**OXIDATION OF C–H BONDS**

*Allylic Oxidation*

**Reagent:**

\[ \text{SeO}_2 \]

**Transformation:**

\[ \begin{array}{c}
\text{R} \rightarrow \text{R} - \text{OH} \\
\end{array} \]

**General Mechanism**

- a series of sigmatropic rearrangements

\[ \begin{array}{c}
\text{R} \rightarrow \text{R} - \text{Se} - \text{OH} \\
\rightarrow \text{R} - \text{Se} - \text{OH} \\
\rightarrow \text{hydrolysis} \\
\rightarrow \text{R} - \text{OH} \\
\end{array} \]

- \( \text{SeO}_2 \) toxic and hard to remove from product
- Catalytic variant developed using TBHP as stoichiometric co-oxidant
- Problem of side-reactions especially if alkene in ring
- Reaction also functions with other reagents such as PDC

**Guidelines for Predicting Product**

1. Hydroxylation occurs \( \alpha \) to the most substituted end of alkene
2. Order of oxidation is \( \text{CH}_2 > \text{CH}_3 > \text{CH} \)
3. If alkene in ring, oxidation will occur in ring if possible (but Bredt's rule applies)
4. Rearrangement products can and will (more often than not) be formed

**Use in Synthesis**

- selective by guideline 1
- selective by guideline 2

\[ \begin{array}{c}
\text{HO} \\
\text{SeO}_2, \text{HCOOH} \quad 50\% \\
\end{array} \]

- wrong stereochemistry

- guideline 2

*Gareth Rowlands (g.rowlands@sussex.ac.uk) Ar402, http://www.sussex.ac.uk/Users/kafj6, Reduction and Oxidation 2002*
Related reaction: Formation of Dicarbonyl Compounds
Transformation:

\[ \text{PhCHO} \]

Mechanism

\[
\begin{align*}
\text{SeO}_2 + \text{H}_2\text{O} &\rightarrow \text{SeOH} \quad \text{OH}
\end{align*}
\]

Use in Synthesis

What have we learnt?
- The position \(\alpha\)-to a double bond can be oxidised
- A set of guidelines allow some degree of predictability to this reaction
- The reaction proceeds via a series of sigmatropic rearrangements
- A related reaction results in the synthesis of dicarbonyl compounds
Oxidation of Activated C–H Bonds
\(\alpha\)-Hydroxylations

Reagent:

Davis’ Oxaziridine

\[
\text{Oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)}
\]

\(\text{MoOPh}\)

Transformation:

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^1 \\
\text{R} & \quad \text{R}^1 \\
\text{R} & \quad \text{R}^1
\end{align*}
\]

General Mechanism

Oxaziridine

\[
\begin{align*}
\text{R} & \quad \text{R}^1 \\
\text{R} & \quad \text{R}^1 \\
\text{R} & \quad \text{R}^1
\end{align*}
\]

MoOPh

Use in Synthesis

\[
\begin{align*}
\text{CH}_2\text{OBn} & \quad \text{CH}_2\text{OBn} \\
\text{H} & \quad \text{H} \\
\text{OMe} & \quad \text{OMe}
\end{align*}
\]

1. LDA
2. Davis’ oxaziridine
70 %
Use in Synthesis

- Chiral oxaziridines can be prepared allowing reagent control asymmetric reactions

Reaction with other Stabilised Anions
Reaction with other Stabilised Anions

\[ \text{Nef-like Reaction} \]

\[ \text{CN} \quad \text{LDA} \quad \text{MoOPh} \quad \text{base} \quad \text{CN} \quad \text{HO} \]

- Use of **oxaziridines** preferable to MoOPh (results & toxicity) but this is **substrate dependant**

**What have we learnt?**
- You can readily introduce hydroxyl group \( \alpha \)-to functionality
- Reaction can be achieved asymmetrically
- Reaction can be used to oxidatively cleave functionality
Miscellaneous C–H Oxidations

- Some recent developments in C–H oxidation
- Katsuki has used Mn-salen complexes to perform enantioselective C–H oxidations

\[
\begin{align*}
R & \quad (X = \text{O, NP}) \\
\text{PhIO, } -30^\circ \text{C, } \\
C_6H_5Cl & \\
\text{yield } &= 41-61 \% \\
e.e. &= 82-90 \%
\end{align*}
\]

