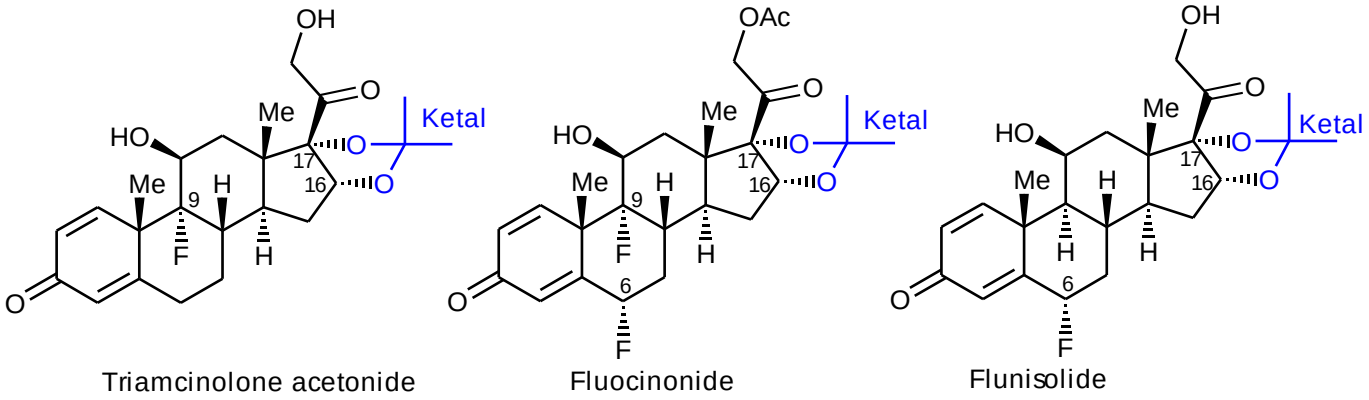
Appendix 1:Functional Group Transformations

App 1.1 Acetals/ketals

Acetals and ketals are not commonly present in drugs, although there are some important anti-inflammatory steroids which *do* contain ketals, such as triamcinolone acetonide, fluocinonide and flunisolide.



The major importance of acetals and ketals is as protecting groups for aldehydes and ketones. When an aldehyde or ketone is treated with an excess of alcohol in the presence of an acid catalyst such as *para*-toluenesulphonic acid, two molecules of alcohol are added to the carbonyl compound to give an acetal or a ketal respectively (Fig. 1). Alcohols are relatively weak nucleophiles, and so the acid catalyst is usually required. The aldehyde or ketone can be regenerated by treating the acetal or ketal with aqueous acid. Water is formed as a byproduct and should be removed from the reaction to shift the equilibrium to products. This can be done by carrying out the reaction under reflux with a Dean and Stark apparatus or with a soxhlet apparatus containing molecular sieves to trap the water. Alternatively, triethylorthoformate can be used as a dehydrating agent.

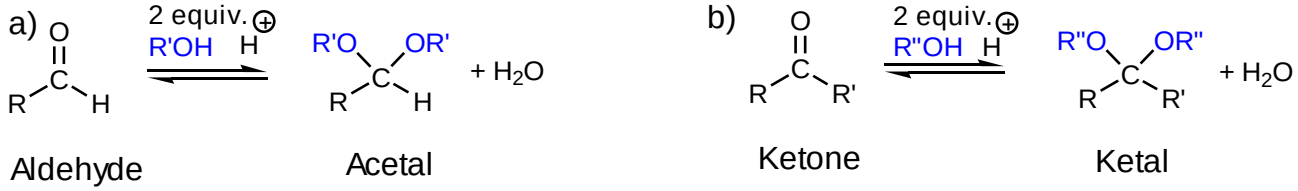


Figure 1 Formation of an acetal and ketal from aldehyde and ketone.

App 1.2 Acid anhydrides

Acid anhydrides are very useful as acylating agents in order to convert alcohols or phenols into esters. For example, acetic anhydride was used to acylate phenol groups in the synthesis of aspirin and heroin - two of the first semi-synthetic drugs to be prepared in the laboratory. Acid anhydrides are best prepared by treating acid chlorides with a carboxylate salt (Fig. 2).

Carboxylic acids are not easily converted to acid anhydrides directly. However five-membered and six-membered cyclic anhydrides can be synthesized from diacids by heating the acyclic structures to eliminate water (Fig. 2).
Because of their reactivity, acid anhydrides are easily hydrolysed in aqueous conditions, and so there are no examples of drugs containing this functional group.

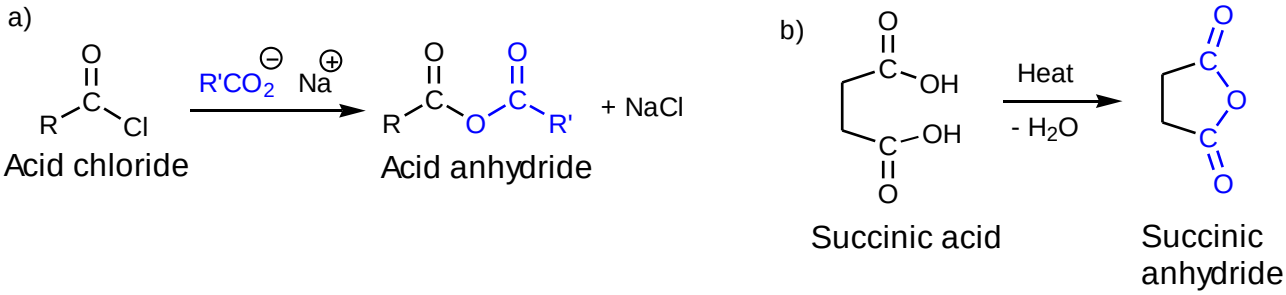


Figure 2 Preparation of acid anhydrides.

App 1.3 Acid chlorides

Like acid anhydrides, acid chlorides are useful acylating agents in organic synthesis. They can be prepared from carboxylic acids using thionyl chloride, phosphorus trichloride or oxalyl chloride (Fig. 3). Carrying out an acylation with an acid chloride is more economical than using an acid anhydride, as one half of the anhydride is wasted. Not surprisingly, acid chlorides are too reactive to survive in aqueous conditions and are not found in drugs.

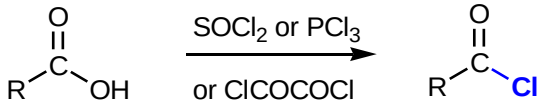
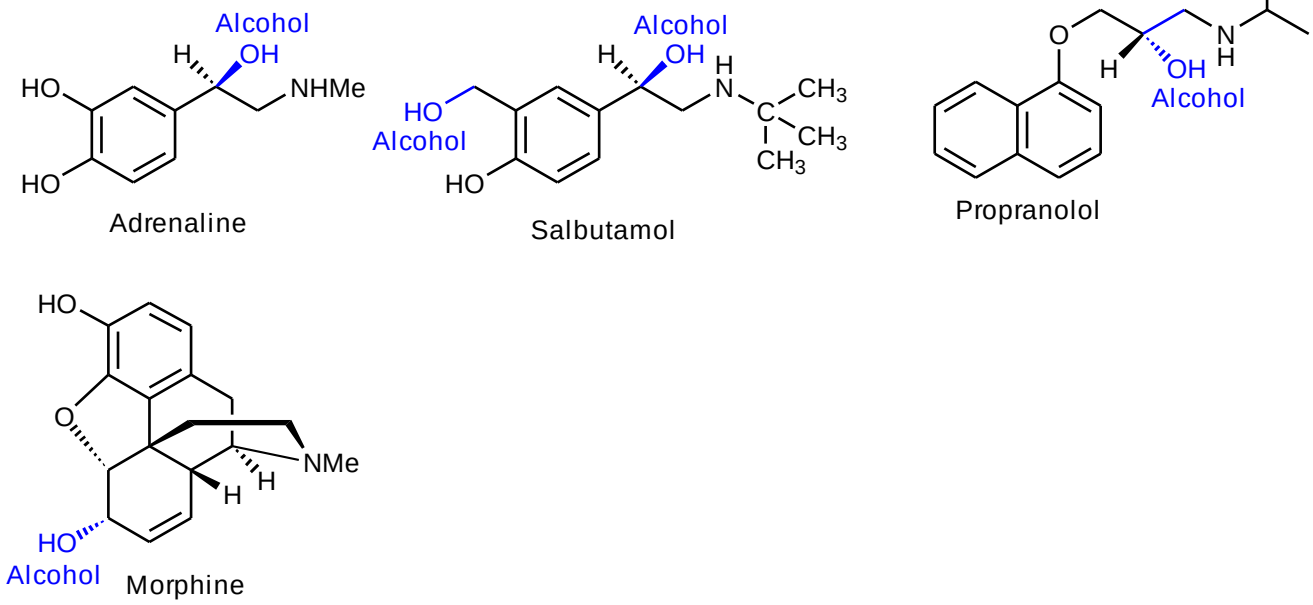


Figure 3 Synthesis of acid chlorides from carboxylic acids.

App 1.4 Alcohols

Alcohols (alkanols) are present in a large number of drugs where they can act as important hydrogen bonding groups. Examples include salbutamol, adrenaline, propranolol, and morphine.



Several functional groups such as esters, alkenes, aldehydes, ketones, carboxylic acids, esters, alkyl halides, and ethers can be converted to an alcohol. Alcohols can also be formed as a result of carbon-carbon bond formations (Appendix 5.1).

App 1.4.1 Hydrolysis of esters to carboxylic acids and alcohols

Esters can be hydrolysed to carboxylic acids and alcohols by heating them under acidic or basic conditions (Fig. 4a). Basic hydrolysis is efficient and irreversible as the resulting carboxylic acid is ionised to a stable carboxylate ion. Acid-catalyzed hydrolysis is not as effective since all the steps in the mechanism are reversible and there is no salt formation to pull the reaction through to products. Therefore, it is important to use an excess of water in order to shift the equilibrium to the products. Only a catalytic amount of acid is required since the protons used during the reaction mechanism are regenerated.

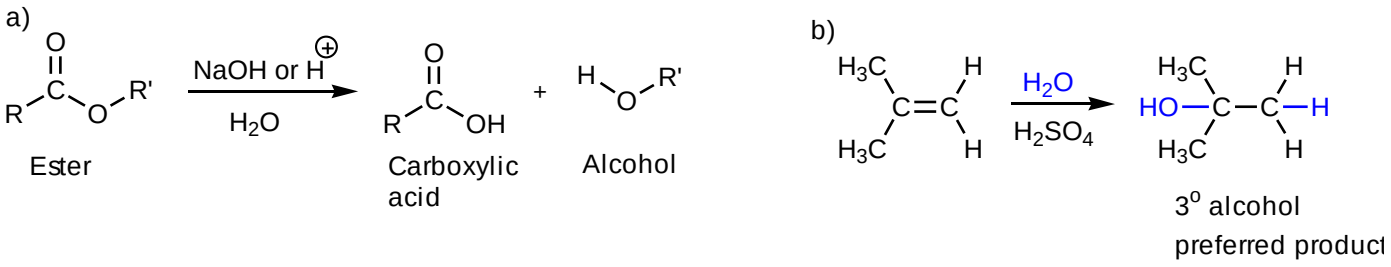


Figure 4 Synthesis of alcohols from a) esters and b) alkenes.

App 1.4.2 Hydration of alkenes to alcohols

Alkenes can be converted to alcohols by treatment with aqueous acid (sulphuric or phosphoric acid) (Fig. 4b). This is an electrophilic addition reaction involving the addition of water across the double bond. With unsymmetrical alkenes, the more substituted alcohol is the preferred product.
The reaction conditions used in this reaction include heating, which can sometimes cause unwanted rearrangement reactions to take place. A milder method which avoids this problem is to treat the alkene with mercuric acetate, then sodium borohydride. The more substituted alcohol is again obtained from unsymmetrical alkenes (Fig. 5).

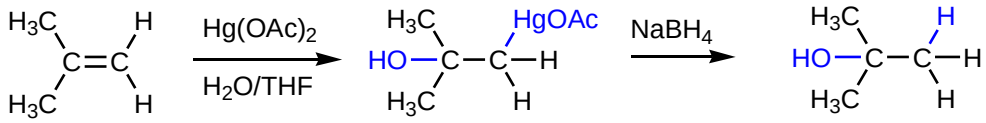


Figure 5 Synthesis of alcohols from alkenes under milder conditions.

Alcohols can also be generated from alkenes by reaction with diborane to give an organoborane intermediate, which can then be oxidized with alkaline hydrogen peroxide to produce the alcohol. With unsymmetrical alkenes, the least substituted alcohol is obtained (the anti-Markovnikov product) (Fig. 6), and so the organoborane reaction is complementary to the electrophilic addition reactions described above.

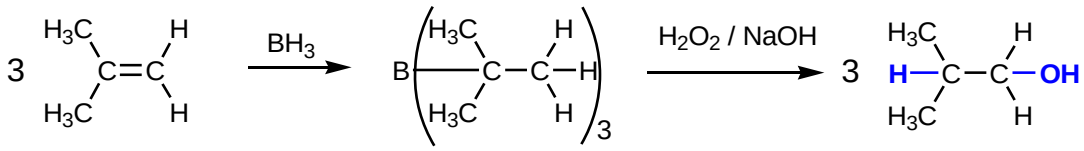


Figure 6 Synthesis of alcohols using diborane and hydrogen peroxide.

App 1.4.3 Reduction of aldehydes and ketones to alcohols
A variety of reducing agents can be used to reduce aldehydes and ketones to alcohols. One of the most convenient of these is sodium borohydride, which reduces aldehydes and ketones to primary and secondary alcohols respectively (Fig. 7). Sodium borohydride is a mild, selective reducing agent which is easy to handle and leaves other functional groups such as alkenes, carboxylic acids, amides, esters and nitriles unaffected. Sodium cyanoborohydride ($NaBH_3CN$) is an even milder reducing agent and will reduce aldehydes but not ketones. Another selective agent is disiamylborane $BH(CHMeCHMe_2)_2$, which reduces aldehydes and ketones without affecting carboxylic acids, esters, or nitriles.
There are times when it is relevant to use a stronger, less selective reducing agent if several functional groups are to be reduced at the same time. For example, lithium aluminium hydride ($LiAlH_4$) or diborane (B_2H_6) can be used to reduce an aldehyde or a ketone at the same time as an ester. Other reducing agents that can be used to reduce a number of functional groups including aldehydes and ketones are aluminium hydride (AlH_3) and diisobutylaluminium hydride (DIBAH).

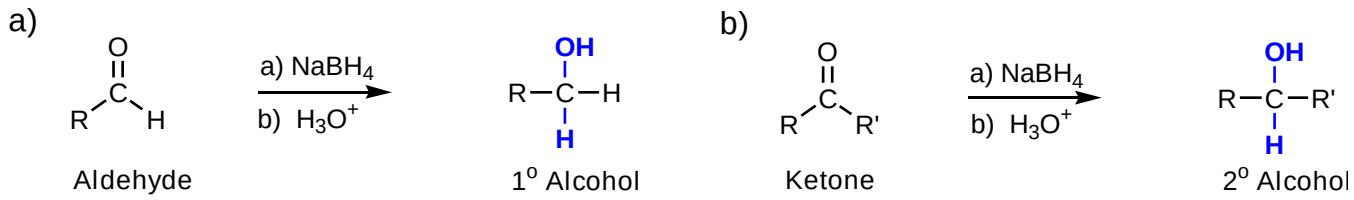


Figure 7 Reduction of aldehydes and ketones to primary and secondary alcohols.

App 1.4.4 Reduction of carboxylic acids and esters to alcohols

Carboxylic acids and esters can be reduced to primary alcohols on treatment with lithium aluminium hydride, with esters being more easily reduced (Fig. 8). The reagent must be handled carefully since it is dusty and ignites with water. Therefore, the reaction must be carried out with an aprotic solvent under a nitrogen atmosphere. Sodium bis(2-methoxyethoxy)aluminium hydride, $NaAlH_2(OCH_2CH_2OMe)_2$ (SMEAH) can be used as an alternative to $LiAlH_4$ and has the advantages of being more soluble and less flammable.

Acid chlorides and acid anhydrides are converted to alcohols with lithium aluminium hydride, but there is little synthetic advantage in this since the same reaction can be achieved on the more readily available esters and carboxylic acids.

Aldehydes and ketones are also reduced by these reagents and would have to be protected if they are to be retained.

Figure 8 Reduction of esters and carboxylic acids to primary alcohols.

Borane is another reagent that can be used to reduce carboxylic acids to primary alcohols. One advantage of using borane rather than lithium aluminium hydride is the fact that borane is selective for electron-rich carbonyl groups and does not reduce any nitro or ester groups which might be present. However, amides and aldehydes are susceptible. DIBAH [$AlH(CH_2CHMe_2)_2$] is more reactive than diborane and will reduce both carboxylic acids and esters.

Sodium borohydride can be used to reduce phenolic esters (ArOCOR) to the phenol and alcohol, but reduction of other esters is usually too slow to be useful. However, lithium borohydride in alcohol solution is a safer alternative to $LiAlH_4$ for the reduction of esters, and leaves amides and carboxylic acids unaffected.

App 1.4.5 Synthesis of alcohols from alkyl halides

The nucleophilic substitution of an alkyl halide with sodium hydroxide can generate alcohols (Fig. 9a). However, alkenes may also be obtained as a result of competing elimination reactions.

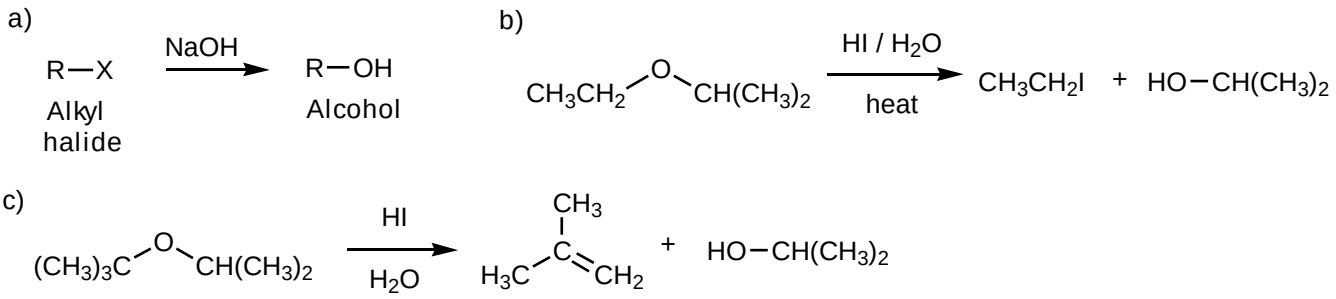


Figure 9 Synthesis of alcohols from alkyl halides or ethers.

App 1.4.6 Synthesis of alcohols from ethers

Ethers are generally unreactive functional groups, but can be cleaved by strong acids such as HI and HBr to produce an alkyl halide and an alcohol (Fig. 9b). Primary and secondary ethers react by the S_N2 mechanism and the halide reacts at the least substituted carbon atom.

Tertiary ethers are likely to give a mixture of an alkene and an alcohol as a result of competing S_N1 and E1 mechanisms (Fig. 9c). Trifluoroacetic acid can be used as the reagent instead of HX.

App 1.5 Aldehydes

Aldehydes (alkanals) are rarely present in drugs as they are easily oxidised by metabolic enzymes in the body. However, they are extremely important in organic synthesis as they are involved in several reactions that lead to carbon-carbon bond formation (Appendix 5.2). Aldehydes can be synthesized by the oxidation of primary alcohols, or by the reduction of esters, acid chlorides or nitriles. They are easily converted to carboxylic acids or primary alcohols once they have served their purpose.

App 1.5.1 Reduction of functional groups to aldehydes

A number of functional groups (nitriles, acid chlorides, amides and esters) can be reduced to aldehydes (Fig. 10).

Nitriles and amides are normally reduced to amines with lithium aluminium hydride, but with a milder, sterically-hindered reducing agent such as diisobutyl aluminium hydride (DIBAH or DIBAL), it may be possible to stop the reaction after the addition of one hydride ion to give the aldehyde instead. However, this is not guaranteed to work in every case. Aromatic nitriles can be reduced to aromatic aldehydes with DIBAH or with stannous chloride and HCl.

Acid chlorides and esters are normally reduced by $LiAlH_4$ to primary alcohols, but aldehydes can be obtained if a milder hydride reducing agent is used. For example, acid chlorides are reduced at -78^{o}C with lithium tri-*tert*-butoxyaluminium hydride. The reagent contains three bulky alkoxy groups that lower the reactivity of the remaining hydride ion such that the reaction stops at the aldehyde. The reagent can also be used to reduce amides to aldehydes. An alternative way of reducing acid chlorides to aldehydes is to carry out a hydrogenation in the presence of a tertiary base and a palladium catalyst on a barium sulphate support. The base serves to neutralise HCl and to reduce the activity of the catalyst.

Esters can be reduced to aldehydes with DIBAH or $NaAlH_2(OCH_2CH_2OMe)_2$. Normally, low temperatures are needed to avoid over-reduction of the aldehyde product to the alcohol. However, it can sometimes prove difficult to control the reaction since the aldehyde is more reactive than the

initial ester, in which case it may be better to reduce the ester to an alcohol and then oxidise that to the aldehyde.

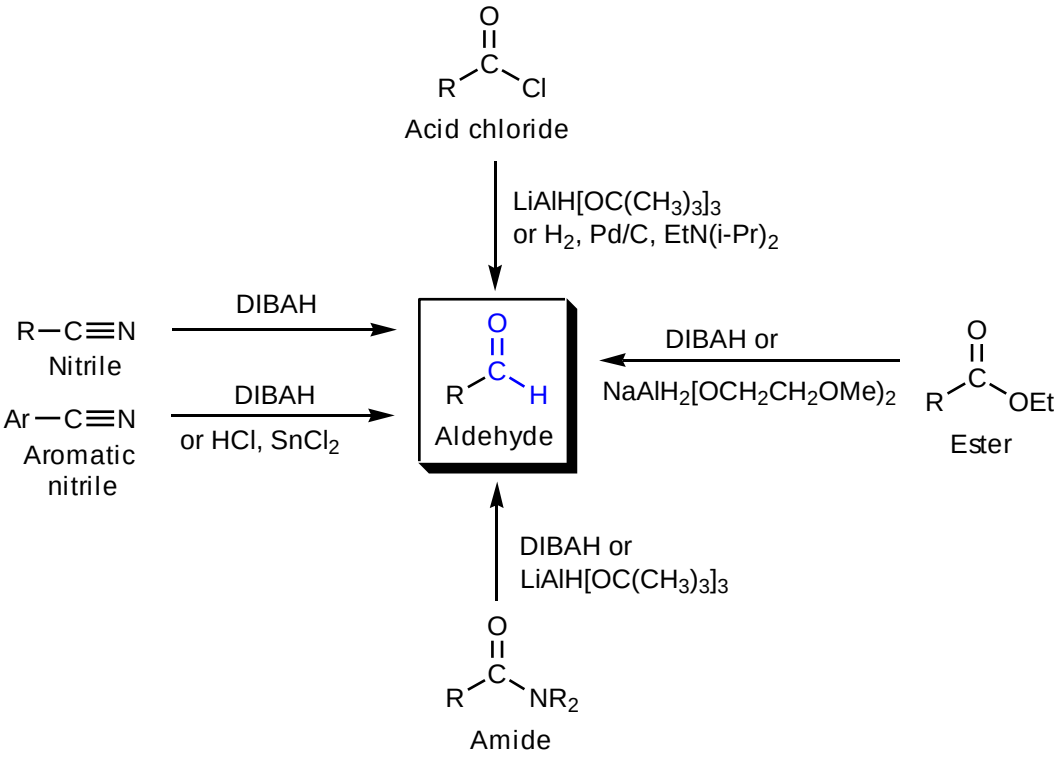


Figure 10 Aldehydes from the reduction of nitriles, esters, amides and acid chlorides (DIBAH = $AlH(CH_2CHMe_2)_2$).

App 1.5.2 Conversion of terminal alkynes to aldehydes

The hydrolysis of terminal alkynes generates methyl ketones rather than aldehydes. However, aldehydes can be obtained by treating the alkyne with 9-BBN, followed by hydrogen peroxide under basic conditions (Fig. 11).

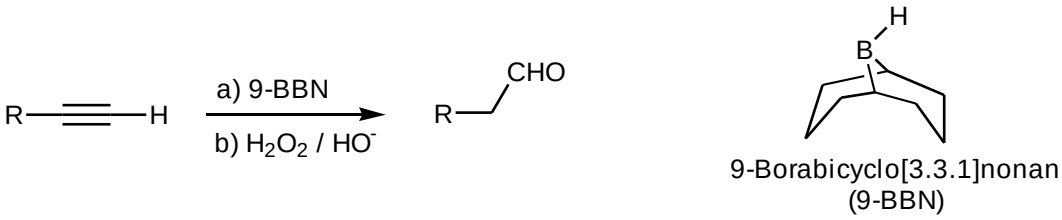


Figure 11 Aldehydes from terminal alkynes.

App 1.5.3 Oxidation of alcohols to aldehydes

Primary alcohols can be oxidized to aldehydes using Jones reagent (CrO_3/H_2SO_4), but the reaction is tricky since there is the danger of over-oxidation to carboxylic acids. With volatile aldehydes, the

aldehydes can be distilled from the reaction solution as they are formed. However, this is not possible for less volatile aldehydes. This problem can be overcome by using a mild oxidizing agent such as pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC) (Fig. 12). The success of these oxidations is solvent dependant and involves the use of methylene chloride rather than aqueous acid. Because the oxidation is not carried out under acidic conditions, acid-sensitive protecting groups such as acetals or silyl ethers are unaffected. Unfortunately, the reaction involves the use of toxic chromium salts and so these procedures are not suitable for large scale syntheses.

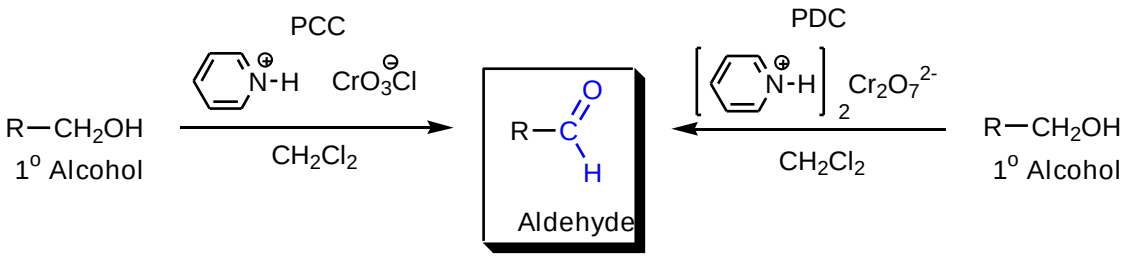


Figure 12 Oxidation of primary alcohols to aldehydes.

The Swern oxidation (Fig. **13**) is an alternative method of oxidising primary alcohols, which avoids the use of toxic chromium salts. Dimethylsulphoxide (DMSO) is activated by an electrophile such as oxalyl chloride to form the oxidising agent i*n situ*. An acid chloride or acid anhydride can be used to activate DMSO instead of oxalyl chloride.

