

Warwick University
Department of Chemistry
Basics of Organic Chemistry and Mechanism
Revision for when you are Lost and Confused
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Unlike many other subjects, organic chemistry ‘builds upon itself’ – you must make sure that you fully understand the earlier concepts before you move on to more challenging work.

In my experience, a lot of students struggle with organic chemistry because they ‘don’t get’ mechanisms. Anyone in this position will probably do badly in their degree course. You can’t succeed just by *memorising*, you have to *understand* the mechanisms.

If you do feel stuck, lost and confused with organic chemistry then please read and work through this document and it should help you. Some is very basic – but none is meant to be patronising – so if you are 100% happy with a section then move on and work through it at your own pace.

The secret to learning this is to be absolutely sure that you know and *understand* what is going on at each stage. Memorising is not good enough. Don’t move on until you are absolutely sure that you understand.

Nomenclature of Organic Compounds

IUPAC has defined systematic rules for naming organic compounds.

These will have already been covered in detail at A-level and will only be mentioned briefly here.

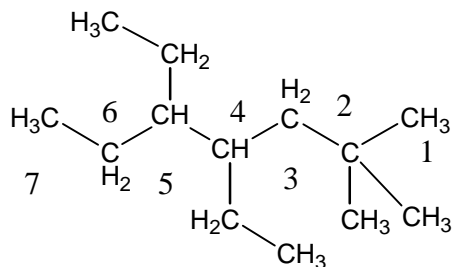
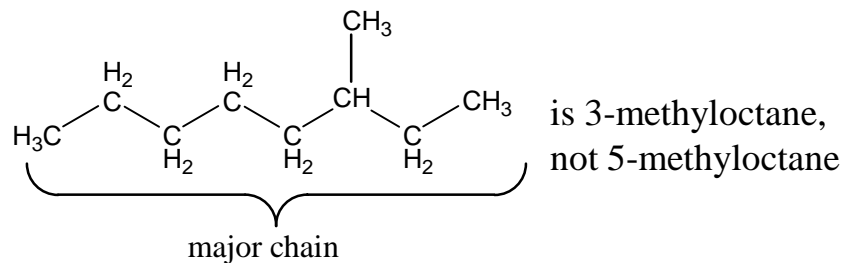
The naming system (and the resulting names) can become very long with complex molecules, therefore this section will be restricted to simple compounds.

The IUPAC naming system involves the following components:

- Identification of major chain or ring
- Side chains and functional groups are added as appropriate, in alphabetical order.
- The sums of numbers for substituents are minimised

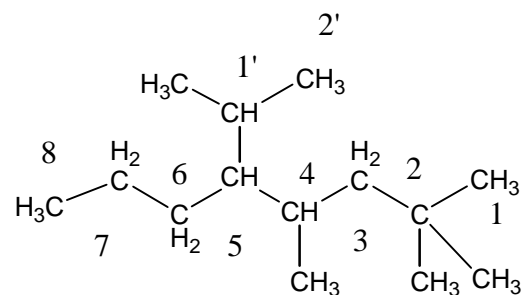
Nomenclature of Organic Compounds

Examples:

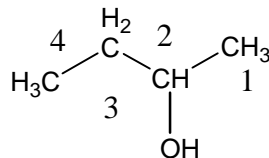


Is 4,5-diethyl-2,2-dimethylheptane

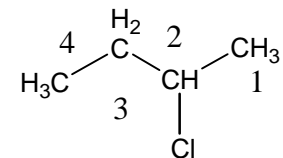
It is **NOT**
3,4-diethyl-6,6-dimethylheptane!



Is 5-(1'-methylethyl)-2,2,4-trimethyloctane



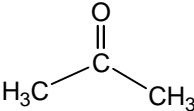
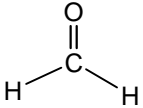
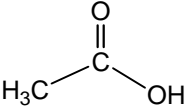
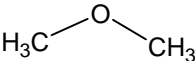
Butan-2-ol



2-chlorobutane

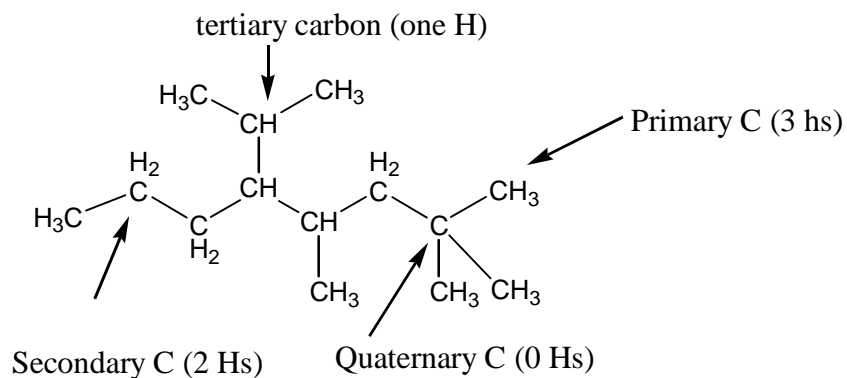
Nomenclature of Organic Compounds

Many common names persist in organic chemistry, despite IUPAC rules, e.g.

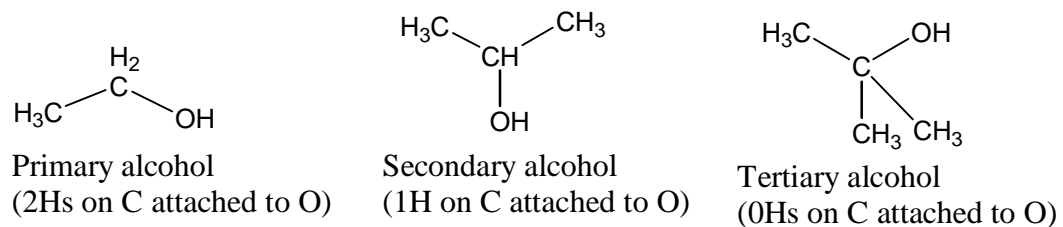
Compound	'common' name	IUPAC name
	Acetone	Propanone
	Formaldehyde	Methanal
	Acetic acid	Ethanoic acid
	Dimethylether	Methoxymethane

Substitution level and functional groups

The 'substitution level' of a carbon atom in an organic compound is determined by the number of attached hydrogen atoms:

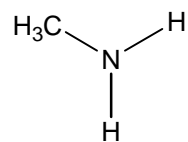


The rules differ for certain functional compounds e.g. alcohols:

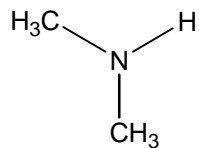


Substitution level and functional groups

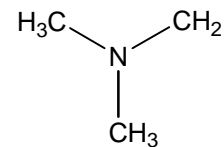
In the case of AMINES, the rules are different:



Primary amine
(2Hs on N)

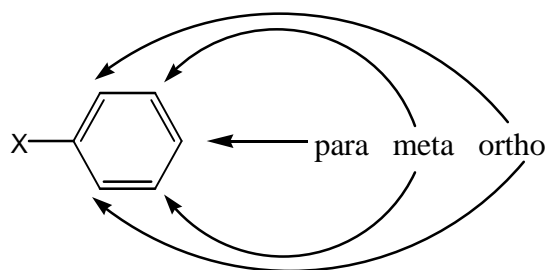


Secondary amine
(1H on N)



Tertiary amine
(0Hs on N)

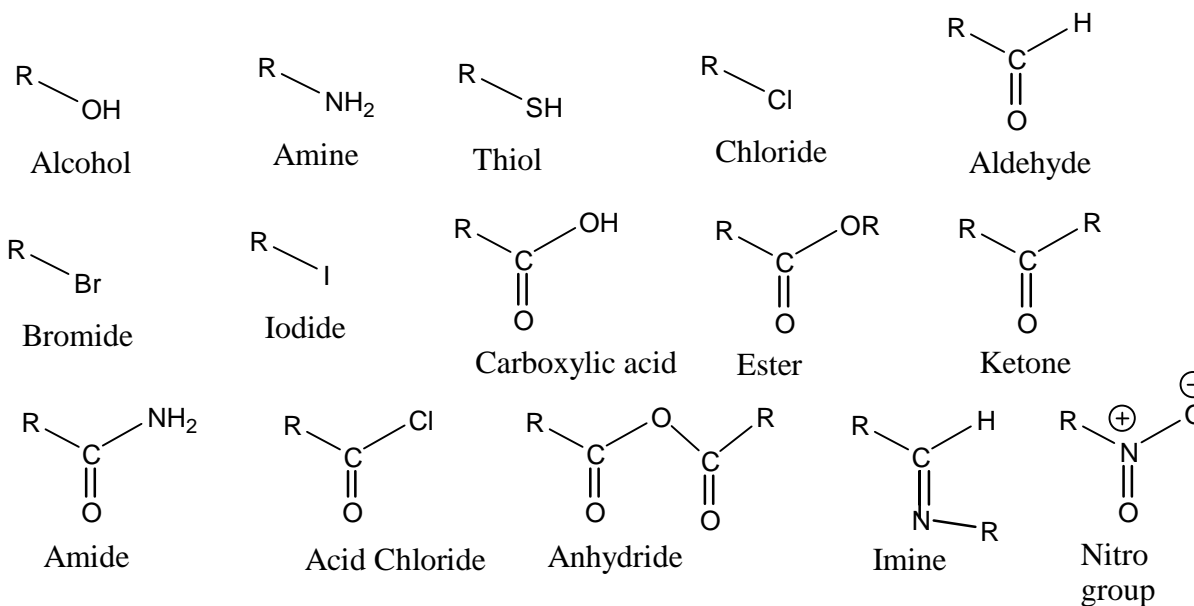
Aromatic compounds: substitution position relative to group 'X'



Substitution level and functional groups

Functional groups will be dealt with as they arise, however the following should be committed to memory:

R= alkyl group, joining at C atom, e.g. CH₃, c-C₆H₁₁, CH₂CH₂CH₃ etc.

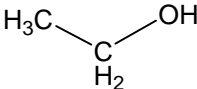
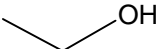
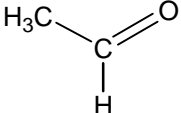
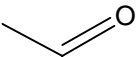
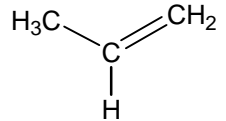
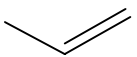
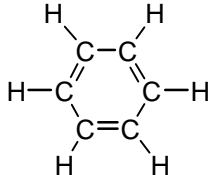



A cyclic ester is called a lactone, a cyclic amide a lactam

Line drawing

Line drawing represents an abbreviated 'shorthand representation of organic structures:

The rules are simple- Structures are written as a series of interconnected lines where each apex is the position of a carbon atom. Heteroatoms (i.e. not H or C) are shown. H atoms are not shown with the exception of those on heteroatoms.

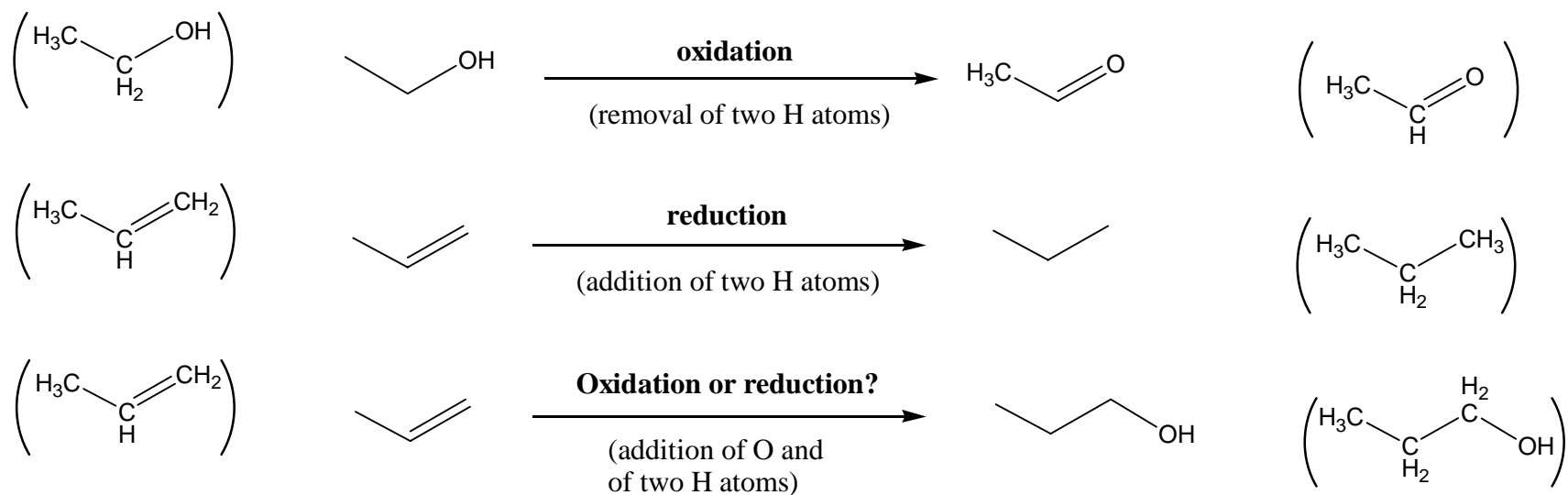
Examples	Full structure	Abbreviated 'line-drawing' structure
Ethanol		
Ethanal		
Propene		
Benzene		

N.b. in some cases the H atom of an aldehyde may be illustrated

Oxidation level

This is a useful tool for the understanding of organic reactions. It is slightly different to the system used for the oxidation level of cations and anions. It is useful to know whether a reduction or oxidation takes place, because this allows a correct selection of reagent to be made.

In some cases it is obvious that a reaction is an oxidation or reduction, in other cases they are not, for example:



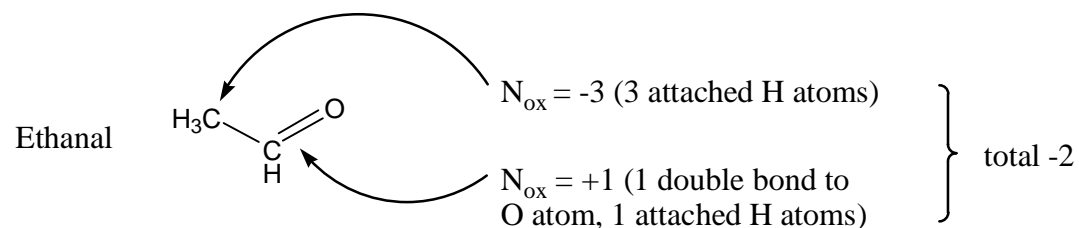
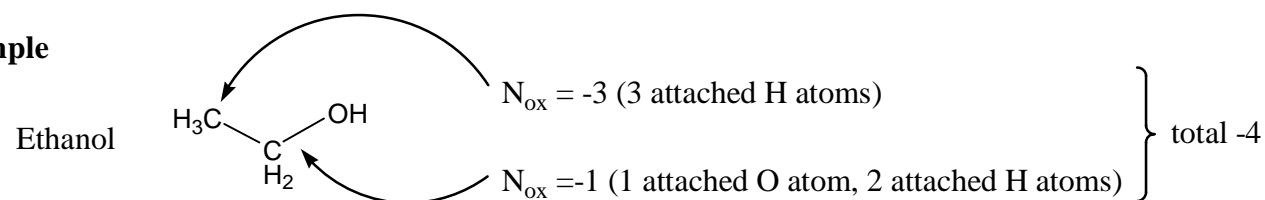
Oxidation level

To assign oxidation number (N_{ox}), there are a number of methods you can use however this one is easy - identify each carbon atom that changes and assign oxidation numbers as follows:

- For each attached H assign '-1'.
- For each attached heteroatom (O, N, S, Br, Cl, F, I etc.) assign '+1'.
- Double or triple bonds to heteroatoms count double or triple respectively.

Then sum them for each molecule.

Example



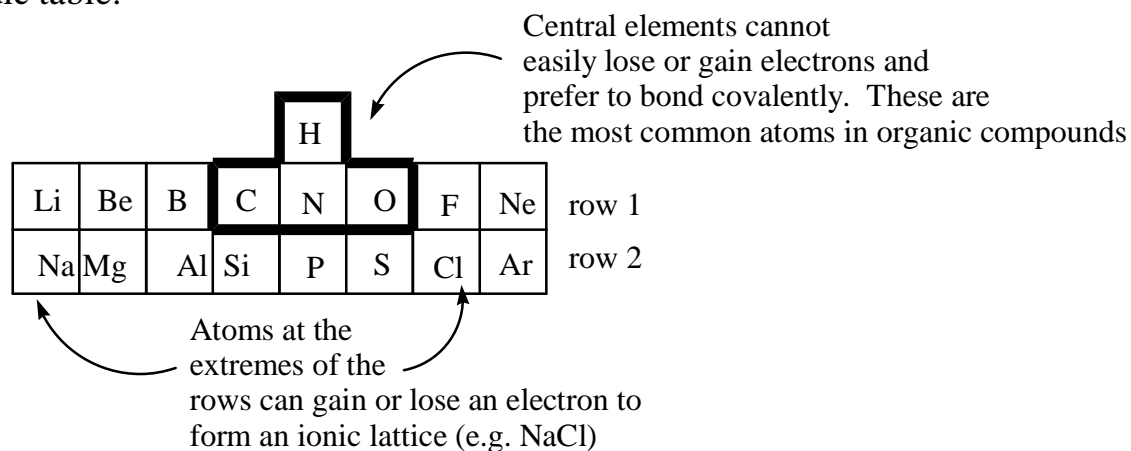
A change of '+2' indicates an oxidation. A change of '-2' indicates a reduction.
note + 2 or -2 is the typical change in oxidation level.

Molecular Stability - covalent vs ionic bonding

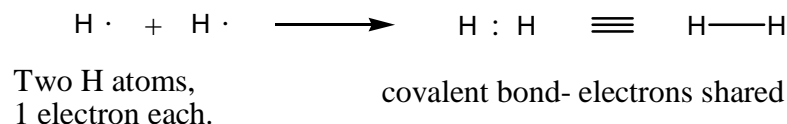
Many factors dictate the stability of atoms and ions. Hydrogen atoms gain stability if there are two electrons in their electron shell. For first and second row elements, significant stability is derived from an outer electronic configuration with 8 electrons.

Atoms can achieve this by i) gaining or losing electrons or ii) sharing them.

In the periodic table:



The simplest example is where two hydrogen atoms combine to form H₂, with a covalent bond between the atoms:



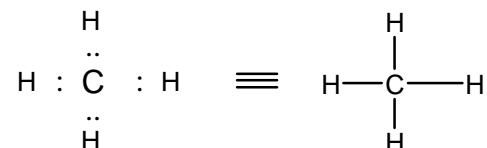
Molecular Stability - covalent vs ionic bonding

Examples

(nb the three dimensional shapes of the molecules will be discussed in a later section)

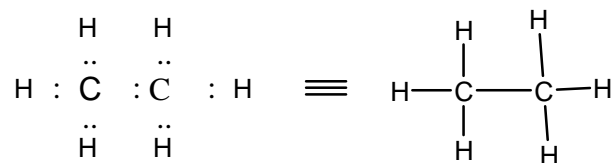
Methane, CH₄

Combine 4 H atoms (1 outer electron each) and 1 C atom (4 outer electrons) to form methane:



Ethane C₂H₆

Combine 6 H atoms (1 outer electron each) and 2 C atom (4 outer electrons) to form ethane



Ethene C₂H₄

Combine 4 H atoms (1 outer electron each) and 2 C atom (4 outer electrons) to form ethen with double bond:

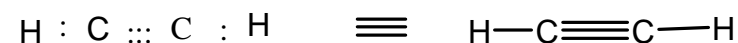


Molecular Stability - covalent vs ionic bonding

Examples of covalent compounds – I realise that this is very basic however some people still struggle with it. It is not meant to be patronising so please move on rapidly if you are OK with this:

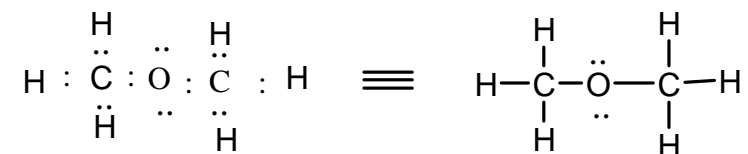
Ethyne C₂H₂

Combine 2 H atoms (1 outer electron each) and 2 C atom (4 outer electrons) to form ethyne with triple bond:



Methoxymethane (dimethylether)

Combine two C atoms (4 electrons), one O atom (6 electrons) and six H atoms (1 electron). Two pairs of electrons (lone pairs) reside on the oxygen atom and the molecule has a 'bent' structure.



Methanal (formaldehyde)

Combine one C atom, one O atom and two H atoms with a C=O double bond. There are two lone pairs on O.



Molecular Stability - covalent vs ionic bonding

Examples of covalent compounds:

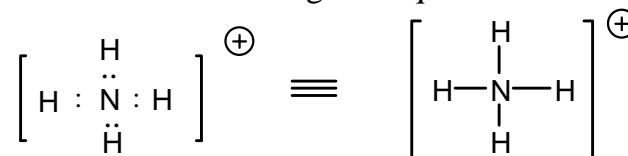
Ammonia NH₃

Combine 3 H atoms (1 outer electron each) and 1 N atom (5 outer electrons) to form ammonia with lone pair on N
The molecule has a *tetrahedral shape*.



Ammonium cation [NH₄]⁺ - an example of when an overall charge is required for stability

Combine 4H atoms (1 outer electron each) and 1 N atom (5 outer electrons), then lose 1 electron to form ammonium cation with an overall positive charge.



Same argument applies to protonated water - see if you can draw it.

More complex example:

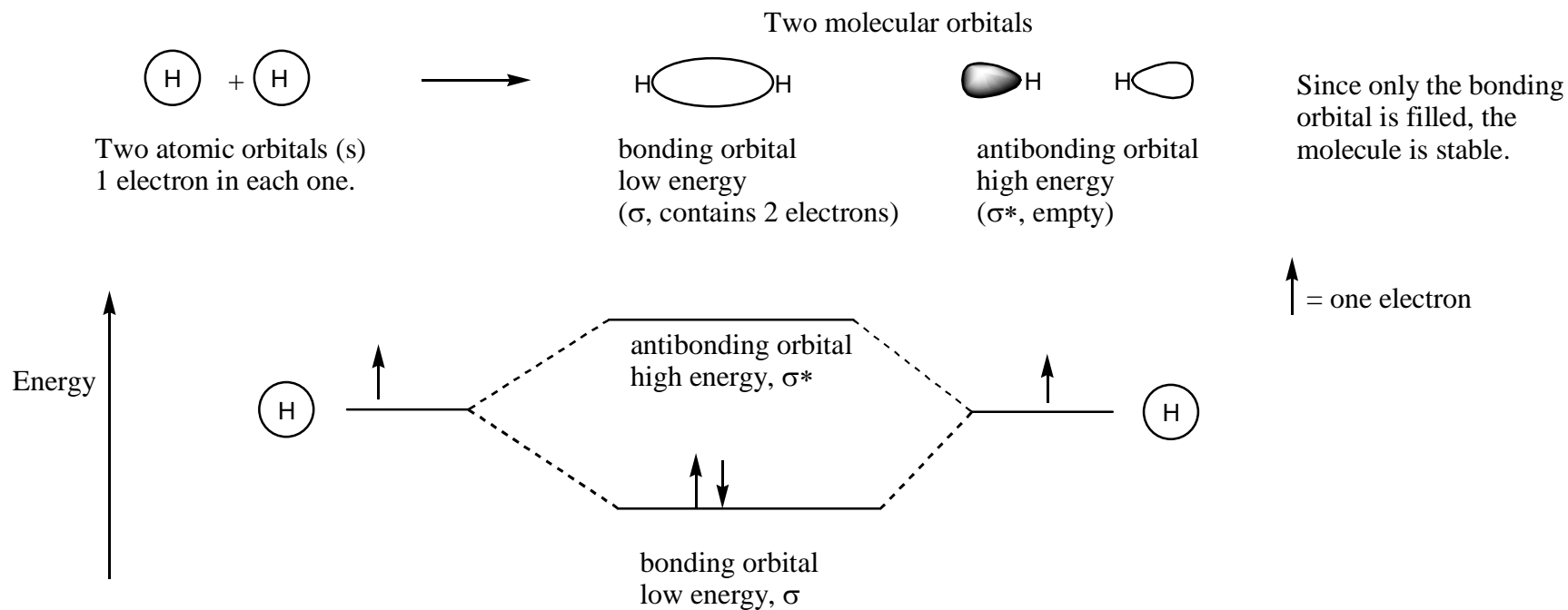
Combine one boron (3 electrons), one N and 6 H atoms to form a complex of borane (BH₃) and ammonia (NH₃).



Molecules in 3D.

Linear combination of atomic orbital (LCAO) model.

This is how the energy of the orbitals would be depicted:

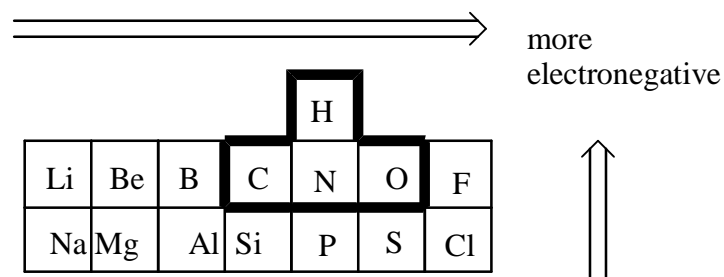


The electrons 'drop' into a lower energy position, which provides a driving force for the reaction, and stability.

Always bear this in mind when thinking about molecular orbital structure.

Bond Polarity

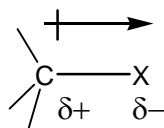
Covalency suggests equal sharing, but this is rarely the case because atoms differ in their inherent ability to stabilise negative charge, I.e. their 'electronegativity. Electronegativity increases in the direction of the arrows shown below (for the first two rows of the periodic table):



Pauling scale of electronegativity allows a quantitative comparison:
e.g. H (2.1), C (2.5), N (3.0), O (3.5), F (4.0), Cl (3.0), Br (2.8), I (2.5) etc.

As a result, most heteroatoms (X) are more electronegative than carbon and C-X bonds are polarised so that there is a partial positive charge on the carbon atom.

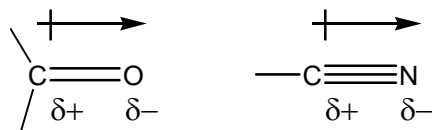
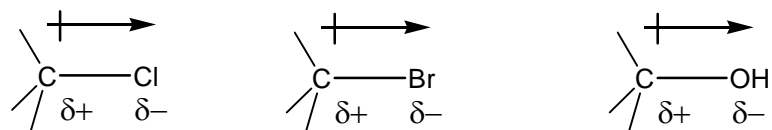
The polarity
is illustrated thus:



See next page for examples

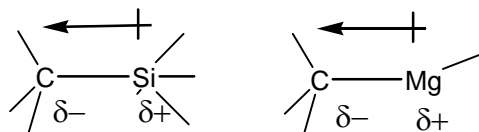
Bond Polarity – although basic, it is very important because it allows us to predict where reactions will take place.

Examples of covalent bonds which contain a dipole:



Note: in the case of double and triple bonds, resonance (delocalisation) effects also contribute to the polarity.

A few elements (notably metals) are less electronegative than C. As a result the dipole is reversed:



This polarity effect is sometimes referred to as the **INDUCTIVE** effect, and operates through sigma bonds in molecules (see a later section).

Formal Charge – this is surprisingly important so make sure you understand,

Formal charge is a method for assigning charge to individual atoms in molecules. Although it does not always give a 'perfect' picture of true charge distribution, it is very helpful when reaction mechanisms are being illustrated.

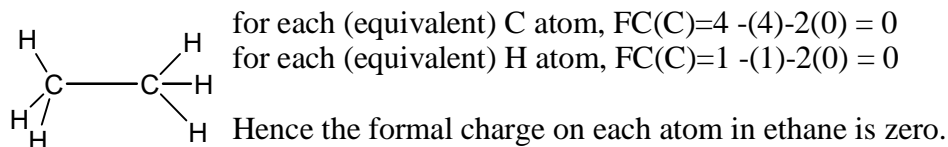
The definition of formal charge on a given (row 1 or 2) atom is as follows:

Formal charge on atom X (FC (X)) = ('atomic group number' of the atom* – ignore transition metals when counting!)-(number of bonds to the atom)- 2(number of lone pairs on the atom).

(You may see a slightly different version of the equation in other places).

Example:

Ethane -



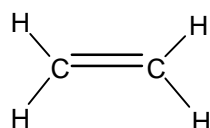
N.b - use a atomic group number of '1' for hydrogen.

* i.e. count from 1 to 8 across the row.

Formal Charge

Further examples:

Ethene -

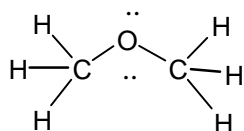


for each (equivalent) C atom, $FC(C) = 4 - (4) - 2(0) = 0$

for each (equivalent) H atom, $FC(H) = 1 - (1) - 2(0) = 0$

Hence the formal charge on each atom in ethene is zero.

Methoxymethane (remember this molecule has two lone pairs on O).



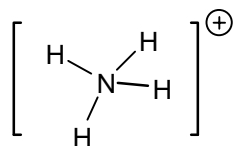
for each (equivalent) C atom, $FC(C) = 4 - (4) - 2(0) = 0$

for each (equivalent) H atom, $FC(H) = 1 - (1) - 2(0) = 0$

for the O atom, $FC(O) = 6 - (2) - 2(2) = 0$

Hence the formal charge on each atom is zero.

Ammonium cation (overall charge of +1)



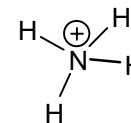
for each (equivalent) H atom,

$FC(H) = 1 - (1) - 2(0) = 0$

for the N atom,

$FC(N) = 5 - (4) - 2(0) = +1$

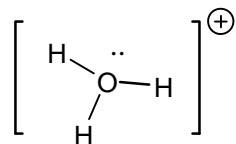
Hence the formal charge on the atoms in the molecule is:.



Formal Charge

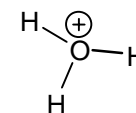
Further examples:

Protonated water (overall charge of +1 and a lone pair on O)

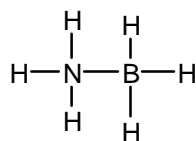


for each (equivalent) H atom,
 $FC(H) = 1 - (1) - 2(0) = 0$
for the O atom,
 $FC(O) = 6 - (3) - 2(1) = +1$

Hence the formal charge on the atoms in the molecule is:.

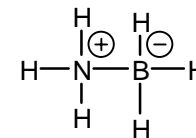


Borane-ammonia complex

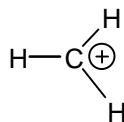


for each (equivalent) H atom,
 $FC(H) = 1 - (1) - 2(0) = 0$
for the N atom,
 $FC(N) = 5 - (4) - 2(0) = +1$
for the B atom $FC(B) = 3 - (4) - 2(0) = -1$

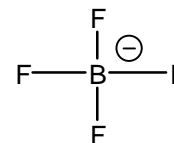
Hence the formal charge on the atoms in the molecule is:.



Methyl cation (only 6 electrons around C):



Tetrafluoroborate anion:



Use the formal charge definition to check the last two examples (n. b. there are three lone pairs on *each* fluorine atom in BF_4^-).

Acidity of organic compounds

Acidity is a measure of the ability of a compound to ionise to a proton and a negatively charged counterion. Group. Organic compounds are not very acidic compared to strong mineral acids, however some are stronger acids than others. **This is a VERY important area to understand for organic chemistry.**

Let's put this into context.

