Appendix 6: Protecting groups

Introduction: Protecting groups - general principles

In order to carry out a reaction on a particular functional group reaction, it may be necessary to 'disguise' or protect other functional groups such that they do not react as well. The ideal features of a protecting group are the following;

* It can be easily added to the target functional group in high yield and under mild conditions.
* It can easily be removed in high yield and under mild conditions.
* It remains stable to the reaction conditions used in a particular synthetic route.
* It can be removed under conditions that are different from those used to remove other types of protecting group - a property known as orthogonality.

It is also useful to have a range of different protecting groups for the same type of functional group, such that they can be removed under different conditions. This allows selective deprotection of similar functional groups.

App 6.1 Protecting groups for carboxylic acids

Carboxylic acids react with a large range of basic and nucleophilic reagents such as Grignard and organolithium reagents due to the presence of the acidic proton, which is abstracted in an acid-base reaction to give the carboxylate ion. Therefore, it is normal to protect a carboxylic acid during a synthesis. The most commonly used protecting group is an ester - typically a methyl, ethyl, benzyl, t-butyl, or trimethylsilyl ester (Fig. 1). The type of ester used needs to be stable to the reagents employed in any particular synthesis, and the choice also depends on whether the conditions for its removal can be tolerated by the rest of the molecule. Alkyl esters can be removed by hydrolysis with base, but this can be problematic if functional groups are present that are susceptible to base. Chiral compounds may also be susceptible to racemisation under basic conditions. One way round this is to use an esterase enzyme as a catalyst for hydrolysis, or to use yeast cells which contain esterase enzymes.

Alternatively, one could use an ester protecting agent that can be removed under milder, non-basic conditions. For example, a benzyl group can be removed by hydrogenolysis or by HBr in acetic acid. A *tertiary* butyl ester can be removed under aqueous acidic conditions, while a trimethylsilyl ester can be removed by treatment with a fluoride ion. The trichloroethyl ester is removed by zinc metal without affecting functional groups that are sensitive to acid, base or reduction.

Ester protecting groups are generally stable to weak bases and electrophiles, but susceptible to strong bases, nucleophiles and reducing agents.