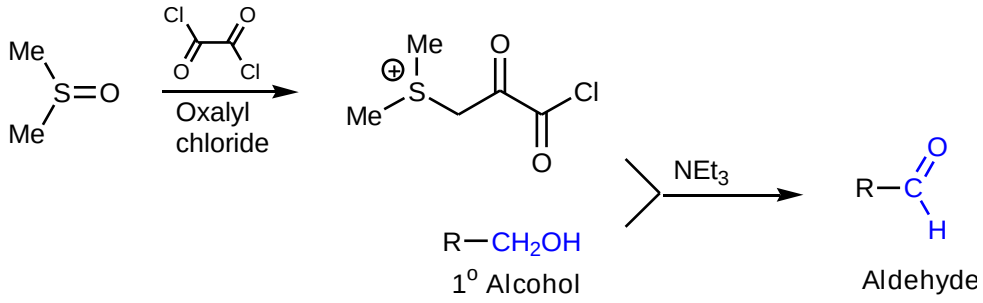


Figure 13 Swern oxidation of primary alcohols to aldehydes.

Dess-Martin periodinane is a very mild oxidising agent which is commonly used to oxidise acid-sensitive alcohols to aldehydes (Fig. 14). Another mild way of oxidising primary alcohols to aldehydes is to use tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) (Fig. **14**). TPAP acts as the oxidising agent while NMO serves to regenerate the TPAP throughout the reaction. This allows TPAP to be used in catalytic quantities.

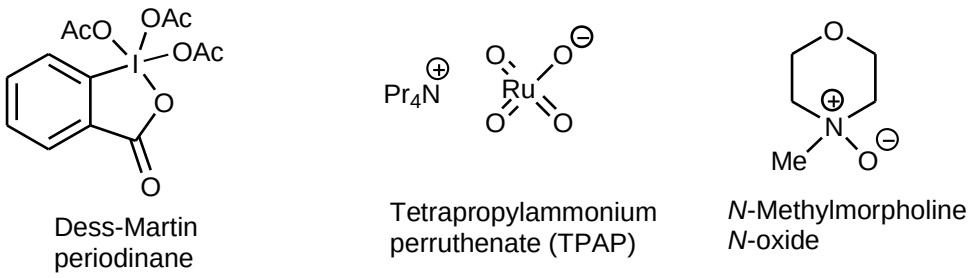


Figure 14 Mild oxidising agents used to convert alcohols to aldehydes.

App 1.5.4 Oxidation of aromatic methyl groups to aromatic aldehydes

Aromatic aldehydes can be synthesised by oxidising aromatic methyl groups with tetraalkylammonium permanganate in acetic acid, or with chromium trioxide in acetic anhydride (Fig. 15). The reaction can also be carried out with chromyl chloride (CrO_2Cl_2) in carbon tetrachloride or carbon disulfide. In these reactions, intermediates or complexes are formed which prevent the aldehydes being oxidised further to carboxylic acids.

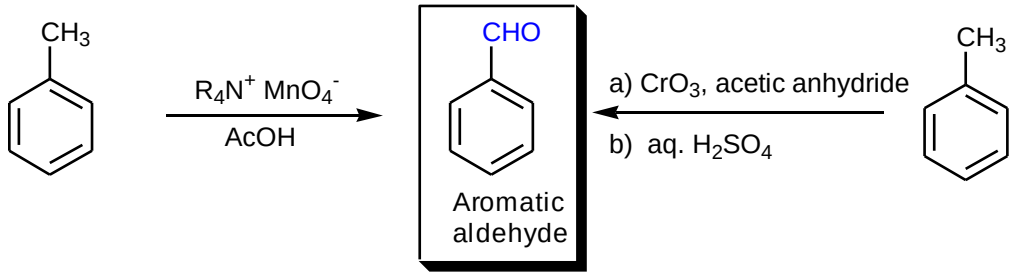


Figure 15 Oxidation of aromatic methyl groups to aromatic aldehydes.

App 1.5.5 Ozonolysis of alkenes to aldehydes and ketones

Treatment of an alkene with ozone results in oxidation of the alkene and formation of an initial ozonide, which then rearranges to an isomeric ozonide. This second ozonide is unstable and potentially explosive and so it is not usually isolated. Instead, it is reduced with zinc and water to form two carbonyl compounds. These will be ketones or aldehydes depending on the substituents present. For example, 3-methyl-2-pentene gives an aldehyde and a ketone (Fig. 16). Ozone shows a high level of selectivity for alkenes over other functional groups, and will react preferentially with electron-rich double bonds. Functional groups such as alcohols, esters and amides are unaffected.

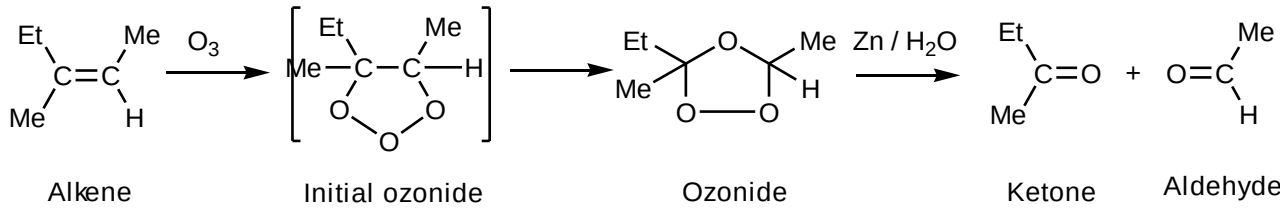


Figure 16 Ozonolysis of alkenes to give aldehydes and/or ketones.

App 1.5.6 Oxidation of 1,2-diols to aldehydes
Another method which produces an aldehyde by the cleavage of a carbon-carbon bond is the reaction of 1,2-diols with sodium periodate or lead tetraacetate (Fig. 17a).

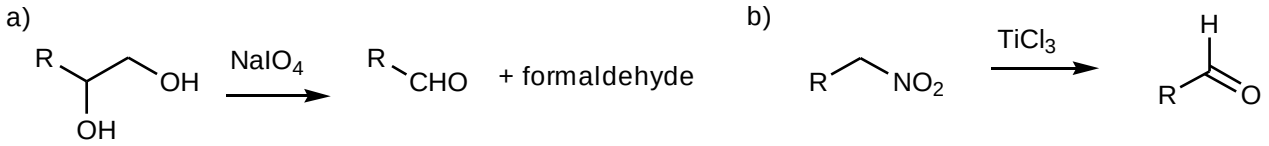
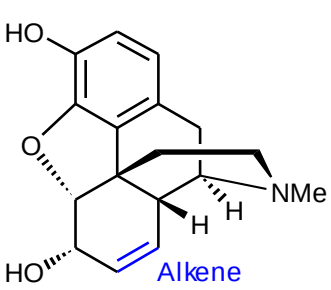


Figure 17 Synthesis of aldehydes from a) the cleavage of 1,2-diols and b) the hydrolysis of aliphatic nitro groups

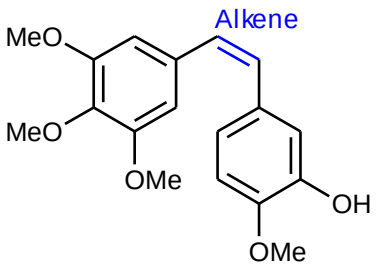
App 1.5.7 Hydrolysis of aliphatic primary nitro groups to aldehydes
A primary aliphatic nitro group can be hydrolysed to an aldehyde in the presence of a titanium chloride catalyst (Fig. 17b). The nitro group can, therefore, be viewed as a latent or 'disguised' aldehyde. This can be useful if the aldehyde is to be revealed late on in a synthetic route, and is an alternative strategy to using an aldehyde protecting group.

App 1.6 Alkenes

Alkenes are not uncommon in clinically useful drugs. For example an alkene is present in the analgesic morphine, the anticancer agent combretastatin and several anti-inflammatory steroids.



Morphine



Combretastatin

Alkenes can be obtained by the transformation of various functional groups such as alkynes, alkyl halides, or alcohols.
Alkenes are also very important in organic synthesis and are viewed as important functional groups in 'click chemistry', since the alkene group is a high energy functional group containing a reactive pi bond.

App 1.6.1 Reduction of alkynes

Alkynes are normally reduced to alkanes by hydrogen over a palladium charcoal catalyst, but with less active catalysts, it is possible to stop the reaction at the alkene stage. In particular, *Z*-alkenes can be synthesized from alkynes by reaction with hydrogen gas and Lindlar's catalyst (Fig. 18a). This catalyst consists of metallic palladium deposited on calcium carbonate, which is then treated with lead acetate and quinoline. The latter treatment 'poisons' the catalyst such that the alkyne reacts with hydrogen to give an alkene, but does not react further. Since the starting materials are absorbed onto the catalytic surface, both hydrogens are added to the same side of the molecule to produce the *Z*-isomer. An alternative catalyst which achieves the same result is nickel boride (Ni_2B) - the P-2 catalyst.

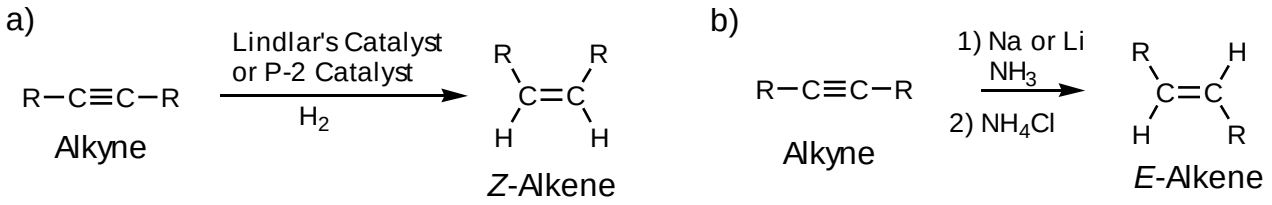


Figure 18 Reduction of alkynes to alkenes.

Reduction of an alkyne to an *E*-alkene can be achieved if the alkyne is treated with lithium or sodium metal in ammonia at low temperatures (Fig. 18b). This is known as a dissolving metal reduction. The reaction conditions are quite 'fierce' and it may not be feasible to carry out this reaction if there are other susceptible functional groups present in the molecule.

App 1.6.2 Dehydrohalogenation of alkyl halides

Elimination reactions of alkyl halides (dehydrohalogenations) are a useful method of synthesizing alkenes. For secondary or tertiary alkyl halides, a base such as sodium ethoxide (NaOEt) should be used in a protic solvent (EtOH). The reaction proceeds by an E2 mechanism, and heating increases the chances of elimination over substitution. The advantage of the E2 mechanism is that it is higher yielding than the E1 mechanism and is also stereospecific. For example, the elimination in Figure 19 gives the *E*-isomer and none of the *Z*-isomer.

For primary alkyl halides, a bulky base (e.g. $NaOBu^t$) should be used. The bulk hinders the possibility of S_N2 substitution and encourages elimination by the E2 mechanism.

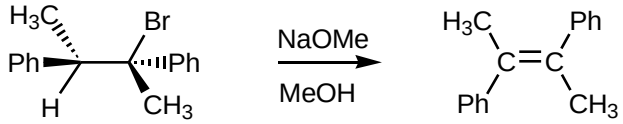


Figure 19 Dehydrohalogenation of alkyl halides.

The E2 elimination requires the presence of a β-proton. If there are several options available, a mixture of alkenes will be obtained, but the favoured alkene will be the most substituted (and most stable) one (**Zaitsev's rule**) (**Fig. 20**). When potassium *tert*-butoxide is used as base, the less substituted alkene is favoured.

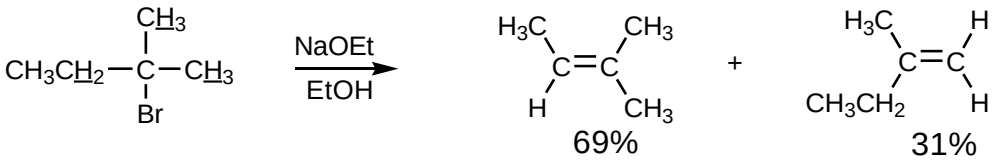


Figure 20 Zaitsev's rule (β-hydrogens underlined).

If the elimination occurs by the E1 mechanism, the reaction is more likely to compete with the S_N1 reaction and a mixture of substitution and elimination products is likely.

App 1.6.3 Dehydration of alcohols to alkenes

Alcohols can undergo elimination reactions to form alkenes (Fig. 21). Since water is eliminated, the reaction is also known as a dehydration. Like alkyl halides, the elimination reaction of an alcohol requires the presence of a susceptible proton at the β-position.

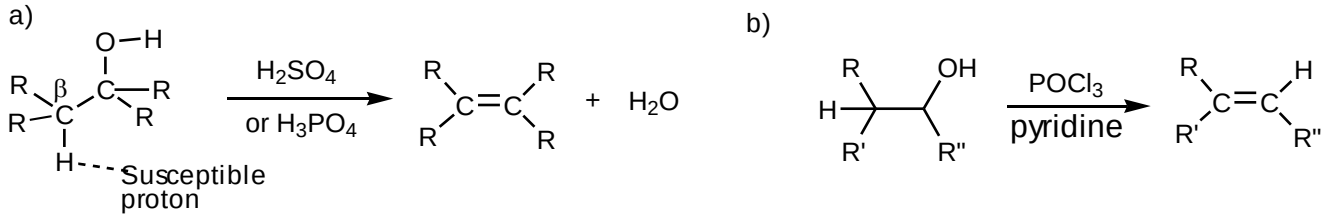


Figure 21 Dehydration of alcohols to alkenes.

Whereas the elimination of alkyl halides is carried out under basic conditions, the elimination of alcohols is carried out under acid conditions using reagents which have non-nucleophilic counterions in order to reduce the risk of competing substitution reactions. Suitable reagents are sulphuric acid or phosphoric acid, but potassium bisulphate is often preferred to sulphuric acid as it is solid and easier to handle. The reaction works best with tertiary alcohols since the elimination proceeds by the E1 mechanism. If different isomeric alkenes are possible, the most substituted alkene will be favoured - another example of Zaitsev's rule (Fig. 20).

Acid-catalysed dehydration often requires vigorous heating to force the reaction and this can result in unwanted rearrangement reactions. Therefore, alternative methods are useful. Reagents such as phosphorus oxychloride ($POCl_3$) dehydrate secondary and tertiary alcohols under mild, basic conditions using pyridine as solvent (Fig. 21b).

App 1.6.4 Conversion of primary amines to alkenes via quaternary salts

Primary amines can be converted to alkenes by first methylating the amine with excess iodomethane to give a quaternary ammonium salt. Once this is formed, it is possible to eliminate triethylamine in the presence of silver oxide to form the desired alkene. The reaction is called the **Hofmann elimination**. Unlike most E2 eliminations, the less substituted alkene is preferred (Fig. 22).

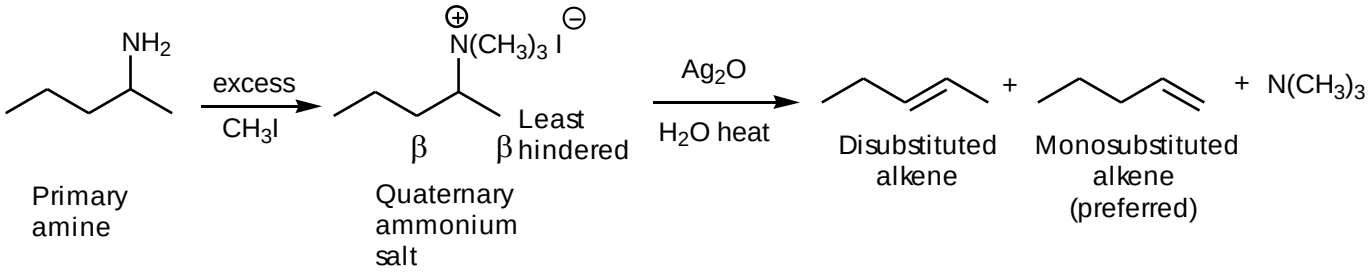


Figure 22 The Hofmann elimination.

Secondary and tertiary amines can also be exhaustively methylated then treated with silver oxide. However, mixtures of different alkenes are likely if the original *N*-substituents are different. The Hofmann elimination is not possible with primary aromatic amines, but secondary and tertiary aromatic amines will react if one of the substituents is a suitable alkyl group. Elimination of the aromatic amine can then occur such that the alkyl substituent is converted to the alkene (Fig. 23).

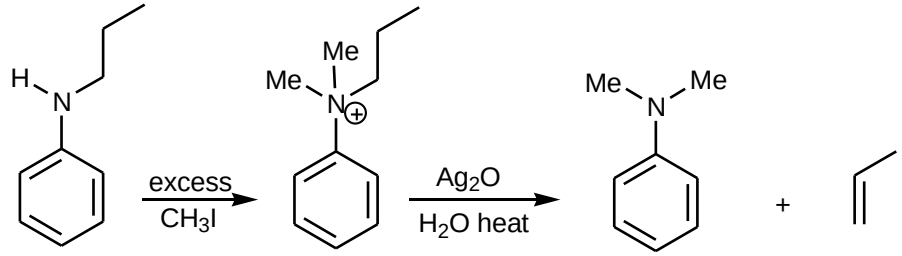


Figure 23 Hoffmann elimination of a secondary aromatic amine.

App 1.6.5 Cleavage of tertiary ethers to form alkenes

Treatment of tertiary ethers with hydrogen iodide results in bond cleavage which can result in alcohol and alkene products (Fig. 9c). Trifluoroacetic acid can be used with primary and secondary ethers to produce the alcohol and the alkene.

App 1.7 Alkyl halides

Alkyl halides (halogenoalkanes) are crucial to many of the carbon-carbon bond formations that are required for the synthesis of a particular carbon scaffold. They are also present in several cytotoxic anticancer agents, and are important to their mechanism of action by acting as alkylating agents with DNA. However, this reactivity is also responsible for serious side effects. Therefore, alkyl halides are usually avoided when designing drugs. There is an exception to every rule though, and alkyl fluorides are that exception. Many successful drugs, including steroidal anti-inflammatory agents, contain fluoro substituents which are often introduced to block metabolism at a particular position of the structure. One of the common metabolic reactions carried out on drugs is oxidation by cytochrome P450 enzymes. The oxidation mechanism involves loss of a proton and so replacement of that proton with a fluorine is effective in preventing the reaction occurring, as the mechanism would require fluorine to depart as a positively

charged ion. Fluorine substituents are similar in size to the proton they are replacing, and so they are unlikely to have any adverse steric effects with target binding sites once they are introduced. The C-F bond is also stronger than other C-X bonds, which means that alkyl fluorides are poor alkylating agents and unlikely to cause side effects. Finally, fluoro substituents increase hydrophobicity, which can be advantageous for binding interactions and pharmacokinetic properties.
Alkyl chlorides, bromides and iodides can be obtained from alkenes, alcohols, mesylates, tosylates and ethers. The synthesis of alkyl fluorides can involve specialised reactions and reagents.

App 1.7.1 Conversion of alkenes to alkyl halides
Alkenes react with hydrogen halides (HCl, HBr and HI) to give an alkyl halide. The reaction proceeds in a **Markovnikov** sense with the hydrogen ending up on the least substituted position, and the halogen ending up on the most substituted position. Markovnikov's rule states that 'in the addition of HX to an alkene, the hydrogen atom adds to the carbon atom that already has the greater number of hydrogen atoms'. This produces the more substituted alkyl halide (Fig. 24).

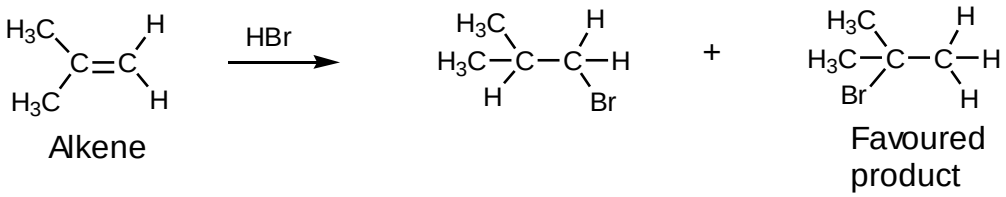


Figure 24 Addition of hydrogen halides to alkenes.

App 1.7.2 Substitution of alcohols to form alkyl halides
Tertiary alcohols can undergo the S_N1 reaction under acidic conditions (HCl or HBr) to produce tertiary alkyl halides (Fig. 25a).

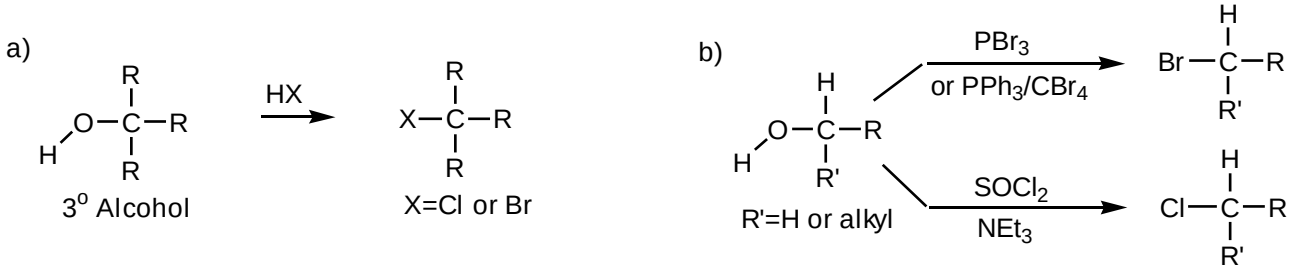


Figure 25 Substitution of alcohols to form alkyl halides.

Primary alcohols and some secondary alcohols react by the S_N2 mechanism. The reaction proceeds with good nucleophiles such as the iodide or bromide ion, but fails with the weaker nucleophilic chloride ion. In this case, a Lewis acid needs to be added to the reaction mixture.

The reaction of primary and secondary alcohols with hydrogen halides can often result in unwanted acid-catalysed rearrangement reactions. To avoid this, alternative procedures can be carried out under milder basic conditions with reagents such as thionyl chloride or phosphorus tribromide (Fig. 25b). In the reaction with thionyl chloride, triethylamine is present to mop up the HCl formed during the reaction. The reaction is also helped by the fact that one of the products (SO_2) is lost as a gas, thus driving the reaction to completion.

App 1.7.3 Substitution of mesylates and tosylates to form alkyl halides

If the direct conversion of an alcohol to an alkyl halide proves problematic, it is worth converting the alcohol to a mesylate or a tosylate, then converting that to the alkyl halide. The mesylate and tosylate groups are both excellent leaving groups and can undergo the S_N2 reaction in the same way as alkyl halides (Fig. 26a).

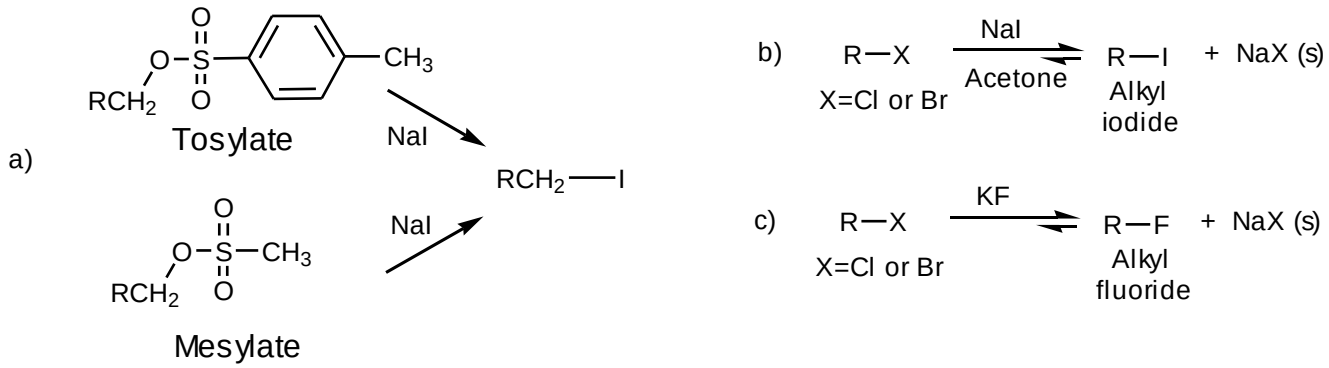


Figure 26 a) Conversion of tosylates and mesylates to alkyl halides. b) Halide exchange.

App 1.7.4 Halide exchange to form alkyl iodides

Alkyl iodides can be prepared from alkyl chlorides or alkyl bromides by halide exchange (Fig. 26b). The reaction is carried out in acetone because sodium chloride or sodium bromide is insoluble in acetone and precipitates once it is formed, thus driving the equilibrium to completion. In contrast, sodium iodide is soluble in acetone. The reaction works best with primary alkyl halides. Alkyl fluorides can also be prepared from other alkyl halides (Fig. 26c). In this case the strength of the C-F bond formed forces the equilibrium to products.

App 1.7.5 Cleavage of ethers to form alkyl halides

Ethers can undergo cleavage by strong acids such as HI and HBr to produce an alkyl halide and an alcohol (Figure 9). Primary and secondary ethers react by the S_N2 mechanism, and the halide reacts at the least substituted carbon atom.

App 1.8 Alkyl fluorides

A number of nucleophilic fluorinating reagents have been used to synthesise alkyl fluorides. It is possible to use hydrogen fluoride, but this is a highly toxic agent which eats into glass and damages bone if it gets on the skin. Potassium fluoride is a more practical reagent and can be used to convert alkyl halides to alkyl fluorides (Fig. 26c). Alkyl mesylates or tosylates can also be converted to alkyl fluorides using potassium fluoride or tetra-n-butylammonium fluoride.

Sulphur tetrafluoride is another fluorinating agent which can be used to convert a carboxylic acid to a trifluoromethyl group (Fig. 27c). However, the reagent is a highly toxic gas and has to be handled with care. Diethylaminosulphur trifluoride (DAST)is a more selective fluorinating agent and easier to handle. It can be used to fluorinate alcohols, aldehydes, ketones and carboxylic acids (Fig. 27a-c). An alternative reagent to DAST is morpholinosulphur trifluoride (MorphoDAST) which is more stable to heating. Triethylamine trihydrofluoride ($Et_3N.3HF$) has also been used as an alternative, non-corrosive reagent to DAST for a large-scale fluorination reaction (Fig. 27d).
Perfluorosulphonyl fluorides have been used to activate alcohol groups, which are then susceptible to nucleophilic substitution by the fluoride ion that is generated (Fig. 27e).