The relative acidity in aqueous solution of a compound is defined by its pK_a .

This is a measure of the inherent ability of any compound to lose a proton in an equilibrium process:



Think about this for a second...

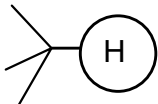
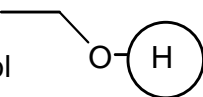
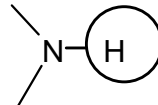
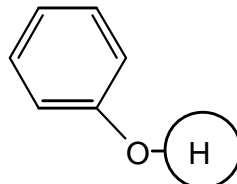
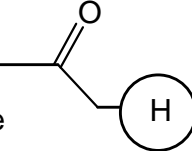
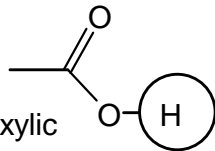
If HXR is a strong acid, the equilibrium will be over to the right hand side. K_a will be high and pK_a will be a low number (possibly even negative). Carboxylic acids, some of the strongest organic acids, have a pK_a of around 5. If HXR is a weak acid the equilibrium will be over to the left hand side, K_a will be low and the pK_a will be quite high. Alkanes ($\text{C}_n\text{H}_{2n+2}$) are *very* reluctant to lose a proton and are weak acids. The pK_a of an alkane is around 40. Most organic compounds have pK_a s between these extremes.

Acidity of organic compounds –it is difficult to overstate how critically important this is!

Nb - a related scale, pH , is a measure of the amount of protons in a solution at any moment.
 pH is defined as $-\log [H^+]$.

Here are a few more examples of pK_a values of organic compounds.
Remember that each unit of pK_a represents a tenfold change in acidity.

Some examples (no. relates to circled proton) are given below:

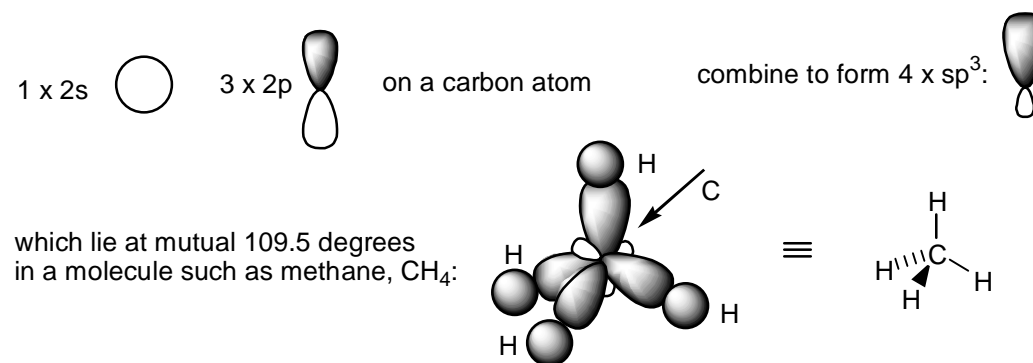
compound	pK_a	compound	pK_a
alkane 	40	alcohol 	16
amine 	30	phenol 	10
ketone 	20	carboxylic acid 	5

Molecules in 3D.

Rehybridisation and VSEPR:

The three-dimensional structure of organic compounds often influences their properties and reactivity. Each carbon atom in an organic molecule can be linked to four, three or two other groups. In each case the orbital structure and three-dimension shape around that carbon atom is different

In the case of a carbon atom attached to four other groups by single bonds, the single 2s and the three 2p orbitals gain stability by mixing (**rehybridisation**) to form four sp^3 orbitals. These are all arranged at mutual 109.5 degree angles to each other and define a *tetrahedral* shape:

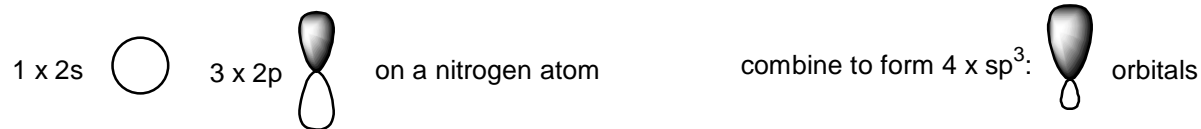


A tetrahedral shape is favoured because this maximises the distance between the filled orbitals, which contain negatively charged electrons, and therefore repel each other. This is known as the '**valence shell electron pair repulsion**' (or VSEPR), and often dominates the shape of molecules.

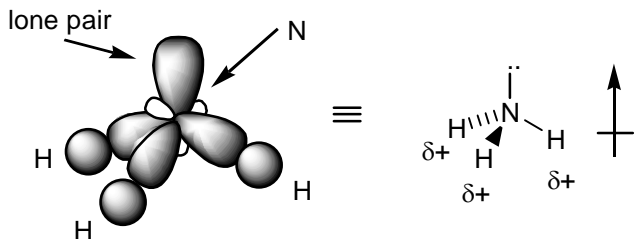
Molecules in 3D.

The VSEPR model for the structure of molecules also explains why molecules such as ammonia and water are not flat or linear respectively. Their structures are 'bent' because of repulsion effect of the electrons in the lone pairs (which are in sp^3 orbitals).

At the nitrogen atom in ammonia, NH_3 :

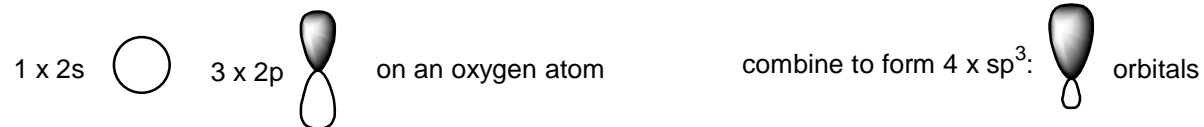


which lie at mutual 109.5 degrees in the ammonia molecule, NH_3 :

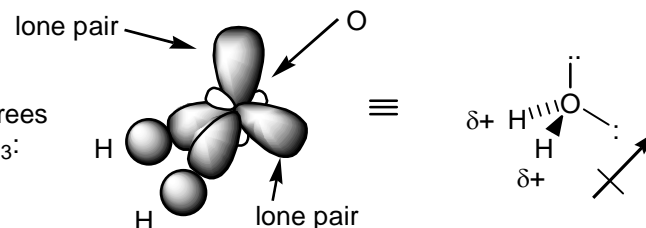


As a result, ammonia is tetrahedral and has a significant dipole.

At the oxygen atom in water, H_2O :



which lie at mutual 109.5 degrees in the ammonia molecule, NH_3 :



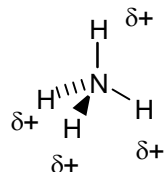
As a result, water is tetrahedral and has a significant dipole.

Molecules in 3D.

Some things to be aware of:

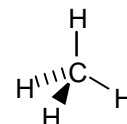
- i) Symmetrical, tetrahedral, compounds have no overall dipole:

For example in the ammonium cation, NH_4^+



The shape is still tetrahedral, and each N-H bond has a dipole, but there is **no overall dipole**, because they cancel out.

For the same reason, methane has no overall dipole either:



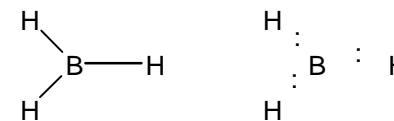
- ii) Molecules which are electron deficient, such as borane (BH_3), retain a trigonal shape. Why? – Well, without an electron pair, there is nothing to repel with!!!

Borane, BH_3 :

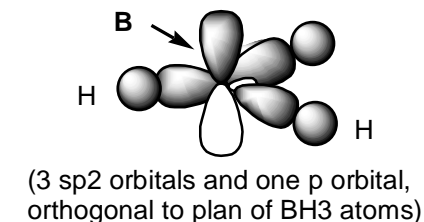
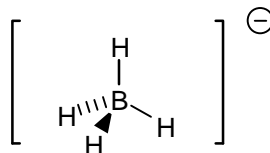


Flat (trigonal), 120° bond angles
no overall dipole

(one B atom with three electrons and three H atoms with one electron each form borane, which has only 6 electrons at the B atom:

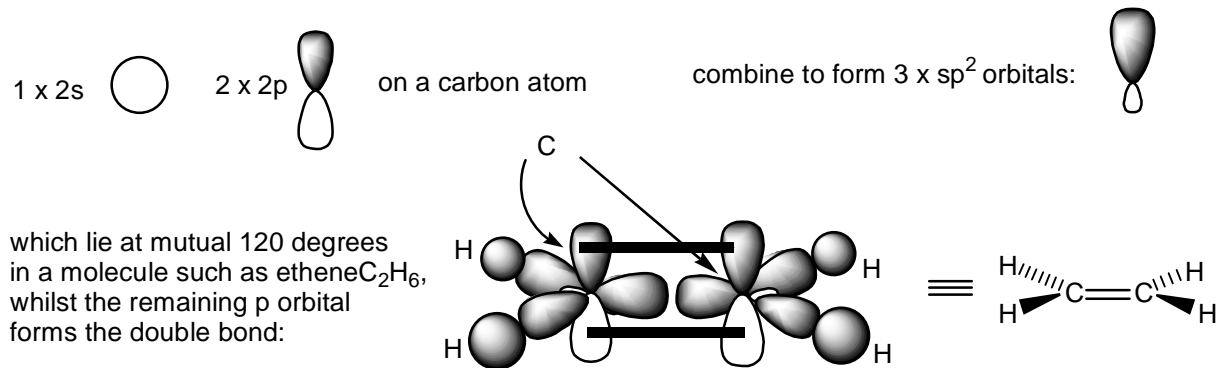


In contrast, borohydride anion, BH_4^- , is tetrahedral, with no overall dipole:



Alkenes

In the case of a carbon atom attached to three other groups (by two single bonds and one double bond) the single 2s and two 2p orbitals mix (rehybridise) to form three sp^2 orbitals. These are all arranged at mutual 120 degree angles to each other and define a *trigonal* shape, the remaining p orbital projects out of the plane of the three sp^2 orbitals and overlaps with an identical orbital on an adjacent atom to form the double bond:

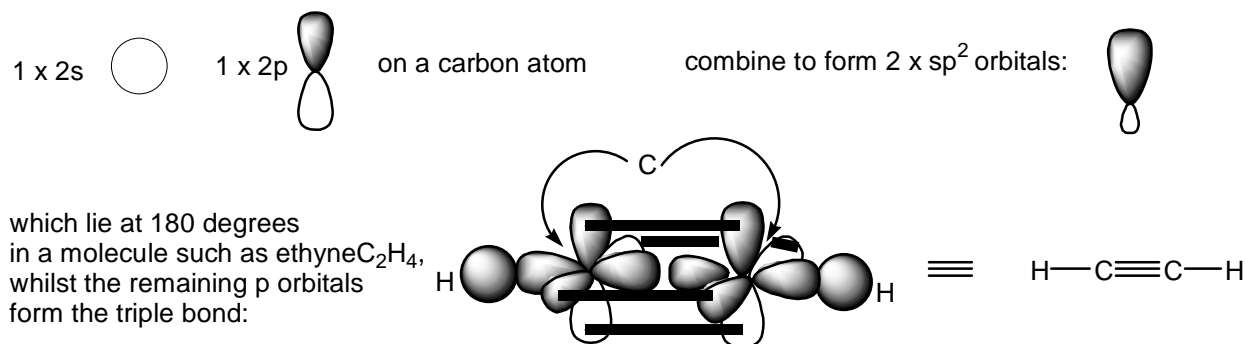


The resulting structure is rigid and cannot rotate about the $C=C$ bond without breakage of the bond between the p-orbitals (the π bond). The can be separated into E and Z configuration isomers.

The π bond is much more reactive than the σ bond – the bonds are not equivalent to each other.

Alkynes:

In the case of a carbon atom attached to two other groups (by one single bonds and one triple bond) the single 2s and one 2p orbitals mix (rehybridise) to form two sp orbitals. These are all arranged at mutual 180 degree angles to each other and define a *linear* shape, the remaining p orbitals projecting out from the sp orbital to overlap with identical orbitals on an adjacent atom to form the triple bond:



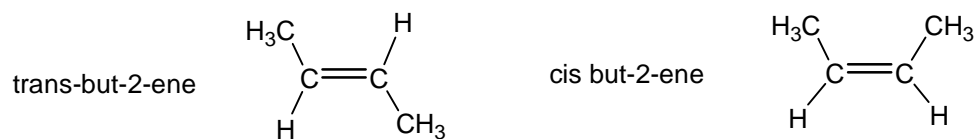
Rehybridisation of orbitals of this type is not limited to carbon, of course. Many other row 1 and 2 atoms (notably N) can rehybridise within organic molecules.

Both π bonds in an alkyne are much more reactive than the σ bond.

Molecules in 3D Conformation and configuration

Configuration is a fixed stereochemical property of compounds. Unlike conformation, a change in *configuration* requires bonds to be broken and formed. Any molecule has a limited number of configurations in which it can exist.

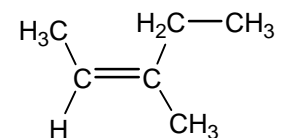
Alkenes can exist in two configurations, for example but-2-ene may have the terminal methyl groups in a *trans* (across from each other) or *cis* (on the same side) position:



Changing *trans* butadiene into *cis*- butadiene (or vice versa) requires the breaking, and subsequent reforming, of the π bond. This is a high- energy process and does not take place at room temperature. At room temperature, but-2-ene (and other alkenes) can be physically separated into the two pure isomers.

Molecules in 3D - Conformation and configuration: E and Z

The *configuration* of an alkene can be obvious in some cases (such as but-2-ene) however in others it is not, for example is the molecule below a cis or trans alkene?



In order to provide an *unambiguous* means for assigning configuration to alkenes (and also to chiral centres as you will see later), organic chemists have adopted the ‘**Cahn-Ingold-Prelog**’ (CIP) rules for configurational assignment.

These are simple to use - first one assigns a ‘priority’ to each group attached to each carbon atom at each end of the alkene. I will describe the priority rules in the next slide. We then define the alkene as either Z (from the German *zusammen*, together) or E (from the German *entgegen*, across):

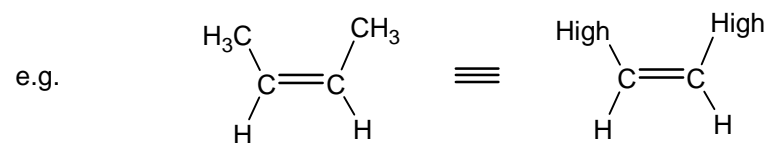


(relative priorities are of a group on a C atom to its partner on the same atom)

Molecules in 3D Conformation and configuration

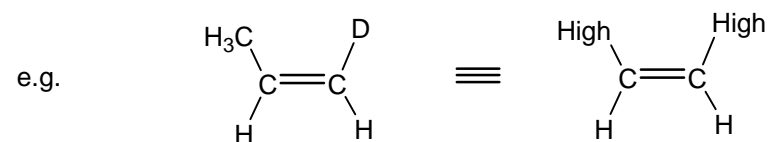
The CIP priority rules are defined as follows, in their own order of priority:

a) Atoms of higher atomic number have priority:



In this molecule the *attached* carbon atoms at each end of the double bond have priority over the attached H atoms, hence this is a Z alkene

b) When the attached atoms are identical on each side, isotopes of higher mass have priority



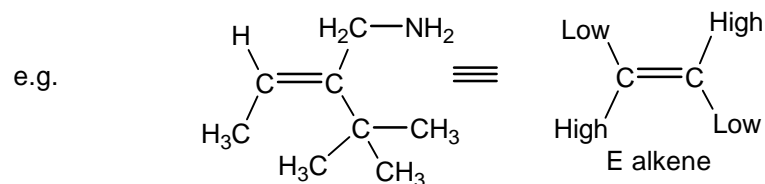
In this molecule the *attached* carbon and deuterium (deuterium is the H-2 isotope) atoms at each end of the double bond have priority over the attached H atoms, hence this is a Z alkene

Molecules in 3D - Conformation and configuration

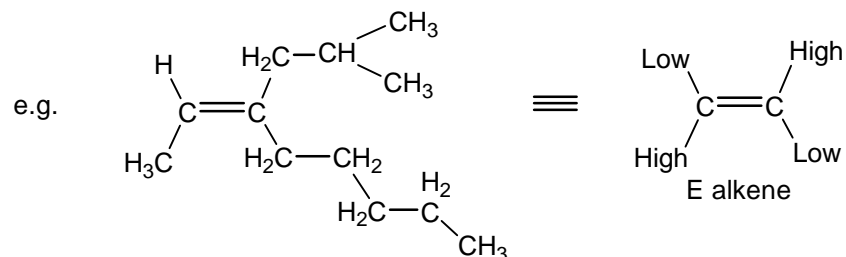
The CIP priority rules are defined as follows, in their own order of priority:

a) When the atoms and isotopes attached on each side are identical, move out until a point of difference is encountered and apply the following rules:

a) Priority goes to the group with the element of highest atomic number at the point of difference.



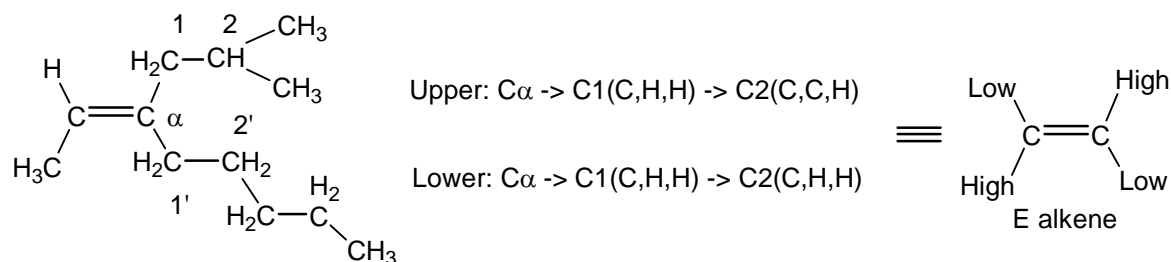
b) Priority goes to the group with the highest sum of atomic numbers if the atoms are of the same types at the point of difference. In the example below, the point of difference on the right hand side is two carbons away from the alkene carbon atom



Molecules in 3D - Conformation and configuration

This is how I worked out the last example (right hand side only):

Imagine you are moving out from the C_α to the adjacent atoms. Going both up (to C1) and down (to C1') leads to a CH_2 group, i.e. no difference. Moving to the next atom reveals that C2 (top branch) is attached to C,C,H but that C2' (lower branch) is attached to C,H,H. The upper branch has the highest sum of attached atomic numbers and therefore has priority.

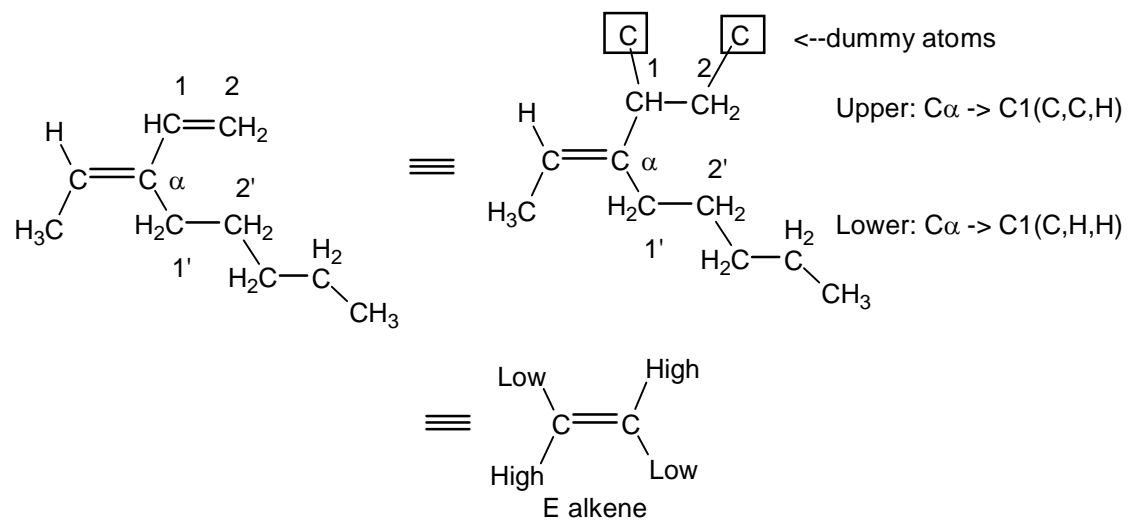


There is one more rule:

d) In the case of double and triple bonds, 'dummy' atoms should be added and counted in the determination of priority. See next slide.

Molecules in 3D - Conformation and configuration

Here is an example of the determination of configuration for an alkene attached to a double bond:

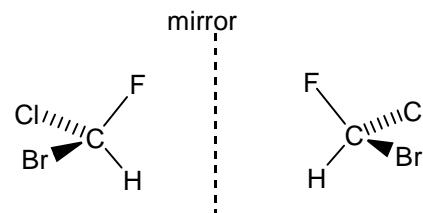


Molecules in 3D - Conformation and configuration

CIP priority rules are also applied to the determination of configuration at chiral centres (a chiral molecule is one which is not superimposable on its mirror image, rather like your hands). The simplest form of a chiral centre is one with a carbon atom attached to four different groups.

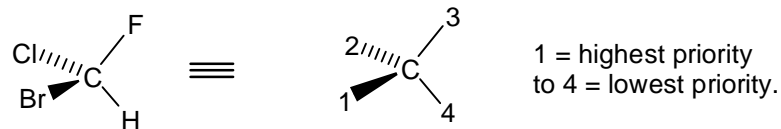
E.g.

CBrClFH is a chiral molecule the two forms (known as enantiomers) can be illustrated thus:



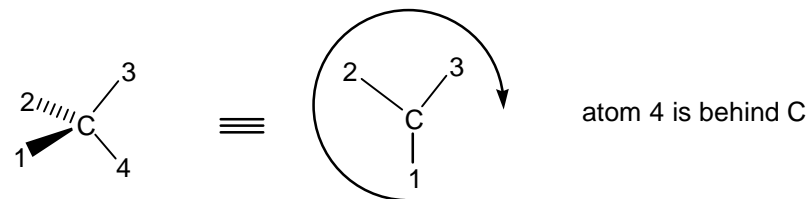
To assign a configuration to a chiral molecule such as the one shown above we first assign CIP priorities to all four groups using the same rules:

e.g.

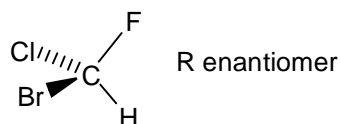


Molecules in 3D - Conformation and configuration

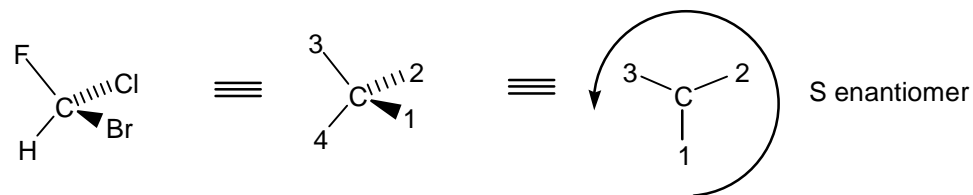
We then view the molecule, with the assigned priorities, along the C-4 bond (with the 4 behind the central carbon atom). Finally, draw an arrow from atom with priority 1 to priority 2 to priority 3 in turn:



In this case the arrow is clockwise; this is therefore referred to as a **R** isomer (R comes from the Latin *rectus*, for 'right'). Isomers of this type are sometimes called 'enantiomers'.

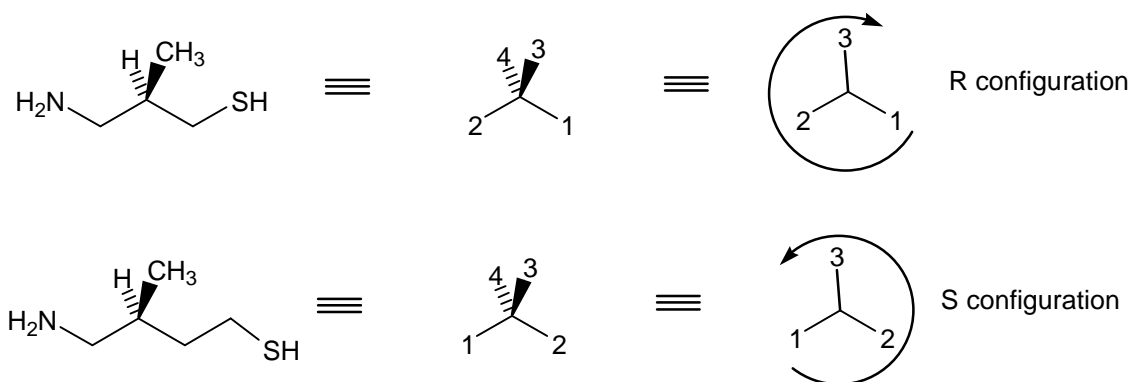


The mirror image of the molecule above is the **S** enantiomer (from the Latin *sinister* for 'left')



Molecules in 3D - Conformation and configuration

Here are a couple of examples - can you see the derivation of the configuration?



One carbon atom makes all the difference!

Molecules in 3D - Conformation and configuration: don't get confused between L/D, l/d and R/S!

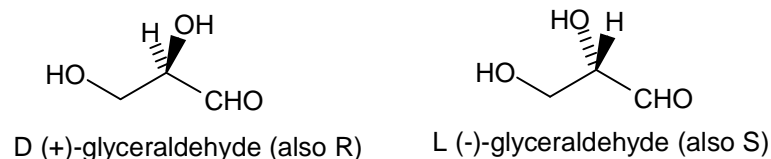
This is very important – please read it.

Some other conventions are used to defined the configuration at chiral centres e.g.

l - molecule with a negative optical rotation (from the Greek for levorotatory; left)

d - molecule with a positive optical rotation (from the Greek for dextrarotatory; right)

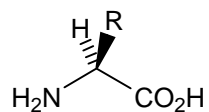
The D/L notation (a very old convention) is derived from the signs of optical rotation of R and S glyceraldehyde respectively:



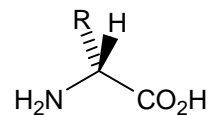
The trivial convention for the absolute configurations of sugars derives from the D/L notation above. D-glucose is the natural enantiomer (costs £20/kg) whilst L-glucose is very rare (£31/g!).

Molecules in 3D - Conformation and configuration

Amino acids are classified into L- (natural) and D- (unnatural)



L - amino acid



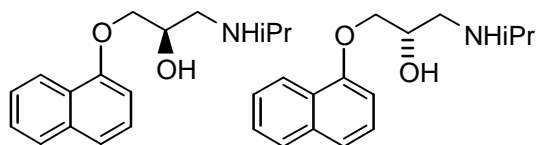
D- amino acid

Most L-amino acids are of S- configuration.

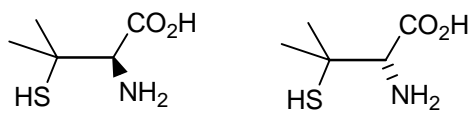
Despite all the different notations, R and S is the one YOU should learn how to use.

Molecules in 3D - Conformation and configuration

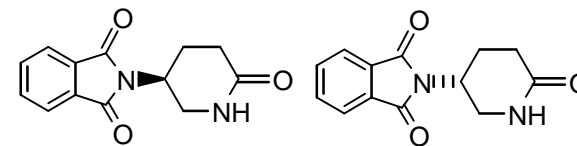
The two mirror-images of chiral compounds can have dramatically different physical properties. That is because we ourselves are made up of molecules of one 'handedness'. Try assigning R/S to these:



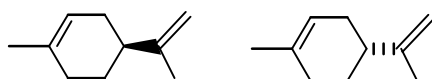
Propranolol:
R is a heart drug
S is a contraceptive



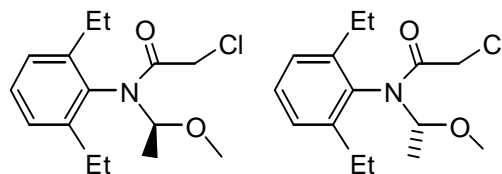
Penicillamine
R is an antiarthritic
S is a highly toxic



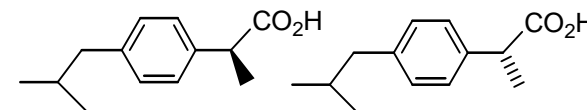
Thalidomide
R is mutagenic
S is anti-emetic



Limonene:
R has a lemon odour
S has an orange odour

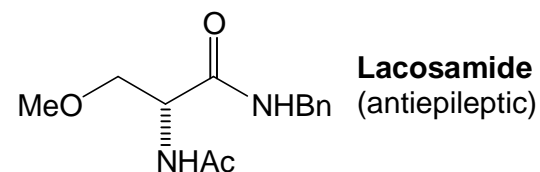
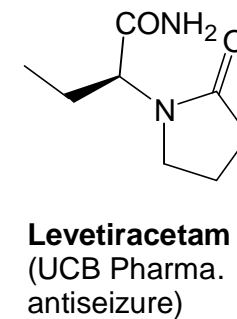
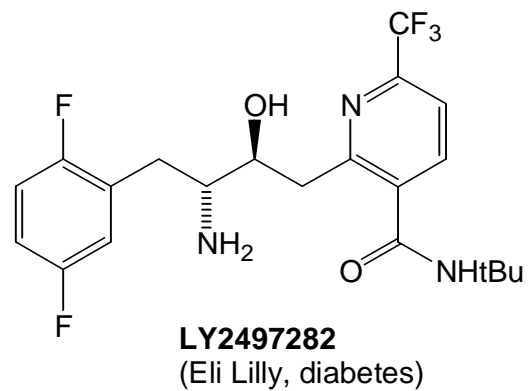
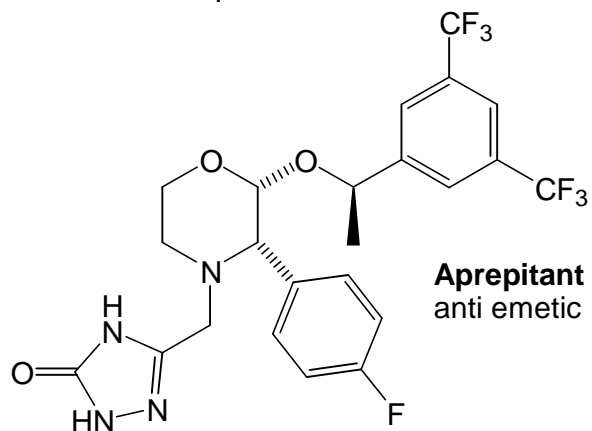
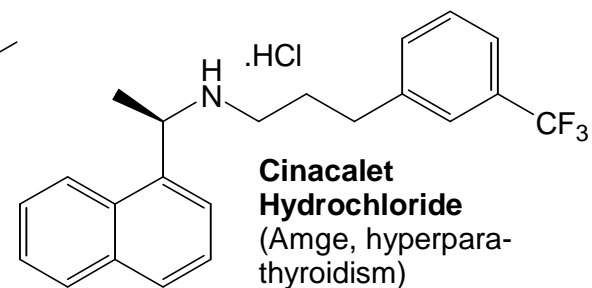
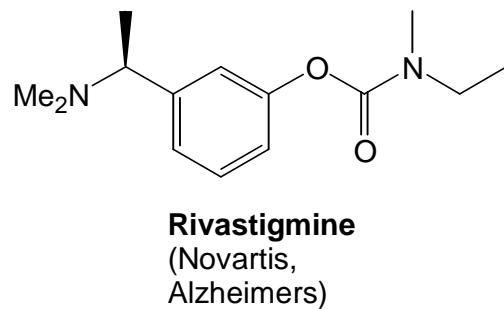
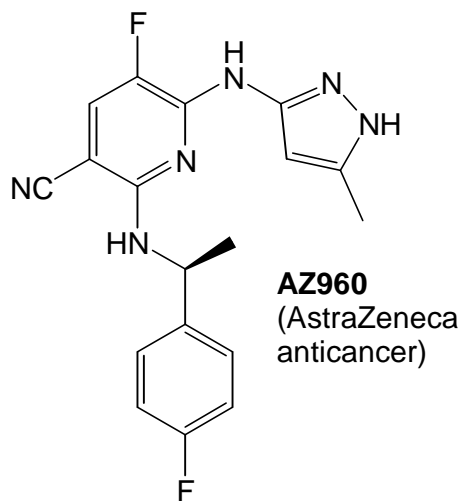


'Dual'
R is an herbicide
S is a pesticide



Ibuprofen
R is anti-inflammatory
S is inactive

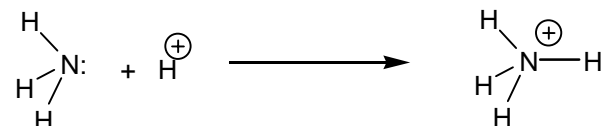
Examples of drugs containing a chiral centre:



Mechanism and 'arrow pushing'. - you must understand this!

