Alkene Epoxidations

- A huge topic which we will only skim the surface of
- References will be included for those who want more detail

*Peracids: The Prilezhaev (Prileschajew) Reaction*

Reagent:

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

Transformation:

\[
\begin{align*}
\text{CH}_2 = \text{CH}_2 & \quad \rightarrow \\
\text{CH}_2 = \text{CH}-\text{O} & \quad \text{O}
\end{align*}
\]

General Mechanism

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

Use in Synthesis

- Peracids much weaker acids than carboxylic acids (\(pK_a\) 8.2 vs 4.8)
- But carboxylic acid is a by-product so buffer with \(\text{NaHCO}_3\)
- Peracids are *electrophilic* so electron withdrawing groups on \(R\) good (\(m\text{CPBA}\))
- Electron-rich alkenes more reactive
- *Hydrogen-bonding* can direct epoxidations

\[
\begin{align*}
\text{HO} \quad \text{ArCO}_3\text{H} & \quad \rightarrow \\
\text{HO} & \quad \text{ArCO}_3\text{H}
\end{align*}
\]

Hydroperoxides

- \(\text{H}_2\text{O}_2\) & alkyl hydroperoxides require the presence of a transition metal to initiate epoxidation
- \(\text{tBuO}_2\text{H} \ (\text{TBHP})\) favoured as safe, soluble and stable in anhydrous solvents and cheap

\[
\begin{align*}
\text{R} & \quad \text{M} \\
\text{O} & \quad \text{O} & \quad \text{M} & \quad \text{R} \\
\text{M} & \quad \text{O} & \quad \text{O} & \quad \text{M} \\
\text{M} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

Gareth Rowlands (g.rowlands@sussex.ac.uk) Ar402, http://www.sussex.ac.uk/Users/kafj6, Reduction and Oxidation 2002
Directed Epoxidations Utilising Hydroperoxides
93CR1307 (directed reactions)
- The use of transition metals can allow directed epoxidations
- Use to control chemoselectivity
- Used to control stereoselectivity

$mCPBA$: TBHP / VO(acac)$_2$

<table>
<thead>
<tr>
<th>1</th>
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- chemo- and stereoselective

Mechanism
- internal delivery
- activation of peroxide
- TBHP rapid ligand exchange
Acyclic systems also show good selectivity

\[
\text{TBHP} \quad \text{VO(acac)}_2 \quad \begin{align*}
\text{19 : 1} & \quad \text{erythro} \\
\text{2.5 : 1} & \quad \text{erythro}
\end{align*}
\]

- biggest effect is \( R'' \)
- therefore use temporary blocking group

\[
\text{TBHP} \quad \text{VO(acac)}_2 \quad \text{TBAF} \quad \begin{align*}
\text{25 : 1} & \quad \text{erythro} \\
& \quad \text{85CC1636}
\end{align*}
\]

- this all leads on to probably the most famous epoxidation system…
Sharpless Asymmetric Epoxidation (S.A.E.)

- It is often forgotten that this was the FIRST GENERAL ASYMMETRIC CATALYST
- Still used extensively, many syntheses have SAE as the keystone or at least introduce chirality via the SAE

Reagent:
TBHP, Ti(OiPr)_4, DCM,
(catalytic when 4Åms used)

Transformation:
\[
\begin{align*}
R^1 & \quad R^2 & \quad R^3 \\
\text{Transformation:} & \quad 70-90\% & \quad >90\% \text{ ee} \\
\text{General Mechanism:} & \quad \text{same as outlined before.} \\
& \quad \text{intermediate believed to look like:} \\
\end{align*}
\]

- Should be noted that there are 8 different binding modes for Ti and tartrate
- Which isomer of DET do you use

- with left-hand point thumb in direction of alcohol (not Faimer bar)
- if you want "O" on top its on your kNuckles so use Negative (−)-DET
- if you want "O" on bottom its on your Palm so use Positive (+)-DET

"O" D-(−)-DET unnatural isomer

"O" L-(+)-DET natural isomer

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

- DCM is an uniquely efficient solvent
- Complex can not be stored
- Catalyst must be aged

**Substrates**

- Yield = good
e.e. = 90%
few examples
but generally good

**Kinetic resolution**

- must stop reaction before
100% completion or you will just
recover a different racemate
- both enantiomers react just
at different rates

- R group hinders attack and
slows epoxidation down

- produced faster

- If allylic alcohol is the desired product use 0.6 equiv. TBHP
- If epoxy alcohol is the desired product use 0.45 equiv. TBHP

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• Although very useful, kinetic resolution only allows a maximum of 50 % yield
• Desymmetrisations allow a theoretical 100 % yield

- desymmetrisation preferentially forms one isomer

  Fast
  \[ \text{Fast} \]
  \[ \text{Slow} \]

- kinetic resolution removes *unwanted* isomer

• Attractive strategy due to combining initial desymmetrisation with a subsequent kinetic resolution to result in very impressive enantiomeric excesses
• e.e. of desired product increases with time (84 % 3hrs → >97 % 140 hrs)

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\[ \text{BF}_3\cdot\text{OEt}_2 \]

\[ \text{KDO} \]

**What have we learnt?**
- Peracids and hydroperoxides are good epoxidising reagents
- Use of transition metals allows directed epoxidations
- SAE is the cornerstone of many total synthesis
- It works well for the majority of *trans* allylic alcohols
- It can be used in kinetic resolution or desymmetrisation reactions

**References:**
- directed: 93CR1307
- Sharpless: 87JACS5765(good), Comp.Org.Syn. Vol.7, Ch.3.2, 91CR437
- Resolution: 81JACS464
- Desymmetrisation: 87JACS1525, 94ACR9
- KDO: 90T4793

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Two building blocks from KC Nicolaou's synthesis of amphotericin B show the power of SAE.

