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
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Selectivity

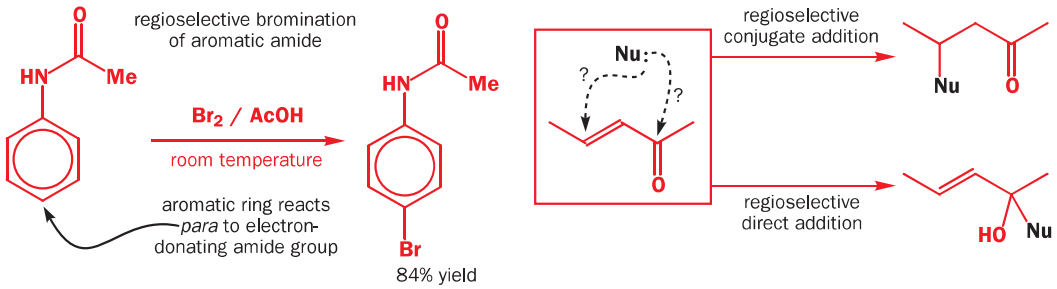
Most organic molecules contain more than one functional group, and most functional groups can react in more than one way, so organic chemists often have to predict *which* functional group will react, *where* it will react, and *how* it will react. These questions are what we call **selectivity**.

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.

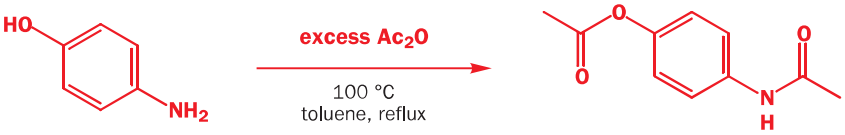
There are three main types of selectivity

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

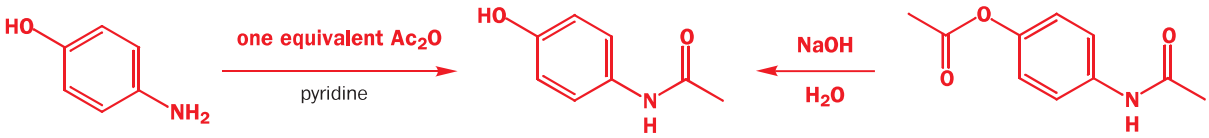
We talked a lot about regioselectivity two chapters ago, when you learned how to predict and explain which product(s) you get from electrophilic aromatic substitution reactions. The functional group is the aromatic ring: *where* it reacts is the reaction's regioselectivity. Going back further, one of 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.

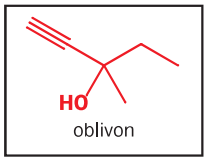


But with just one equivalent of acetic anhydride in the presence of a base (pyridine) only the NH_2 group is acylated, and paracetamol is the product. This is chemoselectivity, and it is to be expected that the NH_2 group is more nucleophilic than the OH group. It is even possible to hydrolyse the doubly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

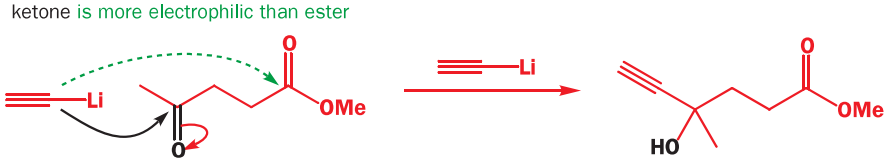


paracetamol

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.

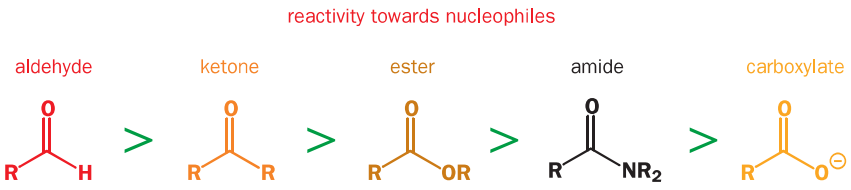


oblivon



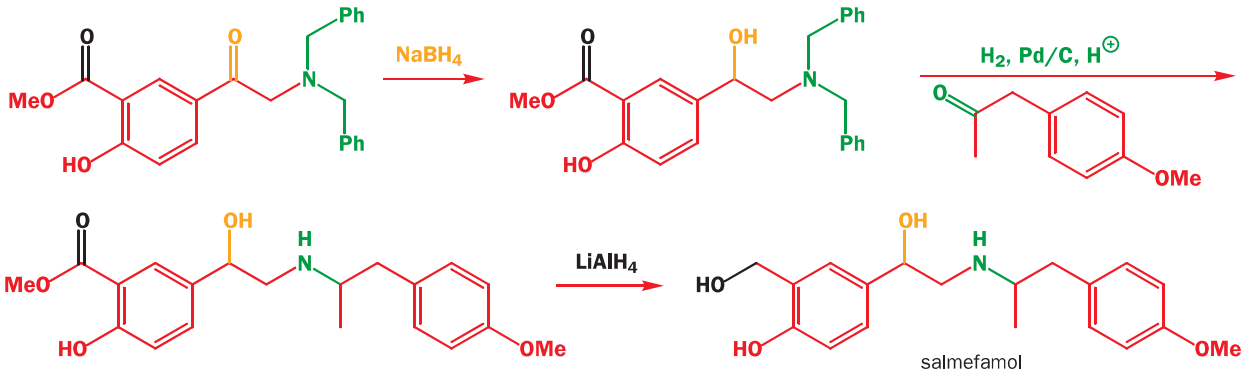
These reactions work because, although each starting material contains two carbonyl groups, one is more electrophilic and therefore more reactive towards nucleophiles (OH^- in the first case; lithium acetylide in the second) than the other. We can order carbonyl compounds into a sequence in which it 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).

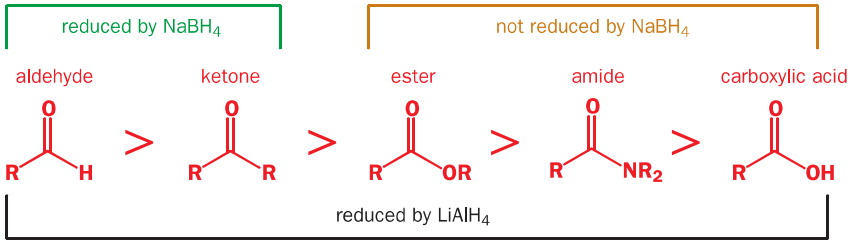


Reducing agents

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.

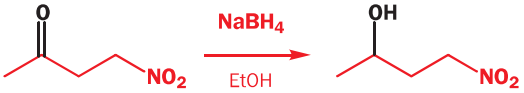
▶ In general, it's best to use the mildest conditions possible for any particular reaction—the potential for unwanted side-reactions is lessened. What is more, $NaBH_4$ is a lot easier to handle than $LiAlH_4$—for example, it simply dissolves in water while $LiAlH_4$ catches fire if it gets wet. $NaBH_4$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

Reduction of carbonyl groups

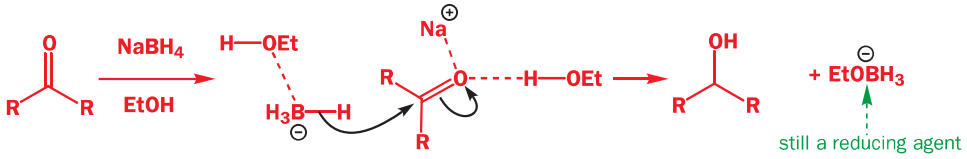
We should now look in detail at reductions of carbonyl compounds, and in doing so we shall introduce a few more specialized reducing agents. Then we will come back to the other type of reduction in the salmefamol synthesis—catalytic hydrogenation.

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.

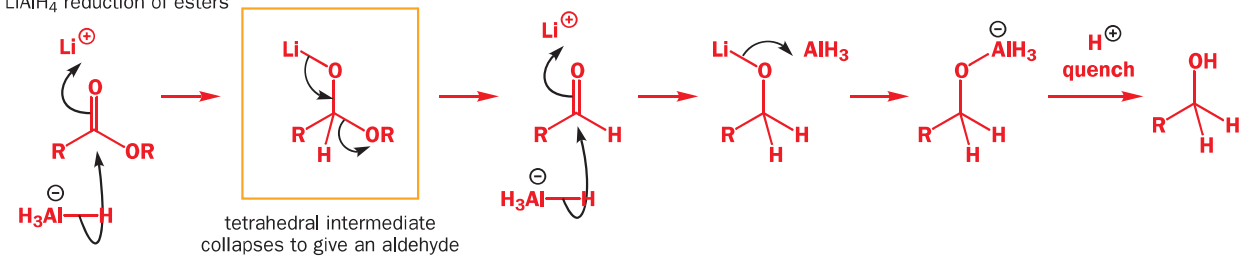
$LiAlH_4$ is often the best reagent, and gives alcohols by the mechanism we discussed in Chapter 12. As a milder alternative ($LiAlH_4$ has caused countless fires through careless handling), lithium borohydride in alcoholic solution will reduce esters—in fact, it has useful selectivity for esters over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

How to reduce amides to amines

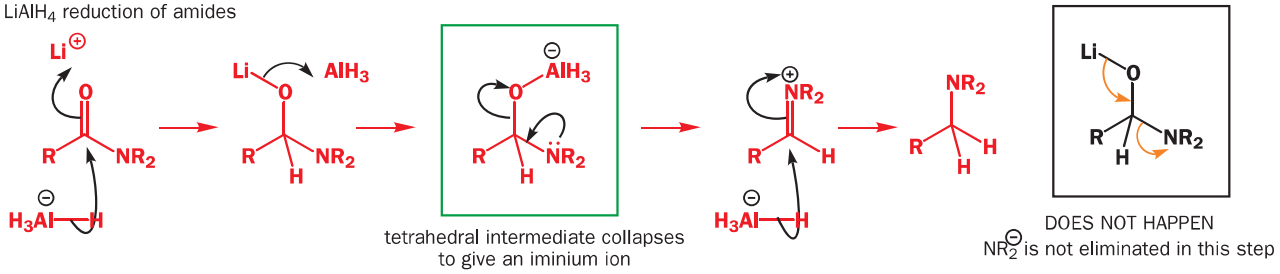
The ester mechanism has rather more detail than the simplified one we presented to you in Chapter 12.

