Appendix 5: Carbon-carbon Bond Formations

Carbon-carbon bond formations play a crucial role in organic synthesis as these are the reactions that allow chemists to create complex molecules from simple building blocks. For these reactions to take place, there must be a functional group present and the reaction will take place at or near to that functional group. A different functional group or pattern of substituents may be formed as a result of the reaction, which can often be characteristic of the reaction and act as a 'molecular signature'. Recognising such signatures is extremely useful when carrying out synthetic design or retrosynthesis. In this appendix we will classify the different reactions by the functional group or 'signature' that is formed in the product.

App 5.1 Alcohols

Several functional group transformations can result in the formation of alcohols and are described in appendix 1.4. Here, we concentrate on carbon-carbon bond formations that result in alcohols. There are various 'signatures' for these reactions including those shown in figure 1. It is also worth noting that several of these 'signatures' are also accessible by reducing ketones that have been formed by carbon-carbon bond formations.

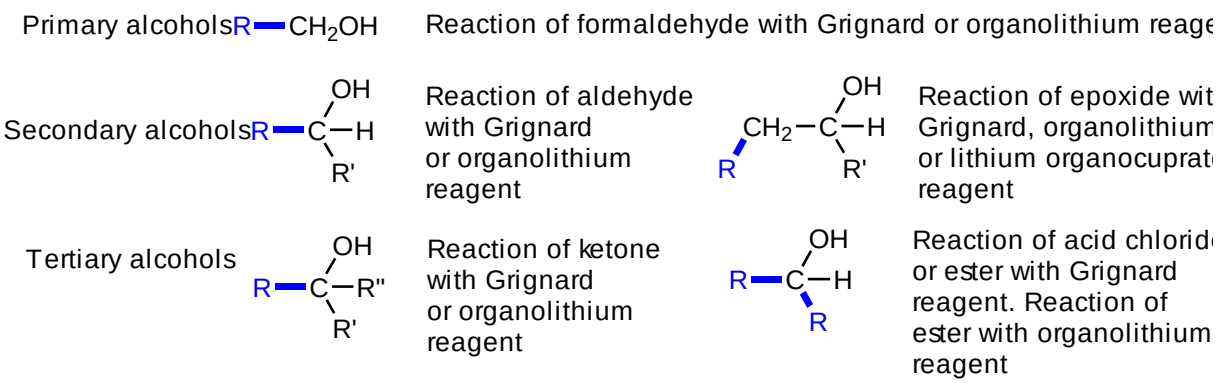


Figure 1 'Signatures' for various alcohols formed by carbon-carbon bond formations. Bold bonds in blue indicate the carbon-carbon bond formed in the reaction.

App 5.1.1 The Grignard Reaction

The Grignard reaction is a popular method for adding alkyl groups to aldehydes and ketones (Fig. 2a-c). The reaction involves nucleophilic addition of a Grignard reagent to the carbonyl group to form an alcohol. Reaction with formaldehyde allows the synthesis of a range of primary alcohols, while reaction with aldehydes and ketones generates secondary and tertiary alcohols respectively. Esters and acid chlorides react with two equivalents of a Grignard reagent to produce a tertiary alcohol where two identical alkyl groups have been added (Fig. 2d-e). Epoxides undergo an S_N2 nucleophilic substitution reaction with Grignard reagents. In this case, the newly added alkyl group is attached to the carbon next to the one bearing the alcohol group (Fig. 2f). With monosubstituted epoxides, the Grignard reagent reacts with the unsubstituted carbon.

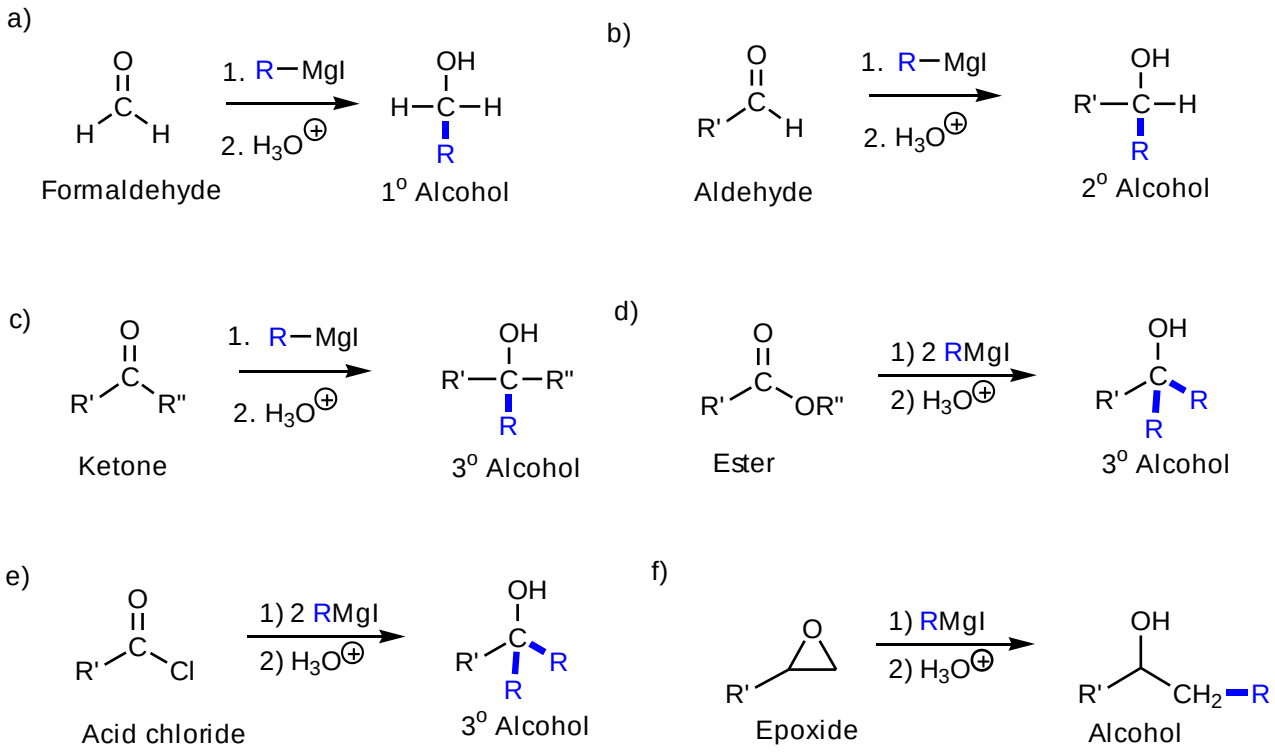


Figure 2 Alcohols generated by the Grignard reaction.

The Grignard reaction must be carried out under anhydrous conditions as the Grignard reagent can act as a base and react with water to give an alkane. Moreover, the same acid-base reaction can take place with any functional group that acts as a proton donor, such as alcohols, carboxylic acids, and amines. Therefore, these functional groups would have to be 'masked' or protected if they are present in the starting material.

App 5.1.2 Organolithium and organocuprate reagents

The reaction of aldehydes or ketones with organolithium reagents is another method of adding alkyl substituents to the carbonyl group to generate primary, secondary and tertiary alcohols (Fig. 3a-c). Esters react with two equivalents of an organolithium reagent to give a tertiary alcohol where two of the alkyl groups are derived from the organolithium reagent (Fig. 3d). Epoxides also react with organolithium reagents in a similar manner to Grignard reagents (Fig. 3e). The addition of a Lewis acid such as $BF_3.Et_2O$ increases the electrophilicity of the epoxide and helps to prevent side products arising from an alternative reductive alkylation reaction (section 5.3.5).

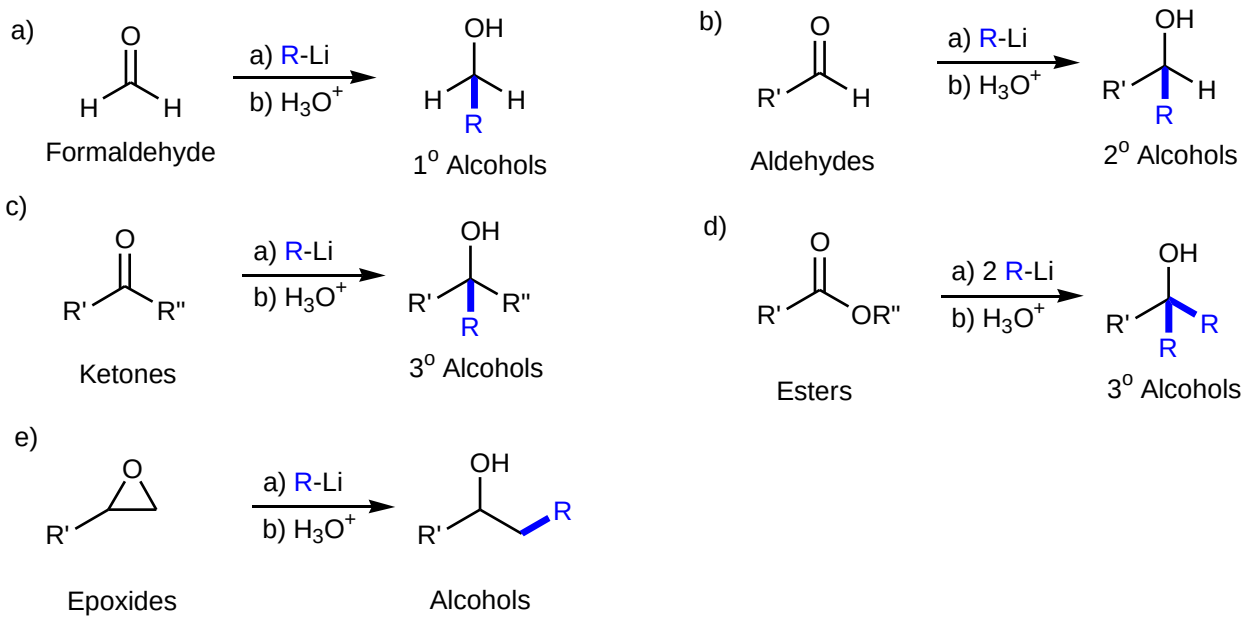


Figure 3 Alcohols generated by organolithium reagents

The reaction of epoxides with lithium organocuprates gives alcohols where the new carbon-carbon bond is formed to the less substituted carbon of the epoxide (Fig. 4). This is analogous to the reaction of epoxides with Grignard reagents and can often be a better method.

Figure 4 Reaction of an epoxide with organocuprate reagents.

App 5.2 Aldehydes

Methods of synthesising aldehydes by functional group transformations were described in appendix 1.5. There are a number of carbon-carbon bond formations that can result in aldehydes having the following 'molecular signatures' (Figure 5).

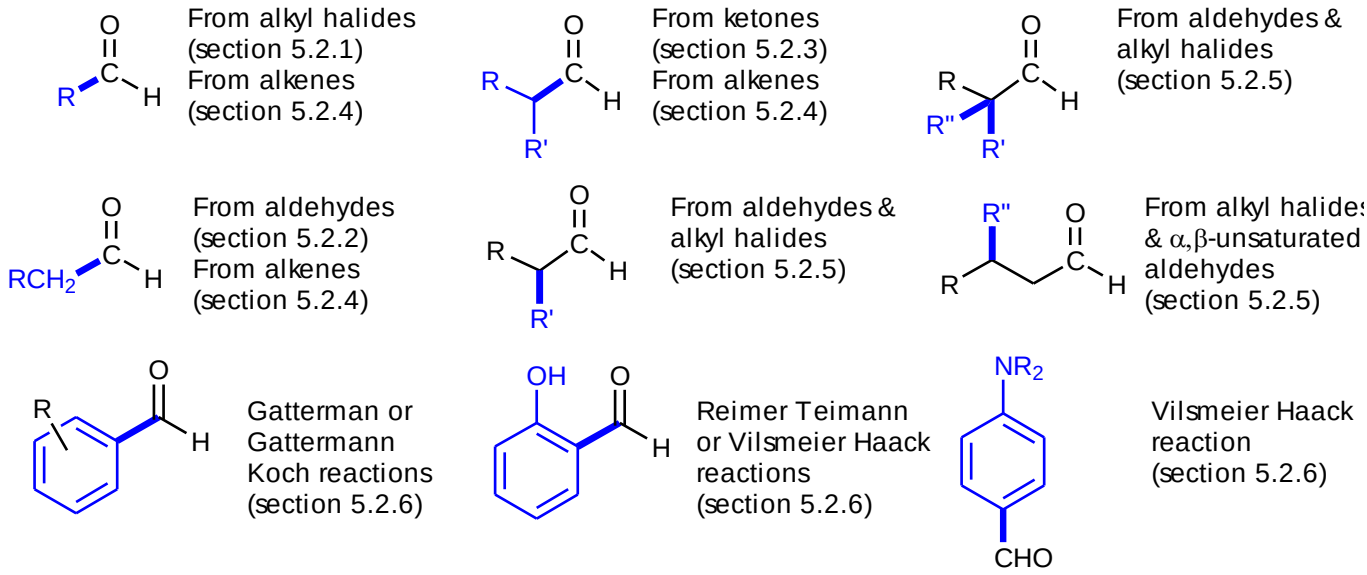


Figure 5 'Molecular signatures' for various aldehydes formed by carbon-carbon bond formations. Bold bonds in blue indicate the carbon-carbon bond formed.

App 5.2.1 Aldehydes from alkyl halides

It is not possible to convert an alkyl halide directly to an aldehyde. This would require using a carbanion where the negative charge was situated on the carbonyl carbon of the aldehyde unit [$^-$:CHO]. However, a carbonyl carbon is electrophilic in nature and not nucleophilic. Therefore, in order to prepare aldehydes, it is necessary to substitute the halogen of the alkyl halide with a nucleophile that can subsequently be converted to the aldehyde. For example, nucleophilic substitution of the halogen with a cyanide ion gives a nitrile, which can then be converted to the aldehyde by reduction (Fig. 6a). Overall, the addition of the aldehyde unit (CHO) involves a 1C chain extension to the original alkyl halide.

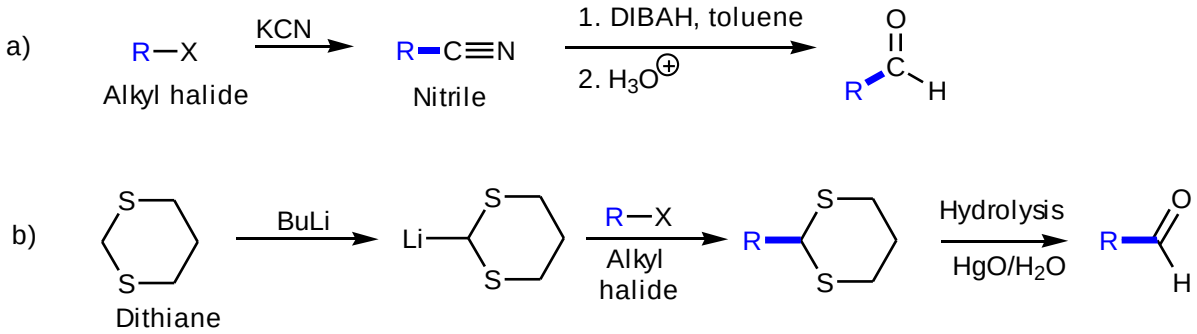


Figure 3.6 Formation of an aldehyde from an alkyl halide.

An alternative method is to react the alkyl halide with a carbanion generated from dithiane, then hydrolyse the alkylated dithiane to the aldehyde (Fig. 6b). The hydrolysis does not occur easily and

requires special conditions; for example the presence of a mercuric salt. Ethyl ethylthiomethyl sulphoxide can be used for this reaction instead of the dithiane.

App 5.2.2 Homologation of aldehydes

An aldehyde can be extended by one carbon unit by reaction with methoxymethylenetriphenylphosphine ($Ph_3P{=}CHOMe$) in a Wittig reaction, then cleaving the resulting enol ether with acid such that it forms the new aldehyde group (Fig. 7). Extending the chain length of an aldehyde in this way is known as a homologation.

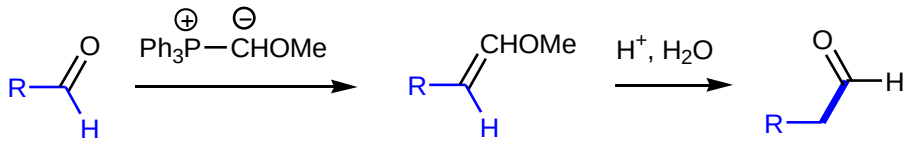


Figure 7 Homologation of aldehydes via enol ethers.

App 5.2.3 Synthesis of aldehydes from ketones

A ketone can be extended by one carbon unit to form an aldehyde by reacting it with a silylated dithiane (Fig. 8). Elimination of TMS-OH results in a double bond which can be reduced. The dithiane ring is then hydrolysed to reveal the aldehyde.

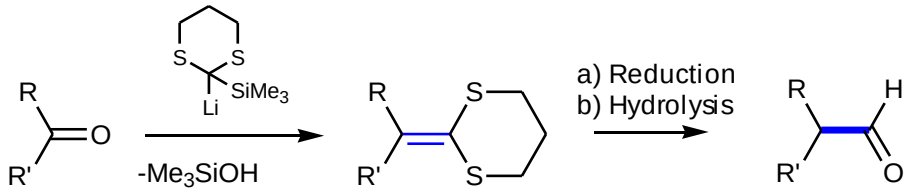


Figure 8 Synthesis of an aldehyde from a ketone.

App 5.2.4 Synthesis of aldehydes from alkenes

An aldehyde group can be added to the least substituted position of an alkene, by first carrying out a hydroboration with the bulky dialkylborane reagent 9-BBN (Fig. 9). The reagent adds across the double bond such that the boron atom is linked to the least substituted carbon of the alkene. Treatment of the resulting trialkylborane with carbon monoxide and $LiAl(OR)_3H$ results in addition of carbon monoxide followed by migration of the 9-alkyl group. Oxidation with hydrogen peroxide then releases the aldehyde product.

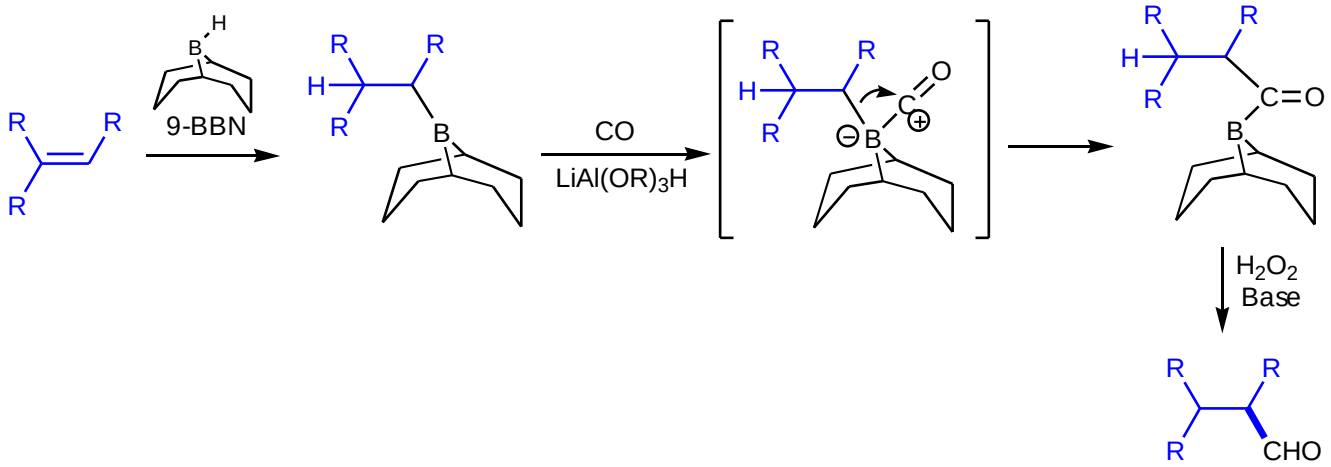


Figure 9 Synthesis of an aldehyde from an alkene.

App 5.2.5 Alkylation of aldehydes and α,β-unsubstituted aldehydes

In appendix 5.1, we looked at the addition of nucleophiles to the carbonyl group of an aldehyde to form alcohols. In these reactions, the aldehyde is acting as an electrophile. It is also possible to carry out reactions where the aldehyde acts as a nucleophile by treating the aldehyde with one equivalent of a strong base to form a carbanion at the α-carbon. Alkylation with an alkyl halide then introduces an alkyl group at the α-position (Fig. 10). However, this reaction is really restricted to branched aldehydes and reactive allyl halides or benzyl halides, as the aldehyde normally undergoes an Aldol reaction instead (appendix 5.18.1) due to the reactivity of the aldehyde group.

A more general approach is to convert the aldehyde to an imine, which can then be treated with base to form a metalloenamine. This can then be alkylated with a primary alkyl, allyl or benzyl halide before being hydrolysed back to the aldehyde (Fig. 11) (see also alkylation of ketones via metalloenamines - appendix 5.22.2).

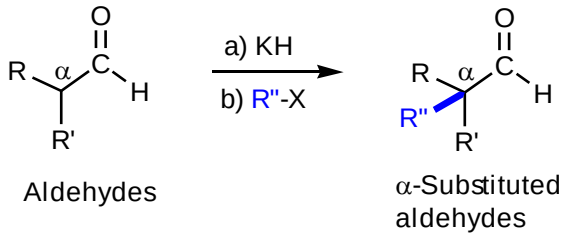


Figure 10 Synthesis of an α-alkylated aldehyde.

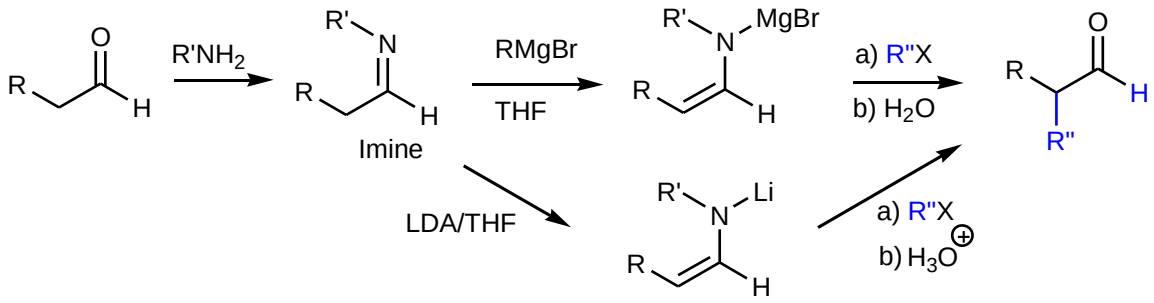


Figure 11 Alkylation of aldehydes via imines.

α,β-Unsaturated aldehydes can be converted to β-substituted aldehydes by reaction with lithium organocuprate reagents (Fig. 12). An alkyl group from the organocuprate agent is added to the unsaturated aldehyde in a 1,4-or conjugated addition reaction. The reaction works best with primary alkyl groups. Only one of the groups from the organocuprate reagent is added to the unsaturated aldehyde and so this method is best used when the reagent is cheap or easily available. Alternatively, one can use a mixed organocuprate reagent containing an alkynyl substituent (R(R'CC)CuLi) or nitrile substituent (R(CN)CuLi). The alkyl group is then transferred preferentially. Aromatic rings can be added to the β-position in the same manner.

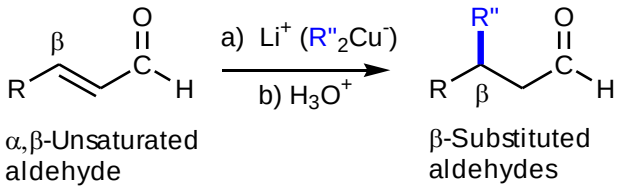


Figure 12 Synthesis of a β-alkylated aldehyde.

A mixed organocuprate reagent with a phenylthio substituent Li[PhS-Cu-R) has been found to be effective in transferring a secondary or tertiary alkyl group to α,β-unsaturated aldehydes.

App 5.2.6 Aromatic aldehydes

Aromatic aldehydes can be synthesised by a number of methods such as the Reimer-Tiemann reaction on phenols (Fig. 13a) the Vilsmeier-Haack formylation of amines and phenols (Fig. 13bc), the Gatterman reaction of phenols, phenyl ethers or alkylbenzenes (Fig. 13d) and the Gatterman-Koch reaction of alkylbenzenes (Fig. 13e).

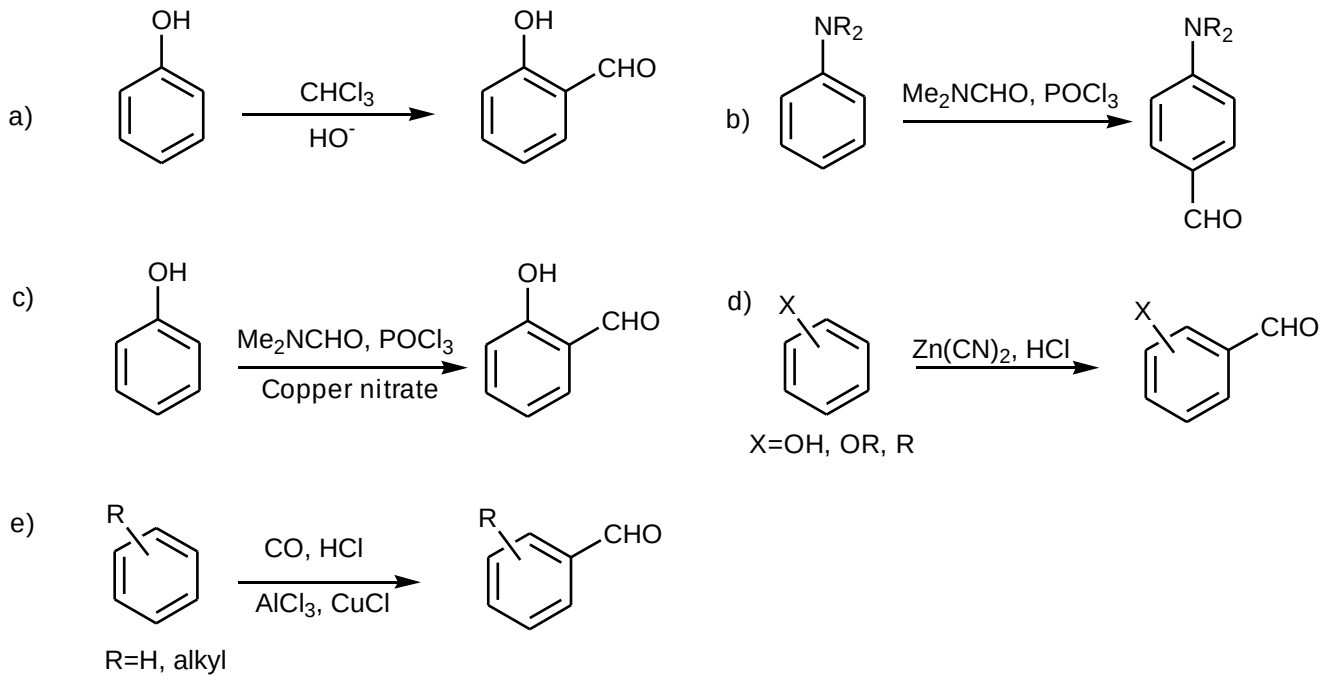


Figure 13 Synthesis of aromatic aldehydes.

App 5.3 Alkenes

The synthesis of alkenes by functional group transformations was covered in appendix 1.6. There are also several methods of producing alkenes by carbon-carbon bond reactions involving aldehydes, ketones, alkynes, and alkyl halides (Fig. 14).

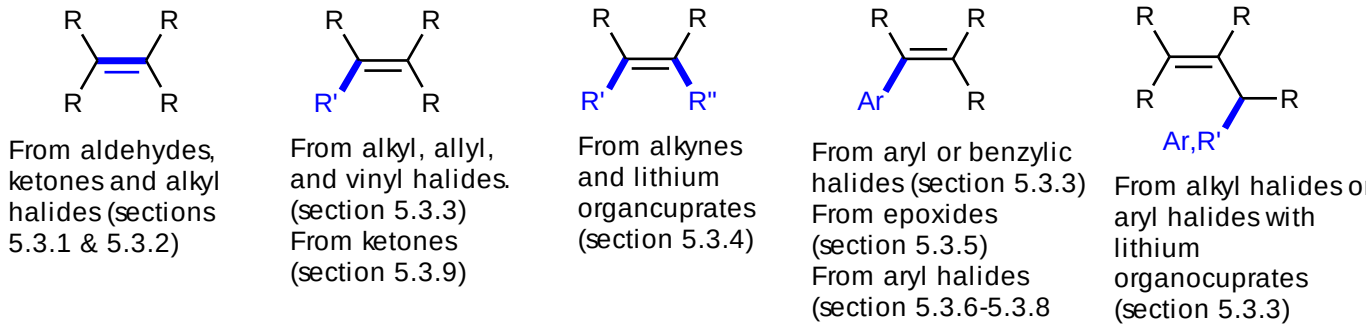


Figure 14 Carbon-carbon bond reactions resulting in alkenes.

App 5.3.1 The Wittig reaction

The Wittig reaction involves the reaction of a phosphorane with an aldehyde or ketone (Fig. 15). Both aliphatic and aromatic aldehydes and ketones can be used. The phosphorane reagent shows good chemoselectivity for aldehydes and ketones and leaves other functional groups such as esters, alkenes, alkynes, amines, ethers, acetals, aromatic nitro groups and aryl halides unaffected. Moreover, the position of the alkene group is unambiguous and will be at the same position as the original carbonyl group.

The phosphorane is generated by reacting an alkyl halide with triphenylphosphine (Ph_3P) to give a phosphonium salt ($Ph_3P^+CHR'R''\ Br^-$), which is then treated with a strong base such as butyllithium (Fig. 16). The phosphorane can be unsubstituted (R'=R''=H), monosubstituted (R'=H, R'' = alkyl or aryl) or disubstituted (R' and R'' = alkyl or aryl).
The Wittig reaction with aldehydes can generate mono, di, and trisubstituted alkenes. When an E or a Z-isomer alkene is possible, the ratio of *E:Z* depends on a number of factors such as the nature of the phosphorane, the type of base, the solvent, and whether the aldehyde is aliphatic or aromatic. The *Z*-isomer is generally favoured with unstabilised phosphoranes such as the ones shown in figures 15 and 16), especially if polar, aprotic solvents are used such as DMF and DMSO. In contrast, the *E*-isomer is favoured when a stabilised phosphorane is used (e.g. (Ph_3P=CH-Ar).

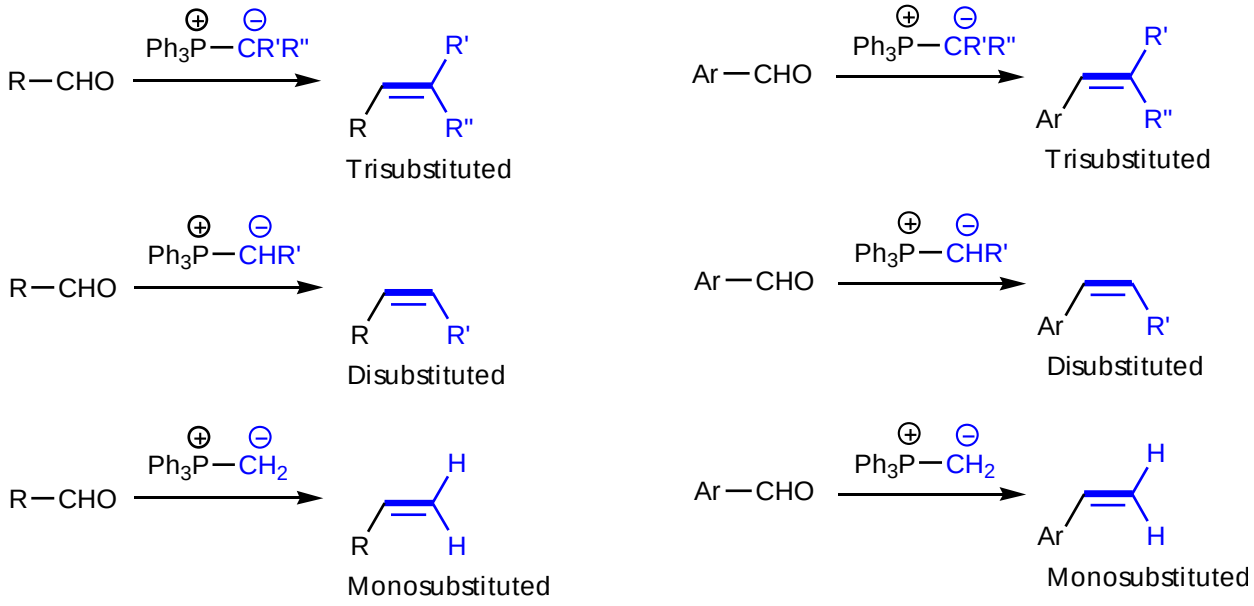


Figure 15 The Wittig reaction with a) aliphatic aldehydes and b) aromatic aldehydes.

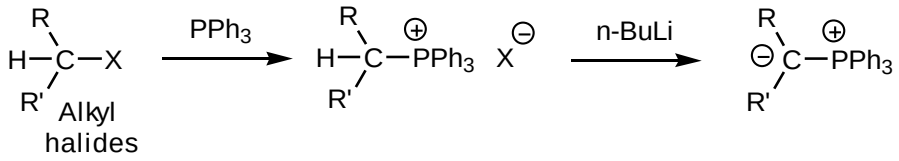


Figure 16 Synthesis of phosphoranes from alkyl halides.

The Wittig reaction is possible with both aliphatic and aromatic ketones (Fig. 17), and works best for the formation of di- or trisubstituted alkenes. However, the reaction of ketones with disubstituted phosphoranes is not very effective in generating tetrasubstituted alkenes. This may well be due to steric hindrance.

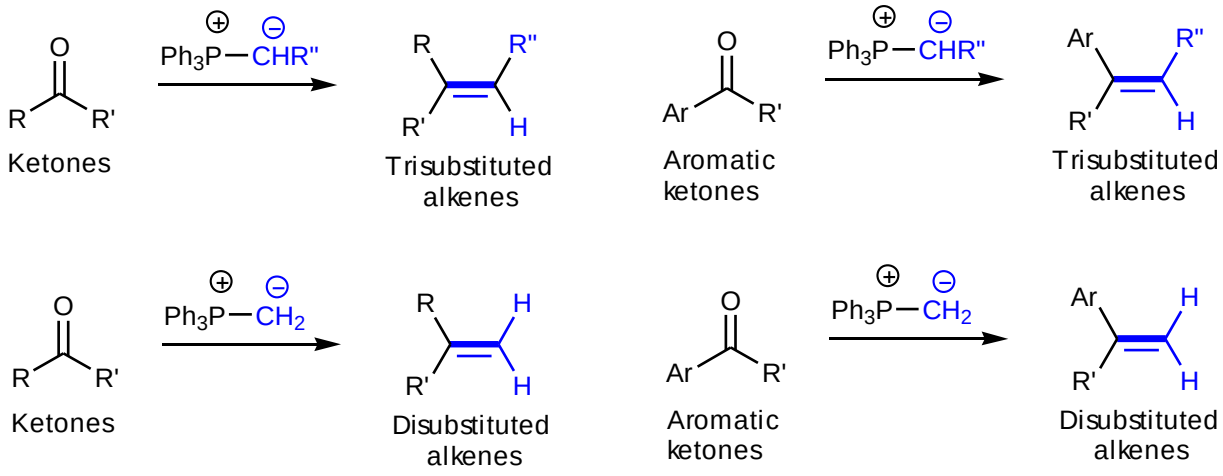


Figure 17 The Wittig reaction with aliphatic and aromatic ketones.

When there is a possibility of the alkene product being the *Z*- or the *E*-isomer, the situation is more complex than with aldehydes. The ratio of *Z* to *E* isomers can differ significantly depending on the type of solvent used.
One problem with the Wittig reaction is the difficulty in removing the by product triphenylphosphine oxide ($Ph_3P{=}O$) from the product. If this is an issue, the Peterson reaction is an alternative procedure.

App 5.3.2 The Peterson Reaction

The Peterson reaction is an alternative method to the Wittig reaction for creating alkenes and involves reacting an aldehyde or ketone with an α-silyl carbanion (Fig. 18). Mono-, di- and trisubstituted alkenes can be synthesised in this manner using aliphatic or aromatic aldehydes and ketones.

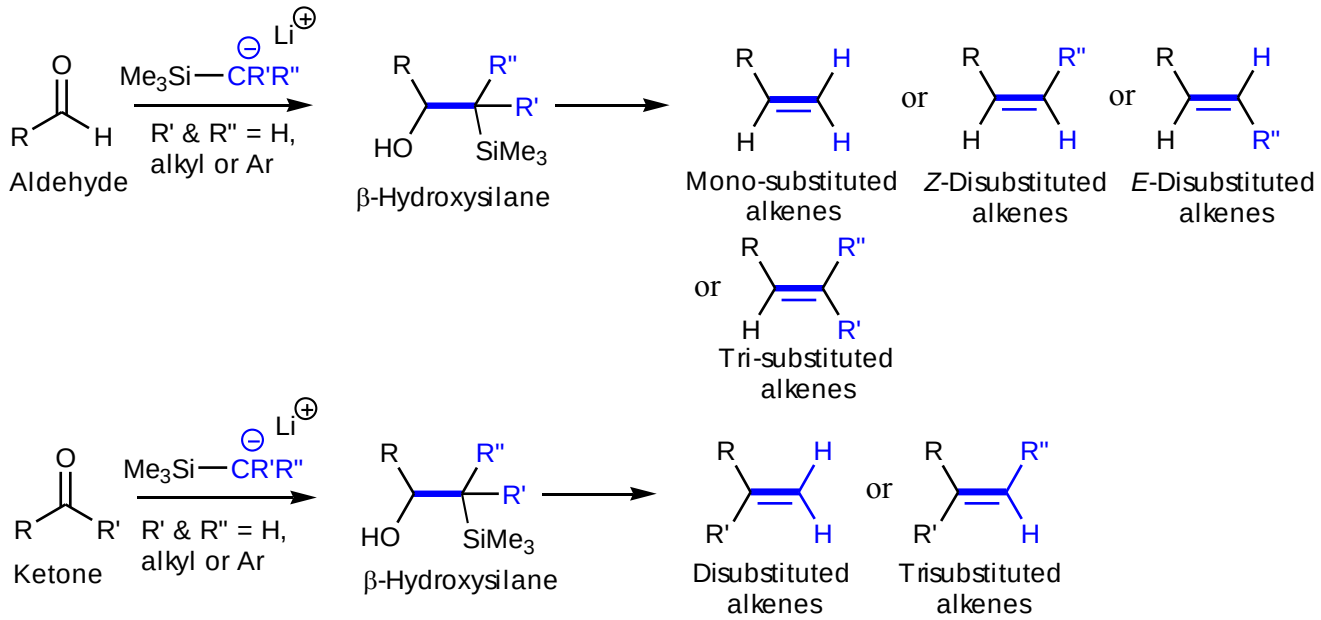


Figure 18 The Peterson reaction.

An advantage of the Peterson reaction over the Wittig reaction is the ability to obtain both the *Z* and the *E* isomers of a product. The intermediate β-hydroxysilane is produced as a mixture of *threo* and *erythro* diastereoisomers and these can be separated and isolated if the groups in the initial α-silyl carbanion are hydrogen or electron-donating alkyl groups. Once separated, each diastereoisomer can be used to produce the *E*- or the *Z*-isomer, depending on whether the work up procedure is carried out under acidic or basic conditions. For example, if the *E*-isomer is obtained from the *threo*-diastereoisomer under basic conditions, then the *E*-isomer can be obtained from the *erythro*-isomer under acidic conditions. The basic conditions used are generally KH/THF. Acidic conditions involve sulphuric acid or a Lewis acid. Another advantage of the Peterson reaction is the fact that the reaction by-product (hexamethyldisiloxane $Me_3SiOSiMe_3$) is volatile and easily removed, unlike the triphenylphosphine by-product produced in the Wittig reaction. It is worth adding that the Peterson reaction is driven by the strong silicon oxygen bonds that are formed in hexamethyldisiloxane.

App 5.3.3 Synthesis of alkenes from vinyl or alkyl halides using lithium organocuprate reagents

The halogen of a vinyl or allyl halide can be replaced with a primary alkyl or aromatic group using lithium organocuprate reagents (Fig. 19). The stereochemistry of the vinyl halide is preserved. In other words, the new substituent replaces the halogen without any change in the alkene's stereochemistry.

