly more important since both compounds are much more reactive towards electrophiles than benzene. However, we did point out that aniline is more reactive than phenol because nitrogen is less electronegative than oxygen and so better able to donate electrons into the π system.

With this in mind, how would you expect fluorobenzene to react? Most electron density is removed first from the *ortho* positions by induction, then from the *meta* positions, and then from the *para* position. Any conjugation of the lone pairs on fluorine with the π system would increase the electron density in the *ortho* and *para* positions. Both effects favour the *para* position and this is where most substitution occurs. But is the ring more or less reactive than benzene? This is hard to say and the honest answer is that sometimes fluorobenzene is more reactive in the *para* position than benzene (for example, in proton exchange and in acetylation—see later) and sometimes it is less reactive than benzene (for example, in nitration). In all cases, fluorobenzene is significantly more reactive than the other halobenzenes. We appreciate that this is a rather surprising conclusion, but the evidence supports it.

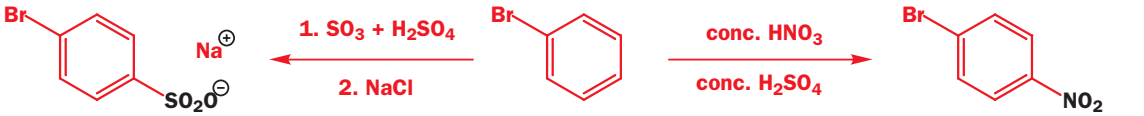
Data for the rate and the products of nitration of halobenzenes show these opposing effects clearly.



Compound	Products formed (%)			Nitration rate
	ortho	*meta*	*para*	(relative to benzene)
PhF	13	0.6	86	0.18
PhCl	35	0.9	64	0.064
PhBr	43	0.9	56	0.060
PhI	45	1.3	54	0.12

- The percentage of the *ortho* product increases from fluorobenzene to iodobenzene. We might have expected the amount to decrease as the size of the halide increases because of increased steric hindrance at the *ortho* position but this is clearly not the case. The series can be explained by the greater inductive effect of the more electronegative atoms (F, Cl) withdrawing electron density mostly from the *ortho* positions
- The relative rates follow a U-shaped sequence; fluorobenzene nitrates most quickly (but not as fast as benzene), followed by iodo-, then chloro-, and then bromo-benzenes. This is a result of two opposing effects: electron donation by conjugation and electron withdrawal by inductive effect

In practical terms, it is usually possible to get high yields of *para* products from these reactions. Both nitration and sulfonation of bromobenzene give enough material to make the synthesis worthwhile. Though mixtures of products are always bad in a synthesis, electrophilic aromatic substitution is usually simple to carry out on a large enough scale to make separation of the major product a workable method.



68% yield

70% yield *p*-bromonitrobenzene

A 68% yield of sodium *p*-bromobenzenesulfonate can be achieved by recrystallization of the sodium salt from water and a 70% yield of *p*-bromonitrobenzene by separation from the *ortho* isomer by recrystallization from EtOH.

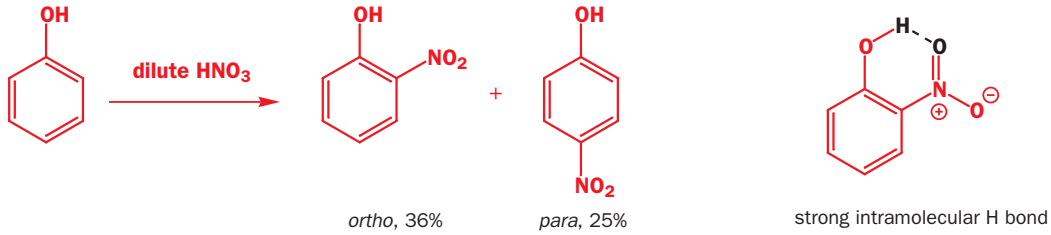
Summary of directing and activating effects

Now we can summarize the stage we have reached in terms of *activation* and *direction*.

Electronic effect	Example	Activation	Direction
donation by conjugation	$-NR_2$, –OR	very activating	*ortho*, *para* only
donation by inductive effect	alkyl	activating	mostly *ortho*, *para* but some *meta*
donation by conjugation *and* withdrawal by inductive effect	F, Cl, Br, and I	deactivating	*ortho* and (mostly) *para*
withdrawal by inductive effect	$-CF_3$, $-NR_3^+$	deactivating	*meta* only
withdrawal by conjugation	$-NO_2$, –CN, –COR, $-SO_3R$	very deactivating	*meta* only

Why do some reactions stop cleanly at monosubstitution?

Reactions such as nitration, sulfonation, and Friedel–Crafts acylation add a very deactivating substituent. They stop cleanly after a single substitution unless there is also a strongly activating substituent. Even then it may be possible to stop after a single substitution. Nitration of phenol is difficult to control because the OH group is very activating and because concentrated nitric acid oxidizes phenol. The solution is to use dilute nitric acid. The concentration of NO_2^+ will be small but that does not matter with such a reactive benzene ring.

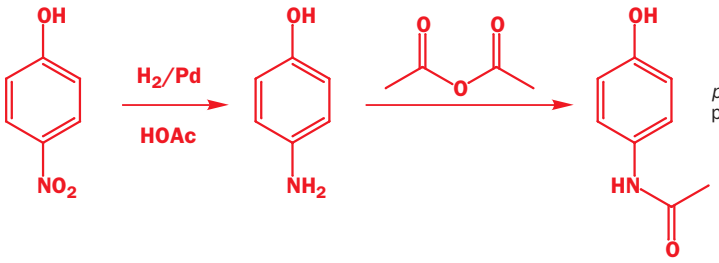


ortho, 36%

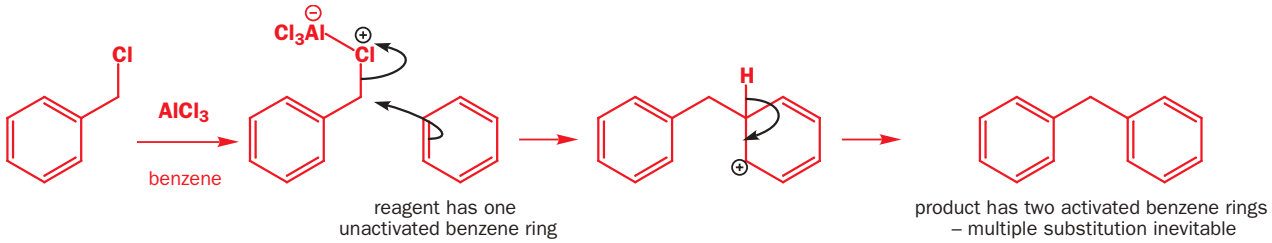
para, 25%

strong intramolecular H bond

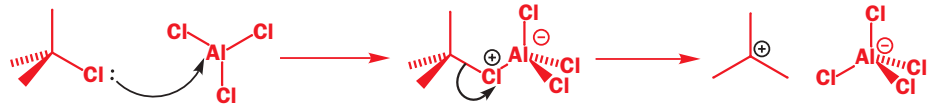
The product is a mixture of *ortho*- and *para*-nitrophenol from which the *ortho* compound can be separated by steam distillation. A strong intramolecular hydrogen bond reduces the availability of the OH group for intermolecular hydrogen bonds so the *ortho* compound has a lower boiling point. The remaining *para*-nitrophenol is used in the manufacture of the painkiller paracetamol.



Weakly electron-withdrawing substituents like the halogens can be added once, but multiple substitution is common with strongly activating substituents like OH and NH_2. When electron-donating substituents are added, multiple substitution is always a threat. As it happens, this threat is not serious as there are no good reagents for adding strongly activating substituents such as 'HO^+' or 'H_2N^+' to aromatic systems. Now you see why adding nitrogen as the deactivating nitro group is such an advantage. The only reactions of this kind where multiple substitution is a genuine problem are likely to be Friedel–Crafts alkylation reactions. Preparation of diphenylmethane from benzene and benzyl chloride is a fine reaction but the product has two benzene rings, each more reactive than benzene itself. A 50% yield is the best we can do and that requires a large excess of benzene to ensure that it competes successfully with the product for the reagent.

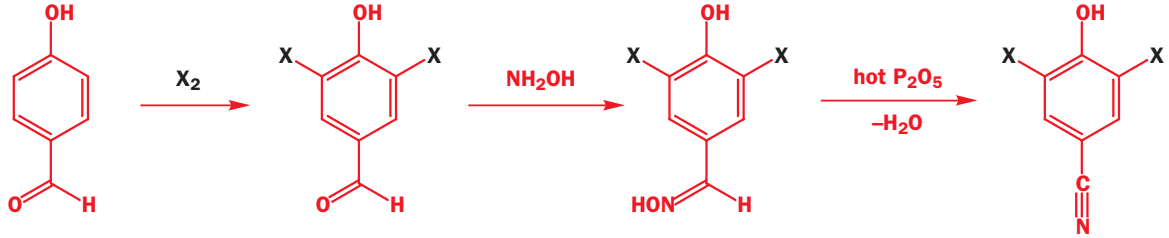


We have drawn the substitution at the benzylic centre as an S_N2 reaction as it would normally be with a primary alkyl halide, though it could be S_N1 in this case as the benzylic cation is stable. Friedel–Crafts alkylation works well with relatively stable cations especially tertiary cations. The cation can be generated in a number of ways such as the protonation of an alkene, the acid-catalysed decomposition of a tertiary alcohol, or the Lewis-acid-catalysed decomposition of a *t*-alkyl chloride.



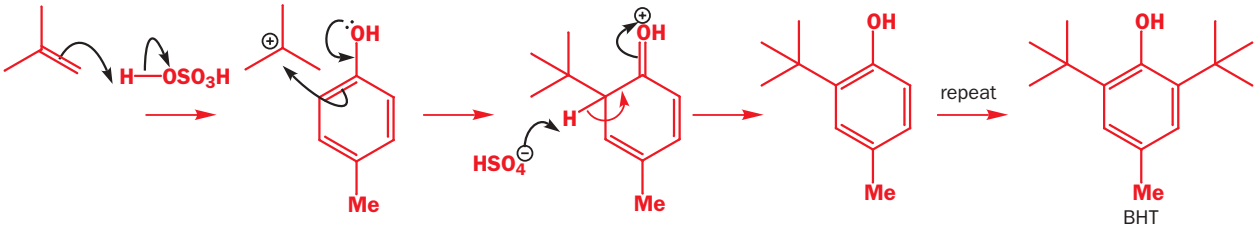
Two or more substituents may cooperate or compete

We can, in a qualitative way, combine the directing effects of two or more substituents. In some cases the substituents both direct to the same positions, as in the syntheses of bromoxynil and ioxynil, contact herbicides especially used in spring cereals to control weeds resistant to other weedkillers. They are both synthesized from *p*-hydroxybenzaldehyde by halogenation. The aldehyde directs *meta* and the OH group directs *ortho* so they both direct to the same position. The aldehyde is deactivating but the OH is activating.



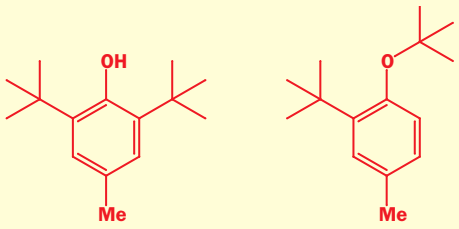
The reaction with NH_2OH is the formation of an oxime from the aldehyde and hydroxylamine and was dealt with in Chapter 14. The reaction with P_2O_5 is a dehydration—phosphorus is used to remove water from the oxime.

In other cases substituents compete by directing to different positions. For example, in the synthesis of the food preservative BHT (p. 000) from 4-methylphenol (*p*-cresol) by a Friedel–Crafts alkylation, the methyl and OH groups each direct *ortho* to themselves. The –OH group is much more powerfully directing than the methyl group because it provides an extra pair of electrons, so it 'wins' and directs the electrophile (a *t*-butyl cation) *ortho* to itself. The *t*-butyl cation can be made from the alkene or *t*-butanol with protic acid or from *t*-butyl chloride with $AlCl_3$.



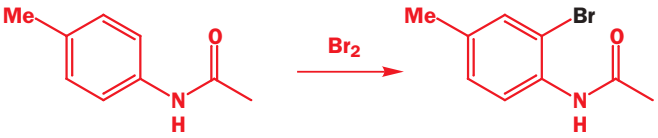
BHT—a case of mistaken identity?

When BHT and other similar phenols were first prepared in the 1940s, chemists were not sure of their structures. The chemical formulae could be determined by elemental analysis, but NMR, which would have instantly revealed the structure, had not yet been discovered. The problem arose because the compound exhibited none of the normal reactions or 'tests' for phenols; for example, it was not soluble in alkali. The chemists thought the second *t*-butyl group had added to oxygen to make an ether. BHT does not behave like other phenols because the –OH group is hindered by the two large *t*-butyl groups.

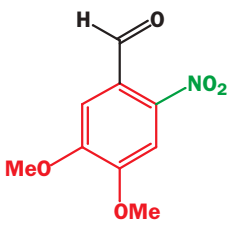


BHT | supposed BHT

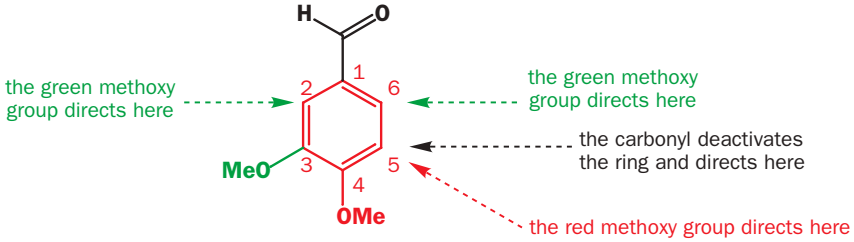
Even a watered-down activating group like the amide –NHCOMe, which provides an extra pair of electrons, will 'win' over a deactivating group or an activating alkyl group. Bromination of this amide goes *ortho* to the –NHCOMe group but *meta* to the methyl group.



When looking at any compound where competition is an issue it is sensible to consider electronic effects first and then steric effects. For electronic effects, in general, any activating effects are more important than deactivating ones. For example, the aldehyde below has three groups—two methoxy groups that direct *ortho* and *para* and an aldehyde that directs *meta*.



main nitration product



3,4-dimethoxybenzaldehyde

▶ If you are in a bar and someone picks a fight with you, it is no help that an inoffensive little man in the corner would prefer not to pick a fight. Aggressive $–NR_2$ and –OR groups are not much affected by inoffensive –Br or carbonyl groups in another corner of the molecule.

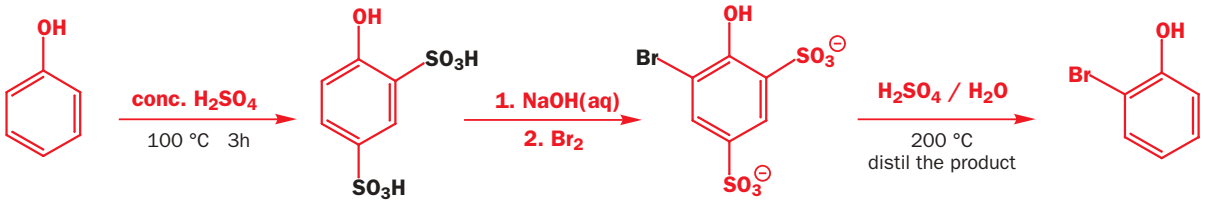
Despite the fact that the aldehyde group withdraws electron density from positions 2 and 6, C6 is still the position for nitration. The activating methoxy groups dominate electronically and the choice is really between C2, C5, and C6. Now consider steric factors—the –OMe groups block the positions *ortho* to them more than the carbonyl does because reaction at C2 or C5 would lead to three adjacent substituents which is why substitution occurs at position 6.

Review of important reactions including selectivity

We shall now return to the main reactions and consider important examples including selectivity.

Sulfonation

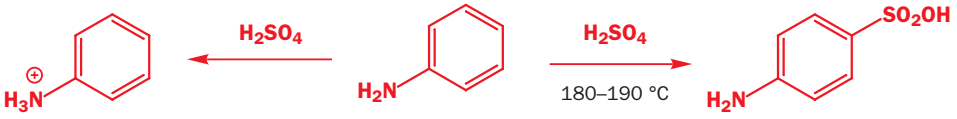
The exact nature of the electrophile in sulfonation reactions seems to vary with the amount of water present. Certainly for oleum (fuming sulfuric acid, concentrated sulfuric acid with added sulfur trioxide) and solutions of sulfur trioxide in organic solvents, the electrophile is sulfur trioxide itself, SO_3. With more water around, $H_3SO_4^+$ and even $H_2S_2O_7$ have been suggested. One important difference between sulfonation and other examples of electrophilic substitution is that sulfonation is reversible. This can be useful because large sulfonic acid groups can act as blocking groups and be removed later. Mixing bromine and phenol at low temperatures produces mainly *p*-bromophenol. At higher temperatures, the tribromo product is formed. The *ortho*-substituted product can be made with the aid of sulfonation.



In stage 1 the phenol is sulfonated twice—the first sulfonic acid group (which adds *para* to the OH group) deactivates the ring, making the introduction of the second group (which goes *ortho* to the OH and *meta* to the first sulfonic acid) harder and that of the third group harder still, which is why we can isolate the disulfonated phenol. In the second stage, the bromination, the OH directs to the *ortho* and *para* positions, but only one *ortho* position is vacant, so the bromine attacks there. Sodium hydroxide is needed to deprotonate the sulfonic acid groups to make them less deactivating. The sulfonation reaction is reversible, and in the third stage it is possible to drive the reaction over by distilling out relatively volatile 2-bromophenol.

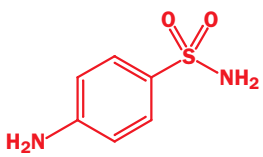
■ The reversibility of sulfonation with sulfuric acid may account for the higher yield of *para* product in the sulfonation of toluene with H_2SO_4 as compared with $ClSO_2OH$ (p. 000).

Direct sulfonation of aromatic amines is even possible. This is very surprising because in sulfuric acid essentially all the amine will be protonated. The protonated amine would react in the *meta* position just like Ph—NMe_3^+ but in these reactions the *para*-sulfonic acid is formed.

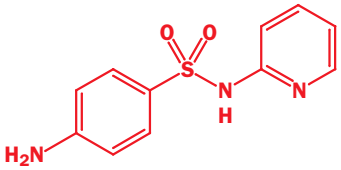


50–60% yield sulfanilic acid

There are two possible explanations for this. Either the very tiny amount of unprotonated amine reacts very rapidly with SO_3 in the *para* position or the reaction is reversible and the *para*-sulfonic acid is formed because it is stabilized by delocalization and least hindered. The product is important because the amides derived from it (sulfanilamides) were the first antibiotics, the 'sulfa' drugs.



sulfanilamide

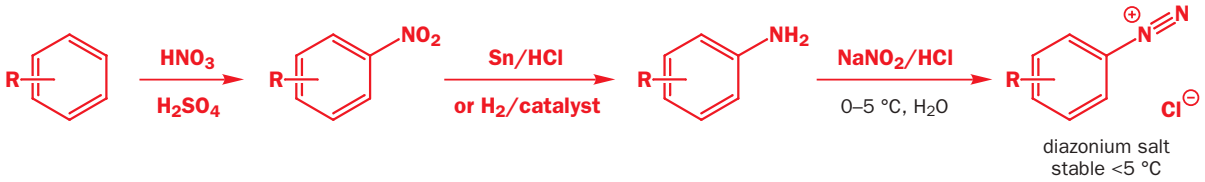


sulfapyridine, a sulfa drug

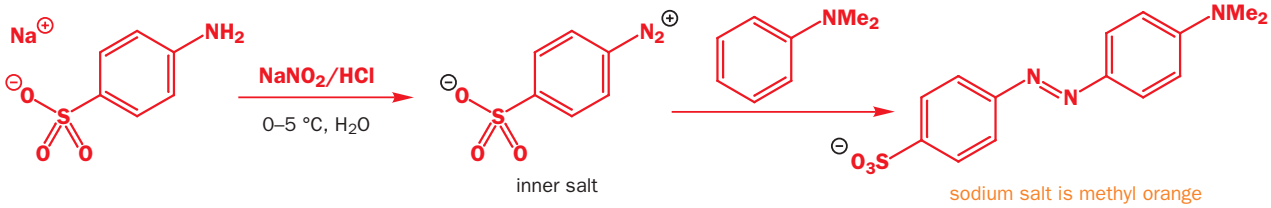
Aromatic nitration and diazo-coupling

We have already described how nitration leads eventually to aromatic amines by reduction of the nitro group. In the next chapter you will meet the further development of these amines into diazonium salts as reagents for nucleophilic aromatic substitution by the S_N1 mechanism with loss of nitrogen. In this chapter we need to address their potential for electrophilic aromatic substitution without the loss of nitrogen as this leads to the important azo dyes. Treatment of the amine with nitrous acid (HON=O) at around 0 °C gives the diazonium salt.

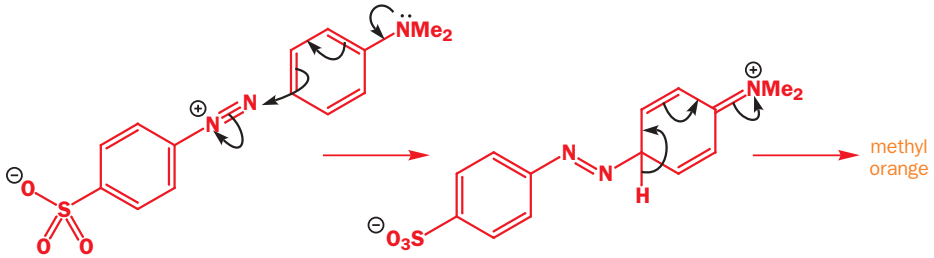
■ The mechanism of formation of NO^+ is discussed in Chapter 21.



These diazonium salts are good electrophiles for activated aromatic rings, such as amines and phenols, and this is how azo dyes are prepared. Diazotization of the salt of sulfanilic acid, which we have just made by sulfonation of aniline, gives an inner salt that combines with *N*,*N*-dimethylaniline to form the water-soluble dye, methyl orange.

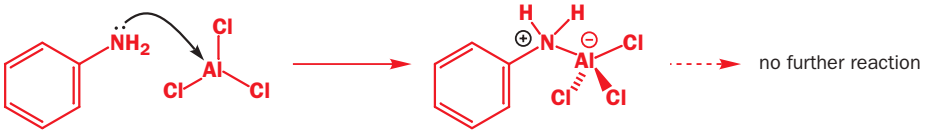


The electrophilic substitution is straightforward, occurring in the *para* position on the activated hindered dialkylamine. Notice that nucleophilic attack must occur on the end nitrogen atom of the diazonium salt to avoid forming pentavalent nitrogen.



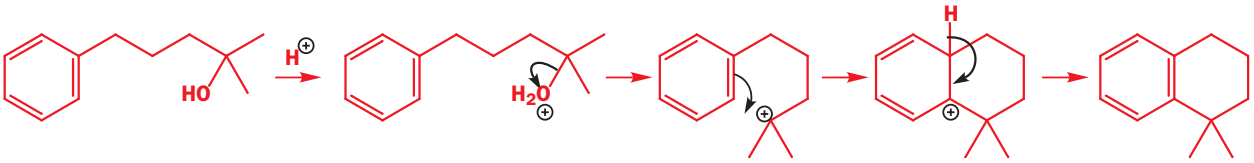
Oxygen and nitrogen can also complex to the catalyst

In Friedel–Crafts alkylation using alkenes and alcohols with strong acids, OH and NH_2 groups activate towards electrophilic attack and direct to the *ortho* or *para* positions. However, in Friedel–Crafts alkylations using *t*-alkyl chlorides and $AlCl_3$, reaction does not proceed much faster than the alkylation of unsubstituted benzene, that is, the –OH group seems to have very little effect on the reaction. This is because oxygen can also complex with the Lewis acid. The Friedel–Crafts alkylation of amines is even worse and normally does not proceed at all—nitrogen forms an even stronger complex with the Lewis acid than oxygen does. This complex then withdraws electrons from the ring, rather than donating electrons as the neutral nitrogen did.



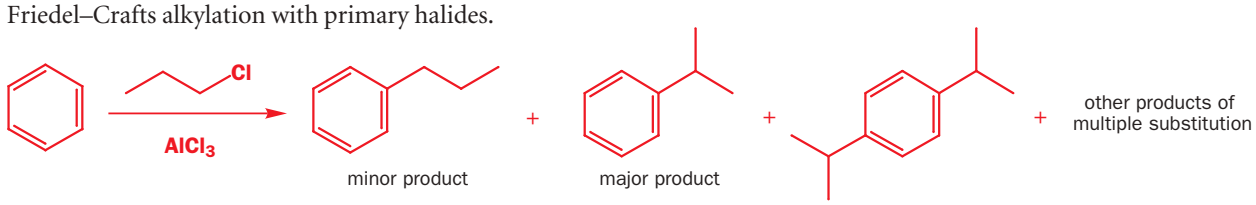
Friedel–Crafts alkylations are especially useful for forming polycyclic compounds. These are usually intramolecular reactions in which the electrophile and the aromatic system are all part of the

same compound. Fairly elaborate examples are discussed in Chapter 51. A simple example reveals the basic plan: an intramolecular Friedel–Crafts alkylation that will be faster than any other, inevitably intermolecular, side reaction.

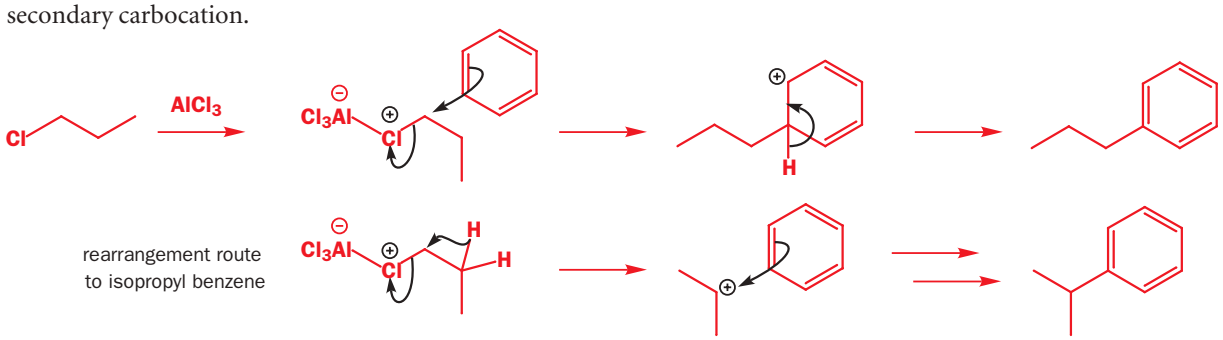


Friedel–Crafts alkylation cannot be used with primary alkyl halides

Even if you successfully prevent multiple substitution from occurring, there is a second and more serious problem—the alkyl cations often rearrange to yield more stable cations. We shall look into such rearrangements more closely in Chapter 37 but for the moment we shall just consider Friedel–Crafts alkylation with primary halides.

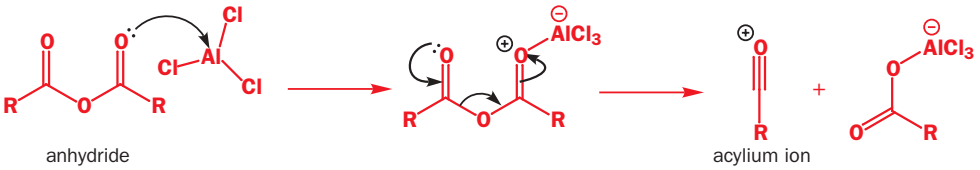


The major product is isopropyl benzene—approximately twice as much as *n*-propyl benzene. The rearrangement in this mechanism occurs because primary cations do not exist in solution (Chapter 17) so that the alkyl halide–$AlCl_3$ complex must either react directly or rearrange to the more stable secondary carbocation.

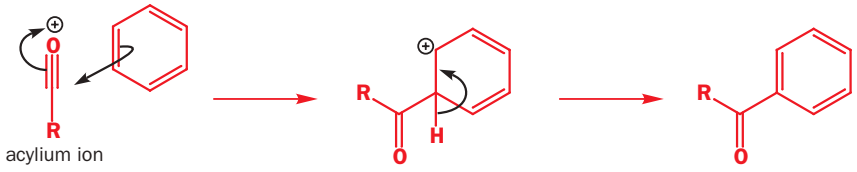


Friedel–Crafts *acylation* is much more reliable

Of more use than Friedel–Crafts alkylation is **Friedel–Crafts acylation**, the introduction of an acyl group (RCO–) on to the ring. Instead of using an alkyl chloride, an acyl chloride (acid chloride) or an acid anhydride is used together with the Lewis acid to produce the reactive acylium ion. We have seen an acid chloride in action (p. 000); here is an anhydride.



The acylium ion is then attacked by the aromatic system in the usual way. Multiple substitution is rarely a problem because the deactivated conjugated ketone is much less reactive than benzene.



▶ In Friedel–Crafts alkylations using an alkyl chloride, the Lewis acid is used in catalytic quantities. In an acylation, however, the Lewis acid can also complex to any oxygen atoms present, to the carbonyl in the product, for example. As a result, in acylation reactions, more Lewis acid is required—just over one equivalent per carbonyl group.

Cyclic anhydrides can be used to make keto-acids. Either carbonyl group is used for the acylation and the other becomes an $AlCl_3$ complex until work-up. Thus 3-benzoylpropanoic acid can be prepared from benzene and succinic anhydride.

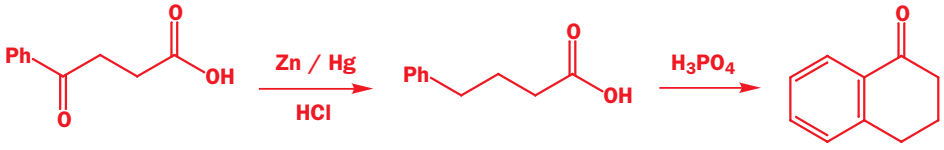
succinic anhydride 3-benzoylpropanoic acid

The advantages of acylation over alkylation

Two problems in Friedel–Crafts alkylation do not arise with acylation.

- The acyl group in the product withdraws electrons from the π system making multiple substitutions harder. Indeed, if the ring is too deactivated to start off with, Friedel–Crafts acylation may not be possible at all—nitrobenzene is inert to Friedel–Crafts acylation and is often used as a solvent for these reactions
- Rearrangements are also no longer a problem because the electrophile, the acylium cation, is already relatively stable

Because the acylation reaction is so much more reliable than Friedel–Crafts alkylation, a common method to alkylate is actually to acylate first and then reduce the carbonyl to a methylene group ($–CH_2–$). For example, the 3-benzoylpropanoic acid just made can be reduced to 4-phenylbutanoic acid using acid and zinc amalgam. This sort of reaction is discussed in Chapter 24. We could go one step further with the 4-phenylbutanoic acid and do an intramolecular Friedel–Crafts acylation. Intramolecular reactions are easy to do and, when starting from carboxylic acids, polyphosphoric acid (represented in the diagram as H_3PO_4) is commonly used to make the OH group into a better leaving group.



3-benzoylpropanoic acid 4-phenylbutanoic acid

One-carbon electrophiles are difficult to use

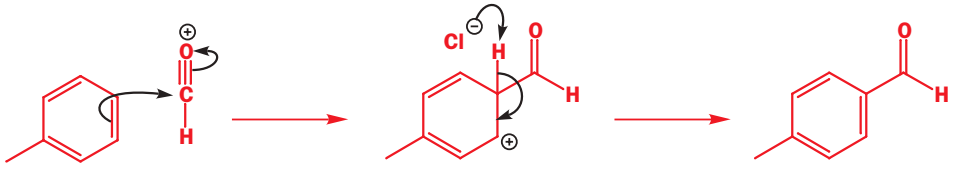
When $R–C{\equiv}O^+$ is used as the electrophile a ketone is produced. If an aldehyde were wanted, $H–C{\equiv}O^+$ would have to be used but it cannot be made from HCOCl because that is unstable. Instead, it can be generated by passing carbon monoxide and hydrogen chloride through a mixture of the aromatic hydrocarbon, a Lewis acid, and a co-catalyst, usually copper (I) chloride. Copper(I) chloride is known to form a complex with carbon monoxide and this probably speeds up the protonation step.

carbon monoxide

■

Ludwig Gatterman (1860–1920) worked at Freiburg and had a taste for danger. He made and studied the dangerously explosive NCl_3 and noticed the strange taste that gaseous HCN gave to a cigar.

This reaction, known as the **Gatterman–Koch reaction**, does not work with phenolic or amino aromatic species due to complex formation with the Lewis acid. It does work well with aromatic hydrocarbons and is used industrially to prepare benzaldehyde and, as here, *p*-tolualdehyde.

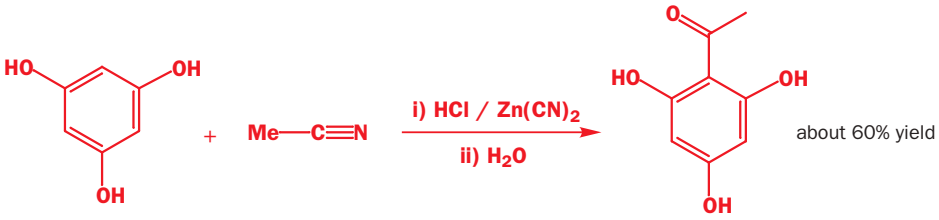


about 50% yield

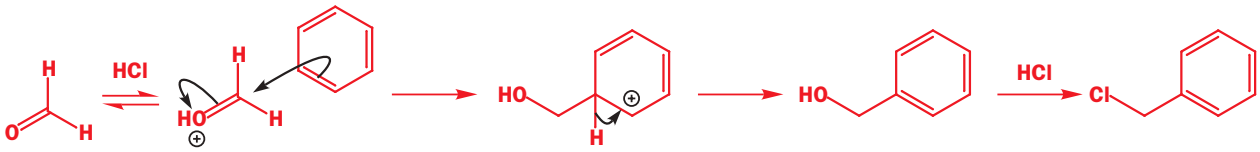
For more reactive aromatic systems such as phenols (but still not amines) a variation of this reaction, called the **Gatterman reaction**, can be useful in preparing aldehydes. Instead of using protonated carbon monoxide, protonated hydrogen cyanide is used (the two are isoelectronic). The reaction goes via an imine intermediate, ArCH=NH, which under the conditions of the reaction is hydrolysed to the aldehyde (see p. 000). When such reactive aromatic species as phenols are involved, the Lewis acid need not be so strong and zinc chloride is often used. With less reactive systems, $AlCl_3$ is needed. The zinc chloride can be conveniently generated from zinc cyanide, $Zn(CN)_2$, and HCl. This has the added advantage of also generating the necessary HCN *in situ* as well.

In a variation of the Gatterman reaction an alkyl cyanide RCN is used in place of HCN as a useful way of preparing ketones from reactive aromatic species that do not react well under Friedel–Crafts conditions. The electrophile involved is effectively $R–C{\equiv}NH^+$, although, perhaps, the imino chloride, R(C=NH)Cl, the analogue of an acyl chloride, RCOCl, is also involved. As in the Gatterman reaction, the imine is an intermediate.

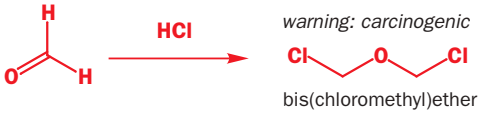
These reactions work even when there are three hydroxyls on the benzene ring.



We have already seen how salicylic acid can be made by reaction of the sodium salt of phenol (PhONa) with CO_2. More important than these reactions is **chloromethylation**, a way of adding a single carbon atom at the alcohol oxidation level. A combination of formaldehyde (CH_2=O) and HCl provides the one-carbon electrophile.



Chloromethylation is an efficient process but it has a serious drawback. Small amounts of the very carcinogenic (cancer-causing) bis(chloromethyl)ether are formed in the reaction mixture so that the process has fallen out of favour.



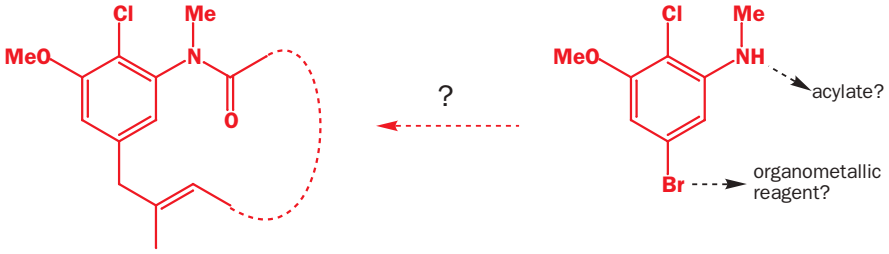
One-carbon electrophiles: summary of methods

Reaction	Substrate	Reagents	Electrophile	Intermediate	Product
Gatterman–Koch	hydrocarbons	CO, HCl, $AlCl_3$, CuCl	$H–C{\equiv}O^+$		ArCHO
Gatterman	phenols	$Zn(CN)_2$, HCl	$H–C{\equiv}NH^+$	ArCH=NH	ArCHO
Hoesch	phenols	RCN, HCl, Zn(II)	$R–C{\equiv}NH^+$	ArRC=NH	ArCOR
chloromethylation	any	CH_2=O, HCl	$H_2C{=}OH^+$	$ArCH_2OH$	$ArCH_2Cl$
Kolbé–Schmidt	phenoxides	NaOH, CO_2	CO_2	$ArCO_2Na$	$ArCO_2H$
Reimer–Tiemann	phenols	$CHCl_3$, NaOH	CCl_2	$ArCHCl_2$	ArCHO

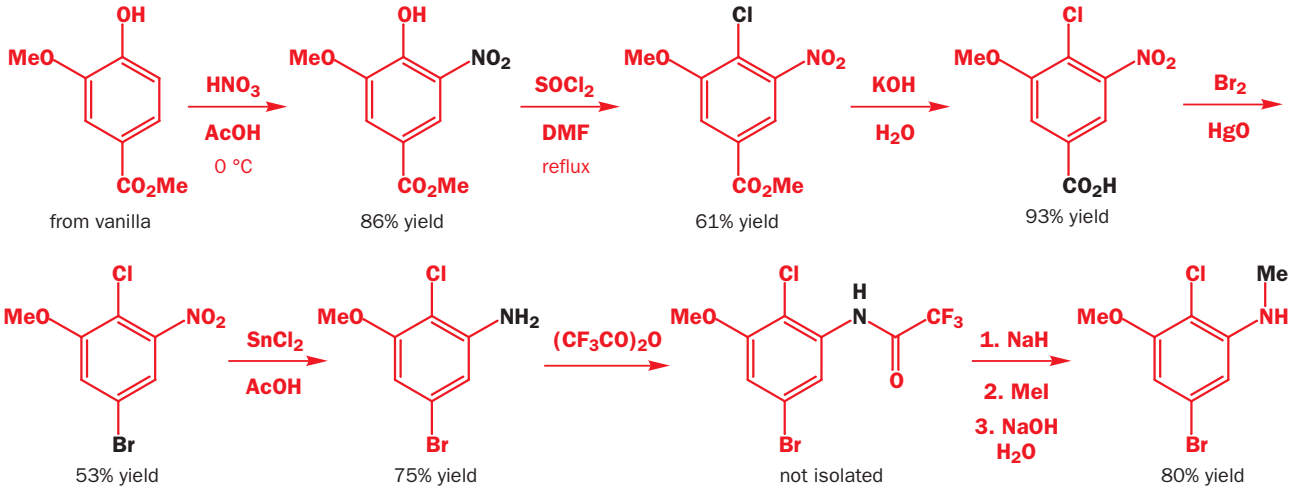
■ The Reimer–Tiemann reaction has dichlorocarbene (CCl_2) as an intermediate and is discussed in Chapter 40.

Electrophilic substitution is the usual route to substituted aromatic compounds

A group of potent anti-leukaemia compounds (the maytansinoids) has an aromatic ring as part of a complex large-ring structure. The synthesis of these molecules could be imagined as starting from a simple aromatic ring with four different substituents in the right positions.

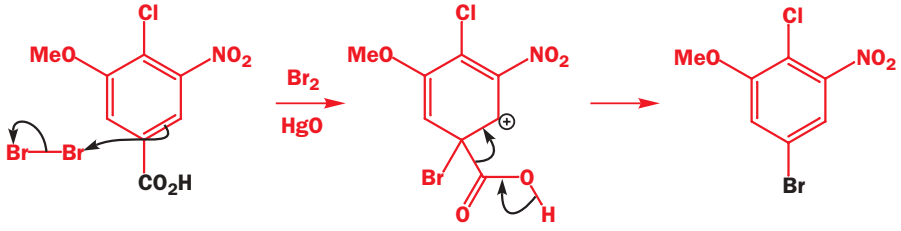


One complete synthesis is shown as the conclusion of this chapter. It is here to demonstrate that manipulation of simple aromatic rings is very much part of modern organic chemistry and because almost all the reactions are ones you have seen so far in the book.



Points to notice:

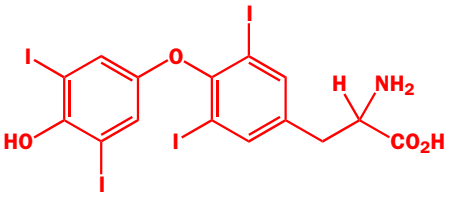
1. The starting material was chosen because it was cheap. It has the right number of substituents in the right places but only one (MeO–) is still there at the end
2. Nitration is used to put in the nitrogen atom as NO_2, later reduced to the required amino group. The nitro group goes in *ortho* to the OH group and *meta* to the CO_2Me group as you might have predicted
3. Step 3, the hydrolysis of the ester, and step 6, amide formation, are familiar reactions
4. Step 2, the replacement of OH by Cl, will be discussed in Chapter 23 as it is a *nucleophilic* aromatic substitution
5. Step 4 is an unusual type of electrophilic aromatic substitution. The leaving group is CO_2 rather than the usual proton and occurs at the only place it can (though it is *meta* to NO_2 and *para* to Cl)



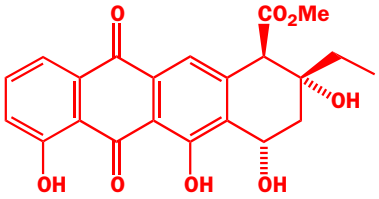
6 The last step is a way to achieve monomethylation of an amino group. Problem 00 gives you a chance to try your hand at a mechanism

Problems

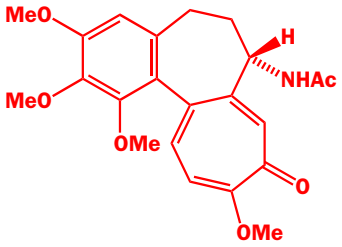
1. All you have to do is to spot the aromatic rings in these compounds. It may not be as easy as you think and you should state some reasons for your choice!



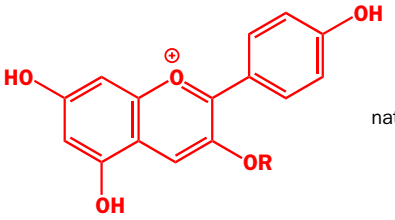
thyroxine
(human hormone)
iodine carrier
in thyroid gland



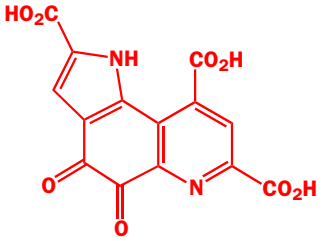
aklavinone
tetracycline antibiotic
[why tetracycline?]



colchicine
compound from
autumn crocus
used to treat gout

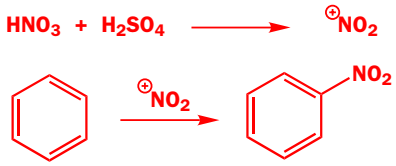


callistephin
natural red flower pigment

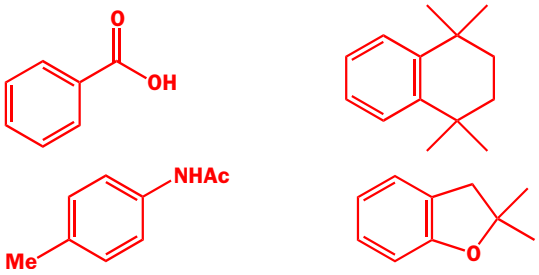


methoxatin
coenzyme from bacteria
living on methane

2. Just to remind you—write out a detailed mechanism for these steps.

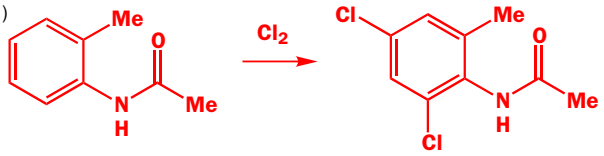


In a standard nitration reaction with, say, HNO_3 and H_2SO_4, each of these compounds forms a single mono-nitration product. What is its structure? Justify your answer with a mechanism.

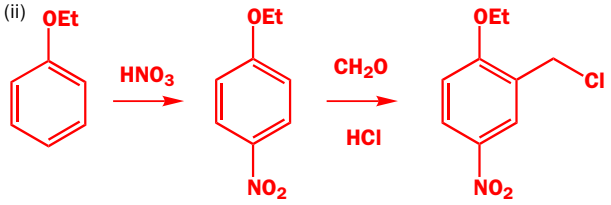


3. Write mechanisms for these reactions, justifying the position of substitution.

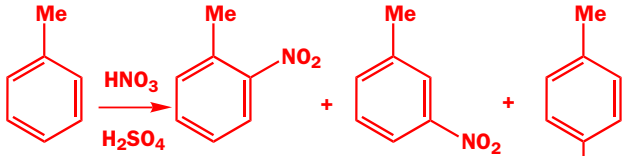
(i)



(ii)

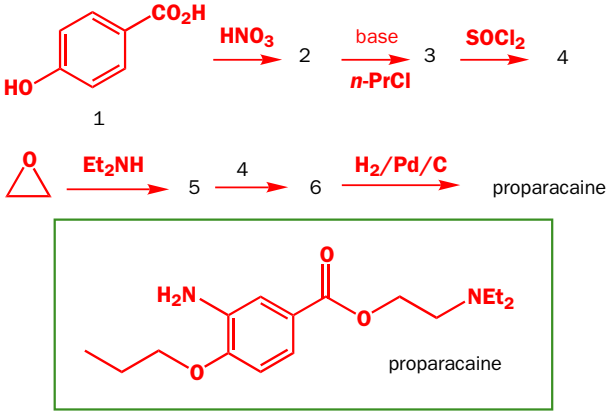


4. How reactive are the different sites in toluene? Nitration of toluene produces the three possible products in the ratios shown. What would be the ratio of products if all sites were equally reactive? What is the actual relative reactivity of the three sites? (You could express this as $x{:}y{:}1$ or as $a{:}b{:}c$ where $a + b + c = 100$.) Comment on the ratio you deduce.

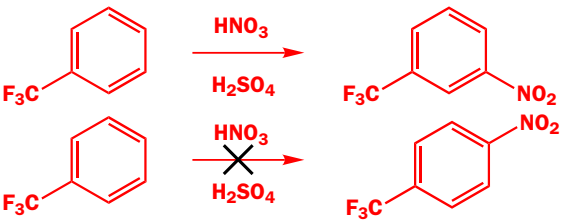


toluene 59% 4% 37%

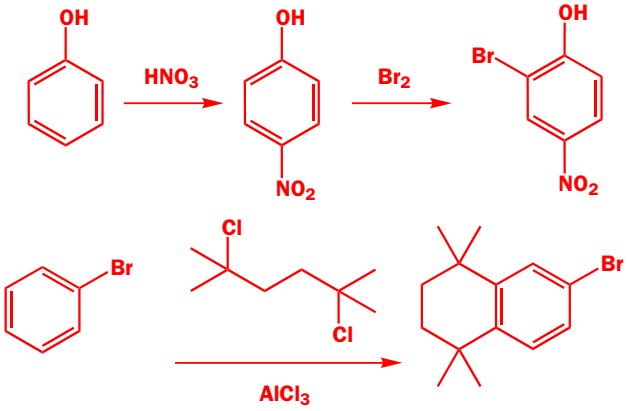
5. Revision problem. The local anaesthetic proparacaine is made by this sequence of reactions. Deduce a structure for each product. Draw a mechanism for each step and explain why it gives that particular product.



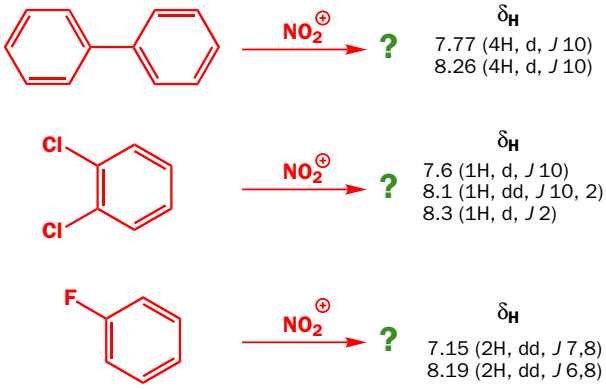
6. In the chapter, we established that electron-withdrawing groups direct *meta*. Among such reactions is the nitration of trifluoromethyl benzene. Draw out the detailed mechanism for this reaction and also for a reaction that does not happen—the nitration of the same compound in the *para* position. Draw all the delocalized structures of the intermediates and convince yourself that the intermediate for *para* substitution is destabilized by the CF_3 group while that for *meta* substitution is not.



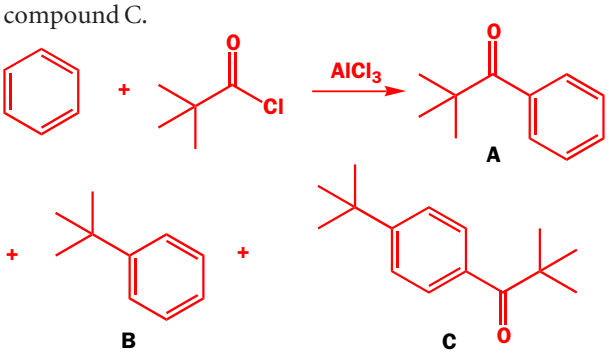
7. Draw mechanisms for the following reactions and explain the position(s) of substitution.