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

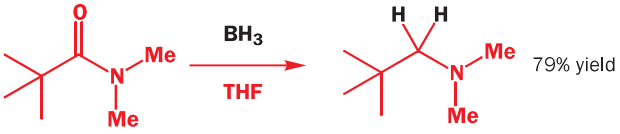


How to reduce carboxylic acids to alcohols

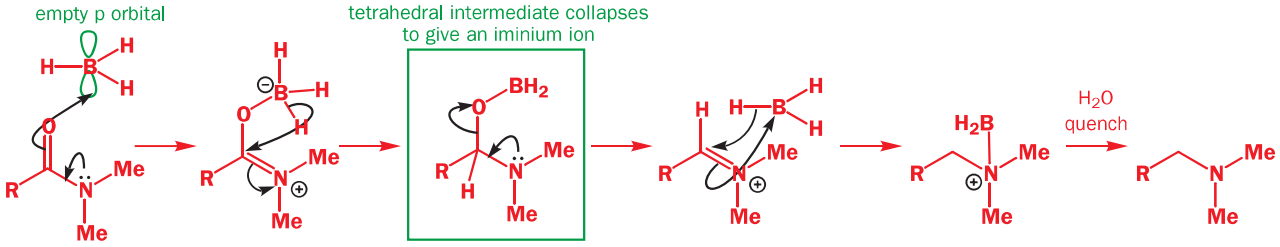
These complexes are Lewis salts: BH_3 is a Lewis acid that accepts a lone pair of electrons from the basic ether or sulfide.

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).

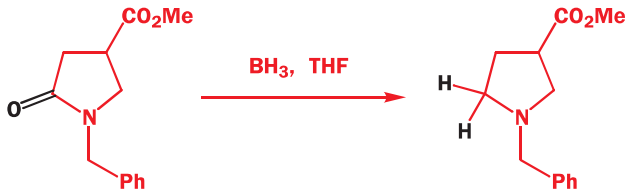
Although borane appears superficially similar to borohydride, it is not an ion and that makes all the difference to its reactivity. Whereas borohydride reacts best with the most electrophilic carbonyl groups, borane's reactivity is dominated by its desire to accept an electron pair into its empty p orbital. 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.



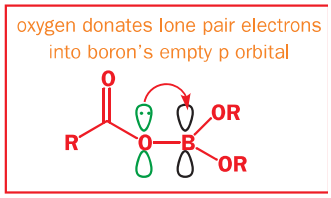
The Lewis basic carbonyl group forms a complex with the empty p orbital of the Lewis acidic borane. Hydride transfer is then possible from anionic boron to electrophilic carbon. The resulting tetrahedral intermediate collapses to an iminium ion that is reduced again by the borane.

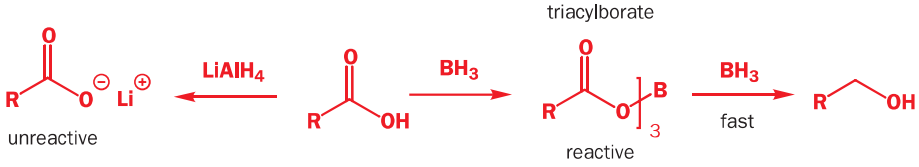


Borane also makes a good alternative to $LiAlH_4$ for reducing amides as the two reagents have slightly different chemoselectivity—in this example borane reduces an amide in the presence of an ester.

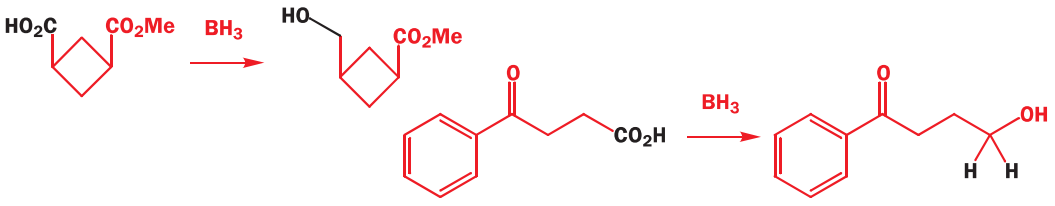


Borane is an excellent reagent for reducing carboxylic acids. It reacts with them first of all by forming triacylborates, with evolution of hydrogen gas. Esters are usually less electrophilic than ketones because of conjugation between the carbonyl group and the lone pair of the sp^3 hybridized oxygen 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 $LiAlH_4$.



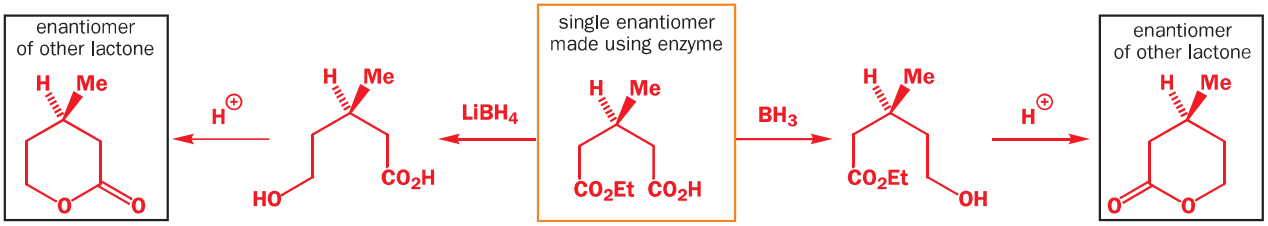


Borane is a highly chemoselective reagent for the reduction of carboxylic acids in the presence of other reducible functional groups such as esters, and even ketones.

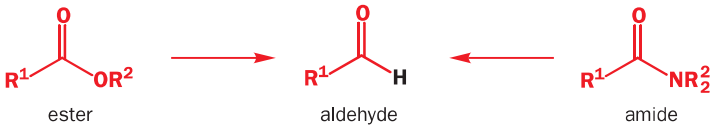


■ This type of asymmetric synthesis is discussed in Chapter 45.

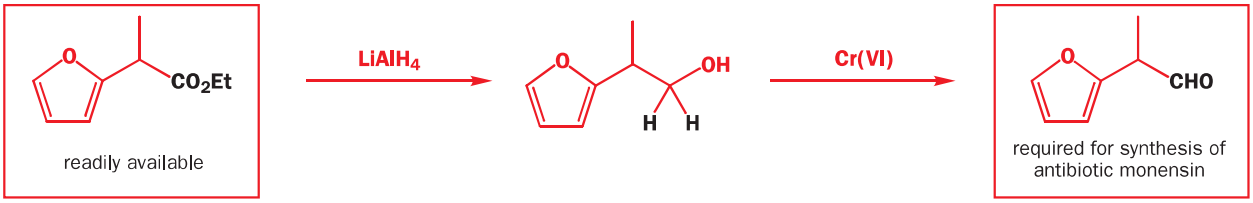
Borane and lithium borohydride are a most useful pair of reducing agents, with opposite selectivities. Japanese chemists used an enzyme to make a single enantiomer of the acid below, and were able to reduce either the ester or the carboxylic acid by choosing lithium borohydride or borane as their reagent.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

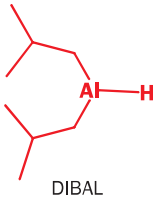


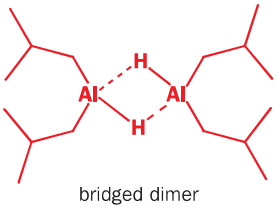
How to reduce esters and amides to aldehydes



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.

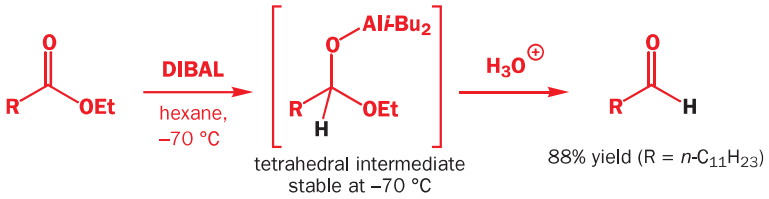




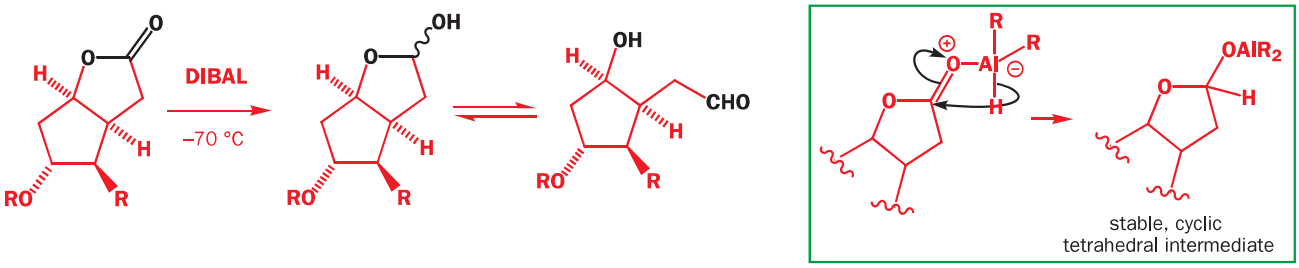


In this case, the chemists decided simply to put up with the fact that $LiAlH_4$ gives the alcohol, and re-oxidize the alcohol back to the aldehyde using chromium(VI) (see later for details of this step). There is, however, a reagent that will sometimes do the job in a single step, though you must bear 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.

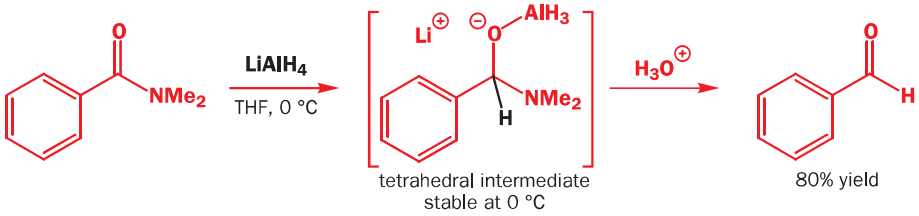


A stable tetrahedral intermediate is more likely in the reduction of lactones, and DIBAL is most reliable in the reduction of lactones to lactols (cyclic hemiacetals), as in E.J. Corey's synthesis of the prostaglandins. The key step, the hydride transfer from Al, is shown in the green frame.



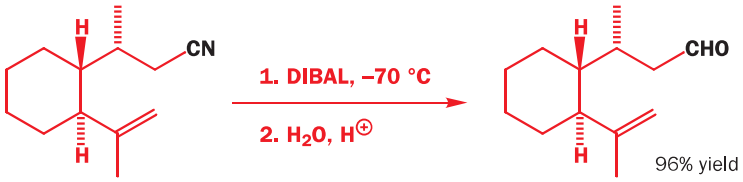
In the amide reduction scheme on p. 000, the step framed in green gives an iminium ion. Stopping the reaction here would therefore provide a way of making aldehydes from amides. Because these tetrahedral intermediates are rather more stable than those from ester reduction, this can often be achieved 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.