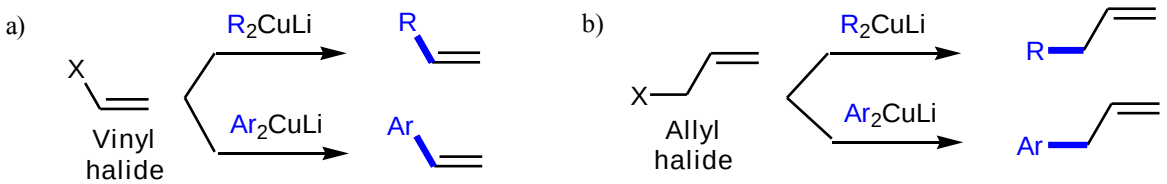


Figure 19 Reaction of vinyl and allyl halides with organocuprate reagents (R=primary alkyl group).

The reaction can also be carried out with alkenyl or allyl lithium organocuprate reagents to substitute the halogen of a primary, aryl or benzyl halide (Fig. 20a-c). Coupling of an alkenyl group to a secondary alkyl halide is possible using the lithium organocuprate reagent shown in figure 20d.

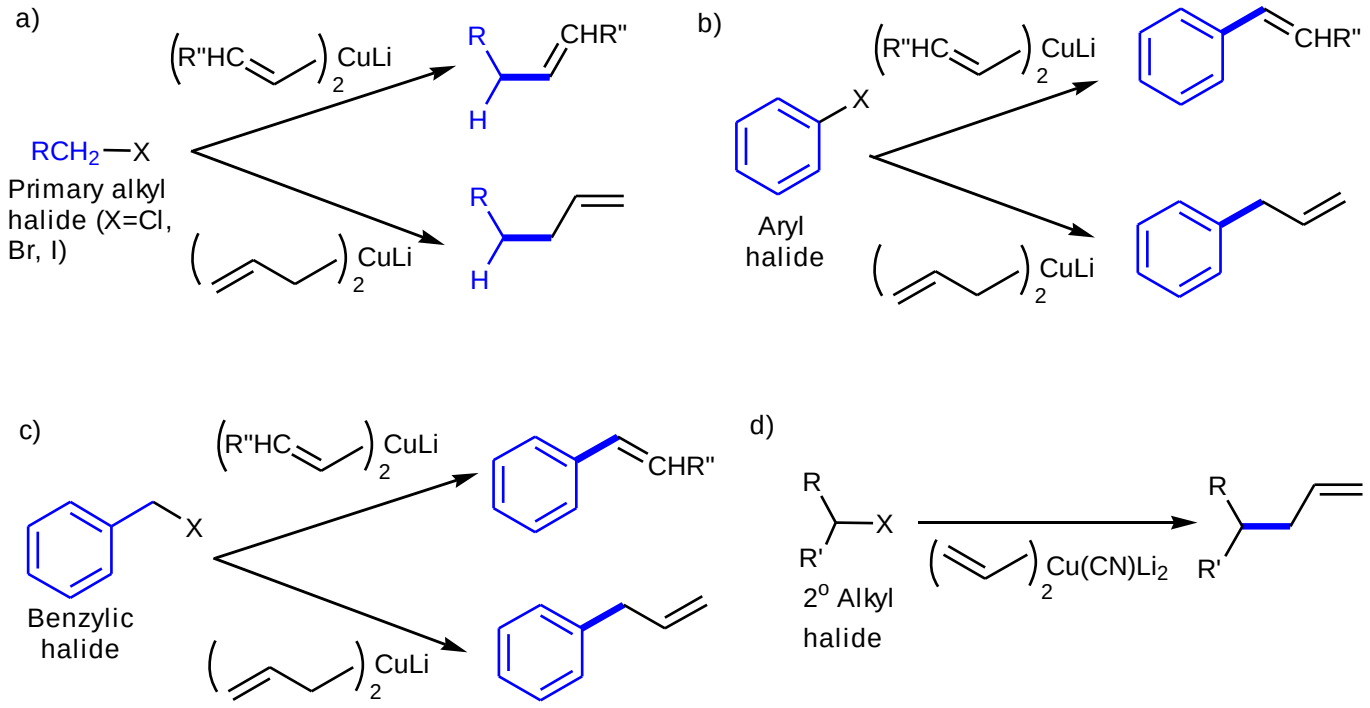


Figure 20 Reactions of primary, aryl and benzyl halides with alkenyl and allyl lithium organocuprate reagents.

App 5.3.4 Synthesis of alkenes from alkynes via lithium organocuprate reagents

Lithium alkenyl organocuprate reagents can be obtained from the reaction of acetylene with a lithium dialkylcuprate reagent. *cis*-Addition takes place and the stereochemistry is preserved following reaction with a primary alkyl halide (Fig. 21a).

A similar approach is to react a terminal alkyne with an organocopper reagent to form an alkenylcopper (I) reagent. The reagent can then be alkylated with an alkyl iodide to produce a trisubstituted alkene where the two additional alkyl groups are cis to each other (Fig. 21b).

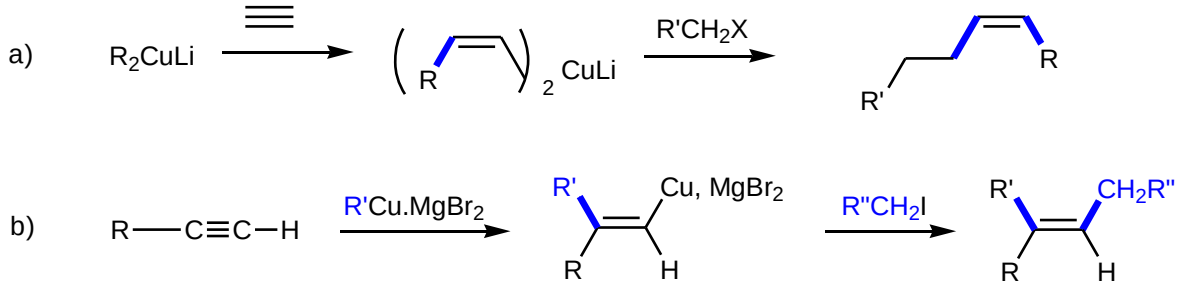


Figure 21 Synthesis of alkenes from alkynes and alkyl halides.

App 5.3.5 Synthesis of alkenes from epoxides by reductive alkylation with organolithium reagents

The reaction of epoxides with organolithium reagents in the presence of a Lewis acid is a method of providing alcohols (appendix 5.1.2). However, it is possible to alter the reaction conditions to carry out a reductive alkylation which produces an alkene instead of an alcohol (Fig. 22). The reaction is carried out with terminal epoxides and an aryl organolithium reagent in the presence of a sterically hindered base called 2,2,6,6-tetramethylpiperidide (LTMP). Under these conditions, a deprotonation takes place, as well as an arylation leading to a dilithiated intermediate. Breakdown of this intermediate then produces the *E*-isomer. The reaction is not so effective with alkyl organolithium reagents.

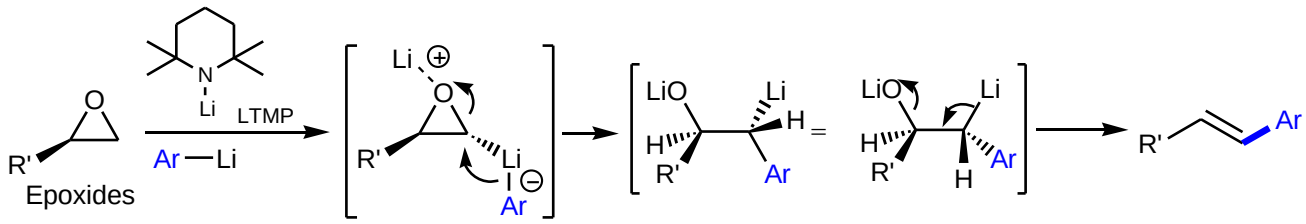


Figure 22 Synthesis of alkenes by reductive alkylation.

App 5.3.6 The Suzuki reaction

The Suzuki reaction is a popular method for linking an aromatic ring to an alkene. The reaction involves treating an aryl halide with an alkenyl organoborane reagent in the presence of a palladium catalyst and a base (Fig. 23). The palladium catalyst is normally $Pd(PPh_3)_4$, but other ligands have been used. The palladium acts as the focus for the reaction and alternates between the 0 and II oxidation states as it binds the reactants and catalyses a series of reactions that ultimately lead to the product. Essentially, the metal captures the two groups that are to be coupled from the reagents, then links them together. The alkenylborane must be *trans* as it is formed by syn hydroboration of an alkyne. Alternatively, a vinyl halide could be treated with an aryl organoborane reagent. In both cases, the stereochemistry of the alkene group used in the reagent is preserved in the product.

The halogen used in the aryl or vinyl halide can be chloride, bromide or iodide, but the bromide and iodide appear to work best. Electron-withdrawing groups in the aryl or vinyl halide increase the reactivity of these reagents.

The organoborane reagent can be either the boronic acid or the boronate.

A recent review of reactions carried out in drug research has shown that the Suzuki reaction is the most commonly used method for creating carbon-carbon bonds, accounting for 40% of all reported reactions over a set time period. This has been aided no doubt by the vast number of boronic acids and boronate esters that are commercially available (over 10,000), as well as over 660,000 aryl halides. The reaction also benefits from the stability, easy synthesis and low toxicity of the organoborane reagents. It is also possible to use water as a solvent, which is attractive on an industrial scale. The Suzuki reaction is readily adaptable to parallel synthetic procedures and shows good chemoselectivity.

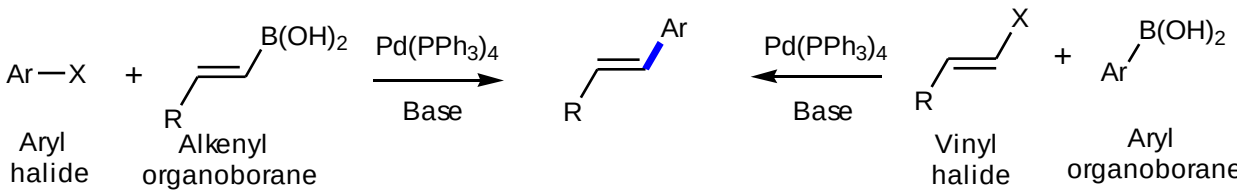


Figure 23 The Suzuki reaction for the synthesis of aromatic alkenes.

The Suzuki reaction is also used for the synthesis of biaryl compounds (appendix 5.10.1).

App 5.3.7 Alkenes from aryl halides and alkenes - Heck-Mizokori reaction

The Heck-Mizokori reaction is very similar to the Suzuki reaction - the difference being that an alkene (instead of an organoborane) is reacted with the aryl halide to produce an E-alkene (Fig. 24).

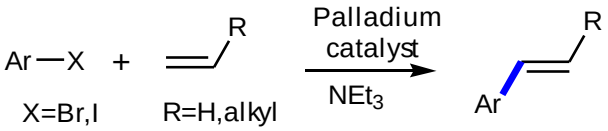


Figure 24 The Heck reaction.

The halogen used in the aryl halide is normally bromine or iodine with aryl iodides being the more reactive. The reaction requires heating if aryl chlorides or electron-rich aryl bromides are used. Aryl triflates can also be used in the reaction and are as effective as aryl bromides.

The palladium catalyst is typically $Pd(OAc)_2$ or $PdCl_2$ and can be recycled. The base is triethylamine or sodium acetate, which acts to neutralise the HX produced in the reaction. Triphenylphosphine is often added along with $Pd(OAc)_2$ to form a more reactive palladium complex. P(o-tolyl)$_3$ is an alternative additive if the reaction is to be carried out using high temperatures, as the resulting palladium complex is thermally more stable. Like the Suzuki reaction, it is possible to use water as a solvent on an industrial scale, where the reaction can be carried out at room temperature in the presence of potassium carbonate, n-$Bu_4N^+X^-$ and PPh_3.

There are limitations to the type of alkene that can be used as reagent. The reaction works well with ethene, but if a monosubstituted alkene is used, the substituent must be electron withdrawing (e.g. CO_2R, CN, $CONH_2$, ketone, Ph, CO_2H) or be capable of acting as a steric shield in order to achieve regioselectivity. Otherwise, the coupling reaction will occur at either end of the double bond.

If there is an allylic proton present, then two different products are possible, defined as the β-hydride and the β'-hydride elimination products (Fig. 25). In the β'-hydride elimination reaction, the β'-hydrogen is eliminated, resulting in the alkene group moving position. Consequently, the newly attached aryl group ends up at the new allylic position, which may result in a new chiral centre. The β'-hydride elimination process is favoured if

R' or R" is an alkene because the product contains a stable, conjugated diene. Similarly, if R' or R" is an alcohol or enol ether, then the β'-hydride elimination process is favoured because a ketone or enol ether is formed respectively. Endocyclic alkenes are also good substrates for cyclisation reactions involving the β'-hydride elimination reaction.

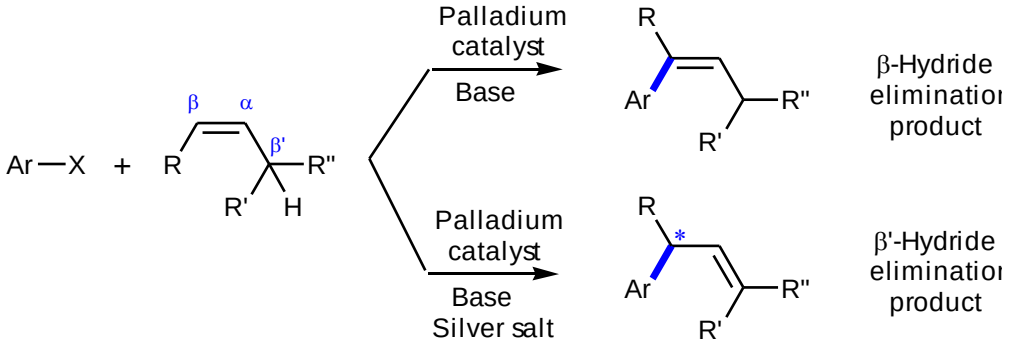


Figure 25 β-Hydride and β'-hydride products of the Heck reaction.

Trisubstituted and tetrasubstituted alkenes generally do not undergo the Heck reaction unless the reaction is an intramolecular cyclisation.

App 5.3.8 Alkenes from aryl halides and vinyl stannane reagents - Stille reaction
The Stille reaction is similar to the Suzuki reaction, except that a stannane reagent is used instead of an organoborane reagent (Fig. 26). The reaction generates an aromatic alkene by reacting an aryl halide with a vinyl stannane. Alternatively a vinyl iodide can be reacted with an aryl stannane. The reaction has the advantage that relatively few other functional groups are likely to be affected, which is good for selectivity. However, the stannanes are highly toxic and often volatile in nature. They also generate toxic tin by-products that can be difficult to remove from the final product and represent a serious environmental hazard. Therefore, the Stille reaction is used relatively rarely compared to the vastly more popular Suzuki reaction. However, the reaction has advantages over other methods when it comes to synthesising complex structures.

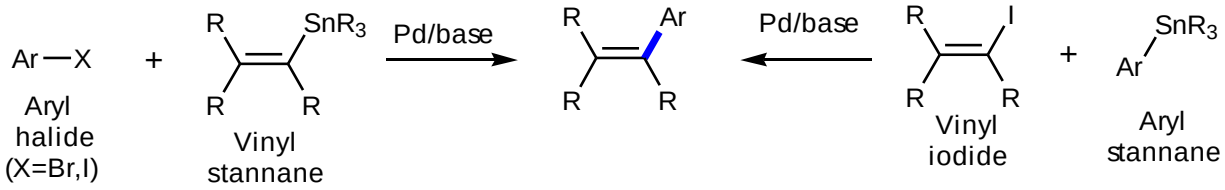


Figure 26 The Stille reaction.

App 5.3.9 Alkenes from aldehydes and ketones via the Grignard reaction
Alkenes can be generated by carrying out a Grignard reaction on an aldehyde or ketone, then dehydrating the alcohol under acid conditions (Fig. 27). This can be effective in some cases, but there

is less control over the ultimate location of the alkene group compared to the Wittig and other reactions. If a choice of alkenes is possible from the dehydration, then the more substituted alkene will be formed.

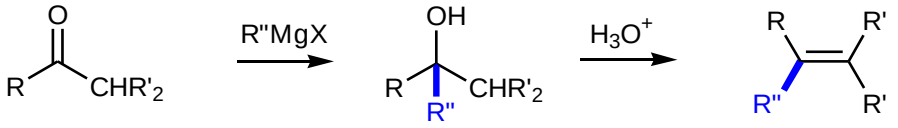


Figure 27 Synthesis of an alkene by dehydration of a Grignard product.

App 5.4 Alkyl fluorides

A particularly useful reaction in drug synthesis is trifluoromethylation of aromatic and heteroaromatic rings, because of the pharmacokinetic and pharmacodynamic advantages that such a group might bring. For example, a CF_3 group can improve the metabolic stability of drugs that contain a metabolically susceptible methyl group. Replacing the methyl group with a trifluoromethyl group prevents that metabolism occurring. Other pharmacokinetic and pharmacodynamic advantages can arise from the increased lipophilicity of a CF_3 group. For example, increased lipophilicity may improve absorption and distribution, or enhance binding interactions with a hydrophobic binding region in a target binding site.

A number of methods of introducing a CF_3 group by functional group transformations were described in appendix 1.8. Here, we discuss methods of introducing the CF_3 moiety by means of carbon-carbon bond formation. A common method of achieving this reaction is to carry out a cross-coupling reaction where an aryl iodide, aryl bromide or vinyl halide is treated with $CuCF_3$ generated *in situ* (Figs. 28 & 29). A number of reagents can be used for this purpose such as CF_3SiEt_3, $FSO_2CF_2CO_2Me$, $ClCF_2CO_2Me$ and CF_3CO_2Na. The first of these reagents is converted to $^-CF_3$ by adding a fluoride ion to the reaction. The fluoride ion forms a strong bond to silicon, thus breaking the bond between silicon and the trifluoromethyl group to generate the $^-CF_3$ carbanion (Fig. 28a). The other three reagents decompose in the presence of CuI to form a carbene ($:CF_2$), which then combines with a fluoride ion to form $^-CF_3$ (Fig. 28b-d).

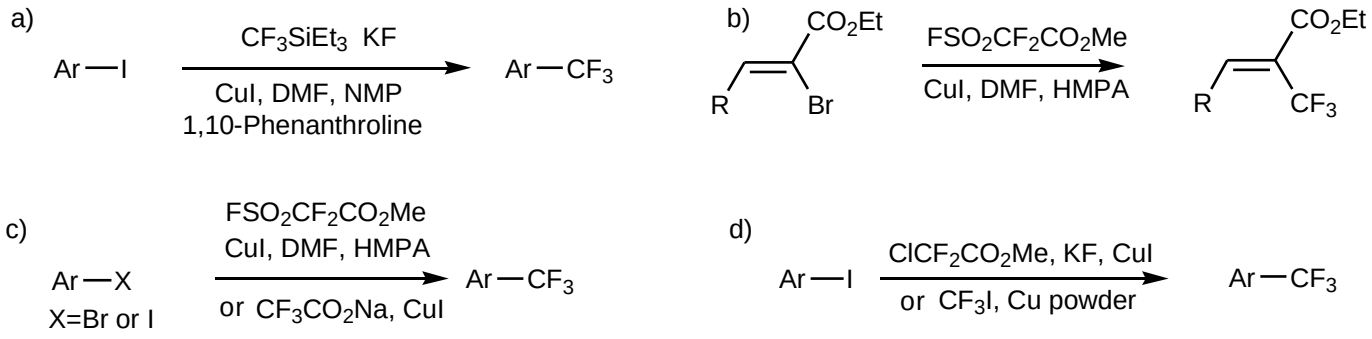


Figure 28 Methods used to introduce a CF_3 group.

A disadvantage with the last three reactions is the need for strong heating and the presence of 1 equivalent of cuprous iodide, and so more recent research has developed methods of carrying out the reaction under milder conditions.
An important step forward was the discovery that catalytic quantities of CuI could be used in trifluoromethylation reactions if 1,10-phenanthrene was included in the reaction.
New reagents have also been developed. Potassium (trifluoromethyl)trimethoxyborate is a relatively new agent that generates $^{-}CF_3$ under mild, non-basic conditions using catalytic quantities of CuI and 1,10-phenanthrene (Fig. 29a). A trifluoromethylcopper(I) reagent ligated with 1,10-phenanthrene has also been isolated and found to react under mild conditions (Fig. 29b).
Further work has shown that it is possible to react aryl and alkenylboronic acids with Me_3SiCF_3 under mild conditions to introduce a trifluoromethyl group, thus extending the reaction to a range of readily available boronic acids (Fig. 29c).
Trifluoromethylation of a carbonyl group is also possible using CF_3SiMe_3 in the presence of tetrabutylammonium fluoride (TBAF). TBAF provides the fluoride ion needed to release $^{-}CF_3$ from the reagent. (Fig. 29d).

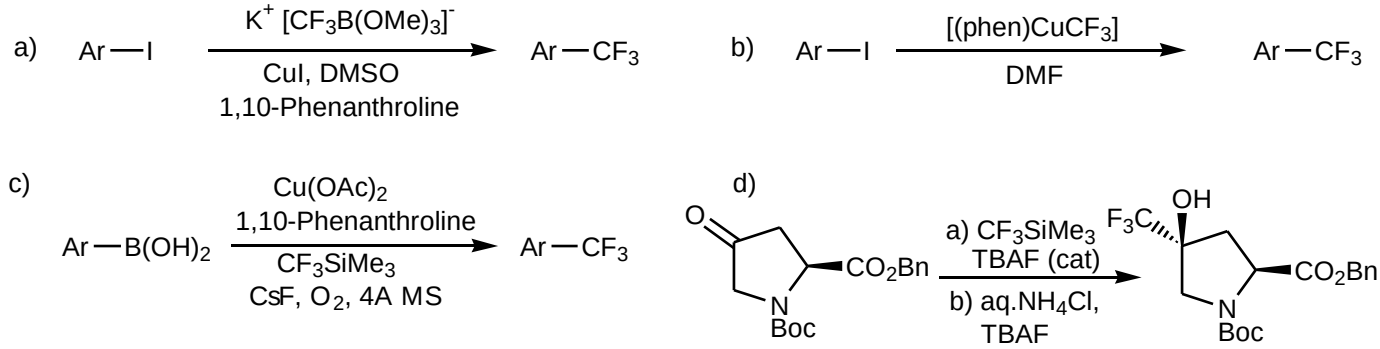


Figure 29 Methods used to introduce a CF_3 moiety (phen = 1,10-phenanthroline).

Palladium-mediated reactions have been tried out as an alternative to copper mediation. A particularly important application is the palladium-catalysed trifluoromethylation of aryl chlorides, as these compounds do not react well in copper-mediated reactions (Fig. 30). However, high temperatures are required for this reaction.

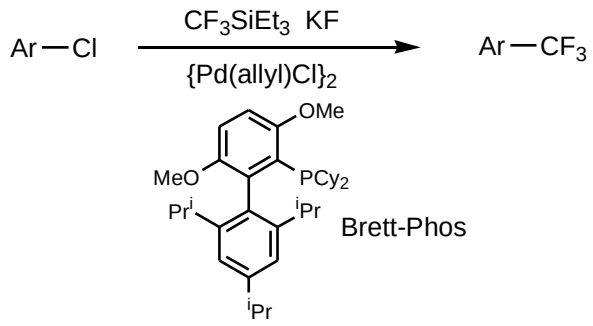


Figure 30 Palladium-catalysed trifluoromethylation of aryl chlorides.

The above reactions all require the starting material to contain a halogen or boronic acid, which is substituted with the trifluoromethyl group. Studies have also been carried out to investigate methods of using electrophilic reagents to trifluoromethylate unactivated positions in heteroaromatic rings. One way of doing this is to use CF_3I, but this reagent is a gas and is not easy to work with. A more convenient method is to use Langlois reagent (sodium trifluoromethanesulphinate), which is decomposed in the presence of tertiary butyl peroxide to release a CF_3 radical. This radical then forms a bond to heterocyclic rings (Fig. 31). The reaction normally takes place at the most nucleophilic position of the heterocyclic ring, but the regioselectivity can be altered by varying the solvents used.

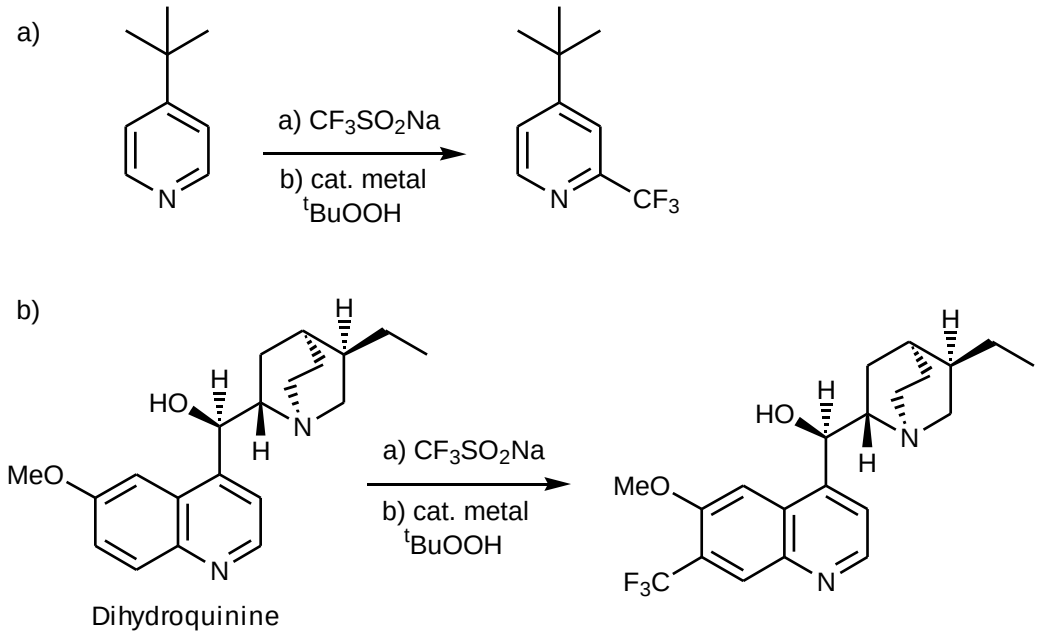


Figure 31 Examples of trifluoromethylation reactions under radical conditions.

An alternative way of incorporating a CF_3 group into a molecule is to take advantage of the large number of simple fluorinated molecules that are now commercially available (Fig. 32). These can be used as reagents or starting materials for conventional synthetic reactions without having to use the specialised reagents or reaction conditions that would otherwise be required to introduce CF_3 and other fluorinated features.

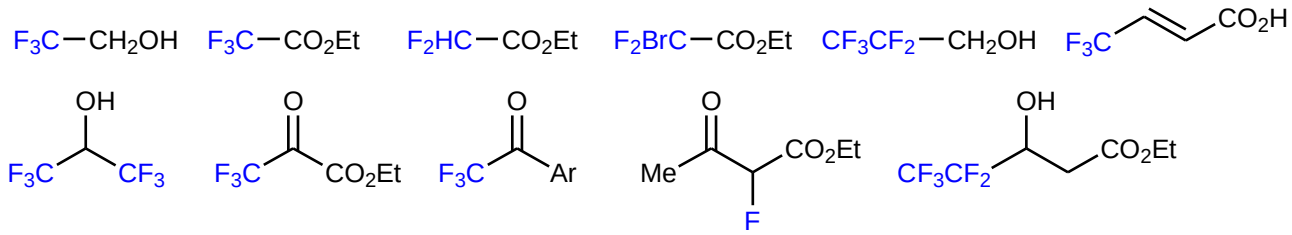


Figure 32 Examples of commercially available compounds containing fluorine.

Finally the reagent CBr_2F_2 has been used to add a CF_2 group to an aldehyde by means of a Wittig reaction (Fig. 33). The Wittig reagent is generated *in situ*.

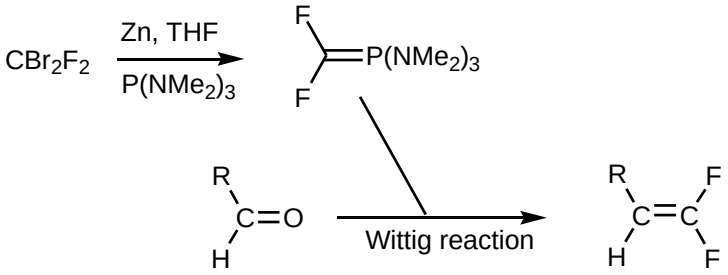


Figure 33 Addition of a CF_2 moiety through the Wittig reaction.

App 5.5 Alkynes

Methods of synthesising alkynes from alkenes and diketones by functional group transformations were described in appendix 1.9. Here we discuss a number of methods of synthesising disubstituted alkynes from terminal alkynes by carbon-carbon bond formation.

App 5.5.1 Alkylation of terminal alkynes

The hydrogen of a terminal alkyne is slightly acidic, which means that it can be removed by a base such as sodium amide ($NaNH_2$) to form an acetylide or alkynide ion. Reaction of the alkynide ion with a primary alkyl halide allows the synthesis of disubstituted alkynes (Fig. 34). When secondary and tertiary alkyl halides are used, the acetylide ion acts as a base and this results in elimination of hydrogen halide from the alkyl halide to form an alkene. The terminal alkyne is recovered unchanged.

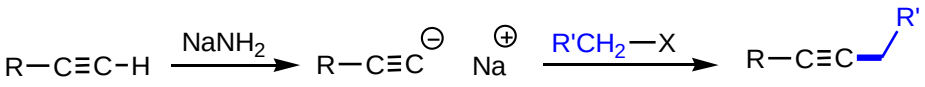


Figure 34 Alkylation of acetylide ions.

App 5.5.2 The Sonagashira reaction

A recent review of reactions used in drug discovery over the last few years has shown that the Sonagashira reaction is second only to the Suzuki reaction as the most commonly used method of creating C-C bonds. The reaction involves a palladium-catalysed coupling of a terminal alkyne to an aryl halide (Fig. 35). Like the Suzuki reaction, the starting materials are generally stable and free from unacceptable toxicity. However, care has to be taken to remove all traces of palladium from the product to avoid toxic effects in bioassays. There are also safety issues related to the use of alkynyl derivatives on large scale.

Aryl iodides react more effectively than aryl bromides, and both of these react more effectively than aryl chlorides. Not surprisingly, aryl iodides and bromides are normally preferred for the reaction. The palladium catalysts are usually $Cl_2Pd(PPh_3)_2$ or $Pd(PPh_3)_4$.

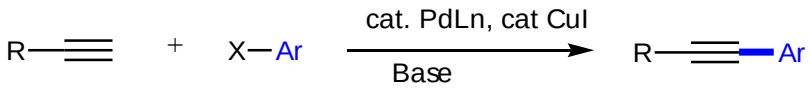


Figure 35 The Sonagashira reaction.

App 5.5.3 The Stephens-Castro coupling

Another method of synthesising aromatic alkynes is to react an aryl iodide with a copper acetylide (the Stephens-Castro coupling) (Fig. 36).

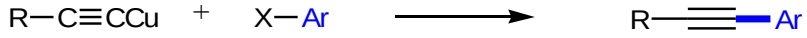
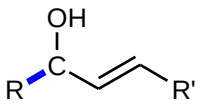


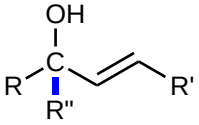
Figure 36 The Stephens-Castro coupling.

App 5.6 Allylic alcohols

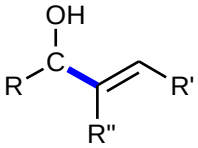
There are a number of functional group transformations that can convert alkenes, epoxides and α,β-unsaturated carbonyl groups to allylic alcohols (appendix 1.10). Methods of generating allylic alcohols by carbon-carbon bond formation involve alkynes, aldehydes, ketones, α,β-unsaturated aldehydes, vinyl halides and alcohols (Fig. 37).



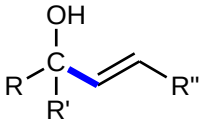
From α,β-unsaturated aldehydes (section5.6.1)



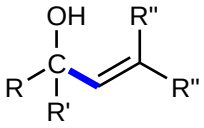
From α,β-unsaturated ketones (section 5.6.1)



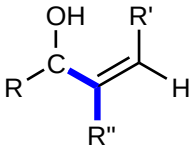
From alkynes, aldehydes, alcohols & vinyl halides (sections 5.6.2- 5.6.3 & 5.6.8)



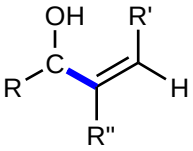
From alkynes, & ketones (sections 5.6.2 & 5.6.4)



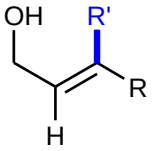
From vinyl halides & ketones (section 5.6.2)



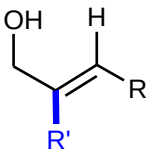
From bromoalkynes or alkynes & aldehydes (section 5.6.2)



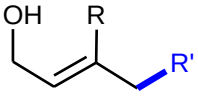
From alkynes, vinyl halides and aldehydes (sections 5.6.4 & 5.6.8)



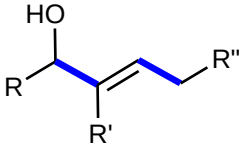
From alkynols & lithium organocuprates (section 5.6.5)



From alkynols & lithium organocuprates (section 5.6.5)



From α,β-unsaturated epoxides & organocuprates (section 5.6.6)



From an alkyl halide & two aldehydes (section 5.6.7)

Figure 37 C-C Bond formations used in the synthesis of allylic alcohols.

App 5.6.1 Allylic alcohols from α,β-unsaturated aldehydes and ketones

α,β-Unsaturated aldehydes or ketones can be converted to allylic alcohols by treatment with a Grignard reagent or an organolithium reagent. Nucleophilic addition takes place by 1,2-addition at the carbonyl group, in preference to 1,4-addition to the alkene. A carbon-carbon bond formation occurs which allows the addition of an alkyl substituent (Fig. 38a&b).

It also possible to carry out a 1,2-addition reaction on α,β-unsaturated aldehydes using dialkylzinc reagents in the presence of $Ti(O^iPr)_4$ and a diamine as catalysts (Fig. 38c). If the diamine is chiral, the reaction is also enantioselective. The dialkylzinc reagents can be generated from alkenes via organoboranes.

1,2-Addition has also been possible with zinc-copper reagents in the presence of boron trifluoride etherate as a catalyst (Fig. 38d).

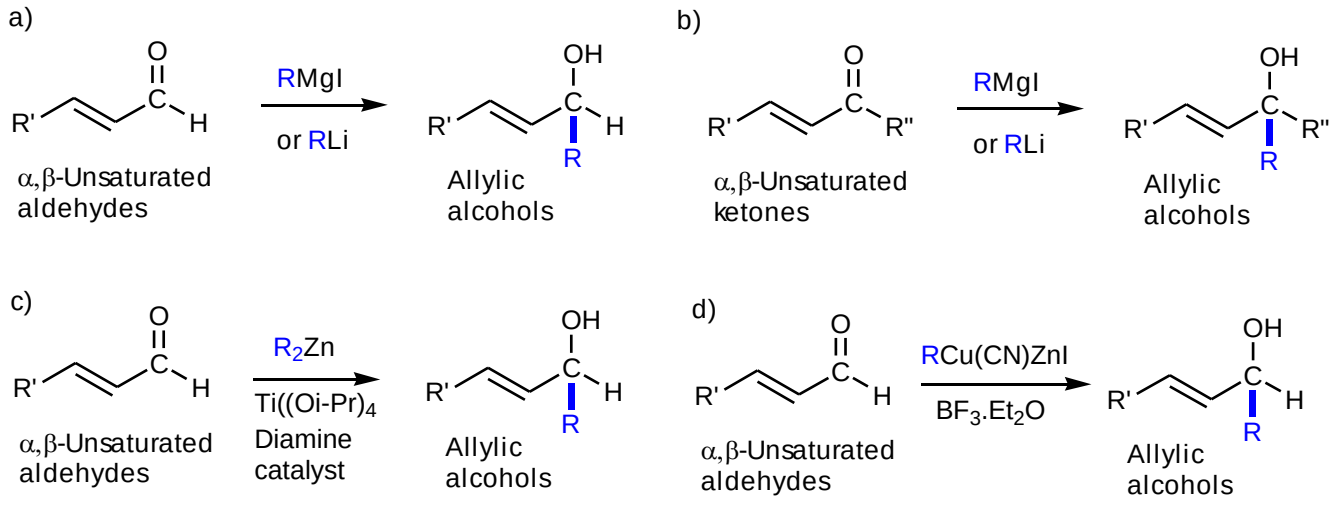


Figure 38 1,2-Nucleophilic addition of organometallic reagents to α,β-unsaturated aldehydes and ketones.

App 5.6.2 Allylic alcohols from alkynes and aldehydes/ketones

(*E*)-Allylic alcohols can be synthesised by the vinylation of aromatic or aliphatic aldehydes using alkenyl zinc reagents in the presence of an amino alcohol (Fig. 39). The amino alcohol serves to catalyse the reaction, and enantioselectivity is possible if the amino alcohol is chiral.

The organozinc reagents required are synthesised from terminal alkynes in a two-step process involving regioselective hydroboration of the alkyne using dicyclohexylborane ($(Cy)_2BH$), followed by transmetallation with either Me_2Zn or Et_2Zn. The organoborane and organozinc reagents can be formed *in situ* and so this method is a one-pot method of preparing the allylic alcohol from an alkyne and an aldehyde. The reaction is the equivalent of adding a vinyl anion ($R_2C{=}CR^-$) to a carbonyl carbon.

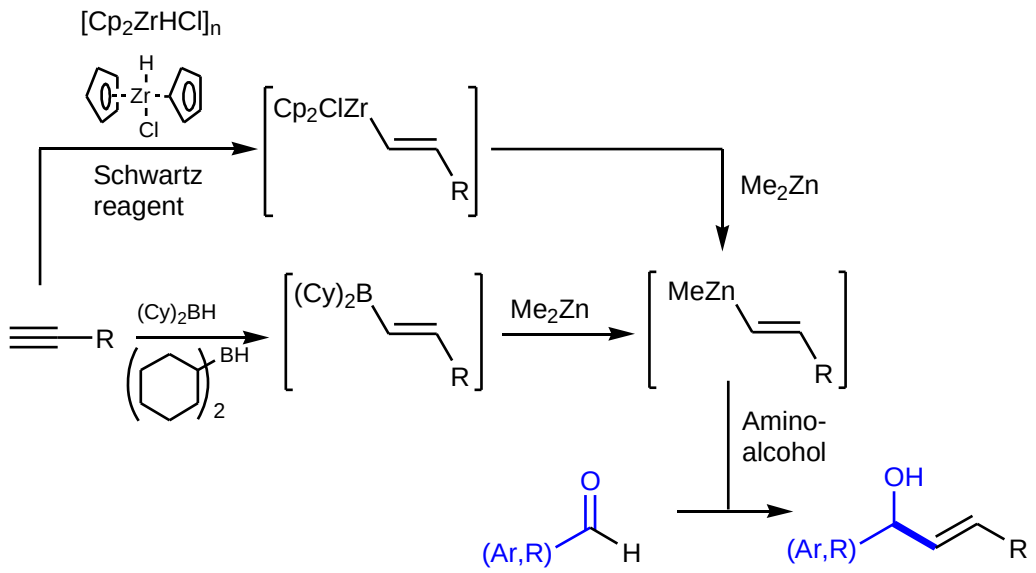


Fig. 39 Synthesis of allyl alcohols by the vinylation of aromatic or aliphatic aldehydes.

A different method of synthesising the organozinc reagent is to carry out a hydrozirconation of the alkyne reactant using Schwartz's reagent, followed by transmetallation with dimethyl zinc. The zirconocene by-products that are formed from this transmetallation act as promoters for the subsequent addition of the organozinc reagents to aromatic and aliphatic aldehydes, thus avoiding the requirement for the presence of amino alcohol ligands. (*E*)-Trisubstituted allylic alcohols can also be synthesised by this method starting from disubstituted alkynes.
It is possible to prepare (*Z*)-trisubstituted allylic alcohols in a 1-pot process by starting with a bromoalkyne. Once the vinyl borane is formed, an alkyl group migrates and displaces the bromo substituent with inversion at the vinylic centre. Transmetallation and subsequent reaction with an aldehyde generates the (Z)-allylic alcohol (Fig. 40).

