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Introduction to Organic Synthesis

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. Several new organic reactions are introduced on the way, but most mechanistic aspects are dealt with later.

The following topics will be covered in this course:

- Introduction to synthesis, chemoselectivity, regioselectivity, functional groups, revision of common functional groups
- Retrosynthesis, retrosynthetic analysis, Functional Group Interconversion (FGI), synthons, synthetic equivalent, target molecule, making simple carbon-carbon and carbon-heteroatom bonds.
- Carbocations, carbanions, electrophilic carbon, nucleophilic carbon.
- Grignard reagents, organocopper compounds, alkyl lithium compounds, stabilised carbanions, carbanion stabilised by two electron withdrawing groups, acid/base activation, Michael addition, reductive amination, imine,
- Malonate ester, enolate formation, alkylation of malonate esters, double alkylation reactions,
- Decarboxylation, kinetic vs. thermodynamic control, β-keto esters, 1,3-diketone, condensation reactions (Knoevenagel, Aldol etc.),
- Pericyclic reactions, Diels-Alder reaction, diene, and dienophiles.
- Formation of double bonds.

Recommended reading:

General:

- Graham Solomons and Craig Fryhle; Organic Chemistry, 7th Edition.
- Francis A. Carey, Organic Chemistry, 4th Edition.
- K. Peter c. Vollhardt and Neil E. Schore, Organic Chemistry, 3rd Edition.

Specific:

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

Very good books that cover all the material:

Organic Chemistry
John McMurry (9th edition)

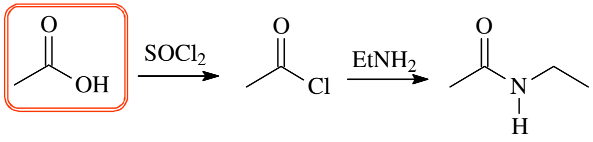
Organic Chemistry
Clayden, Greeves, Warren and Worhers

Introduction

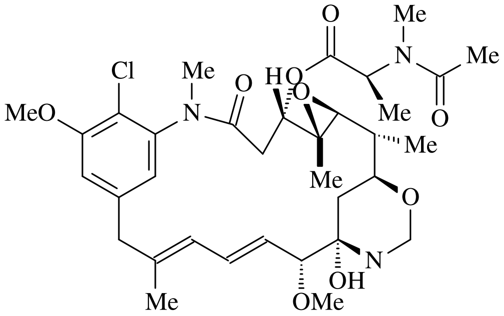
What is organic synthesis?

- 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:



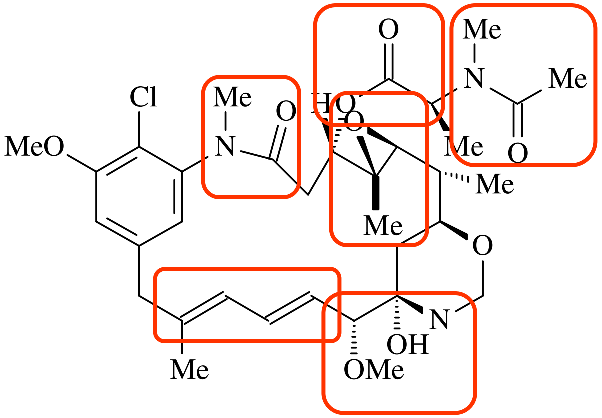
- Of course the structures can contain **many functional groups** and we have to be able to select those we want to react!
- Not just that, if we want to make a given molecule, such as a **NATURAL PRODUCT** we have to be able to **place these functional groups into the molecule at the right places**!
- That can often be a problem, as the following example shows:



MAYTANSINE
A very 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:**



- And there are more!!! Can you spot them?????
- To be able to synthesise a molecule like this, or even the amide on previous 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**
  - ***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!**
- **Next page should remind you!**

- We can see from the above examples that for a successful synthesis we need to be able to have a certain design/target in mind.
- Therefore when designing synthesis that we need to divide our strategy into

Analysis
and
Synthesis

- The **ANALYSIS** would involve:
  1. **Recognise the functional groups in the target molecule.**
  2. **DISCONNECT the product with methods that are KNOWN and 'REALISABLE'.**
  3. **Repeat as often as necessary until reaching available STARTING MATERIAL(S).**
- The **SYNTHESIS** would involve:
  1. **Write out a plan and add the REAGENTS and CONDITIONS.**
  2. **Modify the procedure if needed!**
- **Lets look at some of these definitions…..**

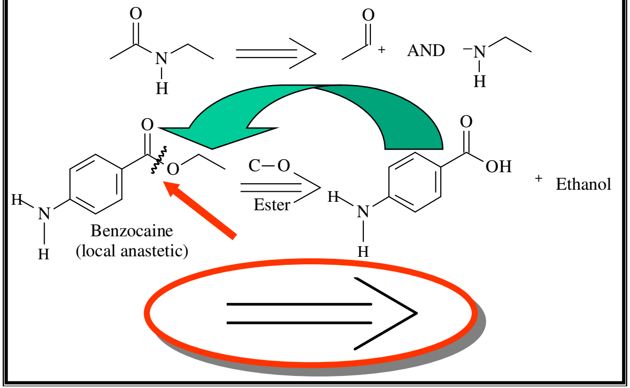
- Often it is better to look at the ***'end product'*** or the final product and see if we can:

Work our way backwards!

(Start with the structure and work backwards)

- This will help us to understand which functional groups we need to take into the account when we choose our ***synthetic strategy***!
- This is called the:

DISCONNECTION



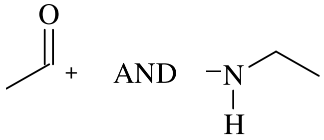
- This kind of analysis is also called:

Retrosynthetic analysis

- What we just saw on last overhead was the breaking of a bond in a single molecule which gave us two new molecules.
- The DISCONNECTION gave us:

SYNTHONS

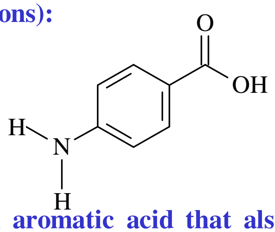
- **We literally reversed the synthetic steps or reactions.**
- **We can only do so when we have got 'reliable reactions'! Hence, something we can recognise!**
- **The SYNTHONS are generalised fragments, usually ions, that are produced by a disconnection.**
- **They might not be the real REAGENTS!!** Hence:



- **As you saw these two SYNTHONS are not likely to be stable because of that we use:**

Synthetic Equivalents

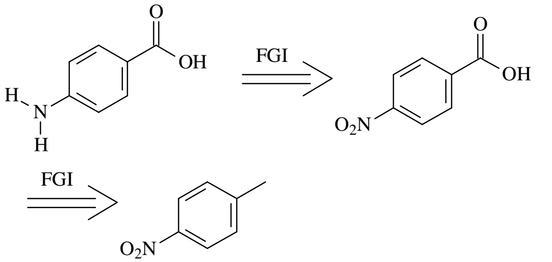
- **These are reagents carrying out the function of the synthon(s) which cannot itself be used.**
- **Lets look at our Benzocaine a bit better (or one of its synthons):**



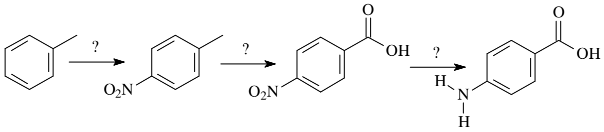
- **We got an aromatic acid that also has got an amino group!**
- **The next step is to remove or disconnect either the $-NH_2$ or the $-CO_2H$ groups! But we don't know of any GOOD METHODS to do so!**
- **Because of this we use what is called:**

FUNCTIONAL GROUP INTERCONVERSION

- ***Functional Group Interconversion*:** the operation of writing one functional group for another so that disconnection becomes possible (written with the arrow with ***FGI*** on top)
- Lets look at our example again:
  - ➡ **Aromatic acids can be formed from oxidation of methyl groups!**
  - ➡ **Amines are made form hydrogenation of NO_2 groups!**

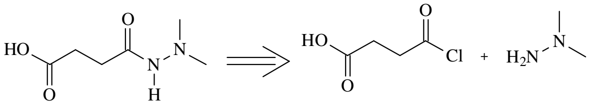


- Here we can do the final disconnect, by removing the NO_2 group and we can start the synthesis with a cheep an easy to get **STRATING MATERIAL:**



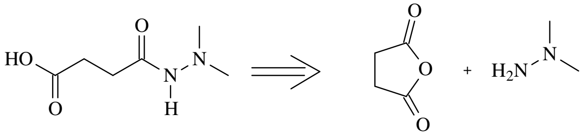
Remember that:

'Disconnection must correspond to known, reliable reaction'



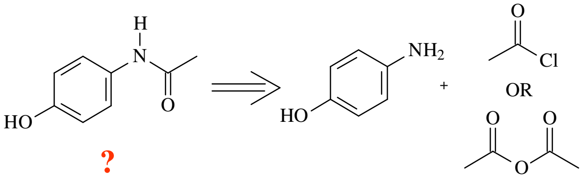
Daminozide an agrochemical

- **Is this a viable DISCONNECTION?**
- **Well in fact it is…..but one of the synthons is not great, since it is unstable……which one?**
- **The acid chloride!**

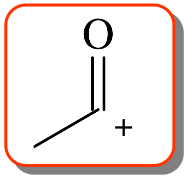


Daminozide an agrochemical

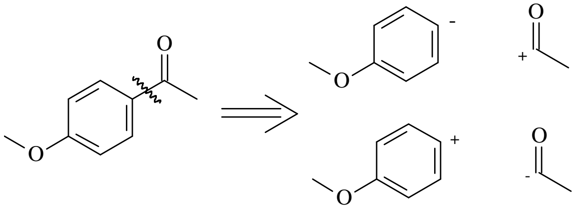
ANHYDRIDE



- In fact the anhydride is used.
- We often see this problem, that more than one starting material are available! We thus use:



- This is **'idealized reagent'; the SYNTHON!**
- We can, by using this kind of 'molecules' to represent the 'polarity' of the product of the disconnection!
- We just have to remember that the synthons have to be replaced by reagents in a suggested synthesis.
- What do you think of this example?