1. Swern
2. Wittig
1. DIBAL
2. tBuCOCl
3. TPSCI
4. DIBAL

1. Red-Al
2. tBuCOCl

(+) DET, Ti(OiPr)_4, TBHP

(-) DET, Ti(OiPr)_4, TBHP

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**Dioxirane Epoxidations**

**Reagent:**

![Dioxirane structure](image)

**Transformation:**

![Epoxidation structure](image)

- *cis*-spiro transition state
- *concerted mechanism*
- *syn-addition*

**General Mechanism**

**Preparation**

- Most common dioxirane is dimethyldioxirane (DMDO)
- Prepared as a pale yellow solution in acetone by the action of oxone or caroate KHSO$_5$

![Preparation reaction](image)

- ~0.08–0.10 M acetone solution "distilled" off with carrier gas to prevent further reaction of oxone and DMDO

**Use in Synthesis**

- *cis*-alkenes react more efficiently for steric reasons (~7-9 times more reactive)

![cis-alkene reaction](image)

- Stereocentrol is a result of steric interactions
- Addition of DCM or H$_2$O decreases stability therefore increases reactivity
- Used at low temperature and neutral conditions (as generates acetone as a by-product)
- Mild so can generate very sensitive epoxides

![Stereocentrol](image)

**Disadvantages:**

- VERY reactive, heteroatoms and hydroxyl groups can be oxidised
- Even *unactivated* C–H can be oxidised

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Catalytic Variant

- As the dioxirane precursor, the ketone, is regenerated during the reaction only a catalytic quantity is required if dioxirane generated in situ
- Possible if pH is kept between 7.0 – 7.5 with phosphate or bicarbonate buffer
- if pH too low then dioxirane formation can not proceed (deprotonation impossible viva supra)
- if pH too high dioxirane destroyed by oxone

Catalytic Asymmetric Variant

- Shi has developed an asymmetric variant using a chiral sugar derivative
- Shi, 97JOC2328

0.2 – 0.3 eq. cat. oxone ph 7-8 H₂O / MeCN

yield 75 %
e.e. 97 %

- High catalyst loadings are required as the ketone decomposes via Baeyer-Villiger reaction

- Armstrong has developed a more robust catalyst (00TA2057)
- Operates < 10 mol% and up to 76 % e.e.

What have we learnt?
- Dioxiranes are extremely powerful oxidants that function under very mild conditions
- Readily generated from ketones
- Ketones can be used catalytically
- Asymmetric variant now possible
Jacobsen–Katsuki Epoxidation

- Aim to develop an asymmetric epoxidation catalyst which would operate on substrates with no functionality for preco-ordination
- A number of reasonably efficient porphyrin based oxo-transfer reagents were developed but the real success story has been the use of SALEN–based reagents

Reagent:

\[
\begin{align*}
\text{NaOCl} \\
(\text{bleach})
\end{align*}
\]

Transformation:

General Mechanism

- Still controversial
  - 97Ang2060
  - Possibilities

concerted

stepwise

(radical or polar)

- oxidations proceed with a degree of scrambling of geometry

> 99 : 1 cis : trans epoxide

78 : 22 cis : trans epoxide

29 : 71 cis : trans epoxide

- Suggests that concerted mechanism is not occurring
- Present believe is probably radical - stepwise mechanism (00Ang589)
Stereoselectivity

- My interpretation would again suggest that Katsuki and Jacobsen disagree on this.
- Both agree that alkene approaches metal oxo complexes side-on.

- Approach so that $\pi$-HOMO of alkene overlaps with $\pi^*$-LUMO of oxo.
- Small substituent passes axial proton.
- Cic alkenes work well.
- Trans alkenes generally bad.

- Jacobsen implies attack on oxo-species occurs from the back face over the diamine bridge.
- Katsuki implies that skewed shape of salen complex results in attack from the side.

- Skewed shape of salen complex shields one side of nucleophile.
- Back face blocked by H of cyclohexane group.
- Large substituent far from bulky front face.
- Bulky tBu groups block approach from front.

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Use in Synthesis

- other oxidants can be used
- Wide range of substrates tolerated
- Cis better than trans

\[
\begin{align*}
&\text{Yields } 63-87 \% \quad e.e. = 86-98 \%
&\text{cis-alkenes}
\end{align*}
\]

\[
\begin{align*}
&\text{Yields } 41-91 \% \quad e.e. = 83-99 \%
&\text{cis-alkenes}
\end{align*}
\]

limited success with trans-alkenes (e.e. 50%)

Recent Development

- use of an achiral salen complex in conjunction with a second ligand gives good (and cheaper, control)

\[
\begin{align*}
&\text{Yields } 63-87 \% \quad e.e. = 86-98 \%
&\text{cis-alkenes}
\end{align*}
\]

\[
\begin{align*}
&\text{Yields } 41-91 \% \quad e.e. = 83-99 \%
&\text{cis-alkenes}
\end{align*}
\]

limited success with trans-alkenes (e.e. 50%)

What have we learnt?
- Unfunctionalised alkenes can be catalytically epoxidised with good selectivity