# *Organic Synthesis Part 2 - Functional Group Interconversions*

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***7 lectures***

***Recommended texts:***

"March's Advanced Organic Chemistry", M.B. Smith and J March, Wiley, 5th edn (£50, but a good investment!)
"Oxidation and Reduction in Organic Synthesis", T.J. Donohoe, OUP primer
"Some Modern Methods of Organic Synthesis", W Carruthers, Cambridge
"Modern Synthetic Methods", H O House, WA Benjamin (a bit old!)

***Aims of course:*** To build on the lectures by Donald Craig and introduce students to the 'tactical' aspects of functional group interconversions. To provide students with the synthetic armoury which, in combination with the first part of the course, will allow the design and execution of simple organic syntheses which are chemo, regio-, stereo- and (where required) enantioselective.

***Course objectives:*** At the end of this course you should be able to:

- Select an appropriate reagent for a given transformation covered within the course, in the context of molecules which you may not have met in the course (ie apply your knowledge)
- Be able to explain, at the level of your colleagues, the mechanistic rationale underpinning any issues of selectivity in the reaction (chemo, regio-, stereo- and enantioselectivity);
- Be ready to apply this knowledge with that from Donald Craig's course to tackle problems in small molecule total synthesis.

***Course content:***

1. Introduction to FGI's. Introduction to classes of reducing agent. Reduction of C=X bonds.
2. Reduction of $CO_2R$ and related functions.
3. Reduction of C-C multiple bonds.
4. Reduction of C-X bonds.
5. Oxidation of C-H bonds bearing no heteroatom.
6. Oxidation of CH-OH groups.
7. Oxidation of olefins.

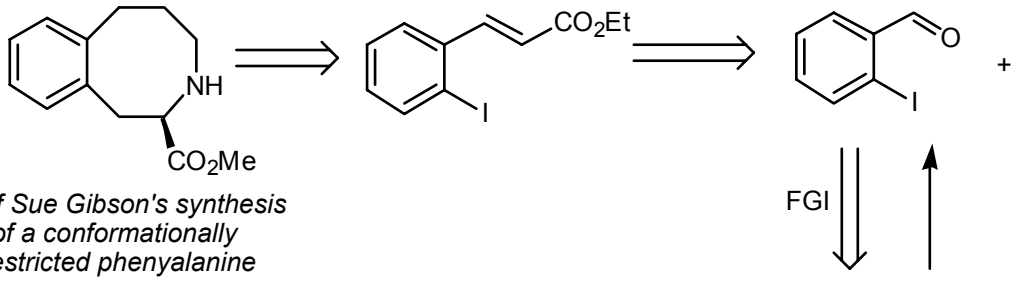
# *Functional Group Interconversions - Lecture 1*

***Background and general principles***

1. *What is a functional group interconversion?*
   It was defined by Stuart Warren as *"the process of converting one functional group into another by **substitution**, **addition**, **elimination**, **oxidation** or **reduction**, and the reverse process used in (retrosynthetic) analysis."*

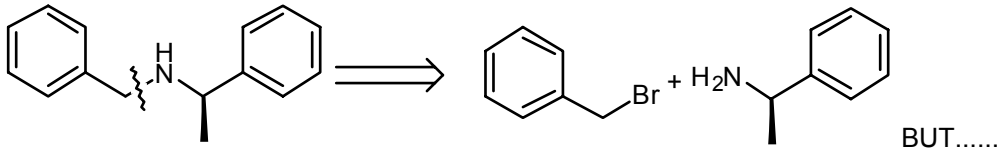
We can easily think of examples of each of these categories. So thats what FGI's are; the next question is why might we want to bother? There are four common reasons for carrying out FGI's (and including them in retrosynthetic analysis):

*1. unavailability of starting materials*



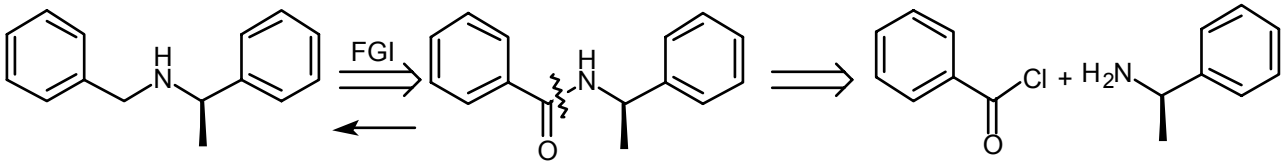

*Prof Sue Gibson's synthesis of a conformationally restricted phenyalanine*

*2. adjustment of functionality at the end of a known reaction*

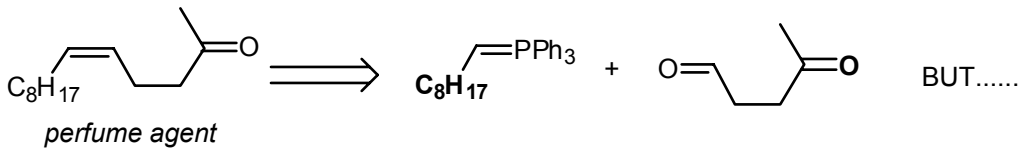



*commonly used chiral amine*

better route involves TWO steps:

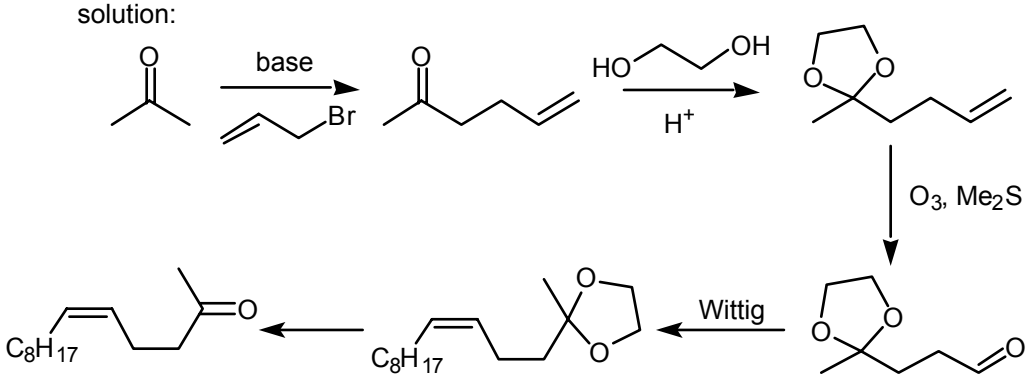


*3. to mask reactive functionality in a molecule*

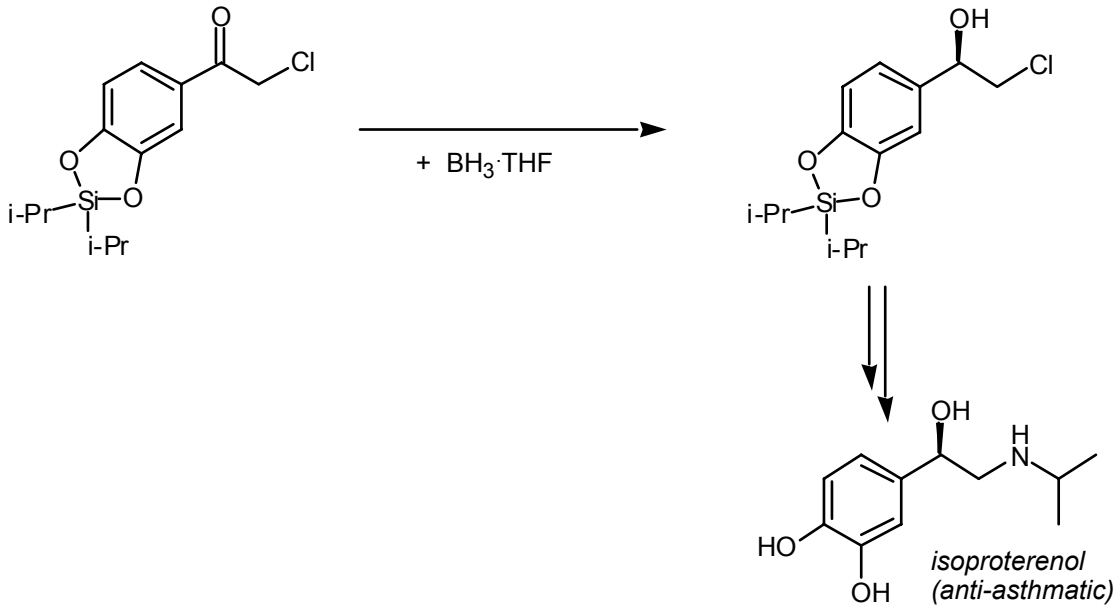



*perfume agent*

solution:




*4. (**VERY** important!) to introduce asymmetry into molecules*




So that's what FGI's are and why we do them. In this course we'll be concentrating on oxidation and reduction (although some of the oxidations of olefins could equally well be regarded as additions), since the addition, elimination and substitution chemistry is pretty well taken care of from first year. We'll start our tour of FGI's by looking at reduction processes. Here are the main classes of reducing agents:

*Main classes of reducing agents*

### *1. Catalytic hydrogenation*

Hydrogen is **CHEAP**!!! But not a good reducing agent on its own - apart from combustion, $H_2$ alone is pretty unreactive. We need a catalyst to weaken or break the H-H bond to make it reactive. The catalysts we use fall into two categories, heterogeneous and homogeneous. The former are usually transition metals or their salts, often supported on an inert carrier. The latter are often soluble transition metal complexes. The advantage of the former method is in the ease of separation of the insoluble catalyst, the advantage of the latter that we can tune the ligands and the metal to achieve selective reductions (chemo- and enantioselectivity).

### *2. Hydride transfer reagents*

Essentially transfer "$H^-$" as a nucleophile, although be aware that $H^-$ is **NOT** a nucleophilic species and NaH, LiH, KH *etc* are **NOT** good reducing agents (they are used as bases). There are two subclasses of hydride transfer reagents: ones which act as nucleophiles directly, and those which are electrophilic and require activation by a Lewis base before they donate hydride.

*i) 'nucleophilic' hydride reagents*

*a) lithium aluminium hydrides -*

the parent compound is $LiAlH_4$ (lithium aluminium hydride, LAH or 'lithal'). It is a **VERY** moisture sensitive grey compound which reacts violently with water and other protic solvents. It is therefore used in **DRY**, aprotic solvents. Ethereal solvents such as $Et_2O$, THF and DME are best, giving usable suspensions of the reagent.

LAH is a **VERY** reactive reducing agent and reduces most functional groups relatively indiscriminately.

Reaction with carbonyl compounds is by donation of hydride, to give a transient alkoxide/alane pair which combines to give an alkoxytrihydroaluminate. This can go on to donate the remaining three hydrides in the same way, although at a reduced rate. We can exploit this by deliberately making trialkoxyaluminiumhydrides, which are mild and selective reducing agents.

*b) sodium borohydrides -*

the parent compound is $NaBH_4$ (sodium borohydride) which is available as a white powder. It is only moderately reactive towards protic solvents ($H_2O$>MeOH>EtOH) and is usually used in ethanolic solution. It is less reactive than LAH, for example it reacts only slowly with esters, making it possible to reduce ketones or aldehydes in their presence.

The mechanism involves the solvent, which helps to activate the carbonyl to attack by H-bonding. Unlike LAH, substitution of the hydrides by -OR **INCREASES** the rate of addition. However, substituting the hydrides by electron withdrawing groups such as acetate or cyanide gives rise to more selective reducing agents.

Next time: other reducing agents and C=X reductions. AA 25.10.02

## *2. Hydride transfer reagents (cont.)*

*1. 'electrophilic' hydride reagents*

*c) diisobutylaluminium hydride*

Available as solutions from Aldrich. The tricoordinate aluminium is, of course, a strong Lewis acid. It won't give up $H^-$ to become an $Bu_2Al^+$ cation; rather it waits until it is complexed by a Lewis base (*eg* a carbonyl group!) then donates its hydride. The fact that only one hydride per molecule of DIBAL-H is delivered, coupled with its electrophilic character makes it a useful reagent - often it can perform selective reductions not available with $LiAlH_4$, *eg* selective reduction of esters to aldehydes (see later).

*b) boranes*

The parent compound is diborane ($B_2H_6$), but it is commonly used as a solution in THF (where the active species is a $BH_3{\cdot}$THF complex) or as its complex with dimethyl sulfide ($BH_3{\cdot}Me_2S$). Since boron is in the same period as aluminium, there are similarities in the mode of action to DIBAL-H (though not in terms of absolute reactivity). Note also the speed of reaction with carboxylic acids, since they rapidly form triacyloxyboranes. Reaction with alkenes and alkynes (hydroboration) is of course facile - we'll discuss this later. Note also that we can replace up to two of the hydrides by alkyl groups (mono and dialkylboranes) which still perform the same reactions, but being bulkier can often offer greater selectivity compared to '$BH_3$'.

## *3. Dissolving metal reductions*

Usually metals such as Li, Na, K, Ca, Mg, Zn, Sn, Fe (often as amalgams - to improve reactivity).
Reactions are often carried out in liquid ammonia, and can be viewed as being caused by 'solvated electrons'. The intermediates are often radical anions, and a range of useful transformations of C=O, C=C and other multiple bonds and C-X bonds can be accomplished.

### *Section 1: C=X reductions*

- *Reductions of aldehydes and ketones to alcohols*
  Suitable reagents include the following:
  $LiAlH_4$, $NaBH_4$, $LiAl(O^tBu)_3H$, ($NaBH_3CN$ in acid)
  DIBAL-H, $BH_3$ (slow, except if catalysed....)
  Na/ROH, $H_2$ and Raney Ni or Ru catalysts, Meerwein-Ponndorf-Verley reduction

*Stereochemistry in the reduction of ketones to alcohols*

As we've already seen, addition of hydride to unsymmetrical ketones gives rise to an asymmetric centre. Reaction of achiral reagents with ketones containing no existing asymmetric centres gives rise to a racemic mixture. This can be altered by the use of chiral reagents (or catalysts) - see later. If the ketone already contains some asymmetric centres, the reaction with even achiral reagents gives rise to diastereomeric products. We can predict the stereochemical outcome using certain models. Basically all of them revolve around

making sure the hydride approaches from the less hindered 'diastereotopic' face of the ketone.

For acyclic ketones, there are three models of most use:
Of historical interest is *Cram's rule* (Professor D J Cram, UCLA, Nobel Prize, 1987) - this helps us to predict facial attack on ketones bearing all carbon substituents on the adjacent asymmetric centre.
*Felkin-Anh model* - most widely accepted model nowadays as it agrees with theoretical studies on the transition state for addition to carbonyl groups. It also allows us to predict facial attack on $\alpha$-alkoxy ketones when a non-chelating reducing agent is used.
*Cram's chelate rule* - helps us to predict facial attack on $\alpha$-alkoxy ketones when chelating metal salts are used as or with reducing agents.
Note that Felkin-Anh and Cram chelate modes of attack on $\alpha$-alkoxy ketones give opposite diastereomers from the same starting compound - can use to our advantage!

For cyclic ketones, again the less hindered face is generally attacked, but this is not always clear cut and depends on both substrate and reagent! Use of dissolving metal reductions usually gives the product with the alcohol in the thermodynamically favoured position.

*Asymmetric reduction*
Can make use of chiral reagents or, better, chiral catalysts. The chiral oxazaborolidine catalysts perfected by Professor E J Corey (Harvard University, Nobel Prize 1990 - you'll hear more of him!) are a beautiful example of design in synthesis.

- *Reduction of imines to amines*

Imines are less electrophilic than ketones, so although $LiAlH_4$ and $H_2$/Pd will reduce them, $NaBH_4$ won't. If you protonate them, they can be reduced by $NaBH_3CN$ - used in reductive amination.

- *Reduction of ketones to alkanes*
  You should have met all of these last year: Clemmenson reaction, the wonderfully named "Huang-Minlon modification of the Wolff-Kischner reaction" and thioketalisation followed by treatment with Raney Ni.

Next time: carboxyl reductions AA 30.10.02

## *Functional Group Interconversions - Lecture 3*

### *Section 2: Carboxyl and related function reductions*

2.1 *Reductions of carboxylic acids*
$RCO_2H$ to $RCH_2OH$, accomplished with $LiAlH_4$, DIBAL-H (rarely) and borane. Note the selectivity of the latter reagent in reducing acids over eg esters.

2.2 *Reduction of esters*
$RCO_2R'$ to $RCH_2OH$ and R'OH, accomplished with $LiAlH_4$ or excess DIBAL-H at ambient temperatures.
Note that the breakdown of the intermediate alumino hemiacetal is slow in the case of DIBAL-H, permitting the selective reduction of $RCO_2R'$ to RCHO and R'OH by use of one equivalent of DIBAL-H at low temperatures.
Lactones give diols under the former conditions and lactols (hydroxy aldehydes) under the latter.

2.3 *Reduction of amides*
RCONR'R" to $RCH_2NR'R"$ by $LiAlH_4$, DIBAL-H or borane. Note the differing electronic character of nitrogen to oxygen is responsible for direct carbonyl reduction as opposed to cleavage/reduction (as seen with esters).

2.4 *Reduction of nitriles*
R-CN to $RCH_2NH_2$, achieved by $LiAlH_4$, excess DIBAL-H or catalytic hydrogenation.
Note that with DIBAL-H (one equivalent), selective reduction to the imine stage can be achieved, although this is usually followed by hydrolysis on work up so the ultimate product is an aldehyde - still useful!

### *Section 3: Reduction of C-C multiple bonds*

3.1 *Hydrogenation*

3.1.1 *Alkynes*
Alkynes can be reduced to alkanes if so desired ($H_2$ and Pt, Pd or Raney Ni catalysts), but this isn't so useful. Much more useful is the fact that we can stereoselectively synthesise either (*E*) or (*Z*)-olefins from alkynes, by either dissolving metal reduction or catalytic hydrogenation over partially poisoned catalysts respectively.

3.1.2 *Isolated olefins*
We'll look at the reduction of enones *etc* later. Reduction of olefins to alkanes is a common synthetic procedure. One can use Pt, Pd, Rh, or Raney Ni catalysts as heterogeneous catalysts, or use homogeneous catalysts such as $(Ph_3P)_3RhCl$ (Wilkinson's catalyst, after the Nobel winning chemist of this department).
Useful facets of hydrogenation include: cis-stereoselectivity in addition of $H_2$; attack of $H_2$ from least hindered face of cyclic olefins, and application in asymmetric synthesis (BIG, BIG industrial process!)

Next lecture: Further C-C reduction; C-X bond reduction AA, 1/11/2002

## *Section 3: Reduction of C-C multiple bonds cont.*

3.2 *Hydroboration*

You've met this in first year. It's (surprise!) the addition of boron and hydrogen across a C-C double or triple bond, and takes place *via* a concerted four-membered transition state. This is a VERY, VERY useful reaction - Nobel Prize for Herbert C Brown (Purdue University) in 1979.

The utility springs from three observations about the reaction: it is **stereospecific** (*cis*-addition); **regioselective** (addition of B to least hindered end of the unsaturation); and the C-B bond is **synthetically useful** (can be used to make C-H, C-C, C-O and C-N bonds with retention of stereochemistry).

*3.2.1 Hydroboration of alkenes*

You met the mechanism last year, but remember that boron attacks the least hindered end of the bond, and that less hindered olefins react quicker. We can use this to make di and monoorganoboranes, which can be used as more selective borane equivalents (and see also aspects of asymmetric induction!).

C-B to C-H bond cleavage is achieved by heating with carboxylic acids; C-C bond formation can be done by a variety of methods (not vital you know these now); C-O bond formation is achieved by basic peroxide (anti-Markownikoff hydration of an olefin overall!) and C-N bond formation by treatment with hydroxylamine O-hydrogen sulfate.

Preparation of chiral mono and di-organoboranes from naturally occurring chiral olefins allows asymmetric hydroboration of olefins - *eg* in the synthesis of chiral alcohols.

*3.2.2 Hydroboration of alkynes*

The formation of vinyl boranes can be useful: transformations of alkynes into olefins, aldehydes/ketones and substituted olefins can be achieved.

3.3 Reduction of aromatic systems

We can reduce aromatic systems to cyclohexanes under very forcing hydrogenolytic conditions, though this isn't a generally useful process. More interesting is the partial reduction of arenes to skipped 1,4-cyclohexadienes by dissolving metal reduction - the Birch reduction. You should have met this in first year.

Recalling that the intermediates are radical anions, we can see why the Birch reduction is so useful - it is regioselective for the 1,4-diene produced when substituted benzenes are used. Thus, electron withdrawing groups end up deconjugated from the olefins (since they stabilise the anionic intermediates) while electron donating groups end up on the olefins - they avoid being adjacent to negative charge.

*3.4 Reduction of $\alpha,\beta$-unsaturated carbonyl compounds*

There are three possible outcomes to this: total reduction to the saturated alcohol ($LiAlH_4$ and heat!); partial reduction to the unsaturated ketone (catalytic hydrogenation or dissolving metal reduction - the latter gives the opportunity for regiospecific enolate chemistry!); and partial reduction to the allylic alcohol (of which more later) - best carried out using the Luche conditions of sodium borohydride and cerium trichloride.

## *Section 4: Reductive cleavage of C-X bonds*

4.1 *Hydride displacements*

$LiAlH_4$, $NaCNBH_3$ and $LiEt_3BH$ (Super hydride!) can all displace halides, tosylates and mesylates from primary and secondary alkyl positions. Since the reactions are $S_N2$ in nature, this is a useful way of making stereospecifically deuterated compounds through the corresponding deutero reducing agents. This is of much use in biosynthetic studies.

Epoxides are a special class of C-X species: there are two possible sites of attack and we can tailor our reaction conditions to gain access to either. Thus, nucleophilic conditions give rise to attack at the least hindered carbon, while the use of a Lewis acid promotes attack at the best cation stabilising centre (usually more substituted) on account of the polarised transition state. Again inversion of stereochemistry is seen.

4.2 *Dissolving metal reductions*

Not greatly synthetically useful, unless you want to make organometallics! Note that if the heteroatom is next door to an anion stabilising group (eg an ester) this is a facile process and can be done with eg zinc metal - the Reformatsky reaction.

4.3 *Radical reactions*

Don't need to worry about these at the moment but they are very useful, and not just for C-X reductions. Much of the work was pioneered by the Nobel laureate Sir Derek Barton, who spent most of his career at Imperial College.

4.4 *Hydrogenolysis*

Cleavage of benzylic ethers and amines by hydrogenolysis gives rise to useful protecting groups for synthesis.

Next lecture: Oxidation of unactivated C-H bonds; oxidation of alcohols.

AA, 6/11/2002

## *Functional Group Interconversions - Lecture 5*

### *Section 5: Oxidation of C-H bonds bearing no heteroatom*

5.1 *Oxidation of benzylic positions*

Alkyl arenes can be oxidised by several reagents (eg $CrO_3/H_2SO_4$, alkaline $KMnO_4$) to benzoic acids (NB regardless of the length of alkyl chain!). Useful only really for manipulation of simple starting materials (*eg* from petrochemicals) or for structural identification.

*5.2 Oxidation of allylic positions*

Many reagents will do this (*eg* $CrO_3$), but most are very strong oxidising agents and so selective oxidation of the allylic position is tricky. Two reagents which will carry this out are selenium dioxide, and singlet oxygen.

5.2.1 *Selenium dioxide*

Oxidises allylic positions with retention of the original double bond position. The mechanism involves ene reaction followed by a [2,3]-sigmatropic rearrangement - the Se(IV) is reduced to Se(II) (which actually disproportionates to Se and $SeO_2$). $SeO_2$ is expensive and very toxic, so a more convenient and economic way to do these reactions is with catalytic $SeO_2$ and a stoichiometric amount of a co-oxidant to reoxidise the Se(II) to $SeO_2$.

The reactions are quite regioselective with non-symmetrical olefins, and the following empirical rules apply:

i) hydroxylation occurs adjacent to the most substituted end of the olefin
ii) the order of reactivity is $CH_2$>$CH_3$>CH (but rule i takes precedence)
iii) 1,1-dimethyl olefins give (*E*)-allylic alcohols
iv) when the olefin is part of a ring, rule i still applies *BUT* the oxidation takes place within the ring if possible
v) note that oxidation of terminal methylenes (*ie* 1,1-disubstituted alkenes) proceeds *via* a different mechanism to give primary alcohols with double bond migration.

5.2.2 *Singlet oxygen*

Singlet oxygen is VERY reactive! It can be generated by photolysing oxygen in the presence of a photosensitiser (usually a dye such as Rose Bengal). Singlet oxygen is nicely complementary to $SeO_2$ in its allylic oxidations in that it forms allyl alcohols with migration of the double bond instead of retention. The mechanism involves an ene reaction, which generates an allyl hydroperoxide; this can be isolated if desired but is more commonly treated with a mild reducing agent to generate the allyl alcohol.

Next lecture: Oxidation of C next to O (alcohols); Oxidation of C=X and C=C bonds

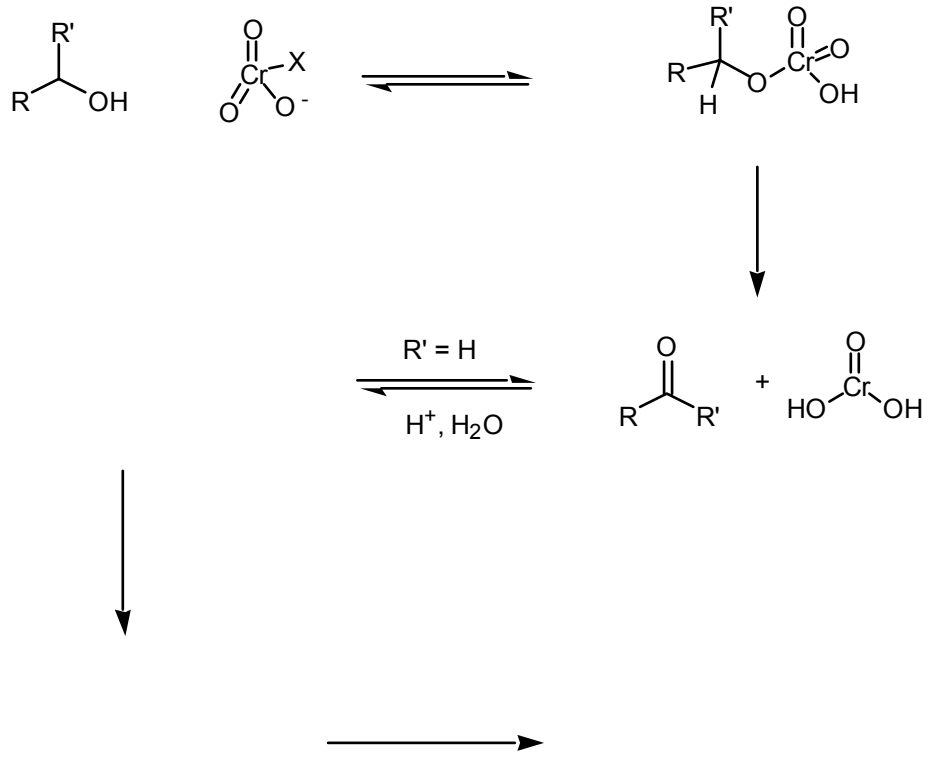
AA, 8/11/2002

## Section 6 *Oxidation of H-adjacent to oxygen*

Here we are talking about the oxidation of secondary alcohols to ketones, and of primary alcohols to either aldehydes or carboxylic acids (preferably selectively!)

### *6.1 Chromium (VI) reagents*

One of the oldest and commonest methods for alcohol oxidation - many reagent combinations have been created. The mechanism generally involves the rapid, reversible formation of a chromate ester, which then breaks down in a slow, rate determining step, to generate the ketone and a Cr(IV) species (which then decomposes further to Cr(III), but you don't need to worry about this).



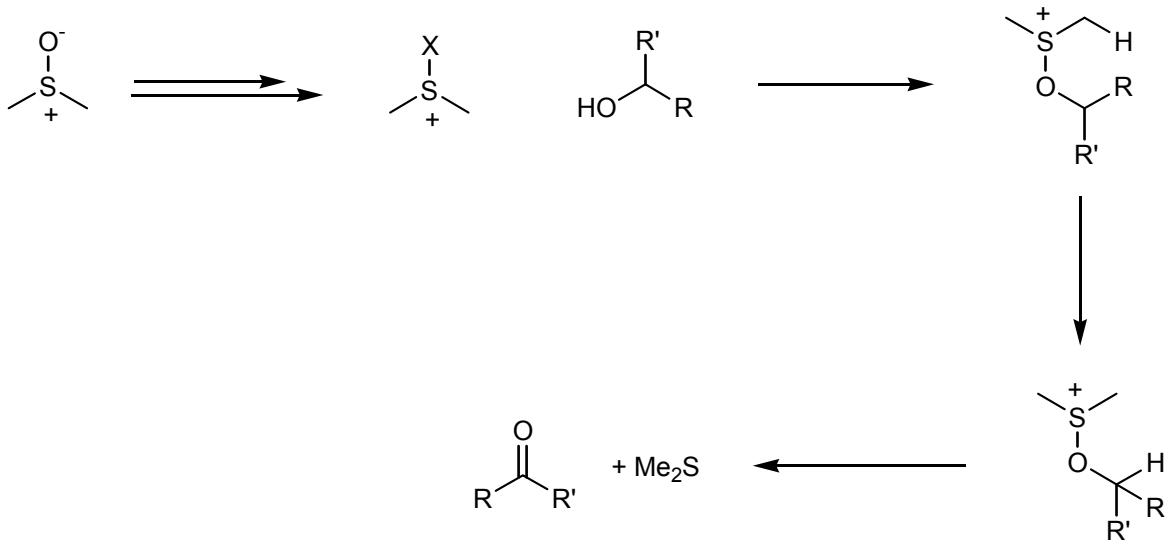

Note that if the reactions are carried out in the presence of water, primary alcohols are almost always oxidised to the acid by way of an intermediate hemiacetal, which then reacts as before. Note also that since the second step of the mechanism is rate determining, then more hindered alcohols oxidise quicker, because of the relief of steric strain on elimination of the chromium species.

Specific reagents include:

a) $CrO_3$ in sulfuric acid - very harsh! Oxidises 2ry alcohols to ketones & 1ry alcohols to acids.
b) $CrO_3/H_2SO_4$/acetone (Jones' oxidation) - a milder version of above, since the reaction is effectively carried out as a titration (red endpoint of excess Cr(VI)). Still oxidises 2ry alcohols to ketones & 1ry alcohols to acids.
c) $CrO_3$-pyridine complex (Collins' reagent) - prepared by adding $CrO_3$ to pyridine. Since it is partially soluble in organic solvents, one can work in a non-aqueous environment and thus oxidise 2ry alcohols to ketones & 1ry alcohols to aldehydes. One drawback is the large excess of reagent generally used.
d) Pyridinium chlorochromate (PCC) another invention of EJ Corey) - made by adding pyridine to an HCl solution of $CrO_3$, and you can buy it. Dissolves in $CH_2Cl_2$, so you can use it in roughly equimolar quantities, and since we're under anhydrous conditions it will selectively oxidise 1ry alcohols to aldehydes (and 2ry to ketones)
e) Pyridinium dichromate (PDC) - made from conc. aqueous $CrO_3$ and pyridine. It's similar to PCC, except it is virtually neutral so can be used on more sensitive substrates.

*6.2 Activated DMSO reagents*

Here DMSO (dimethyl sulfoxide) is the overall oxidant, being reduced itself to dimethyl sulfide - nice! The reactions basically involve activation of the oxygen of the DMSO to form a sulfonium cation, which is then nucleophilically attacked by the hydroxyl oxygen, to form a new sulfonium ether. Treatment with an amine base such as $Et_3N$ first removes the most acidic proton to generate an ylide, which rearranges to give the carbonyl compound and DMS.




The reactions are generally mild. 1ry alcohols are oxidised only as far as the aldehyde, and 2ry alcohols to ketones.

*6.3 Catalytic methods*

The cost and environmental concerns associated with stoichiometric transition metal oxidations has led to much work on the development of methods catalysed by a metal complex and using a cheap, benign co-oxidant. One such system is tetrapropylammonium perruthenate (TPAP), developed by Professor Bill Griffith of this department, and Professor Steve Ley (once of this department, now at Cambridge). The co-oxidant of choice in this case is N-methylmorpholine-N-oxide (NMO for short!).

*6.4 Selective oxidants*

Its worth noting that $MnO_2$ is a wonderfully selective reagent for the oxidation of allylic and benzylic alcohols - even in the presence of other alcohols! This can save you lots and lots of steps in a synthesis.

## *Section 7: Oxidation of C=X bonds*

7.1 *Addition to olefins - Epoxidation*

Epoxides are VERY useful in synthesis - the strain of the three membered ring makes these cyclic ethers very reactive. They react stereospecifically with nucleophiles (ring opening occurs with inversion of configuration in an $S_N2$ manner), and usually we see excellent regiocontrol for attack at the least hindered end as well. Thus there's a lot of interest in methods for their preparation.

7.1.1 *Epoxidation of unfunctionalised olefins*

One way to form epoxides is by halohydrin formation followed by treatment with base - you'll meet this in more detail later in the course. As you found in first year, epoxides can also be prepared directly from alkenes by reactions with peracids. The reactions are concerted and so are stereospecific - the epoxide is formed with retention of olefin geometry. Since the peracid is a source of electrophilic oxygen, the reaction works best with electron poor peracids (*eg meta*-chloroperbenzoic acid, mCPBA) and electron rich olefins.

The reactions are also stereoselective and will attack the less hindered faces of olefins.

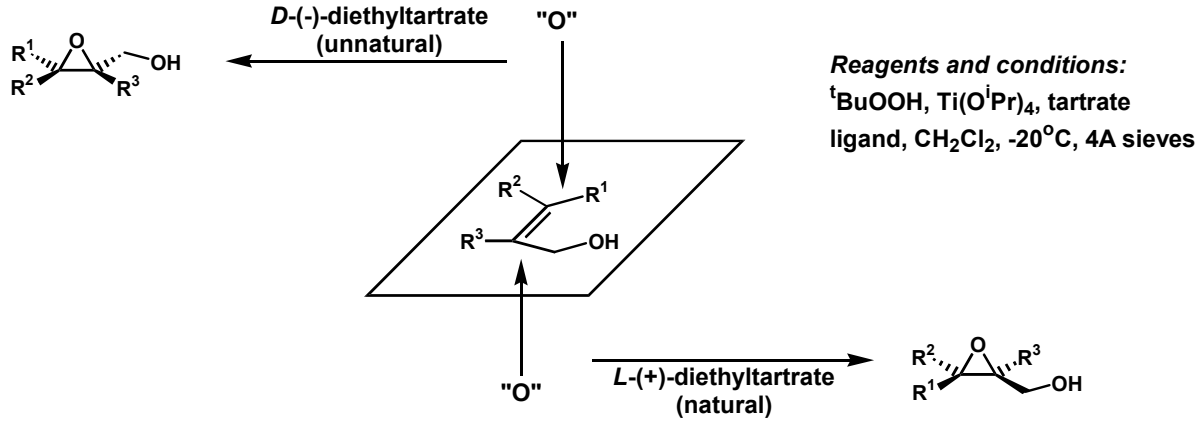
7.1.2 *Epoxidation of allylic alcohols*

Hydroxyl groups can be used to direct epoxidation to that olefin. In the case of mCPBA, this can lead to stereoselective directed epoxidation (eg to the same face of a cyclic allylic alcohol). Certain transition metal salts can also bind to the oxygen and a peroxide species, delivering the oxidant solely to the adjacent olefin even in the presence of others! Not surprisingly, the addition of a metal bearing chiral ligands allows an asymmetric variant of this reaction: the ***Sharpless asymmetric epoxidation (AE) reaction***. Professor K Barry Sharpless (Scripps Research Institute, La Jolla) was awarded the 2001 Nobel Prize for this and his equally useful AD reaction (see later!) The reagents for the reaction are $^{t}BuOOH$, $Ti(O^{i}Pr)_4$, (+) or (-)-diethyl tartrate and 4Å molecular sieves (essential for catalytic activity). Because the metal is bound directly to the hydroxyl group, very good levels of asymmetric induction are observed. The reaction is also extremely predictable - all examples to date fit the mnemonic shown on the scheme below..

This was really the first general, reliable and practical asymmetric reaction, and is done on industrial scale (hundreds of gallons). Nowadays there are also reagents which can

epoxidise unfunctionalised olefins but they are neither as general or reliable as the Sharpless AE.

## *Katsuki-Sharpless asymmetric epoxidation of allylic alcohols*




7.1.3 *Epoxidation of $\alpha,\beta$-unsaturated olefins*

These electron deficient alkenes don't react so well with electrophilic oxidants such as mCPBA, but they'll react nicely in a Michael fashion with peroxy anions. Intramolecular nucleophilic displacement furnishes the epoxide. Note that since we go through an enolate intermediate, the initial olefin geometry does not have to be preserved in the product.

Next time: Formation of 1,2-diols; oxidative cleavage of alkenes AA, 13/11/2002

7.2 *Formation of 1,2-diols*

Ring opening of epoxides with acidic water gives rise to 'trans'-diols overall in two steps from alkenes.

Perhaps more important are the reagents which will cis-dihydroxylate olefins directly in one step - alkaline permanganate and osmium tetroxide.

Both react via a similar mechanism, which is effectively a concerted cycloaddition to the olefin to generate a metal ester, which is then hydrolysed. We'll concentrate more on the osmium tetroxide, since this is the milder and more widely used agent.

Osmium tetroxide is a very toxic solid with a high vapour pressure, which makes it dangerous to handle. Its also very pricey, so its no surprise that people have sought co-oxidants capable of reoxidising the Os(VI) back to Os(VIII). NMO is often the co-oxidant of choice.

As discussed above, the reactions are stereospecific for cis-dihydroxylation of the olefin. They are also stereoselective - attack again occurs on the least hindered face of cyclic olefins.

An asymmetric catalytic version of this reaction would be of great value. Guess who developed it? That man again - Sharpless. Actually the key discovery that enabled Sharpless to develop his system was made by Professor Griffith here at IC - that quinuclidines could accelerate the addition of $OsO_4$ to alkenes. Thus, add a chiral quinuclidine and you should get fast, asymmetric dihydroxylations. Aldrich now sells AD-mixes which contain the osmium, chiral ligand, co-oxidant and buffer for a reaction - just add water! OK, and tert-butanol and alkene.

7.3 *Oxidative cleavage of olefins - indirect methods*

Cleavage of olefins is a useful reaction - we can use it to eg mask a carbonyl group through some reactions where they would normally react, or to manipulate an olefin created through another reaction such as a Diels-Alder reaction.

One method of cleaving olefins is via the 1,2-diols (discussed above) using periodate (either as periodic acid $HIO_4$ or sodium periodate $NaIO_4$) or lead tetraacetate. These reactions stop at the aldehyde stage if either end of the bond is monosubstituted.

7.4 *Oxidative cleavage of olefins - direct methods*

There are many reagents which will cleave olefins, but most aren't selective only for olefin cleavage. Ozonolysis is one of the best methods for olefin bond cleavage. Its useful for both its experimental simplicity and the fact that one can manipulate the intermediates (ozonides) to give a range of products from a single precursor. Thus, treatment of secondary ozonides with sodium borohydride (care!) gives alcohols, mild reduction (with eg Zn or $PPh_3$) gives aldehydes/ketones and oxidative work-up with hydrogen peroxide gives carboxylic acids.

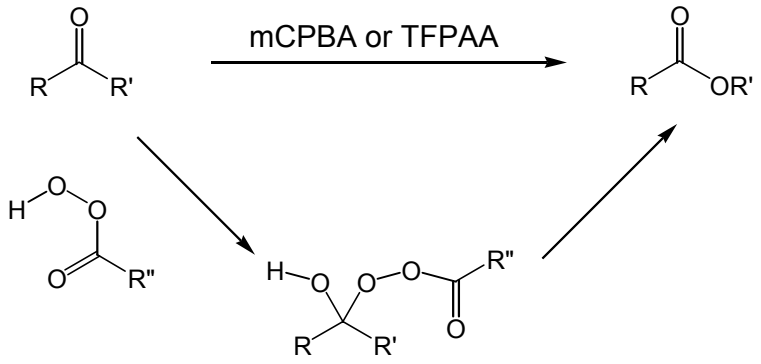
Ozone is prepared by passing an electrical discharge through a stream of oxygen, generating mixtures of 2-10% $O_3$ in $O_2$. Reactions are carried out in solvents such as $CH_2Cl_2$, AcOH or MeOH, often at $0^oC$ or below. Care is required as the ozonides are explosive! The reactions are often self-indicating, as the blue colour of ozone persists once the alkene is consumed.

The mechanism involves [3+2] cycloaddition of the ozone to the olefin to give the primary ozonide; retro-[3+2] cycloaddition breaking a weak O-O bond to give a carbonyl and a carbonyl ylide (which can be trapped!); and finally [3+2]-cycloaddition in the reverse sense to generate the secondary ozonide. Note that ozone is electrophilic and will attack electron rich bonds preferentially.

7.5 *Oxidative cleavage of ketones*

The Baeyer-Villiger reaction, which you will have met in Dr Braddock's course in first year. The reagent is a peracid (usually mCPBA), and the reaction involves attack of the peracid on the ketone, followed by stereospecific migration of the alkyl group with retention of configuration to generate an ester. In unsymmetrical ketones, the order of migrating aptitude parallels roughly the ability to stabilise positive charge (3ry>2ry-phenyl-benzyl>1ry>>Me). The reaction works best with strained cyclic ketones, since the relief of ring strain helps to drive the reaction.

**Baeyer-Villiger oxidation**




- migratory aptitudes: best positive charge stabilising group migrates ie H > tertiary alkyl > secondary alkyl > phenyl > primary alkyl >> methyl
- works very well for small ring ketones (cyclobutanones) or for bicyclic ketones: in both cases relief of ring strain drives the reaction
- reaction proceeds with retention of configuration at R'

**PROTECTING GROUPS IN ORGANIC SYNTHESIS**

One of the themes running through this course of lectures has been that of selectivity. Useful synthetic reagents and procedures are often characterised by their ability selectively to transform a substrate. The selectivity may concern stereo- and regiochemistry, but may also be a question of which functional groups in the molecule are transformed preferentially: this is known as chemoselectivity. Sometimes it simply isn't possible to devise a reaction which carries out a desired transformation whilst leaving other functional groups in the molecule untouched. This is often the case in multi-stage syntheses of complex, polyfunctional molecules. When this happens, it is necessary to mask, or protect functional groups temporarily, in order that they are not affected by reactions transforming functions in other parts of the molecule. The functional group used to effect this protection is called a protecting group. A good protecting group meets several criteria:

- it is readily introduced into the molecule under mild conditions
- it is stable to the reaction conditions used to effect the desired transformation
8. it is readily removed under mild conditions

1. PROTECTION OF ALCOHOLS

Several protecting groups have been developed: we'll look in detail at the following:

*Tetrahydropyranyl (THP) ethers*: These are introduced by the reaction of the alcohol with dihydropyran in the presence of a catalytic amount of acid. They are removed by the action of methanol/catalytic acid.

*Benzyl (Bn) ethers:* These are formed by the reaction of the alcohol with benzyl chloride, or benzyl bromide in the presence of a base. The attractive feature of these ethers is that they may be removed under neutral conditions by catalytic hydrogenation. They can be removed by dissolving metal reduction also: Li + ammonia is standard.

*Silyl ethers:* Trimethylsilyl (TMS) ethers are too acid-sensitive to be good protecting groups in synthesis, but several more stable derivatives have been developed. The most important ones are t-butyldimethylsilyl (TBDMS) and t-butyldiphenylsilyl (TBDPS) ethers. The latter are more acid-stable. They are introduced by the reaction of the alcohol with the appropriate chlorosilane in the presence of a tertiary amine base. Both these groups may be removed by the action of fluoride anion.

*Esters:* These are generally stable to acidic conditions, and are most commonly used to protect an -OH group from oxidation to the corresponding carbonyl compound. Many different esters are used, but acetates (ethanoates) are by far the most common. Acetates are usually formed by reaction of the alcohol with acetic anhydride in pyridine. Primary alcohols react more quickly than secondary alcohols, enabling selective protection in alcohols containing more than one -OH group. Deprotection is usually effected by treatment of the acetate with sodium methoxide in methanol.

**Protection of diols**

In polyhydroxylated compounds (e.g. sugars) it's often desirable to protect two alcohol functions at the same time. This is possible via cyclic acetals/ketals. These are generally stable to neutral, basic and oxidising conditions. For the protection of 1,2-diols, the isopropylidene ketal ('acetonide') is formed, by treatment of the diol with acetone/acid. For 1,3-diols, the benzylidene acetal is formed in an entirely analogous manner, by substituting acetone with benzaldehyde. Both these protecting groups may be removed by the action of aqueous acid.

2. PROTECTION OF CARBONYL GROUPS

We know already that carbonyl groups (aldehydes and ketones) are susceptible to nucleophilic attack (including reduction) and $\alpha$-deprotonation, and therefore the main requirement of any carbonyl protecting group is to withstand these processes. Aldehydes and ketones are usually protected as their acetals or ketals, by reaction with diols (1,2- or 1,3-) under acid catalysis (see above). These acetals/ketals are stable to most neutral, basic and reducing conditions: they are removed by dilute aqueous acid.