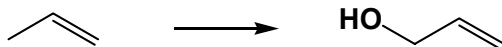
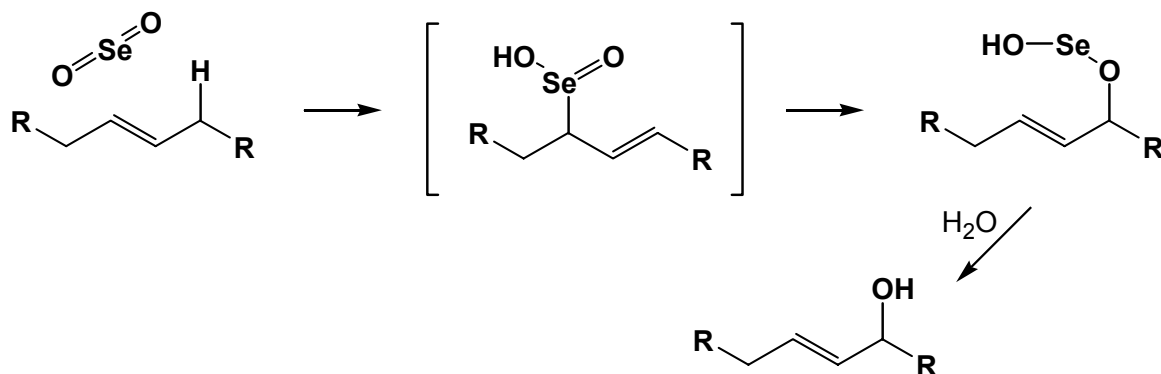


Functional Group Interconversions - Lecture 5**Section 5: Oxidation of C-H bonds bearing no heteroatom****5.1 Oxidation of allylic positions**

Many reagents will do this (eg CrO₃), 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. These reagents are complementary in terms of regiocontrol.....

5.1.1 Selenium dioxide

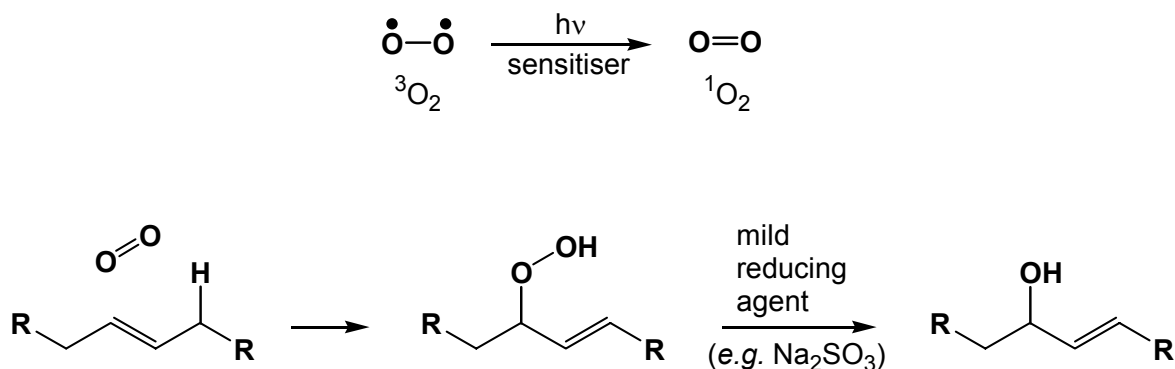
Oxidises allylic positions with retention of the original double bond position. The mechanism involves ene reaction followed by a [2,3]-sigmatropic rearrangement - the Se(IV) is reduced to Se(II). SeO₂ is expensive and very toxic, so a more convenient and economic way to do these reactions is with catalytic SeO₂ and a stoichiometric amount of a co-oxidant (e.g. ^tBuOOH) to reoxidise the Se(II) to SeO₂.



Although we won't go into this, the reactions can be regioselective if non-symmetrical alkenes are used.

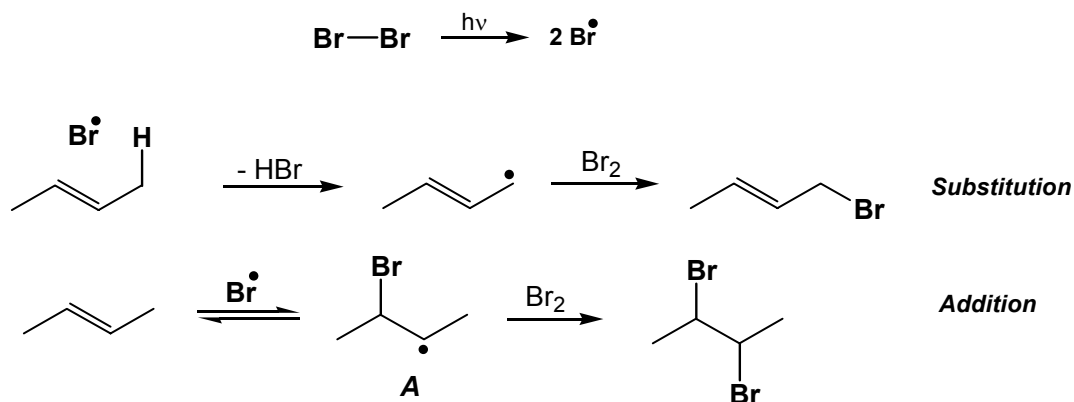
5.1.2 Singlet oxygen

Singlet oxygen (¹O₂) is the first excited electronic state of molecular oxygen, and it 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 SeO₂ in its allylic oxidations in that it forms allylic alcohols with *migration* of the double bond instead of retention of its position. 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 allylic alcohol.

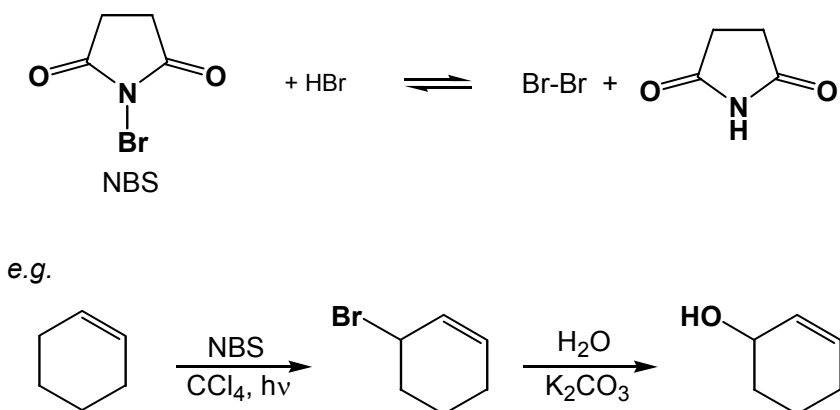


5.2 Allylic bromination

Reaction of an alkene with bromine (in a non-polar solvent to discourage ionic reactions) can lead to competing allylic substitution and addition *via* radical mechanisms:



The trick to achieving selective substitution (*i.e.* allylic bromination) is to know that the addition of Br^\cdot to the alkene is reversible whereas the allylic H-abstraction is effectively irreversible. A high concentration of Br_2 favours the addition product by trapping out the intermediate radical **A**. So to get substitution, we want a low concentration of bromine. This can be done by slow addition, but is much more easily achieved by using a reagent that releases a low concentration of Br_2 (by an ionic mechanism) – N-bromosuccinimide, NBS. Note that hydrolysis can be used to convert the allylic bromide into an allylic alcohol.

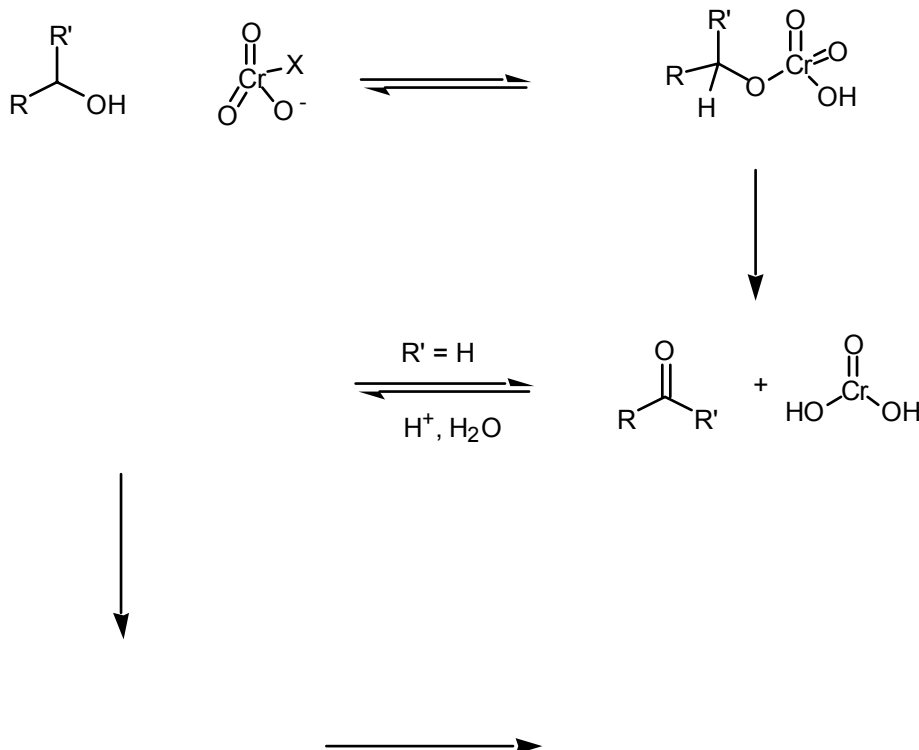


Section 6: Oxidation of H-adjacent to oxygen

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).

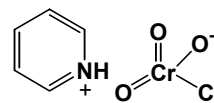


Note that if the reactions are carried out in the presence of water, primary alcohols are almost always oxidised to the acid by way of an intermediate hemiacetal, which then reacts as before. Note also that since the second step of the mechanism is rate determining, then more hindered alcohols oxidise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

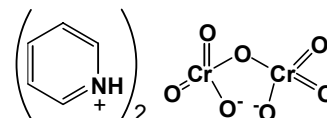
Specific reagents include:

a) $\text{CrO}_3/\text{H}_2\text{SO}_4/\text{acetone}$ (Jones' oxidation) - the reaction is effectively carried out as a titration (red endpoint of excess Cr(VI)). Oxidises secondary alcohols to ketones, and primary alcohols to acids.

b) 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 primary alcohols to aldehydes (and secondary to ketones).

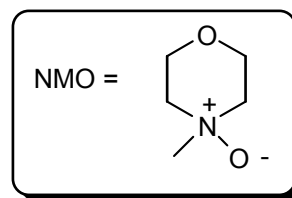
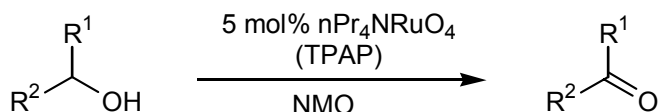


c) Pyridinium dichromate (PDC) - made from conc. aqueous CrO_3 and pyridine. It's similar to PCC, except it is virtually neutral so can be used on more sensitive substrates.



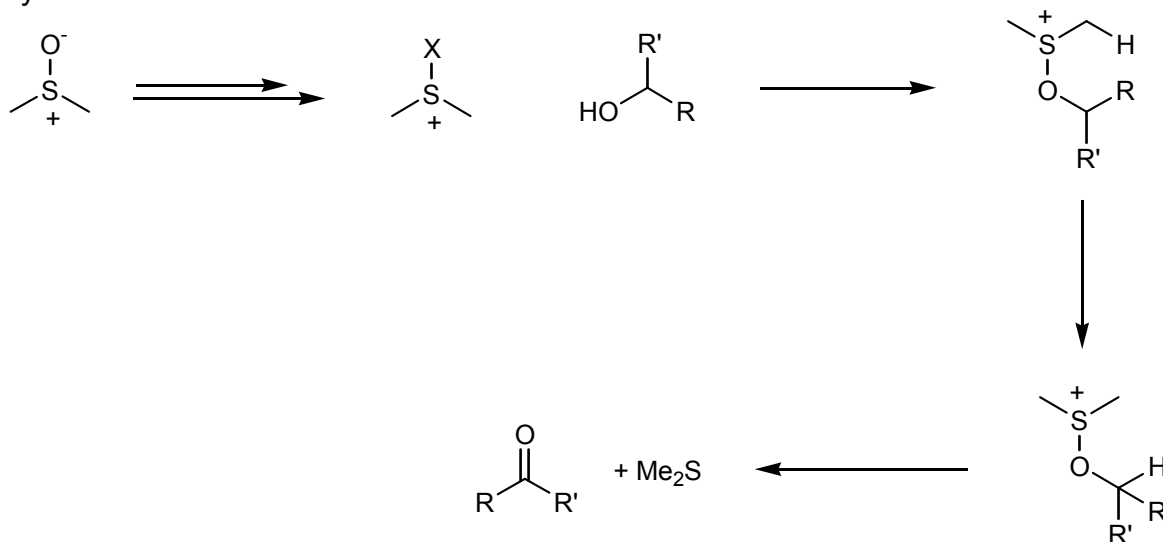
6.2 Catalytic methods

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; $n\text{Pr}_4\text{NRuO}_4$), 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!).



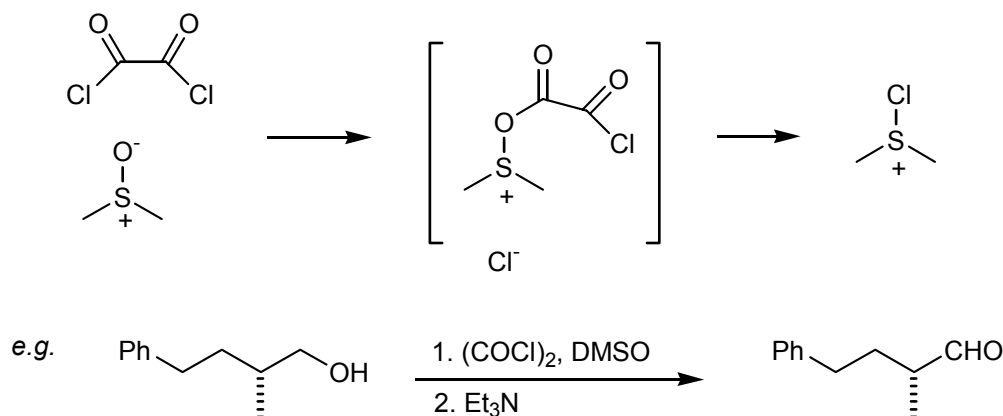
6.3 Activated DMSO reagents

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 dimethyl sulfide.



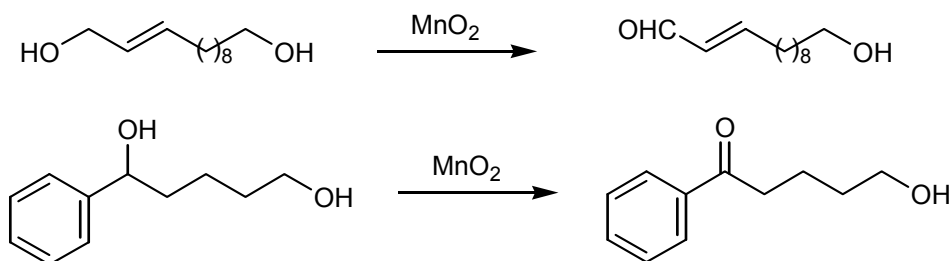
The reactions are generally mild. Primary alcohols are oxidised only as far as the aldehyde, and secondary alcohols to ketones.

The most commonly used method for activating the DMSO is to react it with oxalyl chloride, $(\text{COCl})_2$ – giving an activated species with $\text{X}=\text{Cl}$ in the above Scheme. This is known as the *Swern oxidation* and is one of the most popular methods for oxidizing alcohols.



6.4 Selective oxidation of allylic and benzylic alcohols

It's worth noting that manganese dioxide, 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.



Next time (Thurs 18th Dec at 9am): Oxidation of $\text{C}=\text{X}$ and $\text{C}=\text{C}$ bonds

AA 15.12.03