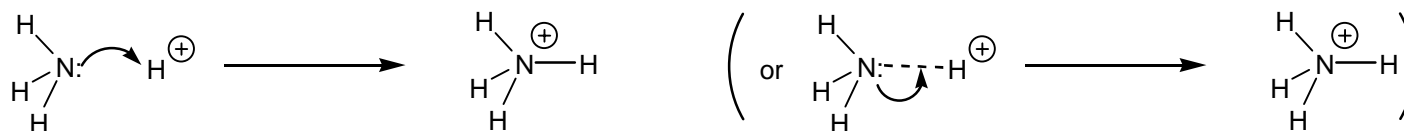
This is a very important section which deals with the mechanism by which one molecule is converted into another. It is a means of showing the way electrons (which make up bonds) move when one compound is transformed into another. 'Arrow pushing' is employed to illustrate mechanisms in organic chemistry.

e.g. consider protonation:



In this process, the lone pair of electrons on N has become a *bonding* pair in the product.

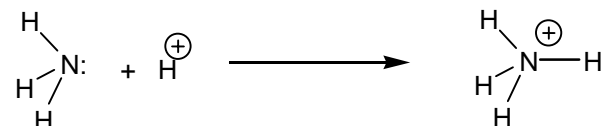
This is how we would show the reaction with a curved mechanistic arrow :



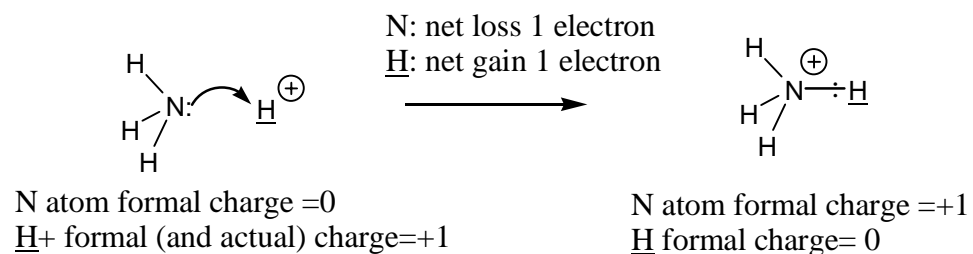
Mechanism and 'arrow pushing' – protonation and deprotonation.

The definition of formal charge means that 'arrow pushing' also shows the movement of *formal charge* during a reaction.

During protonation, the formal charge moves from the proton (H⁺) to the nitrogen atom

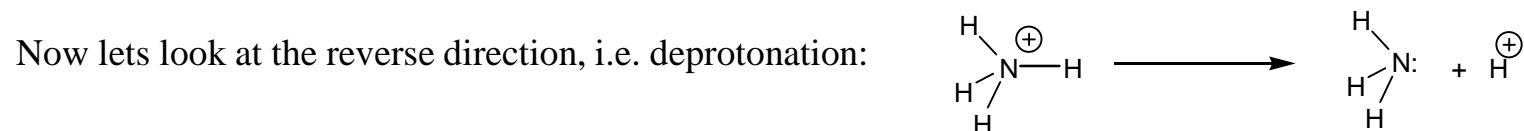


This makes sense because, in the protonation, the nitrogen has donated a full pair of electrons but in the product shares a bonding pair, a net loss of 1 electron. The proton (H⁺), on the other hand, had no electrons originally but now shares a bonding pair, a net gain of one electron (hence the drop in charge from +1 to 0). **We represent this movement of an electron pair as a 'curly arrow' – NOTE THE DIRECTION OF FLOW!**



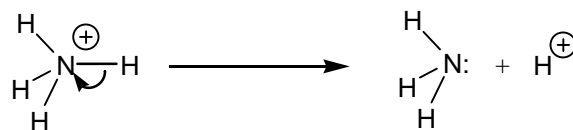
Note that the lone pair on nitrogen becomes the bonding pair in the N-H bond.

Mechanism and 'arrow pushing' – protonation and deprotonation.

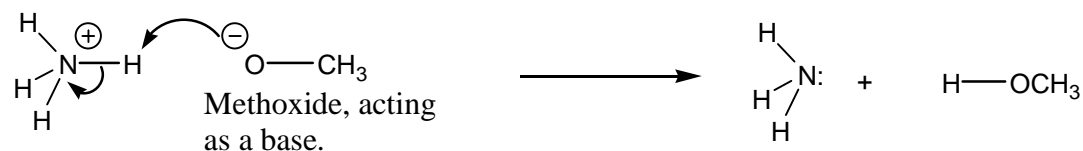


The *formal charge* has moved from N to H. This is because the H was sharing an electron pair on the left hand side, but has none on the right hand side, a net loss of 1 electron.

This is how we would show the reaction with a curved mechanistic arrow - note how it shows the bonding pair moving out of the bond and towards the N atom :



In reality, a proton is usually removed by a base. This is how it would be illustrated:



The *formal charge* also moves. N goes from +1 to 0 because it gains a net 1 electron.

The oxygen goes from -1 to 0 because overall it loses 1 electron.

Note also that the sum of charges in the product (0) should equal the sum of charges on the reagents.

Mechanisms and ‘arrow pushing’ – it does not have to be complicated.

Most organic reactions can be classified into one of four types:

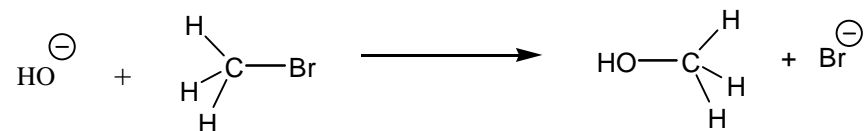
- 1) **Substitution** – replace one group with another, S_N2 , S_N1 etc.
- 2) **Elimination** – take something off, E2, E1 etc. Usually, *two* groups come off and an alkene is formed!
- 3) **Addition** – add something on! Usually you add two groups to an alkene.
- 4) **Rearrangement** – make it look difference.

If you *understand* the mechanisms of these processes then this will greatly assist your knowledge of organic chemistry.

The following slides will run through the key features of substitution, elimination and addition reactions.

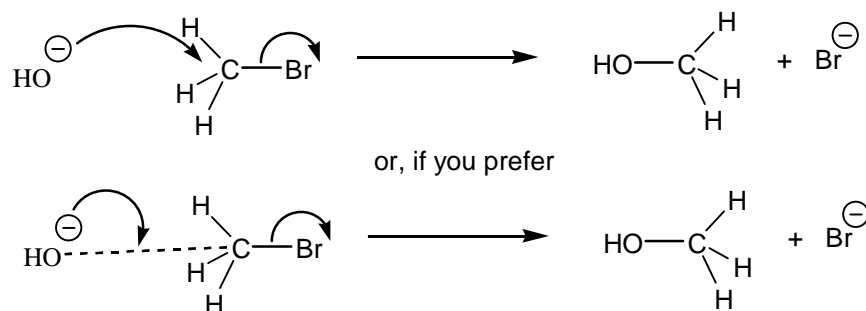
Mechanism and 'arrow pushing' – Substitution reactions.

Now let's consider the reaction of bromomethane (methylbromide) with a nucleophile such as hydroxide anion



This reaction works because the nucleophile (hydroxide) is attracted to the partial positive charge on the carbon atom. Bromide anion must be displaced because the C atom can only be surrounded by a maximum of 8 electrons.

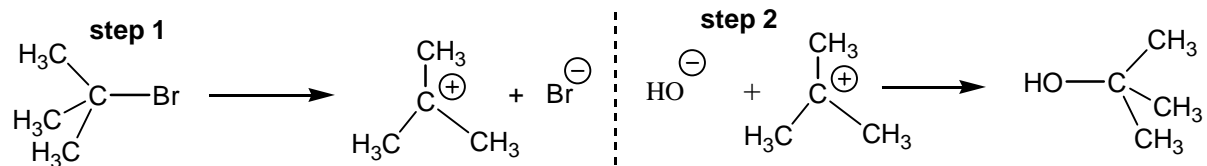
The mechanism is illustrated as shown below (this is called an S_N2 reaction):



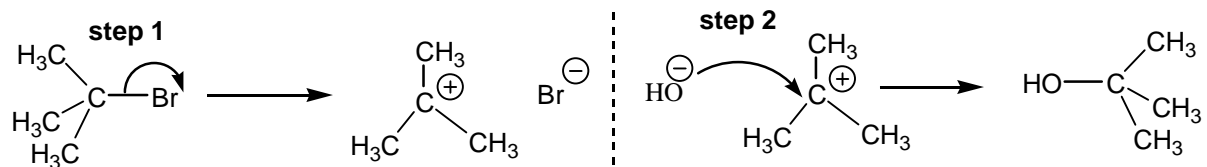
Note how the net negative charge moves from left to right in this mechanism (with the arrows)

Mechanism and 'arrow pushing'.

In some cases (when a hindered halide is used), the reaction proceeds in two steps:



The mechanism is illustrated as shown below (this is called an S_N1 reaction):



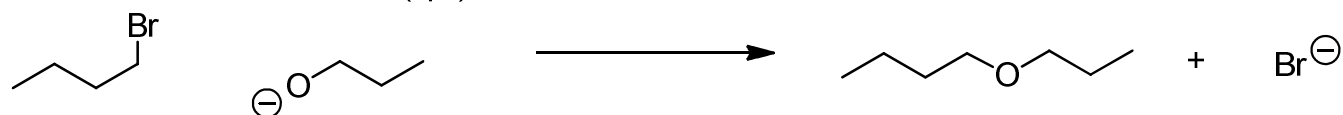
You will learn more about the mechanisms of substitution reactions next term, the important thing for now is to understand the mechanism.

Nucleophilic substitution reactions – overview:

Why these reactions are important and some examples:

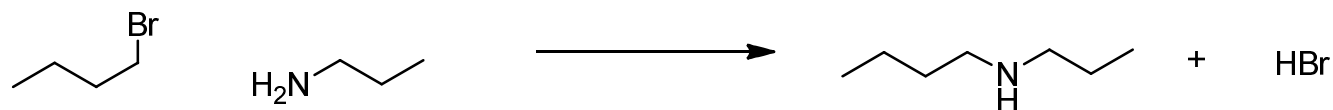
Substitution reaction: replacing one group with another one! Some examples:

Substitution at a saturated (sp^3) carbon atom

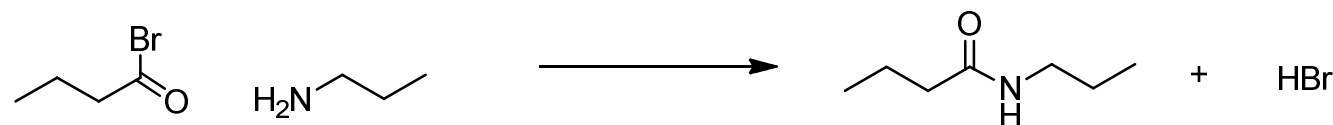


Yes there will be a counterion, but it does not participate in the mechanism as drawn

Substitution at a saturated (sp^3) carbon atom

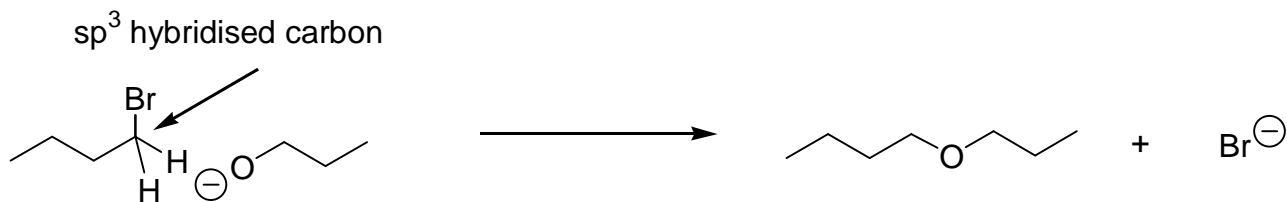


Substitution at an unsaturated (sp^2) carbon atom

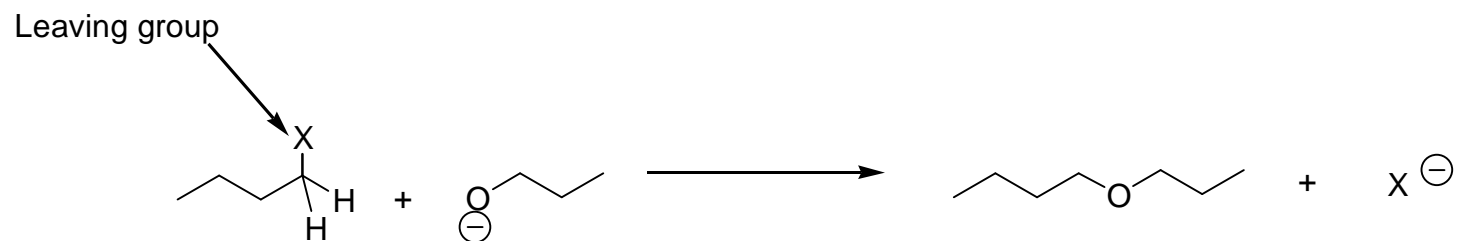


Substitution reactions – some definitions.

What is the significance of the ‘saturated carbon atom’.



Which leaving groups can be used – what ‘drives’ the reaction?



Key point: Good leaving groups are halides (Cl, Br, I), OSO₂R, and other groups which *stabilise a negative charge*.

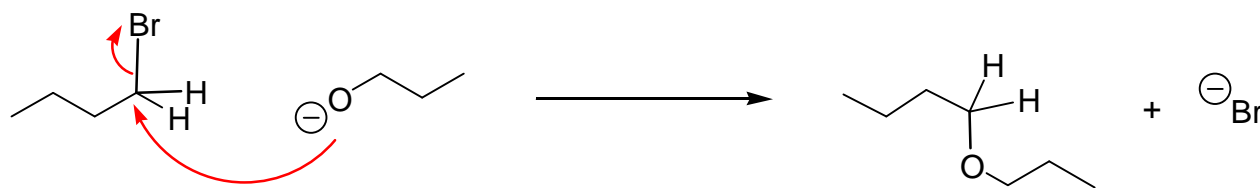
Mechanisms of substitutions reactions: S_N2

There are two major mechanisms of substitution reactions.

The first is called the S_N2 mechanism – Substitution, Nucleophilic, Bimolecular:

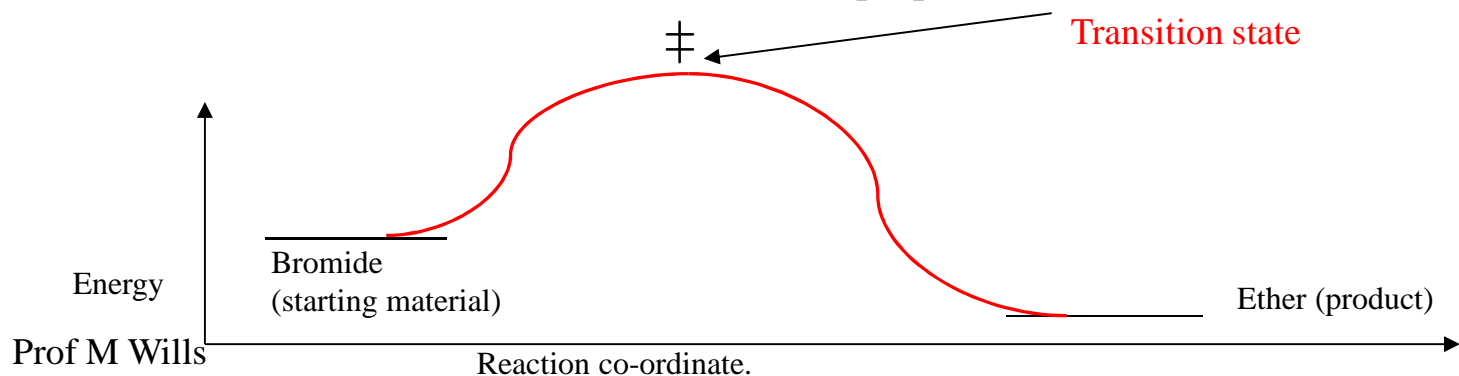
What do these three terms mean?

It is a single step mechanism; the nucleophile adds and the leaving group is simultaneously displaced in the same step. A *concerted* mechanism.



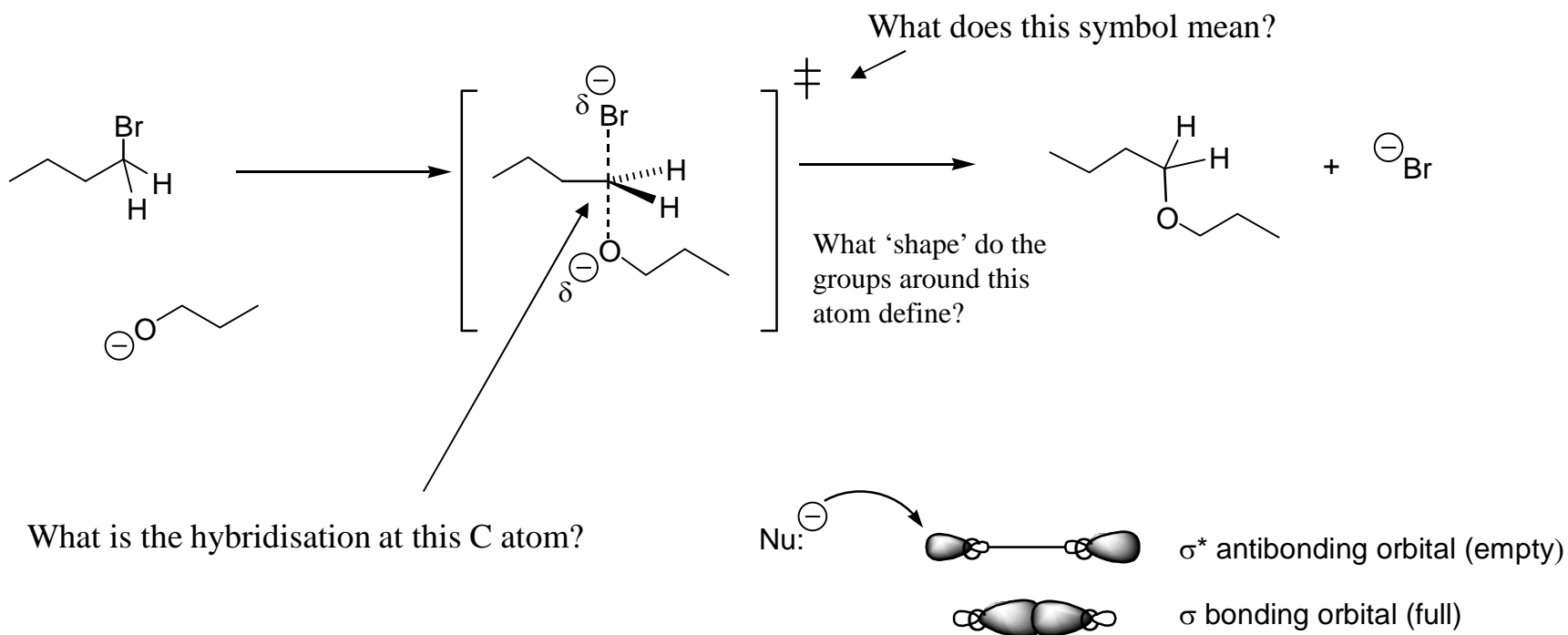
$$\text{Rate} = k [\text{nBuBr}][\text{nPrO}^-]$$

What happens if I double the concentration of bromide? What if I double the concentration of bromide and of propoxide?



The transition state for S_N2 reactions:

The S_N2 mechanism – structure of the transition state.



Note *partial bonds* to nucleophile and leaving group. Nucleophile adds electron density to σ^* antibonding orbital.

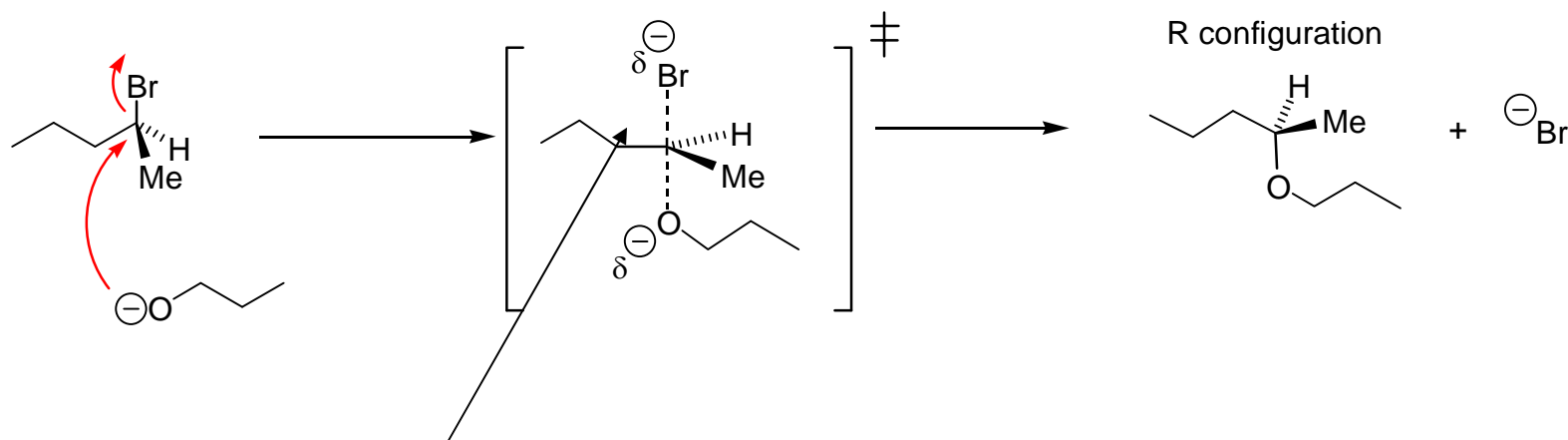
*** Key point of nomenclature; it's S_N2 not SN_2 *** This is important *** If

Prof M Wills someone tells you it is SN_2 then they need to be told that they are incorrect! 51

Stereochemical consequences of S_N2 reactions:

The S_N2 mechanism – What happens at chiral centres:

S configuration:

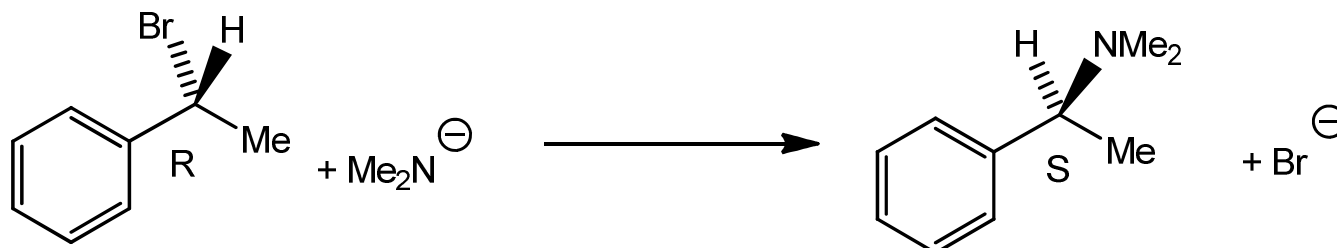


Key concept – inversion of configuration.

*** Key point of nomenclature; INVERSION *** This is important ***

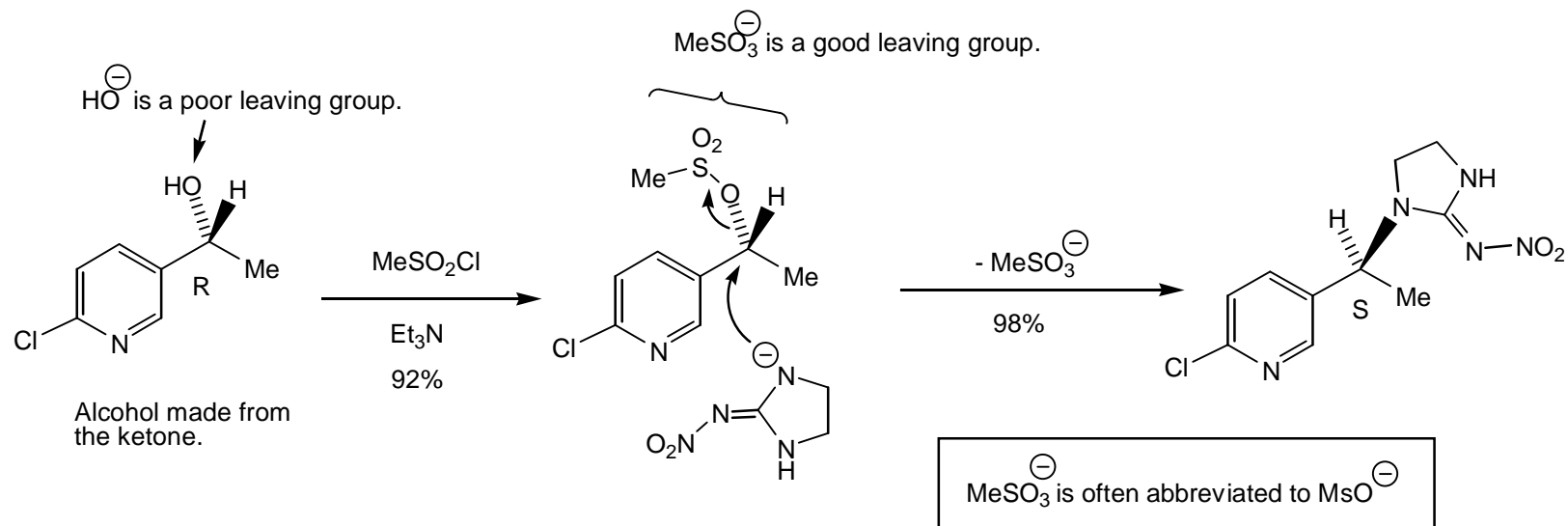
Understanding check;

if you understand why the following happens, then you have 'got it'.



If you cannot see why the NMe₂ group is facing forwards in the product then you have a big problem with your understanding and will probably struggle with organic chemistry so please revise again until you 'get it' or ask your tutor, or both.

Example of an S_N2 reaction in the synthesis of an insecticide – the mechanism is important because it explains how stereochemistry is controlled:



This synthesis depends on the S_N2 reaction for formation of the correct enantiomer of product.

Note the inversion of configuration. What happens if you don't make the mesylate?

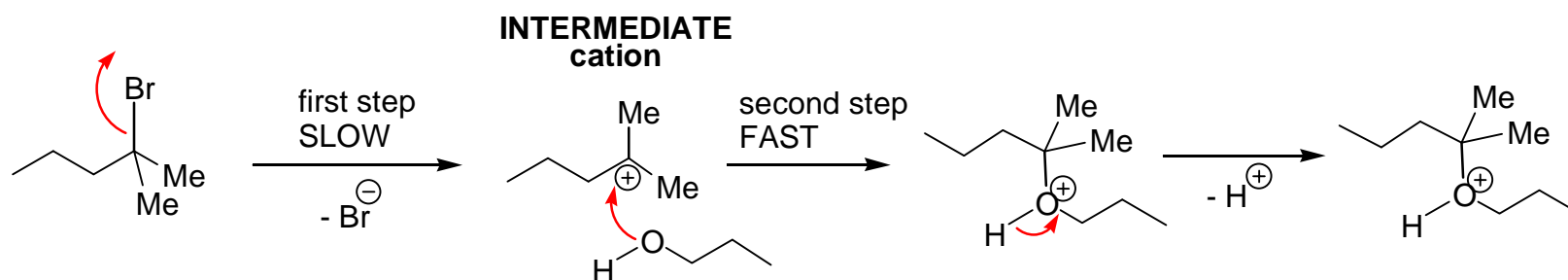
Reference: Krumlinde, P.; Bogar, K.; and Backvall, J.-E. *J. Org. Chem.* **2009**, *74*, 7407-7410.

Mechanisms of substitutions reactions: S_N1

The second is called the S_N1 mechanism – Substitution, Nucleophilic, Unimolecular:

What do these three terms mean?

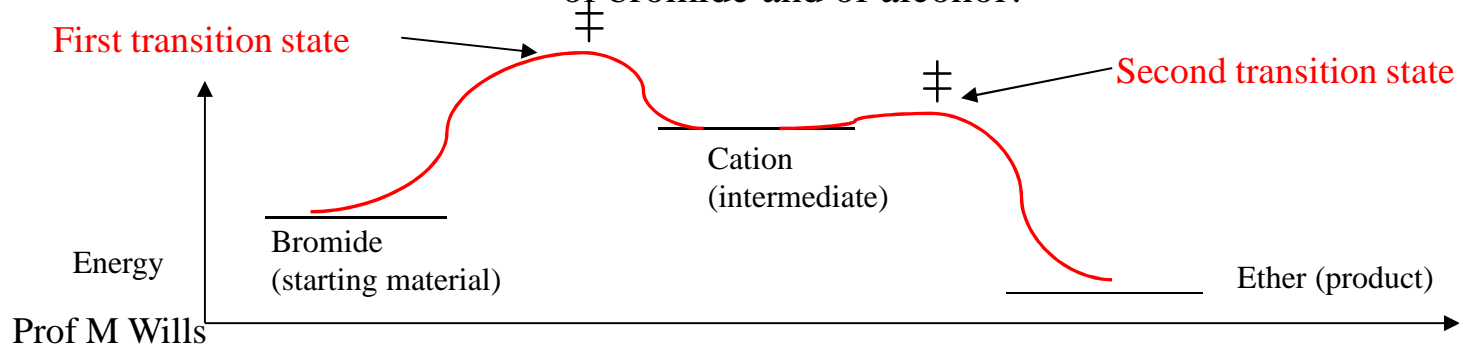
It is a two step mechanism; the leaving group leaves in the first step to form a cationic intermediate and then the nucleophile adds in the second step



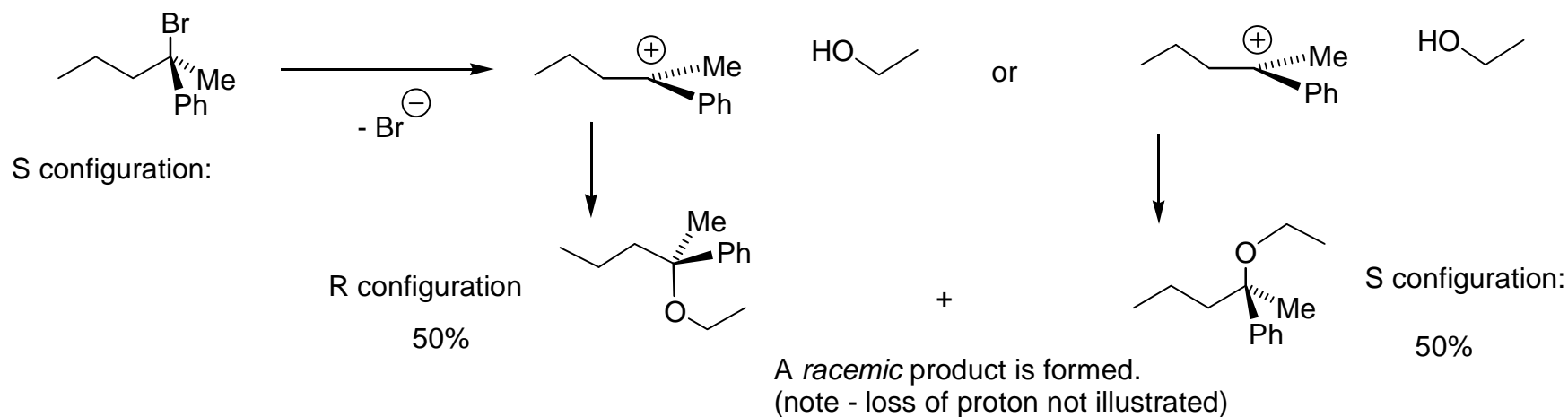
The first step is the rate-determining step (rds)

$$\text{Rate} = k [\text{C}_6\text{H}_{13}\text{Br}] \quad \text{i.e. } [\text{nPrOH (nucleophile)}] \text{ is not featured}$$

What happens if I double the concentration of bromide? What if I double the concentration of bromide and of alcohol?



Stereochemical consequences of S_N1 reactions:



Why are there two products now?
What happened to the square brackets?
What is the ratio of the products?

Two enantiomers are formed in a 1:1 ratio
The cations are intermediates, not *transition states*.

*** Key point of nomenclature; RACEMISATION *** This is important ***
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Nucleophilic substitution reactions: Summary.

S_N1 and S_N2

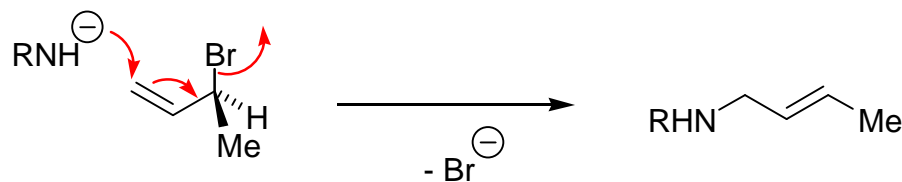
The '1' and '2' refer to the molecularity of the reaction (the number of species in the rate Expression).

S_N1 is a two step reaction. S_N2 is a one step reaction.

S_N2 mechanisms go with inversion of configuration, S_N1 with racemisation.

Make sure you understand the difference between an intermediate and a transition state.

Other substitution mechanisms include the S_N2' :



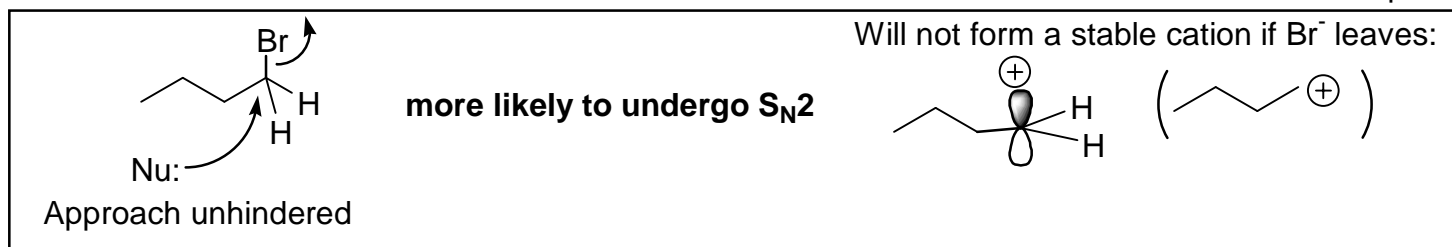
Factors which influence S_N2 and S_N1 reactions:

'If I do a substitution reaction, will it go through an S_N2 or S_N1 mechanism?'

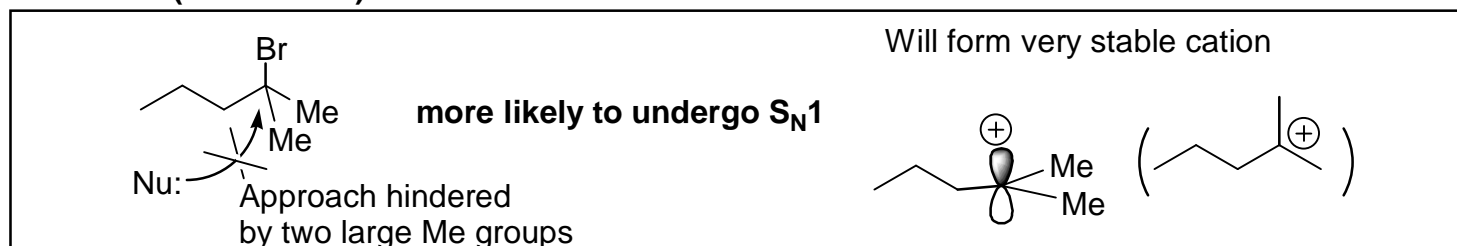
i) Substrate structure. Steric hindrance and cation stability.

Unhindered substrate:

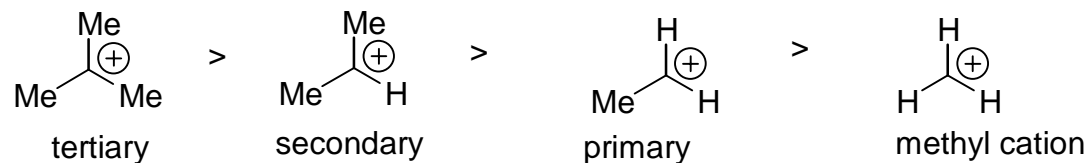
Nu: = nucleophile



Hindered (substituted) substrate



Cation stability:



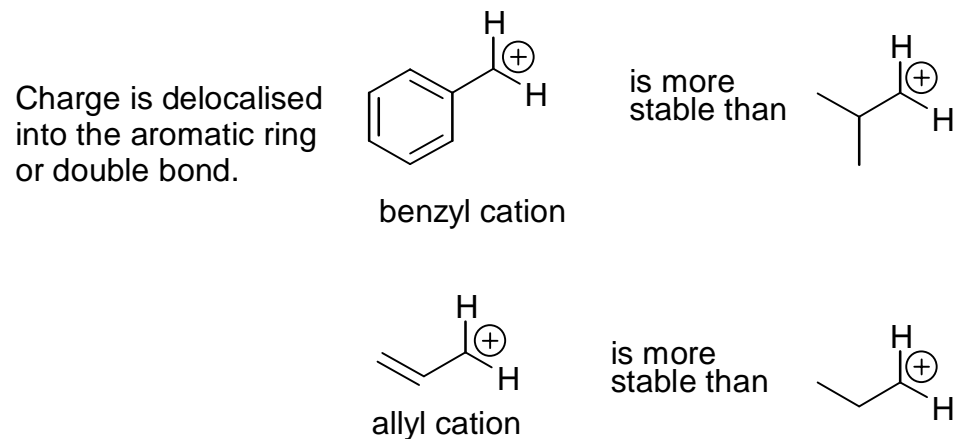
E2
Competes?

A primary halide is more likely to undergo S_N2 , a tertiary S_N1 . A secondary halide may do both, although a good nucleophile would favour S_N2 and a weak nucleophile S_N1 .

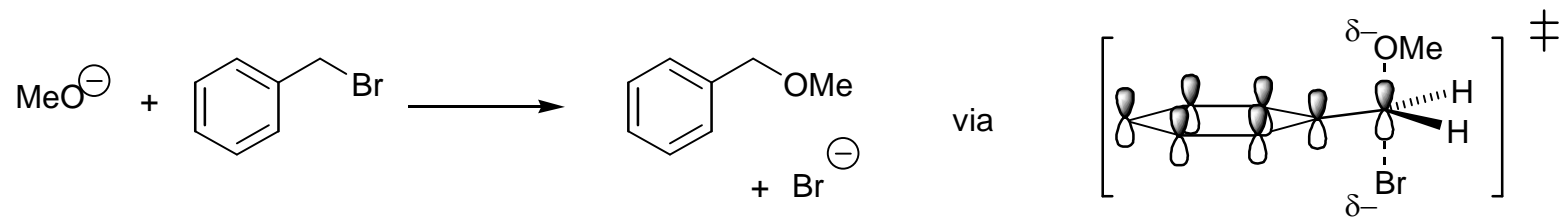
There are exceptions to all these guidelines.

Other factors that increase cation stability.

Cation stability can also be increased by an adjacent double bond or aromatic ring:



However an adjacent benzyl or allyl group can also increase the rate of S_N2 reactions, by stabilising the transition state:



Orbital overlap lowers the transition state energy, and makes the reaction faster.

Factors which influence S_N2 and S_N1 reactions cont:

ii) Effect of the solvent.

Solvent effects can be complex and a good summary can be found on p428-429 of Clayden et al.

Solvents which stabilise cations will tend to increase the rate of S_N1 (because a ions are formed in the rate determining step). These include dipolar aprotic solvents such as dimethylformamide (DMF) and dimethylsulfoxide (DMSO) and dipolar protic solvents such as water or carboxylic acids. For S_N2 reactions the situation is more complex. A nonpolar solvent may speed up the reaction in a situation where the transition state is less polar than the localised anions, and the product is neutral. In situations where a charged product is formed by the reaction of neutral substrates, then a polar solvent such as DMF will be better because the transition state is more polar. Dipolar aprotic solvents such as DMF can also make anionic nucleophiles more reactive in S_N2 reactions because they solvate the cation and make the anion 'freer' to react. Polar protic solvents (e.g. water, alcohols, carboxylic acids) however can retard the rate of S_N2 reactions by solvating the anion and making it less reactive.

iii) Effect of the nucleophile.

In general, more reactive nucleophiles will favour the S_N2 reaction. This is fairly logical and obvious!

Examples of 'reactive' nucleophiles:

Alkoxides: RO[⊖]

Amides: RNH[⊖]

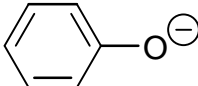
Alkyl anions (for example Grignard (magnesium based) reagents:

R[⊖] (RMgBr)

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Some relatively stable anions are good nucleophiles e.g.

Anions of thiols R-S[⊖]

Anions of phenols 

so are neutral phosphines

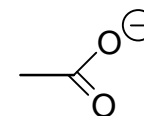
R₃P

Examples of 'less reactive' nucleophiles:

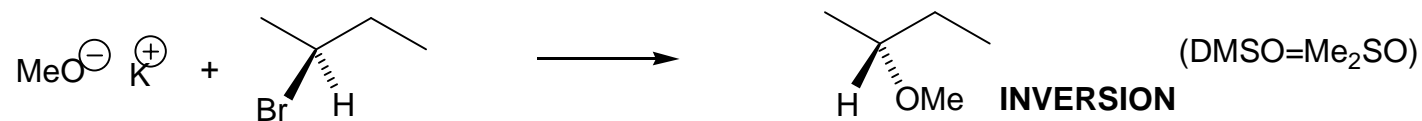
Alcohols (not deprotonated) ROH

Amines (not deprotonated) RNH₂

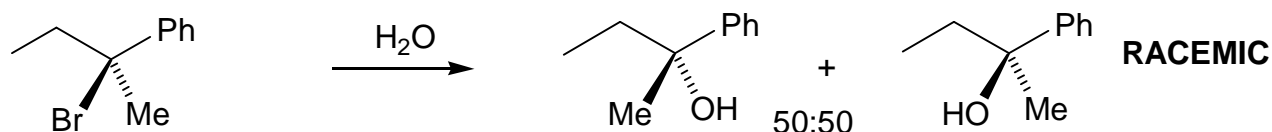
Stabilised nucleophiles e.g. acetate:



S_N2 vs S_N1 – all aspects must be considered:

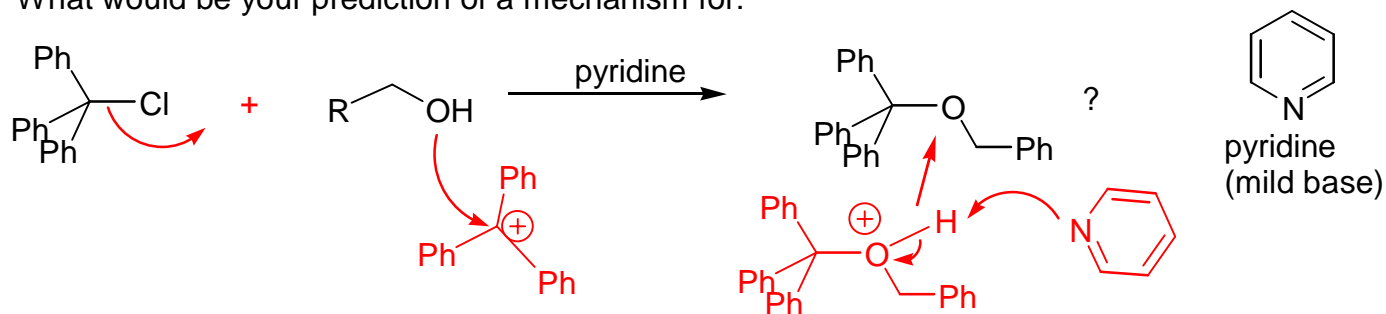


i.e. good nucleophile, not very hindered substrate, good leaving group, hence S_N2 .

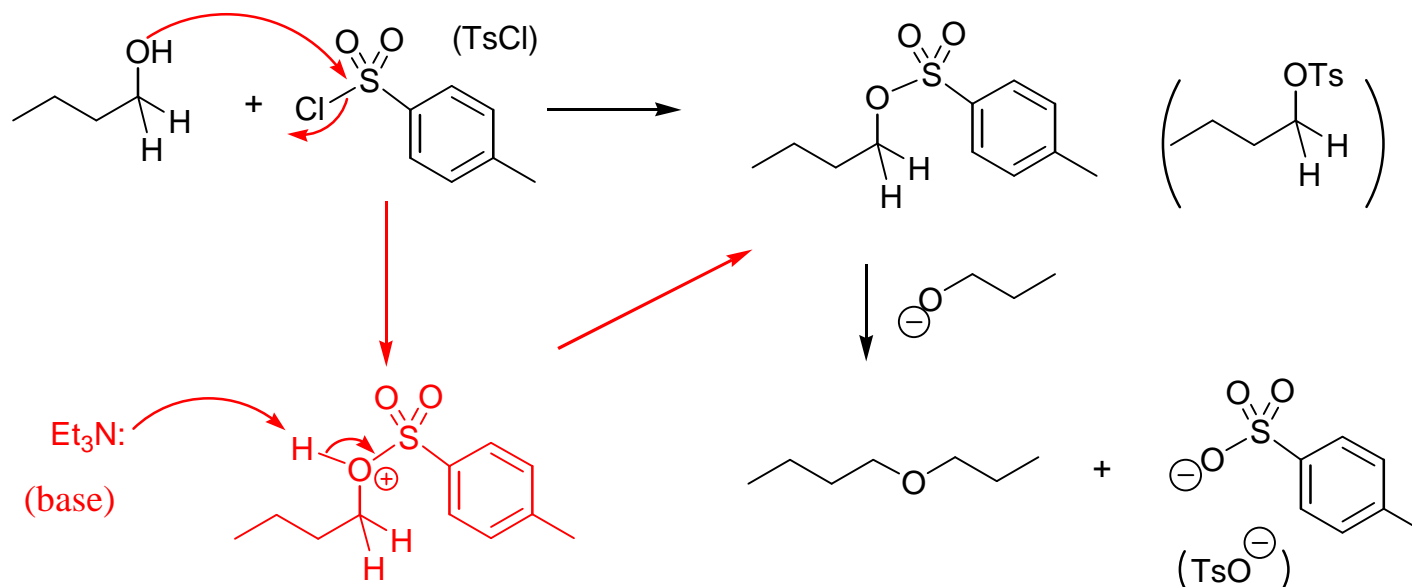


i.e. weak nucleophile, more hindered substrate, potential for stable cation, hence S_N1 .

What would be your prediction of a mechanism for:



Formation and use of the OTs leaving group (very common in synthesis):

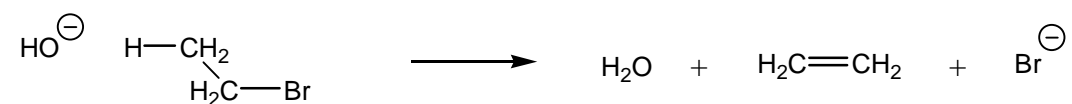


What is the mechanism, and why go to all this trouble, i.e. why is OH a poor leaving group? How else can it be Made into a good leaving group?

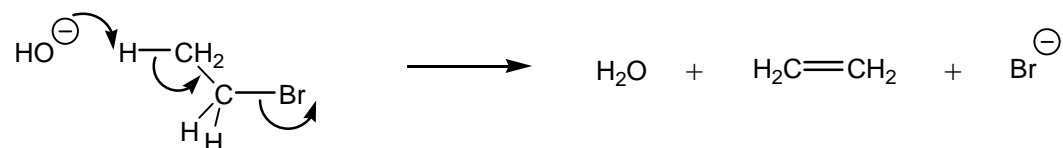
Key point; Learn what a OTs (tosyl group) is – it will come up again!

Mechanism and 'arrow pushing' – Elimination reactions.

Elimination reactions involve the formation of a double bond by loss of two atoms in one process. In the example below hydroxide acts as a base to remove a proton:



One mechanism is illustrated as shown below (this is called an E2 reaction):



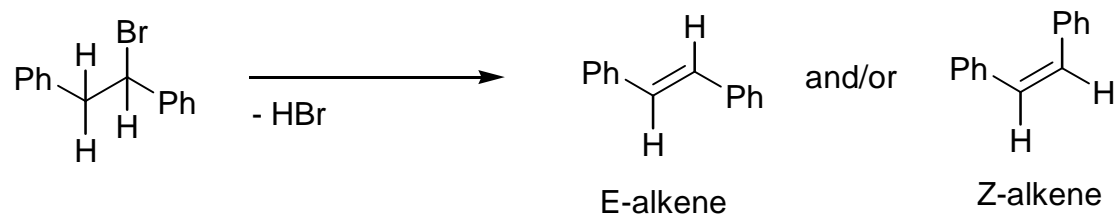
Again note how the negative formal charge flows from left to right - with the arrows

Did you notice that hydroxide can act as a nucleophile (earlier reaction with iodomethane) and as a base (above). Just remember that a nucleophiles and bases are defined by their *actions* not their *structure*.

Alkenes – formation via elimination:

Most (but not all) alkene formation reactions involve an ELIMINATION reaction.

Alkyne reduction is also important (see later).



Recap on alkene structure.

Can you use the Cahn-Ingold-Prelog rules to determine the configuration?

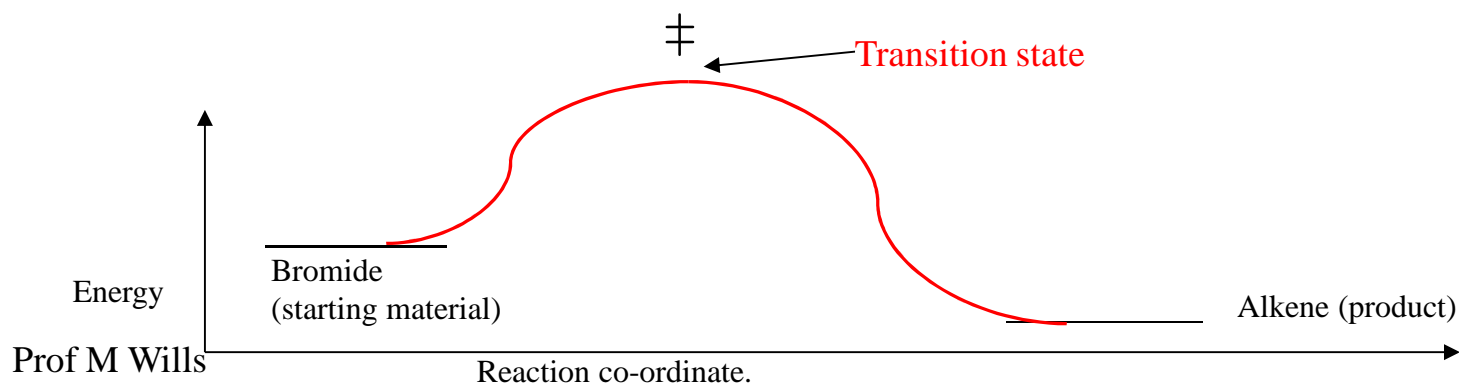
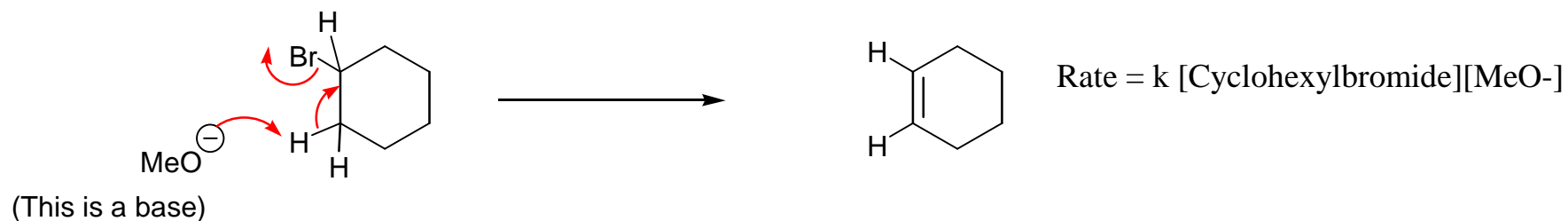
Key point – you lose a H from one carbon atom and a leaving group (typically a halide) from the adjacent carbon atom.

Mechanisms for the formation of alkenes: E1 and E2:

Most elimination reactions, to form alkenes, involve an E2 or E1 elimination.

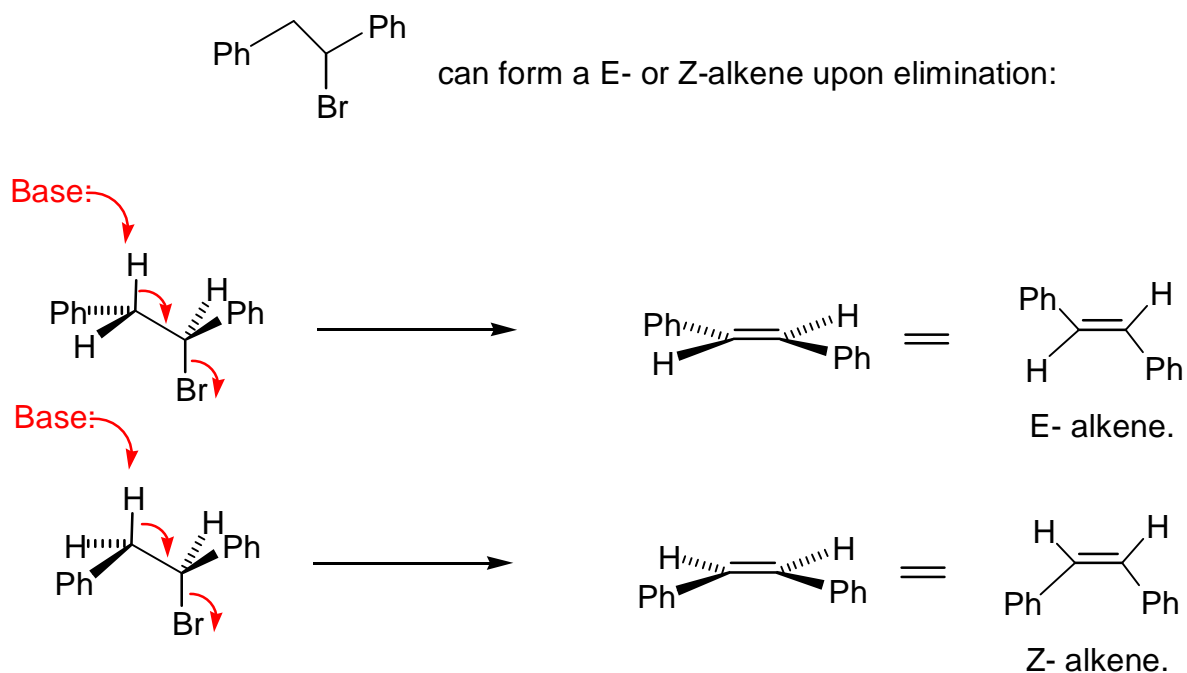
E2 = Elimination, bimolecular. It is a one-step reaction.

A strong base is needed - why is this?



E2 elimination – stereochemical implications: The ‘anti periplanar’ requirement.

E2 reactions require correct orbital alignment in order to work. The optimal arrangement is ‘anti periplanar’, where the ‘H’ and ‘Br’ (in an alkyl bromide) are anti to each other.

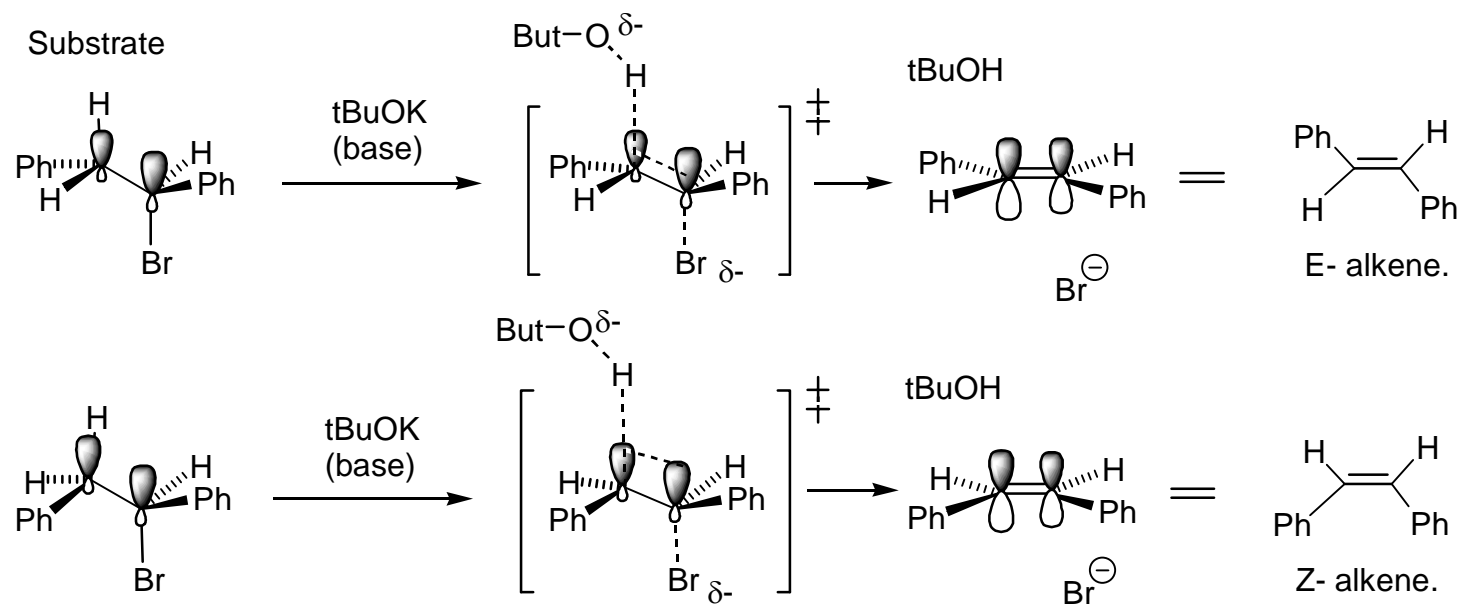


Which base would you use?

EtO⁻, HO⁻, alkoxide. Etc.

E2 elimination – stereochemical implications: orbital alignment:

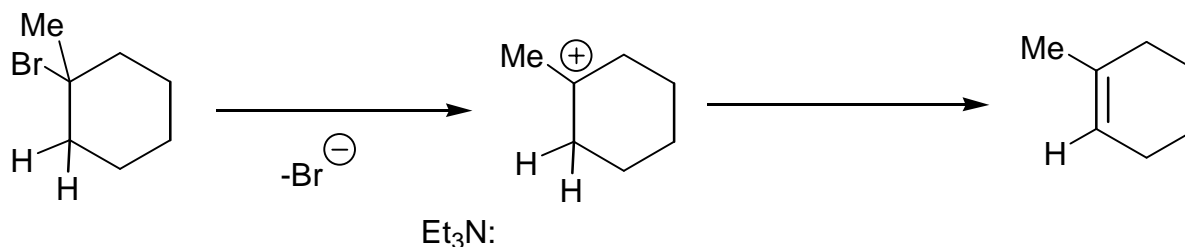
Orbital alignment in E2 elimination reactions:



The alignment of σ and σ^* orbitals in the substrate leads to a smooth transition to a π bond in the product. The E isomer is usually the major product.

The E1 elimination mechanism:

E1 = Elimination, unimolecular. It is a two-step reaction.
It proceeds via a cationic intermediate.

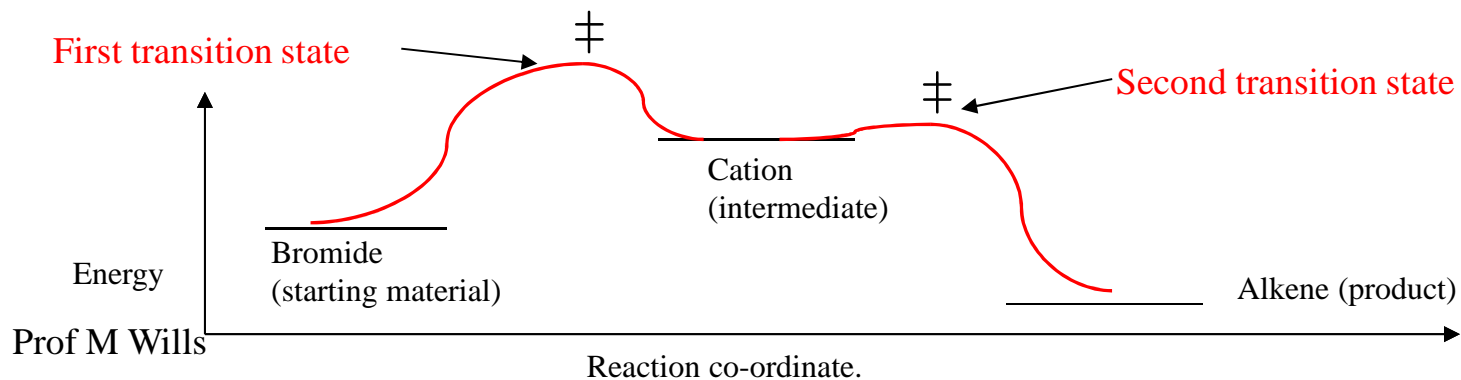


Rate = k [Methylcyclohexylbromide]

Triethylamine (Et₃N)
is a weak base.

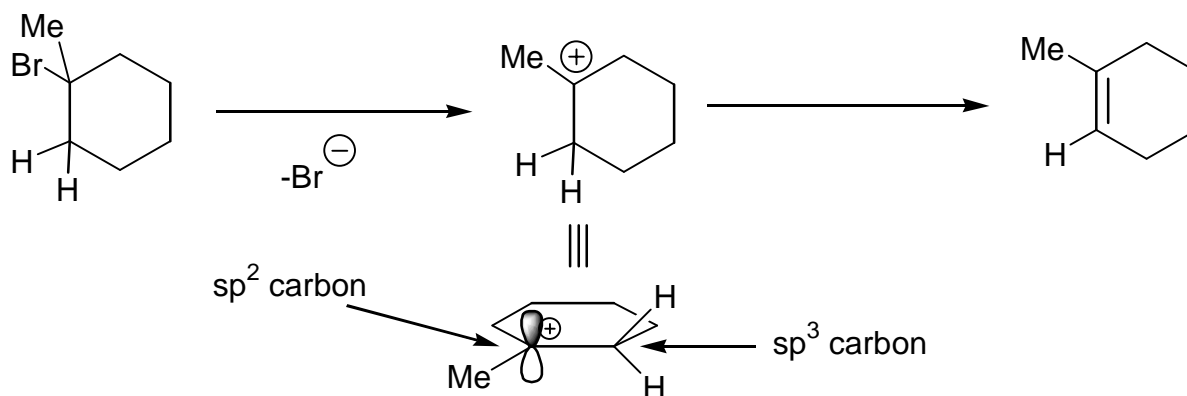
Why does the substrate now have an extra methyl group?

Why was a weak base used in this reaction?

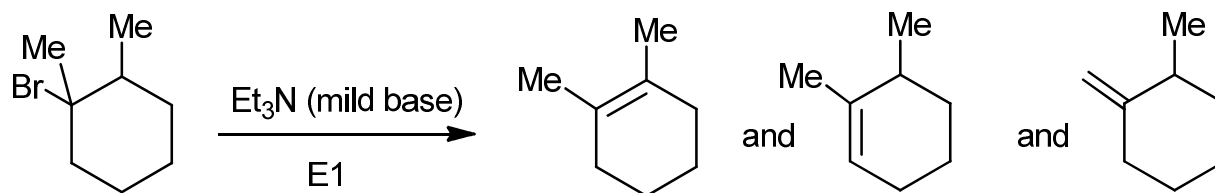


Nature of the intermediate in an E1 reaction:

E1 reactions proceed through a 'flat', i.e. trigonal, cation (like S_N1 reactions).



Sometimes multiple products are formed (irrespective of mechanism):



Formation of alkenes by elimination of alcohols:

Here is a mechanism for an E1 reaction:



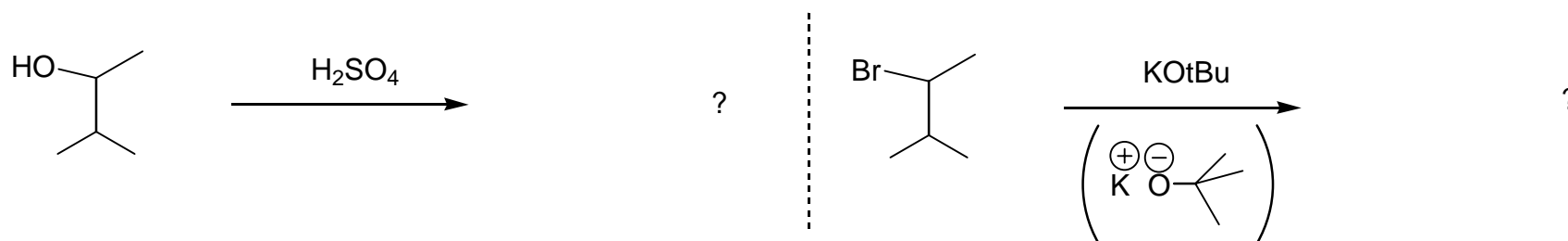
Why is acid needed when the alcohol is the leaving group – why can't we rely on a base?

A: Because the OH would be deprotonated!

What other alkene product can be formed, and how?

A: You would also get the exocyclic alkene – by deprotonation of the methyl group.

Try writing mechanisms and predicting products for the reactions below:



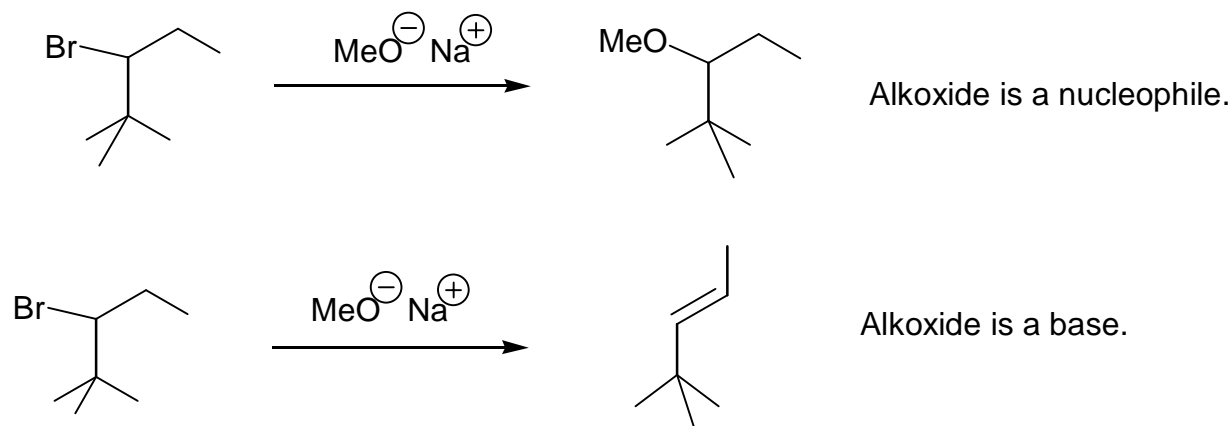
E1_{cb} 'conjugate base' is less common mechanism, but important – look it up if you want to know more.

Substitution vs elimination, base vs nucleophile:

Sometimes a particular substrate can undergo a substitution or an elimination reaction.

The outcome depends on all the factors involved in the reaction;

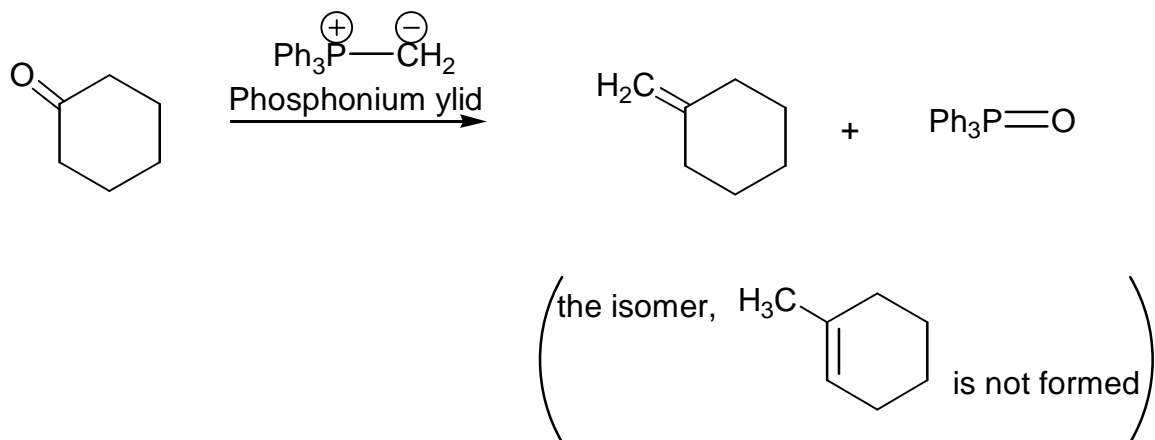
The ‘is an alkoxide a nucleophile or a base?’ question. Answer - depends what it **does**:



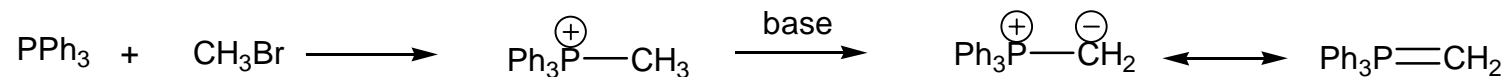
The most important factor is probably the substrate structure – deprotonation may outpace nucleophilic addition when a substrate is very hindered. Certain substrates cannot undergo elimination reactions.

Some alternatives to 'simple' elimination – the Wittig reaction:

The Wittig reaction is one of a number of reactions that provide a means for controlling where the double bond ends up. You'll learn more about it later.



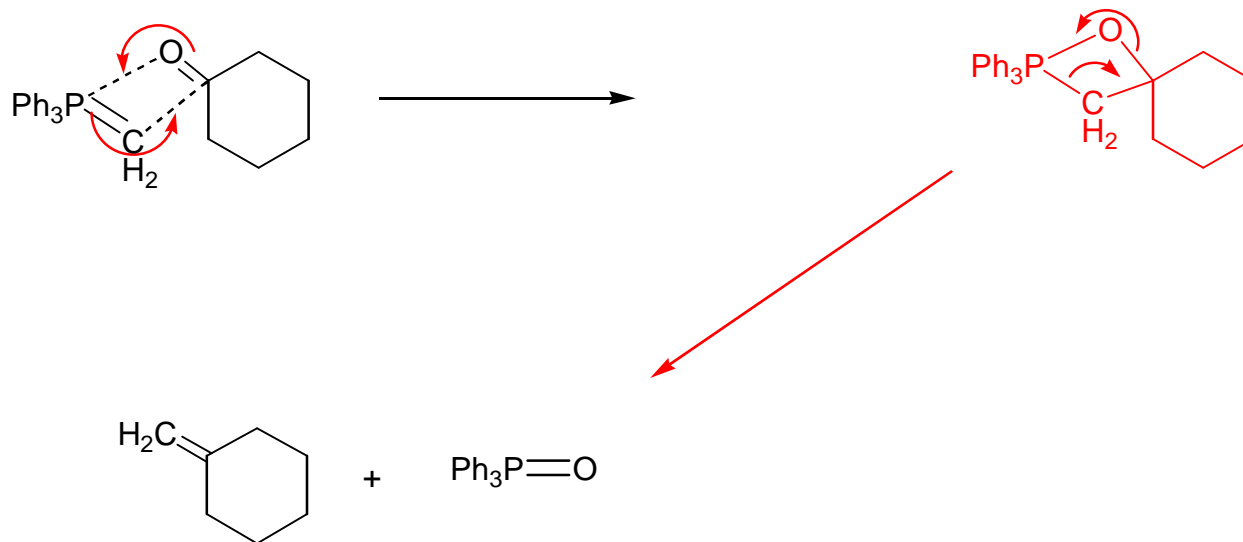
This is how the ylid is formed:



Key point: this is important – learn it

Some alternatives to 'simple' elimination – the Wittig reaction (this is important – learn it)

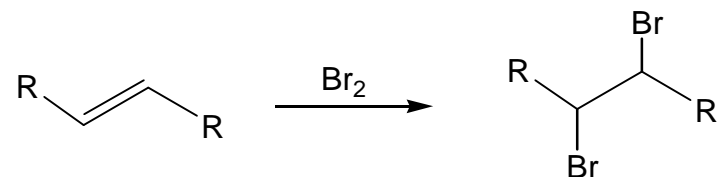
Here is the mechanism of the Wittig reaction – it is pretty easy



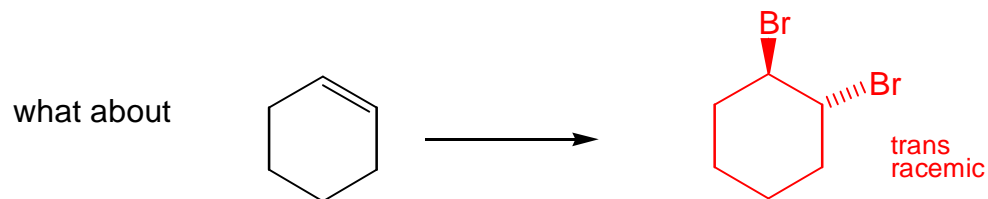
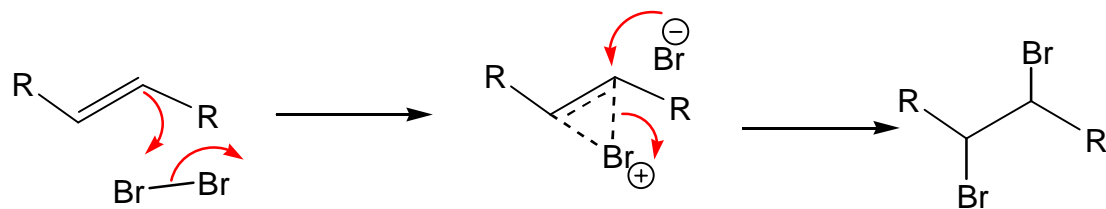
Addition Reactions – often to alkenes or alkynes.

Reactions of alkenes with electrophilic reagents - bromine:

Alkenes are electron rich (in the π system) and react with electrophilic reagents:

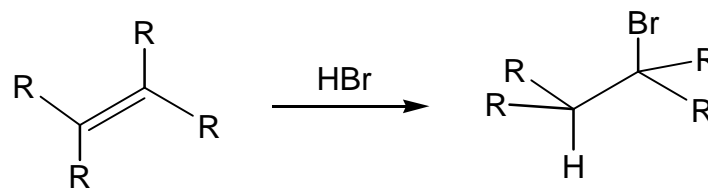


The mechanism is as follows, the intermediate is a bromonium ion:

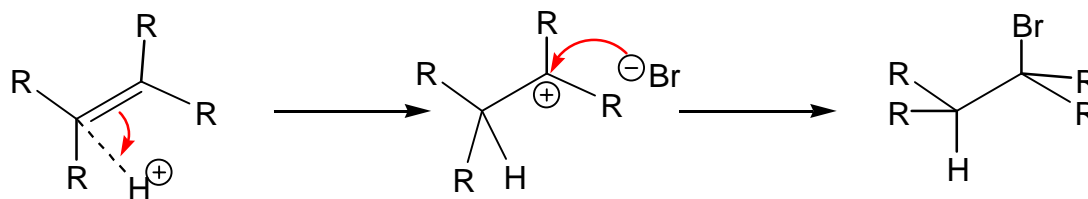


Further additions of electrophiles to double bonds - HBr:

Hydrogen halides (HCl, HBr) also add across double bonds.

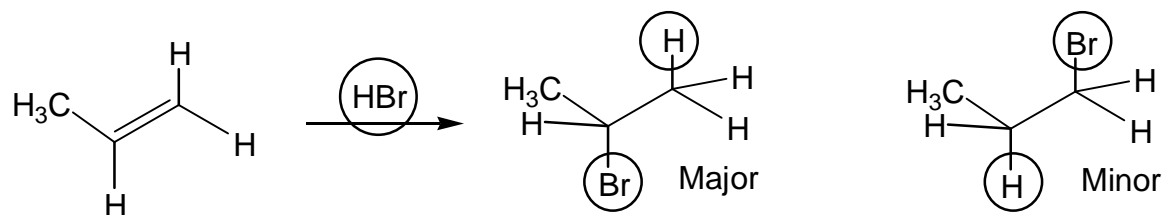


The mechanism involves the addition of a proton first (with the electron-rich alkene), then the bromide. This is logical, because the alkene is electron rich.

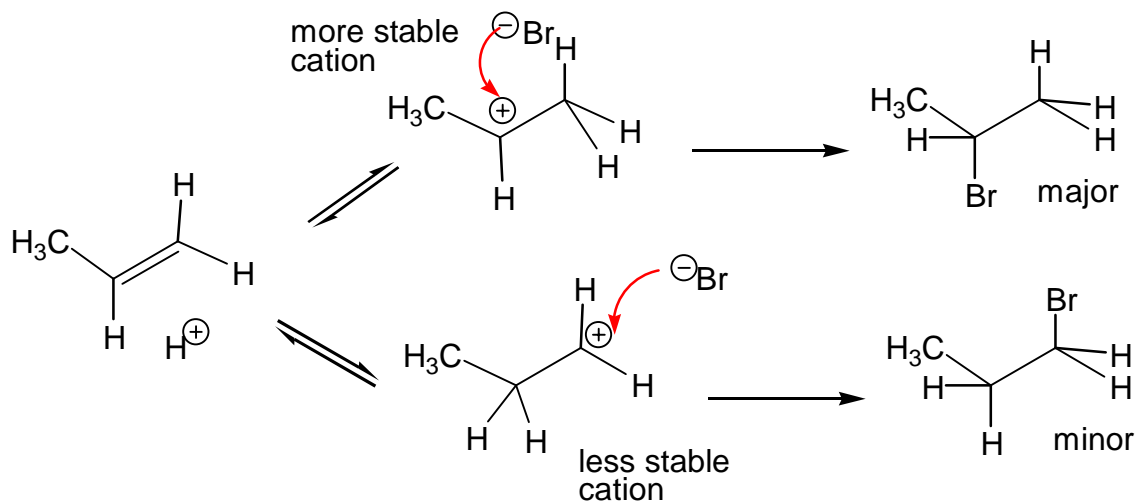


Regioselectivity of electrophilic additions to alkenes:

Addition of HCl and HBr (and other acids) across unsymmetric alkenes results in formation of the more substituted halide (via the more substituted cation).

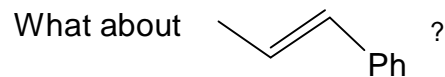


The mechanism involves the addition of a proton first, as before, but in this case the unsymmetrical intermediate has a larger density of positive charge at one end.



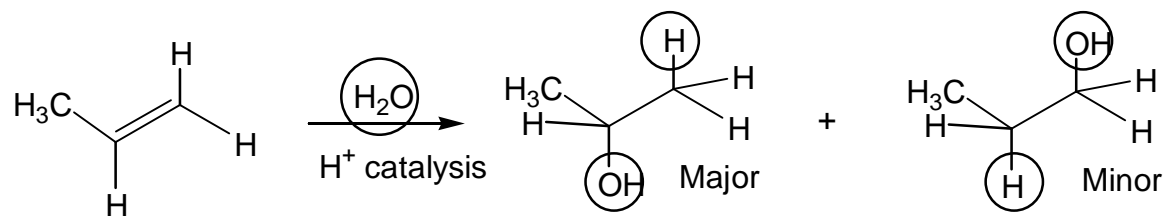
There are two options.

The reaction goes via the most stable (most substituted) cation.

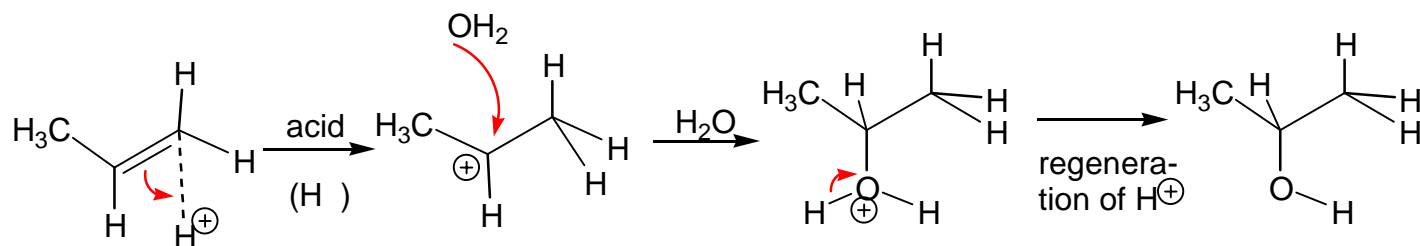


Acid catalysed hydration (addition of water) to alkenes:

Acid catalysed hydration (addition of water) is a *very* important reaction of alkenes:

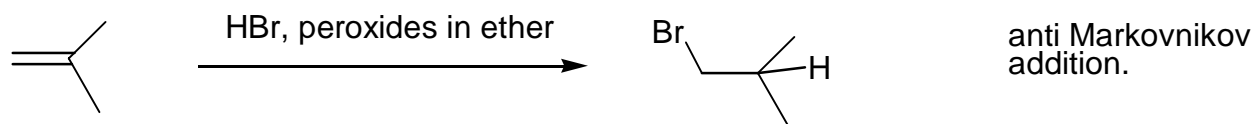


The mechanism involves the addition of a proton first, as before, followed by addition of water, the regioselectivity is the same as for addition of HBr:

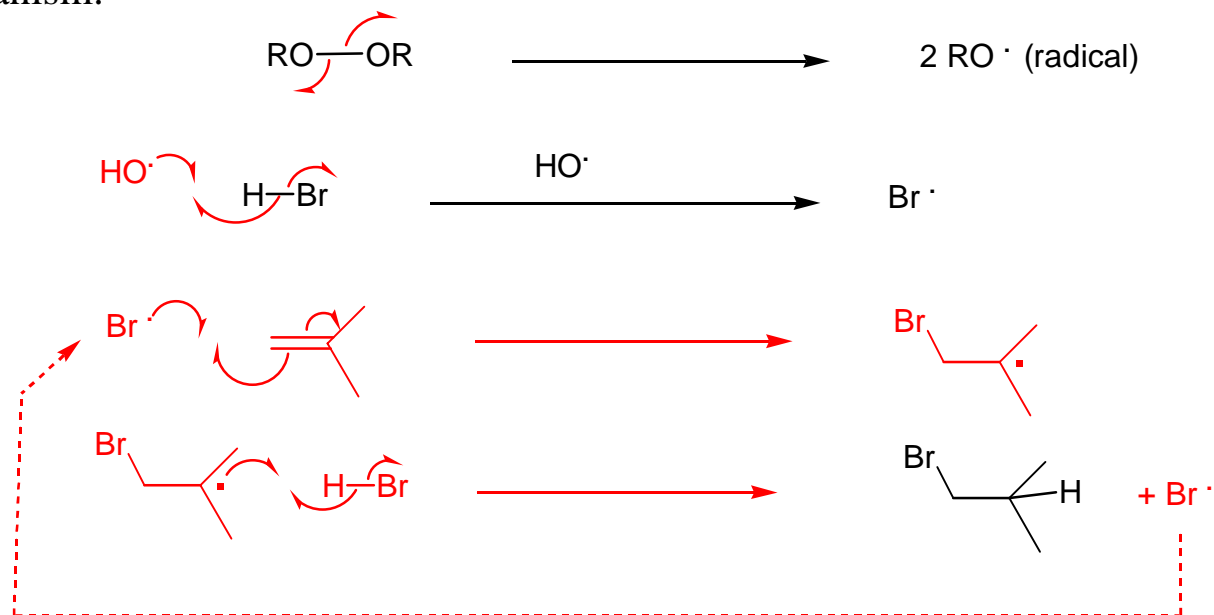


This mode of addition of H_2O is referred to as 'Markonikov' selectivity (i.e. formation of the MOST substituted alcohol via the MOST substituted cation).

Radical reactions of alkenes: HBr in diethylether containing peroxides.

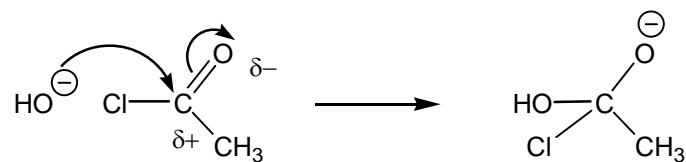


Mechanism (Clayden et al p 1033-1035) –it's a little more complex than the usual addition mechanism:

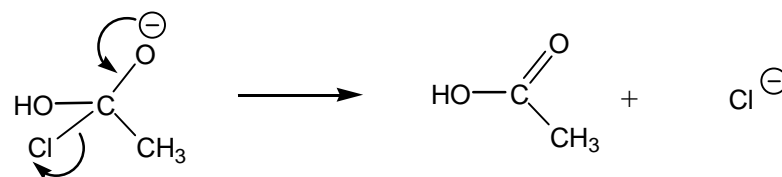
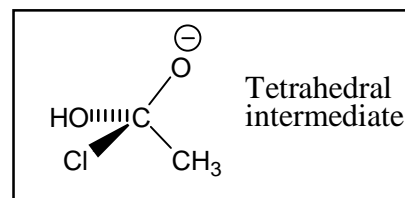


**Reactions with carbonyl groups can result in substitution OR addition.
And the substitution does not go via an S_N2 mechanism!**

An interesting reaction happens when a nucleophile (let's use hydroxide again) attacks a carbonyl group (a C=O bond) which also contains a leaving group. The hydroxide is attracted to the partial positive charge on the carbon atom of the C=O bond:



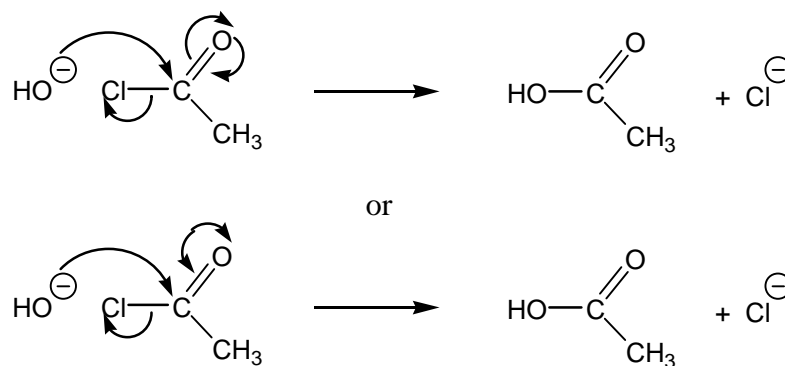
The initial product is called the 'tetrahedral intermediate', because it is an intermediate, and has a tetrahedral shape! It is not stable, and reacts on as shown below:



**Always draw
this process!**

Mechanism and 'arrow pushing'.

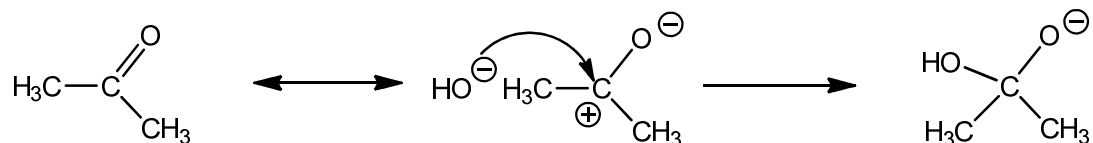
The reaction can be abbreviated into one step:



Remember that you must illustrate that the tetrahedral intermediate is involved in the reaction.

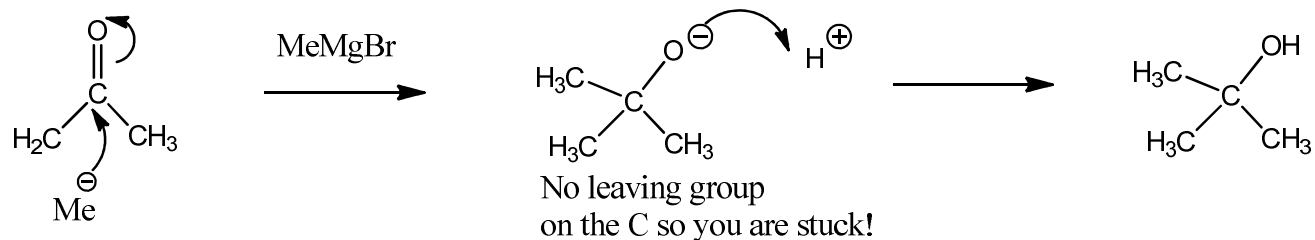
Mechanism and 'arrow pushing'.

Something to avoid: You may have seen a carbonyl addition mechanism illustrated like this:



My advice would be to avoid (unlearn) this two-step process, since it does not properly reflect the true mechanism of the reaction. I.e. the $\text{C}=\text{O}$ bond does not actually break ahead of nucleophilic addition.

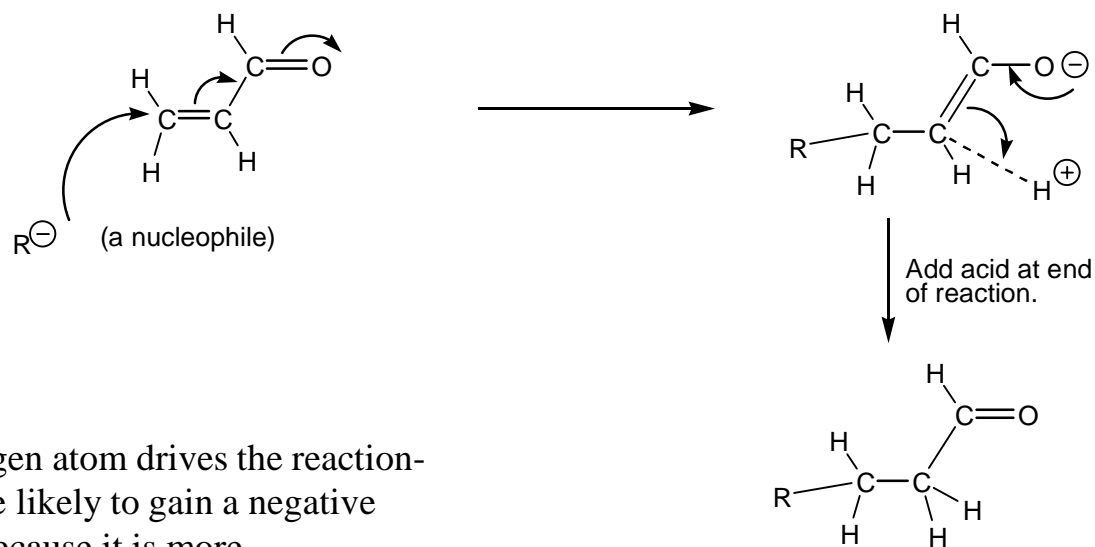
If there is not a leaving group on the tetrahedral intermediate then the overall result will be addition, after protonation of the newly-formed alkoxide:



Mechanism and ‘arrow pushing’ – addition to C=C bonds by nucleophiles can sometimes happen – if there is an electron-withdrawing group nearby.

The polar effects of C=O bonds can be transmitted through adjacent C=C bonds, e.g.

An enone: (a compound with a directly linked C=C and C=O double bond) can react with a nucleophile at either the C of the C=O bond or at the C at the end of the C=C bond. This is called conjugate addition, 1,4-addition and/or ‘Michael’ addition.

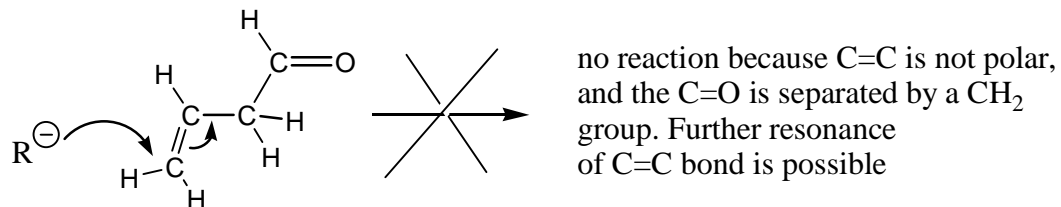


The oxygen atom drives the reaction- it is more likely to gain a negative charge because it is more electronegative than adjacent atoms.

Mechanism and 'arrow pushing' – limits to conjugation.

Note: Resonance/delocalisation involves a movement of charge and electron pairs through unsaturated bonds. It is not possible to extend the electron movement through a saturated atom. (a saturated carbon atom is one attached to a total of four other C or H atoms)

e.g.



Summary:

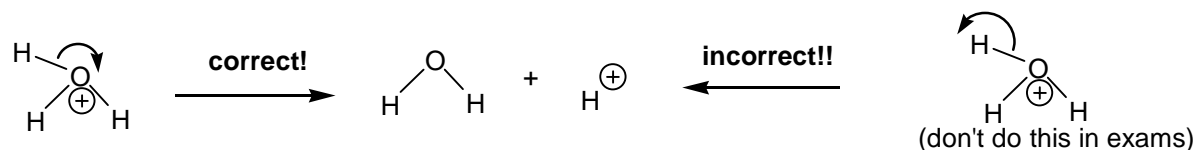
Mechanistic arrows illustrate the movement of a pair of electrons in a molecule. They also show the movement of negative formal charge.

Mechanism and 'arrow pushing' – a few last bit of advice.

Final tips on arrow pushing:

a) remember that curly arrows show the movement of pairs of electrons (and negative formal charge). Any concerted movement of atoms is entirely coincident.

i.e.



b) Mechanistic arrows 'flow' in a head-to-tail fashion (radicals are different - see next page):



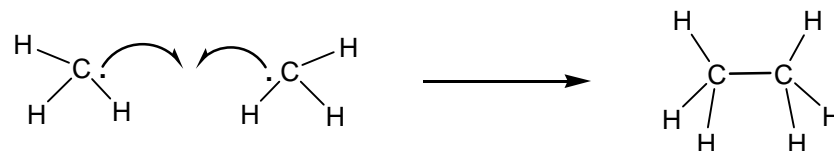
c) Never have 5 full bonds to carbon (this means 10 electrons around it). If you end up with a mechanism a five-bond carbon then think again.

d) Check that the sum of charges in products equals that of the reagents.

Mechanism and ‘arrow pushing’ – the special case of radical reactions.

Radical reactions are different, and involve the use of different arrows (sometimes called ‘fishhooks’). Radical reactions are relatively underdeveloped in synthetic chemistry compared to nucleophile/electrophile reactions, but are becoming more popular.

E.g. each C atom is surrounded by 7 electrons, one comes from each partner to form a bond.

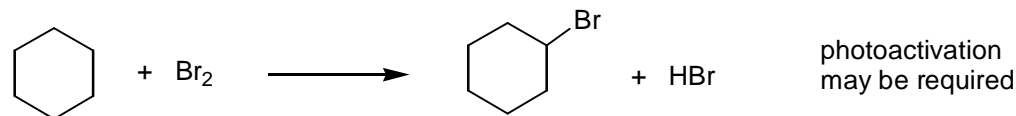


Carbon-carbon bonds (av. 339 kJ/mol) tend to be strong and do not easily cleave in a homolytic manner to give radicals. Other elements with weaker element-element bonds favour this process, e.g. Si-Si (188 kJ/mol), N-N (159 kJ/mol), O-O (138 kJ/mol).

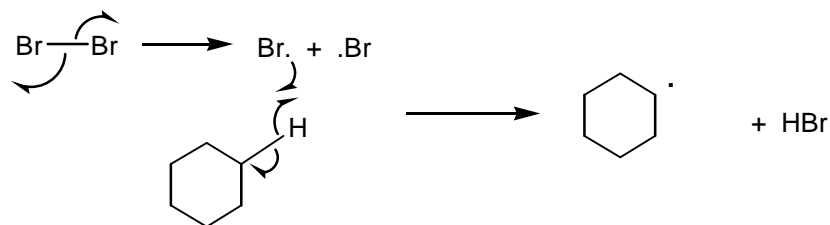
From here on there is a review of the structure and reactivity of specific functional groups – I don't care if some of this repeats what you have already seen, the reiteration is valuable.

Alkanes - the most basic of all organic compounds, composed of only C and H, with no functional groups. General formulae C_nH_{2n+2} (unless cyclic in which case it is C_nH_{2n}).

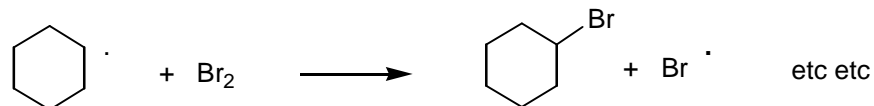
Alkanes are generally quite unreactive and it is difficult to promote reactions at any particular position on them. The bonds are not especially polarised. Radical reactions with halides can be useful:



Mechanism- this is a radical reaction, the first step is initiation:



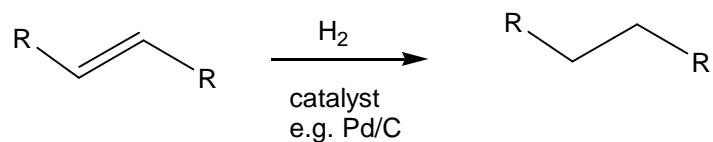
Then the reaction is continued by propagation:



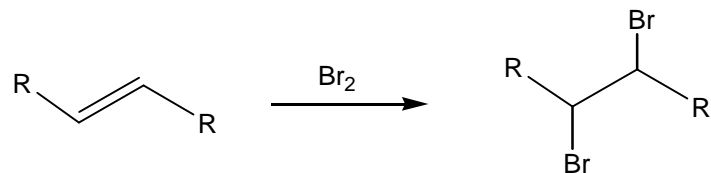
Structure and reactivity of specific functional groups cont...

Alkenes/Alkynes contain reactive double and triple bonds respectively,

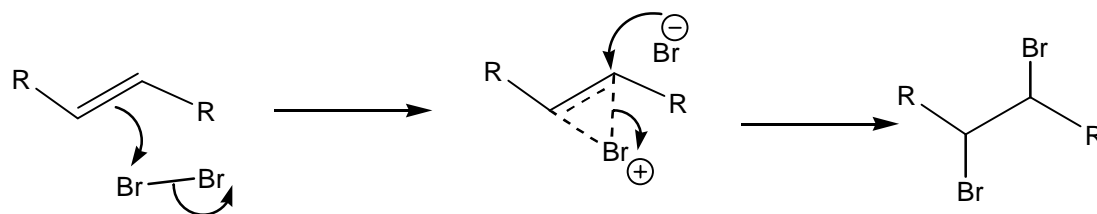
They can be reduced to alkanes by hydrogenation



They are electron rich (in the π system) and react with electrophilic (electron-loving) reagents:



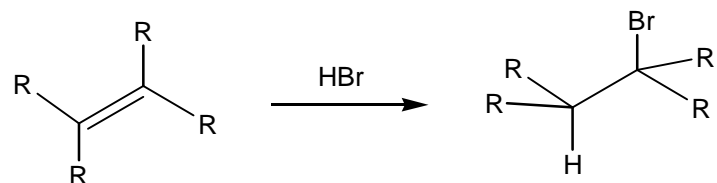
The mechanism is as follows, the intermediate is a bromonium ion:



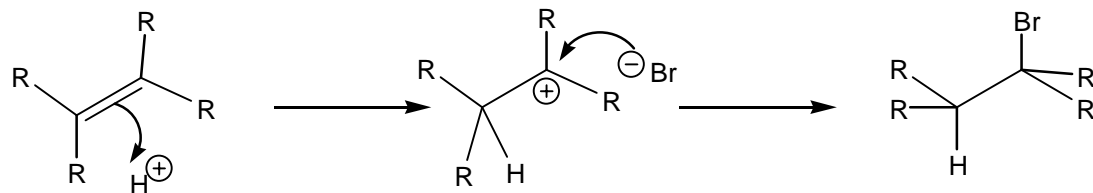
Structure and reactivity of specific functional groups

Alkenes/Alkynes

Hydrogen halides (HCl, HBr) also add across double bonds.



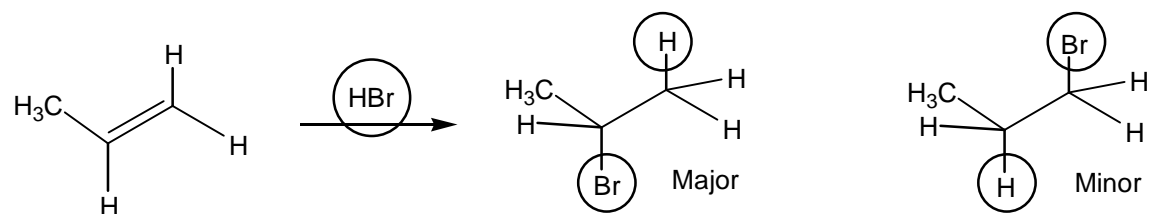
The mechanism involves the addition of a proton first (with the electron-rich alkene), then the bromide.



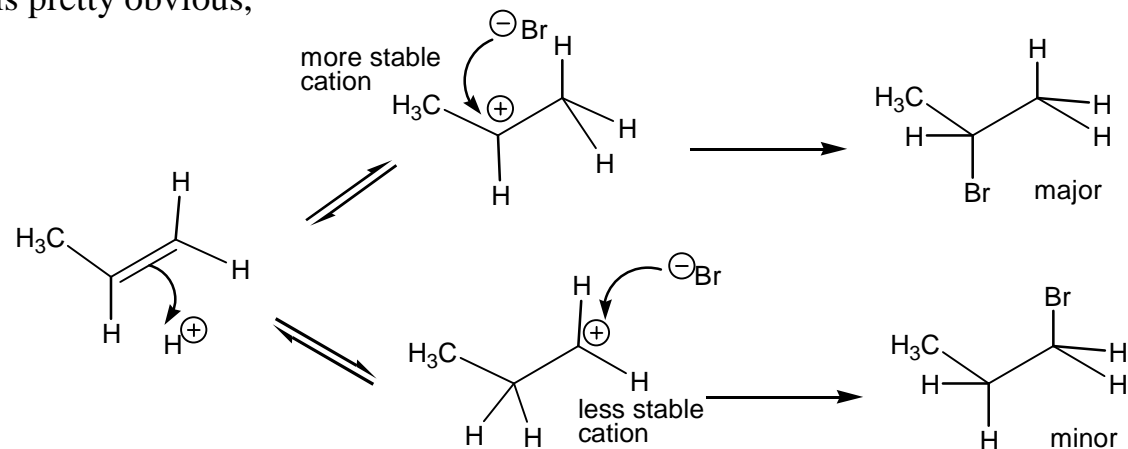
Structure and reactivity of specific functional groups

Alkenes/Alkynes

Addition of HCl and HBr (and other acids) across unsymmetric alkenes results in formation of the more substituted halide (via the more substituted cation).



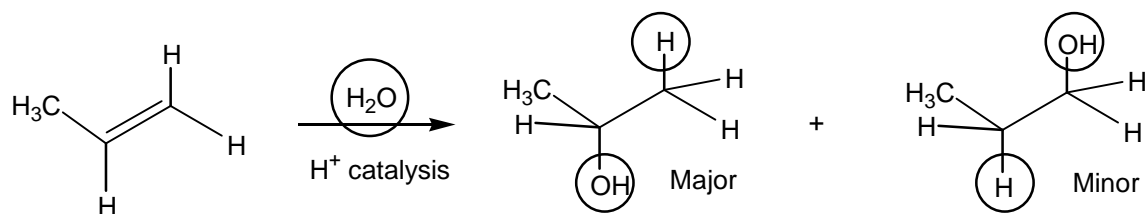
The mechanism involves the addition of a proton first, as before, but in this case the unsymmetrical intermediate has a larger density of positive charge at one end. If you don't understand why the secondary bromide is the major product then you have a big problem and you need to revise again or ask your tutor, as the answer is pretty obvious,



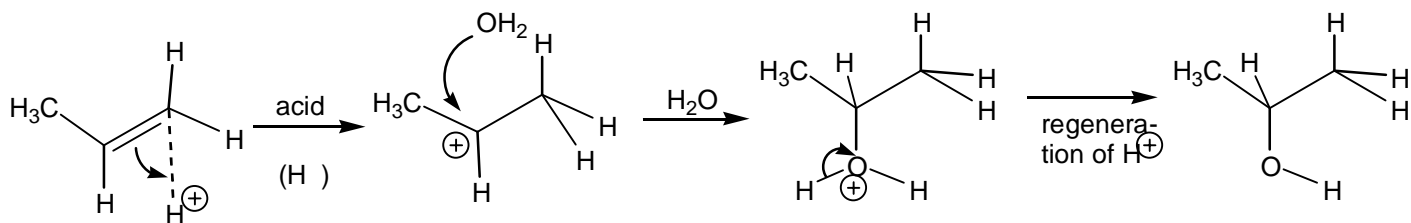
Structure and reactivity of specific functional groups

Alkenes/Alkynes

Acid catalysed hydration (addition of water) is a *very* important reaction of alkenes:



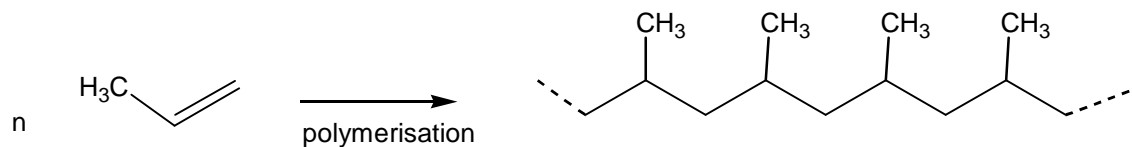
The mechanism involves the addition of a proton first, as before, followed by addition of water, the regioselectivity is the same as for addition of HCl:



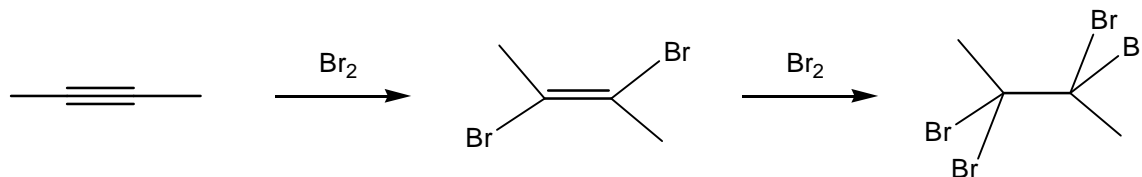
Structure and reactivity of specific functional groups

Alkenes/Alkynes

Another important reaction of alkenes is *polymerisation* : more information to follow, obviously...



Alkynes are capable of many of the same reactions as alkenes, but twice if enough reagent is used, e.g. addition of bromine:



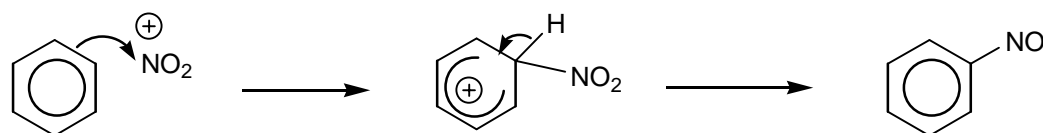
Structure and reactivity of specific functional groups

Aromatic compounds:

Aromatic compounds are stable cyclic systems of conjugated double bonds. There must be $2n+1$ double bonds for the system to be stable. You can illustrate them in two ways, the first of which is more accurate. The structure consists of a system of six sigma (σ) bonds with a π bond system on top which derives from the p orbitals. The carbon atoms are sp^2 hybridised:



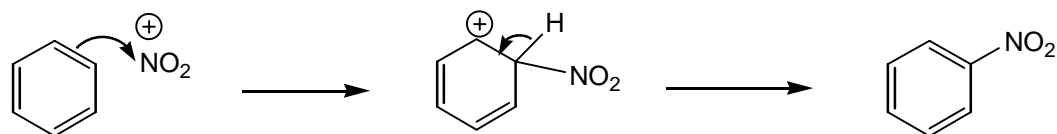
Aromatic compounds are stable to many reactions such as hydrogenation (unless very high pressures are used), polymerisation, etc. However they are also *electron rich*, and as a result electrophilic substitution is a very important reaction. The example below shows nitration of a benzene and the mechanism is always as shown below. Learn it!!



Structure and reactivity of specific functional groups

Aromatic compounds – add the electrophile first!!!!:

You may also see the electrophilic substitution mechanism illustrated for the ‘localised’ version (sorry about the old terminology). Although not a true representative of the real structure, it is a little easier to see how the electrons are moving in this example:

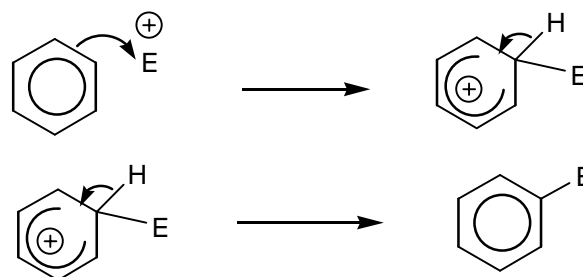


Other important reactions of aromatic compounds include bromination and sulfonylation.

Remember- the mechanism is always the same:

Add electrophile (E, i.e. NO_2^+ , SO_3H^+ , Br^+) first

then remove the proton:



Learn this!!

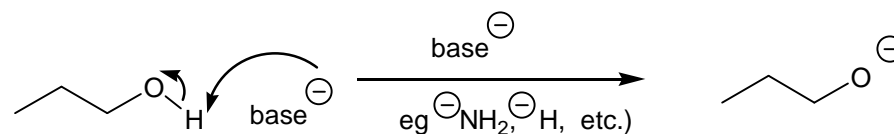
Structure and reactivity of specific functional groups

Alcohols:

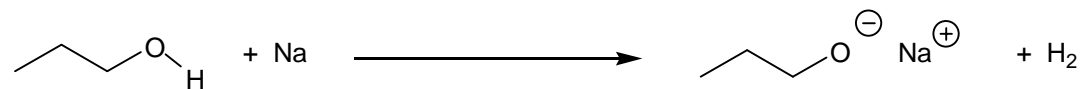
Alcohols are characterised by the presence of the OH group. Many are encountered in daily life, especially ethanol ($\text{CH}_3\text{CH}_2\text{OH}$). Many are used as solvents. All alcohols should be considered toxic and handled with care.

Reactions of alcohols:

i) Removal of a proton to form an alkoxide. The proton on oxygen is *by far* the easiest to remove:



Alkoxides can also be formed by reaction with sodium:

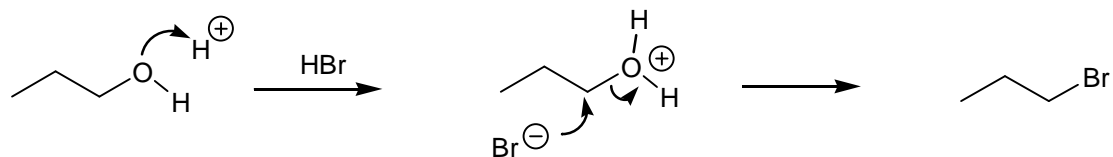


Structure and reactivity of specific functional groups

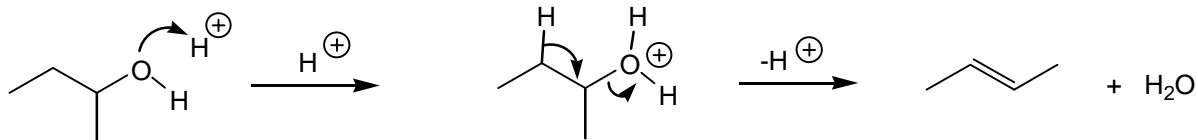
Alcohols:

Reactions of alcohols cont...:

ii) The OH group can be substituted by another group, however acid catalysis is usually essential in order to turn the alcohol into a good leaving group:



iii) Elimination of water leads to the formation of alkenes - again the use of acid is essential:

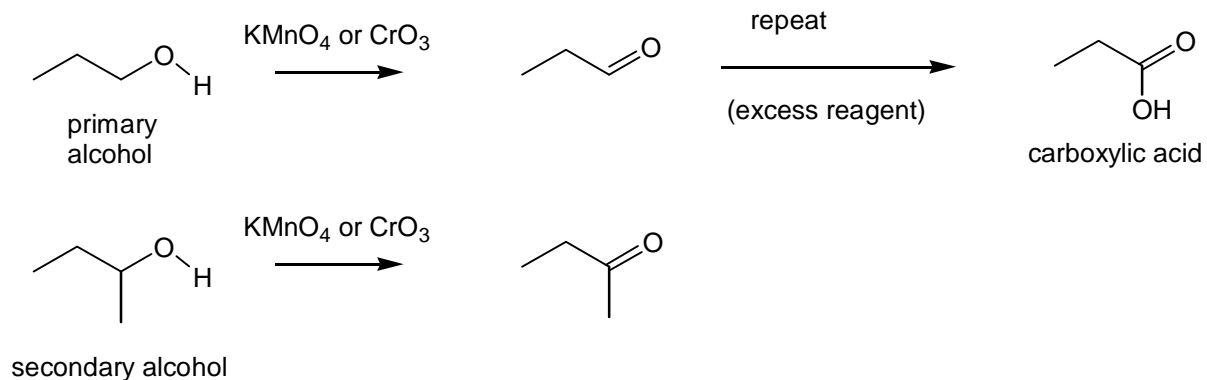


Structure and reactivity of specific functional groups

Alcohols:

Reactions of alcohols cont...:

iv) Oxidation of alcohols leads to the formation of aldehydes, carboxylic acids (from primary alcohols) and ketones (from secondary alcohols):

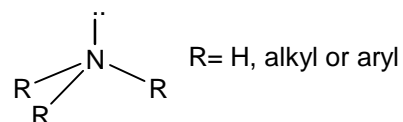


Please make a mental note of the above OXIDISING reagents

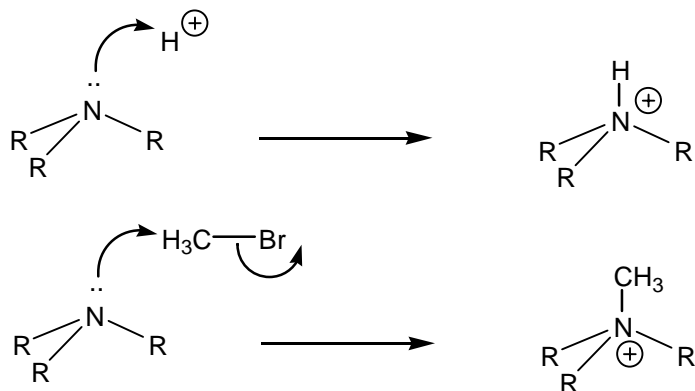
Structure and reactivity of specific functional groups

Amines:

These are nitrogen-containing compounds in which the nitrogen is attached to alkyl or aryl groups only (if N is attached to C=O then the compound is called an AMIDE). The reactivity of amines is dominated by the lone pair on the nitrogen atom, which has a *tetrahedral* shape:



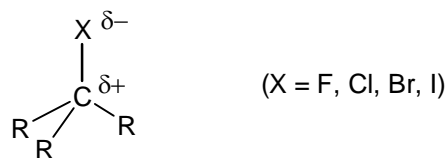
The lone pair is very reactive. It may be protonated (above) or alkylated (below) in which case an ammonium cation is formed:



Structure and reactivity of specific functional groups

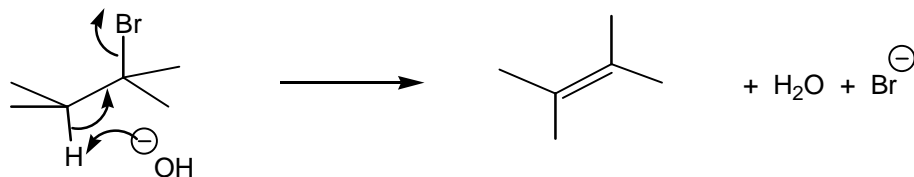
Alkyl halides:

Alkyl halides contain F, Cl, Br or I and are very important synthetic reagents. Their structure and reactivity is dominated by the polarity of the C-X (X=halide) bond.



Reactions of halides:

i) Elimination of HX (e.g. HBr) - a useful method for alkene formation:

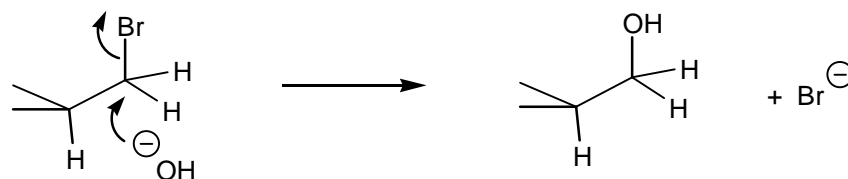


In some cases, more than one product may be formed in an elimination. The major product depends on the exact reaction conditions used.

Structure and reactivity of specific functional groups

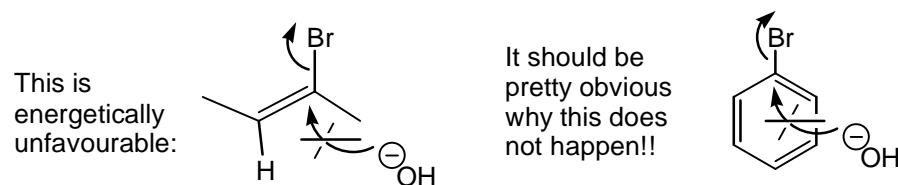
Alkyl halides:

ii) Substitution reactions - replacement of the halide with another group is a common reaction. Again the reaction is guided by the polarity of the C-X bond (C-Br in the case below):



The balance between substitution and elimination is often a close one and depend upon many factors, including the structure of the substrate and the other reagents, the solvent, temperature etc.

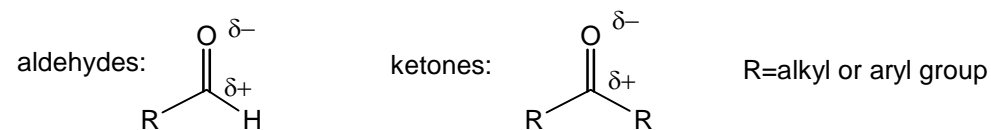
You should also be aware that substitution reactions are not observed at sp^2 C atoms (i.e. on alkenes and aromatic compounds):



Structure and reactivity of specific functional groups

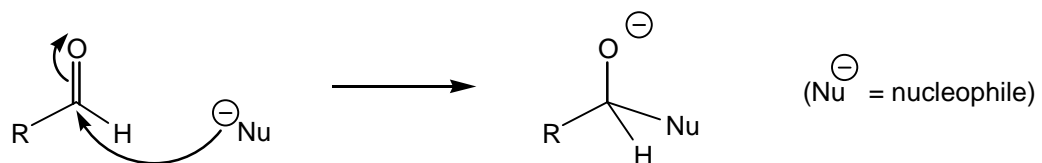
Aldehydes and Ketones:

Aldehydes and ketones contain polarised C=O bonds, which dominate their properties and reactivity.



Reactions of aldehydes and ketones:

i) Addition of nucleophiles is a very common reaction:

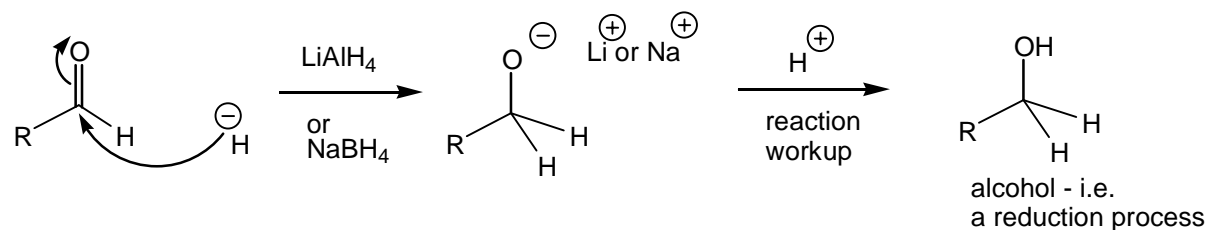


What happens next depends on the nature of the nucleophile which has been used.

Structure and reactivity of specific functional groups

Aldehydes and Ketones:

If the nucleophile is hydride (H^-) from, for example, lithium aluminium hydride or sodium borohydride then the product (after quenching with acid of course) will be an alcohol. Please make a mental note that hydride sources such as lithium aluminium hydride or sodium borohydride are *reducing* agents.



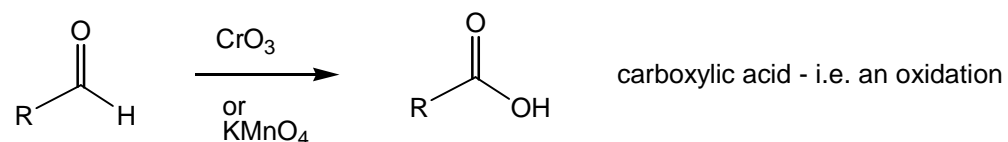
The reduction of ketones in the same way results in the formation of secondary alcohols

The addition of the carbocation part of common organometallic reagents (see later) also results in the formation of alcohols.

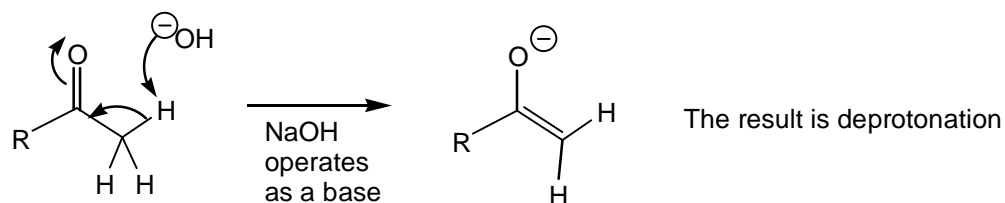
Structure and reactivity of specific functional groups

Aldehydes and Ketones:

ii) The oxidation of aldehydes results in formation of carboxylic acids, as shown below. Ketones are resistant to oxidation by the reagents shown. Remember, as you have seen before, chromium trioxide and potassium permanganate are **oxidising** agents.



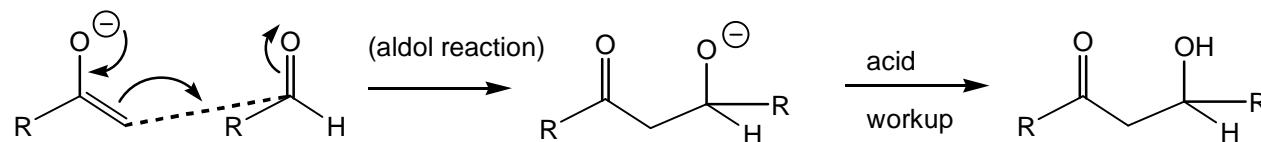
iii) Enolisation: The final key reaction of aldehydes and ketones is deprotonation on the carbon atom next to the C=O bond (but **not** at the C of the C=O bond itself, OK). This is **really important** so learn it!!



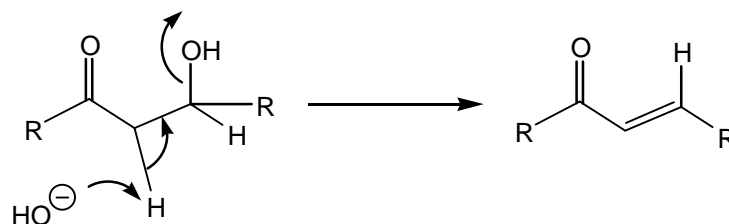
Structure and reactivity of specific functional groups

Aldehydes and Ketones:

The resulting anion, an *enolate*, is very reactive and adds to other reagents, such as another molecule of ketone or aldehyde (the aldol reaction):



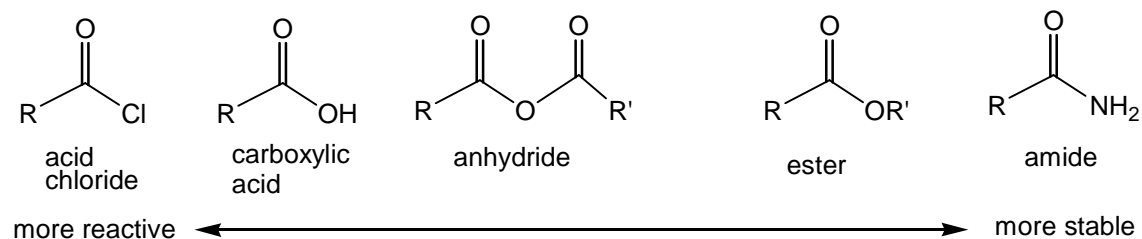
The aldol reaction is a very important reaction for C-C bond formation. The reaction can be catalysed by acid or base and sometimes a mole of water is eliminated.



Structure and reactivity of specific functional groups

Carboxylic acids and their derivatives

Carboxylic acids and derivatives thereof look like aldehydes and ketones but exhibit a very different reactivity pattern. Some examples are shown below:



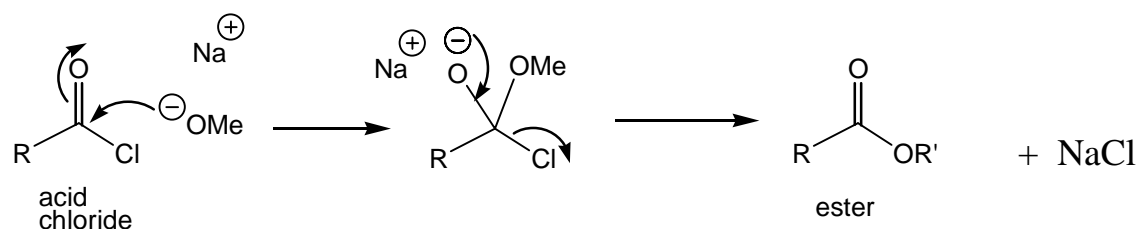
Carboxylic acids are moderately acidic, but not really very strong compared to mineral acids such as HCl and H₂SO₄. Ethanoic acid is about 10¹¹ times as acidic as an alcohol such as ethanol, but HCl is about 10¹⁵ times stronger still (see the section in minimodule A3 on acidity).

The derivatives shown above can all be interconverted through a substitution process. The only limitation is that the product should be more stable than the starting material. The mechanism is always the same and is shown on the next slide.

Structure and reactivity of specific functional groups

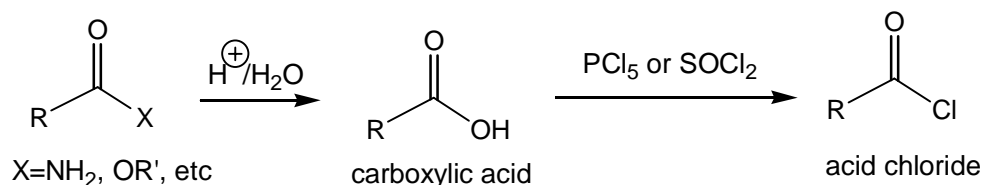
Carboxylic acids and their derivatives

Mechanism of interconversion of carboxylic acid derivatives. The example below is for the conversion of an acid chloride to an ester using sodium methoxide – you've seen it before:



In some cases the reaction can be promoted by the use of acid catalysis (not illustrated).

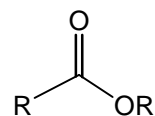
When it is necessary to generate a more reactive derivative, any compound can be hydrolysed to a carboxylic acid (strong aqueous acid) and then to an acid chloride using either phosphorus pentachloride or thionyl chloride (SOCl₂). Can you work out the mechanisms?



Structure and reactivity of specific functional groups

Esters

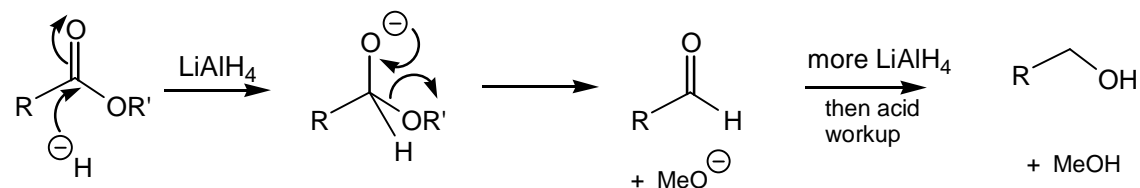
many esters have pleasant odours:



smells like...

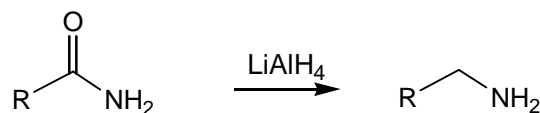
R=CH₃, R'=C₅H₁₁ bananas
R=C₃H₇, R'=C₂H₅ pineapples
R=C₃H₇, R'=C₅H₁₁ apricots
R=CH₃, R'=C₈H₁₇ oranges
R=C₄H₉, R'=C₅H₁₁ apples

Esters are already at a very high oxidation level. Reduction of esters results in the formation of two alcohols, by the mechanism shown:



Amides

Amides are very stable compounds. Hydrolysis with strong aqueous acid converts amides to carboxylic acids. Reduction with lithium aluminium chloride is a useful reaction which leads to the formation of amines:

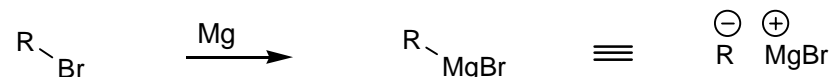


Structure and reactivity of specific functional groups

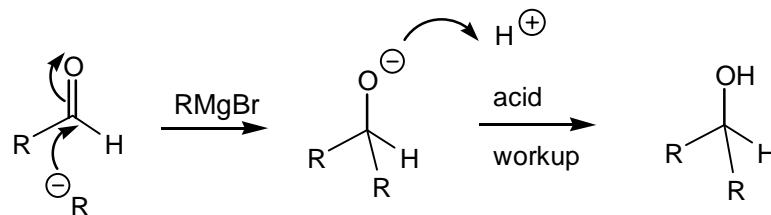
Organometallic Reagents

Organometallic compounds contain a mixture of organic and metallic groups in a covalently (or partly covalently) bonded system. Of these the most common and widely used are based on lithium, magnesium, zinc and copper. Magnesium-based systems are also called *Grignard* reagents (pronounced 'grin-yard').

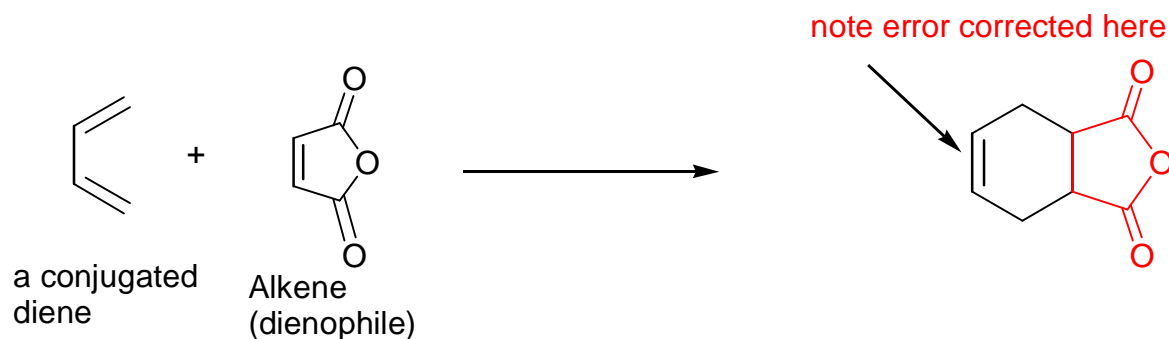
Grignard reagents are prepared by the reaction of metallic magnesium with an alkyl or aryl bromide.



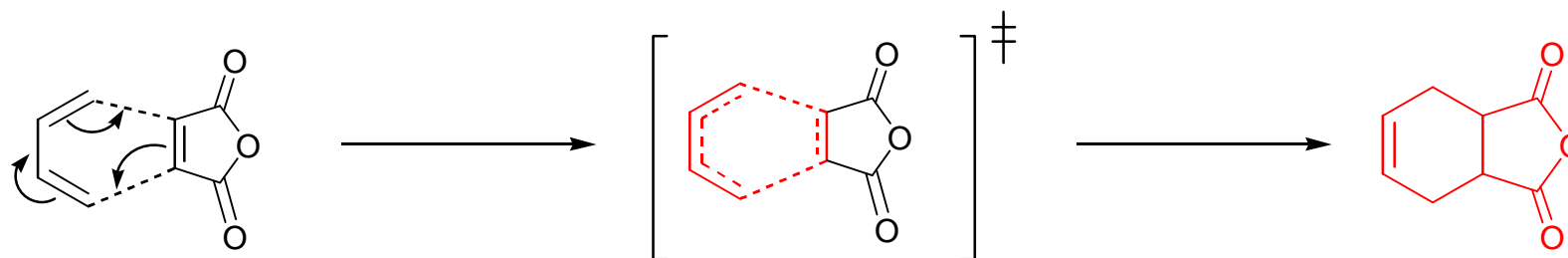
As far as reactions are concerned it is useful to think of these compounds as a negative alkyl group and a positive counterion. The alkyl group is a powerful nucleophile. Reactions with C=O containing compounds lead to formation of alcohols:



Now for a few specialised reactions:
Cycloaddition reactions of alkenes: The Diels-Alder reaction.



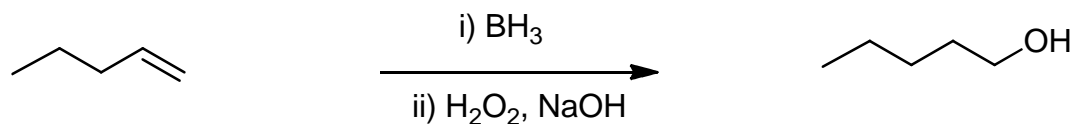
Reaction is concerted i.e. all bonds are formed and broken at the same time:



Stereochemistry: Bonds are formed on one face of the alkene, hence there is a high degree of stereocontrol.

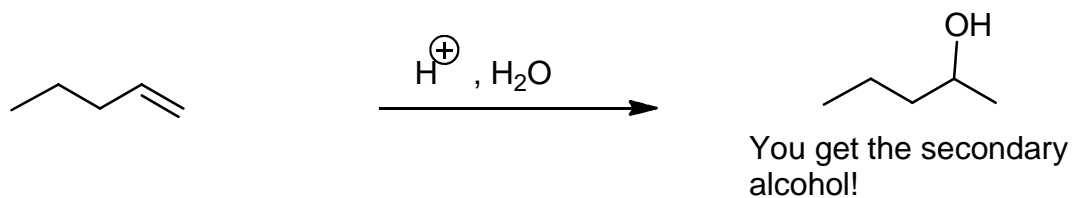
Alkene hydroboration reaction (important)!

Overall reaction (reagents to be added):



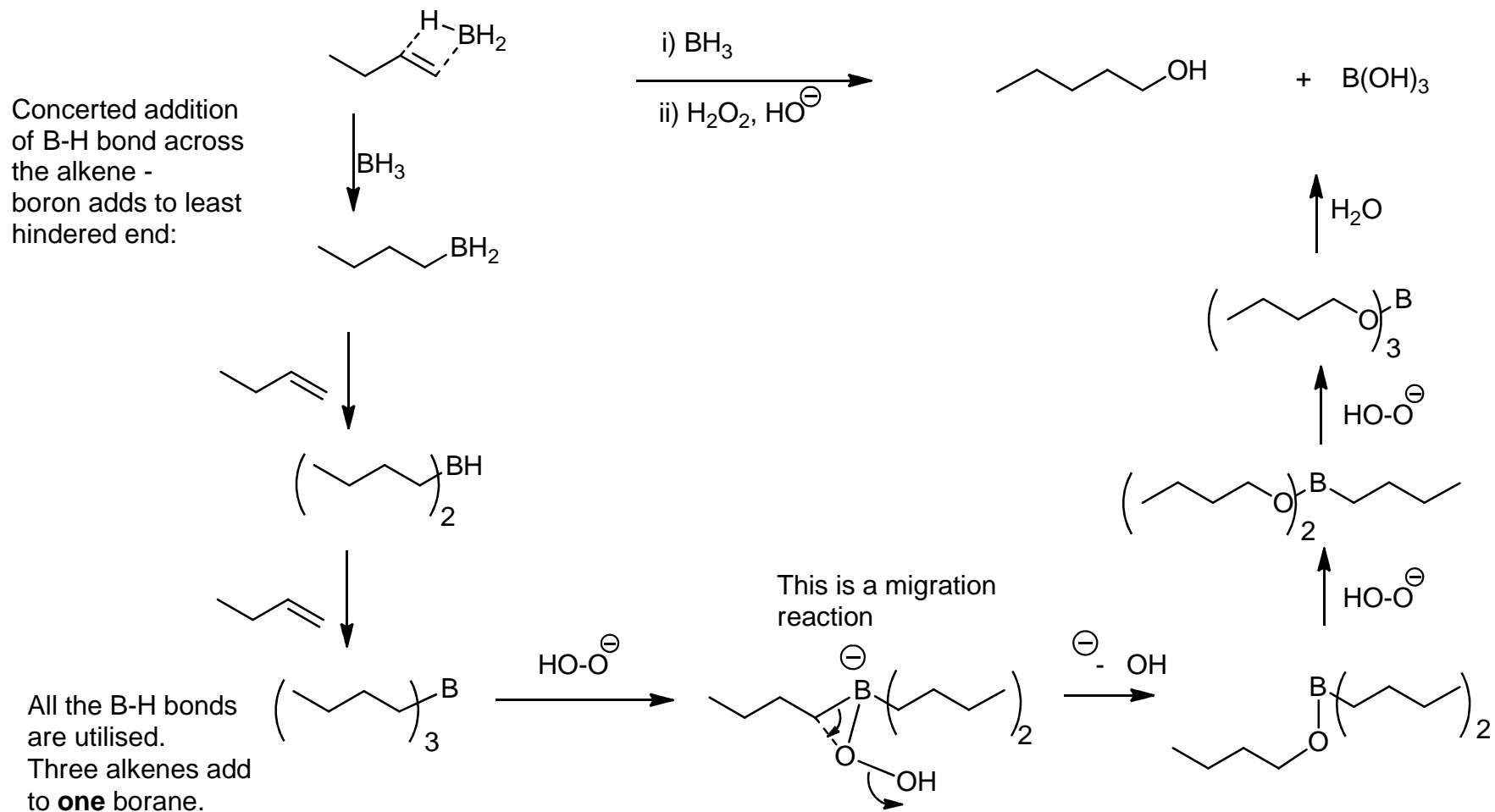
WHY IS IT IMPORTANT? See below...

What happens if you carry out acid-catalysed hydration (addition of water)?



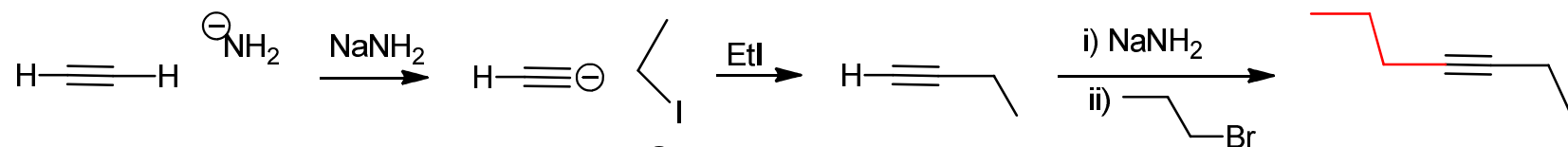
But if you WANT the primary alcohol you need to use hydroboration...

Hydroboration mechanism – don't be intimidated, it isn't that bad:



Reduction reactions of alkenes: and alkynes, stereochemistry – formation of cis alkenes by hydrogenation.

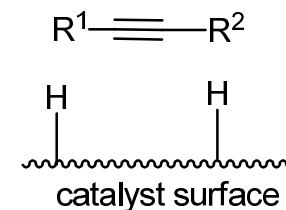
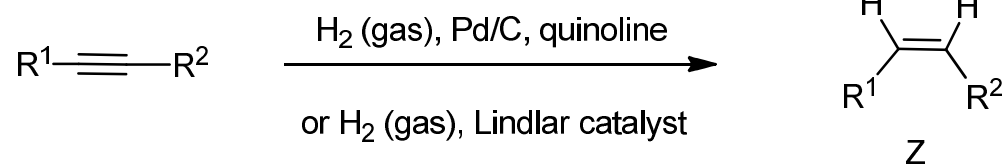
First you need to make a substituted alkyne:



Why do you need to use NH_2^- ? Can you use EtO^- or Et_3N^- ?

These would not be powerful enough as bases.

This is the key reduction reaction:

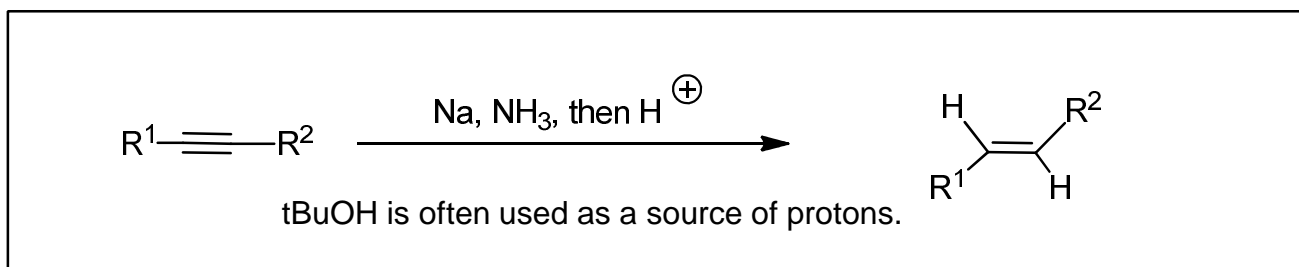


Why is the quinoline added to the catalyst? What happens if you do not add it?

You get reduction right down to the alkane.

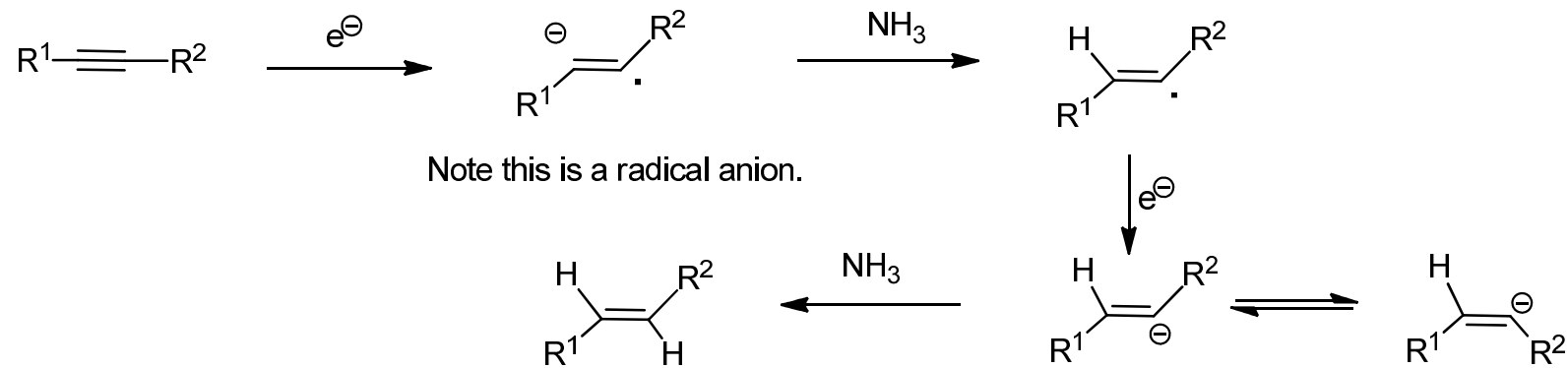
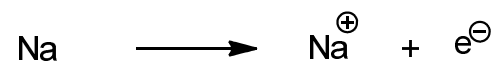
The reduction takes place on a surface, and the hydrogen is transferred to one side of the alkyne, hence the Z (sometimes called cis) product.

trans Alkenes can also be formed from alkynes:



This is commonly known as ‘reducing metal’ reduction. It works by a mechanism in which ‘electrons’ are generated from the metal. Li, K and Mg are also sometimes used.

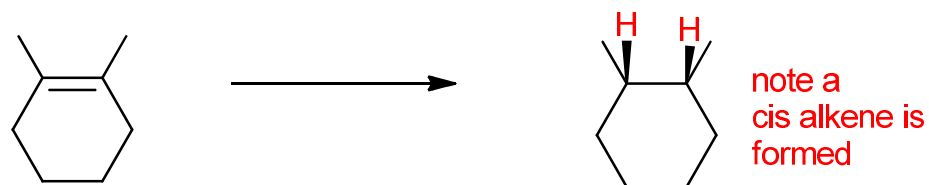
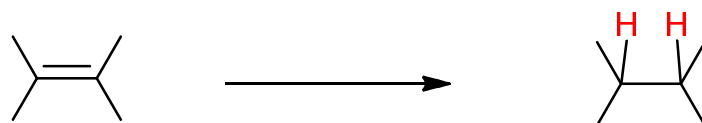
Here is the mechanism:



Reduction of alkenes to alkanes – hydrogenation most commonly used:

Commonly used
Metals: Pd, Rh, Ru, Ir,

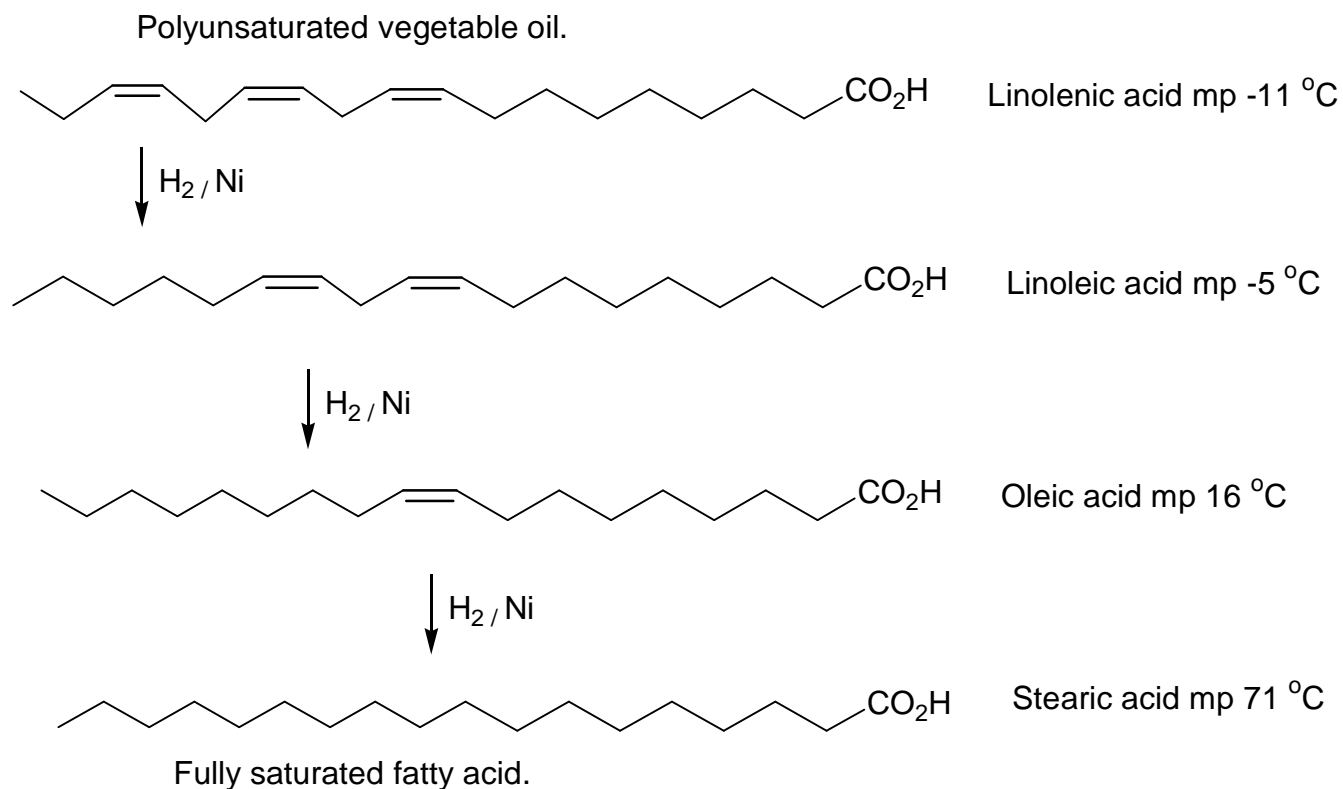
Commonly used
Supports: Carbon (graphite), silica



Stereochemistry is important

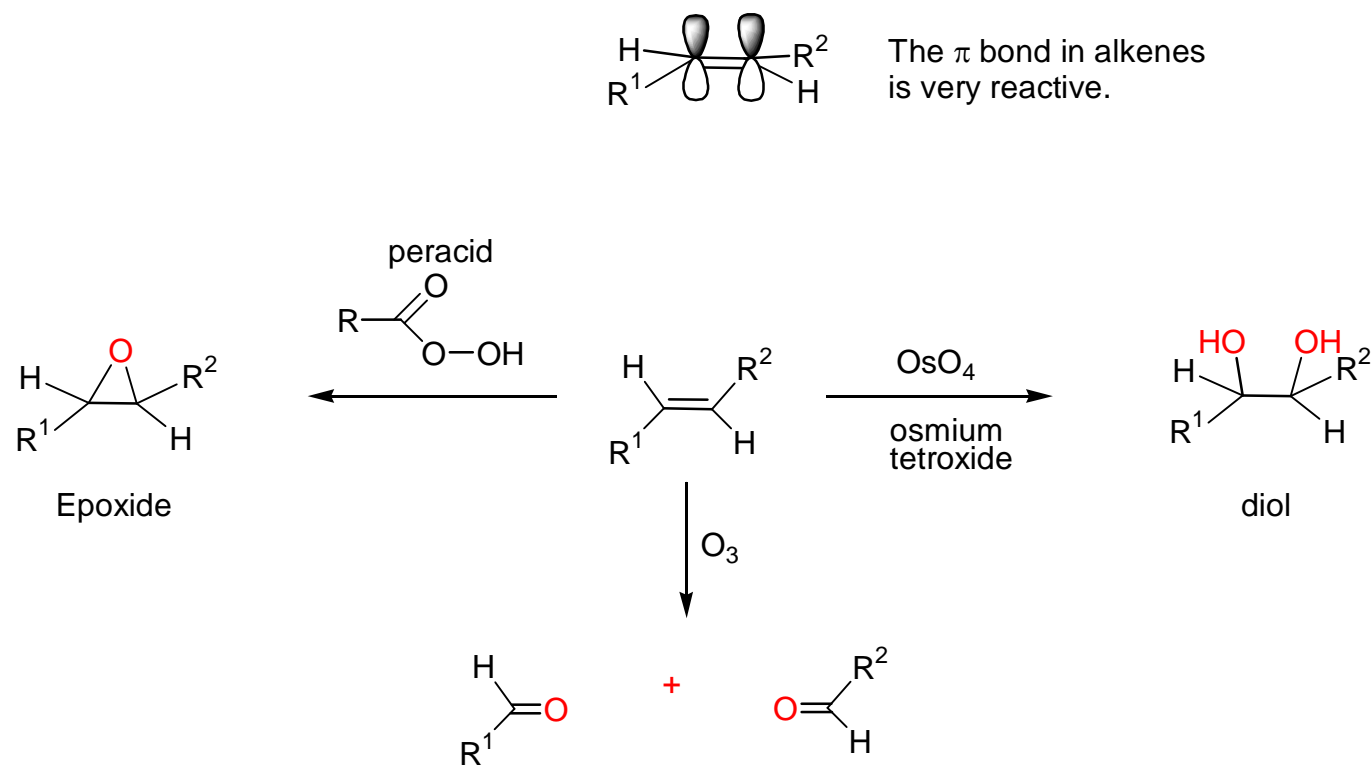
Hydrogenation of alkenes to make margarine:

Polyunsaturated fats are regarded as healthier than saturated ones but tend to be liquids so they are partially hydrogenated to make margarine – solid but still with double bonds in..



Alkene oxidation reactions:

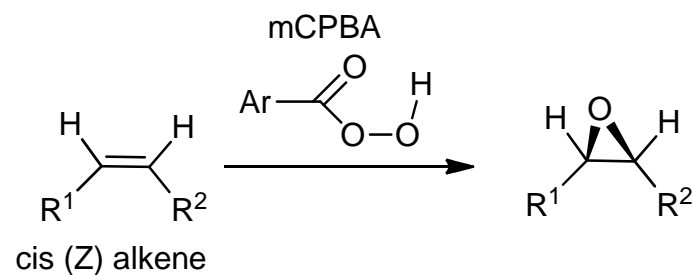
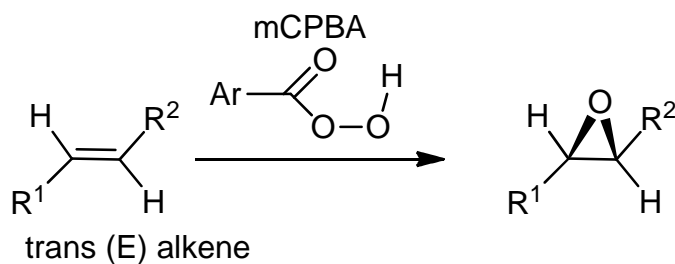
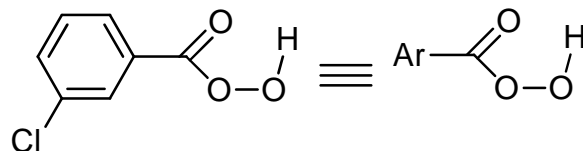
Alkene oxidation reactions can give epoxides, diols, or even ketones from complete cleavage of the alkene.



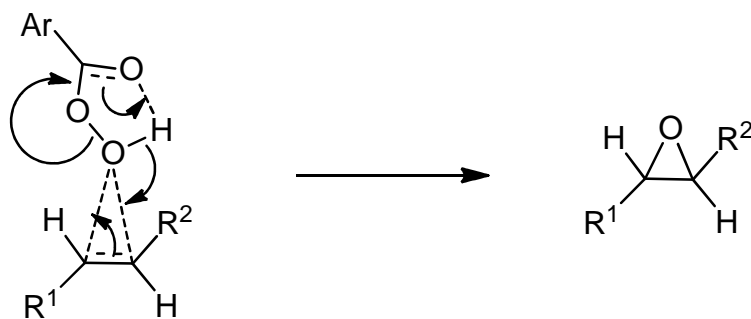
What is the structure of ozone? **Look it up** Why might these products be useful?

Epoxidation of alkenes using peracids:

This is mCPBA,
(*meta*-chloroperbenzoic acid)
which is a commonly used peracid

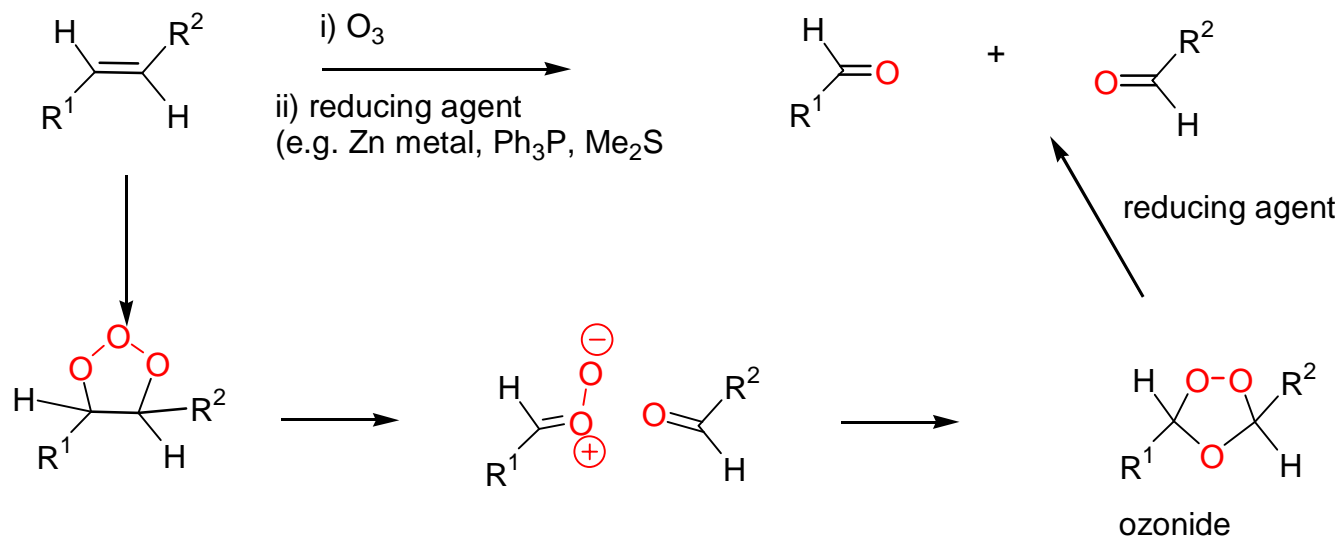


Learn the mechanism:

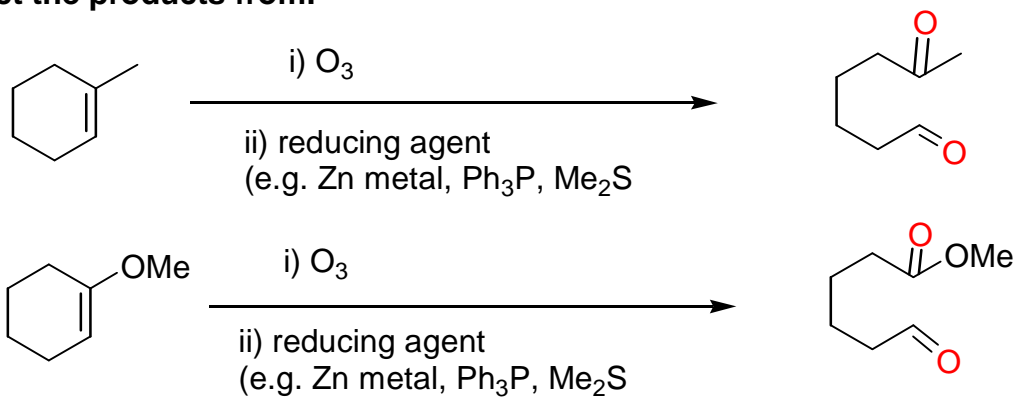


This is one of the best mechanisms!

Ozonolysis of alkenes cleaves the double bond:

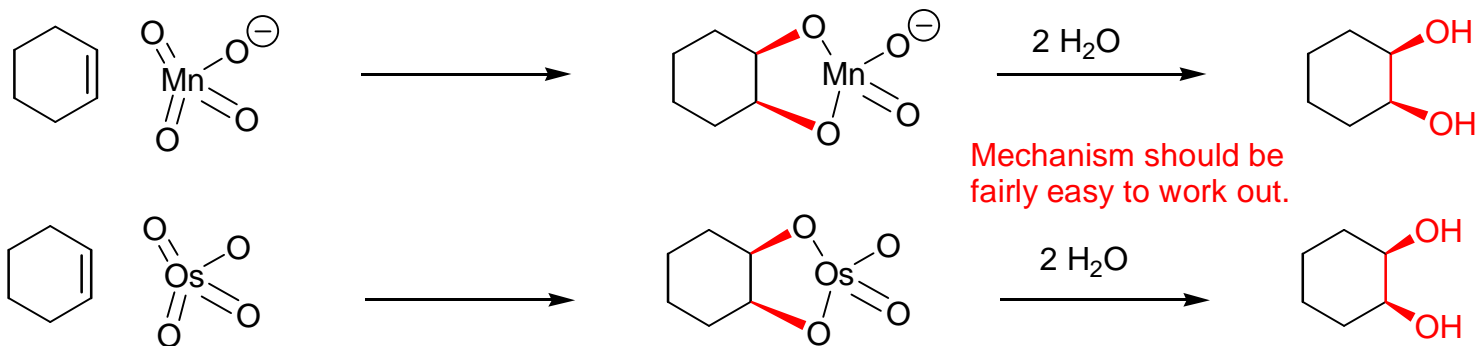


Predict the products from:



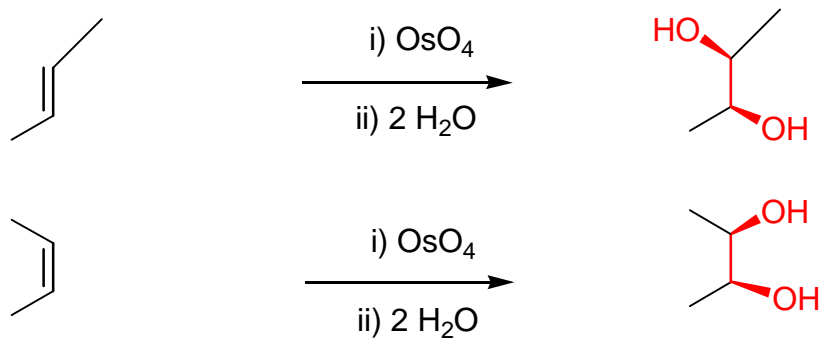
Alkene dihydroxylation:

Potassium permanganate (KMnO_4)



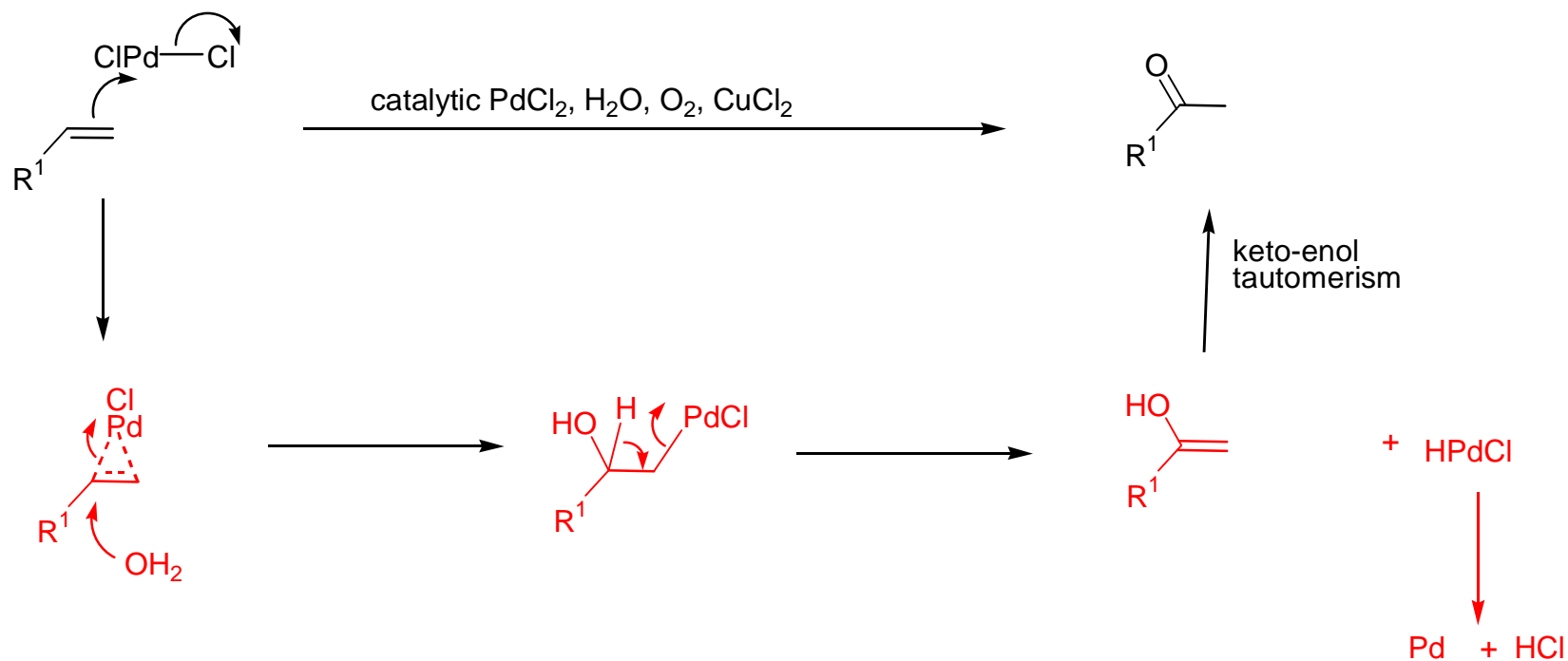
Mechanism should be fairly easy to work out.

What products are formed using the following alkenes and OsO_4 ?



Note – OsO_4 is expensive and very toxic. Better to use it catalytically (how would you do this?).

The Wacker Oxidation:

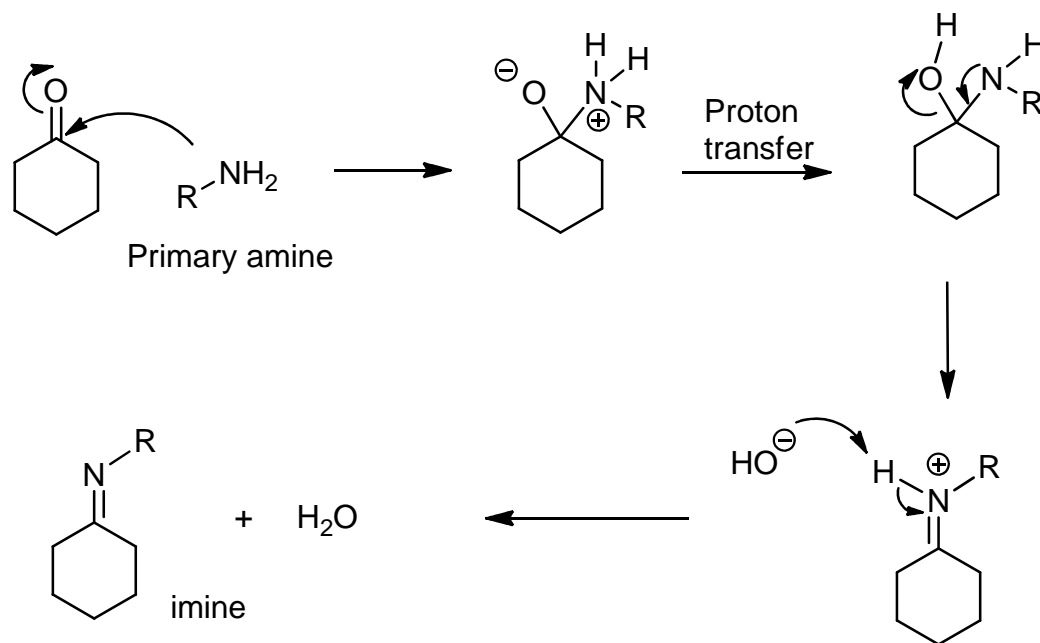


This is a commercial reaction used on a large scale in industry.
The CuCl_2 and O_2 reoxidise the PdCl_2 (Pd is expensive).

Some special reactions you need to know the mechanisms of:

- i) Forming an imine from reaction of a ketone/aldehyde and a primary amine.

(it is actually difficult for me to overstate how important this is!)



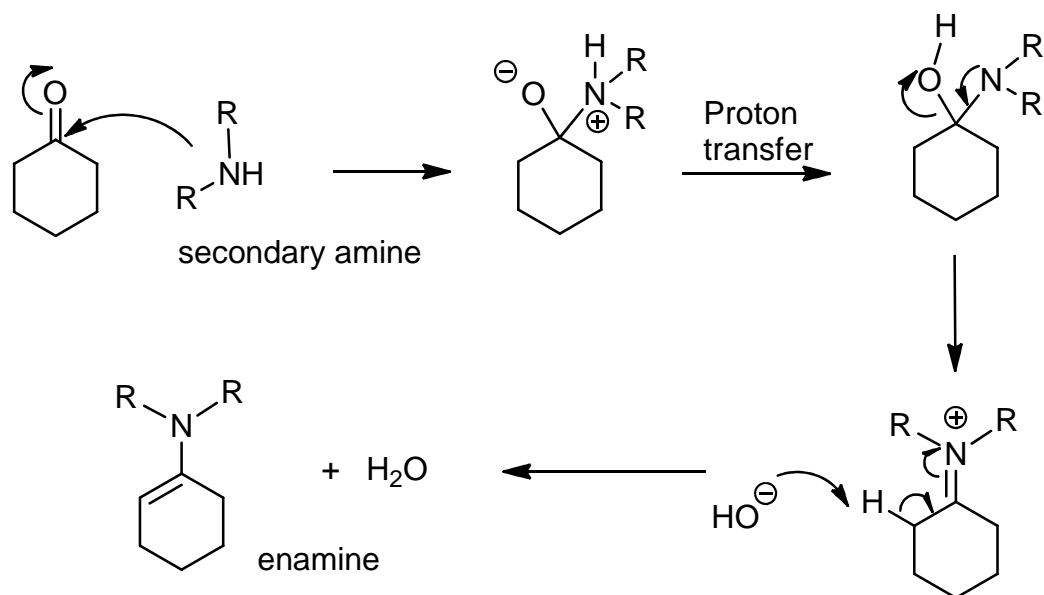
This is not a complex mechanism. Note it is a condensation.

The reaction can be catalysed by acid, in which case the first step is protonation of the ketone.

The non-catalysed version is illustrated.

Some special reactions you need to know the mechanisms of.
ii) Forming an enamine from reaction of a ketone/aldehyde and an secondary amine.

Basically the same reaction as before, but with a secondary amine – in the last step, a proton is removed from C.



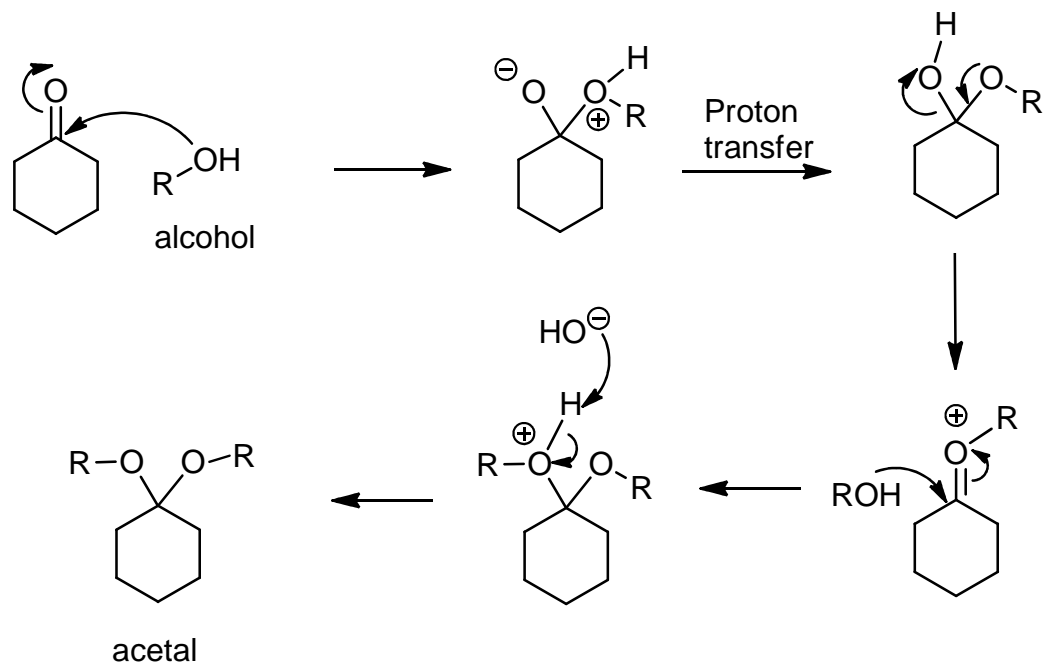
Again it is a condensation, and can be catalysed by acid, in which case the first step is protonation of the ketone.

The non-catalysed version is illustrated.

Some special reactions you need to know the mechanisms of.

iii) Forming an acetal from a ketone/aldehyde and two alcohols.

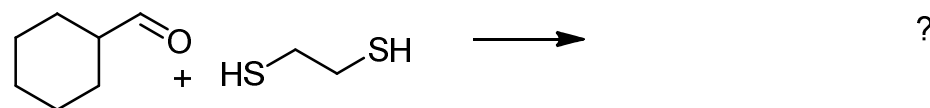
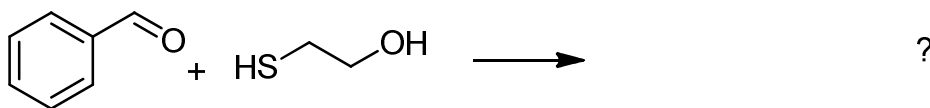
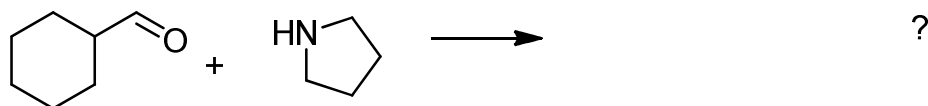
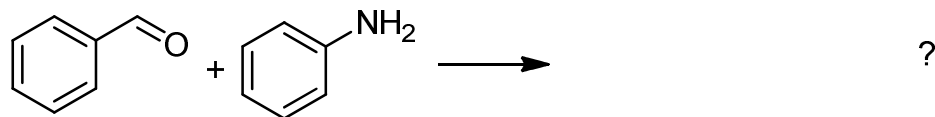
This is again a really important reaction:



Again it is a condensation, and can be catalysed by acid, in which case the first step is protonation of the ketone.

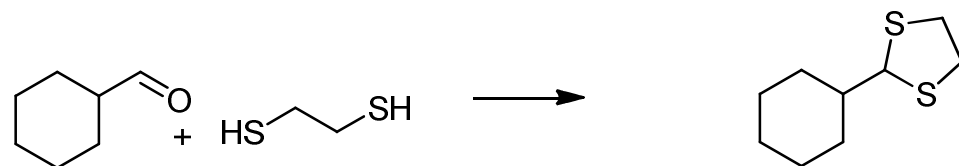
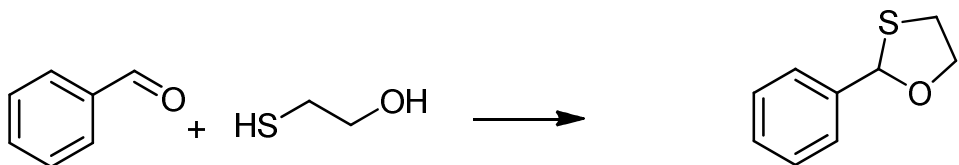
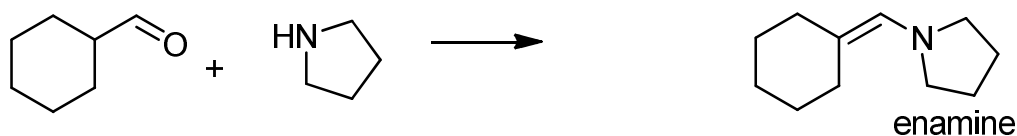
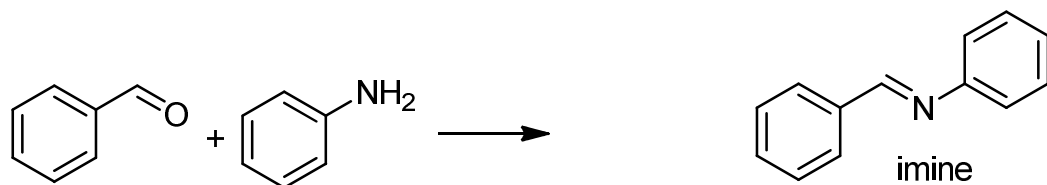
The non-catalysed version is illustrated.

Some special reactions you need to know the mechanisms of.
Now try writing down the products of the following reactions:



The results are on the next slide, but you will get a much better learning experience if you have a try first before looking.

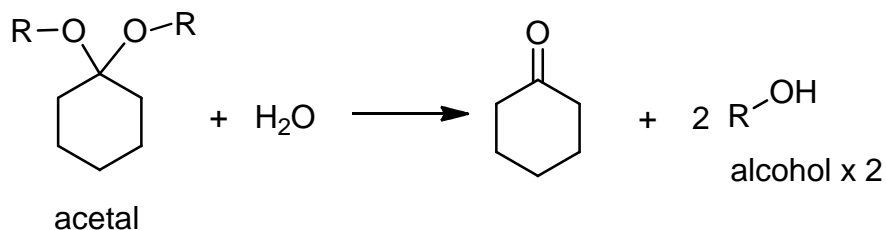
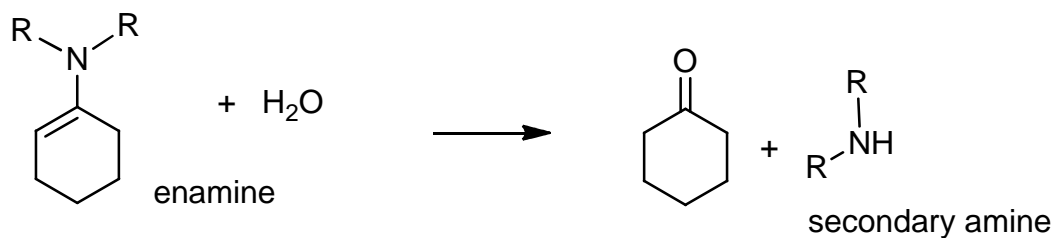
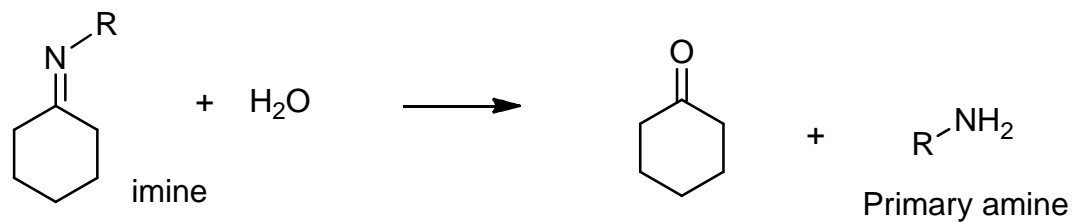
Some special reactions you need to know the mechanisms of.
Here are the answers:



Don't be confused by replacement of O by S, or by both nucleophilic groups being in the same molecule – the mechanism is just the same.

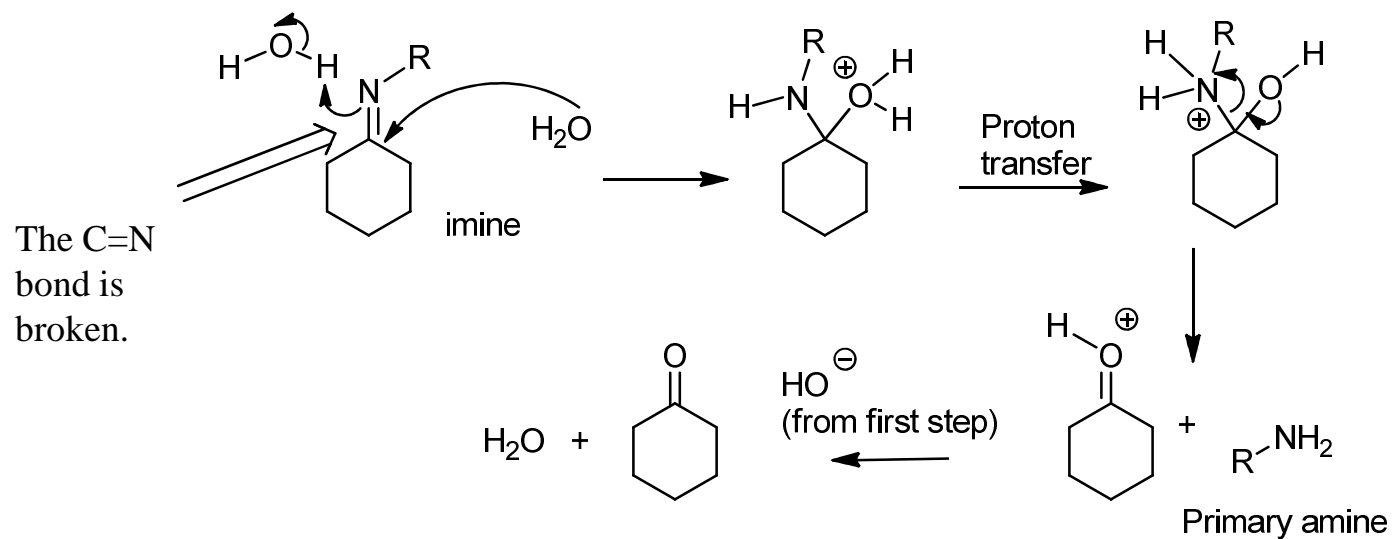
If you didn't get them right then it is probably because you didn't *understand* the mechanisms. Revise the mechanisms and try again.

The reactions are also reversible:



Have a go at writing the mechanisms (I would expect you to be able to do them).
The answers are on the next few slides, but again you are going to get minimal benefit if you just look at them without attempting the questions. So have a go...

Imine hydrolysis:

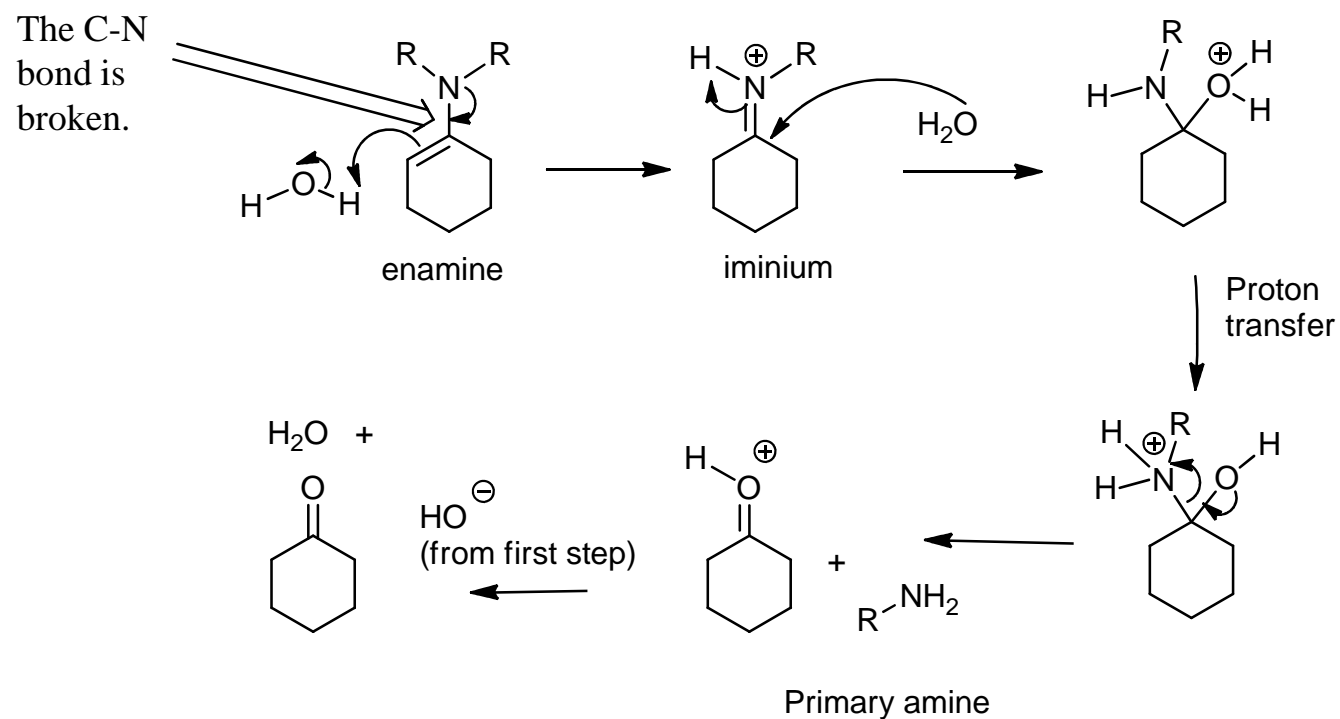


This is not a complex mechanism. Note it is a hydrolysis!

The reaction can be catalysed by acid, in which case the first step is protonation of the imine.

The non-catalysed version is illustrated.

Hydrolysis of an enamine

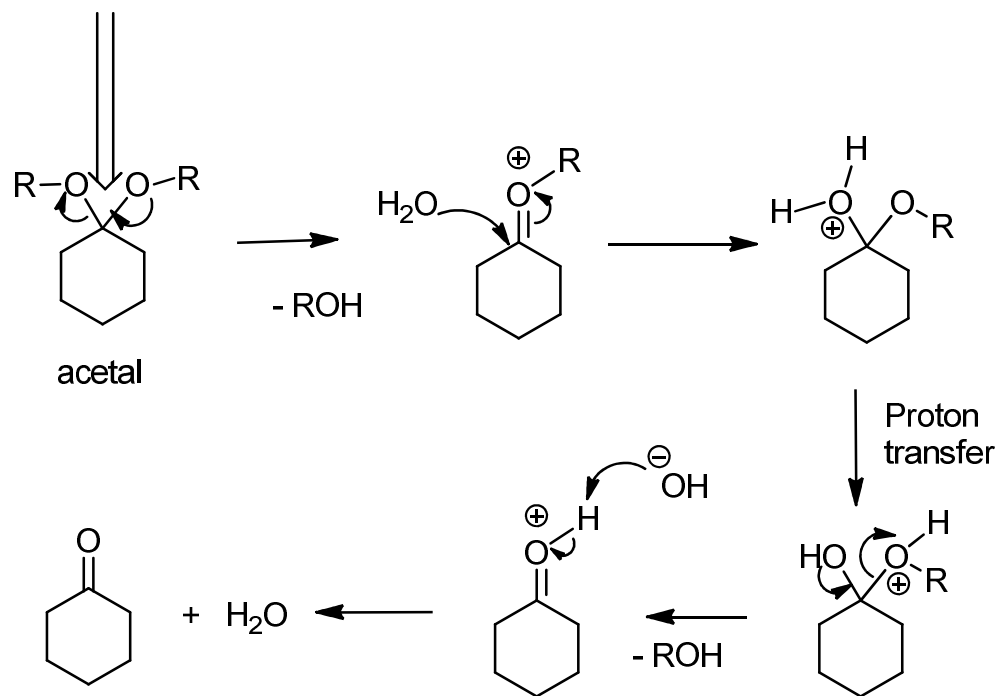


Again it is a hydrolysis, and can be catalysed by acid, in which case the first step is protonation of the enamine, pretty much as shown above.

The non-catalysed version is illustrated.

Hydrolysis of an acetal:

The C-O bonds are broken.



Again it is a hydrolysis, and can be catalysed by acid, in which case the first step is protonation of one of the oxygens on the acetal.

The non-catalysed version is illustrated.