Oxidation of Unactivated C–H Bonds
Dioxirane Strikes Back

- Dioxiranes are amazingly reactive (sometimes)

\[
\begin{align*}
\text{Oxidation} & \\
\text{Dioxirane} & \\
\text{Back} & \\
\text{Dioxiranes} & \\
\text{Reactive} & \\
\text{(sometimes)} & \\
\end{align*}
\]

- Can be quite slow so more reactive dioxiranes have been developed:

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{O} \\
\text{18 min., } -20^\circ \text{C} & \\
& \\
98\% & \\
\end{align*}
\]

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{O} \\
\text{20 equiv., DCM / } & \\
\text{H}_2\text{O, } -20^\circ \text{C} & \\
74\% & \\
\end{align*}
\]

Possible Mechanism

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{R} \\
\text{H} & \quad \text{R} \\
\text{H} & \quad \text{R} \\
\text{H} & \quad \text{R} \\
\end{align*}
\]
**MISCELLANEOUS OXIDATIONS**

*Ozonolysis*

Reagent:

\[ O_3, \text{DMS} \text{ or } PPh_3 \text{ or } \text{LiAlH}_4 \]

Transformation:

\[
\begin{array}{c}
\text{R-} \\
\text{R-} \\
\text{R-} \\
\text{R-} \\
\end{array}
\xrightarrow{\text{O}}
\begin{array}{c}
\text{R-} \\
\text{R-} \\
\text{R-} \\
\text{R-} \\
\end{array}
\]

General Mechanism

- Ozonide then has to be broken down (they can be isolated but not advisable)

Decomposition with DMS, PPh$_3$ or H$_2$Pd / C

\[
\begin{array}{c}
\text{R-} \\
\text{R-} \\
\text{R-} \\
\text{R-} \\
\end{array}
\xrightarrow{\text{PPh}_3}
\begin{array}{c}
\text{R-} \\
\text{R-} \\
\text{R-} \\
\text{R-} \\
\end{array}
+ \text{O=PPh}_3 \text{ or (DMSO)}
\]

Reductive Decomposition with LiAlH$_4$, NaBH$_4$

- Quite shockingly this gives the alcohol

Oxidative Decomposition with peracids or hydroperoxides

\[
\begin{array}{c}
\text{R-} \\
\text{R-} \\
\text{R-} \\
\end{array}
\xrightarrow{H_2O_2}
\begin{array}{c}
\text{R-} \\
\end{array}
\]

Selectivity

- More *electron-rich* alkenes react faster
- Enol ethers give esters on ozonolysis

\[
\begin{array}{c}
\text{OMe} \\
\end{array}
\xrightarrow{O_3, \text{DMS}}
\begin{array}{c}
\text{OMe} \\
\end{array}
\]
Use in Synthesis

Fischer indole

• lactam formation and isomerisation
• attacks electron-rich alkene

O₃, AcOH

The Lemieux–Johnson Reagent

Reagent:
OsO₄, NaIO₄

Transformation:

General Mechanism
• Use catalytic quantities of osmium which is reoxidised by the periodate
• Dihydroxylation as before (vide supra)
• NaIO₄ cleaves the diol...

What have we learnt?
• Alkenes can be oxidatively cleaved in a number of ways
Baeyer-Villiger Oxidation

Reagent:

$RCO_3H$

Transformation:

![Chemical structure](attachment:image.png)

General Mechanism

Migratory aptitude

- Unsymmetric ketones have a choice of which substituent will migrate
- Normally most nucleophilic group / group that can stabilise $\delta^+$ charge best migrates
  $t$-alkyl $> \text{cyclohexyl} = \text{secondary alkyl} = \text{benzyl} > \text{vinylc} > \text{primary alkyl} > \text{methyl}$
- Reason:
  - Migration is concerted
  - During migration 2 $e^-$ spread over 3 atoms
  - Any group stabilising the electron deficiency will be favoured

As the migration is concerted (bonds broken and formed at same time) it occurs with

*retention of stereochemistry*
• The methyl group has a very poor migratory aptitude, consequently the Baeyer-Villiger reaction is an excellent way to make acetates.
• Acetates are readily cleaved, therefore the Baeyer-Villiger is equivalent to:

$\text{R} \xrightarrow{\text{O}} \text{R-OH}$

**Use in Synthesis**

- **Problem:** If alkenes are present a possible competitive reaction is *epoxidation*.
- **Conditions:** Under acidic conditions, Bayer-Villiger favoured.
- **Conditions:** mCPBA + inert solvent at low temperature encourages epoxidation.

