THE UNIVERSITY
OF BIRMINGHAM

CHM2C3-A/B Retrosynthesis

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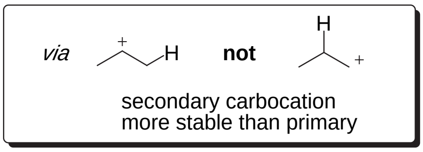
A Summary of Useful Reactions from CHM1C3 and CHM2C3-A

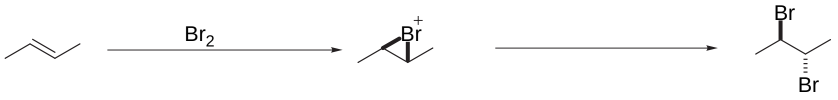
Alkenes

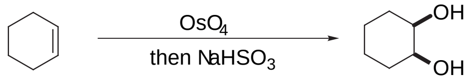
The typical reaction is **electrophilic addition**. This occurs in a Markovnikov fashion, *ie.* it proceeds through formation of the more stable carbocation (carbenium ion). Remember, the order of stability for carbocations is tertiary > secondary > primary > methyl. The alkene attacks the more positive end of the electrophile (X–Y) (work this out on the basis of electronegativity) to give a carbocation and the anion (*e.g.* Y^-). The intermediate is then intercepted by the anion Y^-. Remember atoms like bromine can use one of their lone pairs to stabilise the carbocation, giving a cyclic bromonium ion. This opens up with inversion (like S_N2) to give the *anti* product. Some common reactions that you will find useful are shown below.

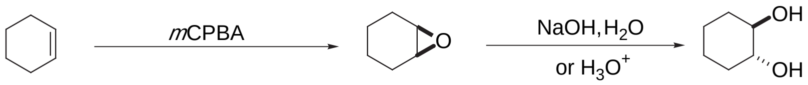
Reactions of alkenes

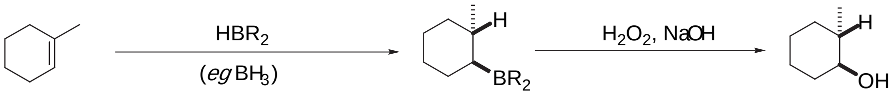


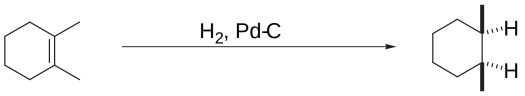
secondary carbocation
more stable than primary







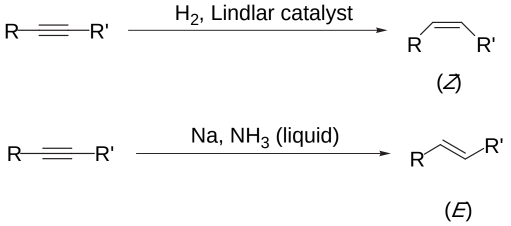




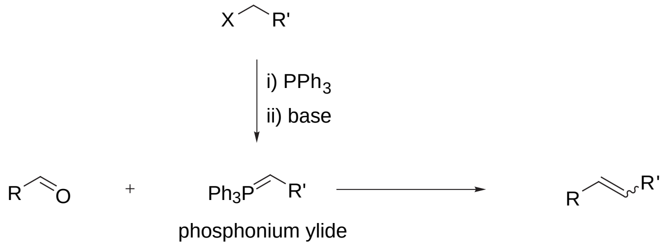
Formation of alkenes

There are many methods available for forming alkenes, some of which you will have seen from earlier courses. In the case of 1,2-substituted alkenes, stereoselectivity issues ((*E*) or (*Z*) stereoisomers) are also important and need to be considered.

1. From alkynes



2. Wittig reaction

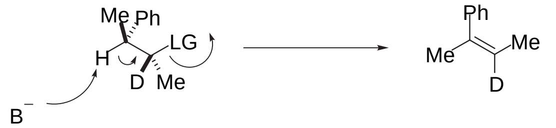


(*Z*)-selective when R' = alkyl

(*E*)-selective when R' = electron-withdrawing group

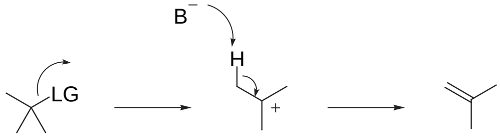
3. Elimination

Elimination can proceed through three basic mechanisms, E_2, E_1 and E_1cb. The E_2 elimination pathway is particularly useful because it proceeds in a stereospecific fashion with antiperiplanar arrangement between the H–C–C–LG (LG = leaving group). Elimination is a common side-reaction in nucleophilic substitution reactions.



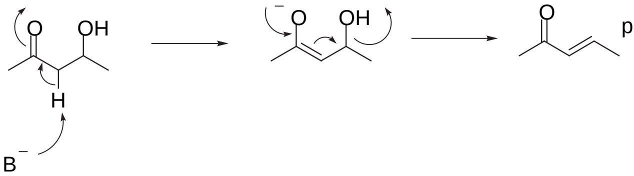
requires H-C and C-LG bonds
to adopt an antiperiplanar arrangement

E_2



only proceeds when a stabilised
carbocation can be formed
(*e.g.* tertiary carbocation)

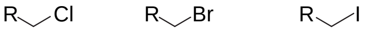
E_1



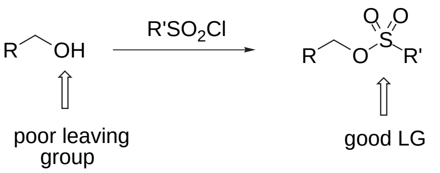
particularly common in base-mediated
dehydration of aldol products

E_1cb

Common leaving groups include halides and sulfonates:



leaving group capacity: $I^- > Br^- > Cl^-$



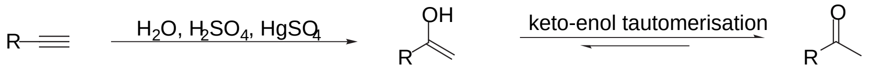
R' = Me (mesylate)

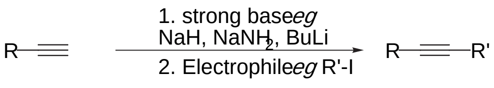
R' = *p*MePh (tosylate)

R' = CF_3 (triflate)

Alkynes

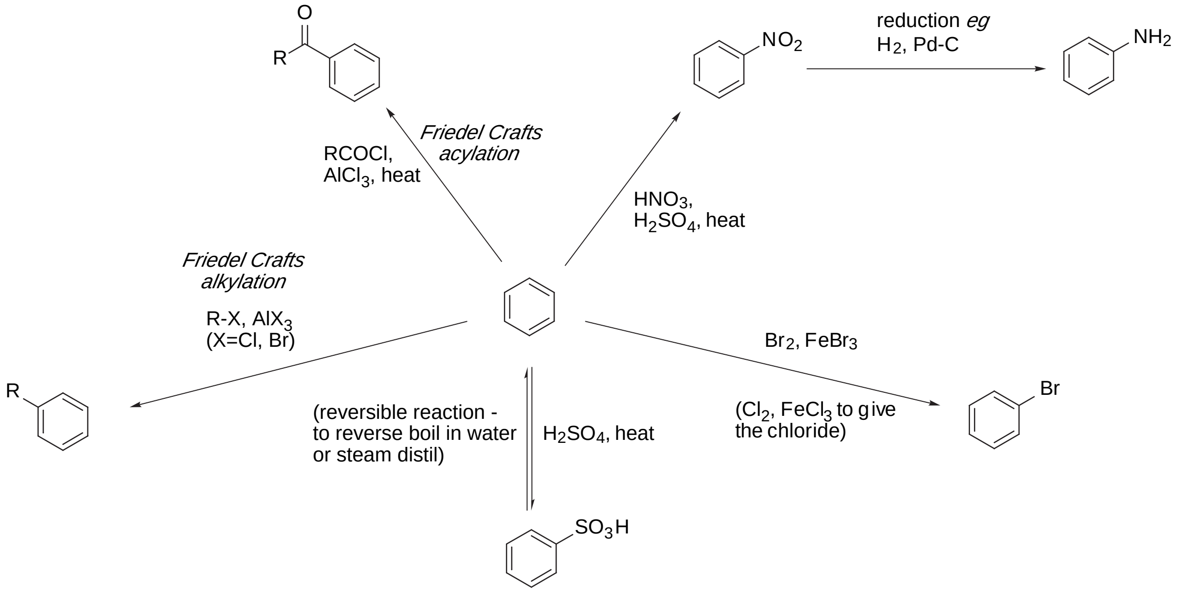
Electrophilic addition reactions of alkynes are less useful than for alkenes. The initially formed vinyl carbocation is relatively unstable and thus slow to form. The product alkene often reacts (to form an alkane) faster than the alkyne, and so a mixture of alkene and alkane products may form. Some of the reactions that are synthetically useful are summarised below.





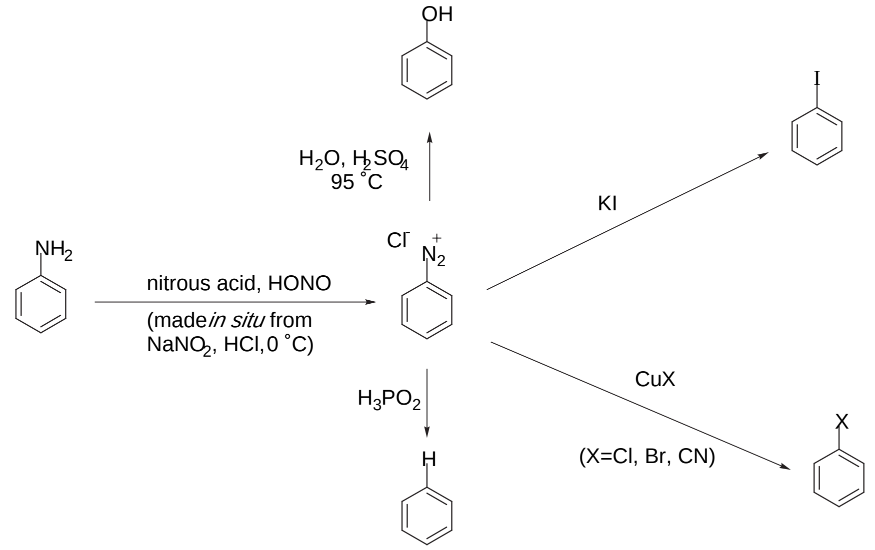
Aromatics

Reaction with electrophiles dominates, but this time we see *substitution* products rather than *addition* products. Because of the aromatic stabilisation energy the intermediate carbocation loses a proton to regain the aromatic ring rather than being attacked by a nucleophile. Some important reactions involving aromatics:



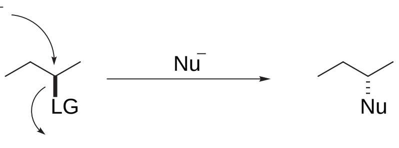
Diazotisation

Nitration of aromatics is a very useful reaction, since the nitro aromatics may be transformed into a wide variety of products. Reduction affords the corresponding aniline, and diazotisation of this gives a very reactive diazonium salt which is synthetically very versatile. Below are some representative examples.

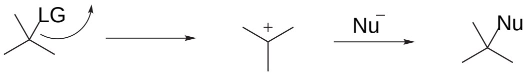


Nucleophilic Substitution Reactions

There are two important nucleophilic substitution reaction mechanisms, S_N1 and S_N2. The most important of these for synthesis is the S_N2 substitution. This reaction is a stereospecific process which proceeds with *inversion of configuration*. A variety of leaving groups can be used (see above in the section on elimination reactions).

