CHEMISTRY 2600

Topic #8: Oxidation and Reduction Reactions

Fall 2018

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Oxidation States of Carbon

- Carbon can have any oxidation state from -4 (CH_4) to +4 (CO_2).

- As a general rule, increasing the number of bonds to oxygen increases a carbon atom's oxidation state while increasing the number of bonds to hydrogen decreases its oxidation state.

- Reactions in which **O is added** to a molecule or **H_2 is removed** from a molecule can be classified as **oxidation reactions**:

- Reactions in which **H_2 is added** to a molecule or **O is removed** from a molecule can be classified as **reduction reactions**:

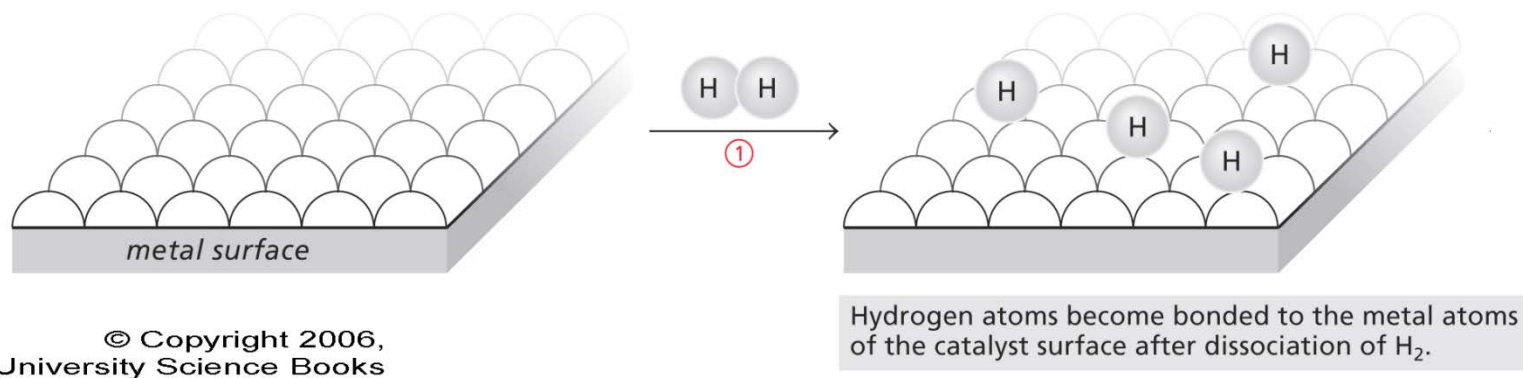- Reactions in which both H_2 and O are added (or removed) are neither oxidations nor reductions.

Reduction Reactions (Hydrogenation)

- We've already seen one reaction which can be considered to be a reduction reaction – the nucleophilic addition of hydrogen to a carbonyl (using $NaBH_4$ or $LiAlH_4$ as the source of "H^-"):

- This was a **chemoselective** reaction – in other words, the reducing agent only reacted with one functional group (the carbonyl) and left others alone (alkenes and alkynes).

- If we want to reduce an alkene or alkyne, we need to use a different kind of hydrogen source – one which can add hydrogen across <u>any</u> π bond. We want our hydrogen source to be, quite literally, hydrogen (H_2).

- Problem: The H-H bond is *very* strong. Why is that?

Reduction Reactions (Hydrogenation)

- Solution: Use a catalyst to help break the H-H bond. A transition metal such as Pd or Pt will do this nicely; however, these metals are expensive and the catalysis only occurs at the surface. So, we coat the metal on something cheap like charcoal to maximize catalytic surface area.

metal surface

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Hydrogen atoms become bonded to the metal atoms of the catalyst surface after dissociation of H_2.

- Thus, the standard choice for a hydrogenation catalyst is 5-10% Pd/C (since Pt is more expensive than Pd and they work equally well for most alkenes and alkynes), and $H_{2(g)}$ is bubbled through a solution of reactant. The catalyst does not dissolve, so stirring is essential to keep it suspended so that alkene (or alkyne) and catalyst come into contact.

4

Reduction Reactions (Hydrogenation)

- The addition of H_2 across a π bond using a transition metal catalyst like this is **always** *syn* (always gives the *cis* **product**):
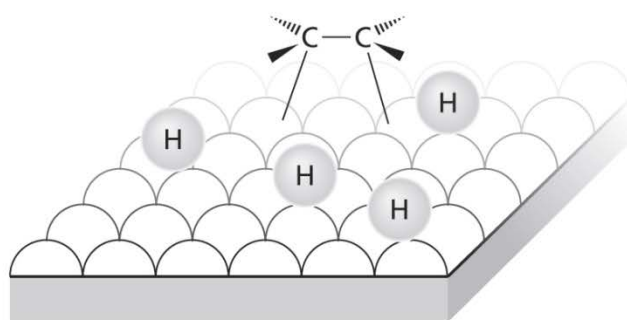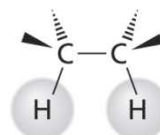

Weak metal–carbon bonds are formed from the reaction between the alkene carbon atoms and the metal surface.
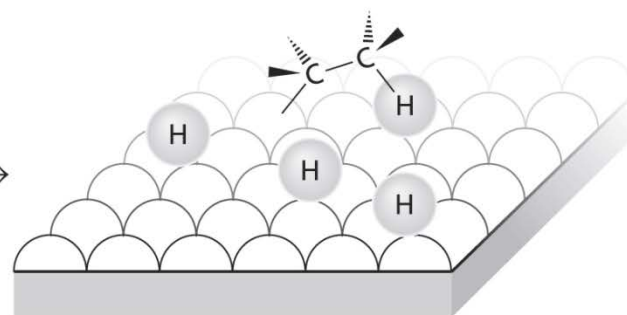
A metal–carbon bond is broken as a carbon–hydrogen bond is formed.

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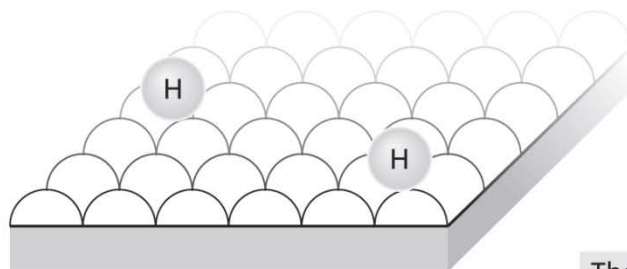
The second metal–carbon bond is broken as another carbon–hydrogen bond is formed; the reduced product dissociates from the surface.

Reduction Reactions (Hydrogenation)

- Any π bond can be hydrogenated, but C=O groups are harder to hydrogenate than C=C, C=N, C≡C or C≡N groups. Hydrogenation of a carbonyl therefore tends to require a more powerful catalyst, heat, and/or a higher pressure of $H_{2(g)}$. Thus, it is not difficult to hydrogenate an alkene or alkyne in the presence of a carbonyl.

- Draw the major organic product of each hydrogenation reaction:
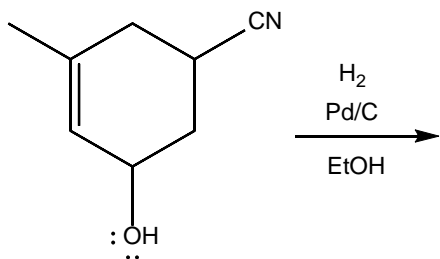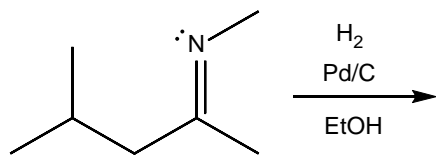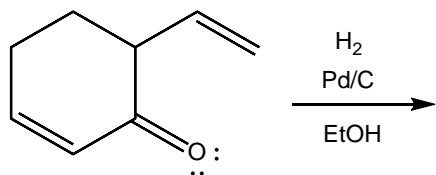
Reduction Reactions (Hydrogenation)

- It is possible to stop hydrogenation of an alkyne at the alkene, but only if a **poisoned catalyst** is used. One "poisoned" hydrogenation catalyst is called Lindlar's catalyst, in which the Pd is coated on $CaCO_3$ instead of charcoal then treated with quinoline and lead(II) acetate to reduce its activity. You can check if your hydrogenation catalyst has been poisoned by checking whether the metal is coated on a salt or on charcoal.

- Hydrogenation of an alkyne with a poisoned catalyst always gives the *cis*-**alkene**:
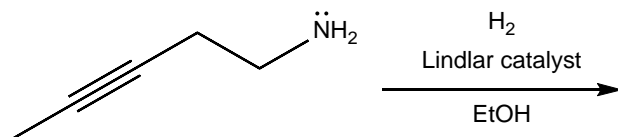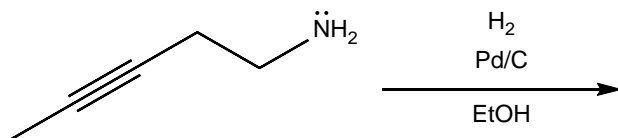
Reduction Reactions (Hydrogenation)

- Azides (R-N$_3$) can also be reduced to amines using H$_2$ and a transition metal catalyst; however, this is technically hydrogenolysis rather than hydrogenation (because a sigma bond is broken or "lysed"):
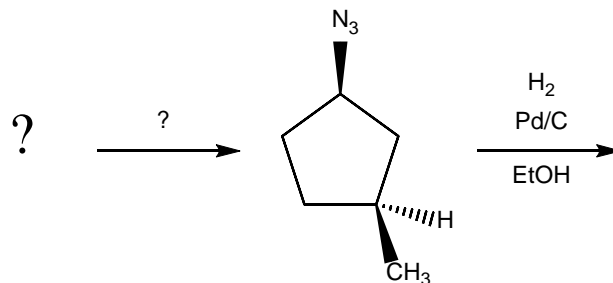

- This is reduction of nitrogen not reduction of carbon.
- Treatment of many organic compounds containing heteroatom-heteroatom bonds with H$_{2(g)}$ gives hydrogenolysis.
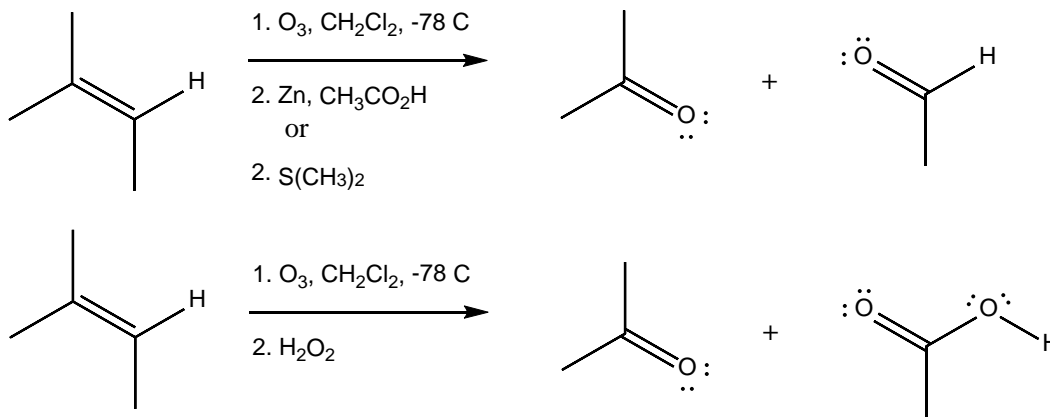
Oxidation Reactions (Ozonolysis)

- An alkene can be "lysed" (broken) to give two carbonyl-containing functional groups via a reaction called ozonolysis (literally, reaction with ozone causing a bond to break)

1. O_3, CH_2Cl_2, -78 C

2. Zn, CH_3CO_2H
   or

2. $S(CH_3)_2$
   or

2. H_2O_2
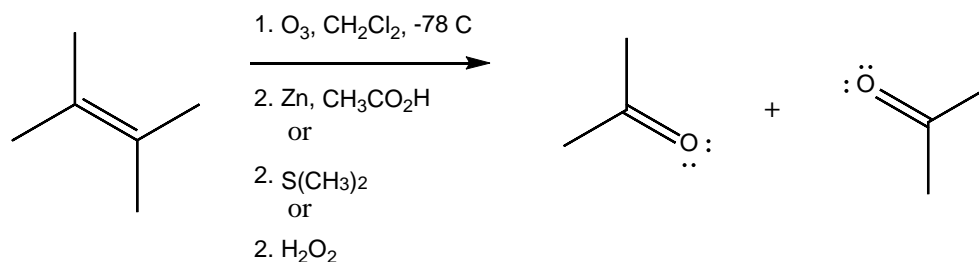
- The three possible sets of conditions for "step 2" are equivalent for the example above, but not if there are any hydrogen atoms attached to the alkene. If there is such a hydrogen, then reductive work-up (Zn/CH_3CO_2H or $S(CH_3)_2$) gives the aldehyde while oxidative work-up (H_2O_2) gives the carboxylic acid:

1. O_3, CH_2Cl_2, -78 C

2. Zn, CH_3CO_2H
   or

2. $S(CH_3)_2$

1. O_3, CH_2Cl_2, -78 C

2. H_2O_2

9

Oxidation Reactions (Ozonolysis)

- How does ozonolysis work?
    - Step 1a: 1,3-Dipolar cycloaddition reaction between the alkene and ozone. (The 1,3-dipolar cycloaddition should look a *lot* like a Diels-Alder reaction; it's another example of a [4+2] cycloaddition.) This gives a very unstable intermediate called a molozonide:
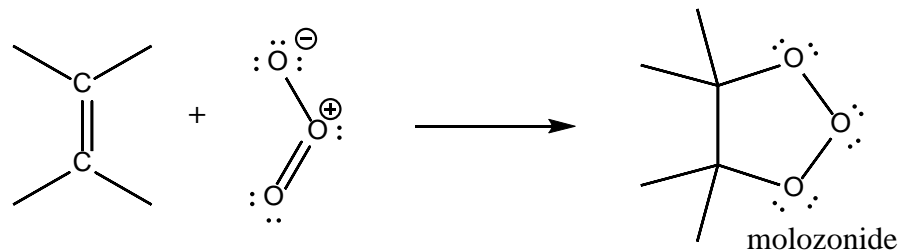

molozonide

    - Step 1b: The molozonide rearranges to a more stable isomer called an ozonide (a kind of cyclic peroxide). This occurs via a retro-1,3-dipolar cycloaddition followed by another 1,3-dipolar cycloaddition!


molozonide

ozonide
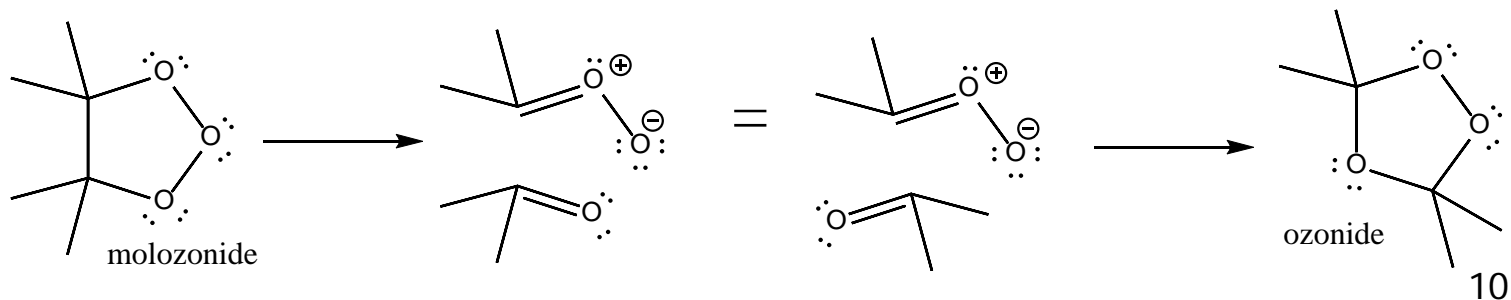
Oxidation Reactions (Ozonolysis)

- Step 2: Work-up. At this point, the mechanism depends on the kind of work-up. Oxidative work-up gives ketones and carboxylic acids (though only one H is replaced by OH in the case of a terminal alkene). Reductive work-up gives ketones and aldehydes. e.g.

ozonide
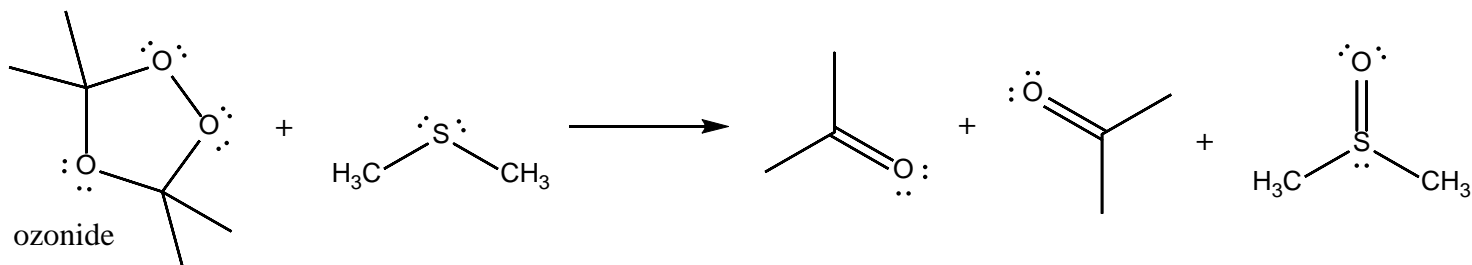
Oxidation Reactions (Ozonolysis)

- Draw the ozonolysis product for each of the following alkenes. Pay attention to whether the work-up is oxidative or reductive!


1. O_3, CH_2Cl_2, -78 C

2. Zn, CH_3CO_2H

1. O_3, CH_2Cl_2, -78 C

2. $S(CH_3)_2$

1. O_3, CH_2Cl_2, -78 C

2. H_2O_2
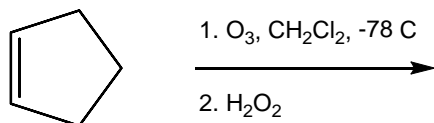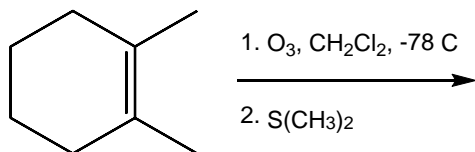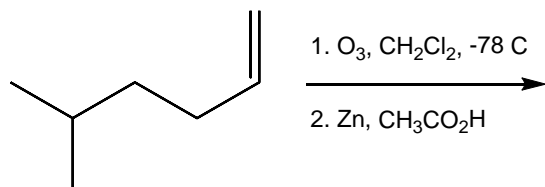
Oxidation Reactions (Ozonolysis)

- Now, we can be very clever when proposing synthetic routes:

Mg

Et$_2$O

1.

2. H$^+$, H$_2$O

1. O$_3$, CH$_2$Cl$_2$, -78 C

2. S(CH$_3$)$_2$

H$_2$SO$_4$
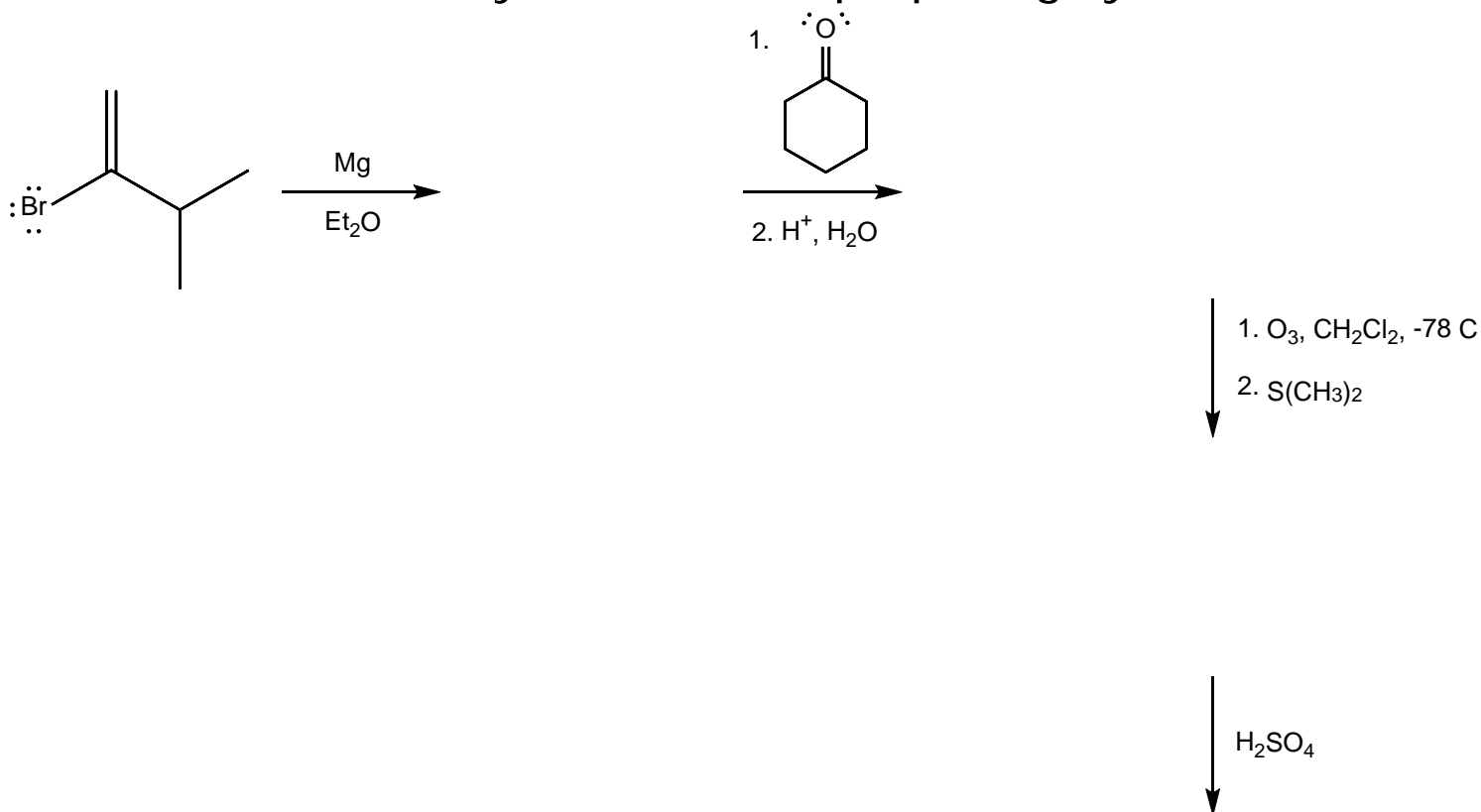
Oxidation Reactions (Dihydroxylation)

- Alkenes can also be converted to vicinal diols (i.e. 1,2-diols) by reaction with an oxidization agent. The two most common choices are:

  - Potassium permanganate ($KMnO_4$). You used this in the CHEM 2000 lab (purple solution for titrating green crystals). It's relatively affordable but fairly toxic and can be quite a harsh reagent.

  - Osmium tetroxide (OsO_4). Don't expect to see this anytime soon in an undergraduate lab! OsO_4 is dangerously toxic and very expensive. It's also gentler than $KMnO_4$, giving better yields and chemoselectivity (will even oxidize an alkene over an alkyne).

- Both oxidizing agents give the *syn* addition product:

$$KMnO_4$$
$$Na_2CO_3, H_2O$$
$$0\ C$$

$$catalytic\ OsO_4$$
$$tBuOOH$$
$$NaOH$$
$$tBuOH$$
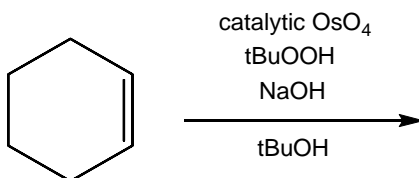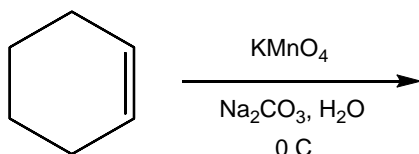
Oxidation Reactions (Dihydroxylation)

- $NaIO_4$ will cleave any C-C bond between two carbons that BOTH have at least one bond to oxygen. Each carbon atom gets oxidized by "one step":
    - Alcohol to ketone (or aldehyde)
    - Ketone (or aldehyde) to carboxylic acid
    - Carboxylic acid to CO_2

- This gives us another means by which to cleave an alkene to two carbonyl groups (an alternative to ozonolysis).
    - First, dihydroxylate with OsO_4 or cold alkaline $KMnO_4$:

    - Then, treat the vicinal diol with aqueous sodium periodate ($NaIO_4$).
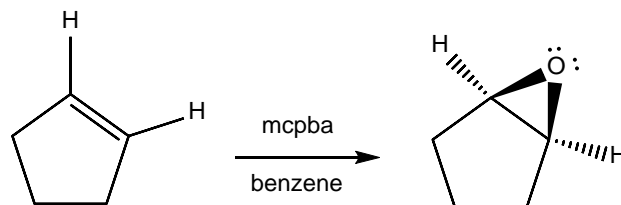
Oxidation Reactions (Dihydroxylation)

- How could you prepare each of the following compounds from an alkene containing no oxygen atoms? It may take more than one step.
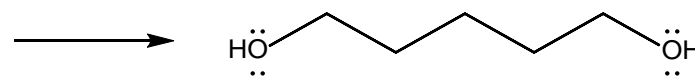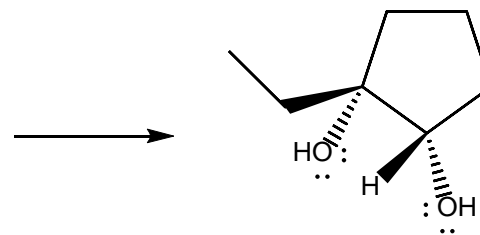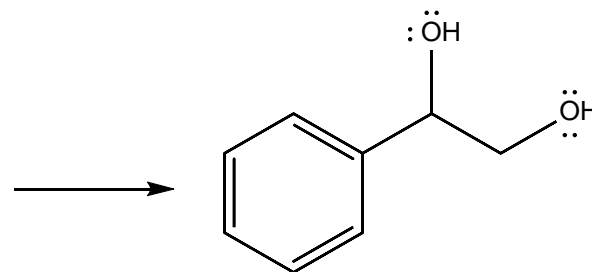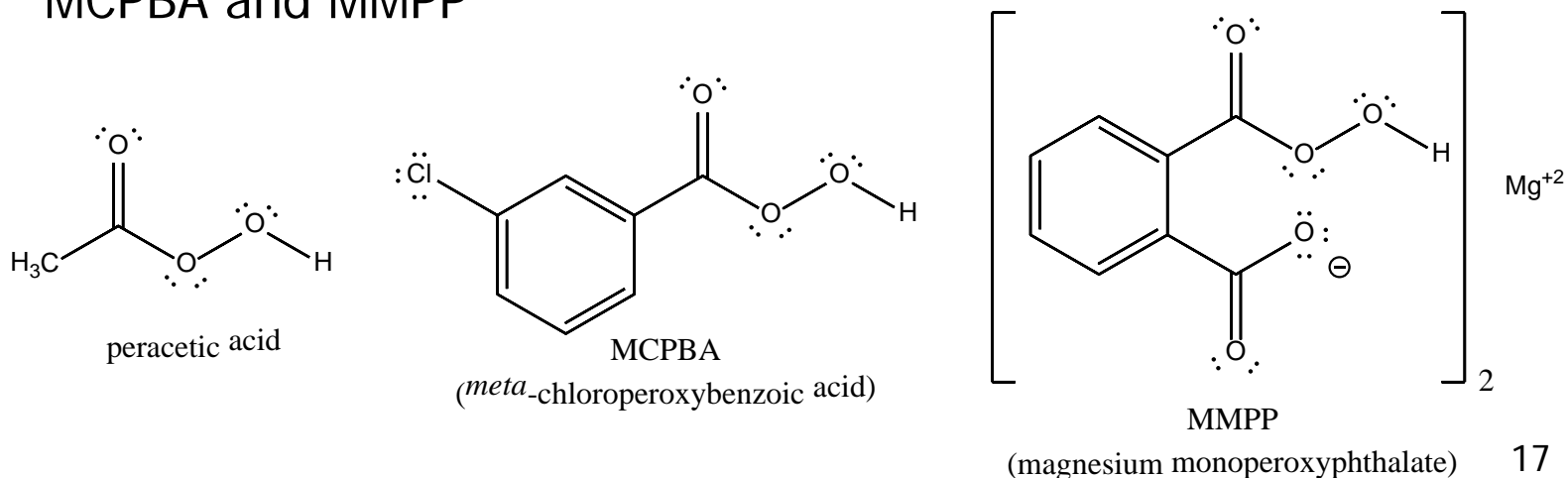
Oxidation Reactions (Epoxidation)

- It's also possible to convert an alkene to an epoxide (3-atom cyclic ether) by oxidation with a peracid ($R\text{-}CO_3H$).

- The most common peracids for this purpose are peracetic acid, MCPBA and MMPP

peracetic acid

MCPBA
(*meta*-chloroperoxybenzoic acid)

MMPP
(magnesium monoperoxyphthalate)

Oxidation Reactions (Epoxidation)

- The exact mechanism for an epoxidation reaction is not known; however, it is known that the alkene serves as nucleophile and the peracid as electrophile.

- Since the alkene acts as the nucleophile, if there are two alkenes in the same molecule, we can predict that the more nucleophilic one (the more electron-rich one) will react first.

- What is the organic product of the reaction below?

1 equiv. MMPP

EtOH
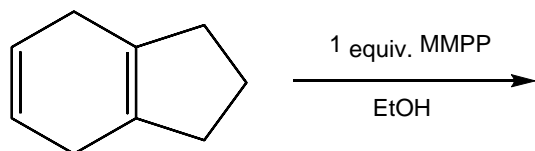
Oxidation Reactions (Alcohol to Carbonyl)

- Alkenes aren't the only groups we might want to oxidize. It's also useful to be able to convert alcohols to ketones and aldehydes. *(Just as it's useful to convert ketones and aldehydes to alcohols – which we've already seen.)*

- To do this, we essentially need to eliminate H_2:

- Effectively, this means that we need to convert the hydrogen atom of the alcohol to a good leaving group (-OH to -OLG) then do an elimination reaction (eliminating H-LG):

Oxidation Reactions (Alcohol to Carbonyl)

- One way to accomplish this is a **Swern oxidation**. This is a multi-step reaction in which:
    - Dimethylsulfoxide [DMSO; $(CH_3)_2SO$] is mixed with oxalyl chloride [$(ClCO)_2$] at low temperature *(usually in CH_2Cl_2 solvent)*
    - The alcohol is then added to the reaction flask and allowed to react.
    - Finally, triethylamine is added and the flask allowed to warm to room temperature.
- Between the DMSO and the Et_3N, this reaction stinks! But it works well and it's very gentle, so it doesn't destroy other functional groups in the molecule. Primary alcohols are oxidized to aldehydes, and secondary alcohols are oxidized to ketones:

1. DMSO, oxalyl chloride, CH_2Cl_2
2. Et_3N
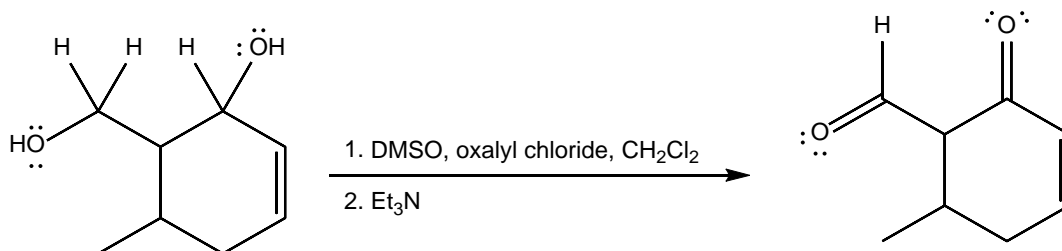
Oxidation Reactions (Alcohol to Carbonyl)

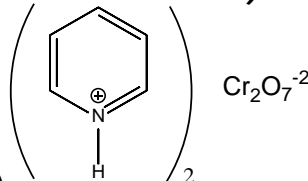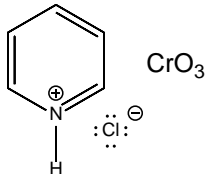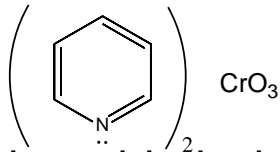- So, how does a Swern oxidation work?
    - Add oxalyl chloride to DMSO:

# Oxidation Reactions (Alcohol to Carbonyl)

- Add alcohol:

- Add Et$_3$N:

Oxidation Reactions (Alcohol to Carbonyl)

- There are a variety of other ways to convert alcohols to carbonyl groups (aldehydes, ketones or carboxylic acids) – many of them involving chromium:

    - 1° alcohols to aldehydes (2° alcohols to ketones)
        - PDC (pyridinium dichromate)

            $Cr_2O_7^{-2}$

        - PCC (pyridinium chlorochromate)

            CrO_3

        - Collins oxidation (2 : 1 pyridine : CrO_3)

            CrO_3

        - Swern oxidation (DMSO + oxalyl chloride; add alcohol; add Et_3N)

    - 1° alcohols and aldehydes to carboxylic acids (2° alcohols to ketones)
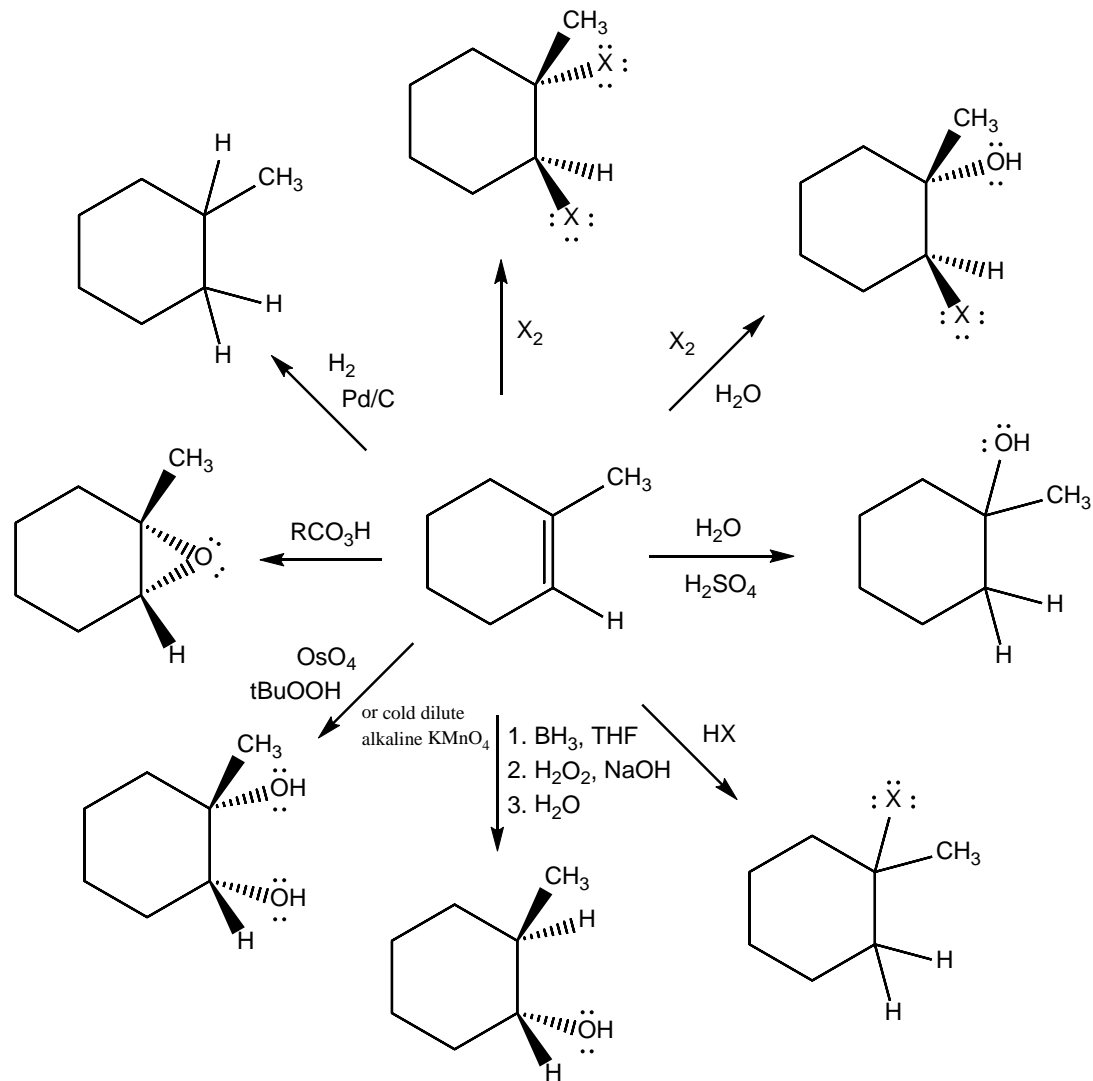   - Jones oxidation (CrO_3 added to H_2SO_4 gives H_2CrO_4)
        - $KMnO_4$ (not cold)

Oxidation Reactions (Alcohol to Carbonyl)

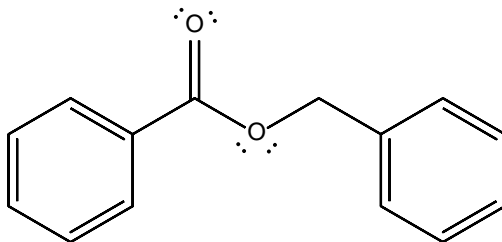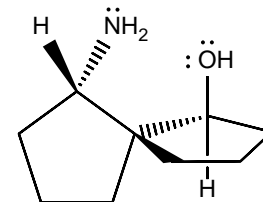- Draw the organic product for each of the following reactions:
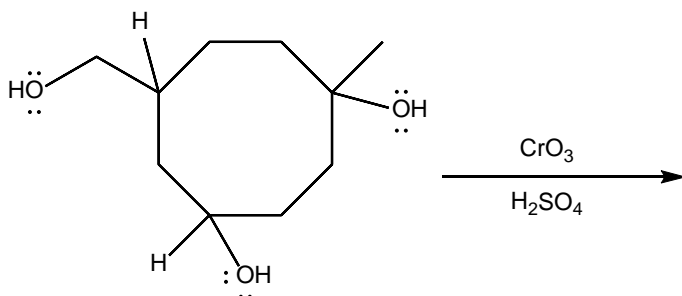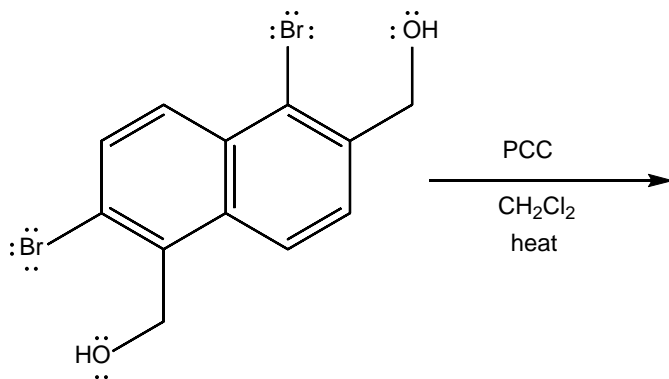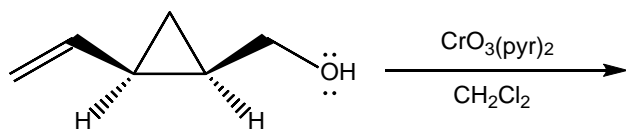
AND ozonolysis cleaves alkene to give two carbonyl groups
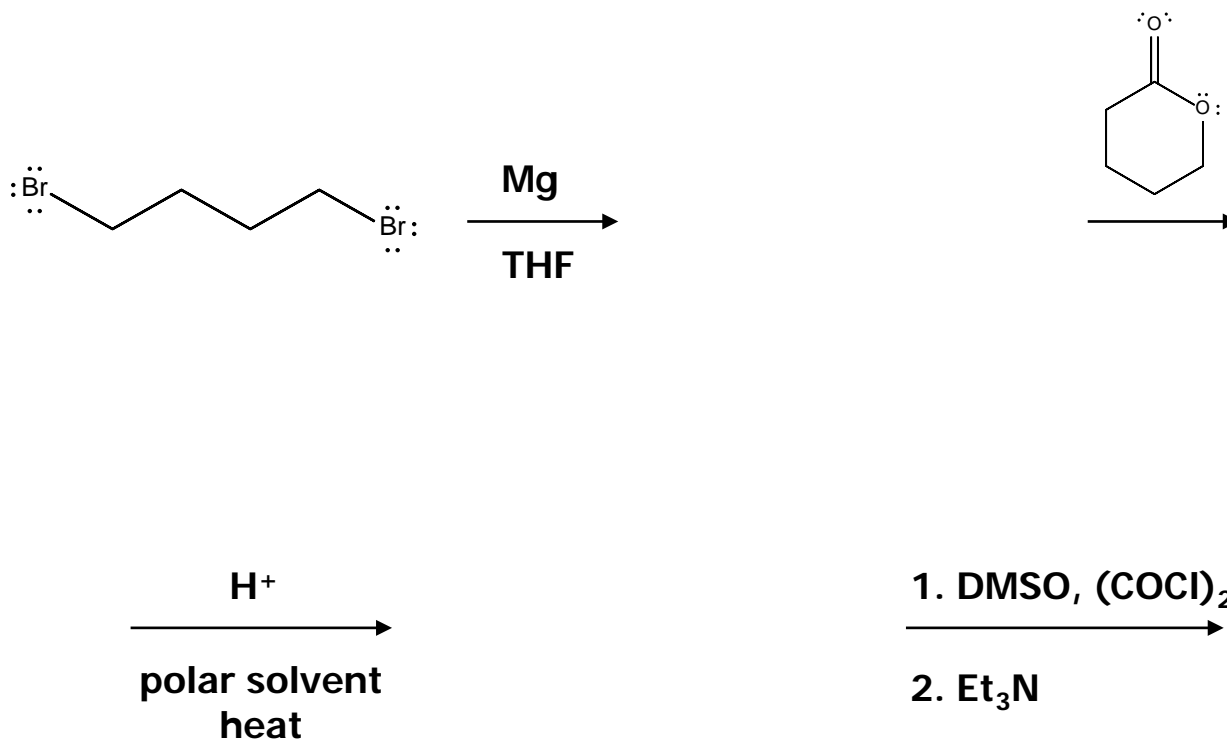
25

Putting It All Together

- How would you make the molecule below? You may use benzyl alcohol as well as any inorganic reagents you like (and/or organic reagents that don't add carbon atoms to the molecule):
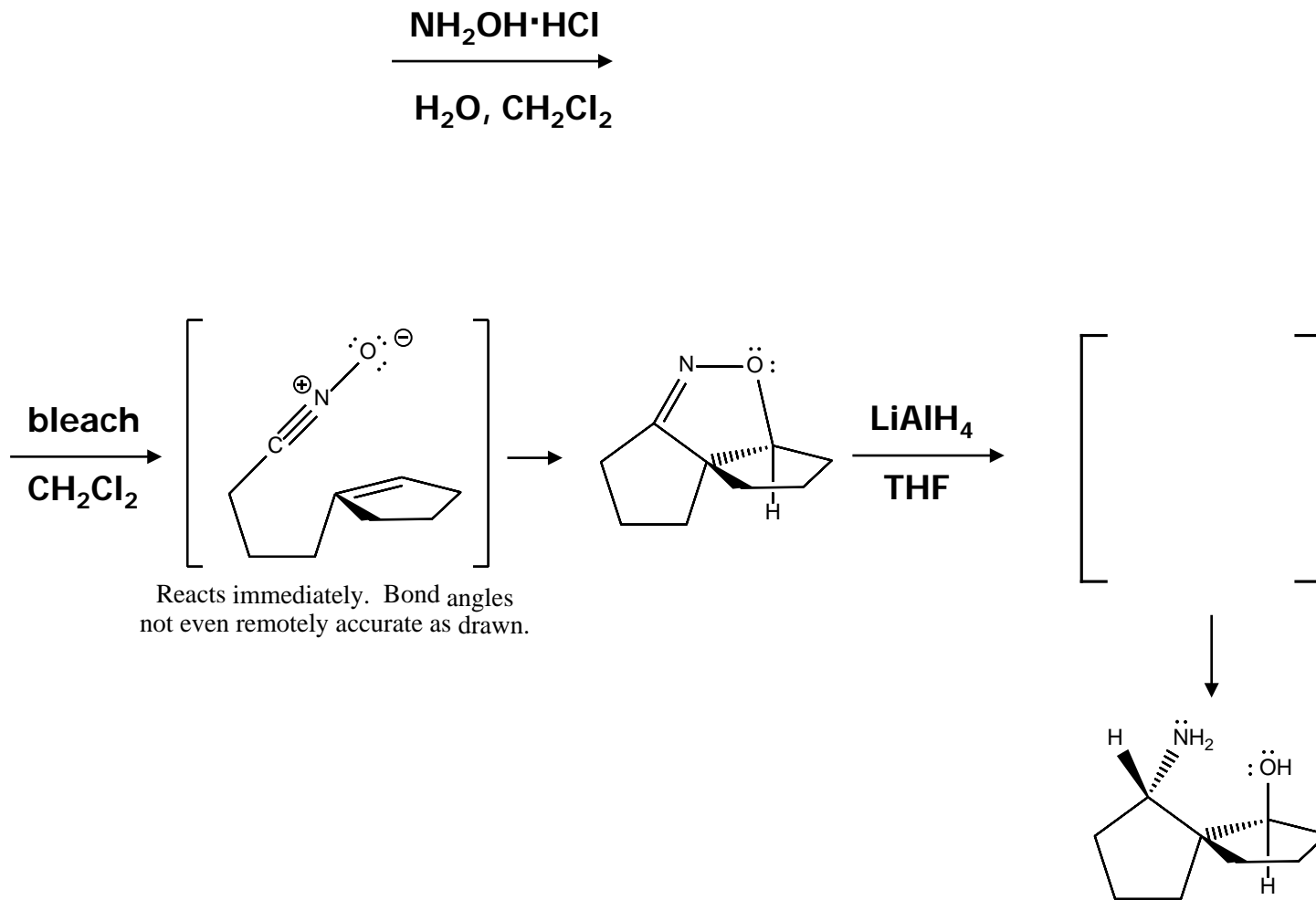
Putting It All Together

- One of my tasks as a PhD student was to put together a synthesis of the amino-alcohol above...

Br—CH₂CH₂CH₂CH₂CH₂—Br →(Mg / THF)

[lactone: 6-membered ring with C=O and ring O]

→ (H⁺ / polar solvent / heat)

→ (1. DMSO, (COCl)₂ / 2. Et₃N)

*I've simplified the reaction conditions for some steps, but they're all reactions you know!

Putting It All Together

$$NH_2OH \cdot HCl$$
$$\xrightarrow{\hspace{3cm}}$$
$$H_2O, CH_2Cl_2$$

Reacts immediately. Bond angles not even remotely accurate as drawn.

bleach / CH$_2$Cl$_2$

LiAlH$_4$ / THF

*I've simplified the reaction conditions for some steps, but they're all reactions you know!