- Is either of these synthons electronically possible?
- The first one is. It is not an idealised fragment, but it helps us to work out which reagent to use!

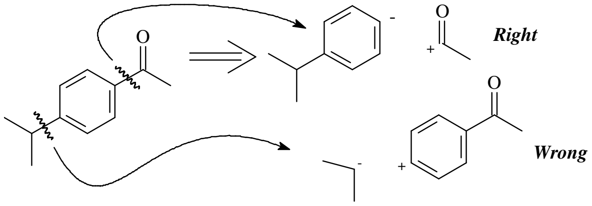
- So what do we have to keep in mind when we are choosing a disconnection?

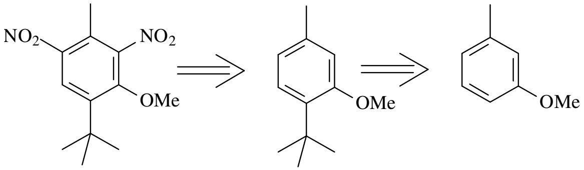
Guideline 1.

Disconnection must correspond to known, reliable reactions.

Guideline 2.

For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom.



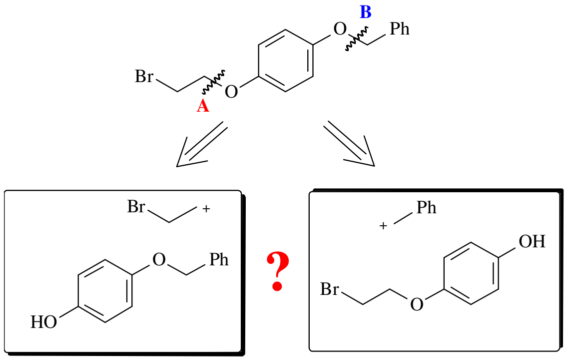


MUSK AMBRETTA
(essential in perfumes)

- Chemoselectivity problems can occur when we have two ore more groups that are reactive within the same molecule.
- To avoid this problem we can try to introduce any reactive groups late in the synthesis!

Guideline 3.

Consider alternative disconnections and choose routes that avoid chemoselectivity problems - often this means disconnecting reactive groups FIRST.



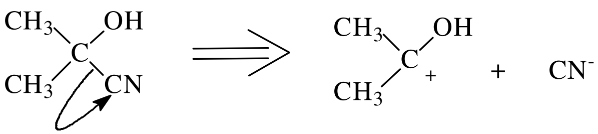
Which one of these disconnections is more logical?

DISCONNECTION HELPS

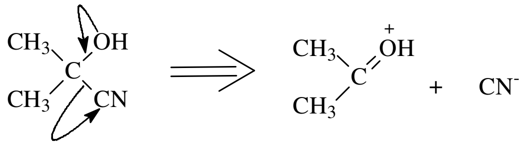
- Lets look at some simple examples, using chemistry that you have seen in your first year!
- It is usually quite easy to achieve the formation of new *C-C, C-N or C-O bonds* from simple starting materials (amines, alcohols, *etc*.)!
- However, this becomes problematic when the molecules become larger.
- What we need to do is to ignore the complex structures of such compounds and rather look at the ***functional group.***

The formation of new C-C bond(s)

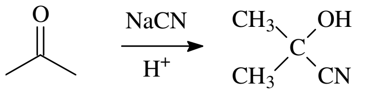
- These are reliable disconnections that we can use almost any time we see one particular functional group in a target molecule!



- Cyanide is a good anion, and the cation is stabilised by the lone pair of the oxygen. We can in fact draw the arrow, starting at the lone pair:

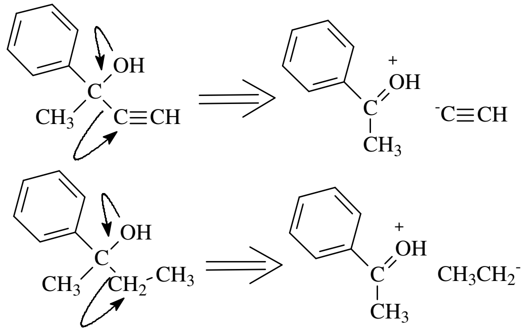


- **The real reaction is in fact:**



CYANOHYDRATE

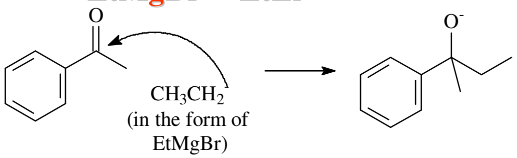
- **It often helps to *'push the arrow'* to chose the most stable anion of the substituent.**
- **We will start by looking at other carbonyl compounds.**



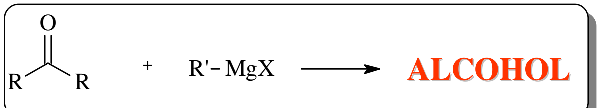
- **Here we have $CH_3CH_2^-$ as synthon. However, it is difficult to form CARBANIONS!!!**

Organometallic reagents

- **We can however use metal based substrates as a reagent for this anion. And for '$CH_3CH_2^-$' we can use EtMgBr or EtLi.**



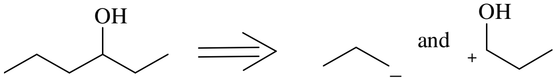
- **This is the Grignard reaction and this is a very nice way (and traditional) to make new C-C bonds:**
  - **Made from simple alkyl or aryl halides (RX) and magnesium (Mg) in dry solvents and are stable in ether/hexane, although they are rapidly decomposed by O_2 and H_2O!**
  - **These molecules can be represented by the *synthon R^-* since they behave as *cabanions.***
  - **The only problem is that these are also good bases and abstract acidic protons (from amines, alcohols and water, *etc*.).**

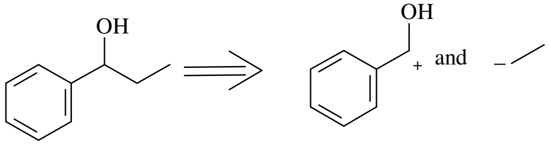


$$R\text{-}MgX + H\text{-}Y \longrightarrow R\text{-}H + Y\text{-}MgX$$

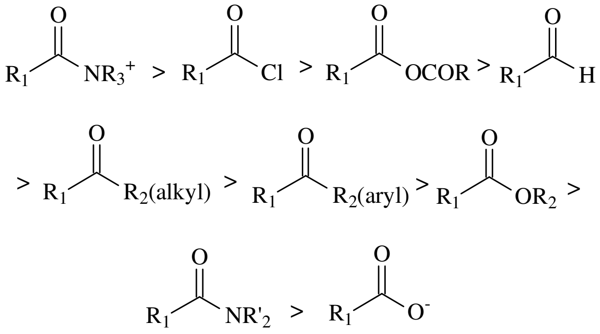
$$\overset{\delta-}{R}\text{-}\overset{\delta+}{MgX} \text{ or } \overset{-}{R}\ \overset{+}{MgX}$$

- **The R-M bond is polarised. And these structures are adequately represented by the synthon R^-.**



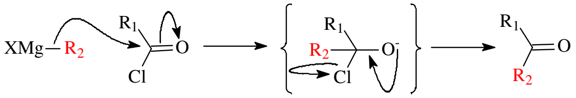


- **$CH_3CH_2CH_2^-$ and $CH_3CH_2^-$ can be represented with *$CH_3CH_2CH_2MgX$* and *CH_3CH_2MgX* as the reagents/synthetic equivalents.**
- **We have seen some of these before, and established that an aldehyde would give a secondary alcohol and a ketone would give tertiary alcohol after washing with H_2O or H_3O^+.**
- **Formaldehyde is also converted into primary alcohol, whereas acid chlorides (RCOCl) would give ketones! But why?**

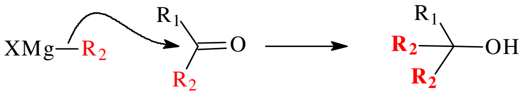


- **For some of these we have good leaving groups and for others we don't!**
- **If we have one (X), it can be eliminated by a carbon nucleophile; this is an acylation reaction.**
- **If we don't, the anion is likely to pick up a proton the reaction medium either during the reaction or in the workup. This is what we saw in last lecture.**
- **Alternatively, if we also have an acidic hydrogen adjacent to the hydroxyl group, then elimination of water my follow the nucleophilic addition.**

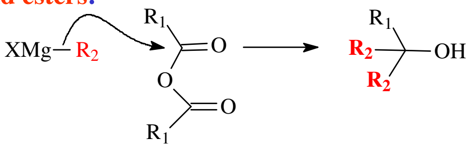
- Well the Cl$^-$ is a good leaving group!

