Lecture Notes
Chem 51B
S. King

Chapter 12 Oxidation & Reduction

I. Introduction

In this chapter we will discuss the oxidation and reduction of akenes, alkynes, alcohols, ethers, and epoxides. Oxidation & reduction reactions are very valuable in organic synthesis. Recognizing whether a compound is oxidized or reduced is an important first step in being able to successfully choose the correct reagents in a chemical transformation.

A. Recognizing Oxidation and Reduction of Organic Compounds

Oxidation-reduction reactions involve the gain and loss of electrons, and a change in the oxidation state of the molecules involved:

Oxidation: *loss* of electrons
Reduction: *gain* of electrons

$$Cu \quad + \quad 2Ag^{+} \longrightarrow Cu^{2+} \quad + \quad Ag$$

Cu	$2Ag^{+}$	Cu^{2+}	Ag
shiny red metal	*colorless*	*blue*	*silver crystals*

✳ If one molecule is oxidized, another is reduced.
✳ Electrons are *TRANSFERRED COMPLETELY* from one molecule to another.

For organic compounds, oxidation-reduction reactions result in a *CHANGE IN ELECTRON DENSITY* around the carbon atom rather than a complete transfer of electrons.

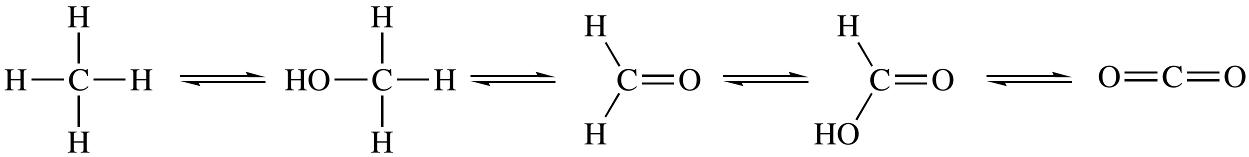
Oxidation: *loss* of "**electron density**"
Carbon "**loses**" electrons by forming bonds with elements that are more electronegative than it is.

loss of:
gain of:

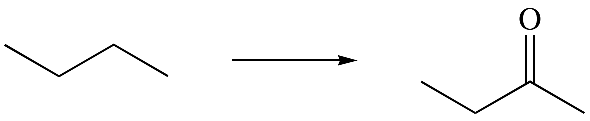
Reduction: *gain* of "**electron density**"
Carbon "**gains**" electrons by giving up bonds to more electronegative elements and forming bonds with hydrogen atoms instead.

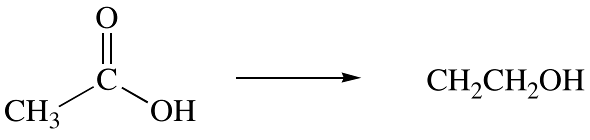
loss of:
gain of:

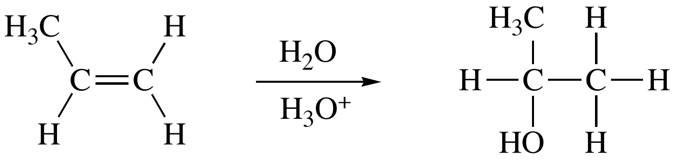
The following shows stepwise oxidation of methane (the most reduced form of carbon) all the way up to carbon dioxide (the most oxidized form of carbon):



Can you recognize oxidation and reduction in the following examples?







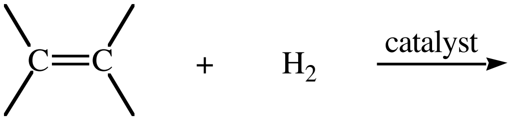
II. Reduction Reactions

A. Reducing Agents:

Reducing agents add the equivalent of two hydrogen atoms to a molecule. There are 3 ways to do this:

1. Add H_2 + catalyst
2. Add two H^+ + $2e^-$
3. Add one H^- followed by one H^+

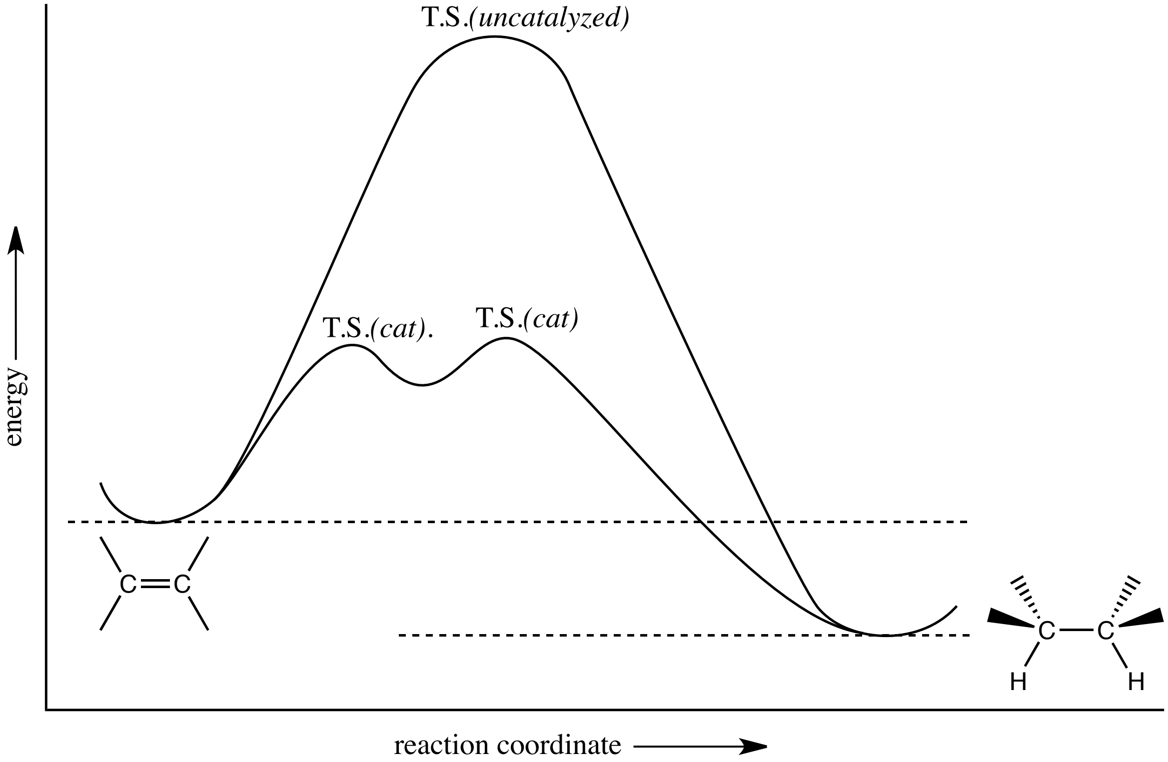
B. Addition of Hydrogen to Alkenes (Catalytic Hydrogenation)



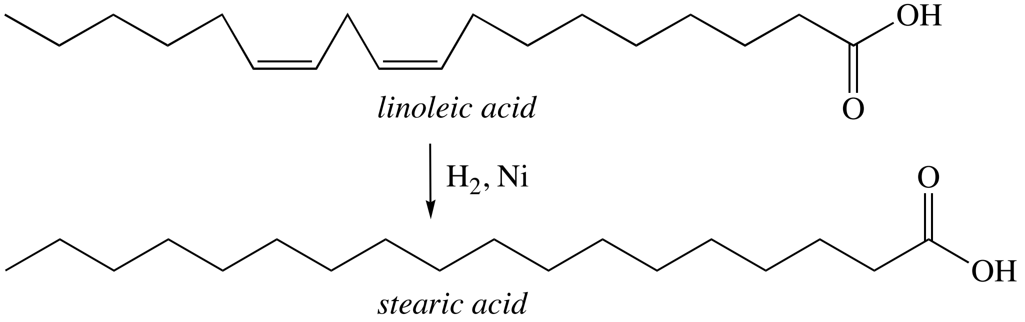
typical catalysts:

- This is a *highly exothermic reaction*, but requires a catalyst because of the *huge energy of activation*.
- The catalyst changes the nature of the transition state, thereby lowering E_a.

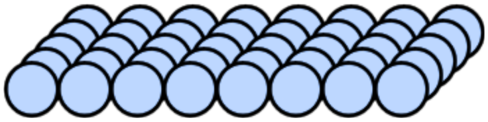
Look @ the energy diagram:

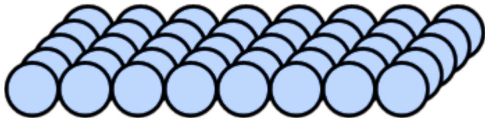


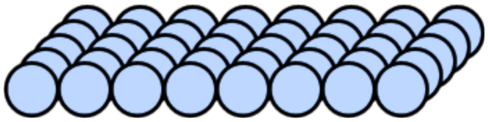
Example:

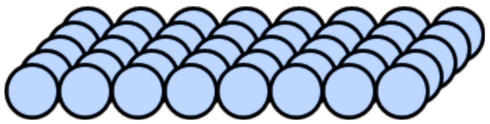


Q. How does this work?
A. The catalyst is in separate solid phase - catalysis occurs at the surface of the metal.







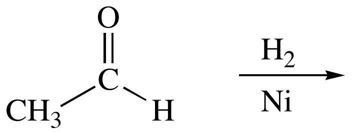


- The alkene is ***adsorbed*** to the metal surface, forming bonds to the metal atom (like a Lewis acid and Lewis base interaction with an alkene and a metal)

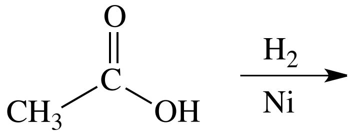
  Result:

B. Hydrogenation of Other Double Bonds

Ketones and *aldehydes* can be reduced with H_2 & Ni, Pd, or Pt, although it is much more common to use $LiAlH_4$ or $NaBH_4$ for the same reduction.



✦ The carbonyl groups of esters, amides, and carboxylic acids are *resistant* to hydrogenation, and will *not* react with H_2, Pd, Pt or Ni. Again, $LiAlH_4$ or DIBAL are the reagents typically used for this type of reduction.



* **NOTICE**: When we hydrogenated linoleic acid on page 90, the carboxylic acid was ***not*** reduced.

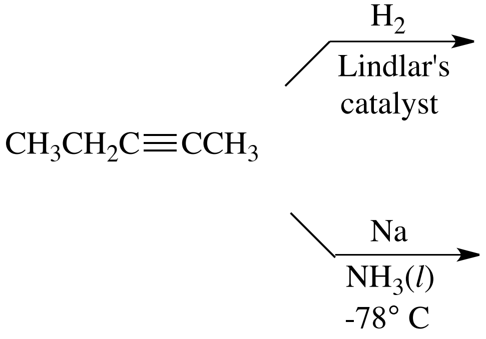
C. Reduction of Alkynes

Hydrogenation of an alkyne leads to addition of H_2 to *one* or to *both* of the π-bonds. Use of Pd, Pt or Ni as a catalyst gives full hydrogenation to an alkane.

$$CH_3CH_2C{\equiv}CCH_3 \xrightarrow[\text{Pd, Pt } or \text{ Ni}]{H_2}$$

✦ *Even if you use 1 eq. of H_2, you will still get full hydrogenation.* *Why?*

For partial hydrogenation of alkynes, two reagents are used, depending upon the desired configuration of the product:



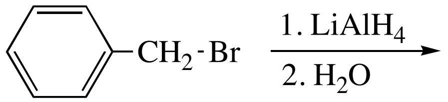
- Lindlar's catalyst is a "poisoned" palladium catalyst. Both lead (Pb) and quinoline are added to reduce the reactivity of the palladium so that partial hydrogenation is possible.

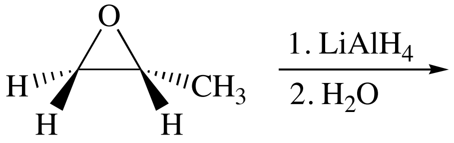
Lindlar's catalyst:

- $Na/NH_3(l)$ is a dissolving metal reduction. Ammonia, which is a gas at room temperature, is cooled down to –78° C in a dry ice/acetone bath. Then a chunk of Na metal is added. The Na becomes Na^+ when it donates an electron to the alkyne, and the NH_3 becomes NH_2^- when it loses a proton.

D. The Reduction of Polar C–X σ-bonds:

Alkyl halides and epoxides are reduced by the hydride reagent lithium aluminum hydride ($LiAlH_4$). The reaction follows an S_N2 mechanism.





- $LiAlH_4$ is a source of the strongly basic hydride ion (H:⁻). Since this is an S_N2 reaction using a strong base, it works well only for unhindered 1° and methyl substrates.
- Because $LiAlH_4$ is a powerful nucleophile, it attacks epoxides at the least substituted side.

III. Oxidation Reactions

A. Oxidizing Agents

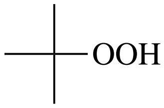
Oxidizing agents fall into two categories:

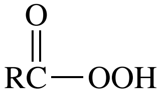
1. Reagents that contain an O-O bond

O_2

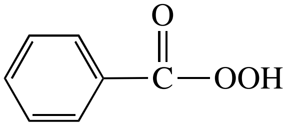
O_3 *ozone*

H_2O_2 *hydrogen peroxide*


tert-butylhydroperoxide

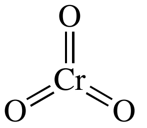

$RC(=O)-OOH$

peroxy acid

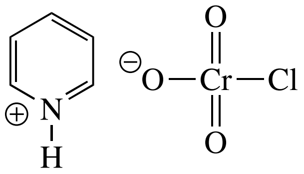

benzoyl peroxide

2. Reagents that contain a metal-oxygen bond.

Cr(VI):


, H_2SO_4

$Na_2Cr_2O_7$, H_2SO_4

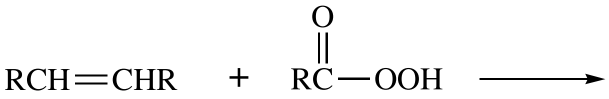

pyridinium chlorochromate
(PCC)

Mn(VII): $KMnO_4$, NaOH *potassium permanganate*

Also: OsO_4 *osmium tetroxide* Ag_2O *silver oxide*

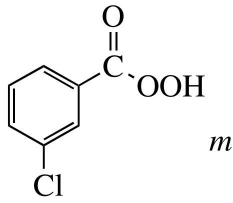
B. Epoxidation

Epoxidation is the addition of a single oxygen atom to an alkene to form an epoxide. The most common way to do this is to use a peroxyacid (AKA: peracids)


$$RCH{=}CHR + RC(=O)-OOH \longrightarrow$$

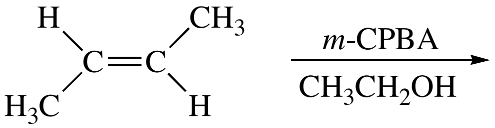
Mechanism:

Common Peroxyacid:



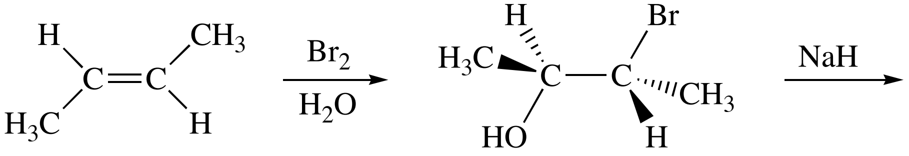
meta-Chloroperoxybenzoic acid

Example:



(E)-2-butene

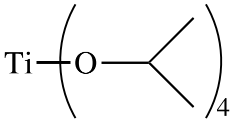
- This reaction is stereoselective! *E*-2-butene gives only *trans*-2,3-dimethyloxirane, and *Z*-2-butene gives only *cis*-2,3-dimethyloxirane.
- This gives the same product obtained with intramolecular nucleophilic substitution of halohydrins:

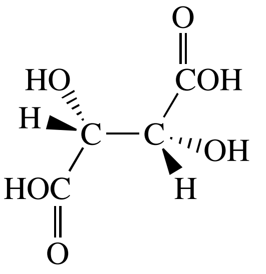


(E)-2-butene

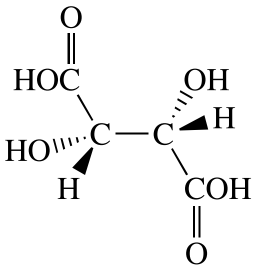
C. Sharpless Asymmetric Epoxidation

One of the most important reactions discovered in the last 25 years is titanium-catalyzed asymmetric epoxidation of *primary allyic alcohols* discovered by Barry Sharpless at MIT. He won the Nobel Prize for this work! The reaction uses tert-butyl hydroperoxide, titanium tetraisopropoxide, and either (+)-diethyl tartrate or (–)-diethyl tartrate.

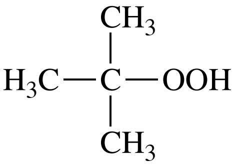




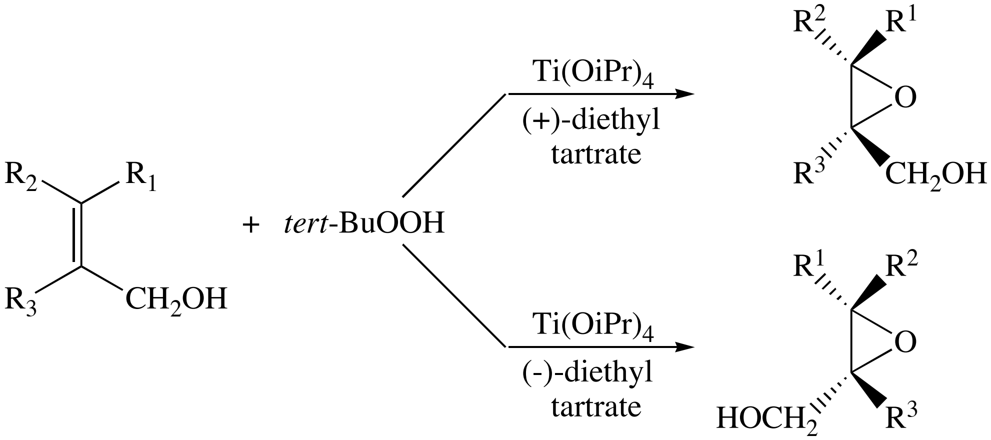
(+)-(*R*,*R*)-tartaric acid



(-)-(*S*,*S*)-tartaric acid

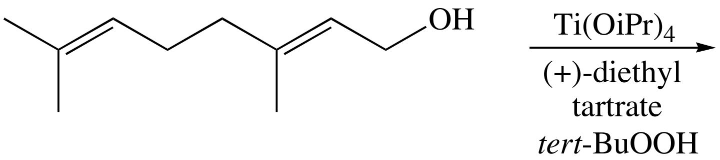


Instead of getting a racemic mixture, asymmetric epoxidation allows the synthesis of only one enantiomer!



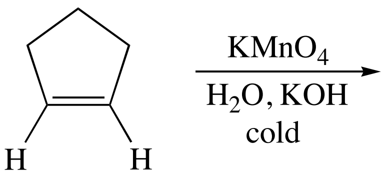
- This reaction is highly enantioselective! You can change the stereochemistry of the product simply by changing which tartrate is used.
- Remember that when you react achiral reagents, to give a product that has a stereocenter, you will always get a racemic mixture unless there is a chiral influence in the reaction. The chiral influence in this reaction is the tartrate.
- This reaction *only works with allylic alcohols*.

Example: Predict the product:



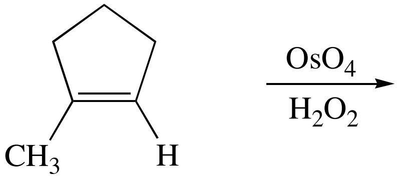
D. Dihydroxylation

Alkenes are readily converted into vicinal diols (AKA: glycol) using either osmium tetroxide (OsO_4) or alkaline potassium permanganate ($KMnO_4$).



NET RESULT:

OsO_4 works in a similar manner:

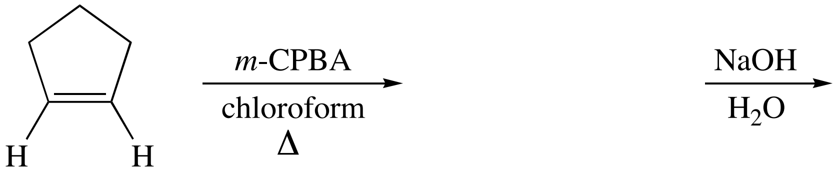


ANTI-dihydroxylation requires 2 steps:

step 1: epoxidation

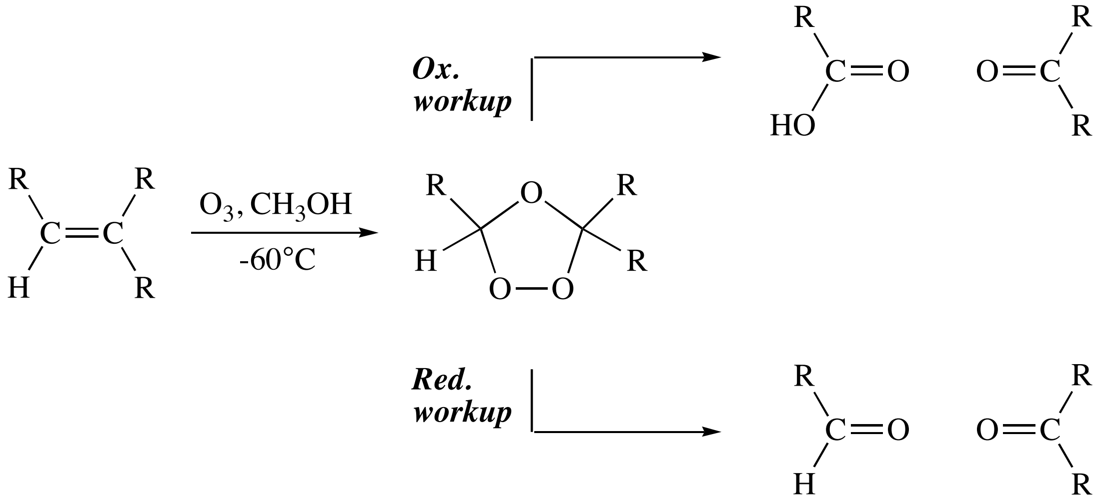
step 2: nucleophilic attack with HO^-, *or* reaction with H_3O^+

Example:



E. Oxidative Cleavage of Alkenes: Ozonolysis

The reaction of an alkene with ozone (O_3) to yield products of double-bond cleavage is called ***ozonolysis***.



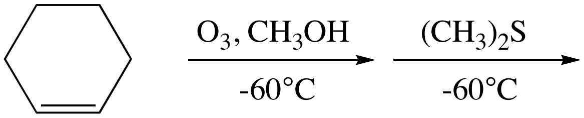
REDUCTIVE WORKUP: X = H

OXIDATIVE WORKUP: X = OH

Ozonolysis also works with alkynes (*With alkynes, H_2O is used in the second step*)

$$R-C\equiv C-H \xrightarrow[-60°C]{O_3,\, CH_3OH} \xrightarrow{H_2O}$$

Example:



☛ Ozonolysis can be used to synthesize aldehydes, ketones, and carboxylic acids from alkenes, and it can be used to break molecules into smaller pieces.

IV. Oxidation of Alcohols

By far the most famous reagent for oxidizing alcohols is Chromic acid (H_2CrO_4). It comes in various different forms, as shown below. Oxidation of primary alcohols gives aldehydes or carboxylic acids, depending on the reagent chosen. Oxidation of secondary alcohols gives ketones. Tertiary alcohols ***are not oxidized!***

A. Oxidation with Chromic Acid

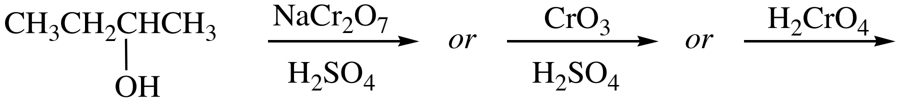
A. Oxidation with Chromic Acid (CrO_3/H_2SO_4 *or* $Na_2Cr_2O_7$, H_2SO_4 *or* $K_2Cr_2O_7$, H_2SO_4), a strong oxidizing agent.

1°: **Forms Carboxylic acids**

$$CH_3CH_2CH_2CH_2OH \xrightarrow[H_2SO_4,\, H_2O]{CrO_3}$$

The reaction doesn't stop here!

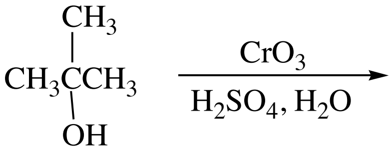
2°: **Forms Ketones**.



$$CH_3CH_2\underset{|}{\underset{OH}{CH}}CH_3 \xrightarrow[H_2SO_4]{NaCr_2O_7} \text{ or } \xrightarrow[H_2SO_4]{CrO_3} \text{ or } \xrightarrow{H_2CrO_4}$$

How?

3°: **No reaction**.



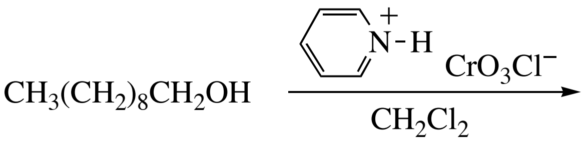
$$CH_3\overset{CH_3}{\underset{OH}{C}}CH_3 \xrightarrow[H_2SO_4,\, H_2O]{CrO_3}$$

Why no reaction???

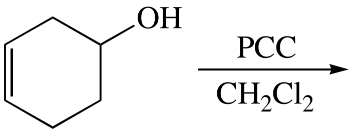
B. Oxidation with Pyridinium Chlorochromate (PCC), a mild oxidizing agent.

Formation of PCC:

1°: Forms aldehydes



2°: Forms ketones.



For molecules containing = & ≡ PCC doesn't react with = & ≡. CrO_3/H_2SO_4 is so acidic it will react with these.

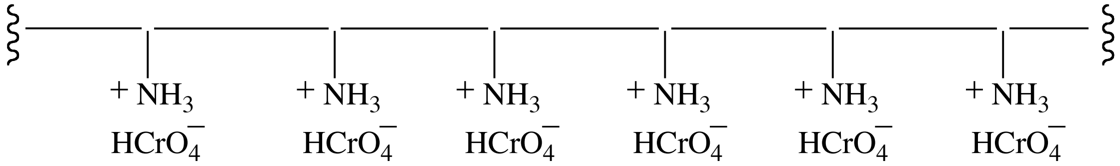
3°: No reaction.

V. Green Chemistry

Several new oxidation methods are based on green chemistry. Green chemistry is the use of environmentally benign methods to synthesize compounds. In “greening” a chemical reaction, efforts are made to minimize waste, by-products, and solvent, and choose safer reagents, especially ones made from renewable resources.

☛ Many oxidation reagents, in particular, are especially toxic:

One especially nice alternative to conventional chromic acid oxidation uses a polymer supported Cr^{6+} reagent, **Amberlyst A-26 resin-$HCrO_4^-$**, that avoids the use of strong acid, and forms a Cr^{3+} by-product that can be easily removed from the product by filtration.



Advantages:

- Alcohol and Amberlyst are heated together without solvent
- Avoids use of strong acid, H_2SO_4
- Cr^{3+} can be filtered off without added solvent
- Cr^{3+} can be regenerated and reused in a subsequent reaction.

Amberlyst A-26 resin-$HCrO_4^-$ oxidized 1° alcohols to aldehydes and 2° alcohols to ketones.

Example:

$$CH_3(CH_2)_8CH_2OH \xrightarrow[\text{Amberlyst A-26 resin}]{HCrO_4^-}$$

VI. Designing Syntheses: Part 2 *(continued from chapter 11)*

Recall:

In planning a synthesis, we have to consider four things:

1. Construction of the carbon skeleton
2. Functional group interconversion
3. Control of regiochemistry
4. Control of stereochemistry

Example: Synthesize 2-bromobutane from compounds of 2 C’s or fewer.

Example: Outline a stereospecific synthesis of *meso*-3,4-dibromohexane starting with compounds of two carbons or fewer.