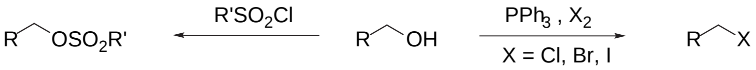


S_N2 good for primary and secondary alkyl halides and sulfonates



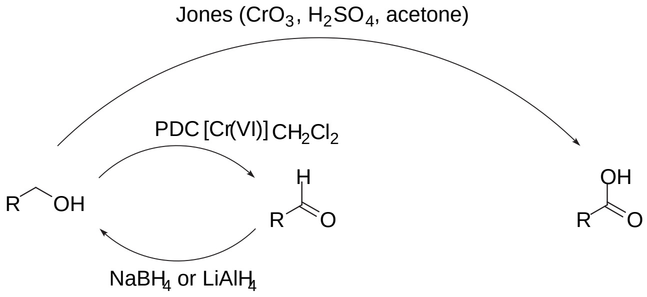
S_N1 good for tertiary alkyl halides and sulfonates

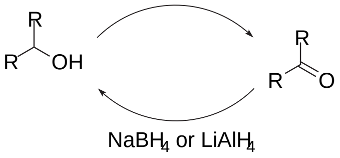
Alkyl halides and sulfonates are commonly used in nucleophilic substitution reactions. They are easily formed from the corresponding alcohols.



Chemistry of the Carbonyl Group

Formation by oxidation and reduction

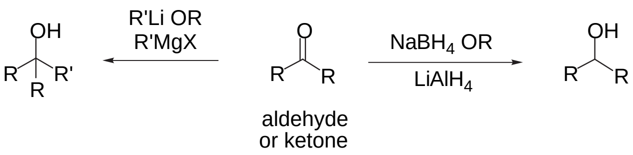




Aldehydes and Ketones

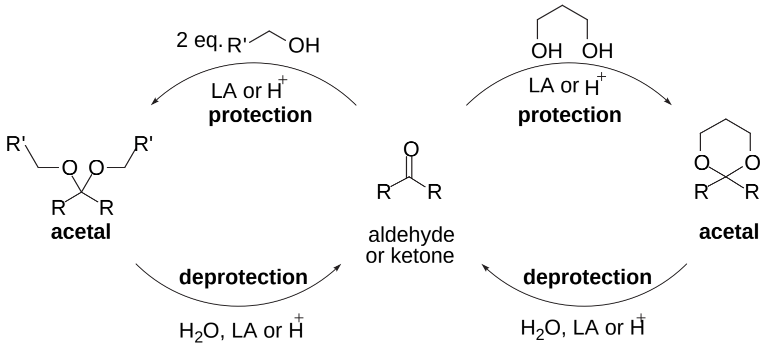
Nucleophilic Addition

The chemistry of aldehydes and ketones is characterised by nucleophilic addition reactions. A wide range of nucleophiles can be used. Common hydride sources include $NaBH_4$ and $LiAlH_4$ ($NaBH_4$ more chemoselective than $LiAlH_4$, which reduces most functional groups containing the C=O group). Common Carbon-nucleophiles are organolithium and organomagnesium (*i.e.* Grignard) reagents. Reaction proceeds through a *tetrahedral intermediate* which is quenched on aqueous work-up to provide an alcohol product.



Acetals

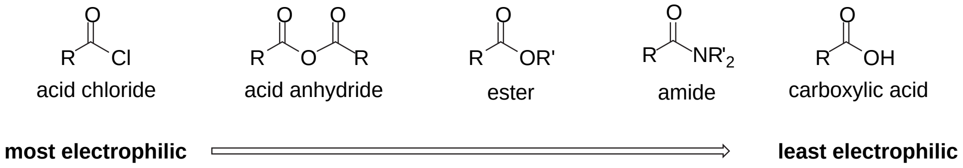
Aldehydes and ketones are good electrophiles. Sometimes we need to mask this reactivity to allow us to perform reactions elsewhere in the molecule. We therefore need a *protecting group* to temporarily mask the C=O group. Acetals are the most common protecting groups for aldehydes and ketones. They are readily prepared under mildly acicic (Brønsted or Lewis acids can be used) conditions and can be hydrolysed back to the parent carbonyl compound by aqueous acid.



Carboxylic Acid Derivatives

These functional groups all contain a C=O group and are therefore also electrophilic. However, their reactivity towards nucleophilic attack depends on the substituent(s) attached.

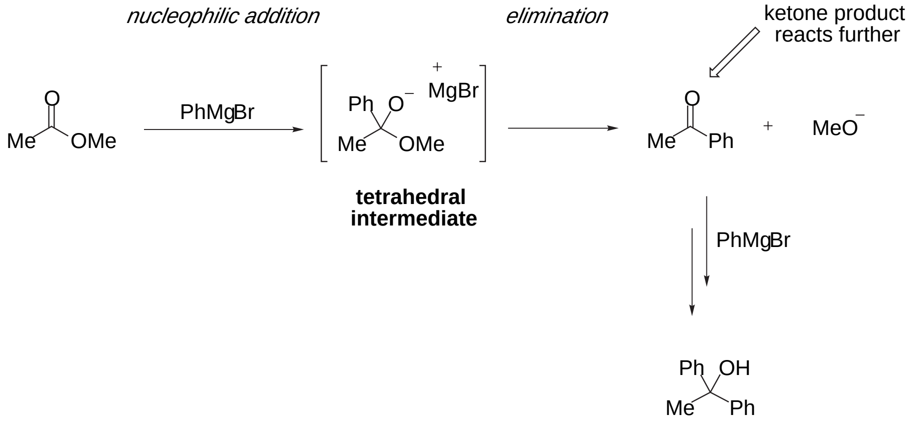
order of reactivity towards nucleophilic addition



Thus acid chlorides can be used to prepare all of the less reactive carboxylic acid derivatives by reaction with the relevant partner *e.g.* for ester synthesis react an acid chloride with an alcohol, for amide synthesis react the acid chloride with the appropriate amine.

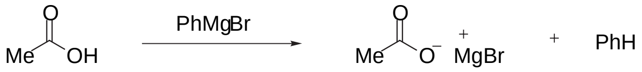
Mechanism of nucleophilic addition / elimination

Carboxylic acid derivatives react with nucleophiles in a similar fashion to aldehydes and ketones, proceeding *via* a tetrahedral intermediate. However the presence of a leaving group means that the carbonyl group can be re-formed by expulsion of the leaving group. In the case of esters, the initial product from the reaction with a Grignard or organolithium reagent is a ketone. This is more electrophilic than the ester starting material and therefore tends to react further. It is therefore generally quite difficult to prepare ketones from carboxylic acid derivatives.

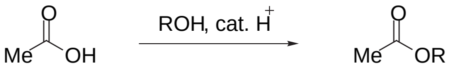


Uses of Carboxylic Acids

The presence of an acidic proton in the carboxylic acid renders these functional groups very weak electrophiles. Reaction with a nucleophile invariably just results in the nucleophile behaving preferentially as a base and forming the corresponding carboxylate salt (acid-base reaction).

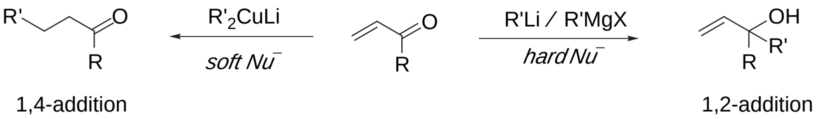


However under acidic conditions, alcohols react with carboxylic acids to generate the corresponding ester. You should know the mechanism of this reaction (the acid is required as a catalyst to create a good leaving group). Note that this reaction is an equilibrium process. To drive the reaction over to the right-hand side it is important to remove the water side-product that is formed, or alternatively use a vast excess of the alcohol.



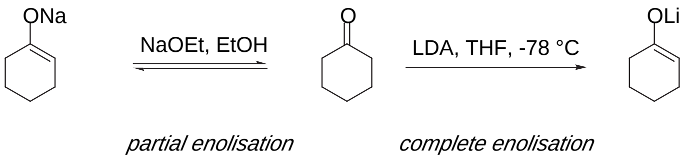
α,β-Unsaturated Carbonyl Compounds

Enones and enoates are *ambident electrophiles* in that there is more than one site at which nucleophiles can react. In general, **hard nucleophiles** (*e.g.* organolithium and Grignard reagents) react in a 1,2-fashion *i.e.* directly at the carbonyl carbon, whereas **soft nucleophiles** (*e.g.* sulfides and organocopper reagents) react in a 1,4-fashion thereby preserving the carbonyl group in the product.

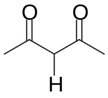


Enolates

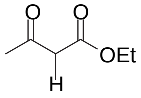
Enolates are formed by treating a carbonyl compound containing an α-C–H group with a base. The pK_a of the α-C–H determines what type of base to use. To get complete enolisation use a base (B$^-$) whose conjugate acid (B–H) has a much higher pK_a that the α-C–H that you are wishing to abstract. To get partial enolisation choose a base whose conjugate acid has a pK_a similar to that of the proton you are wishing to abstract.



Some Important pK_a Values of Carbonyl-Containing Molecules



9.0



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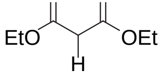

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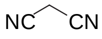

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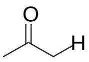

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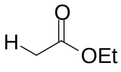

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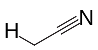

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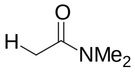

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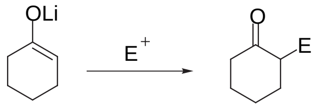
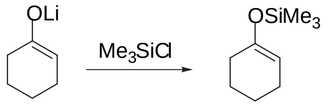
Enolates as Nucleophiles

Enolates are ambident nucleophiles in that they can react at either terminus of the functional group. Most electrophiles react at carbon; the most important exception is silyl electrophiles which react preferentially at oxygen to provide silyl enol ethers.



E = alkyl halides, aldehydes, esters

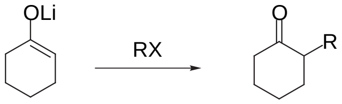
C-alkylation



O-alkylation

Important Reactions involving Enolates

alkylation

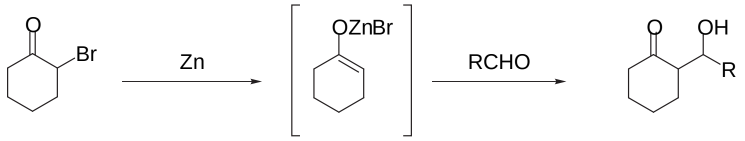


particularly good for primary RX and activated RX such as MeI, allyl bromide and benzyl bromide

aldol reaction

dehydration can be a competing reaction

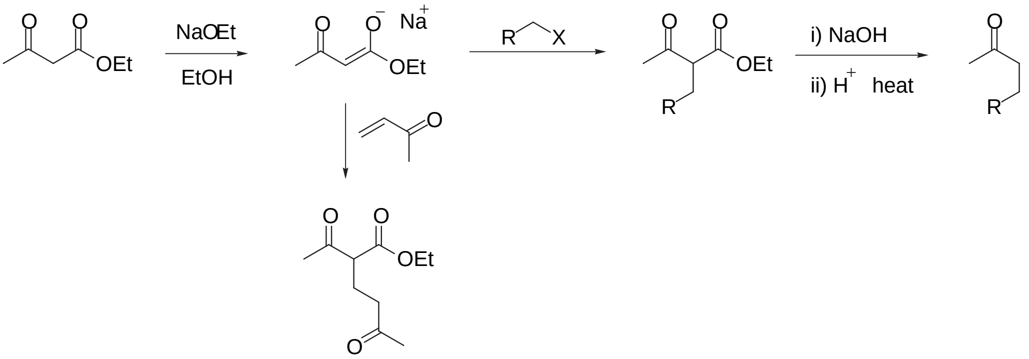
The high reactivity of lithium enolates can cause selectivity problems in these reactions. It is possible to temper the reactivity by changing the metal. For example, zinc enolates are less basic than their lithium analogues but still retain high nucleophilicity in their reaction with aldehydes.



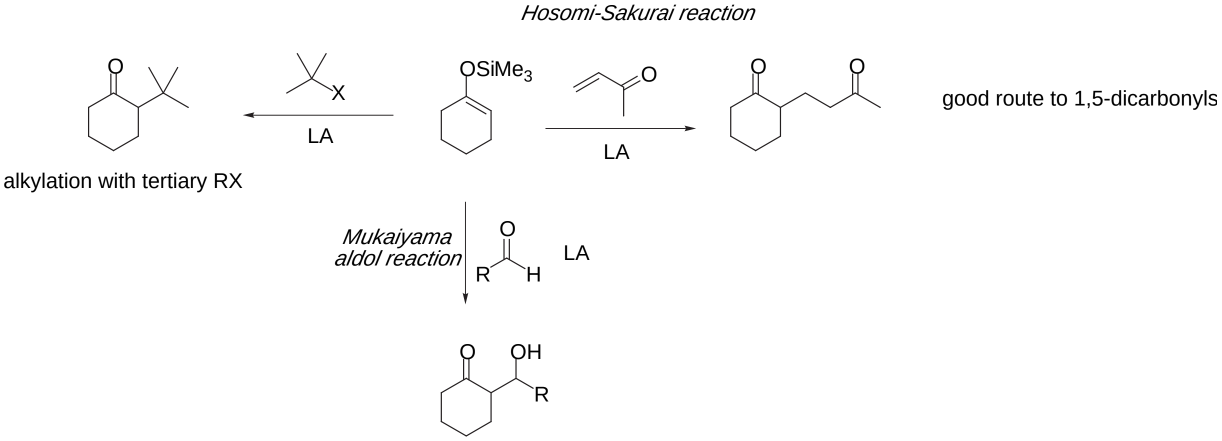
zinc enolate

Reformatski aldol reaction

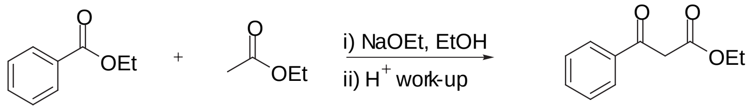
1,3-Dicarbonyl Compounds are also very important enolate nucleophiles. Regioselective enolisation is straightforward and the enolate products are good, soft nucleophiles that react with a range of activated alkyl halides and in a 1,4-fashion with α,β-unsaturated carbonyl compounds. β-Keto esters are very useful latent ketone enolate equivalents since the ester is readily removed by a saponification / decarboxylation process.



Silyl enol ethers are relatively mild soft nucleophiles which react with strong electrophiles. Unlike most enolates, they are stable to strong Lewis acids which allows their use in a range of important reactions:

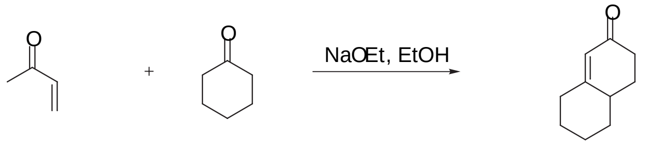


Other Important Reactions involving Enolates



Claisen condensation

a good method for preparing β-keto esters



Robinson annelation

an important method for preparing rings

This hand-out summarises some of the most important areas of organic chemistry that you have covered in years 1 and 2. It contains many of the reactions that you will find useful when proposing syntheses of organic molecules. However, it is by no means exhaustive; you will often need to refer to text books and your original lecture notes to find the reagents and reaction conditions that you desire for carrying out a synthetic transformation.