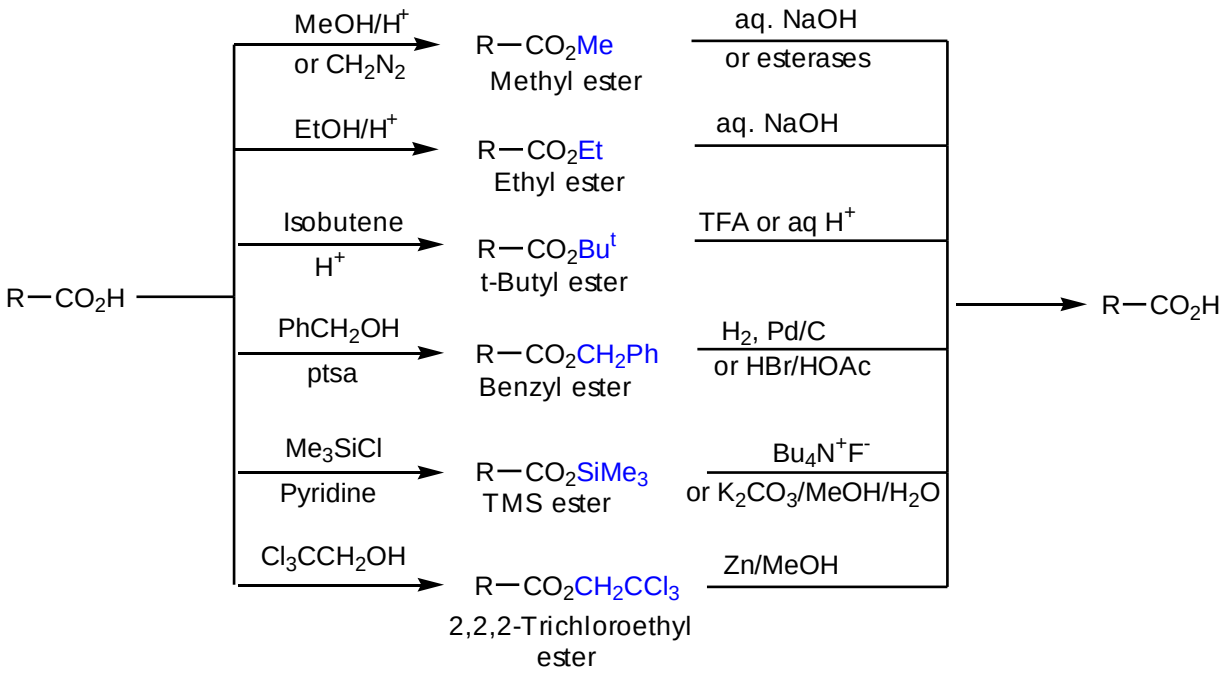

Figure 1 Ester protecting groups for carboxylic acids.

In theory, carboxylic acids could be protected as amides rather than esters, but fiercer reaction conditions are required to hydrolyse the amide group back to the carboxylic acid due to the lower reactivity of amides, and so amides are less useful as protecting groups.
Another useful method of protecting a carboxylic acid is to 'wrap it up' in an oxazoline ring (Fig. 2). The carboxylic acid can be regenerated by treatment with ethanolic HCl. Alternatively, it is possible to take advantage of the protecting group to carry out a functional group transformation that produces an aldehyde. This is carried out by *N*-methylation followed by reduction, before hydrolysis of the ring. Therefore, the oxazoline ring could be viewed as a protecting group for both a carboxylic acid and an aldehyde.

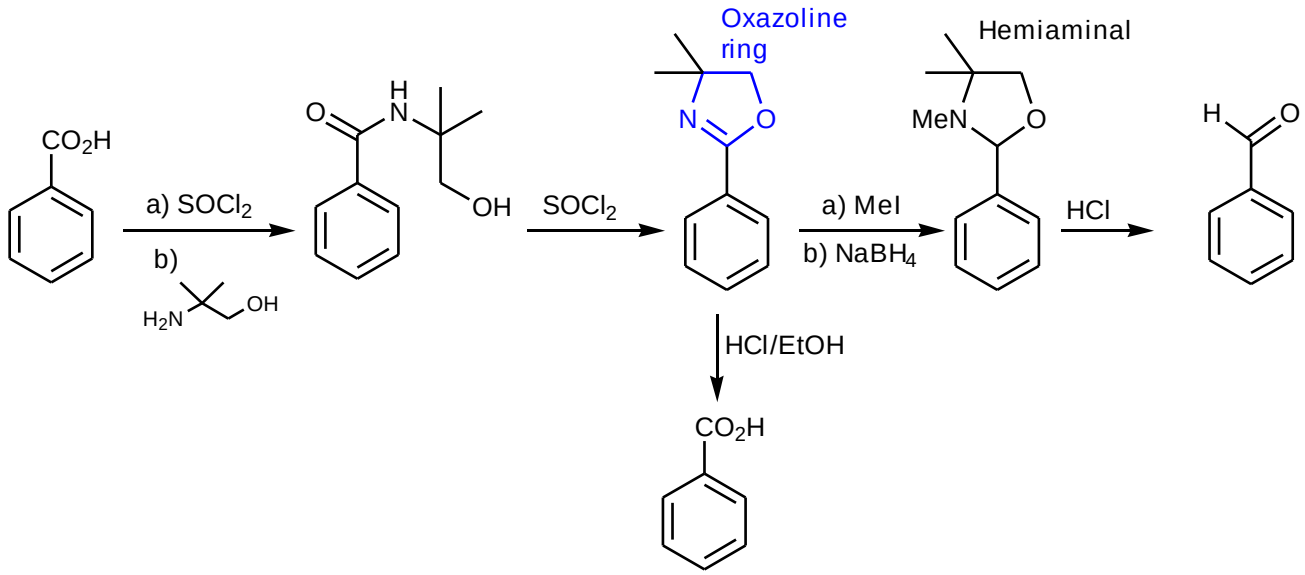

Figure 2 Oxazolines for the protection of a carboxylic acid or for its ultimate conversion to an aldehyde.

