Oxidation States of Organic Functional Groups

The notion of oxidation state is useful in categorizing many organic transformations. This is illustrated by the progression of a methyl group to a carboxylic acid in a series of 2-electron oxidations, as shown at right. Included are several functional group equivalents considered to be at the same oxidation state.

Summary of Reagents for Oxidative Functional Group Interconversions:

- Dimethylsulfoxide-Mediated Oxidations
- Dess-Martin Periodinane (DMP)
- o-Iodoxybenzoic Acid (IBX)
- tetra-n-Propylammonium Perruthenate (TPAP)
- N-Oxocarboximide-Mediated Oxidation
- Manganese Dioxide
- Barium Manganese
- Sodium Chlorite
- Silver Oxide
- Potassium Permanganate
- Pyridinium Dichromate (PDC)
- Manganese Dioxide–NaCN–CH$_2$OH
- Bromine
- Bayer-Villiger Oxidation
- Hydroxamic acid
- orthoester
- Carbonic Acid Ester ROH + CO$_2$ (ROCO$_2$H)

- Ruthenium Tetroxide
- O$_2$/Pt
- Jones Oxidation
- Form enolate; Davis Oxaziridine
- Form enolate; MoOPH
- Form silyl enol ether; mCPBA
- Fetizon's Reagent
- N-Oxocarboximide-Mediated Oxidation

- Alkane R-CH$_3$
- organoboranes RCH$_2$BR$_2$
- organometallics in general RCH$_2$M (M = Li, MgX, ZnX...)
- organosilanes RCH$_2$SiR$_3$
- Alcohol R-CH$_2$OH (R-CH$_2$X)
- alkyl halide X = halide
- alkane sulfonate X = OSO$_2$R'
- alkyl azide X = N$_3$
- alkylamine X = NR'$_2$
- alkylthio ether X = SR'
- alkyl ether X = OR'
- Aldehyde (Ketone) R-CHO (RCOR')
- hemiketal (hemiacetal)
- hydrazone
- oxime
- N-Oxocarboximide-Mediated Oxidation
- ketel (acetal)
- geminal dihalide RCX$_2$R'
- aminal R'O$^+$NR'$_2$$''^-$
- enol ether (enamine)
- dithiane
- imine
- Carboxylic Acid R-CO$_2$H
- ester
- amide
- ketene
- thioester
- trihalomethyl RCX$_3$
- nitrile R-CN
- Hydroxamic acid
- orthoester
- Carbonic Acid Ester ROH + CO$_2$ (ROCO$_2$H)
- carbamate
- alkyl haloformate
- isocyanate R-N=C=O
- carbodiimide R-N=C=N-R'
- urea R-N$^+$N$''$R'$

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Dimethylsulfoxide-Mediated Oxidations

- Reviews


General Mechanism

- Dimethylsulfoxide (DMSO) can be activated by reaction with a variety of electrophilic reagents, including oxalyl chloride, dicyclohexylcarbodiimide, sulfur trioxide, acetic anhydride, and N-chlorosuccinimide.

- The mechanism can be considered generally as shown, where the initial step involves electrophilic (E\(^+\)) attack on the sulfoxide oxygen atom.

- Subsequent nucleophilic attack of an alcohol substrate on the activated sulfoxonium intermediate leads to alkoxy sulfonium salt formation. This intermediate breaks down under basic conditions to furnish the carbonyl compound and dimethyl sulfide.

\[
\text{(CH}_3\text{)}_2\text{S}^\text{O} + \text{E}^+ \rightarrow \text{(CH}_3\text{)}_2\text{S}^\text{X}
\]

\[
\text{RCH}_2\text{OH} + \text{(CH}_3\text{)}_2\text{S}^\text{X} \rightarrow \text{H}_2\text{CH}_3 + \text{X}^-
\]

- Alkoxy sulfonium ylide

- Methylthiomethyl (MTM) ether formation can occur as a side reaction, by nucleophilic attack of an alcohol on methyl(methylene)sulnonium cations generated from the dissociation of sulfoxonium ylide intermediates present in the reaction mixture. This type of transformation is related to the Pummerer Rearrangement.

\[
\text{ROH} + \text{H}_2\text{C}^\text{S} = \text{CH}_3 \rightarrow \text{RO}^\text{S} \text{CH}_3
\]


Swern Procedure

- Typically, 2 equivalents of DMSO are activated with oxalyl chloride in dichloromethane at or below –60 °C.

- Subsequent addition of the alcohol substrate and triethylamine leads to carbonyl formation.

- The mild reaction conditions have been exploited to prepare many sensitive aldehydes. Careful optimization of the reaction temperature is often necessary.


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Pfitzner-Moffatt Procedure

- The first reported DMSO-based oxidation procedure.
- Dicyclohexylcarbodiimide (DCC) functions as the electrophilic activating agent in conjunction with a Brønsted acid promoter.
- Typically, oxidations are carried out with an excess of DCC at or near 23 °C.
- Separation of the by-product dicyclohexylurea and MTM ether formation can limit usefulness.
- Alternative carbodiimides that yield water-soluble by-products (e.g., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)) can simplify workup procedures.

DMSO, DCC
TFA, pyr
87% oxidation


Parikh-Doering Procedure

- Sulfur trioxide-pyridine is used to activate DMSO.
- Ease of workup and at-or-near ambient reaction temperatures make the method attractive for large-scale reactions.


- Examples


SO_3•pyr, Et_3N,
DMSO, CH_2Cl_2
99% oxidation

99.9% ee
190-kg scale


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**Myers**

**Dess-Martin Periodinane (DMP)**

- DMP has found wide utility in the preparation of sensitive, highly functionalized molecules.
- DMP oxidations are characterized by short reaction times, use of a single equivalent of oxidant, and can be moderated with regard to acidity by the incorporation of additives such as pyridine.
- DMP and its precursor o-iodoxybenzoic acid (IBX) are potentially heat and shock sensitive and should be handled with appropriate care.


\[ \text{PhCO}_2\text{H} + \text{KBrO}_3 \xrightarrow{2.0 \text{ M } \text{H}_2\text{SO}_4, 65^\circ \text{C}, 2.5 \text{ h}} \text{PhCO}_2\text{OAc} + \text{Ac}_2\text{O} + \text{AcOH} \]

\[ \text{85}^\circ \text{C then 23}^\circ \text{C, ~24 h}} \xrightarrow{74\% \text{ overall}} \text{DMP} \]

- Addition of one equivalent of water has been found to accelerate the alcohol oxidation reaction with DMP, perhaps due to the formation of an intermediate analogous to II. It is proposed that the decomposition of II is more rapid than the initially formed intermediate I:


\[ \text{DMP} \xrightarrow{\text{R}_1\text{R}_2\text{CHOH} - \text{AcOH}} \]

\[ \text{slow} \]

\[ \text{fast} \]

**Oxidation**

**Examples**

- Use of other oxidants in the following example led to conjugation of the β,γ-unsaturated ketone, which did not occur when DMP was used.


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DMP oxidation in the presence of phosphorous ylides allows for the trapping of sensitive aldehydes.

\[
\text{HO} \quad \begin{array}{c}
\text{Ph}_3\text{P}=\text{CHO}_2\text{CH}_3 \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{DMP, CH}_2\text{Cl}_2, \text{DMSO} \\
\text{PhCO}_2\text{H}
\end{array} \quad \text{CH}_3\text{O}_2\text{C} \quad \begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C}
\end{array}
\]

\[94\% \ (2.2 : 1 \ E : E : Z)\]


DMP has been used to oxidize secondary acyclic and macrocyclic amides to the corresponding imides in moist DMSO/fluorobenzene at elevated temperature.

\[
\begin{array}{c}
\text{HO} \\
\text{SCH}_3
\end{array} \quad \begin{array}{c}
\text{NHFMoc} \\
\text{DMP}
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{SCH}_3
\end{array}
\]

\[>90\%\]


**o-Iodoxybenzoic Acid (IBX)**

- The DMP precursor IBX is gaining use as a mild reagent for the oxidation of alcohols.
- A simpler preparation of IBX has been reported.

\[
\begin{array}{c}
\text{Me} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{N} \\
\text{O'}\text{Bu}
\end{array} \quad \begin{array}{c}
\text{O'}\text{Bu} \\
\text{Me}
\end{array}
\]

\[6.0 \text{ equiv DMP} \quad \text{wet DMSO, PhF} \quad 85^\circ \text{C}, 3.5 \text{ h} \quad 86\%\]


IBX is used as a mild reagent for the oxidation of 1,2-diols without C-C bond cleavage.


Pyridines are not oxidized at a rate competitive with the oxidation of a primary alcohol.


- IBX has been shown to form \(\alpha,\beta\)-unsaturated carbonyl compounds from the corresponding saturated alcohol or carbonyl compound.
- The reproducibility of the results of this and related IBX-mediated oxidations has been found to often depend on the presence of water in the IBX employed (for a discussion, see: http://blog-syn.blogspot.com/2013/03/blog-syn-003a-secret-ingredient.html)


Oxidation of secondary amides in moist DMSO/fluorobenzene at elevated temperature.

\[
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{tBu} \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{N} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{tBu} \\
\text{O}
\end{array}
\]

\[86\%\]


Mark G. Charest, Jonathan William Medley
tetra-n-Propylammonium Perruthenate (TPAP): Pr$_4$N$^+$RuO$_4^-$

- Reviews


- Ruthenium tetroxide (RuO$_4$, Ru(VIII)) and, to a lesser extent, the perruthenate ion (RuO$_4^-$, Ru(VII)) are powerful and rather nonselective oxidants.

- However, perruthenate salts with large organic counterions prove to be mild and selective oxidants in a variety of organic solvents.

- In conjunction with a stoichiometric oxidant such as *N*-methylmorpholine-*N*-oxide (NMO), TPAP oxidations are catalytic in ruthenium, and operate at room temperature. The reagents are relatively non-toxic and non-hazardous.

- To achieve high catalytic turnovers, the addition of powdered molecular sieves (to remove both the water present in crystalline NMO and the water formed during the reaction) is essential.

- The following oxidation state changes have been proposed to occur during the reaction:
  
  Ru(VII) + 2e$^-$ → Ru(V)
  
  2Ru(V) → Ru(VI) + Ru(IV)
  
  Ru(VI) + 2e$^-$ → Ru(IV)


- Examples


**Oxidation**


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**N-Oxoaammonium-Mediated Oxidation**

• Reviews


• *N*-Oxoaammonium salts are mild and selective oxidants for the conversion of primary and secondary alcohols to the corresponding carbonyl compounds. These oxidants are unstable and are invariably generated in situ in a catalytic cycle using a stable, stoichiometric oxidant.

\[
\begin{align*}
X^- & \quad N & \quad R_1 R_2 R_3 \\
\text{N-oxoaammonium salt} & \quad -HX & \quad \text{O} & \quad R_2 R_3 \\
& \quad R_1 N_1 R_1 & \quad + & \quad + \\
\end{align*}
\]

• Three possible transition states have been proposed:


• *N*-Oxoaammonium salts may be formed in situ by the acid-promoted disproportionation of nitroxy radicals. Alternatively, oxidation of a nitroxy radical or hydroxyl amine can generate the corresponding *N*-oxoaammonium salt.

\[
\begin{align*}
2 R_1 N_2 R_1 & \quad \text{disproportionation} \quad -H^+ & \quad \text{R}_1 N_2 R_1 & \quad \text{R}_1 N_2 R_1 \\
\text{nitroxy radical} & \quad + H^+ & \quad \text{R}_1 N_2 R_1 & \quad \text{R}_1 N_2 R_1 \\
\end{align*}
\]


• 2,2,6,6-Tetramethyl-1-piperidinyloxyl (TEMPO) catalyzes the oxidation of alcohols to aldehydes and ketones in the presence of a variety of stoichiometric oxidants, including *m*-chloroperoxybenzoic acid (*m*-CPBA), sodium hypochlorite (NaOCl), [bis(acetoxy)-iodo]benzene (BAIB), sodium bromite (NaBrO2), and Oxone (2KHSO5•KHSO4•K2SO4).


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Manganese Dioxide: MnO₂

- Reviews
  
  
  

- A heterogenous suspension of active manganese dioxide in a neutral medium can selectively oxidize allylic, benzylic and other activated alcohols to the corresponding aldehyde or ketone.

- The structure and reactivity of active manganese dioxide depends on the method of preparation.

- Active manganese oxides are nonstoichiometric materials (in general MnOₓ, 1.93 < x < 2) consisting of Mn (II) and Mn (III) oxides and hydroxides, as well as hydrated MnO₂.

- Hydrogen-bond donor solvents and, to a lesser extent, polar solvents have been shown to exhibit a strong deactivating effect, perhaps due to competition with the substrate for the active MnO₂ surface.

- Examples

  ![Manganese Dioxide: MnO₂](image)


  ![Manganese Dioxide: MnO₂](image)


  ![Manganese Dioxide: MnO₂](image)

  **Cresp, T. M.; Sondheimer, F. J. Am. Chem. Soc. 1975, 97, 4412–4413.**

Oxidation


  ![Oxidation](image)


  ![Oxidation](image)


  ![Oxidation](image)

- Mark G. Charest, Jonathan William Medley
Barium Manganate: BaMnO₄

- Review
- Barium manganate and potassium manganate are deep green salts that can be used without prior activation for the oxidation of primary and secondary allylic and benzylic alcohols.
- Examples

\[
\text{BaMnO}_4, \text{CH}_2\text{Cl}_2 \xrightarrow{23 \text{°C}} \frac{85\%}{\text{Ph}}
\]


\[
\text{BaMnO}_4 \xrightarrow{92\%} \text{H}_2\text{C}_\text{OH}
\]


\[
\text{BaMnO}_4, \text{CH}_2\text{Cl}_2 \xrightarrow{98\%} \frac{\text{H}_3\text{C}}{\text{OH}}
\]


Oxidation

Oppenauer Oxidation

- Review
- A classic oxidation method achieved by heating the alcohol to be oxidized with a metal alkoxide in the presence of a carbonyl compound as a hydride acceptor.
- Effectively the reverse of the Meerwein–Pondorff–Verley Reduction.
- The reaction is an equilibrium process and is believed to proceed through a cyclic transition state. The use of easily reduced carbonyl compounds, such as quinone, helps drive the reaction in the desired direction.

\[
\text{Proposed Transition State}
\]

Djerassi, C. Org. React. 1951, 6, 207.
- Examples

(S)-perillyl alcohol

\[
\text{pivaldehyde, toluene} \xrightarrow{2 \text{ mol \%}} \text{H}_3\text{C}_\text{CHO}
\]

99%

- Highly reactive zirconium alkoxide catalysts undergo rapid ligand exchange and can be used in substoichiometric quantities.

\[
\text{cat. Zr(O-t-Bu)}_4, \text{Cl}_2\text{CHO}, \text{CH}_2\text{Cl}_2 \xrightarrow{3 \text{ Å MS}} \text{H}_3\text{C}_\text{CHO}
\]

86%

Chromium (VI) Oxidants

- Reviews


  * The mechanism of chromic acid-mediated oxidation has been extensively studied and is commonly used as a model for other chromium-mediated oxidations.

  \[ R_2CHOH + HCrO_4^- + H^+ \rightarrow R_2CHOCrO_3H + H_2O \]

  \[ R_2COH \rightarrow R_2C=O + HCrO_3^- + BH^+ \]


  * A competing pathway involving free-radical intermediates has been identified.

  \[ R_2CHOH + Cr(IV) \rightarrow R_2\dot{C}OH + Cr(III) + H^+ \]

  \[ R_2\dot{COH} + Cr(IV) \rightarrow R_2C=O + Cr(III) + H^+ \]

  \[ R_2CHOH + Cr(V) \rightarrow R_2C=O + Cr(III) + 2H^+ \]


  * Fragmentation has been observed with substrates that can form stabilized radicals.

  \[ \text{Ph} \quad \text{O} \quad \text{Cr(IV)} \]

  \[ \text{H} \quad \text{(CH}_3\text{)}_3\text{C} \]

  \[ \quad \rightarrow \quad \text{PhCHO} + (\text{CH}_3)_3\text{C}^+ \]


  * Tertiary allylic alcohols are known to undergo oxidative transposition.

  \[ \text{O} \quad \text{Cr(IV)} \]

  \[ \text{H} \quad \text{(CH}_3\text{)}_2\text{C} \]

  \[ \quad \rightarrow \quad \text{PhCHO} \quad \text{83%} \quad \text{Ph}_2\text{C} \]


Collins Reagent: \( \text{CrO}_3\text{pyr}_2 \)

- \( \text{CrO}_3\text{pyr}_2 \) is a hygroscopic red solid which is easily hydrolyzed to the yellow dipyridinium dichromate (\([\text{Cr}_2\text{O}_7]^{2-}\text{pyrH}^+\))

- Typically, 6 equiv of oxidant in a chlorinated solvent leads to rapid and clean oxidation of alcohols.

- Caution: Collins reagent should be prepared by the portionwise addition of solid \( \text{CrO}_3 \) to pyridine. Addition of pyridine to solid \( \text{CrO}_3 \) can lead to a violent reaction.


- In situ preparation of the reagent circumvents the difficulty and danger of preparing the pure complex.


Pyridinium Chlorochromate (PCC, Corey’s Reagent)

- PCC is an air-stable yellow solid which is not very hygroscopic.
- Typically, alcohols are oxidized rapidly and cleanly by 1.5 equivalents of PCC as a solution in N,N-dimethylformamide (DMF) or a suspension in chlorinated solvents.
- The slightly acidic character of the reagent can be moderated by buffering the reaction mixture with powdered sodium acetate.


- Addition of molecular sieves can accelerate the rate of reaction.


- Examples

\[
\]

\[
\]

Sodium Hypochlorite: NaOCl

- Sodium hypochlorite in acetic acid solution selectively oxidizes secondary alcohols to ketones in the presence of primary alcohols.
- A modified procedure employs calcium hypochlorite, a stable and easily handled solid hypochlorite oxidant.

- Examples:

\[
\]

\[
\]

\[
\]

\[
\]

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Selective Oxidations Using N-Bromosuccinimide (NBS) or Bromine

- NBS in aqueous dimethoxyethane selectively oxidizes secondary alcohols in the presence of primary alcohols.

- Examples:

\[
\text{HO-CH}_3\text{CH}_2\text{OH} + \text{NBS, DME, H}_2\text{O} \rightarrow \text{HO-CH}_3\text{CH}_2\text{CO}_2\text{H} > 98\%
\]


- Bromine has been employed for the selective oxidation of activated alcohols. In the following example, a lactol is oxidized selectively in the presence of two secondary alcohols.

\[
\text{HO-CH}_3\text{CH}_2\text{OH} + \text{Br}_2, \text{AcOH} \rightarrow \text{HO-CH}_3\text{CH}_2\text{CO}_2\text{H} > 51\%
\]


- Stannylene acetals are oxidized in preference to alcohols in the presence of bromine:

\[
\text{HO-CH}_3\text{CH}_2\text{OH} + \text{Bu}_3\text{SnOCH}_3 \rightarrow \text{HO-CH}_3\text{CH}_2\text{CO}_2\text{H} 70\%
\]


Selective Oxidations using Other Methods

- Cerium (IV) complexes catalyze the selective oxidation of secondary alcohols in the presence of primary alcohols and a stoichiometric oxidant such as sodium bromate (NaBrO₃).

\[
\text{Ce(SO}_4)_2\cdot 2\text{H}_2\text{SO}_4, \text{KBrO}_3, 7 : 3 \text{CH}_3\text{CN, H}_2\text{O, 80 °C} \rightarrow \text{HO-CH}_3\text{CO}_2\text{H} 48\%
\]


- In the following example, catalytic tetrahydrogen cerium (IV) tetrakissulfate and stoichiometric potassium bromate in aqueous acetonitrile was found to selectively oxidize the secondary alcohol in the substrate whereas NaOCl with acetic acid and NBS failed to give the desired imide.

\[
\text{Ce(SO}_4)_2\cdot 2\text{H}_2\text{SO}_4, \text{KBrO}_3 \rightarrow \text{HO-CH}_3\text{CO}_2\text{H} \rightarrow \text{(±)-palasonin}
\]


- TEMPO catalyzes the selective oxidation of primary alcohols to aldehydes in a biphasic mixture of dichloromethane and aqueous buffer (pH = 8.6) in the presence of N-chlorosuccinimide (NCS) as a stoichiometric oxidant and tetrabutylammonium chloride (Bu₄N⁺Cl⁻).

\[
\text{TEMPO, NCS, Bu}_4\text{N}^+\text{Cl}^-, \text{CH}_2\text{Cl}_2, \text{H}_2\text{O}, \text{pH 8.6} \rightarrow \text{HO-CH}_3\text{CHO} 77\%, \text{Bu}_4\text{N}^+\text{Cl}^- 0.50\%
\]


- Molybdenum catalysts and H₂O₂ have been used to oxidize secondary alcohols in the presence of primary alcohols:

\[
\text{(NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O} + \text{H}_2\text{O}_2, \text{THF, 23 °C} \rightarrow \text{HO-CH}_3\text{CO}_2\text{H} 88\%
\]


Mark G. Charest, Jonathan William Medley
Sodium Chlorite: NaClO₂

- Sodium chlorite is a mild, inexpensive, and selective reagent for the oxidation of aldehydes to the corresponding carboxylic acids under ambient reaction conditions.
- 2-methyl-2-butene is often incorporated as an additive and has been proposed to function as a scavenger of any electrophilic chlorine species generated in the reaction.


Examples

1. NaClO₂, NaH₂PO₄, 2-methyl-2-butene, t-BuOH, H₂O, 0 °C
2. NaClO₂, NaH₂PO₄, 2-methyl-2-butene, t-BuOH, H₂O, 82%


- The two-step oxidation of an alcohol to the corresponding carboxylic acid is most common.


1. TPAP, NMO, CH₂Cl₂
2. NaClO₂, NaH₂PO₄, 2-methyl-2-butene, THF, t-BuOH, H₂O, >52%


Potassium Permanganate: KMnO₄

Review:

* Potassium permanganate is a mild reagent for the oxidation of aldehydes to the corresponding carboxylic acids over a relatively large pH range. Alcohols, alkenes, and other functional groups are also oxidized by potassium permanganate.

* Oxidation occurs through a coordinated permanganate intermediate by hydrogen atom-abstraction or hydride transfer.


* Potassium permanganate in the presence of tert-butyl alcohol and aqueous NaH₂PO₄ was shown to effectively oxidize the aldehyde in the following polyoxygenated substrate to the corresponding carboxylic acid whereas Jones reagent, RuCl₃(H₂O)ₓ-NaIO₄, and silver oxide failed.


• Examples:


In the following example, a number of other oxidants (including Jones reagent, NaOCl, and RuO₂) failed:

Silver Oxide: Ag₂O

• A classic method used to oxidize aldehydes to carboxylic acids.

• Cis/trans isomerization can be a problem with unsaturated systems under the strongly basic reaction conditions employed.

Examples:


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**Pyridinium Dichromate: (pyrH+)$_2$Cr$_2$O$_7$**

- Review


- PDC is a stable, bright orange solid prepared by dissolving CrO$_3$ in a minimum volume of water, adding pyridine and collecting the precipitated product.

- Non-conjugated aldehydes are readily oxidized to the corresponding carboxylic acids in good yields in DMF as solvent.

- Primary alcohols are oxidized to the corresponding carboxylic acids in good yields.


- In the following example, PDC was found to be effective while many other reagents led to oxidative C-C bond cleavage.

In the following example, all chromium-based oxidants failed to give the desired acid.

Pyridinium Dichromate: (pyrH+)$_2$Cr$_2$O$_7$

- Additional Examples


- PDC can oxidize aldehydes to the corresponding methyl esters in the presence of methanol. It appears that in certain cases, the oxidation of methanol by PDC is slow in comparison to the oxidation of the methyl hemiacetal.

- Attempts to form the ethyl and isopropyl esters were less successful.

- Note that in the following example sulfide oxidation did not occur.


- PDC has also been used to oxidize alcohols to the corresponding carboxylic acids.


- However, a suspension of PDC in dichloromethane oxidizes alcohols to the corresponding aldehyde.


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Manganese Dioxide–NaCN–CH₂OH

- A convenient method to convert unsaturated aldehydes directly to the corresponding methyl esters.
- Cis/trans isomerization, a problem when other reagents such as basic silver oxide are employed, is avoided.
- The aldehyde substrate is initially transformed into a cyanohydrin intermediate. Subsequent oxidation of the cyanohydrin furnishes an acyl cyanide which is then trapped with methanol to give the desired methyl ester.
- Conjugate addition of cyanide ion can be problematic.
- Examples


- In the following example, stepwise addition of reagents proved to be essential to achieve high yields.


Bromine

- Review
- Bromine in alcoholic solvents is a convenient and inexpensive method for the direct conversion of aldehydes into ester derivatives.
- Under the reaction conditions employed, secondary alcohols are not oxidized to the corresponding ketones.
- Oxidation of a hemiacetal intermediate is proposed.
- Olefins, benzylidine acetals and thiketals are incompatible with the reaction conditions.
- A variety of esters can be prepared.
- Examples


- A variation of this reaction using NBS as oxidant has been employed in tandem with the catalytic enantioselective Michael addition of nitromethane to an enal:


Mark G. Charest, Jonathan William Medley
Selective Bayer-Villiger oxidation in the presence of unsaturated ketones and isolated olefins has been achieved.

The migratory preference of alkyl groups has been suggested to reflect their electron-releasing ability and steric bulk.

Typically, the order of migratory preference is tertiary > secondary > allyl > primary > methyl.

The reactivity order of Bayer-Villiger oxidants parallels the acidity of the corresponding carboxylic acid (or alcohol): CF₃CO₂H > p-nitroperbenzoic acid > m-CPBA = HCO₃H > CH₃CO₂H > HOOH > t-BuOOH.

Primary and secondary stereoelectronic effects in the Bayer-Villiger reaction have been demonstrated.

Primary effect: antiperiplanar alignment of RL and \( \alpha_{O-O} \)

Secondary effect: antiperiplanar alignment of \( \alpha_p \) and \( \alpha^*_{C-RL} \)

Primary effect: antiperiplanar alignment of RL and \( \alpha_{O-O} \)

Secondary effect: antiperiplanar alignment of \( \alpha_p \) and \( \alpha^*_{C-RL} \)


The Bayer-Villiger reaction occurs with retention of stereochemistry at the migrating center.

Ruthenium Tetroxide: RuO₄

- RuO₄ is used to oxidize alcohols to the corresponding carboxylic acid. It is a powerful oxidant that also attacks aromatic rings, olefins, diols, ethers, and many other functional groups.

- Catalytic procedures employ 1-5% of ruthenium metal and a stoichiometric oxidant, such as sodium periodate (NaIO₄).

- Sharpless has introduced the use of acetonitrile as solvent to improve catalyst turnover. It is proposed to avoid the formation of insoluble Ru-carboxylate complexes and return the metal to the catalytic cycle.


* Examples

![Chem 115](image)

Molecular Oxygen

- Molecular oxygen in the presence of a platinum catalyst is a classic method for the oxidation of primary alcohols to the corresponding carboxylic acids.

- Examples

![Chem 115](image)


Mark G. Charest
**Jones Oxidation**

- Jones reagent is a standard solution of chromic acid in aqueous sulfuric acid.
- Acetone is often beneficial as a solvent and may function by reacting with any excess oxidant.
- Isolated olefins usually do not react, but some olefin isomerization may occur with unsaturated carbonyl compounds.
- 1,2-diols and α-hydroxy ketones are susceptible to cleavage under the reaction conditions.

- **Examples:**

  ![Chemical structure](image)

  Jones reagent

  $0 \degree C$

  $85\%$


- Silyl ethers can be cleaved under the acidic conditions of the Jones oxidation.

  ![Chemical structure](image)

  Jones reagent

  $-10$ to $23 \degree C$

  $88-97\%$


**N-Oxoammonium-Mediated Oxidation of Alcohols to Carboxylic Acids**

- A general method for the preparation of nucleoside 5'-carboxylates:

  ![Chemical structure](image)

  TEMPO, PhI(OAc)$_2$

  CH$_3$CN, H$_2$O

  B = A (90%)

  B = U (76%)

  B = C (72%, NaHCO$_3$ added)

  B = G (75%, Na salt, NaHCO$_3$ added)


- A brief follow-up treatment with sodium chlorite was necessary to obtain complete oxidation to the bis-carboxylic acid in the following example.

  ![Chemical structure](image)

  1. H$_2$, 20% Pd(OH)$_2$-C, EtOAc, EtOH

  2. PhI(OAc)$_2$, TEMPO

  3. NaClO$_2$, t-BuOH, H$_2$O

  NaH$_2$PO$_4$, isopentene

  49% overall


- Toxicity concerns inherent to chromium(VI) species can be minimized by employing CrO$_3$ as a catalyst in the presence of periodic acid as stoichiometric oxidant.

  ![Chemical structure](image)

  CrO$_3$ (1.1 mol %)

  H$_3$IO$_6$

  90\%


**Oxidation**

19
**Davis Oxaziridine**

- Reviews
- N-Sulfonyloxaziridines are prepared by the biphasic oxidation of the corresponding sulfonimine with m-CPBA or Oxone.
  \[
  RSO_2N=CHR' \overset{m\text{-CPBA or Oxone}}{\rightarrow} RSO_2N\equiv\overset{\text{Davis oxaziridine: } R = R' = \text{Ph}}{\rightarrow}
  \]
- Nucleophilic attack by enolates on the electrophilic oxaziridine oxygen furnishes α-hydroxy ketones.
- Potassium enolates are generally the most successful.
- Examples

  ![Chem 115](Image)

  - Enantioselective hydroxylation of prochiral ketones has been demonstrated.
  \[
  \text{Ph} \overset{\text{1. NaHMDS}}{\rightarrow} \text{Ph} \overset{\text{2. } \text{H}_2\text{C}\text{C}\text{H}_3}{\rightarrow} \text{Ph} \overset{\text{OH}}{\rightarrow}
  \]
  \[
  61% (95\% \text{ ee})
  \]

  - Myers Chem 115

  ![Oxidation](Image)

  - A related diastereoselective conjugate addition/α-oxidation protocol has been employed on industrial scale for the synthesis of an HCV protease inhibitor.

  ![Image](Image)


  ![Image](Image)

  - Reviews
    - Mark G. Charest, Jonathan William Medley
Molybdenum peroxy compounds: MoO₅•pyr•HMPA

![Molybdenum peroxy compounds](image)

- Oxidoperoxo molybdenum(pyridine)hexamethylphosphoramide (MoOPH) is commonly used to oxidize enolates to the corresponding hydroxylated compound.
- It is proposed that nucleophilic attack of the enolate occurs at a peroxyl oxygen atom, leading to O-O bond cleavage.
- β-Dicarbonyl compounds are not hydroxylated.

**Examples**

1. LDA, THF, –78 °C
2. MoOPH

91%

(±)-warburganal


Rubottom Oxidation

- Epoxidation of a silyl enol ether and subsequent silyl migration furnishes α-hydroxylated ketones.
- Silyl migration via an oxocarbenium ion has been postulated.


Silver carbonate absorbed on Celite has been found to selectively oxidize primary diols to lactones.

Fetizon's Reagent

Silver carbonate absorbed on Celite has been found to selectively oxidize primary diols to lactones.


Other Methods

Platinum and oxygen have been used for the selective oxidation of primary alcohols to lactones.

Pt/O2 acetone, water 75-85 °C 77%


• TEMPO has been employed as a catalyst for the preparation of lactones.


• Ru complexes have also been employed.


Mark G. Charest, Jonathan William Medley
Oxidative Cleavage of Diols

Sodium periodate (NaIO₄)

- Reviews:

- One of the most common reagents for cleaving 1,2-diols.

\[
\begin{align*}
\text{HO} & \quad \text{OTBDPS} \\
\text{HO} & \quad \text{OAc} \\
\text{CH₃} & \quad \text{C₆H₅}
\end{align*}
\]


Lead Tetraacetate (Pb(OAc)₄)

- Reviews:

- A common reagent for the cleavage of diols. However, Pb(OAc)₄ is a strong oxidant and can react with a variety of functional groups.

- Examples:

\[
\begin{align*}
\text{HO} & \quad \text{OAc} \\
\text{CH₃} & \quad \text{C₆H₅}
\end{align*}
\]


- Oxidative cyclizations sometimes occur. This process likely proceeds by a free-radical mechanism involving homolytic cleavage of an RO–Pb bond.

\[
\begin{align*}
\text{HO} & \quad \text{OAc} \\
\text{CH₃} & \quad \text{C₆H₅}
\end{align*}
\]


- In addition, Pb(OAc)₄ can oxygenate alkenes, oxidize allylic or benzylic C–H bonds, and has been used to introduce an acetate group α to a ketone.

Landy Blasdel
Ozone

• Ozone is the most common reagent for the oxidative cleavage of olefins.

• The reaction is carried out in two steps:
  1. a stream of O3 in air or O2 is passed through the reaction solution at low temperature (0 °C to –78 °C) until excess O3 in solution is evident from its blue color.
  2. reductive or oxidative work-up.

• Mechanism:

  \[
  \begin{align*}
  &= \text{molozonide} \\
  &\text{reductant} \\
  &= \text{ozonide}
  \end{align*}
  \]

• Considered to be a concerted 3 + 2 cycloaddition of O3 onto the alkene.

• Because ozonides are known to be explosive, they are rarely isolated and typically are transformed directly to the desired carbonyl compounds.

• Dimethyl sulfide is the most commonly used reducing agent. Others include I2, phosphine, thiourea, catalytic hydrogenation, tetracyanoethylene, Zn–HOAc, LiAlH4, and NaBH4. The latter two reductants afford alcohols as products.

• Oxidative workup provides either ketone or carboxylic acid products. The most common oxidants are H2O2, AgO2, CrO3, KMnO4, or O2.

• Alkenes with electron-donating substituents are cleaved more readily than those with electron-withdrawing substituents, see: Pryor, W. A.; Giamalva, D.; Church, D. F. J. Am. Chem. Soc. 1985, 107, 2793–2797.

• Forming the primary ozonide with sterically hindered olefins is difficult, and epoxides can be formed instead:

  \[
  \begin{align*}
  \end{align*}
  \]

• Alkenes are ozonized more readily than alkynes:

  \[
  \begin{align*}
  \end{align*}
  \]

• When a TMS-protected alkyne was used in the example above, the authors observed products arising from ozonolysis of the alkyne as well.

  \[
  \begin{align*}
  \end{align*}
  \]

• Ozonolysis of silyl enol ethers can afford carboxylic acids as products:

  \[
  \begin{align*}
  \end{align*}
  \]
Oxidative Cleavage of Alkenes

OsO₄, NaIO₄


• A two-step procedure involving initial dihydroxylation with OsO₄ to form 1,2-diols, followed by cleavage with periodate.

• This procedure offers an alternative to ozonolysis, where it can be difficult to achieve selectivity for one olefin over another due to difficulties in adding precise quantities of ozone.

• Sharpless dihydroxylation conditions (AD-Mix u/l) can lead to enhanced selectivities.

\[
\begin{align*}
\text{H}_2\text{C} & \text{OCM} & \text{PMBO} & \text{OH} & \text{THF, acetone,} & \text{H}_2\text{O, 23 °C} & \text{PMBO} & \text{OH} & \text{NaIO}_4 & \text{THF, H}_2\text{O, 23 °C} & \text{PMBO} & \text{O} \\
\text{H}_3\text{C} & \text{OPMB} & \text{H}_2\text{C} & \text{PMBO} & \text{H}_3\text{C} & \text{PMBO} & \text{H}_3\text{C} & \text{THF} & \text{NMO} & \text{acetone–H}_2\text{O–t-BuOH (4:2:1)}; & \text{NaIO}_4, \text{THF–H}_2\text{O (3:1)} & \text{O} \\
\end{align*}
\]

93% (two steps)


• The procedure is most often performed in two steps, but the transformation is sometimes accomplished in one:

\[
\begin{align*}
\text{H}_2\text{C} & \text{OPMB} & \text{H}_3\text{C} & \text{THF, H}_2\text{O, 23 °C} & \text{OsO}_4, \text{NaIO}_4, \text{THF–H}_2\text{O (3:1)} & \text{77%} \\
\text{H}_2\text{CO} & \text{CH}_3 & \text{CH}_3 & \text{OsO}_4, \text{NaIO}_4, \text{THF–H}_2\text{O (3:1)} & 77% \\
\end{align*}
\]

1. OsO₄ (cat.), NMO, acetone–H₂O–t-BuOH (4:2:1); 2. NaIO₄, THF–H₂O (3:1) ......................89%

• Frequently the two-step protocol is found to be superior to the one-pot procedure. In the example shown, over-oxidation of the aldehyde was observed in the one-pot reaction.


• An improved one-pot procedure uses 2,6-lutidine as a buffering agent:

\[
\begin{align*}
\text{CH}_3 & \text{OPMB} & \text{OCH}_3 & \text{CH}_3 & \text{OsO}_4, \text{NaIO}_4, \text{2,6-lutidine} & \text{dioxane–H}_2\text{O (3:1)} & \text{90%} \\
\text{CH}_3 & \text{OPMB} & \text{OCH}_3 & \text{CH}_3 & \text{OSMe} & \text{OCH}_3 & \text{CH}_3 & \text{2,6-lutidine} & \text{dioxane–H}_2\text{O (3:1)} & \text{90%} \\
\end{align*}
\]

90% 6%

• Ozonolysis of this substrate resulted in PMB removal.

• The authors found that without base, the α-hydroxyketone was formed in ~30% yield. Using pyridine as base, epimerization of the aldehyde product was observed.


• Notice that in the example above, the less-hindered olefin was cleaved selectively.


Landy Blasdel
Oxidative Cleavage of Alkenes

RuO₄

• References:
  


  RuO₄ is a powerful oxidant that is nevertheless useful in many synthetic transformations.

  RuO₄ has been used to cleave alkenes where other oxidation methods (e.g., O₃, OsO₄/NaIO₄) have failed.

  Reaction conditions are relatively mild and usual involving generation of RuO₄ in situ from RuO₂•2H₂O or RuCl₃•H₂O and an oxidant, such as NaIO₄.

  Solvent mixtures of CCl₄, H₂O and CH₃CN have been determined to be optimal. CH₃CN is a good ligand for low valent Ru, and it prevents formation of stable Ru(II/III)–carboxylate complexes which remove Ru from the catalytic cycle. See: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. J. Org. Chem. 1981, 46, 3936–3938.

  RuO₄ will also oxidize alcohols (to ketones), ethers (to lactones or to two carboxylic acids), diols (to two carboxylic acids), alkynes (to 1,2-diketones), and aryl rings (to carboxylic acid products). It will also remove aryl and alkyne groups, leaving carboxylic acids.


Ketone ➔ α,β- Unsaturated Ketone

See also: o-Iodobenzoic Acid (IBX) earlier in handout

General Reference:

**Saegusa Oxidation**


• A two-step procedure involving silyl enol ether formation, followed by treatment with Pd(II).

• The reaction can be performed with stoichiometric Pd(II), or can be rendered catalytic if a terminal oxidant, such as O₂ or p-benzoquinone, is used.

• Mechanism:


• In this case, diallyl carbonate is used as a terminal oxidant.

Selenation/Oxidation/Elimination


• PhSeBr and PhSeCl can be used to selenate enolates of ketones, esters, lactones and lactams.

• PhSeSePh can be used as well, but ketone enolates are unreactive.

• Aldehydes can be selenated via:

• Mechanism:

  \[
  \text{PhSeBr} + \text{Ac} \xrightarrow{\text{base}} \text{PhSe} \xrightarrow{\text{PhSeBr}} \text{SePh} \rightarrow [\text{O}] \text{PhSeOH} + \text{Ac} \xrightarrow{\text{O}}
  \]

• Common oxidants include H₂O₂, O₃, and NaIO₄.


• Electron withdrawing groups on the phenyl ring facilitate the elimination step, which can be difficult with primary or β- or γ-branched selenoxides: Sharpless, K. B.; Young, M. W. J. Org. Chem. 1975, 40, 947–948.

• Examples:

  1. LDA, THF, –78 °C
  2. PhSeBr

  \[
  \text{PhO} \xrightarrow{\text{H₂O₂, pyridine}} \text{PhSePh} \xrightarrow{\text{25 °C, 30 min}} \text{Ph}
  \]

  66%

• Generating the enolate under kinetic conditions can allow for formation of the less-substituted double bond.


  \[
  \begin{align*}
  \text{H₂C} & \xrightarrow{1. \text{LDA; PhSeCl}} \text{H₃C} \\
  \text{H₂C} & \xrightarrow{2. \text{H₂O₂}} \text{H₃C}
  \end{align*}
  \]

  64%


• The example above illustrates how the stereospecificity (syn) of the elimination can be used to achieve selectivity in olefin formation.

  \[
  \text{H₂O₂, THF, H₂O, AcOH, 0 °C}
  \]

  96%

  \[
  \text{H₂O₂, THF, H₂O, AcOH, 0 °C}
  \]

  96%

  \[
  \begin{align*}
  \text{H₂O₂, THF, H₂O, AcOH, 0 °C}
  & \rightarrow \text{H₂O₂, THF, H₂O, AcOH, 0 °C} \\
  \text{cis-fused} & \rightarrow \text{trans-fused}
  \end{align*}
  \]

  85%

  10 : 90

SeO$_2$ Oxidation of Alkenes to Allylic Alcohols

- References

- General method for oxidizing alkenes to allylic alcohols.
  Although the reaction can be performed with stoichiometric SeO$_2$, catalytic methods employing a stoichiometric oxidant (e.g., t-BuOOH) are more frequently used.

- Mechanism:

\[
\text{H}_3\text{C} = \text{CH}_3 \xrightarrow{\text{O=Se=O}} \text{H}_3\text{C} = \text{CH}_2 \xrightarrow{[2,3]-	ext{sigmatropic rearrangement}} \text{H}_3\text{C} \xrightarrow{\text{OSe}} \text{OH}
\]


Selectivity:
(a) oxidation typically occurs at the more highly substituted terminus of the alkene
(b) the order of reactivity of C–H bonds is CH$_2$ > CH$_3$ > CH
(rule (a) takes precedence over rule (b))
(c) when the double bond is within a ring, oxidation occurs within the ring
(4) gem-dimethyl trisubstituted alkenes form (E)-$\alpha$-hydroxy alkenes stereoselectively