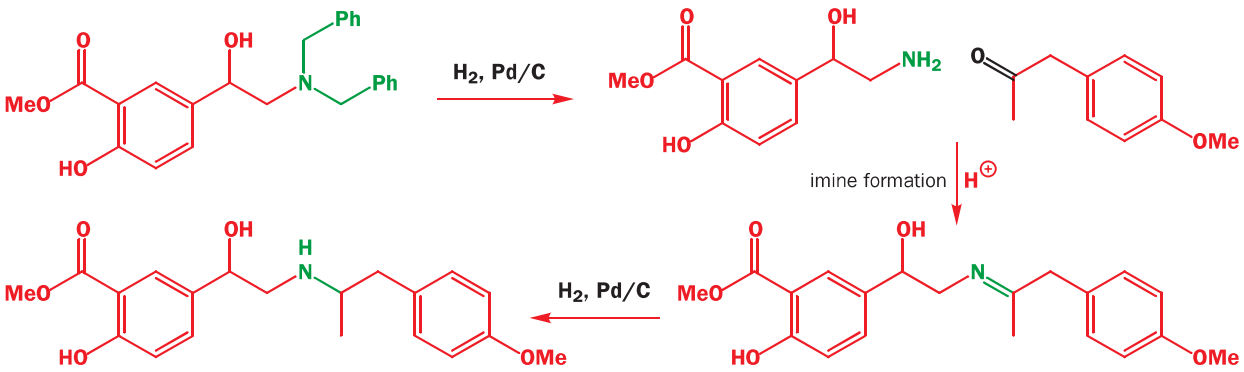
DIBAL is also good for reducing nitriles to aldehydes. Indeed, this reaction and the reduction of lactones to lactols are the best things that DIBAL does.

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



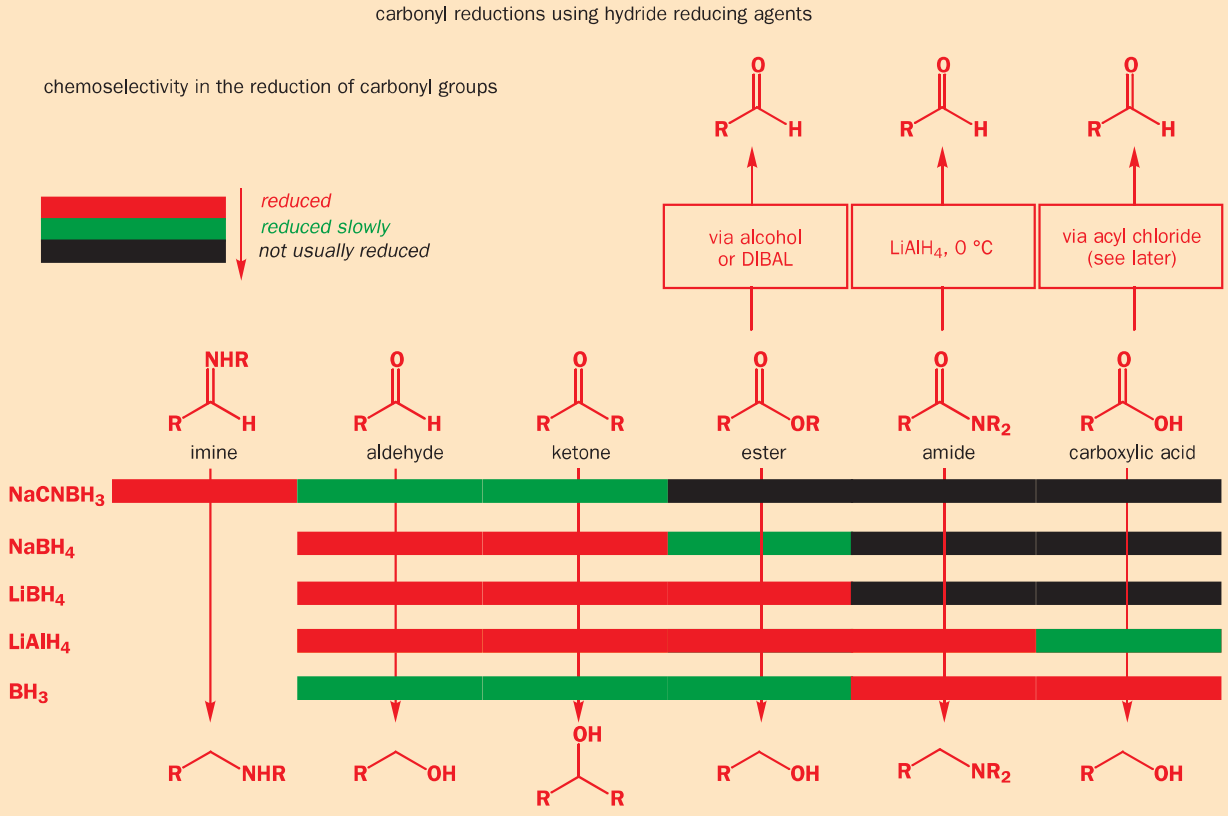
Now, let's go back to the salmefamol synthesis we started with on p. 000. The other reducing agent used in the sequence is hydrogen gas over a palladium catalyst. Catalytic hydrogenation has two functions here: firstly, it removes the two benzyl groups from the nitrogen, revealing a primary amine (this 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.

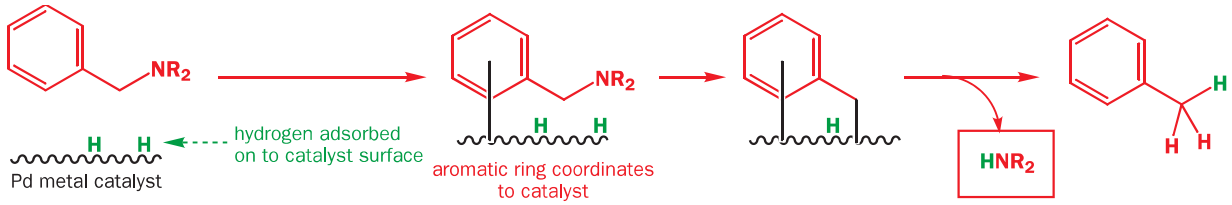


Catalytic hydrogenation reduces the imine (as the protonated iminium ion) but not the ketone from which it is formed. This chemoselectivity (reduction of iminium ions but not ketones) is also displayed by sodium cyanoborohydride and we can add $NaCNBH_3$ to complete our table of reactivity, if we insert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

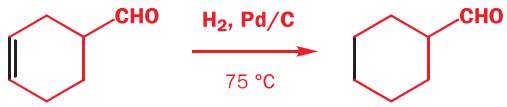


We put 'mechanism' in inverted commas because this isn't really a proper chemical mechanism, more a scheme with a suggested sequence of events. The key points are that the benzyl amine coordinates to the metal catalyst via the electron-rich aromatic ring. The C–N bond is now in close proximity to the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

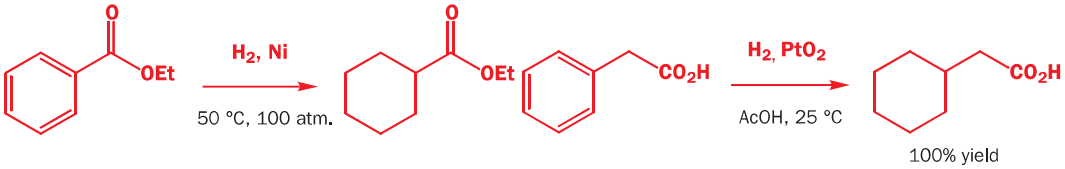
Because of the need for initial coordination with the catalyst, only benzylic or allylic C–X bonds can be reduced, but the X can be oxygen as well as nitrogen. We will come back to benzyl groups, and their hydrogenolysis, as a means for temporary protection of amines and alcohols later in the chapter. 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.

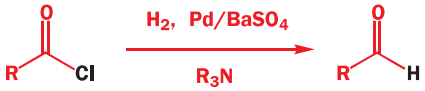


▶ Some hydrogenations, like this one, require high pressures of hydrogen gas to get them to go at a reasonable rate. They are usually done in a sealed apparatus known as a **Parr hydrogenator.**

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.

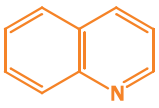
Substrate	Usual choice of metal
benzyl amine or ether	Pd
alkene	Pd, Pt, or Ni
aromatic ring	Pt or Rh, or Ni under high pressure

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.

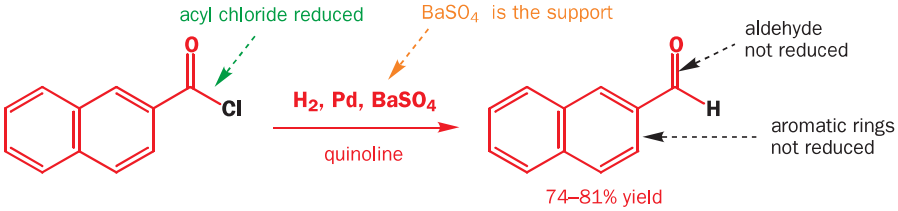


This is a good way of reducing compounds at the carboxylic acid oxidation level to aldehydes, which is why we included it in the table of carbonyl reductions on p. 000. The tertiary amine is needed both to neutralize the HCl produced in the reaction and to moderate the activity of the catalyst (and prevent 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

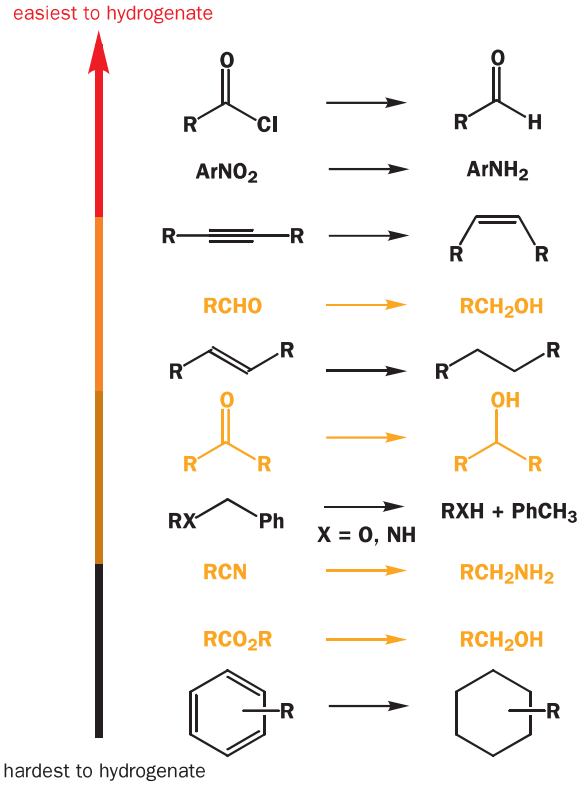


quinoline

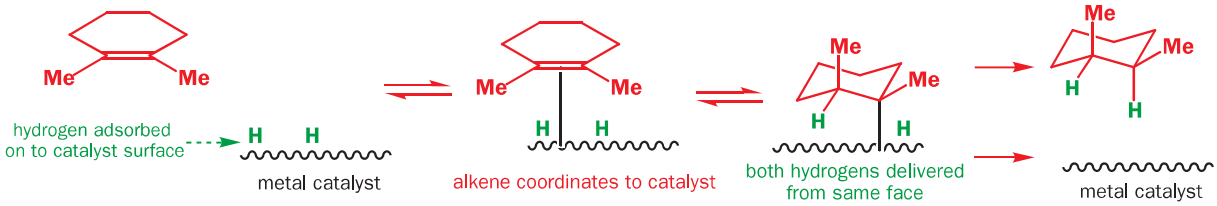


Although aromatic rings can be hydrogenated, as you saw on p. 000, neither they nor the aldehyde product are reduced under these conditions and, as with hydride reductions of carbonyl compounds, we can draw up a sequence of reactivity towards hydrogenation. The precise ordering varies with the catalyst, 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

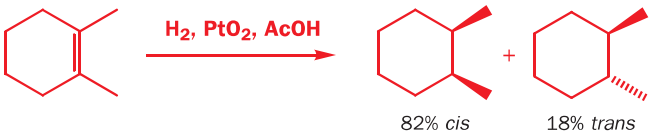
towards certain classes of compound—for example, Pt, Rh, and Ru will selectively hydrogenate aromatic rings in the presence of benzylic C–O bonds, while with Pd catalysts the benzylic C–O bonds are hydrogenolysed faster.