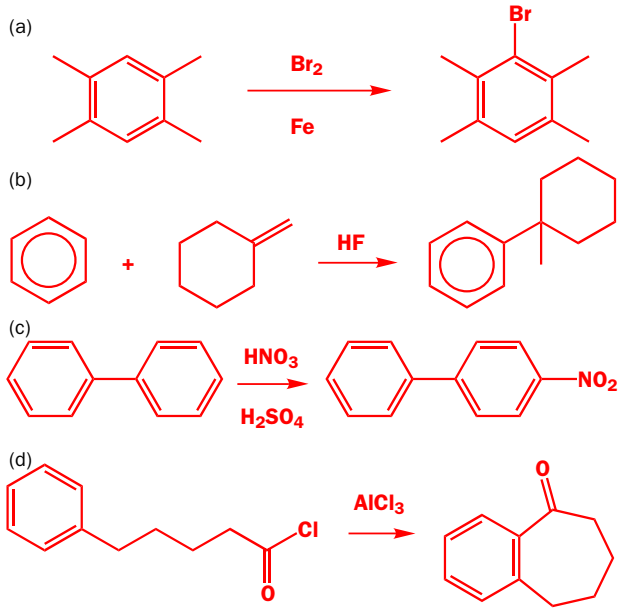
8. Nitration of these compounds gives products with the proton NMR spectra shown. Deduce the structures of the products from the NMR and explain the position of substitution.



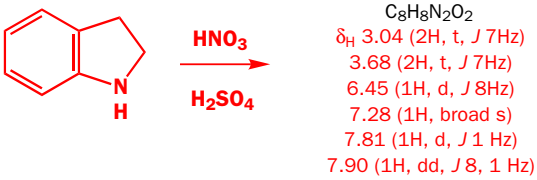
9. Attempted Friedel–Crafts acylation of benzene with *t*-BuCOCl gives some of the expected ketone, as a minor product, and also some *t*-butyl benzene, but the major product is the disubstituted compound C. Explain how these compounds are formed and suggest the order in which the two substituents are added to form compound C.



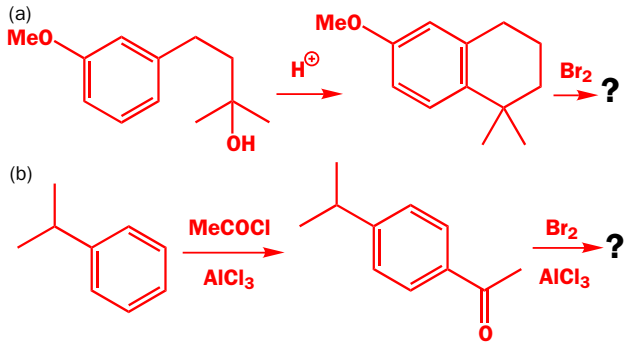
10. Draw mechanisms for the following reactions.



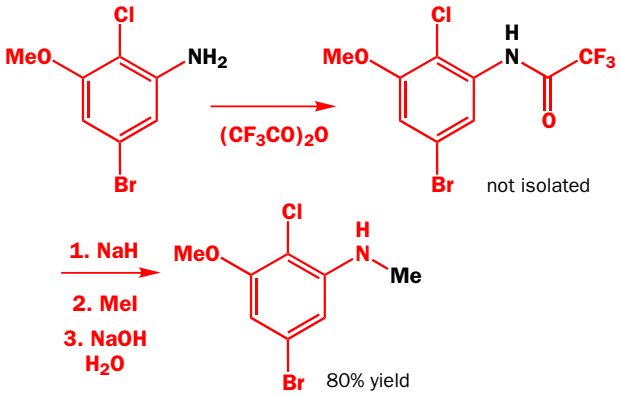
11. Nitration of this aromatic heterocycle with the usual mixture of HNO_3 and H_2SO_4 gives a product whose NMR spectrum is given. Though you have not yet met heterocycles you should be able to deduce the structure of the product and explain why it is formed.



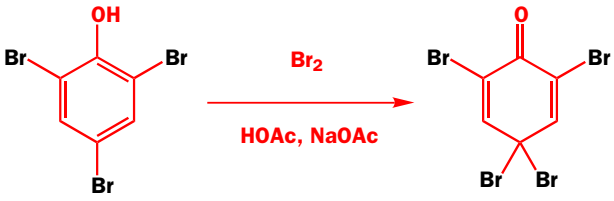
12. Explain the position of substitution in the following reactions and predict the structure of the final product. Why is a Lewis acid necessary for the second bromination but not for the first?



13. Suggest mechanisms for the methylation step at the end of the synthesis that concludes the chapter. Why is it necessary to go to these lengths rather than just react with MeI?

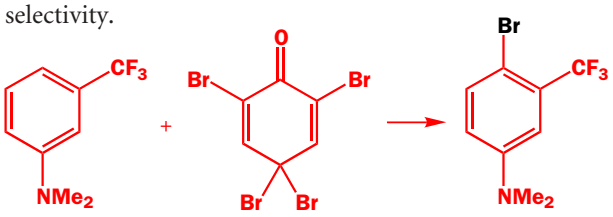


14. So what happens if we force phenol to react again with bromine? Will reaction then occur in the *meta* positions? It is possible to brominate 2,4,6-tribromophenol if we use bromine in acetic acid. Account for the formation of the product.



2,4,6-tribromophenol

This product can be used for bromination as in the mono-bromination of this amine. Suggest a mechanism and explain the selectivity.



90% yield

Electrophilic alkenes

23

Connections

Building on:

- Conjugate addition ch10
- Electrophilic additions to alkenes ch20
- Electrophilic substitution on aromatic rings ch22

Arriving at:

- Conjugate addition: conjugation of alkenes with electron-withdrawing groups other than C=O (CN and NO_2), which makes them electrophilic and allows nucleophilic attack
- Conjugate substitution: electrophilic alkenes bearing leaving groups can promote substitution reactions at C=C related to those at C=O
- Nucleophilic aromatic substitution: electron-poor aromatic rings that allow substitution reactions with nucleophiles rather than the usual electrophiles
- Special leaving groups and nucleophiles that allow nucleophilic aromatic substitution on electron-rich rings
- Allylic systems: how double bonds adjacent to leaving groups share the electrophilic character of the carbon atom carrying the leaving group, and may allow more than one product to form

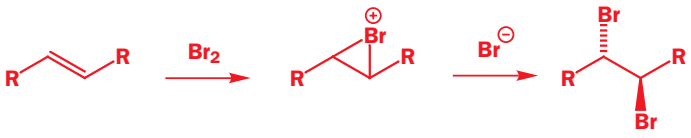
Looking forward to:

- Conjugate addition of enolate-type nucleophiles ch29
- Reactions of heterocyclic aromatic compounds ch43

This chapter is also the last chapter in the second cycle of chapters within this book, with which we complete our survey of the important elementary types of organic reactions. We follow it with two review chapters, before looking in more detail at enolate chemistry and how to make molecules.

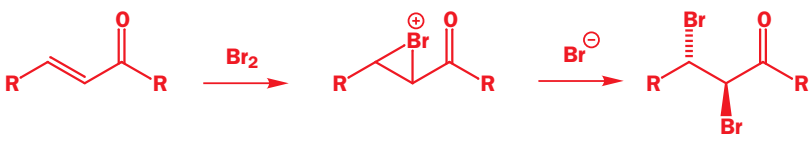
Introduction—electrophilic alkenes

Alkenes are nucleophilic. Almost regardless of their substituents, they react with electrophiles like bromine to form adducts in which the π bond of the alkene has been replaced by two σ bonds.



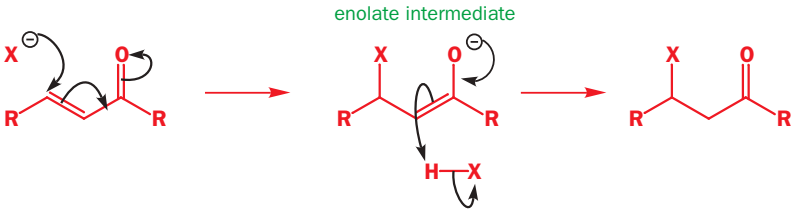
■ Reactions like this were discussed in Chapter 20.

Even when the alkene is conjugated with an electron-withdrawing group, bromine addition still occurs, though less readily. As we said, alkenes are nucleophilic.



■ We saw examples of this reaction in Chapter 10.

But this last type of alkene is also electrophilic. The carbonyl group dominates the alkene in the interaction between the two groups and nucleophiles add so that the enolate is an intermediate and the negative charge resulting from conjugate addition is stabilized by conjugation. This intermediate is protonated on carbon to give the conjugate addition product—the result of a nucleophilic addition of HX to the alkene. The final product has an unchanged carbonyl group but without that carbonyl group no nucleophilic addition could have occurred.



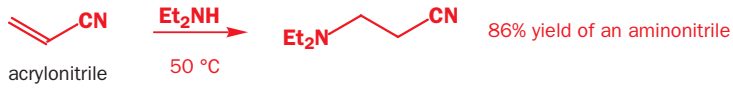
We are going to extend this idea now and show that other groups besides the carbonyl group can promote nucleophilic addition to alkenes and then extend the idea further into the reactions of allylic and aromatic compounds. First of all we are going to look at other conjugating electron-withdrawing groups.

Nucleophilic conjugate addition to alkenes

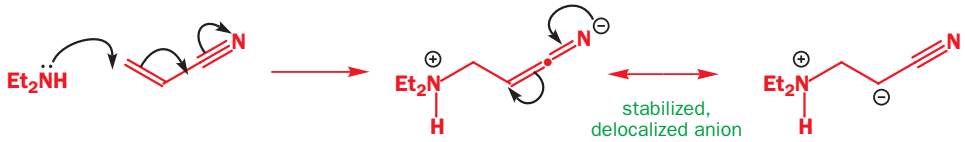
Unsaturated nitriles

The essential requirement for these reactions is a conjugating substituent that is about as anion-stabilizing as a carbonyl group. One we have seen before is cyanide and we shall look first at conjugated nitriles. The simplest is acrylonitrile. This compound adds amines readily.

■ Like many simple acrylic derivatives, this nitrile is readily available as it is manufactured on a large scale for polymer synthesis. Superglue is a polymerized acrylonitrile. There is more about this in Chapter 52.



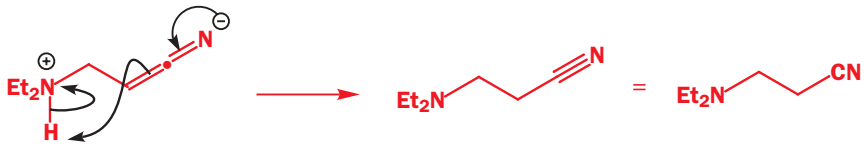
The amine first attacks the alkene in a typical conjugate addition to make a stable anion. Notice that the nucleophile must attack the far end of the alkene to do this—attack next to the electron-withdrawing group would not work.



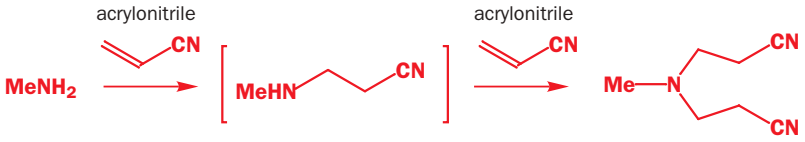
The anion can have its charge drawn on the nitrogen atom but it is really delocalized over the two neighbouring carbon atoms and is very like an enolate. Do not be put off by the odd appearance of the 'enolate'. The dot between the two double bonds is a reminder that there is a linear sp carbon atom at this point.

Protonation at carbon restores the cyanide and gives the product—an amino-nitrile. The whole process adds a 2-cyano-ethyl group to the amine and is known industrially as **cyanoethylation**.

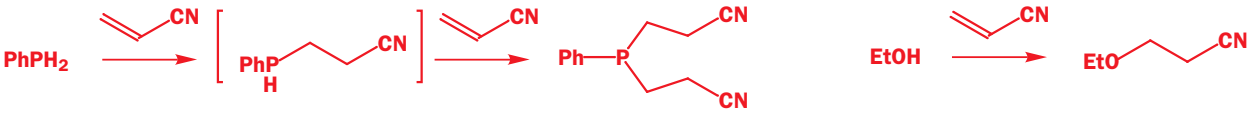
▶ You will see a few mechanisms in this chapter where we have written an intramolecular deprotonation. This saves writing two steps—protonation of the enolate and deprotonation of N (here)—but quite possibly this is not the actual mechanism by which the proton transfer takes place. Any proton will do, as will any base—do not take the arrows here too literally.



With a primary amine, the reaction need not stop at that stage as the product is still nucleophilic and a second addition can occur to replace the second hydrogen atom on nitrogen.



Other elements add too. Phenyl phosphine can undergo a double addition just as in the last example, but alcohols can add only once.



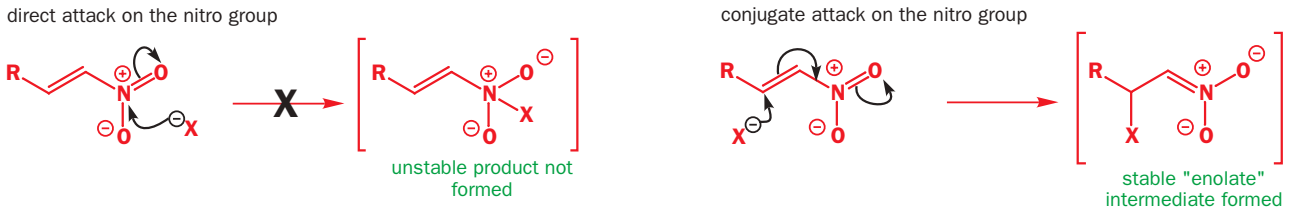
If there is a competition between a second row (for example, N or O) and a third row (for example, S or P) element, the third row element normally wins. The lone pair electrons are of higher energy ($3sp^3$) in the third-row element than in the second-row element ($2sp^3$).

The cyanide group is a typical group for promoting conjugate addition. It is possible for nucleophiles to attack directly at the CN group but it is not very electrophilic so that these reactions tend to be thermodynamically controlled and attack is preferred in the conjugate position.

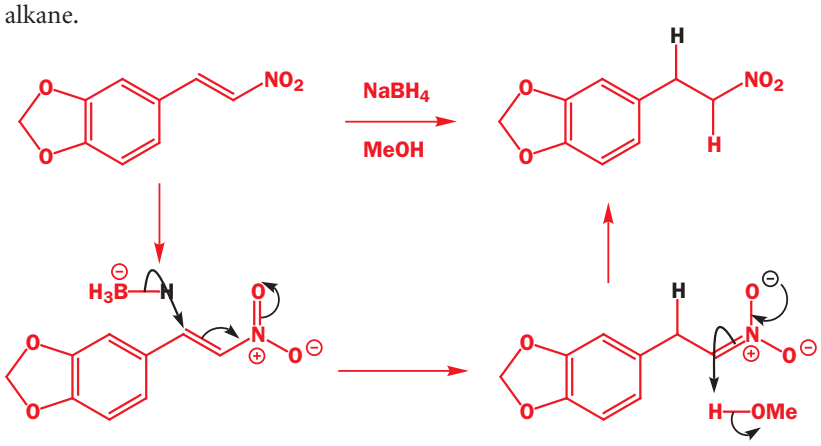
Unsaturated nitro compounds

The nitro group (NO_2) is extremely electron-withdrawing—about twice as electron-withdrawing as a carbonyl group. This should theoretically make it prefer direct attack rather than conjugate attack but in practice direct attack at NO_2 is almost unknown. The products from direct attack are very unstable compounds and revert to starting materials easily. You may rely on conjugate addition to nitro-alkenes.

■ We discussed factors favouring direct versus conjugate attack in Chapter 10, p. 000.

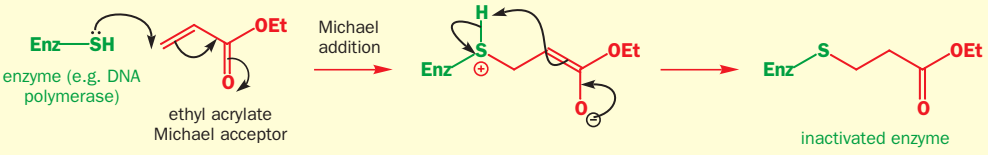


The intermediate is rather like an enolate anion, with a negatively charged oxygen atom conjugated to a (N=C) double bond. It reacts like an enolate, picking up a proton on carbon to re-form the nitro group and give a stable product—the result of conjugate addition of HX. Here is the full mechanism with borohydride acting as the nucleophile, reducing the nitroalkene to a nitroalkane.

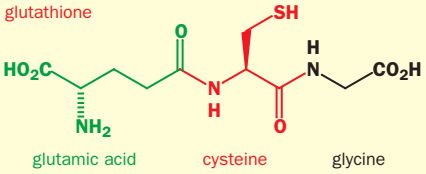


Michael acceptors are dangerous

Any compound capable of conjugate addition (a **Michael acceptor**—conjugate additions are also known as **Michael additions**) is potentially dangerous to living things. Even simple compounds like ethylacrylate are labelled 'cancer suspect agent'. They attack enzymes, particularly the vital DNA polymerase involved in cell division by conjugate addition to thiol and amino groups in the enzyme.

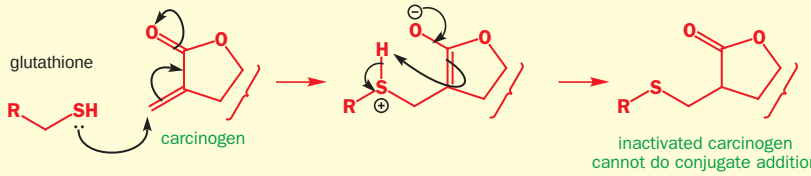


Any compound that is good at conjugate addition is probably toxic and carcinogenic (cancer-causing). In Chapter 10, we mentioned some anticancer drugs that work by this same mechansim, but do it more selectively in rapidly proliferating cancer cells. Most Michael acceptors are less benign, and damage the DNA replication process unselectively. Fortunately, we are offered some degree of protection by an important compound present in most tissues. The compound is glutathione, a tripeptide—a compound made from three amino acids. We shall discuss such compounds in more detail later in the book (Chapter 49) but notice for the moment that this compound can be divided into three at the two amide bonds.



The business end of glutathione is the thiol (SH) group, which scavenges carcinogenic compounds by conjugate addition. If we use an 'exomethylene lactone'—a highly reactive Michael acceptor—as an example and represent glutathione as RCH_2SH, you can see the sort of thing that happens.

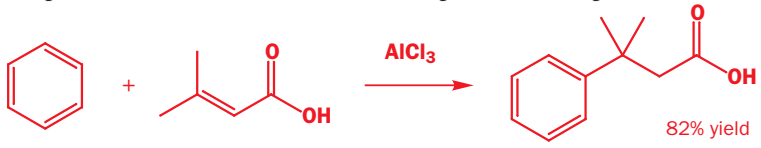
detoxification of carcinogens by glutathione



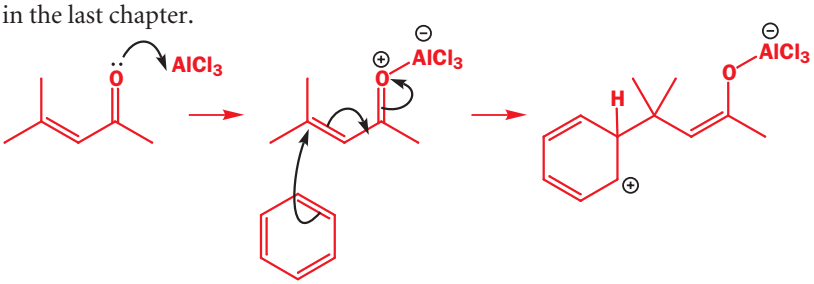
If the normally abundant glutathione is removed by such processes as oxidation (Chapter 46) and cannot any longer scavenge toxins, then the organism is in danger. This is one reason why vitamin C is so beneficial—it removes stray oxidizing agents and protects the supply of glutathione. Keep eating the fruit and vegetables!

Other nucleophiles in conjugate addition

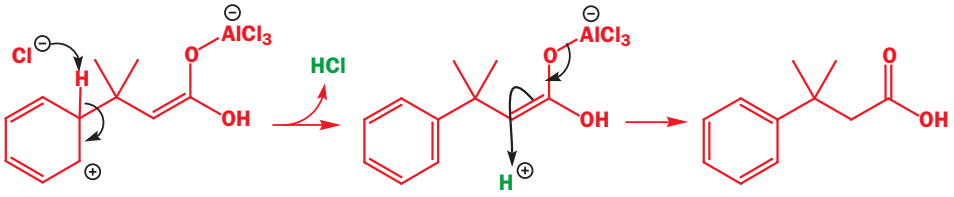
Since we introduced conjugate addition in Chapter 10, a number of new reactions have been covered and a number of new nucleophiles introduced. Some of these can lead to conjugate addition. One important new reaction is electrophilic aromatic substitution, which we met in the last chapter. Michael acceptors can combine with Lewis acids to provide electrophiles for reactions with benzene derivatives.



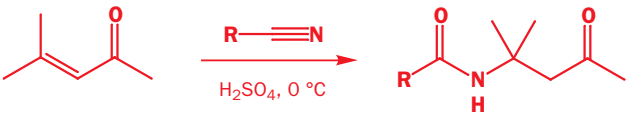
The Lewis acid ($AlCl_3$) must combine with the carboxylic acid to create a reactive electrophile that is attacked by a benzene molecule. The first step is just like the reactions of benzene we discussed in the last chapter.



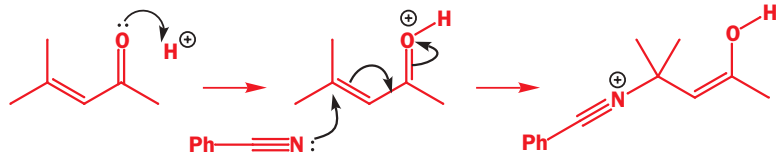
The next step must be the restoration of the aromaticity of the ring by the removal of the proton at the site of attack. This gives the aluminium enolate of the ketone. There is a proton now available to convert the aluminium enolate to the ketone and this is the final product. This is a useful reaction because it has added a benzene ring to a quaternary carbon atom—conjugate addition has overcome steric hindrance.



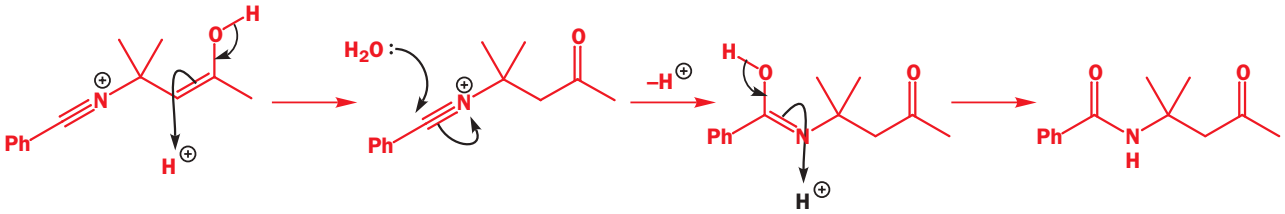
Another less-common class of nucleophile that does conjugate addition is nitriles. We used unsaturated nitriles a moment ago as Michael acceptors, and nitriles are usually electrophiles rather than nucleophiles. We did see in Chapter 17 that nitriles will act as nucleophiles in the S_N1 reaction (the Ritter reaction). The next reaction is related to the Ritter reaction.



Protonation of the carbonyl group gives a very electrophilic cation that is reactive enough to persuade the nitrile to do conjugate addition.

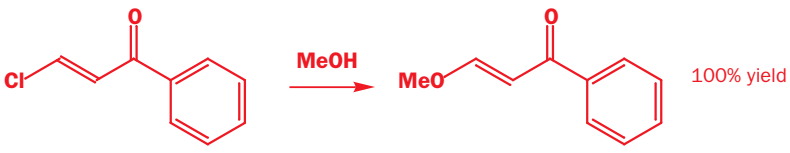


Tautomerization of the enol to a ketone, addition of water, and another tautomerization to an amide complete the mechanism. Notice here that a nitrogen has been added to a tertiary centre—this is not an easy result to accomplish and it is worth noting that conjugate addition is a good way to make bonds to crowded centres.



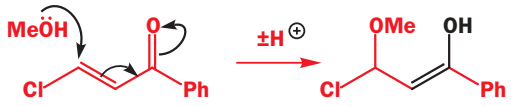
Conjugate substitution reactions

Just as direct addition to C=O (Chapter 6) becomes substitution at C=O (Chapter 12) when there is a leaving group at the carbonyl carbon, so conjugate *addition* becomes conjugate *substitution* if there is a leaving group, such as Cl, at the β carbon atom. Here is an example: substitution has replaced Cl with OMe, just as it would have done in a reaction with an acyl chloride.



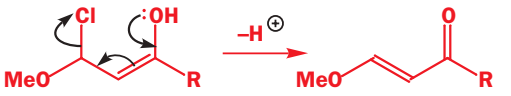
This apparently simple substitution does *not* involve a direct displacement of the leaving group in a single step! As you will see again shortly, S_N2 reactions do not occur at sp^2 hybridized carbon. The mechanism starts in exactly the same way as for conjugate addition, giving an enol intermediate.

formation of the enol intermediate

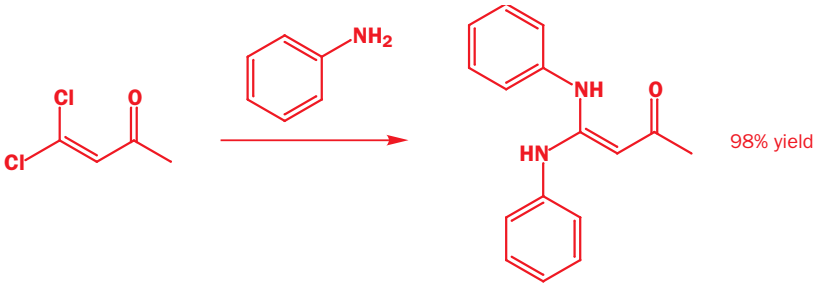


Now the leaving group can be expelled by the enol: the double bond moves back into its original position in this step, which is exactly the same as the final step of an E1cB reaction (Chapter 19). The 'new' double bond usually has the *E* configuration as the molecule can choose which of the two possible perpendicular conformations to eliminate.

expulsion of the leaving group from the enol intermediate

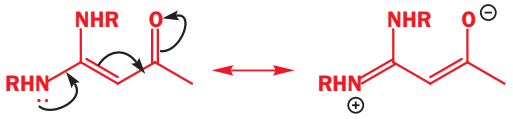


Halogens are excellent leaving groups and are often used in conjugate substitution reactions. In the next example, two consecutive conjugate substitution reactions give a diamine.

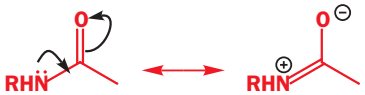


At first sight, the product looks rather unstable—sensitive to water, or traces of acid perhaps. But, in fact, it is remarkably resistant to reaction with both. The reason is conjugation: this isn't really an amine (or a diamine) at all, because the lone pairs of the nitrogen atoms are delocalized into the carbonyl group, very much as they are in an amide. This makes them less basic, and makes the carbonyl group less electrophilic.

delocalization of the nitrogen's lone pair



delocalization in an amide

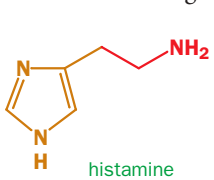


Compounds like this are for this reason known as **vinylogous amides**—the C=C bond between the N and C=O allows conjugation still to take place but at a greater distance. This is the essence of vinylogous behaviour.

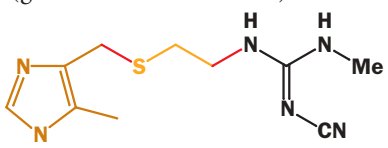
Just as the cyanide (CN) and nitro (NO_2) groups can be used to bring about conjugate addition, so also they can initiate conjugate substitution. Examples of these reactions play vital roles in the synthesis of two of the most important drugs known—the anti-ulcer drugs Tagamet (SmithKline Beecham) and Zantac (GlaxoWellcome).

Preventing ulcers (1): Tagamet

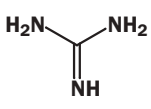
One cause of ulcers is excess acid secretion by the stomach, and one method of prevention is to stop this by blocking the acid-releasing action of histamine. You can see here the resemblance between histamine and Tagamet (generic name cimetidine).



histamine



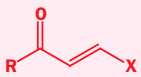
cimetidine—SmithKline Beecham's Tagamet



guanidine

▶ Vinylogous behaviour

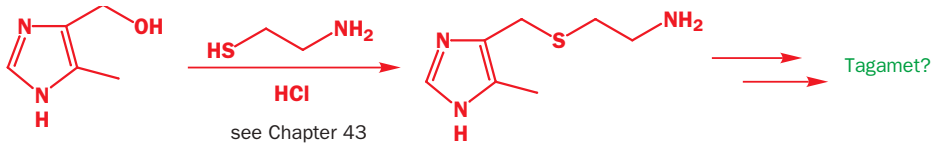
The conjugated double bond serves as an electronic linker between the carbonyl group and the halogen or other heteroatom, which makes the chemical and spectroscopic behaviour of the composite functional group similar to that of the simple relative. You could think of the β-chloro enone at the beginning of this section as a vinylogous acyl chloride that reacts with methanol to give a vinylogous ester.



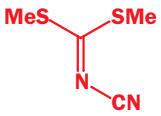
is the vinylogous version of, and reacts similarly to,

As well as the histamine-like portion of the molecule, Tagamet has a sulfur atom and then, at the end of a short chain of carbon atoms, a complicated functional group based on guanidine. It is easy to add the sulfur atom and the short carbon chain to the heterocyclic building block (see Chapter 43 for more about this) so that the only problem is how to build on the guanidine at the end of the molecule.

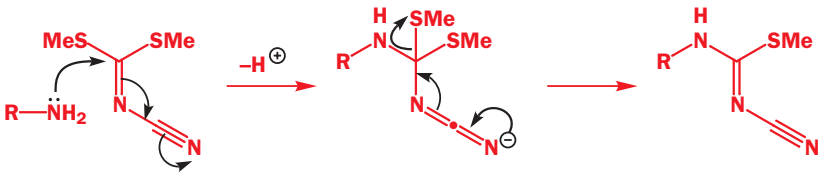
■ Guanidine is an organic base, as strong as NaOH, and it was discussed in Chapter 8.



Now enter the star of the show! This simple cyanoimine, with two SMe groups as built-in leaving groups, is readily available and reacts with amines to give guanidines in two stages.

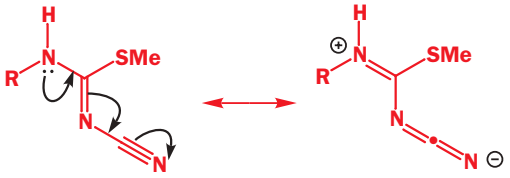


Each of the reactions is a conjugate substitution. It will be clearer if we draw the reaction with a generalized primary amine RNH_2 first.

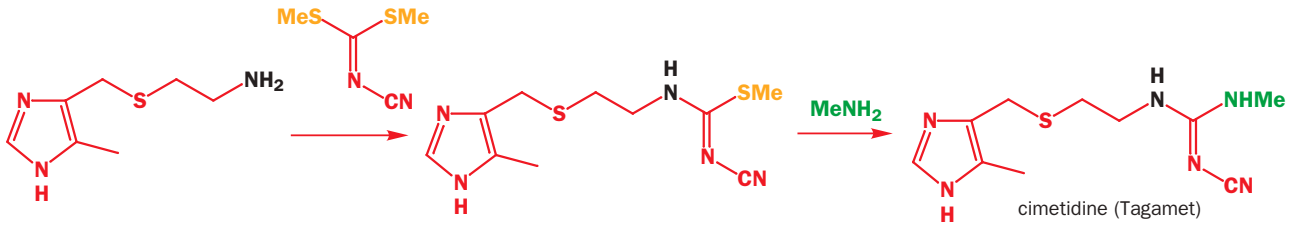


The first step is conjugate addition, exactly as we saw with acrylonitrile at the beginning of this chapter. The second step shows the return of the negative charge and the expulsion of the best leaving group. Thiols are acidic compounds, and MeS^- is a better leaving group than RNH^-.

The reaction stops cleanly at this point and more vigorous conditions are required to displace the second MeS^- group. This is because the first product is less reactive than the starting material. Why is this? The introduced amino group is electron-donating and a strong conjugation is established between it and the cyano group.



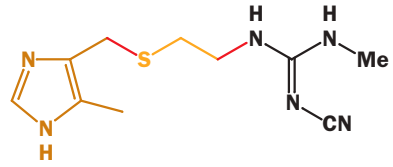
Now a second and different amine can be introduced and the second MeS^- group displaced. In the Tagamet synthesis; the second amine is $MeNH_2$, and the synthesis is complete.



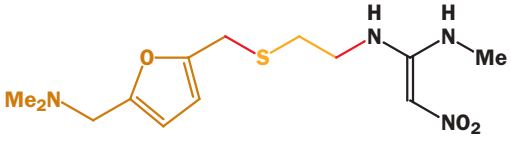
cimetidine (Tagamet)

Preventing ulcers (2): the best selling drug of all time—GlaxoWellcome's Zantac

This anti-ulcer drug has some obvious similarities to Tagamet, and some differences too. Here are the two structures side-by-side.



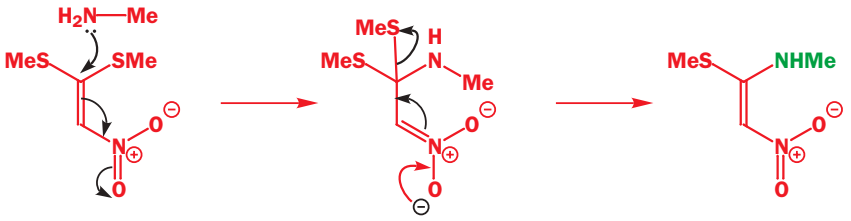
cimetidine—SmithKline Beecham's Tagamet



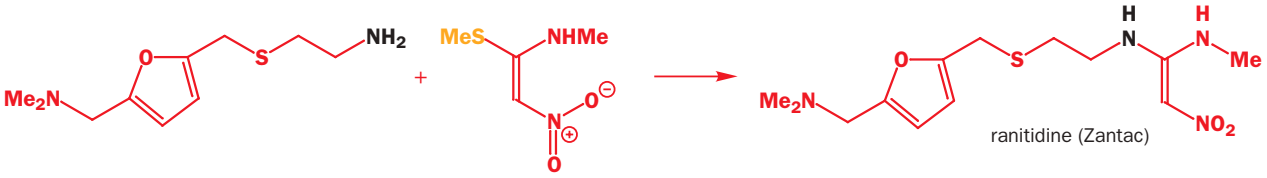
ranitidine—GlaxoWellcome's Zantac

The heterocyclic ring is still there but it is very different. The sulfur and its surrounding CH_2 groups are the same and the guanidine seems to be still there. But it isn't. Look closely at this

'guanidine' and you will see that there are only *two* nitrogen atoms around the central carbon atom instead of the *three* in a guanidine. This is an **amidine**. The nitrile has also been replaced by a nitro group. The synthesis is ,however, remarkably similar to that of the real guanidine in Tagamet. Two conjugate substitutions use MeS^- as leaving groups and amine as nucleophiles. Here is the first, with mechanism.



The first step is conjugate addition, just like the conjugate additions to nitroalkenes at the beginning of this chapter, and the second step brings the negative charge back and expels the best leaving group. Again the reaction can be made to stop at this stage because this product is stabilized by conjugation between the green amino group and the nitro group. A second substitution puts together the two halves of the drug.

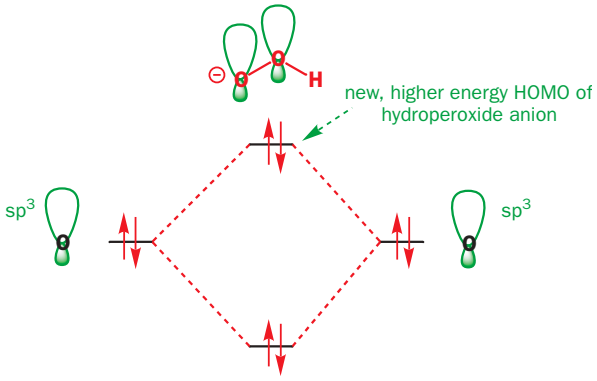


Nucleophilic epoxidation

The conjugate substitutions we have just been discussing rely on a starting material containing a leaving group. In this section we are going to look at what happens if the leaving group is not attached to the unsaturated carbonyl compound, but instead is attached to the nucleophile. We shall look at this class of compounds—nucleophiles with leaving groups attached—in more detail in Chapter 40, but for the moment the most important will be hydroperoxide, the anion of hydrogen peroxide.

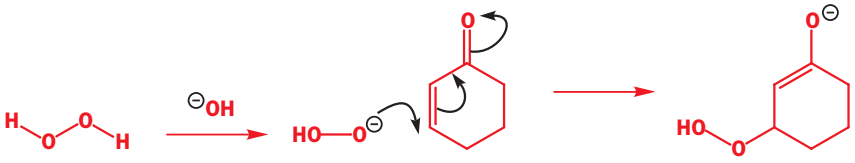
hydrogen peroxide | hydroperoxide anion

Hydroperoxide is a good nucleophile because of the **alpha effect**: interaction of the two lone pairs on adjacent oxygen atoms raises the HOMO of the anion and makes it a better and softer nucleophile than hydroxide.



Hydroperoxide is also less basic than hydroxide because of the inductive electron-withdrawing effect of the second oxygen atom. Basicity and nucleophilicity usually go hand in hand—not here though. This means that the hydroperoxide anion can be formed by treating hydrogen peroxide with aqueous sodium hydroxide.

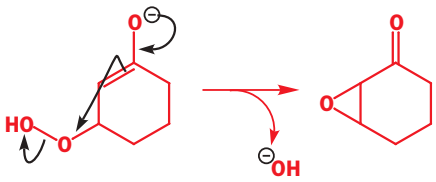
This is what happens when this mixture is added to an enone. First, there is the conjugate addition.



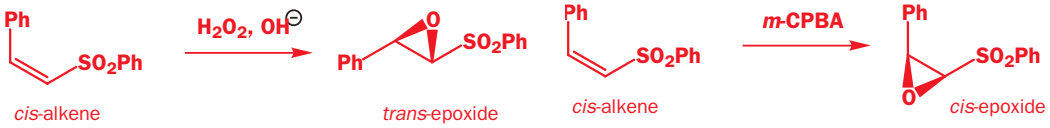
▶ The same effect explains why hydroxylamine and hydrazine are more nucleophilic than ammonia: p. 000.

▶ The pK_a of hydrogen peroxide is 11.6.

The product is not stable, because hydroxide can be lost from the oxygen atom that was the nucleophile. Hydroxide is fine as a leaving group here—after all, hydroxide is lost from enolates in E1cB eliminations, and here the bond breaking is a weak O–O bond. The product is an epoxide.

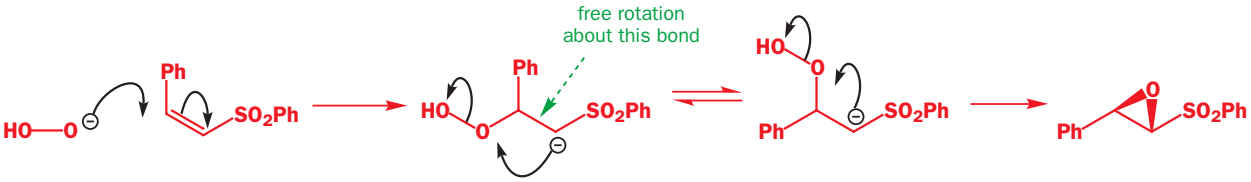


The electrophilic epoxidizing agents such as *m*-CPBA, which you met in Chapter 20, are less good with electron-deficient alkenes: we need a nucleophilic epoxidizing agent instead. There is another significant difference between hydrogen peroxide and *m*-CPBA, highlighted by the pair of reactions below.



cis-alkene *trans*-epoxide *cis*-alkene *cis*-epoxide

m-CPBA epoxidation is stereospecific because the reaction happens in one step. But nucleophilic epoxidation is a two-step reaction: there is free rotation about the bond marked in the anionic intermediate, and the more stable, *trans*-epoxide results, whatever the geometry of the starting alkene.



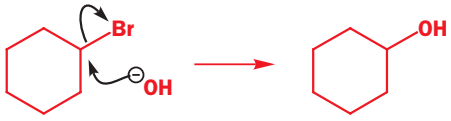
In general, conjugate substitution is not nearly as important as the next topic in this chapter—nucleophilic aromatic substitution. Before we describe in detail those reactions that do occur, we need to explain why the most obvious reactions do not occur.

Nucleophilic aromatic substitution

The simplest and most obvious nucleophilic substitutions on an aromatic ring, such as the displacement of bromide from bromobenzene with hydroxide ion, do *not* occur.

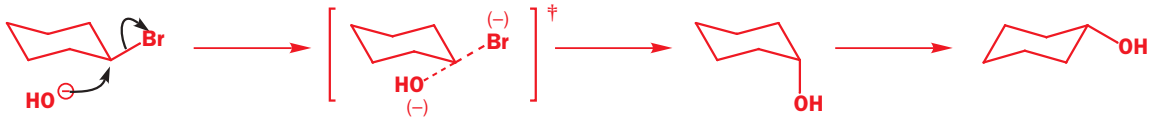
reaction doesn't happen

Please note—this mechanism is *wrong*! No such reactions are known. You might well ask, 'Why not?' The reaction looks all right and, if the ring were saturated, it *would* be all right.



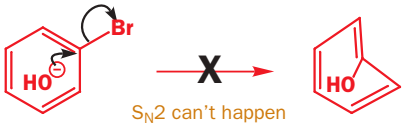
reaction does happen

This is an S_N2 reaction, and we know (Chapter 17) that attack must occur in line with the C–Br bond from the back, where the largest lobe of the σ* orbitals lies. That is perfectly all right for the aliphatic ring because the carbon atom is tetrahedral and the C–Br bond is not in the plane of the ring. Substitution of an equatorial bromine goes like this.



line of attack is not in plane of ring

But in the aromatic compound, the C–Br bond is in the plane of the ring as the carbon atom is trigonal. To attack from the back, the nucleophile would have to appear inside the benzene ring and invert the carbon atom in an absurd way. This reaction is not possible!



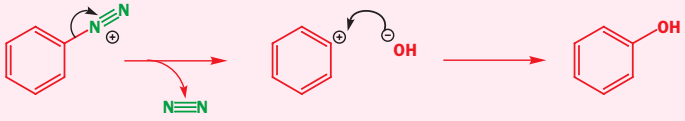
S_N2 can't happen

This is another example of the general rule.

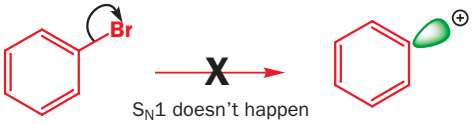
> ● S_N2 at sp^2 C does *not* occur.

If S_N2 is impossible, what about S_N1? This is possible but very unfavourable. It would involve the unaided loss of the leaving group and the formation of an aryl cation. All the cations we saw as intermediates in the S_N1 reaction (Chapter 17) were planar with an empty p orbital. This cation is planar but the p orbital is full—it is part of the aromatic ring—and the empty orbital is an sp^2 orbital outside the ring.

▶ In fact, the mechanism *can* occur, but only with the best leaving group—a molecule of gaseous nitrogen—as we shall see later.



S_N1 does happen



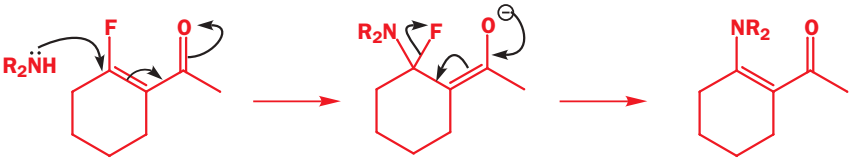
S_N1 doesn't happen

unstable phenyl cation with empty sp^2 orbital

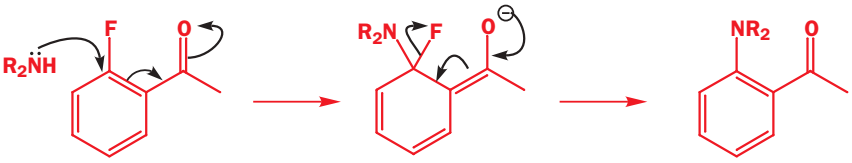
The most important mechanism for aromatic nucleophilic substitution follows directly from conjugate substitution and we shall introduce it that way. It is called the 'addition–elimination mechanism'.

The addition–elimination mechanism

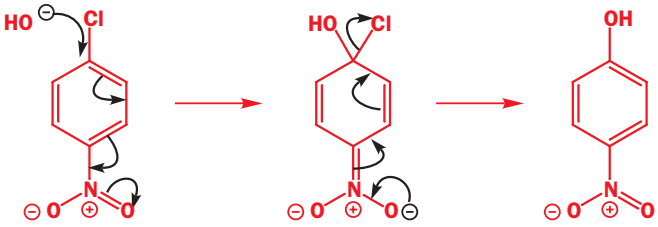
Imagine a cyclic β-fluoro-enone reacting with a secondary amine in a conjugate substitution reaction. The normal addition to form the enolate followed by return of the negative charge to expel the fluoride ion gives the product.



Now imagine just the same reaction with two extra double bonds in the ring. These play no part in our mechanism; they just make what was an aliphatic ring into an aromatic one. Conjugate substitution has become nucleophilic aromatic substitution.



The mechanism involves *addition* of the nucleophile followed by *elimination* of the leaving group—the **addition–elimination mechanism**. It is not necessary to have a carbonyl group—any electron-withdrawing group will do—the only requirement is that the electrons must be able to get out of the ring into this anion-stabilizing group. Here is an example with a *para*-nitro group.



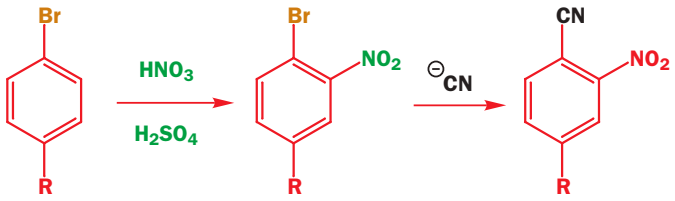
Everything is different about this example—the nucleophile (HO^-), the leaving group (Cl^-), the anion-stabilizing group (NO_2), and its position (*para*)—but the reaction still works. The nucleophile is a good one, the negative charge can be pushed through on to the oxygen atom(s) of the nitro group, and chloride is a better leaving group than OH.

A typical nucleophilic aromatic substitution has:

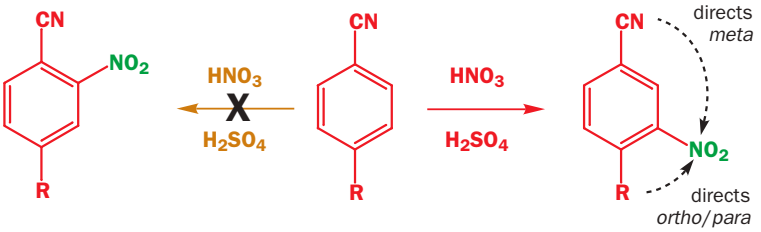
- an oxygen, nitrogen, or cyanide nucleophile

- a halide for a leaving group
- a carbonyl, nitro, or cyanide group *ortho* or *para* to the leaving group

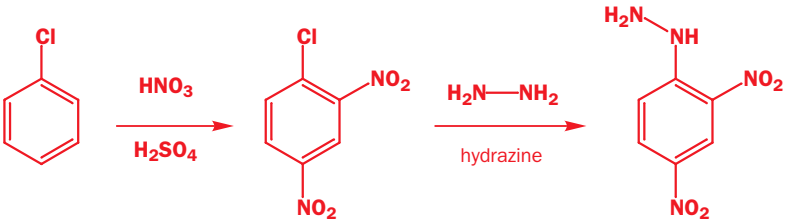
Since the *nitro* group is usually introduced by electrophilic aromatic substitution (Chapter 22) and halides direct *ortho/para* in nitration reactions, a common sequence is nitration followed by nucleophilic substitution.



This sequence is useful because the nitro group could not be added directly to give the final product as nitration would go in the wrong position. The cyanide is *meta*-directing, while the alkyl group (R) is *ortho*, *para*-directing.



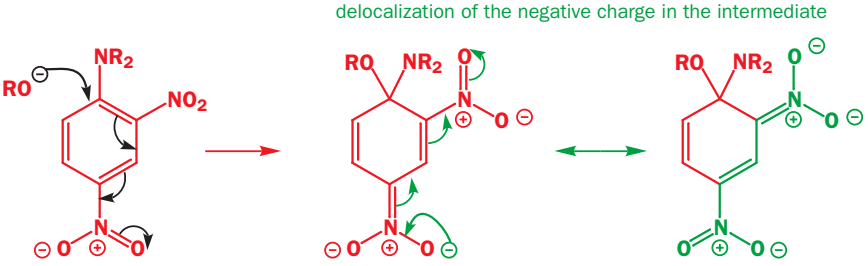
Two activating electron-withdrawing groups are better than one and dinitration of chlorobenzene makes a very electrophilic aryl halide. Reaction with hydrazine gives a useful reagent.



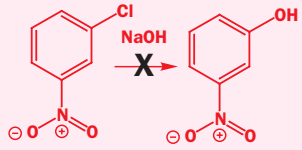
This compound forms coloured crystalline imines (hydrazones) with most carbonyl compounds—before the days of spectroscopy these were used to characterize aldehydes and ketones (see p. 000).

The intermediate in the addition–elimination mechanism

What evidence is there for intermediates like the ones we have been using in this section? When reactions like this last example are carried out, a purple colour often appears in the reaction mixture and then fades away. In some cases the colour is persistent and thought to be due to the intermediate. Here is an example with RO^- attacking a nitrated aniline.

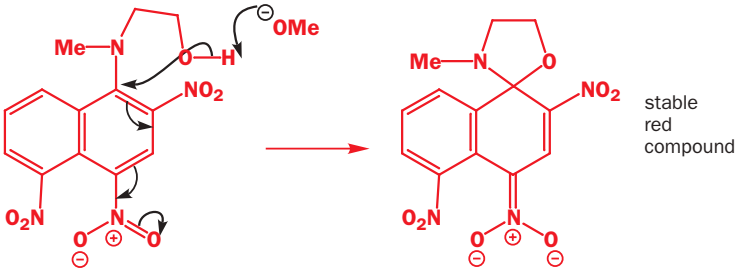


▶ If you try and do the same reaction with a *meta* anion-stabilizing group, it doesn't work. You can't draw the arrows to push the electrons through on to the oxygen atom. Try it yourself.

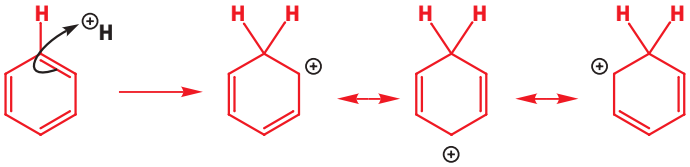


▶ It also makes a very toxic one! The reason is the same as with Michael acceptors—this compound is carcinogenic.

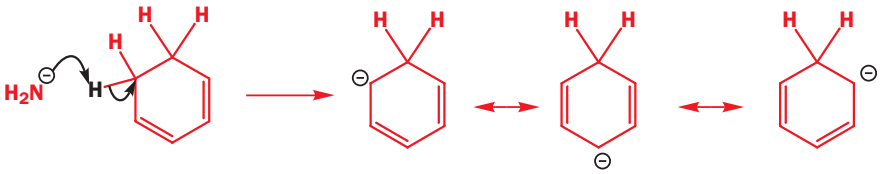
This intermediate is persistent because neither potential leaving group (NR_2 or OR) is very good. If the nucleophile is part of the same molecule, the intermediate becomes a stable cyclic compound and can be isolated. It is more stable because neither leaving group can get away from the molecule as it is tethered by the rest of the ring. Notice that there are *three* active nitro groups in this molecule all stabilizing the negative charge.



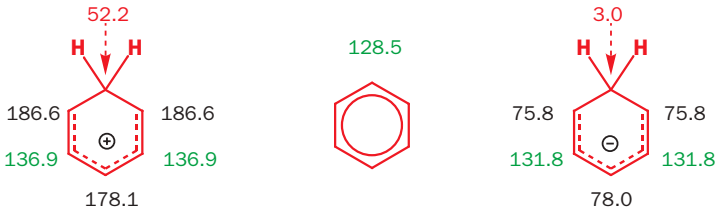
What is the nature of this intermediate? We can best answer that by comparing the ^{13}C NMR spectra of three species: benzene itself; the simplest version of our carbanion intermediate (that is, with no substituents); and the simplest version of the cationic intermediate in electrophilic aromatic substitution. Direct protonation of benzene gives this last compound.



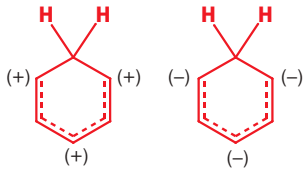
The intermediate in nucleophilic substitution cannot be made by adding H^- to benzene as no reaction occurs. Olah, the carbocation pioneer (p. 000), managed to make it by treating dihydrobenzene (cyclohexadiene) with a strong base. Deprotonation creates the anion.



Here are the details of the NMR spectra side-by-side with those of benzene. We shall use a summary structure for each ion showing delocalized charges around the five trigonal atoms in the ring. You may judge whether the NMR spectra justify these structures.



▶ *A reminder.* A larger shift means less electronic shielding and a smaller shift more electronic shielding.

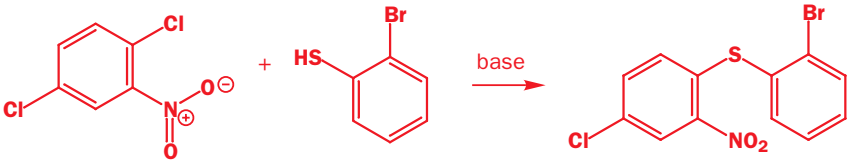


These results are very striking. The shifts of the *meta* carbons in both ions are very slightly different from those of benzene itself (about 130 p.p.m.). But the *ortho* and *para* carbons in the cation have gone downfield to much larger shifts while the *ortho* and *para* carbons in the anion have gone upfield to much smaller shifts.

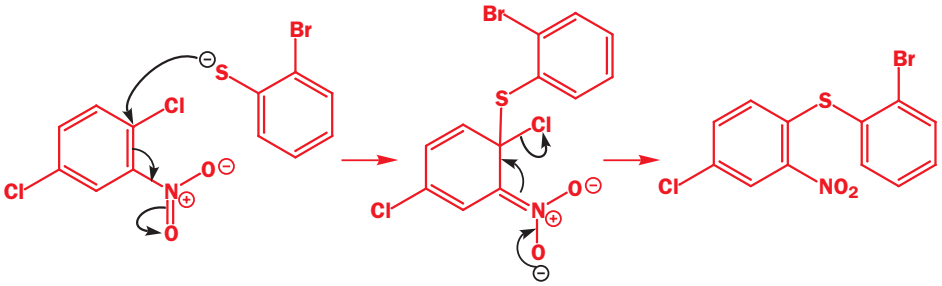
The differences are very great—about 100 p.p.m. between the cation and the anion! It is very clear from these spectra that the ionic charge is delocalized almost exclusively to the *ortho* and *para* carbons in both cases. The alternative structures in the margin show this delocalization.

This means that stabilizing groups, such as nitro or carbonyl in the case of the anion, must be on the *ortho* or *para* carbons to have any effect. A good illustration of this is the selective displacement of

one chlorine atom out of these two. It is the *ortho* chlorine group that is lost and the *meta* one that is retained.

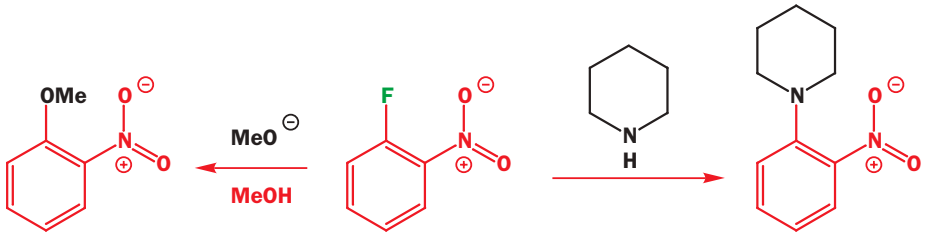


The mechanism works well if we attack the chlorine position *ortho* to the nitro group with the anion of the thiol nucleophile as the negative charge can then be pushed into the nitro group. Satisfy yourself that you cannot do this if you attack the other chlorine position. This is a very practical reaction and is used in the manufacture of a tranquillizing drug.



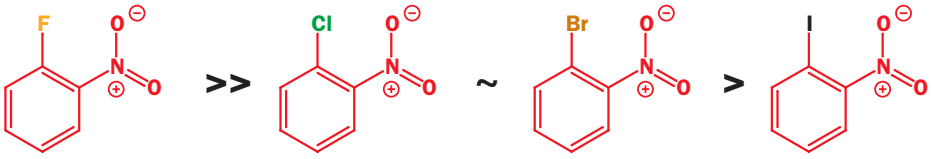
The leaving group and the mechanism

In the first nucleophilic aromatic substitution that we showed you, we used fluoride ion as a leaving group. Fluoride works very well in these reactions, and even such a simple compound as 2-nitrofluorobenzene reacts efficiently with a variety of nucleophiles, as in these examples.



The same reactions happen with the other 2-nitro-halobenzenes but less efficiently. The fluoro-compound reacts about 10^2–10^3 times faster than the chloro- or bromo-compounds and the iodo-compound is even slower.

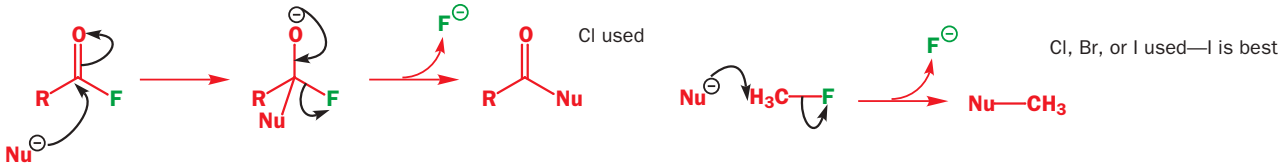
reactivity of 2-halo-1-nitrobenzenes in nucleophilic aromatic substitution



fastest reactions slowest reactions

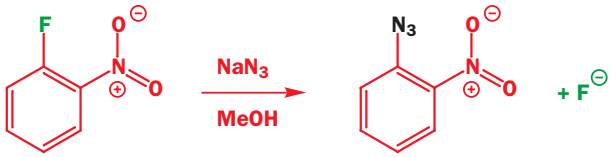
This ought to surprise you. When we were looking at other nucleophilic substitutions such as those at the carbonyl group or saturated carbon, we never used fluoride as a leaving group! The C–F bond is very strong—the strongest of all the single bonds to carbon—and it is difficult to break.

these reactions are not used:

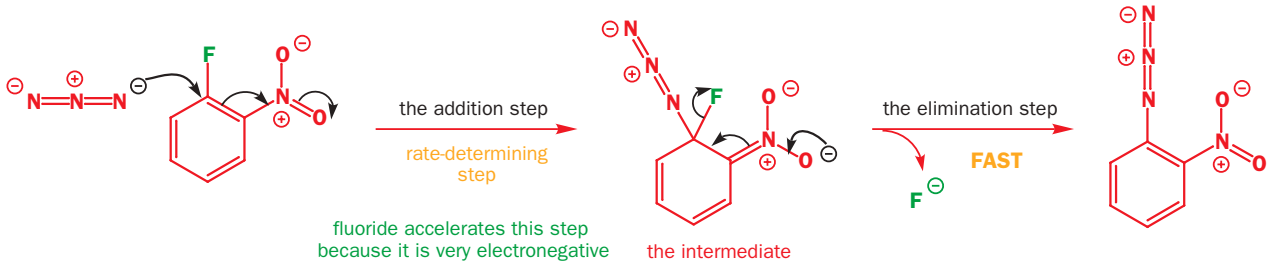


▶ Azide is a good nucleophile because of its shape—it is like a needle—and because it is equally nucleophilic at either end. We discussed azides in Chapter 17, p. 000.

So why is fluoride often preferred in nucleophilic aromatic substitution and why does it react faster than the other halogens when the reverse is true with other reactions? You will notice that we have *not* said that fluoride is a better leaving group in nucleophilic aromatic substitution. It isn't! The explanation depends on a better understanding of the mechanism of the reaction. We shall use azide ion as our nucleophile because this has been well studied, and because it is one of the best.



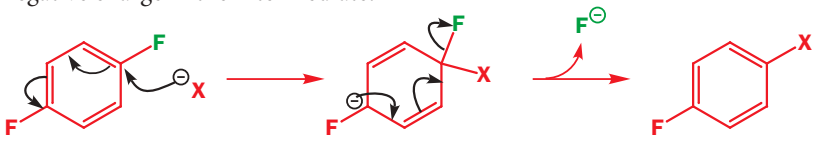
The mechanism is exactly the same as that we have been discussing all along—a two-stage addition–elimination sequence. In a two-step mechanism, one step is slower and rate-determining; the other is unimportant to the rate. You may guess that, in the mechanism for nucleophilic aromatic substitution, it is the first step that is slower because it disturbs the aromaticity. The second step restores the aromaticity and is faster. The effect of fluoride, or any other leaving group, can only come from its effect on the first step. How good a leaving group it might be does not matter: the rate of the second step—the step where fluoride leaves—has no effect on the overall rate of the reaction.



▶ Note carefully that this is an *inductive* effect: there are no arrows to be drawn to show how fluorine withdraws electrons—it does it just by polarizing C–F bonds towards itself. Contrast the electron-withdrawing effect of the nitro group, which works (mainly) by conjugation.

Fluoride does, in fact, slow down the second step (relative to Cl^-, say), but it accelerates the first step simply by its enormous inductive effect. It is the most electronegative element of all and it stabilizes the anionic intermediate, assisting the acceptance of electrons by the benzene ring.

A dramatic illustration of the effect of fluorine is the reactions of benzene rings with more than one fluorine substituent. These undergo nucleophilic substitution without any extra conjugation from electron-withdrawing groups. All the fluorine atoms that are not reacting help to stabilize the negative charge in the intermediate.

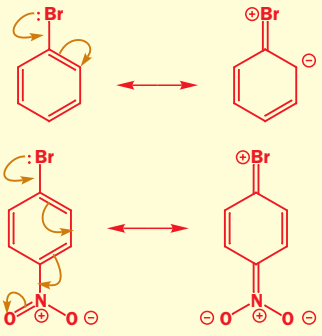


delocalized negative charge stabilized by two fluorines on ring

Intellectual health warning!

Some textbooks tell you that nucleophilic aromatic substitution doesn't happen with ordinary aryl halides because of conjugation between the lone pairs of the halide and the aromatic system.

This is supposed to stop the reaction by making the C–Br bond stronger. This is nonsense. The reaction doesn't happen on simple aryl halides because there is no available mechanism. It is easy to show that the false textbook reason is wrong. The conjugation in this nitro compound is much better than in bromobenzene, so it should be even less reactive.

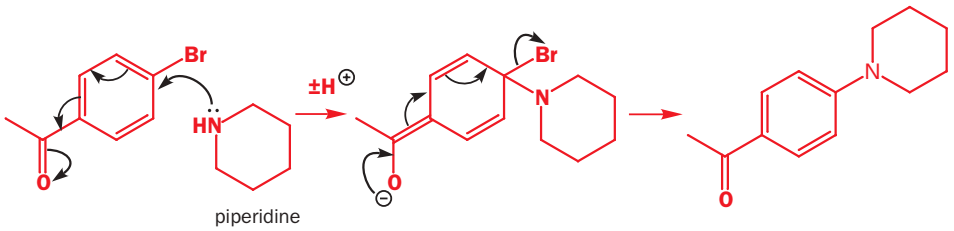


In fact, as you now know, this compound is much *more* reactive towards nucleophiles. The false textbook reason would also suggest that fluoride would work really badly because this same conjugation is stronger with fluoride than with the other halogens as its p orbitals are the right size ($2sp^2$) to conjugate with carbon p orbitals. Again, you already know the opposite to be true.

The strength of the bond to the leaving group does not affect the efficiency of nucleophilic aromatic substitution because that bond is not broken in the rate-determining step. Understand the mechanism and it all becomes clear.

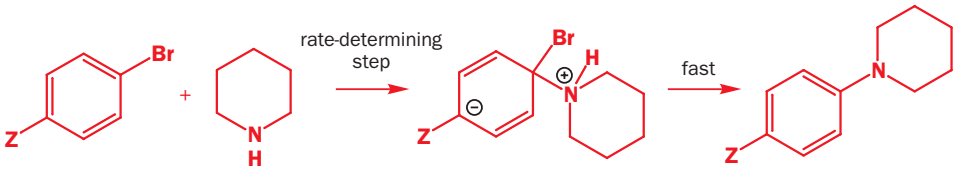
The activating anion-stabilizing substituent

We have used nitro groups very extensively so far and that is only right and proper as they are the best at stabilizing the anionic intermediate. Others that work include carbonyl, cyanide, and sulfur-based groups such as sulfoxides and sulfones. Here is a direct comparison for the displacement of bromide ion by the secondary amine piperidine. First the reaction with a carbonyl group.

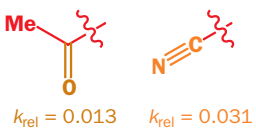


piperidine

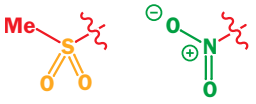
Now we are going to give the rates for the same reaction but with different activating groups. The mechanism is the same in each case; the only difference is the electron-withdrawing power of the activating group. You recall that this is vital for the rate-determining first step and for stabilization of the intermediate. The symbol Z represents the anion-stabilizing group and the margin shows what Z might be. The numbers are the relative rates compared with Z = nitro.



Z =



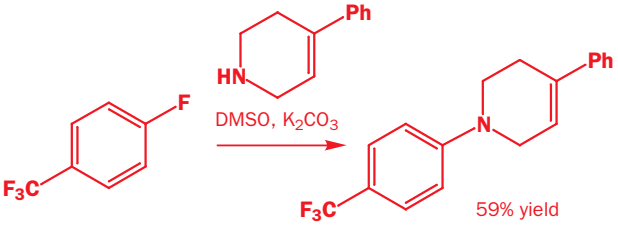
k_{rel} = 0.013 k_{rel} = 0.031



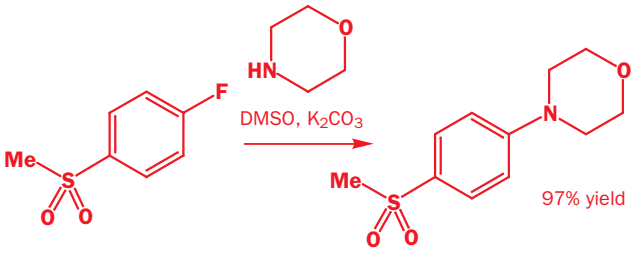
k_{rel} = 0.053 k_{rel} = 1.0

All the compounds react more slowly than the nitro-compound. We have already mentioned (Chapters 8 and 22) the great electron-withdrawing power of the nitro group—here is a new measure of that power. The sulfone reacts twenty times slower, the nitrile thirty times slower, and the ketone a hundred times slower.

The nitro is the best activating group, but the others will all perform well especially when combined with a fluoride rather than a bromide as the leaving group. Here are two reactions that work well in a preparative sense with other anion-stabilizing groups. Note that the trifluoromethyl group works by using only its powerful inductive effect.



59% yield



97% yield

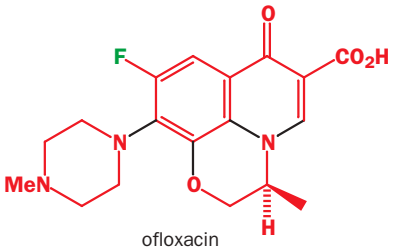
To summarize

Any anion-stabilizing (electron-withdrawing) group *ortho* or *para* to a potential leaving group can be used to make nucleophilic aromatic substitution possible.

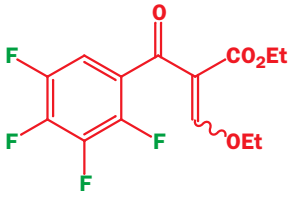
Some medicinal chemistry—preparation of an antibiotic

We want to convince you that this chemistry is useful and also that it works in more complicated molecules so we are going to describe in part the preparation of a new antibiotic, ofloxacin. The sequence starts with an aromatic compound having four fluorine atoms. Three are replaced specifically by different nucleophiles and the last is present in the antibiotic itself. As a reminder of the first

section of this chapter, the preparation also involves a conjugate substitution. The structure of ofloxacin (below) highlights the remaining fluorine atom and (in black) the four bonds made by reactions discussed in this chapter. Underneath is the starting material with its four fluorine atoms.

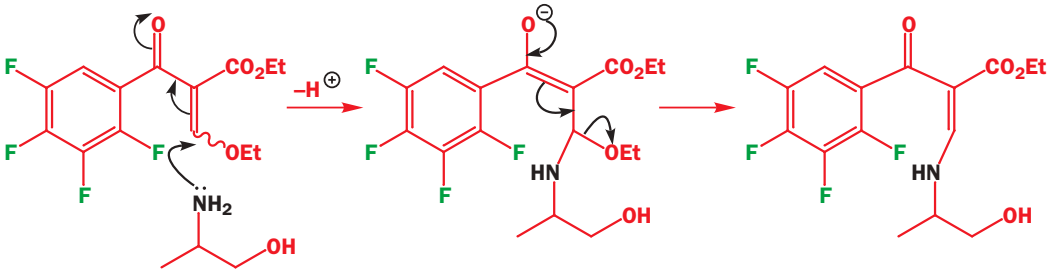


ofloxacin

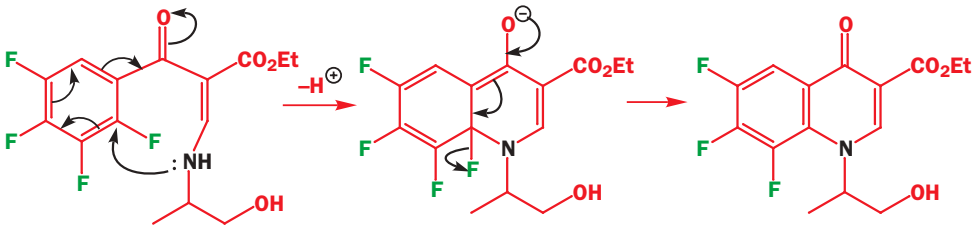


starting material for ofloxacin synthesis

The preparation of the starting material involves reactions that we will meet later in the book and is described in Chapter 28. The next reaction is the conjugate substitution. An amino alcohol is used as the nucleophile and it does a conjugate addition to the double bond. Notice that it is the more nucleophilic amino group that adds to the alkene, not the hydroxyl group. And, when the negative charge comes back to complete the conjugate substitution, the better leaving group is alkoxide rather than a very unstable amine anion.

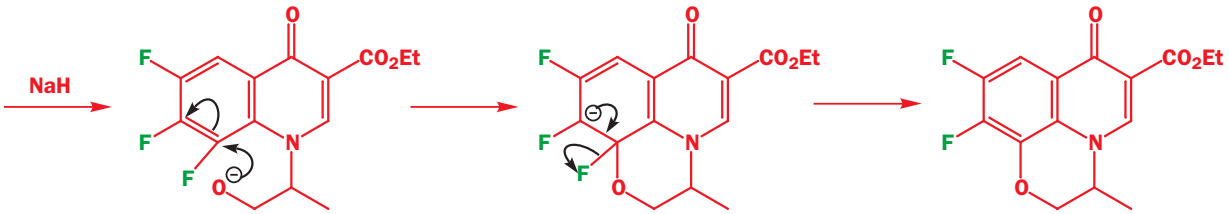


The next step is the first nucleophilic aromatic substitution. The amino group attacks in the position *ortho* to the carbonyl group so that an enolate intermediate can be formed. When the charge returns, the first fluoride is expelled.



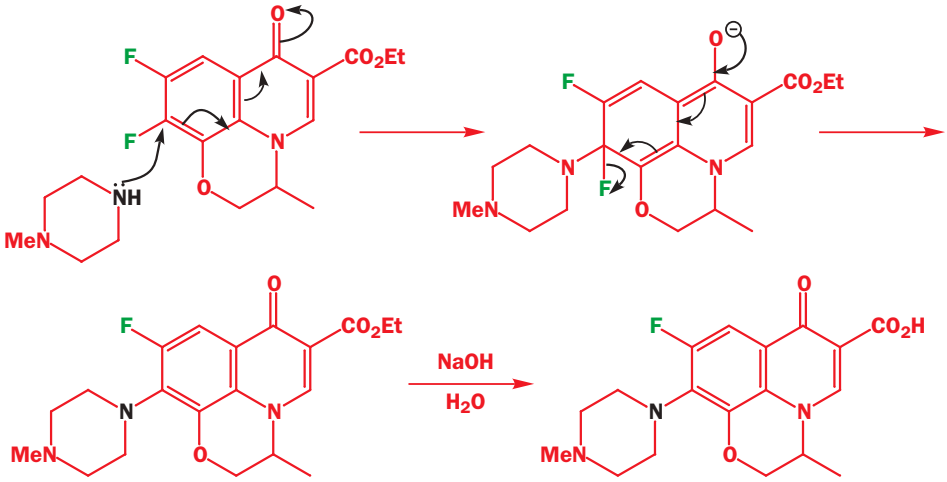
▶ We had to draw the arrows going the long way round the ring in the addition step because we happened to draw the double bonds in those positions in the starting material: this is the sort of thing you will find happens when you write mechanisms—there is no significance in it and it doesn't matter which way round the arrows go.

Treatment with base (NaH can be used) now converts the OH group into an alkoxide and it does the next aromatic nucleophilic substitution. In this reaction we are attacking the position *meta* to the ketone so we cannot put the negative charge on the oxygen atom. The remaining three fluorines must stabilize it by the inductive effect we described earlier.



negative charge stabilized by inductive effect only

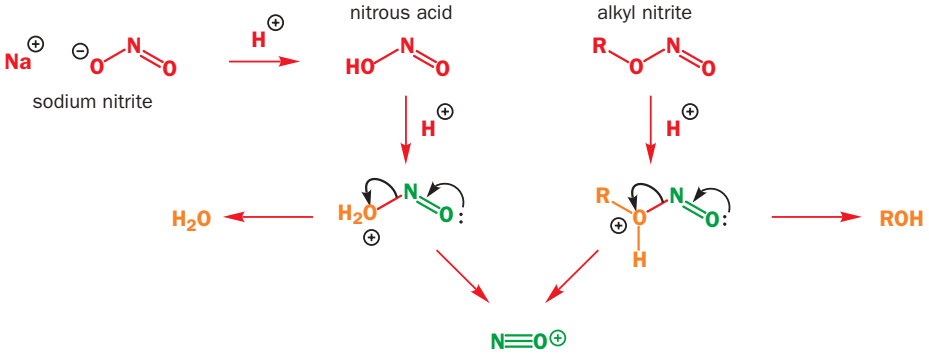
When this charge returns to restore the benzene ring, the second fluoride is expelled and only two are left. One of these is now displaced by, for the first time, an external nucleophile—an amine. It is easy to predict which one because of the need to stabilize the charge in the intermediate.



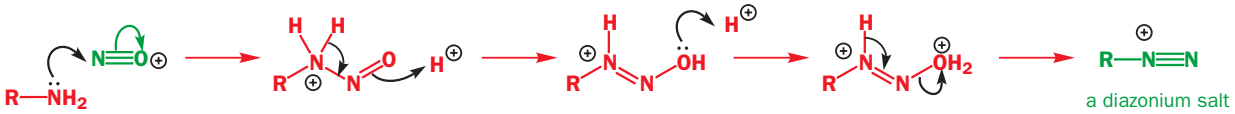
This displaces the third fluorine and all that is left is to hydrolyse the ester to the free acid with aqueous base (Chapter 12). Every single reaction in this quite complicated sequence is one that you have met earlier in the book, and it forms a fitting climax to this section on the addition–elimination mechanism for aromatic nucleophilic substitution. We now need to mention two other less important possibilities.

The S_N1 mechanism for nucleophilic aromatic substitution—diazonium compounds

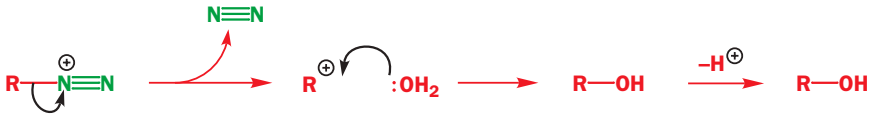
When primary amines are treated with nitrous acid (HONO), or more usually with a nitrite salt or an alkyl nitrite in acid solution, an unstable **diazonium salt** is formed. You met diazonium salts in Chapter 22 undergoing coupling reactions to give axo compounds, but they can do other things as well. First, a reminder of the mechanism of formation of these diazonium salts. The very first stage is the formation of the reactive species NO^+.



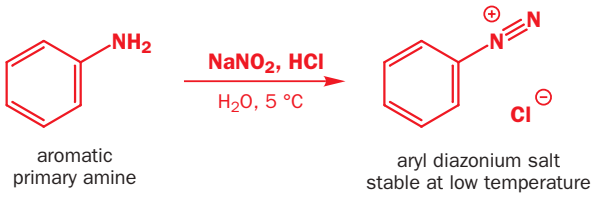
The NO^+ cation then attacks the lone pair of the amine and dehydration follows. The mechanism is quite simple—it just involves a lot of proton transfers! There is, of course, an anion associated with the nitrogen cation, and this will be the conjugate base (Cl^- usually) of the acid used to form NO^+.



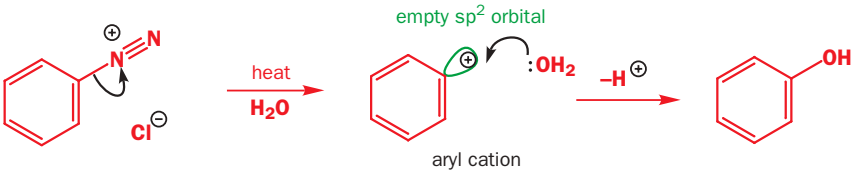
If R is an alkyl group, this diazonium salt is very unstable and immediately loses nitrogen gas to give a planar carbocation, which normally reacts with a nucleophile in an S_N1 process (Chapter 17) or loses a proton in an E1 process (Chapter 19). It may, for example, react with water to give an alcohol.



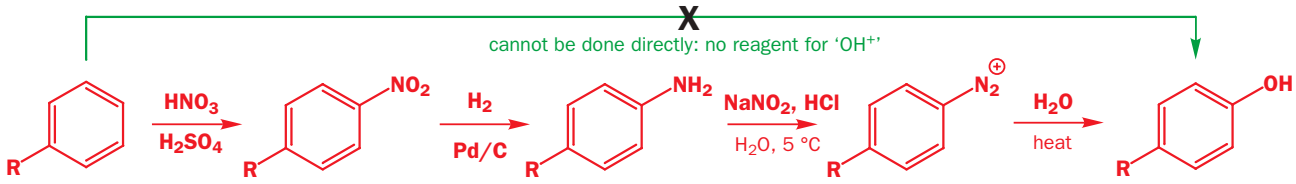
If R is an aryl group, the carbocation is much less stable (for the reasons we discussed earlier—chiefly that the empty orbital is an sp^2 rather than a p orbital) and that makes the loss of nitrogen slower. If the diazotization is done at lowish temperatures (just above 0 °C, classically at 5 °C), the diazonium salt is stable and can be reacted with various nucleophiles.



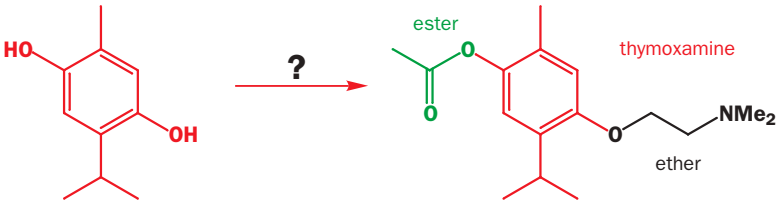
If the aqueous solution is heated, water again acts as the nucleophile and a phenol is formed from the amine. The aryl cation is an intermediate and this is an S_N1 reaction at an aromatic ring.



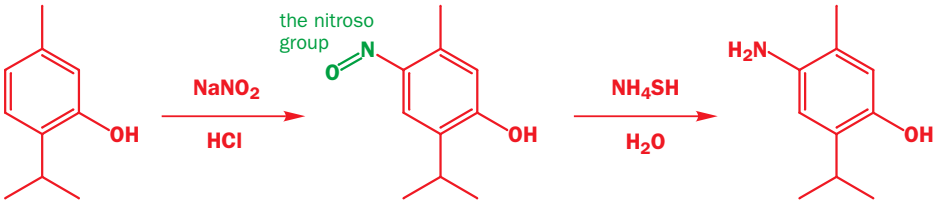
The point of this reaction is that it is rather difficult to add an oxygen atom to a benzene ring by the normal electrophilic substitution as there is no good reagent for 'OH^+'. A nitrogen atom can be added easily by nitration, and reduction and diazotization provide a way of replacing the nitro group by a hydroxyl group.



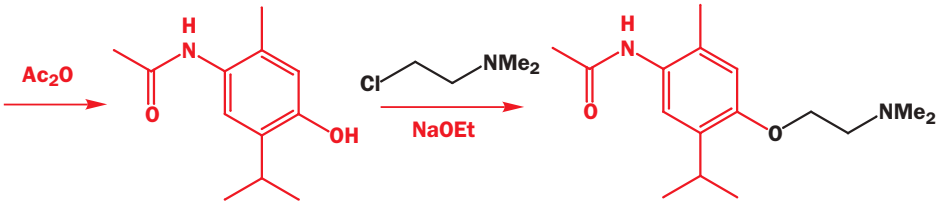
This is a practical sequence and is used in manufacturing medicines. An example is the drug thymoxamine (Moxysylyte), which has a simple structure with ester and ether groups joined to a benzene ring through their oxygen atoms.



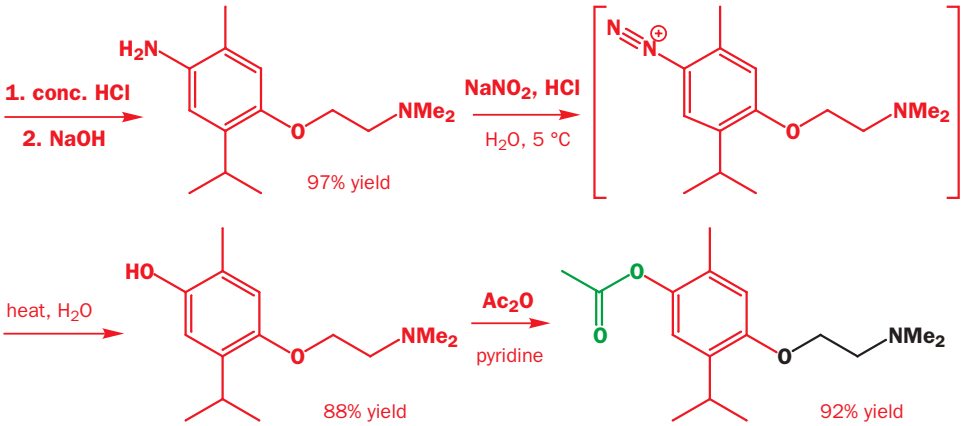
It seems obvious to make this compound by alkylation and acylation of a dihydroxybenzene. But how are we to make sure that the right phenol is acylated and the right phenol alkylated? French pharmaceutical chemists had an ingenious answer. Start with a compound having only one OH group, alkylate that, and only then introduce the second using the diazonium salt method. They used a simple phenol and introduced nitrogen as a nitroso (NO) rather than a nitro (NO_2) group. This means using the same reagent, HONO, as we used for the diazotization. These were the first two steps.



The reduction of NO is easier than that of NO_2, and HS^- is enough to do the job. The amine can now be converted to an amide to lessen its nucleophilicity so that alkylation of the phenol occurs cleanly.



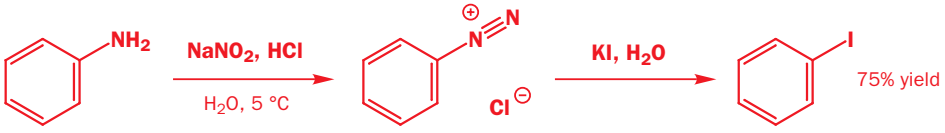
Finally, the amide must be hydrolysed, the amino converted into an OH group by diazotization and hydrolysis, and the new phenol acetylated.



This is yet another synthesis in which almost every step is a reaction that you have already met in this book! There are three nucleophilic substitutions at the carbonyl group, one S_N2 reaction, one electrophilic and one nucleophilic aromatic substitution (the latter being an S_N1 reaction), and a reduction. The chemistry you already know is enough for a patented manufacture of a useful drug.

Other nucleophiles

Because aryl diazonium salts are reasonably stable, other nucleophiles may be introduced to capture the aryl cation when the diazonium salt is heated. Among these, iodide ion is important as it allows the preparation of aryl iodides in good yield. These compounds are not so easy to make by electrophilic substitution (Chapter 22) as aryl chlorides or bromides because iodine is not reactive enough to attack benzene rings. Aryl iodides are useful in the more modern palladium chemistry of the Heck reaction, which you will meet in Chapter 48.



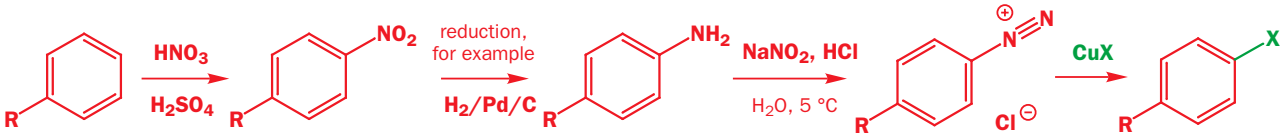
Other nucleophiles, such as chloride, bromide, and cyanide, are best added with copper(I) salts. These reactions are almost certainly radical in character (Chapter 39). Since aromatic amines

▶ The nitrosation uses the same intermediate (NO^+) used in the diazotization and is really very like the nitrosation of the enol we described on p. 000. There it tautomerized to an oxime—it can't do that here. Make sure you can draw a mechanism for this reaction and explain why the NO group goes in that position.

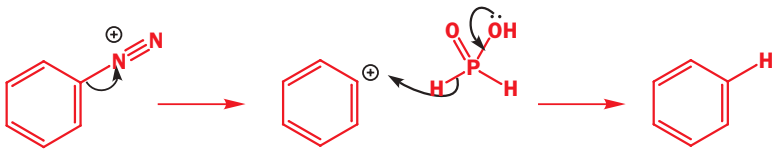
■ Reduction of $-NO_2$ groups is discussed in Chapter 24, p. 000.

▶ This is 'protection' of the amine as an amide: protecting groups are discussed in the next chapter. The amino group is more nucleophilic than the phenol so it would be alkylated if we did not protect it. Protection is selective for the same reason—the amino group attacks the anhydride preferentially. Now the amide is less nucleophilic than the phenol so alkylation occurs at oxygen. You should draw mechanisms for all these steps and make sure you understand why they happen in the way that they do.

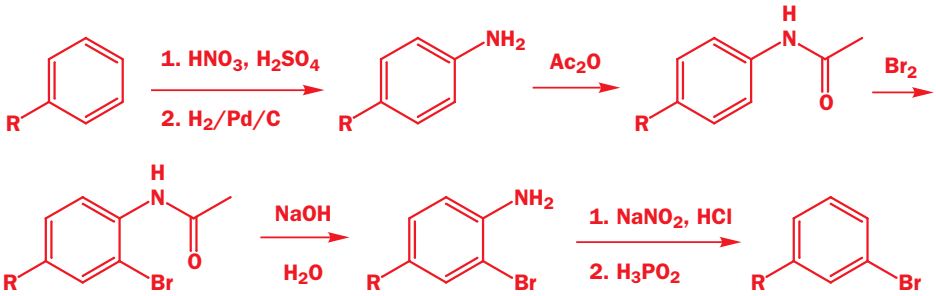
are usually made by reduction of nitro-compounds, a common sequence of reactions goes like this.



A reaction that may seem rather pointless is the reduction of diazonium salts, that is, the replacement of N_2^+ by H. A good reagent is H_3PO_2.



It would indeed be pointless to make benzene in this way, but this reaction allows the introduction of an amino group for the purpose of directing an electrophilic substitution and then its removal once its job is done. Here is a famous example.



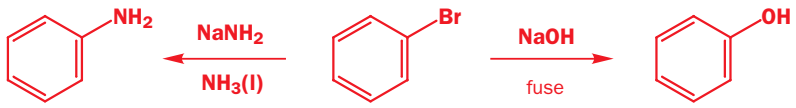
■ This chemistry is very long-winded, and now rather old-fashioned. Difficult-to-make substitution patterns are more usually set up using variants of the directed metallation (ortholithiation) chemistry we introduced in Chapter 9.

Nitration puts in a substituent *para* to the alkyl group, which, after reduction, becomes a powerful *ortho* director so that the bromine is directed *meta* to the original alkyl group (Chapter 22). Removal of the amino group by reduction allows the preparation of *meta* bromo alkyl benzenes that cannot be made directly.

The benzyne mechanism

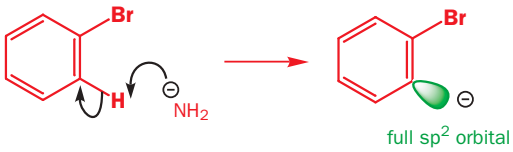
There is one last mechanism for aromatic nucleophilic substitution and you may well feel that this is the weirdest mechanism you have ever seen with the most unlikely intermediate ever! For our part, we hope to convince you that this mechanism is not only possible but useful.

At the start of the section on 'Nucleophilic aromatic substitution' we said that 'the displacement of bromide from bromobenzene with hydroxide ion do(es) not occur'. That statement is not quite correct. Substitution by hydroxide on bromobenzene can occur but only under the most vigorous conditions—such as when bromobenzene and NaOH are melted together (fused) at very high temperature. A similar reaction with the very powerful reagent $NaNH_2$ (which supplies NH_2^- ion) also happens, at rather lower temperature.



These reactions were known for a long time before anyone saw what was happening. They do not happen by an S_N2 mechanism, as we explained at the start of the section, and they can't happen by the addition–elimination mechanism because there is nowhere to put the negative charge in the intermediate. The first clue to the true mechanism is that all the nucleophiles that react in this way

are very basic, and it was suggested that they start the reaction off by removing a proton *ortho* to the leaving group.

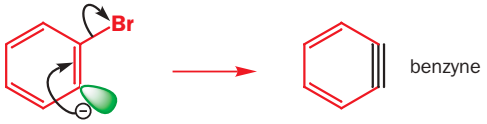


The carbanion is in an sp^2 orbital in the plane of the ring. Indeed, this intermediate is very similar to the aryl cation intermediate in the S_N1 mechanism from diazonium salts. That had no electrons in the sp^2 orbital; the carbanion has two.

▶ It is important that you see for yourself why an aryl anion is a more stable intermediate than an aryl cation. Having an empty sp^2 orbital means that there are electrons in a (higher energy) p orbital that would be more stable in the sp^2 orbital. Having a full sp^2 orbital on the other hand leaves no empty low-energy orbitals.

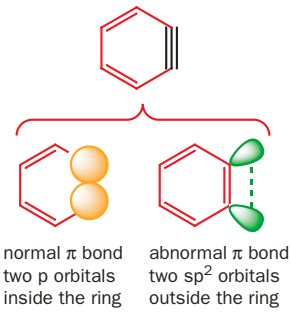
Why should this proton be removed rather than any other? The bromine atom is electronegative and the C–Br bond is in the plane of the sp^2 orbital and removes electrons from it. The stabilization is nonetheless weak and only strong bases will do this reaction.

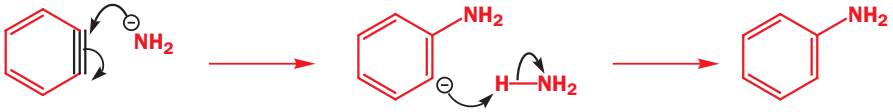
The next step is the loss of bromide ion in an elimination reaction. This is the step that is difficult to believe as the intermediate we are proposing looks impossible. The orbitals are bad for the elimination too—it is a syn- rather than an anti-periplanar elimination. But it happens.



The intermediate is called benzyne as it is an alkyne with a triple bond in a benzene ring. But what does this triple bond mean? It certainly isn't a normal alkyne as these are linear. In fact one π bond is normal—it is just part of the aromatic system. One π bond—the new one—is abnormal and is formed by overlap of two sp^2 orbitals outside the ring. This external π bond is very weak and benzyne is a very unstable intermediate. Indeed, when the structure was proposed few chemists believed it and some pretty solid evidence was needed before they did. We shall come to that shortly, but let us first finish the mechanism. Unlike normal alkynes, benzyne is electrophilic as the weak third bond can be attacked by nucleophiles.

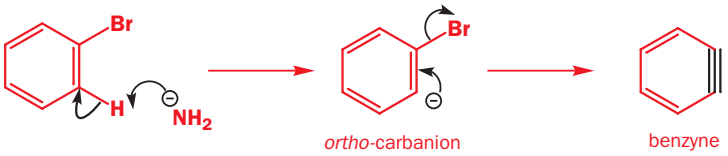
the π orbitals of benzyne



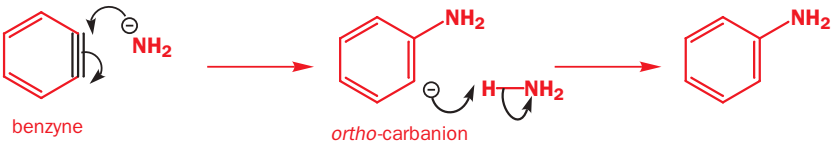


Notice the symmetry in this mechanism. Benzyne is formed from an *ortho* carbanion and it gives an *ortho* carbanion when it reacts with nucleophiles. The whole mechanism from bromobenzene to aniline involves an elimination to give benzyne followed by an addition of the nucleophile to the triple bond of benzyne. In many ways, this mechanism is the reverse of the normal addition–elimination mechanism for nucleophilic aromatic substitution and it is sometimes called the **elimination–addition mechanism**.

the elimination step

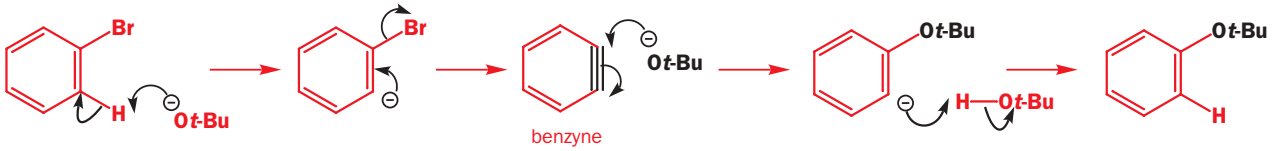


the addition step



Any nucleophile basic enough to remove the *ortho* proton can carry out this reaction. Known examples include oxyanions, amide anions (R_2N^-), and carbanions. The rather basic alkoxide *t*-butoxide will do the reaction on bromobenzene if the potassium salt is used in the dipolar aprotic solvent DMSO to maximize reactivity.

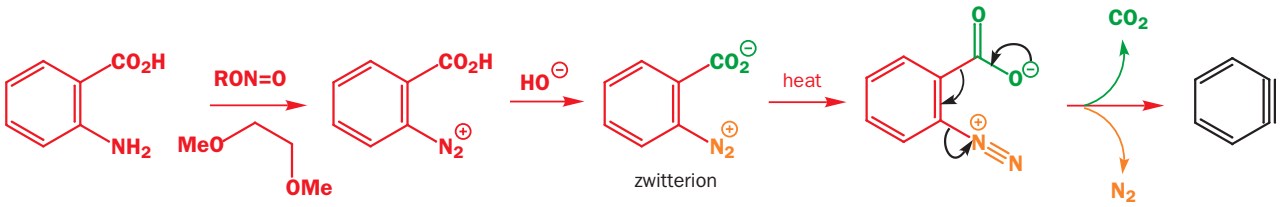
■ Remember. DMSO solvates K^+ but not RO^- so RO^- is left as a reactive 'naked anion'.



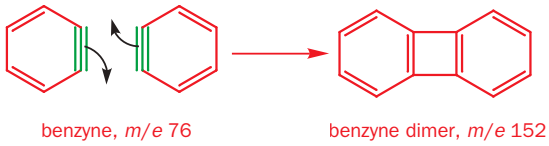
Evidence for benzyne as an intermediate

As you would expect, the formation of benzyne is the slow step in the reaction so there is no hope of isolating benzyne from the reaction mixture or even of detecting it spectroscopically. However, it can be made by other reactions where there are no nucleophiles to capture it. The most important is a diazotization reaction.

This diazotization is particularly efficient as you can see by the quantitative yield of the *ortho*-iodo-acid on capture of the diazonium salt with iodide ion. However, if the diazonium salt is neutralized with NaOH, it gives a zwitterion with the negative charge on the carboxylate balancing the positive charge on the diazonium group. This diazotization is usually done with an alkyl nitrite in an organic solvent (here, dimethoxyethane, DME) to avoid the chance that nucleophiles such as chloride or water might capture the product. When the zwitterion is heated it decomposes in an entropically favourable reaction to give carbon dioxide, nitrogen, and benzyne.

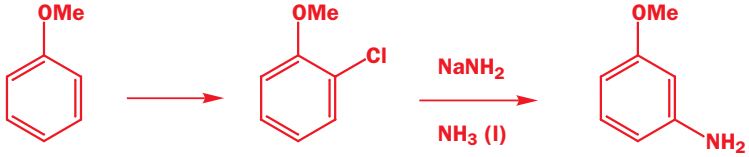


You can't isolate the benzyne because it reacts with itself to give a benzyne dimer having a four-membered ring between two benzene rings. If the zwitterion is injected into a mass spectrometer, there is a peak at 152 for the dimer but also a strong peak at 76, which is benzyne itself. The lifetime of a particle in the mass spectrometer is about 20 ns (nanosecond = 10^{-9} second) so benzyne can exist for at least that long in the gas phase.



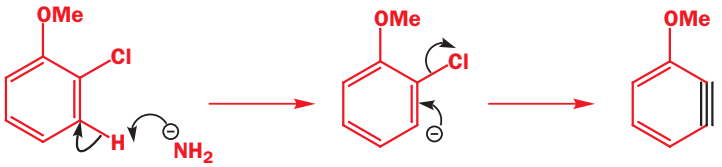
Benzyne produced from the zwitterion can also be captured by dienes in a Diels–Alder reaction (see Chapter 35). But this merely shows that benzyne can exist for a short time. It does not at all prove that benzyne is an intermediate in aromatic substitution reactions. Fortunately, there is very convincing evidence for this as well.

There is one very special feature of the benzyne mechanism. The triple bond could be attacked by nucleophiles at either end. This is of no consequence when we are dealing with bromobenzene as the products would be the same, but we can make the ends of the triple bond different and then we see something interesting. *ortho*-Chloro aryl ethers are easy to prepare by chlorination of the ether (Chapter 22). When these compounds are treated with $NaNH_2$ in liquid ammonia, a single amine is formed in good yield.

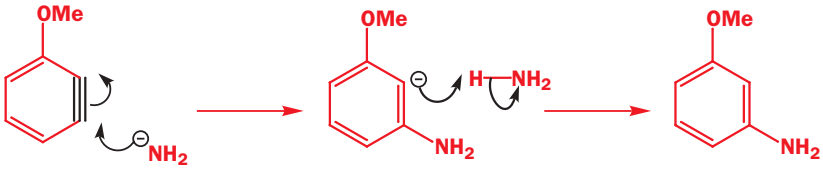


There is no mistake in this scheme. The amine is really at the *meta* position even though the chlorine was at the *ortho* position. It would be very difficult to explain this by any other mechanism but very easy to explain using a benzyne mechanism. Using the same two steps that we have used before, we can write this.

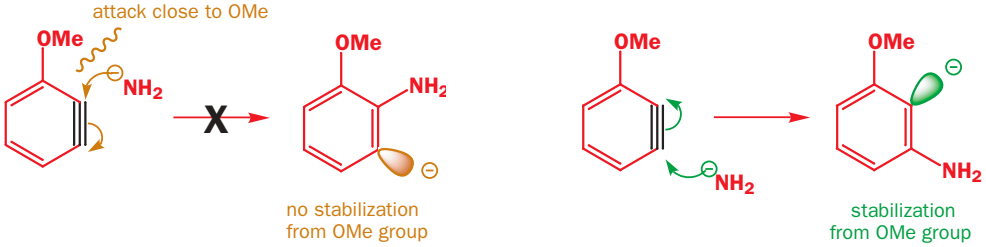
the elimination step



the addition step

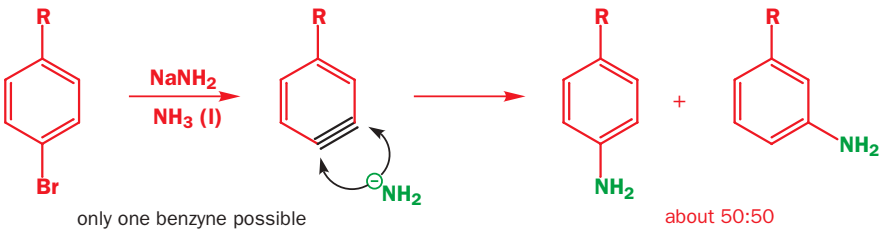


That shows *how* the *meta* product might be formed, but *why* should it be formed? Attack could also occur at the *ortho* position, so why is there no *ortho* product? There are two reasons: electronic and steric. Electronically, the anion next to the electronegative oxygen atom is preferred, because oxygen is inductively electron-withdrawing. The same factor facilitates deprotonation next to Cl in the formation of the benzyne. Sterically, it is better for the amide anion to attack away from the OMe group rather than come in alongside it. Nucleophilic attack on a benzyne has to occur in the plane of the benzene ring because that is where the orbitals are. This reaction is therefore very sensitive to steric hindrance as the nucleophile must attack in the plane of the substituent as well.



This is a useful way to make amino ethers with a *meta* relationship as both groups are *ortho*, *para*-directing and so the *meta* compounds cannot be made by electrophilic substitution. The alternative is the long-winded approach using a diazonium salt that was described in the previous section.

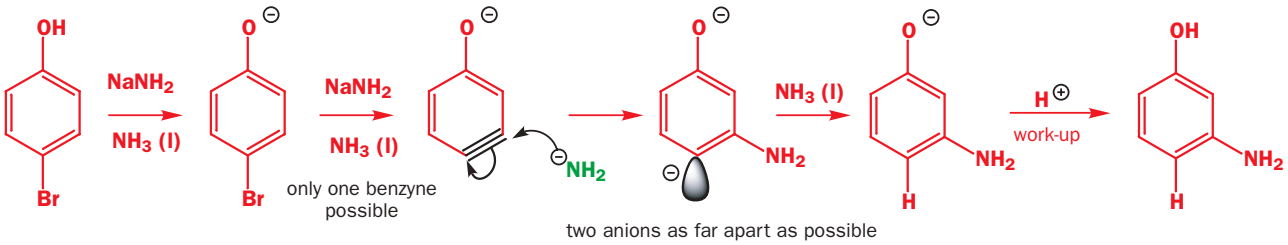
para-Disubstituted halides can again give only one benzyne and most of them give mixtures of products. A simple alkyl substituent is too far away from the triple bond to have much steric effect.



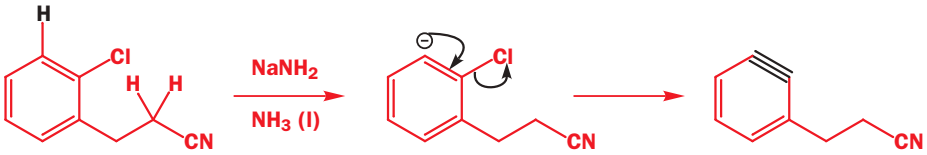
If the substituent is an electron-repelling anion, then the *meta* product is formed exclusively because this puts the product anion as far as possible from the anion already there. This again is a useful result as it creates a *meta* relationship between two *ortho*, *para*-directing groups.

▶ Oxygen is an electron-withdrawing group here because the anion is formed in the plane of the ring and has nothing to do with the benzene's π orbitals. Of course, as far as the π orbitals are concerned, oxygen is electron-*donating* because of its lone pairs.

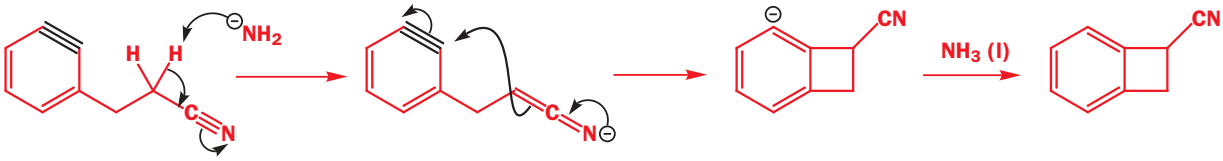
▶ Steric hindrance is not nearly as important in electrophilic substitution or in nucleophilic substitution by the addition–elimination mechanism. In both of these reactions, the reagent is attacking the p orbital *at right angles* to the ring and is some distance from an *ortho* substituent.



One case where selectivity of attack is no problem is in reactions with intramolecular nucleophiles. These cyclizations simply give the only possible product—the result of cyclization to the nearer end of the triple bond. One important example is the making of a four-membered ring. Only one benzyne can be formed.



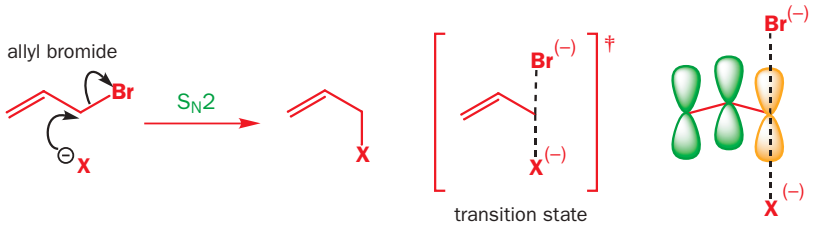
There are acidic protons next to the cyanide, and the amide ion is strong enough to form an 'enolate' by the removal of one of those. The enolate cyclizes on to the benzyne to give a four-membered ring. As it happens, the nucleophile adds to the position originally occupied by the chlorine, but that is not necessary.



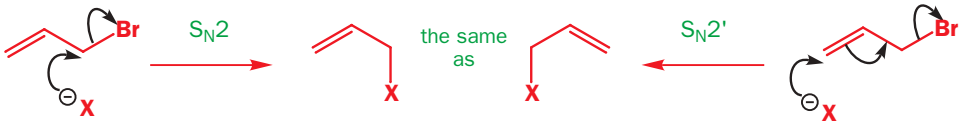
Nucleophilic attack on allylic compounds

We shall finish this chapter with some alkenes that are electrophilic, not because they are conjugated with another π system, but because they have a leaving group adjacent to them. We shall start with some substitution reactions with which you are familiar from Chapter 17. There we said that allyl bromide is about 100 times more reactive towards simple S_N2 reactions than is propyl bromide or other saturated alkyl halides.

The double bond stabilizes the S_N2 transition state by conjugation with the p orbital at the carbon atom under attack. This full p orbital (shown in yellow in the diagram below) forms a partial bond with the nucleophile and with the leaving group in the transition state. Any stabilization of the transition state will, of course, accelerate the reaction by lowering the energy barrier.



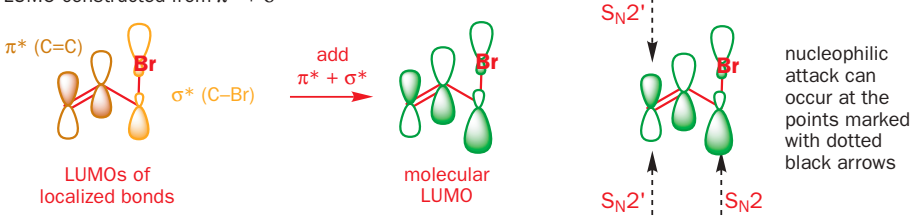
There is an alternative mechanism for this reaction that involves nucleophilic attack on the alkene instead of on the saturated carbon atom. This mechanism leads to the same product and is often called the S_N2' (pronounced 'S-N-two-prime') mechanism.



We can explain both mechanisms in a unified way if we look at the frontier orbitals involved. The nucleophile must attack an empty orbital (the LUMO) which we might expect to be simply σ* (C–Br) for the S_N2 reaction.

But this ignores the alkene. The interaction betweenπ* (C=C) and the adjacent σ* (C–Br) will as usual produce two new orbitals, one higher and one lower in energy. The lower-energy orbital, π* + σ*, will now be the LUMO. To construct this orbital we must put all the atomic orbitals parallel and make the contact between π* + σ* a bonding contact.

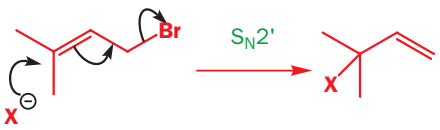
LUMO constructed from π* + σ*



If the allylic halide is unsymmetrically substituted, we can tell which process occurs and the normal result is that nucleophilic attack occurs at the less hindered end of the allylic system whether that means S_N2 or S_N2'. This important allylic bromide, known as 'prenyl bromide', normally reacts entirely via the S_N2 reaction.

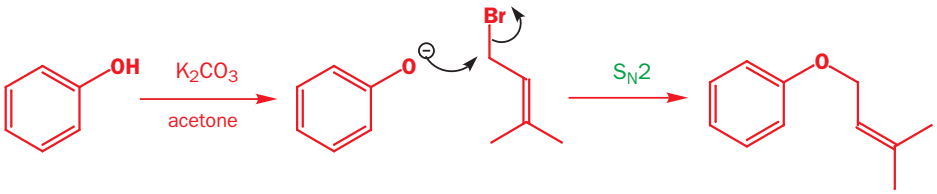
prenyl bromide reacts like this

and not like this

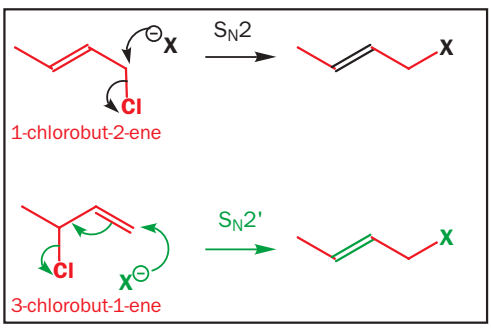


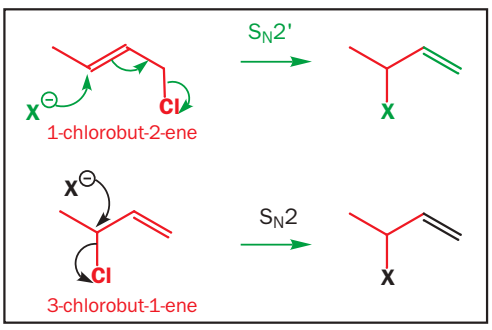
The two ends of the allylic system are contrasted sterically: direct (S_N2) attack is at a primary carbon while allylic (S_N2') attack is at a tertiary carbon atom so that steric hindrance favours the S_N2 reaction. In addition, the number of substituents on the alkene product means that the S_N2 product is nearly always preferred—S_N2 gives a trisubstituted alkene while the S_N2' product has a less stable monosubstituted alkene.

An important example is the reaction of prenyl bromide with phenols. This is simply carried out with K_2CO_3 in acetone as phenols are acidic enough ($pK_a \sim 10$) to be substantially deprotonated by carbonate. The product is essentially entirely from the S_N2 route, and is used in the Claisen rearrangement (Chapter 36).

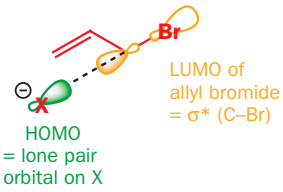


If we make the two ends of the allyl system more similar, say one end primary and one end secondary, things are more equal. We could consider the two isomeric butenyl chlorides.



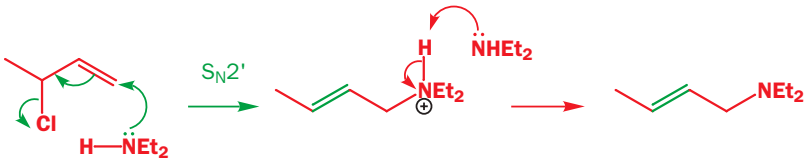


orbitals treated as for 'simple' S_N2

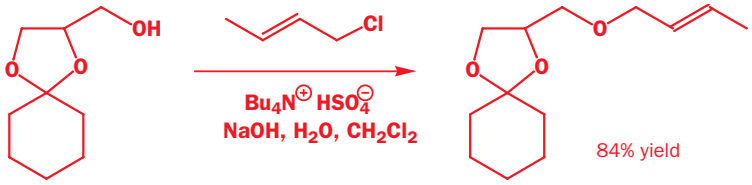


So far we have used the word 'allyl' to describe these compounds. Strictly, that word applies only to specific compounds CH_2=CH–CH_2X with no substituents other than hydrogen. Allyl is often used loosely to describe any compound with a functional group on the carbon atom *next to* the alkene. We shall use 'allylic' for that and 'allyl' only for the unsubstituted version.

All routes look reasonable, though we might again prefer attack at the primary centre kinetically and the disubstituted alkene thermodynamically and this is the usual outcome. The reactions in the left-hand box are preferred to those in the right-hand box. But there is no special preference for the S_N2 over the S_N2' mechanism or vice versa—the individual case decides. If we react the secondary butenyl chloride with an amine we get the S_N2' mechanism entirely.

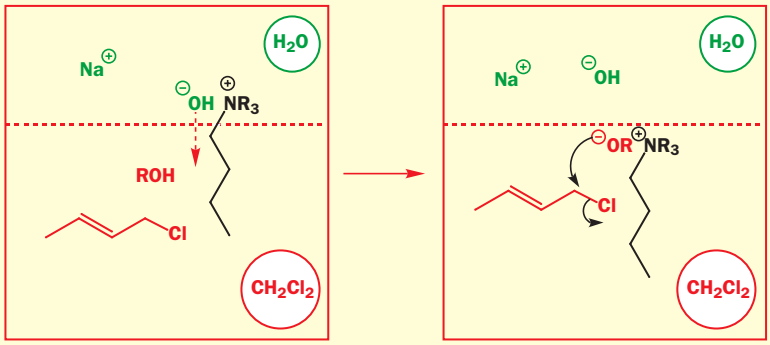


If the primary chloride is used, only the S_N2 reaction normally occurs so that once again we get nucleophilic attack at the primary centre and the more stable product with the more highly substituted alkene. Here is a slightly more advanced example.



Phase transfer catalysis

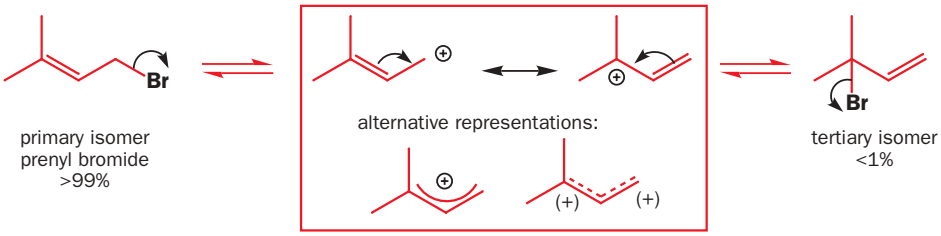
The last example is interesting because the starting material contains an acetal as well as a primary alcohol group. Acetals are very easily destroyed by acid so the conditions must be kept strictly alkaline. Sodium hydroxide does this but it is insoluble in organic solvents. The method shown here uses a two-phase system of water and dichloromethane (CH_2Cl_2). The organic molecules are in the CH_2Cl_2 layer and the NaOH is in the water layer. The tetraalkyl ammonium salt has a polar group (N^+) and hydrocarbon side chains (butyl groups). These chains mean that, although it is charged, $Bu_4N^+HO^-$ ion pairs are soluble in the organic layer. The ammonium salt allows a low concentration of hydroxide ions to pass into the CH_2Cl_2 layer where they act as a base catalyst for the reaction. Here are the layers shown schematically.



This method is called **phase transfer catalysis** because the tetraalkyl ammonium salt acts as a phase transfer agent, allowing ions to pass into the organic phase. The ether product is, of course, soluble in the organic phase and the work-up is very simple—separation of the phases removes unchanged NaOH and the inorganic by-product, NaCl.

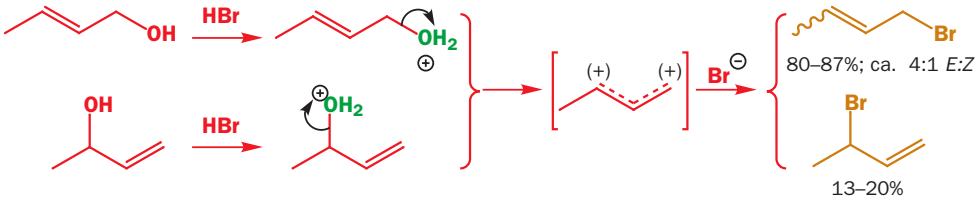
Notice that these reactions take place with allylic *chlorides*. We should not expect an alkyl chloride to be particularly good at S_N2 reactions as chloride ion is only a moderate leaving group and we should normally prefer alkyl bromides or iodides. *Allylic* chlorides are more reactive because of the alkene. Even if the reaction occurs by a simple S_N2 mechanism without rearrangement, the alkene is still making the molecule more electrophilic.

You might ask a very good question at this point. How do we know that these reactions really take place by S_N2 and S_N2' mechanisms and not by an S_N1 mechanism via the stable allyl cation? Well in the case of prenyl bromide, we don't! In fact, we suspect that the cation probably *is* an intermediate, because prenyl bromide and its allylic isomer are in rapid equilibrium in solution at room temperature.

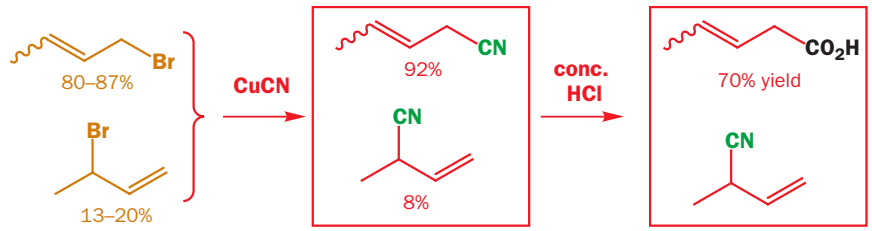


The equilibrium is entirely in favour of prenyl bromide because of its more highly substituted double bond. Reactions on the tertiary allylic isomer are very likely to take place by the S_N1 mechanism: the cation is stable because it is tertiary and allylic and the equilibration tells us it is already there. Even if the reactions were bimolecular, no S_N2' mechanism would be necessary for the tertiary bromide because it can equilibrate to the primary isomer more rapidly than the S_N2 or S_N2' reaction takes place.

Even the secondary system we also considered is in rapid equilibrium when the leaving group is bromide. This time both allylic isomers are present, and the primary allylic isomer (known as 'crotyl bromide') is an *E*/*Z* mixture. The bromides can be made from either alcohol with HBr, and the same ratio of products results, indicating a common intermediate in the two mechanisms. You saw at the beginning of Chapter 17 that this reaction (Chapter 16) is restricted to alcohols that can react by S_N1.

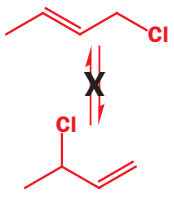


Displacement of the bromide by cyanide ion, using the copper(I) salt as the nucleophile, gives a mixture of nitriles in which the more stable primary nitrile predominates even more. These can be separated by a clever device. Hydrolysis in concentrated HCl is successful with the predominant primary nitrile but the more hindered secondary nitrile does not hydrolyse. Separation of compounds having two different functional groups is easy: in this case the acid can be extracted into aqueous base, leaving the neutral nitrile in the organic layer.



Once again, we do not know for sure whether this displacement by cyanide goes by the S_N1, S_N2, or S_N2' mechanism, as the reagents equilibrate under the reaction conditions. However, the chlorides do *not* equilibrate and so, if we want a clear cut result on a single well-defined starting material, the chlorides are the compounds to use.

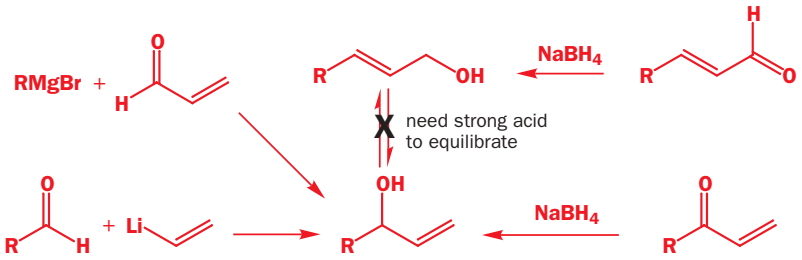
allylic chlorides do not equilibrate



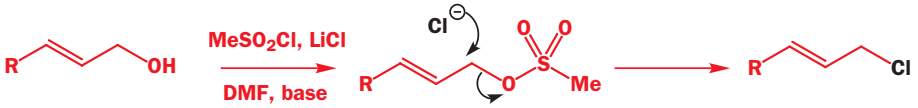
Regiospecific preparation of allylic chlorides

Allylic alcohols are good starting materials for making allylic compounds with control over where the double bond and the leaving group will be. Allylic alcohols are easily made by addition of Grignard reagents or organolithium compounds to enals or enones (Chapter 9) or by reduction of enals or enones (Chapter 24). More to the point, they do not equilibrate except in strongly acidic solution, so we know which allylic isomer we have.

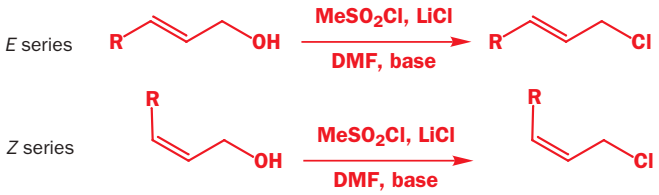
▶ By analogy with *stereospecific*, we can define **regiospecific** to mean a reaction where the regiochemistry (that is, the location of the functional groups) of the product is determined by the regiochemistry of the starting material.



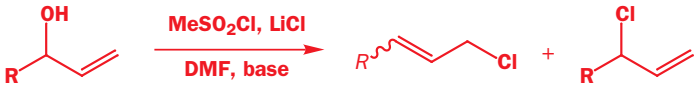
Conversion of the alcohols into the chlorides is easier with the primary than with the secondary alcohols. We need to convert OH into a leaving group and provide a source of chloride ion to act as a nucleophile. One way to do this is with methanesulfonyl chloride ($MeSO_2Cl$) and LiCl.



This result hardly looks worth reporting and, anyway, how do we know that equilibration or S_N1 reactions aren't happening? Well, here the mechanism must be S_N2 because the corresponding *Z*-allylic alcohol preserves its alkene configuration. If there were equilibration of any sort, the *Z*-alkene would give the *E*-alkene because *E* and *Z* allylic cations are not geometrically stable.

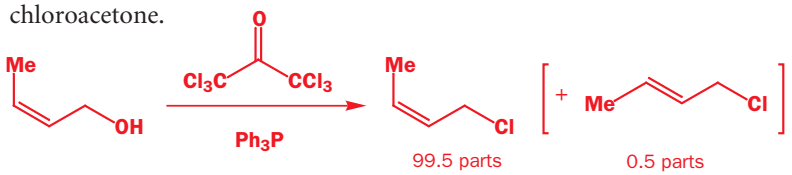


Sadly, this method fails to preserve the integrity of the secondary allylic alcohol, which gives a mixture of allylic chlorides.



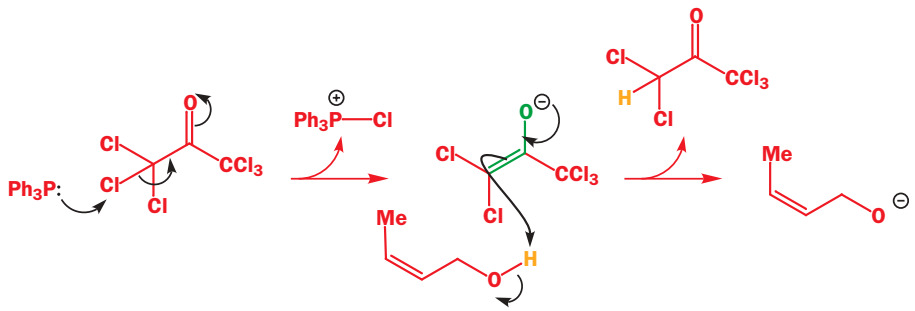
■ The Mitsunobu reaction was discussed in Chapter 17, p. 000. Mitsunobu chemistry involves using a phosphorus atom to remove the OH group, after the style of PBr_3 as a reagent to make alkyl bromides from alcohols.

Reliable clean S_N2 reactions with secondary allylic alcohols can be achieved only with Mitsunobu chemistry. Here is a well-behaved example with a *Z*-alkene. The reagents have changed since your last encounter with a Mitsunobu-type reaction: instead of DEAD and a carboxylic acid we have hexachloroacetone.

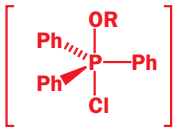


The first thing that happens is that the lone pair on phosphorus attacks one of the chlorine atoms in the chloroketone. The leaving group in this S_N2 reaction at chlorine is an enolate, which is a basic species and can remove the proton from the OH group in the allylic alcohol.

▶ Phosphorus doing a substitution at a C–Cl bond the wrong way round! But P is soft, so it cares little about the polarization of the bond, only about the energy of the C–Cl σ*. The energy is the same whichever end of the bond is attacked. You may see similar reactions of PPh_3 with CBr_4 or CCl_4: all produce stabilized carbanions.

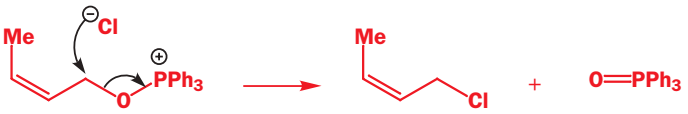


Now the alkoxide anion can attack the positively charged phosphorus atom. This is a good reaction in two ways. First, there is the obvious neutralization of charge and, second, the P–O bond is very strong. This reaction, which we have drawn as an S_N2 reaction at phosphorus, really goes through a pentacovalent intermediate shown to the right, but you will usually see it drawn in a concerted fashion.

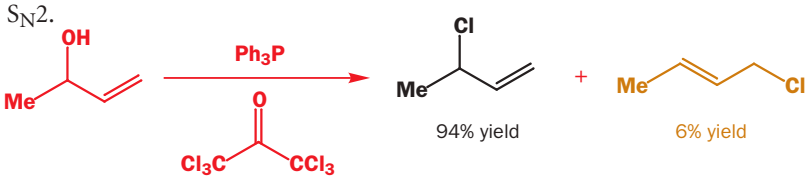


probable intermediate

The next step is a true S_N2 reaction at carbon as the very good leaving group is displaced. The already strong P–O single bond becomes an even stronger P=O double bond to compensate for the loss of the strong C–O single bond.

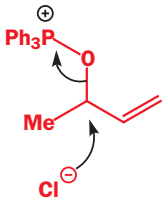


There is obviously no S_N1 component in this displacement (otherwise the *Z*-alkene would have partly isomerized to the *E*-alkene) and very little S_N2' as only 0.5% of the rearrangement product is formed. These displacements of $Ph_3P{=}O$ are often the 'tightest' of S_N2 reactions. Now for the really impressive result. Even if the alcohol is secondary, and the rearranged product would be thermodynamically more stable, very little of it is formed and almost all the reaction is clean S_N2.



There is a bit more rearrangement than there was with the other isomer but that is only to be expected. The very high proportion of direct S_N2 product shows that there is a real preference for the S_N2 over the S_N2' reaction in this displacement.

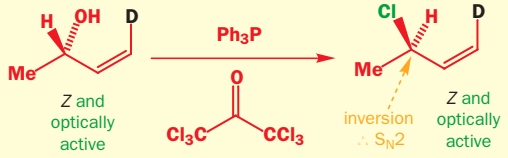
S_N2 preferred to S_N2'



More evidence for S_N2 on the phosphonium intermediate

It is possible to show that the stereochemistry of the double bond is not affected during this reaction and that it goes with clean inversion by using an optically active alcohol with a labelled hydrogen (deuterium) on the alkene.

Note the inversion at the stereogenic centre (see discussion of this as a criterion of the S_N2 reaction in Chapter 17) but retention in the geometry of the alkene. This is clear evidence for an S_N2 reaction at the secondary centre.



Now that we know how to make allylic chlorides of known structure—whether primary or secondary—we need to discover how to replace the chlorine with a nucleophile with predictable regioselectivity. We have said little so far about carbon nucleophiles (except cyanide ion) so we shall concentrate on simple carbon nucleophiles in the S_N2' reaction of allylic chlorides.

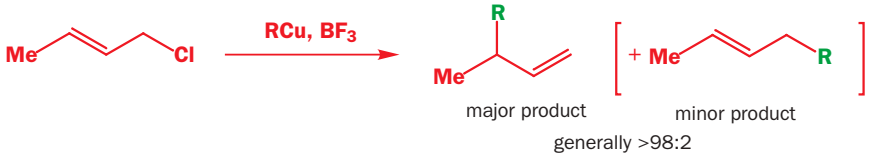
The S_N2' reaction of carbon nucleophiles on allylic chlorides

Ordinary carbon nucleophiles such as cyanide or Grignard reagents or organolithium compounds fit the patterns we have described already. They usually give the more stable product by S_N2 or S_N2' reactions depending on the starting material. If we use copper compounds, there is a tendency—no more than that—to favour the S_N2' reaction. You will recall that copper(I) was the metal we used to ensure conjugate addition to enones (Chapter 10) and its use in S_N2' reactions is obviously related.

▶ Probably all 'S_N2 reactions' at Si, P, and S go through addition intermediates because these elements can sustain five full bonds. The substitution mechanism is then: (1) addition to give an anionic species; (2) elimination of the best leaving group. Do you see an analogy with some reactions from earlier in this chapter?

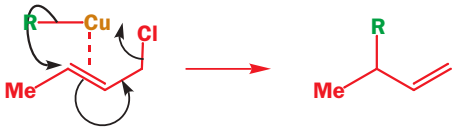
■ We looked at the converse—'loose' S_N2 transition states with considerable S_N1 character—in the reactions of bromonium ions and protonated epoxides in Chapter 19.

Simple alkyl copper reagents (RCu, known as Gilman reagents) generally favour the S_N2' reaction but we can do much better by using RCu complexed with BF_3.

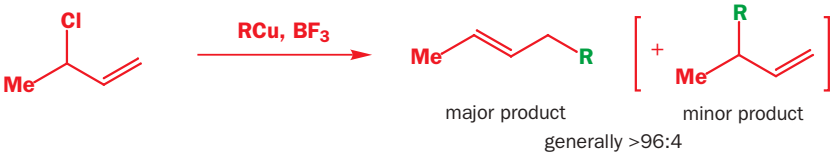


■ The nature of metal–alkene complexes is discussed in Chapter 48.

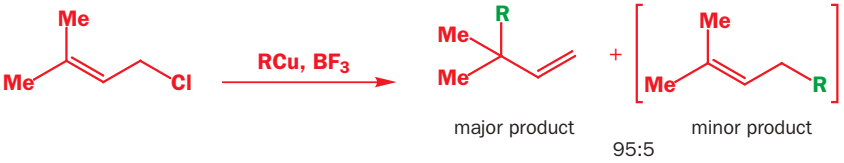
The copper must complex to the alkene and then transfer the alkyl group to the S_N2' position as it gathers in the chloride. This might well be the mechanism, though it is often difficult to draw precise mechanisms for organometallic reactions.



The secondary allylic isomer also gives almost entirely the rearranged product. This is perhaps less surprising, as the major product is the more stable isomer, but it means that either product can be formed in high yield simply by choosing the right (or should we say *wrong*, since there is complete allylic rearrangement during the reaction) isomer. The reaction is regio*specific*.

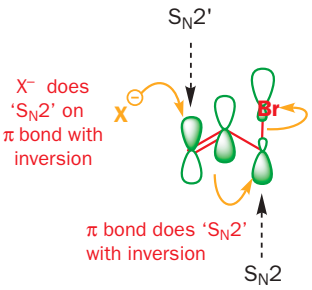


The most remarkable result of all is that prenyl chloride gives rearranged products in good yield. This is about the only way in which these compounds suffer attack at the tertiary centre by S_N2' reaction when there is the alternative of an S_N2 reaction at a primary centre.



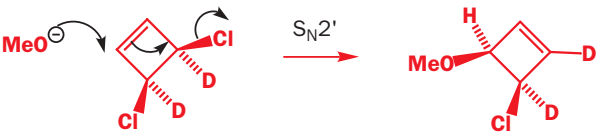
Stereochemistry of the S_N2' reaction

retention in S_N2' reactions?

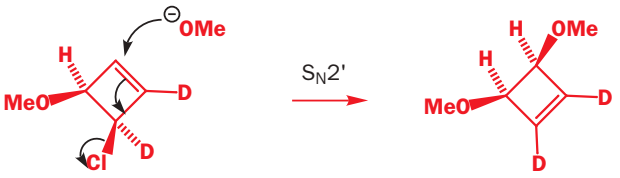


There is some controversy over this issue. There is, of course, none over the S_N2 reaction on these allylic compounds—inversion occurs as in all S_N2 reactions. It used to be supposed than S_N2' reactions went with 'retention'—that is, the nucleophile attacked the same face of the allylic system (we shall call this ***syn* attack**). The attractive rationalization was that the π bond attacked the C–Br bond from the back and then was itself attacked from the back by the nucleophile. This results in an *anti* reaction of the π bond and overall *syn* attack of the nucleophile with respect to the leaving group.

We now know that the picture is not as simple as this. *syn* S_N2' reactions are preferred but *anti* S_N2' reactions are also possible and the result found depends on the molecule under observation. Here is a convincing example of S_N2' reactions going with *syn* stereochemistry. The molecule is a planar cyclobutene, which makes the stereochemistry easy to see.



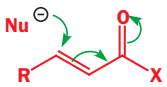
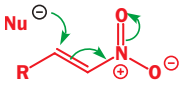
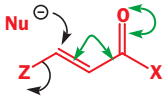
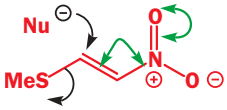
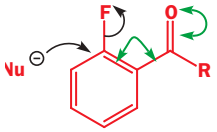
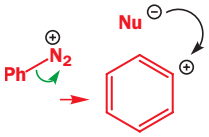
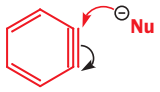
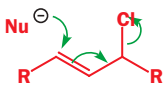
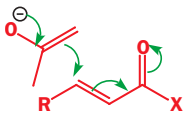
The deuterium labels are there so that we can see that the S_N2' reaction is indeed taking place. This reaction is entirely *syn* even though the methoxide nucleophile must attack alongside the other chlorine atom. The reaction does not stop there since a second methoxide displaces the other chloride—also in a *syn* fashion. Here too there must be considerable resistance to *syn* attack as the second methoxide anion must approach alongside the first.



In other cases, especially in open-chain compounds, the stereochemical outcome is not so clear cut and mixtures are often formed. The best generalization is that the S_N2' reaction prefers *syn* stereochemistry but that *anti* stereochemistry is also possible. In the absence of other evidence, you should first suggest a *syn* course for the reaction—but do not be surprised if your suggestion turns out to be wrong.

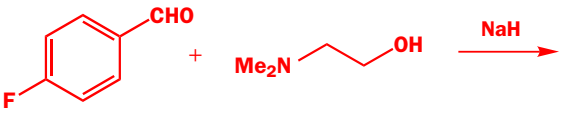
To conclude . . .

This chapter is about electrophilic alkenes. We started by saying that alkenes are really nucleophilic and not electrophilic but in this chapter (and in Chapter 10) we have managed to find a remarkable collection of electrophilic alkenes from various types of chemistry. Here is a summary chart.

Page no.	Type of alkene	Examples	Reaction
000 (ch. 10)	unsaturated carbonyl compounds		conjugate addition
000	unsaturated nitriles and nitroalkenes		conjugate addition
000	enones, etc. with β-leaving group		conjugate substitution
000	guanidines, amidines, and nitroalkenes with β-leaving group		conjugate substitution
000	benzene rings with electron-withdrawing substituents and leaving groups		nucleophilic aromatic substitution: addition–elimination mechanism
000	aryl cations		nucleophilic aromatic substitution: S_N1 mechanism
000	benzyne		nucleophilic aromatic substitution: elimination–addition mechanism
000	allylic halides and esters of allylic alcohols		nucleophilic substitution (S_N2 and S_N2')
Still to come:			
000 (ch. 29)	enolates and enolate equivalents as nucleophiles		conjugate addition

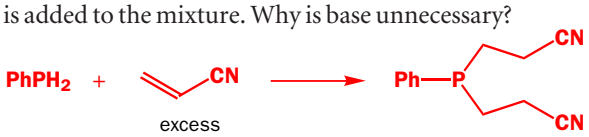
Problems

1. What is the structure of the product of this reaction and how is it formed?

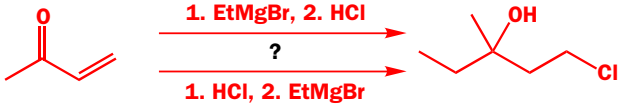


$C_{11}H_{15}NO_2$
$\nu_{max}(cm^{-1})$ 1730
δ_C(p.p.m.) 191, 164, 132, 130, 115, 64, 41, 29
δ_H(p.p.m.) 2.32 (6H, s), 3.05 (2H, t, *J* 6 Hz), 4.20 (2H, t, *J* 6 Hz), 6.97 (2H, d, *J* 7 Hz), 7.82 (2H, d, *J* 7 Hz), 9.97 (1H, s)

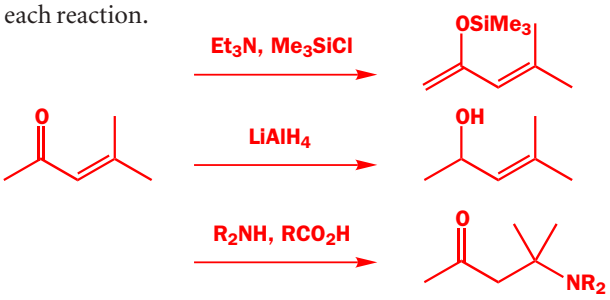
2. Draw a detailed mechanism for this reaction. Note that no base is added to the mixture. Why is base unnecessary?



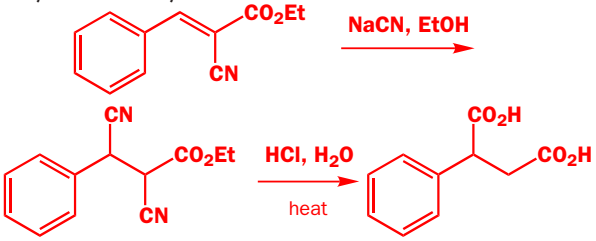
3. Which of the two routes suggested here would actually lead to the product? What might happen in the other sequence?



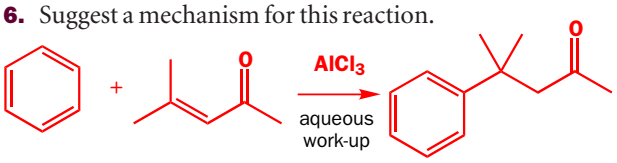
4. Suggest reasons for the different outcome of each of these reactions. Your answer must, of course, include a mechanism for each reaction.



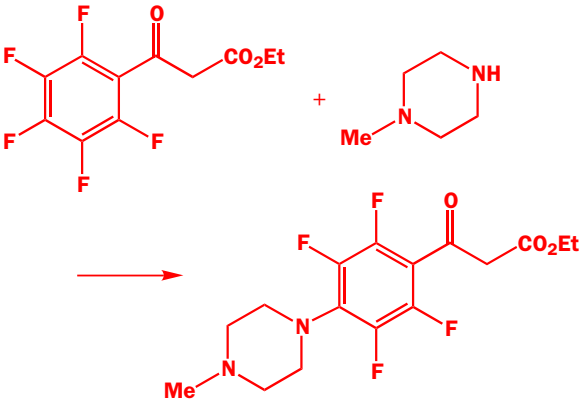
5. Suggest mechanisms for these reactions. You should explain why one of the cyanides is lost but not the other.



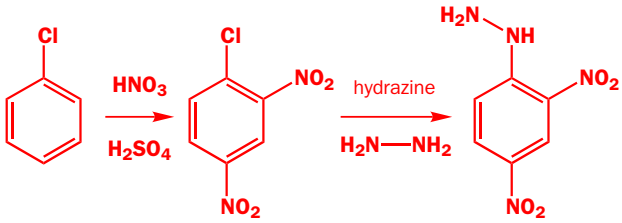
6. Suggest a mechanism for this reaction.



7. Suggest a mechanism for this reaction explaining the selectivity.

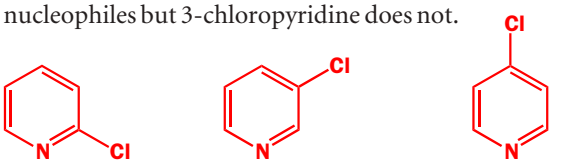


8. Suggest mechanisms for all of the steps in this synthesis of 2,4-dinitrophenylhydrazone given in the chapter.



2,4-dinitrophenylhydrazine

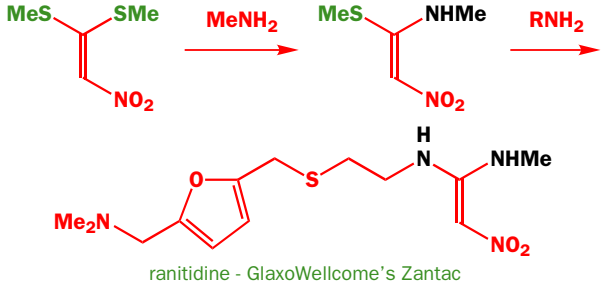
9. Pyridine is a six-electron aromatic system like benzene. You have not yet been taught anything systematic about pyridine but see if you can work out why 2- and 4-chloropyridines react with nucleophiles but 3-chloropyridine does not.



2-chloropyridine 3-chloropyridine 4-chloropyridine

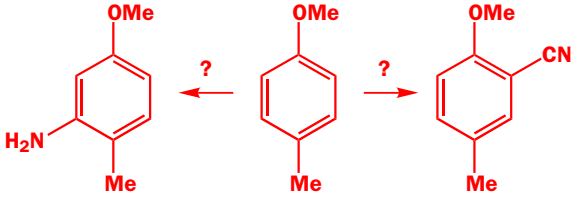
2-chloropyridine

10. Draw detailed mechanisms for the last two steps in the ranitidine synthesis that involve conjugate substitution. Why is it possible to replace one MeS group at a time?

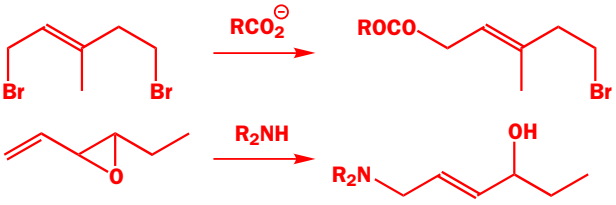


ranitidine - GlaxoWellcome's Zantac

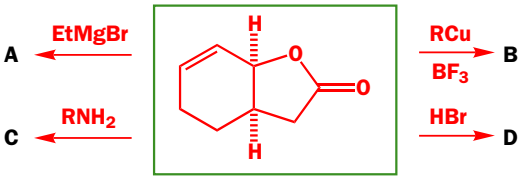
11. How would you convert this aromatic compound into the two derivatives shown?



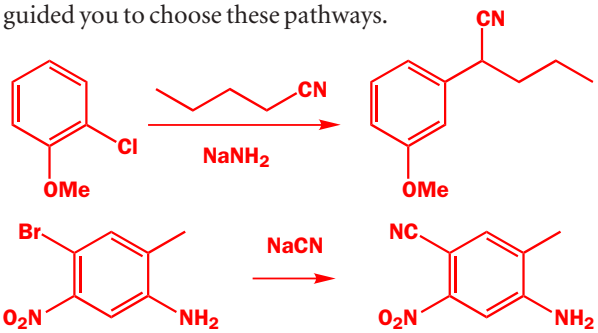
12. Comment on the selectivity shown in these reactions.



13. Suggest what products might be formed from the unsaturated lactone and the various reagents given and comment on your choice.



14. Suggest mechanisms for these reactions, pointing out what guided you to choose these pathways.



Chemoselectivity: selective reactions and protection

24

Connections

Building on:

- Carbonyl addition and substitution ch6, ch12, & ch14
- Conjugate addition ch10
- Mechanisms and catalysis ch13
- Electrophilic addition to alkene ch20
- Nucleophilic aromatic substitution ch23

Arriving at:

- Regio-, stereo-, and chemoselectivity
- Reagents for reduction of alkenes and carbonyl compounds
- Removal of functional groups
- Reduction of benzene rings
- Protection of aldehydes, ketones, alcohols, and amines
- Reagents for oxidation of alcohols

Looking forward to:

- Synthesis in action ch25
- Enolates especially aldol chemistry ch26–ch29
- Retrosynthetic analysis ch30
- Cycloadditions ch35
- Rearrangements ch37
- Sulfur chemistry ch46

Selectivity

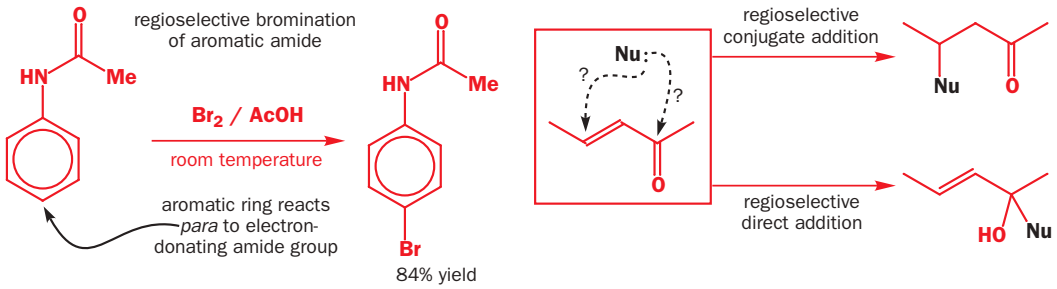
Most organic molecules contain more than one functional group, and most functional groups can react in more than one way, so organic chemists often have to predict *which* functional group will react, *where* it will react, and *how* it will react. These questions are what we call **selectivity**.

Selectivity comes in three sorts: chemoselectivity, regioselectivity, and stereoselectivity. **Chemoselectivity** is *which* group reacts; **regioselectivity** is *where* it reacts. **Stereoselectivity** is *how* the group reacts with regard to the stereochemistry of the product.

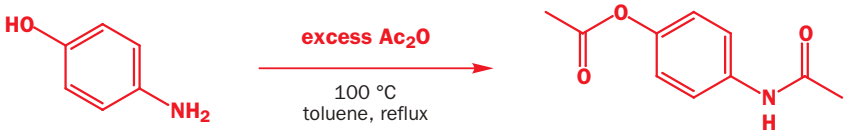
There are three main types of selectivity

- Chemoselectivity: *which* functional group will react
- Regioselectivity: *where* it will react
- Stereoselectivity: *how* it will react (stereochemistry of the products)

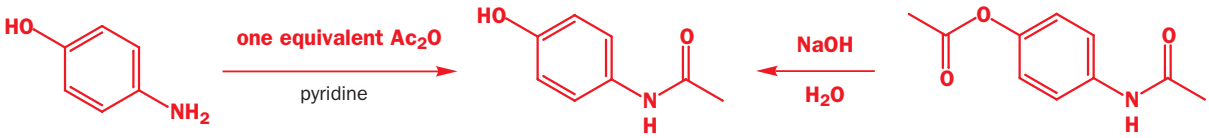
We talked a lot about regioselectivity two chapters ago, when you learned how to predict and explain which product(s) you get from electrophilic aromatic substitution reactions. The functional group is the aromatic ring: *where* it reacts is the reaction's regioselectivity. Going back further, one of the first examples of regioselectivity you came across was nucleophilic addition to an unsaturated ketone. Addition can take place in a 1,2- or a 1,4-fashion—the question of which happens (*where* the unsaturated ketone reacts) is a question of regioselectivity, which we discussed in Chapters 10 and 23. We shall leave all discussion of stereoselectivity until Chapters 31–34.



This chapter is about chemoselectivity—in a compound with more than one functional group, which group reacts? Let's start with a straightforward example—the synthesis of paracetamol briefly described in Chapter 22. 4-Aminophenol could react with acetic anhydride on both nitrogen and oxygen to give a compound containing an amide and an ester functional group. This is what happens on heating with excess Ac_2O in toluene.

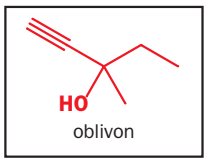


But with just one equivalent of acetic anhydride in the presence of a base (pyridine) only the NH_2 group is acylated, and paracetamol is the product. This is chemoselectivity, and it is to be expected that the NH_2 group is more nucleophilic than the OH group. It is even possible to hydrolyse the doubly acetylated product to paracetamol with aqueous sodium hydroxide. The ester is more reactive than the amide and hydrolyses much more easily (Chapter 12).



paracetamol

We know that ketones are more reactive towards Grignard reagents and organolithiums than esters because you can't isolate a ketone from the reaction of an ester with a Grignard reagent or an organolithium (in Chapter 12 we devoted some time to what you *can* react with an organometallic compound to get a ketone—p. 000). So it should come as no surprise that, when some chemists at Pfizer were developing anticonvulsants related to the tranquillizer oblivon by adding lithium acetylide to ketones, they were successful in making a tertiary alcohol by chemoselective reaction of a ketone in the presence of an ester.



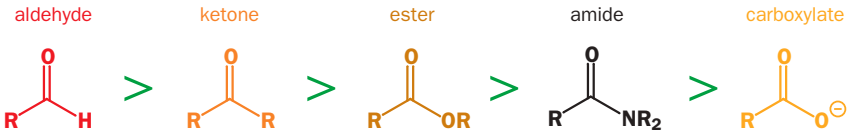
oblivon

ketone is more electrophilic than ester

These reactions work because, although each starting material contains two carbonyl groups, one is more electrophilic and therefore more reactive towards nucleophiles (OH^- in the first case; lithium acetylide in the second) than the other. We can order carbonyl compounds into a sequence in which it will *usually* be possible to react those on the left with nucleophiles in the presence of those on the right.

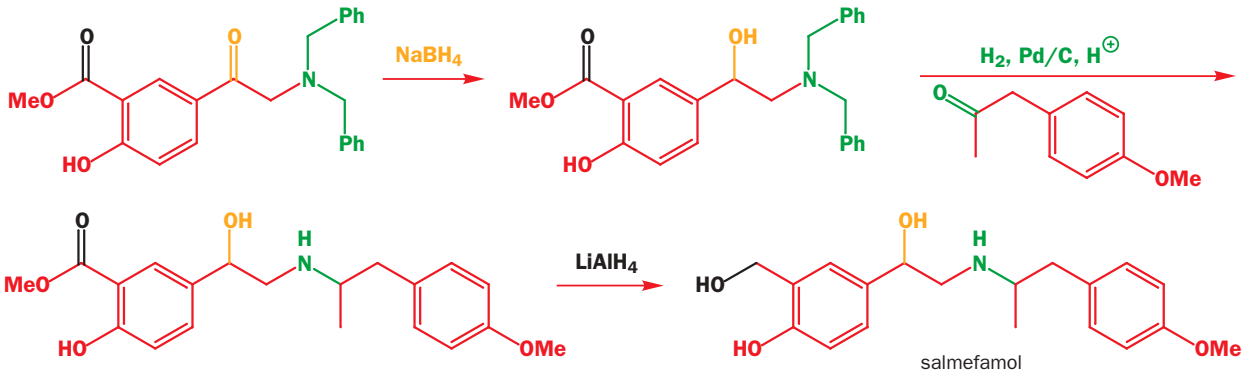
■ We've already discussed this sequence of reactivity in relation to acid derivatives in Chapters 12 and 14—make sure you understand the reason for the ordering of ester > amide > carboxylate. Here we're adding on aldehyde (the most reactive, for steric reasons—it is the least hindered) and ketone (more reactive than esters because the carbonyl group is not stabilized by conjugation with a lone pair).

reactivity towards nucleophiles

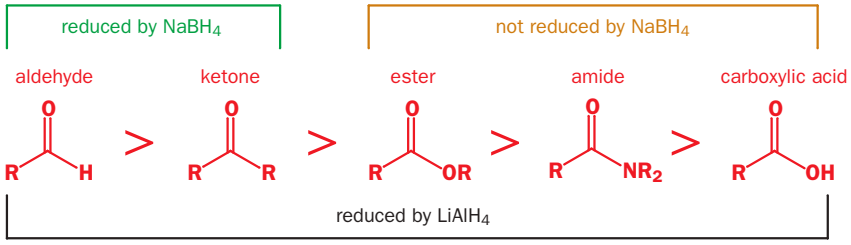


Reducing agents

Chemists at Glaxo exploited this reactivity sequence in their synthesis of the anti-asthma drug, salmefamol (sister of the best seller salbutamol, which will be discussed in Chapter 25). Three reducing agents are used in the sequence: sodium borohydride ($NaBH_4$); lithium aluminium hydride ($LiAlH_4$); and hydrogen gas over a palladium catalyst.



We shall use this synthesis as a basis for discussion on chemoselectivity in reductions. In the first step, sodium borohydride leaves the black carbonyl group of the ester untouched while it reduces the ketone (in yellow); in the last step, lithium aluminium hydride reduces the ester (in black). These chemoselectivities are typical of these two most commonly used reducing agents: borohydride can usually be relied upon to reduce an aldehyde or a ketone in the presence of an ester, while lithium aluminium hydride will reduce almost any carbonyl group.



Each reduction gives an alcohol, apart from the reduction of an amide with $LiAlH_4$, which gives an amine, which we shall explain next. We shall return to the salmefamol synthesis later to explain the reductions with hydrogen gas catalysed by palladium.

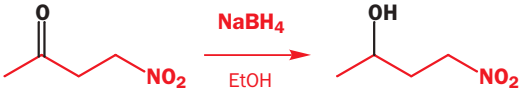
▶ In general, it's best to use the mildest conditions possible for any particular reaction—the potential for unwanted side-reactions is lessened. What is more, $NaBH_4$ is a lot easier to handle than $LiAlH_4$—for example, it simply dissolves in water while $LiAlH_4$ catches fire if it gets wet. $NaBH_4$ is usually used to reduce aldehydes and ketones, even though $LiAlH_4$ also works.

Reduction of carbonyl groups

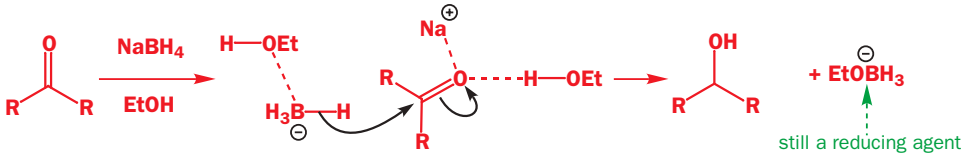
We should now look in detail at reductions of carbonyl compounds, and in doing so we shall introduce a few more specialized reducing agents. Then we will come back to the other type of reduction in the salmefamol synthesis—catalytic hydrogenation.

How to reduce aldehydes and ketones to alcohols

We don't need to spend much time on this—sodium borohydride does it very well, and is a lot easier to handle than lithium aluminium hydride. It is also more selective: it will reduce this nitroketone, for example, where $LiAlH_4$ would reduce the nitro group as well.



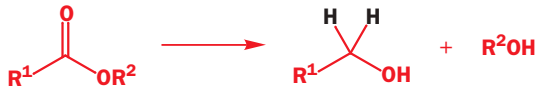
You met borohydride in Chapter 6, where we discussed the mechanism of its reactions. Sodium borohydride will reduce only in protic solvents (usually ethanol, methanol, or water) or in the presence of electrophilic metal cations such as Li^+ or Mg^{2+} ($LiBH_4$ can be used in THF, for example). The precise mechanism, surprisingly, is still unclear, but follows a course something like this with the dotted lines representing some association, perhaps coordination or bond formation.



The essence of the reaction is the transfer of a hydrogen atom with two electrons (called **hydride transfer** though no hydride ion is involved). In addition, the developing negative charge on oxygen gets help from the alcohol or the sodium ion or both and a molecule of alcohol adds to the boron during or immediately after the reduction. The by-product, an alkoxyborohydride anion, is itself a reducing agent, and can go on to reduce three more molecules of carbonyl compound, transferring step-by-step all of its hydrogen atoms.

How to reduce esters to alcohols

■ Why not try writing the mechanism out now to make sure you understand it, before checking back to p. 000? In a moment, we will show you a slightly more sophisticated version, in which we account for the fate of the Li and Al species.



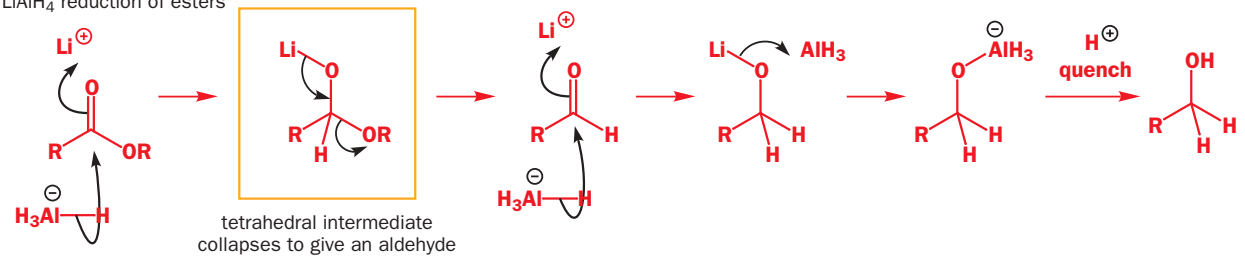
$LiAlH_4$ is often the best reagent, and gives alcohols by the mechanism we discussed in Chapter 12. As a milder alternative ($LiAlH_4$ has caused countless fires through careless handling), lithium borohydride in alcoholic solution will reduce esters—in fact, it has useful selectivity for esters over acids or amides that $LiAlH_4$ does not have. Sodium borohydride reduces most esters only rather slowly.

How to reduce amides to amines

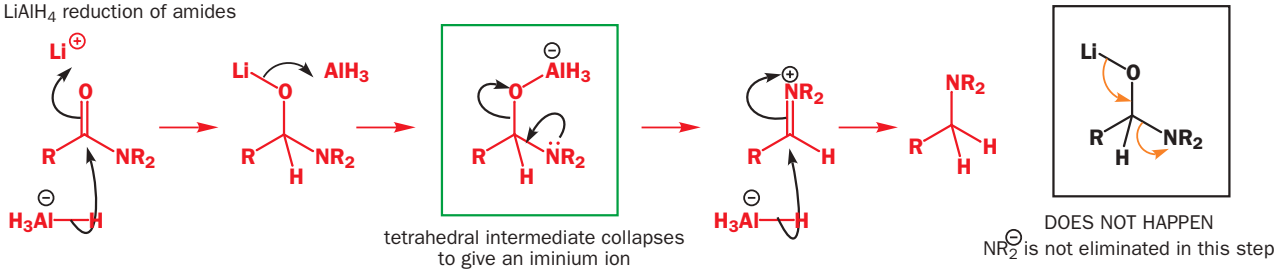
■ The ester mechanism has rather more detail than the simplified one we presented to you in Chapter 12.

Again, $LiAlH_4$ is a good reagent for this transformation. The mechanism follows very much the same course as the reduction of esters, but there is a key difference at the steps boxed in yellow and in green.

$LiAlH_4$ reduction of esters



$LiAlH_4$ reduction of amides

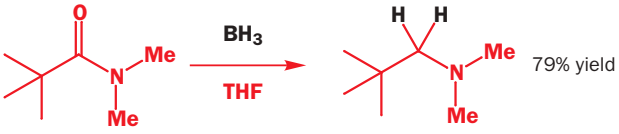


How to reduce carboxylic acids to alcohols

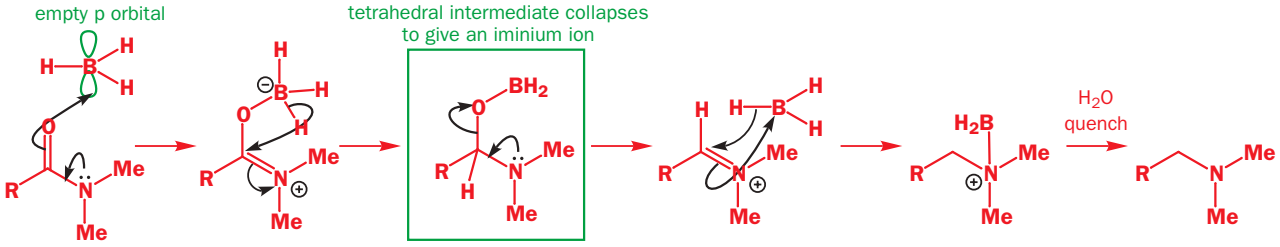
■ These complexes are Lewis salts: BH_3 is a Lewis acid that accepts a lone pair of electrons from the basic ether or sulfide.

The best reagent for this is borane, BH_3. Borane is, in fact, a gas with the structure B_2H_6, but it can be 'tamed' as a liquid by complexing it with ether (Et_2O), THF, or dimethyl sulfide (DMS, Me_2S).

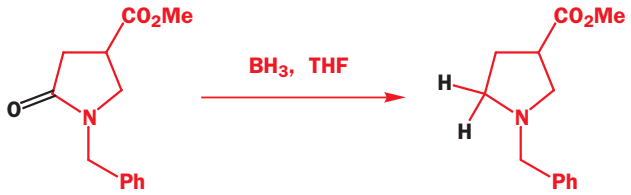
Although borane appears superficially similar to borohydride, it is not an ion and that makes all the difference to its reactivity. Whereas borohydride reacts best with the most electrophilic carbonyl groups, borane's reactivity is dominated by its desire to accept an electron pair into its empty p orbital. In the context of carbonyl group reductions, this means that it reduces electron-rich carbonyl groups fastest. The carbonyl groups of acyl chlorides and esters are relatively electron-poor (Cl and OR are very electronegative); borane will not touch acyl chlorides and reduces esters only slowly. But it will reduce amides.



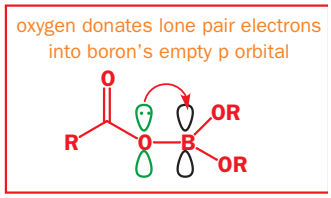
The Lewis basic carbonyl group forms a complex with the empty p orbital of the Lewis acidic borane. Hydride transfer is then possible from anionic boron to electrophilic carbon. The resulting tetrahedral intermediate collapses to an iminium ion that is reduced again by the borane.

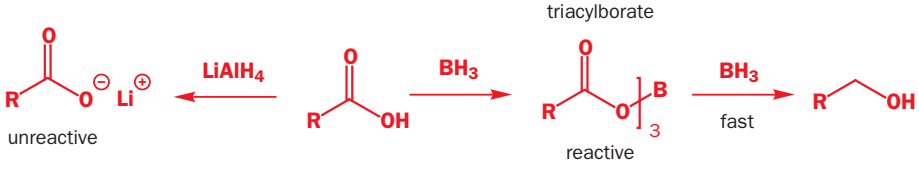


Borane also makes a good alternative to $LiAlH_4$ for reducing amides as the two reagents have slightly different chemoselectivity—in this example borane reduces an amide in the presence of an ester.

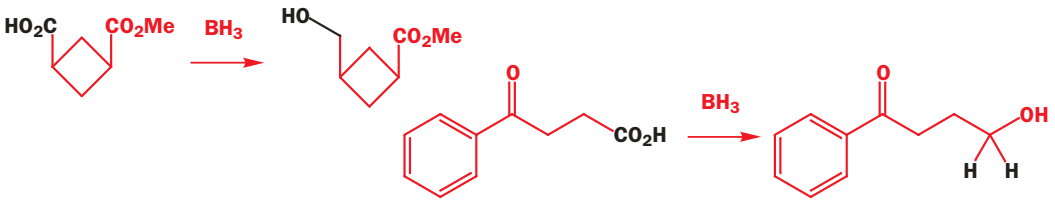


Borane is an excellent reagent for reducing carboxylic acids. It reacts with them first of all by forming triacylborates, with evolution of hydrogen gas. Esters are usually less electrophilic than ketones because of conjugation between the carbonyl group and the lone pair of the sp^3 hybridized oxygen atom—but, in these boron esters, the oxygen next to the boron has to share its lone pair between the carbonyl group and the boron's empty p orbital, so they are considerably more reactive than normal esters, or the lithium carboxylates formed from carboxylic acids and $LiAlH_4$.



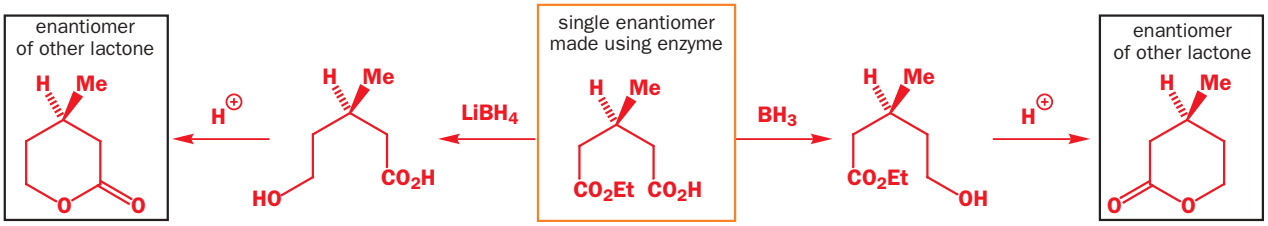


Borane is a highly chemoselective reagent for the reduction of carboxylic acids in the presence of other reducible functional groups such as esters, and even ketones.

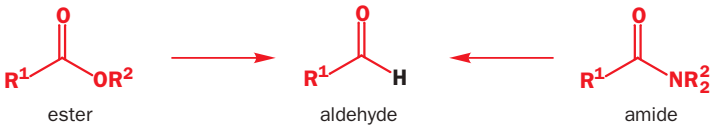


■ This type of asymmetric synthesis is discussed in Chapter 45.

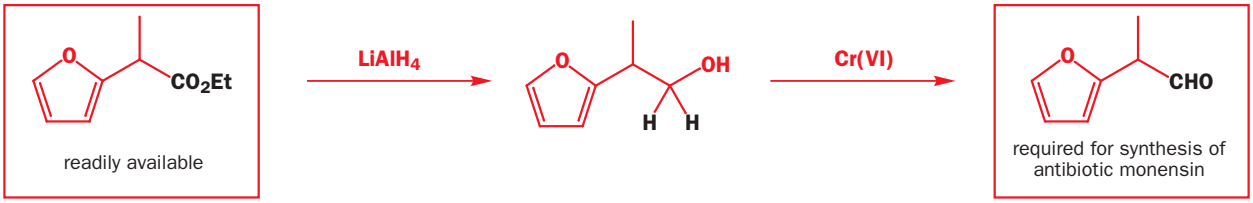
Borane and lithium borohydride are a most useful pair of reducing agents, with opposite selectivities. Japanese chemists used an enzyme to make a single enantiomer of the acid below, and were able to reduce either the ester or the carboxylic acid by choosing lithium borohydride or borane as their reagent. Check for yourself that the lactones (cyclic esters) in black frames are enantiomers.

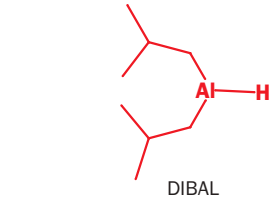


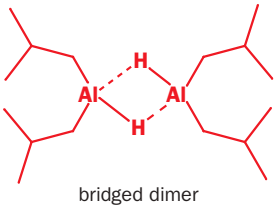
How to reduce esters and amides to aldehydes



The step boxed in yellow in the ester reduction scheme on p. 000 gave an aldehyde. The aldehyde is more readily reduced than the ester, so the reduction doesn't stop there, but carries on to the alcohol oxidation level. How, then, can you reduce an ester to an aldehyde? This is a real problem in synthetic chemistry—the ester below, for example, is easy to make by methods you will meet in Chapter 27. But an important synthesis of the antibiotic monensin requires the aldehyde.

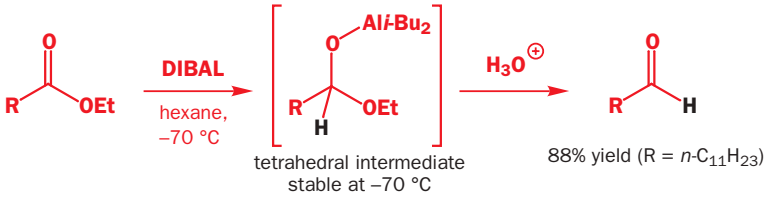




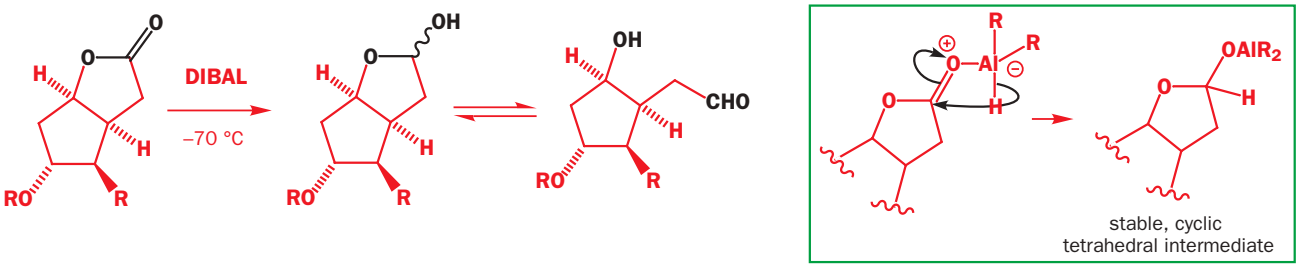


In this case, the chemists decided simply to put up with the fact that $LiAlH_4$ gives the alcohol, and re-oxidize the alcohol back to the aldehyde using chromium(VI) (see later for details of this step). There is, however, a reagent that will sometimes do the job in a single step, though you must bear in mind that this is not at all a general reaction. The reagent is known as DIBAL (or DIBAH or DIBALH—diisobutyl aluminium hydride, *i*-Bu_2AlH).

DIBAL is in some ways like borane—it exists as a bridged dimer, and it becomes a reducing agent only after it has formed a Lewis acid–base complex, so it too reduces electron-rich carbonyl groups most rapidly. DIBAL will reduce esters even at –70 °C, and at this temperature the tetrahedral intermediate may be stable. Only in the aqueous work-up does it collapse to the aldehyde when excess DIBAL has been destroyed so that no further reduction is possible.

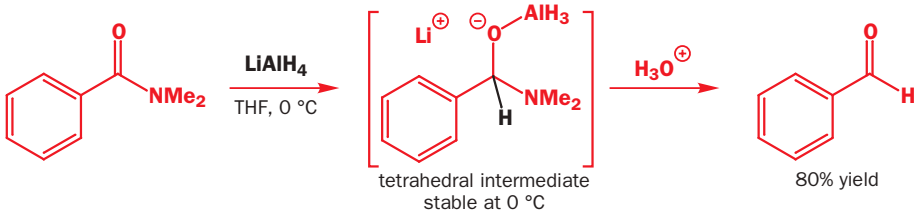


A stable tetrahedral intermediate is more likely in the reduction of lactones, and DIBAL is most reliable in the reduction of lactones to lactols (cyclic hemiacetals), as in E.J. Corey's synthesis of the prostaglandins. The key step, the hydride transfer from Al, is shown in the green frame.



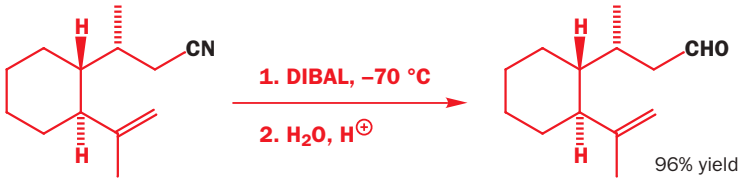
In the amide reduction scheme on p. 000, the step framed in green gives an iminium ion. Stopping the reaction here would therefore provide a way of making aldehydes from amides. Because these tetrahedral intermediates are rather more stable than those from ester reduction, this can often be achieved simply by carrying out the amide reduction, and quenching, at 0 °C (–70 °C is usually needed to stop esters overreducing to alcohols).

▶ *Reminder.* Cyclic hemiacetals are more stable than acyclic ones. Note how the product stays as a lactol—an acyclic hemiacetal would revert to alcohol plus aldehyde.



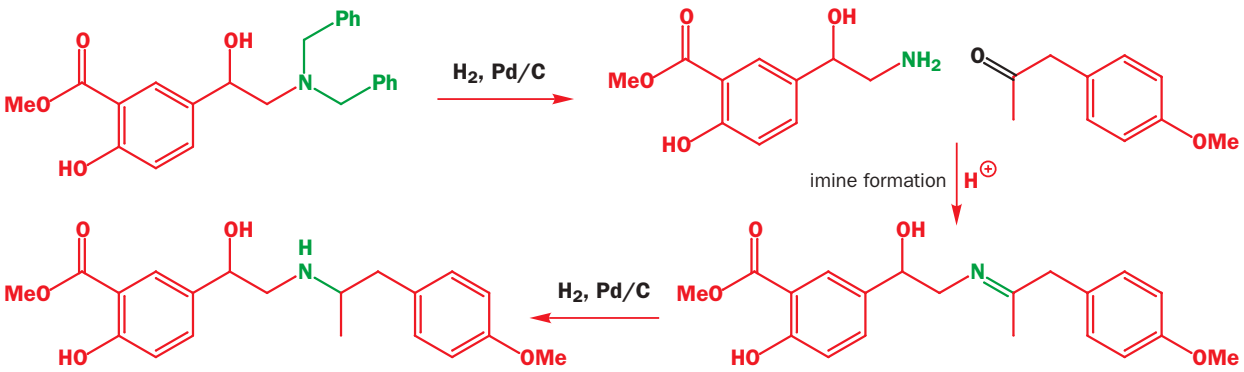
DIBAL is also good for reducing nitriles to aldehydes. Indeed, this reaction and the reduction of lactones to lactols are the best things that DIBAL does.

▶ Carboxylic acids can be reduced to aldehydes via their acyl chlorides using the *Rosenmund reaction*—see below.



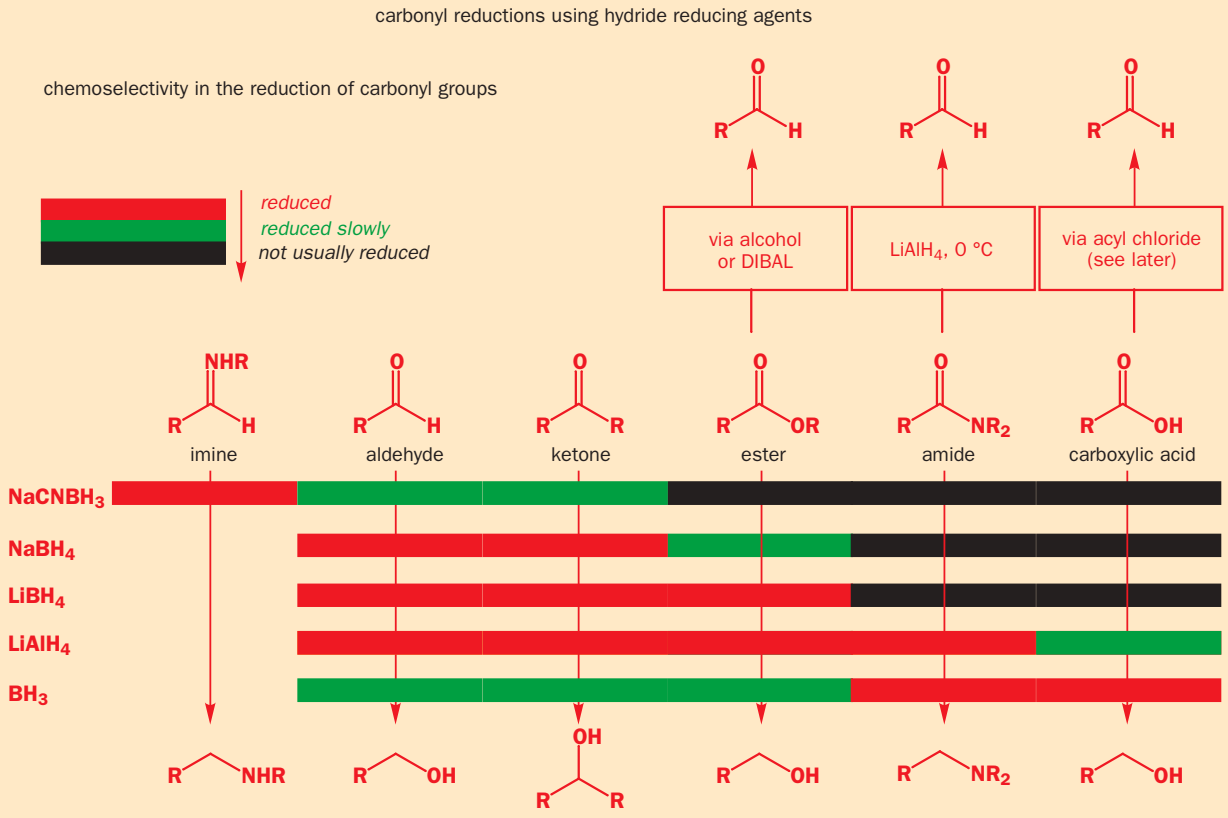
Now, let's go back to the salmefamol synthesis we started with on p. 000. The other reducing agent used in the sequence is hydrogen gas over a palladium catalyst. Catalytic hydrogenation has two functions here: firstly, it removes the two benzyl groups from the nitrogen, revealing a primary amine (this reaction is discussed later in this chapter), and, secondly, it reduces the imine that forms between this amine and the ketone added in this second step—an instance of **reductive amination**. We shall consider the second first, because it is another example of chemoselectivity in the reduction of a carbonyl-like group. You met reductive amination in Chapter 14, but as a reminder, here is the process again.

▶ 'Pd/C' means palladium metal dispersed on a charcoal support—usually 5–10% by mass Pd and 90–95% C. It is made by suspending charcoal powder in a $PdCl_2$ solution, and then reducing the $PdCl_2$ to Pd metal, usually with H_2 gas, but sometimes with formaldehyde, HCHO (which becomes oxidized to formic acid, HCO_2H). The palladium metal precipitates on to the charcoal, which can be filtered off and dried. The fine Pd particles present maximum surface area to the reaction they catalyse and, while Pd is an expensive metal, it is recyclable since the Pd/C is insoluble and can be recovered by filtration.

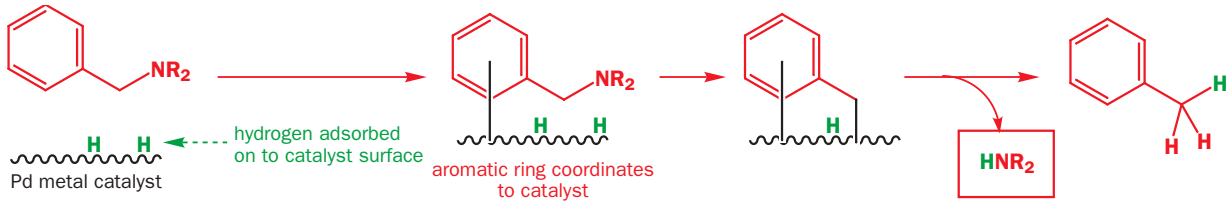


Catalytic hydrogenation reduces the imine (as the protonated iminium ion) but not the ketone from which it is formed. This chemoselectivity (reduction of iminium ions but not ketones) is also displayed by sodium cyanoborohydride and we can add $NaCNBH_3$ to complete our table of reactivity, if we insert imines at the left-hand end.

Summary



Now, what about the removal of the *N*-benzyl groups? This reaction is a **hydrogenolysis**—a cleavage of a C–X single bond by addition of hydrogen—and is just one of the many reactions hydrogen will do over metal catalysts. The 'mechanism' probably goes something like this.

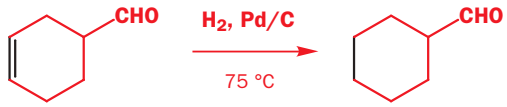


We put 'mechanism' in inverted commas because this isn't really a proper chemical mechanism, more a scheme with a suggested sequence of events. The key points are that the benzyl amine coordinates to the metal catalyst via the electron-rich aromatic ring. The C–N bond is now in close proximity to the palladium-bound hydrogen atoms, and is reduced.

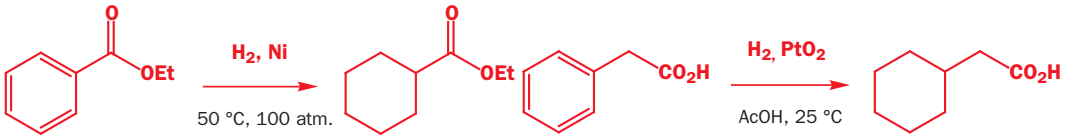
Because of the need for initial coordination with the catalyst, only benzylic or allylic C–X bonds can be reduced, but the X can be oxygen as well as nitrogen. We will come back to benzyl groups, and their hydrogenolysis, as a means for temporary protection of amines and alcohols later in the chapter. For the moment, though, we should take a broader look at catalytic hydrogenation as our second (after hydride reduction) important class of reductions.

Catalytic hydrogenation

You need to know about three sorts of hydrogenation reactions: the hydrogenation of a triple bond to a *Z*-alkene using 'Lindlar's catalyst', a poisoned form of palladium on barium sulfate; the hydrogenation of alkenes (including the imine above); and the hydrogenolysis of benzyl ethers and amines. We shall discuss each of these. The mechanism of hydrogenations is quite different from that of reductions by nucleophilic reducing agents like borohydride and, for this reason, catalytic hydrogenations have a totally different chemoselectivity. For example, it is quite possible to hydrogenate double bonds in the presence of aldehydes.



Even aromatic rings can be reduced by hydrogenation: in these examples the carbonyl groups survive while phenyl is reduced to cyclohexyl.

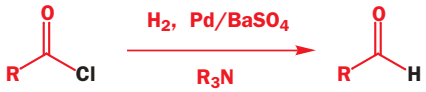


▶ Some hydrogenations, like this one, require high pressures of hydrogen gas to get them to go at a reasonable rate. They are usually done in a sealed apparatus known as a **Parr hydrogenator**.

The catalyst in each of these three reductions is a different metal. Palladium and platinum are the most commonly used metal catalysts for hydrogenation, but hydrogenation can also work with nickel, rhodium, or ruthenium. The choice of catalyst depends on the compound to be reduced.

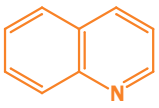
Substrate	Usual choice of metal
benzyl amine or ether	Pd
alkene	Pd, Pt, or Ni
aromatic ring	Pt or Rh, or Ni under high pressure

Catalytic hydrogenation is often chosen as a method for reduction because of its chemoselectivity for C=C double bonds and benzylic C–X bonds over C=O groups. The most important hydrogenation involving a carbonyl compound is not actually a reduction of the C=O double bond. Hydrogenation of acyl chlorides gives aldehydes in a reaction known as the **Rosenmund reaction**—really a hydrogenolysis of a C–Cl bond.

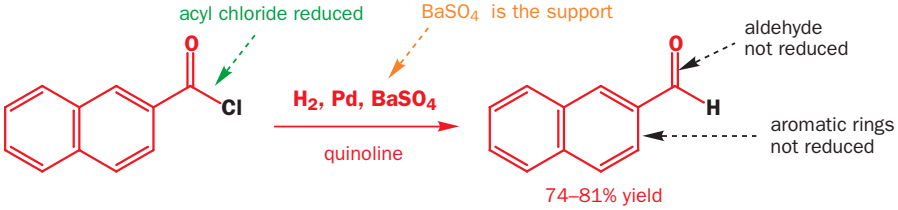


This is a good way of reducing compounds at the carboxylic acid oxidation level to aldehydes, which is why we included it in the table of carbonyl reductions on p. 000. The tertiary amine is needed both to neutralize the HCl produced in the reaction and to moderate the activity of the catalyst (and prevent overreduction). You will notice too that the catalyst support is different: Pd/$BaSO_4$ rather than Pd/C. $BaSO_4$ (and $CaCO_3$) are commonly used as supports with more easily reduced substrates because they allow the products to escape from the catalyst more rapidly and prevent overreduction. Acyl chlorides are among the easiest of all compounds to hydrogenate—look at this example.

the tertiary amine

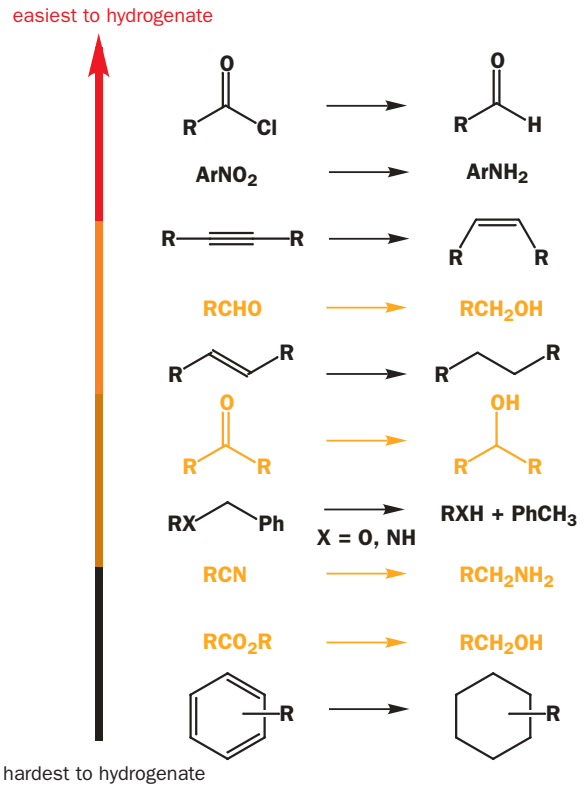


quinoline

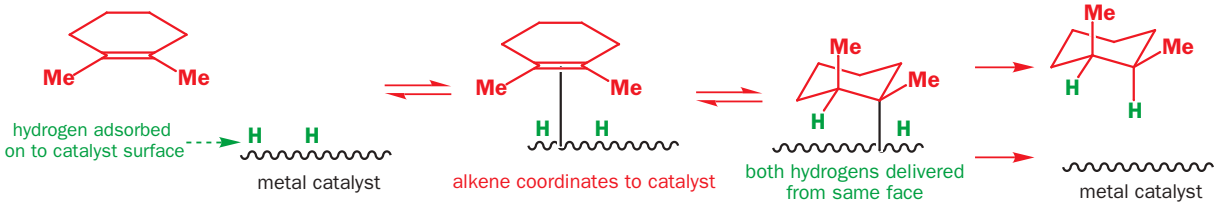


Although aromatic rings can be hydrogenated, as you saw on p. 000, neither they nor the aldehyde product are reduced under these conditions and, as with hydride reductions of carbonyl compounds, we can draw up a sequence of reactivity towards hydrogenation. The precise ordering varies with the catalyst, especially with regard to the interpolation of the (less important, because other methods are usually better) carbonyl reductions (in yellow). Some catalysts are particularly selective

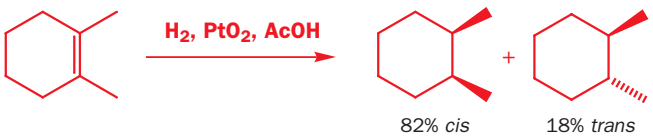
towards certain classes of compound—for example, Pt, Rh, and Ru will selectively hydrogenate aromatic rings in the presence of benzylic C–O bonds, while with Pd catalysts the benzylic C–O bonds are hydrogenolysed faster.



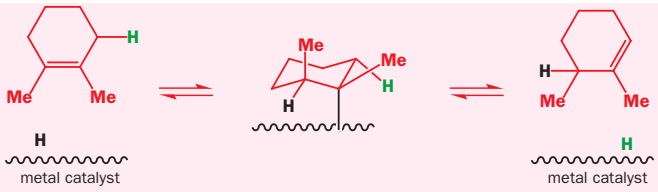
Like hydrogenolysis, the mechanism of the hydrogenation of C=C double bonds starts with coordination of the double bond to the catalyst surface.



Two hydrogen atoms are transferred to the alkene, and they are often both added to the same face of the alkene. In Chapter 20 you met other reactions of alkenes: some, like bromination, were *anti*-selective, but others like epoxidation were *syn*-selective like hydrogenation.



▶ This cannot be relied upon though! The same reaction with Pd as catalyst gives mainly the *trans* isomer, because of the reversibility of the hydrogenation process. This intermediate can easily escape from the catalyst as an isomeric alkene, which can be re-hydrogenated from the other face. Isomerizations of this sort sometimes accompany hydrogenations.



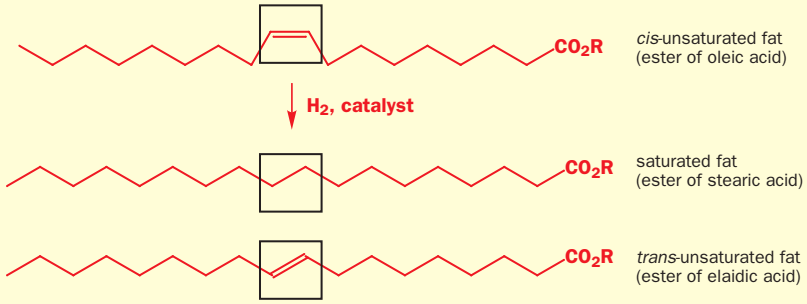
Hydrogenated vegetable oil

Plants such as soya, rapeseed, cottonseed, and sunflower are useful sources of edible vegetable oils, but these oils are unsuitable as 'butter substitutes' because of their low melting points. Their low melting points relative to animal fats are largely due to *cis* double bonds that disrupt the packing of the alkyl chains in the solid state. Treating the crude vegetable oil with hydrogen over a metal catalyst removes some of these double bonds, increases the proportion of saturated fat in the oil, and raises its melting point, making it suitable for making margarine.

Not all the double bonds are hydrogenated, of course: margarine manufacturers are desperate to tell us that their products are still 'high in unsaturated fatty acids'. Many also advertise that they are 'low in *trans* unsaturated fatty acids', because of a suggested link between incidence of coronary heart disease and *trans* unsaturated fatty acid intake.

Where have the *trans* double bonds come from? Well, partial hydrogenation can lead to significant double-bond isomerization, not just to regioisomers (as in the example in the marginal box above) but to geometrical isomers too.

In Chapter 31 we shall come back to double-bond geometry and how to control it. There is more on fats in Chapter 49.



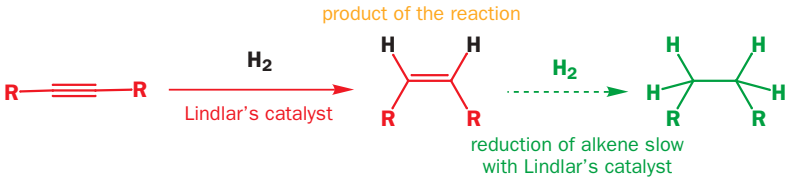
A note on some catalysts

Catalytic hydrogenations take place only on the surface of the particles of a metal catalyst. The metal must therefore be very finely divided and is often mixed with a **support**—this is what Pd/C or $Pd/BaSO_4$ means—palladium particles deposited on a support of powdered charcoal or barium sulfate. Palladium on charcoal is probably the most commonly used catalyst, but three others deserve special mention.

1 You will meet **Lindlar's catalyst** in Chapter 31 but we will mention it now because of its special chemoselectivity. Unlike the other hydrogenations we have described, the Lindlar catalyst will hydrogenate alkynes to alkenes, rather than alkenes to alkanes. This requires rather subtle chemoselectivity: alkenes are usually hydrogenated at least as easily as alkynes, so we need to be sure the reaction stops once the alkene has been formed. The Lindlar catalyst is a palladium catalyst ($Pd/CaCO_3$) deliberately poisoned with lead. The lead lessens the activity of the catalyst and makes further reduction of the alkene product slow: most palladium catalysts would reduce

alkynes all the way to alkanes. Best selectivities are obtained if quinoline is added to the reaction, just as in the Rosenmund reaction, and, in fact, alkyne to alkene reductions work with $Pd/BaSO_4$ + quinoline too. Even so, Lindlar reactions often have to be monitored carefully to make sure that overreduction is not taking place

Lindlar's catalyst = **Pd, $CaCO_3$, $Pb(OAc)_2$**

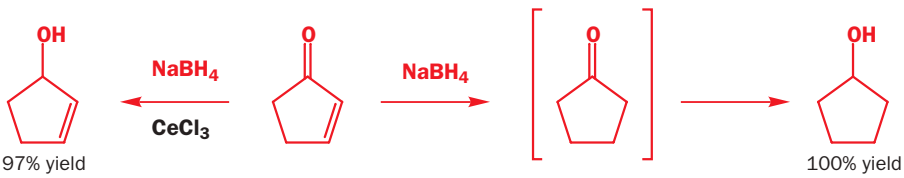


2 **Adams's catalyst** is formally PtO_2, and you have already seen this at work in one or two examples. The actual catalyst is, however, not the oxide of platinum, but the platinum metal that forms by reduction of PtO_2 to Pt *during the hydrogenation*

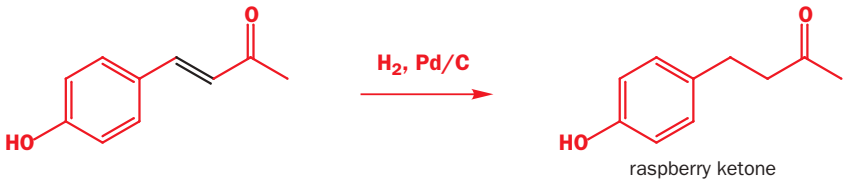
3 **Raney nickel** (often abbreviated to RaNi) is a finely divided form of nickel made from a nickel–aluminium alloy. The aluminium is dissolved away using concentrated aqueous sodium hydroxide, leaving the nickel as a fine powder. The process liberates H_2 (check this for yourself—on paper!), and some of this hydrogen remains adsorbed on to the nickel catalyst. This means that some hydrogenations, particularly those of C–S bonds, which you will come across later in this chapter and in Chapter 46, can be carried out just by using freshly prepared Raney nickel, with no added H_2 (RaNi as reagent, not catalyst)

How to reduce unsaturated carbonyl compounds

Where reduction of an α,β-unsaturated carbonyl compound takes place is really a question of regioselectivity, not chemoselectivity, but it's useful to discuss the problem here having just introduced you to these hydrogenation methods. When we first covered conjugate addition in Chapter 10, we pointed out that hydride reducing agents are not good choices for the selective reduction of the C=O bond of unsaturated carbonyl compounds because they tend to add to the double bond as well, giving first the saturated carbonyl compound, which is then reduced to the alcohol. The way to get regioselective addition directly to the carbonyl group is to add a hard, Lewis-acidic metal salt, such as $CeCl_3$.

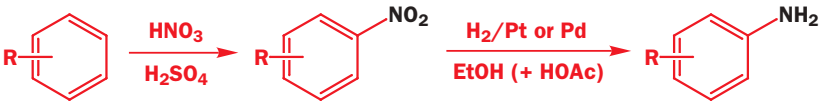


It should not surprise you that regioselective reduction of the C=C double bond alone is best done using catalytic hydrogenation as the C=C bond is weaker than the C=O bond. The flavouring compound known as 'raspberry ketone' is made by this method.



Nitro group reduction

Near the top of the list of reactivity towards hydrogenation lies the NO_2 group and in Chapter 22 we saw how the sequence of nitration of aromatic rings followed by reduction was a useful route to aromatic amines. The reduction can be carried out by Sn/HCl but catalytic hydrogenation is much simpler. The reaction is usually done in ethanol with a Pd or Pt catalyst and it may be necessary to add a weak acid to prevent the amine produced from poisoning the catalyst.



usually ~100% yield

The real gain over the Sn/HCl method is in the work-up. Instead of separating and disposing of voluminous toxic tin residues, a simple filtration to remove the catalyst, evaporation, and crystallization or distillation gives the amine.

Getting rid of functional groups

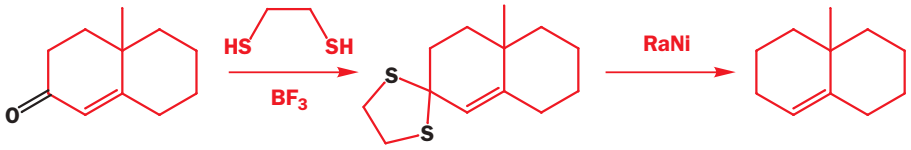
Functional groups can be useful for putting a molecule together, but their presence may not be required in the final product. We need ways of getting rid of them. Hydrogenation of alkenes is one way that you have seen, and alcohols can be got rid of either by elimination and then hydrogenation or by tosylation and substitution using borohydride to provide a nucleophilic hydrogen atom.

▶ Lithium triethylborohydride is used here, but other powerful hydride reducing agents would do as well.

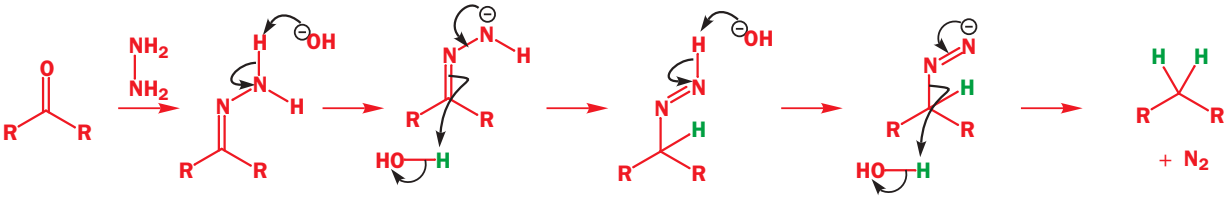
99% yield

Removal of carbonyl groups is harder, though there are several possible methods. C–O bonds are strong, but C–S bonds are much weaker, and are often easily reduced with Raney nickel (we come back to this in Chapter 46). We can get rid of aldehyde and ketone carbonyl groups by making them into **thioacetals**, sulfur analogues of acetals, formed in a reaction analogous to acetal formation (p. 000) but using a dithiol with a Lewis acid catalyst. Freshly prepared Raney nickel carries enough H_2 (p. 000) to reduce the thioacetal without added hydrogen.

▶ This is sometimes known as the **Mozingo reaction**.



A slightly more vigorous method, known as the **Wolf–Kishner reduction**, is driven by the elimination of nitrogen gas from a hydrazone. Hot concentrated sodium hydroxide solution deprotonates the hydrazone, which can then eliminate an alkyl anion—a reaction you would usually be wary of writing, but which is made possible by the thermodynamic stability of N_2.



The third method is the simplest to do, but has the most complicated mechanism. The **Clemmensen reduction** is also rather violent, and really reasonable only for compounds with just the one functional group. It uses zinc metal dissolv*ing* in hydrochloric acid. As the metal dissolves, it gives up two electrons—in the absence of something else to do, these electrons would reduce the H^+ in the acid to H_2, and give $ZnCl_2$ and H_2. But in the presence of a carbonyl compound, the electrons go to reduce the C=O bond.

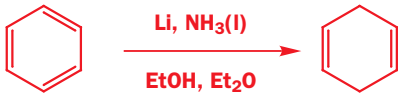
88%, R = $C_{17}H_{35}$

The mechanism has a good deal in common with a whole class of reductions, of which the Clemmensen is a member, known as **dissolving metal reductions**. We shall now look at these as our third (after metal hydrides and catalytic hydrogenation) important class of reducing agents.

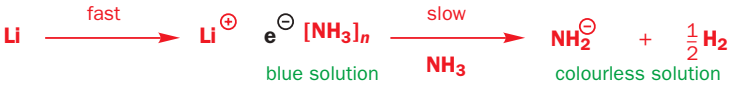
Dissolving metal reductions

Group 1 metals, such as sodium or lithium, readily give up their single outer-shell electron as they dissolve in solvents such as liquid ammonia or ethanol. Electrons are the simplest reducing agents, and they will reduce carbonyl compounds, alkynes, or aromatic rings—in fact any functional group with a low-energy π^* orbital into which the electron can go.

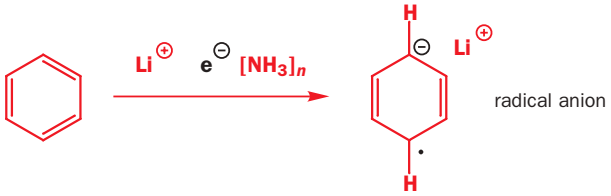
We shall start by looking at the dissolving metal reduction of aromatic rings, known as the **Birch reduction**. Here is the reaction of benzene with lithium in liquid ammonia. At first sight, this reaction looks quite improbable, with an aromatic ring ending up as an unconjugated diene! The mechanism explains why we get this regiochemistry, and also why the reaction stops there—in other words why the dissolving lithium reduces an aromatic ring more readily than an alkene.



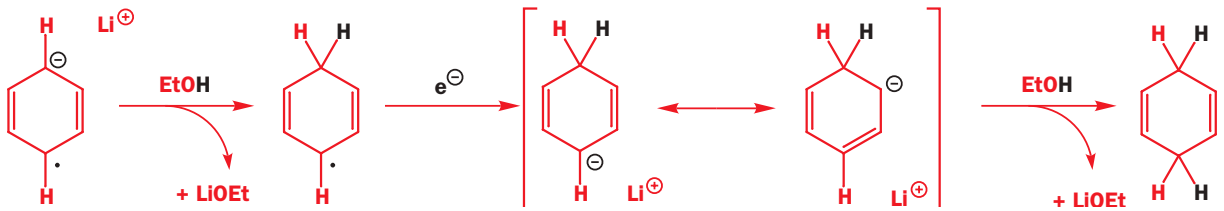
The first thing to note is that when lithium or sodium dissolve in ammonia they give an intense blue solution. Blue is the colour of solvated electrons: these group 1 metals ionize to give Li^+ or Na^+ and $e^-(NH_3)_n$—the gaps between the ammonia molecules are just the right size for an electron. With time, the blue colour fades, as the electrons reduce the ammonia to NH_2^- and hydrogen gas. Sodium amide, $NaNH_2$, the base you met early in this book, is made by dissolving Na in liquid NH_3 *and then waiting till the solution is no longer blue.*



Birch reductions use those blue solutions, with their solvated electrons, as reducing agents. The reduction of NH_3 to NH_2^- and H_2 is quite slow, and a better electron acceptor will get reduced in preference. In the example above, the electrons go into benzene's lowest lying antibonding orbital (its LUMO). The species we get can be represented in several ways, all of them radical anions (molecules with one excess, unpaired electron).



The radical anion is very basic, and it picks up a proton from the ethanol that is in the reaction mixture. The molecule is now no longer anionic, but it is still a radical. It can pick up another electron, which pairs with the radical to give an anion, which is quenched again by the proton source (ethanol).



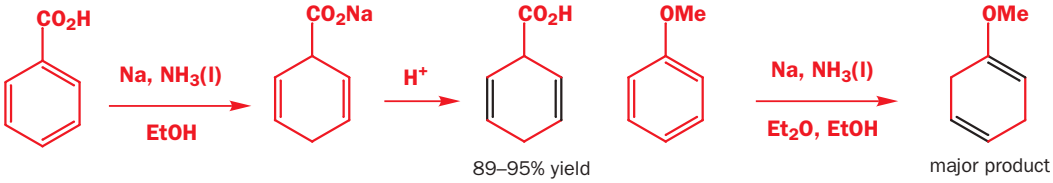
The regiochemistry of the reaction is determined at the final protonation step—the anion itself is of course delocalized and could react at either end to give a conjugated diene, which would be more

stable. Why then does it choose to pick up a proton in the middle and give a less stable isomer? Well, the full explanation is beyond the scope of this book, but suffice it to say that kinetically controlled reactions of pentadienyl anions with electrophiles typically take place at this central carbon.

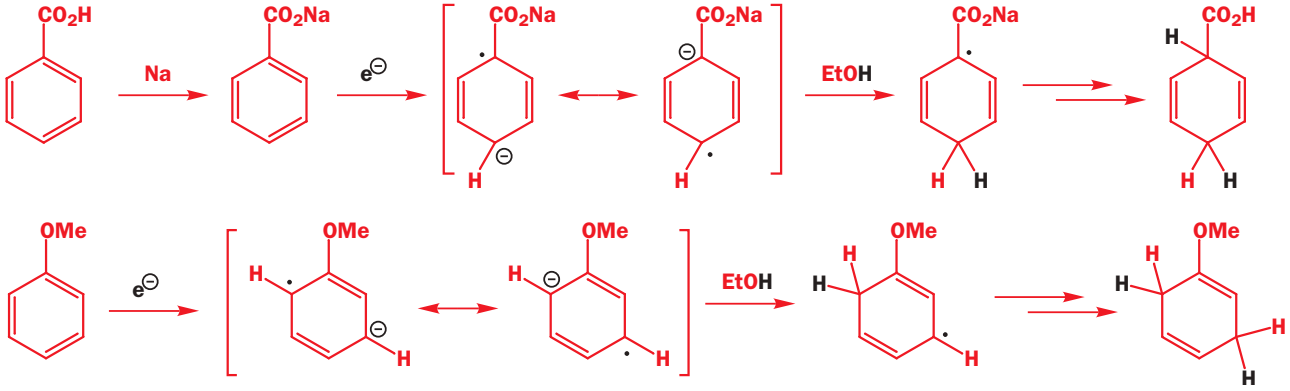
Further questions of regioselectivity arise when there are substituents around the aromatic ring. Here are two examples. The second product was used by Evans in his synthesis of the alkaloid luciduline. These examples serve to illustrate the general principle that electron-withdrawing groups promote *ipso, para* reduction while electron-donating groups promote *ortho, meta* reduction.

■ You can read more in Ian Fleming (1976). *Frontier orbitals and organic reaction mechanisms*. Wiley, Chichester.

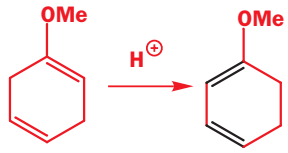
■ Alkaloids appear in Chapter 51.



The explanation must lie in the distribution of electron density in the intermediate radical anions. Electron-withdrawing groups stabilize electron density at the *ipso* and *para* positions, and protonation occurs *para*, while electron-donating groups stabilize *ortho* and *meta* electron density.

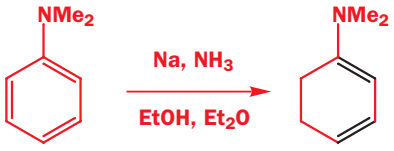


If you want the conjugated dienes as products, it is quite a simple matter to isomerize them using an acid catalyst. In fact, a small amount (about 20%) of the conjugated product is produced anyway in the reaction of anisole above.



■ Make sure you can write a mechanism for this isomerization. *Hint*. Start as though you were protonating an enol ether on carbon. You saw this sort of thing in Chapter 21.

With anilines, it is impossible to stop the isomerization taking place during the reaction, and Birch reduction always gives conjugated enamines.

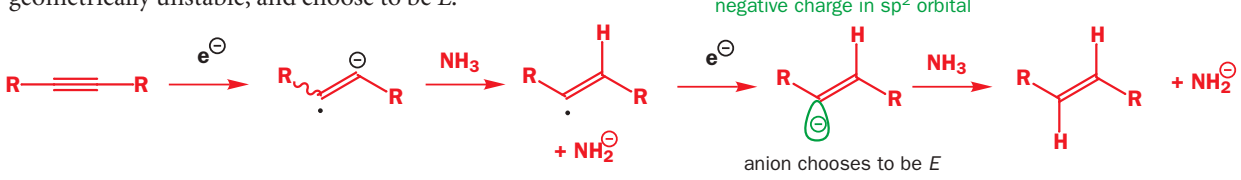


■ Birch-style reduction of α,β-unsaturated carbonyl compounds is described in Chapter 26.

Birch reduction works for alkynes too, and is a good way of reducing them, to *trans* double bonds (the best way to reduce them to *cis*-alkenes is via H_2 and the Lindlar catalyst).

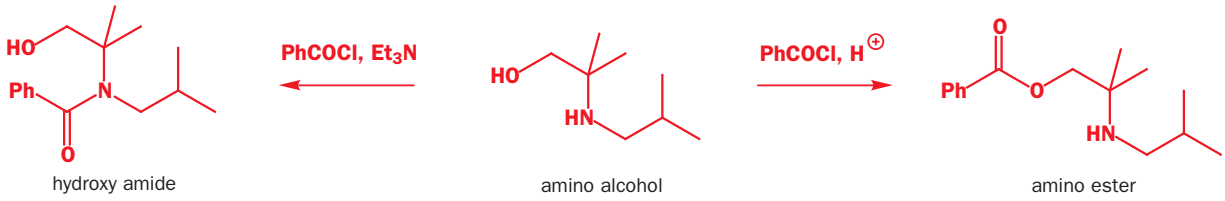
▶ We come back to dissolving metals in Chapter 39, where we will also introduce another type of reduction—a good way of reducing C–halogen bonds to C–H.

The mechanism follows the same course as the reduction of aromatic rings, but the vinyl anion is basic enough to deprotonate ammonia, so no added proton source is required. Vinyl anions are geometrically unstable, and choose to be *E*.



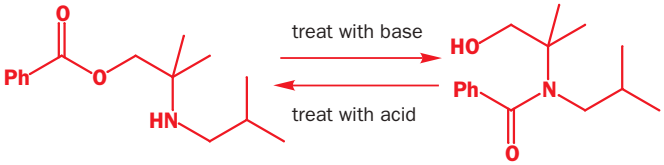
One functional group may be more reactive than another for *kinetic* or for *thermodynamic* reasons

We hope that our survey of the important methods for reduction has shown you that, by choosing the right reagent, you can often react the functional group you want. The chemoselectivity you obtain is kinetic chemoselectivity—reaction at one functional group is simply faster than at another. Now look at the acylation of an amino alcohol (which is, in fact, a synthesis of the painkiller isobucaine) using benzoyl chloride under *acid* conditions. The hydroxyl group is acylated to form an ester. Yet under *basic* conditions, the selectivity is quite different, and an amide is formed.



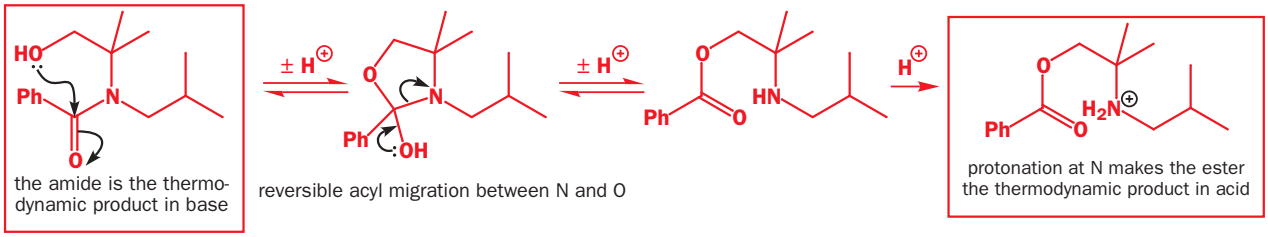
hydroxy amide — amino alcohol — amino ester

A clue to why the selectivity reverses is shown below—it is, in fact, possible to interconvert the ester and the amide simply by treating either with acid or with base.



■ We first met examples of kinetic and thermodynamic control in Chapter 13.

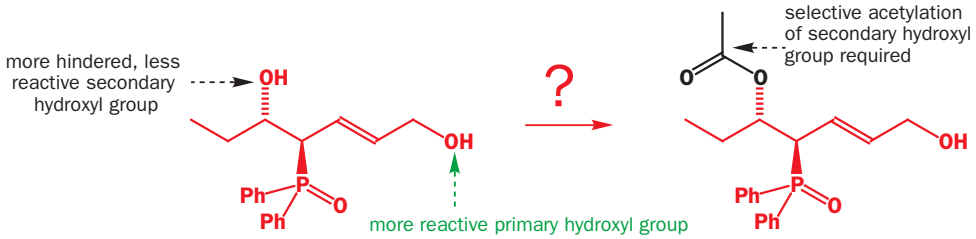
The selectivity in these reactions is *thermodynamic* chemoselectivity. Under conditions in which the ester and amide can equilibrate, the product obtained is the more stable of the two, not necessarily the one that is formed faster. In base the more stable amide predominates, while in acid the amine is protonated, which prevents it from acting as a nucleophile and removes it from the equilibrium, giving the ester.



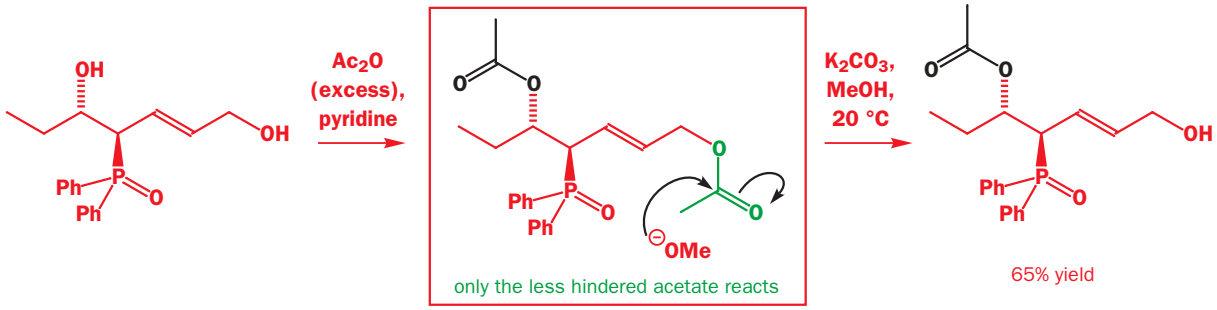
the amide is the thermodynamic product in base — reversible acyl migration between N and O — protonation at N makes the ester the thermodynamic product in acid

How to react the less reactive group (I)

The relative reactivity of the alcohol and amine in the example just given could be overturned by conducting a reaction under thermodynamic control. In kinetically controlled reactions, the idea that you can conduct chemoselective reactions on the more reactive of a pair of functional groups—carbonyl-based ones, for example—is straightforward. But what if you want to react the less reactive of the pair? There are two commonly used solutions. The first is illustrated by a compound needed by chemists at Cambridge to study an epoxidation reaction. They were able to make the following diol, but wanted to acetylate only the more hindered secondary hydroxyl group.



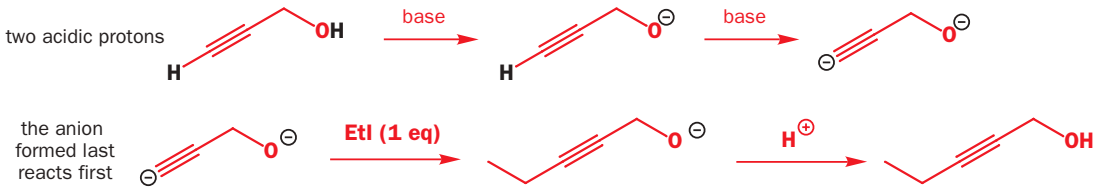
Treatment with one equivalent of an acyl chloride agent is no good because the primary hydroxyl group is more reactive; instead, the chemists acetylated both hydroxyl groups, and then treated the bis-acetate with mildly basic methanol (K_2CO_3, MeOH, 20 °C), which reacted only at the less hindered acetoxy group and gave the desired compound in 65% yield.



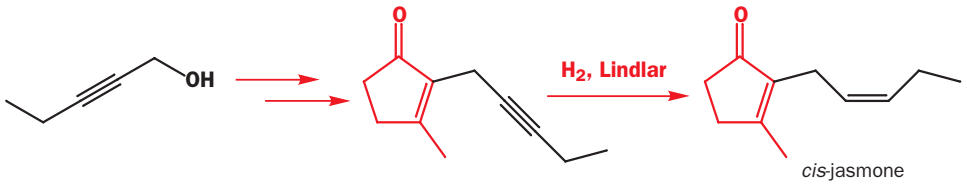
In other words, start by letting both groups react, and then go backwards but reverse the reaction at only one of the groups. The likelihood is that the less favourable reaction (in other words, reaction at the less reactive group) will be less readily reversed.

Chemoselectivity in the reactions of dianions

The idea that a reaction that is less easy to do will be easier to undo is central to a useful bit of chemoselectivity that can be obtained in the reactions of dianions. 1-Propynol can be deprotonated twice by strong bases—first, at the hydroxyl group to make an alkoxide anion (the pK_a of the OH group is about 16) and, secondly, at the alkyne (pK_a of the order of 25) to make a 'dianion'. When this dianion reacts with electrophiles it always reacts at the alkynyl anion and not at the alkoxide.



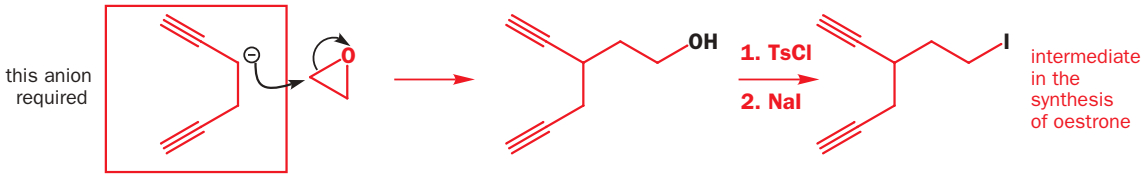
This reaction is important in a synthesis of the perfumery compound *cis*-jasmone. The alkyne is the precursor to *cis*-jasmone's alkene side chain.



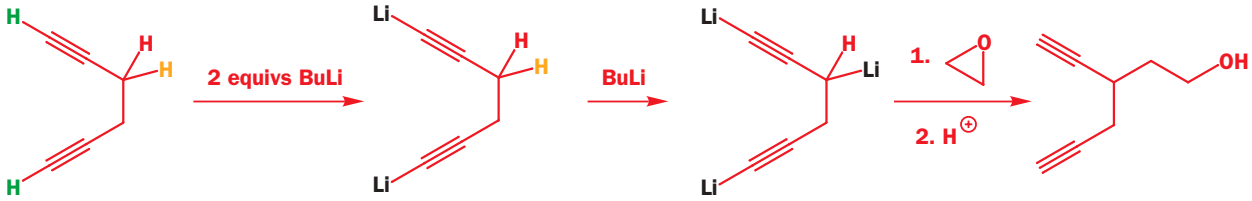
?Heading?

The principle here is that the anion that is formed *last* reacts *first*.

Vollhardt used this sort of chemoselectivity in his 1977 synthesis of the female sex hormone oestrone. He needed an alkyl iodide, which could be made by reacting an anion of a bis-alkyne with ethylene oxide.



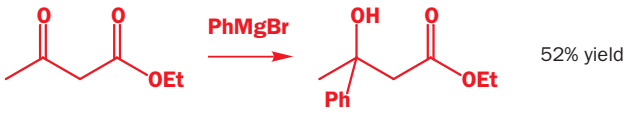
Although anions can often be formed straightforwardly next to alkynes, there are two other more acidic protons (green) in the molecule that would be removed by base before the yellow proton. However, treatment with *three* equivalents of butyl lithium removes all three, and the trianion reacts with ethylene oxide at the last-formed anionic centre to give the required compound.



How to react the less reactive group (II): protecting groups

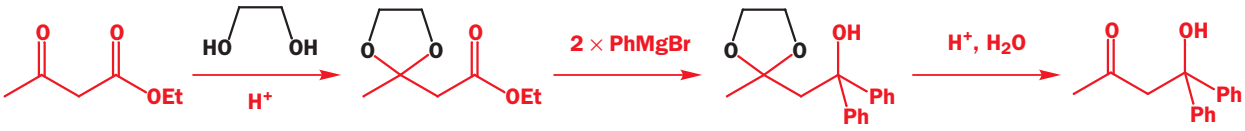
The usual way of reacting a less reactive group in the presence of a more reactive one is to use a protecting group. This tertiary alcohol, for example, could be made from a keto-ester if we could get phenylmagnesium bromide to react with the ester rather than with the ketone.

As you would expect, simply adding phenylmagnesium bromide to ethyl acetoacetate leads mainly to addition to the more electrophilic ketone.



■ Five-membered cyclic acetals like these are known as dioxolanes. You met them first in Chapter 14 when we were discussing acetal formation and hydrolysis.

One way of making the alcohol we want is to protect the ketone as an acetal. An **acetal-protecting group** (shown in black) is used.

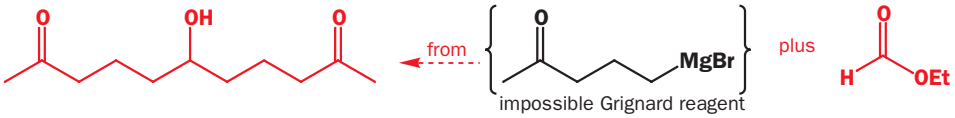


▶ This table of protecting groups will grow, line by line, as we move through this chapter and the next.

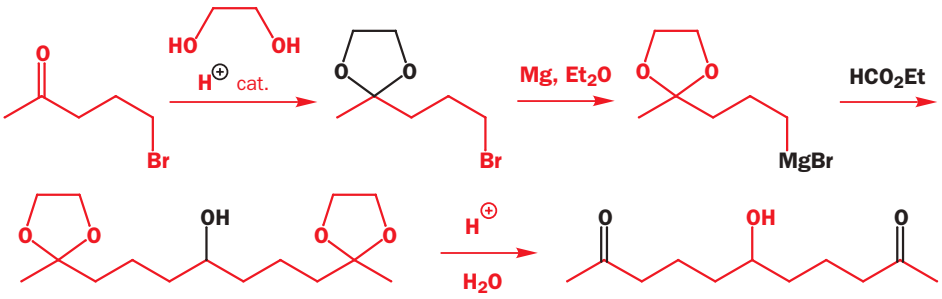
The first step puts the protecting group on to the (more electrophilic) ketone carbonyl, making it no longer reactive towards nucleophilic addition. The Grignard then adds to the ester, and finally a 'deprotection' step, acid-catalysed hydrolysis of the acetal, gives us back the ketone. An acetal is an ideal choice here—acetals are stable to base (the conditions of the reaction we want to do), but are readily cleaved in acid.

Protecting group	Structure	Protects	From	Protection	Deprotection
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		water, H^+ cat.

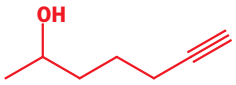
By protecting sensitive functional groups like ketones it becomes possible to make reagents that would otherwise be unstable. In a synthesis of the natural product porantherine, a compound based on this structure was needed.



One way to make it is to add a Grignard reagent twice to ethyl formate. But, of course, a ketone-containing Grignard is an impossibility as it would self-destruct, so an acetal-protected compound was used.



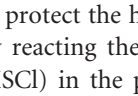
Strongly nucleophilic reagents like Grignard reagents and organolithiums are also strong bases, and may need protecting from acidic protons as well as from electrophilic carbonyl groups. Among the most troublesome are the protons of hydroxyl groups. When some American chemists wanted to make the antiviral agent Brefeldin A, they needed a simple alkynol.

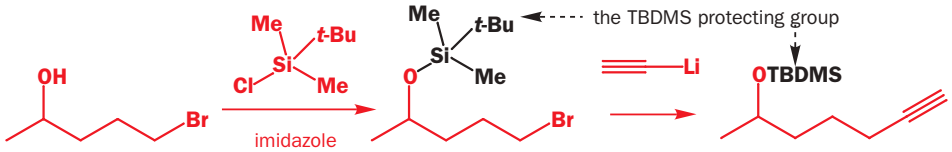


A synthesis could start with the same bromoketone as the one above: reduction gives an alcohol, but alkylation of an alkynyl anion with this compound is not possible, because the anion will just deprotonate the hydroxyl group.

The answer is to protect the hydroxyl group, and the group chosen here was a **silyl ether**. Such ethers are made by reacting the alcohol with a trialkylsilyl chloride (here *t*-butyl dimethyl silyl chloride, or TBDMSCl) in the presence of a weak base, usually imidazole, which also acts as a nucleophilic catalyst (Chapter 12).

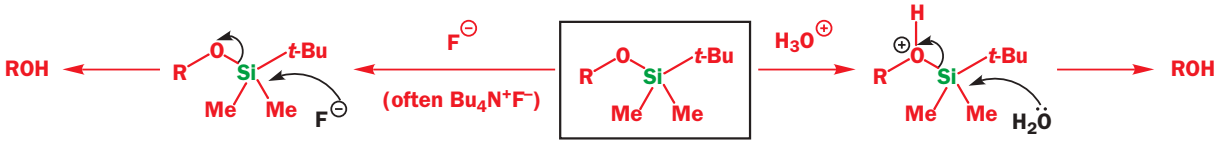
imidazole = (a weak base)





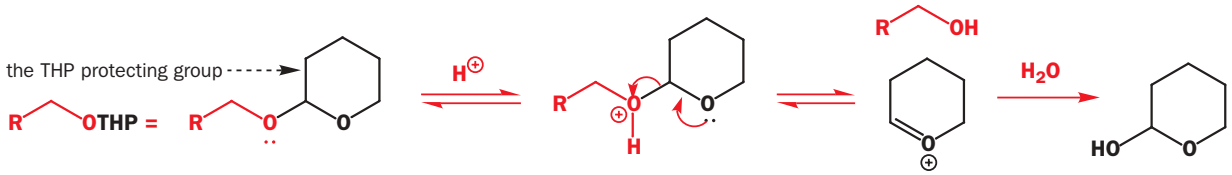
Silicon has a strong affinity for electronegative elements, particularly O, F, and Cl, so trialkylsilyl ethers are attacked by hydroxide ion, water, or fluoride ion but are more stable to carbon or nitrogen bases or nucleophiles. They are usually removed with aqueous acid or fluoride salts, particularly $Bu_4N^+F^-$ which is soluble in organic solvents. In fact, TBDMS is one member of a whole family of trialkylsilyl protecting groups and their relative stability to nucleophiles of various kinds is determined by the three alkyl groups carried by silicon. The most labile, trimethylsilyl (TMS), is removed simply on treatment with methanol, while the most stable require hydrofluoric acid.

■ Although not important to our discussion here, these substitution reactions are not the simple S_N2 reactions (Chapter 17) they might appear to be. The nucleophile adds to silicon first to form a five-valent anion which decomposes with the loss of the alcohol (Chapter 21).



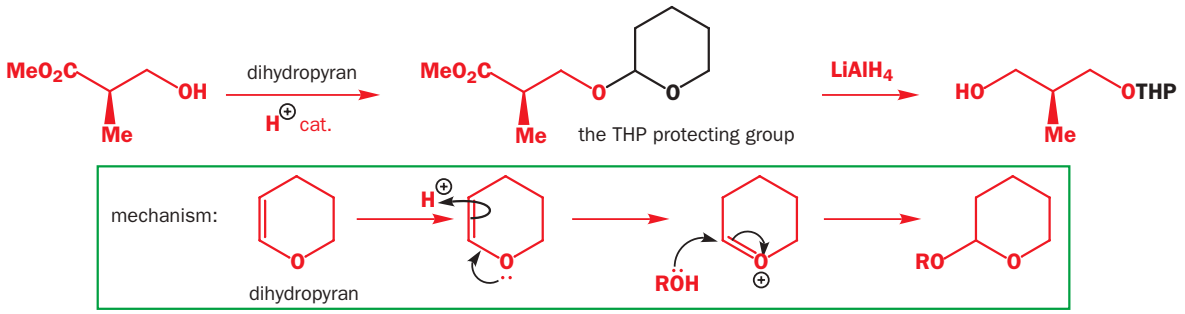
Protecting group	Structure	Protects	From	Protection	Deprotection
trialkylsilyl (R_3Si-, e.g. TBDMS)	RO—$SiMe_3$ RO—$SiMe_2Bu^t$	alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-

Why can't we just use a simple alkyl ether (methyl, say) to protect a hydroxyl group? There is no problem making the ether, and it will survive most reactions—but there *is* a problem getting an ether off again. This is always a consideration in protecting group chemistry—you want a group that is stable to the conditions of whatever reaction you are going to do (in these examples, strong bases and nucleophiles), but can then be removed under mild conditions that do not result in total decomposition of a sensitive molecule. What we need then, is an ether that has an 'Achilles' heel'—a feature that makes it susceptible to attack by some specific reagent or under specific conditions. One such group is the tetrahydropyranyl (THP) group. Although it is stable under basic conditions, as an ether would be, it is an acetal—the presence of the second oxygen atom is its 'Achilles' heel' and makes the THP protecting group susceptible to hydrolysis under acidic conditions. You could see the lone pair on the second oxygen atom as a 'safety catch' that is released only in the presence of acid.



Making the THP acetal has to be done in a slightly unusual way because the usual carbonyl compound plus two alcohols is inappropriate. Alcohols are protected by reacting them with an enol ether, dihydropyran, under acid catalysis. Notice the oxonium intermediate (formed by a familiar mechanism from Chapter 14)—just as in a normal acetal-forming reaction. In this example the THP group is at work preventing a hydroxyl group from interfering in the reduction of an ester.

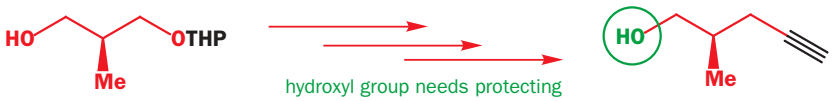
■ Some chemistry of enol ethers is in Chapter 21.



▶ A little further inspection will show you that the THP group here is not just stopping the OH interfering with the $LiAlH_4$ reduction, but is also crucial to the preservation of the chirality of this compound. The wedged bond shows you that the starting material is a single enantiomer: without a protecting group on one of the hydroxyls, they would be identical and the compound would no longer be chiral. More detailed inspection shows that the THP group also complicates the situation by introducing an extra chiral centre, and hence the potential for two diastereoisomers, which we will ignore.

Protecting group	Structure	Protects	From	Protection	Deprotection
tetrahydropyranyl (THP)	RO O	alcohols (OH in general)	strong bases	O dihydropyran and acid	H^+, H_2O

The THP-protected compound above is an intermediate in a synthesis of the insecticide milbemycin as a single enantiomer. It needs to be converted to this alkyne—and now the *other* hydroxyl group will need protecting.

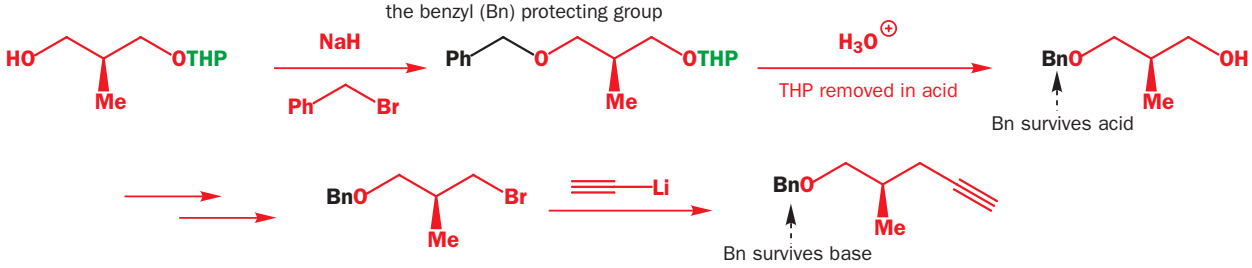


This time, though, TBDMS will not do, because the protecting group needs to withstand the acidic conditions needed to remove the THP protecting group! What is more, the protecting group needs to be able to survive acid conditions in later steps of the synthesis of the insecticide. The answer

is to use a third type of hydroxyl-protecting group, a benzyl ether. Benzyl (Bn) protecting groups are put on using strong base (usually sodium hydride) plus benzyl bromide, and are stable to both acid and base.

▶ Note the abbreviation for a benzyl ether, $ROCH_2Ph$, is RO**Bn**. Contrast this with benz*oyl esters*, ROCOPh, which may be abbreviated RO**Bz**.

the benzyl (Bn) protecting group



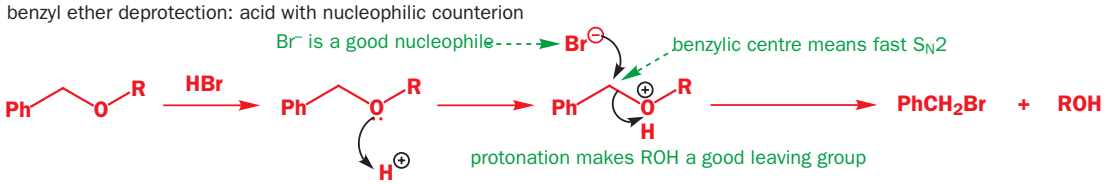
The benzyl ether's Achilles' heel is the aromatic ring and, after reading the first half of this chapter, you should be able to suggest conditions that will take it off again: hydrogenation (hydrogenolysis) over a palladium catalyst.

▶ It must be a *palladium* catalyst—platinum would catalyse hydrogenation of the aromatic ring.

benzyl ether deprotection: catalytic hydrogenation

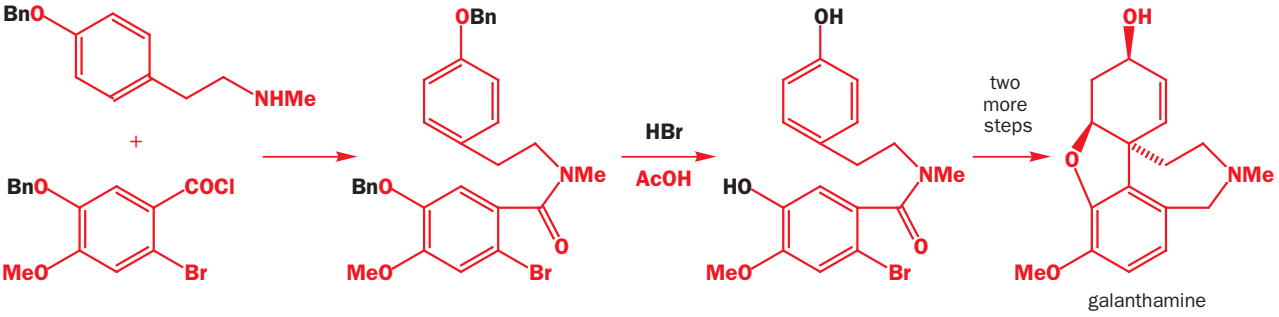
Benzyl ethers can sometimes be removed by acid, if the acid has a *nucleophilic* conjugate base. HBr, for example, will remove a benzyl ether because Br^- is a good enough nucleophile to displace ROH, though only at the reactive, benzylic centre.

benzyl ether deprotection: acid with nucleophilic counterion



HBr in acetic acid (just the solvent) is used to remove the benzyl ether protecting groups in this example, which forms part of a synthesis of the alkaloid galanthamine.

■ Alkaloids appear in Chapter 51.



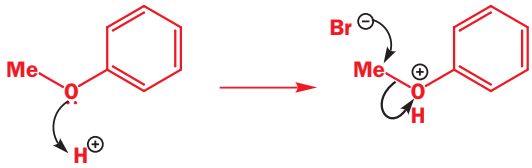
Protecting group	Structure	Protects	From	Protection	Deprotection
benzyl ether (OBn)	RO, ROBn	alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)	MeO, R	phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI

We said earlier that simple methyl ethers are inappropriate as protecting groups for OH because they are too hard to take off again. That is usually true, but not if the OH is phenolic—ArOH is an

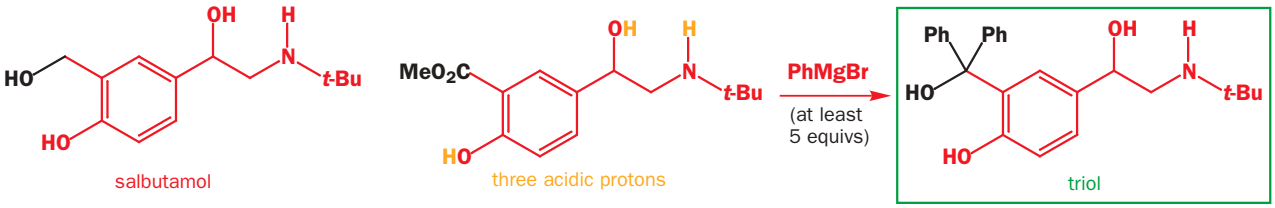
▶ Alternatives to HBr include BBr_3, usually the favoured reagent, HI, and Me_3SiI. You met the reaction of phenyl ethers with BBr_3 in Chapter 17.

even better leaving group than ROH, so HBr will take off methyl groups from aryl methyl ethers too. You will see an example in Chapter 25.

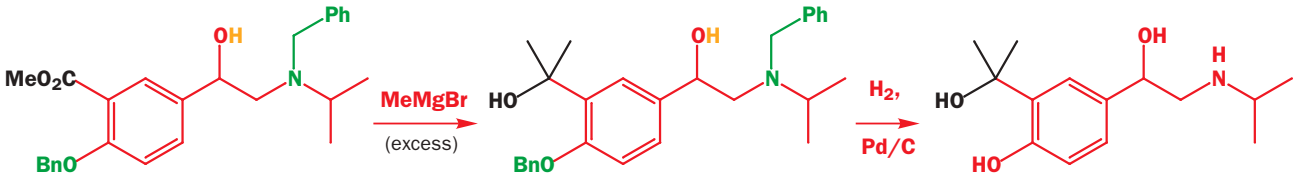
deprotection of aryl methyl ethers



Protecting groups may be useful, but they are also wasteful—both of time, because there are two extra steps to do (putting the group on and taking it off), and of material, because these steps may not go in 100% yield. Here's one way to avoid using them. During the development of the best-selling anti-asthma drug salbutamol, the triol boxed in green was needed. With large quantities of salbutamol already available, it seemed most straightforward to make the triol by adding phenylmagnesium bromide to an ester available from salbutamol. Unfortunately, the ester also contains three acidic protons, making it look as though the hydroxyl and amine groups all need protecting. But, in fact, it was possible to do the reaction just by adding a large excess of Grignard reagent: enough to remove the acidic protons *and* to add to the ester.

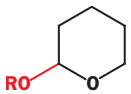


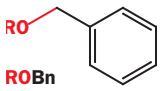
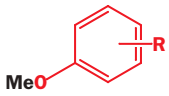
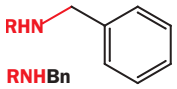
This strategy is easy to try, and, providing the Grignard reagent isn't valuable (you can buy PhMgBr in bottles), is much more economical than putting on protecting groups and taking them off again. But it doesn't always work—there is no way of telling whether it will until you try the reaction in the lab. In this closely related reaction, for example, the same chemists found that they needed to protect both the phenolic hydroxyl group (but not the other, normal alcohol OH!) as a benzyl ether and the amine NH as a benzyl amine. Both protecting groups come off in one hydrogenation step.



■ This is the last appearance of the table of protecting groups in this chapter but it is extended in Chapter 25.

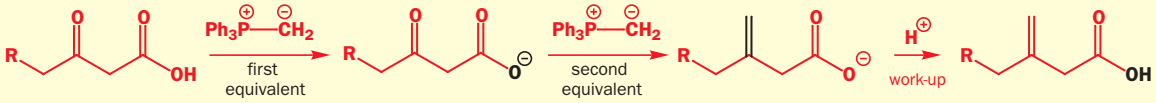
Benzyl groups are one way of protecting secondary amines against strong bases that might deprotonate them. But it is the nucleophilicity of amines that usually poses problems of chemoselectivity, rather than the acidity of their NH groups, and we come back to ways of protecting them from electrophiles when we deal with the synthesis of peptides in Chapter 25.

Protecting group	Structure	Protects	From	Protection	Deprotection
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		water, H^+ cat.
trialkylsilyl (R_3Si-, e.g. TBDMS)		alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	 dihydropyran and acid	H^+, H_2O

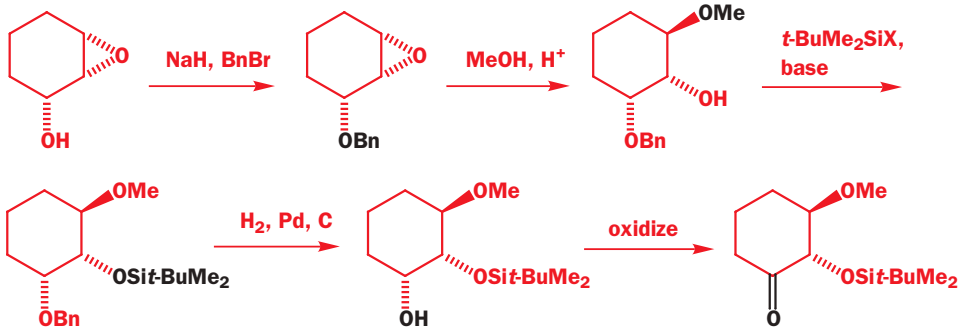
Protecting group	Structure	Protects	From	Protection	Deprotection
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI
benzyl amine (NBn)		amines	strong bases	BnBr, K_2CO_3	H_2, Pd

Bergamotene

An acidic proton posed a potential problem during E.J. Corey's synthesis of bergamotene (a component of the fragrance of Earl Grey tea). You met the Wittig reaction in Chapter 14, and phosphonium ylids are another type of basic, nucleophilic reagent that –OH groups often need protecting against. But, in this synthesis, a successful Wittig reaction was carried out even in the presence of a carboxylic acid, again by using an excess of the phosphonium ylid. We talk about carboxylic acid protection in the next chapter. In fact the carboxylate anion is itself a kind of protecting group as it discourages the rather basic Wittig reagent from removing a proton to form an enolate.



We have dealt with protecting groups for C=O, OH, and NH that resist nucleophiles, acids, and base. Sometimes functional groups need protecting against oxidation, and we finish our introduction to protecting groups with an example. During a synthesis of the bacterial product rapamycin, an epoxy alcohol needed converting to a ketone through a sequence that involves selective oxidation of only one of two hydroxyl groups. The group to be oxidized is there in the starting material, so it can be protected straight away. The protecting group (Bn) needs to be acid-stable, because the next step is to open the epoxide with methanol, revealing the second hydroxyl group. This then needs protecting—TBDMS was chosen, so as to be stable to hydrogenolysis, which deprotects the hydroxyl that we want to oxidize. Finally, oxidation gives the ketone.



In this chapter we have talked about most of the steps in this sequence, except the epoxide-opening reaction (for which read Chapters 17 and 18) and the oxidation step. Which reagent would a chemist choose to oxidize the alcohol to the ketone, and why? We shall now move on to look at oxidizing agents in detail.

Oxidizing agents

We dealt in detail earlier in the chapter with reducing agents and their characteristic chemoselectivities. Oxidizing agents are equally important, and in the chapter on electrophilic addition to alkenes we told you about peracids as oxidizing agents for C=C double bonds—they give epoxides. But

▶ In Chapter 37 you will find out that peracids also react with ketones, but that need not concern us here.

peracids do not react with alcohols: they are chemoselective oxidants of C=C double bonds only. Later in the book, you will meet more oxidizing agents, such as osmium tetroxide (OsO_4) and ozone (O_3)—these are also chemoselective for double bonds, because they react with the C=C π bond, and we shall leave them until Chapter 35. In this section we will be concerned only with oxidizing agents that oxidize alcohols and carbonyl compounds.

The most commonly used methods for oxidizing alcohols are based around metals in high oxidation states, often chromium(VI) or manganese(VII), and you will see that mechanistically they are quite similar—they both rely on the formation of a bond between the hydroxyl group and the metal. Another class of oxidations, those that use halogens, sulfur, or nitrogen in high oxidation states, we will deal with relatively briefly.

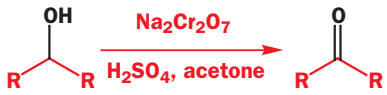
Oxidizing agents

Chemoselective for C=C double bonds[a]	Chemoselective for alcohols or carbonyl compounds
peracids, RCO_3H (Chapter 20)	Cr(VI) compounds
osmium tetroxide, OsO_4 (Chapter 35)	Mn(VII) compounds
ozone, O_3 (Chapter 35)	some high oxidation state Hal, N, or S compounds

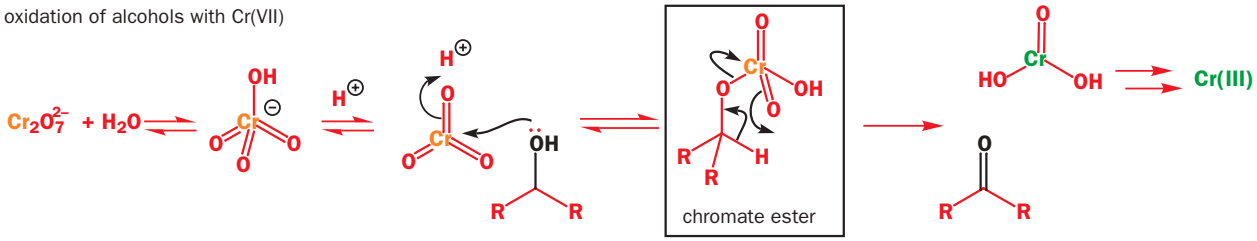
[a]not dealt with in this chapter.

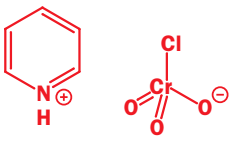
How to oxidize secondary alcohols to ketones

We start with this, because overoxidation is difficult. Provided the alcohol is not acid-sensitive, a good method is sodium dichromate in dilute sulfuric acid. This is usually added to a solution of the alcohol in acetone, and is known as the **Jones oxidation**.



The mechanism starts with the formation of $HCrO_4^-$ ions, that is, Cr(VI), from dichromate ion in solution. In acid, these form chromate esters with alcohols. The esters (boxed in black) decompose by elimination of the Cr(IV) $HCrO_3^-$, which subsequently reacts with a Cr(VI) species to yield 2 × Cr(V). These Cr(V) species can oxidize alcohols in the same way, and are thereby reduced to Cr(III) (the final metal-containing by-product). Cr(VI) is orange and Cr(III) is green, so the progress of the reaction is easy to follow by colour change.



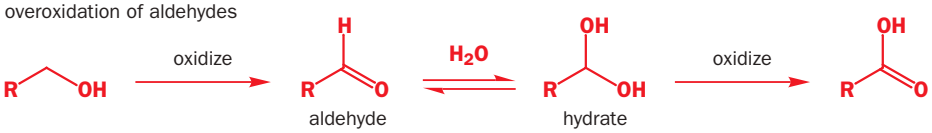


pyridinium chlorochromate, PCC

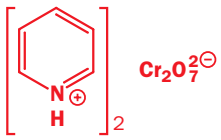
Chromic acid is best avoided if acid-sensitive alcohols are to be oxidized, and an alternative reagent for these is PCC (pyridinium chlorochromate), which can be used in dichloromethane.

How to oxidize primary alcohols to aldehydes

Aqueous methods like the Jones oxidation are no good for this, since the aldehyde that forms is further oxidized to acid via its hydrate. The oxidizing agent treats the hydrate as an alcohol, and oxidizes it to the acid.

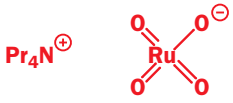


The key thing is to avoid water—so PCC in dichloromethane works quite well. The related reagent PDC (pyridinium dichromate) is particularly suitable for oxidation to aldehydes.



pyridinium dichromate, PDC

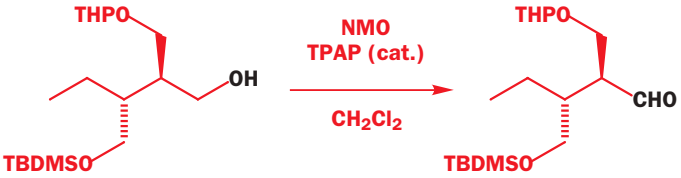
Some very mild oxidizing agents are being more and more widely used for the synthesis of very sensitive aldehydes. One of these is known as TPAP (tetra-*n*-propylammonium perruthenate, pronounced 'tee-pap').



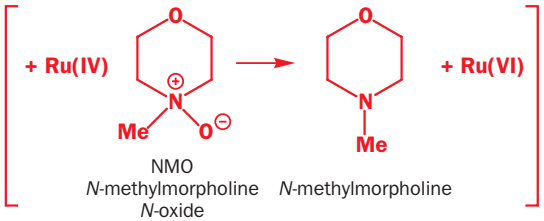
TPAP
tetrapropylammonium perruthenate

TPAP can be used catalytically, avoiding the large amounts of toxic heavy metal by-products generated by most chromium oxidations. The stoichiometric oxidant in this reaction is 'NMO' (*N*-methylmorpholine-*N*-oxide), which is reduced to the amine, reoxidizing the ruthenium back to Ru(VI).

▶ Notice that the two protecting groups, both acid-sensitive, survive these conditions very well.



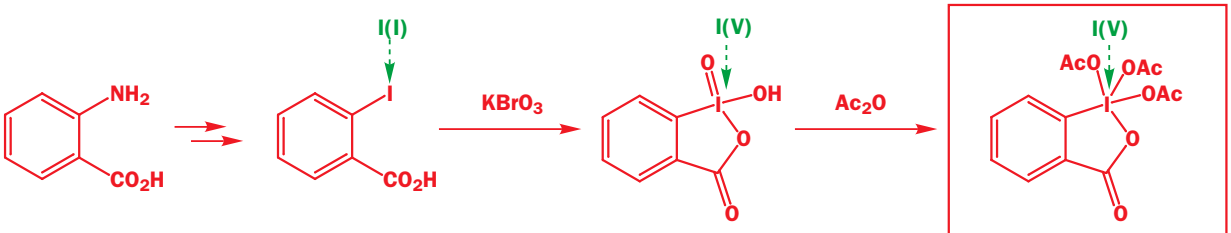
97% yield



NMO
N-methylmorpholine *N*-oxide

N-methylmorpholine

Another important modern reagent (discovered in 1983) is known as the **Dess–Martin periodinane**, and is an iodine compound that can be made from 2-iodobenzoic acid, itself available from anthranilic acid via the diazonium salt route, as described in the last chapter.



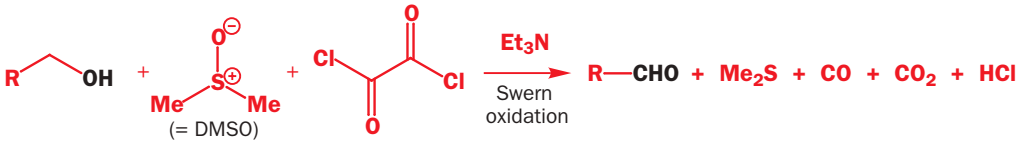
anthranilic acid

WARNING!
explosive when dry!

Dess–Martin periodinane—
handled and used in solution

It will oxidize even very sensitive alcohols to carbonyl compounds—few others, for example, would give a *cis*-α,β-unsaturated aldehyde from a *cis*-allylic alcohol without isomerizing it to *trans*, or producing other by-products.

We shall leave detailed discussion of one more method till much later, in Chapter 46 (p. 000), since the mechanism involves some sulfur chemistry you will meet there. But we introduce it here because of its synthetic importance. Known as the **Swern oxidation**, it uses a sulfoxide [S(IV)] as the oxidizing agent. The sulfoxide is reduced to a sulfide, while the alcohol is oxidized to an aldehyde.

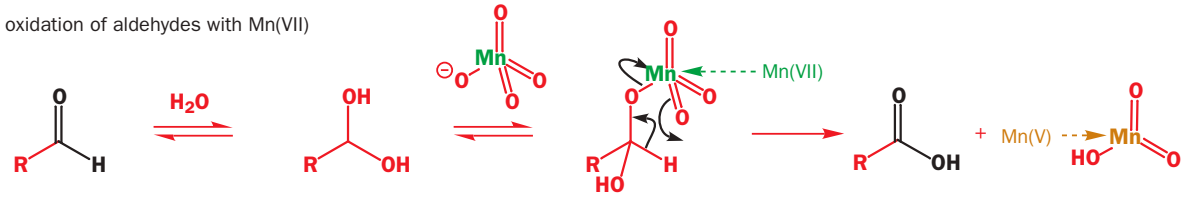


How to oxidize primary alcohols or aldehydes to carboxylic acids

This is the 'overoxidation' we were trying to avoid in oxidizing alcohols to aldehydes, and is best done with an aqueous solution of Cr(VI) or Mn(VII). Acidic or basic aqueous potassium perman-

ganate is often a good choice. From alcohols in acidic solution the mechanism follows very much the lines of the chromic acid mechanism; from aldehydes, the mechanism is very similar.

oxidation of aldehydes with Mn(VII)

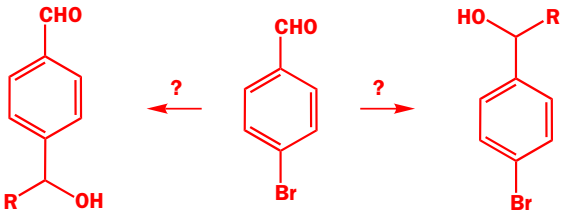


To conclude...

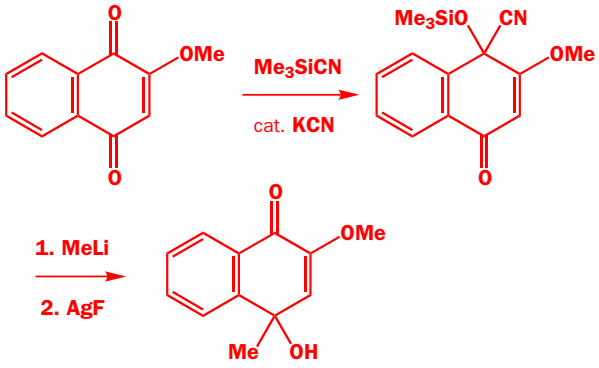
In the next chapter we will look at the ways in which the ideas and principles we have talked about in this chapter, and the reactions you have met in the 23 preceding ones, can be used in a practical way to make useful and interesting molecules. We will look at the synthesis of some of the molecules found in nature, such as hormones, plant-derived products with medicinal properties, and insect pheromones, as well as others that Nature has not made but that for one reason or another man has chosen to make.

Problems

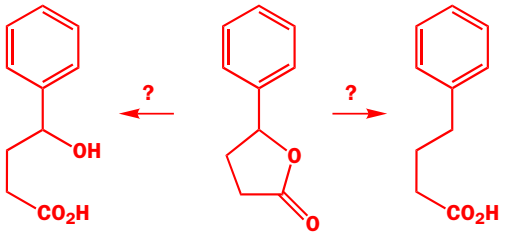
1. How would you convert this bromoaldehyde chemoselectively into the two products shown?



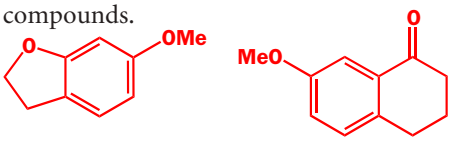
2. Explain the chemoselectivity of these reactions. What is the role of the Me_3SiCN?



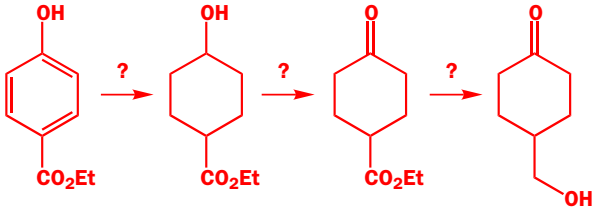
3. How would you convert this lactone selectively either into the hydroxy-acid or into the unfunctionalized acid?



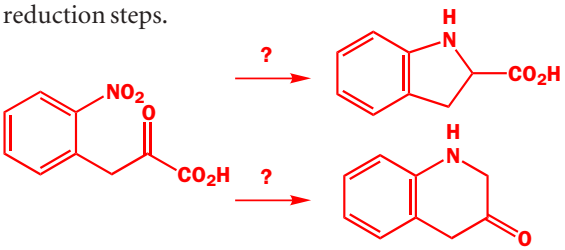
4. Predict the products of Birch reduction of these aromatic compounds.



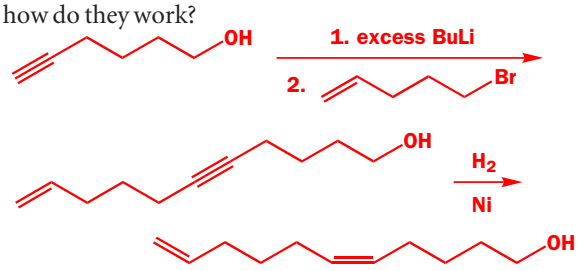
5. How would you carry out these reactions? In some cases more than one step may be needed.



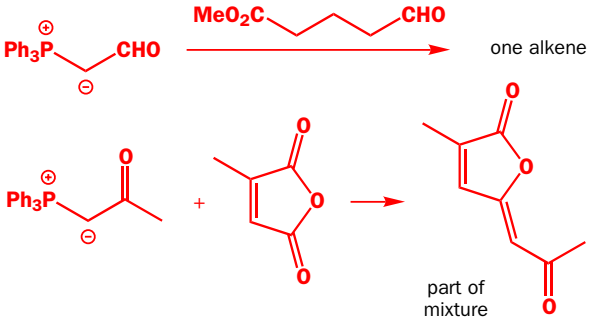
6. How would you convert this nitro compound into the two products shown? Explain the order of events with special regard to reduction steps.



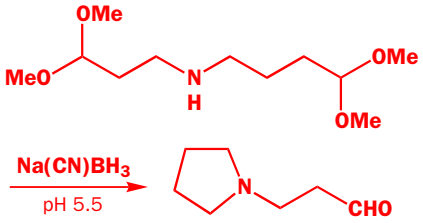
7. What kinds of selectivity are operating in these reactions and how do they work?



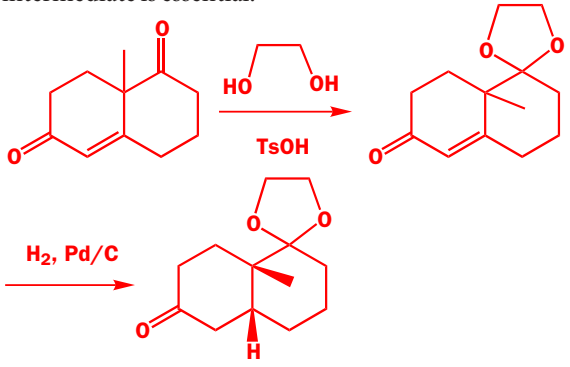
8. These two Wittig reactions (Chapter 14) give very different results. The first gives a single alkene in high yield (which?). The second gives a mixture from which one alkene can be separated with difficulty and in low yield. Why are they so different?



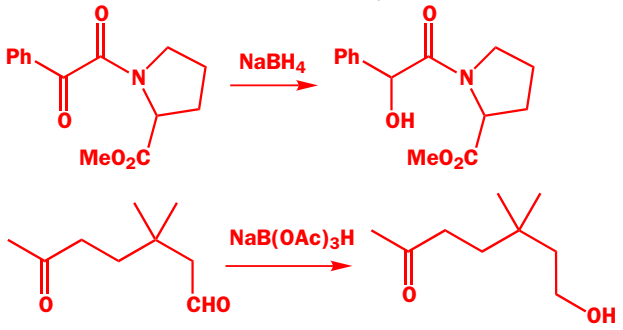
9. Why is this particular amine formed by reductive amination?



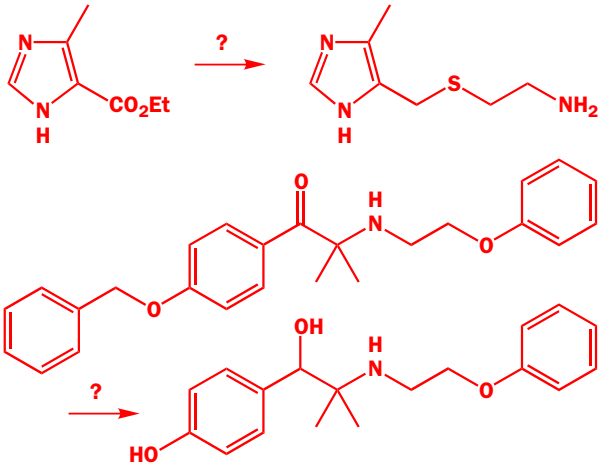
10. Account for the chemoselectivity of the first reaction and the stereoselectivity of the second. A conformational drawing of the intermediate is essential.



11. Account for the chemoselectivity of these reductions.



12. How would you carry out the following conversions? More than one step may be needed and you should comment on any chemoselective steps.



Synthesis in action

25

Connections

Building on:

- Carbonyl addition and substitution ch6, ch12, & ch14
- Mechanisms and catalysis ch13
- S_N1 and S_N2 mechanisms ch17
- Electrophilic aromatic substitution ch22
- Chemoselectivity ch24
- Protecting groups ch24
- Oxidation and reduction ch24

Arriving at:

- Introduction to synthesis
- More chemoselectivity
- Combining reactions from all previous chapters in practical applications
- Further protection of amines and carboxylic acids
- When to avoid protecting groups
- Synthesis of peptide hormones
- Solid phase chemistry

Looking forward to:

- Chemistry of enolates ch26–ch29
- Retrosynthetic analysis ch30
- Diastereoselectivity ch33–ch34
- Synthesis of aromatic heterocycles ch43
- Asymmetric synthesis ch45
- The chemistry of life ch49
- Natural products ch51
- Organic synthesis ch53

Introduction

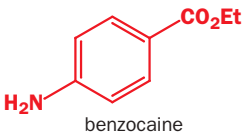
In the last chapter, you saw examples of groups of sequential reactions used together to construct more complex organic molecules. We call these sequences **syntheses**, and our aim in this chapter is to show you how the reactions you have met in the first 24 chapters of this book can be used to make molecules.

Why make molecules?

Making molecules, the job of the synthetic chemist, developed from a rather random process in the nineteenth century into a well-ordered and well-understood science during the course of the twentieth century. Syntheses can even be planned (and, in some specialized cases, executed) by computers. But why do it?

Historically, the first reason was to prove structures. If you make a compound by a series of known reactions, and understand what happened at each step, you can compare the compound of known structure that you have made with, say, a compound extracted from a plant whose structure you do not know. As methods like NMR arrived on the scene, this became less and less necessary—structures could be deduced spectroscopically. Instead chemists started making molecules in order to do things—to combat diseases, for example, or to develop new fragrances or materials. Many drugs are the product of 'fine tuning' of a naturally occurring compound to alter its properties and, in the course of the development of a drug, an enormous variety of compounds are made by chemists. Some drugs are themselves natural products, but are available in quantities too small to be widely used—so chemists are called upon to make them in gram, kilo, and eventually tonne quantities. Other chemists make molecules in order to find out about the molecules themselves, perhaps because the molecules have particular theoretical interest or because they shed light on the mechanism of a chemical (or biochemical) reaction. Finally, chemists make molecules simply because they are not there (yet) but are a challenge to make. Many of the great advances in the science of synthesis have occurred during the synthesis of natural products, and a frequent test of a new synthetic method is—can it be used to make a natural product?

In this chapter we will look in detail at a few syntheses of important molecules. We hope you will appreciate that the chemistry you encountered in the first 24 chapters is being used all the time in chemical and pharmaceutical labs, in hospitals, and in industrial plants across the world to make valuable, sometimes life-saving, compounds. We start with two simple compounds made from one starting material: toluene.



benzocaine

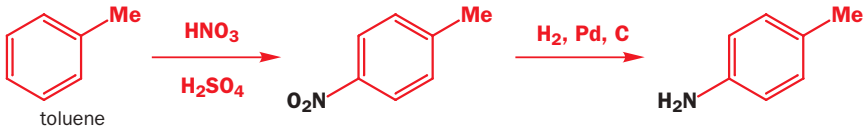
Benzocaine

Benzocaine is a local anaesthetic with a range of applications (see box). It is manufactured from toluene in a few steps using some quite simple chemistry.

Uses of benzocaine

Benzocaine has been used as a component of appetite suppressants; astringents; analgesics; burn and sunburn remedies; cough tablets, drops, and lozenges; haemorrhoidal creams, suppositories, and enemas; oral and gingival products for teething, toothaches, canker sores, and denture irritation; and in oral antibacterial agents; treatments for athlete's foot, corns, calluses, and warts; and sore throat sprays and lozenges.

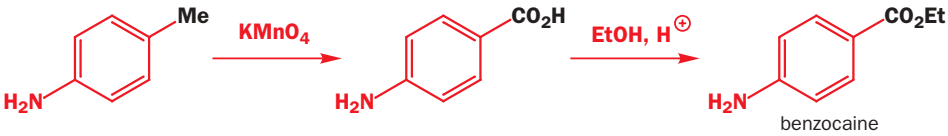
First, one of the classical reactions of aromatic chemistry: the nitration of toluene. The methyl group directs the nitration to the *para* position, so we get the right substitution pattern for benzocaine. But we also get the wrong oxidation levels: first, the nitro group needs reducing to NH_2: this can be done with catalytic hydrogenation (Chapters 22 and 24).



toluene

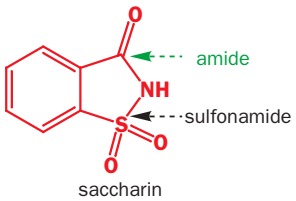
▶ Formation of the acid chloride followed by reaction with the alcohol would not be suitable here, for chemical reasons as well as economical ones. Why not?

Benzocaine needs an ester (CO_2Et) in place of our methyl group: an oxidation is needed, and the reagent used is $KMnO_4$. This rather odd-looking oxidation is worth remembering: $KMnO_4$ oxidizes aromatic methyl groups (in other words, methyl groups attached directly to benzene rings) to carboxylic acids. And, finally, the esterification: heating with an excess of ethanol in acid gives benzocaine.



benzocaine

▶ Notice that a synthesis is drawn out as a scheme showing starting materials, reagents, and products connected by reaction arrows. Intermediates that are formed but not isolated are usually shown [in square brackets]. Reagents shown on one arrow are all present at the same time. The most important are usually on top of the arrow—those underneath may be catalyst or solvent but this is not a universal convention. Conditions and yields may be added if important or interesting. We do not usually show mechanisms in the scheme but, if an explanation of an unusual reaction or selectivity is needed, then a mechanism might be included.



saccharin

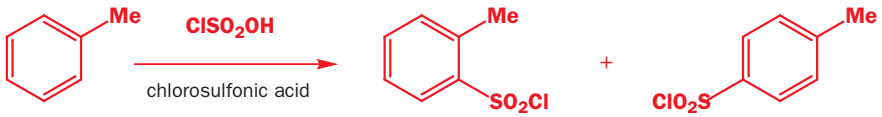
Saccharin

Saccharin is, of course, the famous artificial sweetener. It was discovered at Johns Hopkins University in 1879 in the days before disposable gloves. Ira Remsen (1846–1927) asked a research fellow Constantin Fahlberg (1850–1910) to oxidize a sulfonamide he had made. Fahlberg did so and found that evening that the food he was eating tasted remarkably sweet. Saccharin is a cyclic imide with a nitrogen atom acylated on one side by a sulfonic acid and on the other by a carboxylic acid.

■ Some of the reactions used in the synthesis were discussed in Chapter 22.

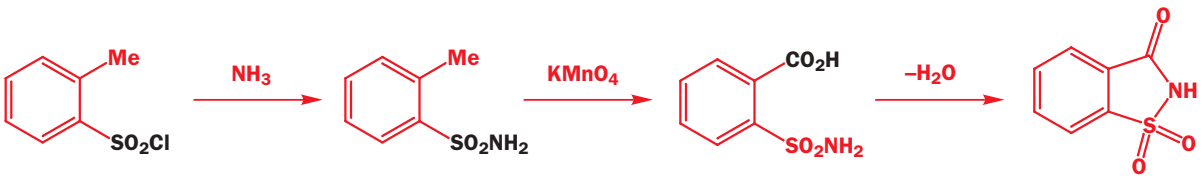
The first step in the synthesis of saccharin is an electrophilic substitution reaction, like the first step of the benzocaine synthesis, but this time we want the *ortho*-substituted product. Chlorosulfonic acid gives a mixture of *ortho* and *para* products—it is impossible to find conditions that completely avoid forming the *para*-toluenesulfonyl chloride. However, you may recognize an old friend here—the by-product is, of course, TsCl. You may have wondered why we always use TsCl and not $PhSO_2Cl$ to make OH into a leaving group: now you know.

■ The details of this reaction are analysed in Chapter 22.



ortho-toluenesulfonyl chloride *para*-toluenesulfonyl chloride = TsCl

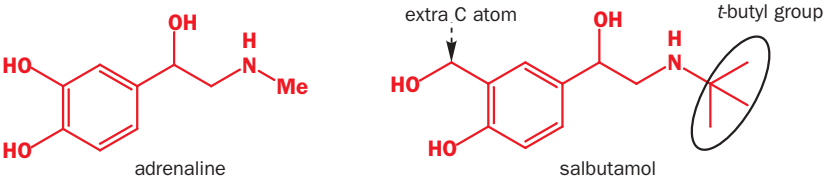
The sulfonyl chlorides react with ammonia to give sulfonamides. Notice that this compound's aromatic methyl group is at the wrong oxidation level, so we again use $KMnO_4$ to make the acid before dehydrating to give saccharin.



saccharin

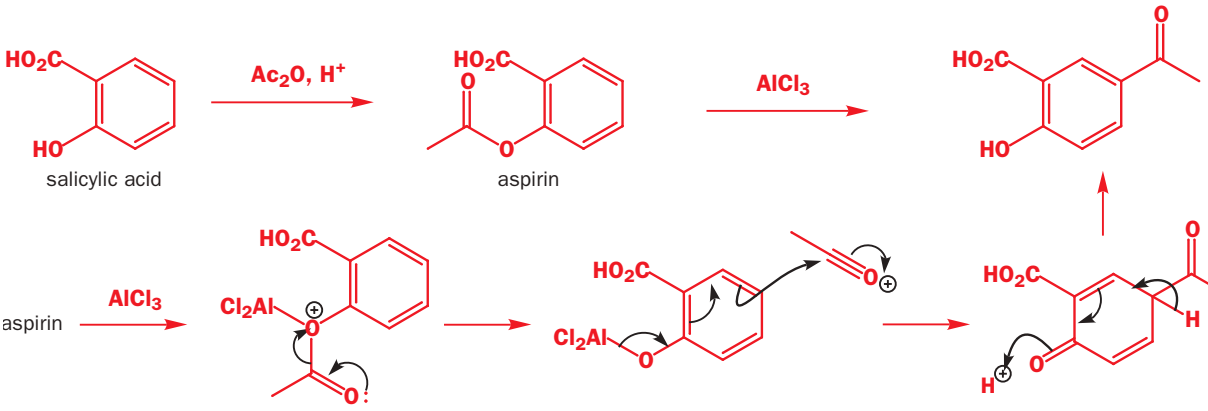
Salbutamol

Anti-asthma drugs work by dilating the air passages of the lungs, releasing the constriction that characterizes the disease. Salbutamol does this by imitating the action of the hormone adrenaline (epinephrine). Adrenaline has other effects—it increases heart rate for example—but the medicinal chemists at Glaxo working on asthma found that adding on the extra carbon atom avoided dangerous side-effects on the heart. The *t*-butyl group increases the stability of the drug, so its effects last longer.



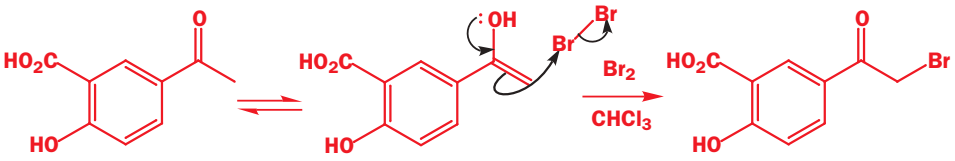
adrenaline salbutamol

Salbutamol is made from aspirin, itself simply the acetate ester of the natural product salicylic acid, by a series of substitution reactions. The first is a Friedel–Crafts acylation (an electrophilic substitution) in which aspirin itself is the acylating agent: it is an isomerization in which the acetyl group gets transferred from O to C. Acylation occurs *para* to the electron-donating alkoxy substituent, and gives this ketone.

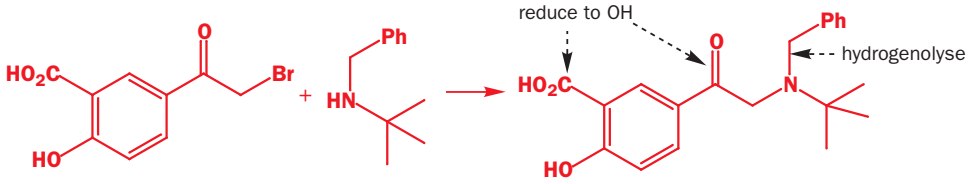


Because this is an unusual Friedel–Crafts acylation, we think it worthwhile to draw a mechanism in the description of a synthesis. This is just such a situation as we described above. Another electrophilic substitution occurs when this ketone reacts with bromine via its enol (Chapter 21).

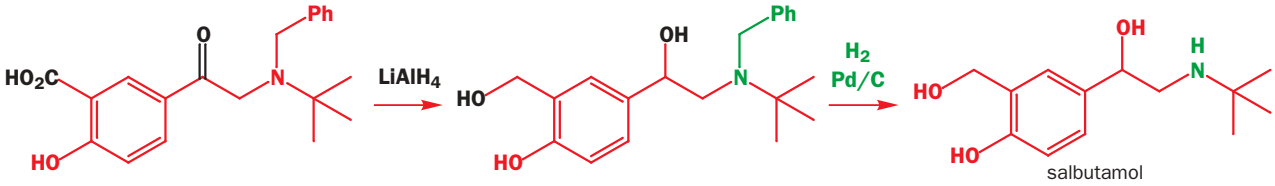
▶ It is given another name, the **Fries rearrangement**.



Next, a nucleophilic substitution reaction at saturated carbon. α-Halo ketones are excellent electrophiles and react rapidly with nucleophiles, such as this secondary amine, by the S_N2 mechanism (Chapter 17). All that remains is to reduce the ketone and the acid to alcohols and remove the benzyl protecting group (both discussed in Chapter 24).

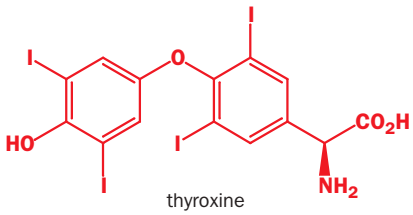


$LiAlH_4$ is ideal for the reduction of both the CO_2H group and the ketone as it carries out both reductions in a single step. The other reduction is a hydrogenolysis of the benzyl group, for which we need catalytic hydrogenation.

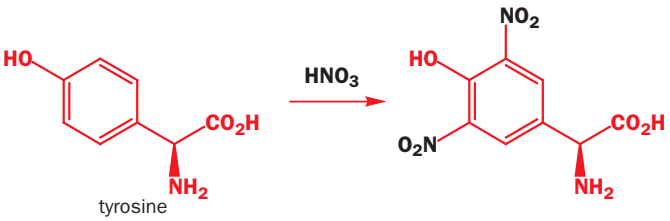


Thyroxine

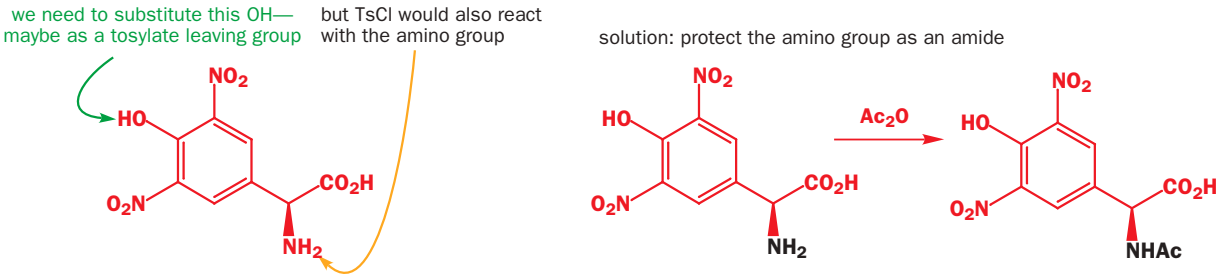
Salbutamol works by imitating the action of a hormone: thyroxine *is* a hormone—it is part of the body's control over its metabolic rate. Lack of thyroxine (or rather, of the iodine needed to make it) causes hyperthyroidism, or goitre. Our next synthesis is one that has been used on an industrial scale for the manufacture of synthetic thyroxine (identical with, but less macabre than, naturally extracted thyroxine).



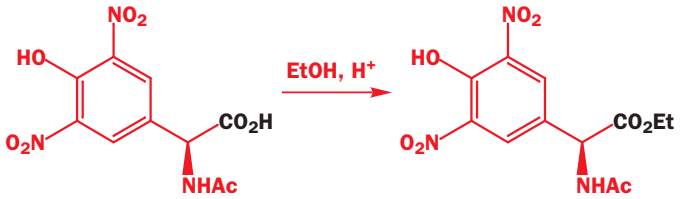
Thyroxine has two aromatic rings, and you should be prepared to draw upon what you learned about aromatic chemistry in Chapters 22 and 23. It is also an amino acid and, in order to make the synthesis as cheap as possible, the chemists at Glaxo who developed the method used the amino acid tyrosine as a starting material. Nitration of tyrosine puts two nitro groups *ortho* to the OH group in an electrophilic aromatic substitution (make sure that you understand why!).



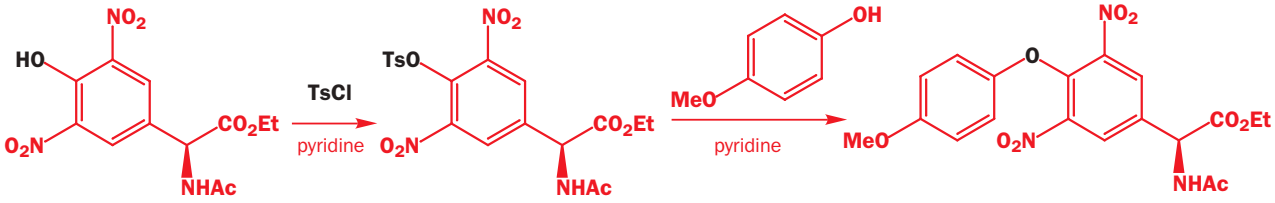
These make the aromatic ring electron-poor, ready for a nucleophilic aromatic substitution that will introduce the other aromatic ring of the target. We need to displace OH, but OH^- is a bad leaving group, so we must first make it into a tosylate. The trouble is—there is a free amine in the starting material and we do not want that to react with the TsCl. The answer—as you should be able to predict after Chapter 24—is to protect the amine.



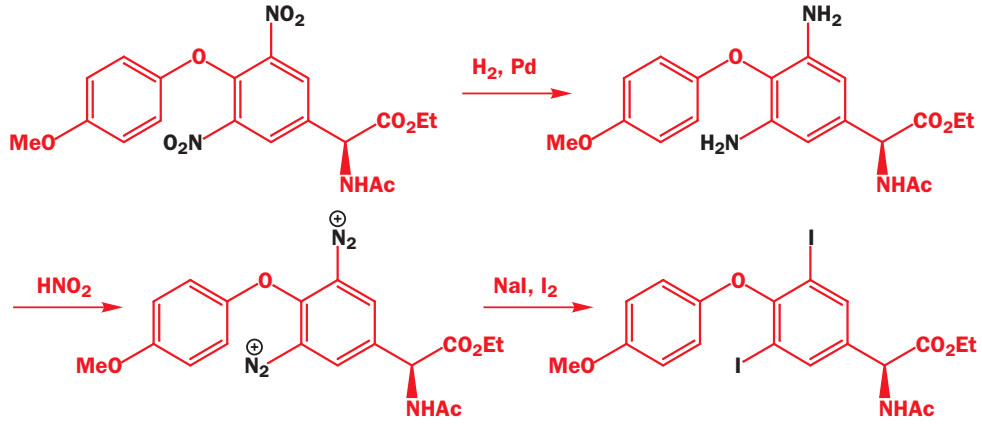
We haven't yet discussed amine protection (that will come later in this chapter) but, since it is the amino group's nucleophilicity that is the problem, it makes sense to react it with an acylating agent: an amide is much less nucleophilic than an amine because the nitrogen's lone pair is involved in conjugation with the carbonyl group. The same method was used to reduce the nucleophilicity of aromatic amines in bromination (Chapter 22). The carboxylic acid also needs protecting, and it is made into an ethyl ester.



Now the tosylation—under the usual conditions—followed by the nucleophilic aromatic substitution (Chapter 23). The leaving group is *ortho* to two electron-withdrawing groups, and so the substitution pattern is right for nucleophilic aromatic substitution. The nucleophile is 4-methoxyphenol, deprotonated by pyridine.

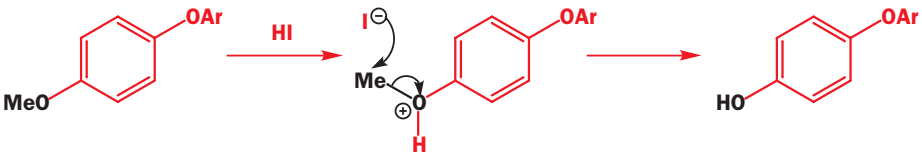


The nitro groups need replacing by iodine atoms, and you should not be surprised that they were reduced to amino groups by hydrogenation over palladium and then diazotized. Sodium iodide substitutes I^- for N_2^+.

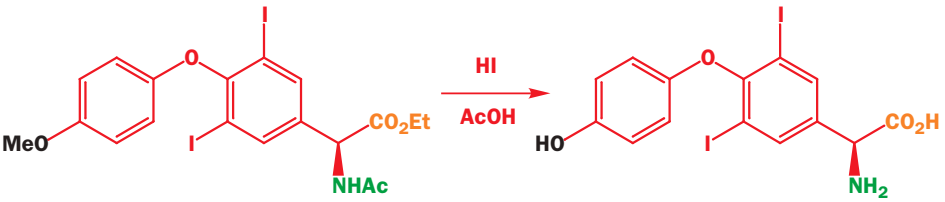


The methyl ether is really a protected version of the phenolic OH we need in thyroxine, and its deprotection uses a method that you met in Chapter 24. Most ethers are very hard to cleave—phenyl

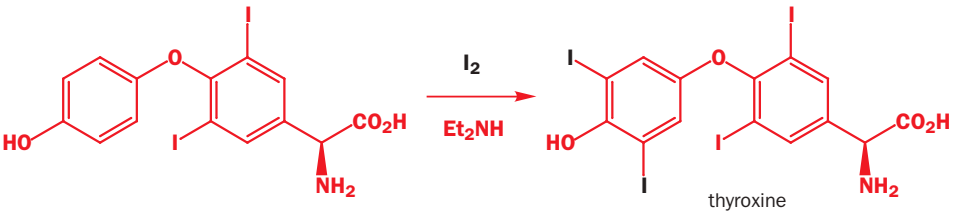
ethers are a bit easier, because phenols are reasonable leaving groups. HI in AcOH protonates the oxygen atom, and now attack of the good nucleophile I^- on the electrophilic Me centre can kick out the phenol.



Remarkably, the same conditions hydrolyse the amide- and ester-protecting groups too—very useful for an industrial process where every step means another reaction vessel.



Finally, electrophilic substitution on the left-hand ring in the manner of the first nitration step puts in the third and fourth iodine substituents of thyroxine. Notice that the free O^- (the phenol is ionized with Et_2NH) group is more activating (electron-donating) than the ether oxygen atom.



thyroxine

This synthesis shows how important electrophilic substitution in aromatic compounds is in industrial processes. It involves four separate such reactions as well as three nucleophilic aromatic substitutions. The chemistry of Chapters 22 and 23 is well represented here.

Muscalure: the sex pheromone of the house-fly

Many insects attract a mate by releasing a volatile organic compound known as a pheromone. Pheromones are highly specific to species, and provide a cunning means of controlling pests: place a pad of cotton wool soaked in male pheromone inside a trap, and in drop all the female pests—no next generation. If insect control is to rely on a supply of the pheromone, that supply has to be synthetic—it takes enormous numbers of squashed insects to provide even a few milligrams of most pheromones.

▶ The name muscalure comes from the generic name of the house-fly, *Musca*.

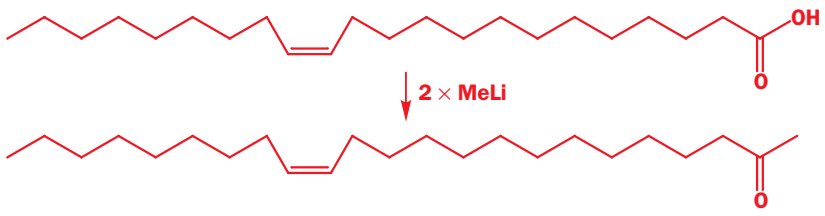
We will start by looking at two syntheses of the very simple pheromone of a very common insect—the house-fly. The pheromone, known as **muscalure**, is a *Z*-alkene.

muscalure, the pheromone of the house-fly

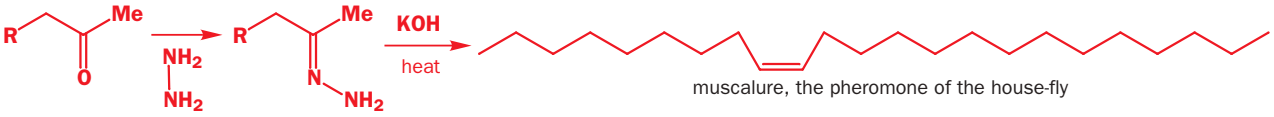
■ You met this reaction in Chapter 12 as one of the few ways of adding a nucleophile to a carboxylic acid derivative to give a ketone.

One approach, used by some American chemists in the early 1970s, was very simple. These chemists noted the similarity between the structures of muscalure and the fatty acid known as erucic acid, which is abundant in rapeseed oil, and decided to make muscalure from erucic acid. They first reacted the acid with two equivalents of methyllithium—the first equivalent deprotonates the acid to make a lithium carboxylate salt, while the second reacts with the lithium carboxylate to make a ketone.

erucic acid, a fatty acid extracted from rapeseed oil

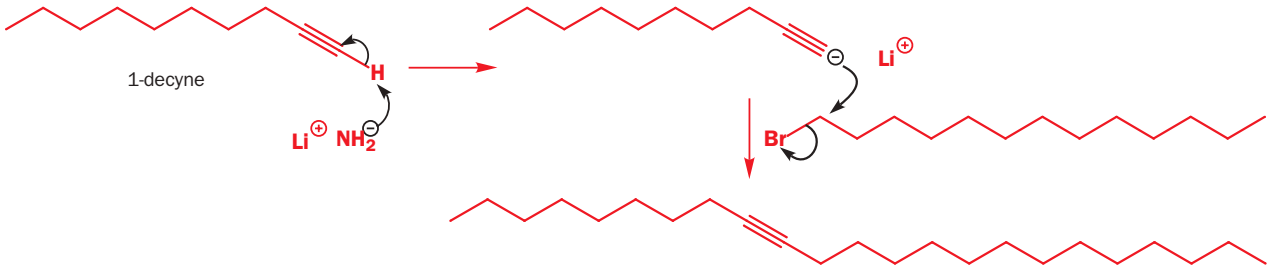


The next step is to remove the ketone functional group. You met a few ways of doing this in the last chapter; here the method chosen was to make a hydrazone and heat in the presence of base. Muscalure is the product.

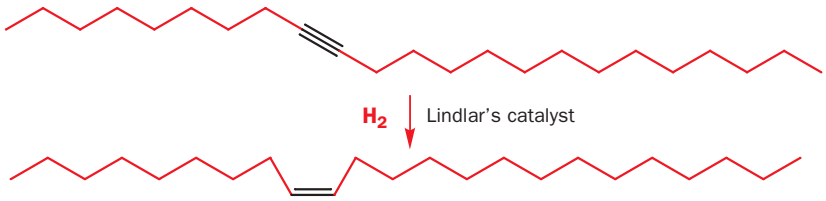


muscalure, the pheromone of the house-fly

In 1977, some Russian chemists made the same compound by a different route. They chose to introduce the *Z* double bond by hydrogenation of an alkyne over Lindlar's catalyst. To make the alkyne they needed, they took 1-decyne, treated it with $LiNH_2$ to remove the acidic terminal proton, and reacted the anion with an *n*-alkyl bromide.

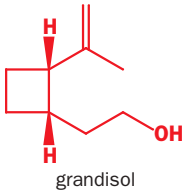


By stirring the alkyne with Lindlar's catalyst under an atmosphere of hydrogen they were able to make muscalure.



■ In Chapter 24 you saw that Lindlar's catalyst is a weak catalyst that only allows hydrogenation of alkynes, and gives *Z* double bonds.

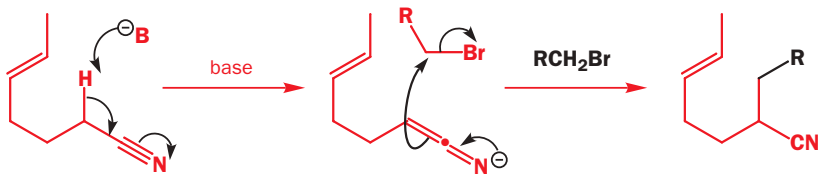
Grandisol—the sex pheromone of the male cotton boll weevil



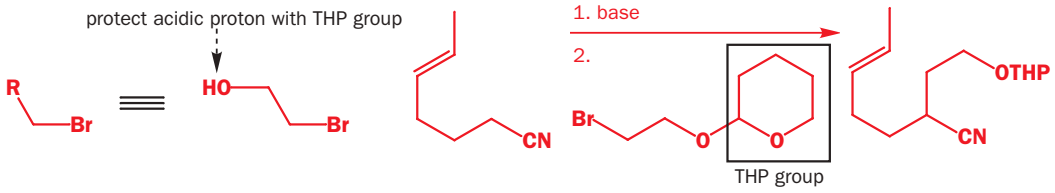
grandisol

House-flies are irritating and a minor health hazard, but the cotton boll weevil is an enormously destructive pest of the American cotton crop and is responsible for vast economic losses. The weevil has a pheromone called grandisol. The structure and synthesis of grandisol are rather more complicated than the syntheses of muscalure, but *all the reactions are ones you have met in the first 24 chapters of the book.*

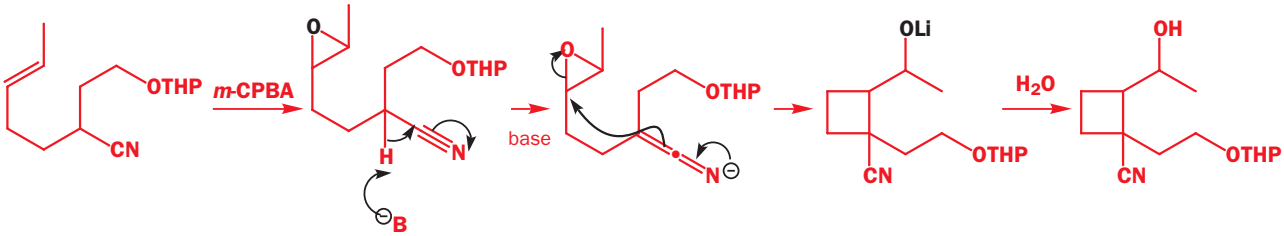
You saw in Chapter 21 how carbonyls form enolates when they are treated with base. On p. 000, you met nitriles doing something very similar, and the first step of the grandisol synthesis is the reaction of the 'enolate' of a nitrile with an electrophile—an alkyl bromide.



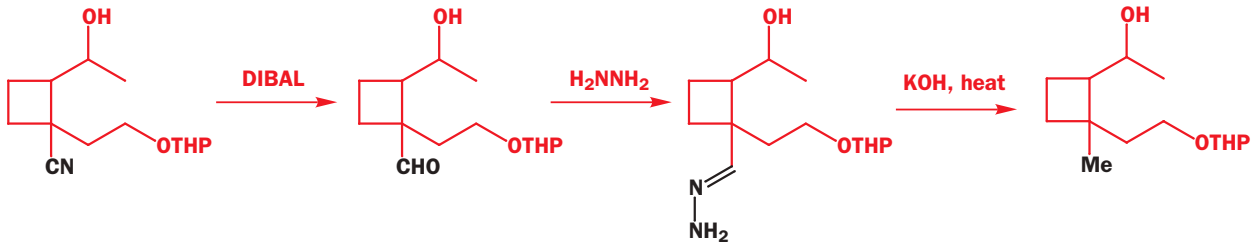
The electrophile required carries a hydroxyl group. But this is no good because the acidic OH proton will react with the basic enolate—we need a protecting group, and the one chosen here was THP. So, here is the first step presented in a way that you will find useful. Because the base is added first and the alkyl bromide afterwards when all the base has reacted, the synthesis is written as : 1. base; 2. RCH_2Br.



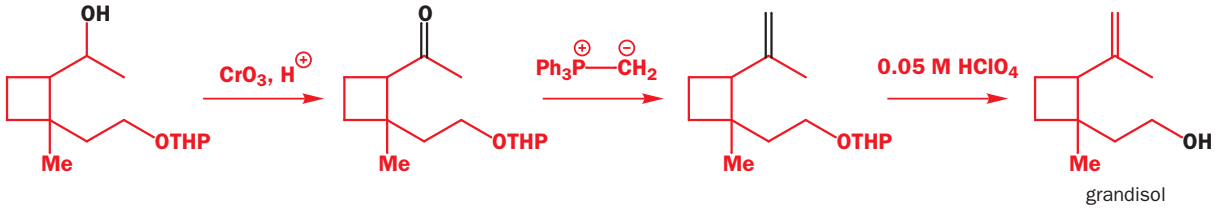
Next, the double bond is made into an epoxide with *m*-CPBA. Epoxides react with nucleophiles, and this is the way that the four-membered ring of grandisol was formed: the nitrile still has a proton next to it, and a strong base will remove this proton as before to give an 'enolate'. The enolate reacts with the epoxide to give a four-membered ring.



You can now clearly see the similarity with our 'target molecule', grandisol, but there are several more steps to carry out yet. The nitrile needs to be got rid of completely—we showed you a few ways of getting rid of functional groups in the last chapter, and the one used here was the Wolff–Kishner reduction of an aldehyde. The aldehyde comes from reduction of the nitrile with DIBAL.



Now we need to put in the C=C double bond, using a Wittig reaction. The Wittig reaction turns aldehydes or ketones into alkenes, turning the C=O bond into a C=C bond (Chapter 14). Of the many methods for oxidizing secondary alcohols to ketones (Chapter 24), these chemists chose CrO_3. Finally, the protecting group needs to come off. THP-protected alcohols are acetals, and THP groups are removed in aqueous acid: the product is grandisol.



We hope that you can see from this example that all the steps in this important synthesis use chemistry that you have already met. The art in synthesis is to put the steps together in the right order, and we aren't asking you to think about that (that can wait until Chapter 30)—at this stage see these syntheses as a way of revising what you have already learned.

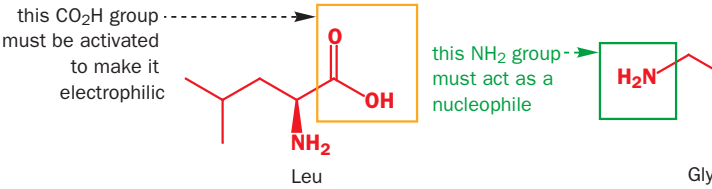
▶ Neither at this stage are we asking you to think about the stereochemistry of the molecules we are making. Grandisol is, in fact, a single diastereoisomer and a single enantiomer, as shown on p. 000, and this synthesis makes a racemic mixture of a single diastereoisomer. Why the product is racemic should be evident to you after reading Chapter 16; why it gives a single diastereoisomer you might like to think about once you have read beyond Chapter 33.

Peptide synthesis: carbonyl chemistry in action

In this part of the chapter we will talk in detail about the synthesis of a single class of biologically important molecules, peptides. In doing so, we will introduce you to protecting groups for two more important functional groups: amines and carboxylic acids. The ability to control the reactivity of these groups is vital to the controlled synthesis of peptides. This field has grown vastly since the introduction of the Z or Cbz protecting group (which you will meet shortly) in 1932, and today machines can be programmed to synthesize peptides automatically.

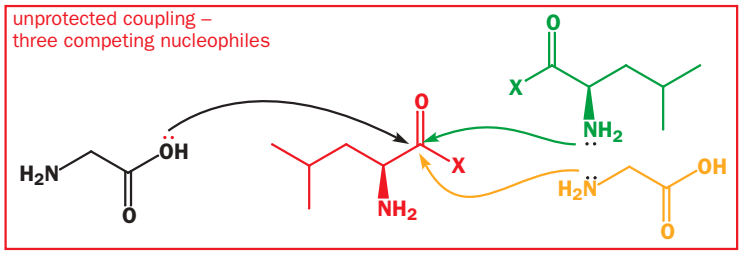
Let's start by thinking how you might react two amino acids together, to make a dipeptide—leucine and glycine, for example. If we want the NH_2 group of alanine to react with the CO_2H group of glycine we will first have to activate the carboxylic acid towards nucleophilic substitution—by making the acyl chloride, say, or a particularly reactive ester.

■ The names, structures, and abbreviations for the natural amino acids are in Chapter 49.



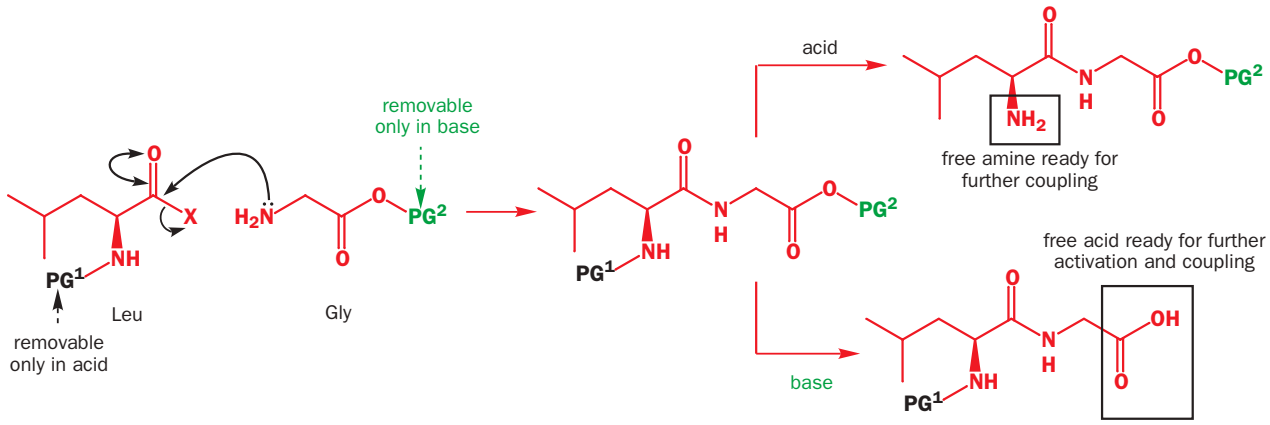
▶ In fact, the use of acyl chlorides in peptide synthesis is rare because of the potential for unwanted side-reactions, including racemization and dimerization to form by-products known as diketopiperazines. We will represent our activated acid as RCOX, where X is some other good leaving group such as a phenol.

The main problem, though, is that there is another free CO_2H, which could react with the COX group to form an anhydride, and two different free amines, either of which might react, giving both LeuLeu (which we don't want) and LeuGly (which we do).



For this reason, we need to protect both the NH_2 group of leucine and the CO_2H group of glycine. What sort of protecting groups do they need to be? We will need to be able to take them off again once they have done their job, so there is no point using, say, an amide to protect the amine since we would have great difficulty hydrolysing the amide in the presence of the amide bond we are trying to form. Ideally, not only do we want the protecting groups to be removable under mild conditions that will not destroy the rest of the molecule, but we want two groups (one for each of NH_2 and CO_2H) which we can take off under *different* conditions. We then have the opportunity to modify either end of the dipeptide at will.

A good choice for a pair of conditions might be acid and base—we might protect the NH_2 group with a protecting group we can remove only in acid, and the CO_2H group with protection we can remove only in base.



The Cbz protecting group—oxytocin

We introduced the dipeptide LeuGly as an example because it forms the *C*-terminus of the peptide hormone oxytocin.

H_2N–Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly–$CONH_2$
oxytocin

Synthetic hormones

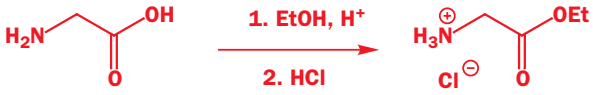
Oxytocin is a hormone involved in controlling the onset of labour in women and the subsequent release of milk. It was the first peptide hormone to be synthesized, in 1953, and the synthetic 'version' of the hormone, Syntocinon (identical, of course, with the 'natural' version isolated from human placentas, though probably purer), is regularly used in modern obstetrics to induce labour in women whose babies are overdue. Several other peptide hormones have been synthesized in the lab, and we will come back to one of them, gastrin, shortly.

▶ ***C*-terminus** means the end of the peptide that carries the terminal CO_2H group. The other end, carrying the NH_2 group, is the ***N*-terminus**. By convention, we write the *N*-terminus on the left and the *C*-terminus on the right. The structure of oxytocin is represented here in terms of the three-letter codes for amino acids—there is a full list in Chapter 49.

■ du Vigneaud won the Nobel Prize for Chemistry in 1955 for his work on the synthesis of peptides.

■ Problem 12.5 depends on understanding this.

The first step in the synthesis of oxytocin is indeed the coupling of glycine (through its amino group) with leucine. This is how it was done by du Vigneaud and Bodanszky. First, the carboxylic acid of the glycine was protected as an ethyl ester. Making an ester is the obvious way to stop CO_2H groups interfering as acids or as nucleophiles. However, simple methyl and ethyl esters may pose problems—they can still react with such nucleophiles as amines. Ethyl esters of amino acids are therefore stable only if the NH_2 group is protected. The glycine ethyl ester had to be stored as its hydrochloride salt: in effect, the $-NH_2$ group is 'protected' as $-NH_3^+$.

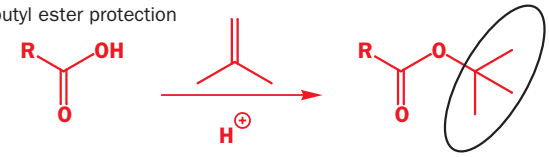


glycine — glycine ethyl ester hydrochloride

▶ This method is preferable in this case to the usual way of making esters—from acyl chloride plus alcohol—since steric hindrance makes that a very slow reaction with *t*-butanol.

If du Vigneaud and Bodanszky had wanted a carboxylic-acid-protecting group that was more stable towards attack by nucleophiles, they could have made a *t*-butyl ester with isobutene in sulfuric acid.

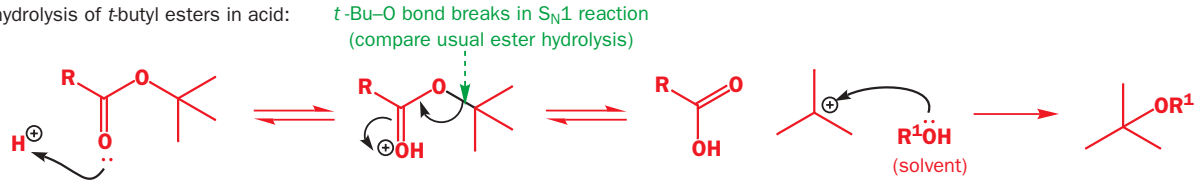
t-butyl ester protection



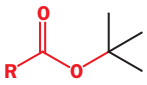
steric hindrance protects the carbonyl group from attack

Steric bulk means that *t*-butyl esters are resistant to nucleophilic attack at the carbonyl group, and that includes hydrolysis under basic conditions (nucleophilic attack by HO^-). But they do hydrolyse relatively easily in acid, because the mechanism of hydrolysis of *t*-butyl esters in acid is quite different. It does not involve nucleophilic attack at the carbonyl group and is a favourable S_N1 reaction at the *t*-butyl group (Chapter 17).

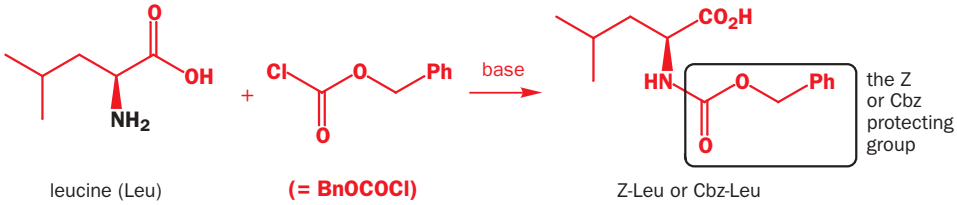
hydrolysis of *t*-butyl esters in acid:



This is a good point to continue our growing table of protecting groups started in Chapter 24. We need only one new entry for *t*-butyl esters.

Protecting group	Structure	Protects	From	Protection	Deprotection
***t*-butyl ester** (CO_2Bu-*t*)		carboxylic acid (RCO_2H)	bases, nucleophiles	isobutene, H^+	H_3O^+

In the event, the chemists needed a group that they could later react with ammonia to make the amide that is present in oxytocin. They also wanted a group that was stable to mild acid—so they chose the ethyl ester. As for the leucine residue, it had to have its NH_2 group protected using a base-stable protecting group, because base would be needed to release the NH_2 group of the glycine hydrochloride salt. The group that was used is one of the most important nitrogen-protecting groups and is known, rather uninformatively, as the **Z group** (also known as **Cbz**, or carboxybenzyl). Cbz (Z) groups are put on by treating with benzyl chloroformate (BnOCOCl) and weak base.

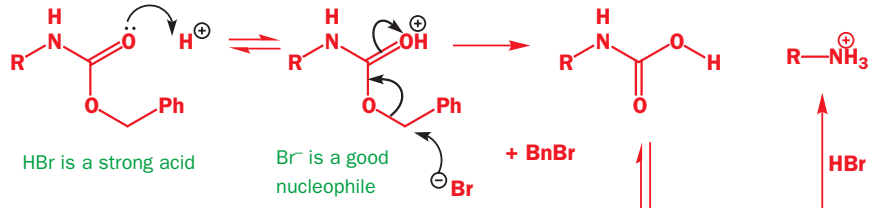


leucine (Leu) (= BnOCOCl) Z-Leu or Cbz-Leu

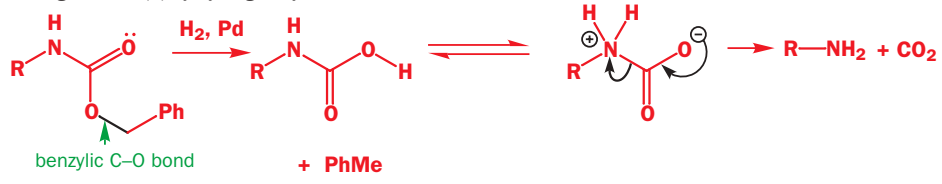
Cbz-protected amines behave like amides—they are no longer nucleophilic, because the nitrogen's lone pair is tied up in conjugation with the carbonyl group. They are resistant to both aqueous acid and aqueous base, but they have, to use the analogy we developed in the last chapter, an Achilles' heel or safety catch—the benzyl ester. The same conditions that removed benzyl ethers in Chapter 24 will remove Cbz: HBr or hydrogenolysis.

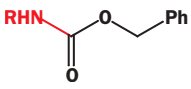
▶ You can tell the difference between Z as a protecting group and *Z* as a label for the stereochemistry of an alkene because the latter is in *italics*. It's less confusing to use Cbz for the protecting group and *Z* for the alkene.

cleavage of Cbz (Z) in HBr/AcOH

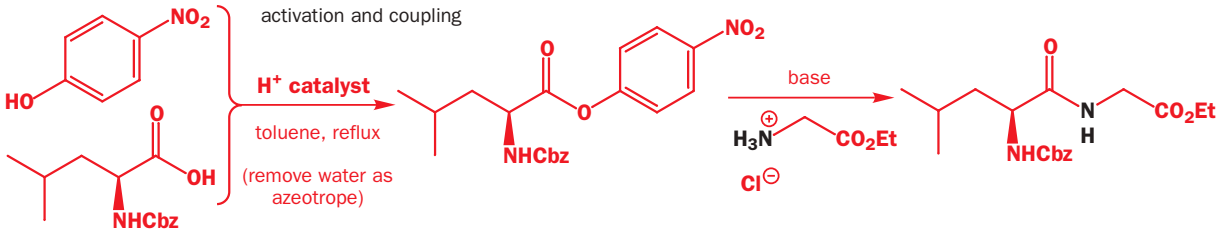


cleavage of Cbz (Z) by hydrogenolysis

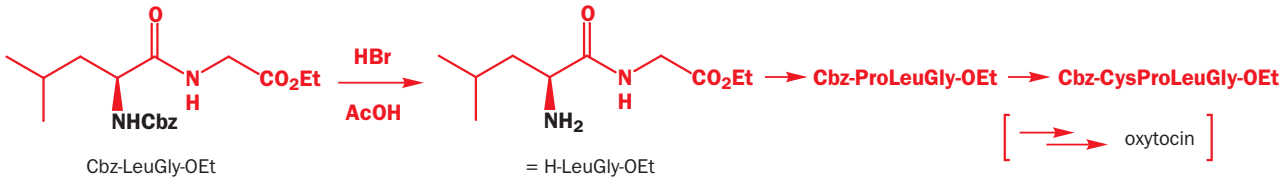


Protecting group	Structure	Protects	From	Protection	Deprotection
Cbz (Z) (OCOBn)		amines	electrophiles	BnOCOCl, base	HBr, AcOH or H_2, Pd

The Cbz-protected leucine next had to be activated so that it would react with the glycine. The acyl chloride won't do as it is unstable, and a common alternative in peptide chemistry is to make a *p*-nitrophenyl or 2,4,6-trichlorophenyl ester. Phenoxide, especially when substituted with electron-withdrawing substituents, is a good leaving group, and Cbz-leucine *p*-nitrophenyl ester reacts with the glycine hydrochloride ethyl ester in the presence of a weak base (triethylamine, to release the glycine's NH_2 group). Notice the chemoselectivity in this step—the glycine's NH_2 group has three carbonyl groups to choose from, but reacts only with the most electrophilic—the one bearing the best leaving group.



The dipeptide is now coupled—but is still protected. Deprotection (HBr/AcOH) gave the HCl salt of LeuGly ethyl ester for further reaction. The rest of the peptide was built up in much the same way—each amino acid being introduced as the Cbz-protected *p*-nitrophenyl ester before being deprotected ready for the next coupling, until all nine of oxytocin's amino acids had been introduced.

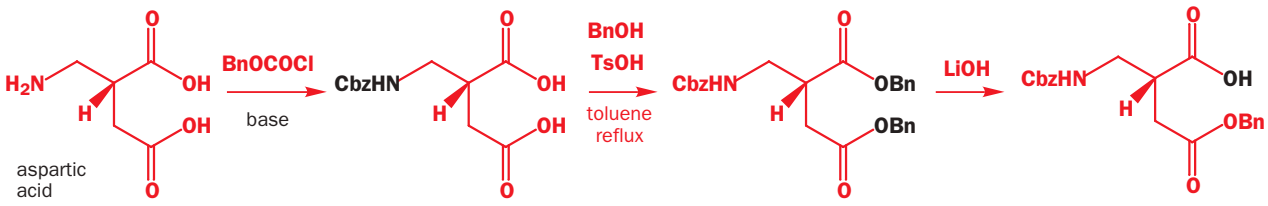


The *t*-Boc protecting group—gastrin and aspartame

H_2N–Tyr-Met-Asp-Phe–$CONH_2$
gastrin *C*-terminal tetrapeptide

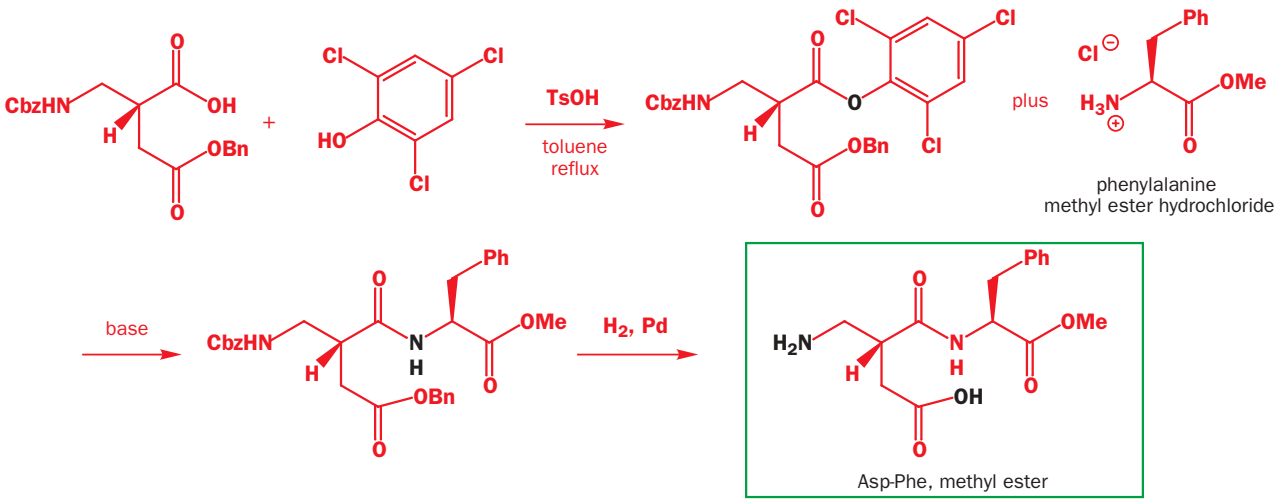
Gastrin is a hormone released from the stomach that controls the progress of digestion. Early work on the hormone showed that only the four *C*-terminal amino acids of the peptide were necessary for its physiological activity.

The synthesis starts with the coupling of two more amino acids: aspartic acid and phenylalanine. As you would expect, the carboxylic acid group of phenylalanine is protected, this time as a methyl ester, and the NH_2 group of aspartic acid is protected as a Cbz-derivative. Since aspartic acid has two carboxylic acid groups, one of these also has to be protected. Here is the method—first the Cbz-group is put on; then both acids are protected as *benzyl* esters. Then just one of the benzyl esters is hydrolysed. It may seem surprising to you that this chemoselective hydrolysis is possible, and you could not have predicted that it would work, without trying it out in the lab.



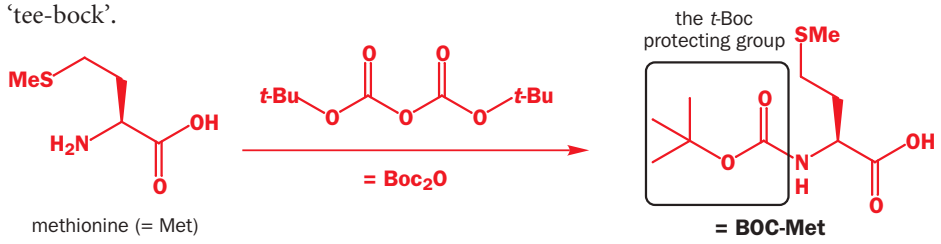
■
Again—note the chemoselectivity! Phenylalanine's NH_2 group attacks only one of the four carbonyl groups in this molecule.

The protected acid is activated as its 2,4,6-trichlorophenyl ester, ready for coupling with the phenylalanine methyl ester in base. Now you see why the benzyl ester was chosen to protect Asp's side-chain carboxylic acid group—hydrogenolysis can be used to cleave both the Cbz-group and the benzyl ester at the same time.

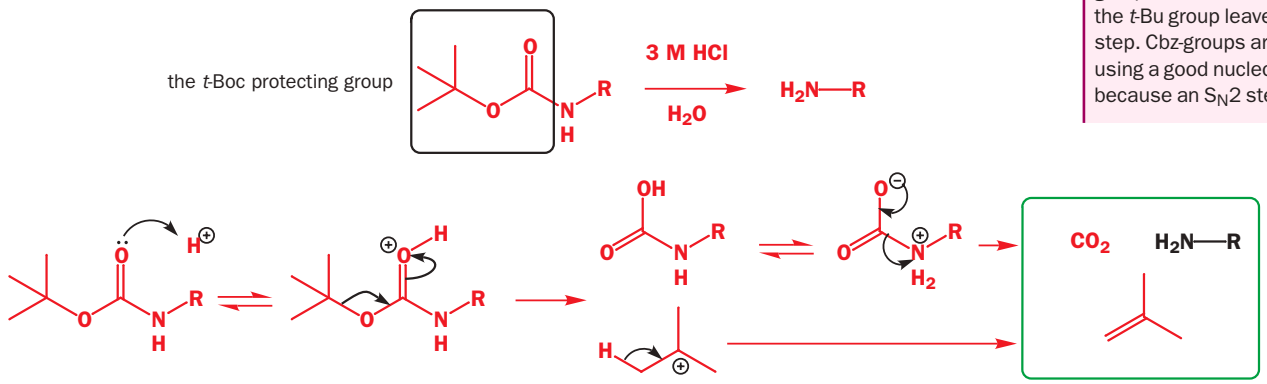


At this point in one synthesis of the tetrapeptide in the laboratories of Searle, the American pharmaceutical company, a remarkable discovery occurred. The AspPhe methyl ester was accidentally found to taste sweet: extremely sweet—about 200 times as sweet as sucrose. AspPhe is now known as aspartame, marketed under the brand name Nutrasweet.

The next amino acid in the peptide is methionine, and it will of course need *N*-protecting and *C*-activating. The *N*-protecting group used this time was different—still a carbamate, not Cbz or Z but *t*-Boc (or just Boc or BOC)—standing for *t*-butyloxycarbonyl and pronounced 'bock' or 'tee-bock'.

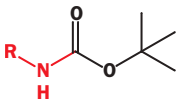


Like Cbz, the *t*-Boc group is a carbamate protecting group. But, unlike Cbz, it can be removed simply with dilute aqueous acid. Just 3M HCl will hydrolyse it, again by protonation, loss of *t*-butyl cation, and decarboxylation.

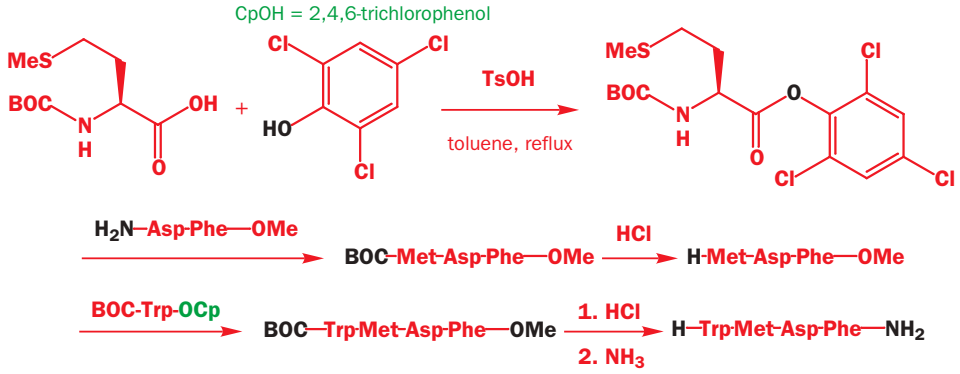


▶ The mechanism for this hydrolysis is comparable to the acid-catalysed cleavage of Cbz groups, but remember that here the *t*-Bu group leaves in an S_N1 step. Cbz-groups are cleaved by using a good nucleophile, Br^-, because an S_N2 step is involved.

Base, on the other hand, cannot touch the *t*-Boc group—the carbonyl group is too hindered to be attacked even by OH^-, and *t*-Boc is strongly resistant to basic hydrolysis: again, another example of an amide with an Achilles' heel. The obvious way to make carbamates from amines is to react them with a carbamoyl chloride—this is how Z-groups are usually put on. Unfortunately, *t*-BuOCOCl is unstable, and we have to use some other electrophilic derivative—usually the anhydride Boc_2O as here, for example.

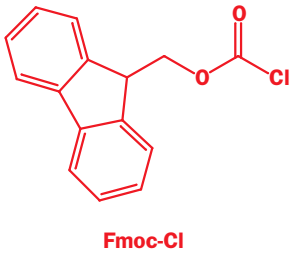
Protecting group	Structure	Protects	From	Protection	Deprotection
***t*-Boc** (OCOBu-*t*)		amines	electrophiles	(*t*-BuOCO)$_2$O, base	H^+, H_2O

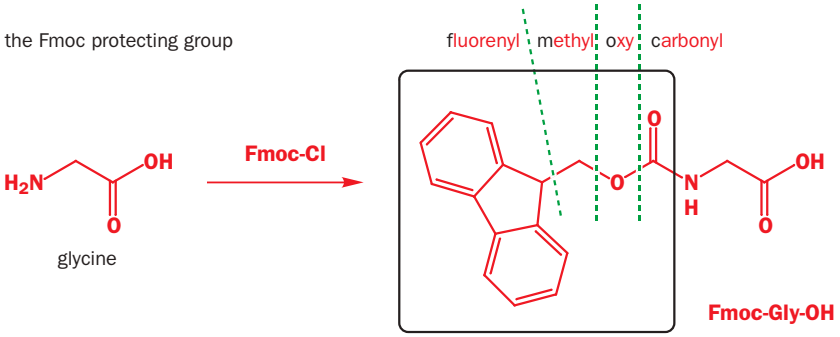
Meanwhile, back at the tetrapeptide synthesis, methionine (Met) has been BOC-protected, and is ready for activation—as a 2,4,6-trichlorophenyl ester (Cp) this time and coupling with the deprotected Asp-Phe-OMe. Aqueous acid takes off the BOC group without hydrolysing peptide or ester bonds, and a repeat of this cycle with BOC-tryptophan trichlorophenyl ester (BOC-Trp-OCp) finally gives the tetrapeptide.



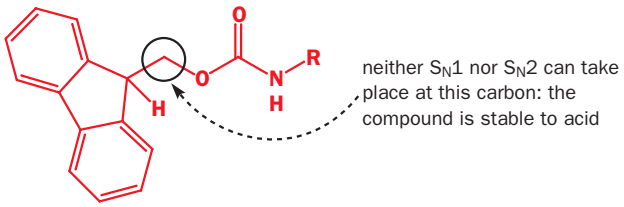
The Fmoc protecting group—solid-phase synthesis

You have already met our next and last amine-protecting group in Chapter 8.

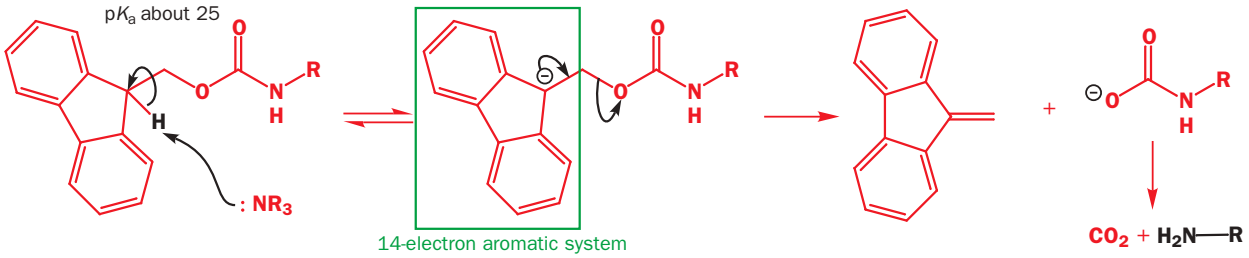




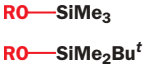
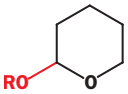
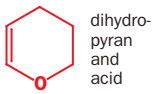
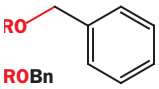
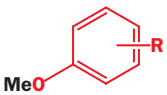
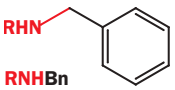
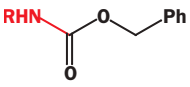
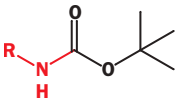
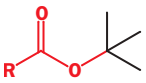
It is called Fmoc (pronounced 'eff-mock'), for fluorenylmethyloxycarbonyl, and has a susceptibility inverse to that of *t*-Boc. It cannot be lost by substitution in the manner of Cbz or *t*-Boc because neither S_N1 nor S_N2 mechanisms can operate at the ringed carbon atom: it is both primary *and* hindered.



So, where is the safety catch? The important point about Fmoc is that is has a rather acidic proton (pK_a about 25), shown in black. The proton is the Achilles' heel: treatment of Fmoc-protected amines with base eliminates a fulvene to reveal the NH_2 group.



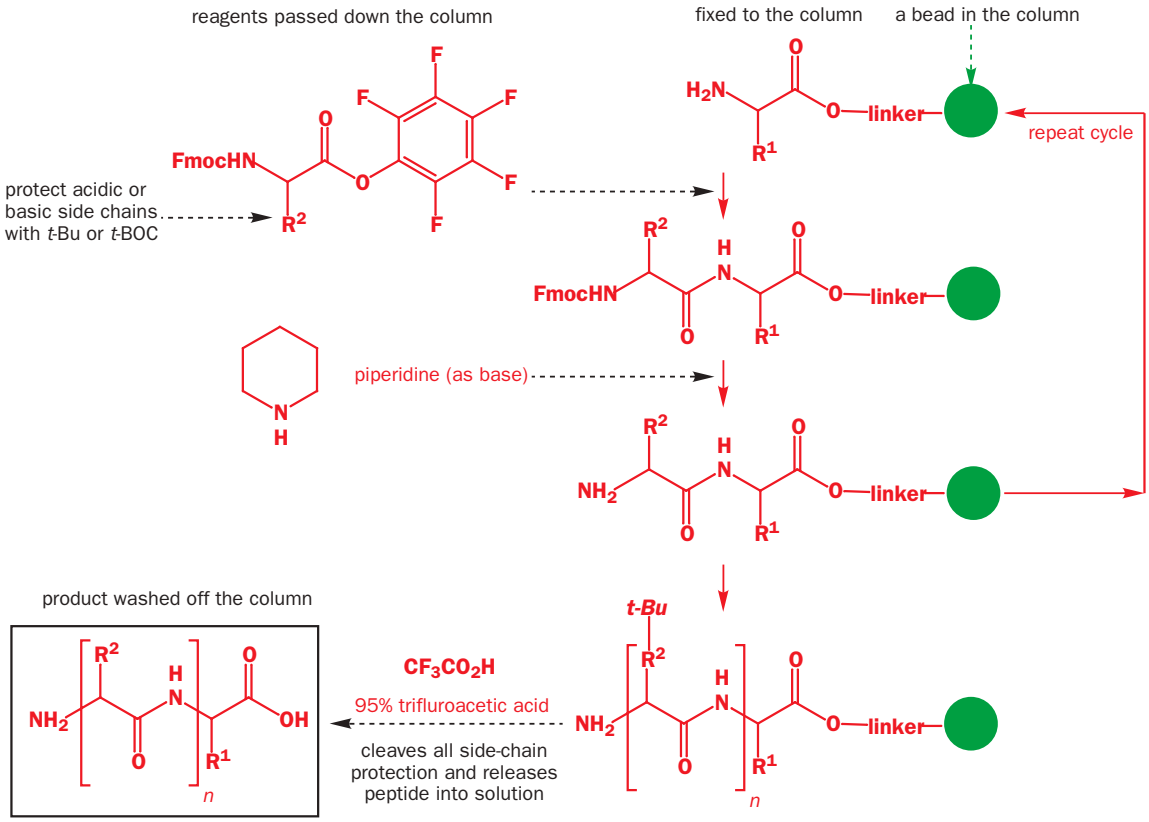
The table of protecting groups, built up slowly over this chapter and the last, is now complete.

Protecting group	Structure	Protects	From	Protection	Deprotection
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		water, H^+ cat.
trialkylsilyl (R_3Si-, e.g. TBDMS)		alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	 dihydro-pyran and acid	H^+, H_2O
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI
benzyl amine (NBn)		amines	strong bases	BnBr, K_2CO_3	H_2, Pd
Cbz (Z) (OCOBn)		amines	electrophiles	BnOCOCl, base	HBr, AcOH, or H_2, Pd
***t*-Boc** (OCOBu-*t*)		amines	electrophiles	$(t\text{-BuOCO})_2O$, base	H^+, H_2O
Fmoc fluoroenyloxycarbonyl	see text	amines	electrophiles,	Fmoc-Cl	base, e.g. amine
***t*-butyl ester** (CO_2Bu-*t*)		carboxylic acid (RCO_2H)	bases, nucleophiles	isobutene, H^+	H_3O^+

The synthesis of peptides on a solid support, usually beads of either polystyrene (the **Merrifield approach**) or polyamide (the **Sheppard approach**) resins has become extremely important, because it allows peptides to be synthesized by machines, and a key feature of the Sheppard approach is the use of Fmoc-protected amino acid residues. The idea is that the *C*-terminus amino acid is tethered to the resin by means of a carbamate linker that is stable to mild acid or base. The peptide chain is then built up using the sorts of methods we have been discussing and, when complete, is released by cleaving the linker with strong acid.

The side chains of the amino acids in this approach are also protected with acid-labile groups (*t*-butyl esters and BOC, for example), so that they too are revealed only in the final deprotection step.

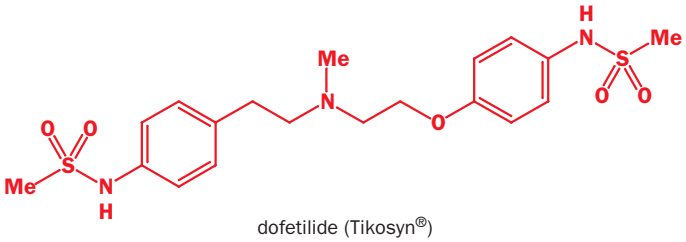
Acid cannot therefore be used for protection for the *N*-terminus of the chain as it grows, so the solution is to use Fmoc. Each amino acid is introduced as its Fmoc-protected pentafluorophenyl ester (yet another electrophilically activated electron-poor phenyl ester), and then the Fmoc group is cleaved with piperidine ready for the next residue to be added. The green blob in the diagram represents a polystyrene or polyamide bead, each of which carries many linkers and many growing peptide chains.



Once the first amino acid is fixed to the column, reagents are added simply by passing solutions down the column. Any excess or by-products are washed off. Finally, the product is released by passing a solution of CF_3CO_2H down the column. The simplicity and reliability of this type of simple iterative process, with two steps per cycle, has made automated peptide synthesis common laboratory practice.

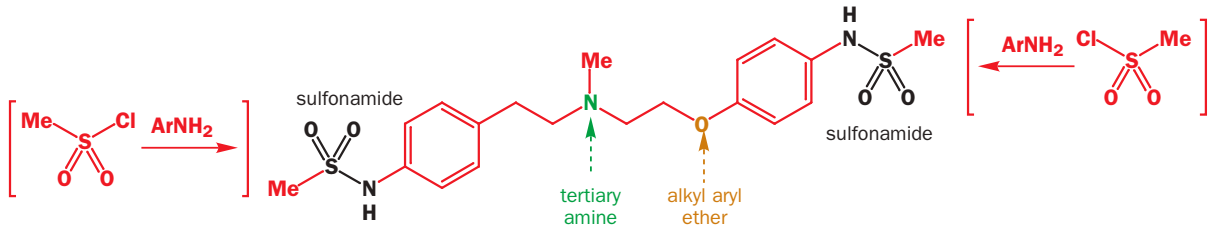
The synthesis of dofetilide, a drug to combat erratic heartbeat

The chapter ends with a complete synthesis of an important new drug. Cardiac arrhythmia (erratic and inefficient heart action) is a major problem in the modern world causing poor lifestyle (exhaustion) and death by blood clots. A new drug dofetilide (Tikosyn®) is being introduced by Pfizer to treat this problem. It works by blocking the passage of potassium ions out of heart muscle and so delays the onset of an irregular beat until the next normal beat takes over.

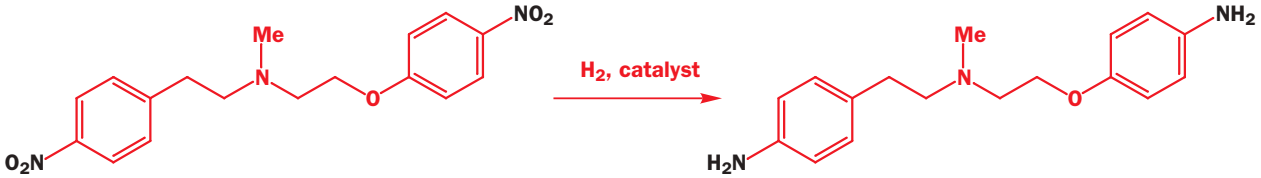


dofetilide (Tikosyn®)

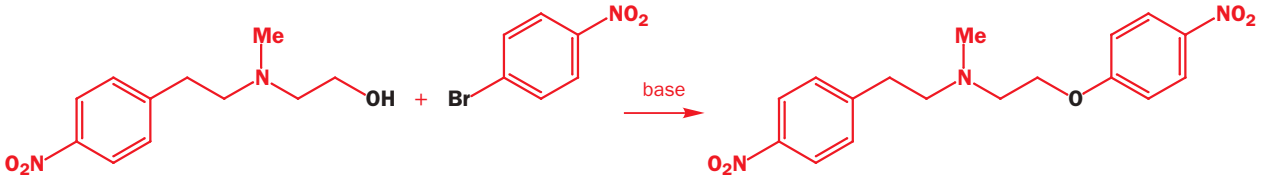
We are going to do a little more than simply give the reactions that eventually made up the synthesis of dofetilide. We are going to put ourselves in the place of the chemists who invented the synthesis and try to see what led them to the reactions they chose. First, we should inspect the structure of the molecule. There are two sulfonamides, one at each end. We have seen how to make sulfonamides earlier in this chapter when saccharin was being discussed. The usual way is to react the amine with a sulfonyl chloride. In this case we shall need to react methane sulfonyl chloride ($MeSO_2Cl$ or MsCl) with the aromatic amines. This is a well-known reaction and should work well here. The other functional groups—tertiary amine and alkyl aryl ether—should not interfere so no protection is needed.



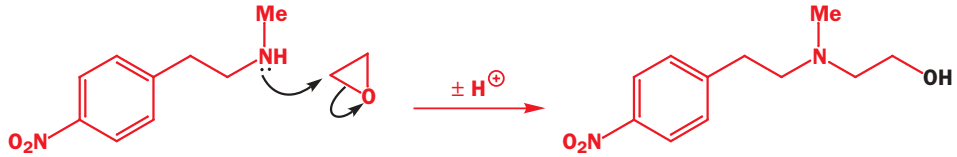
So we need to make the required aromatic diamine. We might guess from what we did earlier in this chapter as well as from Chapter 22 that this is likely to be achieved by nitration and reduction so we should check that double nitration of our proposed starting material will occur in the right positions (regioselectivity). Remember that at this stage we are just making proposals—we can only predict whether the reactions will actually occur or not.



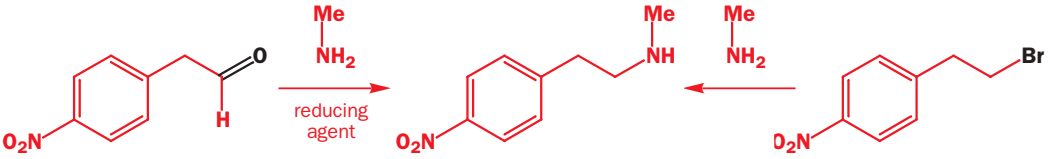
The substituents on both rings are activating and *ortho, para*-directing so there is reasonable hope that *para* selectivity can be achieved in both cases. However the left-hand ring is only weakly activated by an alkyl group whereas the ring on the right is strongly activated by the oxygen atom. It might be difficult to get the left-hand ring to react even once before the right-hand ring reacts three times (Chapter 22). A good solution would be to build the dinitro compound with each separate ring already previously nitrated once only. So we need to think how to link the rings together. The most obvious approach is to combine some organic electrophiles (alkyl halides, carbonyl compounds) with nitrogen and oxygen nucleophiles. We might, for example, join up the right-hand ring by nucleophilic aromatic substitution using the convenient *para* nitro group.



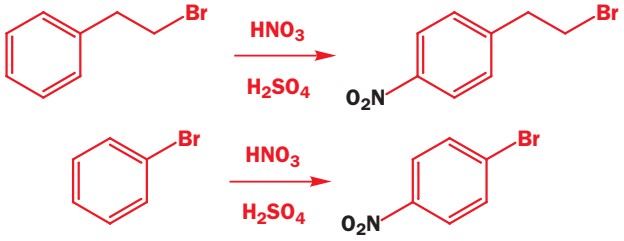
Then we could make the amino alcohol by adding an amine to an epoxide—that $N–CH_2–CH_2–OH$ group looks as though it comes from ethylene oxide and an amine.



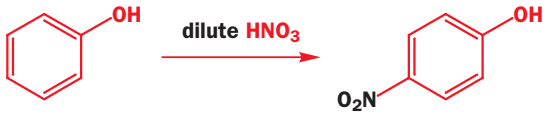
In its turn the amine could come from a reductive amination (Chapter 24) or by an alkylation, using in both cases $MeNH_2$ as the nucleophile and an aldehyde or an alkyl halide as the electrophile.



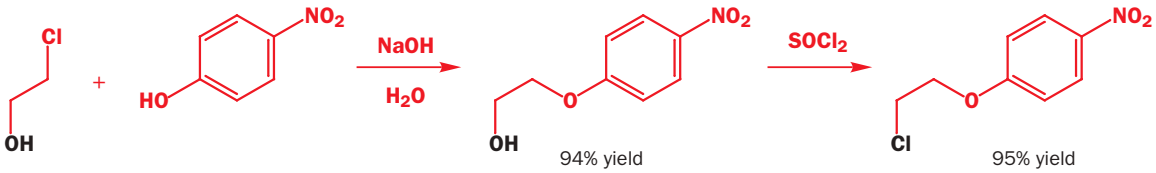
Now we have a selection of possible starting materials and we should consider which might be available commercially as that will make the job so much easier. In fact, two of the nitro compounds we want can be made so easily by direct nitration that they are available commercially.



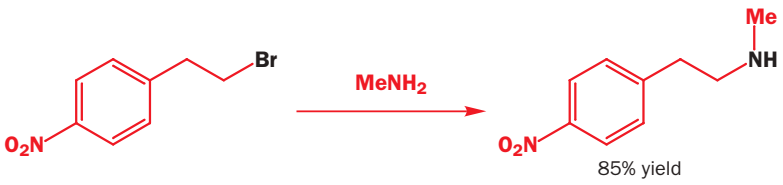
Only the aldehyde is not a commercial product and we might guess that the oxidizing power of nitric acid might convert the aldehyde into an acid. An even cheaper compound is *para*-nitro phenol, which can be made very easily from phenol and dilute nitric acid (Chapter 22).



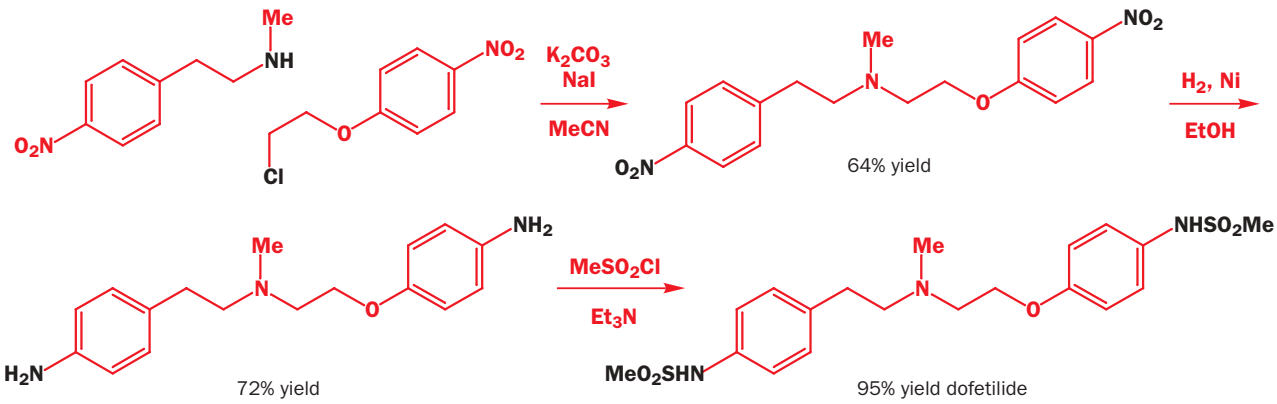
From the many possible approaches, Pfizer chose the one summarized below. The question of cheapness and availability of starting materials matters more in large-scale manufacture than in laboratory work but we can only guess at some of the choices. The last stages are as we suggested but the first stages are not. The ether is made from *para*-nitro phenol and 2-chloroethanol. This is an unusual electrophile and this reaction forms the subject of a problem at the end of the chapter. The resulting alcohol is converted into the chloride with $SOCl_2$, a standard method from Chapter 17. The yields are excellent and this too is an important consideration in manufacture.



The amine is made by a simple alkylation reaction on methylamine. This choice is made chiefly because of the cheapness of the alkyl bromide and the good yield. There could be a real problem here with further alkylation of the product but they probably use a large excess of methylamine to prevent that.



Now that the parts have been assembled, they can be joined together and these last steps follow the plan we outlined earlier. The worst step in the synthesis is the joining together of the two halves and even that gives a respectable 64% yield. This approach to synthesis—analysing the problem first and then proposing solutions—will be the subject of Chapter 30.



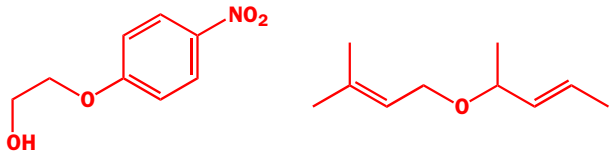
This is a commercial synthesis of an important new compound and uses only chemistry that you have met in the first 24 chapters of the book. Though new syntheses are completed and new methods invented daily, the basic organic reaction types remain the foundation on which these inventions are constructed.

Looking forward

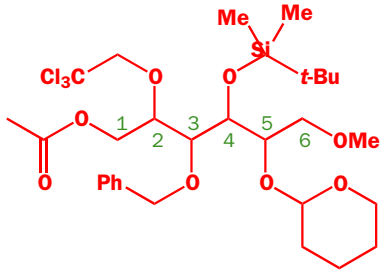
So far, most of the reactions presented in the book that are useful in synthesis have made C–O, C–N, or C–halogen bonds and only a few (Wittig, Friedel–Crafts, and reactions of cyanides and alkynes) make C–C bonds. This limitation has severely restricted the syntheses that we can discuss in this chapter. This is by design as we wanted to establish the idea of synthesis before coming to more complicated chemistry. The next four chapters introduce the main C–C bond-forming reactions in the chemistry of enols and enolates. You met these valuable intermediates in Chapter 21 but now you are about to see how they can be alkylated and acylated and how they add directly to aldehydes and ketones and how they do conjugate addition to unsaturated carbonyl compounds. Then in Chapter 30 we return to a more general discussion of synthesis and develop a new approach in the style of the last synthesis in this chapter.

Problems

1. Suggest two different syntheses for these ethers and say which you prefer (and why!).



2. This hexa-alcohol can be deprotected, one OH at a time, by the sequence of reagents shown below. Explain how each reagent works, stating, of course, which protecting group it removes! Would any other order of events be successful?



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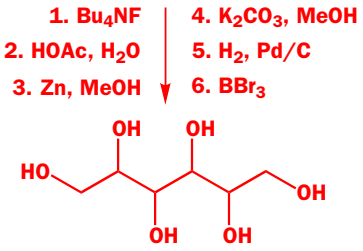
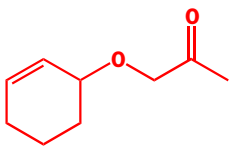
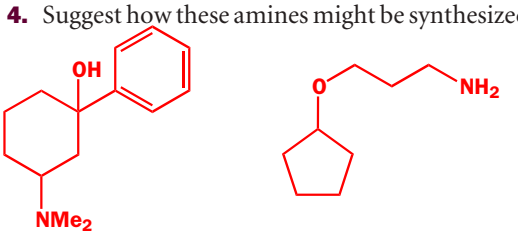


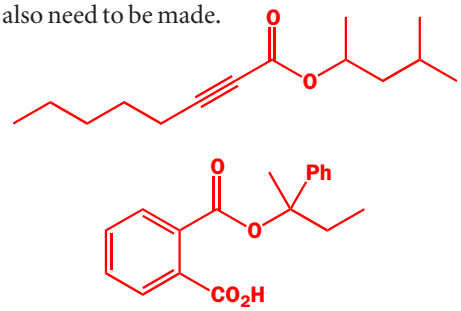
3. Suggest syntheses for this simple compound. What selectivity problems must be overcome?



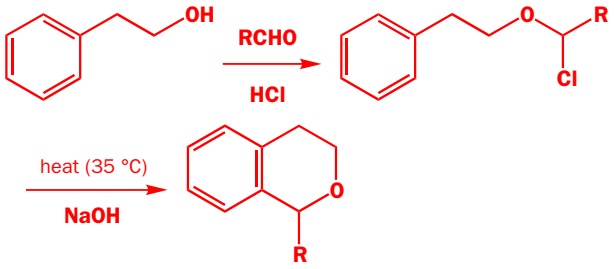
4. Suggest how these amines might be synthesized.



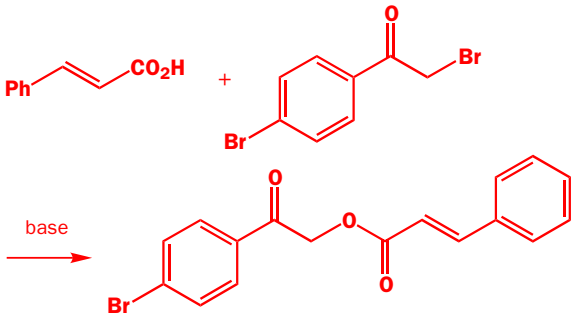
5. Suggest syntheses for these esters. The starting materials might also need to be made.



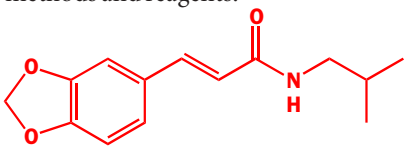
6. Suggest a synthesis of the starting material and give mechanisms for the reactions. Why does the last step go under such unusual conditions?



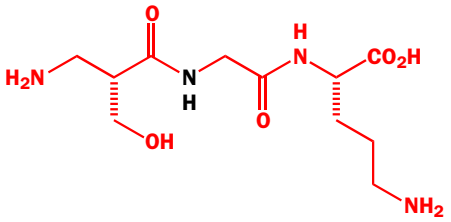
7. Esters are normally made from alcohols and activated acids. This one is made by a completely different method. Why?



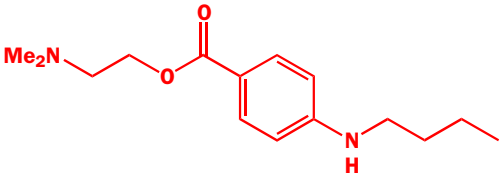
8. Suggest a synthesis for this compound. Justify your choice of methods and reagents.



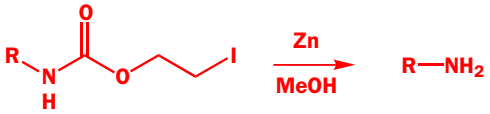
9. Suggest a synthesis of this non-protein peptide, emphasizing the choice of protecting groups.



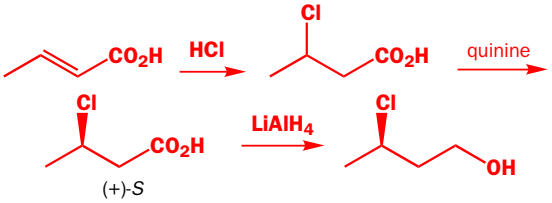
10. Suggest a synthesis for this local anaesthetic.



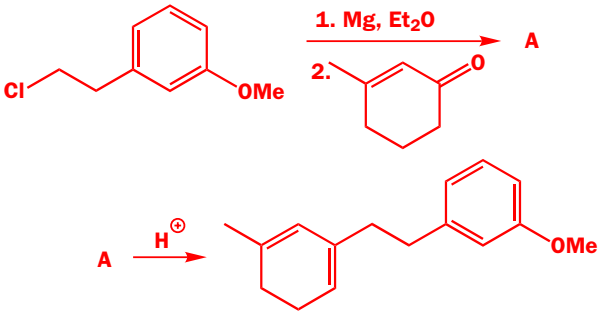
11. The β-iodoethoxycarbonyl group has been suggested as a protecting group for amines. It is removed with zinc in methanol. How would you add this protecting group to an amine and how does the deprotection occur? What other functional groups might survive the deprotection?



12. Revision of Chapters 10 and 16. Give mechanisms for this synthesis and suggest why this route was followed.



13. Revision of Chapters 9 and 19. Draw the structures of the intermediates in this synthesis of a diene and comment on the selectivity of the last step.



14. Suggest ways to make these compounds.