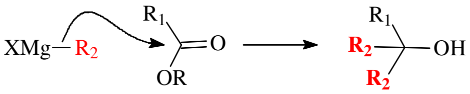


- However, this is not the full story since we now have formed a new species that is very reactive (although less then the acid chloride). So what can happen?

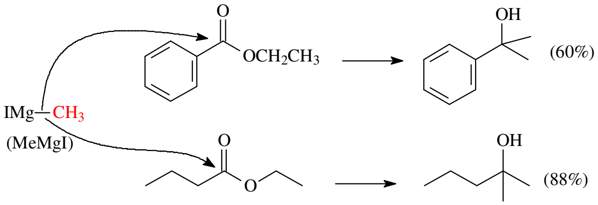


- The final product is the tertiary alcohol where we have added two Grignard reagents to the original. This will happen when we react the Grignard reagent with acyl halides, anhydrides and esters:

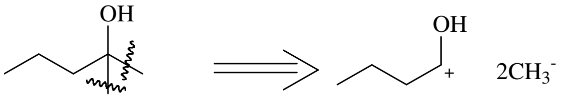




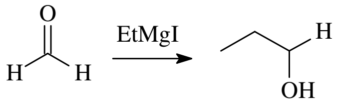
- Of these the esters are the most reliable and give the best yield:



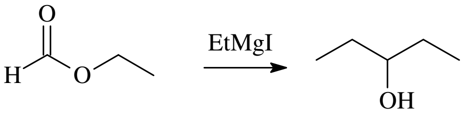
- The disconnection can be done twice, and overall would give us:



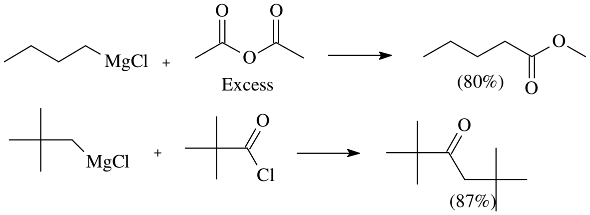
- As stated above, fomaldehyde gives us primary alcohol:



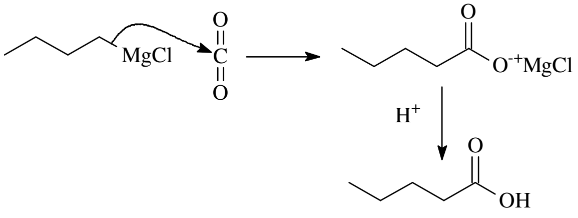
- In the same way, formate esters give secondary alcohols:

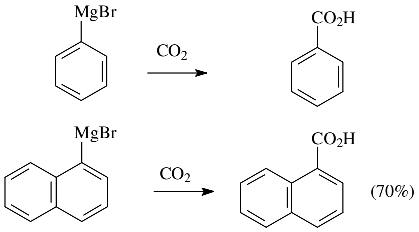


- Even though, one would expect to get the di-substituted product all the time, then it is possible to isolate the mono substituted product (*e.g.* the ketone) in acceptable yields by controlling the reaction conditions, *e.g.* when:
    - The acyl compound is in excess.
    - The reacting temperature is low.
    - The product is sterically hindered.

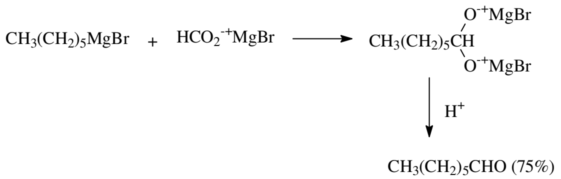


- One carbonyl function that we have not looked at is carbon dioxide. CO_2 can react with Grignard regents and gives carboxylic acids:



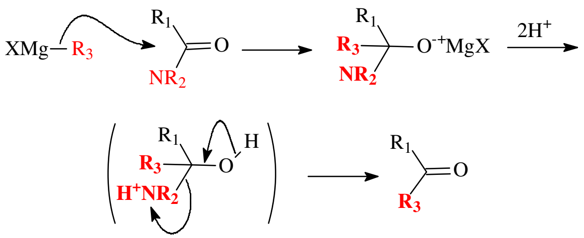


$CH_3CH_2MgBr + HCO_2H$ (format ions) $\longrightarrow HCO_2^{-+}MgBr + C_2H_6$

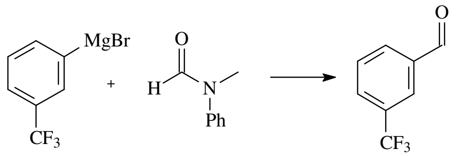


$$CH_3(CH_2)_5MgBr + HCO_2^{-+}MgBr \longrightarrow CH_3(CH_2)_5CH(O^{-+}MgBr)_2 \xrightarrow{H^+} CH_3(CH_2)_5CHO \ (75\%)$$

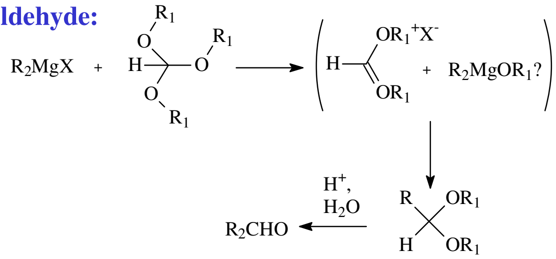
- Though we can form the aldehyde using the above procedure, then carboxylation is carried out by using large excess of CO_2 and the acid is the primary product.
- In the case of primary and secondary amides the principal role of the Grignard reaction is to remove the acidic protons the the nitrogen (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:



- Here it is essential to protonate the amine for the intermediate to collapse to give the new carbonyl compound.
- This reactions can be used to give aldehydes:



- However, using orthoformate ester (trialkoxy-methanes) is a better way of forming the aldehyde:



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

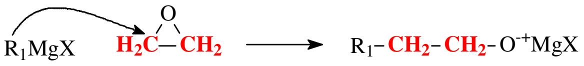
$$\boxed{R_1MgX + R_2\text{-}Y \longrightarrow R_1\text{-}R_2 + MgXY}$$

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

- We can also use other electrophiles such as the sulfonates (Tosyl: $CH_3C_6H_4SO_2$-R):

$$PhCH_2MgI + CH_3(CH_2)_3OS(O_2)PhCH_3 \longrightarrow Ph(CH_2)_4CH_3$$

- However, usually this type of reaction is not very successful due to various side reactions. The one reaction that does proceeds well is the opening of oxirane (ethylene oxide):



$$R_1MgX \quad H_2C\overset{O}{—}CH_2 \longrightarrow R_1\text{-}CH_2\text{-}CH_2\text{-}O^{-+}MgX$$

- Because of the problem with side effects in alkylation Grignard reactions other organo-metalic regents are used. These are:
  - Organolithium
  - Organozinc
  - Organocadmium
  - Organocopper
- We will look at selcted examples of these next.

