Oxidations

Oxidation is one of the most important & useful reactions in chemistry

Most of the chemicals are obtained by the oxidation of petrochemicals

Definition:

Inorganic Chemists & Organic Chemists differ in defining oxidation

Inorganic Chemists:
(1) Loss of electrons
(2) Increase in oxidation number

Organic Chemists:
The same rules can not be applied because
(1) Mechanisms of most of the oxidation reactions do not involve a direct electron transfer
(2) It is also not possible to apply oxidation number uniformly
Oxidations

Addition of Oxygen

\[ \text{H}_3\text{C} \equiv \text{CH}_3 \rightarrow \text{H}_3\text{C} \equiv \text{C}^\text{OH} \rightarrow \text{H}_3\text{C} \equiv \text{CHO} \rightarrow \text{H}_3\text{C} \equiv \text{CO}_2\text{H} \]

Replacement of hydrogen atom bonded to carbon with another, more electronegative element like oxygen

Elimination of Hydrogen

\[ \text{H}_3\text{C} \equiv \text{CH}_3 \rightarrow \text{H}_2\text{C} \equiv \text{CH}_2 \rightarrow \text{HC} \equiv \text{CH} \]

Simplest Definition

Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen

The reverse is true for reduction

There is no oxidation without a concurrent reduction
Oxidations

Oxidation

- At single carbon
- Vicinal Carbon
- Hetero atom
- Unfunctionalized Carbon atom

Reagents

1. Metal based
2. Non-metal based
Metal Based Oxidations

Chromium based oxidation
Manganese based oxidation
Ruthenium based oxidation
Osmium based oxidation
Molybdenum based oxidation
Lead based oxidation
Titanium based oxidation
Metal Based Oxidations

Chromium Based Reagents

$\text{CrO}_3$

Jones oxidant

PCC

PDC

Collins reagent

Chromyl chloride

Reactivity & selectivity depends on the (1) Solvents & (2) Chromium ligands

Substantial selectivity can be achieved by choice of the particular reagent or conditions

The most widely employed transition metal oxidations are Cr(VI) based reagents
Oxidations

CrO₃

\[
\ce{CrO3 + H2O -> HO-Cr-O}\]

\[
\ce{2 HO-Cr-O <-> O-Cr-O-Cr-O + H2O}\]

In dilute solution the chromate ion is present. As concentration increases the dichromate ion dominates.

The extent of protonation of these ions depend on the pH.

In acetic acid, CrO₃ exists as mixed anhydride of acetic acid & chromic acid.

\[
\ce{CH3COOH + CrO3 -> \ce{HO}CrO \rightarrow \ce{ACrO}O}\
\]
Oxidations

\[ \text{CrO}_3 \]

In pyridine, \( \text{CrO}_3 \) exists as an adduct involving Cr-N bond

\[
\text{N} + \text{CrO}_3 \rightarrow \text{N-Cr-O}^+\text{N}
\]

The most common transformation effected on with Cr(VI) is the conversion of the alcohols into ketones or aldehydes

\[
\text{R-OH} \xrightarrow{\text{CrO}_3} \text{R-O}^+\text{Cr-OH} \rightarrow \text{R-} + \text{H}_2\text{CrO}_3
\]

A variety of experimental conditions have been used for oxidation of alcohols by Cr(VI) on a synthetic scale.
Chromium Based Oxidation

Jones Oxidation

Jones Reagent: Acidic aqueous solution of chromic acid. Generally added to an acetone solution of the alcohol

\[
\text{CrO}_3 + \text{H}_2\text{SO}_4 + \text{H}_2\text{O}
\]

Use: For simple, unfunctionalized alcohols Jones reagent can be used.

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Chromium Based Oxidation

Jones Oxidation

Advantages:
(1) Cr(VI) → Cr(III)
Precipitate

Acetone can be decanted. Easy to work up
(2) Good reagent to oxidize primary alcohol to acid

Disadvantages:
(1) Saturated primary alcohols are oxidized to carboxylic acids

(2) Not good method for acid sensitive groups & compounds
(3) Under acidic condition dehydration may also take place
Chromium Based Oxidation

\[ \text{CrO}_3 \cdot 2\text{Pyridine (Collins Reagent)} \]

**Preparation:**

\[ \text{CrO}_3 \text{ (anh.)} + 2 \text{ Pyridine (anh.)} \rightarrow \text{CrO}_3 \cdot 2\text{pyridine (Solid)} \]

**Uses:**

1. Where other functional groups are susceptible to oxidation
2. When the molecule is sensitive to strong acid
3. Primary & secondary alcohols are oxidized to aldehydes & ketones in non-aqueous solution (Generally DCM was used) without over oxidation
4. Neither markedly basic, nor acidic
Chromium Based Oxidation

**CrO$_3$. 2Pyridine (Collins Reagent)**

Disadvantages:

1. **Must use a large excess of the reagent**
2. **It is moisture sensitive & loses its activity in aqueous solution**

The double bond did not migrate
Chromium Based Oxidation

Pyridinium Chlorochromate (PCC)

Preparation:

\[
\text{CrO}_3 + 6\text{N HCl} \rightarrow \text{HO-Cr-Cl} \quad \text{Pyridine} \rightarrow \text{Orange-yellow crystalline solid, Less hygroscopic}
\]

Advantages:

(1) Reagent can be used in stoichiometric amounts with substrate

(2) It is less hygroscopic. So, it can be stored for a long time

(3) PCC is slightly acidic, but can be buffered with NaOAc
Chromium Based Oxidation

Pyridinium Chlorochromate (PCC)

Oxidation of Organoboranes:

\[
\begin{align*}
\text{BH}_3 \cdot \text{THF} & \quad \rightarrow \quad \text{CHO} \\
(1) & \quad \rightarrow \quad (2) \quad \text{PCC, 0°C}
\end{align*}
\]

Deoximation:

\[
\begin{align*}
\text{CHO} & \quad \rightarrow \quad \text{CO}_2 \\
\text{PCC} & \quad \rightarrow \quad \text{CO}_2
\end{align*}
\]
Chromium Based Oxidation

Pyridinium Chlorochromate (PCC)

Oxidation of Tertiary Allylic Alcohols:

1. MeMgBr, CeCl₃
2. PCC, CH₂Cl₂

1. MeMgBr, CeCl₃
2. PCC, CH₂Cl₂
Chromium Based Oxidation

Pyridinium Chlorochromate (PCC)

Oxidation of Tertiary Allylic Alcohols:

\[ \text{OH} \quad \text{PCC} \quad \text{OH} \]

\[ \text{Pyridinium Chlorochromate (PCC)} \]

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Chromium Based Oxidation

Pyridinium Chlorochromate (PCC)

Oxidative Cationic Cyclization:

[Chemical structures and reaction mechanisms as shown in the image]
Chromium Based Oxidation

Pyridinium Chlorochromate (PCC)

Oxidation of Enol Ethers to Lactones:

\[
\text{Oxidation of Furan Ring System:}
\]

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Chromium Based Oxidation

Pyridinium Chlorochromate (PCC)

Oxidation of Active Methylene Group:

\[
\text{PCC} \quad \begin{array}{c}
\text{Oxidation}
\end{array} \quad \begin{array}{c}
\text{active methylene group}
\end{array}
\]
Chromium Based Oxidation

Pyridinium Dichromate (PDC)

Preparation:

\[ 2\text{CrO}_3 + \text{H}_2\text{O} \rightarrow \text{HO-Cr-O-Cr-OH} \]

Pyridine

Solubility:

Soluble in water, DMF, DMSO, dimethylacetamide. It is sparingly soluble in dichloromethane.
Chromium Based Oxidation

Pyridinium Dichromate (PDC)

Advantages:

1. Excellent reagent for oxidation of allylic alcohols
2. There is no over-oxidation of aldehydes
3. No $E/Z$-isomerization
4. Unlike conjugated aldehydes, non-conjugated aldehydes are readily oxidized to acids by PDC in DMF at 25°C
Chromium Based Oxidation

Pyridinium Dichromate (PDC)

Uses:

\[
R\text{-}\text{OH} \xrightarrow{\text{PDC}, \text{CH}_2\text{Cl}_2} R\text{-}\text{CHO}
\]

\[
R\text{-}\text{OH} \xrightarrow{\text{PDC}, \text{CH}_2\text{Cl}_2} R\text{-}\text{CHO}
\]

\[
R\text{-}\text{OH} \xrightarrow{\text{PDC}, \text{CH}_2\text{Cl}_2} R\text{-}\text{CHO}
\]

\[
\text{OH} \xrightarrow{\text{PDC}} \text{O}
\]

\[
\text{O} \xrightarrow{\text{PDC, DCM}} \text{O}
\]

\[
\text{O} \xrightarrow{\text{PDC, DCM}} \text{O}
\]
Chromium Based Oxidation

Pyridinium Dichromate (PDC)

This reaction is complicated by the cationic cyclization when PCC was used.
Chromium Based Oxidation

Miscellaneous Oxidation of $\text{CrO}_3$

\[
\text{Cyclohexanone} \xleftrightarrow{\text{CrO}_3/\text{AcOH}} \text{Cyclohexene} \xrightarrow{\text{H}_2\text{O}} \text{Cyclohexanone}
\]

\[
\text{Cyclohexene} \xrightarrow{\text{CrO}_3/\text{AcOH}} \text{CrO}_3 \xrightarrow{\text{H}_2\text{O}} \text{Cyclohexanone}
\]

\[
\text{Cyclohexanone} \xrightarrow{\text{CrO}_3/\text{AcOH}} \text{HO}_2\text{C} \xrightarrow{\text{H}_2\text{O}} \text{HO}_2\text{C}
\]

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Chromium Based Oxidation

Etard Reaction

\[ \text{OR} \xrightarrow{\text{CrO}_2\text{Cl}_2, \text{CH}_2\text{Cl}_2} \text{CHO} \]

\[ \text{CH}_3 \xrightarrow{\text{CrO}_3, \text{Ac}_2\text{O}} \text{CHO} \]

\[ \text{CrO}_3 \xrightarrow{\text{Ac}_2\text{O}} \text{AcO}_\text{H}_\text{OAc} \]

\[ \text{Hydrolysis} \rightarrow \text{CHO} \]
Chromium Based Oxidation

Supported Reagents

(1) PCC on alumina
(2) PCC on polyvinylpyridine

Improved yields due to simplified work up

Advantage:

Improved yields due to simplified work up
Chromium Based Oxidation

Transformation

\[ R\text{OH} \rightarrow R\text{-CHO} \]

\[ R\text{HOR}' \rightarrow R\text{R'} \]

\[ R\text{OH} \rightarrow R\text{-COOH} \]

Chromium Reagents

- PCC, Collins reagent, PDC in DCM
- PCC, Collins reagent, PDC, Jones reagent
- Jones reagent, PDC in DMF
- Etard reaction
Manganese Based Oxidation

Potassium Permanganate (KMnO₄)

Under mild condition KMnO₄ can effect conversion of alkenes to glycol

KmnO₄ is such a powerful oxidant that it can cleave the glycol further. So, careful control is required.
Manganese Based Oxidation

Potassium Permanganate (KMnO$_4$)

**In Water Medium:**

- $\text{R} = \text{R'}$  
  $\text{R} = \text{R'}$  
  $\text{HO} = \text{HO}$  
  $\text{Ar}$  
  $\text{Ar}$

$\text{KMnO}_4$, $\text{H}_2\text{O}$  

$\rightarrow$  

- $\text{R} = \text{R'}$  
  $\text{O} = \text{O}$  
  $\text{OH}$  
  $\text{ArCO}_2\text{H}$  
  $\text{ArCO}_2\text{H}$

- $\text{Ar}$  
  $\text{CH}_3$

$\text{KMnO}_4$, $\text{H}_2\text{O}$  

$\rightarrow$  

- $\text{R} = \text{R'}$  
  $\text{O} = \text{O}$  
  $\text{OH}$  
  $\text{ArCO}_2\text{H}$  
  $\text{ArCO}_2\text{H}$
Manganese Based Oxidation

Potassium Permanganate (KMnO₄)

In Organic Solvents:

3.3 mol KMnO₄
Benzene polyether

1.0 mol KMnO₄
R₄NCl

Oxidation of Acetylenes:

Ph≡CH₂CH₂CH₃
KMnO₄
R₄N⁺, DCM

CH₂CH₂CH₃
CH₂CH₂CH₃

CH₂CH₂CH₃

CH₂CH₂CH₃
Manganese Based Oxidation

Potassium Permanganate (KMnO$_4$)

Oxidation of Aromatic Side Chain:

\[
\text{Ar–R} \xrightarrow{\text{KMnO}_4} \text{Ar–CO}_2\text{H}
\]

Oxidation of Amino Compounds:

\[
\text{R}_3\text{C–NH}_2 \xrightarrow{\text{KMnO}_4} \text{R}_3\text{C–NO}_2
\]

Tertiary alkylamines can be oxidized to nitro compounds

Oxidation of Sulphides:
Manganese Based Oxidation

Potassium Permanganate (KMnO₄)

Oxidation of Terminal Alkynes:

Application in the Synthesis of Saccharin:

\[
\text{Saccharin}
\]
Manganese Based Oxidation

**Manganese dioxide (MnO\textsubscript{2})**

**Uses:**
Selective oxidation of allylic & benzylic alcohols

\[
\text{MnO}_2, \text{KCN} \quad \text{EtOH} \quad \text{CN} \quad \text{OH} \\
\text{MnO}_2 \quad \text{CH}_2\text{Cl}_2
\]

Excess of MnO\textsubscript{2} is required
Manganese Based Oxidation

Manganese dioxide (MnO$_2$)

\[
\text{MnO}_2 + \text{ROH} + \text{NaCN} \rightarrow \text{RCO}_2\text{R}
\]

\[
\text{MnO}_2 + \text{OH}^- \rightarrow \text{CN}^-
\]

\[
\text{MnO}_2 + \text{R}^+ \rightarrow \text{RC}^-
\]
Manganese Based Oxidation

Manganese dioxide (MnO$_2$)
Manganese Based Oxidation

Manganese(III) acetate $\text{Mn(OAc)}_3$

$\text{Mn(OAc)}_3$ reacts with various functional groups to form acetate esters. The reactions include the oxidation of alcohols and ketones to form esters and carboxylic acids, respectively. The mechanism involves the formation of an active manganese species which then abstracts a hydrogen atom from the substrate, leading to the formation of an alkene and a manganese species. This process is repeated to form the final product.
Manganese Based Oxidation

Manganese(III) acetate $\text{Mn(OAc)}_3$

\[
\text{OH} \quad \xrightarrow{\text{Mn(OAc)}_3} \quad \text{O} \quad \xrightarrow{\text{OH}} \quad \text{Me}
\]

\[
\text{O} \quad \xrightarrow{\text{Mn(OAc)}_3} \quad \text{Me}
\]

\[
\text{OH} \quad \xrightarrow{\text{Mn(OAc)}_3} \quad \text{Me}
\]

\[
\text{O} \quad \xrightarrow{\text{Mn(OAc)}_2} \quad \text{Me}
\]

\[
\text{OH} \quad \xrightarrow{\text{Mn(OAc)}_3} \quad \text{Me}
\]

\[
\text{OH} \quad \xrightarrow{\text{Mn(OAc)}_3} \quad \text{Me}
\]
Silver-Based Oxidation

\[ Ag_2O \]

Mild oxidant to oxidize aldehyde to carboxylic acid

\[ RCHO + Ag_2O \rightarrow RCOOH + 2Ag \]

\[ Ag_2CO_3 \text{ on Celite (Fetizon's Reagent)} \]

Conversion of diols to lactones

\[ \text{OH} \]

\[ \text{OH} \]

\[ \text{OH} \]

\[ \text{OH} \]
Silver-Based Oxidation

$\text{Ag}_2\text{CO}_3$ on Celite (Fetizon’s Reagent)

Highly Selective:

Mono-Oxidation:

Mechanism:

$\text{Ag}^+ \cdot \text{O}_2^- \cdot \text{O}_2^- \cdot \text{Ag}^+ \rightarrow \text{R}^+ \cdot \text{R}^+ \rightarrow \text{R}^+ \cdot \text{R}^+ + \text{H}_2\text{O} + \text{CO}_2 + 2\text{Ag}$
Silver-Based Oxidation

Silver acetate

In absence of water, Prevost Hydroxylation, *trans*-product

In presence of water, Woodwards hydroxylation, *cis*-product
Other Metal-Based Oxidation

Hunsdiecker Reaction:

\[
\text{CO}_2\text{Ag} + \text{Br}_2 \rightarrow \text{Br} \\
\]

\[
\text{RCOOAg} + \text{X}_2 \rightarrow \text{RCOOX} + \text{AgX} \\
\]

\[
\Delta \quad \text{RCOOX} \rightarrow \text{RCOO}^* + \text{X}^* \quad \text{(Initiation)} \\
\]

\[
\text{RCOO}^* \rightarrow \text{R} + \text{CO}_2 \\
\]

\[
\text{R} + \text{RCOOX} \rightarrow \text{RX} + \text{RCOO}^* \quad \text{(Propagation)} \\
\]
Ruthenium & Osmium tetroxide Oxidation

Mechanism seems to be same in both cases

Uses:

Alkenes are generally oxidized to cis-diols
Alkynes are oxidized to diketones as in case of KMnO$_4$
Ruthenium & Osmium tetroxide Oxidation

Osmium tetroxide ($\text{OsO}_4$)

OsO$_4$ is highly toxic, cannot be used at industrial scale

Use of NMO as co-oxidant along with catalytic amount of OsO$_4$ can be used for higher scale

Selectivity:

Directed by hydroxyl group
Ruthenium & Osmium tetroxide Oxidation

Ruthenium tetroxide (RuO₄)
Prepared in-situ by mixing RuCl₃, NaIO₄, CH₃CN, CCl₄, H₂O

Primary Alcohols:

\[
\text{Ph} - CH₂ - CH₂ - OH \xrightarrow{\text{RuO}_4} \text{Ph} - CH₂ - CH₂ - CO₂H
\]

Secondary Alcohols:
Secondary alcohols oxidized to ketones

\[
\text{HO} - \text{C₆H₆} - \text{CH₂} \xrightarrow{\text{RuCl}_3, \text{NaIO}_4} \text{C₆H₆} - \text{CO}_2 \text{H}
\]

Diols:
Diols are further oxidized to carboxylic acids

\[
\text{Ph} - \text{OH} - \text{CH₂} \xrightarrow{\text{RuO}_4, \text{NaIO}_4} \text{Ph} - \text{CO}_2 \text{H}
\]
Ruthenium tetroxide Oxidation

Ruthenium tetroxide (RuO$_4$)

**Oxidation of Ethers:**

- Ruthenium tetroxide Oxidation

- Oxidation of Phenyl Groups:

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Ruthenium & Osmium tetroxide Oxidation

Tetra-n-propylammonium perruthenate (TPAP)

A catalytic amount of TPAP with NMO as the co-oxidant oxidizes a range of functional groups.

The performance of this reagent is improved by the addition of MS.
Ruthenium & Osmium tetroxide Oxidation

Tetra-n-propylammonium perruthenate (TPAP)

Groups Tolerant are:

Alkenes
THP ethers
Epoxides
Lactones
Silyl ethers
Indoles
Other Metal-Based Oxidation

Lead tetraacetate, LTA, \( \text{Pb(OAc)}_4 \)

Lead tetraacetate is a very good reagent for glycol cleavage

Particularly LTA is useful for glycols that have low solubility in aqueous media

Carboxylic acids are oxidized by LTA
**Other Metal-Based Oxidation**

**Lead tetraacetate, LTA , Pb(OAc)$_4$**

\[
Pb(OAc)_{4} + RCO_2H \rightarrow RCOO-Pb(OAc)_3 + CH_3COOH
\]

\[
RCOO-Pb(OAc)_3 \rightarrow \cdot R + CO_2 + Pb(OAc)_3
\]

\[
\cdot R + Pb(OAc)_3 \rightarrow R^+ + Pb(OAc)_2 + CH_3COO^-
\]

The reductive step is promoted by hydrogen donor solvents.

Acetate arise by the capture of an acetate ion.

In presence of lithium chloride, the product is the corresponding chloride.
α-hydroxy carboxylic acids undergo oxidative decarboxylation to give ketone

\[
\begin{align*}
\text{O-H} & \quad \text{O-H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{Pb(OAc)}_3 & \quad \text{H} \\
\text{CO} & \quad + \text{CO}_2 + \text{Pb(OAc)}_2 + \text{CH}_3\text{CO}_2\text{H}
\end{align*}
\]

γ-keto carboxylic acid preferentially yield α,β-unsaturated ketone

Presumably it goes via oxidation of carboxylic acid to the carbocation followed by deprotonation
Other Metal-Based Oxidation

Lead tetraacetate, LTA, Pb(OAc)$_4$

LTA is toxic in nature

Other Metal-Based Oxidation
Other Metal-Based Oxidation

Lead tetraacetate, LTA, Pb(OAc)$_4$

\[ \text{H-O-C} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{O-Pb(OAc)$_3$} \quad \rightarrow \quad \text{CO}_2 + \text{Alkene} + \text{Pb(OAc)$_2$} + \text{CH}_3\text{CO}_2\text{H} \]

\[ \text{CO}_2 \quad \text{H} \quad \text{O} \quad \text{O-Pb(OAc)$_3$} \quad \rightarrow \quad \text{Pb(OAc)$_2$} + \text{CO}_2 + \text{AcOH} \]
Other Metal-Based Oxidation

Lead tetraacetate, LTA, Pb(OAc)_4

\[
\begin{align*}
\text{LTA} & \quad \text{LTA} \\
\text{CO}_2 & + \text{AcOH} \\
\text{Pb(OAc)}_3 & + \text{Pb(OAc)}_2
\end{align*}
\]

Other Metal-Based Oxidation
Other Metal-Based Oxidation

Oxymercuration

Addition of water to an alkene

When water is used as solvent, it opens the mercurinium ion and gives alcohols.

\[
\text{R} = \text{C-Hg bond is very weak and it can be easily replaced with hydrogen by reducing agents. Generally NaBH}_4 \text{ is used.}
\]
Other Metal-Based Oxidation

Oxymercuration

Addition of water to an alkyne

\[ R\equiv \xrightarrow{Hg(OAc)_2} R\overset{Hg^{2+}}{-\equiv} \xrightarrow{H_2O} HO\overset{\text{HgOAc}}{-\overset{\text{HgOAc}}{\equiv}} \]

This is what we should have expected. But what we get is a ketone

Since AcOH is the byproduct, this protonates the carbonyl group

For hydration of alkynes, we do not need NaBH₄. Moreover, if you use NaBH₄ in the last step, it will reduce the ketone
Other Metal-Based Oxidation

Oxymercuration

\[
\text{OH} \quad \text{Hg(OAc)}_2 \quad \text{OH} \quad \text{NaBH}_4
\]

Deoxydaunomycinone

\[
\text{OH} \quad \text{Hg(OAc)}_2 \quad \text{H}_2\text{O}
\]

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Other Metal-Based Oxidation

Wacker Oxidation

O₂, HCl

CuCl₂ → PdCl₂

Pd⁰ + HCl

HPdⁿCl

β-elimination

R

HO

Wacker oxidation

MgBr

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Other Metal-Based Oxidation

Molybdenum Peroxy Complexes:

MoOPH (MoO₅ Py. HMPA complex)

It contains two electrophilic bridged peroxy ligands and a single oxo-unit.

\[
\begin{align*}
\text{R} & \quad \text{R'} \\
\text{Li}^+ & \quad \text{Mo} \quad \text{O} \quad \text{O} \\
\text{L} & \quad \text{L'} \\
\text{L} = \text{HMPA} & \quad \text{L'} = \text{Pyridine}
\end{align*}
\]

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Non-Metal Based Oxidation
Activated Dimethyl Sulfoxide (DMSO)

\[ \text{S}^+\text{O}^- + \text{E}^+ \rightarrow \text{S}^+\text{O}\text{E} \rightarrow \text{S}^+\text{O} \rightarrow \text{R} \text{CHOH} \rightarrow \text{R} \text{C}=\text{O} \] + Me₂S

Electrophiles

SOCl₂, (COCl)₂, Cl₂, TsCl, (CH₃CO)₂O,
SO₃/pyridine, CF₃SO₃H

Nucleophiles

ROH, PhOH, PhNH₂, R₂C=N-OH, Enols

Swern Oxidation
Moffatt Oxidation
Kornblum Oxidation
Corey-Kim Oxidation
DMSO-Ac₂O

Most of these reactions take place at very low temperature
Non-Metal Based Oxidation

Swern Oxidation

Trifluoroacetic anhydride also can be used instead of \((\text{COCl})_2\)
Non-Metal Based Oxidation

Swern Oxidation

Survives protecting groups

\[
\text{CH} \left( \text{OEt} \right)_2 \xrightarrow{\text{Swern Oxidation}} \text{CH} \left( \text{OEt} \right)_2
\]

No epimerization of aldehydes

\[
\text{H} \quad \text{CH}_3 \\
\text{H} \\
\text{OH}
\xrightarrow{\text{Swern Oxidation}}
\text{H} \quad \text{CH}_3
\]

\[
\text{CH}_3
\]

\[
\text{H} \\
\text{CH}_3
\text{OH}
\xrightarrow{\text{Swern Oxidation}}
\text{H} \\
\text{CH}_3
\text{CHO}
\]

\[
\text{H} \quad \text{CH}_3 \\
\text{H} \\
\text{OH}
\xrightarrow{\text{Swern Oxidation}}
\text{H} \quad \text{CH}_3
\text{CHO}
\]
Non-Metal Based Oxidation

Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]

Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]

Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]

Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]

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\[ \text{Non-Metal Based Oxidation} \]

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\[ \text{Non-Metal Based Oxidation} \]

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\[ \text{Non-Metal Based Oxidation} \]

Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]

Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]

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Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]

Moffatt Oxidation

\[ \text{Non-Metal Based Oxidation} \]
Non-Metal Based Oxidation

DMSO, Ac₂O

Disadvantage: Alcohol may attack acetate

DMSO- SO₃⁻ Py

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Non-Metal Based Oxidation

Kornblum Oxidation

Oxidation of alkyl halides to aldehydes

\[ \text{RCH}_2\text{Br} \xrightarrow{\text{S}^+\text{O}^-} \text{H} \xrightarrow{\text{NaHCO}_3} \text{RCHO} + \text{Me}_2\text{S} \]

Corey-Kim Oxidation

\[ \text{Cl-N} \xrightarrow{\text{S}^+\text{Cl}} \text{HO} \xrightarrow{\text{Base}} \text{R}_2\text{CO} + \text{Me}_2\text{S} \]
Non-Metal Based Oxidation

Hypervalent Iodine(V) Containing Oxidizing Agents

2-Iodoxybenzoic acid (IBX)

Preparation:

IBX  DMP

\[
\text{Oxone, } H_2O \
\text{70 °C}
\]

\[
\text{KBrO}_3 \
2N \text{H}_2\text{SO}_4, 75 \, ^\circ \text{C}
\]
Non-Metal Based Oxidation

2-Iodoxybenzoic acid (IBX)

Mechanism:

Uses:
1. Oxidation of Alcohols:
Non-Metal Based Oxidation
2-Iodoxybenzoic acid (IBX)

2. Introduction of Unsaturation:

OH
\[
\text{IBX (2 eqv)} \rightarrow \text{IBX (2 eqv)}
\]
Toluene-DMSO

\[
\text{IBX (4 eqv)} \rightarrow \text{IBX (4 eqv)}
\]
Toluene-DMSO

3. Selective Oxidation of Benzylic Carbon:

Ar\_R \rightarrow \text{IBX (4 eqv)} \rightarrow Ar\_R

Fluorobenzene-DMSO
Non-Metal Based Oxidation
Dess-Martin Periodinane (DMP)

**Preparation:**

\[
\begin{align*}
\text{IO} & \quad \text{AcO} \\
\text{IO} & \quad \text{OAc} \\
\text{IO} & \quad \text{OAc}
\end{align*}
\]

\[
\text{Ac}_2\text{O}
\]

**Mechanism:**

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{AcO} & \quad \text{OAc} \\
\text{AcO} & \quad \text{OAc}
\end{align*}
\]

\[
\text{HO} \quad \text{R}
\]

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{AcO} & \quad \text{OAc} \\
\text{AcO} & \quad \text{OAc}
\end{align*}
\]

\[
\text{R} \quad \text{H}
\]

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{AcO} & \quad \text{OAc} \\
\text{AcO} & \quad \text{OAc}
\end{align*}
\]

\[
\text{R} \quad \text{H}
\]
Non-Metal Based Oxidation
Dess-Martin Periodinane (DMP)

Uses:

\[
\begin{align*}
\text{OH} & \quad \text{TBSO} & \quad \text{OH} & \quad \text{TBSO} \\
\text{TBSO} & \quad \text{OH} & \quad \text{OH} & \quad \text{TBSO} \\
\text{Ph} & \quad \equiv & \quad \text{OH} & \quad \text{Ph} \\
\text{CF}_3 & \quad \equiv & \quad \text{CF}_3 & \quad \equiv \\
\text{HO} & \quad \equiv & \quad \text{O} & \quad \equiv \\
\text{O} & \quad \equiv & \quad \text{O} & \quad \equiv
\end{align*}
\]
Non-Metal Based Oxidation

Tetramethylpiperididine nitroxide (TEMPO)

It is a stable nitroxide and is the active reagent in oxidizing alcohols.

TEMPO can be used in catalytic amount if NaOCl or NCS is used in stoichiometric amount.

TEMPO (2 mol%)

PhCH₂O(CH₂)₂CH₂OH + TEMPO (2 mol%) NaOCl → PhCH₂O(CH₂)₂CHO
Tetramethylpiperididine nitroxide (TEMPO)

This reagent can selectively oxidize primary alcohols in the presence of secondary alcohols

\[
\text{CH}_3\text{CH(CH)CH}_2\text{OH} \xrightarrow{\text{TEMPO (10 mol%)}} \text{CH}_3\text{CH(CH)CHO}
\]

\[
\text{CH}_3\text{CH(CH)CH}_2\text{OH} \xrightarrow{\text{NCS (1.5 eq)} \text{ TBACl}} \text{CH}_3\text{CH(CH)CHO}
\]

It can also oxidize primary alcohols to carboxylic acids by a subsequent oxidation with hypochlorite ion

\[
\text{RCH}_2\text{OH} \xrightarrow{\text{TEMPO}} \text{RCOOH}
\]

\[
\text{RCH}_2\text{OH} \xrightarrow{\text{NaOCl (3 eq) TBACl}} \text{RCOOH}
\]
Non-Metal Based Oxidation

Epoxidation

Electron rich substrate and electrophilic reagent

Electron deficient substrate and nucleophilic reagent

R = EWG

Stabilized
Non-Metal Based Oxidation
Epoxidation

Electrophilic Reagents:

1. Peracetic acid
2. Perbenzoic acid
3. m-CPBA
4. KHSO$_5$ (Oxone)
5. Dimethyldioxirane (DMDO)

Peracids

Peracids can be prepared from the corresponding acids & H$_2$O$_2$

$$\text{RCO}_2\text{H} + \text{H}_2\text{O}_2 \rightarrow \text{RCO}_3\text{H} + \text{H}_2\text{O}$$
Non-Metal Based Oxidation

**Peracids**

**Mechanism:**

It is believed to be a concerted process

Stereospecific *syn* addition is constantly observed

Epoxides are always *syn*. *Trans* epoxide means substituents are *trans*

The rate of epoxidation

The reactivity of the peracid is increased by EWG's
Non-Metal Based Oxidation

Peracids

Stereoselectivity:

Addition of oxygen comes preferentially from the less hindered side of the molecule.

Regioselectivity:

More electron rich double bond participated in epoxidation.
Non-Metal Based Oxidation

Peracids

Henbest Epoxidation:

Epoxidation directed by a polar group

Hydrogen bonding between hydroxyl group & the reagent stabilizes the transition states

\[
\begin{align*}
\text{Henbest Epoxidation:} & \\
\text{Epoxidation directed by a polar group} & \\
\text{Hydrogen bonding between hydroxyl group & the reagent stabilizes} & \\
\text{the transition states} & \\
\end{align*}
\]
Non-Metal Based Oxidation

**Henbest Epoxidation:**

![Chemical structures](image)

- Reaction with $m$-CPBA:
  - Transformation of a hydroxyl group to an epoxide.

\[ \text{CO}_2\text{Me} \rightarrow \text{CO}_2\text{Me} \]
Non-Metal Based Oxidation

Peracids

Rubottom Oxidation:

Epoxides derived from vinyl silanes are converted into aldehydes or ketones under mild acidic condition.
Non-Metal Based Oxidation

Can you do epoxidation in non-acidic medium? Yes

Nitrile & \( H_2O_2 \)

\[
R-\text{C}≡\text{N} + H_2O_2 \rightarrow \text{R} \text{O} \text{O} \text{N} \text{H}
\]

By product is amide, not acid

DCC-\(H_2O_2\)

Looks like peracid
Non-Metal Based Oxidation

**Methyltrioxorhenium (MeReO$_3$)**

$$\text{MeReO}_3 \xrightarrow{\text{Py, CH}_2\text{Cl}_2, 30\% \text{ H}_2\text{O}_2} \text{PhO}$$

**Dioxiranes (Murray’s Reagent)**

Dimethyldioxirane (DMDO)

[Chemical structures of Methyltrioxorhenium and Dioxiranes]

**Uses:**

- Epoxidation of olefins
- Oxidizes sulfides to sulfoxides & sulfones
- Oxidation of amines to amino N-oxides
- Oxidation of aldehydes to carboxylates

[Chemical structures and reactions]

**More reactive analogue of DMDO**

[Chemical structures and reactions]
Non-Metal Based Oxidation

Dioxiranes (Murray's Reagent)

Mechanism:

\[
\begin{align*}
\text{N,N-Dialkylpiperidin-4-one salts are also good catalysts for epoxidation.}
\end{align*}
\]

The quarternary nitrogen enhances the reactivity of the ketone towards nucleophilic addition.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
+ & \quad \text{Ph} & \quad \text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{KHSO}_5 & \quad \text{K}_2\text{CO}_3 & \quad \text{Ph} & \quad \text{OH} \\
\text{93%} & \quad \text{89% ee}
\end{align*}
\]
Non-Metal Based Oxidation

Epoxidation of Electrophilic Alkenes

\[ \text{Cyclohexene} + \text{H}_2\text{O}_2 + \text{NaOH} \rightarrow \text{Cyclohexene oxide} \]

\[ \text{Cyclohexene} + \text{KOH} \rightarrow \text{Cyclohexene oxide} \]
Non-Metal Based Oxidation

Epoxidation of Electrophilic Alkenes

Strong EWG attached to olefin makes it less reactive

H$_2$O$_2$/NaOH cannot be used as ester will get hydrolyzed and $m$-CPBA is unreactive
Non-Metal Based Oxidation

Baeyer-Villiger oxidation

\[
\begin{align*}
R'\text{CO}_3\text{H} & \quad \rightarrow \quad R'\text{O}_\text{O}_2\text{OH} & \quad \rightarrow & \quad R'\text{O}_\text{O}_3\text{H} + \text{R'COOH} \\
\text{CO}_3\text{H} & \quad \rightarrow \quad \text{CO}_3\text{H} & \quad \rightarrow & \quad \text{CO}_3\text{H} \\
\text{CH}_3\text{CO}_3\text{H} & \quad \rightarrow \quad \text{CH}_3\text{CO}_3\text{H} & \quad \rightarrow & \quad \text{CH}_3\text{CO}_3\text{H} \\
\text{CF}_3\text{CO}_3\text{H} & \quad \rightarrow \quad \text{CF}_3\text{CO}_3\text{H} & \quad \rightarrow & \quad \text{CF}_3\text{CO}_3\text{H}
\end{align*}
\]
Non-Metal Based Oxidation

Transformation of Epoxides

\[ \text{Nu} \]
\[ \text{BF}_3\cdot\text{Et}_2\text{O} \]
\[ \text{MeOH} \]

\[ \text{H}_2\text{O}_2 \]

\[ \text{HCO}_2\text{H} \]
Non-Metal Based Oxidation

Transformation of Epoxides

Base catalyzed ring opening of epoxides leads to allylic alcohols

\[
\begin{align*}
\text{O} & \quad \text{Base} \\
\text{LDA} & \\
\text{HO} & \\
\end{align*}
\]

\[
\begin{align*}
\text{LiClO}_4, \text{CF}_3\text{SO}_3\text{Li}, \text{Mg(ClO}_4)_2, \text{Zn(OTf)}_2, \text{Yb(OTf)}_3 & \text{ catalyze the epoxide ring opening.}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \rightarrow \\
\text{OH} & \\
\text{NR}_2 & \\
\end{align*}
\]

LAH acts as a nucleophilic agent & attacks at the less substituted carbon atom of the epoxide ring. DIBAL-H also serves the purpose

\[
\begin{align*}
\text{OH} & \quad \text{LAH} \\
\text{CH}_3 & \\
\end{align*}
\]

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Non-Metal Based Oxidation

Oxidation with Singlet Oxygen

Generation of Singlet Oxygen:

\[
\text{Photosensitizer} + h\nu \rightarrow ^1[\text{Photosensitizer}]^* \\
^1[\text{Photosensitizer}]^* \rightarrow ^3[\text{Photosensitizer}]^* \\
^3[\text{Photosensitizer}]^* + ^3O_2 \rightarrow \text{Photosensitizer} + ^1O_2 \\
H_2O_2 + ^\cdot OCl \rightarrow ^1O_2 + H_2O + Cl^- \\
(RO)_3P + O_3 \rightarrow (RO)_3P=O \rightarrow (RO)_3P=O + ^1O_2 \\
\]

Diagram: (Reaction mechanisms with structures and molecules)
Non-Metal Based Oxidation

Oxidation with Singlet Oxygen

Mechanism:

1. Concerted mechanism

2. Peroxide-intermediate mechanism

There is a preference for removal of a hydrogen from more congested side of the double bond.
Non-Metal Based Oxidation

Oxidation with Singlet Oxygen

\[
\begin{align*}
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\end{align*}
\]
Non-Metal Based Oxidation

SeO$_2$ Oxidation

Mechanism:

1. SeO$_2$

2. H$_2$O$_2$

Cat. SeO$_2$ t-BuOOH
Non-Metal Based Oxidation

**SeO$_2$ Oxidation**

![Chemical reaction diagram for SeO$_2$ oxidation.]

**PhSeCl Oxidation**

![Chemical reaction diagram for PhSeCl oxidation.]

**Phenyl Sulfoxide Oxidation**

![Chemical reaction diagram for phenyl sulfoxide oxidation.]

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Elimination Reactions

\[
\text{LDA} \quad \text{PhSeSePh} \quad \rightarrow \quad \text{LDA} \quad \text{PhSeSePh} \quad \rightarrow \quad \text{LDA} \quad \text{PhSeSePh} \quad \rightarrow \quad \text{LDA} \quad \text{PhSeSePh} \quad \rightarrow
\]

\[
\text{OAc} \quad \rightarrow \quad \text{OAc} \quad \rightarrow \quad \text{OAc} \quad \rightarrow \quad \text{OAc} \quad \rightarrow
\]

\[
\text{OH} \quad \rightarrow \quad \text{OH} \quad \rightarrow \quad \text{OH} \quad \rightarrow \quad \text{OH} \quad \rightarrow
\]

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Non-Metal Based Oxidation

**NaIO₄ Oxidation**

\[ R\underbrace{\begin{array}{c} R \\ \text{HO} \\ \text{OH} \end{array}}_{\text{OH}} + \text{IO}_4^- \rightarrow \begin{array}{c} R \\ \text{R} \\ \text{R} \end{array} \begin{array}{c} \text{O} \\ \text{P} \\ \text{O} \\ \text{O} \\ \text{OH} \end{array} \rightarrow 2 \text{RCHO} + \text{H}_2\text{O} + \text{IO}_3^- \]

\[ \text{CH}_3\text{COOH} + \text{IO}_3^- + \text{H}_2\text{O} \rightarrow \begin{array}{c} \text{OH} \\ \text{OH} \\ \text{OH} \end{array} \begin{array}{c} \text{O} \\ \text{P} \\ \text{O} \\ \text{O} \\ \text{O} \\ \text{O} \\ \text{OH} \end{array} \]

Non-Metal Based Oxidation
Non-Metal Based Oxidation

Ozonolysis

\[ \text{R} = \text{R}' \quad \xrightarrow{\text{O}_3} \quad \text{RCHO} + \text{R'C}=\text{O} \]

[3+2]

\[ \text{RCH}_2\text{OH} \]

\[ \text{Me}_2\text{S}=\text{O} \]

\[ \text{PPh}_3 \quad \xrightarrow{\text{NaBH}_4 / \text{EtOH}} \quad \text{Ph}_3\text{P}=\text{O} \]

\[ \text{Zn} \quad \xrightarrow{} \quad \text{ZnO} \]

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Non-Metal Based Oxidation

Ozonolysis

MeO

\[ \text{will undergo ozonolysis faster than other} \]

Reductive Workup:

\[
\text{Ozonolysis} \quad 1. \text{O}_3 \quad 2. \text{Na}_2\text{SO}_3
\]

Oxidative Workup:

\[
\text{Ozonolysis} \quad 1. \text{O}_3, \text{HCOOH} \quad 2. \text{H}_2\text{O}_2
\]
Non-Metal Based Oxidation

Oxidation with $N$-sulfonyloxaziridines

1. KHMDS

2. $\text{Ph}\,\text{NSO}_2\text{Ph}$

Example:

1. KHMDS

2. $\text{Ph}\,\text{NSO}_2\text{Ph}$
Non-Metal Based Oxidation

Oxidation of Unfunctionalized Carbon

Barton Reaction:

\[
\text{OH} \xrightarrow{\text{NOCl}} \text{ONO} \xrightarrow{\text{hv}} \text{O} \]

\[
\text{ONO} \xrightarrow{\text{hv}} \text{NO} \xrightarrow{\text{hv}} \text{OH}
\]