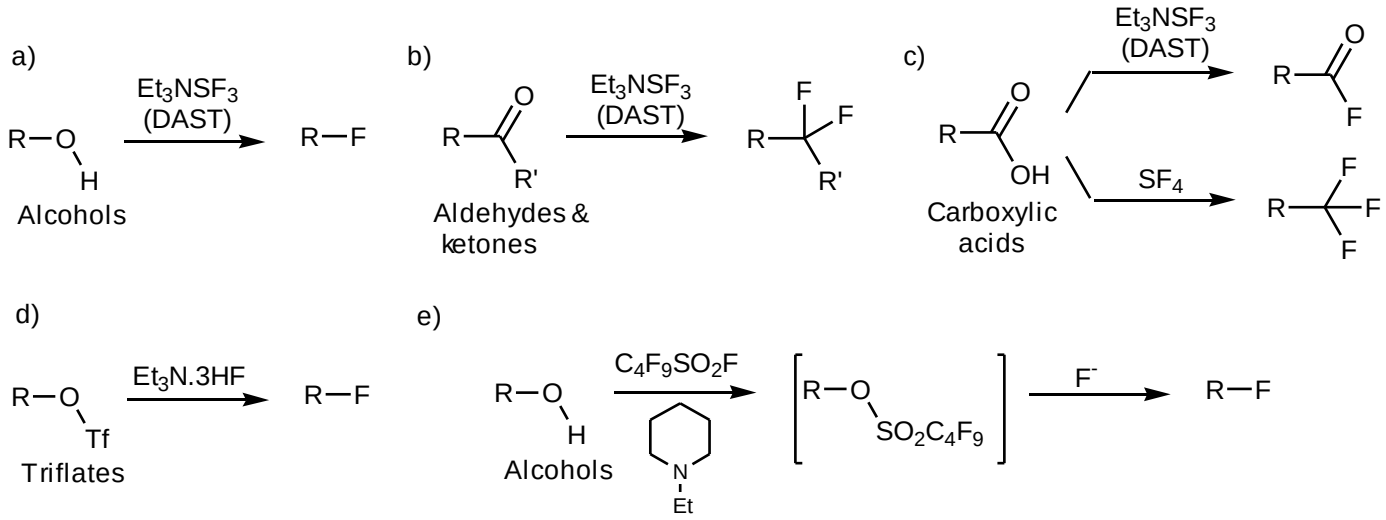


Figure 27 Fluorination with nucleophilic reagents.

A methyl group on an aromatic ring can be converted to a trifluoromethyl group by chlorinating the methyl group, then reacting it with antimony (V) fluoride (Fig. 28).

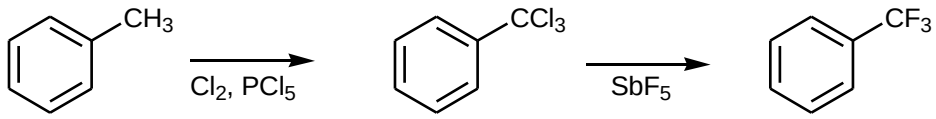
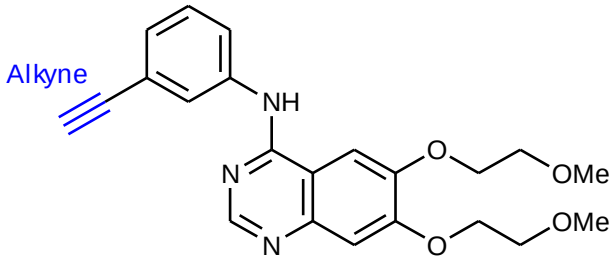


Figure 28 Conversion of an aromatic methyl group to a trifluoromethyl group.

App 1.9 Alkynes

Alkynes are present in a number of drug structures, including steroid oral contraceptives, the anticancer agent erlotinib, the antiviral agent efavirenz, and the antidepressant agent clorgiline. Selegiline which is used in the treatment of Parkinson's disease also contains an alkyne group.



Erlotinib

Alkynes can be synthesized from alkenes through a two-step process which involves the electrophilic addition of bromine to the alkene to form a vicinal dibromide then dehydrohalogenation with strong base (Fig. 29). The second stage involves the loss of two molecules of hydrogen bromide, and so two equivalents of base are required.

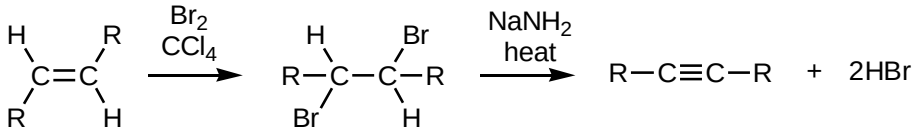


Figure 29 Conversion of an alkene to an alkyne.

Alkynes can also be synthesised directly from α-diketones by reaction with $P(OR)_3$, or in a two stage process involving oxidation of a bis-hydrazone (Fig. 30).

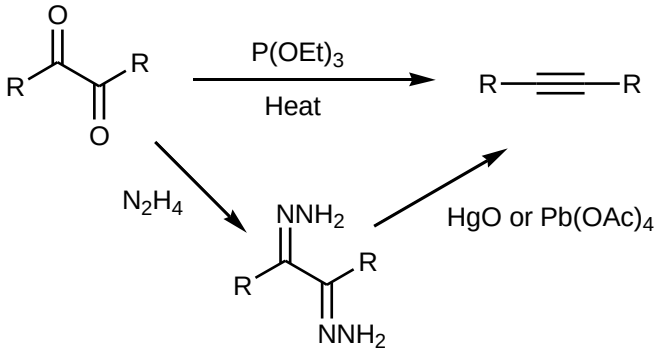


Figure 30 Synthesis of alkynes from α-diketones.

App 1.10 Allylic alcohols

Allylic alcohols are present in several opioid analgesics, a number of statins and an agent called clavulanic acid which is used in antibacterial preparations. In synthetic terms, allylic alcohols are key starting materials for an asymmetric reaction called the Sharpless epoxidation (Chapter 5.8.3). There are a number of functional group transformations that can convert alkenes, epoxides and α,β-unsaturated carbonyl groups to allylic alcohols.

App 1.10.1 Allylic alcohols from the reduction of α,β-unsaturated ketones

The reduction of α,β-unsaturated ketones to allylic alcohols is best carried out using lithium aluminium hydride under carefully controlled conditions (Fig. 31). The hydride ion reacts by 1,2-addition to the carbonyl group, rather than by 1,4-addition to the alkene. With sodium borohydride, some reduction of the alkene takes place, in addition to hydride addition to the carbonyl group. The addition of $CeCl_3$ increases selectivity for the carbonyl group.

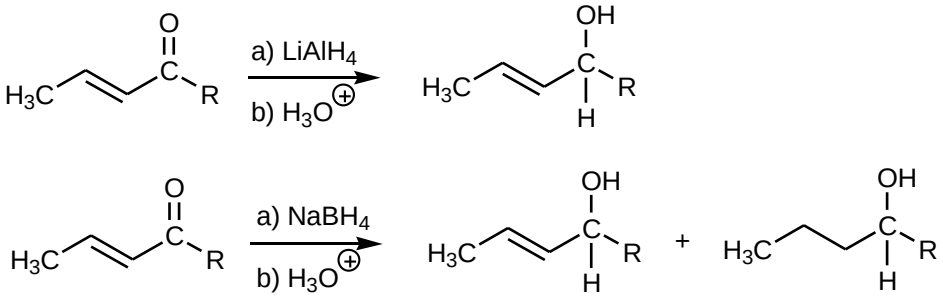


Figure 31 Reduction of α,β-unsaturated ketones to allylic alcohols.

App 1.10.2 Allylic alcohols from alkenes or epoxides

Alkenes can be brominated at the allylic position by treatment with *N*-bromosuccinimide in the presence of a peroxide initiator (Fig. 32). The reaction involves a radical mechanism and the reagent reacts at the allylic position rather than the alkene itself, with a preference for secondary allylic positions over primary. The resulting allyl bromide then undergoes a nucleophilic substitution with a hydroxide ion to give the allylic alcohol.

Alternatively, the alkene can be oxidised with a catalytic quantity of selenium oxide in the presence of a hydroperoxide (Fig. 32). The reaction involves selenium oxide adding initially to the least hindered side of the olefin, which is followed by dehydration and a [2,3]sigmatropic rearrangement. If two allylic positions are available, the oxidation may be regioselective. The hydroperoxide serves to regenerate the selenium oxide.

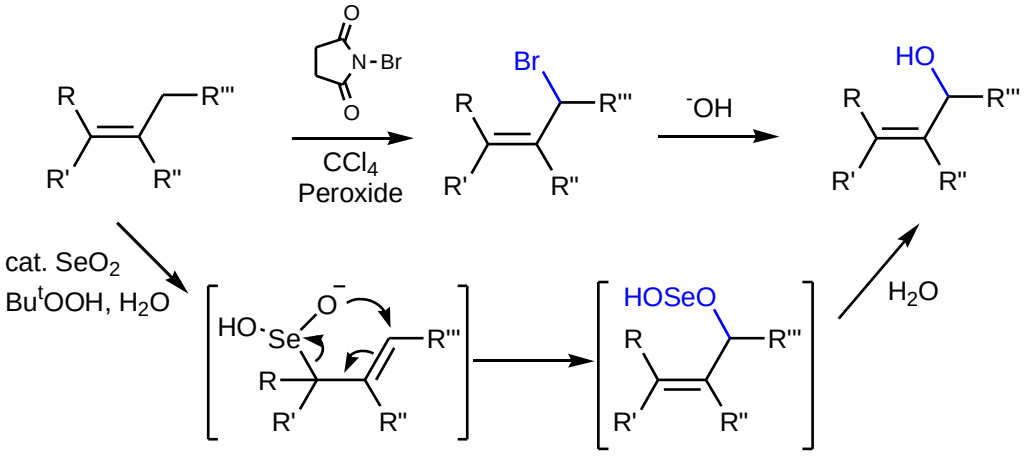


Figure 32 Conversion of alkenes to allylic alcohols.

Alkenes can also be converted to allylic alcohols via an epoxide (Fig. 33). The epoxide is treated with a phenylselenide ion (generated *in situ* by the reaction of PhSeSePh with $NaBH_4$) to form a β-hydroxyselenide. Oxidation with hydrogen peroxide generates a selenoxide which spontaneously decomposes to give the *trans* allylic alcohol. The reaction occurs under mild, non-basic conditions and produces an allylic alcohol where the alkene group has shifted from its original position.
An alternative method is to treat the epoxide with a strong non-nucleophilic base such as lithium diethylamide. With unsymmetrical epoxides, the favoured product has the least substituted alkene group.

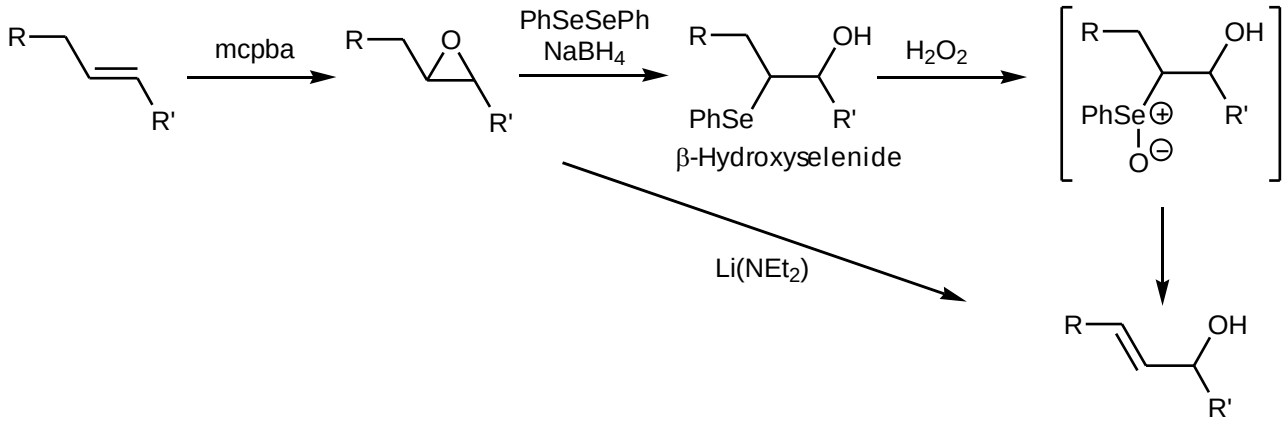


Figure 33 Synthesis of allylic alcohols from alkenes via an epoxide.

App 1.10.3 Allylic alcohols from α,β-unsaturated aldehydes and ketones
A couple of functional group transformations can be used to convert an α,β-unsaturated aldehyde or ketone to an allylic alcohol. Firstly, the unsaturated carbonyl group is oxidised with a peroxide to form an α,β-epoxyaldehyde or α,β-epoxyketone. Reduction with hydrazine then results in the formation of an allylic alcohol (Fig. 34).

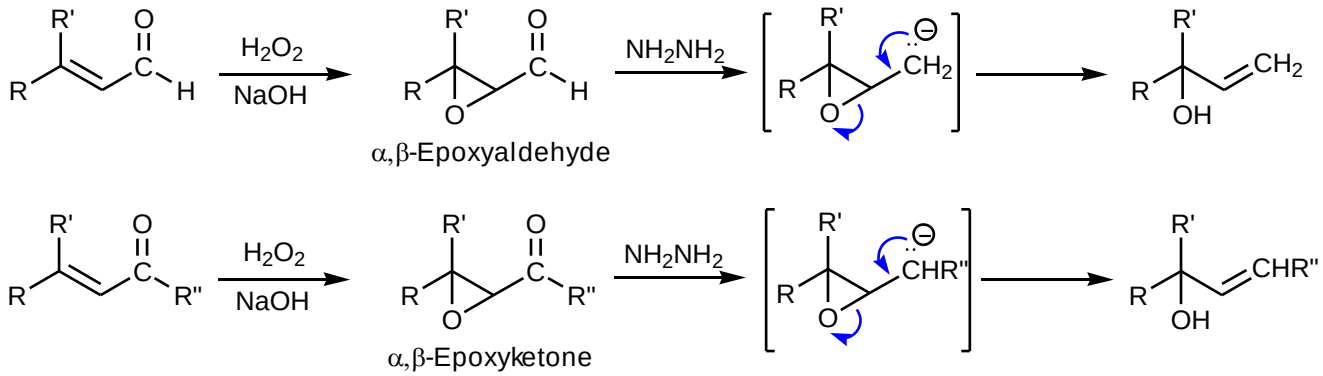


Figure 34 Synthesis of allylic alcohols from α,β-unsaturated aldehydes and ketones.

App 1.11 Amides

Amides are relatively common in drugs. For example, the antibacterial penicillins and cephalosporins contain an amide group, as do several kinase inhibitors that are used as anticancer agents. Peptide-based drugs contain amide groups as these are the links that make up the peptide backbone. Similarly, many drugs which have been developed from peptide lead compounds are likely to have amide groups present. Compared to other carboxylic acid derivatives (acid chlorides, acid anhydrides and esters), amides are relatively stable groups and can survive a wide range of chemical reagents. However, they can be prone to enzyme-catalysed hydrolysis in the body due to the action of peptidases.

Considering their prevalence in drugs, it is not surprising that amide formation is one of the most common reactions carried out in drug synthesis. Secondary and tertiary amides are relatively common in drugs, whereas primary amides are less common. The tetracyclines are one example of a class of drugs containing a primary amide group.

App 1.11.1 Conversion of acid chlorides, acid anhydrides or esters to amides

Amides can be prepared by the reaction of an amine with an acid chloride by nucleophilic substitution (Fig. 35a). Treatment of the acid chloride with ammonia gives a primary amide, treatment with a primary amine gives a secondary amide and treatment with a secondary amine gives a tertiary amide. Tertiary amines cannot be used in this reaction because they do not give a stable product.

Two equivalents of amine are required for the reaction since one equivalent of the amine is used up in forming a salt with the hydrochloric acid that is produced as a by product. This is clearly wasteful on the amine, especially if the amine is expensive and not easily synthesised. To avoid this, one equivalent of sodium hydroxide or pyridine can be added to the reaction in order to neutralize the HCl produced.

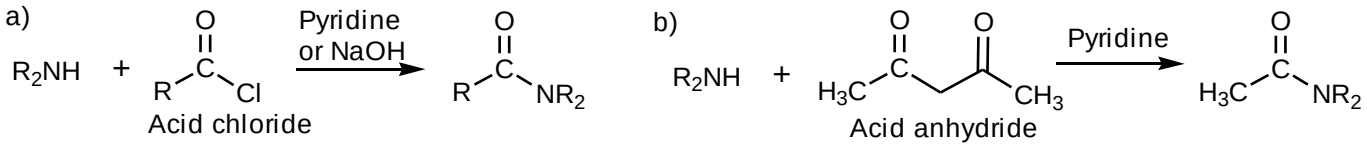


Figure 35 Reactions of amines with carboxylic acid derivatives.

Amides can also be synthesized from acid anhydrides and esters, but in general these reactions offer no advantage over acid chlorides since acid anhydrides and esters are less reactive. Furthermore, with acid anhydrides half of the parent carboxylic acid is lost as the leaving group. This is wasteful and so acid anhydrides are only used for the synthesis of amides if the acid anhydride is cheap and freely available (e.g. acetic anhydride) (Fig. 35b).

App 1.11.2 Coupling an amine with a carboxylic acid to form an amide

The synthesis of amides directly from carboxylic acids and amines is not straightforward since an acid-base reaction is more likely to take place to form a salt. Therefore, an activating or coupling agent is used to promote the reaction. One of the most popular coupling agents is dicyclohexylcarbodiimide (DCC). This structure reacts with the carboxylic acid to form an activated

intermediate, which then reacts with the amine (Fig. 36). This procedure is commonly used in peptide synthesis, but there can be problems with side reactions and epimerisation. These problems can be eased to a large extent by adding a further reagent called 1-hydroxybenzotriazole (HOBt). This reagent reacts with the activated intermediate to form a second intermediate which then reacts with the amine with less risk of epimerisation.

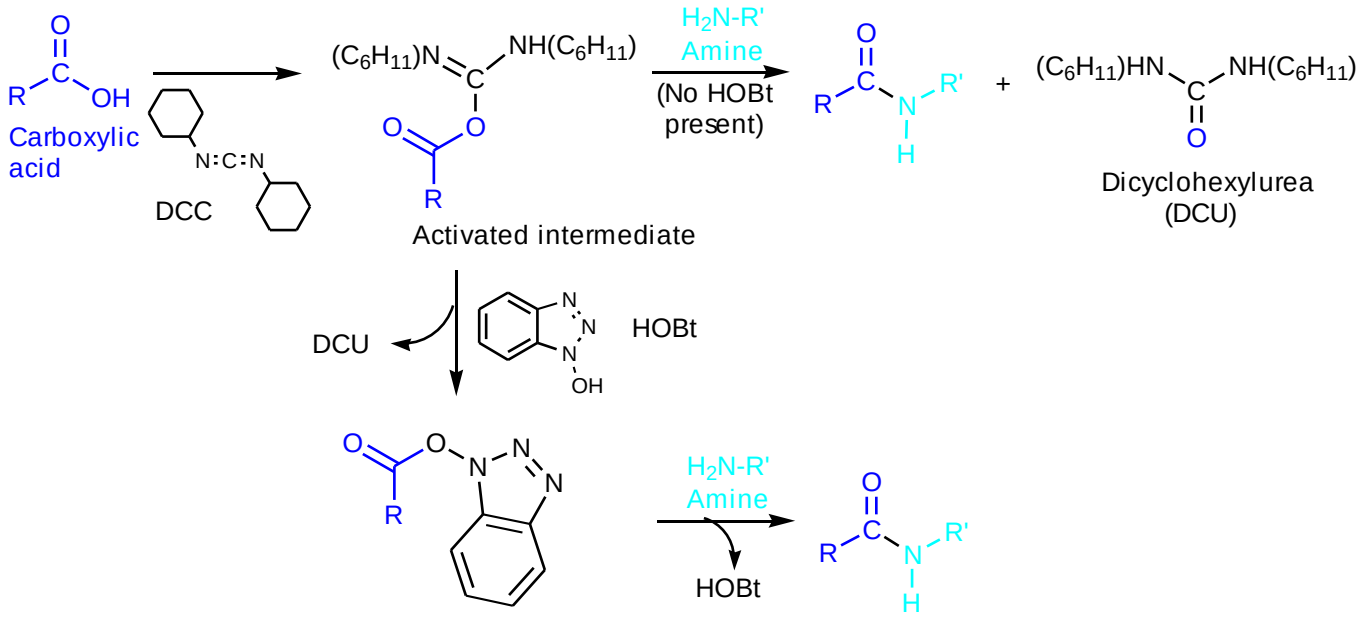


Figure 36 Coupling of an amine with a carboxylic acid in the presence of dicyclohexylcarbodiimide (DCC).

Another problem with the use of DCC is the formation of dicyclohexylurea which is poorly soluble and difficult to remove. An alternative coupling agent is diisopropylcarbodiimide (DIC) (Me_2HC-N=C=N-$CHMe_2$) which forms a urea (DIU) which is soluble in dichloromethane. This makes it a better choice for solid phase coupling reactions. A vast number of other coupling agents have been studied and used in amide formation, including 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (Et-N=C=N-$(CH_2)_3$-NMe_2), which is a water-soluble coupling agent.
The coupling agents benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) are commonly used in solid phase synthesis to carry out coupling reactions.

App 1.11.3 Methylation of secondary amides to form tertiary amides
Secondary amides can be treated with sodium hydride to deprotonate the amide, then methylated with iodomethane to give an *N*-methylated tertiary amide (Fig. 37). This feature is present in several drugs that have been derived from peptide lead compounds. The presence of the *N*-methyl group can prevent peptidases catalysing the hydrolysis of the original amide or peptide bond.

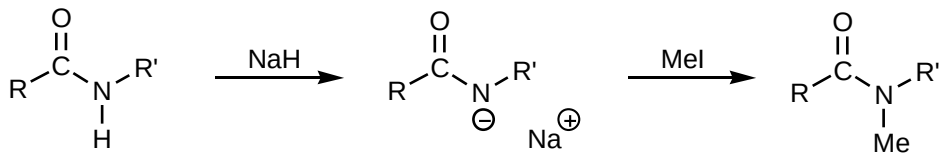


Figure 37 *N*-Methylation of secondary amides.

App 1.12 Amines

Amines are one of the most common functional groups in drug-like structures and are present in a large variety of clinically-important drugs. Tertiary amines are particularly common, whereas primary amines are relatively scarce. Amines can be extremely important to both the pharmacodynamic and pharmacokinetic properties of a drug. In many cases, the amine has a pK_a value which is close to blood pH (7.4), which means that there is an equilibrium between the free base and the ionised form. The free base is more hydrophobic than the ionised form and allows the drug to cross hydrophobic cell membranes. This aids oral absorption of the drug across the gut wall and access to targets within cells. In the ionised form, the amine confers water solubility. In many drugs, the ionised group is capable of forming strong ionic and hydrogen bonding interactions with target binding sites. Amines can be synthesised from amides, nitriles, azides, ketones, aldehydes, nitro groups and alkyl halides.

App 1.12.1 Hydrolysis of amides to amines

Amides can be hydrolyzed to carboxylic acids and amines under acidic conditions (Fig. 38). Since amines are basic, they will react with the mineral acid to form a water soluble aminium ion. This is an irreversible step which pulls the equilibrium through to the products. As a result, at least one equivalent of mineral acid is required for the reaction to proceed effectively.

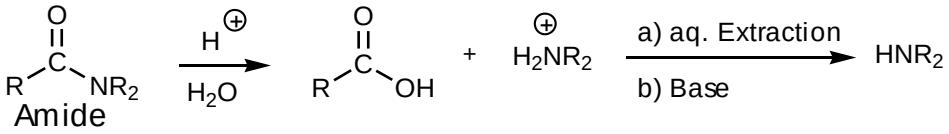


Figure 38 Hydrolysis of amides to carboxylic acids and amines.

App 1.12.2 Reduction of nitro groups to amines

A nitro group can be converted to a primary amine by catalytic hydrogenation or by treatment with $LiAlH_4$ (Fig. 39a). The nitro group frequently serves as a 'masked' amine throughout a reaction sequence and can be converted to the amine towards the end of the synthetic route. This is a useful alternative to the protection and deprotection of an amine. Moreover, the nitro group has a powerful electron-withdrawing effect which allows carbon-carbon bond formations to be carried out at the α-carbon (Appendix 5.24).

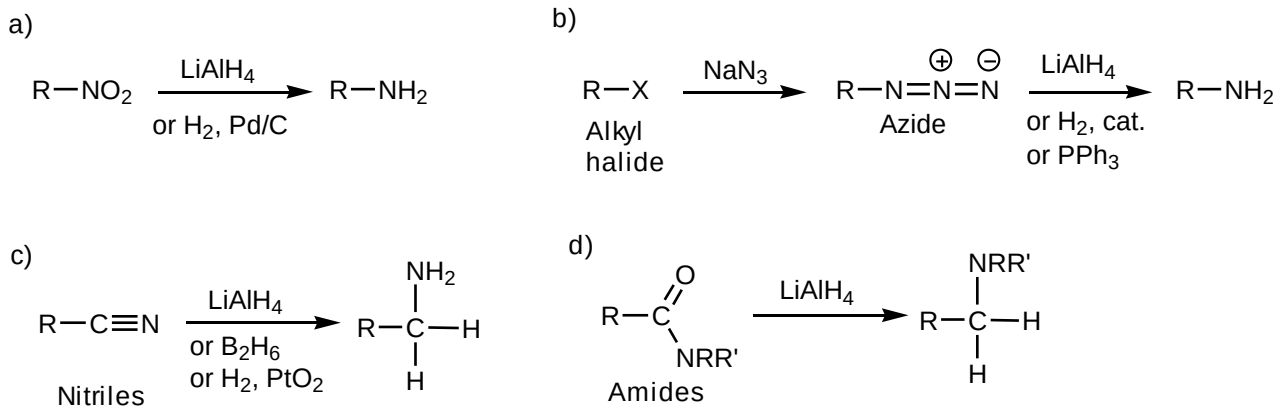


Figure 39 Reduction of nitro groups, azides, nitriles and amides to amines.

App 1.12.3 Reduction of azides to amines

Azides are also reduced to primary amines by $LiAlH_4$ or by catalytic hydrogenation (Fig. 39b). Another method is to use triphenylphosphine or tributylphosphine in a method called the **Staudinger reaction**. Since the azide ion is a good nucleophile, it can be used to substitute a primary alkyl halide. Therefore, primary alkyl halides can be converted to amines in a two-step process via azides (Fig. 39b). Some secondary alkyl halides can be converted to amines in a similar manner.

App 1.12.4 Reduction of nitriles to amines

Nitriles can be reduced to primary amines with lithium aluminium hydride (Fig. 39c). An alternative reducing agent is diborane which is unreactive to acid chlorides or esters. Hydrogenation with a platinum oxide catalyst has also been used. It should be evident that these methods are restricted to the formation of primary amines having the general formulas RCH_2NH_2.

App 1.12.5 Reduction of amides to amines p

Amides can be reduced to amines by treatment with lithium aluminium hydride (Fig. 39d), allowing the synthesis of primary, secondary and tertiary amines depending on the nature of the amide Diborane can also be used for the reduction of amides to amines, and has an advantage over $LiAlH_4$ in that it shows selectivity for amide groups over ester groups.
Sodium bis(2-methoxyethoxy)aluminium hydride, $NaAlH_2(OCH_2CH_2OMe)_2$ (SMEAH) can be used as another alternative to $LiAlH_4$, and has the advantages of being more soluble and less flammable. It will also leave any nitrile group present unaffected.

App 1.12.6 Conversion of alkyl halides to primary amines

We have already seen that some alkyl halides can be converted to an amine via an azide (Fig. 39b). The overall reaction is equivalent to replacing the halogen atom of the alkyl halide with an NH_2 unit. Another method of achieving the same result is the **Gabriel synthesis** of amines (Fig. 40). This involves treating phthalimide with KOH to abstract the N-H proton. The phthalimide ion can then be alkylated by treating it with an alkyl halide in a nucleophilic substitution. Subsequent hydrolysis releases a primary amine. An alternative method of releasing the primary amine is to cleave the substituted phthalimide with hydrazine.