Other Organometallic Reagents/Reactions

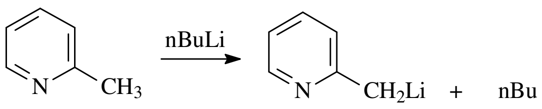
Organolithium reagents (RLi)

- **Lithium is a very electropositive metal and highly polarised towards carbon**
- **These are usually made either from the appropriate halide and metallic lithium, or by halogen-metal exchange:**

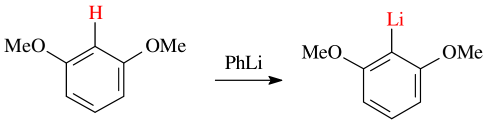
$$RBr + 2Li \longrightarrow RLi + LiBr$$

$$RBr + R'Li \longrightarrow RLi + R'Br$$

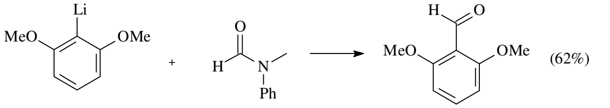
- **If acidic compounds are used, these can be deprotonated and lithiated:**

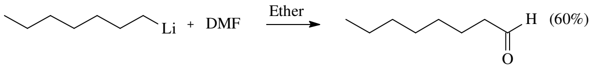


- **Even benzene derivatives can be lithiated:**

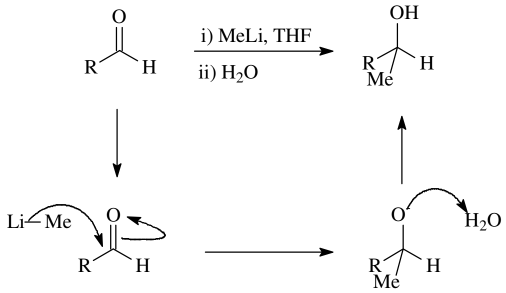


- **As the examples shown above, the organolithium reagents are more strongly nucleophilic then the corresponding Grignard reagents.**
- **They undergo all the same reactions as the Grignard reagents, and often more efficiently:**



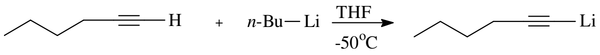


- **Here the aldehyde is formed even when using DMF. The attack of other carbonyl compounds such as aldehydes and ketones is also effective:**

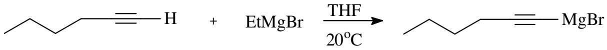


- **When the organolithium compound reacts with water it is destroyed in the same way as the Grignard reagent, giving the alkane and MOH.**

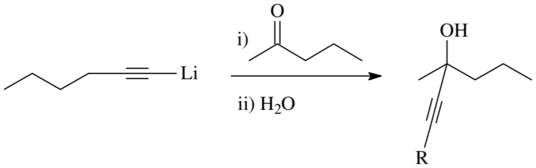
- **As before, the reaction of RLi with aldehydes and ketones gives secondary and tertiary alcohols respectively.**
- **Since the RLi is quite a strong base, they can be used (as shown earlier) to deprotonate acidic moieties such as alkynes:**



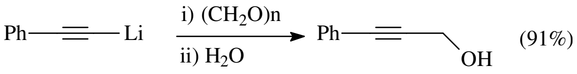
- **This is also possible using Grignard reagents, but only at higher temperatures:**



- **Both of these can now be used as effective nucleophiles:**



- **The reaction of RLi with formaldehydes give primary alcohols, just like using Grignard:**



Organocopper:

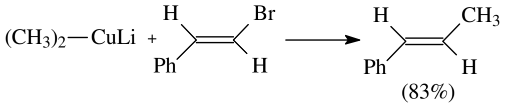
- **The reaction of organolithium compounds with copper(I) haldide gives organocopper species. These can be either formed as:**
  - **RCu or**
  - **R_2CuLi**

$$R-Li + CuX \longrightarrow R-Cu + LiX$$

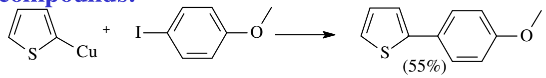
$$2R-Li + CuI \longrightarrow R_2-CuLi + LiI$$

- **The former (simple alkylcopper) is sparingly soluble in organic solvents.**
- **The second is soluble in ethers and is of great use in organic synthesis, like in the displacement of halogens:**

$$R-Cu + CH_3(CH_2)_9-I \longrightarrow CH_3(CH_2)_9-R$$



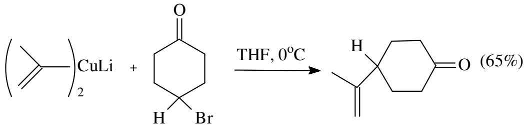
- **These reactions are most successful with lithium dialkyl or dialkenyl cuprates and aryl copper compounds:**



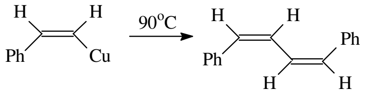
- **The displacement of a halogen from an acyl halide occurs easily, often at –78°C:**

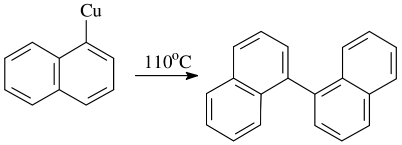
$$(CH_3)_2\text{—}CuLi \;+\; CH_3(CH_2)_9\text{−}COCl \xrightarrow[\text{15 min.}]{-78^{o}C} CH_3(CH_2)_9\text{−}COCH_3$$

- **When using ketones or aldehyde the unreactivity of the copper reagent is apparent:**

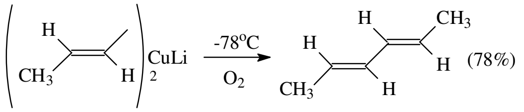


- **The copper(I) reagents are very valuable synthetic tools since they can undergo coupling reactions that involve one electron transfer:**



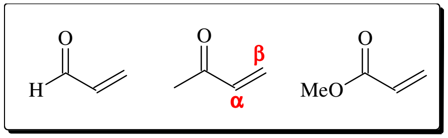


- **When using lithium dialkyl cuprates and oxygen (O_2) these coupling reactions go very well:**

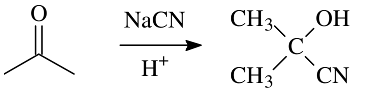


Conjugated Addition
(using organometallic and other reagents)

- **There is one reaction that we have not looked at, but is of great synthetic relevance when using organometallic (and other) reagents! This the reaction of α,β-unsaturated carbonyl groups:**

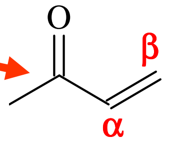


- **One of the first reaction we looked at was the formation of cyanohydrate:**



CYANOHYDRATE

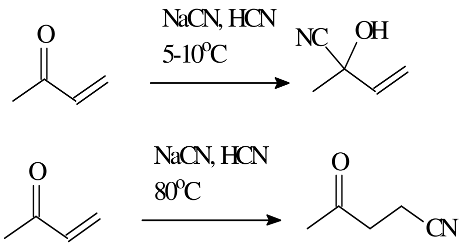
- **If we were to do carry out this reaction using the above ketone, then what could happened?**



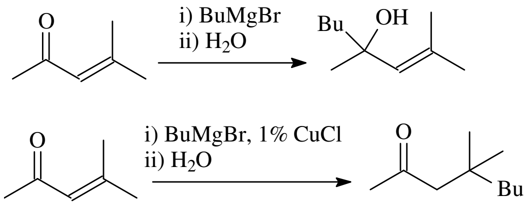
Attack on the carbonyl

Attack on the alkene

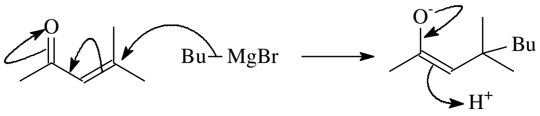
- **In fact both of these reactions can take place:**



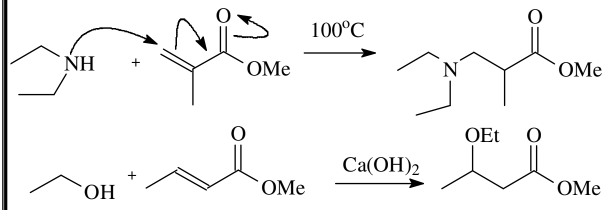
- **We could also carry out such reactions using a Grignard reagent:**



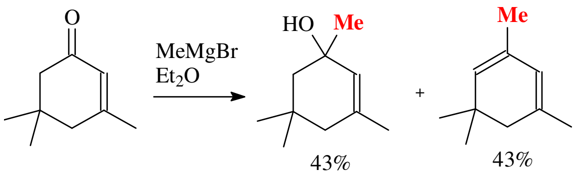
- **C=C double bonds conjugated with carbonyl groups are electrophilic, whereas isolated C=C double bonds are nucleophilic!**
- **Because of this, the nucleophile can attack the alkene:**



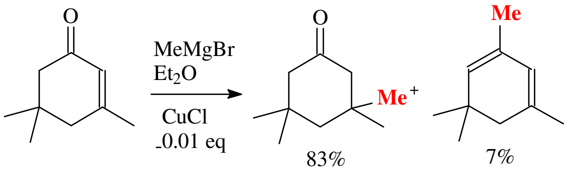
- **A range of nucleophiles will participate in such reactions : amines, alcohols, thiols and halides:**



- **Copper (I) salts are particularly good in directing organometallic reagents to the α,β–bond. In the case of using a Grignard reagents, the ketone is attached preferentially:**

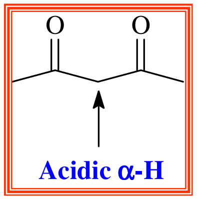


- **Using 1% of CuCl gives however:**

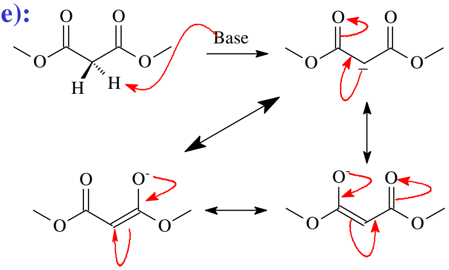


Stabilised carbanions: formation of C-C bonds

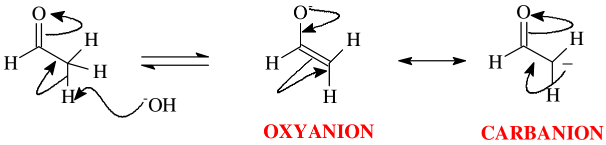
- When a **-CH$_2$-, CHR- group** in a molecule is flanked by **one or two electron withdrawing groups**, then it can be easily deprotonated and the resulting anion is stabilised by delocalisation.
- This occurs in molecules such as **α,β–dicarbonyl compounds**:



- The protons are called **α-protons**, and are quite acidic.
- The deprotonation of the **α-proton** gives the following delocalisation (stabilisations *via* resonance):

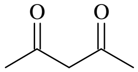


- The anions formed by deprotonation of the carbon alpha to the carbonyl group bear most of the negative charge on oxygen and are commonly referred to as **ENOLATES**:

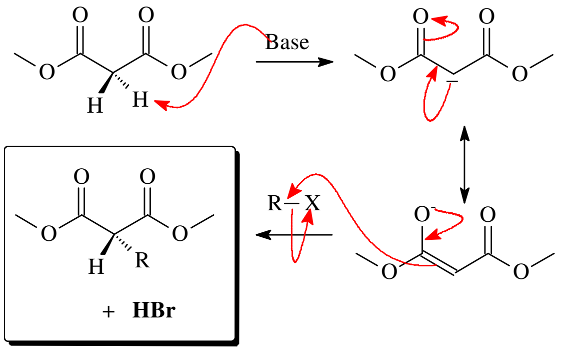


- What we have made here is a carbon nucleophile (by deprotonation).
- The stability of the anion is governed by the way we can delocalise the charge, i.e. by *resonance*

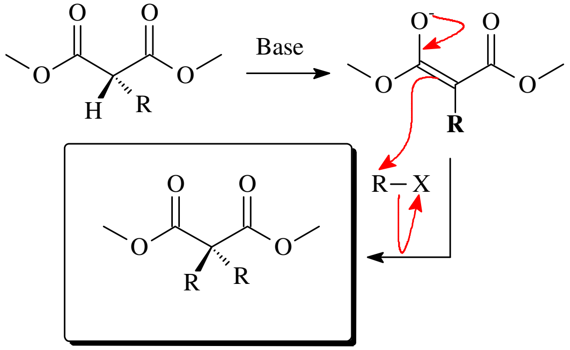
Both the rate and the stabilisation of the carbanion are enhanced by the presence of substituents groups that can stabilise the negative charge

	$CH_2(NO_2)_2$	$CH_2(CO_2CH_2CH_3)_2$
pKa = 9	pKa = 4.4	pKa = 13

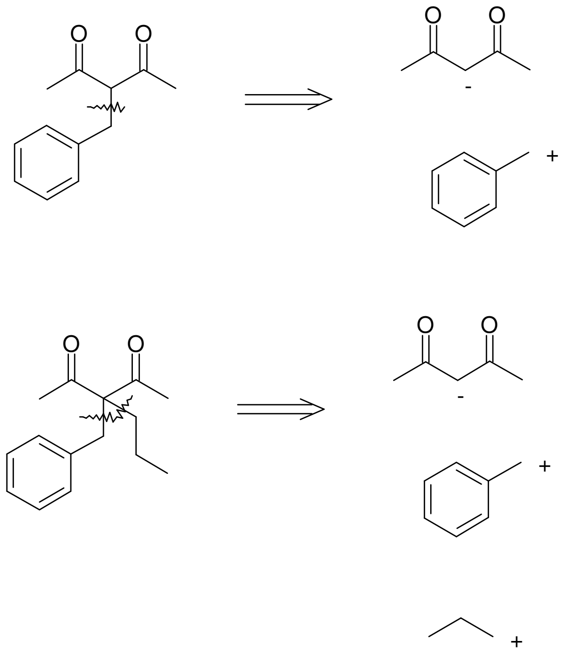
- These compounds can thus be completely deprotonated by bases such as **Na^{+-}OEt**, called sodium ethoxide.
- They can then undergo alkylation reactions.



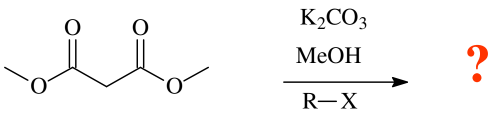
- Notice that we have two α-protons, the pKa of the latter is higher than that of the first one, but still we can get **di-alkylation if the base is strong enough:**



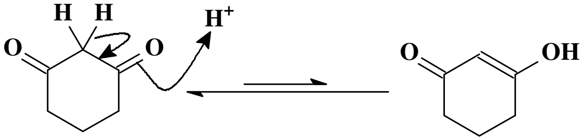
Retrosynthetic analysis



- We can overcome this if we use milder base (notice the solvent!):

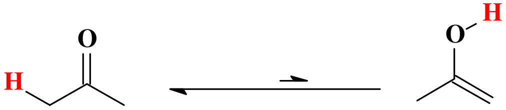


- Very often carbonyl molecules can have 'two types of structures'. In fact they can exist in equilibrium:



KETO FORM **ENOL FORM**

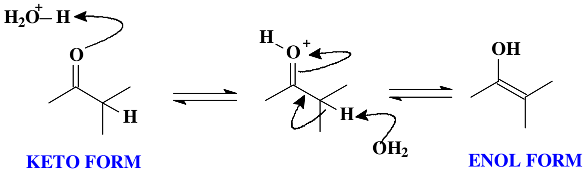
- Usually simple aldehydes and ketones do not exist as enols ('ene-ol') (such as acetone) since the combination of the C=C double bond and the O-H single bond is (slightly) less stable then the C=O double bond and a C-H single bond:



Keto fom of acetone

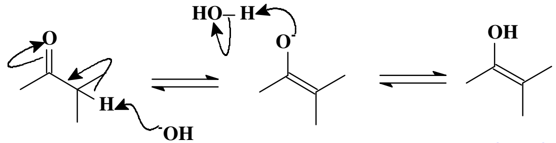
Enol fom of acetone

- **Enolization** is usually quite a slow process in neutral solution (See notes from last year).
- 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**

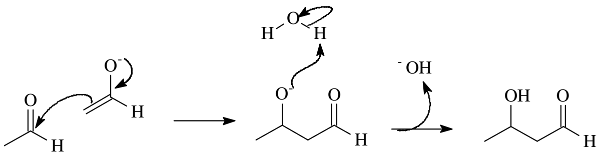
- In the base-catalysed reaction, the α-proton is first deprotonated, and then the proton is added to the oxygen atom in a second step:



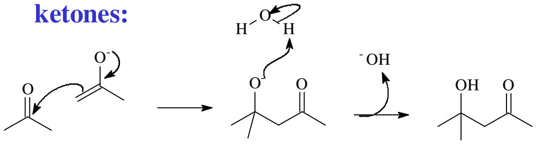
KETO FORM **ENOL FORM**

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

- The NaOH is not strong enough (basic enough) to *enolize* the aldehydes completely.
- The enolate is thus surrounded by other aldehyde molecules, *i.e.* these *aldehyde molecules are all electrophilic* whiles *the enolate is nucleophilic*.
- Each enolate ion will thus attack one of these aldehyeds, forming an alkoxide ion which can be protonated by water to give alcohol.

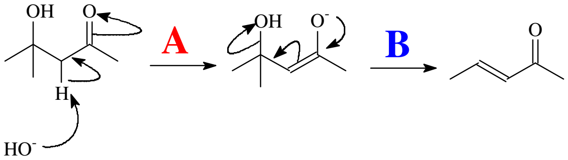


- The product is an aldehyde with a hydroxy group. The name of this reaction is the Aldol reaction and the trivial name of the product is *'aldol'*. You did this in your first practical class! (See Experiment 1)
- Such reactions can also take place if you use ketones:



4-Hydroxy-4-methylpentan-2-one

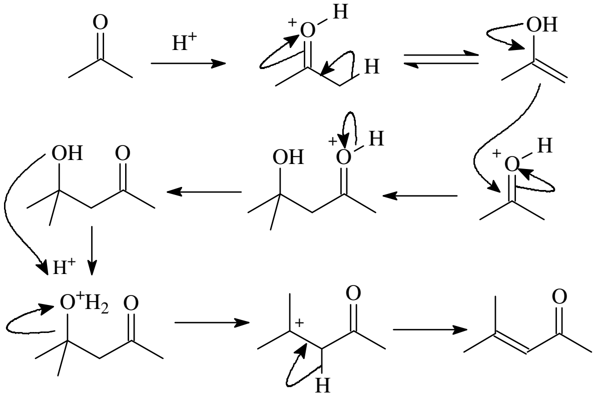
- The above acetaldehyde reactions works well with a drop of diluted sodium hydroxide. The acetone reactions is best done if we add barium hydroxide [$Ba(OH)_2$)]. Both of these keep the base concentration low.
- In both of the above examples we have formed a new C-C single bond, and we can *isolate the aldol product*.
- 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:



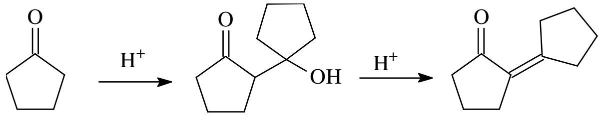
- The first step here is the enolization (A), and the second step is the elimination (B).
- Because of this very often it is possible to get either the aldol product, the eliminated product or mixture of both!
- The elimination product is, however, quantitatively formed if we tune the reaction conditions:

- Strong Base
- High(er) Temperatures
- Longer Reaction Times
- (also on the Structure of the Reagents!)

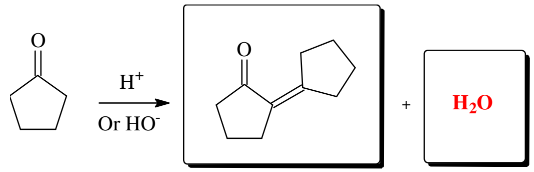
- The elimination step (E1) is even more easier if we use acid. Acid catalysed aldol reactions usually give the unsaturated product instead of aldols:



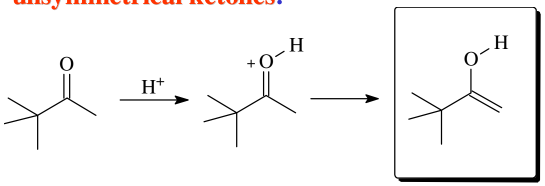
- Here is what happened if we use cyclopentanone:



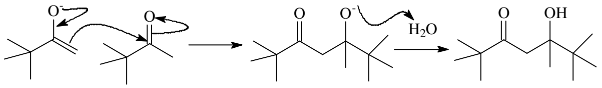
- These kind of reactions are often called CONDENSATION REACTIONS:



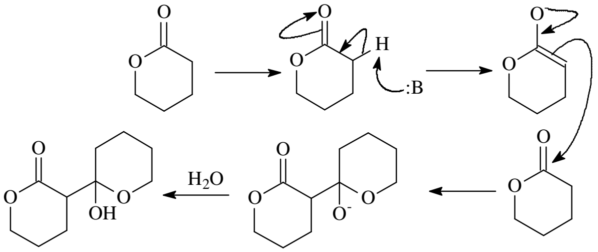
- For this particular reaction we can say that the *"two molecules of cyclopentanone condense together to give a conjugated enone".*
- The aldol reaction can also be carried out using unsymmetrical ketones:



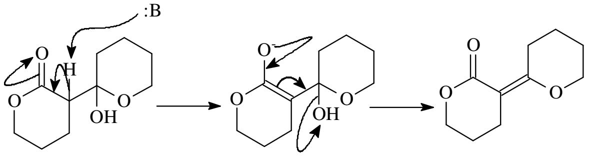
- Here only one side of the ketone is blocked (no α-proton) and only one enol is formed.
- We say that the enolization can only occur towards the methyl group but not towards the *t*-butyl group.
- There are many molecules that do this, an aryl ketone being an example.



- These kind of reactions can also take place if you use cyclic esters, called lactones:

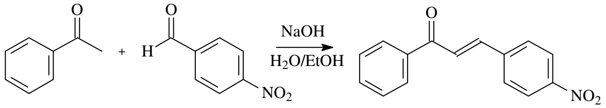


- Here the elimination will occur via the enolate of the aldol production, called E1cB :

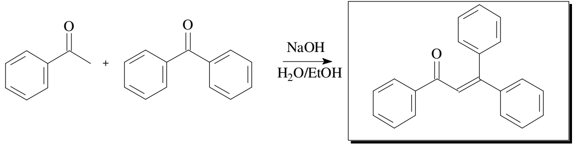


- Acyclic esters are different since they have got a leaving group which is the one that departure. In the case of the lactone this is possible but the equilibrium will favour the condensation.

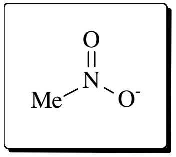
- Another type of condensation reactions are the CROSS-Condensation reactions.
- In comparison to what we have been looking at then these occur between two different carbonyl compounds, whereas up to now we have discussed SELF-Condensation reactions.
- An example of such cross-condensation reaction is the reaction between PhCOMe and 4-nitrobenzaldehyde:



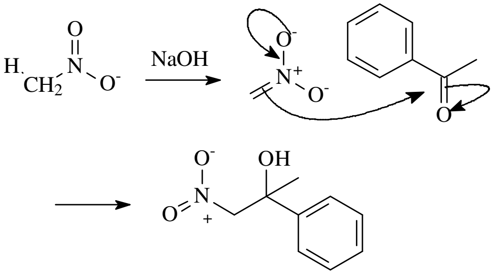
- Here only the ketone can be enolized.
- These molecules are called chalcones, and they are of course enones.
- Such reactions are also possible between other carbonyl compounds, where one of the carbonyls does not have an α-proton, such as the dipheynlketone:



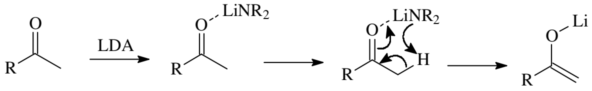
- There are several other compounds that can enolized but are not electrophilic.
- For instance **nitromethan**:



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

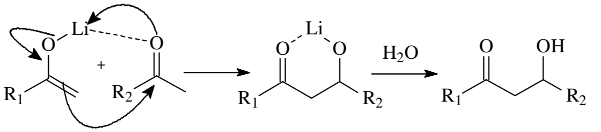


- If a strong base is used such as LDA (lithium diisopropyl amine) a specific enolate can be formed.
- This occurs through fast deprotonation and stabilisation by the Li^+ ion.

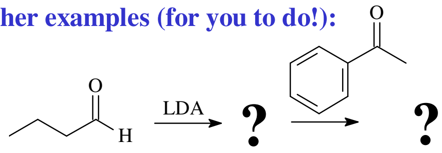


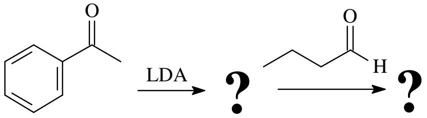
- The reaction is carried out at -78^{o}C.

- 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!):



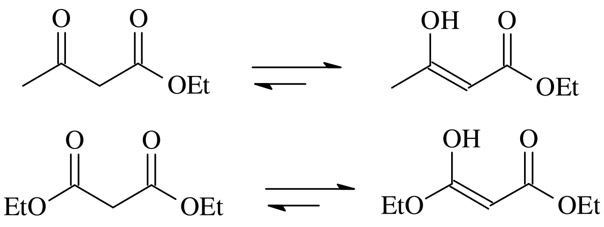


- It is also possible to make other kind of stabilised enoles such as by using **silyl enol ether** and **enamines**. We will look at these in next lecture.

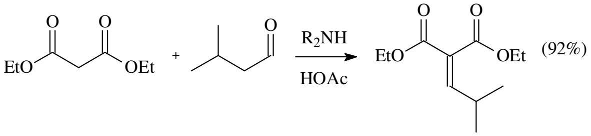
Quick Summary

- We have looked formation of stabilised anions (enolates) and the various condensation reactions they can undergo.
- We looked at specific enaolates (lithium enolates)
- In this lecture we will revisit enolate chemistry where the anion is stabilised by two electron withdrawing groups.