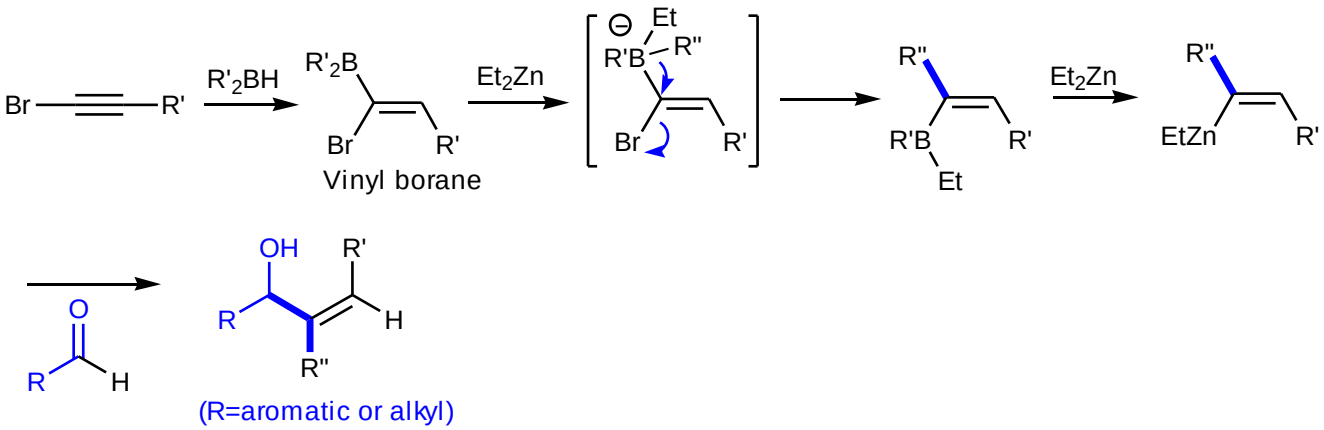


Fig. 40 Synthesis of (*Z*)-trisubstituted allylic alcohols

It has proved possible to synthesise (*E*)-disubstituted tertiary allylic alcohols by reacting the organozinc reagent with aromatic or aliphatic ketones in the presence of a $Ti(O^iPr)_4$ catalyst and a chiral ligand. Dimethylzinc ($ZnMe_2$) is also added to mop up any isopropanol released from the catalyst (Fig. 41). Divinylzinc reagents prepared from vinyl halides have also been reacted with ketones to produce trisubstituted tertiary allylic alcohols.

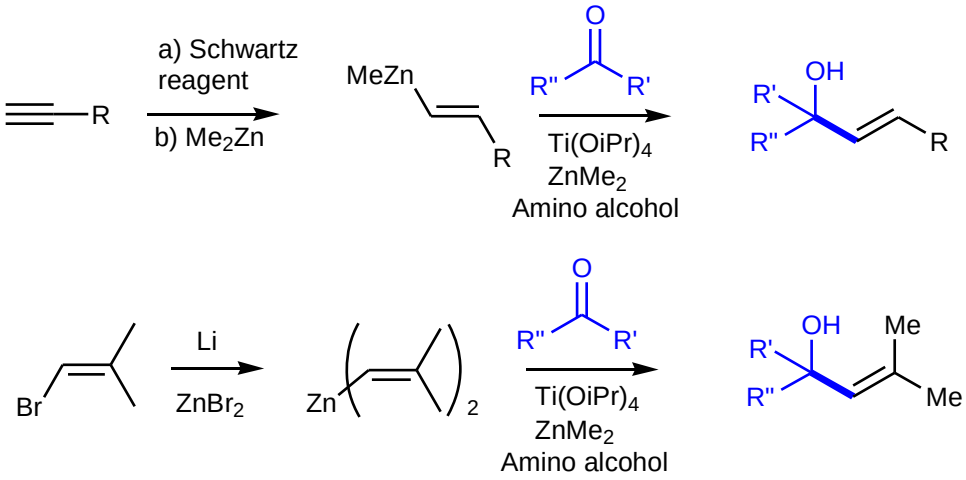


Fig. 41 Synthesis of tertiary allylic alcohols.

A distinct disadvantage of these methods is the need for four organometallic reagents and the requirement to remove the metallic byproducts produced. To avoid this problem, methods have been devised to carry out the direct coupling of an alkyne with an aromatic or aliphatic aldehyde without the need for organometallic reagents. For example, direct coupling is possible in the presence of a nickel catalyst under reducing conditions (Fig. 42). Varying the conditions can affect the regioselectivity of the reaction (Fig. 42b & c)

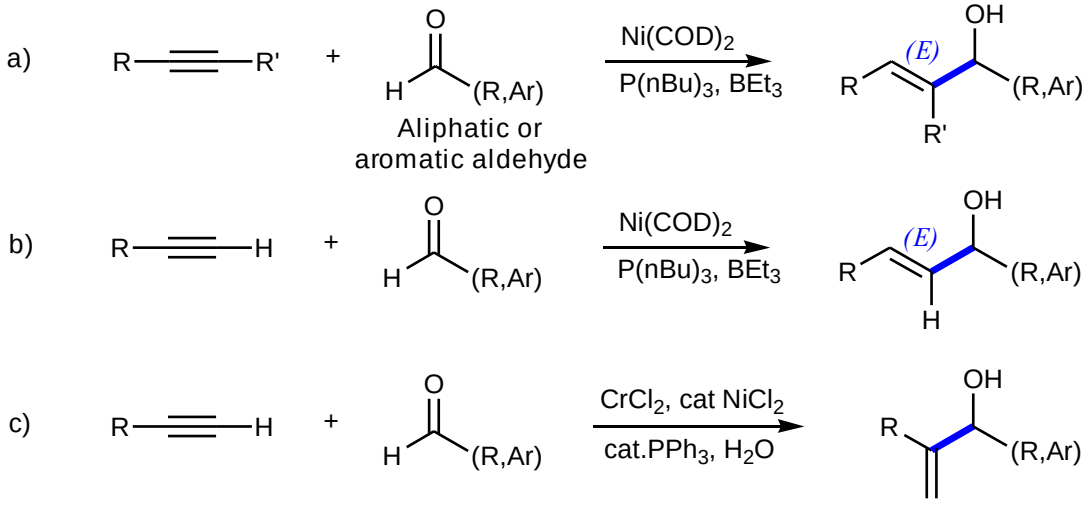


Fig. 42 Reductive coupling of alkynes with aldehydes. COD = cyclooctadiene.

A more recent method makes use of a ruthenium catalyst under reducing conditions (Fig. 43). Formic acid is present as a reductant and sodium iodide helps to prevent the formation of enone side products. This is known as a ruthenium-catalysed transfer hydrogenative coupling.

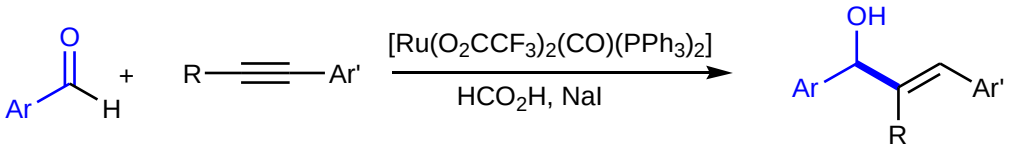


Fig. 43 Synthesis of allylic alcohols from aromatic aldehydes and alkynes in the presence of a ruthenium catalyst.

An older method of coupling an alkyne with an aldehyde is by means of an organoborane reagent (Fig. 44). The alkyne is treated with 9-borabicyclo[3.3.1]nonane (9-BBN) to give a vinyl borane. Treatment with an aliphatic or aromatic aldehyde results in the vinyl borane adding across the carbonyl group. Work up with base and hydrogen peroxide generates the allylic alcohol with the alkene retaining its stereochemistry.

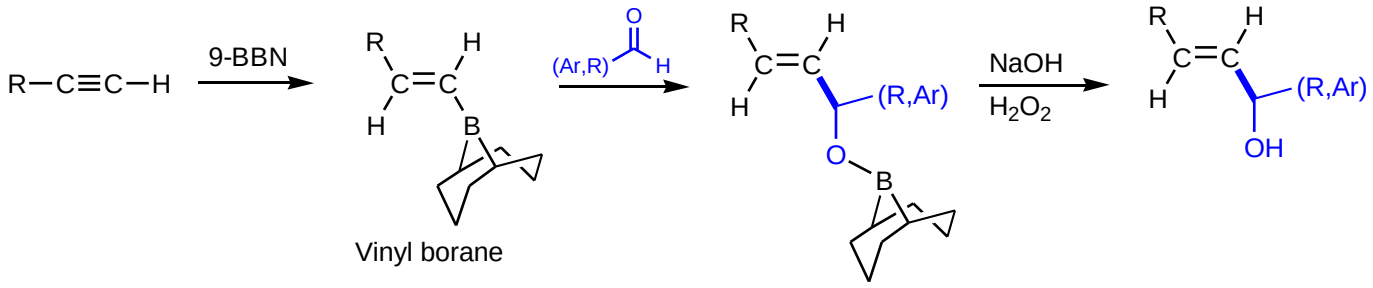


Fig. 44 Synthesis of allylic alcohols via a vinyl borane.

App 5.6.3 Allylic alcohols from alkynes reacting with alcohols or aldehydes

The ruthenium-catalysed transfer hydrogenative coupling shown in figure 43 has also been applied to the coupling of alkynes to benzyl or aliphatic alcohols (Fig. 45). In this scenario, isopropanol is present as a source of hydrogen for the reduction process.

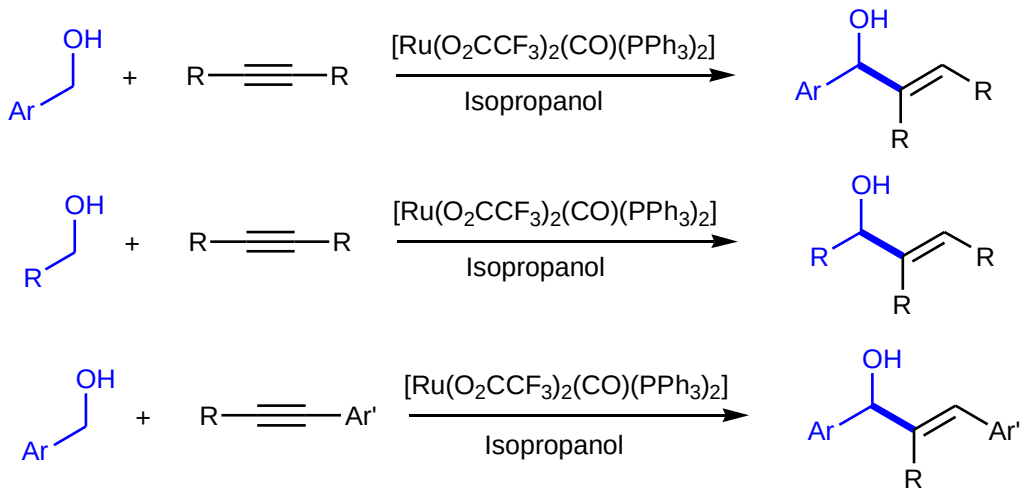


Figure 45 Ruthenium-catalysed alkyne aldehyde transfer hydrogenative coupling.

App 5.6.4 Allylic alcohols from symmetrical alkynes and aldehydes via alkenyl alanes
Symmetrical alkynes can be hydroaluminated with lithium hydridodiisobutylmethylaluminate, then treated with formaldehyde or acetaldehyde to form allylic alcohols (Fig. 46).

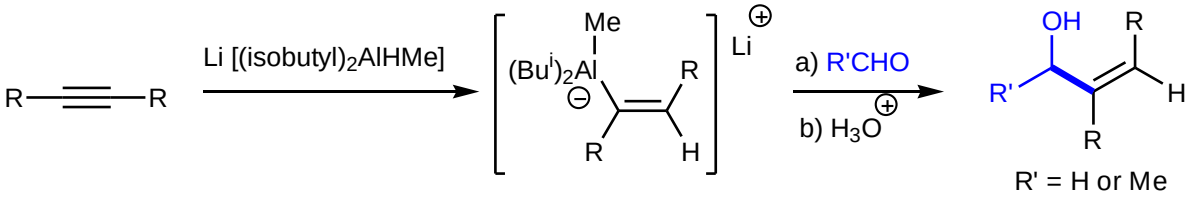


Figure 46 Vinylation of aldehydes with alkenyl alanes.

The reaction with aliphatic ketones is more difficult and requires more reactive alkenylating agents. However, alkenyl aluminium reagents react with aromatic ketones to produce tertiary allylic alcohols (Fig. 47). The alkenylating agents can be generated i*n situ* from a terminal alkyne and DIBAL.

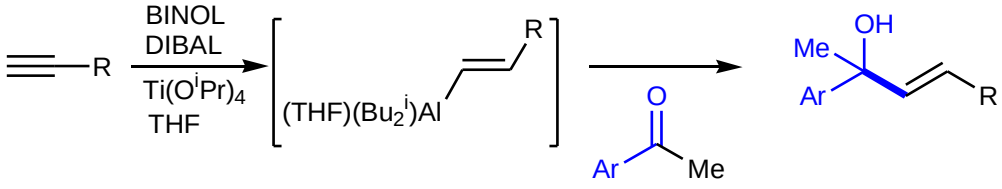


Figure 47 Alkenylation of aromatic ketones with alkenyl alanes.

App 5.6.5 Allylic alcohols from alkynols
Allylic alcohols containing a trisubstituted alkene group can be synthesised from alkynols by a reduction with $LiAlH_4$, followed by iodine treatment to give an iodoallylic alcohol (Fig. 48) (the

conditions can be varied to determine which carbon is iodinated). Alkylation with a lithium organocuprate then generates the trisubstituted allylic alcohol.

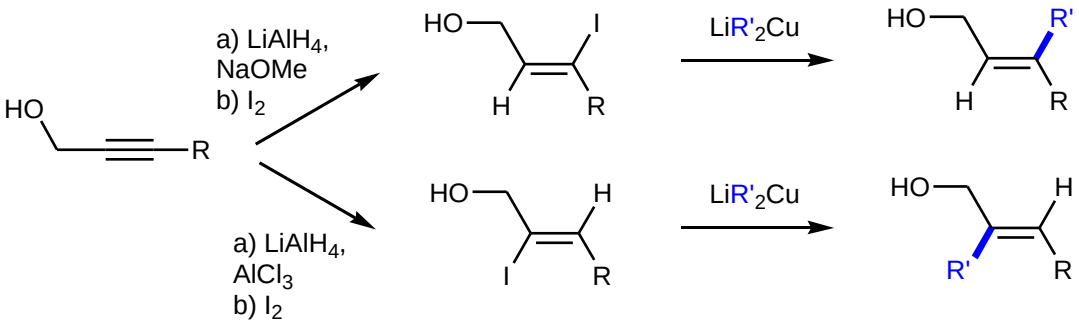


Figure 48 Allylic alcohols from alkynols.

App 5.6.6 Allylic alcohols from α,β-unsaturated epoxides

α,β-Unsaturated epoxides react with organocuprates to form *trans*-allylic alcohols by 1,4-addition (Fig. 49), allowing the addition of a substituent at a different allylic position from that of the alcohol.

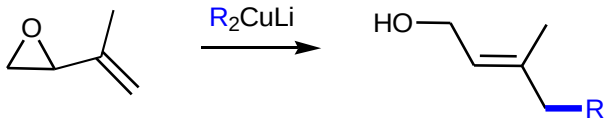


Figure 49 Allylic alcohols from α,β-unsaturated epoxides

App 5.6.7 Allylic alcohols from an alkyl halide and two aldehydes

It is possible to synthesise allylic alcohols by carrying out a modification of the Wittig reaction. Reaction of an aldehyde with the Wittig reagent would normally give an alkene, but if the betaine intermediate is treated with base and a second aldehyde, then it is possible to get an (*E*)-trisubstituted allylic alcohol where two new C-C bonds have been created (Fig. 50).

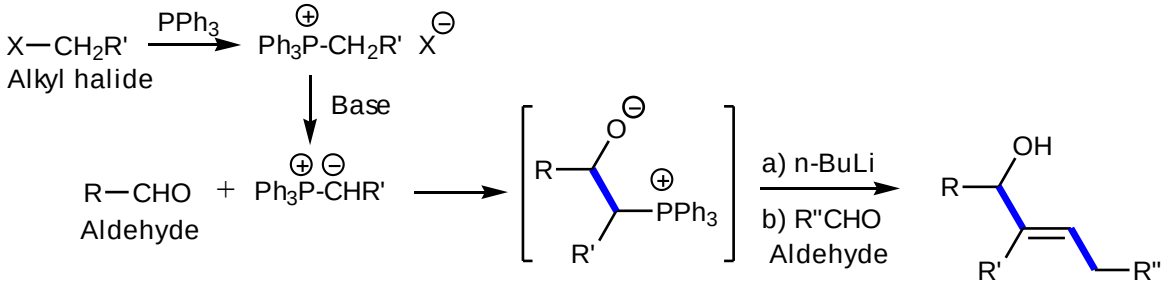


Figure 50 Allylic alcohols from two aldehydes and an alkyl halide.

App 5.6.8 Allylic alcohols from coupling vinyl halides with aldehydes

The coupling of a vinyl halide with an aldehyde is a common method of preparing allylic alcohols. The reaction is carried out under oxygen free conditions in the presence of

$CrCl_2$ and a catalytic amount of nickel chloride ($NiCl_2$) or palladium acetate ($Pd(OAc)_2$). Other functional groups which might be present in the molecule, such as esters, amides, nitriles, ketones, acetals, ketals, ethers, silyl ethers, alcohols and olefins, are unaffected. The halogen of the vinyl halide can be iodine or bromine and the stereochemistry of the vinyl halide is retained in the product if a disubstituted or *E*-trisubstituted vinyl halide is used (Fig. 51a-c). Vinyl triflates can also be used in the reaction (Fig. 51d). Curiously, an inversion of stereochemistry occurs if a *Z*-trisubstituted vinyl halide is used (Fig. 51e).

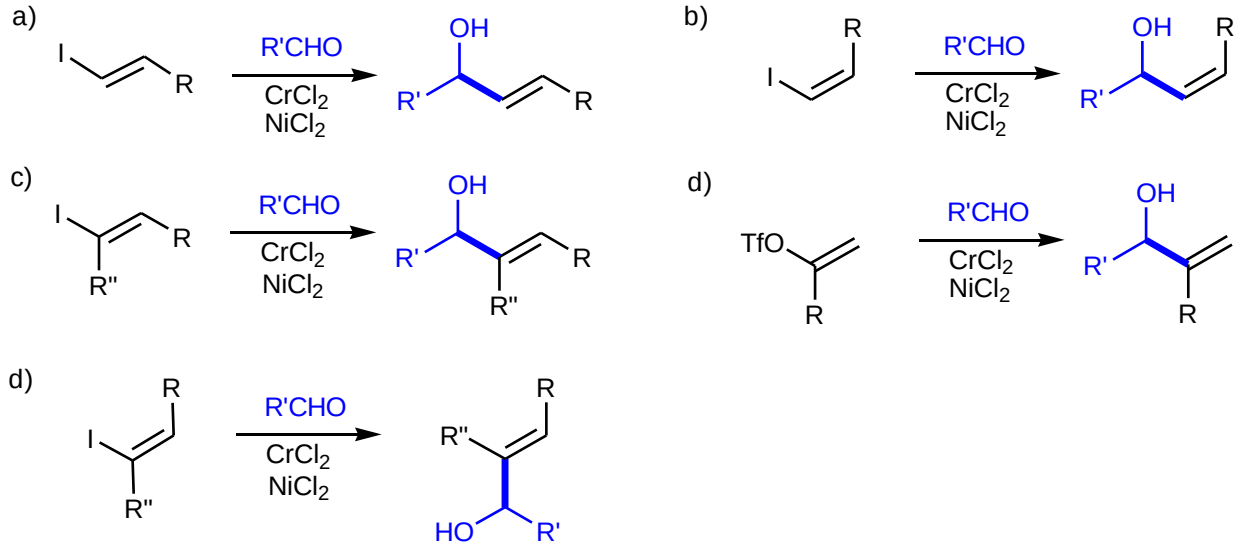


Figure 51 Allylic alcohols from vinyl iodides and aldehydes.

App 5.7 Amino acids

The synthesis of amino acids through carbon-carbon-bond formations is possible from aldehydes or alkyl halides (Fig. 52). The methods used to synthesise carboxylic acids and allylic alcohols are also relevant due to the functional group transformations described in appendix 1.13.

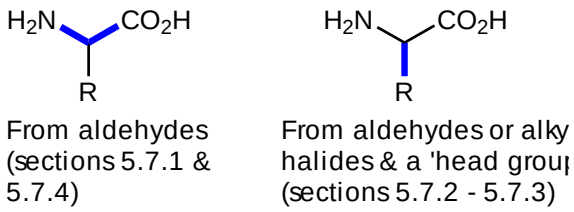


Figure 52 C-C Bond formations used in the synthesis of amino acids.

App 5.7.1 Synthesis of amino acids from aldehydes (Strecker Synthesis)

A common method of synthesising both natural and unnatural amino acids is the Strecker synthesis (Fig. 53), which involves reacting an aldehyde with hydrogen cyanide and ammonium carbonate, followed by hydrolysis of the nitrile group. The final product is a racemate, but enantioselectivity is possible with suitable reagents (chapter 5.8.5).

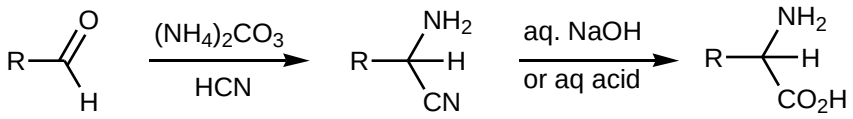


Figure 53 The Strecker synthesis of amino acids.

App 5.7.2 The synthesis of amino acids from aldehydes and functionalised glycine moieties
Amino acids can be synthesised from aldehydes by treating the aldehyde with an oxazolone generated from an *N*-acylated glycine (Fig. 54). This oxazolone represents the amino acid head group containing both functional groups and the alpha carbon. The resulting azlactone is hydrolysed to produce the protected dehydroamino acid (*N*-acylaminoacrylic acid), which is then hydrogenated and deprotected. The synthesis of the *N*-acylaminoacrylic acid is known as the **Erlenmeyer synthesis** and works best with aromatic aldehydes. Aliphatic aldehydes are not generally good reactants because they are unstable to the reaction conditions, although some success has been achieved by varying the reaction conditions. For example, adsorbing the azlactone and the aliphatic aldehyde onto neutral alumina and irradiating with microwave radiation for a couple of minutes has proved successful.
This method does not work with ketones and cannot be used to synthesise amino acids where the side chain has a tertiary carbon linked to the α-carbon. The reaction is best for the synthesis of amino acids with a side chain corresponding to CH_2Ar.

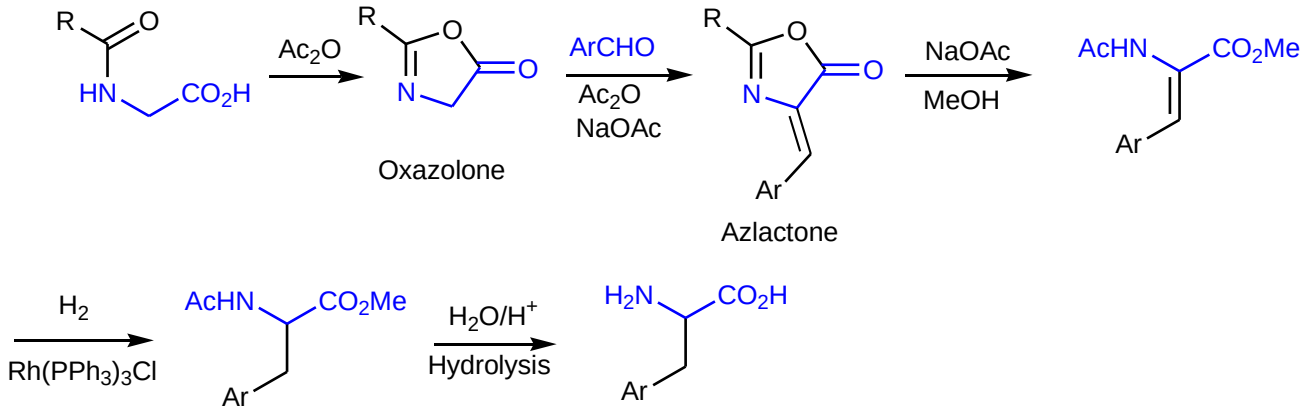


Figure 54 Synthesis of amino acids from aldehydes and *N*-acylated glycine (R=Me or Ph).

Another common approach is to carry out a Horner-Emmons olefination of an aldehyde with a phosphonate reagent representing the amino acid head group (Fig 55). The resulting (*Z*)-dehydroamino acid derivative is then hydrogenated, before the protecting groups are removed.

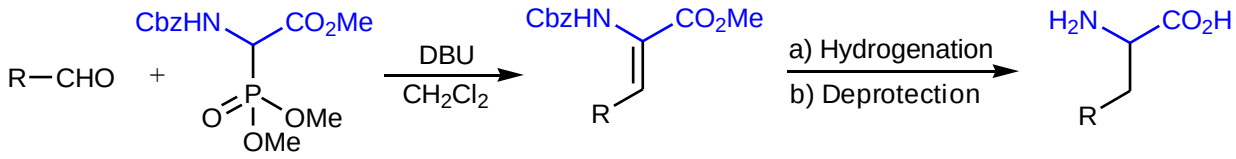


Figure 55 Synthesis of amino acids via a Horner-Emmons olefination.

App 5.7.3 Synthesis of amino acids from alkyl halides and functionalised glycine moieties
Other functionalised glycine moieties have been used in the synthesis of amino acids where an alkyl halide is used to introduce the side chain rather than an aldehyde. The Sorenson method (Fig. 56a) starts off with an *N*-acetylaminomalonic ester, which is treated with base to form a carbanion, then alkylated with the alkyl halide. Hydrolysis and decarboxylation generates the amino acid.
Another method is to take an imine derivative of glycine methyl ester and treat it with base to form a carbanion. This is then alkylated with the alkyl halide, and hydrolysed to the amino acid (Fig. 56b).

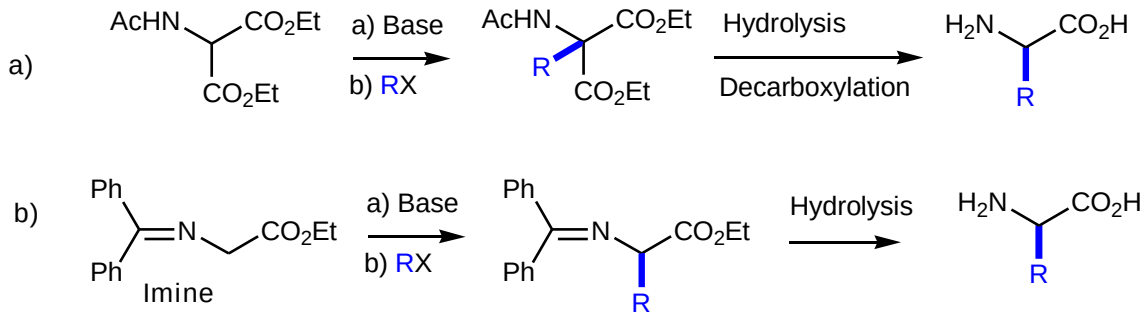


Figure 56 Synthesis of amino acids from alkyl halides and an amino acid 'head group'.

App 5.7.4 Synthesis of amino acids from aldehydes via the Knoevenagel reaction.
Amino acids can be synthesised by reacting aldehydes with dimethylmalonate, to form an α,β-unsaturated diester which is then hydrogenated and converted to an oxime with isoamyl nitrite. Oxime hydrolysis then gives the protected amino acid (Fig. 57).

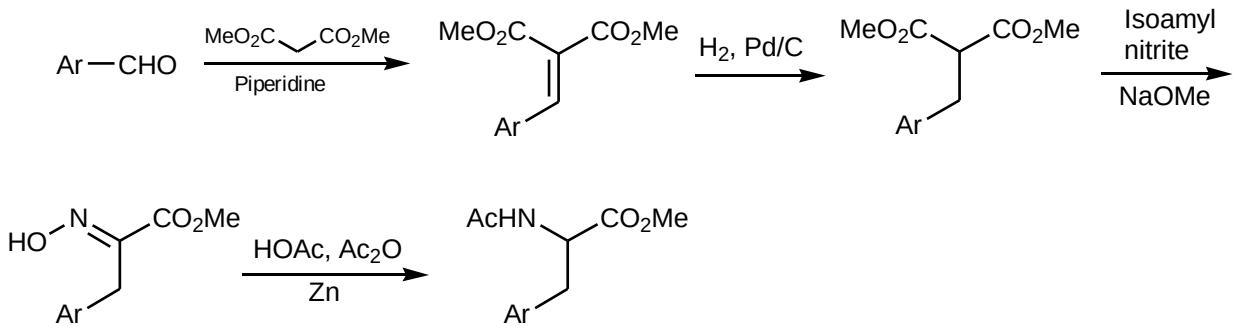


Figure 57 Synthesis of amino acids from aldehydes via the Knoevenagel reaction.

App 5.8 Amino alcohols

1,2-Amino alcohols can be prepared by functional group transformations of epoxides as described in appendix 1.14. They can also be prepared by C-C bond formation. For example, aldehydes or ketones can be reacted with a cyanide ion to produce a cyanohydrin, which is then reduced to the amino alcohol (Fig. 58).

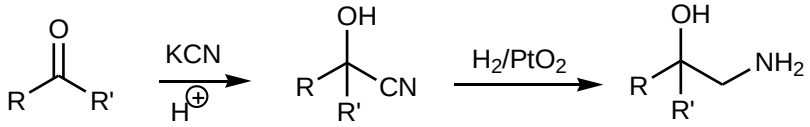


Figure 58 Synthesis of 1,2-amino alcohols from aldehydes or ketones.

Other types of amino alcohols can be synthesised from amino ketones by nucleophilic addition with a carbanion (Fig. 59).

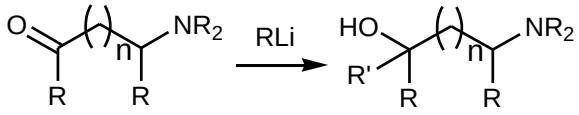


Figure 59 Synthesis of amino alcohols by functional group transformations.

App 5.9 Aromatic rings - acylation and alkylation

App 5.9.1 The Friedel Crafts Reaction

Aromatic rings can be alkylated with alkyl halides in the presence of a Lewis acid such as $AlCl_3$ or BF_3 as catalyst. This is known as the Friedel Crafts alkylation (Fig. 60) and is an example of an electrophilic substitution reaction. The order of reactivity of alkyl halides is RF > RCl > RBr > RI, with the order of reactivity of the different types of alkyl halide being allylic, benzylic > tertiary > secondary > primary. Lewis acids differ in strength. Milder ones can be used with reactive alkyl halides and stronger ones with the less reactive alkyl halides. The relative reactivity of some Lewis acids is $AlCl_3$ > $FeCl_3$ > $SnCl_4$ > BF_3.

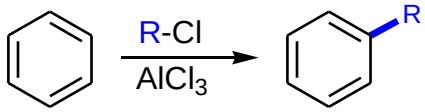


Figure 60 Friedel Crafts alkylation.

There are limitations to the Friedel Crafts alkylation. It does not proceed well with aromatic amines as the Lewis acid forms a complex with the basic amine. The presence of a strongly deactivating nitro substituent prevents reaction and yields are low with other deactivating groups. The reaction can also give poor yields when primary alkyl halides are used. For example, the reaction of 1-chlorobutane with benzene gives two products with only 34% of the desired product (Fig. 61). This is due to rearrangement reactions undergone by the carbocation intermediate.

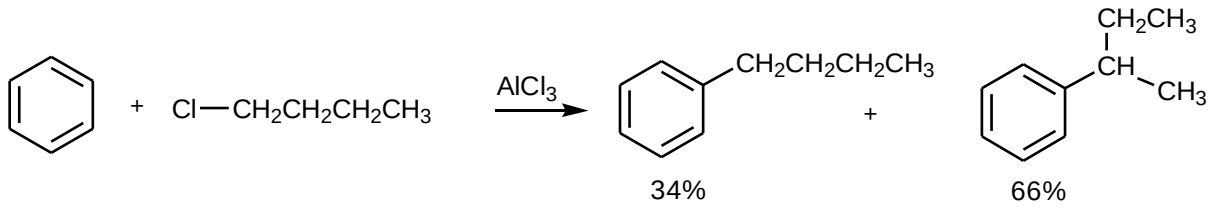


Figure 61 Friedel Crafts reaction of 1-chlorobutane with benzene.

One way round this problem is to carry out a Friedel Crafts acylation to produce an aromatic ketone, and then reduce the ketone. For example, the linear butyl substituent in figure 61 can be added more effectively as shown in figure 62.

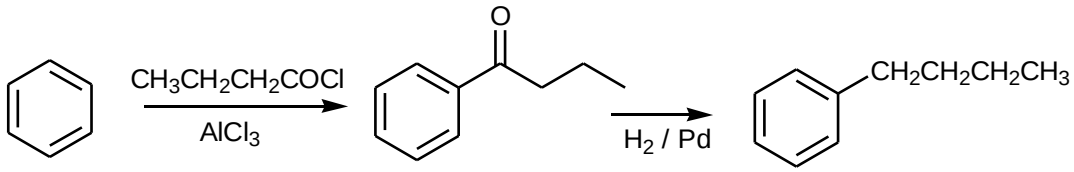


Figure 62 Synthesis of 1-butylbenzene by Friedel Crafts acylation and reduction.

Friedel Crafts alkylations can also be carried out using alkenes instead of alkyl halides. A Lewis acid is not required, but a mineral acid is. Treatment of the alkene with the acid leads to a carbocation which can then react with an aromatic ring by electrophilic substitution (Fig. 63).

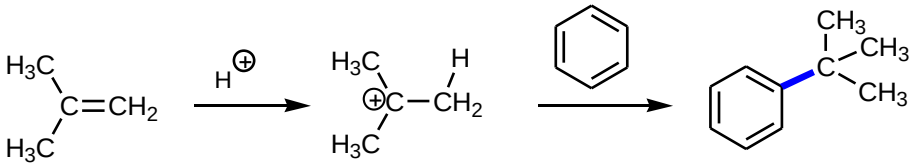


Figure 63 Friedel Crafts alkylation of benzene with an alkene.

In a similar fashion, Friedel Crafts reactions can be carried out with alcohols in the presence of a mineral acid such as sulphuric acid. The acid catalyses the elimination of water from the alcohol resulting in the formation of an alkene, which can then be converted to a carbocation as already described (Fig. 64).

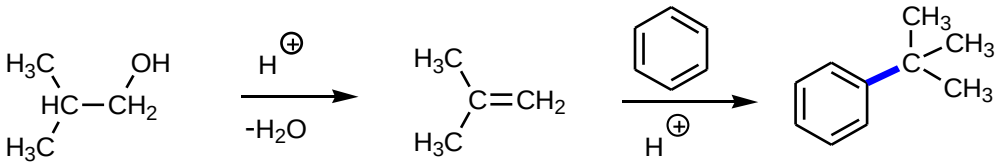


Figure 64 Friedel Crafts alkylation of benzene with an alkene generated from an alcohol.

Intramolecular Friedel-Crafts reactions are a popular method of creating cyclic systems (chapter 4.5.1).

App 5.9.2 Coupling aryl and alkyl groups with organocuprate reagents

An alternative procedure to the Friedel Crafts alkylation is to react an aryl halide with an organocuprate reagent (Fig. 65a). It is also possible to carry out this reaction using an alkyl halide and an arylorganocuprate reagent.(Fig. 65b).

Figure 65 Coupling aryl and alkyl groups with organocuprate reagents.

App 5.9.3 Suzuki reaction

The Suzuki reaction was described earlier as a method of synthesising aromatic alkenes (appendix 5.3.6). It can also be used to alkylate an aromatic ring (Fig. 66). One advantage over the Friedal Crafts reaction is that there is no risk of the alkyl group rearranging.

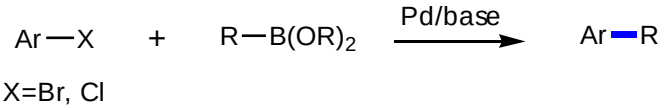


Figure 66 Alkylation of an aromatic ring using the Suzuki reaction.

App 5.9.4 Alkylation of deactivated aromatic rings

An aromatic halide containing a strong deactivating group such as a nitro group can undergo nucleophilic substitution of the halogen atom with nucleophiles such as amides, hydrazines, azides, nitriles, thiolates, or alkoxides. Under oxidative conditions, however, it is possible to replace a hydrogen atom from the aromatic ring and introduce a third substituent with a Grignard or organolithium reagent (Fig. 67).

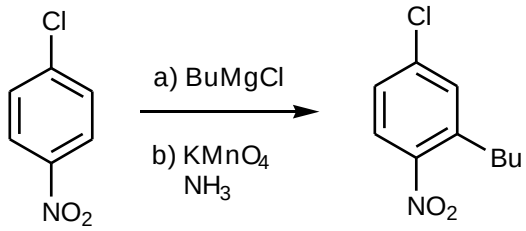


Figure 67 Alkylation of deactivated aromatic rings.

App 5.9.5 The Claisen rearrangement

A useful method of introducing an alkyl substituent to the *ortho* position of a phenol is by the **Claisen rearrangement** (Fig. 68). The phenol is converted to the phenoxide ion, then treated with 3-bromopropene (an allyl bromide) to form an aromatic ether. On heating, the allyl group (-CH_2-$CH{=}CH_2$) is transferred from the oxygen to the *ortho* position of the aromatic ring. The mechanism

of the final step involves a concerted process of bond formation and bond breaking called a **pericyclic reaction.** The alkene can then be reduced to give a propyl substituent if desired.

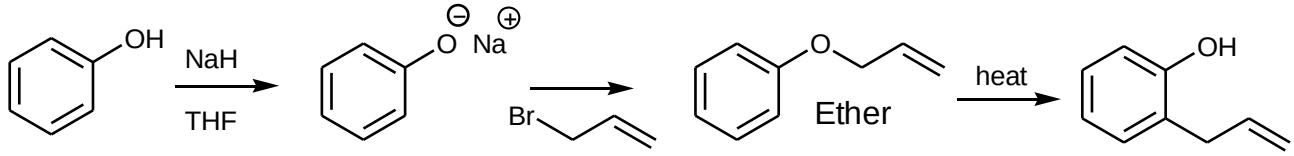


Figure 68 Claisen rearrangement.

App 5.10 Biaryls

Biaryl groups involving aromatic or heteroaromatic rings are present in an increasing number of drugs. These include various kinase inhibitors used as anticancer agents (e.g. imatinib and nilotinib) and the antibacterial agent radezolid.

App 5.10.1 The Suzuki-Miyaura reaction

The Suzuki-Miyaura reaction is an effective method of synthesising biaryl structures in good yield and selectivity under milder conditions than alternative coupling methods involving Grignard reagents or tin compounds (Fig. 69). The reaction involves the coupling of an aryl halide with an aryl boronate (or aryl boronic acid) in the presence of a palladium or nickel catalyst. Due to the popularity of this reaction, there are a large variety of commercially available aryl halides and aryl boronic acids. The latter have proved to be relatively safe reagents, and the boron-containing by products are easy to handle and remove. Moreover, the reaction can be carried out in the presence of a range of other functional groups.

Aryl iodides and bromides are normally used, but it is also possible to use aryl triflates. An aryl iodide is more reactive than an aryl bromide, and so it is possible to be selective in the coupling if more than one of these halogens is present. Aryl chlorides react too slowly to be effective, unless special reactions conditions are used such as nickel catalysts.

The solvent is usually ether or THF, but it is also possible to carry out the reaction with water, which is beneficial on large scale. The base is normally sodium carbonate, but other bases have been used. The most frequently used catalyst is $Pd(PPh_3)_4$. The palladium essentially captures the aryl rings from both reagents, with displacement of the halide and boronate ions. The rings are then coupled and the palladium catalyst is released to catalyse another coupling reaction. The palladium catalyst can be used in very small quantities, which is particularly important on large scale.

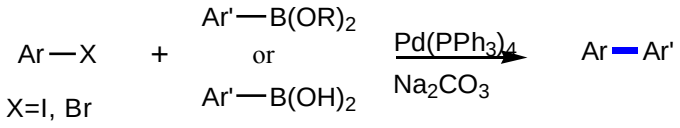


Figure 69 Synthesis of biaryls using the Suzuki-Miyaura reaction (Ar = aromatic or heteroaromatic ring).

Cross coupling can also be carried out on heteroaromatic rings to produce products such as aryl-substituted pyridines, pyrroles and indoles. Unlike aryl chlorides, heteroaryl chlorides are sufficiently reactive to undergo reaction under the normal reaction conditions.

App 5.10.2 The Kosugi-Migita-Stille reaction

The Kosugi-Migita-Stille reaction is another method that has proved useful in the synthesis of biaryl compounds in good yield and selectivity (Fig. 70a). The reaction is between an arylstannane and an aryl halide (or triflate) in the presence of a palladium catalyst. The addition of copper salts is often beneficial and it is thought that these may result in a more reactive organocopper reagent being formed *in situ*. When the organostannane is being linked to an aryl triflate, lithium chloride is normally added. Like the Suzuki reaction, the Stille reaction can be carried out in the presence of water. However, a serious disadvantage with the Stille reaction is the fact that the organotin reagents and by products are toxic, making the reaction unsuitable for large scale syntheses. Moreover the organostannanes are expensive.

The reaction has also been used to couple aromatic rings with heteroaromatic rings.

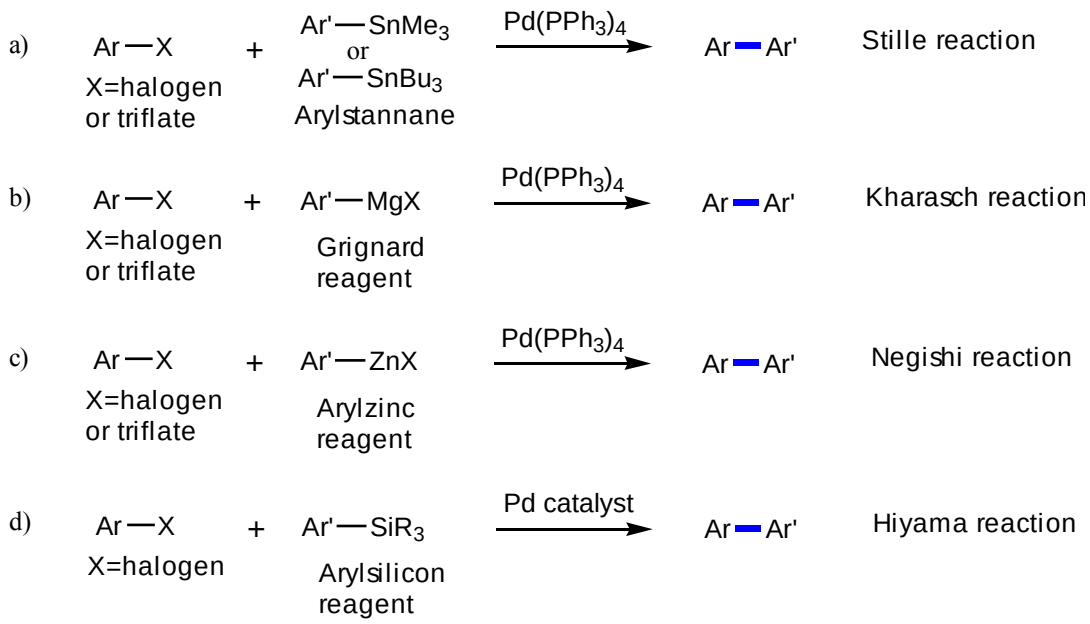


Figure 70 Synthesis of biaryls by palladium-catalysed coupling reactions. (Ar = aromatic or heteroaromatic ring)

App 5.10.3 The Karasch-Kumada-Corriu-Tamao reaction

Biaryls can be synthesised by reacting an aryl Grignard reagent with an aryl halide in the presence of a palladium or a nickel catalyst (Fig. 70b). However, the reaction suffers the disadvantage that it is not possible to have nitrile, ester or cyano groups present in the starting materials, as these would react with the Grignard reagent. Nevertheless, the method is convenient for the synthesis of relatively simple biaryl structures.

App 5.10.4 The Negeshi reaction

The Negeshi reaction involves the reaction of an arylzinc reagent with an aryl halide (or aryl triflate) in the presence of a palladium or nickel catalyst (Fig. 70c). The reaction goes in good yield and selectivity, and the organozinc reagent can be generated *in situ*. However, the reaction cannot be carried out in water, and there are safety issues when they are carried out on large scale.

App 5.10.5 The Hiyama reaction
The Hiyama reaction involves organosilanes and aryl halides (iodides or bromides) in the presence of a palladium catalyst (Fig. 70d). The reaction goes in good yield and selectivity, and the organosilanes have low toxicity. However, special reactors are required if a fluoride ion is being used as an activating group.

App 5.11 Carboxylic acids

Methods of generating carboxylic acids by functional group transformations were covered in appendix 1.18. A number of methods involving C-C bond formations are also available as described below.

App 5.11.1 Carboxylic acids from alkyl halides with chain extension.
There are two methods by which alkyl halides can be converted to a carboxylic acid and, in both cases, the carbon chain is extended by one carbon (Fig. 71). One method involves substituting the halogen with a cyanide ion, then hydrolyzing the cyanide group. This works best with primary alkyl halides, allylic halides and benzylic halides. The other method involves the formation of a Grignard reagent which is then treated with carbon dioxide. This reaction works well for both aliphatic and aromatic Grignard reagents.

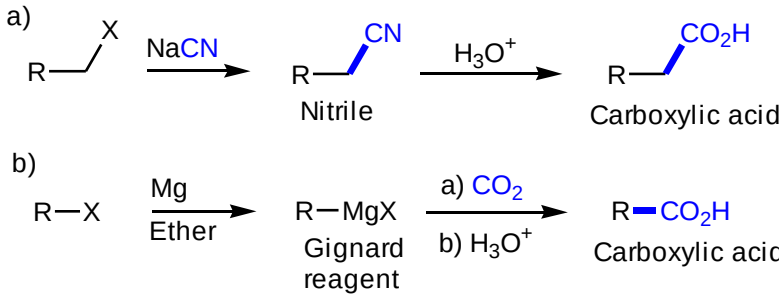


Figure 71 Extending an alkyl halide by one carbon unit.

App 5.11.2 Carboxylic acids from diethyl malonate
Diethyl malonate can be alkylated or dialkylated to provide straight chain or branched chain esters which can then be hydrolysed and decarboxylated to carboxylic acids (Fig. 72a&b). This is also a method of synthesising the corresponding esters and is covered in appendix 5.16.1.

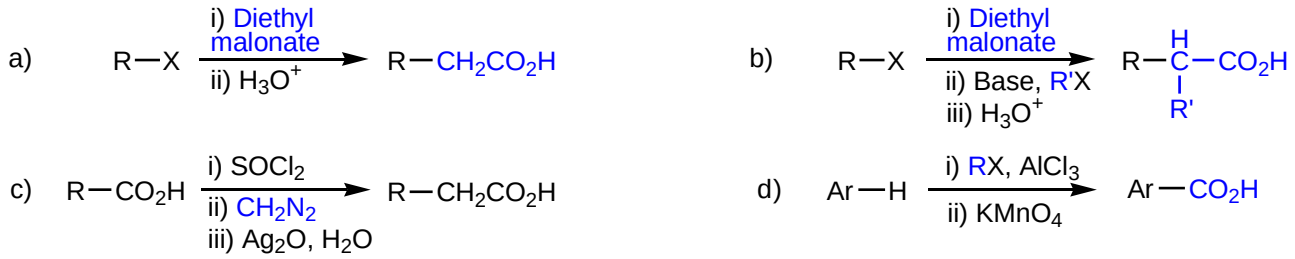


Figure 72 Synthesis of carboxylic acids.

App 5.11.3 Carboxylic acids from the Arndt-Eistert reaction

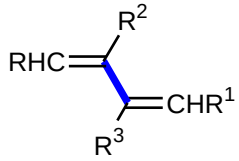
Carboxylic acids can be extended by one carbon unit using the Arndt-Eistert reaction (Fig. 72c). This is also used to prepare esters (appendix 5.16.3).

App 5.11.4 Aromatic carboxylic acids

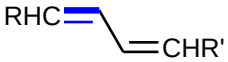
Carboxylic acids cannot be added directly to aromatic rings, and so it is necessary to add a different group to the ring that can subsequently be converted to the carboxylic acid by functional group transformation. For example, a methyl group can be added directly to the ring by Friedel Crafts alkylation then oxidised (Fig. 72d).

App 5.12 Dienes (conjugated)

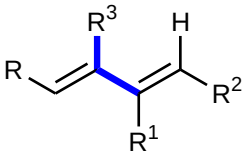
Conjugated dienes can be synthesised by functional group transformations (appendix 1.20) or by carbon-carbon bond formations involving vinyl halides, organocuprate reagents, and organoboronic acids (Fig. 73).

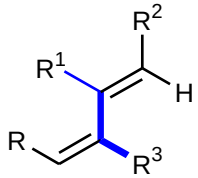


From vinyl halides,alkenyl organometallics, alkenes, alkynes, chloroalkynes, epoxides (sections 5.12.1,5.12.3-5.12.4).

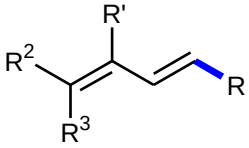


From aldehydes, ketones, α,β-unsaturated aldehydes, allylic halides and alkyl halides (section 5.12.2)





From dibromoalkenes and alkylzinc reagents (section 5.12.1)



From dienolphosphates and Grignard reagents (section 5.12.5).

Figure 73 C-C Bond formations in the synthesis of conjugated dienes.

App 5.12.1 Conjugated dienes from vinyl halides or vinyl tosylates

Dienes can be synthesised by treating vinyl halides with alkenylcopper reagents, as long as zinc bromide and a catalytic amount of $Pd(PPh_3)_4$ is present (Fig. 74a). The reaction preserves the stereochemistry of both alkenes used in the reaction.

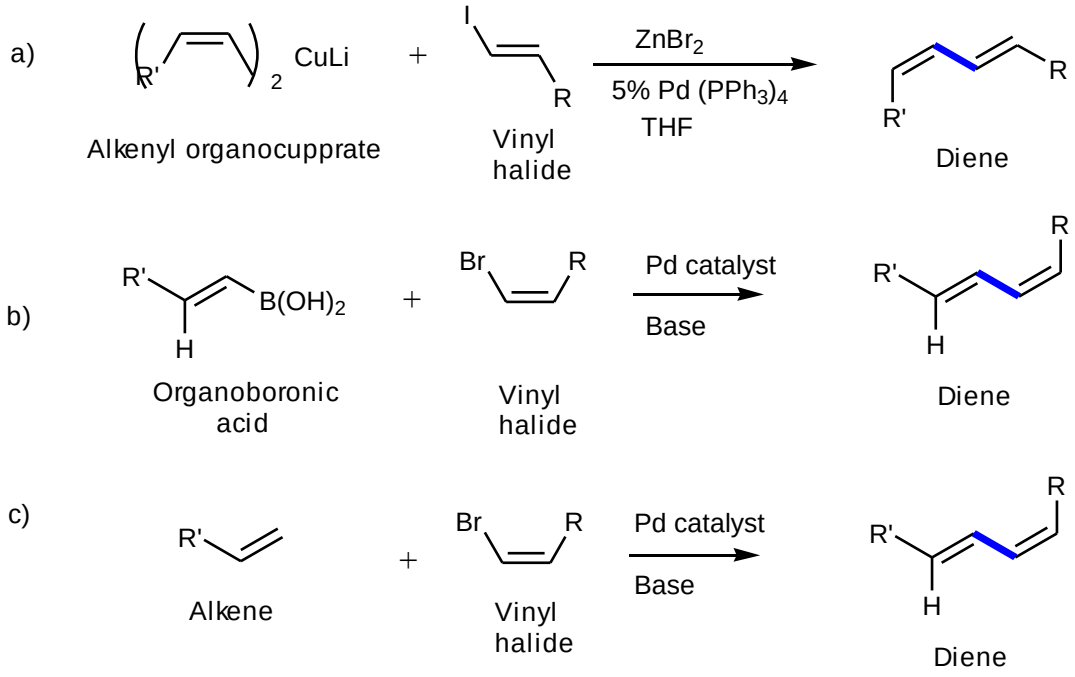


Figure 74 Synthesis of dienes from vinyl halides.

An alternative method of converting vinyl halides to conjugated dienes is to use the Suzuki reaction, which involves reacting the vinyl halide with a vinyl organoboronic acid in the presence of palladium as a catalyst (Fig. 74b). The stereochemistry of the alkenes in both reactants is preserved in the product. The Heck reaction can also be used to generate conjugated dienes, by reacting vinyl halides or vinyl tosylates with alkenes in the presence of a palladium catalyst (Fig. 74c).

1,1-Dibromo-1-alkenes have served as starting materials for a two-stage process leading to conjugated dienes (Fig. 75). The dibromo alkene is first alkenylated to form a bromo diene. Reaction with an alkylzinc reagent then replaces the surviving bromine substituent with an alkyl substituent. The stereochemistry of the reaction is dependent on the type of palladium catalyst used. With $Pd(PPh_3)_4$, an inversion takes place at the reaction centre, whereas the stereochemistry is retained if $Pd(^tBu_3P)_2$ is used.

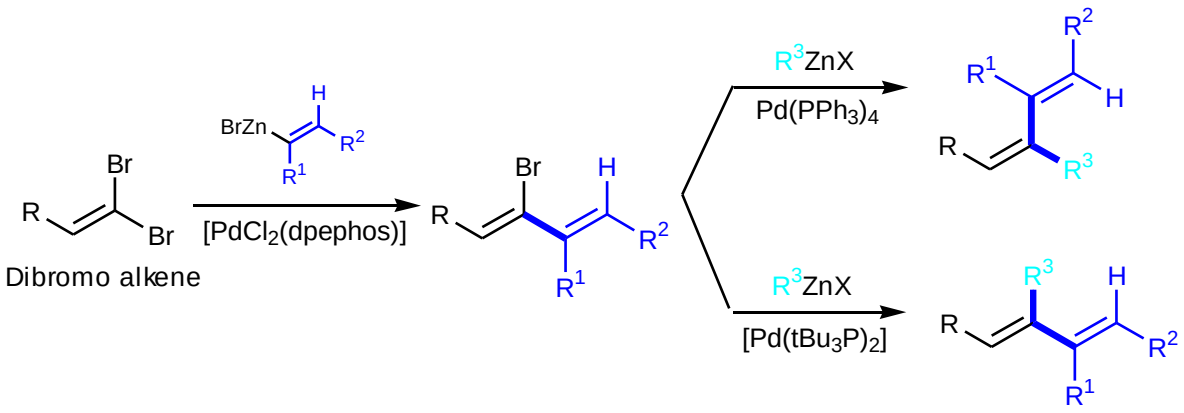


Figure 75 Synthesis of dienes from a dibromo alkene.

App 5.12.2 Synthesis of dienes from aldehydes, ketones and allylic halides

Conjugated dienes can be synthesised by reacting aldehydes or ketones with a Wittig reagent derived from an allylic halide (Fig. 76a). The negative charge in the Wittig reagent is stabilised by the neighbouring alkene group and this favours the *E*-stereochemistry in the newly formed alkene group. The stereochemistry of the alkene in the Wittig reagent is preserved. However, side products may be formed as a result of the Wittig reagent reacting at the γ-carbon instead of the α-carbon.

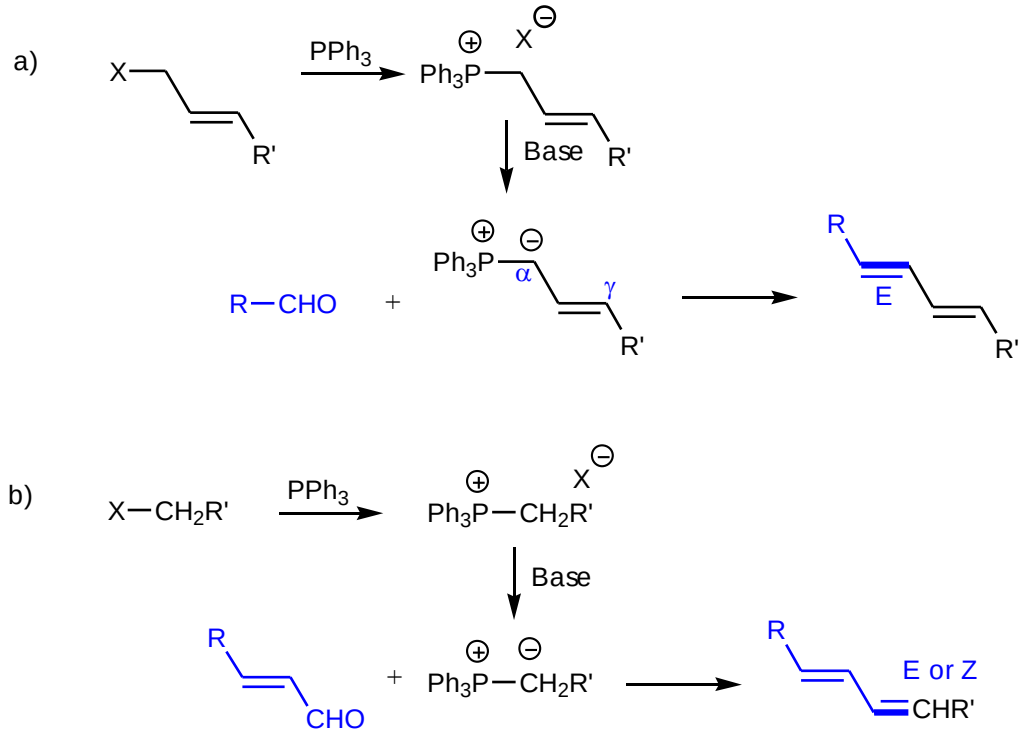


Figure 76 Synthesis of dienes from allylic halides, aldehydes and ketones.

An alternative approach is to react an α,β-unsaturated aldehyde with a phosphorane derived from an alkyl halide(Fig. 76b). The stereochemistry of the newly formed alkene may be E or Z depending on whether the phosphorane is stabilised or unstabilised.

App 5.12.3 Synthesis of dienes from chloro alkynes and alkynes

A *trans,trans*-diene can be synthesised by linking a chloro alkyne with an alkyne using organoborane chemistry (Fig. 77). The chloro alkyne is reacted with t-hexylborane to give an alkenyl borane, which is then added to the other alkyne. Treatment with sodium methoxide results in the two alkenyl groups being linked together, then acid treatment releases the diene. An alternative work up generates an α,β−unsaturated ketone instead (appendix 5.27.10).

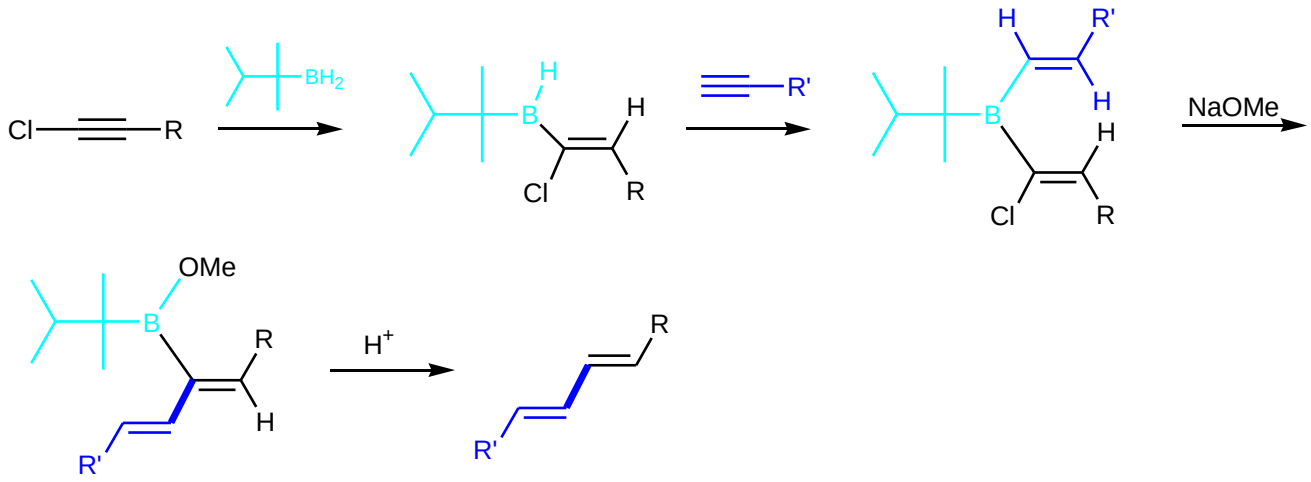


Figure 77 Synthesis of dienes from a chloroalkyne and an alkyne.

A different approach involves treating one alkyne with Schwartz's reagent to give a vinyl zirconium structure (Fig. 78). This is treated with methyl lithium or methyl magnesium bromide, followed by the second alkyne. Treatment with acid then releases the diene.

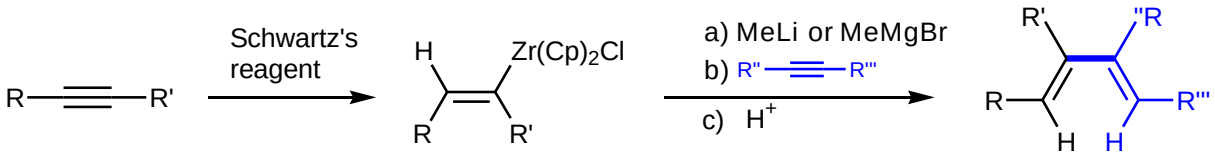


Figure 78 Synthesis of dienes from two alkynes.

App 5.12.4 Synthesis of dienes from epoxides and alkenyl lithium reagents

The reaction of epoxides with alkenyl lithium reagents in the presence of a sterically hindered base has been effective in generating dienes (Fig. 79). The reaction is a reductive alkylation and is similar to that described in section 5.3.5 for the synthesis of alkenes.

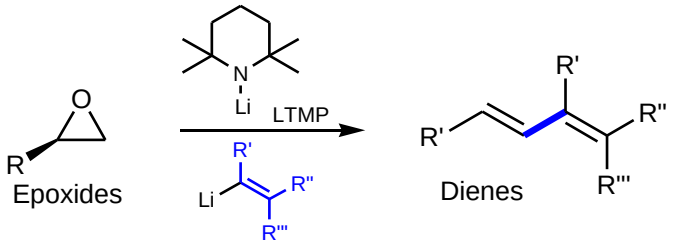


Figure 79 Synthesis of dienes from an epoxide and organolithium reagent.

App 5.12.5 Coupling a conjugated diene with a Grignard reagent

It is possible to couple dienol phosphates with Grignard reagents in the presence of an iron catalyst ($Fe(acac)_3$). The reaction has proved useful in preparing terminal conjugated dienes (Fig. 80). The reaction is stereoselective with the alkyl group adding to the alkene group at the *trans*-position.

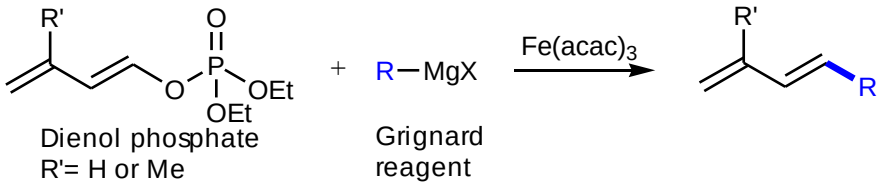


Figure 80 Synthesis of terminal conjugated dienes.

The reaction also works with a number of other conjugated dienol phosphates (Fig. 81).

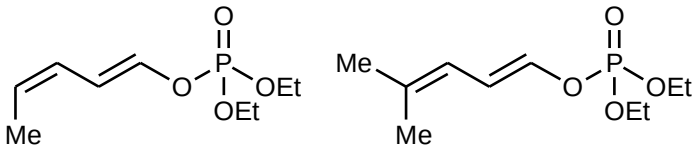


Figure 81 Other dienol phosphates that act as substrates.

App 5.13 Diketones

The synthesis of diketones by functional group transformation is described in appendix 1.22. Diketones can also be prepared by carbon-carbon bond formations (Fig. 82). A number of these are described in the following sections.

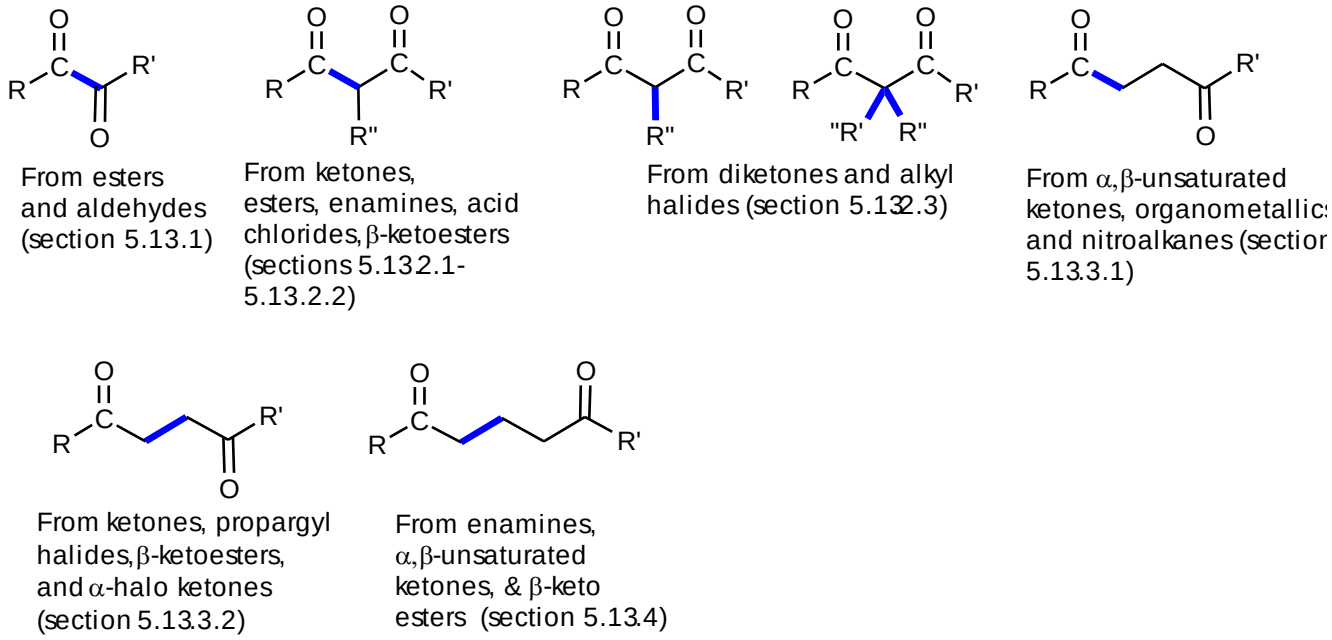


Figure 82 Diketones as a result of carbon-carbon bond formation.

App 5.13.1 Synthesis of 1,2-Diketones

1,2-Diketones can be synthesised from an ester and an aldehyde if the aldehyde is first converted to a 1,3-dithiane (Fig. 83). The dithiane can be deprotonated with base, then acylated with the ester. Oxidative hydrolysis then gives the diketone.

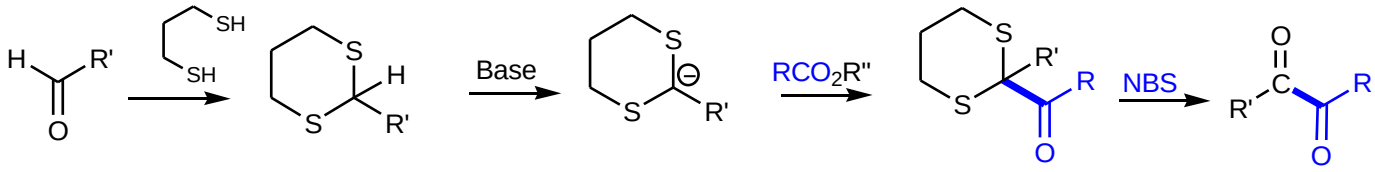


Figure 83 Synthesis of 1,2-diketones from aldehydes and esters

App 5.13.2 Synthesis of 1,3-Diketones

App 5.13.2.1 Condensation of a ketone with an ester

A limited number of β-diketones (1,3-diketones) can be synthesized from the condensation of an enolisable ketone with a non-enolisable ester (Fig. 84) in a mixed Claisen condensation. Reaction of the ketone with base generates an enolate ion which then reacts with the ester by a nucleophilic substitution reaction to give a stabilised enolate. Treatment with acid then generates the diketone. The reaction works best with ketones that can only form the one enolate - such as aromatic or symmetrical ketones. This avoids the problem of different products arising from two possible enolates. It is also advisable to use an ester which cannot form an enolate; for example an aromatic ester. This avoids the problem of a competing Claisen condensation between two esters (see appendix 5.21.2.1). Having said that, successful reactions have been carried out using ethyl acetate.

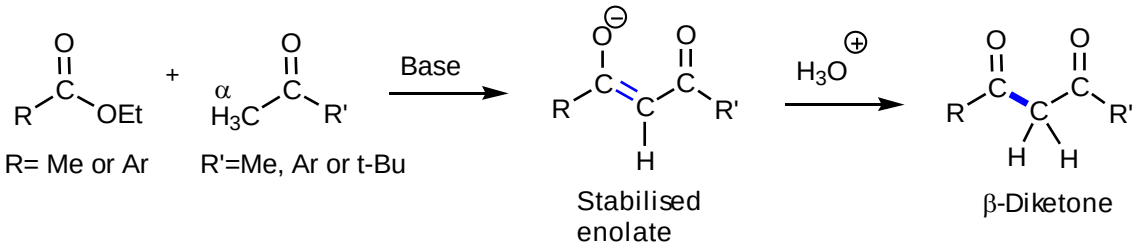


Figure 84 Mixed Claisen condensation between an ester and a ketone.

There is also the possibility that the ketone could react with itself in an Aldol reaction (appendices 5.18.1) but the product from this reaction is less stable than the product from the mixed Claisen condensation, since the latter reacts with base to form a stabilised enolate ion. Moreover, the Aldol reaction is reversible and so the reaction is shuttled towards the Claisen product.
To conclude, the condensation reaction is best carried out with an aromatic or acetate ester, and a methyl ketone that can only form a single enolate ion.

App 5.13.2.2 Synthesis of 1,3-diketones from ketones or β-keto esters with acid chlorides
Another approach to 1,3-diketones is to convert the ketone to an enamine by treating it with a secondary cyclic amine such as piperidine, morpholine or pyrrolidine in the presence of a catalytic amount of *para*-toluenesulphonic acid (ptsa) (Fig. 85a). Water is formed as a by product and is removed by heating the reaction to reflux such that an azeotrope is formed between the solvent and the water. The water content can be removed by collecting it in a Dean and Stark apparatus or absorbing it onto molecular sieves in a soxhlet apparatus. Once the enamine is formed, it is acylated with an acid chloride, then hydrolysed to give the diketone.

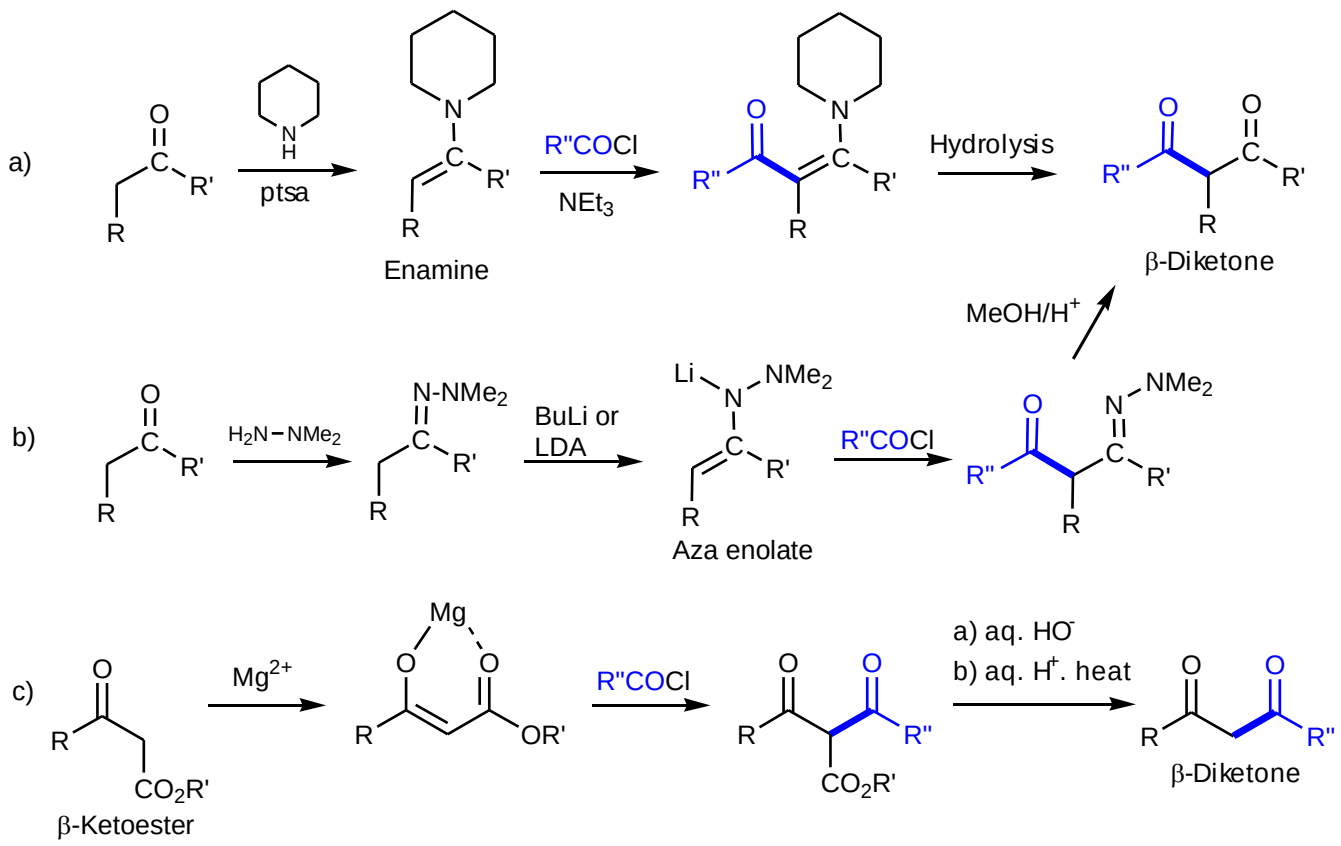


Figure 85 Synthesis of 1,3-diketones from ketones and acid chlorides.

Alternatively, the ketone can be converted to a hydrazone. This is then treated with base to form an aza-enolate, which can be acylated with an acid chloride. The product can then be hydrolysed under mild conditions to the diketone product (Fig. 85b).
It is also possible to acylate a β-ketoester with an acid chloride via a magnesium enolate (Fig. 85c). The magnesium chelates the oxygens and prevents O-acylation.

App 5.13.2.3 Alkylation of β-diketones

The methylene moiety between the carbonyl groups of a 1,3-diketone contains protons that are acidic enough to be deprotonated with a base such as sodium hydroxide or sodium carbonate. The carbanion that is formed can be alkylated with an alkyl halide, then deprotonated again to react with a different alkyl halide (Fig. 86). Alkylation is possible using primary and secondary alkyl halides, allylic halides and benzylic halides. However, a significant side reaction can be O-alkylation. Tertiary alkyl halides tend to eliminate to alkenes under basic conditions, but it may be possible to alkylate the diketone under non-basic conditions if the alkyl halide is converted to a carbocation in the presence of a Lewis acid.

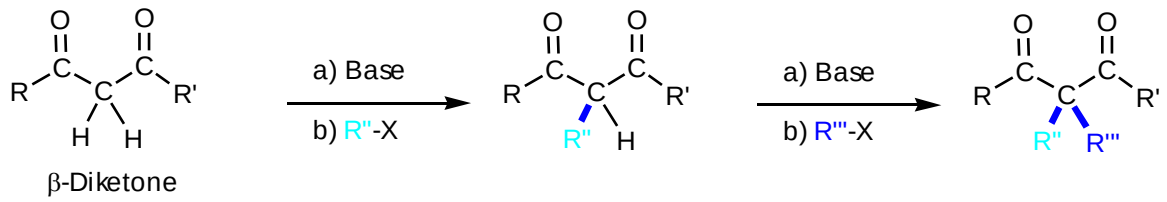


Figure 86 Alkylation of β-diketones.

App 5.13.3 Synthesis of 1,4-Diketones

App 5.13.3.1 From α,β-unsaturated ketones

It would be nice to create 1,4-diketones by adding an acyl anion to an α,β-unsaturated ketones in a 1,4-conjugate addition reaction (Fig. 87). However, it is impossible to generate an acyl anion since the carbonyl carbon is electrophilic in nature. Therefore, an acyl anion is an example of umpulong (chapter 3.4) - a structure which has an unnatural charge. To get round this problem, it is better to add a group which is naturally nucleophilic and then convert it to the ketone group by functional group transformations. The reagents concerned could, therefore, be viewed as providing a 'masked' acyl anion. There are several reagents that can be used for this purpose.

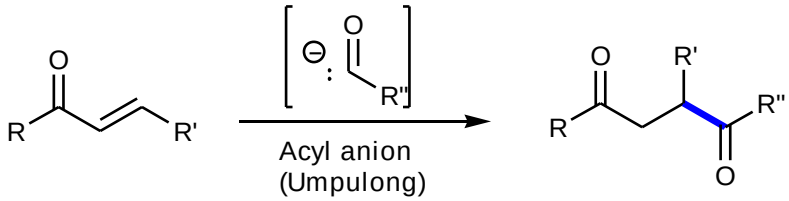


Figure 87 1,4-Diketones from an α,β-unsaturated ketone and an acyl anion equivalent (umpulong).

For example, reaction of the α,β-unsaturated ketone with an alkenyl organocuprate reagent provides a vinyl ether, which can be treated with acid to generate the diketone (Fig. 88a). 1,4-Diketones can also be synthesised by reacting the α,β-unsaturated ketone with an organolithium compound in the presence of $Ni(CO)_4$ (Fig. 88b), or with a organocuprate reagent in the presence of carbon monoxide. Alternatively, the α,β-unsaturated ketone can be reacted with a carbanion generated from a nitroalkane (Fig. 88c). The nitro group is a strong electron-withdrawing group, and so a relatively weak base can be used to remove a proton from the carbon that is α to the nitro group. Once the nitroketone has been formed, it can be treated with titanium trichloride to convert the nitro group to an imine, which can then be hydrolysed to a ketone group.

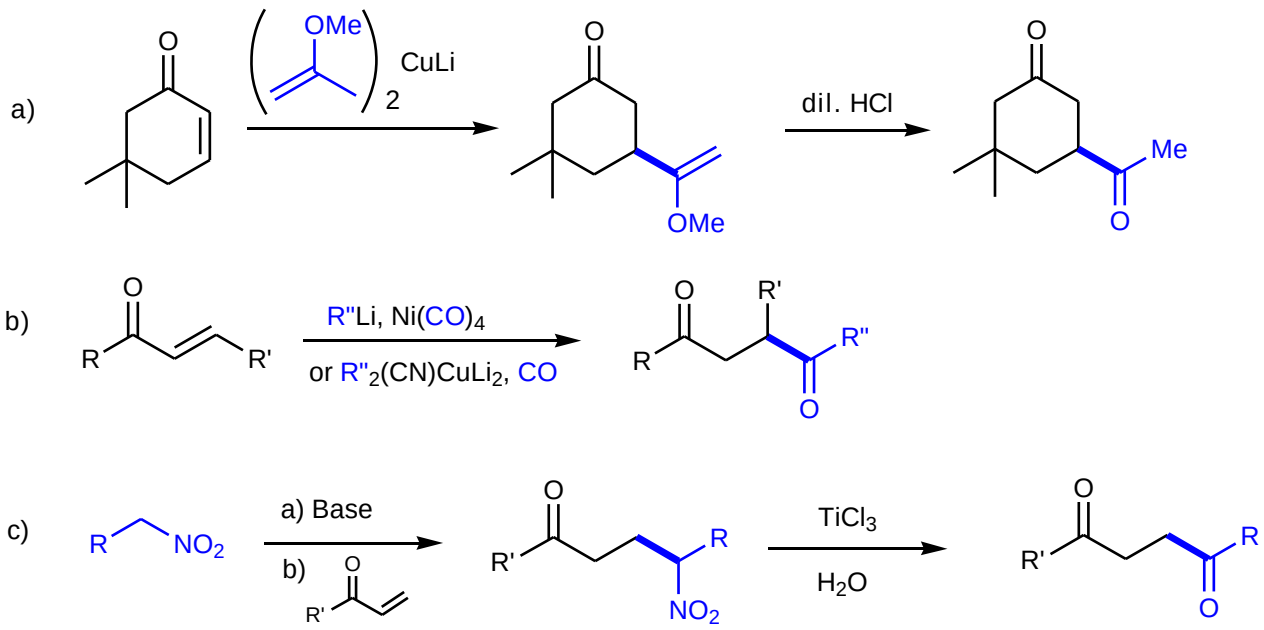


Figure 88 Methods of synthesising 1,4-diketones from an α,β-unsaturated ketone.

App 5.13.3.2 From ketones and β-keto esters

Treatment of a methyl ketone with base generates a carbanion which can be alkylated with a propargyl halide (Fig. 89a). The resulting alkyne group can then be hydrolysed to a ketone in the presence of a mercury salt as catalyst.

Alternatively, the ketone can be converted to an enamine then reacted with an α-halo ketone (Fig. 89b). A different method having the same result would be to treat a β-keto ester with the halo ketone (Fig. 89c). Hydrolysis and decarboxylation then generates the diketone.

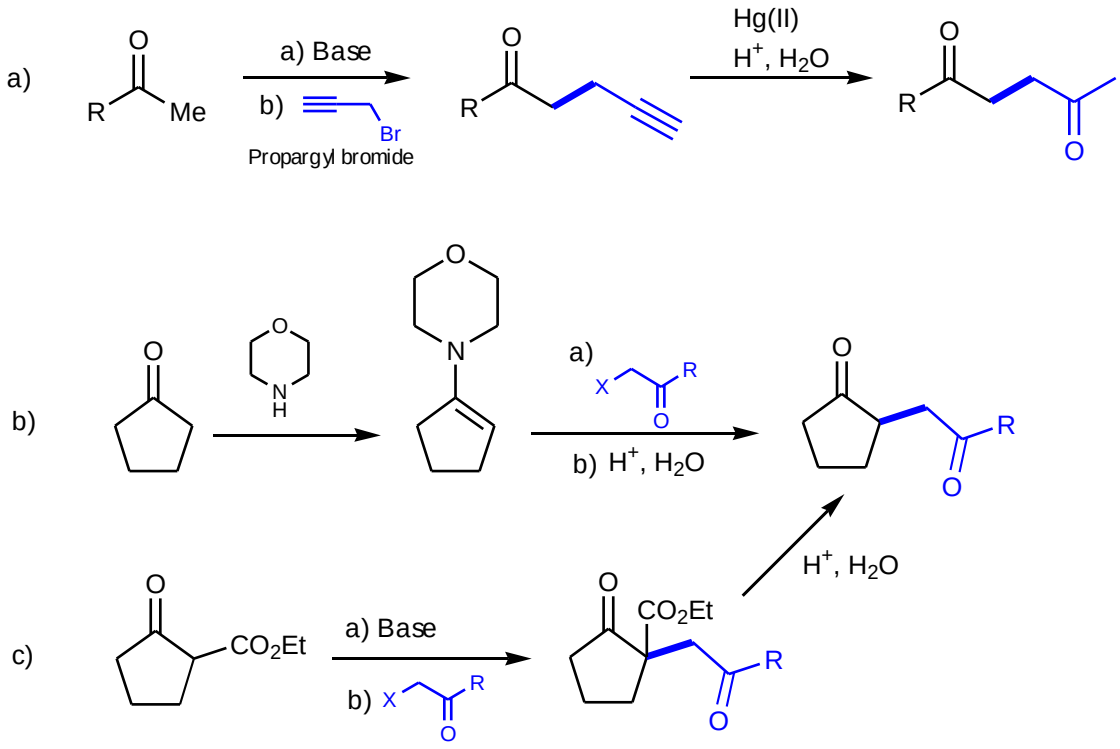


Figure 89 Synthesis of 1,4-diketones from ketones and β-keto esters.

App 5.13.4 Synthesis of 1,5-Diketones

1,5-Diketones can be synthesised by carrying out a Michael reaction on an α,β-unsaturated ketone with a carbanion generated from a β-keto ester. Treatment of the β-keto ester with a base generates a carbanion on the carbon between the two carbonyl groups (Fig. 90a). A relatively mild base can be used for this because of the influence of the two carbonyl groups increasing the acidity of the protons on the α-carbon. Once the carbanion has been formed, it is treated with the α,β-unsaturated ketone. A Michael reaction take place where the carbanion undergoes a 1,4-conjugate addition to the α,β-unsaturated ketone. The ester activating group is then removed by hydrolysis and decarboxylation to give the 1,5-diketone.

Enamines can also be reacted with α,β-unsaturated ketones in the Michael reaction to produce 1,5-diketones (Fig. 90b).

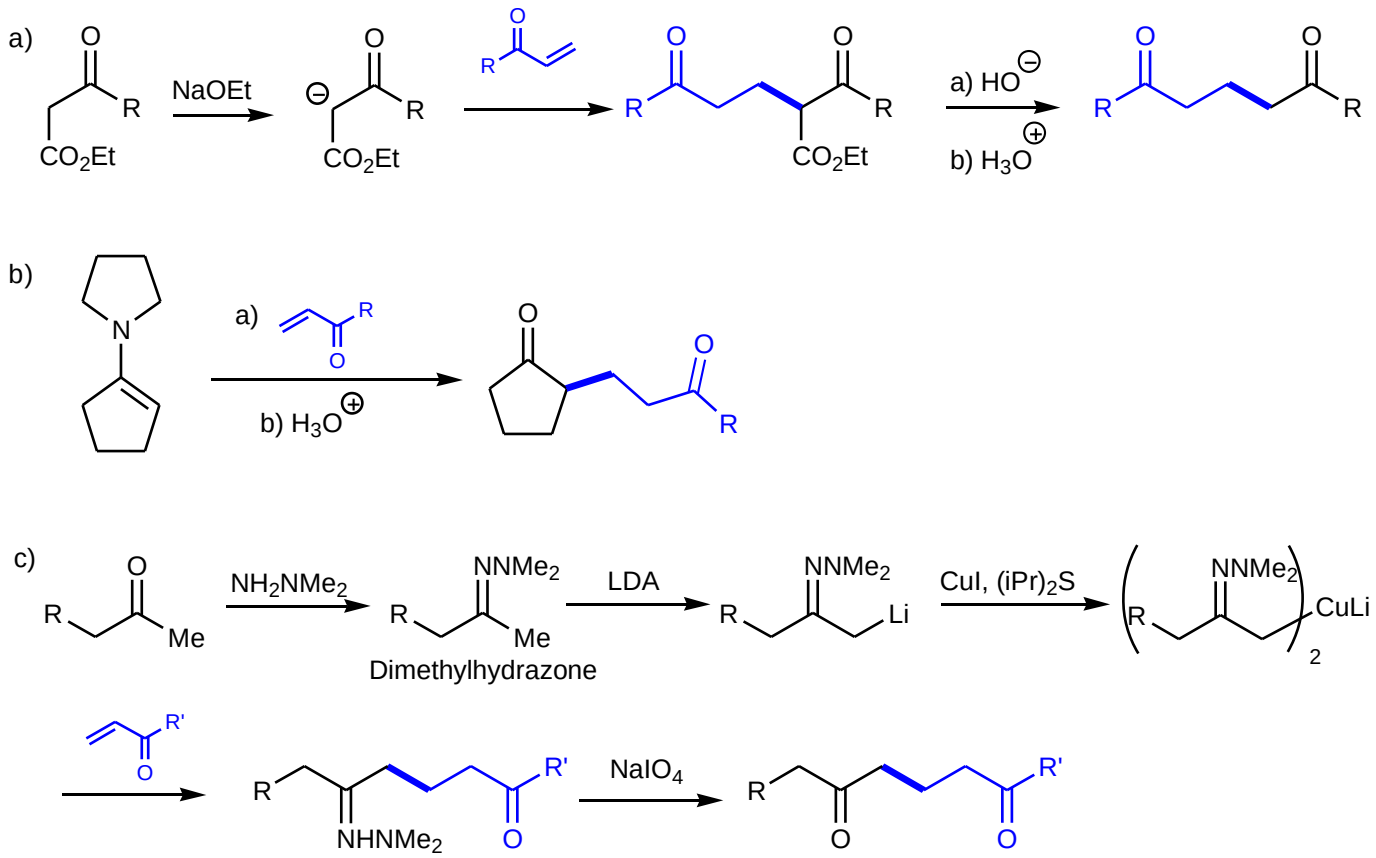


Figure 90 Synthesis of 1,5-diketones.

A third method is to convert a ketone into a dimethylhydrazone, which is treated with a strong base such as lithium diisopropylamide (LDA) to produce a carbanion at the less substituted position (Fig. 90c). This is then converted to a cuprate reagent which undergoes the Michael addition with the α,β-unsaturated ketone. The hydrazone group is finally removed under oxidative conditions.

App 5.14 Diols

Methods of synthesising diols by functional group transformations are given in appendix 1.23. A number of methods of synthsising diols by C-C bond formation are also used for particular patterns of diols (Fig. 91).

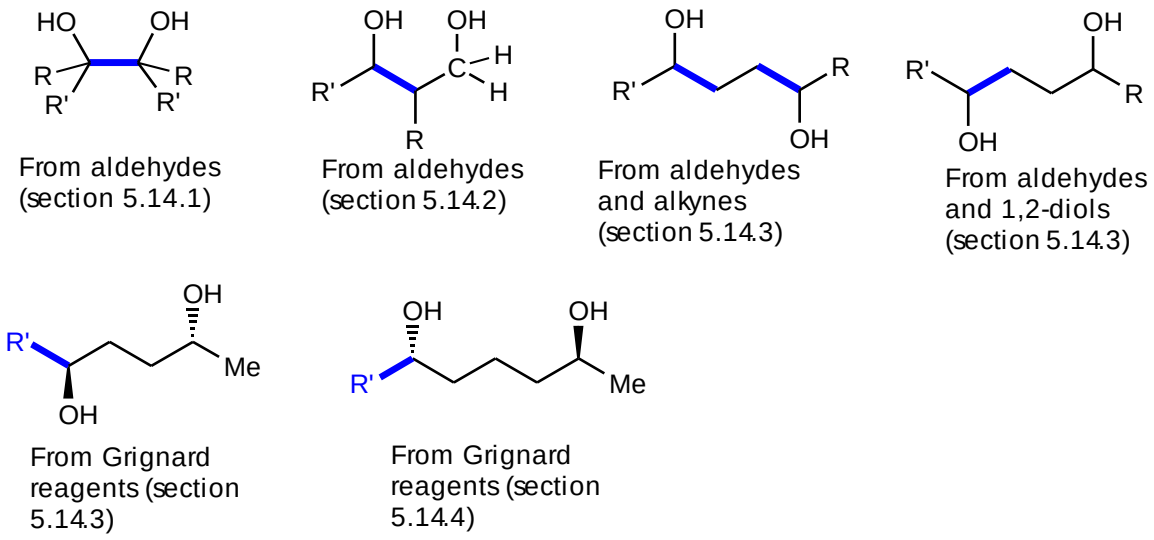


Figure 91 Methods of preparing diols by C-C bond formation.

App 5.14.1 Synthesis of 1,2-Diols

Symmetrical diols are possible from ketones using the Pinacol reaction (Fig. 92). This reaction involves a radical mechanism and works for most ketones. The acyloin reaction used for cyclisation has a similar mechanism.

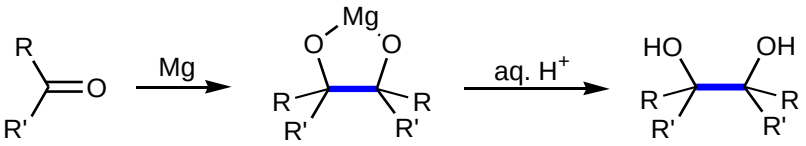


Figure 92 The Pinacol reaction.

App 5.14.2 Synthesis of 1,3-Diols

1,3-diols can be obtained by reducing β-hydroxyaldehydes (Fig. 93). These, in turn, can be obtained from aldehydes by the Aldol reaction (appendix 5.18.1).

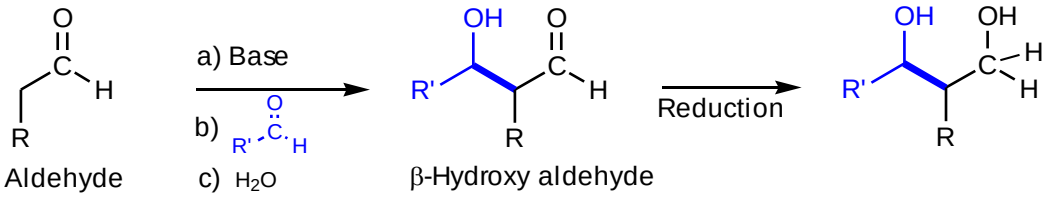


Figure 93 Synthesis of 1,3-diols via the Aldol reaction.

App 5.14.3 Synthesis of 1,4-Diols

1,4-Diols are found in a variety of natural products that are currently being studied as lead compounds for novel anticancer and antibacterial agents.

App 5.14.3.1 From acetylene and aldehydes

The 1,4-diols can be obtained by the reduction of γ-hydroxy ketones, but it is also possible to build the diol structure from acetylene and different aldehydes. Acetylene is treated with base to form an acetylide ion which undergoes an Aldol addition with an aldehyde structure. The process can be repeated and the resulting disubstituted alkyne is reduced by hydrogenation (Fig. 94).

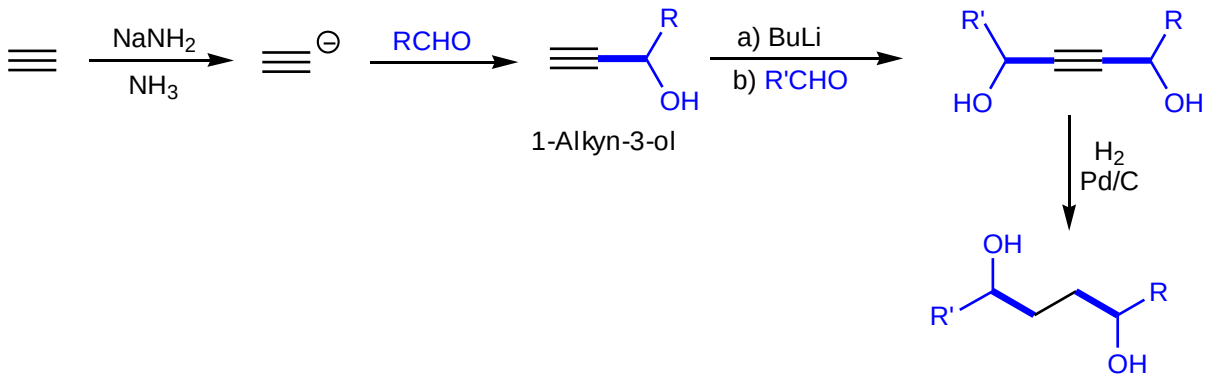


Figure 94 Synthesis of 1,4-diols from acetylene and aldehydes

App 5.14.3.2 From 1,2-diols and aldehydes via the Wittig reaction

The Wittig reaction can be used to create the required skeleton of a 1,4-diol from a 1,2-diol and an aldehyde (Fig. 95). The 1,2-diol is selectively tosylated such that the primary alcohol group reacts and not the secondary alcohol. The tosylate is then substituted with triphenylphosphine and treated with base to give the Wittig reagent, which can be reacted with an aldehyde. The resulting structure contains a double bond which can be reduced to give the 1,4-diol.

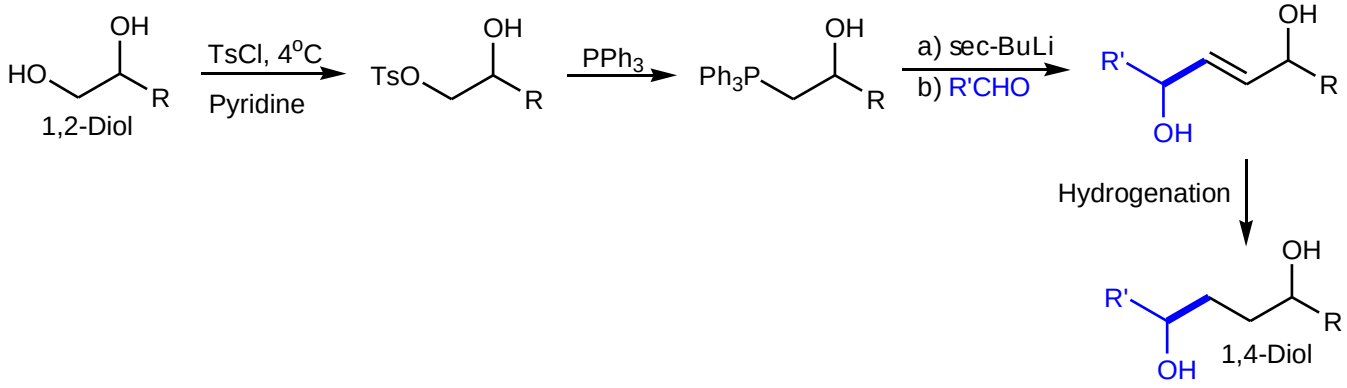


Figure 95 Synthesis of 1,4-diols from 1,2-diols and aldehydes via a Wittig reaction.

App 5.14.3.3 From conjugated dienes

A method of generating 1,4-diols through a similar unsaturated intermediate has been derived from a conjugated diene, where the diene is first epoxidised (Fig. 96). The epoxides are then ring opened using titanocene(III) chloride.

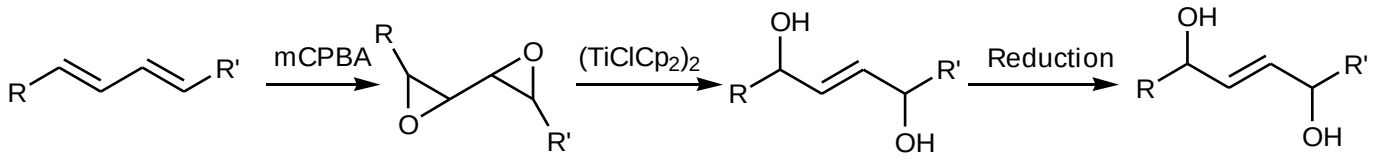


Figure 96 Synthesis of 1,4-diols from conjugated dienes.

App 5.14.3.4 From an ene acetal and Grignard reagents

Another approach which has been used to generate 1,4- and 1,5-diols is to take an ene acetal and treat it with an iodinating agent ($(collidine)_2ClO_4$ or $I(collidine)_2PF_6$) to induce a rearrangement reaction (Fig. 97). Reaction with a Grignard reagent displaces the ether substituent and introduces an alkyl group with retention of stereochemistry. Finally, the diol masking group is removed to give the 1,4-diol.

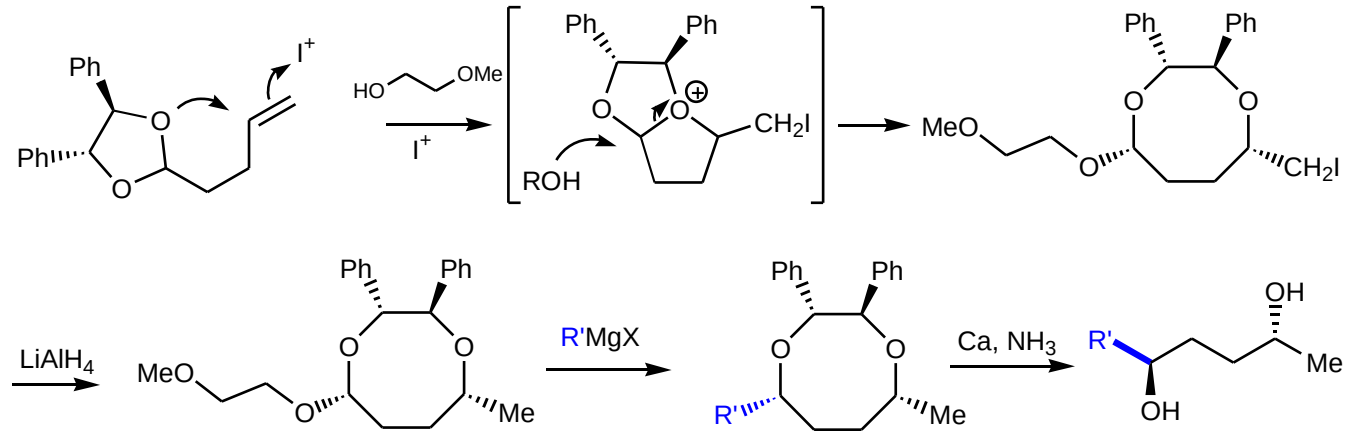


Figure 97 Synthesis of 1,4-diols from an ene acetal and Grignard reagents.

App 5.14.4 Synthesis of 1,5-Diols

1,5-Diols are present in a number of natural products which have interesting antifungal, antibacterial and antimalarial activity. They can be synthesised from an ene acetal in a similar manner to that described for the synthesis of 1,4-diols above (Fig. 98).

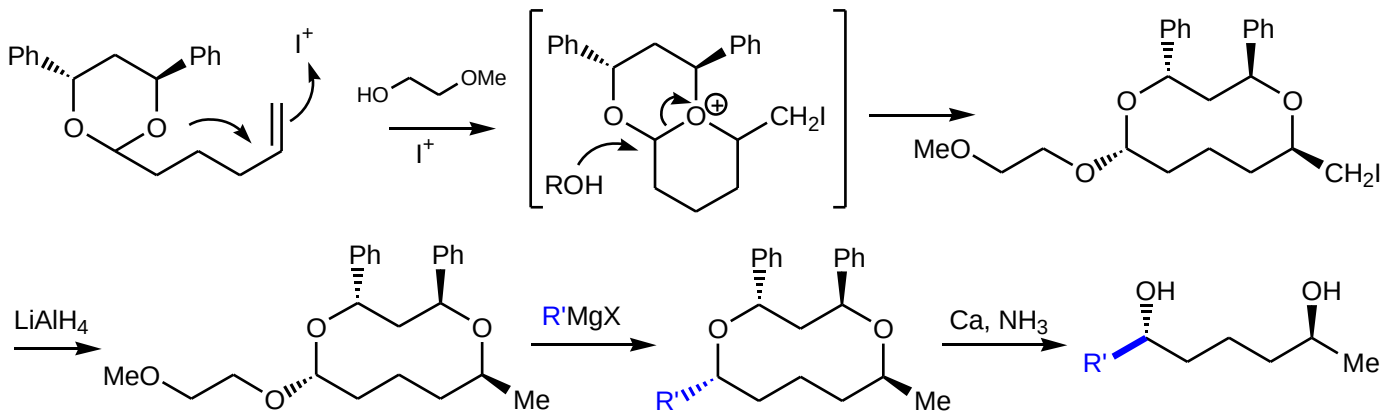


Figure 98 Synthesis of 1,5-diols from an ene acetal and Grignard reagents.

App 5.15 Epoxides

Epoxides can be generated by functional group transformations of alkenes (appendix 1.26). It is also possible to synthesise them through a carbon-carbon bond formation by reacting an aldehyde or a ketone with a sulphur ylide (Fig. 99). The sulphur ylide undergoes a nucleophilic addition with the carbonyl group to form a tetrahedral intermediate containing a very good thioether leaving group. Further reaction involves ring closure to form the epoxide with loss of the thioether leaving group.

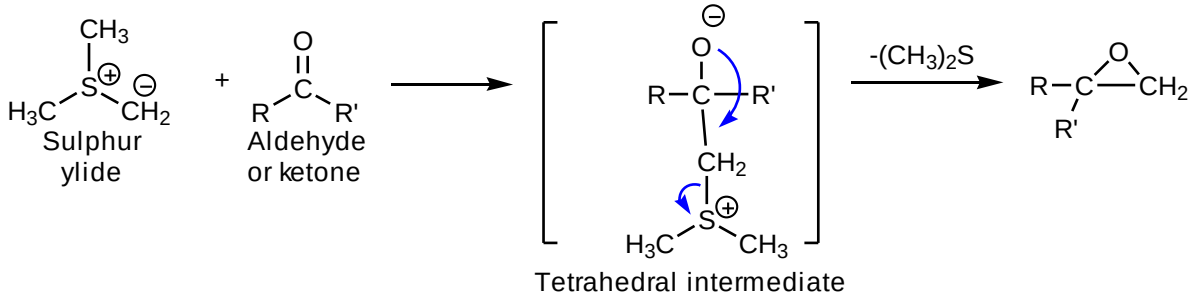


Figure 99 Reaction of aldehydes and ketones with sulphur ylides.

A number of other sulphur ylids have been used in this reaction to produce trisubstituted epoxides. For example, epoxides with an aromatic substituent have been prepared (Fig. 100).

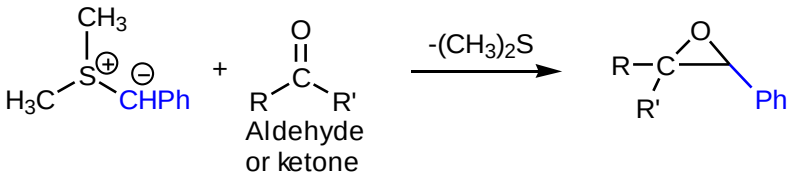
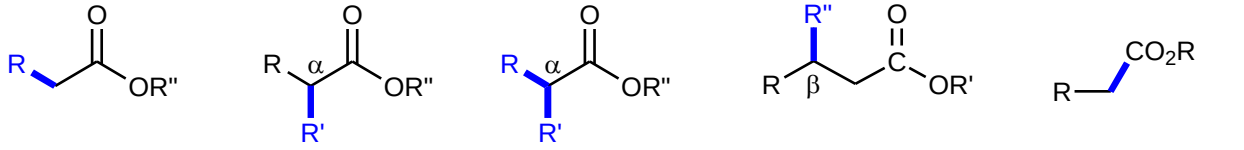


Figure 100 Synthesis of epoxides with an aromatic substituent.

App 5.16 Esters

Methods of synthesising esters by functional group transformations were described in appendix 1.27. It is also possible to synthesise esters by a number of carbon-carbon bond formations involving esters, α,β-unsaturated esters, or carboxylic acids (Fig. 101).



Alkylation of an ester or diethyl malonate (section 5.16.1)

Alkylation of an ester (section 5.16.1)

Alkylation of diethyl malonate (section 5.16.1)

Alkylayion of an α,β–unsaturated ester (section 5.16.2)

From carboxylic acids (section 5.16.3)

Figure 101 Synthesis of esters by C-C bond formation.

App 5.16.1 Alkylation of esters

Esters with an α-hydrogen can be treated with a strong base to form an enolate ion, which can then be alkylated with an alkyl halide (Fig. 102).

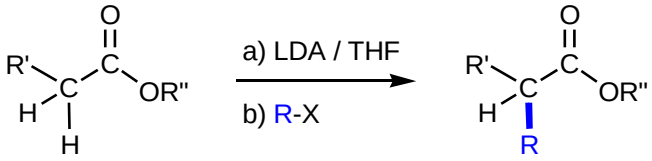


Figure 102 α-Alkylation of esters (LDA=Lithium diisopropylamide).

Although simple esters can be alkylated in this manner, the use of a molecule such as diethyl malonate is far more effective (Fig. 103). This is because the α-protons of diethyl malonate are more acidic (pK_a 10-12) than the α-protons of a simple ester such as ethyl acetate (pK_a 25), and can be removed by a milder base. For example, diethyl malonate is deprotonated by sodium ethoxide, whereas a much stronger base such as lithium diisopropylamide (LDA) is required to deprotonate ethyl acetate. A further point worth noting is that sodium ethoxide is strong enough to totally deprotonate diethyl malonate, such that all the diethyl malonate is converted to the enolate ion. This prevents the possibility of any competing Claisen reaction (see appendix 5.21.2.1) since that reaction requires the presence of unaltered ester.

Diethyl malonate can be treated with one equivalent of sodium ethoxide and alkylated with an alkyl halide, then treated with another equivalent of base and alkylated with a different alkyl halide (Fig. 103). Subsequent hydrolysis and decarboxylation of the diethyl ester results in the formation of a carboxylic acid, which can then be esterified. Therefore, this method is suitable for synthesising a wide range of carboxylic acids and esters.

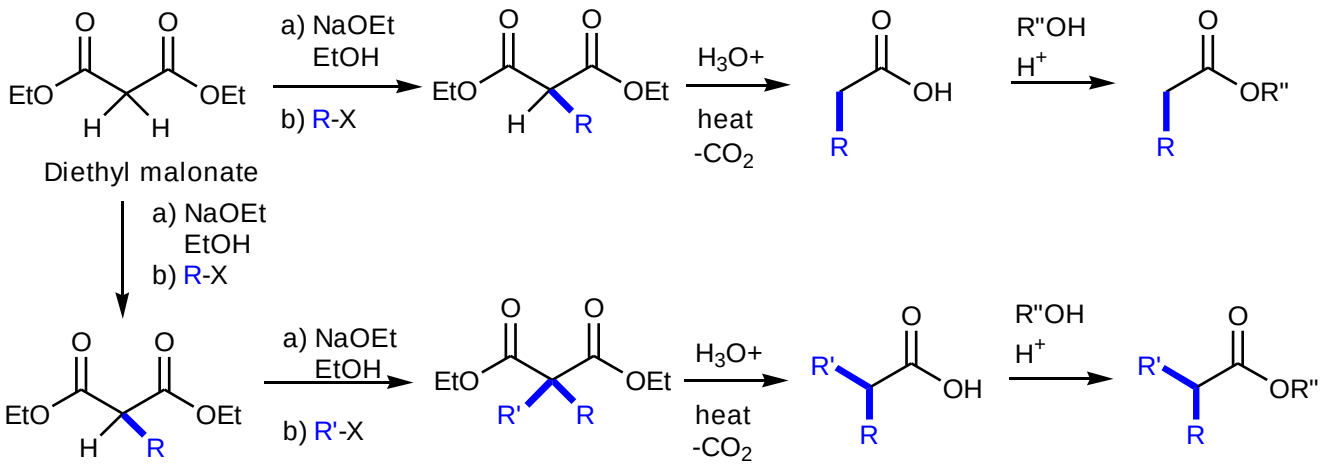


Figure 103 Dialkylation of diethyl malonate.

App 5.16.2 Alkylation of an α,β-unsaturated ester at the β-position

The reaction of an organocuprate reagent with an α,β-unsaturated ester results in the addition of a primary alkyl, vinyl or aryl group to the β-position (Fig. 104). The product no longer has a double bond and is now branched at the β-position. This is known as a 1,4-addition or a conjugate addition reaction. Other reactive functional groups would have to be protected (e.g. alcohols carboxylic acids, epoxides and halides). Only one of the alkyl groups from the organocuprate reagent is added to the unsaturated ester, and so this method is best used when the reagent is cheap or easily available. Alternatively, one can use a mixed organocuprate reagent containing an alkynyl or nitrile substituent. Both of these substituents are relatively unreactive and so an alkyl group is transferred preferentially. α,β-Unsaturated esters are less reactive than α,β-unsaturated aldehydes and ketones in this reaction and the reactions work best when a primary alkyl group is being transferred.

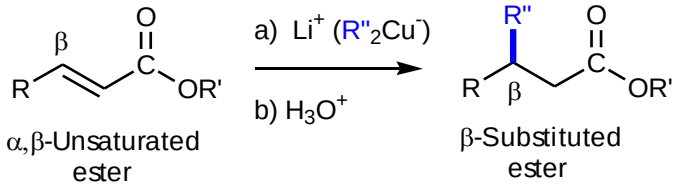


Figure 104 Synthesis of branched esters from α,β-unsaturated esters.

App 5.16.3 The Arndt-Eistert reaction

An aliphatic or aromatic carboxylic acid can be converted to a carboxylic acid or an ester with a 1C extension of the carbon backbone by the Arndt-Eistert reaction (Fig. 105). The carboxylic acid is converted to an acid chloride, then treated with diazomethane to give a diazoketone. Treatment with silver oxide and water results in a rearrangement reaction to form a ketene, which adds a molecule of the solvent to form the carboxylic acid or ester.

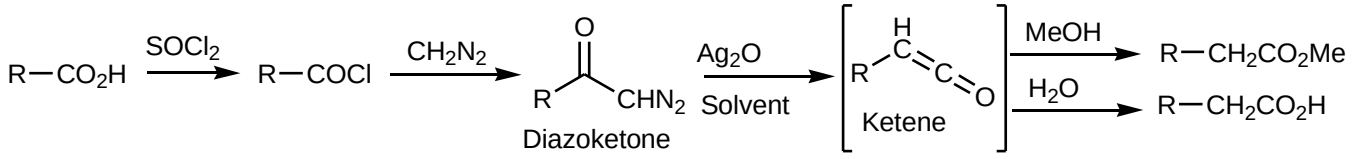


Figure 105 The Arndt-Eistert reaction (R = aliphatic or aromatic substituent).

App 5.17 α-Hydroxy aldehydes and ketones

α-Hydroxy ketones can be synthesised from aldehydes by the benzoin condensation, but only if the aldehyde cannot enolise (Fig. 106a). The reaction is essentially a dimerisation of the original aldehyde, which rather limits its use. The condensation involves nucleophilic addition of the cyanide ion to a carbonyl group to give a cyanohydrin which then ionises and reacts with a second molecule of the aldehyde.

If the cyanohydrin is, instead, reduced with DIBAL, then an α-hydroxy aldehyde is obtained (Fig. 106b&c).

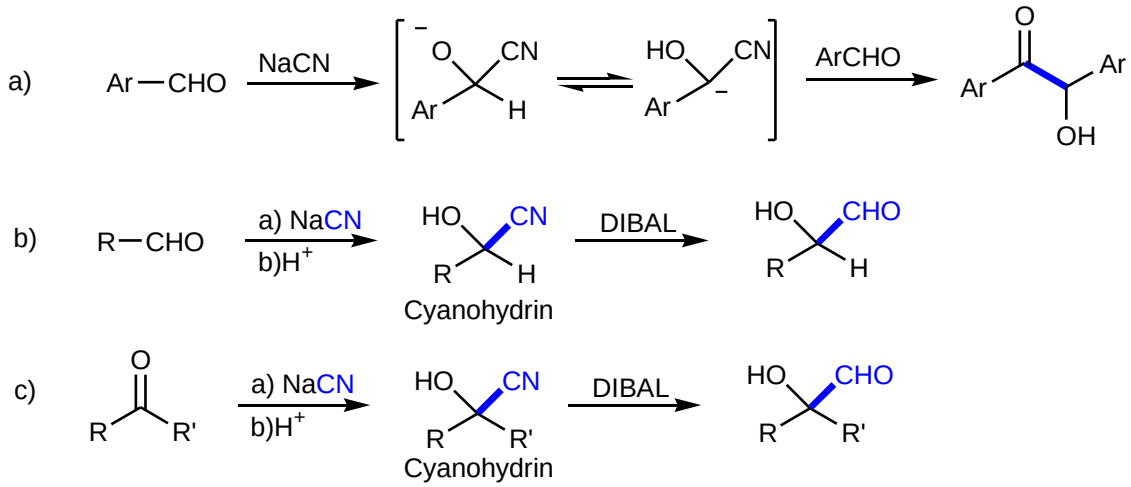


Figure 106 Synthesis of α-hydroxy aldehydes and ketones.

Another approach is to react a ketone with an acyl anion equivalent. For example, treatment of a terminal alkyne with base produces an acetylide ion which can undergo a nucleophilic addition with a ketone. The resulting product can then be hydrolysed in the presence of mercuric ion to give an α-hydroxy ketone (Fig. 107a).

Aldehydes can be converted to a thioketal, which can be deprotonated with base and reacted with aldehydes in a nucleophilic addition reaction. Hydrolysis of the ketal generates an α-hydroxy aldehyde (Fig. 107b).

α-Hydroxyketones are possible by an acyloin reaction in the presence of trimethylsilyl chloride (TMSCl) (Fig. 107c). TMSCl traps the dianion that results from the acyloin reaction and removes the

ethoxide by-product, thus preventing side reactions. Hydrolysis of the silylated product generates the hydroxy ketone.

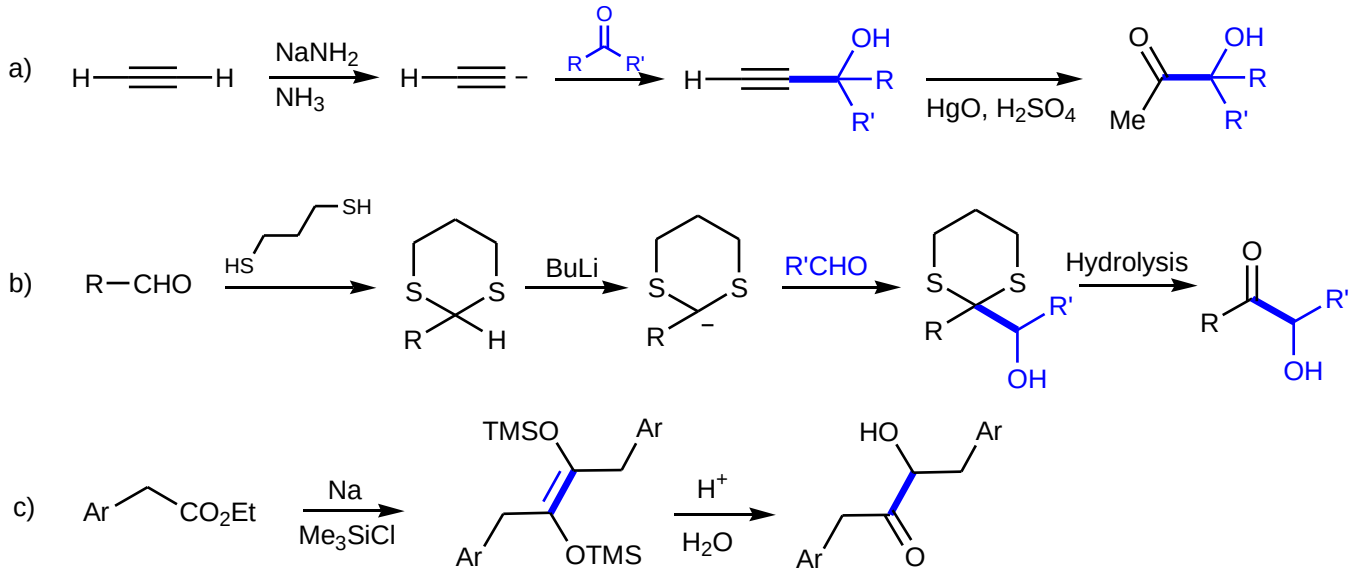


Figure 107 Methods of synthesising α-hydroxy aldehydes and ketones.

App 5.18 β-Hydroxy aldehydes and ketones

App 5.18.1 The Aldol reaction

The Aldol reaction can be carried out on an aldehyde or ketone bearing an acidic proton at the α-carbon. The reaction involves treating the carbonyl structure with a catalytic amount of base, such that only some of the starting material is converted to the enolate ion. Once the enolate ion has been formed, it can undergo a nucleophilic addition with a molecule of unreacted starting material to form the β-hydroxy carbonyl product (Fig. 108). The base is reformed as a result of the addition reaction and so more enolate can be formed to allow the reaction to continue. A weaker base (e.g. sodium hydroxide or sodium ethoxide) is normally used for this reaction than would be needed for the alkylation of an aldehyde or ketone (appendices 5.25 & 5.22.1). The best chances of isolating the β-hydroxy product is from an aldehyde of general structure (RCH_2CHO). With branched aldehydes (R_2CHCHO) and most ketones, the more likely product is an α,β–unsaturated carbonyl structure (appendices 5.25.1 & 5.27.1) due to the stabilisation of the resulting conjugated system. Indeed, the Aldol reaction is a common procedure employed for the synthesis of α,β–unsaturated aldehydes and ketones.

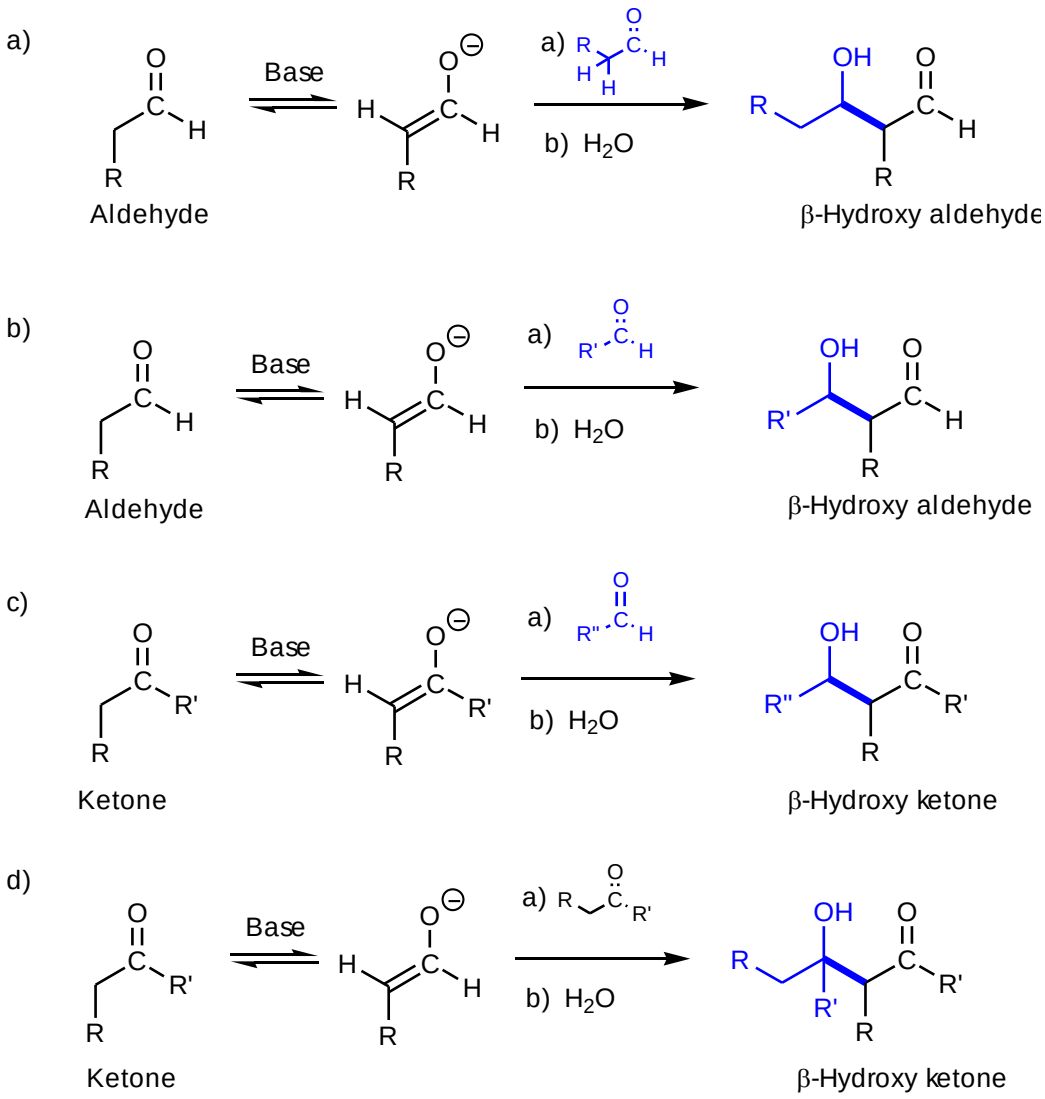


Figure 108 The Aldol reaction.

β-Hydroxy aldehydes are feasible if the Aldol reaction is between two molecules of the same aldehyde (Fig. 108a). It also possible to obtain β-hydroxy aldehydes when two different aldehydes are present in the reaction, as long as one of the aldehydes lacks an α-hydrogen (Fig. 108b). β-Hydroxy ketones are feasible from a ketone and an aldehyde as long as the ketone structure is the only one that can form the enolate. In other words, the aldehyde should have no α-protons (Fig. 108c). The last two types of reaction are known as the **Claisen-Schmidt reaction**. The Aldol reaction between two molecules of the same ketone is not favoured under normal reaction conditions as the equilibrium favours the starting material over the product (Fig. 108d). However, it is possible to carry out the reaction with volatile ketones by heating the solution to reflux such that the ketones pass through a Soxhlet extractor containing the base. A small amount of the hydroxy ketone is then formed and the mixture is siphoned back into the main vessel. The hydroxy ketone has a higher boiling point than the

ketone and so the process can be continued with the desired product gradually building up in the main vessel.
With other combinations of aldehydes and ketones, a mixture of products is likely.
With unsymmetrical ketones capable of forming two different enolates, the reaction is best done by using a preformed enolate as described in the following sections to ensure that the desired product is obtained. These reactions are known as directed Aldol reactions.

App 5.18.2 Crossed Aldol reaction with preformed enolates

A crossed Aldol reaction involves condensation between two different structures such as the enolate of a ketone reacting with an aldehyde. Under the normal conditions used for the Aldol reaction (section 5.18.1), the ketone and the aldehyde are both present along with a base such as sodium hydroxide. However, there is a risk that a mixture of products would be obtained, especially if both the aldehyde and the ketone could form enolates.
This can be avoided by starting with a solution that contains only the ketone, and adding a very strong base such as lithium di-isopropylamide (LDA) at low temperature. A lithium enolate is rapidly formed and all of the ketone is converted to the enolate before any self reaction can occur. The aldehyde can then be added to form a complex which is converted to the enolate of the desired product through a favoured cyclic mechanism (Fig. 109a). The reaction is so effective in linking ketones to aldehydes that it does not rally matter whether the aldehyde can form an enolate ion or not.

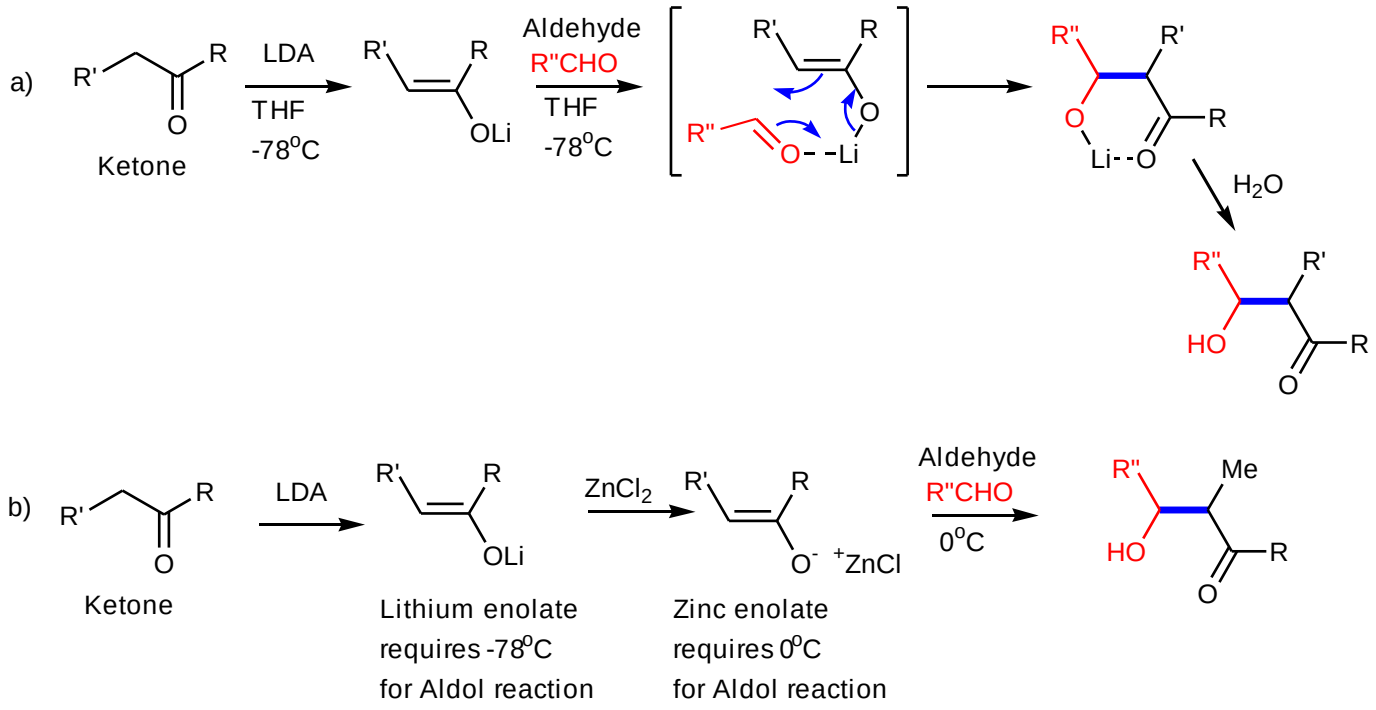


Figure 109 Cross Aldol reaction involving lithium or zinc enolates.

A variant on this method is to convert the preformed lithium enolate to a zinc enolate, then react that with the aldehyde (Fig. 109b). This has the advantage that the reaction can be carried out at 0°C, rather than at -78°C, since the zinc enolate is less reactive.

In both cases, a β-hydroxy ketone may be obtained, whereas the unsaturated product is obtained under normal Aldol reaction conditions. This is because the enolate product forms a chelate with the lithium or zinc ion.

App 5.18.3 Crossed Aldol reaction with a TMS ether

A ketone with an α-proton can be converted to a trimethylsilyl enol ether, which on treatment with a Lewis acid, such as $TiCl_4$, reacts with an aldehyde or ketone to form a β-hydroxy ketone (Fig. 110). The advantage of this approach is the lack of any base in the reaction, which ensures that the second carbonyl structure cannot form an enolate.

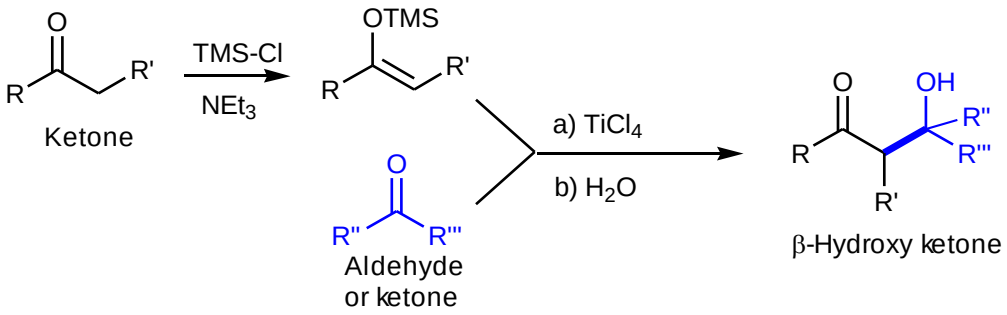


Figure 110 Crossed Aldol condensations with TMS enol ethers.

App 5.18.4 Crossed Aldol reactions with boron enolates

A crossed Aldol reaction can also be carried out with boron enolates. These have the advantage that the reaction is stereoselective due to a 6-membered chair-shaped transition state (Fig. 111).

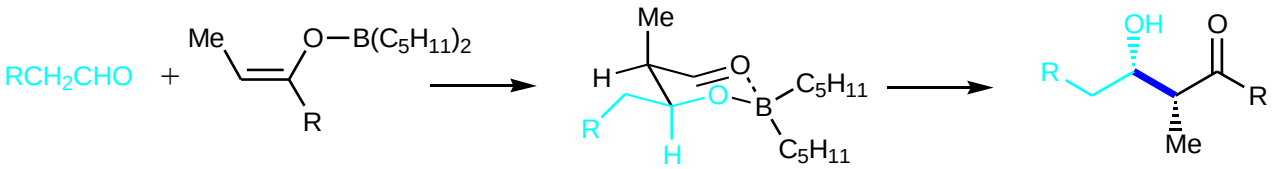


Figure 111 Boron enolates in the Aldol synthesis.

App 5.18.5 Directed Aldol reactions with imines or hydrazones

Under normal Aldol conditions, it is not practical to react the enolate of an aldehyde with a ketone, as the aldehyde is more likely to self condense. However, this reaction can be achieved by first converting the aldehyde to an imine or a dimethylhydrazone, then treating the product with a strong base (LDA) to create a carbanion (Fig. 112). Reaction with a ketone then produces the Aldol product. It is also possible to carry out Aldol reactions starting with the dimethylhydrazones of ketones.

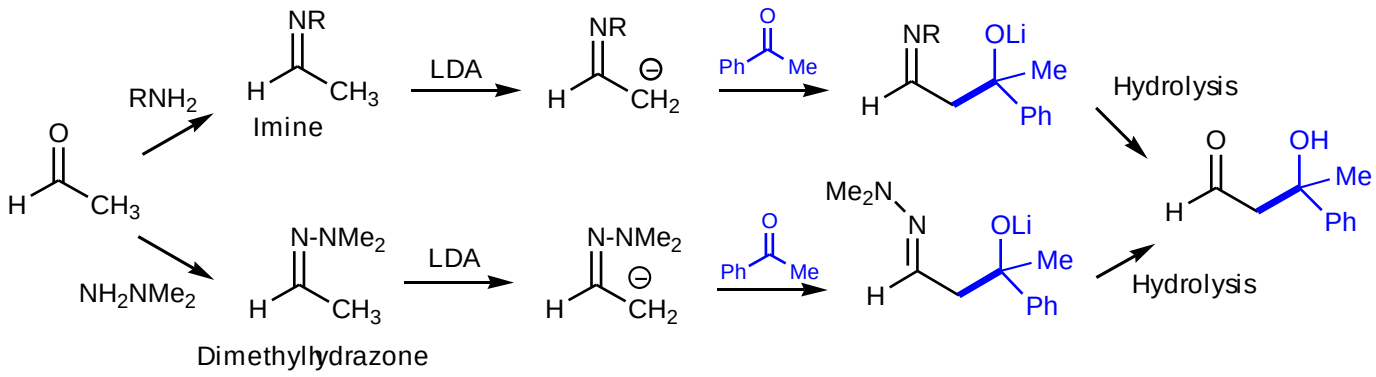


Figure 112 Directed Aldol reaction.

App 5.19 β-Hydroxy esters

The Reformatsky reaction is a convenient method of synthesising β-hydroxy esters from a carboxylic acid starting material (Fig. 113). The carboxylic acid must have an α-proton present, which can be replaced with bromine by treatment with bromine and red phosphorus. The carboxylic acid is also converted to an acid bromide which is easily converted to an ester by addition of an alcohol. The resulting bromoester is then treated with zinc and an aldehyde or ketone to give the desired product.

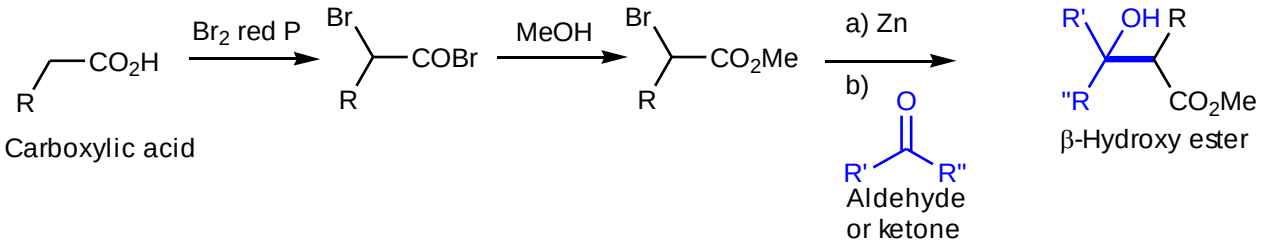


Figure 113 The Reformatsky reaction.

A different approach involves the use of diethyl malonate and epoxides (Fig. 114). The diethyl malonate is treated with base and the resulting carbanion reacts with an epoxide to open up the epoxide ring. Hydrolysis and decarboxylation gives access to a β-hydroxy acid which can then be esterified.

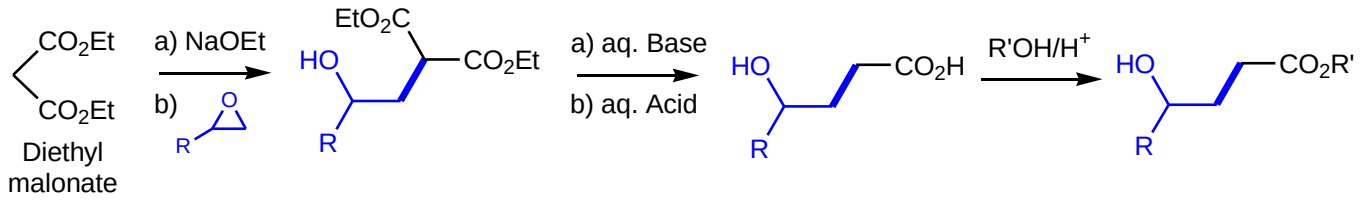


Figure 114 Synthesis of β-hydroxy acids and esters.

App 5.20 α-Hydroxy ethers

α–Hydroxy ethers are not particularly prevalent in drug structures. However, the antibiotics erythromycin and clarithromycin contain the feature, as well as several pharmacologically active natural products that are being studied as lead compounds. The latter include geldanamycin and maytansine which have anticancer activity.

α–Hydroxy ethers can be formed by the ring opening of epoxides with an alkoxide ion. With unsymmetrical epoxides, the S_N2 reaction will occur at the least substituted position if it is carried out under basic conditions (Fig. 115a). Alternatively, the reaction can be carried out under acidic conditions with an alcohol, which will usually attack the most substituted position (Fig. 115b).

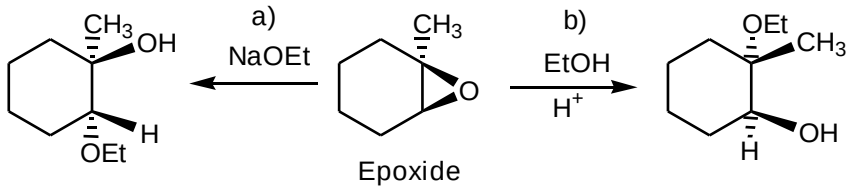


Figure 115 Formation of α-hydroxy ethers.

App 5.21 Keto acids and esters

Keto esters are very important intermediates in organic synthesis. There are various methods of synthesising different keto acids and keto esters by functional group transformations and carbon-carbon bond formations (Fig. 116).

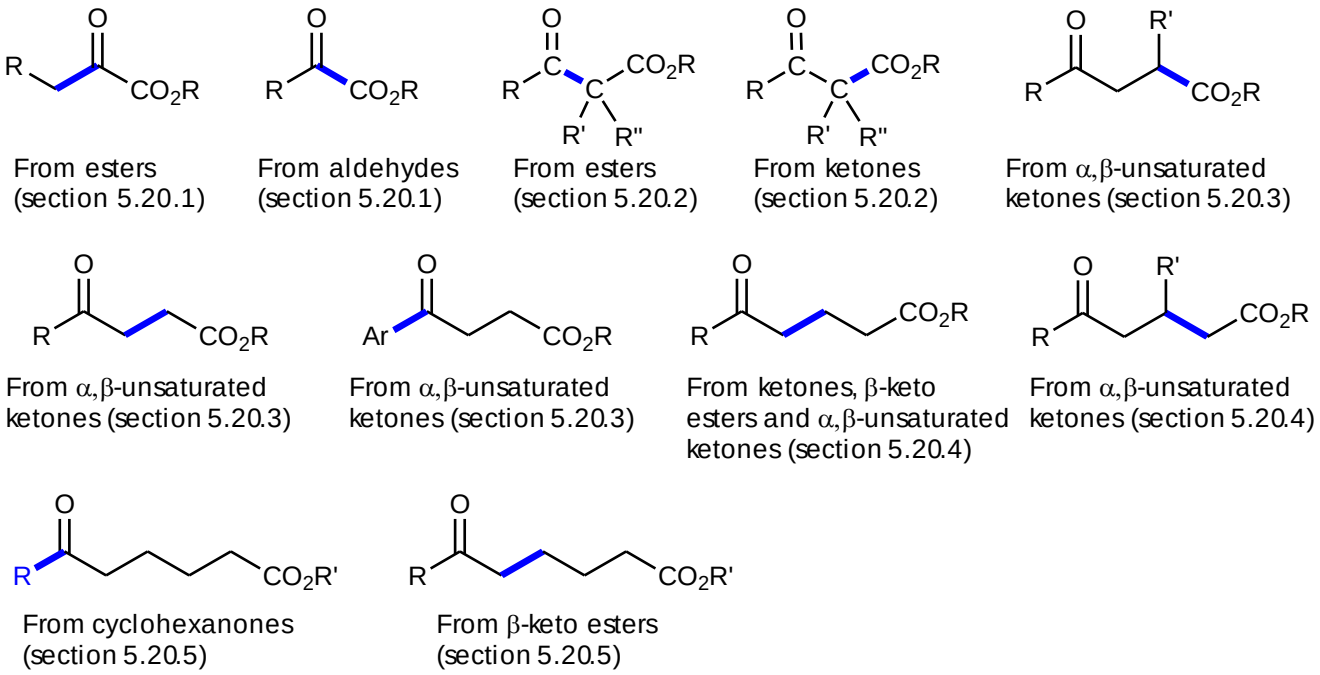


Figure 116 Carbon-carbon bond formations used in the synthesis of keto acids and keto esters.

App 5.21.1 α-Keto acids and esters (1,2-keto acids and esters)

α-Keto acids and esters can be obtained by the ozonolysis of an α,β-unsaturated ketone (appendix 1.33). Another approach is to carry out a mixed Claisen condensation between an ester and diethyl oxalate (Fig. 117a). The product obtained is then hydrolysed and decarboxylated to give the α-ketoacid.

Alternatively, α-keto esters can be prepared from aldehydes by converting the aldehyde to a 1,3-dithiane, then carrying out an acylation reaction with ethylchloroformate. The dithiane is then removed by treatment with *N*-bromosuccinimide (NBS) (Fig. 117b).

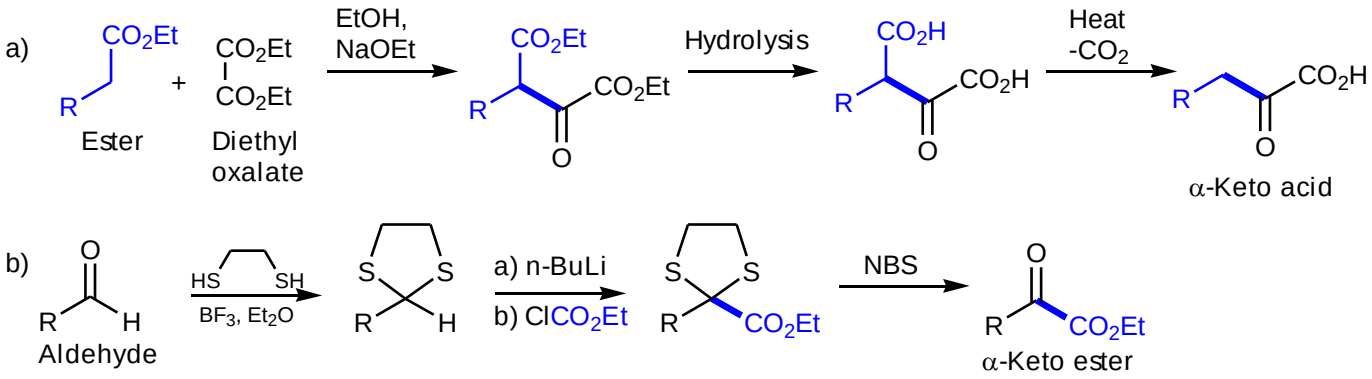


Figure 117 Formation of α-keto acids and esters.

App 5.21.2 β-Keto acids and esters (1,3-keto acids and esters)

5.21.2.1 The Claisen condensation

The Claisen condensation reaction is a popular method of synthesising β-keto esters, and involves the condensation of two identical ester molecules (Fig. 118). The ester must have an acidic α-proton for this reaction to occur.

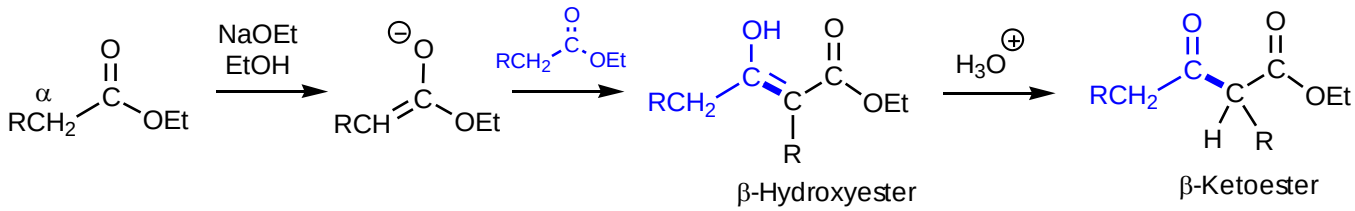


Figure 118 Claisen condensation.

This reaction can be viewed as the ester equivalent of the Aldol reaction (appendix 5.18.1). It involves the formation of an enolate ion from one ester molecule, which then undergoes nucleophilic substitution with an un-enolised ester molecule. If the product obtained can also form an enolate, then a strong base is not required. For example, one can use sodium ethoxide. If the product cannot form an enolate, then a strong base is required. This is necessary if the ester has a branch at the α-position and has only one acidic proton available (Fig. 119).

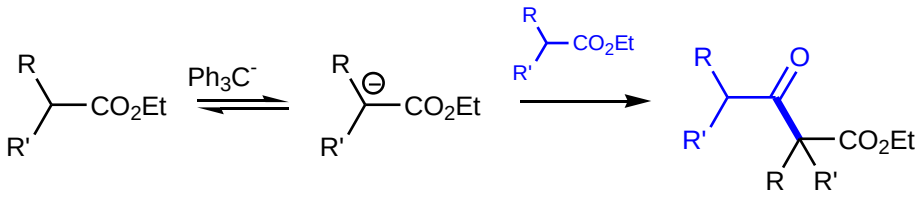


Figure 119 Claisen condensation with branched esters.

5.21.2.2 The mixed Claisen condensation with different esters

Two different esters can be used in a mixed Claisen condensation, as long as one of the esters has no α-protons and cannot form an enolate ion. For example, an aromatic ester has no α-protons and can be reacted with the enolate of the other ester (Fig. 120). A very strong base (e.g. LDA) is used such that the enolate ion is formed quantitatively from the enolisable ester. This prevents the possibility of self Claisen condensation.

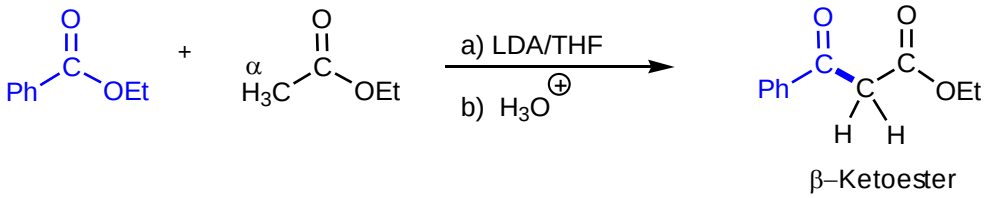


Figure 120 Mixed Claisen condensation involving two different esters.

5.21.2.3 β-Keto esters from ketones

β-Keto esters can also be synthesised from ketones by reacting the enolate ion of the ketone with diethylcarbonate (Fig. 121). Regioselectivity is possible if reaction at one side results in a stable enolate ion, whereas reaction at the other side does not. The β-keto ester obtained contains an α-carbon between the ketone and ester groups which is activated by both functional groups. This makes the α–protons more acidic than in the original ketone, and allows the possibility of further carbanion chemistry being carried out; for example alkylation at the α-position. The activating ester group can be hydrolysed and decarboxylated at a later stage if desired to synthesise different ketones (appendix 5.22.3).

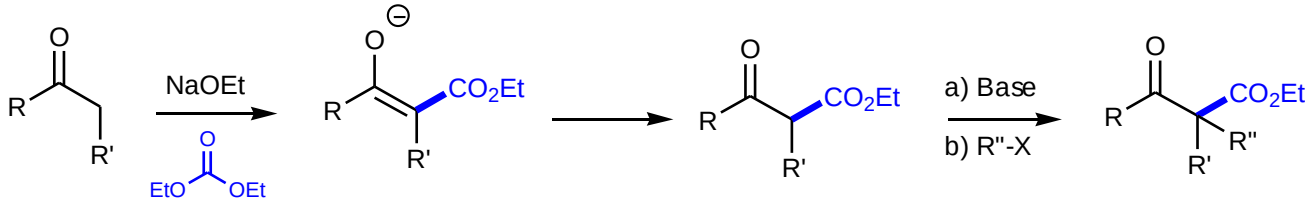


Figure 121 β-Keto esters from ketones.

App 5.21.3 γ-Keto acids and esters (1,4-keto acids and esters)

γ-Keto esters can be prepared by the conjugate addition of suitable lithium organocuprates to α,β-unsaturated ketones (Fig. 122). The organocuprate acts as a masked acyl anion, and the reaction is an example of the concept of umpulong (chapter 3.4). An alternative method is to carry out the Michael reaction with cyanide, then hydrolyse the product.

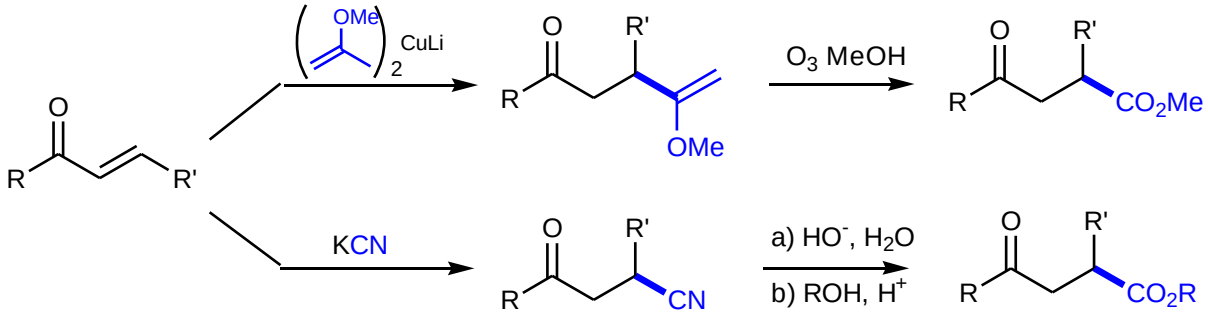


Figure 122 γ-Keto esters from α,β-unsaturated ketones.

Reacting an α-halo ester with an enolate or enamine is another approach to the synthesis of γ-keto esters (Fig. 123).

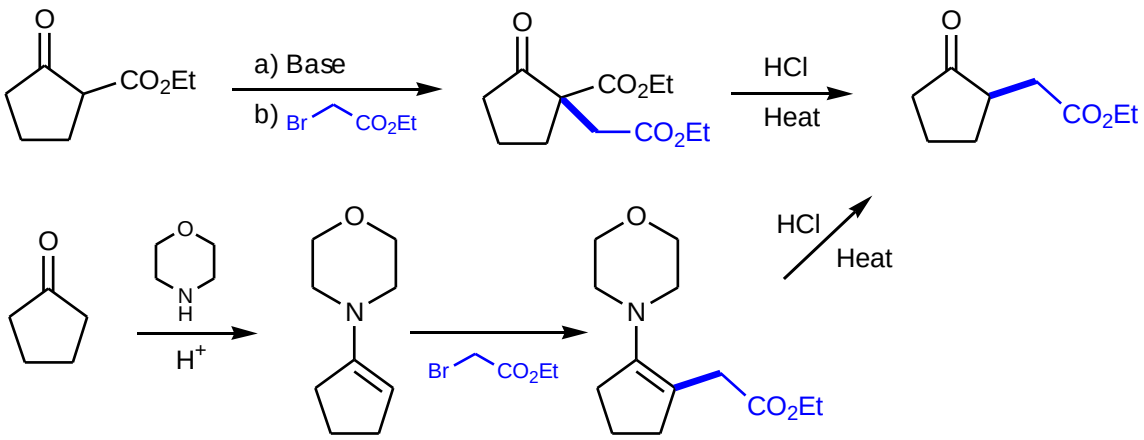


Figure 123 γ-Keto esters from ketones or β-keto esters.

Aromatic γ-keto acids can be synthesised by a Friedel-Crafts acylation of an aromatic ring with succinic anhydride (Fig. 124). Esterification produces aromatic γ-keto esters.

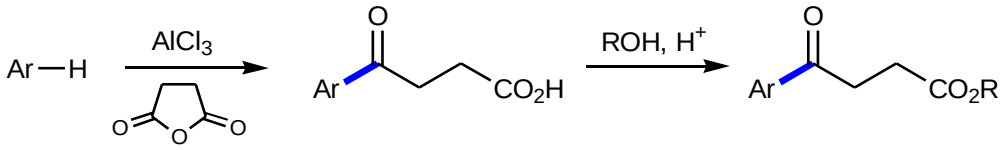


Figure 124 Aromatic γ-keto acids and esters.

App 5.21.4 δ-Keto acids and esters (1,5-keto acids and esters)

δ-Keto acids and esters can be synthesised by converting a ketone to a β-keto ester (appendix 5.21.2.3) then carrying out a Michael reaction on an α,β-unsaturated ester (Fig. 125a). Hydrolysis and decarboxylation of the Michael product removes the activating ester group to give the γ–keto acid, which can be esterified to the γ–keto ester. A strong base is not required for the Michael addition as there is no need to convert all of the keto ester to the enolate. Moreover, only a catalytic amount of the base is required. The reaction can also be carried out via an enamine instead of a β-ketoester (Fig. 125b).

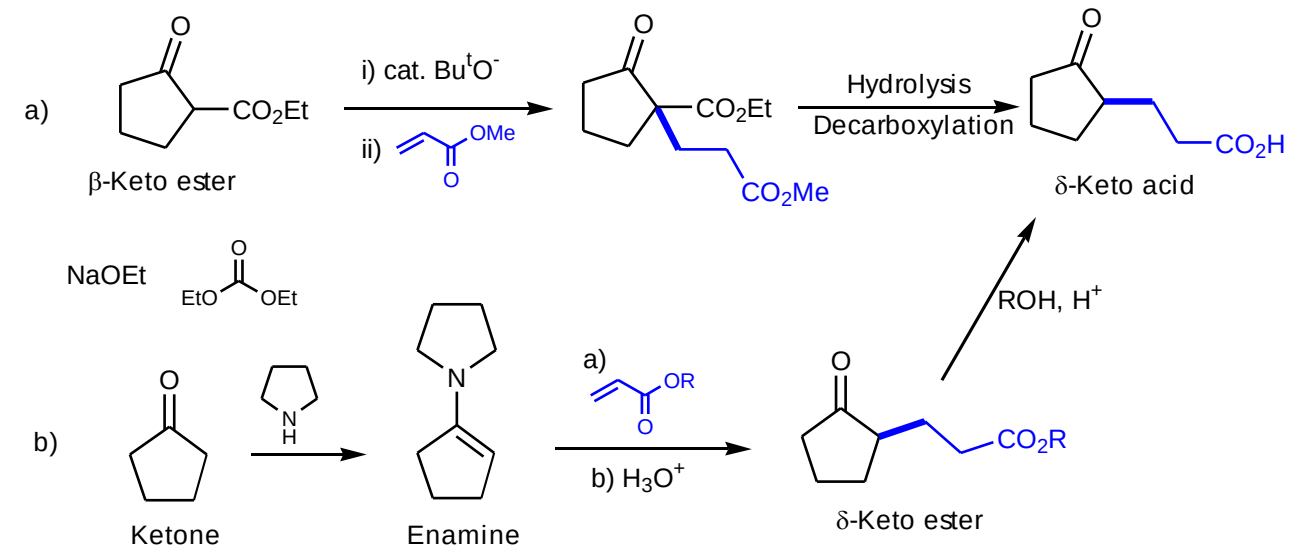


Figure 125 Synthesis of δ-ketoesters by the Michael reaction.

A related approach is to react diethyl malonate with an α,β-unsaturated ketone, followed by hydrolysis and decarboxylation to give the γ-keto acid (Fig. 126).

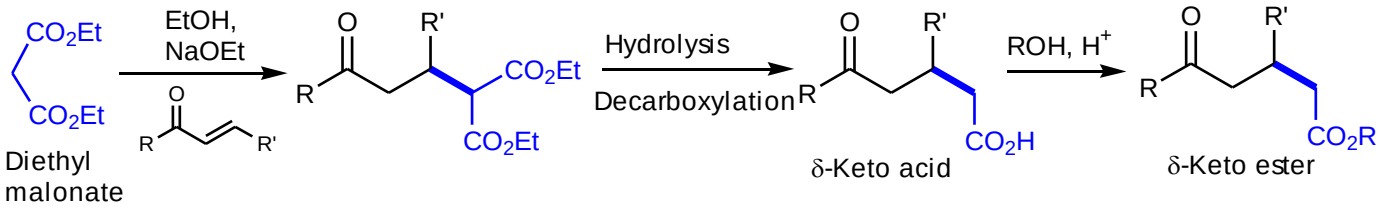


Figure 126 Synthesis of δ-ketoesters by the Michael reaction.

App 5.21.5 ε-Keto acids and esters (1,6-keto acids and esters)
1,6-Keto acids and esters can be synthesised from cyclohexanone by means of a Grignard reagent, followed by dehydration and ozonolysis (Fig. 127).

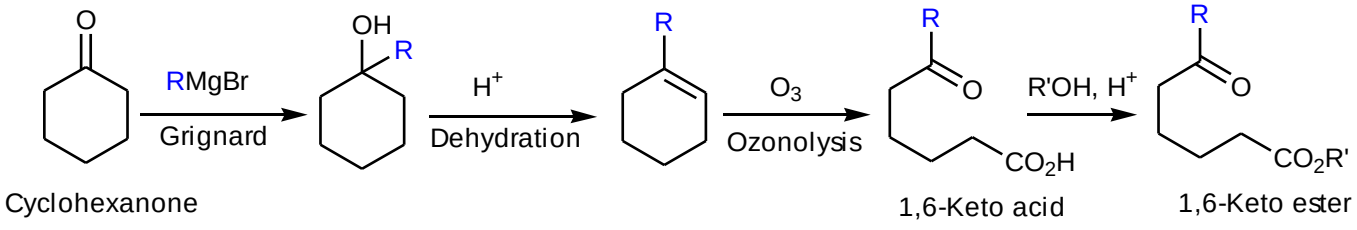


Figure 127 Synthesis of 1,6-keto acids and esters.

1,6-Keto acids and esters can also be obtained from β-keto esters and 4-bromo esters (Fig. 128). The β-keto ester is converted to a carbanion in the presence of base, then alkylated with the bromo ester.

Hydrolysis and decarboxylation of the ester activating group provides the 1,6-keto acid which can be esterified to the 1,6-keto ester.

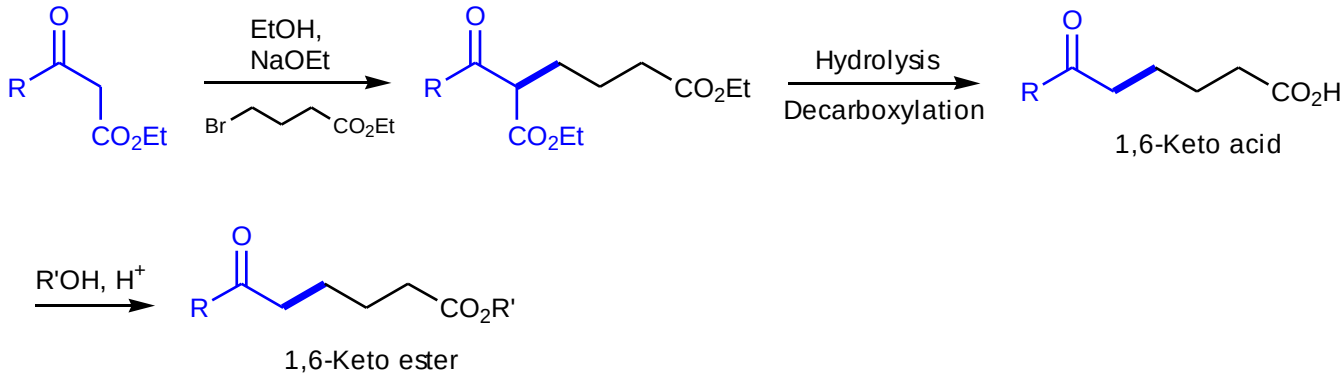


Figure 128 Synthesis of 1,6-keto acids and esters.

App 5.22 Ketones

Methods of synthesising ketones by functional groups transformations were described in appendix 1.34. Ketones are extremely important in organic synthesis and there is a large number of reactions involving C-C bond formation which can be used to synthesise them (Fig. 129). Common starting materials are β-ketoesters, enamines, α,β-unsaturated ketones, acid chlorides, nitriles, carboxylic acids, aldehydes and ketones themselves.

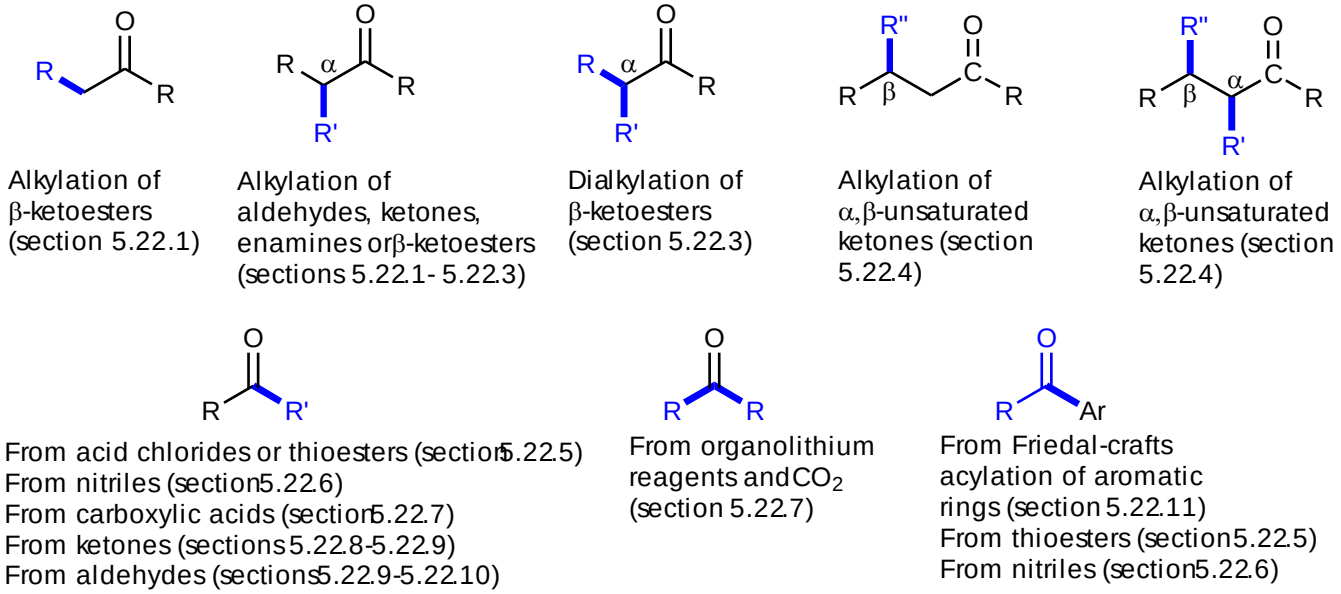


Figure 129 Molecular signatures for ketones.

Note that the ketones obtained from these reactions can be easily reduced to alcohols and so these methods are an alternative method of creating several of the alcohols described in appendix 5.1.

App 5.22.1 Alkylation of ketones at the α-position

Ketones containing an α-proton can be alkylated at the α-carbon. The α-proton is slightly acidic, and can be removed by a strong base such as lithium diisopropylamide (LDA) to form an enolate ion. This can then be treated with an alkyl halide to give the alkylated ketone (Fig. 130). It is important to add the ketone slowly to one equivalent of a strong base to fully convert the ketone to the enolate, and to avoid the possibility of a competing Aldol reaction (appendix 5.18.1). The reaction is an S_N2 nucleophilic substitution with respect to the alkyl halide, and so the reaction works best with primary alkyl (RCH_2X), primary benzylic ($ArCH_2X$) and primary allylic halides ($R_2C{=}CH\text{-}CH_2X$). The enolate ion is a strong base and, if it is reacted with secondary and tertiary halides, elimination of the alkyl halide takes place to give an alkene, leaving the ketone unaffected.

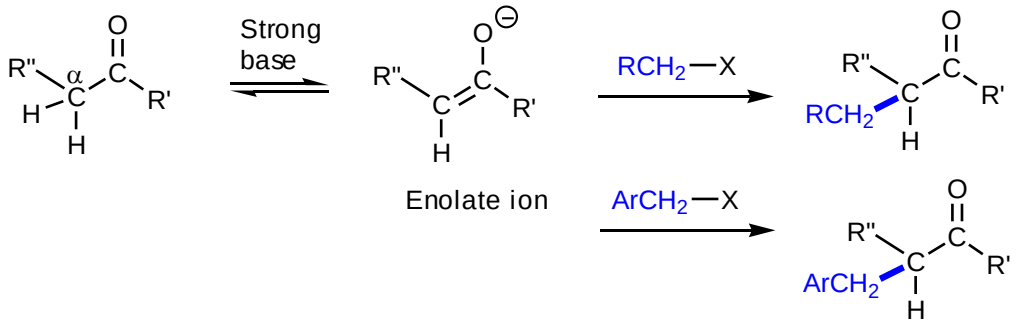


Figure 130 Alkylation of ketones.

App 5.22.2 Alkylation of ketones via enamines or imines

An alternative method of alkylating cyclic ketones is to convert the ketone to an enamine (cyclic ketones are converted to the enamine more easily than acyclic ketones), which can be alkylated then hydrolysed back to the ketone (Fig. 131).

The enamine is synthesised by treating the ketone with a secondary cyclic amine (such as piperidine, morpholine or pyrrolidine) in the presence of a catalytic amount of *para*-toluenesulphonic acid (ptsa). Water is formed as a by-product and can be removed by heating the reaction to reflux such that an azeotrope is formed between the solvent and the water. The water content can then be removed by collecting it in a Dean and Stark apparatus, or absorbing it onto molecular sieves in a Soxhlet apparatus, before allowing the solvent to return to the reaction vessel. With an unsymmetrical ketone, there are two possible enamines, with the less substituted enamine being the more favoured.

Once the enamine is formed, it can be treated with a reactive alkylating agent such as an allylic halide or benzylic halide (Fig. 131). The advantage of this method over the direct alkylation of a ketone is that the reaction proceeds under milder conditions without the need for a base, and so there is no risk of self-condensation reactions. Also, alkylation favours the less substituted α-carbon due to the preference for the less substituted enamine, and is easier to control than direct alkylation of the ketone. Finally, there is less chance of a second alkylation taking place, if that should prove possible. The disadvantage of the procedure is the fact that the enamines do not react particularly well with alkyl halides.

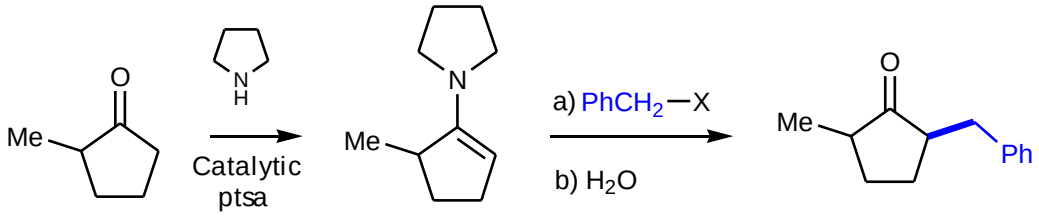


Figure 131 Alkylation of ketones via an enamine.

Although enamines themselves do not react very well with alkyl halides, it has been found that metalloenamines do (Fig. 132). These compounds are formed by reacting an aldehyde or ketone with a primary amine to form an imine, then treating the imine with a Grignard reagent or lithium di-isopropylamide (LDA). The resulting metalloenamine can then be alkylated with primary or secondary alkyl halides (as well as allylic or benzylic halides), then hydrolysed to the ketone.

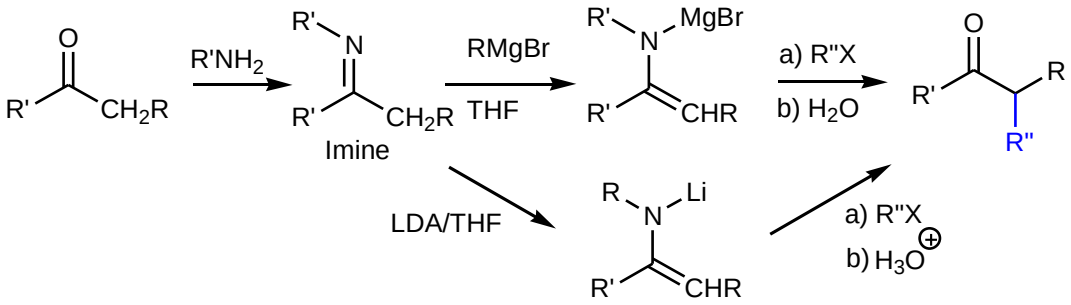


Figure 132 Alkylation of aldehydes or ketones via an metalloenamines (R'=H or alkyl group).

App 5.22.3 Ketones from β-keto esters

The α-protons of a simple ketone are only weakly acidic and so a powerful base such as lithium diisopropylamide (LDA) is required to generate the enolate ion required for an alkylation (appendix 5.22.1). An alternative method of preparing the same product with a milder base is to start with a β-keto ester (Fig. 133). The α-protons in this structure are more acidic because they are flanked by two carbonyl groups. As a result, the enolate can be formed using sodium ethoxide. Once the enolate has been alkylated, the ester group can be hydrolyzed and decarboxylated on heating with aqueous hydrochloric acid. The decarboxylation mechanism involves the β-keto group and would not occur if this group was absent (Fig. 134).

The reaction works well with benzyl halides and primary allyl halides, as well as primary and secondary alkyl halides. Tertiary alkyl halides are more of a problem due to a competing elimination reaction which converts the alkyl halide to an alkene. In such cases, the corresponding tertiary mesylate or tosylate may be worth using.

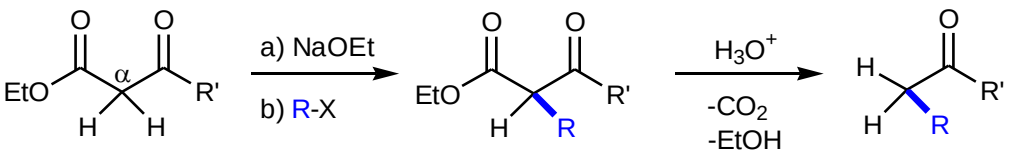


Figure 133 α-Alkylation of β-keto esters.

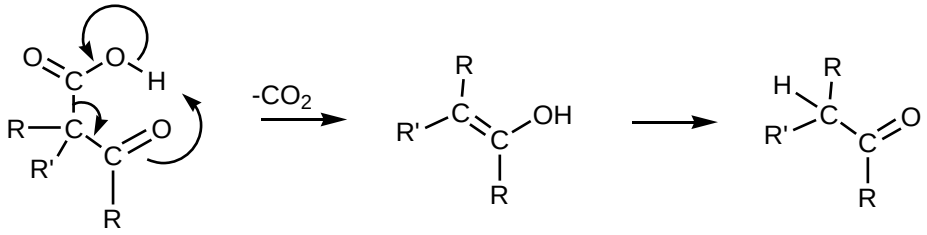


Figure 134 Decarboxylation mechanism.

It is possible for two different alkylations to be carried out on a β-keto ester if there is more than one α-proton present (Fig. 135).

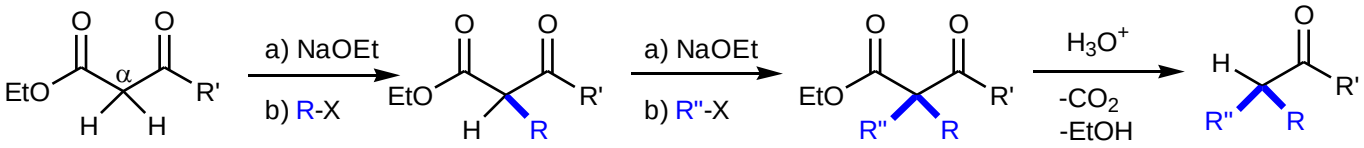


Figure 135 Dialkylation of β-keto esters.

β-keto esters are also useful in solving a problem involved in the alkylation of unsymmetrical ketones. For example, alkylating butanone with methyl iodide leads to two different products because there are α-protons on either side of the carbonyl group (Fig. 136).

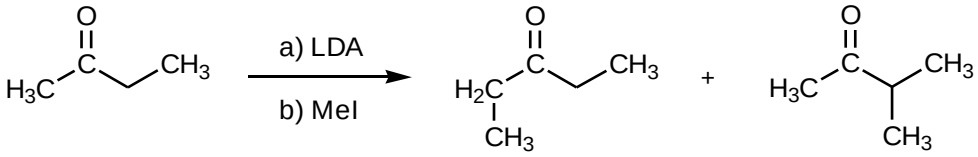


Figure 136 Alkylation of butanone.

These products can be obtained specifically by using relevant β-keto esters to make the target alkylation site more acidic (Fig. 137).

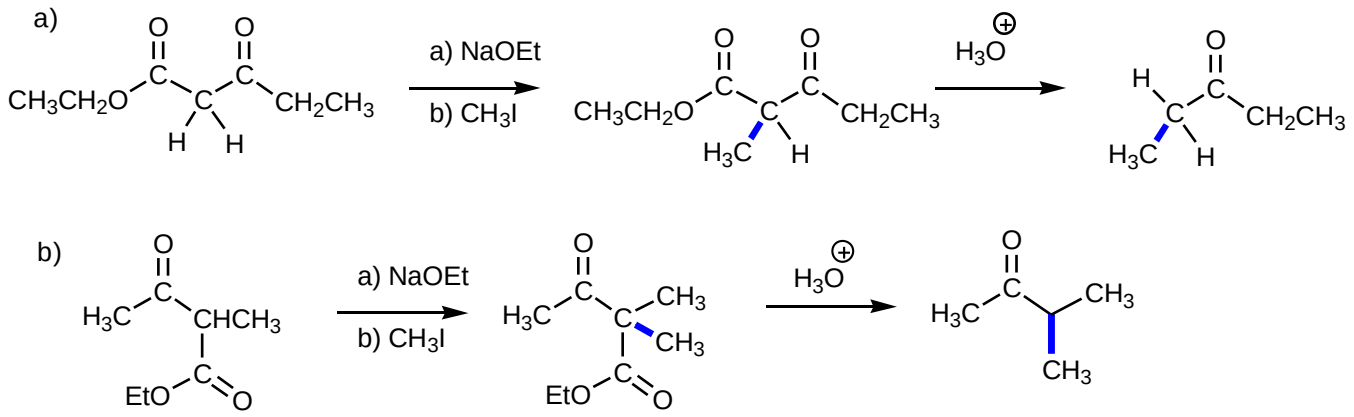


Figure 137 Targeted alkylations.

It may not always be possible to start a synthesis with a β-ketoester, in which case it would be useful to introduce the ester group as a temporary activating group. One way of doing this is to react a ketone with base, then ethyl carbonate (Fig. 138) (see also appendix 5.21.2.3).

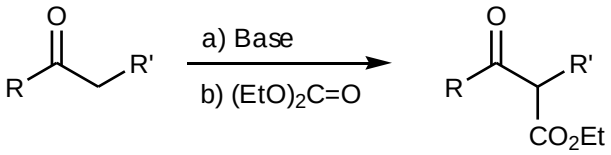


Figure 138 Introduction of an ester activating group.

App 5.22.4 Alkylation of α,β-unsaturated ketones at the β-position

The reaction of a lithium diorganocuprate reagent (Gilman reagent) with an α,β-unsaturated ketone (R' = alkyl or aryl) allows the addition of a primary alkyl, vinyl or aryl group to the β-position in a 1,4-conjugate addition reaction (Fig. 139). The product no longer has a double bond and is now branched at the β-position. Other reactive functional groups in the molecule would have to be protected (alcohols carboxylic acids, epoxides and halides).

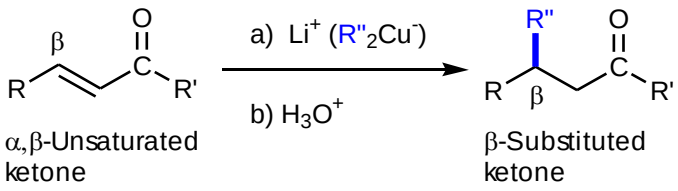


Figure 139 Synthesis of ketones from α,β-unsaturated ketones.

Only one of the alkyl groups from the organocuprate reagent is added to the unsaturated ketone and so this method is best used when the reagent is cheap or easily available. Alternatively, one can use a mixed organocuprate reagent where one of the substituents is an alkynyl or nitrile group. The alkynyl

or nitrile substituents are relatively unreactive and so the alkyl group is transferred preferentially (Fig. 140). A mixed organocuprate reagent with a phenylthio substituent Li[PhS-Cu-R) has been found to be effective if a secondary or tertiary alkyl group is to be transferred to the α,β-unsaturated ketone. It is possible to carry out similar conjugate additions using Grignard reagents in the presence of copper salts.

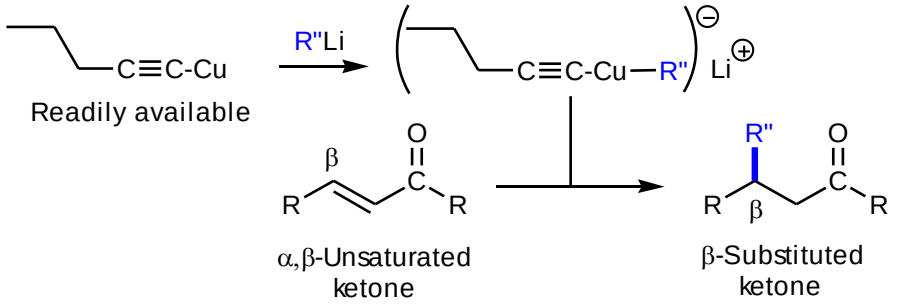


Figure 140 Use of a mixed organocuprate reagent.

It is sometimes possible to introduce alkyl substituents to both the α and β positions of an α,β-unsaturated ketone (a tandem vicinal difunctionalisation) by carrying out the reaction in the presence of an alkyl halide (Fig. 141). The alkyl group from the organocuprate reagent is added to the β-position by the conjugate addition reaction, then the resulting enolate may react with an allyl or primary alkyl halide to introduce a substituent at the α-position.

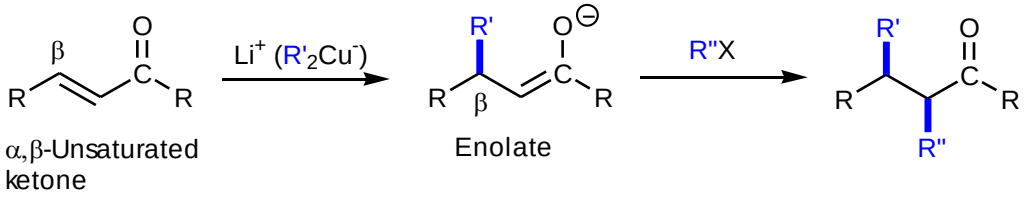


Figure 141 Alkylation at both the α– and β-positions of a ketone.

App 5.22.5 Synthesis of ketones from acid chlorides

Aliphatic and aromatic acid chlorides react with lithium diorganocuprate reagents to form ketones (Fig. 142a). The alkyl group of the aliphatic acid chloride can be primary, secondary or tertiary. An alkyl group from the organocuprate reagent displaces the chloride ion to produce the ketone. Unlike the Grignard reaction, the reaction stops at this stage and the mechanism is thought to be radical based rather than a nucleophilic substitution. No reaction takes place with carboxylic acids, acid anhydrides, esters or amides.

Only one of the alkyl groups is transferred from the organocuprate reagent and a mixed organocuprate reagent may be applicable if the alkyl group is expensive or difficult to synthesise (compare appendix 5.22.4).

The reaction works best when the group transferred from the organocuprate reagent is a vinyl group or a primary alkyl group. If a secondary or tertiary alkyl group is to be added, it is better to use the mixed organocuprate reagent Li[PhS-Cu-R) (Fig. 142b).

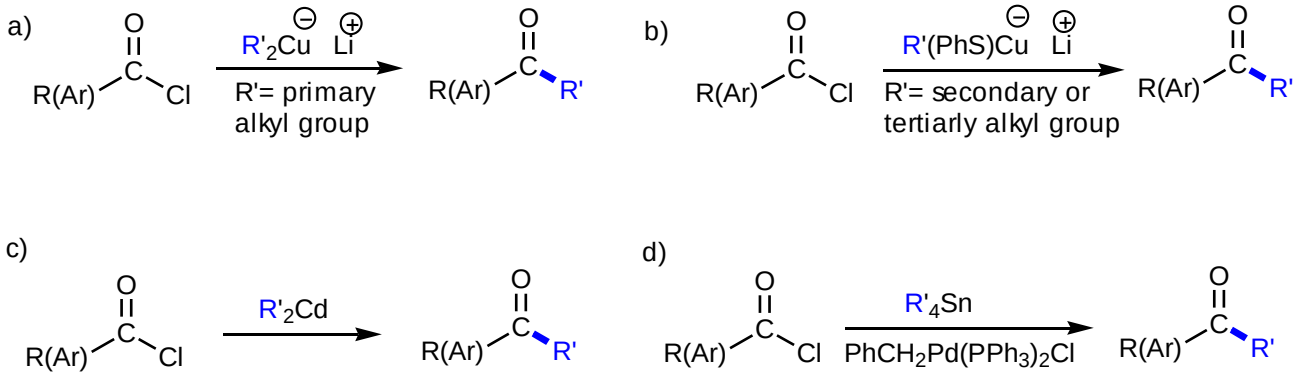


Figure 142 Reaction of acid chlorides with organometallic reagents.

The organocuprates can also be reacted with thioesters (RCOSR) instead of acid chlorides to create ketones. In these cases, it is possible to transfer an aryl group or an alkyl group that is either primary or secondary.
Organocadmium reagents (R'_2Cd) are an alternative to organocuprate reagents in the reaction with acid chlorides, and allow the transfer of a primary alkyl group or an aryl group (Fig. 142c).
Organotin reagents (R'_4Sn) also react with aliphatic and aromatic acid chlorides to produce ketones in high yield if a palladium catalyst is present ($BzPd(PPh_3)_2Cl$) (Fig. 142d). The reaction can be carried out in the presence of nitro, nitrile, arylhalo, olefin, methoxy, ester and aldehyde groups. An aryl group is transferred from the organotin reagent more easily than an alkyl group. For example, the use of triphenylmethyl tin will result in an aromatic ketone rather than a methyl ketone.

App 5.22.6 Synthesis of ketones from nitriles
Nitriles can be treated with Grignard reagents to give ketones (Fig. 143). The reaction initially gives an imine, which is then hydrolysed with acid to provide the ketone. Better yields are obtained when aromatic ketones are synthesised compared to aliphatic ketones.

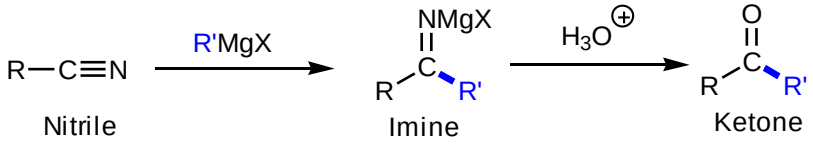


Figure 143 Reaction of nitriles with Grignard reagents.

App 5.22.7 Synthesis of ketones from carboxylic acids
The reaction of an aromatic or aliphatic carboxylic acid with an excess of organolithium agent generates a carboxylate ion. This reacts further to give an adduct which can be converted to a ketone with an aqueous acid work up (Fig. 144a). The group that is added (R') can be aryl, or a primary, secondary or tertiary alkyl group.
Symmetrical ketones can be synthesised by treating organolithium reagents with carbon dioxide. This generates a carboxylate ion, which then reacts as above (Fig. 144b).

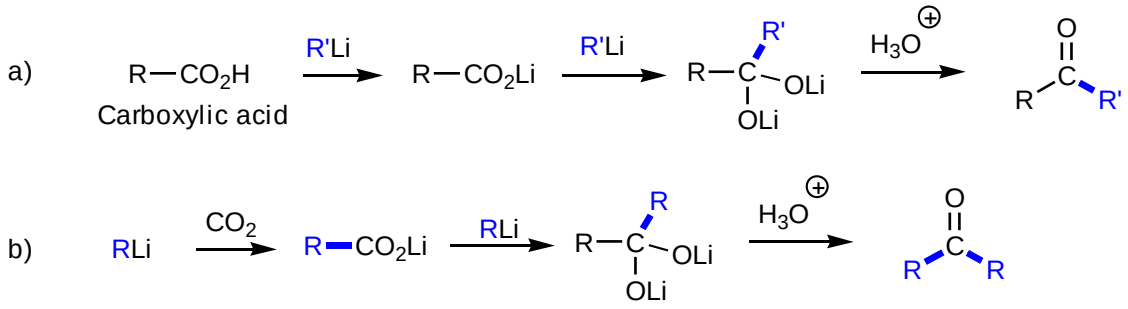


Figure 144 Synthesis of ketones from carboxylic acids.

App 5.22.8 Synthesis of ketones from diols by the Pinacol rearrangement

The Pinacol rearrangement of 1,2-diols is a useful method of preparing ketones with a neighbouring tertiary alkyl group (Fig. 145). A symmetrical ketone can be dimerised under reducing conditions to produce a tetrasubstituted diol, then treatment with acid results in a rearrangement reaction involving migration of one of the substituents. Both alkyl and aromatic groups can migrate.

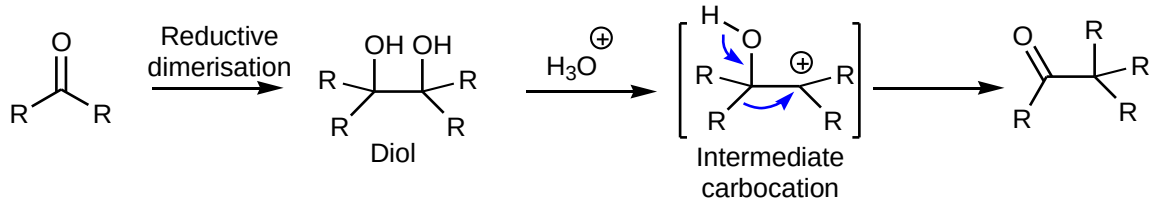


Figure 145 The Pinacol rearrangement.

If the diol has different substituents, then a mixture of ketones is likely to be obtained. The preferred product will be determined by a number of factors. First of all, the reaction should proceed through the more stable carbocation intermediate. Secondly, an aromatic ring is more likely to migrate than an alkyl group or a hydrogen atom, especially if the ring contains electron-donating substituents.

App 5.22.9 Synthesis of methyl ketones

A modification of the Peterson reaction (appendix 5.3.2) can be used to synthesise methyl ketones from aldehydes or ketones (Fig. 146a).

Another method of synthesising methyl ketones is to react an aldehyde with diazomethane (Fig. 146b). In the subsequent rearrangement reaction the hydrogen atom migrates in preference to the alkyl group.

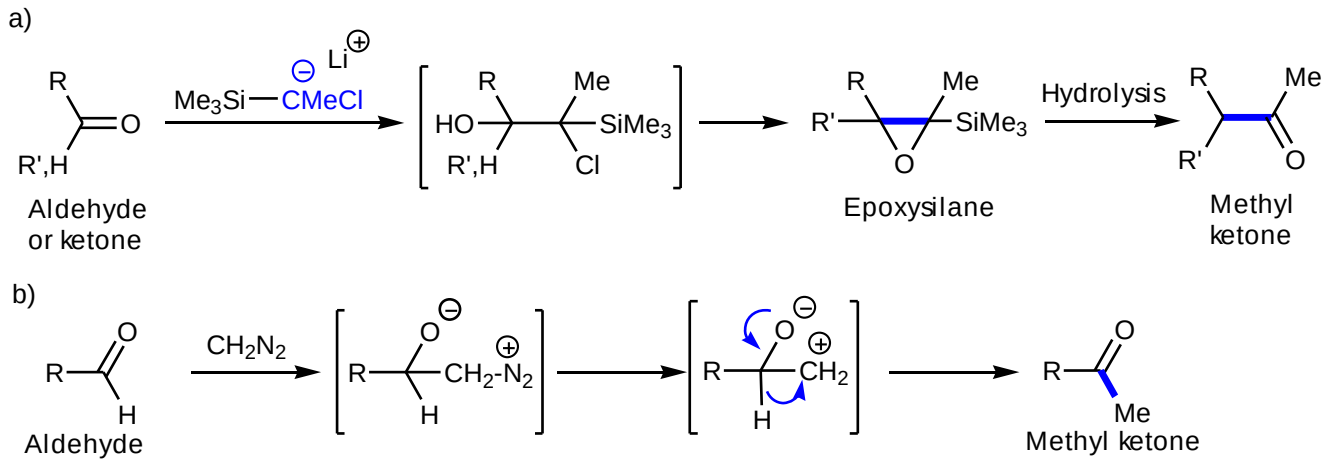


Figure 146 Synthesis of methyl ketones.

App 5.22.10 Synthesis of ketones from aldehydes

Aldehydes can be converted to dithianes, then treated with base to form a carbanion which is stabilised by the neighbouring sulphur atoms. This can be alkylated and the dithiane ring removed to provide ketones (Fig. 147). This is an example of umpulong (chapter 3.4).

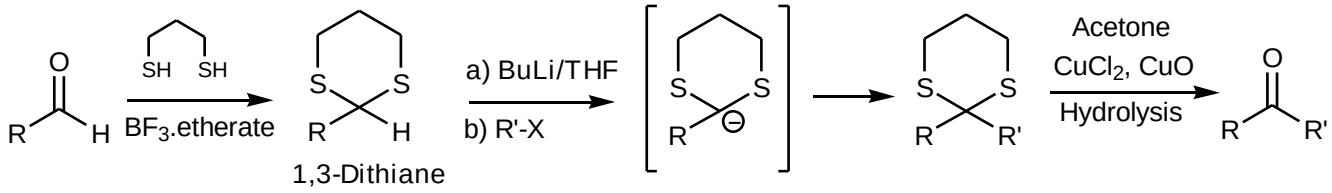


Figure 147 Synthesis of ketones from aldehydes.

App 5.22.11 Aromatic ketones by the Friedel-Crafts acylation

A number of methods for preparing aromatic ketones have already been described in previous sections where C-C bond formation involves a functional group that is already linked to the aromatic ring. Alternatively, an aromatic reagent is used to react with a functional group on an aliphatic starting material. For example, aromatic ketones can be synthesised by the reaction of an aromatic Grignard reagent with a nitrile (appendix 5.22.6) or by reacting an arylorganocuprate reagent with a thioester (appendix 5.22.5).

Here, we look at reactions where a new carbon-carbon bond is formed between the aromatic ring and the newly introduced ketone group. The most common method for carrying out this reaction is the Friedel-Crafts reaction, which involves an electrophilic substitution reaction of the aromatic ring by an acid chloride in the presence of a Lewis acid catalyst (Fig. 148). The acylation only occurs once and there is no risk of the rearrangement reactions that can occur with carbocations used in the Friedel-Crafts alkylation. Therefore, this is also a good method of introducing alkyl substituents that would be difficult to introduce using the Friedel-Crafts alkylation, since the ketone group can be removed by reduction (appendix 3.2).

Acid chlorides are normally used because they are more readily available, but the reaction is also possible with acid iodides, bromides and fluorides. A slight excess of Lewis acid is required, as 1 equivalent is complexed to the oxygen of the acid halide.
It is also possible to carry out the acylation with a carboxylic acid in the presence of a mineral acid such as sulphuric acid.
As far as the aromatic substrate is concerned, the reaction does not go well if the aromatic ring has an amine substituent or a *meta*-directing substituent.
The Friedel-Crafts acylation reaction is also very useful in intramolecular cyclisations (chapter 4.5.1).

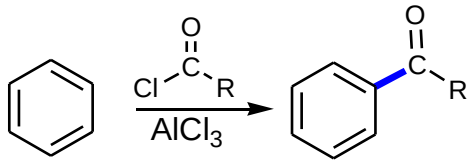


Figure 148 Friedel Crafts acylation.

App 5.23 Nitriles

Nitriles can be synthesised by substituting the halogen of an alkyl halide with a cyanide ion (Fig. 149). This works best with primary alkyl halides. The nitrile can then be converted to other functional groups, giving access to carboxylic acids or aldehydes (appendices 1.18.1 & 1.5.1). Ketones can also be synthesised from nitriles by C-C bond formations (appendix 5.22.6).

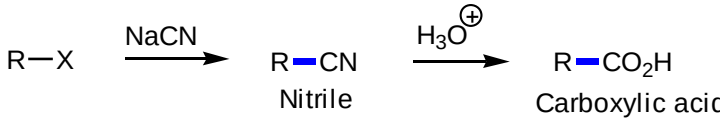


Figure 149 Synthesis of a nitrile.

App 5.24 Nitroalkanes

The nitro functional group has a powerful electron-withdrawing effect, which means that any protons at the alpha carbon are slightly acidic and can be removed by base. Therefore, it is possible to alkylate the α-carbon in a similar manner to the α-alkylation of carbonyl compounds (Fig. 150). The resulting compounds can be easily converted to the corresponding primary amines by reducing the nitro group (appendix 1.12.2).

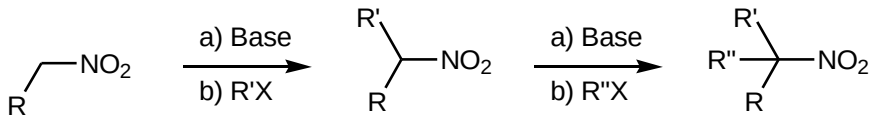


Figure 150 Alkylation of nitroalkanes.

App 5.25 α,β-Unsaturated aldehydes

There are various carbon-carbon bond formations that can be used to synthesise α,β-unsaturated aldehydes starting from aldehydes, ketones or α,β-unsaturated aldehydes (Fig. 151).

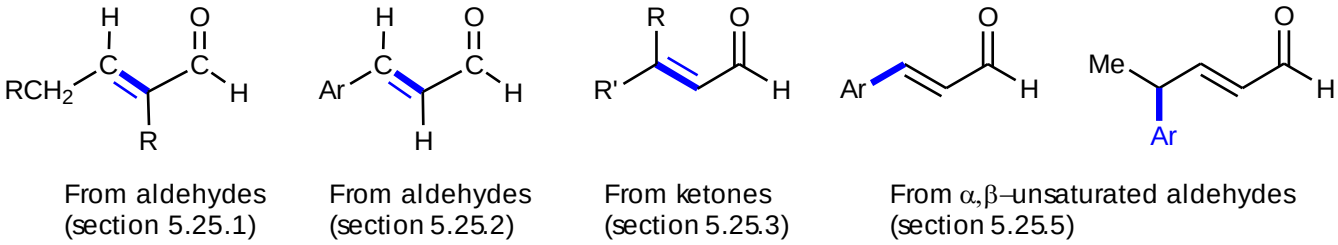


Figure 151 Carbon-carbon bond formations used in the synthesis of α,β-unsaturated aldehydes.

App 5.25.1 Aldol condensation

The Aldol reaction was described previously as a method of synthesising β-hydroxy aldehydes (appendix 5.18.1). If the reaction is carried out with heating, then water is eliminated (dehydration) to form α,β-unsaturated aldehydes (Fig. 152).

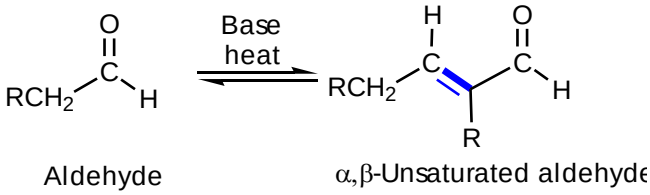


Figure 152 The Aldol condensation.

App 5.25.2 Crossed Aldol reaction with different aldehydes

As described in appendix 5.18.1 & 5.18.2, it is possible to link two different carbonyl compounds to form β-hydroxy aldehydes in a reaction known as the **crossed Aldol reaction.** The reaction conditions can be set such that dehydration occurs to give α,β-unsaturated aldehydes instead. For example, benzaldehyde and ethanal can be linked in the presence of sodium hydroxide to give cinnamaldehyde (Fig. 153).

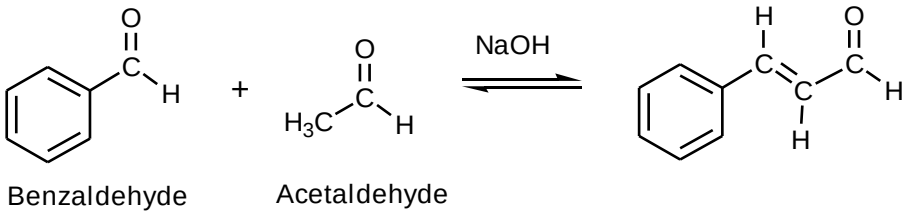


Figure 153 The crossed Aldol reaction.

In this example, acetaldehyde reacts with sodium hydroxide to form an enolate ion, which then reacts with benzaldehyde. Elimination of water occurs easily to give an extended conjugated system

involving the aromatic ring, the double bond and the carbonyl group. This reaction works well because the benzaldehyde has no α-protons and cannot form an enolate ion. Therefore, there is no chance of benzaldehyde undergoing self condensation. It can only act as the electrophile for another enolate ion. However, what is to stop the acetaldehyde undergoing an Aldol addition with itself ? The reaction can be controlled by only having benzaldehyde and sodium hydroxide initially present in the reaction flask. Since benzaldehyde has no α-protons, no reaction can take place. A small quantity of acetaldehyde can now be added. Reaction with excess sodium hydroxide turns most of the acetaldehyde into the enolate ion and there will only be a very small amount of 'free' acetaldehyde left compared to benzaldehyde. Therefore, the enolate ion is more likely to react with benzaldehyde. Once the reaction is judged to have taken place, the next small addition of acetaldehyde is made and the process is repeated.

App 5.25.3 Conversion of a ketone to a homologated α,β-unsaturated aldehyde

The Wittig reaction was discussed previously as a method of synthesising alkenes (appendix 5.3.1). The Horner-Wadsworth-Emmons reaction is a similar reaction which involves a phosphonate reagent, and is a good method of synthesising α,β-unsaturated carbonyl compounds. One example of this is a reaction which extends a ketone by two carbon units to generate an α,β-unsaturated aldehyde (Fig. 154a). The phosphonate reagent used contains a masked aldehyde group and represents the equivalent of the carbanion $^{-}CH_2CHO$.

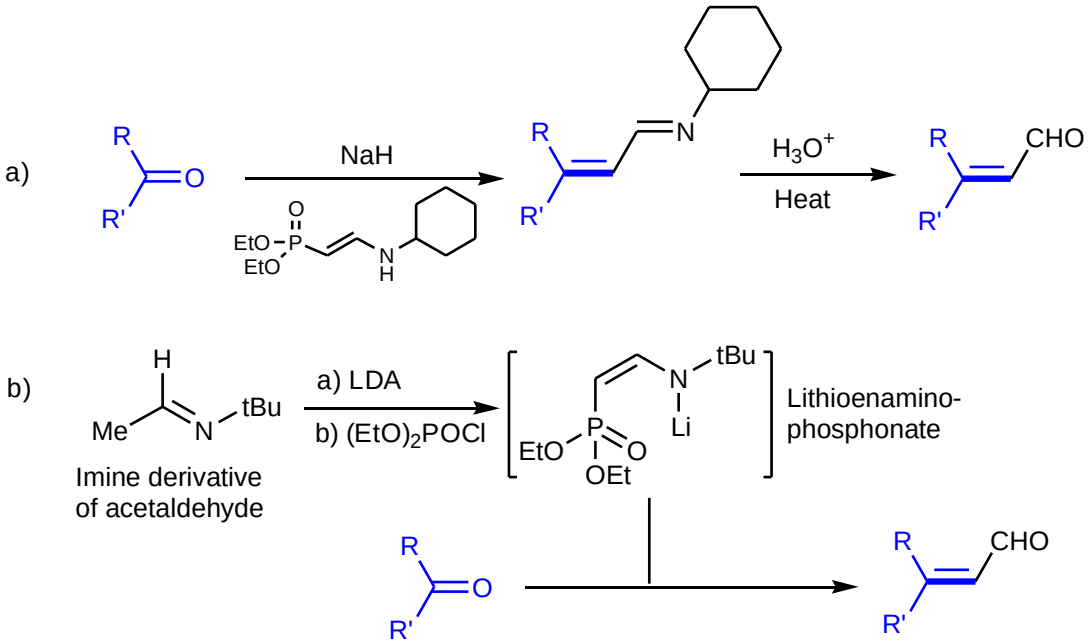


Figure 154 Extension of a ketone to form an α,β-unsaturated aldehyde.

An alternative one-pot method that achieves the same result is to treat an imine derivative of acetaldehyde with lithium diisopropylamide (LDA), followed by diethyl chlorophosphate to generate a lithioenaminophosphonate (Fig. 154b). This is reacted immediately with the ketone, and the α,β-unsaturated aldehyde is obtained on work up.

App 5.25.4 α,β-Unsubstituted aldehydes by the Corey-Peterson reaction

The Corey-Peterson olefination using a silylated imine and a carbonyl compound has been used to create an unsaturated aldehyde in one step (Fig. 155). This was used in a synthesis of Taxol.

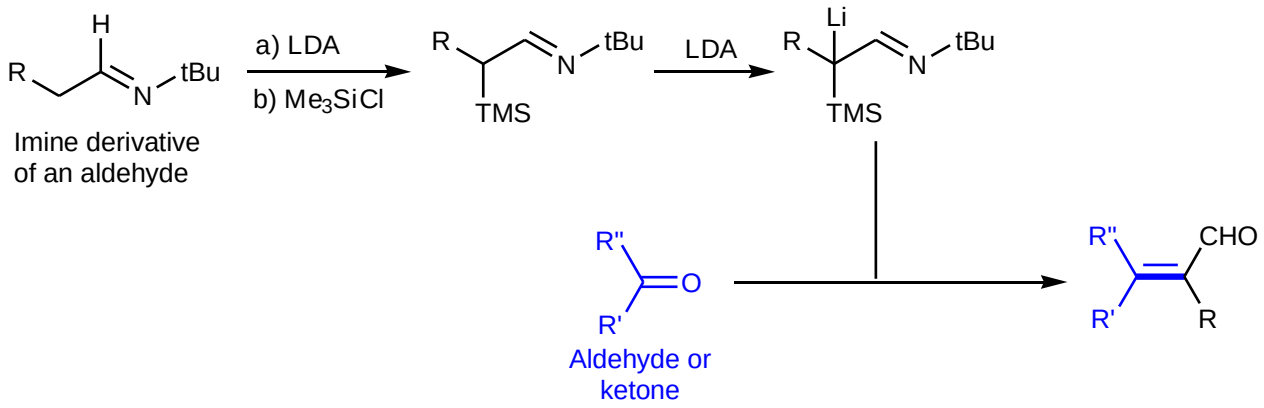


Figure 155 The Corey-Peterson reaction.

App 5.25.5 The Heck reaction

It has been possible to link acrolein to a range of aromatic boronic acids under base-free conditions using a palladium (I) catalysed oxidative Heck reaction (Fig. 156a).

Under different reaction conditions, it has proved possible to carry out arylations at the allylic position of α,β-unsaturated aldehydes (Fig. 156b).

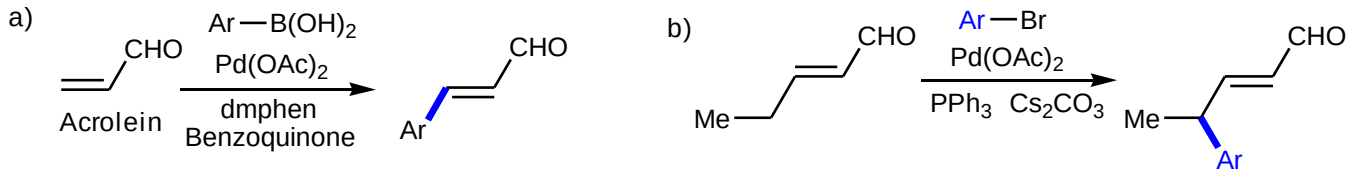


Figure 156 α,β-Unsaturated aldehydes synthesised by the Heck reaction.

App 5.26 α,β-Unsaturated Acids and Esters

α,β-Unsaturated acids are found in antibacterial agents such as fusidic acid and the cephalosporins. α,β-Unsaturated esters are not so common, although some natural products with such groups are being studied as lead compounds. For example, the microbial metabolite eleuthrobin is a microbial metabolite that contains an α,β-unsaturated ester and has anticancer properties. Sarcodictyins are simplified analogues of this compound. Phyllanthoside obtained from tree roots also contains this functional group and has anticancer activity.

Most of the carbon-carbon bond formations used in the synthesis of α,β-Unsaturated acids or esters involve formation of the C=C bond.

App 5.26.1 α,β-Unsaturated esters from ketones and α-bromo esters

The Reformatsky reaction was described in appendix 5.19 as a method of synthesising β-hydroxy esters from α-bromo esters and an aldehyde or ketone. By varying the reaction conditions to encourage dehydration, the corresponding α,β-unsaturated esters can be synthesised (Fig. 157). For example, the presence of Bu_3P encourages formation of the unsaturated product.

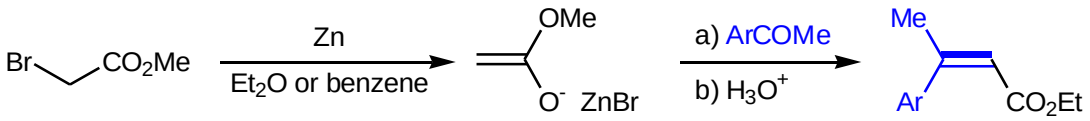


Figure 157 The Reformatsky reaction and dehydration.

App 5.26.2 α,β-Unsaturated esters from aldehydes and α-halo esters Aldehydes can be converted to α,β-unsaturated esters by the Wittig reaction using a phosphorane reagent that includes the ester group (Fig. 158). The preferred stereochemistry of the product is generally the *E*-isomer. The ester group serves to stabilise the charge in the ylide, which means that a milder base can be used to generate the ylide than for an unstabilised ylide. The reaction works well with aliphatic and aromatic aldehydes, but not with ketones, since the stabilised phosphorane is not sufficiently reactive.

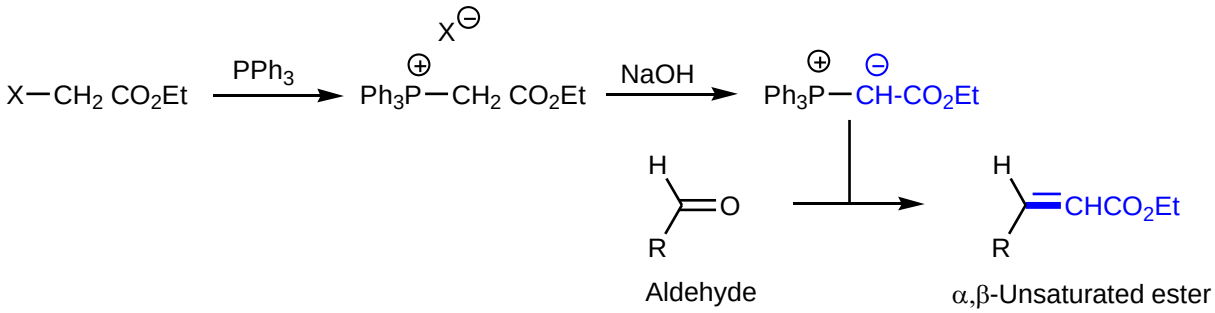


Figure 158 Use of the Wittig reaction to generate α,β-unsaturated esters.

App 5.26.3 α,β-Unsaturated esters from aldehydes and ketones
The Horner-Wadsworth-Emmons reaction is a variation of the Wittig reaction and involves a phosphonate reagent reacting with a ketone or an aldehyde (Fig. 159). If there is the possibility of geometric isomers, the *E*-isomer is generally preferred, especially if an aldehyde is used as starting material. However, the reaction conditions can be varied to favour the *Z*-isomer.

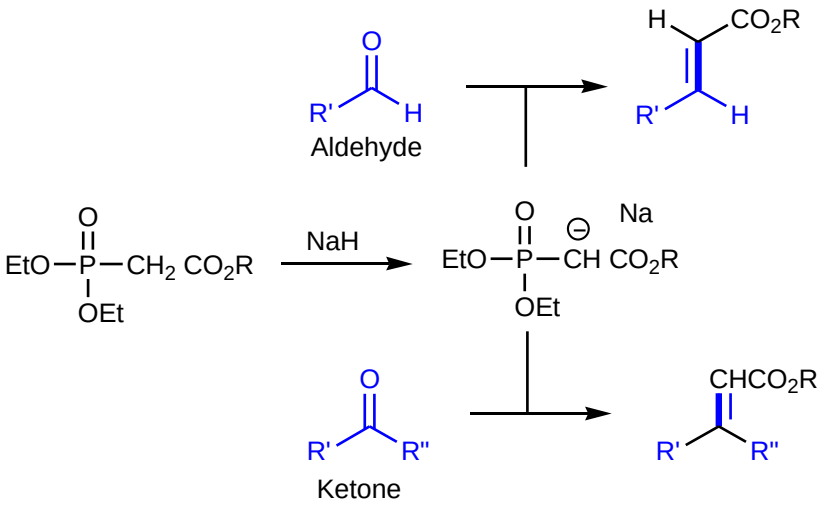


Figure 159 Use of the Horner-Wadsworth-Emmons reaction to generate α,β-unsaturated esters.

App 5.26.4 The Peterson Reaction

The Peterson reaction is an alternative method to the Horner-Wadsworth-Emmons reaction for creating α,β-unsaturated esters, and involves reacting an aldehyde or ketone with an α-silyl carbanion (Fig. 160). The silicon reagent is generally more reactive than the corresponding phosphorus reagent.

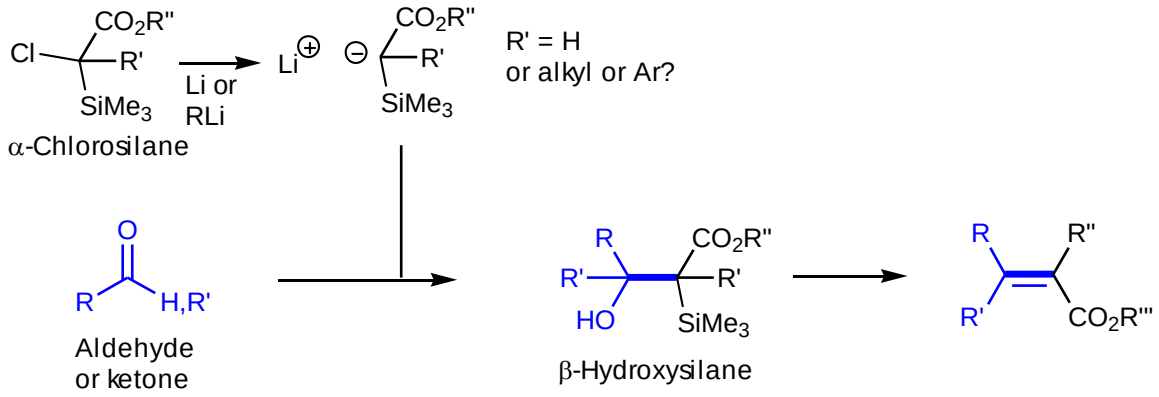


Figure 160 Synthesis of α,β-unsaturated esters by the Peterson reaction.

App 5.26.5 Synthesis of α,β-unsaturated esters by the Heck reaction

Aromatic and heteroaromatic α,β-unsaturated esters can be synthesised by coupling an aromatic halide with an α,β-unsaturated ester in the presence of a palladium catalyst (Fig. 161). Mono-, di- and trisubstituted unsaturated esters have been used in the reaction, as well as α,β-unsaturated acids. The reaction requires *in situ* reduction of palladium (II), which is achieved by adding tri(o-tolyl)phosphine ($P(o\text{-}Tol)_3$).

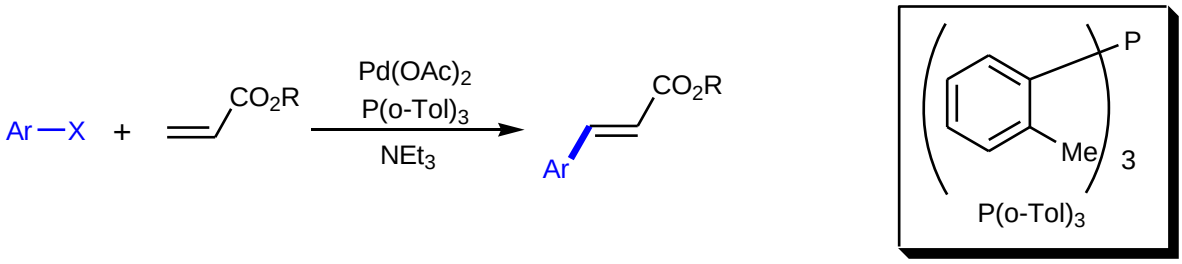


Figure 161 Synthesis of α,β-unsaturated esters by the Heck reaction.

App 5.26.6 Synthesis of α,β-unsaturated esters by the Knoevenagel reaction

The Knoevenagel reaction can be carried out between diethyl malonate and an aldehyde in the presence of a weak acid (HOAc) and a weak base (R_2NH) to give an α,β-unsaturated ester (Fig. 162). Self condensation involving diethyl malonate or the aldehyde does not occur. Diethyl malonate is largely enolised under normal conditions and the weak base serves to generate a small amount of the enolate ion. However the ester groups of the diethyl malonate are not sufficiently reactive to react. In contrast, the aldehyde has a more electrophilic carbonyl group and so the enolate of diethyl malonate reacts exclusively with the aldehyde. The aldehyde itself does not self condense because the base is too weak to remove its α-proton to form an enolate.

The final steps involve hydrolysis of the ester groups with base, followed by decarboxylation under acid conditions. Esterification of the surviving carboxylic acid generates the unsaturated ester.

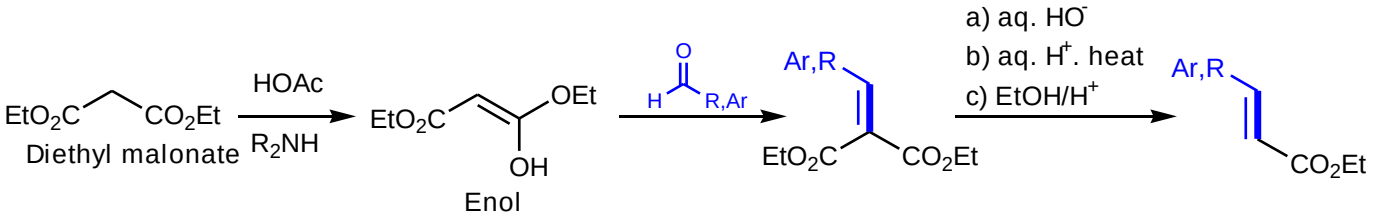


Figure 162 Synthesis of α,β-unsaturated esters by the Knoevenagel reaction.

This reaction can also be carried out using malonic acid (Fig 163a). This has the advantage that decarboxylation occurs under the reaction conditions to give the α,β-unsaturated acid directly.

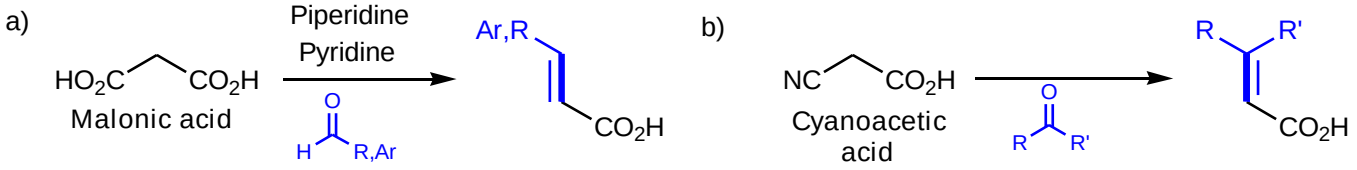


Figure 4.163 Other reagents capable of forming stabilised carbanions for the Knoevenagel reaction.

The Knoevenagel reaction works better with aromatic aldehydes than with aliphatic aldehydes, as the product from an aliphatic aldehyde can react further to give unwanted side products.

Ketones do not react with either malonic acid or diethyl malonate, but the reaction can be successfully achieved using cyanoacetic acid or its esters (Fig. 163b). However, diethyl malonate can react with ketones in the presence of $TiCl_4$ and pyridine in THF.

App 5.27 α,β-Unsaturated ketones

There are a number of functional group transformations that can be used to synthesise α,β-unsaturated ketones from ketones or alkenes (appendix 1.46). They can also be synthesised from aldehydes, ketones, alkynes, acid chlorides and α,β-unsaturated acid chlorides by C-C bond formations (Fig. 164).

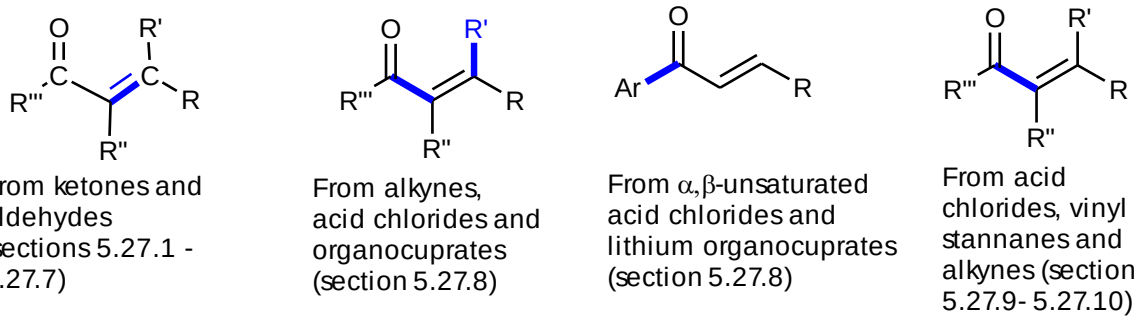


Figure 164 C-C Bond formations used in the synthesis of α,β–unsaturated ketones

App 5.27.1 α,β-Unsaturated ketones from the Aldol condensation

The Aldol reaction has previously been described as a method of synthesising β-hydroxy ketones from a ketone (appendix 5.18.1). If the reaction is carried out under different conditions (e.g. increasing the amount of base, using a stronger base, or heating more strongly over a longer period), then water is eliminated to form an α,β-unsaturated ketone (Fig. 4.165). This is called the Aldol condensation as water is being lost in a dehydration process. Carrying out the reaction under acid conditions also encourages formation of the unsaturated product.

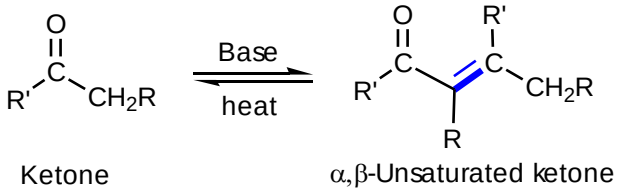


Figure 165 The Aldol reaction followed by dehydration.

Only one condensation product can be obtained from a symmetrical ketone. With unsymmetrical ketones, a mixture of products is possible if there are α-protons on either side of the carbonyl group. Therefore, the reaction works best on unsymmetrical ketones where there are α-protons on only one side of the carbonyl group; for example aromatic ketones.

App 5.27.2 Crossed Aldol reaction between a ketone and an aldehyde

Ketones and aldehydes can be linked together by a crossed Aldol reaction - a reaction known as the **Claisen-Schmidt** reaction. The most successful reactions are those involving a ketone that only forms one kind of enolate, reacting with an aldehyde that does not have an α-proton (Fig. 166). Since the aldehyde cannot enolise, there is no chance of a competing Aldol reaction between two molecules of the aldehyde. The chances of the ketone self condensing are low because the aldehyde has a more electrophilic, reactive carbonyl group than the ketone. Therefore, once the enolate of the ketone has been formed, it is more likely to react with the more reactive aldehyde.

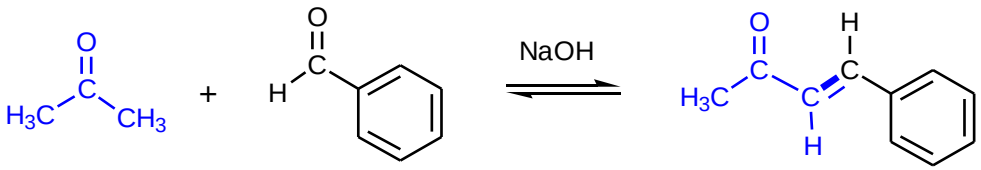
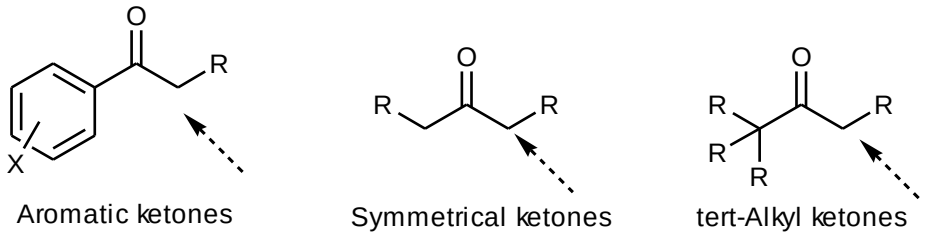


Figure 166 The Claisen-Schmidt reaction.

Examples of suitable ketones and aldehydes include aromatic aldehydes and ketones, symmetrical ketones, formaldehyde and *tertiary*-butyl aldehydes and ketones (Fig. 4.167). Trying to react an enolisable aldehyde with a non-enolisable ketone will not succeed as self condensation of the aldehyde is far more likely.

a) Ketones capable of forming only one type of enolate



b) Aldehydes incapable of forming an enolate

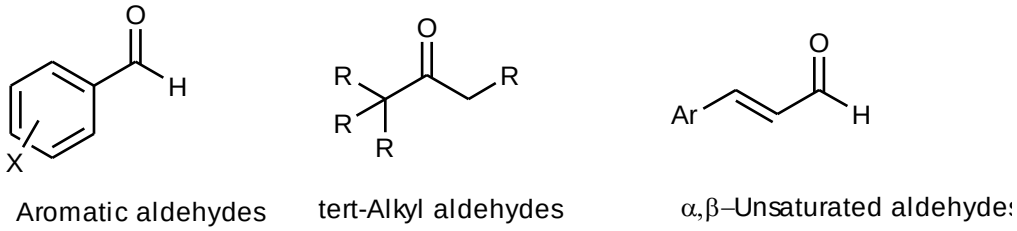


Figure 167 Suitable ketones and aldehydes for a crossed Aldol reaction.

With unsymmetrical ketones capable of enolising on both sides of the carbonyl group, two different products are possible (Fig. 168). The preference can be determined by whether the reaction is carried

out under acidic or basic conditions, but it is usually better to use preformed enolates as described in the following sections.

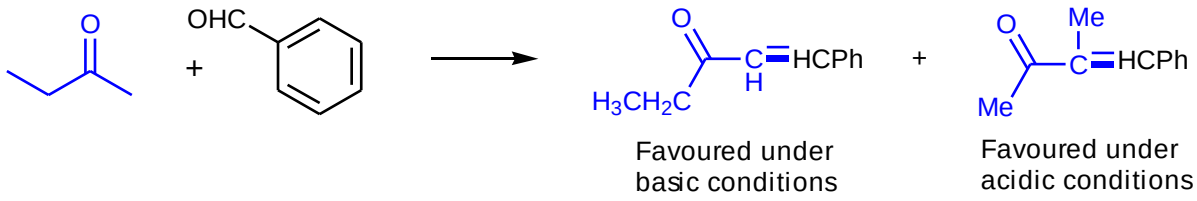


Figure 168 The Claisen-Schmidt reaction between an aromatic aldehyde and an unsymmetrical ketone.

App 5.27.3 Crossed Aldol reaction with preformed enolates or enamines

An alternative way of carrying out crossed Aldol reactions is to use preformed enolates as described in appendices 5.18.2-5.18.4. The hydroxy ketones generated in this way can be easily converted to the corresponding unsaturated ketones by acid treatment (Fig. 169a&b). Another approach is to use enamines which are, in turn, synthesised from aldehydes or ketones (Fig. 169c).

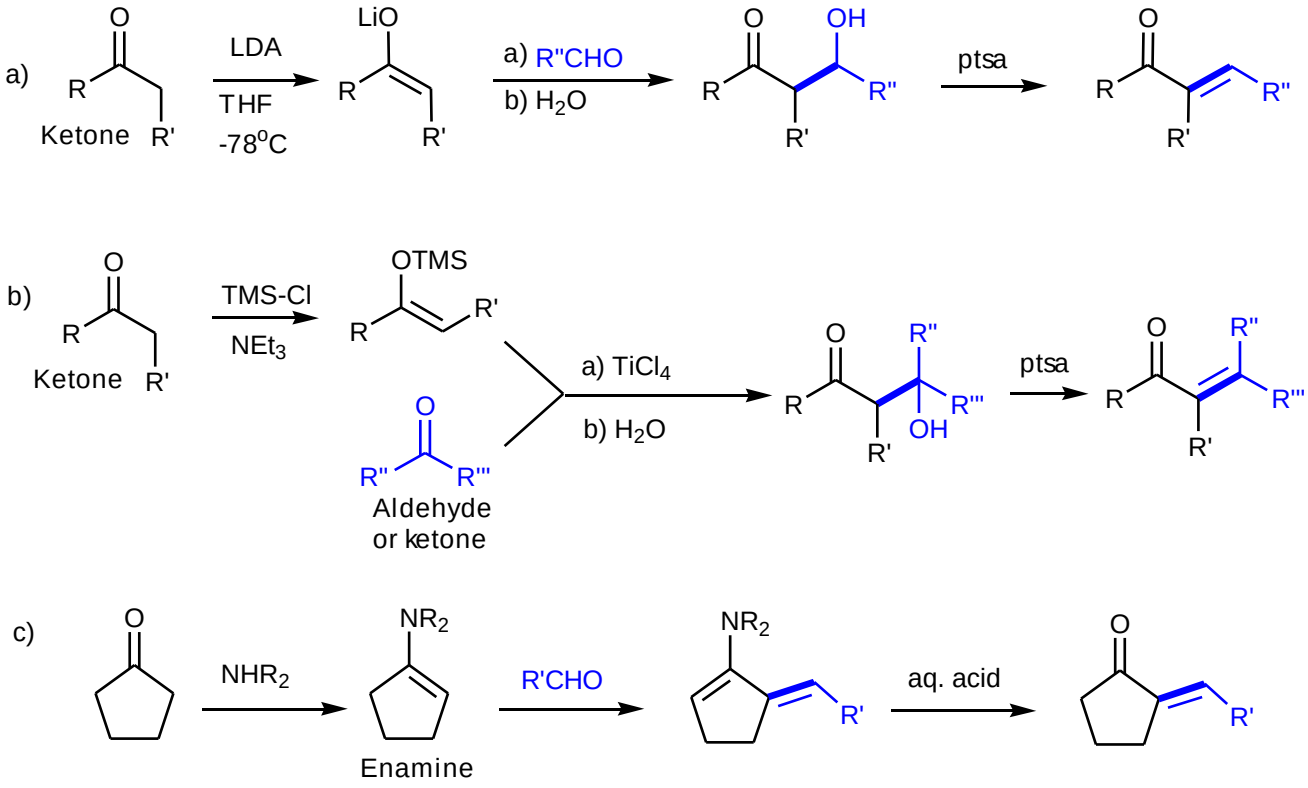


Figure 4.169 The Aldol reaction with preformed enolates or enamines.

App 5.27.4 α,β-Unsaturated ketones from β-ketoesters

α,β-Unsaturated ketones can be generated from β-ketoesters by carrying out the crossed Aldol condensation with an aldehyde, followed by hydrolysis and decarboxylation of the ester group (Fig. 170). The reaction works with most aldehydes whether they have an enolisable proton or not.

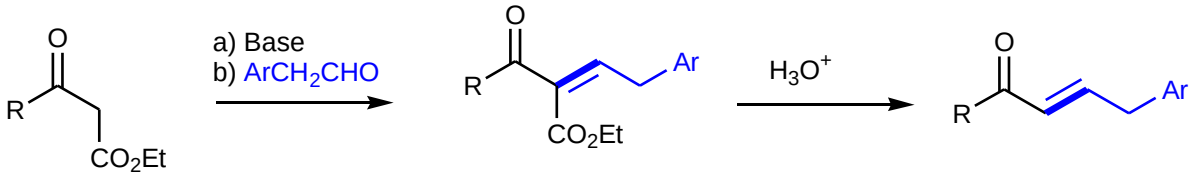


Figure 170 Synthesis of an α,β-unsaturated ketone from a β-ketoester.

App 5.27.5 The Mannich reaction

The Mannich reaction involves reacting an aliphatic or aromatic ketone containing an α-hydrogen with a secondary amine and formaldehyde to form a β-amino ketone (Fig. 171). Further reaction with iodomethane followed by base generates an α,β-unsubstituted ketone with a terminal alkene group. This kind of product would be difficult to synthesise by other methods and can be used for the Michael reaction.

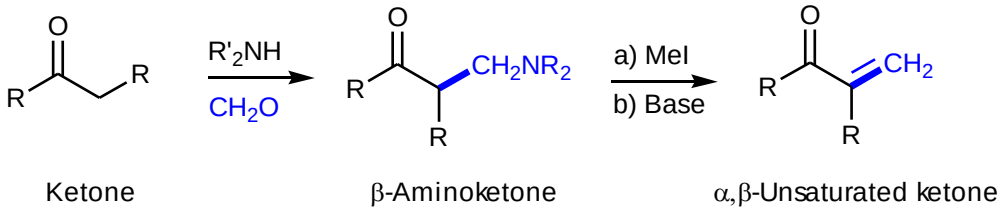


Figure 171 Synthesis of an α,β-unsaturated ketone via a β-aminoketone.

App 5.27.6 The Horner-Wadsworth-Emmons Reaction

The Horner-Wadsworth-Emmons reaction is similar to the Wittig reaction used for the synthesis of alkenes (appendix 5.3.1), but involves a phosphonate reagent which includes a ketone group (Fig. 172). Unlike the Wittig reaction, the preferred stereochemistry is the *E*-isomer over the *Z*-isomer. The reaction can be carried out on both aldehydes and ketones.

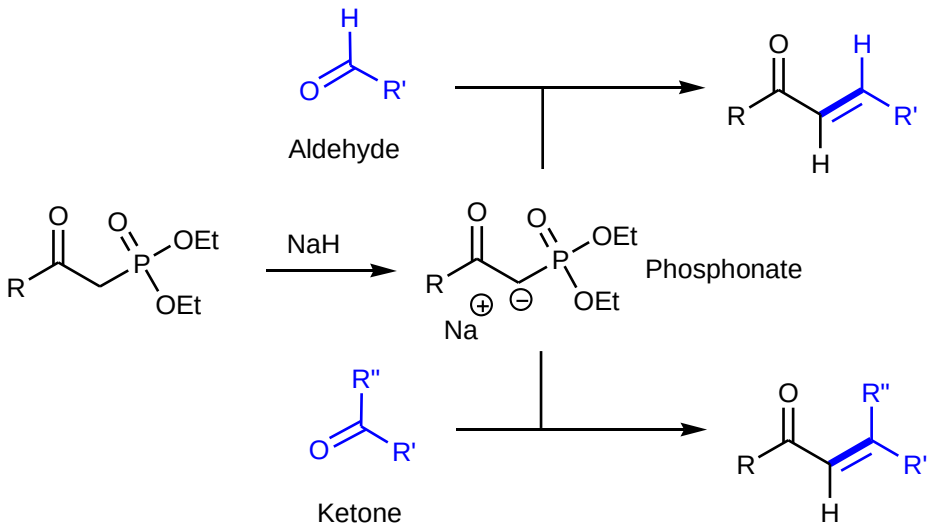


Figure 172 The Wadsworth-Emmons reaction.

App 5.27.7 The Wittig reaction

It is possible to synthesise α,β–unsaturated ketones by reacting a stabilised phosphorane derived from an α-bromo ketone with an aromatic or aliphatic aldehyde (Fig. 173). The preferred stereochemistry is the *E*-isomer of the alkene. The stabilised phosphorane is not sufficiently reactive to react with ketones. In such cases, it is better to use the more reactive phosphonate reagents (appendix 5.27.6)

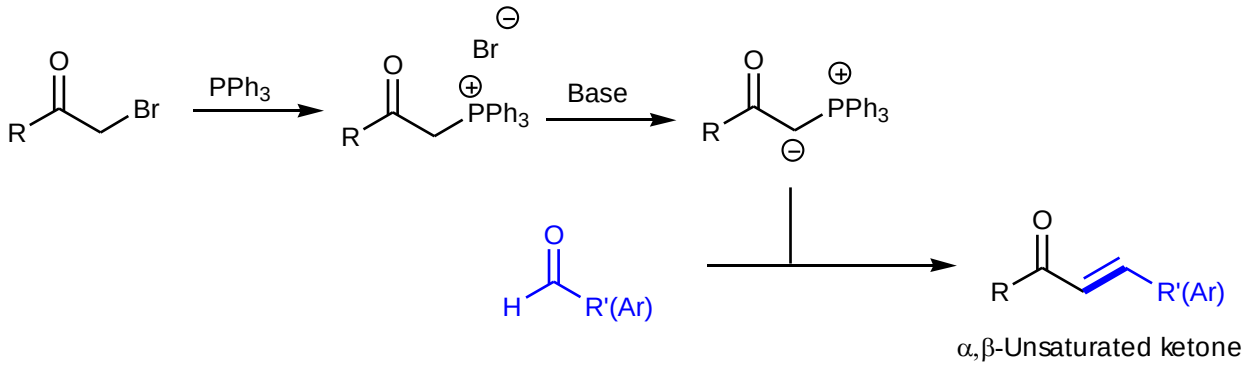


Figure 173 The Wittig reaction with aromatic or aliphatic aldehydes to generate α,β–unsaturated ketones.

App 5.27.8 α,β-Unsubstituted ketones from acid chlorides and organocuprate reagents

The reaction of an acid chloride with organocuprate reagents can be used to synthesise ketones (appendix 5.22.5). Reaction of an acid chloride with an alkenylcopper (I) reagent results in an α,β-unsubstituted ketone with preservation of the alkene stereochemistry (Fig. 174a). The reaction is carried out with cooling and there is no reaction with any chloro substituents, ethers or esters that might be present in the starting material.

Another approach is to react an α,β-unsaturated acid chloride with a diorganocuprate reagent (Fig. 174b).

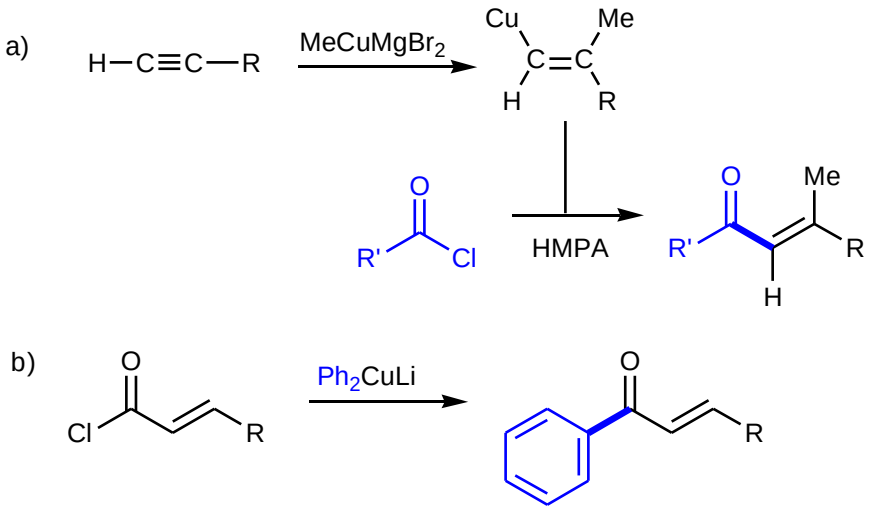


Figure 174 Organocuprate reagents in the synthesis of α,β–unsaturated ketones.

App 5.27.9 The Stille reaction

Vinyl stannanes react with acid chlorides in the presence of a palladium catalyst and carbon monoxide to give α,β-unsaturated ketones (Fig. 175). The reaction involves both reactants binding to the palladium metal in an oxidative process, before they link together in a reductive-elimination step. The carbon monoxide is present to prevent decarbonylation of the acid chloride once it is bound to the palladium catalyst.

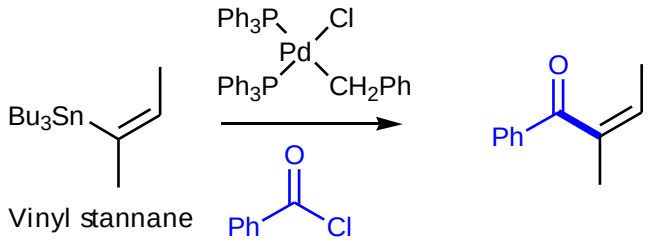


Figure 175 α,β-Unsaturated ketones from the Stille reaction.

App 5.27.10 α,β-Unsaturated ketones from alkynes

The reaction of organoborane reagents with alkynes has already been described as a method of synthesising conjugated dienes (appendix 5.12.3). If the final reaction with acid is replaced with an oxidative work up using hydrogen peroxide, then an α,β-unsaturated ketone is obtained (Fig. 176).

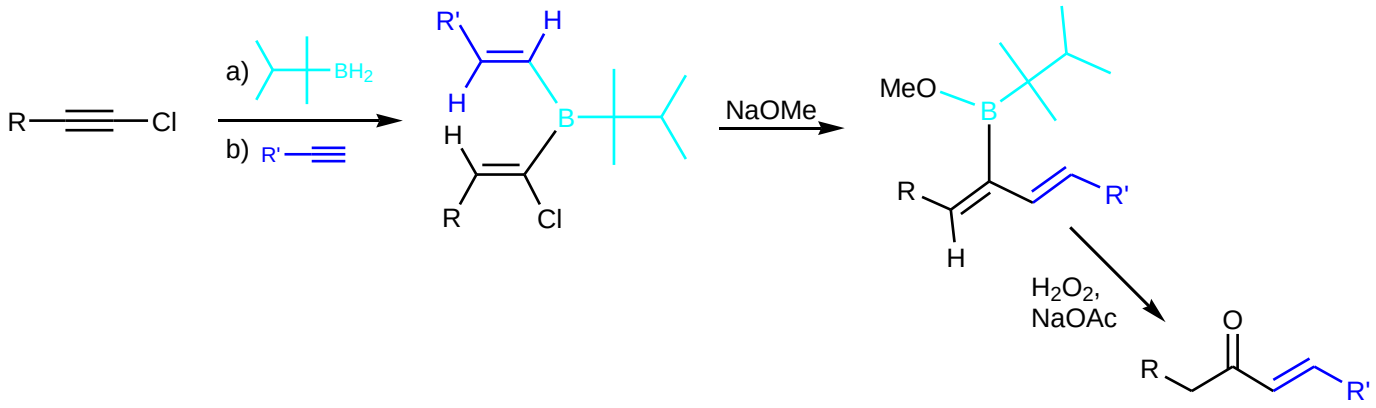


Figure 176 α,β-Unsaturated ketones from organoboranes and alkynes.

App 5.28 α,β-Unsaturated nitriles

α,β-Unsaturated nitriles are not commonly found in drugs. An exception is rilpivirine, which is a second-generation non-nucleoside reverse transcriptase inhibitor used in the treatment of HIV.

App 5.28.1 Horner -Wadsworth-Emmons

α,β-Unsaturated nitriles can be synthesised by the Horner-Wadsworth-Emmons reaction (Fig. 177). The *E*-isomer is generally preferred if a choice of *E* and *Z*-isomers is possible.

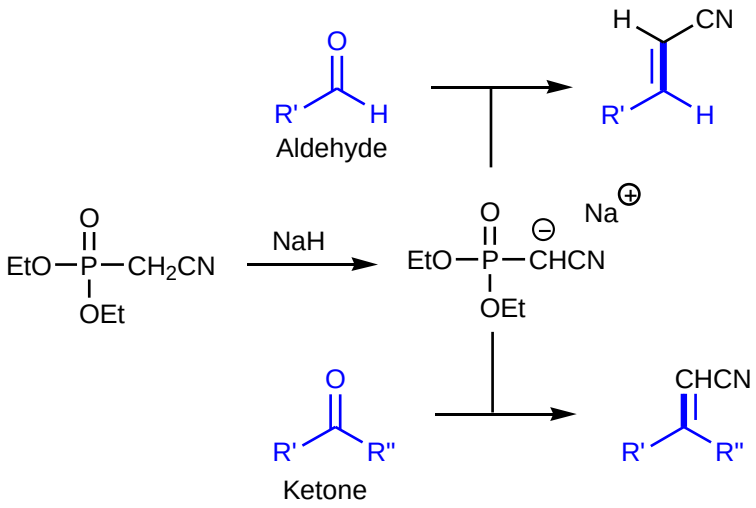


Figure 177 Synthesis of α,β-unsaturated nitriles.

The Wittig reaction involves the use of a stabilized phosphorane which is sufficiently reactive to react with an aldehyde but not a ketone.

App 5.28.2 The Heck reaction

The Heck reaction has been used to synthesise α,β-unsaturated nitriles by reacting aryl halides with acrylonitrile in the presence of a palladium catalyst (Fig. 178).

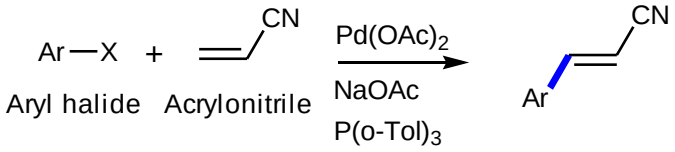


Figure 178 Synthesis of α,β-unsaturated nitriles using the Heck reaction.