App 6.2 Protecting groups for phenols

Although the OH proton of a phenol is not as acidic as a carboxylic acid, it is acidic enough to react with a wide range of bases and nucleophiles including Grignard reagents. Therefore, it is normal to protect phenol groups during most synthetic routes. The phenol OH group is also a powerful activating group for the aromatic ring, and so protecting it helps to control any electrophilic substitution reactions that are to be carried out on the ring. The phenol can be protected as an ester or an ether (Fig. 3). A variety of different ethers can be used which involve different deprotection conditions. Ether protecting groups are generally resistant to bases and weak electrophiles.

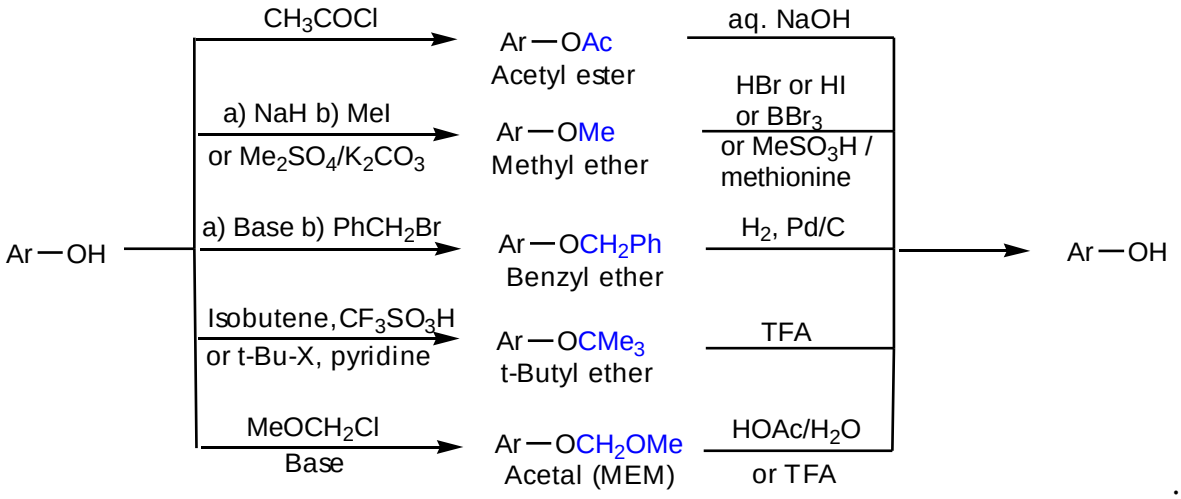

Figure 3 Protecting groups for phenols.

App 6.3 Protecting groups for alcohols

Alcohols have a slightly acidic proton which can be abstracted by strong bases and nucleophiles such as Grignard reagents. Primary and secondary alcohols are also susceptible to oxidising agents. As the alcohol group is slightly nucleophilic, it may also react with some electrophiles. Alcohols are often protected during synthetic routes, but there are some reactions where protection is not required; for example, the coupling reaction involving serine in Case Study 4; figure CS4.3 and the first stage of the synthesis of dapoxetine in chapter 5, Box 5.6. The semi-synthetic route used to produce paclitaxel is an example where some alcohol groups need protection but some do not (chapter 2.13; Fig. 2.59).
Alcohols can be protected as esters or ethers (Fig. 4) which are resistant to electrophiles and oxidising agents, and a similar variety of protecting groups to those described in appendix 6.2 can be used. Protecting groups can be applied or removed selectively with the least hindered alcohol groups being favoured (chapter 2.13; Fig. 2.60).
Alkyl ethers are effective protecting groups which are stable to a wide variety of reagents and reactions. However, that very stability can be a problem as more forcing conditions are needed for their removal, and these conditions may not be compatible with other groups in the structure. However, certain types of ethers are susceptible to less rigourous conditions for their removal. For example, a benzyl ether can be removed by hydrogenolysis using hydrogen gas and a catalyst under mild conditions.
A variety of silyl ethers are commonly used as protecting groups for alcohols, such as the trimethylsilyl group and the more bulky *tertiary* butyldimethylsilyl group. Silyl ethers are stable to nucleophiles, carbanions and bases, but can be removed with a fluoride ion due to the strong Si-F bond that is formed. Alternatively, they can be deprotected in aqueous acid. The TMS ether is more labile than most other silyl ethers and can be removed with methanol. A recent survey showed that silyl protecting groups are the most commonly used alcohol protecting groups in drug synthesis, accounting for about a quarter of all the protection strategies reported.
The THP (tetrahydropyranyl) and MEM (methoxymethyl) protecting groups are examples of acetal protecting groups which are resistant to bases and can be removed under acid conditions.