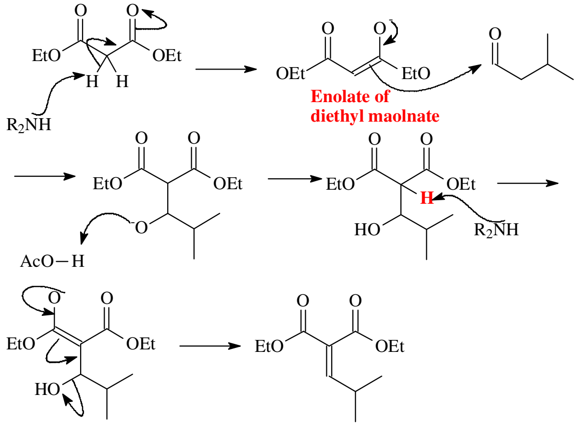
- We will also look at the formation of six member ring systems, and the reaction of these compounds with Grignard Reagents.
- But first we look at enolate chemistry of 1,3-dicarbonyl compounds
- 1,3-dicarbonyl compounds undergo enolization under normal conditions:



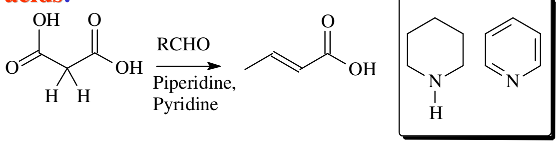
- However, these enolates are very stable and and the carbonyl groups in the unenolized fraction of the two examples are poor electrophiles.
- Because of these these do not undergo self condensation reactions so easily.
- However cross-condensation reactions are easily done:



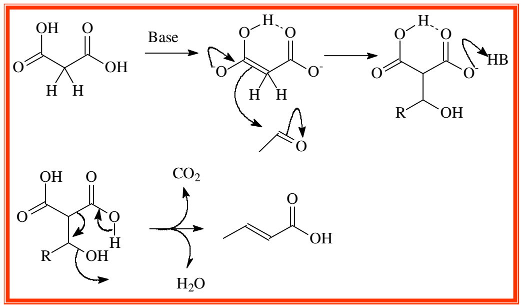
- We need a weak acid or a base to accelerate the reaction:

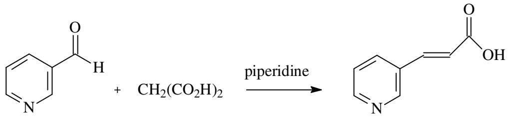


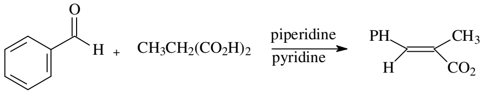
- **The reaction of malonic acid with an aldehyde under similar conditions gives *a,b*-unsaturated acids:**



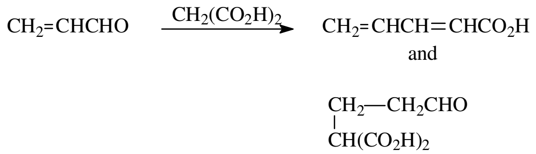
- **This is the Knoevenagel reaction. It involves the loss of CO_2, thorough decarboxylation process:**







- **Sometimes both the Knoevengel type and Michael addition can occur:**

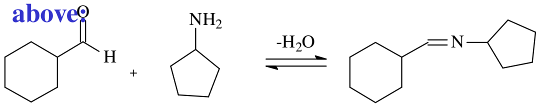


$CH_2{=}CHCHO \xrightarrow{CH_2(CO_2H)_2} CH_2{=}CHCH{=}CHCO_2H$

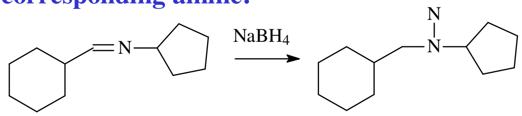
and

$\begin{array}{l} CH_2\text{—}CH_2CHO \\ | \\ CH(CO_2H)_2 \end{array}$

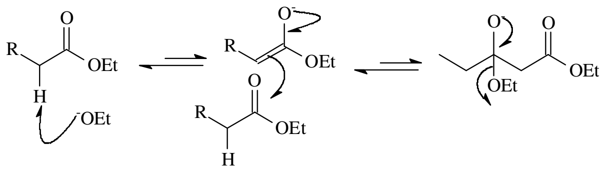
- **Aldehydes can undergo condensation reaction with primary amines (and sometime secondary) to give imines, and these are related to the above?**



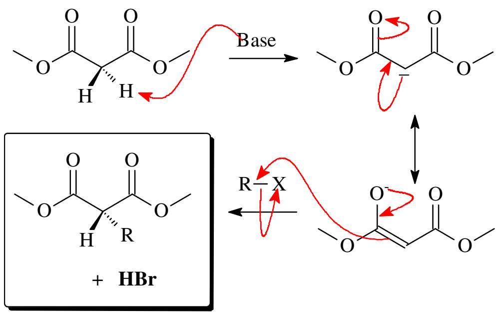
- **Reduction of this imine with $NaBH_4$ gives the corresponding amine:**



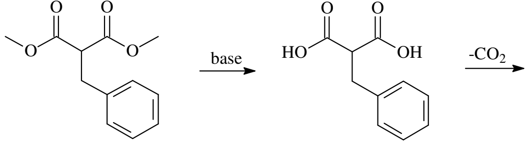
- **This is called reductive ammination!**
- **On the bases of these you might guess the product of the self condensation of ethyl acetate?**
- **This is the Claisen ester condensation and requires the use of base.**
- **Usually the base is of the same nature as the ester!**

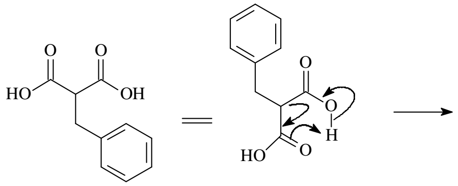


- Can we do alkylations of these enolates, form a other C-C bonds?
- Yes, we have already seen one example:

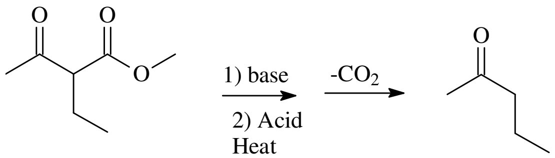


- In the same way as shown above we can also loos one of the carboxylic functions through decarboxylation:





- We can do the same thing with β-keto esters:



Regioselectivity and Stereoselectivity

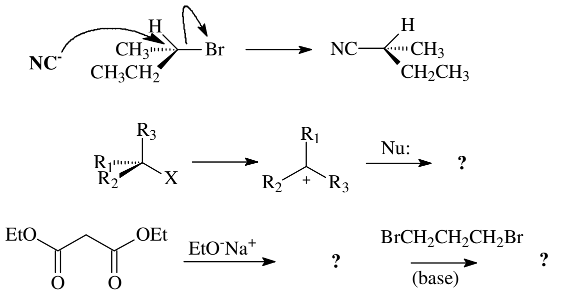
- An unsymmetrical dialkyl ketone can from two regioisomeric enolates on deprotonation:

$$R_2CH_2\overset{\overset{O}{\|}}{C}CH_2R' \xrightarrow{B^-}$$

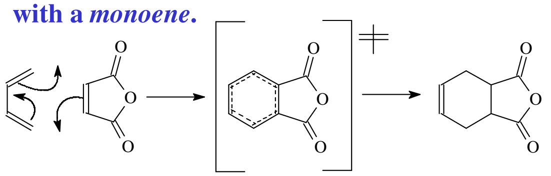
- We need to be able to control this regisoselectivity!
- This can often be done by choosing the right experimental conditions.

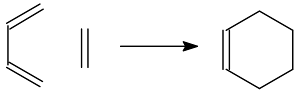
PERICYCLIC REACTIONS

- We have investigate several different types of reactions:

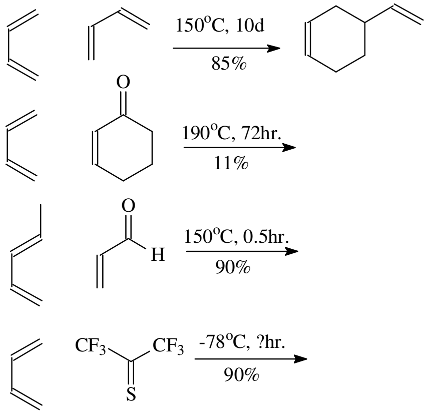


- One thing we did see on the tutorial sheets were ring compounds!
- 6 member ring compounds can be formed by using electrocyclic ring closure reactions, called the *Diels-Alder reaction.*
- The Diels-Alser reaction in its simplest form consists of the reaction of a conjugated *diene* with a *monoene*.

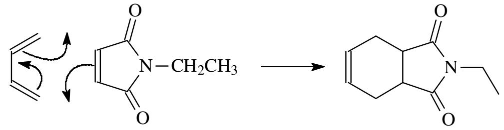


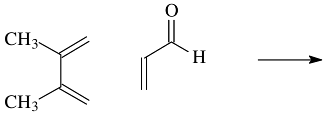


- This reaction is often shown in textbooks, but it is very slow and by heating it at 165^{o} and 900 atm. for 17 hours do we get our DA product.
- The reason is that the dienophile does not have attached to it one or more electron withdrawing groups such as carbonyl, nitrile, nitro or sulfonyl groups.
- Substitutions on the diene also increase the rate, provided that they are electron-donating! Try to do these:

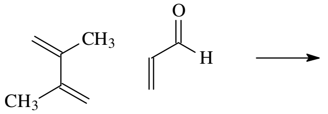


- **These reactions cannot be described adequately in terms of electrophilic-nucleophilic interactions**
- **Furthermore these can not be described by radical pathways**
- **In fact they are representatives of a large group of reactions that involve the interactions of π-electron systems in a concerted manner and via a cyclic transitions state**
- **Such reactions are generally described as pericyclic or symmetry controlled.**





Reaction

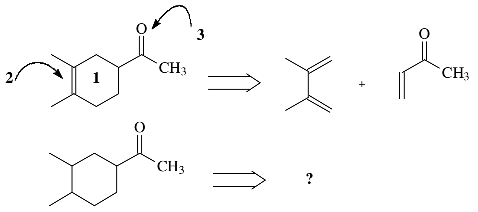


No Reaction

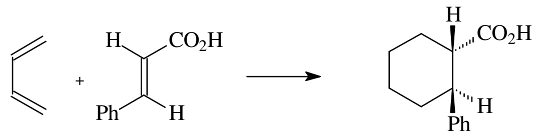
- **We say that the *diene* can adapt two types of conformations: *cisoid* and *transoid***

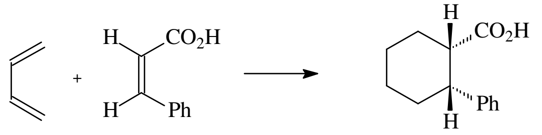
- All the reactions go in a single step simply by heating the two starting materials together.
- Since these reactions do not include an intermediate, we don't have to stabilize the transition state and hence we often **don't need to have solvent present** in the reaction!
- For the first two above, 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:

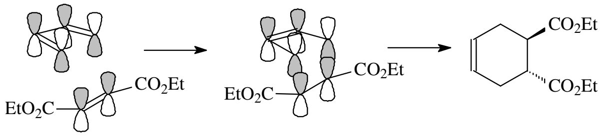
1. **They have a new six member ring**
2. **A double bond in the ring (positioned quite precisely)**
3. **Have got a conjugated group that is outside the ring and opposite to the double bond:**



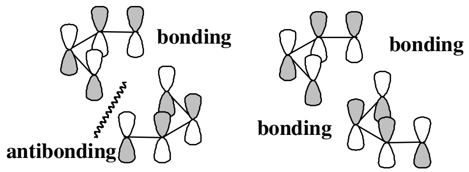
- **In the reaction above we have a 4π-electron system (the diene) interacting with the 2π-electron system of the monene, or DIENOPHILE, yielding a [4+2]-cycloaddition.**
- **Because of this the relative configuration of the starting material is retained in the product:**



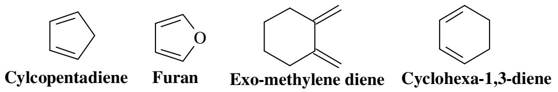


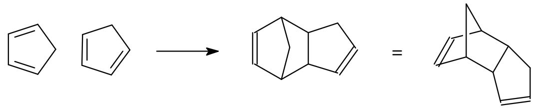


- **For the above DA reactions we obtain a transition state that has six delocalised π-electrons:**

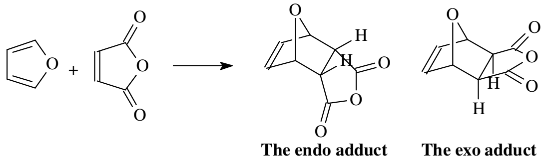


- In both of these cases, the diene is in its *cis*-configuration. We saw earlier that when it is trans no reaction occur. But the *trans*- configuration is the more stable one!
- **Cyclic diene** have no way of taking up the trans configuration. Because the DA reactions proceed much faster for cyclic dienes.



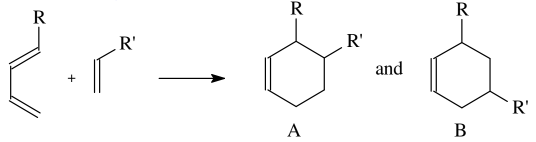


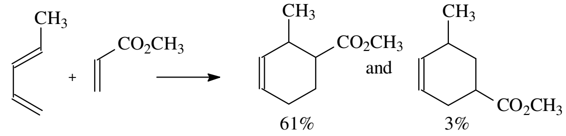
- We can also get (possible) mixture of products:



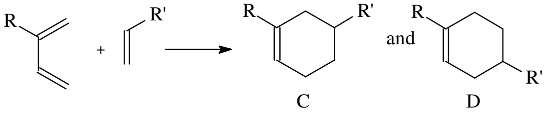
THE DA REACTION:

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

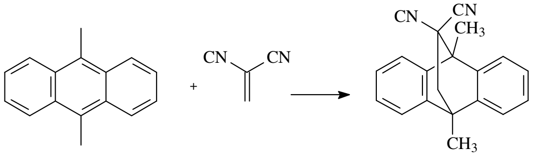




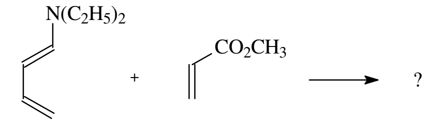
- However, usually the reaction is very regioselective and one of the product is produced dominantly *A*
- *This is can be explained in terms of frontier orbital theory*
- When the diene is substituted at the 2 position the major product is *D*:

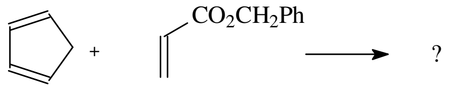


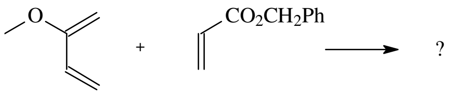
- A variety of components may participate in the Diels-Alder reaction, so this procedure is of considerable synthetic importance:
- Benzene derivatives do not participate in the Diels-Alser reaction sine the product would be non-aromatic!
- However, benzyne (dehydrobenzene) and polycyclic compounds such as anthracene does:



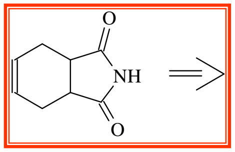
Examples:



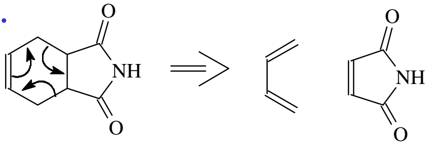




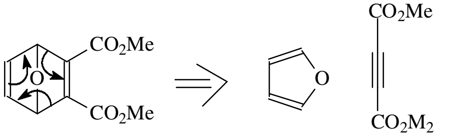
- So if you are asked to show the disconnection of a DA product such as the one below you should be able to do so since you only show the arrows going in a reverse!



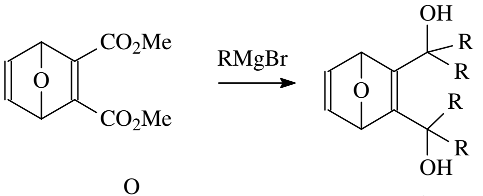
- The double bond in the six-membered ring showed us where to start the disconnection
- All you need to do is to find the six-membered ring containing the double bond and draw the arrows.

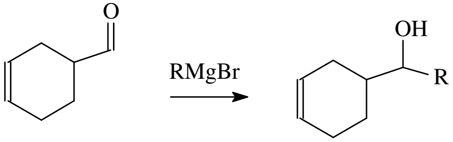


A

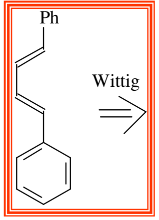


- When you have got esters, ketones, aldehydes etc. you can couple these reactions with the organometalic chemistry we did before. Hence what will happened if you reacted RMgX with A above? Look at the tutorial sheets!

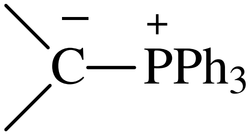




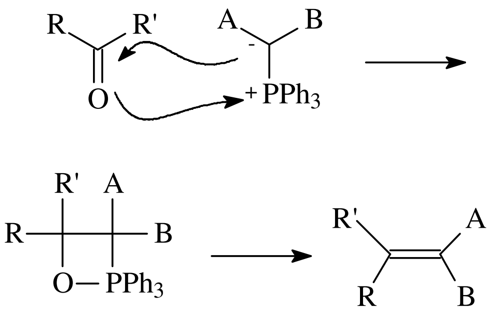
- Very often we need to make the diene or the dionophile:



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

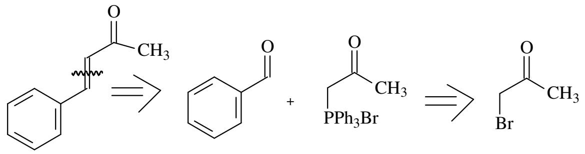


- This is called *triphenylphosphonium ylide*.
- This compound can react with carbonyls such as ketones and aldehydes to form an *oxaphosphetane*, which breaks up to give *trihenylphosphine oxide* and *an alkene:*

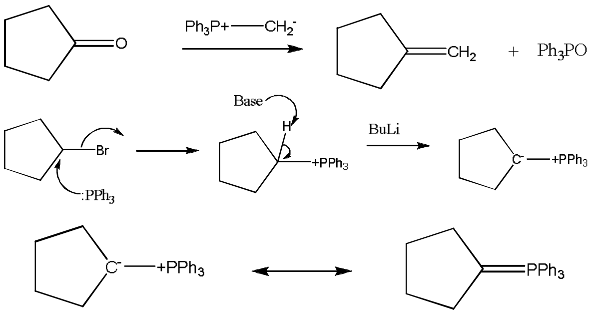


oxophosphetane

- 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.



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: