I. Basic Principles

ID. Miscellaneous Oxidation Reactions

Boger Notes: p. 41 - 86 (Chapter IV)
Carey/Sundberg: B p. 786-820 (Chapter B 12.3 - 12.7)
Problem of the Week: Provide a mechanism for this transformation:

![Chemical structure diagram]

2. Bayer-Villiger Oxidations

Ketones react with peroxycacids or hydrogen peroxides to give esters via a C→O rearrangement. Both acid- and base-catalyzed mechanisms have been proposed.

![Mechanism diagram]

The migratory aptitudes are t-alkyl > cyclohexyl = 2°alkyl = benzyl = phenyl > vinylic > 1°alkyl > cyclopropyl > methyl.
Baeyer-Villiger oxidations are highly stereoselective; migration occurs with retention of configuration. Recent work also demonstrates that alkoxyalkyl groups have an extremely high migratory aptitude:


\[
\begin{align*}
\text{BnO} & \quad \text{mCPBA, NaHCO}_3, \\
\text{CH}_2\text{Cl}_2, 0 \degree \text{C to rt.} & \quad \text{BnO} \\
\end{align*}
\]

The bond antiperiplanar to the dissociating peroxide bond is always the bond that migrates, even when electronically disfavored from doing so (Goodman, R. M.; Kishi, Y., "Experimental support for the primary stereoelectronic effect governing Baeyer-Villiger oxidation and Criegee rearrangement." *J. Am. Chem. Soc.* **1998**, *120*, 9392).
When an alkene and a carbonyl are present in the same molecule, an increase in the acidity of the medium favors attack at the carbonyl. Acid-catalyzed side reactions can be suppressed by a phosphate buffer.

![Chemical structures](image1)

Jacobi, P. A.; Herradura, P., "Enantioselective syntheses of (+)- and (-)-blastmycinolactol." *Tetrahedron Lett.*, **1997**, *38*, 6621-6624. *Syn*-selective Nicholas-Schreiber condensation. The methyl ketone was unreactive to the usual reagents, including MCPBA, AcOOH, CF₃CO₂H, and PhSe(O)OH/H₂O₂. The best results were obtained using bis(trimethylsilyl)peroxide [(TMSO)₂], which was initially introduced by Noyori for the chemoselective oxidation of ketones in the presence of alkene double bonds.

![Chemical structures](image2)
Aldehydes usually give acids, with the exception of electron-rich aldehydes. Migration occurs with retention of configuration.


\[
\begin{array}{c}
\text{HO} - \text{CF}_{3} \quad \text{O} - \text{CHO} \\
\uparrow \quad \downarrow \\
\text{HO} \quad \text{CF}_{3} \quad \text{O} - \text{CHO}
\end{array}
\text{MCPBA} \quad \text{CH}_{2}\text{Cl}_{2} \quad 81\% \\
\downarrow \quad \uparrow
\begin{array}{c}
\text{HO} - \text{CF}_{3} \quad \text{O} - \text{CHO} \\
\uparrow \quad \downarrow \\
\text{HO} \quad \text{CF}_{3} \quad \text{O} - \text{CHO}
\end{array}
\]

3. Dehydrogenations


\[
\begin{array}{c}
\text{MeO} \quad \text{O} \\
\uparrow \quad \downarrow \\
\text{MeO}
\end{array}
\text{MnO}_{2}, 70 \degree C \\
\text{methylcyclohexane} \quad 36h, 83\%
\]


\[
\begin{array}{c}
\text{MeO} \quad \text{N} \quad \text{O} \\
\text{TBDMSO} \quad \text{TBDMSO}
\end{array}
\text{CuBr}_{2}, \text{HMTA} \\
\text{DBU, CH}_{2}\text{Cl}_{2} \quad 82\%
\]

![Thiazolines Reaction](image)

**Tawicyclamide B** → **Dehydrotawicyclamide B**


![Thiazolidines Reaction](image)

BocNH\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{CO}_2\text{Me}
\end{array}
\] → BocNH\[
\begin{array}{c}
\text{N} \\
\text{SCO}_2\text{Me}
\end{array}
\]

MnO\text{2}, benzene, 55 °C, 2-4 h 69%
4. Oxidations of Organometallics


After a sulfoxide/magnesium exchange reaction, a carbenoid homologation reaction provides a chiral secondary Grignard reagent that can be oxidized enantioselectively.

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoO2·Py·DMPU</td>
<td>84%</td>
<td>92%</td>
</tr>
<tr>
<td>PhO2·S·N·Ph</td>
<td>80%</td>
<td>91%</td>
</tr>
<tr>
<td>O·B·O</td>
<td>80%</td>
<td>88%</td>
</tr>
<tr>
<td>TMS-O·O·TMS</td>
<td>20%</td>
<td>82%</td>
</tr>
<tr>
<td>Tr(OHP)4·BuOOH</td>
<td>82%</td>
<td>71%</td>
</tr>
<tr>
<td>Li·O·O·Bu</td>
<td>75%</td>
<td>32%</td>
</tr>
<tr>
<td>O·O</td>
<td>89%</td>
<td>15%</td>
</tr>
</tbody>
</table>

5. Allylic Oxidations


(a) PCC, pyr. 4Å MS, CH2Cl2 (79%)
(b) Red-Al, CuBr; AcOH, THF (89%)
(c) BH4·OEt2, THF; PCC, 4 Å MS, CH2Cl2 (60%)
6. Benzylic Oxidations


- IBX (3-4 equiv), PhF/DMSO, 80 °C
- IBX (3-4 equiv), PhF/DMSO, 80 °C
- IBX (3-4 equiv), PhF/DMSO, 80 °C
- IBX (10 equiv), DMSO, 110 °C, 24 h

7. Ozonolysis

According to the Criegee mechanism, 1,3-dipolar cycloaddition gives a 1,2,3-trioxolane product that rearranges to a 1,2,4 trioxolane (the ozonide) by fragmentation into a ketone and a carbonyl oxide followed by a second dipolar addition. In addition to catalytic hydrogenation, LAH, NaBH₄, Zn/AcOH, and Me₂S/MeOH can be used to decompose the ozonide.

1,3-Dipolarophiles, such as ketones, methyl formate, phenanthrene quinone and methyl pyruvate have been employed to trap the carbonyl oxides to give tri- and tetra-substituted ozonides. The goal of these trapping experiments is simply to prepare the ozonides which are difficult to obtain by normal procedures (*Tetrahedron* 1997, 53, 5217-5232).

Alkenes can usually be ozonized in the presence of alkynes (since ozone is an electrophilic reagent, it actually prefers alkenes). Non-compatible functional groups are:


The nonoxidative decomposition of cyclohexene ozonide gives an aldehyde-carboxylate.

- Pyridine serves to attenuate the reactivity of ozone toward electron-rich functional groups such as a PMB-ether:

![Diagram]

8. High-Valent TM(0) Epoxidations

Mo, V, W (H₂WO₄), Ti, Al serve as catalysts with t-BuO₂H or other peroxides as stoichiometric oxidants. Toluene is a frequent solvent. Mo(CO)₆ is the catalyst of choice for substrates lacking directing groups.

\[
\text{mechanism:} \quad \begin{array}{c}
\text{O} \\
\text{M} \\
\text{O}
\end{array} \quad \begin{array}{c}
t-\text{Bu} \\
\leftarrow \text{L}_n \\
\rightarrow \text{M}
\end{array} \quad \text{syn-epoxidation}
\]

with directing groups such as -OH: ca. 1000x faster than parent alkene, esp. with allylic and homoallylic OH, ester, etc.

\[
\begin{align*}
\text{substrate} & \quad \text{TBHP, Mo(CO)₆} \\
& \quad 66\% \\
\text{product} & \quad \text{MCPBA} \\
& \quad 94\% \\
\text{product} & \quad \text{t-BuOOH/VO(acac)₂} \\
& \quad 6\%
\end{align*}
\]

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPBA</td>
<td>64 : 36</td>
</tr>
<tr>
<td>t-BuOOH/VO(acac)₂</td>
<td>29 : 71</td>
</tr>
<tr>
<td>t-BuOOH/Mo(CO)₆</td>
<td>62 : 38</td>
</tr>
<tr>
<td>t-BuOOH/Al(t-Bu)₃</td>
<td>64 : 36</td>
</tr>
</tbody>
</table>
The extent to which a hydroxyl group is involved in the epoxidation of cyclic alkenes and alkadienes is determined not only by its position relative to the double bond but also by the conformation of the molecule as a whole (Dryuk, V. G.; Kartsev, V. G., "Mechanism of the directing influence of functional groups and the geometry of reactant molecules on peroxide epoxidation of alkenes." Russ. Chem. Rev. 1999, 68, 183-201):
9. Sharpless Asymmetric Epoxidations

1980: Katsuki & Sharpless; Ti(IV)alkoxide, tartrate, t-BuOOH.

"O" with D(-)-DIPT (unnatural; 2S,3S)

\[ \text{CH}_2\text{Cl}_2, -20^\circ\text{C} \rightarrow \text{epoxyalcohol} \]

70-90% yield >90% ee

"O" with L-(+)-DIPT (natural; 2R,3R)


- incompatible functional groups: amines, -CO\(_2\)H, -SH, phenols, phosphines.
Stoichiometry: 5% Ti / 6% tartrate to 10% Ti / 12% tartrate:

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\rightarrow & \quad 3 \text{ Å MS, TBHP} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

5% / 6% → 92% ee
2% / 2.5% → 69% ee


-O with (-)-DIPT

1:1

If stopped at 50% conversion, this diastereomer is enriched

-O' with (-)-DIPT

If stopped at 50% conversion, this diastereomer is enriched
Especially interesting in this context is the potential of the Sharpless asymmetric epoxidation in bi-directional synthesis and for the differentiation of diastereotopic alkenes:

\[
\text{anti/syn } 98:2 \\
\text{with (+)-DIPT} \\
\text{anti/syn } 38:62
\]

\[
\frac{k_{\text{fast}}}{k_{\text{slow}}} = 104
\]

Relative rates at 0 °C:

<table>
<thead>
<tr>
<th>DIPT</th>
<th>DET</th>
<th>DMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Bulkier esters improve kinetic resolution
Assuming that no significant bi-epoxidation has occurred after 3 h, the ee of this reaction would be 84% for the major product, and the de would be 87% (anti/syn) for the reaction.


How would you make this?

Preparation of starting diepoxide:
