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Room 2.4 School of Chemistry

Introduction to

Organic Synthesis 2011

Lectures 1-7

This course gives a basic introduction to organic synthesis. The aim is to show the use of several common reactions, introduce the concept of synthetic organic chemistry and how organic chemists design and carry out multi step synthesis.

The following topics will be covered in this course:

- **Introduction to synthesis, chemoselectivity, regioselectivity and functional groups**
- **Radical Reactions**
- **Carbocations and carbanions (electrophilic carbon and nucleophilic carbon).**
- **The use of Grignard reagents, organocopper compounds and alkyl lithium compounds.**
- **Aldol and carbonyl chemistry: Stabilised carbanions, acid/base activation, Michael addition.**
- **Malonate ester, enolate formation, alkylation of malonate esters, double alkylation reactions,**
- **Carbanion stabilised by two electron withdrawing groups, β-keto esters, 1,3-diketone, condensation reactions such as Knoevenagel, etc., kinetic vs. thermodynamic control and decarboxylation.**
- **Hard and soft acid base (HSAB) theory**
- **Pericyclic reactions, Diels-Alder reaction, diene, and dienophiles.**
- **Formation of double bonds.**

Recommended reading

Very good books that cover all the material:

- **Organic Chemistry by John McMurry**
- **Organic Chemistry by Clayden, Greeves, Warren and Worhers**
- **Organic Chemistry by Brown, Foote, Iverson and Anslyn**
- **Many more…….**

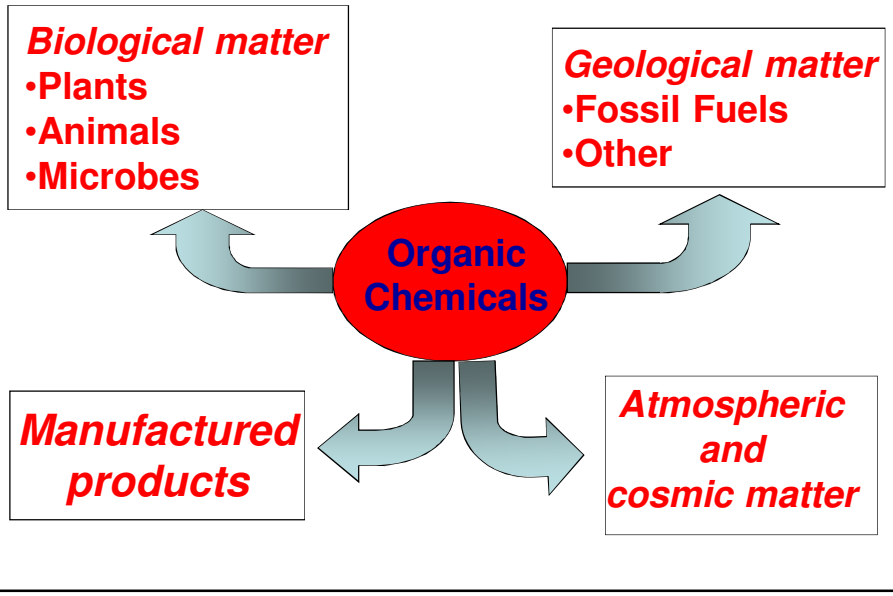
Specific:

- Guidebook to Organic Synthesis 3rd. Ed. Mackie, Smith and Aitken.
- Organic Synthesis the Disconnection Approach, Stuart Warren.
- Designing Organic Synthesis, Stuart Warren

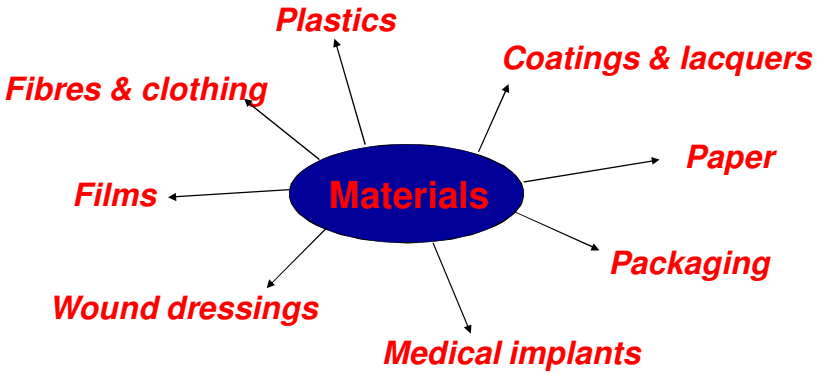
Lecture 1:

- **Introduction to organic synthesis**
- **Radical chemistry an introduction**

Organic chemicals are universal



Organic chemicals in manufactured products produced in Ireland

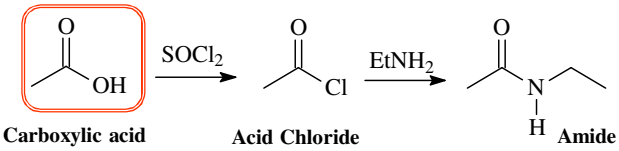


Introduction

What is organic synthesis?

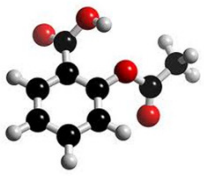
- Organic compounds can be **SYNTHESISED** from smaller subunits that have functional groups.
- **Functional groups** are moieties within a given structure that we can use as **'handles'**! We use these to extend structures, or add new components to a given molecule.
  - These groups are said to be **'reactive'** in comparison to ordinary carbon-carbon or carbon-hydrogen bonds, hence we could say that:

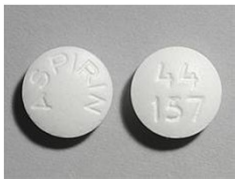
they import specific types of reactivity to organic molecules….hence this acid:

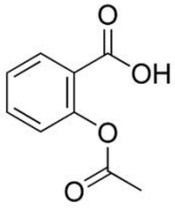


Carboxylic acid **Acid Chloride** **Amide**

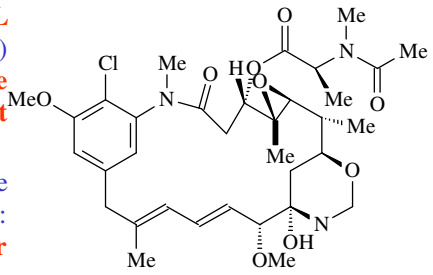
- Of course the structures can contain **many functional groups** and we have to be able to select those we want to react!





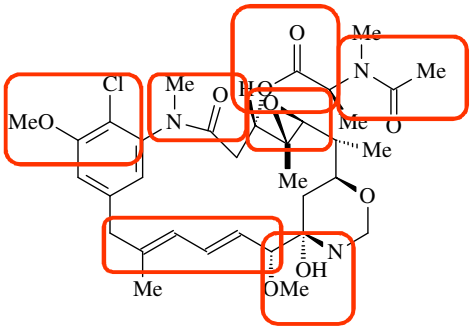


- Not just that, if we want to make a given molecule, such as a **NATURAL PRODUCT** (like TAXOL shown earlier) we have to be able to **place these functional groups into the molecule at the right places**!
- That can often be a problem, as the following example shows: **MAYTANSINE : A potent anti-tumour agent (E. J. Corey *et. al.* 1978-1980)**



- Here we not just have many functional groups but also **STEREOCHEMISTRY** to think about!

- **Lets look at Maytansine a bit more and try to identify some of the functional groups you saw and learned about last year:**



- **And there are more!!!**
- **To be able to synthesise a molecule like this, or even the amide on the first slide, we have to be able to:**

BREAK OR MAKE NEW BONDS BETWEEN ATOMS

- **This lecture course is all about doing that kind of chemistry……**

- The reaction steps are the actual synthesis, when we form or break **C-C, C-O, C-X** bonds etc.
- These reactions can often occur at more than one possible place! **Which obviously is a problem!!**
- This would lead to other products that we are not interested in and are called **side-products**.
- If however the reaction occurs at dominantly at one place we say that the reaction is:

REGIOSELECTIVE

However, if the reaction occurs at on place only (in 100% yield) the reaction is:

REGIOSPECIFIC

- Furthermore, as you may remember since last lecture course, that many reactions can lead to products that are capable of exhibiting:

STEREOISOMERISM

- When we carry out a reaction one can thus produce compounds which have:
  - ***E vs. Z isomers or stereogenic centres***

The bottom line is that we need to be able to understand and know the reactions that functional groups can undertake!

You have in your previous courses seen many of these functional groups such as:

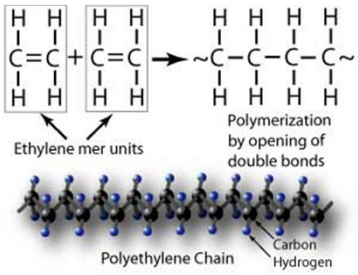
Halides, Alcohols,

Amines, Alkenes

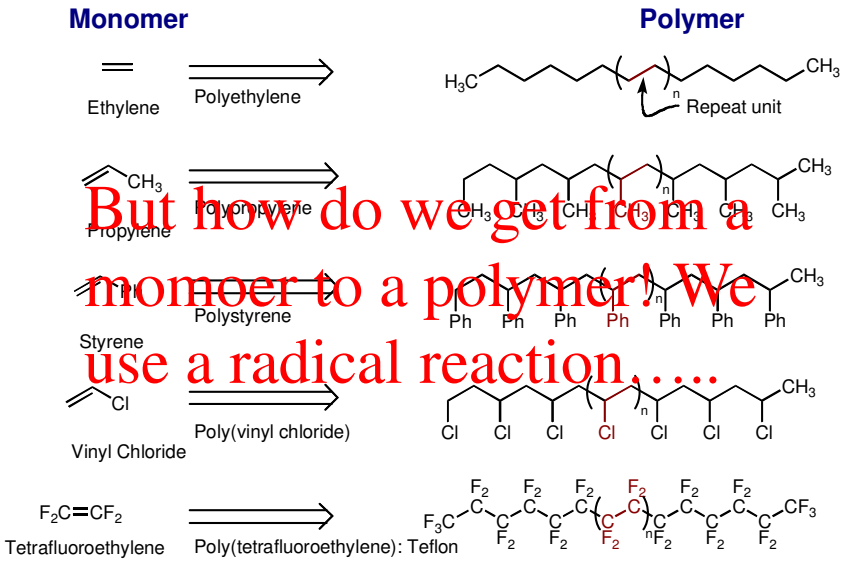
Aromatic compounds, etc.

- **If you have forgotten all of these you better go and take a second look at them!**

Radical chemistry



Common synthetic polymers:



But how do we get from a monomer to a polymer? We use a radical reaction….

‘Radicals and Radical Reactions

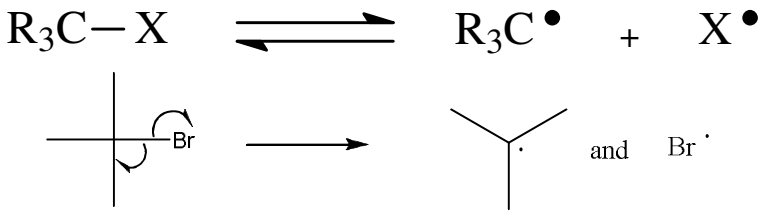
Chapter 39 in Clyden

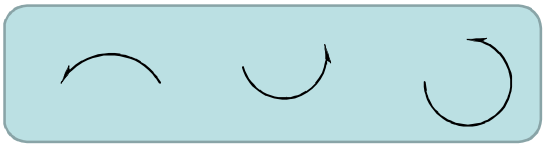
We have studied reactions that have intermediates or are formed in a concerted manner where a nucleophile attaches an electrophile, in a single step.

These are formed through **HETEROLYTIC FISSION.**

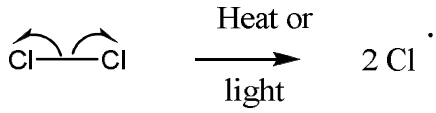
We are now going to look at reactions that occur through **HOMOLYTIC FISSION.**

That is to say that these give species that have unpaired electrons:

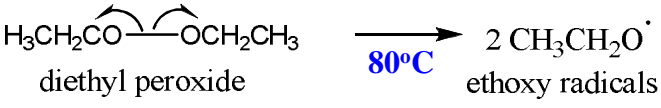




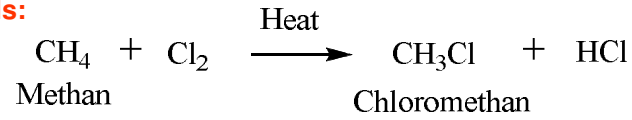
Fishhook arrows



Here the bond is broken using either heat or light energy



Hence, we should be able to do some synthesis with these radicals:



If chloromethan is allowed to react with more Cl_2, then further chlorination will occur and you will form….?

Here we use the curly '**fish-hook**' (half-arrow).

The **homlolytic** fission of an R_3C-X in the gas-phase is always less energy demanding than for **heterolytic** fission.

However, in polar solvents, the reverse is often seen. This is due to solvation of the developing ions.

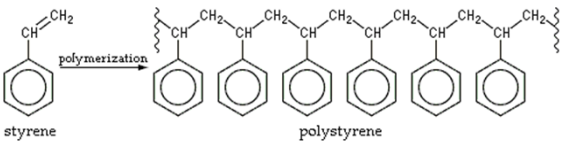
Radial reactions occur widely in the gas-phase. In fact the combustion of any organic compounds is almost always a radical reaction:

Hence the internal combustion engine!

Some organometallic compounds such as **organocobalts and organomercury compounds** have very weak carbon-metal bonds that undergo homolysis very easily to give carbon cantered radicals:

Similarly, tetraethyllead used to be added to petrol to prevent 'knocking' but now $MeOBu^t$ is used.

Radical reactions also occur in solutions, particularly **in non-polar solvents**. These are often catalysed by light or other radicals- ***i.e as in the formation of plastics.***



Once formed in solution, the radicals show chemistry that is less selective than for other species. Hence, side-reactions can occur.

As radical usually react fast, they are often referred to as 'free'…

A free-radical process consists of at least two steps.

- The first steps involves the **FORMATION** of a radical; the **INITIATION STEP!**
- The second step is the **DESTRUCTION** of the free-radical; which is the combination of two like or unlike radicals to give a new bond; the **TERMINATION STEP!**

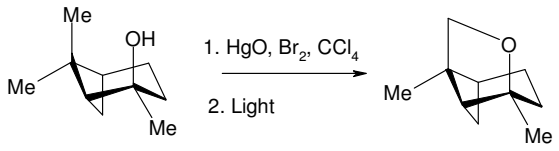
Summary of Radical reactions

Radicals can react by three possible ways:

- **Radical + radical give: spin-paired molecule!**
- **Radical + spin-paired molecule give: a new radical + a new spin-paired molecule!**
- **Radical give: new radical + spin-paired molecule!**

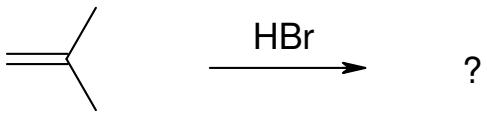
Examples of these reactions include:

- **Coupling**
- **Addition**
- **Substitution**
- **Reduction**
- **Fragmentation**
- **Rearrangement**

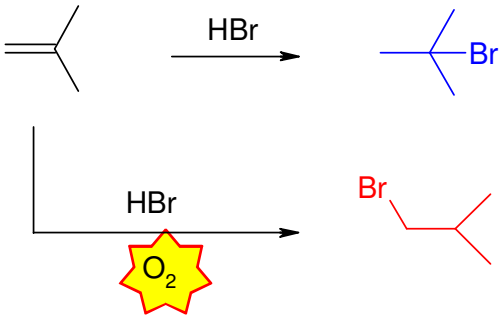


These can be both INTER- or INTRAMOLECULAR reactions.

One of the first radical reaction to be investigated was:



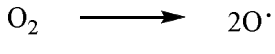
Morris Kharasch found that the regioselectivity of adding H-Br to isobutene dependent on if or not you had O_2 or HO-OH present!



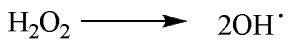
In the former reaction- you have an addition reaction involving the initial formation of a stable carbocation.

Here the Br-radical attacks the less hindered end of the alkene. This then generates a 3° radical.

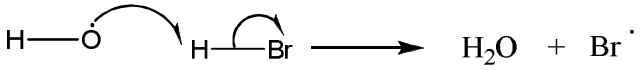
Overall this reaction is as following:



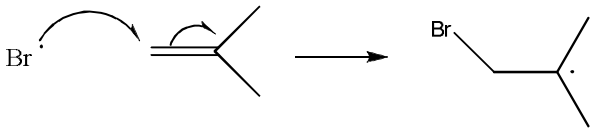
or



These radicals then 'help' break the H-Br bond to generate a new radical. In the case of peroxide this would occur like this:

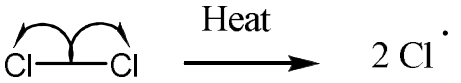


This is a 'radical abstraction' by the peroxide radical. And we use the 'fish-hook' to describe the movement of the 'single electron'

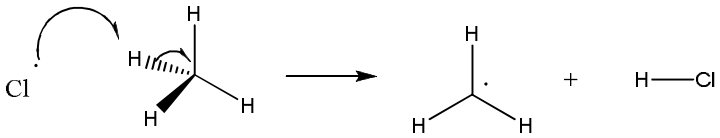


We have now generated a carbon centred radical, by using a radical addition reaction. This radical will then react further.

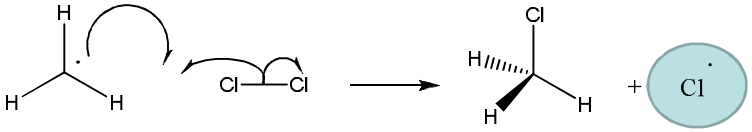
We can now look back at the free radical chlorination of methane, which is a substitution reaction:



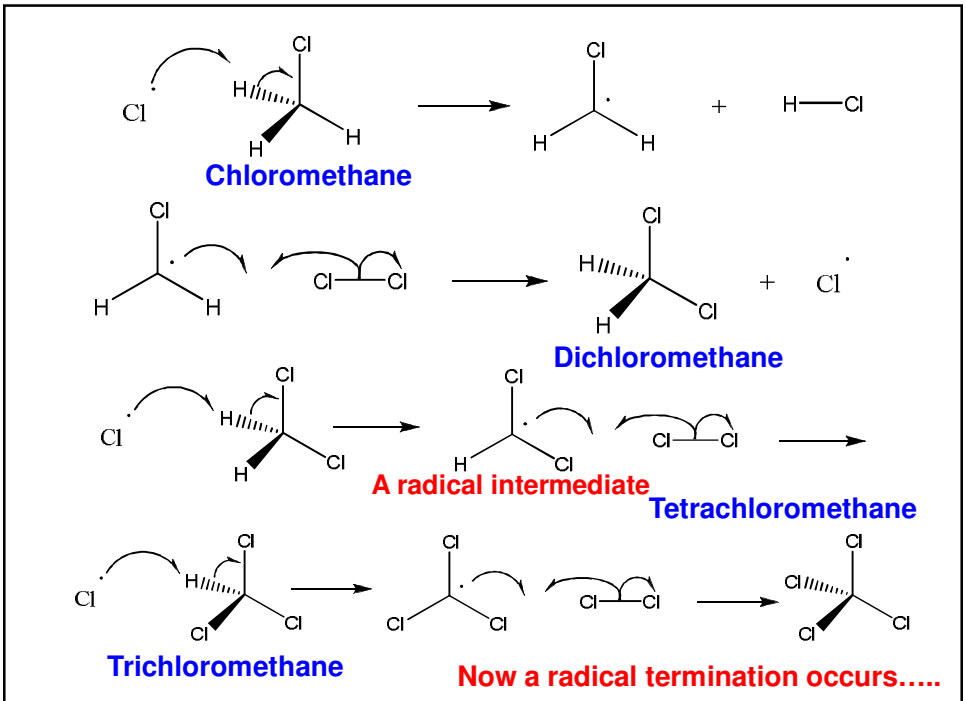
This is radical initiation



The Cl-radical now reacts with methane and generates a new carbon based radical and HCl. And if we got more Cl_2 there the reaction will proceed even further.

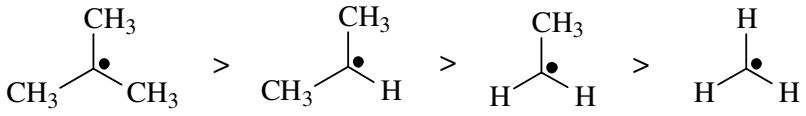


This is radical propagation



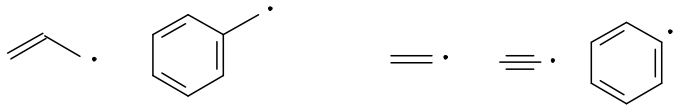
The stability of the radical is depended on the strength of the X-Y bond to give X• and Y•!

For C-H bonds, the decrease in the strength of the R-H bond when R goes from primary to tertiary is seen very clearly in the stability of the radical:



The tertiary alkyl radicals are more stable than the methyl radicals.

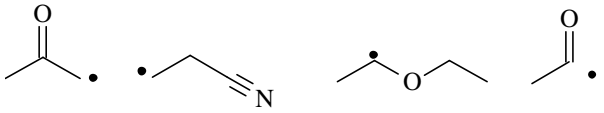
If the radical can be delocalised, an extra stability is observed. This is seen for:



More stable than alkyl radicals

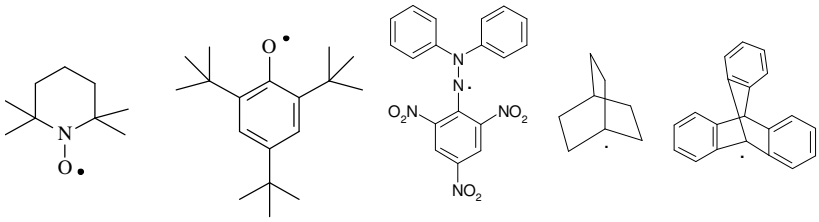
Less stable than alkyl radicals

Adjacent functional groups stabilise radicals independent of whether they are electron withdrawing or donating!



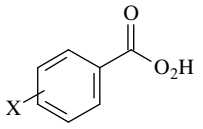
These are all more stable than tertiary alkyl radicals.

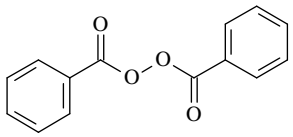
The Ph_3C• radical we saw earlier is very stable, but that is due to steric affect. We have seen a few examples of those before, here are more:



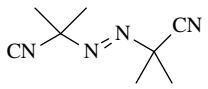
As we saw above, then the initial formation of a radical is often initiated by another radical!

These are called RADICAL INITIATORS:





Dibenzoyl peroxide



AIBN (azoisobutyronitrile)

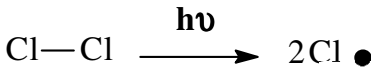
The formation of a radical is formed by homolysis of weak bonds such as:

Bond X-Y	ΔG for X-Y → X· + Y·
(C-H	*414 kJ mol^{-1})*
Br-Br	192 kJ mol^{-1}
I-I	151 "
HO-OH	213 "
MeO-OMe	151 "
H-Br	366 "
H-I	298 "
CH_3-Cl	349 "

Temperatures above 200 °C will homolyse most bonds (e.g. car engines). However, this is not ideal! However, some weak bonds do undergo homolysis at elevated temperatures (above RT).

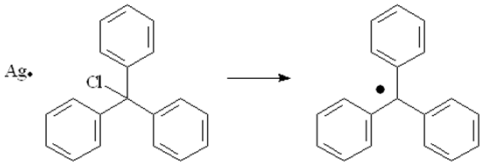
However, light can be used to cleave bonds (photochemistry) when the energy required is between *ca,* 167-293 kj mol^{-1}

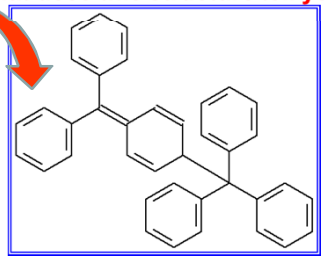
- This corresponds to RED and Blue light respectively!
- However, the molecule must be able to absorb the light energy!



What does this structure tell you!

One of the first radical reactions to be investigated was:

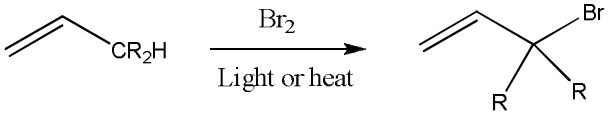




Can form a dimer

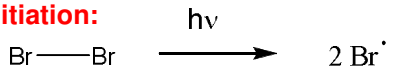
The stability of allylic and benzylic radicals will explain why these react different than 'isolated alkenes or benzene'.

And using the table above we can predict that for both attach occurs on the sp^3-hybridysed carbon atom:



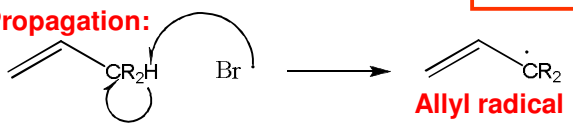
The mechanism (the step-by-step description) for this reaction is:

Initiation:

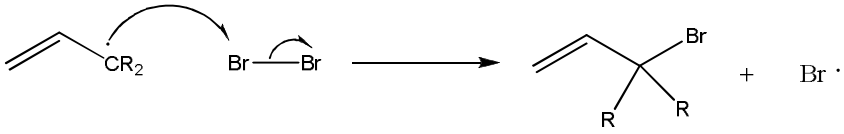


Same as 2 :Br •

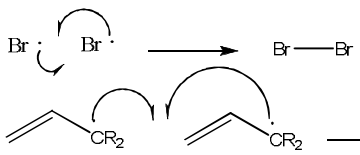
Propagation:



Allyl radical



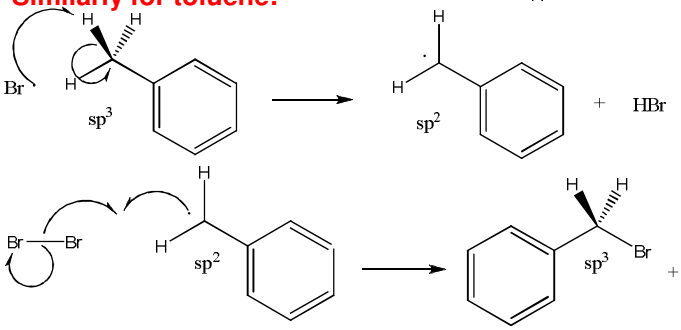
Termination:

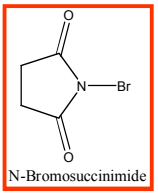


Likely but only when the allyl 'fuel' is completed.

Unlikely to occur in any real quantity.

Similarly for toluene:





This is a good example of radical chain reaction

Reaction is unlikely to occur on the benzene ring but can give '*over bromination*' on the methyl position.

Summary

As you have seen then when formed in solution, the radicals show chemistry that is less selective than for other species. And that they often also proceed with great rapidity due to fast CHAIN REACTIONS.

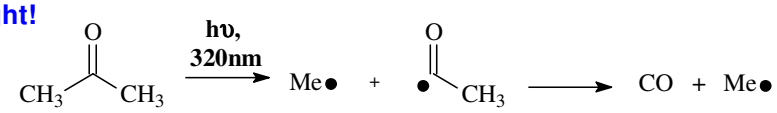
As we have seen then the three main ways of making radicals is to use:

- **PHOTOLYSIS**
- **THERMOLYSIS**
- **REDOX REACTIONS**

We looked at the first two in some details. And looking back at our chloromethylation reaction (or the bromination, *NB.* bromine radicals are less reactive than chlorine radicals), the cycle proceeds without the need for further photochemical generation of $Cl^{\cdot}$ and because of that, the reaction is said to be 'self-perpetuating'.

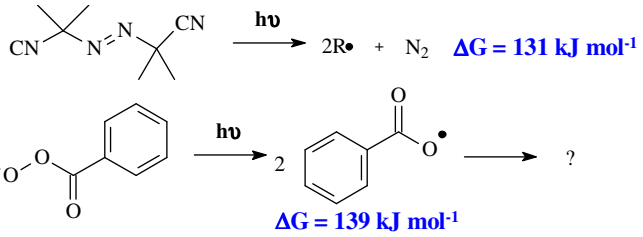
However, such reaction be inhibit by adding a substrate that themselves react particularly readily with the radical (quenching). These are called RADICAL INHIBITORS: phenols, quinines, diphenylamines, iodine, *etc.*

Importantly, for PHOTOLYSIS, the molecule has to be able to absorb light!



Here the carbonyl compound absorbs the light at 320 nm which is equivalent of 375 kJmol^{-1}. Alkyl hypochlorides and nitrites do the same.

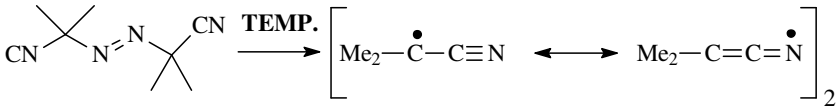
The advantage of photolysis over thermolysis is that radical is formed at reasonable temperatures, and very often these are very strong bonds that are broken, like for the azoalkanes and peroxides shown previously (the initiators):



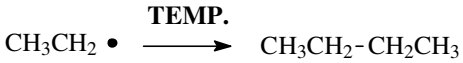
For THERMOLYSIS, we often need high temperatures. These are often done in the gas phase through the decomposition of metal alkyls (*i.e.* car engines).

However, majority of radicals in solutions are formed by the thermal decomposition of peroxides or azo compounds. These however, often need long reaction times and high temperatures.

Alkyl azo compounds can be substituted to increase the rate of this decomposition (i.e as for AIBN, $\tau_{½}$ = 1.0h @ 80°C).



Finally….In the absence of other species, the radical can in solution abstract a hydrogen atom from the solvent. This can lead to the formation of dimers, but it is very concentration dependent:



The formation of new C-C bond(s)

Having looked at radical reactions in previous lectures we now going to go back to reactions involving the transfer of electron pairs.

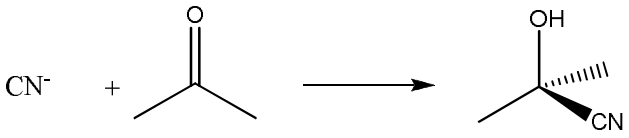
Hence these are reactions that involve the use of nucleophiles.

Nucleophiles **donates electrons**, but can often react as bases as well, and this will depend on their strength (soft *vs.* hard).

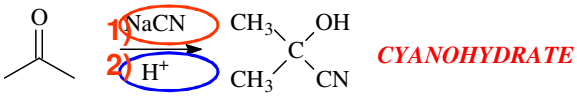
Nucleophiles can be either negatively charged, such as RO-, or neutral, but possessing a per of electron in a high energy filled orbital.

The most common types of nucleophiles have non-bonding lone pair of electrons, and they usually placed on heteroatoms such as O, N, S or P.

Cyanide is a good **anion**, and can be used to add to an electrophile such as a ketone. This gives a new C-C bond between the carbon atom of the carbonyl moiety and the CN^-.



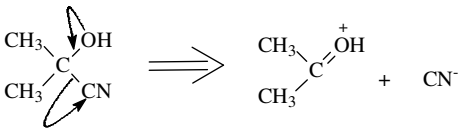
The real reaction is in fact:



CYANOHYDRATE

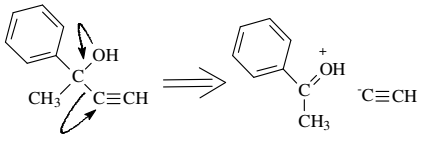
We will look at these kind of reactions using various types of nucleophiles in our next few lectures.

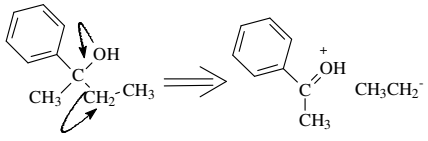
When analysing products such as the cyanohydrate, it often helps to ***'push the arrow backwards'*** to chose the most stable anion of the substituent as in the case of these carbonyl compounds:



This will help you in understand what kind of nucleophiles you might need to make:

We will start with the use of strong nucleophiles made by using organometallic compounds.



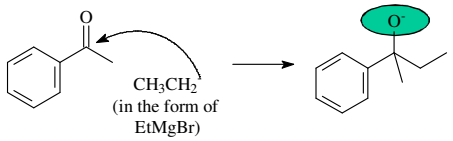


Formation of C-C bonds using organometallic reagents

On previous slide we used NaCN as source of a nucleophile.

We can also use metal based substrates as a reagent for nucleophiles.

An example is the use of nucleophile '$CH_3CH_2^-$' which we can 'generate' by using organometallic reagents such as EtMgBr (Ethyl magnesium bromide)or EtLi (ethyl lithium).



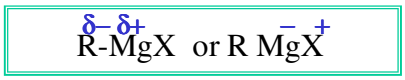
Need to protonate the alkoxide

This is the Grignard reaction; a very traditional way of making new C-C bonds. The reagent is formed:

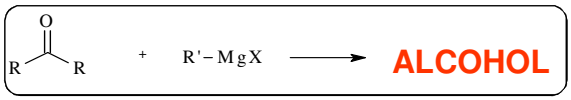
- From simple alkyl or aryl halides (RX) and magnesium (Mg) in dry solvents and these are stable in ether/hexane, although they are rapidly decomposed by O_2 and H_2O!
- The only problem is that these are also good bases and abstract acidic protons (from amines, alcohols and water, *etc.*).

Nucleophiles such as $CH_3CH_2CH_2^-$ and $CH_3CH_2^-$ can be represented with $CH_3CH_2CH_2MgX$ and CH_3CH_2MgX as the reagents/synthetic equivalents for such reactions (where X = Cl, Br or I)

As carbon is more electron negative than magnesium, a polarisation occurs making the carbon partially negative, which gives it its nucleophilic status:

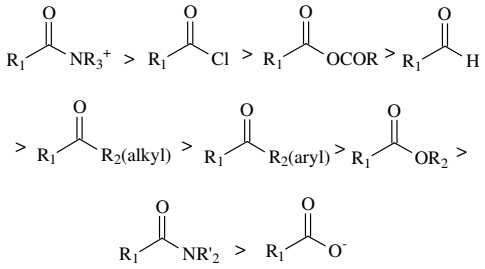


Carbonyl compounds are often used in Grignard reactions where aldehyde would give a secondary alcohol and a ketone would give tertiary alcohol after washing with H_2O or H_3O^+.



Formaldehyde can also be converted into primary alcohol, whereas acid chlorides (RCOCl) would give ketones! But why?

The carbonyls are electrophiles (electron difficient) and their reactivity depends on their structure:



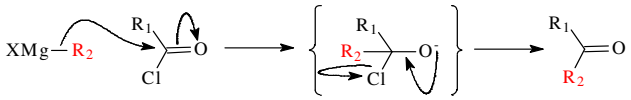
For some of these structures we have good leaving groups and for others we don't! And that dictates their reactivity towards RMgX.

If we have a good leaving group (X), it can be eliminated by a carbon nucleophile (such as RMgX or amine) this is an acylation reaction.

If we don't, the anion (alkoxide) is likely to pick up a proton the reaction medium either during the reaction or in the workup.

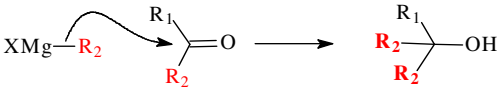
Alternatively, if we also have an acidic hydrogen adjacent to the hydroxyl group, then elimination of water my follow the nucleophilic addition.

An example of a reaction where two Grignard Reactions can occur is when we use acid chloride as Cl^- is a good leaving group!



First step

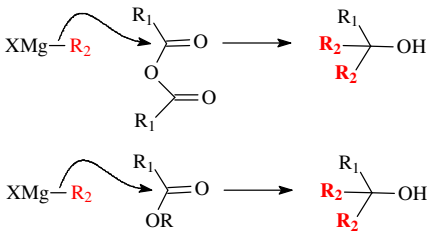
Since we now have formed a new species that is very reactive (although less then the acid chloride), a second attack can occur:



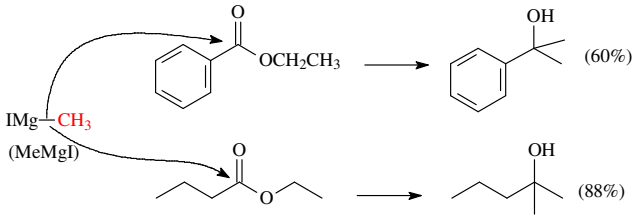
Second step, giving the alcohol after workup

The final product is a tertiary alcohol where we have added two Grignard reagents to the original reagent.

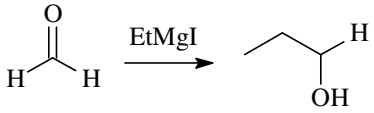
This will happen when we react the Grignard reagent with acyl halides, anhydrides and esters (*NB.* Need to protonate the alcoxide):



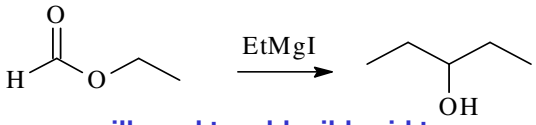
Of these the esters are the most reliable and give the best yield:



As stated above, fomaldehyde gives us primary alcohol:



An in the same way, formate esters give secondary alcohols:



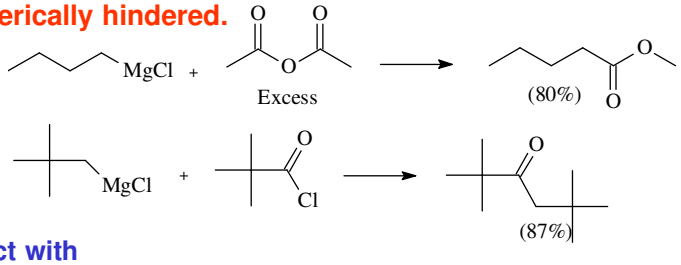
For all of these you will need to add mild acid to generate the R-OH

Even though, one would expect to get the di-substituded product all the time, then it is possible to isolate the mono substituted product by controlling the reaction conditions! *e.g.* when:

The acyl compound is in excess;

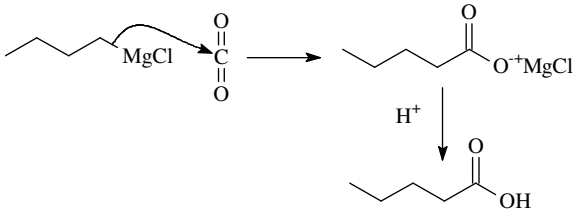
The reacting temperature is low;

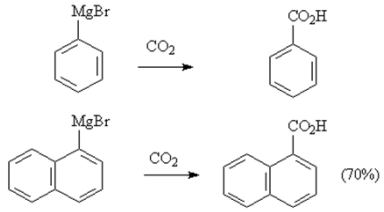
The product is sterically hindered.



CO_2 can also react with Grignard regents and gives carboxylic acids.

This is a very useful reaction and often done by using dry ice (solid CO_2).

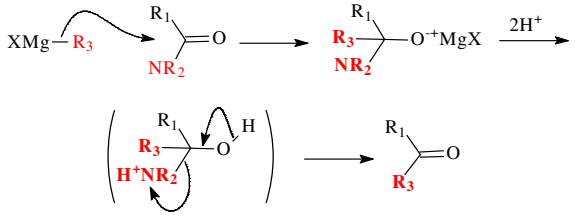




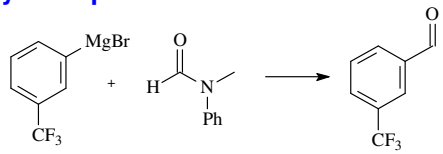
Here the carboxylation is carried out by using large excess of CO_2 and the acid is the primary product.

In the case of primary and secondary amides the principal role of the Grignard reaction is to remove the acidic protons the the nitrogen (as in the case of the acid above).

However, if using tertiary amide, the corresponding ketone is formed, since the leaving group is the tertiary amine:



It is essential to protonate the amine for the 'intermediate to collapse' to give the new carbonyl compound. This reactions can also be used to give aldehydes:



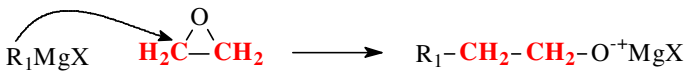
In the same way that Grignard reagents undergo acylation with carbonyl compounds, they also undergo alkylation to give alkanes:

$$R_1MgX + R_2\text{-}Y \longrightarrow R_1\text{-}R_2 + MgXY$$

$$CH_3(CH_2)_{11}MgI + CH_3(CH_2)_{11}I \longrightarrow CH_3(CH_2)_{22}CH_3 \quad (63\%)$$

However, often various side-reactions can occur.

The one reaction that does proceeds well is the opening of oxirane (ethylene oxide):

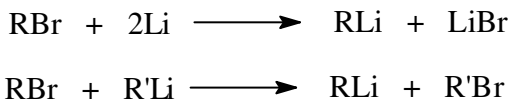


Because of side effects in alkylation Grignard reactions other organo-metalic regents are used such as: Organolithium; Organozinc; Organocadmium and Organocopper

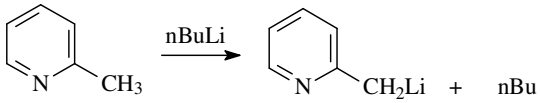
Organo lithium reagents (RLi)

We looked at organo-Mg reagents. Lithium (Li) is also a very electropositive metal and highly polarised towards carbon.

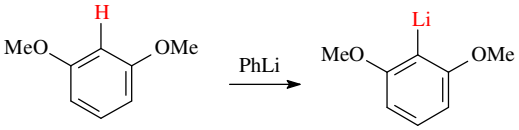
Organolithium reagents are made either from the appropriate halide and Li(s), or by halogen-metal exchange:



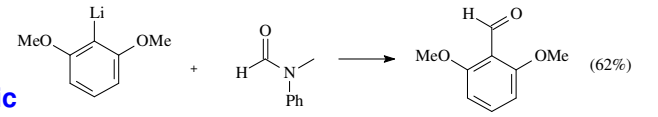
If acidic compounds are used, these can be deprotonated and lithiated:

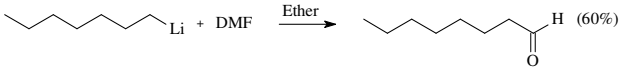


Even benzene derivatives can be lithiated:



The organolithium reagents are more strongly nucleophilic then the corresponding Grignard reagents.

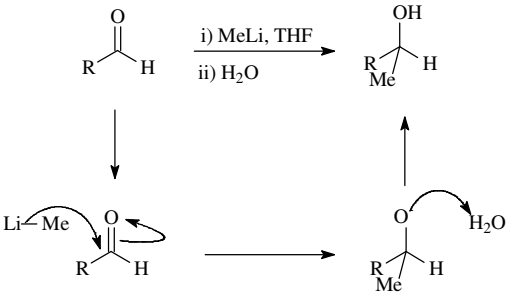




Organolithium ragents undergo all the same reactions as the Grignard reagents, and often more efficiently.

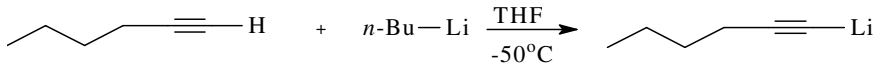
Here the aldehyde is formed even when using DMF. The attack of other carbonyl compounds such as aldehydes and ketones is also effective:

When the organolithium compound reacts with water it is destroyed in the same way as the Grignard reagent, giving the alkane and LiOH.

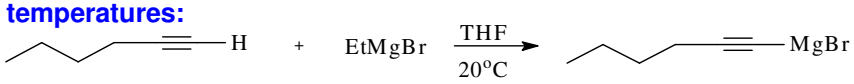


As before, the reaction of RLi with aldehydes and ketones gives secondary and tertiary alcohols respectively.

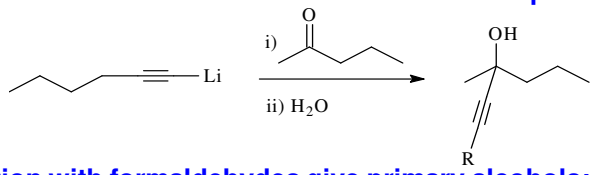
Since the RLi is quite a strong base, they can be used (as shown earlier) to deprotonate acidic moieties such as alkynes:



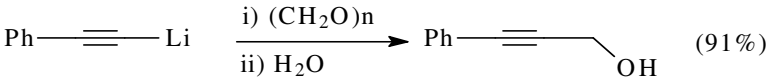
This is also possible using Grignard reagents, but only at higher temperatures:



Both of these can now be used as effective nucleophiles:

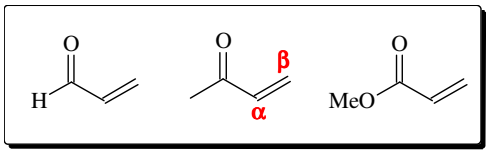


The reaction with formaldehydes give primary alcohols:



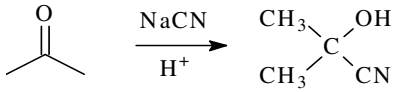
Conjugated Addition Reactions (Michael addition reactions)

In the last section we used of organometallic reagents as nucleophiles and many carbonyles as electrophiles. Now we will look at similar reactions using α,β-unsaturated carbonyl based compounds:



These structures area also called Michael acceptors!

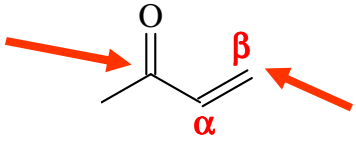
We have already looked at the formation of cyanohydrate:



CYANOHYDRATE

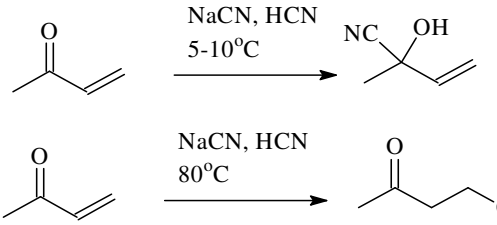
If we were to do carry out this reaction using the above α,β-unsaturated ketone, then what could happened?

We could get an attack on the carbonyl

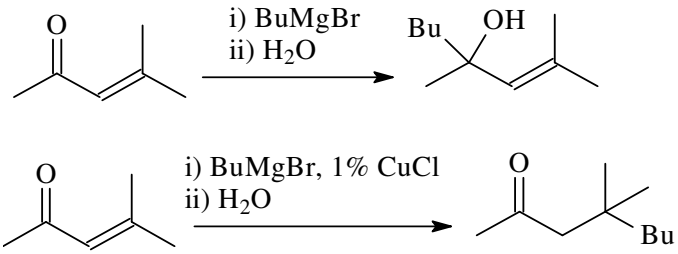


Or an attack on the alkene!

In fact both of these reactions can take place:



We could also carry out such reactions using a Grignard reagent:

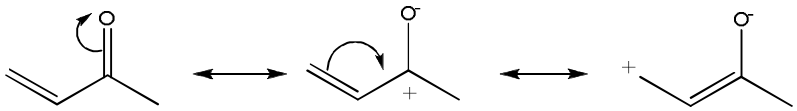


But why does this occur???

The reason for this is that the double bond is electron deficient because it is in conjugated to the carbonyl part!

It does not behave like an isolated double bond which we would consider a weak nucleophile that could react with strong eletrophiles.

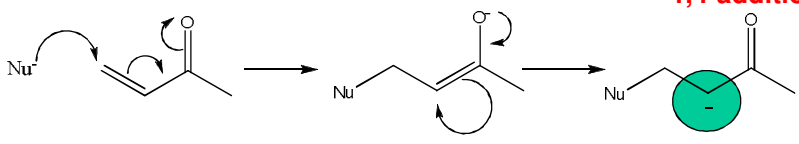
This behaviour can be rationalised if we look at the resonance structures of a α,β-unsaturated carbonyl compound:



One of these resonance structures places a positive charge at the end of the double bond (at the β-position).

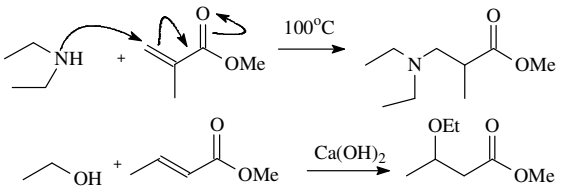
Because of this we can refer to such double bonds as being activated and the nucleophile can add on to the β-position:

1,4-addition!

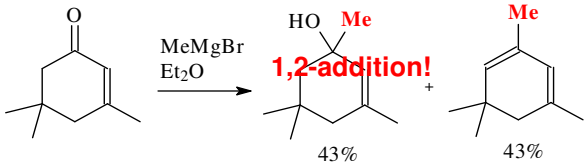


Formation of a resonance-stabilized (enolate) anion

A range of nucleophiles will participate in such reactions: amines, alcohols and thiols (RSH):

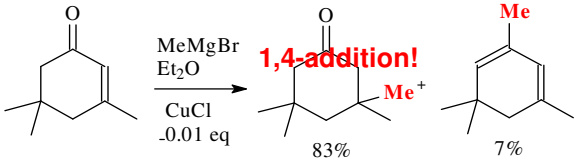


Copper (I) salts are particularly good in directing reagents to the α,β-bond.



In the case of using a Grignard reagents, the ketone is attached preferentially as shown here:

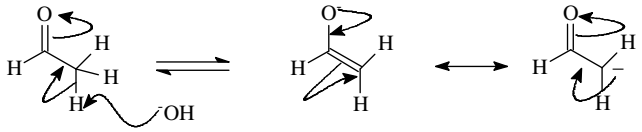
Using 1% of a copper salt, such as CuCl, gives, however:



Stabilised carbanions: formation of C-C bonds

We just seen the formation of a resonance stabilized anion.

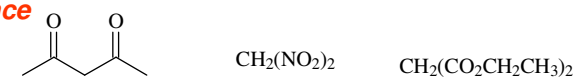
Such anions can be formed by a deprotonation of a carbon moiety next to a carbonyl group, and are commonly referred to as ENOLATES:



What we have made here is a carbon based nucleophile, the stabilisation of which is enhanced by the presence of substituents groups that can stabilise the negative charge, *i.e.* Oxygen.

The stability of the anion is governed by the way we can delocalise the charge, i.e. by *resonance*

A measure of which is their pKa:

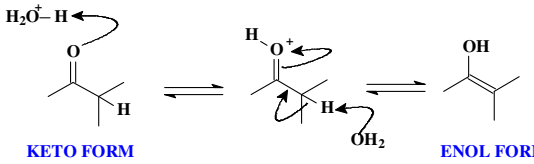


These compounds can thus be completely deprotonated by bases such as $Na^{+-}OEt$, called sodium ethoxide, after which they can then undergo alkylation reactions.

Enolization itself (without a catalyst) is usually quite a slow process in neutral solution. But it can be catalysed by using either:

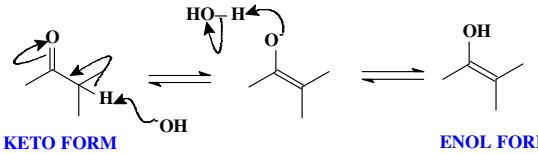
Acid or Base

In the *acid-catalysed reaction*, the molecule is first protonated on oxygen and then loses the C-H proton in a second step:



KETO FORM ENOL FORM

In the *base-catalysed reaction*, the α-proton is first deprotonated, and then the proton is added to the oxygen atom in a second step:

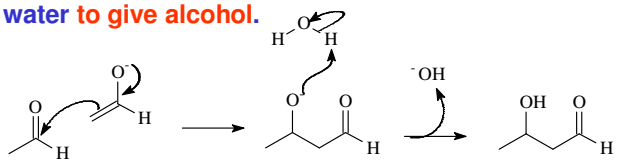


KETO FORM ENOL FORM

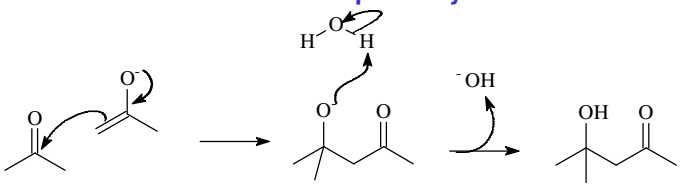
The intermediate in the base-catalysed reaction is the enolate ion, the conjugated base of the enol.

Using NaOH is not strong enough (*basic enough*) to *enolize* an aldehydes completely.

Because of this the enolate is thus surrounded by other aldehyde molecules, *i.e.* these *aldehyde molecules are all electrophilic* whiles *the enolate is nucleophilic*. So each enolate ion can thus attack one of these aldehyeds, forming an alkoxide ion which can be protonated by water to give alcohol.



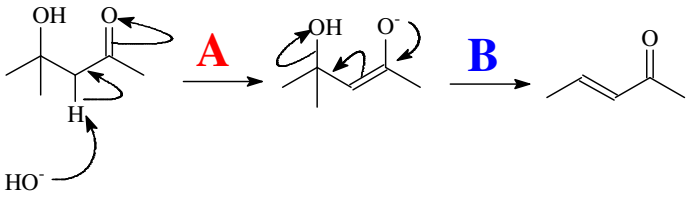
The product is an aldehyde with a hydroxy group. The name of this reaction is the Aldol reaction and the trivial name of the product is *'aldol'*. You did this in your first practical class! (See Experiment 1) Such reactions can also take place if you use ketones:



4-Hydroxy-4-methylpentan-2-one

The above acetaldehyde reactions works well with a drop of diluted sodium hydroxide. The acetone reactions is best done if we add barium hydroxide [$Ba(OH)_2$)]. Both of these keep the base concentration low.

However, if we add more base, we can push the reactions a bit further, since we can carry out dehydration on these two products. This gives stable conjugated unsaturated carbonyl compounds:

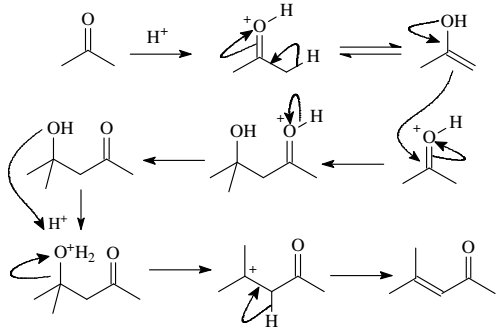


The first step here is the enolization (A), and the second step is the elimination (B). Because of this very often it is possible to get either the aldol product, the eliminated product or mixture of both!

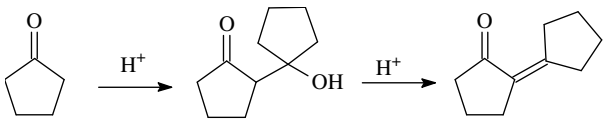
The elimination product is, however, quantitatively formed if we tune the reaction conditions:

Strong Bass; High(er) Temperatures; Longer Reaction Times and the structure of the reagents!

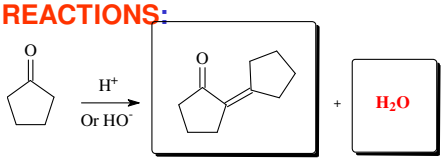
The elimination step (E1) is even more easier if we use acid. Acid catalysed aldol reactions usually give the unsaturated product instead of aldols:



Here is what happened if we use cyclopentanone:

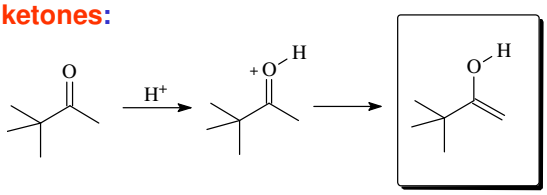


These kind of reactions are often called CONDENSATION REACTIONS:



For this particular reaction we can say that the *"two molecules of cyclopentanone condense together to give a conjugated enone"*.

The aldol reaction can also be carried out using unsymmetrical ketones:



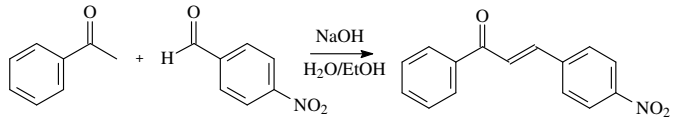
Here only one side of the ketone is blocked (no a-proton) and only one enol is formed.

We say that the enolization can only occur towards the methyl group but not towards the *t*-butyl group. There are many molecules that do this, an aryl ketone being an example.

Another type of condensation reactions are the CROSS-Condensation reactions.

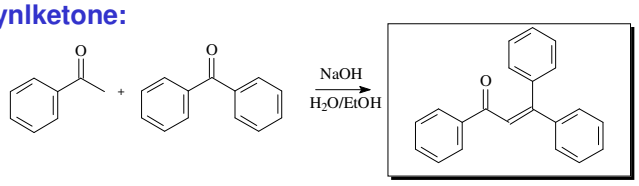
In comparison to what we have been looking at then these occur between two different carbonyl compounds, whereas up to now we have discussed SELF-Condensation reactions.

An example of such cross-condensation reaction is the reaction between PhCOMe and 4-nitrobenzaldehyde:



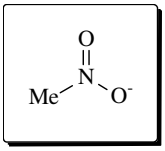
Here only the ketone can be enolized. These molecules are called chalcones, and they are of course enones.

Such reactions are also possible between other carbonyl compounds, where one of the carbonyls does not have an a-proton, such as the dipheynlketone:

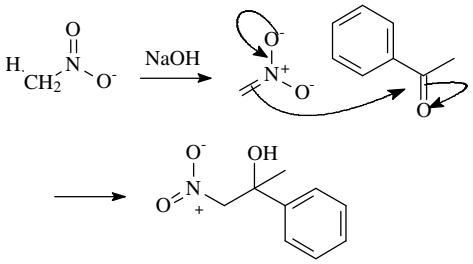


There are several other compounds that can enolized but are not electrophilic.

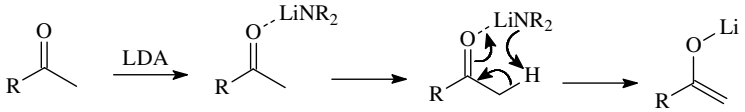
For instance nitromethan:



The anion of nitromethan is called nitronates, and it can react with aldehydes and ketones:

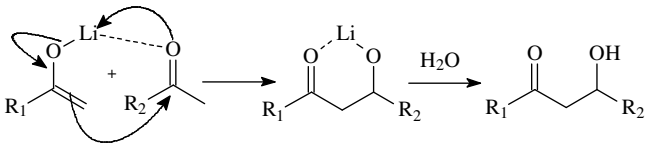


If a strong base is used such as LDA (lithium diisopropyl amine) a specific enolate can be formed. This occurs through fast deprotonation and stabilisation by the Li^+ ion.



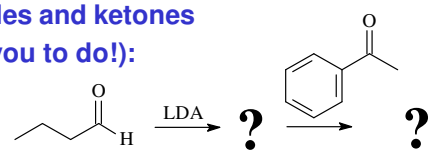
The reaction is carried out at –78°C.

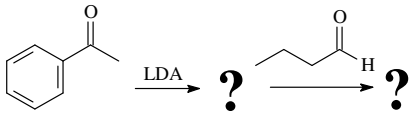
The reaction is also very quick so all the ketone is converted to the lithium-enolate. Then we can add a second ketone/aldehyde to the reaction and carry out a condensation:



This is necessary to use when using esters since they are less reactive then aldehydes and ketones

Other examples (for you to do!):

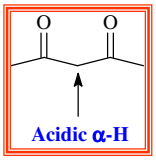




Malonate chemistry: Formation of stabilized enolate

In previous examples we have generated an enolate anion that has been stabilized by a single carbonyl (or equivalent) group.

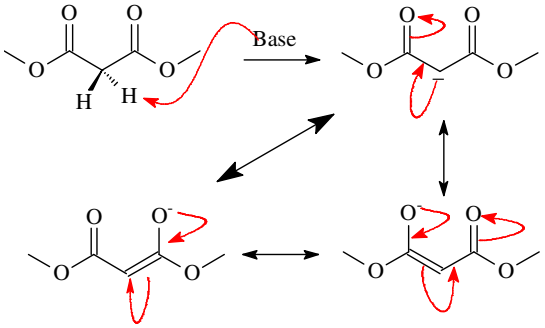
When a -CH_2-, CHR- group in a molecule is flanked by one or two electron withdrawing groups, then it can be easily deprotonated and the resulting anion is stabilised by delocalisation.



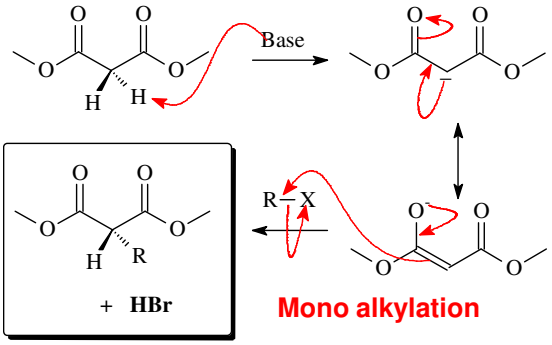
This occurs in molecules such as α,β–dicarbonyl compounds:

The protons are called α-protons, and are quite acidic.

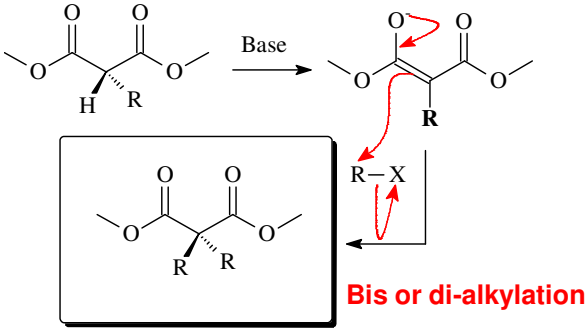
The deprotonation of the α–proton gives the following delocalisation (stabilisations *via* resonance):



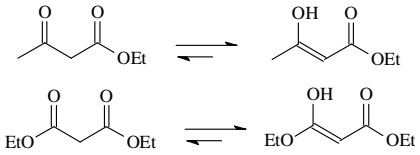
We now have *generated an enolate anion and we can use that to react with electrophiles* such as alkyl halides, *etc.*:



Since we have two α-protons, the pKa of the latter is higher than that of the first one, but still we can get di-alkylation if the base is strong enough:

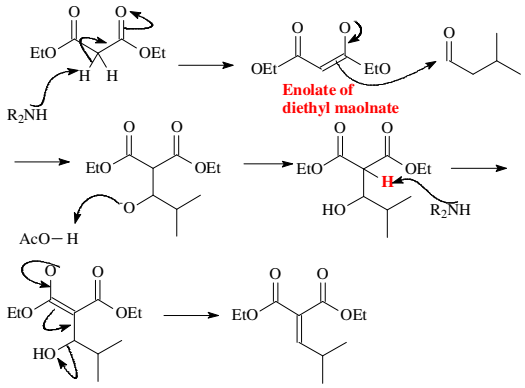


1,3-dicarbonyl compounds undergo enolization under normal conditions:

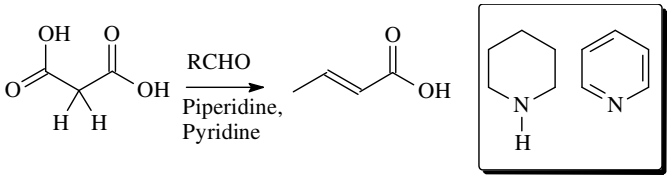


However, these enolates are very stable and the carbonyl groups in the unenolized fraction of the two examples are poor electrophiles.

Because of this, these structures do not undergo self condensation reactions so easily. However, cross-condensation reactions are easily achievable:



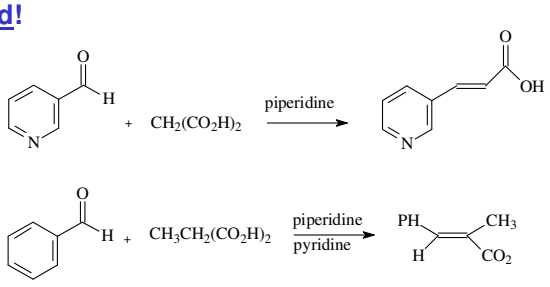
The reaction of malonic acid with an aldehyde under similar conditions gives α,β-unsaturated acids:



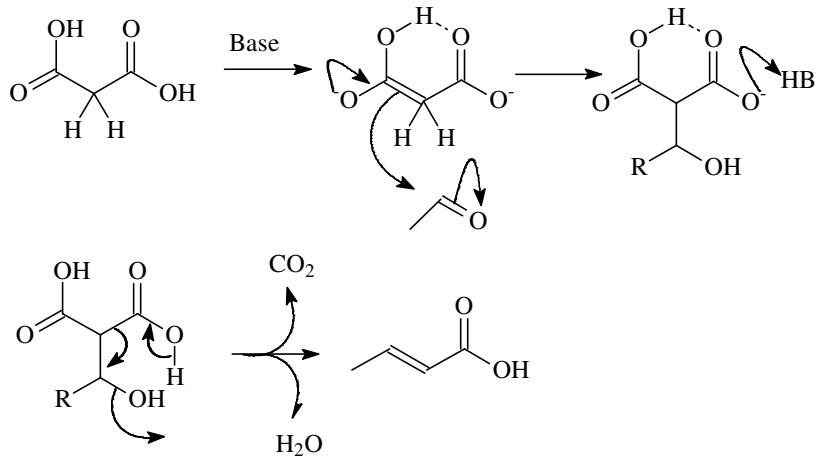
This is the Knoevenagel reaction. It involves the loss of CO_2, thorough a decarboxylation process (see next slide).

This is a very useful reaction as it gives us a single carboxylic acid from a dicarbonyl compound!

The driving force for this reaction is the loss of CO_2 from the di-carbonyl compound, which is an irreversible process:



In the Knoevenagel reaction the loss of CO_2 occurs thorough a process called decarboxylation, the mechanism of which is shown belwo:

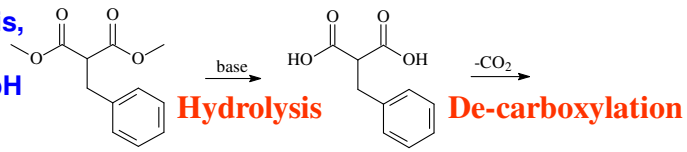


Sometimes both the Knoevengel type and Michael addition can occur in one step:

$CH_2{=}CHCHO \xrightarrow{CH_2(CO_2H)_2} CH_2{=}CHCH{=}CHCO_2H$ and $CH_2(CH_2CHO)CH(CO_2H)_2$

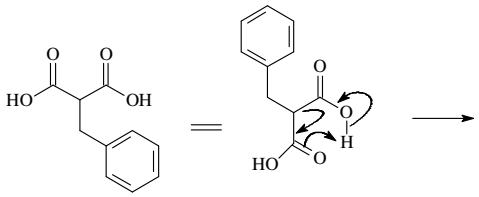
In a similar manner, de-carboxylation can also occur from di-esters, such as malonates, which we used previously in our C-C bond formation. However, we need to form the acid first through hydrolysis.

i.e. base hydrolysis, followed by pH change to acidic pH and heading:



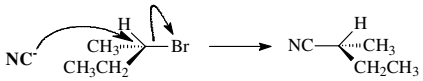
Hydrolysis De-carboxylation

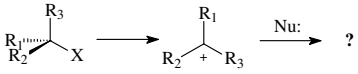
Again, sometimes it is better to redraw the structure in a six-member ring conformation. Then the de-carboxylation becomes more clearer:

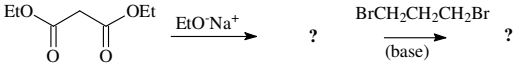


PERICYCLIC REACTIONS

We have investigate several different types of reactions:



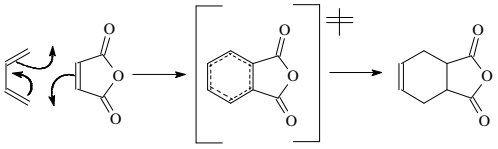


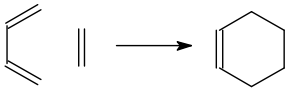


One thing we did see on the tutorial sheets were ring compounds!

6 member ring compounds can be formed by using electrocyclic ring closure reactions, called the *Diels-Alder reaction*.

The Diels-Alser reaction in its simplest form consists of the reaction of a conjugated *diene* with a *monoene*.

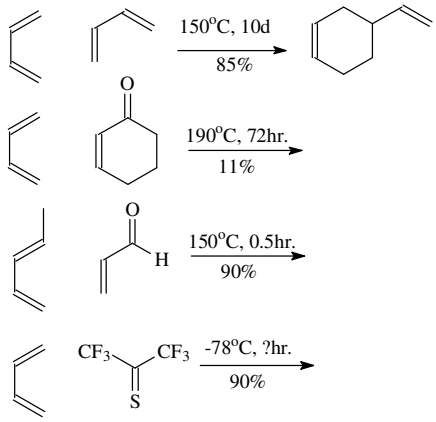




This reaction is often shown in textbooks, but is slow; needs heating it at 165° and 900 atm. for 17 hours do we get our DA product.
The reason is that the dienophile does not have attached to it one or more electron withdrawing groups such as carbonyl, nitrile, etc.

Substitutions on the diene also increase the rate, provided that they are electron-donating!
Try to do these:

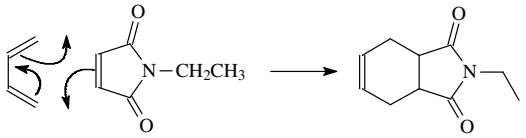
All the reactions go in a single step simply by heating the two starting materials together.

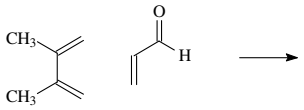


These reactions cannot be described adequately in terms of *electrophilic-nucleophilic* interactions

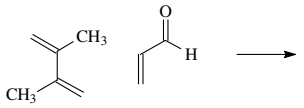
Furthermore these cannot be described by radical pathways either!

In fact they are representatives of a large group of reactions that involve the interactions of π-electron systems in a concerted manner and via a cyclic transitions state:





Reaction



No Reaction

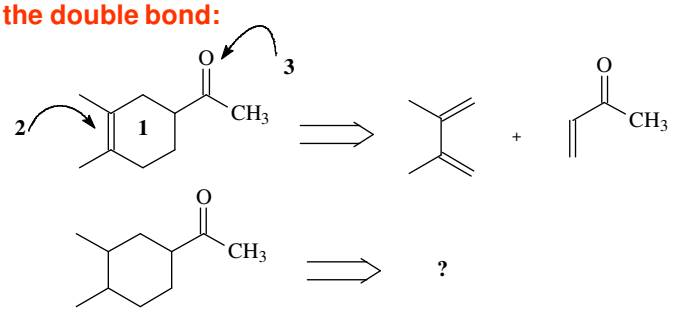
We say that the *diene* can adapt two types of conformations: *cisoid (works)* and *transoid (does not work)*

Since these reactions do not include an intermediate, we don't have to stabilize the transition state and hence we often don't need to have solvent present in the reaction!

For the first two above, each arrow leads directly to the next, and the last arrow connects to the first. This is like an electron rotating circle!

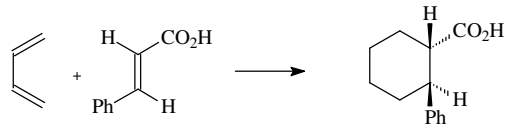
The reactions we have been looking at are 'typical' CYCLOADDITION REACTIONS. The products have always a few things in common:

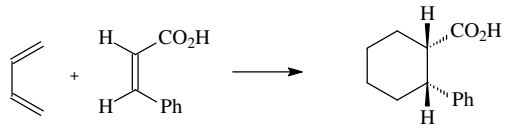
1. They have a new six member ring
2. A double bond in the ring (positioned quite precisely)
3. Have got a conjugated group that is outside the ring and opposite to the double bond:

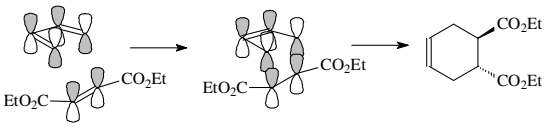


In the reaction above we have a 4p-electron system (the diene) interacting with the 2p-electron system of the monene, or DIENOPHILE, yielding a [4+2]-cycloaddition.

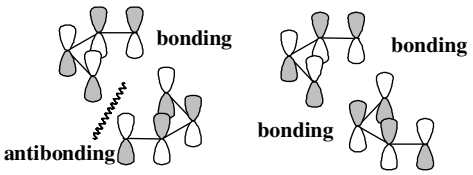
Because of this the relative configuration of the starting material is retained in the product:





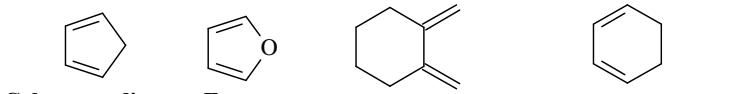


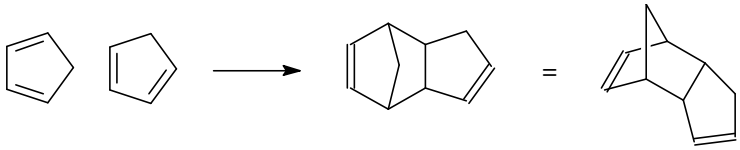
For the above DA reactions we obtain a transition state that has six delocalised π-electrons:



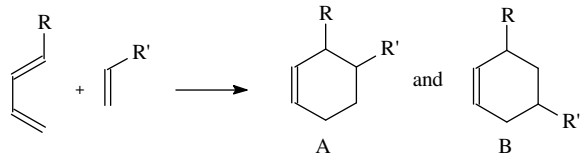
In both of these cases, the diene is in its *cis*-configuration. We saw earlier that when it is trans no reaction occur. But the *trans*-configuration is the more stable one!

Cyclic diene have no way of taking up the trans configuration. Because the DA reactions proceed much faster for cyclic dienes.

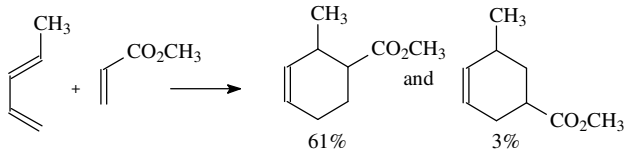




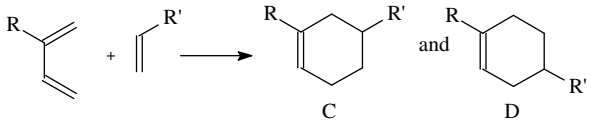
If the *diene* and the *dienophile* are both un-symmetrical the Diels-Alder addition may occur in two ways:



However, usually the reaction is very regioselective and one of the product is produced dominantly *A*.



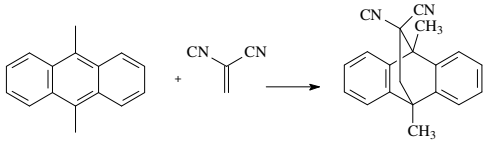
When the diene is substituted at the 2 position the major product is *D*:



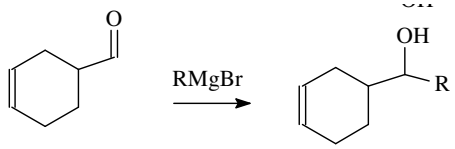
A variety of components may participate in the Diels-Alder reaction, so this procedure is of considerable synthetic importance:

Benzene derivatives do not participate in the Diels-Alser reaction sine the product would be non-aromatic!

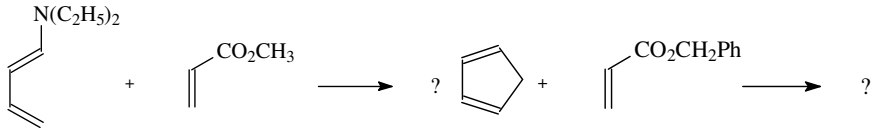
However, polycyclic compounds such as anthracene do:



When you have got esters, ketones, aldehydes etc. you can couple these reactions with the organometalic chemistry we did before.

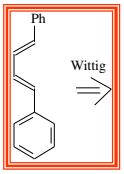


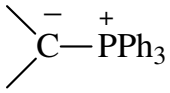
Examples for you:



Very often we need to make the diene or the dionophile:

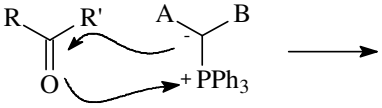
This can be done by using the Wittig reactions, which introduces new C-C double bonds into molecules by using:



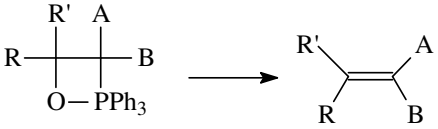


This is called *triphenylphosphonium ylide*.

This compound can react with carbonyls such as ketones and aldehydes to form an *oxaphosphetane*, which breaks up to give *trihenylphosphine oxide* and *an alkene:*

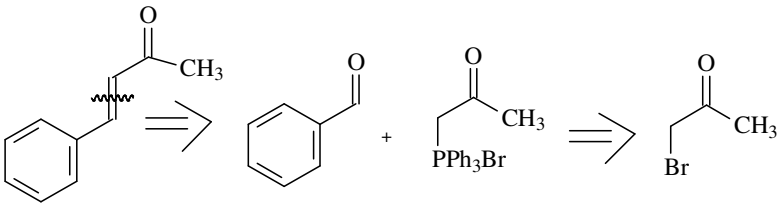


oxophosphetane

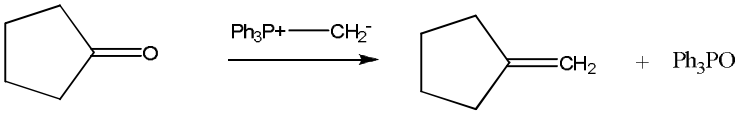


We can thus make a large range of alkenes that we can use in the DA synthesis.

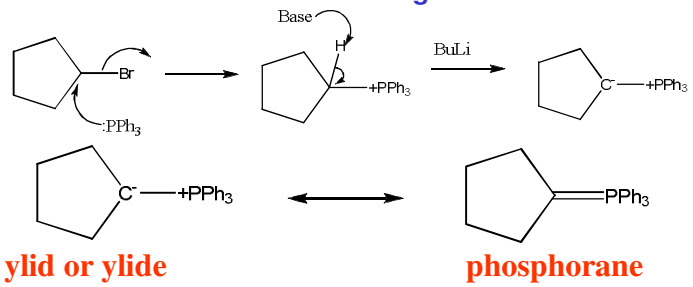
So remember you might have to disconnect all the way to the two starting materials above!



This is reaction enables us to place a double bond within a structure in a precise location, not like is often seen for the eliminate of alcohols as water, where we can get two structural isomers. Hence, the overall reaction is:



The mechanism for its formation being:



ylid or ylide **phosphorane**

What about *E vs. Z stereochemistry*?

The stereochemistry of the Wittig Reaction generally gives *E* selectivity for *stabilized ylids* and *Z* selectivity for *unstabalized ylids*.

The stabilized ylids are those which have conjugated or anion stabilized substituent's adjacent to the negative charge: