#### **Oxidation Reactions**

Based on the discussion at the beginning of reductions, it's apparent what is meant in organic terms by oxidation - the removal of H atoms or the addition of O atoms.

The most common oxidation is the oxidation of an alcohol.

Usually, the most well known oxidation reagents are inorganic reagents containing metal atoms in very high oxidation states.

i.e., 
$$Cr^{+6}$$
  $CrO_3$ ,  $K_2Cr_2O_7$   $KmnO_4$ 

-these oxidations are usually performed in an acidic medium, such as the Jones reagent  $CrO_3 + H_2SO_4 + H_2O/acetone$ 

The result of addition of these oxidants to alcohols depends of the alcohol used.

Tertiary alcohols (3°) don't have an  $\alpha$ -H, so they don't oxidize, although they may eliminate to alkenes (E1) under the strongly acidic conditions.

Secondary alcohols oxidize cleanly to ketones

Primary alcohols oxidize to aldehydes, but aldehydes themselves are <u>very</u> easily oxidized in turn up to carboxylic acids. It is usually impossible, with Jones type conditions, to stop the oxidation of a 1° alcohol at the aldehyde stage.

So how do you stop the oxidation of a 1° alcohol at the aldehyde. Much like in the reduction of alkynes problem, by tempering the reactivity of the oxidant. This was originally done by making a pyridine complex of  $CrO_3$ .

If this complex is used in an inert solvent, such as  $CH_2Cl_2$  or pyridine itself, the  $1^\circ$  alcohol oxidation will stop at the aldehyde.

 $CrO_3$ -2pyr isn't often used anymore, however. Equivalent variations on this reagent are pryridinium chlorochromate (PCC, essentially  $CrO_3$  + HCl + pyridine) and pyridinium dichromate (PDC). These are widely used in  $CH_2Cl_2$  and give very high yields of aldehyde. For the purposes of this course, these three reagents are interchangeable. By the way, the  $2^\circ$  alcohol to ketone oxidation also works quite nicely with these reagents.

Mechanism: The mechanism of  $Cr^{VI}$  or related oxidations is a bit of a mess, since it's very complex, and  $Cr^{VI}$ ,  $Cr^{VI}$ , and  $Cr^{IV}$  are all participating. For acid dichromate, the following is at least one of the mechanisms occurring simultaneously:

One of the mechanisms occurring simultaneously.

$$R_{2}C-H + HCrO_{4} + HG \longrightarrow R_{2}C-O_{3}H \longrightarrow$$

There is another very mild oxidation for sensitive alcohols, which also stops the 1° alcohol oxidation at the aldehyde stage. This employs sulphur in a higher oxidation state (namely a sulphoxide) as the oxidation, in addition to oxalyl chloride and triethylamine. It's name is **Swern Oxidation**. (MARCH 9-20)

The mechanism is also fairly involved, but at least there's only one of them going on here.

$$H_{3}C = \frac{1}{S-0} + C_{1} - \frac{1}{C} - \frac{1}{C} - C_{1} = \frac{CH_{2}C_{12}}{-60^{\circ}} \left[ \begin{array}{c} H_{3}C \\ H_{3}C \\ \end{array} \right] = \frac{C}{S-0} - \frac{C}{C} - \frac{C}{C} - C_{1} = \frac{C}{C} - C_{2} = \frac{C}{C} - C_{2} = \frac{C}{C} - C_{1} = \frac{C}{C} - C_{2} = \frac{C}{C} - C_{1} = \frac{C}{C} - C_{2} = \frac{C}{C} - C_{2} = \frac{C}{C} - C_{1} =$$

To reemphasize, this is very mild. Any HCl liberated is consumed by the NEt<sub>3</sub>, so that acid sensitive groups (i.e., protecting groups) are not affected. Furthermore, the side products are gases or low boiling liquids (CO, CO<sub>2</sub>, Me<sub>2</sub>S), so that the product is easily separable. The *only* drawbacks are that the actual reagent is only stable at low temperature (< -50 °C) and the dimethyl sulphide stinks.

# Allylic Oxidations - Manganese Dioxide

One more conventional oxidation reagent is useful for its specificity. MnO<sub>2</sub> is not an especially active oxidant, so it will oxidize only the most reactive alcohol, These are normally restricted to allylic alcohols (or propargylic alcohols, or benzylic alcohols); alcohols not immediately next to a  $\pi$ -system simply don't oxidize. As a result, one can do a selective oxidation on a system with two functional groups which at first glance look pretty much the same. This ability to distinguish them is very useful.

distinguish them is very useful.

$$R \longrightarrow CH_2Cl_2$$

$$R \longrightarrow R'$$

$$S_{MILARLY}$$

$$R \longrightarrow R'$$

$$S_{MILARLY}$$

### Oxidation of C=X Compounds

### 1)Epoxidation - Peracids (March 5-36)

Peracids have the structure
i.e., an ester of HOOH

They are normally prepared by oxidation of an aldehyde. The O-O bond of these is relatively weak, and they can be used for oxidation purposes. There most common reaction is with the C=C of an alkene to give epoxides. This is probably the most common way of preparing an epoxide.

Comments: The peracid induced epoxidation of alkene is stereospecific; one gets **cis** addition across the C=C. (Aside: You should look up the term stereospecific, as it is distinguished from the term stereoselective)

Common peracids: The most common ones are m-chloroperbenzoic acid and peracetic acid.

This reaction is very useful because of the subsequent reactivity of the epoxide products:

Certain peracids lead to further reaction of the epoxide, particularly performic acid I) (HCOOOH)

$$\left( \begin{array}{c} HCOOOH \\ H \end{array} \right) = \left[ \begin{array}{c} H \\ H \end{array} \right] + \left[ \begin{array}{c} H \\ H \end{array} \right] = \left[ \begin{array}{c} H \\ H \end{array} \right] + \left[ \begin{array}{c} H \\ H \end{array} \right] = \left[ \begin{array}{c} H \\ H \end{array} \right] + \left[ \begin{array}{c} H \\ H \end{array} \right] = \left$$

This occurs due to the fact that formic acid is a relatively strong acid - it is an excellent way to make trans 1,2-diols (starting from cis alkenes).

Ring opening by nucleophiles 2) -Epoxides are susceptible to nucleophilic attack due to the ring strain in the three membered ring. Therefore, many nucleophiles which participate in  $S_N 2$  type reactions will open the epoxide ring.

Ring opening by reduction 3)

This is really just a variation on 2), but LiAlH4 (but not normally NaBH4 will also open epoxides (by an S<sub>N</sub>2 mechanism), to the alcohol.

Note: There are other reagents which will epoxidize alkenes. The most common of these are alkyl peroxides (usually tBuOOH), catalyzed by a transition metal complex { Ti(OiPr4), V(O)(OR)3 }. These are especially useful, because they are amenable to chiral epoxidations. This will be left for future courses, though.

The peracid induced epoxidation of alkenes appears to be a concerted, one step, mechanism. The alkene is clearly the electron rich partner, and the peracid the electron deficient one. As a result, more electron rich alkenes are normally epoxidized more rapidly, and peracids with more electron withdrawing groups (i.e., CF<sub>3</sub>CO<sub>3</sub>H) are especially reactive peracids for this

Electron poor alkenes:

Since the C=C has an EWG on it,  $\alpha$ , $\beta$ -unsaturated ketones are too electron poor to epoxidize with a peracid. These can be epoxidized, but one normally uses a different set of reagents ( $H_2O_2$  + NaOH). This works by a different mechanism (essentially a conjugate addition followed by enolate attack on the weak O-O bond). As a result, the addition is non longer stereospecifically  $\alpha$ .

# Baeyer Villiger Oxidation (March 8-20)

Although alkenes are <u>more</u> reactive, ketones will also react with peracids, by a different mechanism, to give esters (or lactones). This is called a **Baeyer-Villiger oxidation** (or rearrangement), and it amounts to stuffing an oxygen atom between the carbonyl carbon of a ketone and the next carbon.

etone and the next carbon.

$$CH_3CO_3H$$

$$CH_2CI_2$$

$$CH_3CO_3H$$

$$CH_2CI_2$$

$$CH_2CI_2$$

$$CH_3CO_3H$$

The mechanism of the Baeyer-Villiger features formation of a hemi acetal of the ketone, using the peracid, and then loss of carboxylate ion and migration of a R group over to the oxygen atom which remains. This is really the first of a class of reactions called 'nucleophilic rearrangements', which we've see more of right at the end of the course.

H<sub>3</sub>C 
$$H_3$$
C  $H_3$ C  $H$ 

The immediate question which should come to mind is in regards to which R group migrates, seeing as ketones have two of them. The answer stems from the fact that in the transition state, positive charge is developing partially on the O atom which is being migrated to, and partially from the C atom which was originally the carbonyl carbon. As a result, the more electron donating