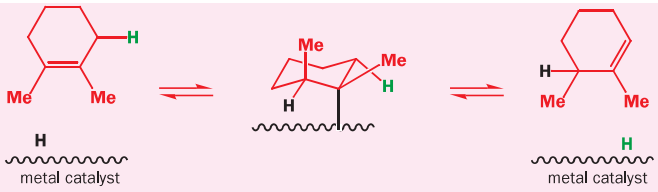
Like hydrogenolysis, the mechanism of the hydrogenation of C=C double bonds starts with coordination of the double bond to the catalyst surface.



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.



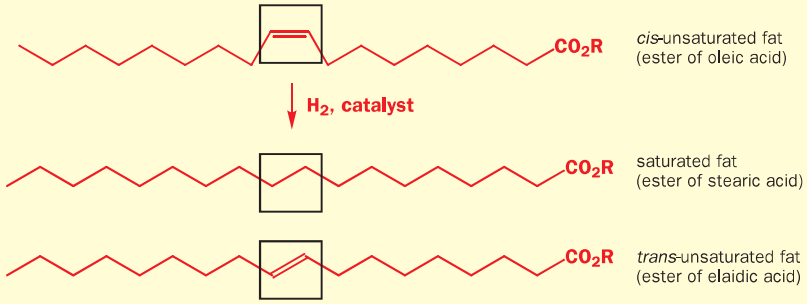
Hydrogenated vegetable oil

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.



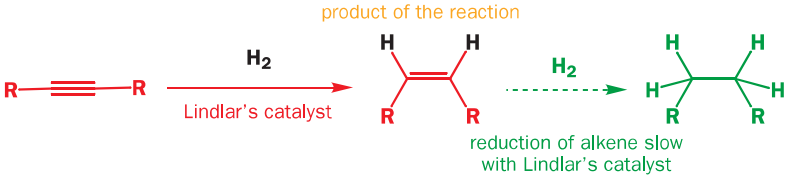
A note on some catalysts

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, $CaCO_3$, $Pb(OAc)_2$**

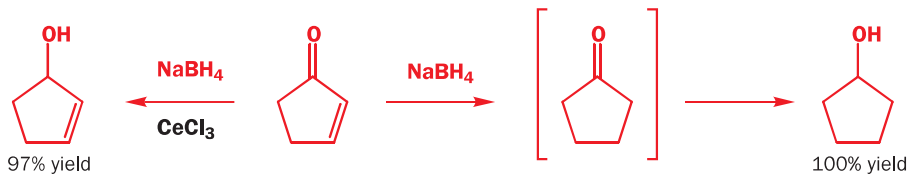


2 **Adams's catalyst** is formally PtO_2, and you have already seen this at work in one or two examples. The actual catalyst is, however, not the oxide of platinum, but the platinum metal that forms by reduction of PtO_2 to Pt *during the hydrogenation*

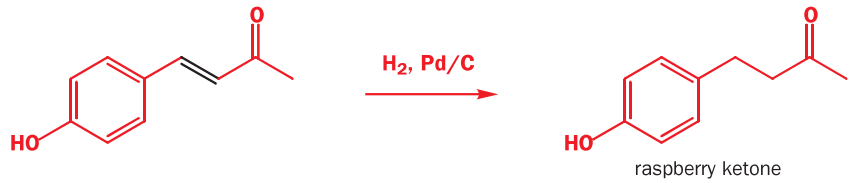
3 **Raney nickel** (often abbreviated to RaNi) is a finely divided form of nickel made from a nickel–aluminium alloy. The aluminium is dissolved away using concentrated aqueous sodium hydroxide, leaving the nickel as a fine powder. The process liberates H_2 (check this for yourself—on paper!), and some 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 $CeCl_3$.

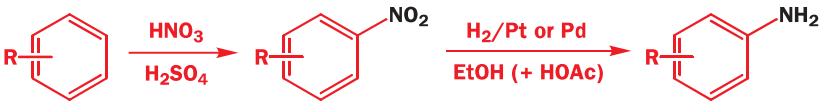


It should not surprise you that regioselective reduction of the C=C double bond alone is best done using catalytic hydrogenation as the C=C bond is weaker than the C=O bond. The flavouring compound known as 'raspberry ketone' is made by this method.



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

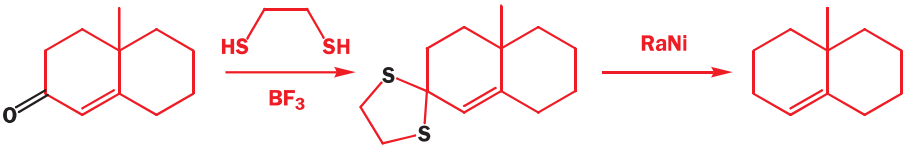
Functional groups can be useful for putting a molecule together, but their presence may not be required in the final product. We need ways of getting rid of them. Hydrogenation of alkenes is one way that you have seen, and alcohols can be got rid of either by elimination and then hydrogenation or by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

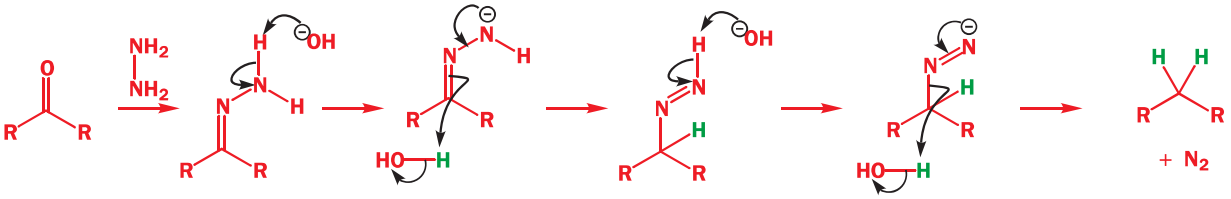
99% yield

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.

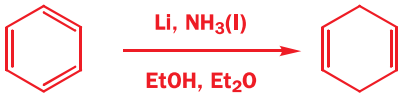
88%, R = $C_{17}H_{35}$

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.

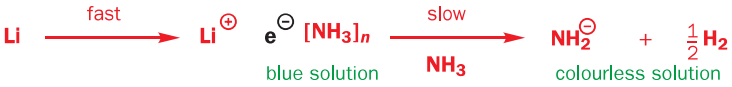
Dissolving metal reductions

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.

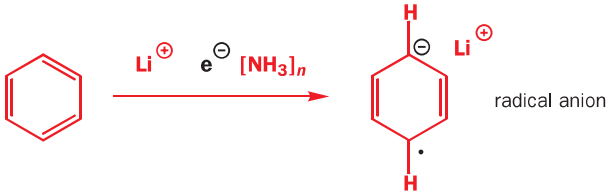
We shall start by looking at the dissolving metal reduction of aromatic rings, known as the **Birch reduction**. Here is the reaction of benzene with lithium in liquid ammonia. At first sight, this reaction looks quite improbable, with an aromatic ring ending up as an unconjugated diene! The mechanism 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.



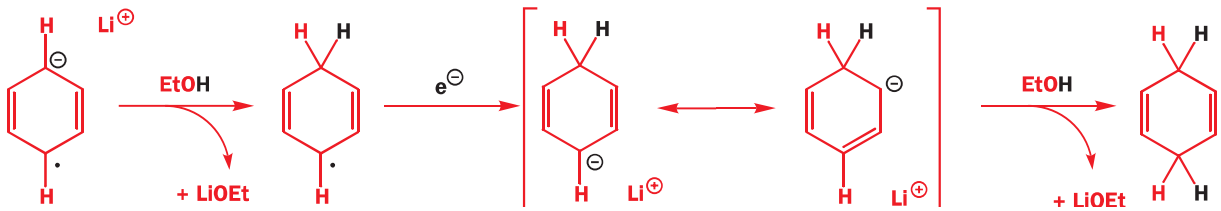
The first thing to note is that when lithium or sodium dissolve in ammonia they give an intense blue solution. Blue is the colour of solvated electrons: these group 1 metals ionize to give Li^+ or Na^+ and $e^-(NH_3)_n$—the gaps between the ammonia molecules are just the right size for an electron. With time, the blue colour fades, as the electrons reduce the ammonia to $\overline{NH_2}$ 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 $\overline{NH_2}$ 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).



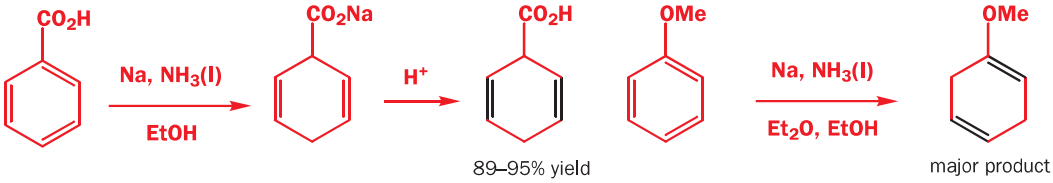
The regiochemistry of the reaction is determined at the final protonation step—the anion itself is of course delocalized and could react at either end to give a conjugated diene, which would be more

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.

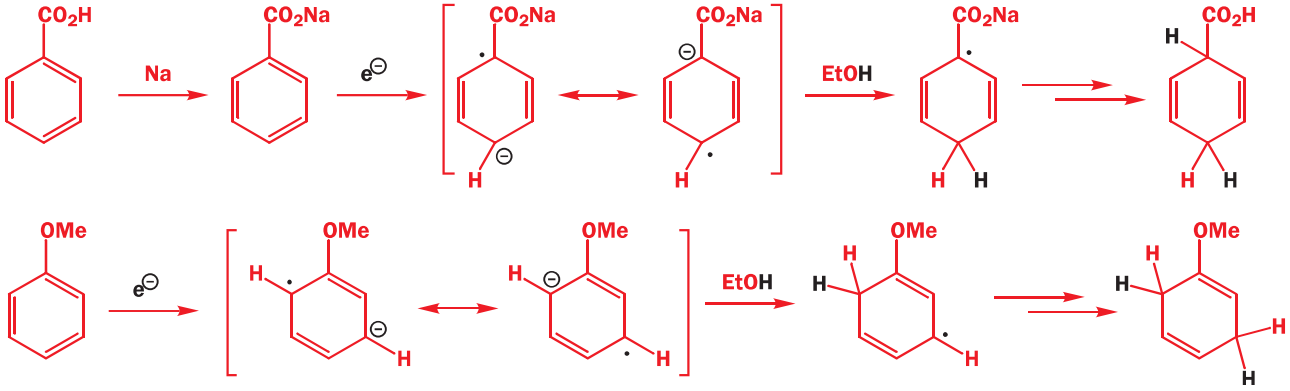
Further questions of regioselectivity arise when there are substituents around the aromatic ring. Here are two examples. The second product was used by Evans in his synthesis of the alkaloid luciduline. These examples serve to illustrate the general principle that electron-withdrawing groups promote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

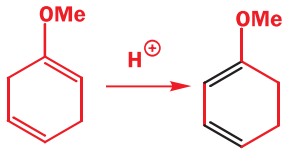
Alkaloids appear in Chapter 51.



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.

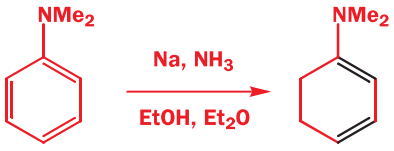


If you want the conjugated dienes as products, it is quite a simple matter to isomerize them using an acid catalyst. In fact, a small amount (about 20%) of the conjugated product is produced anyway in the reaction of anisole above.



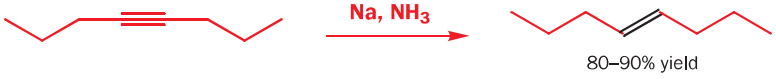
Make sure you can write a mechanism for this isomerization. *Hint.* Start as though you were protonating an enol ether on carbon. You saw this sort of thing in Chapter 21.

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



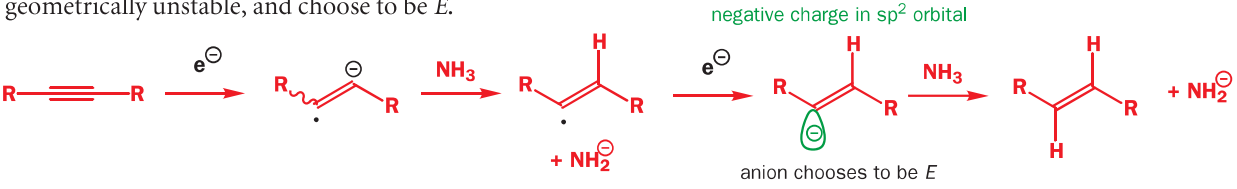
Birch-style reduction of α,β-unsaturated carbonyl compounds is described in Chapter 26.

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).



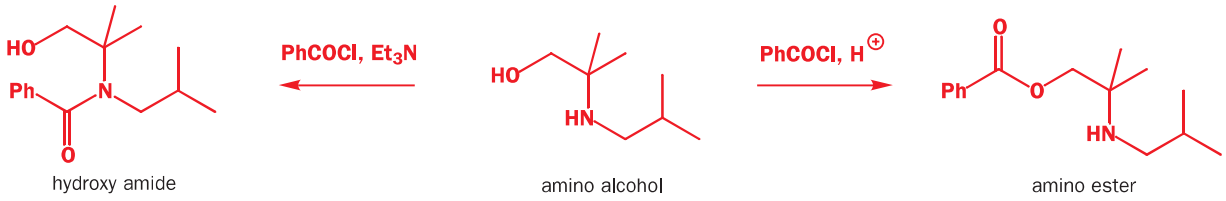
We come back to dissolving metals in Chapter 39, where we will also introduce another type of reduction—a good way of reducing C–halogen bonds to C–H.

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*.

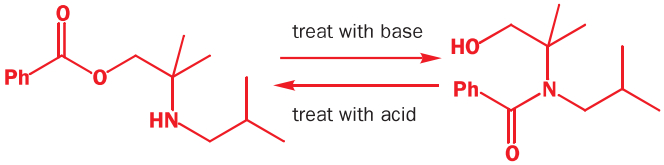


One functional group may be more reactive than another for *kinetic* or for *thermodynamic* reasons

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.

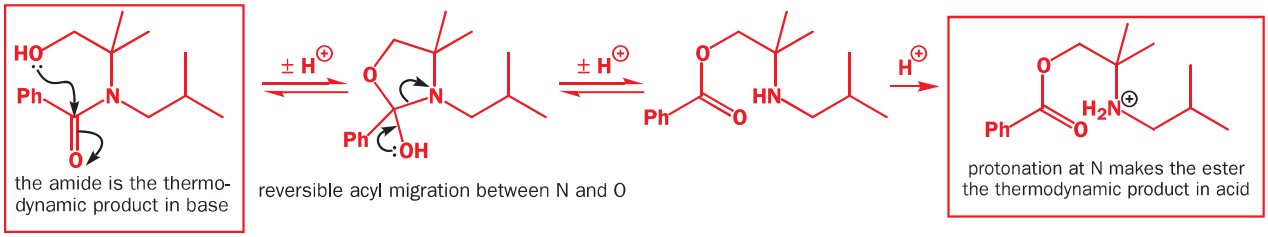


A clue to why the selectivity reverses is shown below—it is, in fact, possible to interconvert the ester and the amide simply by treating either with acid or with base.



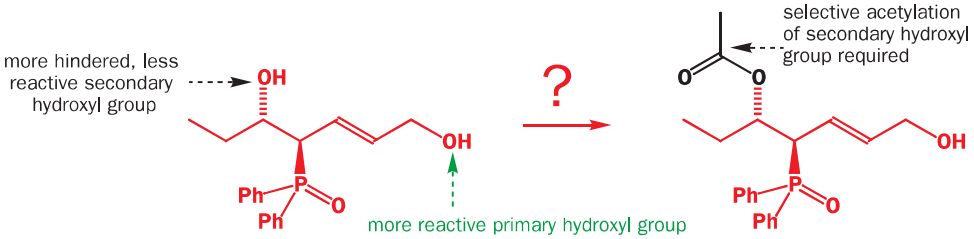
■ We first met examples of kinetic and thermodynamic control in Chapter 13.

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.

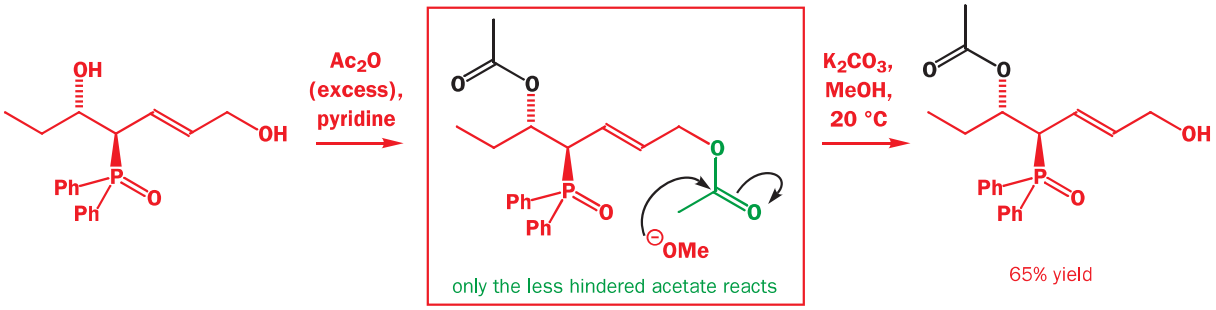


How to react the less reactive group (I)

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.



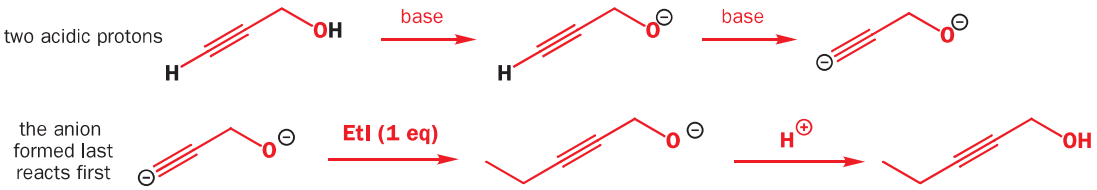
Treatment with one equivalent of an acyl chloride agent is no good because the primary hydroxyl group is more reactive; instead, the chemists acetylated both hydroxyl groups, and then treated the bis-acetate with mildly basic methanol (K_2CO_3, MeOH, 20 °C), which reacted only at the less hindered acetoxy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



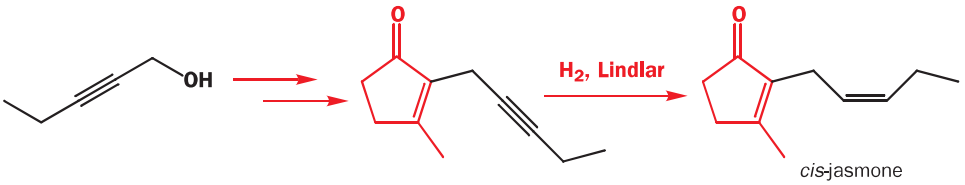
In other words, start by letting both groups react, and then go backwards but reverse the reaction at only one of the groups. The likelihood is that the less favourable reaction (in other words, reaction at the less reactive group) will be less readily reversed.

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.



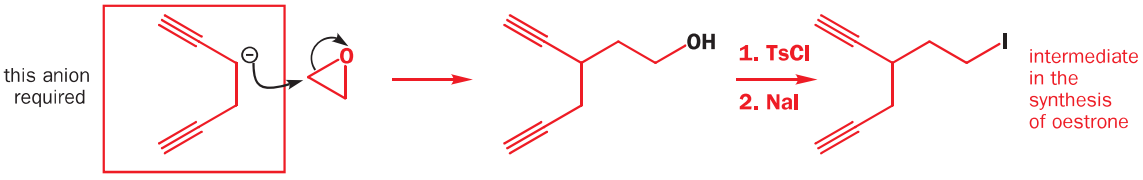
This reaction is important in a synthesis of the perfumery compound *cis*-jasmone. The alkyne is the precursor to *cis*-jasmone's alkene side chain.



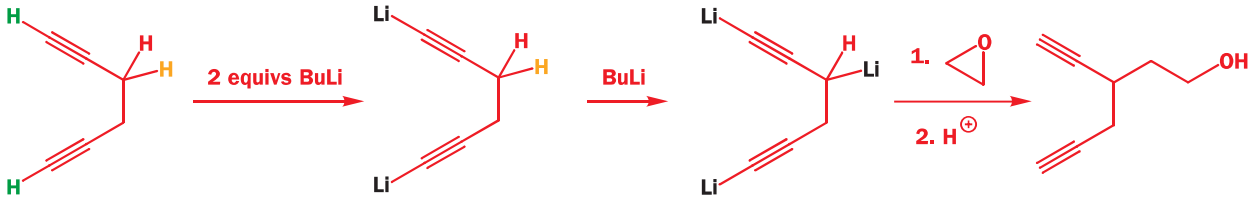
?Heading?

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.



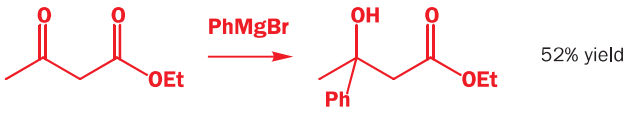
Although anions can often be formed straightforwardly next to alkynes, there are two other more acidic protons (green) in the molecule that would be removed by base before the yellow proton. However, treatment with *three* equivalents of butyl lithium removes all three, and the trianion reacts with ethylene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



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

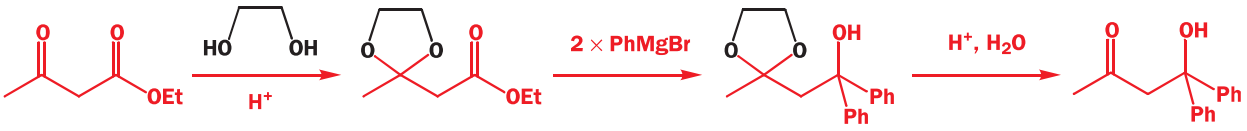
The usual way of reacting a less reactive group in the presence of a more reactive one is to use a protecting group. This tertiary alcohol, for example, could be made from a keto-ester if we could get phenylmagnesium bromide to react with the ester rather than with the ketone.

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.

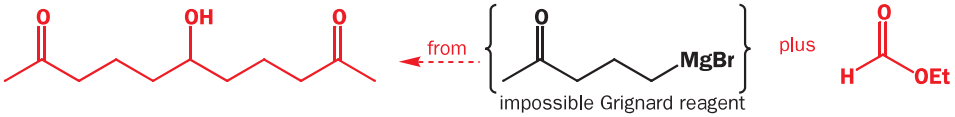


▶ This table of protecting groups will grow, line by line, as we move through this chapter and the next.

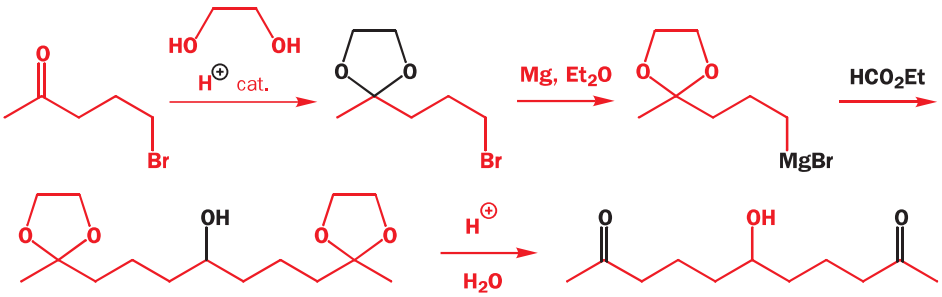
The first step puts the protecting group on to the (more electrophilic) ketone carbonyl, making it no longer reactive towards nucleophilic addition. The Grignard then adds to the ester, and finally a 'deprotection' step, acid-catalysed hydrolysis of the acetal, gives us back the ketone. An acetal is 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.

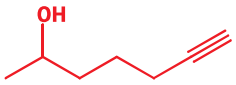
By protecting sensitive functional groups like ketones it becomes possible to make reagents that would otherwise be unstable. In a synthesis of the natural product porantherine, a compound based on this structure was needed.



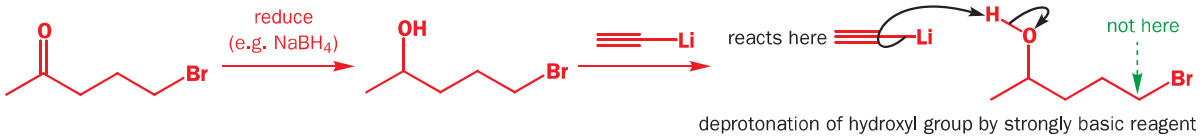
One way to make it is to add a Grignard reagent twice to ethyl formate. But, of course, a ketone-containing Grignard is an impossibility as it would self-destruct, so an acetal-protected compound was used.



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.

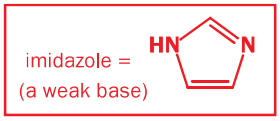


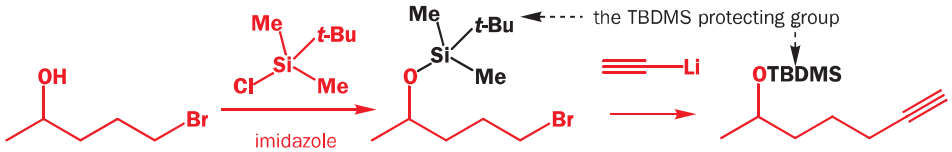
A synthesis could start with the same bromoketone as the one above: reduction gives an alcohol, but alkylation of an alkynyl anion with this compound is not possible, because the anion will just deprotonate the hydroxyl group.



deprotonation of hydroxyl group by strongly basic reagent

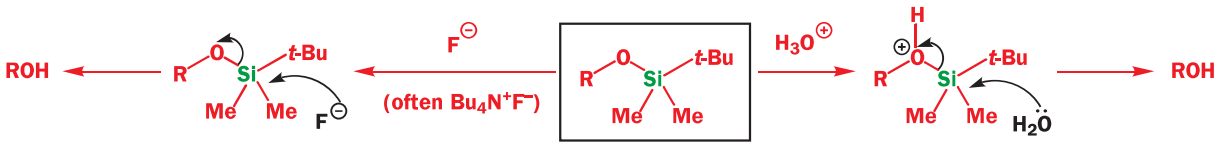
The answer is to protect the hydroxyl group, and the group chosen here was a **silyl ether**. Such ethers are made by reacting the alcohol with a trialkylsilyl chloride (here *t*-butyl dimethyl silyl chloride, or TBDMSCl) in the presence of a weak base, usually imidazole, which also acts as a nucleophilic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





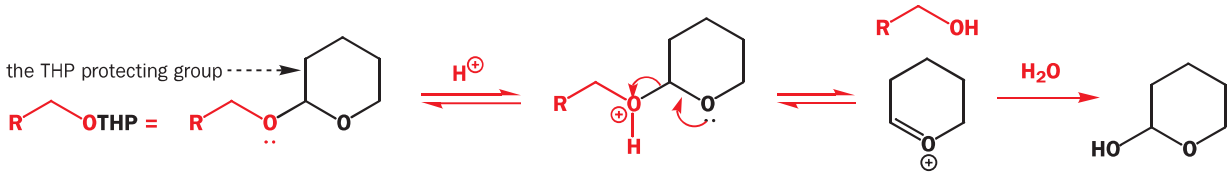
Silicon has a strong affinity for electronegative elements, particularly O, F, and Cl, so trialkylsilyl ethers are attacked by hydroxide ion, water, or fluoride ion but are more stable to carbon or nitrogen bases or nucleophiles. They are usually removed with aqueous acid or fluoride salts, particularly $Bu_4N^+F^-$ 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).



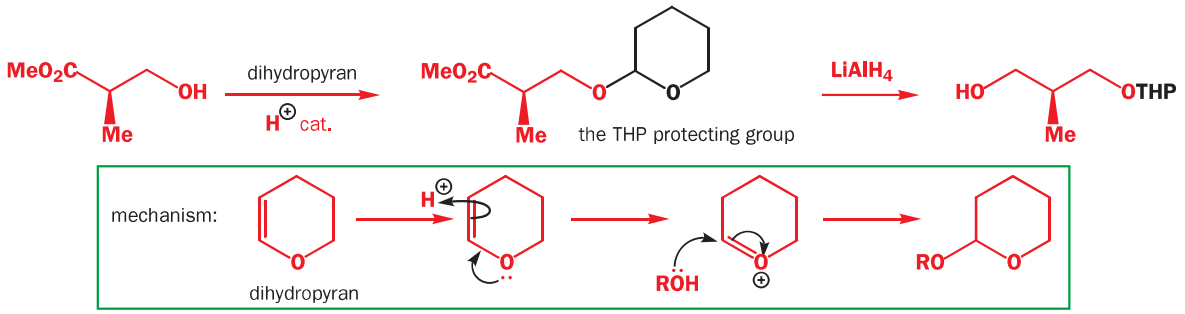
Protecting group	Structure	Protects	From	Protection	Deprotection
trialkylsilyl (R_3Si-, e.g. TBDMS)	RO—$SiMe_3$ RO—$SiMe_2Bu^t$	alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-

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.

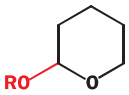


Making the THP acetal has to be done in a slightly unusual way because the usual carbonyl compound plus two alcohols is inappropriate. Alcohols are protected by reacting them with an enol ether, dihydropyran, under acid catalysis. Notice the oxonium intermediate (formed by a familiar mechanism from Chapter 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.

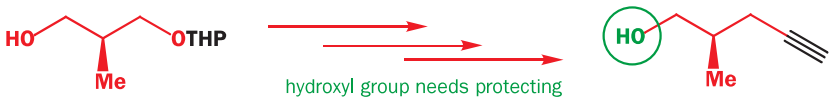
■ Some chemistry of enol ethers is in Chapter 21.



▶ 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)		alcohols (OH in general)	strong bases	 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.

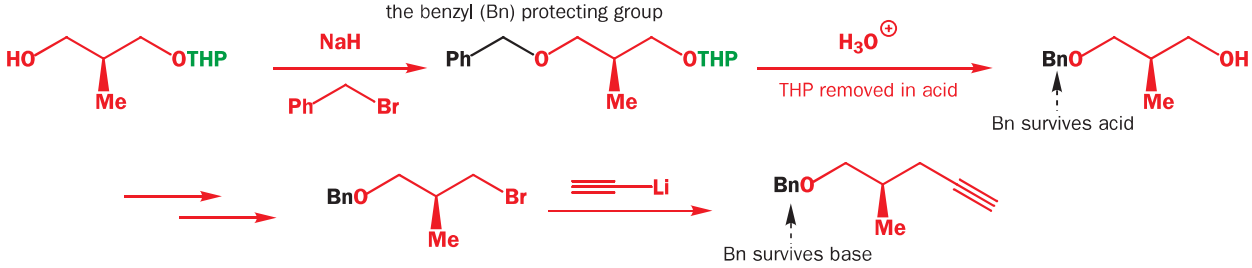


This time, though, TBDMS will not do, because the protecting group needs to withstand the acidic conditions needed to remove the THP protecting group! What is more, the protecting group needs to be able to survive acid conditions in later steps of the synthesis of the insecticide. The answer

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 benzoyl *esters*, ROCOPh, which may be abbreviated RO**Bz**.

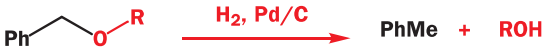
the benzyl (Bn) protecting group



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.

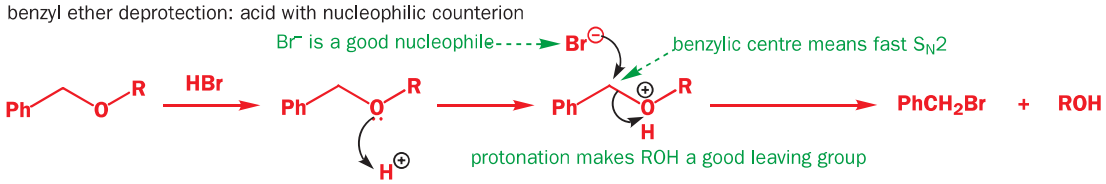
▶ It must be a *palladium* catalyst—platinum would catalyse hydrogenation of the aromatic ring.

benzyl ether deprotection: catalytic hydrogenation



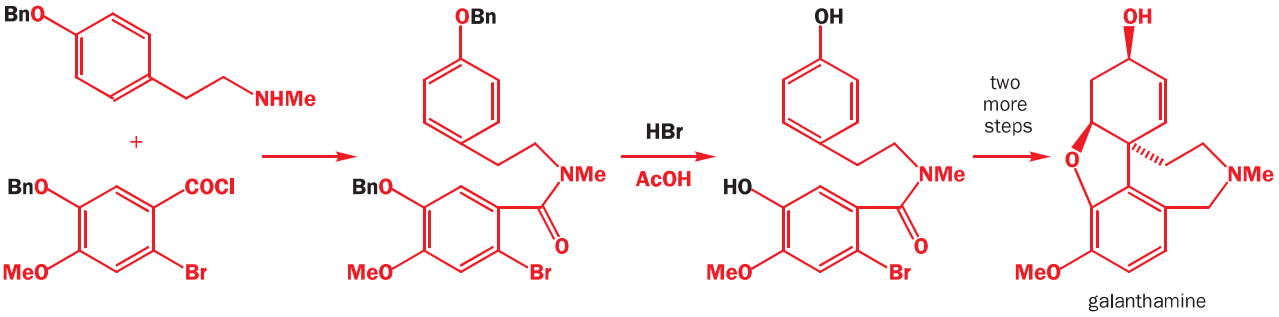
Benzyl ethers can sometimes be removed by acid, if the acid has a *nucleophilic* conjugate base. HBr, for example, will remove a benzyl ether because Br^- is a good enough nucleophile to displace ROH, though only at the reactive, benzylic centre.

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.



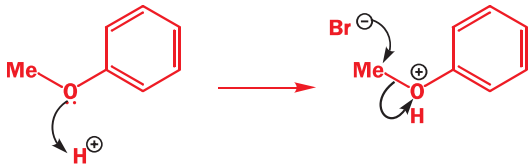
Protecting group	Structure	Protects	From	Protection	Deprotection
benzyl ether (OBn)	RO, ROBn	alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)	MeO, R	phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI

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

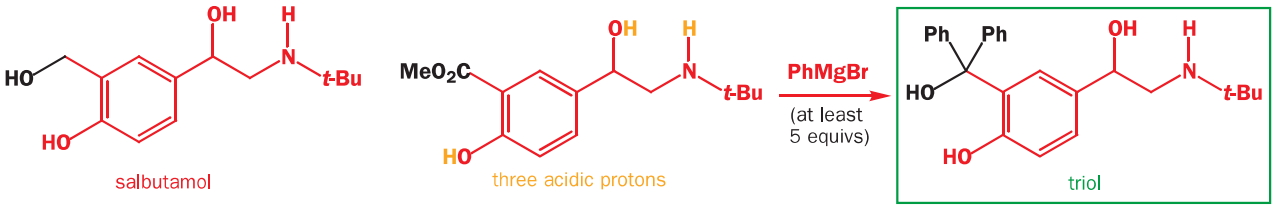
▶ Alternatives to HBr include BBr_3, usually the favoured reagent, HI, and Me_3SiI. You met the reaction of phenyl ethers with BBr_3 in Chapter 17.

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.

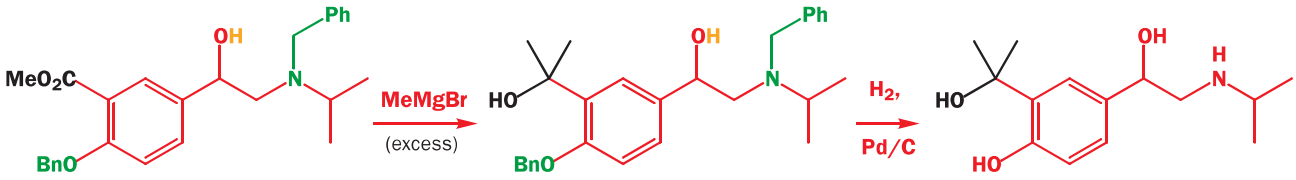
deprotection of aryl methyl ethers



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.

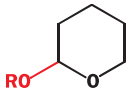


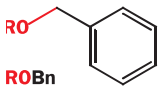
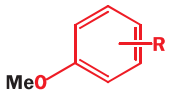
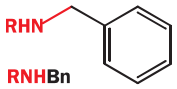
This strategy is easy to try, and, providing the Grignard reagent isn't valuable (you can buy PhMgBr in bottles), is much more economical than putting on protecting groups and taking them off again. But it doesn't always work—there is no way of telling whether it will until you try the reaction in the 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.

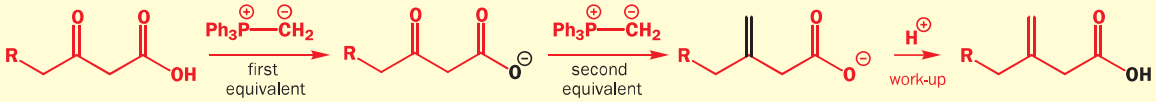
Benzyl groups are one way of protecting secondary amines against strong bases that might deprotonate them. But it is the nucleophilicity of amines that usually poses problems of chemoselectivity, rather than the acidity of their NH groups, and we come back to ways of protecting them from electrophiles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

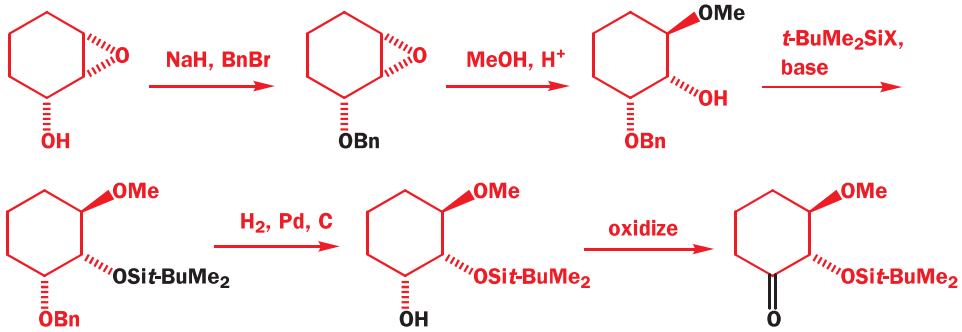
Protecting group	Structure	Protects	From	Protection	Deprotection
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI
benzyl amine (NBn)		amines	strong bases	BnBr, K_2CO_3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

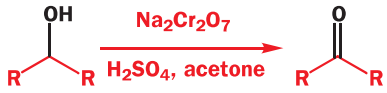
● Oxidizing agents

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

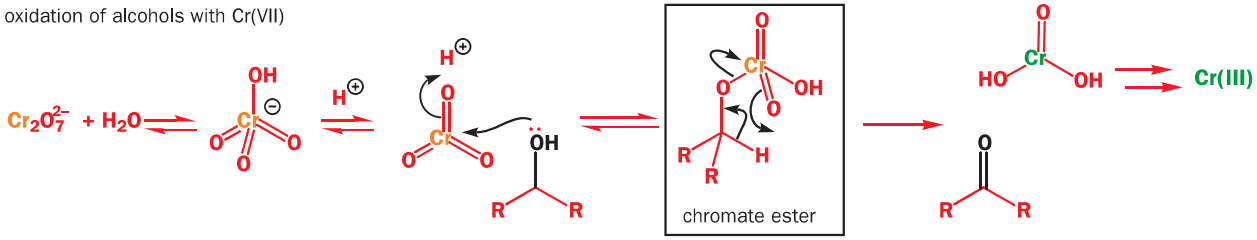
[a]not dealt with in this chapter.

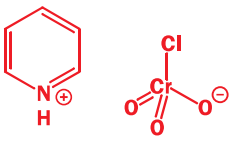
How to oxidize secondary alcohols to ketones

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.



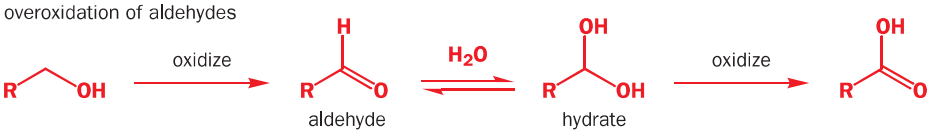


pyridinium chlorochromate, PCC

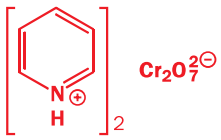
Chromic acid is best avoided if acid-sensitive alcohols are to be oxidized, and an alternative reagent for these is PCC (pyridinium chlorochromate), which can be used in dichloromethane.

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.

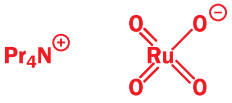


The key thing is to avoid water—so PCC in dichloromethane works quite well. The related reagent PDC (pyridinium dichromate) is particularly suitable for oxidation to aldehydes.



pyridinium dichromate, PDC

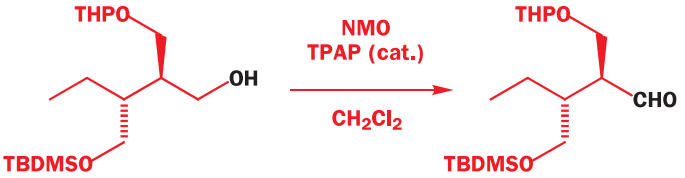
Some very mild oxidizing agents are being more and more widely used for the synthesis of very sensitive aldehydes. One of these is known as TPAP (tetra-*n*-propylammonium perruthenate, pronounced 'tee-pap').



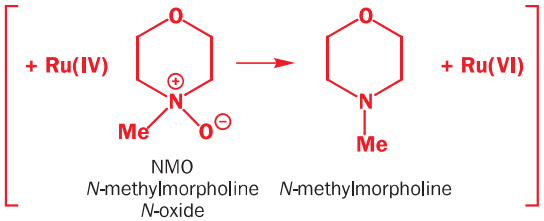
TPAP
tetrapropylammonium perruthenate

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.

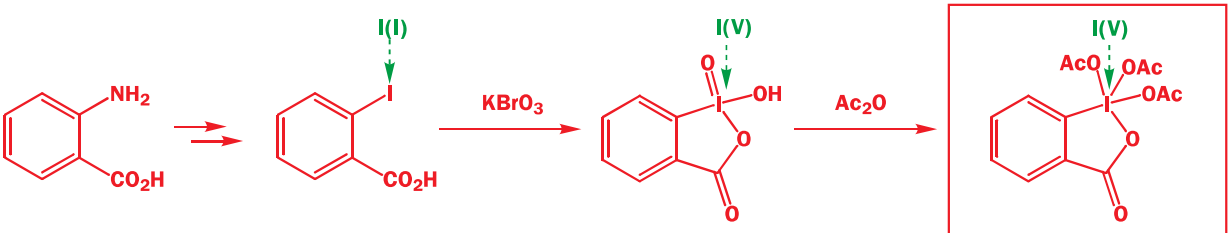


97% yield



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.



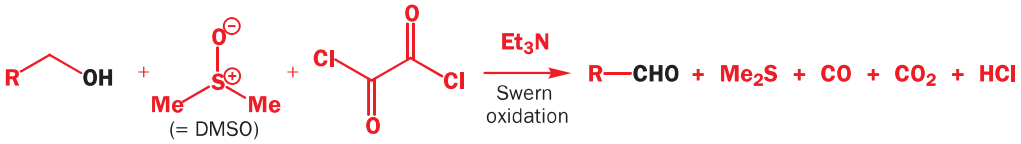
anthranilic acid

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.

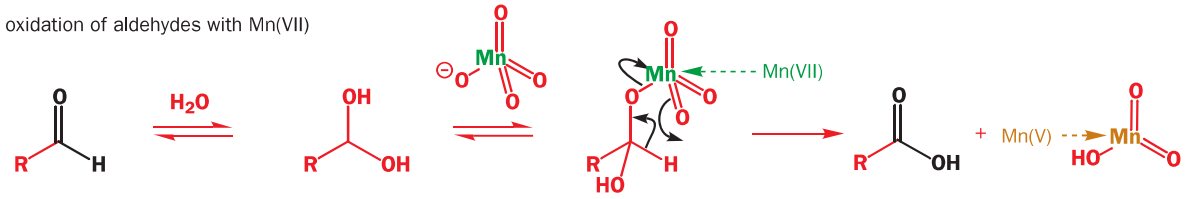
We shall leave detailed discussion of one more method till much later, in Chapter 46 (p. 000), since the mechanism involves some sulfur chemistry you will meet there. But we introduce it here because of its synthetic importance. Known as the **Swern oxidation**, it uses a sulfoxide [S(IV)] as the oxidizing 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.

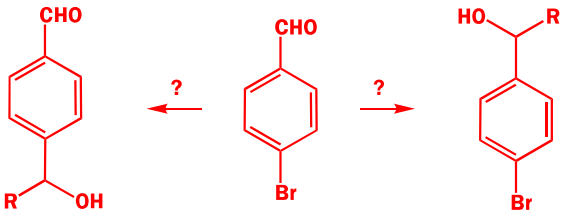


To conclude...

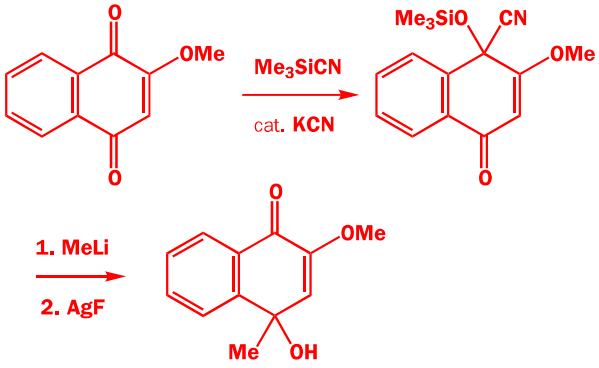
In the next chapter we will look at the ways in which the ideas and principles we have talked about in this chapter, and the reactions you have met in the 23 preceding ones, can be used in a practical way to make useful and interesting molecules. We will look at the synthesis of some of the molecules 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

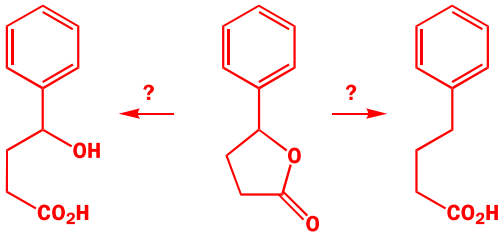
1. How would you convert this bromoaldehyde chemoselectively into the two products shown?



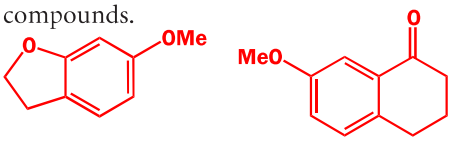
2. Explain the chemoselectivity of these reactions. What is the role of the Me_3SiCN?



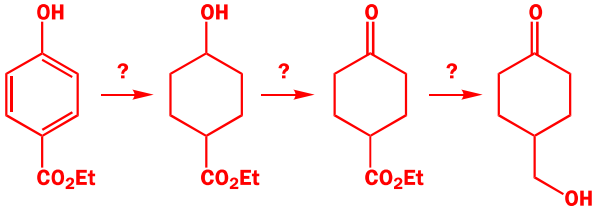
3. How would you convert this lactone selectively either into the hydroxy-acid or into the unfunctionalized acid?



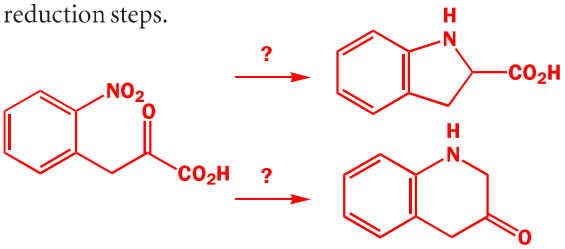
4. Predict the products of Birch reduction of these aromatic compounds.



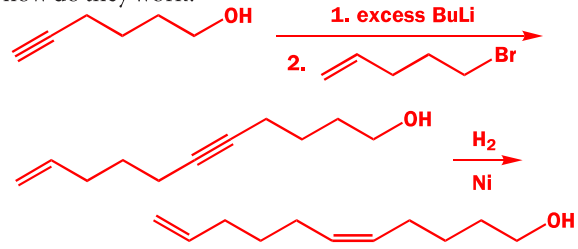
5. How would you carry out these reactions? In some cases more than one step may be needed.



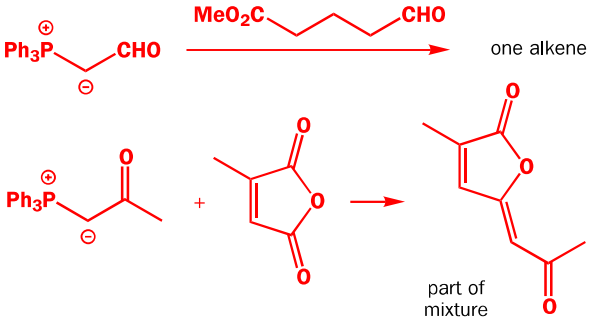
6. How would you convert this nitro compound into the two products shown? Explain the order of events with special regard to reduction steps.



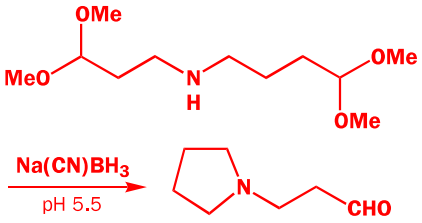
7. What kinds of selectivity are operating in these reactions and how do they work?



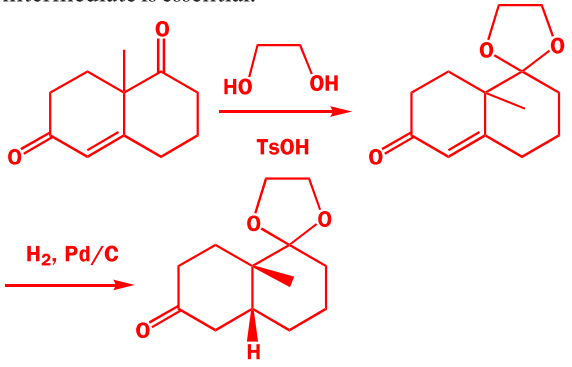
8. These two Wittig reactions (Chapter 14) give very different results. The first gives a single alkene in high yield (which?). The second gives a mixture from which one alkene can be separated with difficulty and in low yield. Why are they so different?



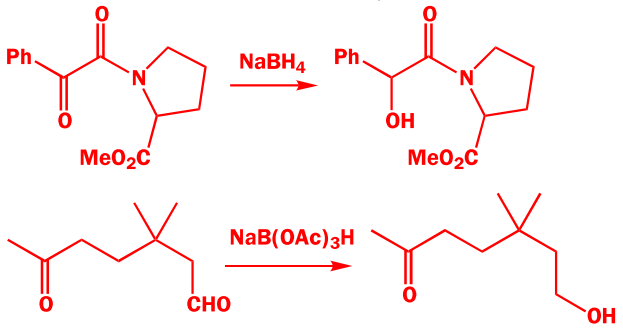
9. Why is this particular amine formed by reductive amination?



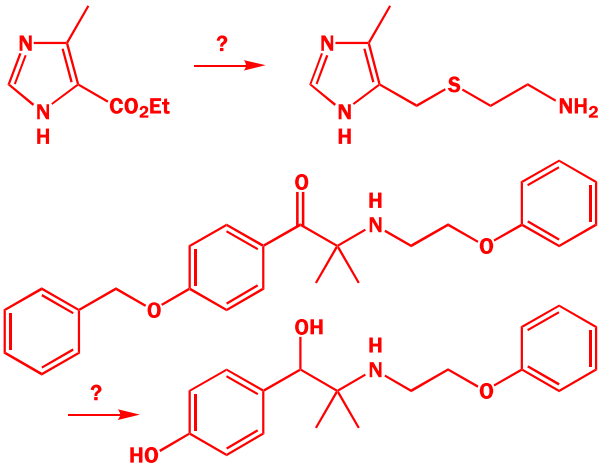
10. Account for the chemoselectivity of the first reaction and the stereoselectivity of the second. A conformational drawing of the intermediate is essential.



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.