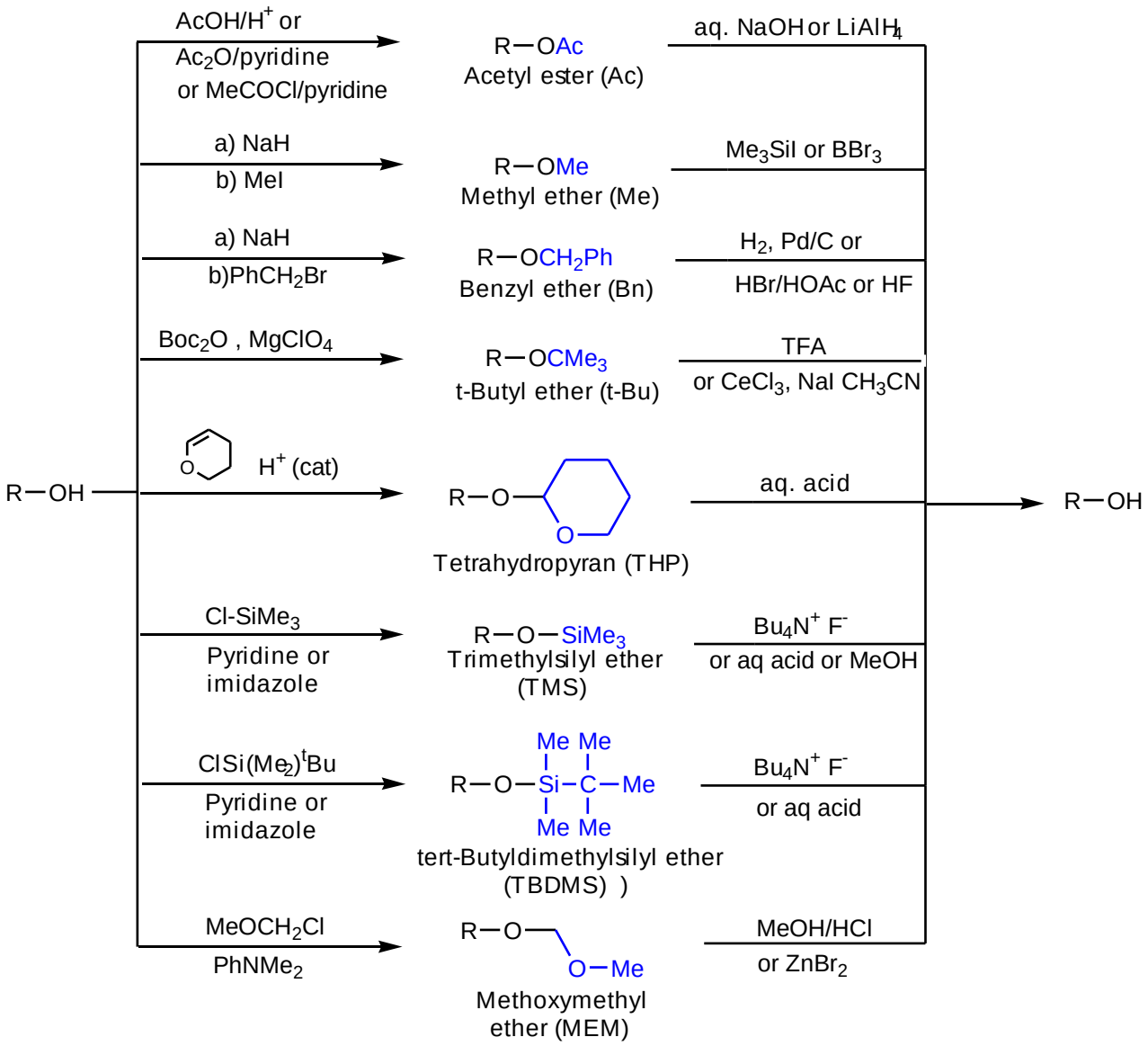

Figure 4 Protecting groups for alcohols.

App 6.4 Protecting groups for amines

It is normal to protect amines during a synthesis because of their basic and nucleophilic properties, which would cause them to react with most electrophilic reagents such as alkyl halides. Primary and secondary amines can also potentially lose a proton to a nucleophilic reagent such as a Grignard reagent.