![Chemical diagram showing the Baeyer-Villiger reaction and catalytic asymmetric variation.](image-url)

*Catalytic Asymmetric Baeyer-Villiger*

Yield = 62%
e.e. = 91%
97SL1151

_Gareth Rowlands (g.rowlands@sussex.ac.uk) Ar402, http://www.sussex.ac.uk/Users/kafj6, Reduction and Oxidation 2002_
**Tamao-Fleming Oxidation**

**Reagent:**

KF, KHCO₃, H₂O₂ or EX / RCO₃H / base

**Transformation:**

\[ \text{SiR}_2X \rightarrow \text{OH} \]

**General Mechanism**

X = heteroatom or H

- concerted migration so retention of stereochemistry

**Use in Synthesis**

- Silyl groups relatively unreactive
- C–Si bond only easily broken when carbon functionality allows it *eg:*

\[ \text{SiR}_2X \rightarrow \text{Me}_3\text{Si} \rightarrow \text{OH} \]

- Silyl group very useful - can be thought of as *super-proton* - it activates double bonds, encourages substitution rather than addition, controls regio- and stereochemistry (97CR2063)

**Tamao Oxidation**

\[ \text{SiR}_2X \stackrel{\text{KF, KHCO}_3}{\rightarrow} \text{OH} \]

**Fleming Oxidation**

- More useful silyl groups BUT harsher conditions

1. BuLi
2. \(\text{BF}_3\)
3. 1. \(\text{H}_2\text{O}_2\), NaHCO₃, KF
4. \(\text{SiPh}_2\text{Cu}\)

Gareth Rowlands (g.rowlands@sussex.ac.uk) Ar402, http://www.sussex.ac.uk/Users/kaff6, Reduction and Oxidation 2002
**Wacker-Type Oxidations**

**Reagent:**

PdCl$_2$(cat), or CuCl, O$_2$

**Transformation:**

\[ R\ce{\text{-}}\text{CH}_2\text{-}R' \xrightarrow{\text{PdCl}_2\text{L}_n} \text{R}\text{-CH}_2\text{-OH} \]

**General Mechanism**

\[ \text{Pd(2)L}_n \xrightarrow{\beta\text{-elimination}} \text{Pd(0)L}_n \xrightarrow{\text{re-oxidises palladium}} \text{PdClL}_n \]

**Use in Synthesis**

- allows these 2 stereocentres to be set-up via the reliable Brown or Roush crotylation

\[ \text{Me}\text{CO}_2\text{O} + \text{MeO} \xrightarrow{20 \text{ mol}\% \text{PdCl}_2\text{, CuCl}, \text{O}_2\text{, H}_2\text{O} / \text{DMF}} \text{85\%} \]

\[ \text{OMe} \text{OTBS} \text{CO}_2\text{Me} \]

**Problems:**

- alkene isomerisation
- chlorination (especially if CuCl$_2$ used)
- regiochemistry
- acid sensitivity of molecule as HCl produced

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**Modifications to the Wacker Reaction**

**Smith’s Modifications**

- HCl destroying product
- Replace CuCl with Cu(OAc)₂ - no HCl generated only the weaker AcOH
- Yield increased to 86%

**Oxo-mercurial Variant**

\[
\text{NBn} \quad \text{PhSO}_2 \quad \text{Bu} \quad 1. \text{THF}:\text{H}_2\text{O}, \text{Hg(OAc)}_2 \\
2. \text{THF}, \text{PdCl}_2, \text{CuCl}_2 \\
\]

- Proceeds via oxo-mercuriation then transmetallation
- Standard Wacker resulted in a maximum yield of 45%

**Intramolecular Wacker-Type Oxidation**

**Asymmetric Intramolecular Variant**

\[
\text{Pd(O}_2\text{CCF}_3)_2 \\
\]

Gareth Rowlands (g.rowlands@sussex.ac.uk) Ar402, http://www.sussex.ac.uk/Users/kaff6, Reduction and Oxidation 2002