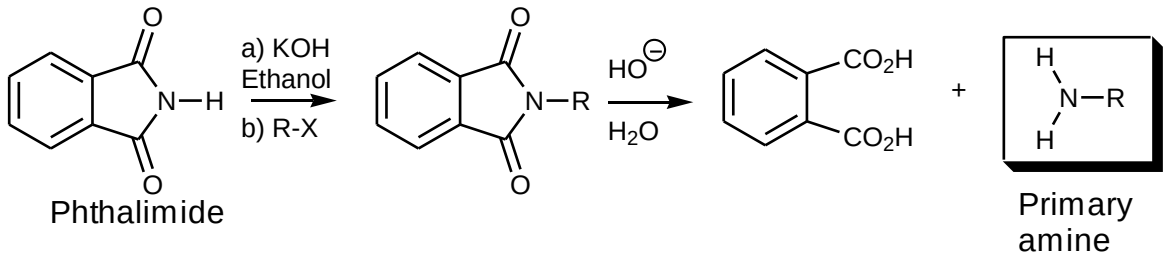


Figure 40 Gabriel synthesis of amines.

App 1.12.7 Rearrangements of carboxylic acid derivatives to primary amines

There are two rearrangement reactions which can be used to convert carboxylic acid derivatives into primary amines, where the carbon chain in the product has been shortened by one carbon unit (Fig. 41). These are known as the Hofmann and the Curtius rearrangements. The Hofmann rearrangement involves the treatment of a primary amide with bromine under basic conditions, while the Curtius rearrangement involves heating an acyl azide. The end result is the same - a primary amine with loss of the original carbonyl group.

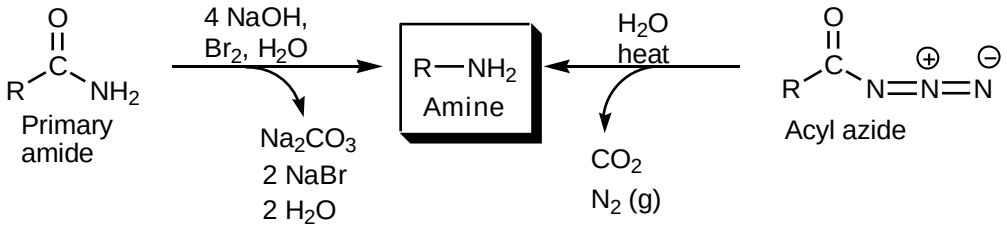


Figure 41 Hoffmann and Curtius rearrangements.

In both reactions, the alkyl group (R) is transferred from the carbonyl group to the nitrogen to form an intermediate isocyanate (O=C=N-R). This is then hydrolyzed by water to form carbon dioxide and the primary amine. The Curtius rearrangement has the added advantage that nitrogen is lost as a gas, which helps to drive the reaction to completion.

App 1.12.8 Alkylation of amines

Ammonia, primary amines and secondary amines can undergo the S_N2 reaction with alkyl halides to produce a range of primary, secondary and tertiary amines. The amines are produced as aminium salts which are converted to the free amine by treatment with sodium hydroxide (Fig. 42a).

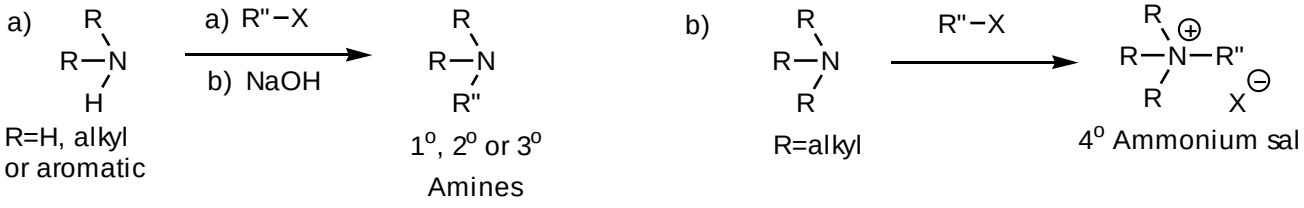


Figure 42 Alkylation of amines.

In theory, it should be possible to synthesize primary amines from ammonia, secondary amines from primary amines, and tertiary amines from secondary amines. In practice, over-alkylation is common. For example, reaction of ammonia with methyl iodide leads to a mixture of primary, secondary, and tertiary amines along with a small quantity of the quaternary ammonium salt (Fig. 2.43).

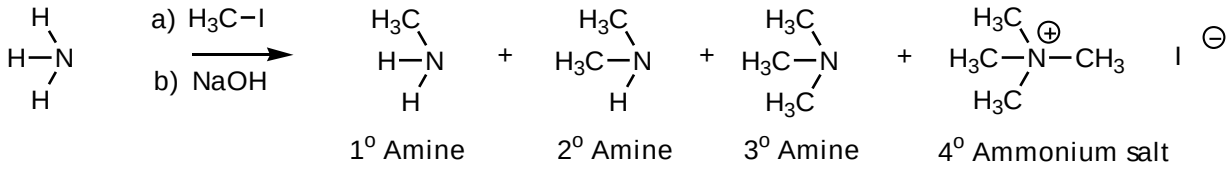


Figure 43 Over-alkylation of ammonia.

Alkylation of tertiary amines by this method is a good way of obtaining quaternary ammonium salts (Fig. 42b) since no other products are possible. However, alkylation of lower order amines is not so satisfactory. One way round this problem is to acylate the amine to form an amide then reduce the amide to an amine (Fig. 44). Acylation can only occur once. Despite the problems of *N*-alkylation, it is one of the most frequently used reactions carried out in drug synthesis.

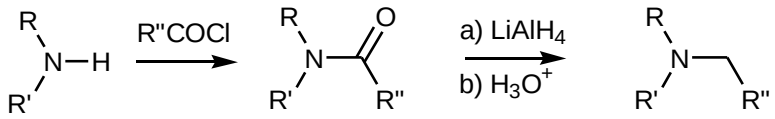


Figure 44 Alternative method of adding an alkyl substituent.

App 1.12.9 Alkylating an amine by reductive amination of ketones or aldehydes

Another method of alkylating a primary or secondary amine is to treat the amine with a ketone or an aldehyde in the presence of the reducing agent sodium cyanoborohydride (Fig. 45). This reaction is known as a reductive amination and is one of the most common reactions used in drug synthesis. The reaction proceeds through an imine or an iminium ion which is reduced *in situ*. Over alkylation cannot occur by this method. $NaBH_4$ and $LiAlH_4$ have also been used as the reducing agent.

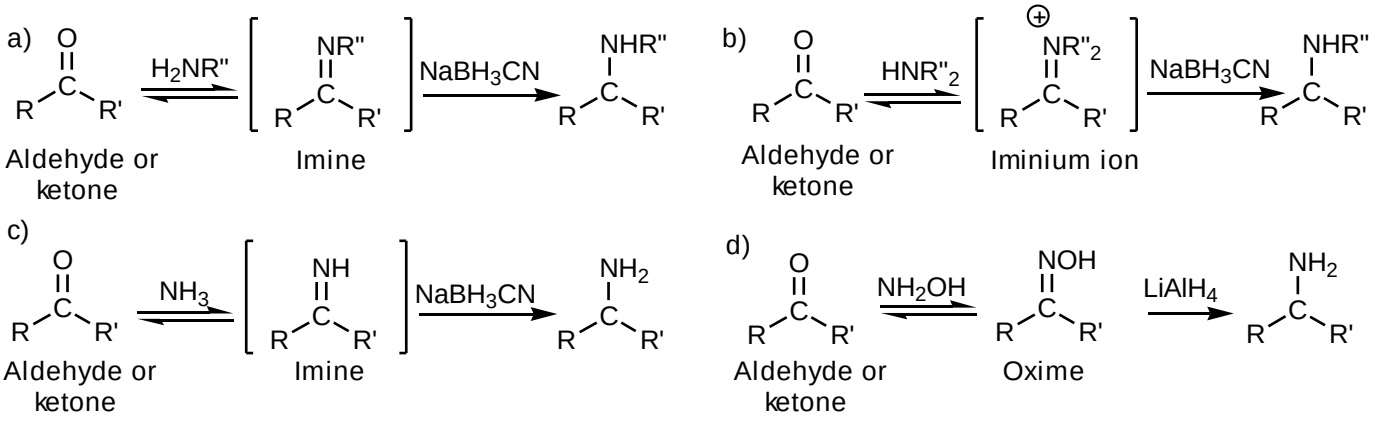


Figure 45 Reductive aminations of carbonyl compounds.

Primary amines are converted to secondary amines (Fig 45a) and secondary amines are converted to tertiary amines (Fig. 45b). The reaction is also suitable for the synthesis of primary amines if ammonia is used instead of an alkylamine. In this case, the imine intermediate is unstable and so the reduction should be carried out without isolating the imine (Fig. 45c). An alternative method for synthesising primary amines is to use hydroxylamine instead of ammonia. The resulting oxime is reduced to the amine by $LiAlH_4$ or by hydrogenation (Fig. 45d).
Reductive amination has an advantage over the 2-stage acylation and reduction of an amine described in figure 44 as a branched alkyl group can be added (Fig. 46).

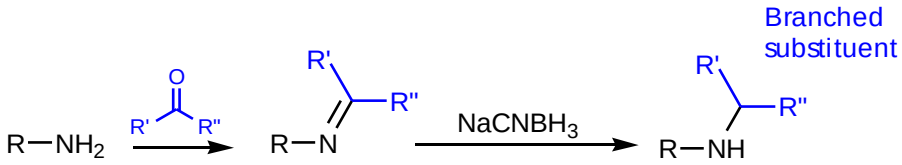


Figure 46 Reductive amination of a ketone to add a branched substituent.

App 1.12.10 *N*-Demethylation of tertiary amines
A large number of natural product lead compounds contain an *N*-methyl group. *N*-Demethylation is extremely useful, since it produces a secondary amine which can be alkylated to provide a vast range of analogues with different alkyl groups. The reaction can be carried out under mild conditions using vinyloxycarbonyl chloride (VOC-Cl) and methanol (Fig. 47).

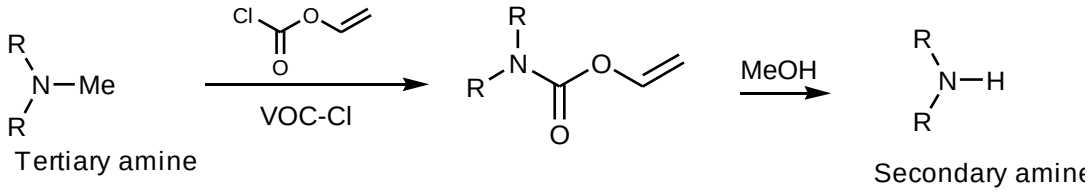


Figure 47 *N*-Demethylation of tertiary amines.

App 1.12.11 Aromatic amines
The direct introduction of an amine group to an aromatic ring is not normally possible unless the aromatic ring contains a halogen substituent and a powerful electron-withdrawing substituent, in which case a nucleophilic substitution reaction may be feasible.
If a nucleophilic substitution is not feasible, then the amine has to be introduced indirectly. This can be achieved by adding a nitro group by means of an electrophilic substitution, and then reducing the nitro group to the amine using tin and hydrochloric acid (Fig. 48). Alternative reducing agents are sodium hydrosulphite or hydrogen gas over a palladium catalyst. In the latter case, the amine product can poison the catalyst, in which case the addition of acetic acid can counteract that effect. The tin/HCl method is not favoured for the large scale syntheses of drugs due to toxic tin residues that have to be removed.

Once an amine group has been introduced to an aromatic ring, it can be alkylated with an alkyl halide, acylated with an acid chloride or converted to a higher amine by reductive animation as described above.
Reducing an aromatic nitro group to an amine has been frequently useful in heterocyclic synthesis, where the resulting amine reacts spontaneously with an electrophilic group in a cyclisation reaction.

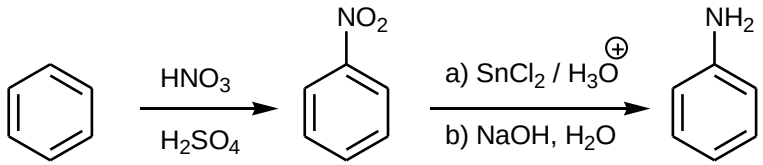
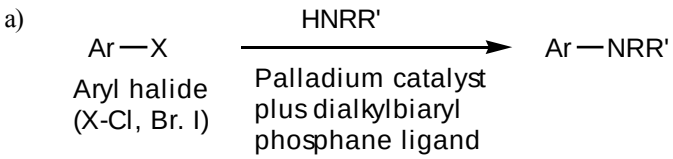


Figure 48 Introducing an amine group to an aromatic ring.

App 1.12.12 Palladium-catalysed aminations of aromatic rings
Palladium-catalysed aminations have been used successfully to couple a primary or secondary amine with an aromatic or heteroaromatic ring (Fig. 49a). An aryl halide is used as starting material and the halogen is eventually replaced with an amine substituent.



b) Examples of dialkylbiaryl phosphane ligands

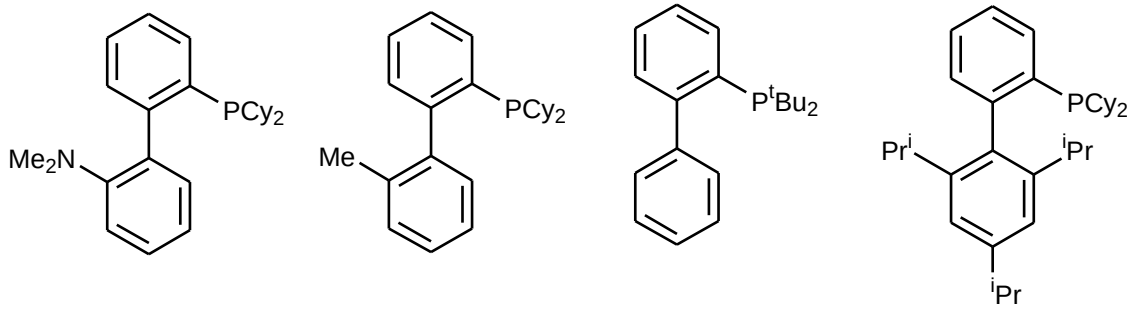


Figure 49 a) Palladium-catalysed aminations b) Examples of dialkylbiaryl phosphane ligands.

A dialkylbiaryl phosphane ligand is required and the nature of the ligand plays an important role in allowing the reaction to be carried out under mild conditions. The ligand also serves to shorten the reaction time, and lower the amount of catalyst required. There are a large variety of these ligands now available (Fig. 49b).

App 1.13. Amino acids

Amino acids are the building blocks for proteins and are commonly used in the synthesis of peptide-based drugs. Functional group transformations can be carried out to convert carboxylic acids, acid chlorides, dehydroamino acids and allylic alcohols to amino acids.
Aliphatic carboxylic acids can be converted to amino acids by bromination with PBr_3 to give a haloacid, which is then treated with an excess of ammonia to give the amino acid (Fig. 50). Alternatively, the haloacid can be treated with phthalimide under basic conditions, and the resulting *N*-substituted phthalimide is then hydrolysed with KOH. Although the latter procedure involves an extra step, it can usually provide a better yield. The R group in the carboxylic acid represents the side chain of the eventual amino acid and so numerous amino acids can be synthesised from carboxylic acids that are formed by the methods described in appendices 1.18 & 5.11.

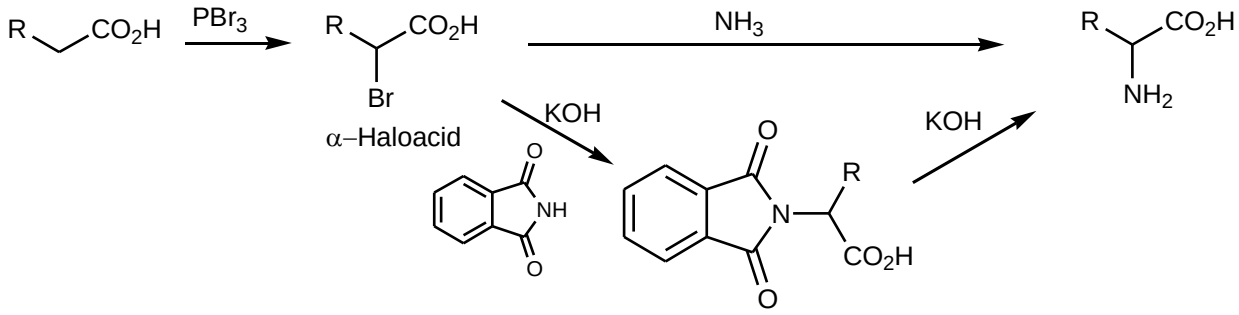


Figure 50 Synthesis of amino acids from carboxylic acids.

An approach which has proved useful in synthesising amino acids with bulky or branched side chains has been to synthesise allylic alcohols (appendices 1.10 & 5.6), then react these with trichloroacetonitrile to form a trichloroacetimidate (Fig. 51). This undergoes a [3,3] sigmatropic rearrangement to form an allylic amide. The alkene can then be split by oxidation with $NaIO_4$ in the presence of a ruthenium catalyst, or by ozonolysis.

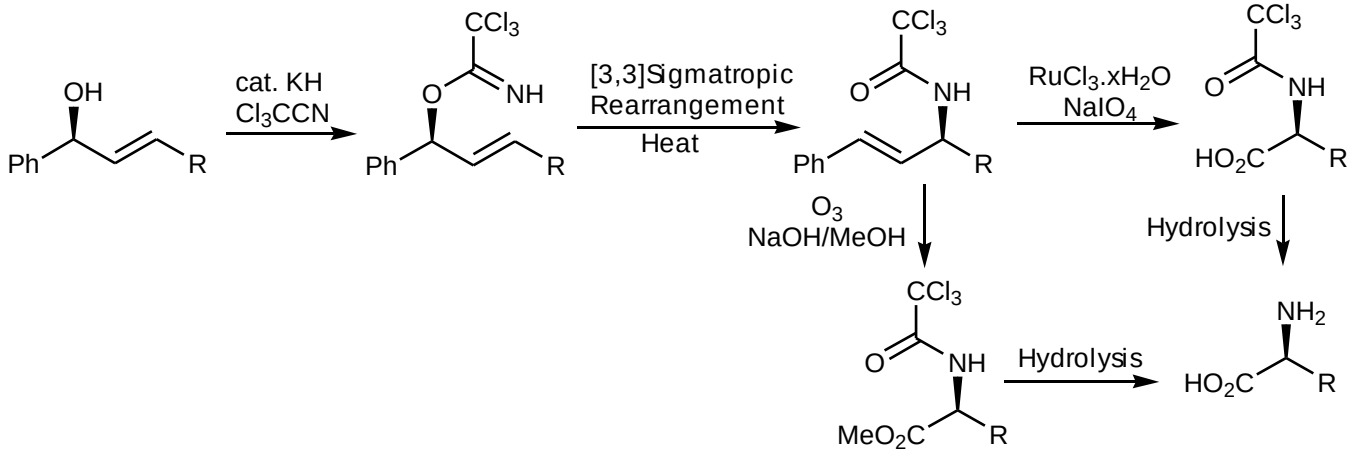


Figure 51 Synthesis of amino acids from allylic alcohols.

Amino acids can also be synthesised by the rhodium-catalysed hydrogenation of *N*-acylaminoacrylic acids (Fig. 52a). It works best when the alkene group is trisubstituted, rather than tetrasubstituted. The *N*-acylaminoacrylic acids can be synthesised as described in appendix 5.7.2.

Finally, α-keto acids or esters can be converted to imines, then reduced to amino acids or their esters (Fig. 52b&c).

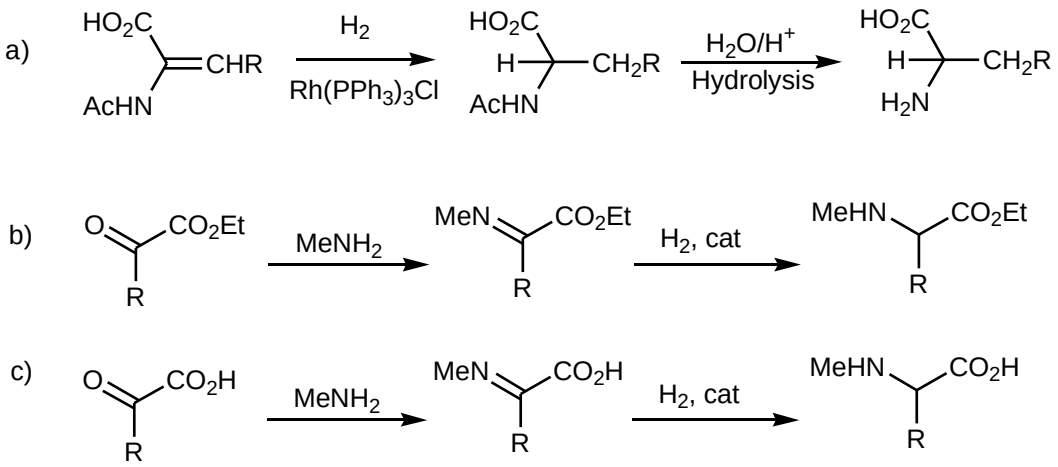


Figure 52 Synthesis of amino acids from functional group transformations.

App 1.14. Amino alcohols

1,2-Amino alcohols are commonly found in drug-like structures. Examples include a wide range of adrenergic agonists and antagonists such as salbutamol and propranolol, the anticancer agent mitoxantrone, the antiviral agents avridine, indinavir, and saquinavir, the antibacterial agents ethambutol and vancomycin, and the antihypertensive agent aliskiren.

An effective method of synthesising a 1,2-amino alcohol is to react an epoxide with an amine (Fig. 53a). Substitution takes place at the least substituted carbon of the epoxide. An example of this can be seen in chapter 2.3.1 in the synthesis of salmeterol.

Another approach is to react an epoxide with the azide ion, and then reduce the azide group (Fig. 53b).

Both reactions are stereospecific and result in a *trans*-arrangement between the alcohol and the amine if the epoxide is part of a cyclic system. If the *cis*-arrangement is wanted, then a different method has to be used.

Since epoxides are formed from alkenes, the above methods can also be used to convert an alkene to a 1,2-amino alcohol via an epoxide. An effective method of adding the amino and alcohol groups to the same face of the alkene is to react the alkene with the *N*-chloro, *N*-sodio salt of a primary amine in the presence of an osmium catalyst (Fig. 53c). With a suitable ligand the reaction can be diastereoselective. The reaction works better for conjugated alkenes than for non-conjugated alkenes.

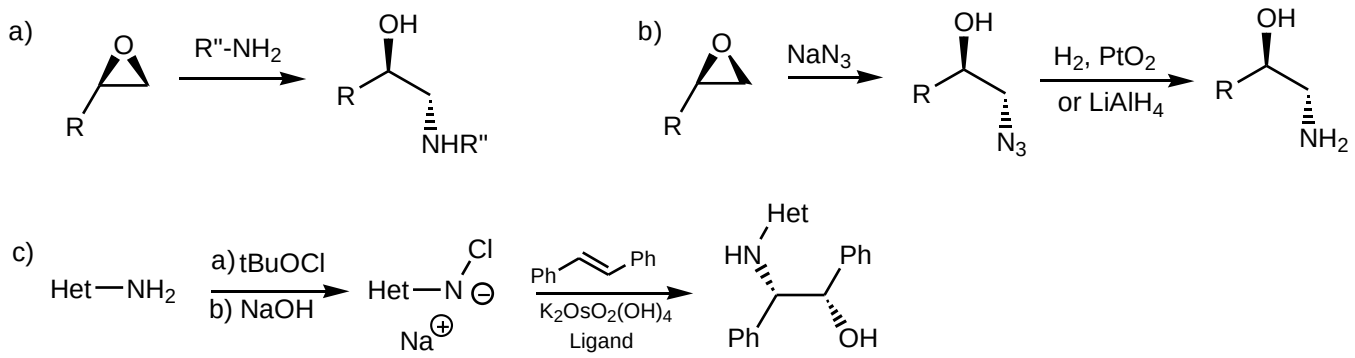


Figure 53 Synthesis of 1,2-amino alcohols.

Other types of amino alcohols can be synthesised from amino ketones by reduction (Fig 54).

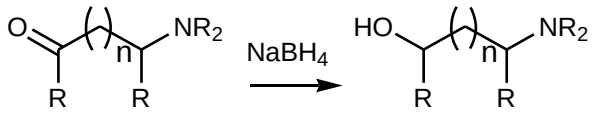


Figure 54 Synthesis of amino alcohols by reduction of a ketone.

App 1.15. Aryl halides

Aryl halides are found in a large variety of clinically important drugs and can serve a number of purposes. In some drugs, the halogen forms an important hydrophobic binding interaction with a target binding site, while in other drugs, it has been added to protect the aromatic ring from an oxidative metabolic reaction. The electron-withdrawing properties of halogens can also have an important influence on the physicochemical and pharmacokinetic properties of a drug.
Unlike alkyl halides, aryl halides are stable groups under physiological conditions and so there are far fewer risks of toxic properties. By the same token, aryl halides are stable to many of the chemical reagents used in synthesis and can be incorporated early on in a synthetic route. Aryl fluorides and chlorides are commonly found in drugs. Aryl bromides and iodides are less common, but they are extremely important in synthesis as they are important reagents for palladium-catalysed carbon-carbon bond formations such as the Suzuki, Stille, Heck and Sonagashira reactions.

App 1.15.1 Electrophilic substitution

Halogen substituents can be introduced to aromatic rings by electrophilic substitution reactions. For example, the bromination of benzene is carried out with bromine in the presence of a Lewis acid as catalyst (Fig. 55a). If substituents are already present in the ring, then these will influence the reactivity and substitution positions for bromination. For example, a phenol is highly activated towards electrophilic substitution resulting in tri-bromination, even in the absence of a Lewis acid catalyst (Fig. 55b). The same holds true for aniline (Fig. 55c). With less activating groups such as alkyl groups, ethers, aliphatic esters (Ar-OCOR) and aliphatic amides (Ar-NHCOR), mono-substitution takes place at the *ortho* or *para* positions, the latter being favoured if the substituent is bulky and blocks reaction at the *ortho* position. Deactivating groups such as carboxylic acids, ketones, aldehydes, aromatic esters ($ArCO_2R$) and aromatic amides ($ArCONHR_2$) direct substitution

to the *meta* position. Halogens are anomalous in that they deactivate the ring and direct substitution to the *ortho* and *para* positions.

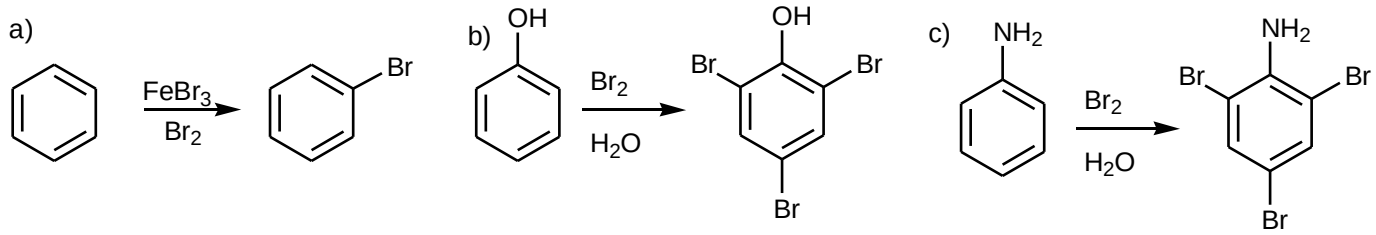


Figure 55 Bromination of aromatic rings.

App 1.15.2 Conversion of aromatic amines to aryl halides via diazonium salts
A popular method of introducing a range of halogens into an aromatic ring is to use a diazonium salt, which can be formed from an aromatic amine by reaction with nitrous acid. Once the diazonium salt has been formed, it can be treated with various nucleophiles (Fig. 56). The nucleophile displaces the diazonium group from the aromatic ring as nitrogen gas which is lost from the reaction mixture, thus helping to drive the reaction to completion. Those reactions involving Cu(I) are also known as the **Sandmeyer reaction.** The overall reaction is equivalent to replacing the primary amine with a halogen. These kinds of reactions have proved crucial in the synthesis of tetracycline analogues.

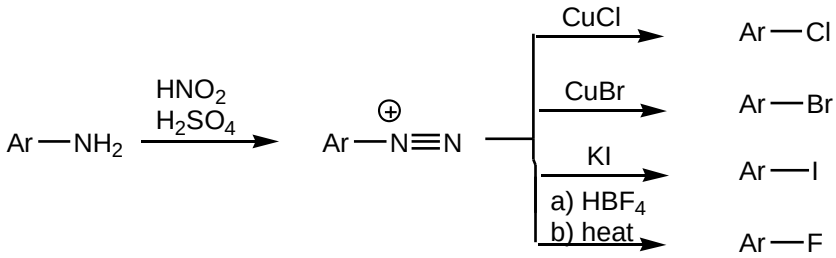


Figure 56 Reactions of diazonium salts to produce aryl halides.

App 1.16 Azides

Azides are not usually found in drugs due to their reactivity. However, the antiviral drug zidovudine contains such a group. Azides are useful in synthesis and are obtained by the nucleophilic substitution of alkyl halides with the azide ion (Fig. 57).

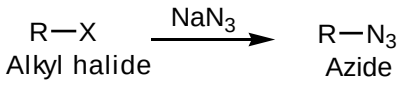


Figure 57 Reactions of diazonium salts to produce aryl halides.

App 1.17 Aziridines

Aziridines are not commonly present in drugs, although the ring has been incorporated into a number of structures that have been studied as potential drugs. The aziridinium cation is formed as a reactive intermediate during the mechanism of action of alkylating anticancer drugs.

Aziridines are useful intermediates in the formation of vicinal diamines, and can be synthesised from vicinal halo amines (Fig. 58a) or from epoxides via amino alcohols (Fig. 58b) (see also the synthesis of oseltamivir - box 5.4).

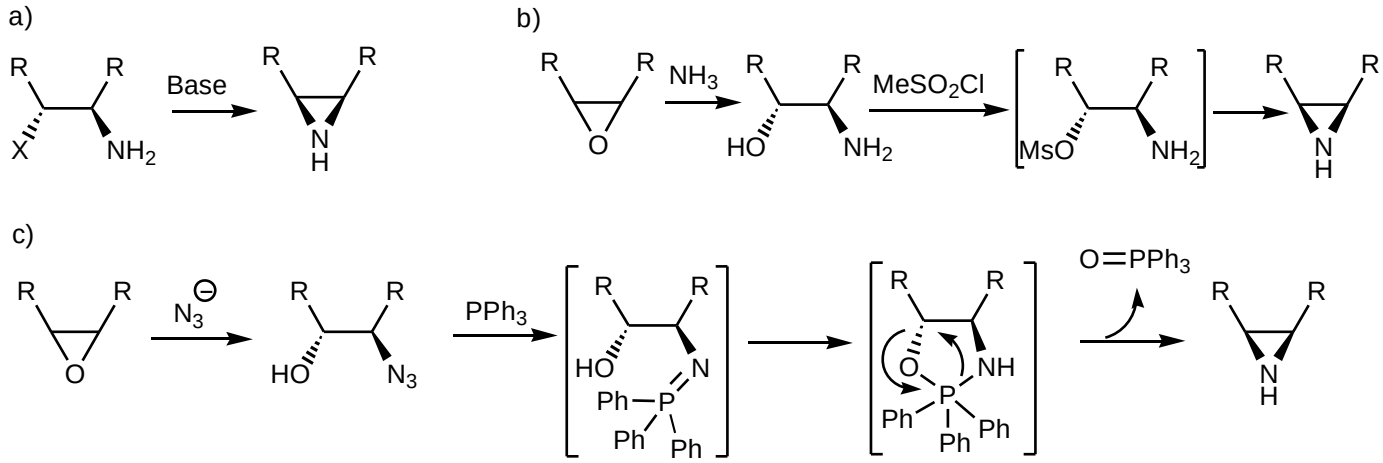


Figure 58 Methods of synthesising aziridines.

Epoxides can also be converted to aziridines in a two-stage process by first carrying out a ring opening reaction with an azide ion. Reaction of the azide group with triphenylphosphine then generates the aziridine ring. Triphenylphosphine is normally used to reduce an azide group to an amine. However, an aziridine can be formed if there is a vicinol alcohol group present (Fig. 58c). Alkenes can be converted directly to aziridines by reaction with chloramine T (TsNClNa)or the *N*-chloramine salt of *tert*-butylsulphonamide, as long as a catalyst ($PhNMe_3^+Br^-$) is present (Fig. 59).

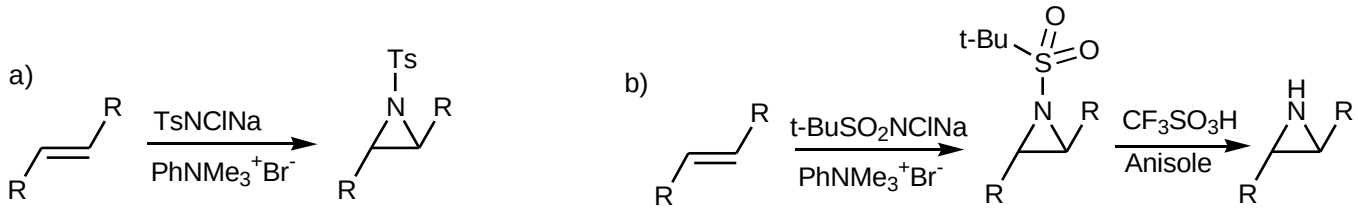


Figure 59 Synthesis of aziridines directly from alkenes.

App 1.18 Carboxylic acids

Carboxylic acids are present in a number of important drugs such as penicillins and cephalosporins, as well as some antihypertensive agents known as ACE inhibitors (ACE stands for angiotensin converting enzyme). When ionised, the carboxylate ion can form strong ionic and hydrogen bonding interactions with amino acid residues in protein binding sites. It can also act as a ligand for metal cofactors in metalloenzymes.

In organic synthesis, carboxylic acids are frequently used to synthesise amides, esters and heterocyclic rings. Carboxylic acids can be obtained from esters, amides, nitriles, primary alcohols, aldehydes, alkenes, and methyl ketones. Aromatic carboxylic acids can be obtained from alkyl benzenes.

App 1.18.1 Hydrolysis of esters, amides and nitriles to carboxylic acids

Carboxylic acids can be obtained by the hydrolysis of esters under acidic or basic conditions with heating (Figs. 60a). Amides can be hydrolyzed to carboxylic acids and amines under acid conditions (Fig. 60b).

Although acid chlorides and anhydrides are easily hydrolyzed to carboxylic acids, the reaction serves no synthetic purpose since acid chlorides and acid anhydrides are synthesized from carboxylic acids in the first place. Nitriles are also hydrolyzed to carboxylic acids in acidic or basic aqueous solutions (Fig. 60c).

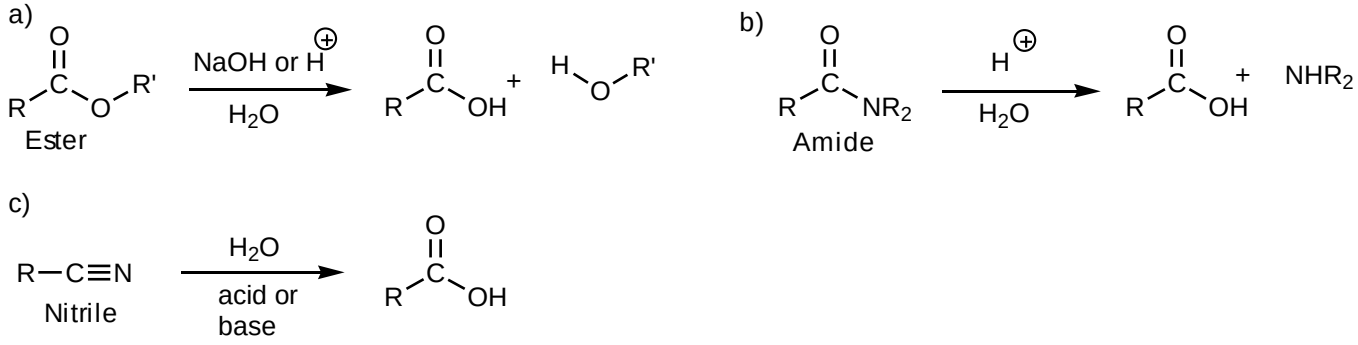


Figure 60 Hydrolysis of a) esters, b) amides and c) nitriles to carboxylic acids.

App 1.18.2 Oxidation of primary alcohols and aldehydes to carboxylic acids

Primary alcohols can be oxidized to carboxylic acids with chromium trioxide under acidic conditions (Fig. 61a). Potassium permanganate can also be used. Oxidation of an aldehyde with chromium trioxide or potassium permanganate results in the formation of a carboxylic acid (Fig. 61b). Some compounds may be sensitive to the acid conditions used in this reaction and an alternative method is to use a basic solution of silver oxide (Fig. 61c). Aldehydes can also be oxidised to carboxylic acids with peroxycarboxylic acids (Fig. 61d).

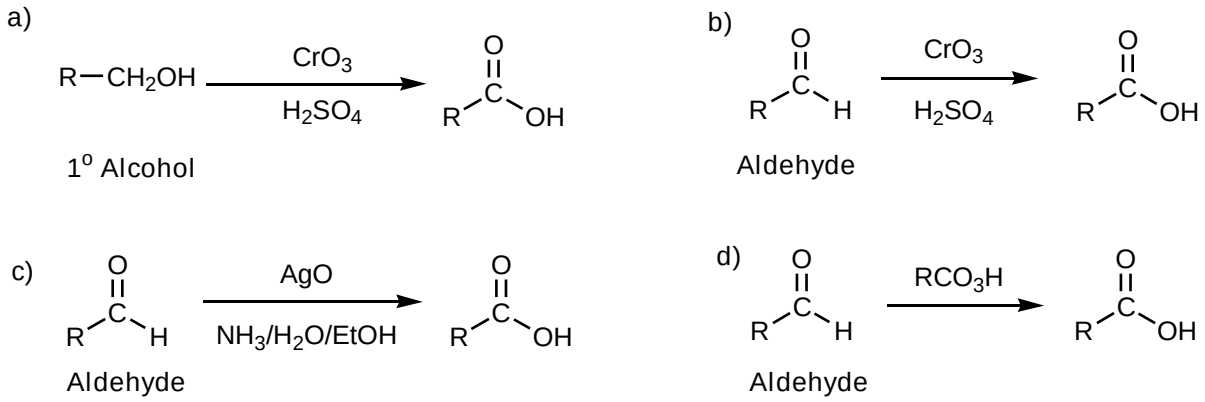


Figure 61 Oxidation of primary alcohols and aldehydes to carboxylic acids.

App 1.18.3 Oxidation of alkyl substituents to aromatic carboxylic acids

Aromatic rings are remarkably stable to oxidation from oxidizing agents such as potassium permanganate or sodium dichromate. In contrast, alkyl substituents on the aromatic ring are surprisingly susceptible. This can be put to good use in the synthesis of aromatic carboxylic acids by oxidising an alkyl substituent to a carboxylic acid without affecting the aromatic ring (Fig. 62). It does not matter how large the alkyl group is as long as a benzylic hydrogen is present (i.e. the carbon directly attached to the ring must contain a hydrogen). Alkyl groups lacking a benzylic hydrogen are not oxidized.

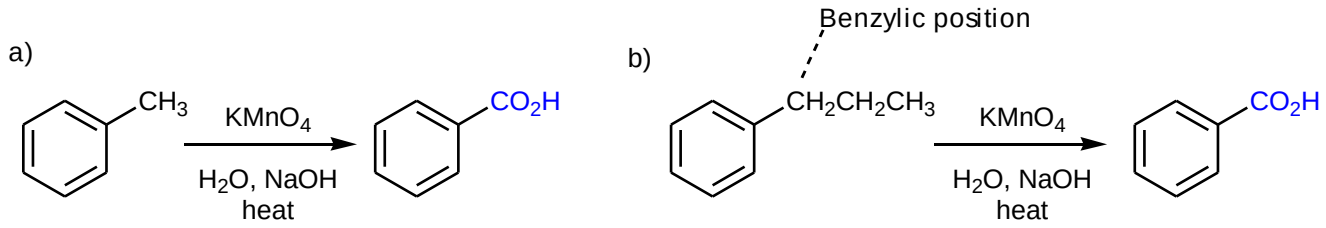


Figure 62 Oxidation of aromatic alkyl substituents.

App 1.18.4 Cleavage of alkenes to carboxylic acids and ketones

Alkenes can be oxidatively cleaved with hot permanganate solution to give carboxylic acids and/or ketones (Fig. 63a). The products obtained depend on the substituents present on the alkene. A vinylic proton has to be present if a carboxylic acid is to be formed; i.e. a proton directly attached to the double bond.

Ozonolysis of relevant alkenes with an oxidative work up using hydrogen peroxide will also generate carboxylic acids. Because of this, a terminal alkene can be viewed as a 'latent' carboxylic acid (Fig. 63b).

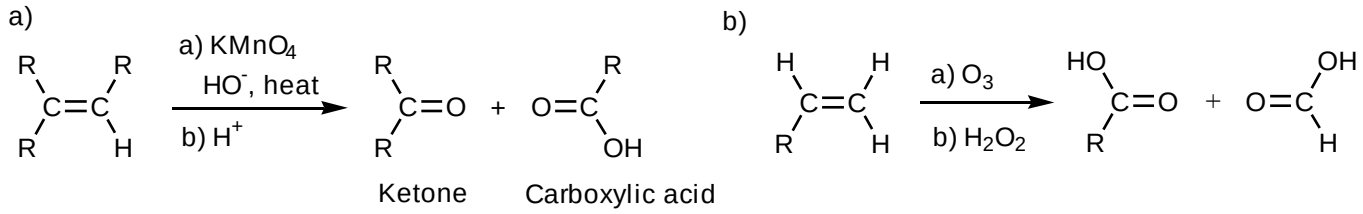


Figure 63 Oxidative cleavage of alkenes.

App 1.18.5 Conversion of methyl ketones to carboxylic acids

Methyl ketones undergo α-halogenation with excess iodine and base such that all three methyl protons are replaced with iodine (Fig. 64). The product obtained is then susceptible to nucleophilic substitution whereby the hydroxide ion substitutes the tri-iodomethyl ($^{-}CI_3$) carbanion - a good leaving group due to the three electron-withdrawing iodine atoms. This is known as the **Iodoform reaction**.

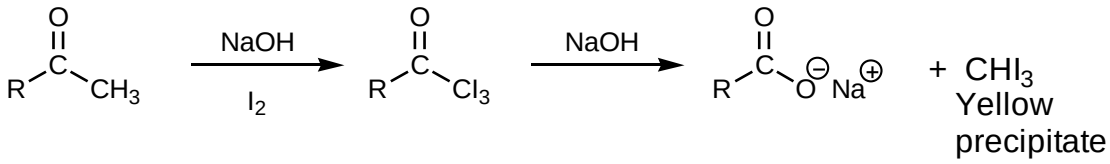


Figure 64 The Iodoform reaction.

App 1.19 Cyanohydrins

Cyanohydrins are not found in drugs and can be potentially toxic, but they can be useful intermediates in organic synthesis as they can be converted to amino acids or hydroxy acids. Aliphatic aldehydes and ketones react with HCN in the presence of a catalytic amount of KCN to form cyanohydrins (Fig. 65**)**. Aromatic ketones can be converted to cyanohydrins by using diethylaluminium cyanide (Et_2AlCN).

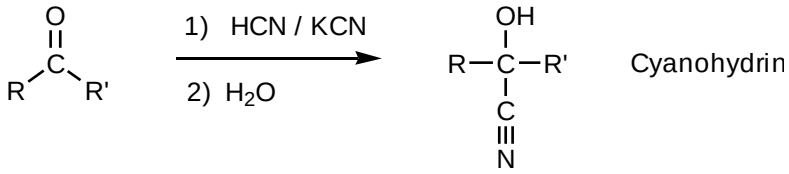


Figure 65 Formation of a cyanohydrin from an aldehyde or ketone (R' = alkyl group or H).

App 1.20 Dienes (conjugated)

Conjugated dienes are present in several drugs, such as the anticancer agents cyproterone acetate and megestrol acetate, the antibacterial agent rifampicin and statins such as lovastatin and simvastatin. A number of promising lead compounds with anticancer activity contain conjugated diene systems such as bryostatin, maytansine, and spongistatin. More extended conjugated systems of alkenes are present in the immunosuppressant rapamycin, the antifungal agent amphotericin, and the anticancer agents temsirolimus and everolimus.

Conjugated dienes are extremely important reagents in organic synthesis as they can be used in the Diels Alder reaction. For example, the natural product thebaine contains a conjugated diene and is used as the starting material in an important group of opioid analgesics and sedatives known as the oripavines (chapter 4.6.1).

Conjugated dienes can be synthesised from propargyl diols by reduction with $LiAlH_4$ (Fig. 66) (the Whiting reaction). Alkenes can be converted to dienes by brominating the allylic position, then dehydrating with base (Fig. 66b). α,β–Unsaturated ketones can be converted to conjugated dienes by converting them to tosylhydrazones, then treating them with strong base (Fig. 66c). The unconjugated dienes produced by the Birch reaction (appendix 1.21) can be isomerised to conjugated dienes by treatment with an acid catalyst (Fig. 66d)

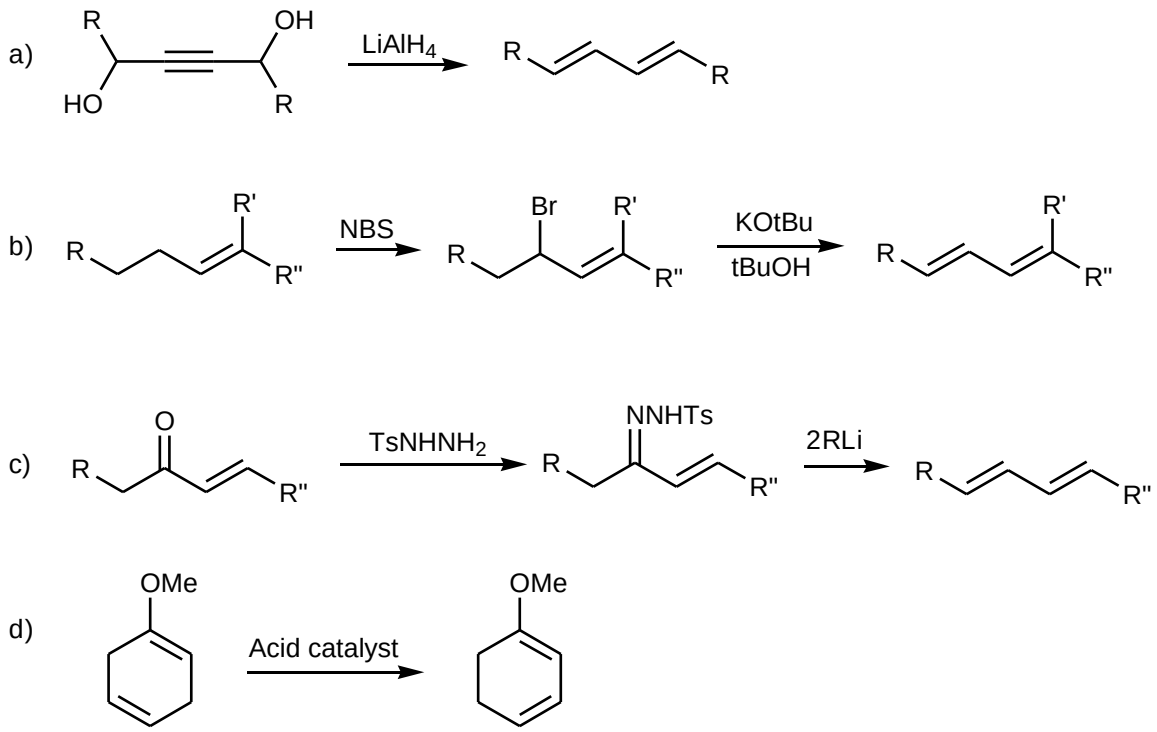


Figure 66 Synthesis of conjugated dienes from functional group transformations.

App 1.21 Dienes (unconjugated)

There are many instances of drugs and promising lead compounds containing two or more alkenes within their structure. Examples include eleutherobin, which is a lead compound with anticancer properties, and lipstatin which was the lead compound for the anti-obesity agent orlistat. The different alkenes concerned are normally synthesised in a step-wise fashion using the same procedures described for the synthesis of alkenes, but some methods are useful for synthesising a diene in one step with control over the relative position of the two alkene groups. For example, the Birch reduction is a method of converting an aromatic ring into an unconjugated cyclic diene, and has been extremely important in synthesising conjugated dienes in a number of steroid structures such as prednisolone, prednisone, betamethasone and dexamethasone. The reaction is a dissolving metal reduction where the aromatic ring is treated with lithium or sodium metal in a mixture of liquid ammonia and ethanol. When the metal dissolves, electrons are produced which react with the aromatic system, leading ultimately to the diene system (Fig. 67a). The ethanol acts as the proton source in the mechanism. The position of the diene is affected by whether any substituents present are electron withdrawing or electron donating (Fig. 67b&c). With anilines, an isomerisation takes place which means that a conjugated diene is obtained rather than an unconjugated diene (Fig. 67d).

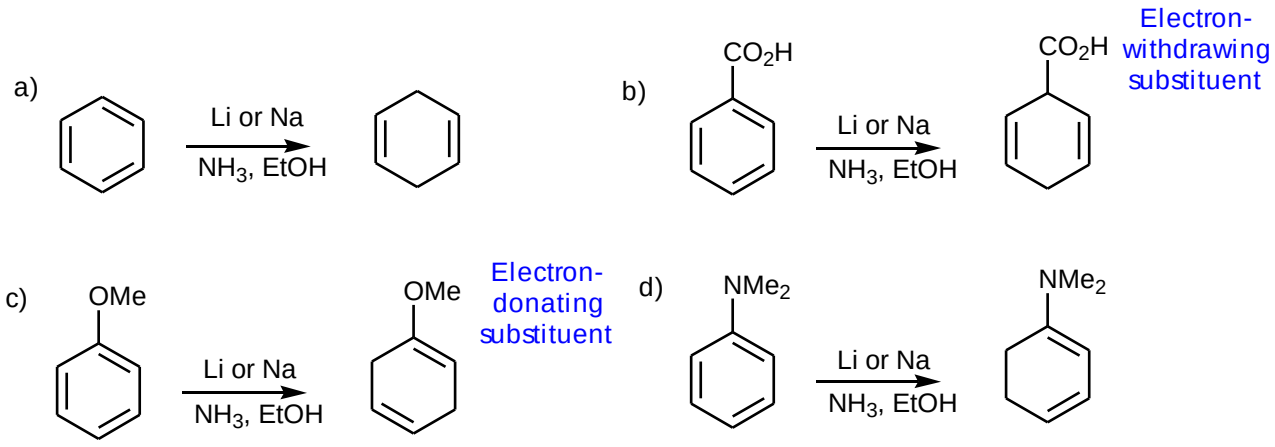


Figure 67 Birch reduction of aromatic rings.

App 1.22 Diketones

Diketones are found in a number of drugs and are very important reagents in organic synthesis. Diketones can generally be synthesised by the oxidation of diols and hydroxy ketones (Fig. 68).

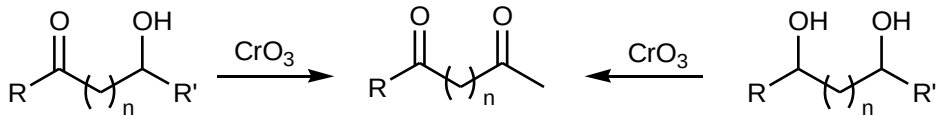


Figure 68 Oxidation of diols and hydroxy ketones to diketones.

App 1.22.1 Synthesis of 1,2-Diketones

A number of functional group transformations can be used to generate a 1,2-diketone. For example, oxidation of a ketone with nitrous acid results in a 1,2-diketone, as long as there is a methylene group (CH_2) present at the α-position (Fig. 69a). The reaction involves formation of an enol and, if more than one enol is possible, the more stable one is preferred.

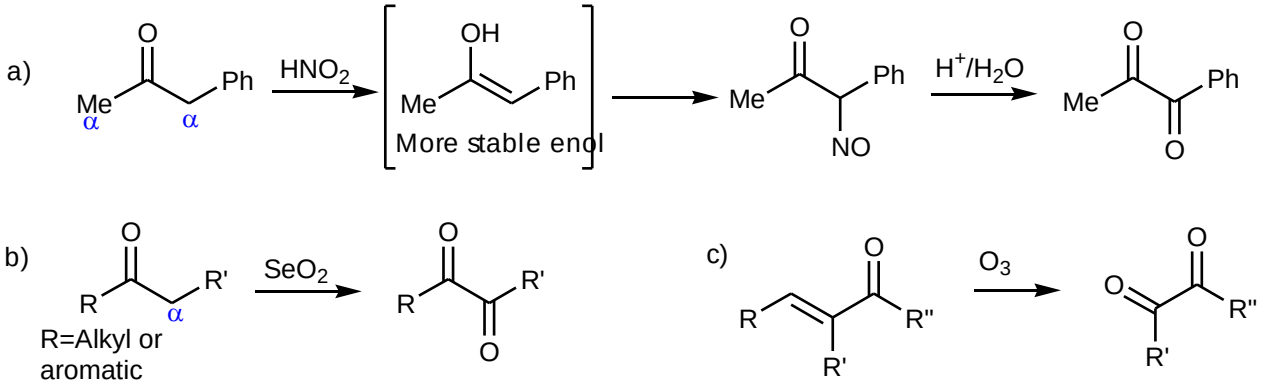


Figure 69 Oxidation of a ketone to a 1,2-diketone.

Alternatively, the ketone can be oxidised at the α-position with selenium dioxide (Fig. 69b). If oxidation occurs at the end of a chain, a ketoaldehyde is obtained rather than a diketone. Another approach is the ozonolysis of α,β-unsaturated ketones (Fig. 69c).

App 1.22.2 Synthesis of 1,3-Diketones

1,3-Diketones can be synthesised by hydrolysing conjugated alkynes (Fig. 70). The hydrolysis is easier than the hydrolysis of isolated alkynes and does not require a metal catalyst.

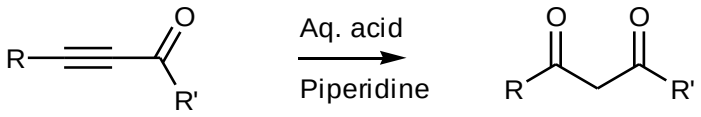


Figure 70 Hydrolysis of conjugated acetylenes to 1,3-diketones.

App 1.22.5 1,6-Diketones

One method of synthesising 1,6-diketones is to carry out an ozonolysis of substituted cyclohexene rings (Fig. 71).

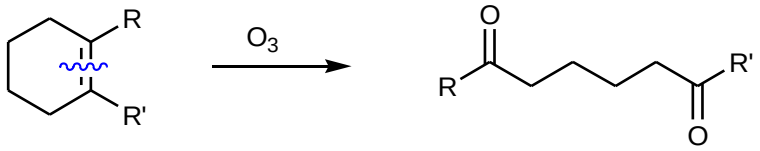


Figure 71 Synthesis of 1,6-diketones.

App 1.23 Diols

1,2-Diols are present in a significant number of drugs. Examples include the antibiotics erythromycin, vancomycin, tobramycin and mupirocin, the antiviral agents ribavirin and zanamivir, and the anticancer agents capecitabine, eleutherobin and pancratistatin, as well as the expectorant guaifenesin.

App 1.23.1 General synthesis of diols

Diols can be synthesised by the reduction of the corresponding diketones or hydroxy ketones (Fig. 72).

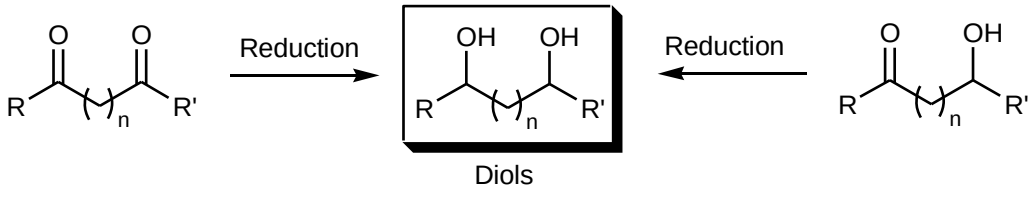


Figure 72 General preparations of diols by functional group transformation.

App 1.23.2 Synthesis of 1,2-Diols

1,2-Diols can be formed from alkenes or epoxides.

Alkenes are oxidised with osmium tetroxide (OsO_4) to give a 1,2-diol, also known as a glycol (Fig. 73a). The reaction involves the formation of a cyclic intermediate where the osmium reagent is attached to one face of the alkene. On treatment with sodium bisulphite, the intermediate is cleaved such that the two oxygen atoms linking the osmium remain attached. This results in both alcohols being added to the same side of the double bond - *syn* hydroxylation. With acyclic alkenes, different diastereoisomers are obtained depending on whether you start with the *Z* or the *E*-alkene. If there is more than one alkene present in the molecule, the reaction takes place at the most electron-rich or most substituted double bond, and at the least hindered face. Hydrolysis of the osmium glycolate intermediate can be accellerated in the presence of the sulphonamide $MeSO_2NH_2$. Asymmetric dihydroxylations are possible using $K_2OsO_2(OH)_2$ as a non-volatile source of osmium, along with a chiral cinchona alkaloid-based ligand.
Dihydroxylation can also be carried out using cold alkaline potassium permanganate ($KMnO_4$) followed by treatment with aqueous base (Fig. 73b). It is important to keep the reaction cold since potassium permanganate can cleave the diol by further oxidation (appendix 1.34.2). The reaction actually works better with osmium tetroxide. However, this is a highly toxic and expensive reagent and has to be handled with care.

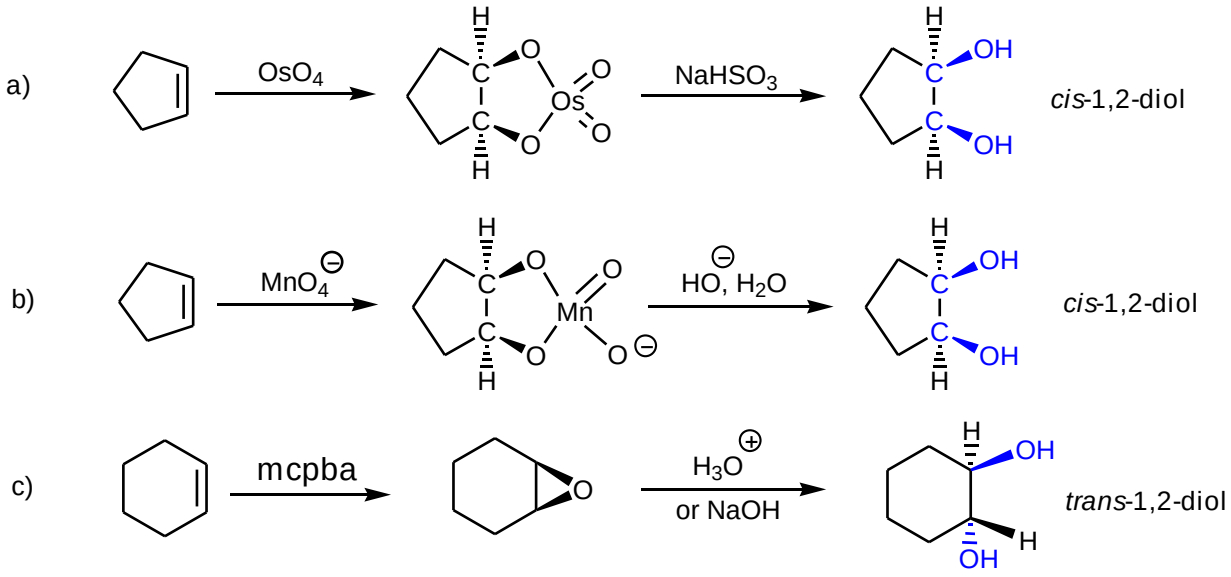


Figure 73 Oxidation of an alkene to a 1,2-diol.

Anti-hydroxylation of an alkene bond can be achieved by forming an epoxide, then carrying out an acid-catalyzed hydrolysis (Fig. 73c). Epoxides are cyclic ethers, but they are more reactive than normal ethers because of the ring strain involved in a three-membered ring. Therefore, ring opening can take place through an S_N2 nucleophilic substitution reaction under acidic or basic conditions to give a 1,2-diol. The incoming nucleophile attacks the epoxide from the opposite direction of the epoxide ring, resulting in a *trans* arrangement of the diol system when the reaction is carried out on

the epoxides of cycloalkenes. With the epoxides of acyclic alkenes, different diastereoisomers are obtained depending on the stereochemistry of the initial alkene.

App 1.24 Disulphides

Disulphide bonds are present in proteins and some peptide hormones such as vasopressin and oxytocin. The anticancer agent depsipeptide also contains a disulphide bond. Disulphide bonds can be easily formed by the oxidation of thiols with mild oxidizing agents such as bromine or iodine (Fig. 74).

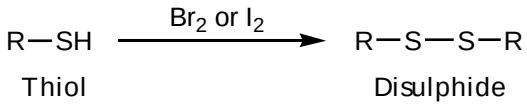


Figure 74 Conversion of a thiol to a disulphide.

App 1.25 Enamines

Enamines are not prevalent in drug structures, but they are extremely useful reagents for reactions involving carbon-carbon bond formation. Enamines can be formed by the reaction of a secondary amine with an aldehyde or ketone, as long as there is an α-proton present in the aldehyde or ketone (Fig. 75). This proton is lost in order to form the enamine, and an acid catalyst is usually required. The yield can be improved by adding a dehydrating agent such as titanium tetrachloride to remove the water that is formed from the reaction. With unsymmetrical ketones, there is the possibility of two different enamines, in which case the more stable enamine is preferred.

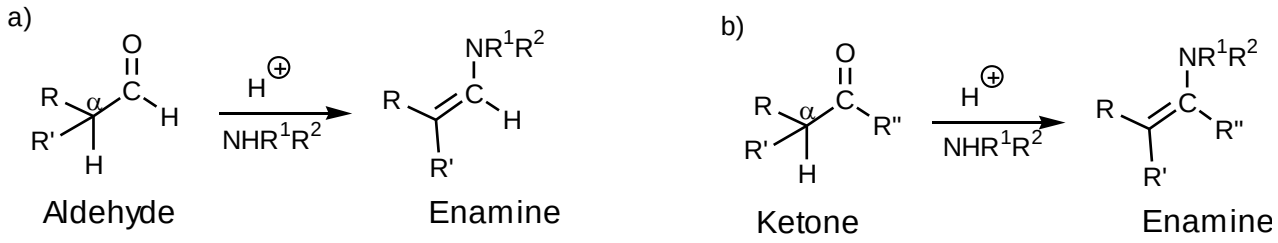
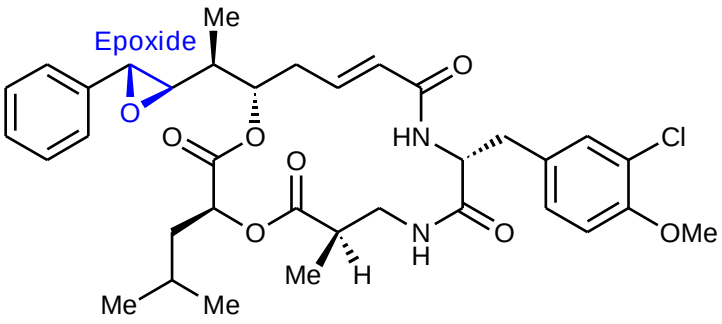


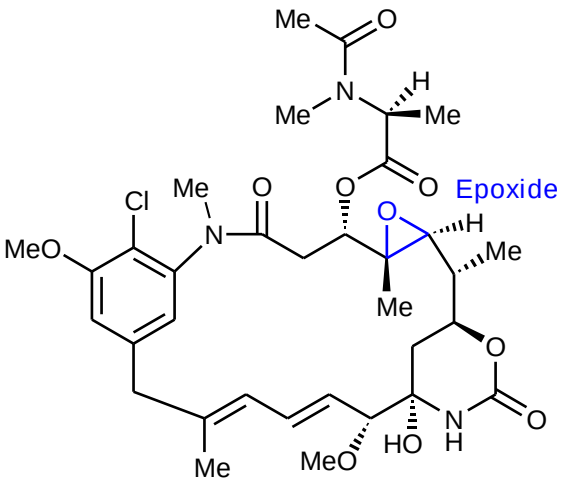
Figure 75 Enamines from reaction of a secondary amine with a) an aldehyde or b) a ketone.

App 1.26 Epoxides

Epoxides are present in a number of natural products that are used as drugs or lead compounds. Examples include the antibiotic mupirocin and a range of natural products currently being studied as lead compounds for novel anticancer agents (phyllanthoside, the epothilones, cryptophycins and maytansine).



Cryptophycin 1



Maytansine 1

Epoxides are also important synthetic intermediates in the preparation of 1,2-diols and α-hydroxyamines. They can be prepared by treating an alkene with a peroxyacid such as *meta*-chloroperoxybenzoic acid (mcpba), with the epoxide being formed on the least hindered face of the alkene (Fig. 76**).** If more than one alkene group is present, the reaction shows a preference for the more substituted, electron-rich alkene. If there is an allylic alcohol present, the reaction takes place on the allylic alkene rather than with any isolated alkene that might be present. In this situation, the reaction takes place at the *more* hindered face. For example, the Sharpless epoxidation is an asymmetric epoxidation that occurs at the alkene group of allylic alcohols, with no reaction at isolated alkenes.

Methyltrioxorhenium ($MeReO_3$)has been used as a catalyst for the epoxidation of alkenes with aqueous hydrogen peroxide (Fig. 76**)**. The presence of a heterocyclic structure such as pyridine or pyrazole helps to protect and stabilise the resulting epoxide products and prolong the lifetime of the catalyst.

An alternative route to epoxides from alkenes is a two step process involving the formation of a halohydrin (Fig. 76). Epoxides can also be synthesized by treating aldehydes or ketones with sulphur ylides.

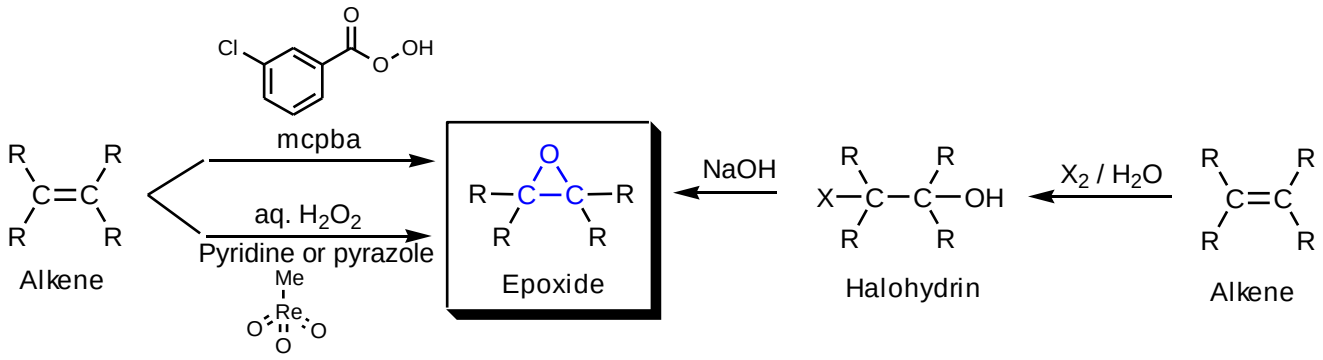
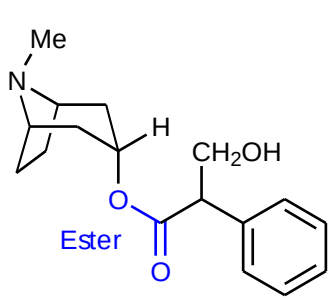


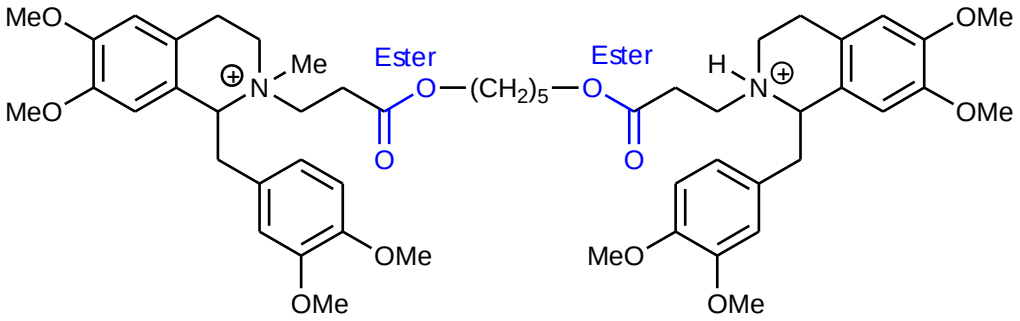
Figure 76 Epoxidation of an alkene.

App 1.27 Esters

A large number of drugs include an ester functional group; for example the cholinergic antagonists atropine and atracurium. In many cases, the drugs concerned are prodrugs where the ester is masking a polar functional group, such as an alcohol, phenol or carboxylic acid in order to improve oral absorption. The ester is then hydrolysed by esterase enzymes once it is absorbed.



Atropine



Atracurium

In synthetic terms, esters can act as important protecting groups and are also important in carbon-carbon bond formations. There are many different ways in which esters can be synthesized.

App 1.27.1 Esters from the reaction of alcohols with acid chlorides or acid anhydrides

A very effective method of synthesis is to react an acid chloride with an alcohol in the presence of pyridine (Fig. 77a). Acid anhydrides also react with alcohols to give esters, but are less reactive. Furthermore, the reaction is wasteful since half of the acyl content in the acid anhydride is lost as the leaving group (i.e. the carboxylate ion). This is not a problem if the acid anhydride is cheap and readily available. For example, acetic anhydride is useful for the synthesis of a range of acetate esters (Fig. 77b).

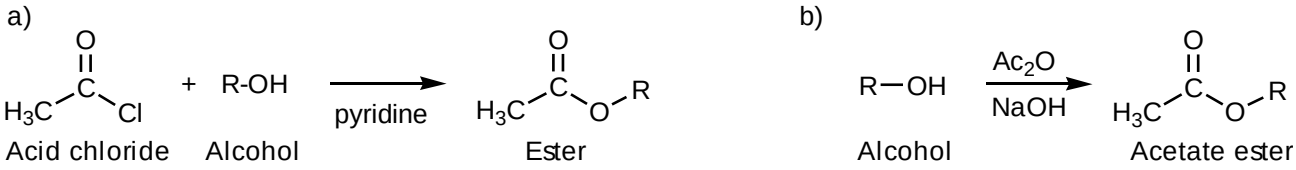


Figure 77 Synthesis of esters from alcohols reacting with acid chlorides or acid anhydrides.

App 1.27.2 Synthesis of esters from carboxylic acids

A very common method of synthesizing esters is to treat a carboxylic acid with an alcohol in the presence of a catalytic amount of a mineral acid (Fig. 78a), while an excellent method of preparing methyl esters is to treat carboxylic acids with diazomethane (Fig. 78b). Good yields are obtained in the latter reaction because nitrogen is formed as one of the products and is lost as a gas, thus driving

the reaction to completion. However, diazomethane is an extremely hazardous chemical which can explode, and strict safety precautions are necessary when using it.
A carboxylic acid can also be converted to a carboxylate ion and then treated with an alkyl halide (Fig. 78c). The reaction involves the S_N2 nucleophilic substitution of an alkyl halide and so the reaction works best with primary alkyl halides.

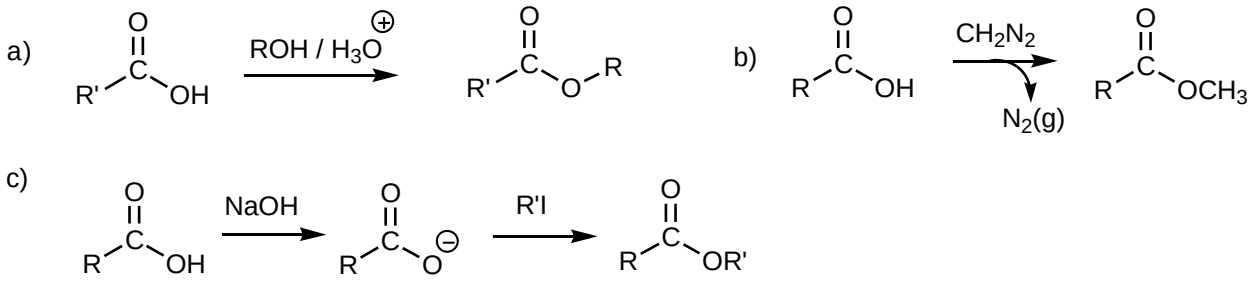


Figure 78 Synthesis of esters from carboxylic acids.

Another method of creating esters from carboxylic acids is through the **Mitsunobu reaction** where the carboxylic acid is reacted with an alcohol in the presence of triphenylphosphine (PPh_3) and diethyl azodicarboxylate - the latter reagent being given the ominous acronym (DEAD) (Fig. 79). DEAD serves to activate triphenylphosphine such that it becomes linked to the alcohol group to form an alkoxyphosphonium salt containing a strong oxygen-phosphorus bond. The carboxylic acid is also converted to a carboxylate ion which then carries out a nucleophilic substitution reaction on the alkoxyphosphonium salt to give the ester product. Although the carboxylate ion is a poor nucleophile, the reaction is driven by the formation of triphenylphosphine oxide which contains a very strong P=O bond. The reaction can be classed as a redox reaction since DEAD is reduced and triphenylphosphine is oxidised as a result of the mechanism. Note that an inversion of configuration takes place for chiral alcohols, which would not occur with the methods previously described.

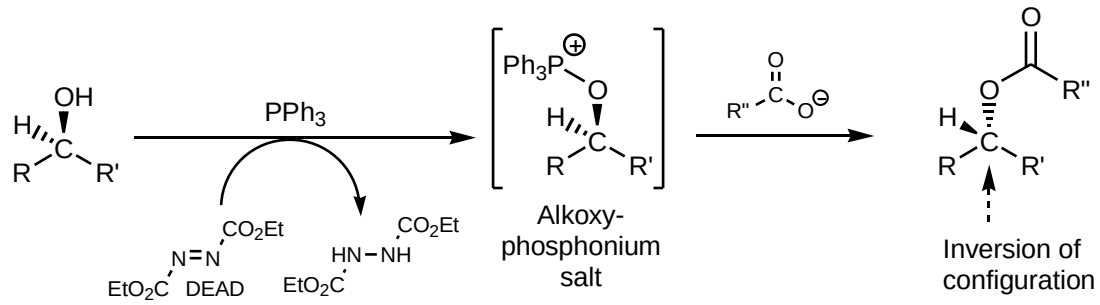


Figure 79 Synthesis of esters by the Mitsunobu reaction.

App 1.27.3 Esters by transesterification
Esters can be converted by nucleophilic substitution from one type of ester to another - a process called transesterification. For example, a methyl ester can be dissolved in ethanol in the presence of

an acid catalyst and converted to an ethyl ester (Fig. 80a). The reaction is an equilibrium reaction, but when an alcohol is used as solvent, it is in large excess and the equilibrium is shifted to the desired ester. Furthermore, if the alcohol to be replaced has a low boiling point, it can be distilled from the reaction as it is formed, thus shifting the equilibrium further to the desired product.

Figure 80 Synthesis of esters by a) transesterification and b) hydrolysis of nitriles.

App 1.27.4 Phenyl esters
Phenols (ArOH) can be converted into phenyl esters (ArOCOR) by reaction with acid chlorides or acid anhydrides. However, unlike alcohols, phenols are not converted to esters by reaction with a carboxylic acid under acid catalysis.

App 1.27.5 Hydrolysis of nitriles to esters
Nitriles (RCN) can be hydrolyzed to esters by reaction with an alcohol under acid conditions (Fig. 80b).

App 1.27.6 Synthesis of esters by the Baeyer Villiger oxidation of ketones
Treatment of a ketone with a peroxy acid leads to the synthesis of an ester where one of the alkyl groups of the original ketone migrates to the oxygen of the ester (Fig. 81). With unsymmetrical ketones, there are two possible products, depending on which alkyl group migrates. However, there is a marked preference between different types of migratory groups, which follows the order tertiary > secondary > benzyl > aryl > primary > Me. Chiral groups retain their absolute configuration when they migrate.

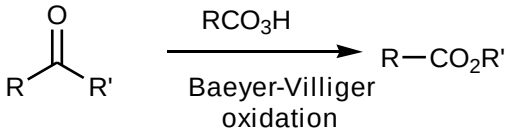
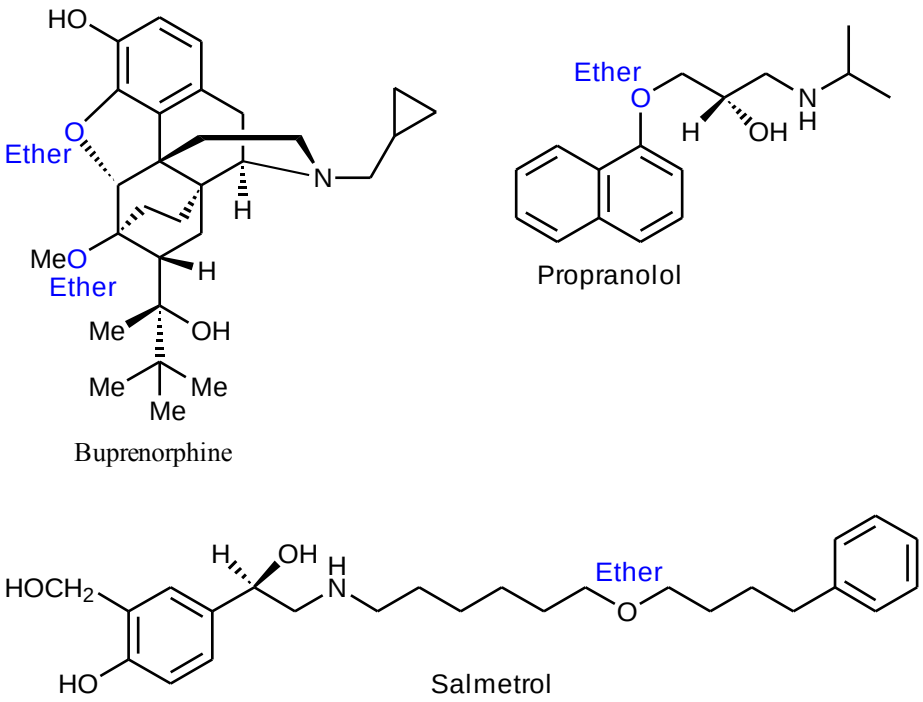


Figure 81 The Baeyer-Villiger oxidation of ketones.

App1.28 Ethers
Aliphatic and aromatic ethers are found in a wide variety of drug structures, including the analgesic buprenorphine, the beta-blocker propranolol, and the anti-asthmatic agent salmeterol. They have the potential to act as hydrogen bond acceptors in binding sites. Synthetically, they are generally unreactive groups.



App 1.28.1 Aliphatic ethers from alcohols and alkyl halides

The Williamson ether synthesis is the best method of preparing aliphatic ethers (Fig. 82a). The procedure involves the S_N2 reaction between a metal alkoxide and a primary alkyl halide or tosylate. The alkoxide required for the reaction is prepared by treating an alcohol with a strong base such as sodium hydride or metallic sodium. An alternative procedure is to treat the alcohol directly with the alkyl halide in the presence of silver oxide, thus avoiding the need to prepare the alkoxide beforehand.

If an unsymmetrical ether is being synthesized, the most hindered alkoxide should be reacted with the simplest alkyl halide, rather than the other way round. Since this is an S_N2 reaction, primary alkyl halides react better then secondary or tertiary alkyl halides.

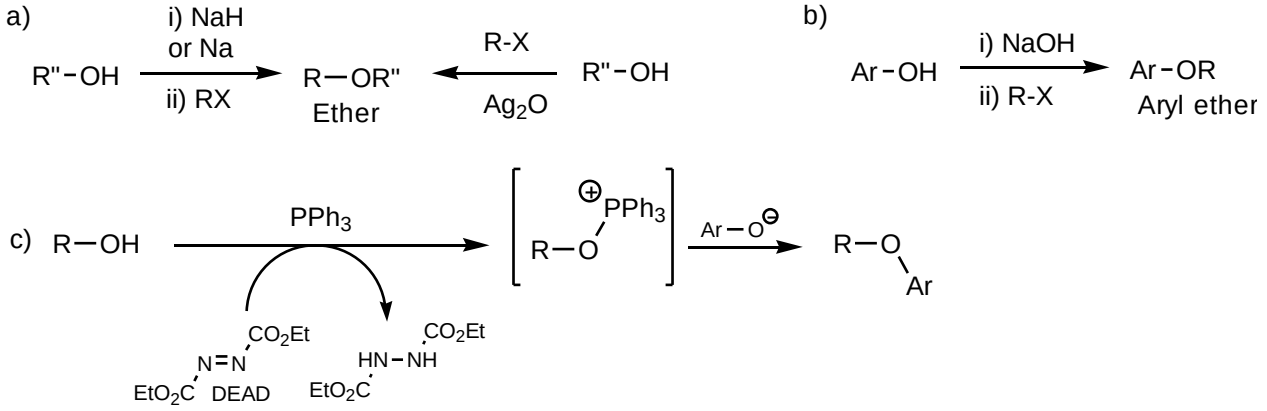


Figure 82 Synthesis of ethers from alkyl halides and alcohols.