Amines are generally protected as amides or as urethanes (Fig. 5). There are a selection of urethane functional groups available; benzyloxycarbonyl (Z or Cbz), t-butyloxycarbonyl (Boc), and fluorenylmethyloxycarbonyl (Fmoc), which can be removed under different conditions. The most popular of these is the Boc group.

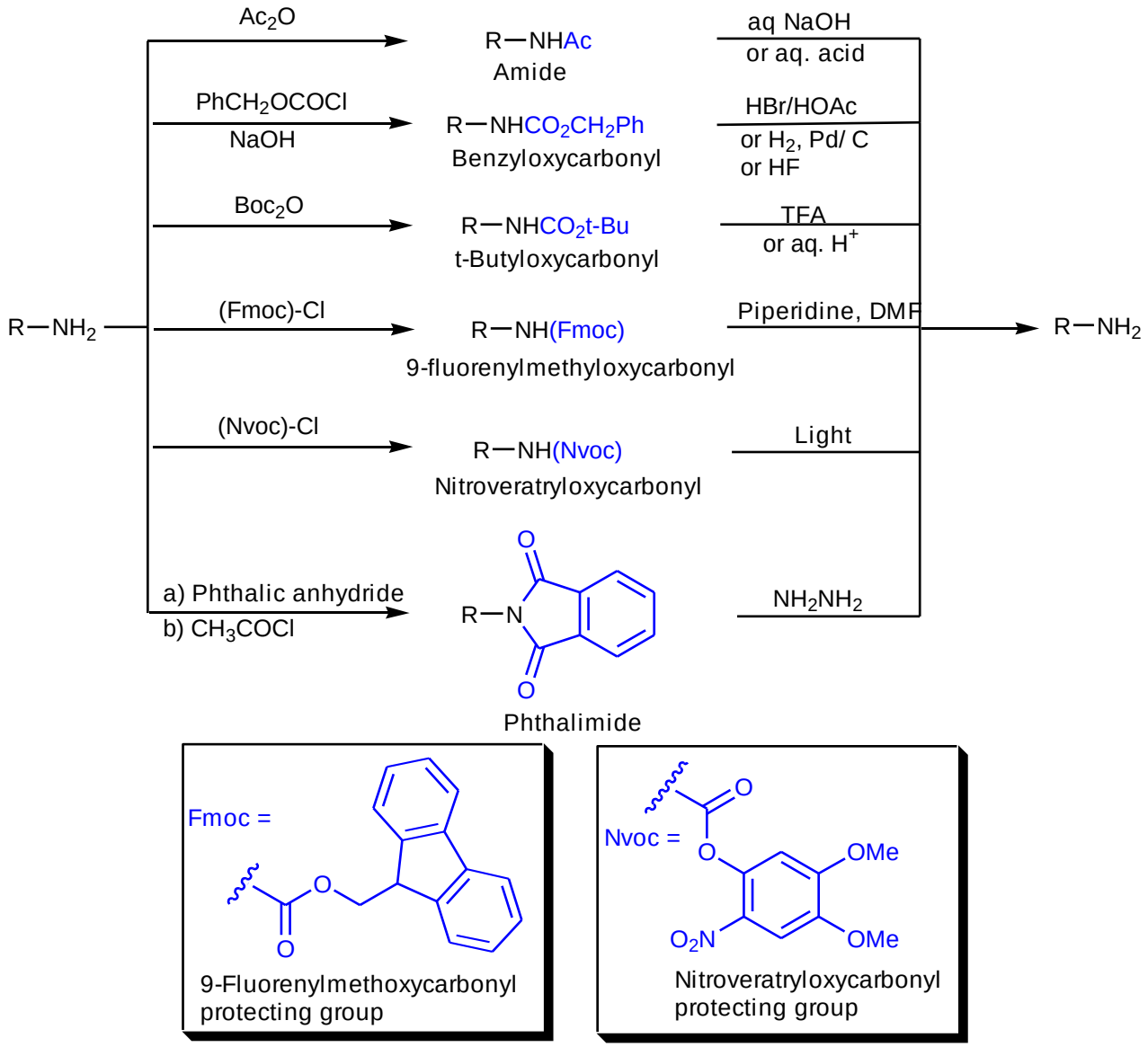

Figure 5 Protecting groups for amines.

An aromatic amine acts as a strong activating group for electrophilic substitution reactions in the aromatic ring. Sulphonation and nitration can be carried out without the need for protection, but there are problems related with other types of electrophilic substitution. It is difficult to control halogenation to a single substitution, whereas Friedel Crafts alkylation and acylation are unsuccessful because the amine group forms an acid-base complex with the Lewis acid that is required for these reactions. These problems can be avoided by protecting the group as an amide. With aromatic compounds, the conditions required to hydrolyse the amide afterwards are not usually a problem. An alternative approach to amine protection is to carry out an organic synthesis with a nitro group present instead of the amine. Reduction of the nitro group generates the amine (appendix 1.12.2), and so the nitro group can be viewed as a 'masked' amine.

App 6.5 Protecting groups for aldehydes and ketones

Aldehydes and ketones react with a wide range of nucleophiles, while aldehydes are susceptible to oxidising agents. Therefore, it is normal to protect these groups to avoid unwanted reactions. Typical protecting groups are acetals or thioacetals for aldehydes, and ketals or thioketals for ketones (Fig. 6). It is possible to protect an aldehyde selectively in the presence of a ketone due to the greater reactivity of the aldehyde group. Similarly, it is possible to protect an aliphatic ketone selectively in the presence of an aromatic ketone.

Acetals and ketals are formed when the aldehyde or ketone is treated with an excess of alcohol in the presence of an acid catalyst. The catalyst is necessary as alcohols are relatively weak nucleophiles. Cyclic acetals or ketals can be used as protecting groups by reacting the carbonyl group with a suitable diol. Acetal and ketal protecting groups are resistant to bases, nucleophiles and reducing agents, but are susceptible to electrophiles and oxidising agents. They are normally removed by treatment with aqueous acid.

Aldehydes and ketones can also be protected as thioacetals or thioketals respectively. The protecting group can be applied under acid conditions. However, the hydrolysis of the group is more difficult than the hydrolysis of acetals and ketones, and a large variety of conditions have been developed to try and tackle this problem.