App 1.28.2 Aromatic ethers from the reaction of phenols with alkyl halides or alcohols

Phenols can be converted into aryl ethers by reaction with alkyl halides in the presence of base (Fig. 82b). The reactions can be carried out under milder conditions than those used for alcohols due to the greater acidity of phenols. Thus phenols can be converted to phenoxide ions with sodium hydroxide rather than metallic sodium. Dimethyl sulphate can be used instead of iodomethane to form aromatic methyl ethers.
Another method of alkylating phenols is to carry out the reaction with an alcohol in the presence of triphenylphosphine and diethyl azodicarboxylate in a **Mitsunobu coupling** (Fig. 82c; compare Fig. 79). This method was used to prepare an aromatic ether in a synthesis of the antidepressant tomoxetine (chapter 5.8.4; Fig. 5.58). Another example of its use can be seen in chapter 6.5.8; Fig 6.52.

App 1.28.3 Aliphatic ethers from alcohols and alkenes

Alkenes can be converted to ethers by the electrophilic addition of mercuric trifluoroacetate, followed by addition of an alcohol (Fig. 83). An organomercuric intermediate is obtained which can be reduced with sodium borohydride to give the ether.

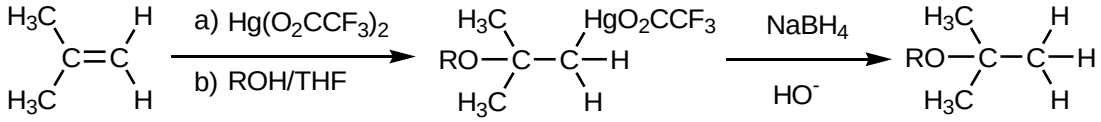


Figure 83 Synthesis of ethers from alkenes and alcohols.

App 1.29 α-Halo aldehydes and α-halo ketones

α-Halo aldehydes and ketones are useful reagents in drug synthesis and can be formed by reacting an aliphatic aldehyde or ketone with chlorine, bromine or iodine in acidic solution, resulting in halogenation at the α-carbon (Fig. 84). An α-proton must be present in the aldehyde or ketone for this reaction to occur, and acid conditions are necessary to avoid polyhalogenation. As far as ketones are concerned, the reaction is best carried out on aromatic ketones, or ketones which can only enolise on one side of the carbonyl group. Otherwise, a mixture of products is obtained.

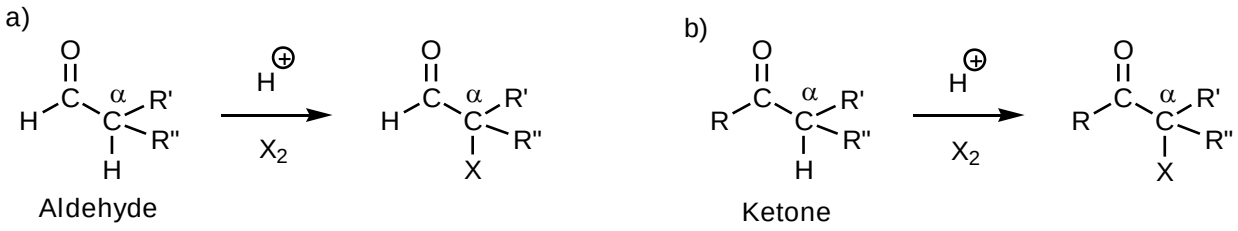


Figure 84 Formation of a) α-halo aldehydes and b) α-halo ketones.

Halogenation at the α-carbon of aldehydes and ketones is a useful method of introducing a fluorine substituent using an electrophilic fluorinating agent. Fluorine (F_2) itself has been used for this purpose, but fluorine is very reactive, non-selective and difficult to handle. Moreover, toxic HF is formed as a by product of the reaction. A more convenient reagent is Selectfluor (Fig. 85), which is

sufficiently stable to be handled safely and reacts more selectively. *N*-Fluorobenzenesulphonimide (NFSi) is another electrophilic fluorinating reagent that is commonly used (Fig. 86).

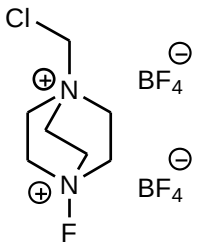


Figure 85 Selectfluor.

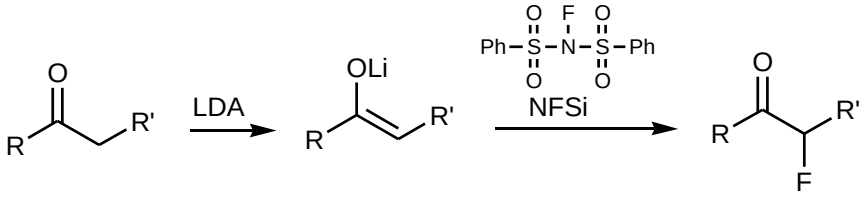


Figure 86 Fluorination of a ketone.

App 1.30 Halo amines

β–Halo amines are a common feature in many of the anticancer alkylating agents used in medicine. They can be synthesised by treating β–hydroxy amines with phosphorus oxychloride (Fig. 87).

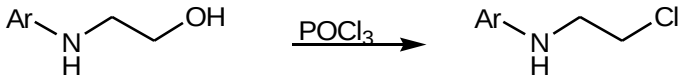


Figure 87 Synthesis of β-halo amines.

App 1.31 α-Hydroxy ketones

α-Hydroxy carbonyl compounds are found in several natural products with biological activity. They also have an important application as chiral auxiliaries in asymmetric synthesis. If a ketone has an acidic α-proton, then treatment with the base potassium hexamethyldisilazine (KHMDS) generates an enolate ion, which can be oxidised with *N*-sulphonyloxaridines to introduce a hydroxyl group (Fig. 88). This method was used to introduce a hydroxyl group as part of a full synthesis of tetracyclines (Chapter 12.5, Fig. 12.33).

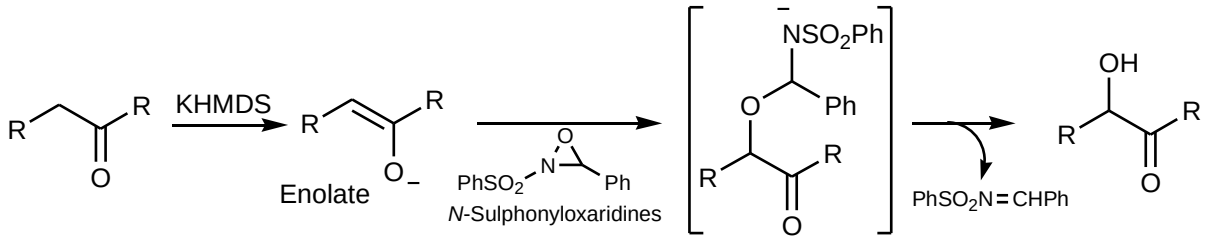


Figure 88 α-Hydroxylation of a ketone.

App 1.32 Imines

The reaction of primary amines with aldehydes and ketones in the presence of an acid catalyst generates imines which are also known as **Schiff bases** (Fig. 89). Water is formed as a by-product and can be removed by heating the reaction to reflux such that the water is azeotroped off into a Dean and Stark apparatus, or absorbed by molecular sieves held in a soxhlet apparatus. Alternatively, trimethylorthoformate can be used as a dehydrating solvent without the need for acid catalysis.

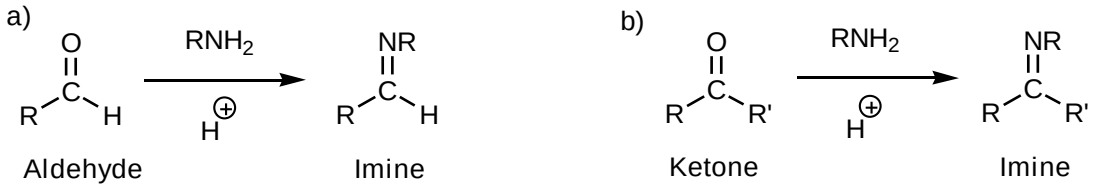


Figure 89 Formation of imines from aldehydes and ketones with amines.

App 1.33 α-Keto acids and α-keto esters

α-Keto acids and esters can be obtained by the ozonolysis of an α,β-unsaturated ketone (Fig. 90a).

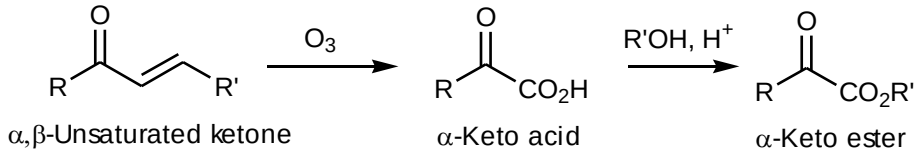
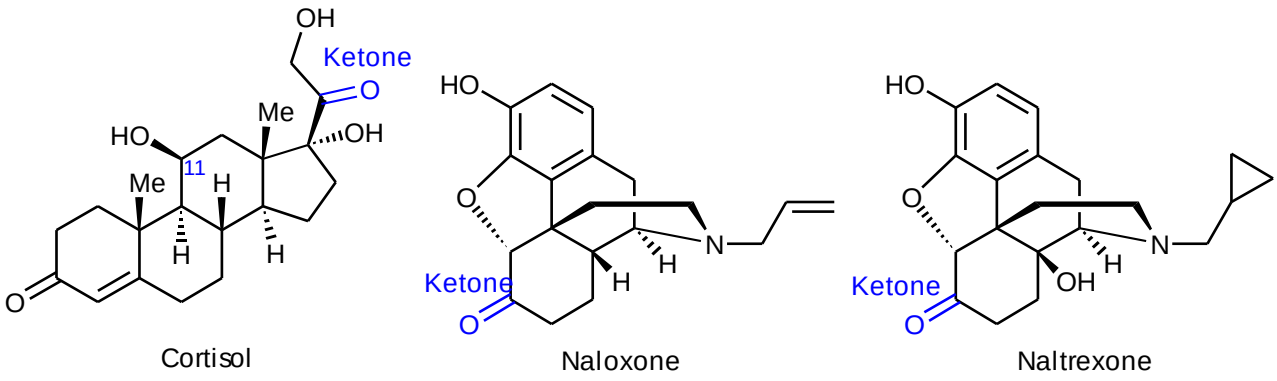


Figure 90 Synthesis of α-keto acids and esters.

App 1.34 Ketones

Ketones are found in a variety of drugs including the opioid antagonists naloxone and naltrexone, the anti-smoking drug bupropion, the antipsychotic haloperidol, and a variety of steroidal anti-inflammatory agents such as cortisol.



In synthetic terms, ketones are extremely important functional groups for carbon-carbon bond formations. They can be synthesized from secondary alcohols, alkynes, alkenes and α,β-unsaturated ketones.

App 1.34.1 Oxidation of secondary alcohols to ketones

A common method of obtaining ketones is by oxidising secondary alcohols with chromium trioxide or sodium dichromate (the Jones oxidation) (Fig. 91a). If the starting material is not stable to acid conditions, then pyridinium chlorochromate can be used instead. The Oppenauer oxidation involves the use of an aluminium alkoxide in acetone (Fig. 91b), and has been a popular method of oxidising secondary alcohols to ketones during the synthesis of various steroids (e.g. Chapter 9.3 Fig. 9.7). The aluminium alkoxide reacts with the alcohol group to form an alkoxide derivative which then reacts with acetone through a cyclic transition state. This leads to oxidation of the secondary alcohol and reduction of acetone.

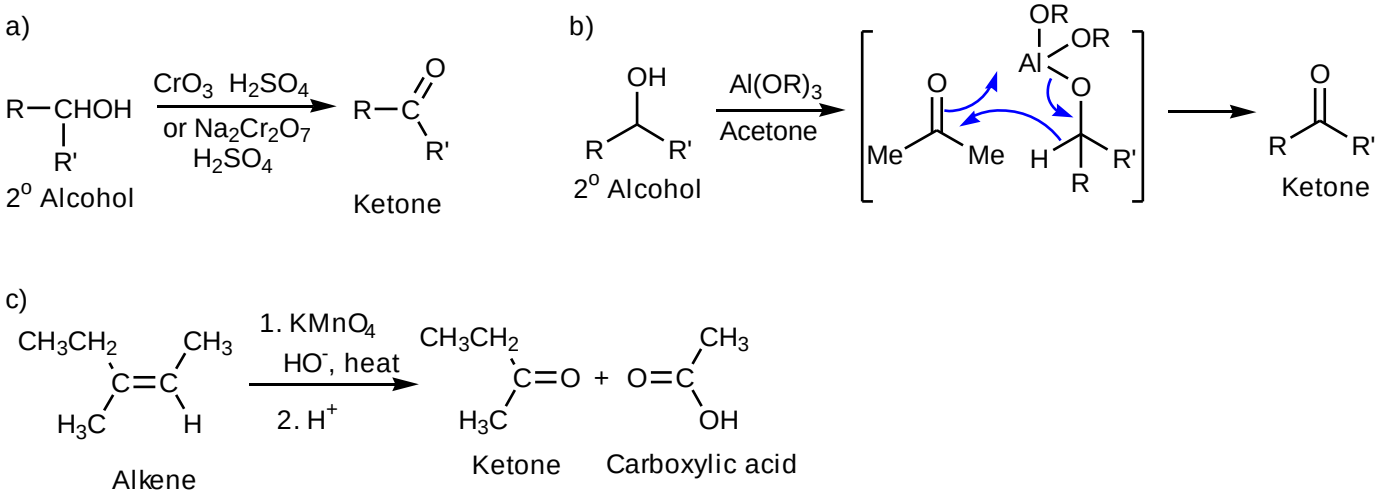


Figure 91 Oxidation of a) & b) secondary alcohols and c) alkenes to ketones.

App 1.34.2 Oxidation of alkenes

Ozonolysis of an alkene followed by a reductive work up is a method of splitting an alkene across the double bond to give two carbonyl compounds. These will be ketones or aldehydes depending on the

substituents present. Alkenes can also be oxidatively cleaved with hot permanganate solution to give carboxylic acids and/or ketones (Fig. 91c).

App 1.34.3 Reduction of α,β-unsaturated ketones to form ketones

The alkene group of an α,β-unsaturated ketone can be reduced using hydrogen gas in the presence of a metal catalyst such as palladium or platinum (Fig. 92a). Both hydrogen atoms are added to the least hindered face of the alkene in a *cis* fashion. Aromatic rings and carbonyl groups are unaffected, but alkynes and nitro groups are susceptible to reduction.

If the reaction proves difficult to carry out with more hindered molecules, it is possible to reduce the alkene group with sodium and ammonia. The conditions are harsh, though, and may not be feasible if there are other functional groups present in the molecule.

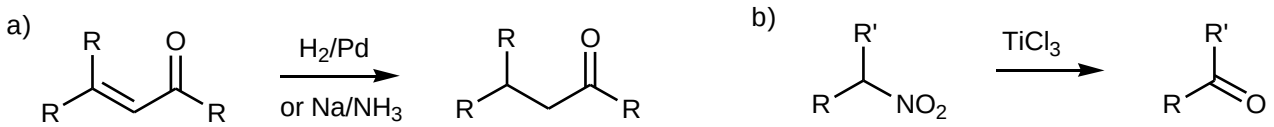


Figure 92 a)Reduction of an α,β-unsaturated ketone. b) Hydrolysis of a nitro group.

App 1.34.4 Hydrolysis of nitro groups to form ketones

A secondary aliphatic nitro group can be hydrolysed in the presence of a titanium chloride catalyst to form a ketone (Fig. 92b). The nitro group can, therefore, be viewed as a latent ketone group that can be revealed when required during a synthetic route.

App 1.34.5 Ketones from alkynes

Symmetrical alkynes react with aqueous acid in the presence of a catalyst (mercuric sulphate) to generate a ketone (Fig. 93a). The reaction goes through an enol, which undergoes keto-enol tautomerism to provide the ketone.

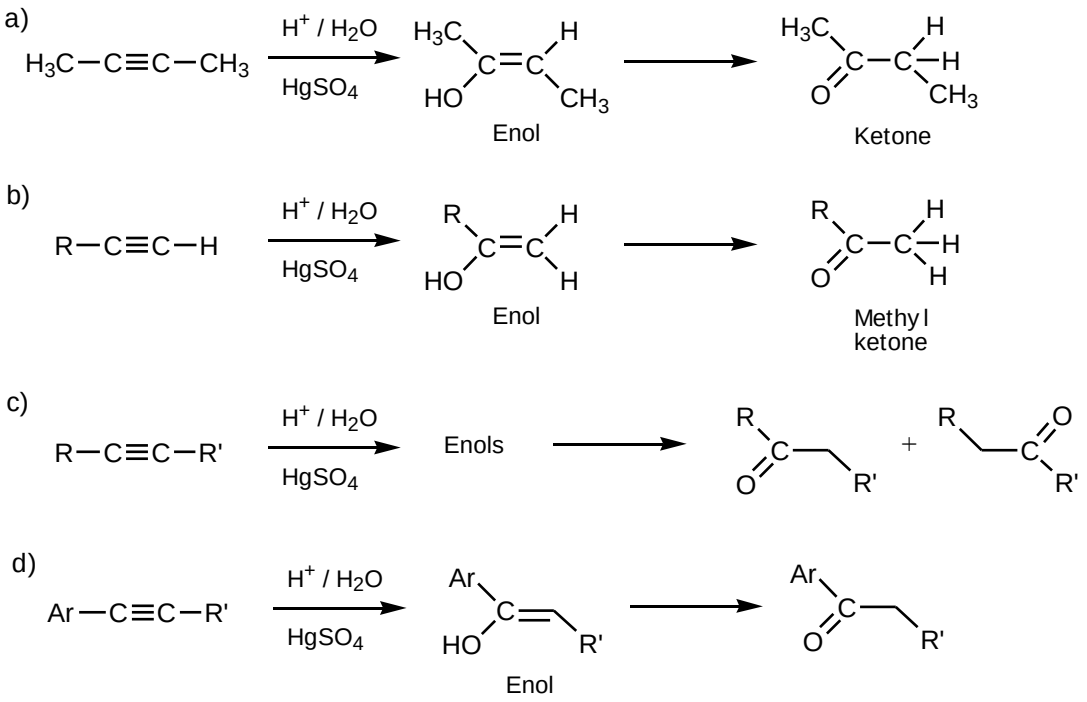
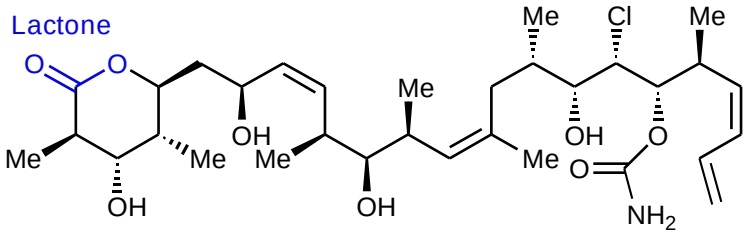


Figure 93 Conversion of alkynes to ketones.

With terminal alkynes, water is added across the triple bond according to Markovnikov's Rule which states that the additional hydrogen ends up on the carbon which already has the most hydrogens. This means that a methyl ketone is formed after keto-enol tautomerism, instead of an aldehyde (Fig. 93b). With unsymmetrical alkynes, a mixture of both possible ketones is likely (Fig. 93c). However, the hydrolysis of aromatic alkynes tends to show selectivity for the aromatic ketone (Fig. 93d).

App 1.35 Lactones

Lactones are present in a number of drugs including the cholesterol-lowering drugs lovastatin and simvastatin, the muscarinic agonist pilocarpine, the anticancer agent discodermolide, the antiviral agents podophyllotoxin and tipranavir, and the antibacterial agents azithromycin, telithromycin and daptomycin.



Discodermolide

A convenient method for generating lactones is to carry out the Baeyer-Villiger oxidation of cyclic ketones (Fig. 94). This is analogous to the Baeyer-Villiger oxidation of acyclic ketones to produce esters (appendix 1.27.6). Lactones can also be prepared by intramolecular cyclisations (chapter 4.5.2).

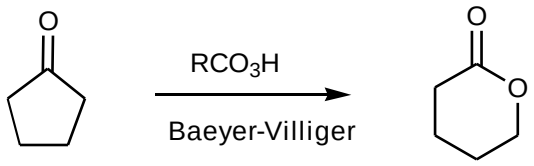


Figure 94 Bayer-Villiger oxidation of cyclic ketones to lactones.

App 1.36 Nitriles

Nitriles are present in a significant number of drugs, often as an aryl substituent. For example, a nitrile group is present in the antihypertensive agent cromakalim and the antidepressant citalopram. Nitriles are electron-withdrawing and can strongly influence neighbouring groups. The anti-ulcer agent cimetidine contains a nitrile group which was added to decrease the basicity of a guanidine group.

Aliphatic nitriles are commonly prepared by the S_N2 reaction of a cyanide ion with a primary alkyl halide (Fig. 95a). However, this limits the nitriles which can be synthesized to those having the general formula RCH_2CN. A more general synthesis of nitriles involves the dehydration of primary amides with reagents such as thionyl chloride ($SOCl_2$), phosphorus pentoxide (P_2O_5), phosphoryl trichloride ($POCl_3$) or acetic anhydride (Fig. 95b). Aromatic nitriles are generated from diazonium salts by the Sandmeyer reaction (Fig. 95c).

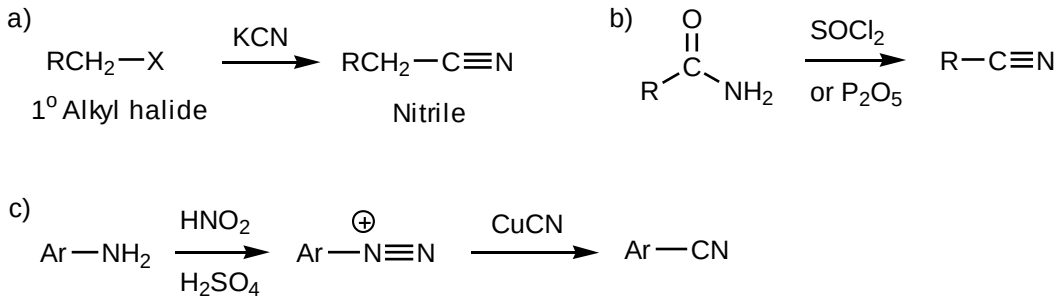


Figure 95 Synthesis of nitriles by a) substitution of alkyl halides b) dehydration of primary amides and c) the Sandmeyer reaction.

App 1.37 Organometallic reagents

Organometallic reagents are extremely important to many of the synthetic reactions involved in carbon-carbon bond formation (Appendix 5). There are a large variety of such reagents. The ones described here provide the equivalent of carbanions which can act as nucleophiles in nucleophilic additions or substitutions.

App 1.37.1 Grignard reagents

Alkyl halides of all types (1º, 2º and 3º) react with magnesium in dry ether to form Grignard reagents, where the magnesium is 'inserted' between the halogen and the alkyl chain (Fig. 96). These reagents are extremely useful in organic synthesis and can be used in a wide variety of carbon-carbon bond forming reactions. Their reactivity reflects the polarity of the atoms present. Since magnesium is an electropositive metal, the neighbouring carbon atom of the alkyl group will be slightly negative and can act as a nucleophilic centre. In essence, a Grignard reagent can be viewed as providing the equivalent of a carbanion.

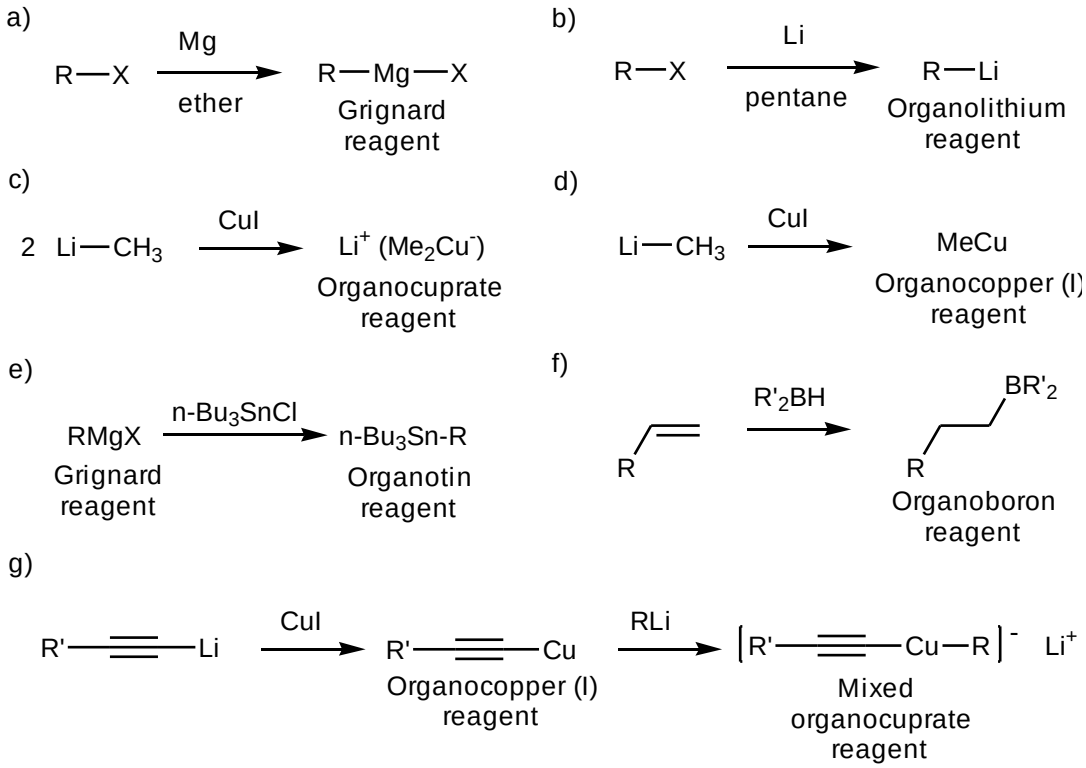


Figure 96 Formation of organometallic reagents.

App 1.37.2 Organolithium reagents

Alkyl halides can be converted to organolithium reagents using lithium metal in an alkane solvent (Fig. 96b). Like Grignard reagents, the carbon linked to the metal is slightly negative and can act as a nucleophile.

App 1.37.3 Organocuprate reagents

Organocuprate reagents (another source of carbanion equivalents) are prepared by the reaction of one equivalent of cuprous iodide with 2 equivalents of an organolithium reagent (Fig. 96c). With 1 equivalent of the organolithium reagent, an organocopper(I) reagent is obtained (Fig. 96d). This allows the synthesis of mixed organocuprates (Fig. 96g), which are useful reagents in several reactions.

App 1.37.4 Organotin reagents

Organotin reagents can be synthesised by the reaction of a Grignard reagent with tributyltin chloride (Fig. 96e). The reagents are useful in palladium-catalysed coupling reactions.

App 1.37.5 Organoborane reagents

Organoborane reagents can be synthesised by the reaction of a dialkylborane with an alkene (Fig. 96f).

App 1.38 Oximes and Oxime Ethers

Oximes are not particularly common in drugs. However, an oxime group is present in pralidoxime (an antidote to organophosphate nerve agents) and nocardicin A. Oxime ethers are more common and can be found in the antidepressant fluvoxamine, the antibacterial agent aztreonam, and a range of antibacterial cephalosporins called the oximinocephalosporins. Oximes can be prepared by the reaction of aldehydes or ketones with hydroxylamine (Fig. 97). *O*-Alkylation can be achieved with diazomethane, alkyl halides or alkyl sulphates to give the oxime ethers.