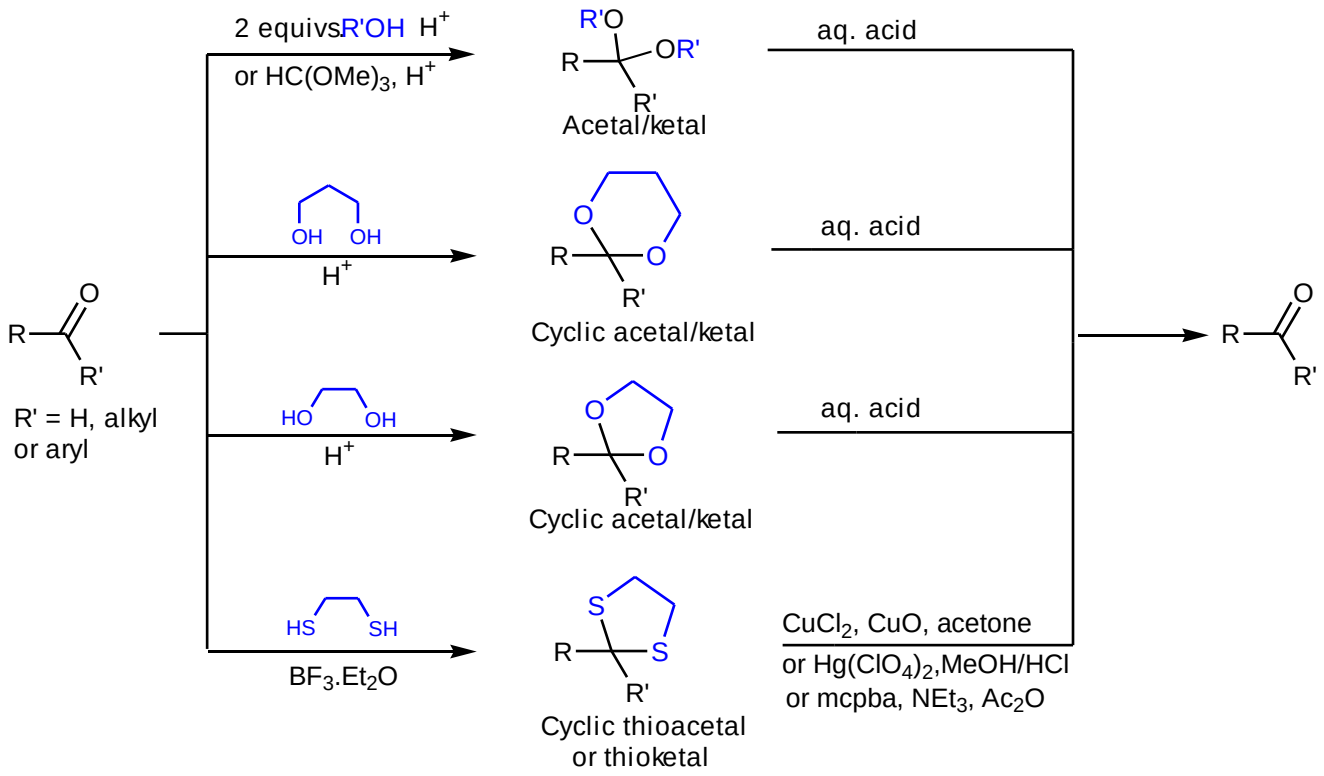

Figure 6 Protecting groups for aldehydes and ketones.

App 6.6 Protecting groups for thiols

Thiols are highly susceptible to oxidation to disulphides, and so they are normally protected during a synthesis. Thiols can be protected as thioethers (Fig. 7). However, the deprotection of thioethers can be quite harsh, which might affect other functional groups that are present. Thioester protecting groups could be used in such situations. The simplest thioester protecting group would be a thioacetate, although the 2-methoxyisobutyryl group has been recommended when a Suzuki reaction is being carried out.

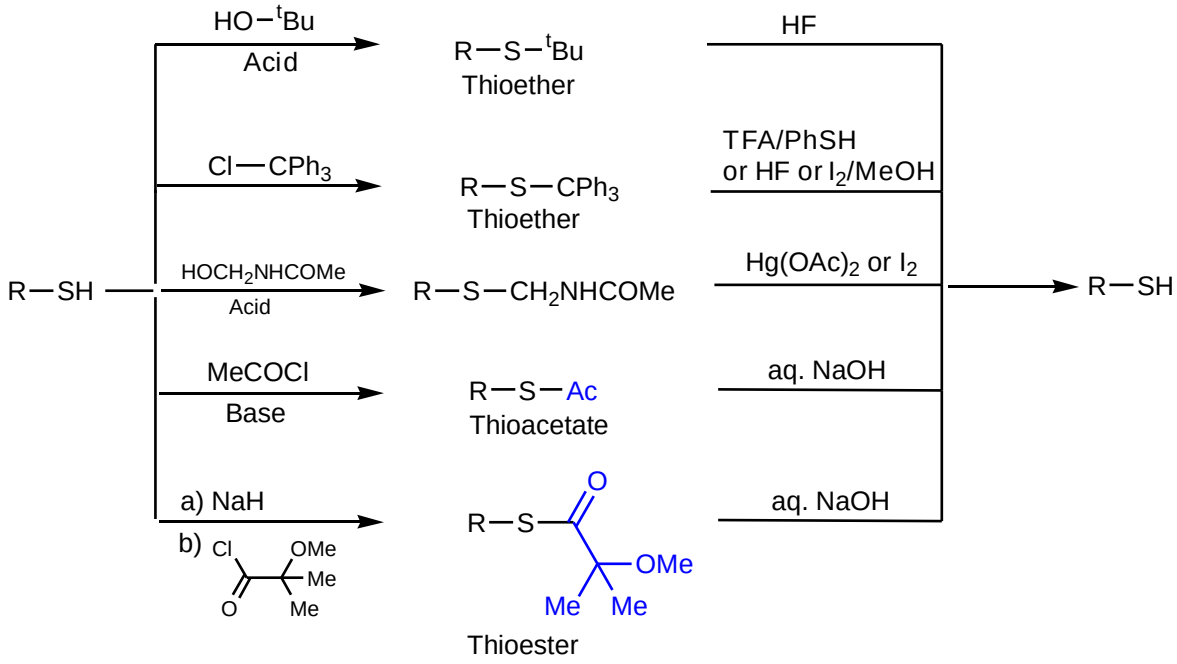

Figure 7 Protecting groups for thiols.

A different approach to the protection of thiols is to introduce a thiouronium salt (Fig. 8). The thiouronononium group acts as a masked thiol group, and can be converted to the thiol by treatment with base.

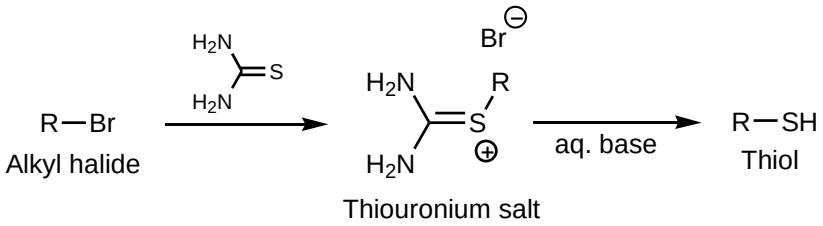

Figure 8 Introducing a masked thiol group.

App 6.7 Protecting groups for alkenes

It is not usually necessary to protect alkenes as they are 'immune' from a large number of reagents. However, if necessary, it is possible to protect an alkene with bromine by means of an electrophilic addition (Fig. 9). Deprotection then involves a debromination reaction which is carried out by treating the dibromoalkane with sodium iodide in acetone, or with zinc dust in acetic acid.

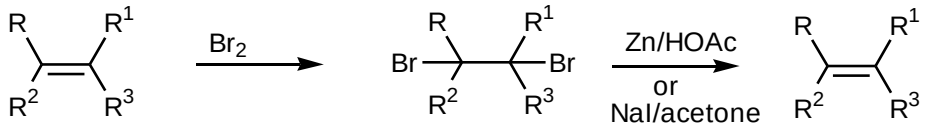

Figure 9 Protection of an alkene.

App 6.8 Protecting groups for terminal alkynes

The proton of a terminal alkyne is slightly acidic and needs to be protected if strong bases or nucleophiles are going to be used during a synthesis. The group can be protected with a trialkylsilyl group or converted to a propargyl alcohol (Fig. 10). A fluoride reagent will deprotect the trialkylsilyl group, while treatment with base converts the propargyl alcohol back to the alkyne.

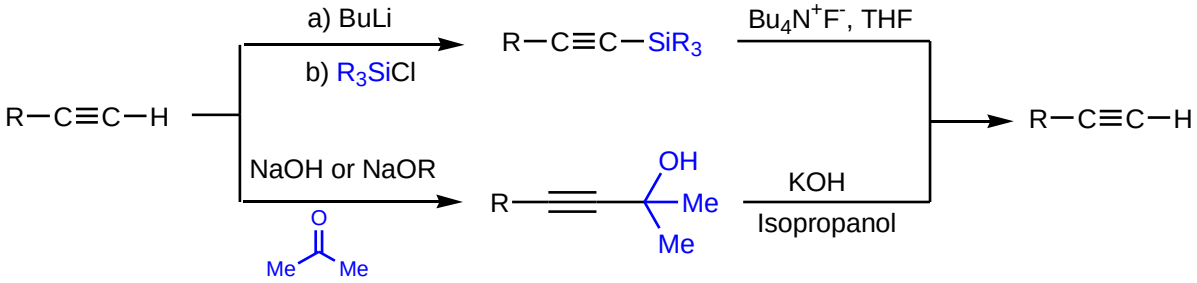

Figure 10 Protection of a terminal alkyne.

App 6.9 Protecting groups for diols

Diols can be protected by treatment with acetone to form a ketal. The diols have to be situated such that a 5, 6 or 7-membered ring is formed without undue strain (Fig. 11).

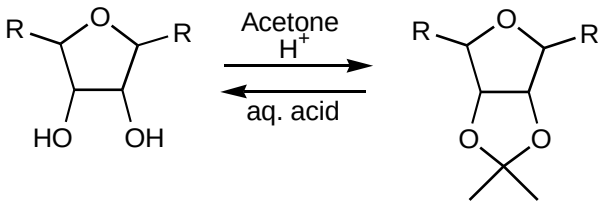

Figure 11 Protection and deprotection of a diol.