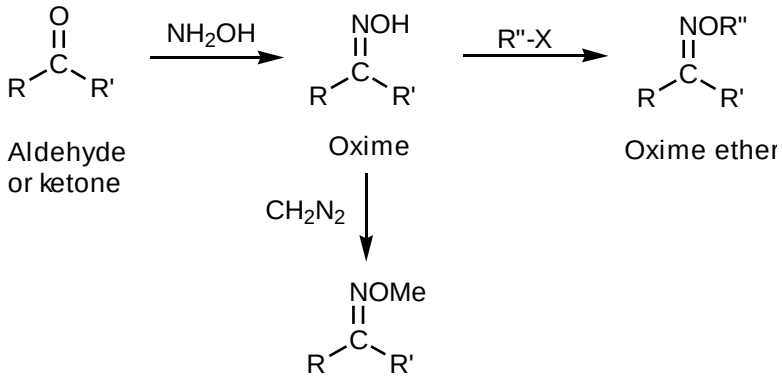
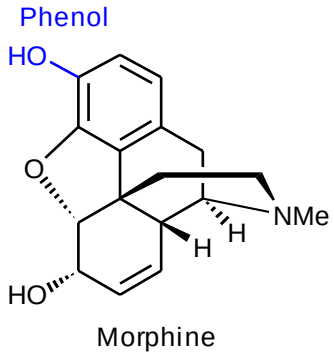


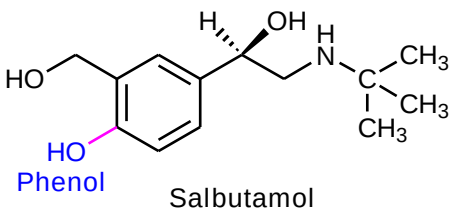
Figure 97 Synthesis of oximes and oxime ethers from aldehydes and ketones.

App 1.39 Phenols

Phenols are commonly present in drug structures. Examples include the anti-asthmatic agent salbutamol, the analgesic morphine, and antibiotics such as valinomycin and the tetracyclines. The phenol OH group often forms an important hydrogen bond with a target binding site.



Morphine



Salbutamol

It is not possible to introduce the phenol group directly to an aromatic ring, but it is possible to obtain phenols from various functional group transformations.

App 1.39.1 Phenols from aryl esters

Aryl esters can be hydrolysed under acidic or basic conditions in the same way as alkyl esters (Fig. 98a; cf Fig. 4a).

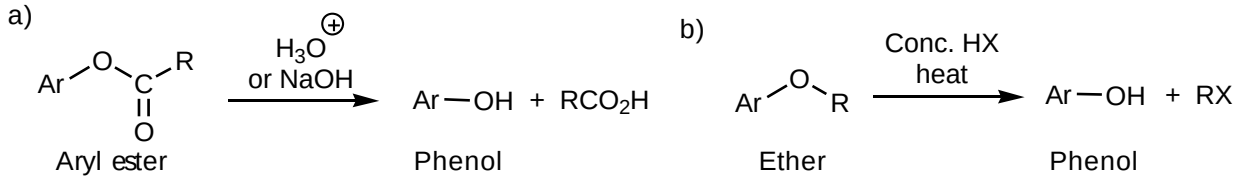


Figure 98 Synthesis of phenols from a) aryl esters and b) ethers.

App 1.39.2 Phenols from aromatic ethers

An aomatic ethers can be cleaved to a phenol and an alkyl halide using the same method used to cleave an aliphatic ether (Fig. 98b; cf. Fig. 9). The bond between the alkyl group and oxygen is specifically cleaved since it is weaker than the Ar-O bond.

A popular method of cleaving an aromatic methyl ether in opioid chemistry is to use methanesulphonic acid along with the amino acid methionine (see also chapter 8.6.7; Fig. 8.64). The methanesulphonic acid acts as a hard acid which interacts with the ether oxygen atom (a hard base), whereas the methionine acts as a soft nucleophile and interacts with the methyl group of the methyl ether (a soft acid). The process of cleavage is known as a **push-pull mechanism**, where the methionine does the pushing and the methanesulphonic acid does the pulling (Fig. 99).

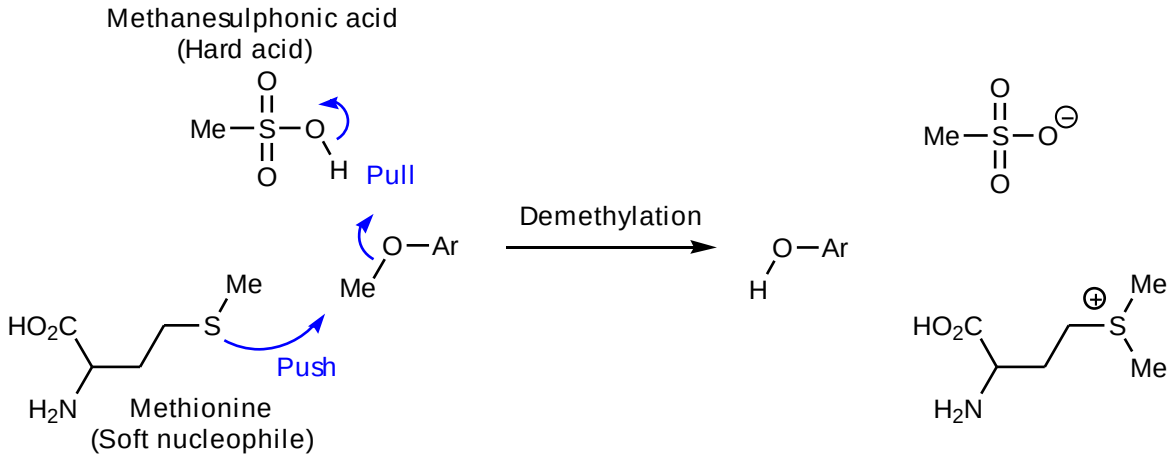


Figure 99 The push-pull mechanism in the cleavage of an aromatic methyl ether.

App 1.39.3 Phenols from primary aromatic amines

A general method for introducing a phenol group is to convert a primary aromatic amine to a diazonium salt, and then carry out a hydrolysis reaction (Fig. 100a). Alternatively, a dilute solution of the diazonium salt can be treated with cupric nitrate and cuprous oxide.

Figure 100 Synthesis of phenols from a) primary aromatic amines and b) aromatic sulphonic acids.

App 1.39.4 Phenols from aromatic sulphonic acids

A sulphonic group can be converted to a phenol group by melting the starting material with sodium hydroxide (Fig. 100b). The reaction conditions are harsh and only alkyl-substituted phenols can be prepared by this method.

App 1.40 Sulphonamides

The best known sulphonamides in medicinal chemistry are the antibacterial sulphonamides, but sulphonamide functional groups are present in a large number of other drugs used in different therapeutic fields. Examples include the anticancer agent prinomastat, the antiviral agents tipranavir, amprenavir, darunavir and delavirdine, the anti-impotence drug sildenafil, the dopamine antagonist sultopride, the serotonin agonist sumatriptan, and the cholesterol-lowering drug rosuvastatin.

Sulphonamides can be formed by reacting primary and secondary amines with a sulphonyl chloride in the presence of pyridine (Fig. 101). Tertiary amines do not give a stable product and are recovered unchanged. The reaction works for both aliphatic and aromatic amines.

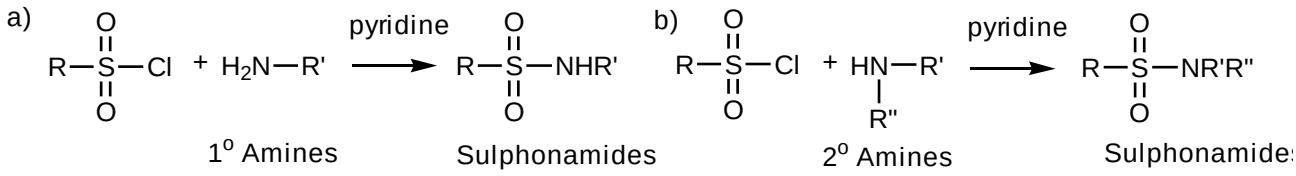


Figure 101 Synthesis of sulphonamides.

App 1.41 Sulphonates

Sulphonates are synthesised by treating alcohols with sulphonyl chlorides in the presence of a base such as pyridine or triethylamine. For example, reaction with methanesulphonyl chloride or *p*-toluenesulphonyl chloride gives a methane sulphonate (mesylate) and a *p*-toluenesulphonate (tosylate) respectively (Fig. 102a,b). The base serves to 'mop up' the HCl which is formed during the reaction and prevents acid-catalyzed rearrangement reactions.

Mesylates and tosylates are excellent leaving groups and undergo nucleophilic substitution with a range of nucleophiles. For that reason, they are useful reagents in organic synthesis and can be used in the same way as alkyl halides.

The trifluoromethylsulphonate group is called a triflate group and is an even better leaving group than the mesylate or tosylate. Alcohols are converted to triflates by reaction with trifluorosulphonyl anhydride in the presence of pyridine (Fig. 80c).

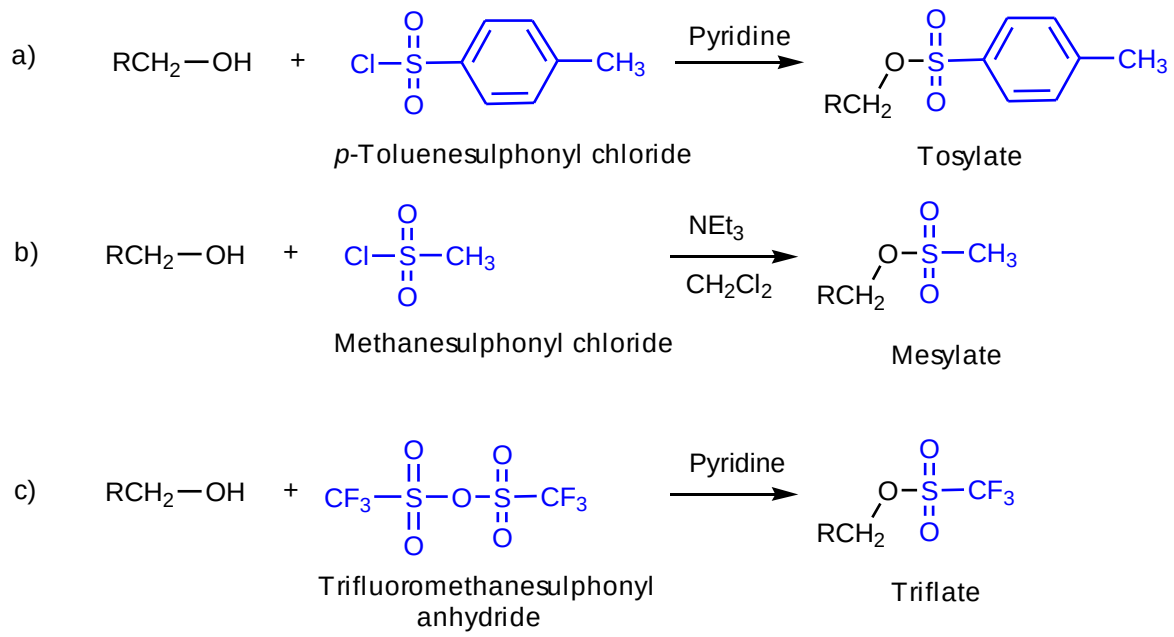


Figure 102 Synthesis of mesylates, tosylates and triflates from alcohols.

App 1.42 Sulphoxides and sulphones

Sulphoxides and sulphones are present in a number of drugs. For example, the anti-protozoal drug oxamniquine and the anticancer drug fulvestrant both contain a sulphoxide group. Lapatinib (an anticancer drug), rofecoxib (a COX inhibitor) and several antileprosy drugs all contain a sulphone group.

Sulphoxides can be obtained by oxidising thioethers with hydrogen peroxide. Further oxidation with a peroxyacid gives a sulphone (Fig. 103).

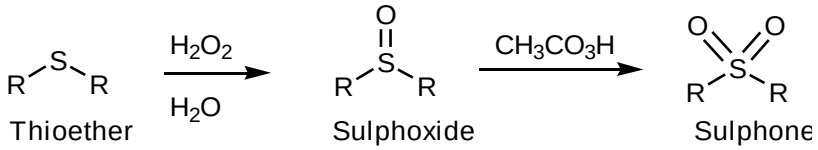


Figure 103 Synthesis of sulphoxides and sulphones.

App 1.43 Thioethers

Thioethers (or sulphides) are present in a limited number of drugs such as the anti-ulcer drugs cimetidine and ranitidine, the antibacterial drug cafazolin, and the immunosuppressant azathioprine. The functional group is prepared by the S_N2 nucleophilic substitution of primary or secondary alkyl halides with a thiolate anion (RS^-), which is generated by reacting a thiol with base (Fig. 104a). The reaction is similar to the Williamson ether synthesis. Symmetrical thioethers can be prepared by treating an alkyl halide with KOH and an equivalent of hydrogen sulphide. The reaction produces a thiol which is ionized again by KOH and reacts with another molecule of alkyl halide (Fig. 104b).

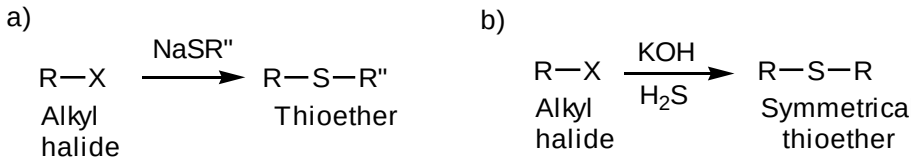


Figure 104 Synthesis of thioethers from alkyl halides and thiols.

App 1.44 Thiols

Thiols are present in a small number of drugs such as the antihypertensive agent captopril, the anticancer agent 6-mercaptopurine and the enkephalinase inhibitor thiorphan.

The functional group can be introduced by treating an alkyl halide with an excess of KOH and hydrogen sulphide (Fig. 105a). A hydrogen sulphide anion (HS^-) is formed and reacts with the alkyl halide by means of an S_N2 nucleophilic substitution reaction. A problem with this reaction is the possibility of the product being ionized and reacting with a second molecule of alkyl halide to produce a thioether (RSR) as a by product. Therefore, an excess of hydrogen sulphide is normally used to avoid this problem. Thioether formation can also be avoided by using an alternative procedure involving a thiourea (Fig. 105b). The thiourea acts as the nucleophile in the S_N2 reaction to produce an *S*-alkylisothiouronium salt which is then hydrolyzed with aqueous base to give the thiol. Finally, thiols can be formed by reducing disulphides with zinc in the presence of acid (Fig. 105c).

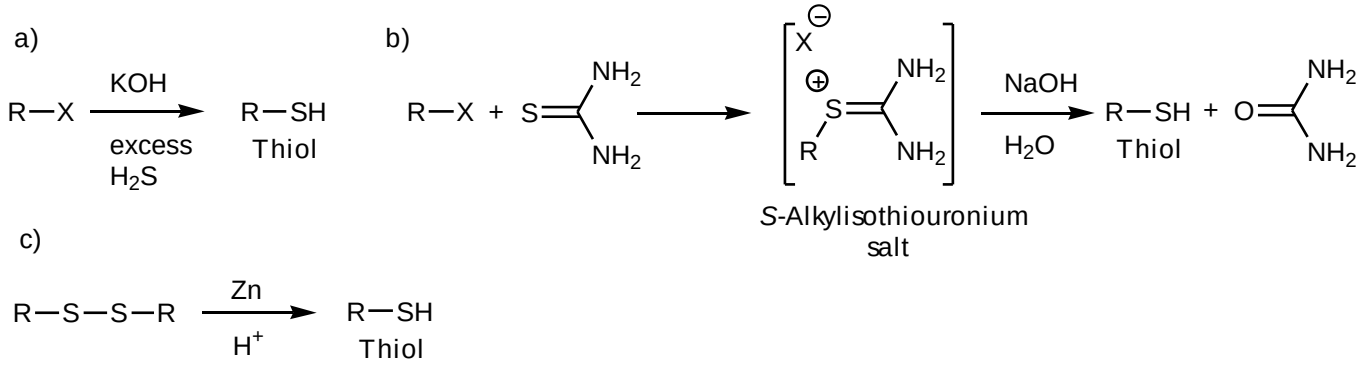


Figure 105 Synthesis of thiols from alkyl halides or disulphides.

App 1.45 α,β-Unsaturated aldehydes

α,β-Unsaturated aldehydes are not found in drugs due to the reactivity of the aldehyde group. However, they are an important group in organic synthesis.

α,β-Unsaturated aldehydes can be synthesised by oxidising allylic alcohols with Dess-Martin periodinane (Fig. 106) (cf appendix 1.5.3). Methods of synthesising allylic alcohols are described in appendices 1.10 & 5.6.

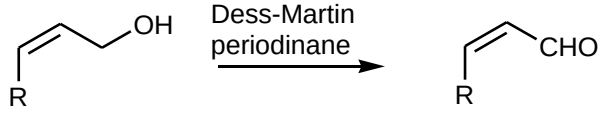


Figure 106 Oxidation of allylic alcohols to α,β–unsaturated aldehydes.

App 1.46 α,β-Unsaturated ketones

α,β-Unsaturated ketones are present in several types of drugs including steroids used in hormone replacement therapy, anticancer treatment and as anti-inflammatory agents. The group is also present in several opioid analgesics.

There are a number of functional group transformations that can be used to synthesise them from ketones or alkenes.

α,β-Unsaturated ketones can be synthesised from ketones in a two stage process involving α-bromination followed by dehydrohalogenation (Fig. 107a). Alternatively, the ketone can be treated with base to form an enolate ion which is then reacted with phenylselenyl bromide. Further treatment with hydrogen peroxide oxidises the selenium, leading to an elimination reaction and formation of the α,β-unsaturated ketone (Fig. 107b). Another method is to convert the ketone to a silyl enol ether, then oxidise that with $Pd(OAc)_2$ (Fig. 107c).

Alkenes can be oxidised at the allylic position to give α,β-unsaturated ketones using selenium oxide (SeO_2) or CrO_3/pyridine (Fig. 107d).

Finally, β-hydroxy ketones obtained from the Aldol reaction (appendix 5.18.1) are easily dehydrated in the presence of *para*-toluenesulphonic acid (ptsa) to form α,β-unsaturated ketones (Fig. 107e).

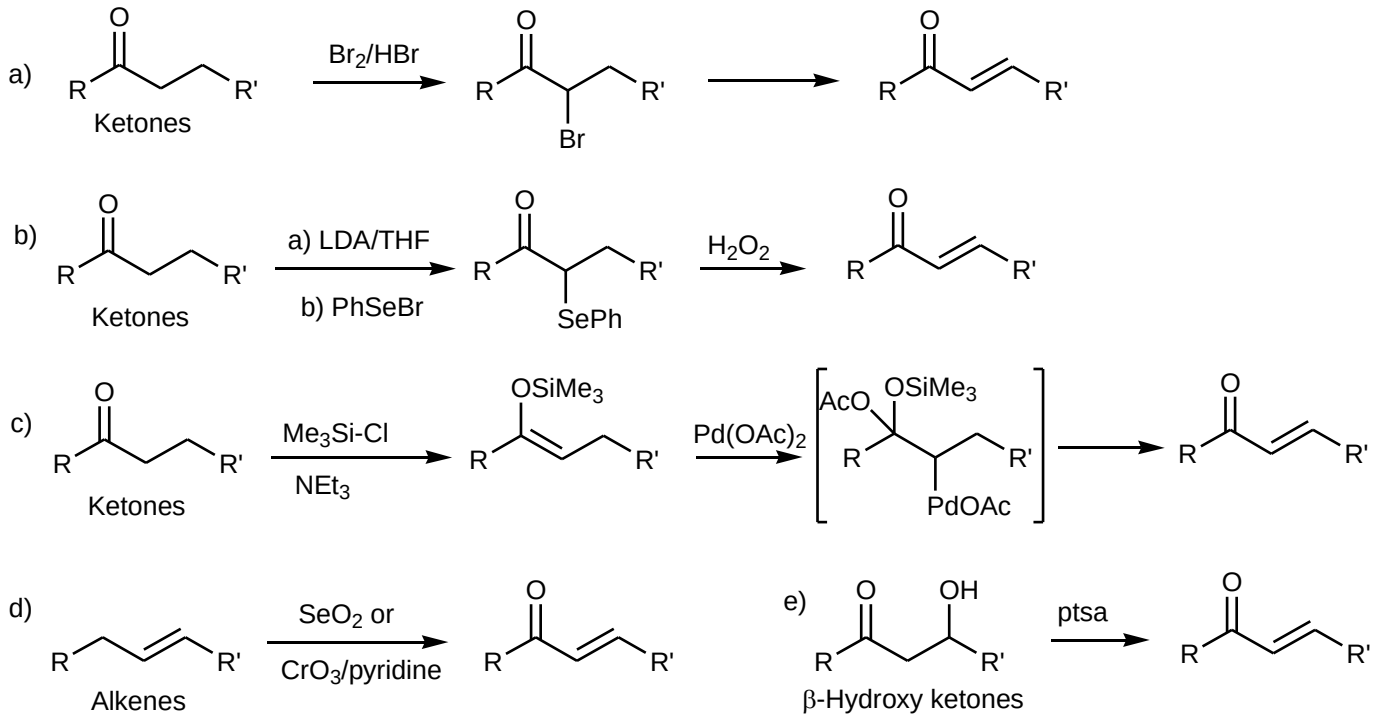


Figure 107 α,β–Unsaturated ketones from functional group transformations.

App 1.47 Ureas

The urea functional group is found in a number of drugs including the anticancer drug sorafenib and the antiviral drug ritonavir. The carbonyl oxygen can act as an effective hydrogen bond acceptor and the N-H hydrogens are potential hydrogen bond donors. Ureas can be synthesised from amines and isocyanates or alcohols and cyanamides.

App 1.47.1 Reaction of an amine with an isocyanate
Ureas can be formed by reacting an amine with an isocyanate (Fig. 108). The amine acts as a nucleophile and adds to the central carbon of the isocyanate. Primary and secondary amines can be used for the reaction, as well as ammonia.

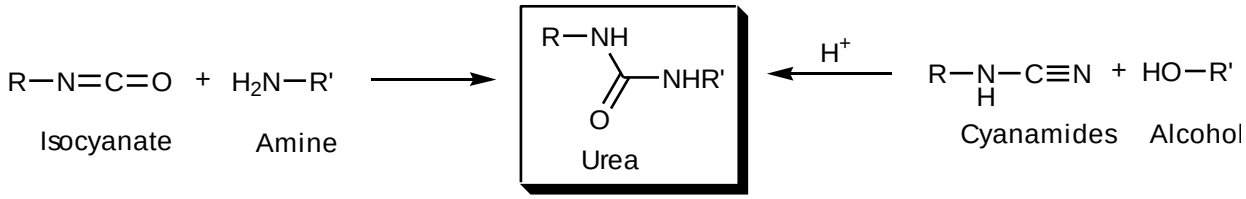


Figure 108 Synthesis of ureas.

App 1.47.2 Reaction of an alcohol with a cyanamide
The reaction of an alcohol with a cyanamide under strong acid conditions can also generate ureas (Fig. 108). The reaction involves protonation of the alcohol and loss of water to produce a cation, and so it works best for secondary, tertiary and benzylic alcohols as these generate stable carbocations.

App 1.48 Urethanes

Urethanes (or carbamates) are found in a wide variety of drugs used in different fields of medicine. Examples include the anticholinesterase drug physostigmine, the cholinergic agonist bethanechol, the anticancer drugs geldanamycin and capecitabine, the antiviral drugs amprenavir and ritonavir, and the antibacterial agent cefuroxime. A urethane functional group is frequently introduced in place of an ester group as the urethane group is more resistant to enzyme-catalysed hydrolysis.
Urethanes are also useful protecting agents for amine groups during synthesis (Appendix 6.4). They can be prepared from isocyanates or chloroformates.

App 1.48.1 Reaction of an alcohol with an isocyanate
The reaction of an alcohol with an isocyanate generates a urethane (Fig. 109). The alcohol group acts as a nucleophile and adds to the carbon centre of the isocyanate.

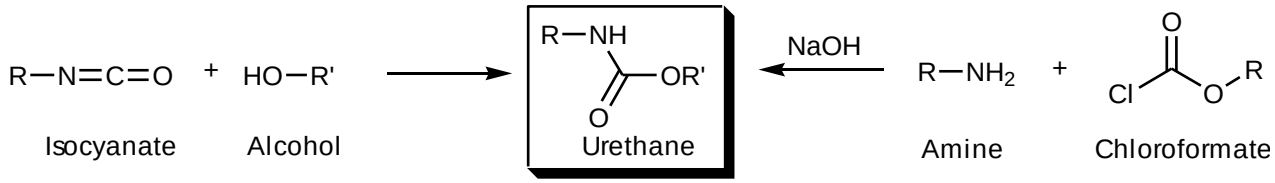


Figure 109 Synthesis of urethanes.

App 1.48.2 Reaction of an amine with a chloroformate

Treatment of an amine with a chloroformate also generates a urethane (Fig. 109). This reaction is frequently used to protect amine groups in peptide synthesis (Appendix 6.4). The chloroformate is added dropwise along with a solution of sodium hydroxide to a solution of the amine. The base is required to neutralise HCl which is formed during the reaction.

App 1.49 Vinyl esters and ethers

Vinyl esters and ethers are rarely found in drugs, but are useful in drug synthesis. They can be formed by treatment of an aldehyde with a base to generate an enolate ion. Alkylation or acylation of the enolate oxygen is then possible with highly reactive alkylating and acylating agents such as chlorotrialkylsilanes, α-haloketones, alkyl tosylates and acid chlorides. The reaction works best in a polar, aprotic solvent such as HMPA, and the aldehyde must have an α-proton present to form the enolate (Fig. 110).

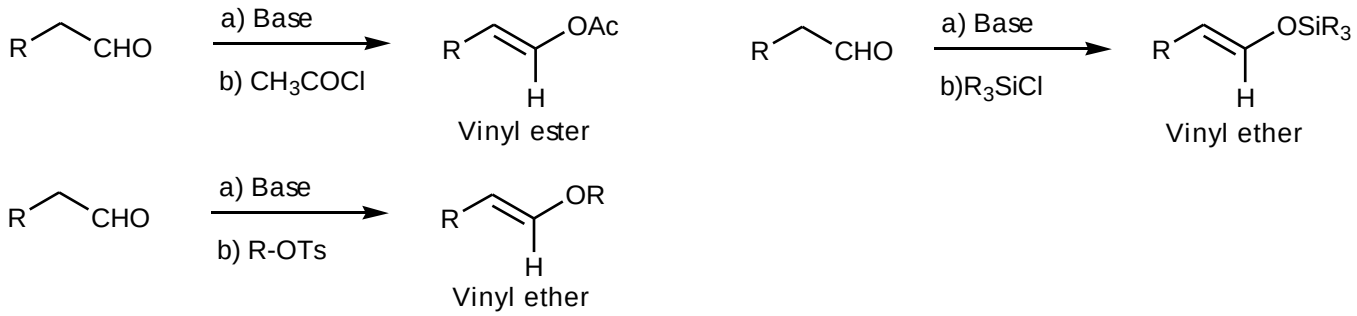


Figure 110 Formation of vinyl esters and ethers.