**Metal catalysed asymmetric epoxidation of olefins**

First report: chiral molybdenum peroxo complexes

\[
\text{squalene} \xrightarrow{\text{MoO}_2(\text{acac})_2, \text{tBuOOH}} \xrightarrow{\text{di-isopropyl tartrate}} \quad \text{14\% ee}
\]


Iron porphyrin complexes act as mimics for cytochrome P450 enzymes

\[
\text{R = Fe}
\]

Metal salen complexes as catalysts for AE reactions

Advantages of metal salen catalysed AE:

- Chiral centres close to metal centre
- Simple to prepare - substituted salicylaldehyde plus chiral diamine
- Relatively stable to oxidation: range of co-oxidants extended

Manganese salen catalysed asymmetric epoxidation of unfunctionalised olefins

- di-t-butyl substituted chiral manganese salen complexes catalyse the efficient asymmetric epoxidation of Z-olefins with good selectivities; the reaction is poor for terminal (low selectivity), E- or trisubstituted olefins (low reactivity). Note that the co-oxidant is bleach!

3rd generation:

\[
\text{catalyst:} \begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\end{array} \quad 92\% \text{ ee}
\]

\[
\text{NaOCl, CH}_2\text{Cl}_2
\]

\[
\text{RL} \text{ Rs}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{RL} \\
\text{O}
\end{array}
\end{array} \quad 34\% \text{ ee}
\]

\[
\text{RL} \text{ Rs}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\end{array} \quad 97\% \text{ ee} \quad 4:1
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\end{array} \quad 78\% \text{ ee}
\]

\[
\text{tBu} \quad 86\% \text{ ee}
\]

Manganese salen catalysed asymmetric epoxidation - mechanism and stereochemistry

- as seen on the previous slide, dialkyl substituted olefins react with retention of configuration (concerted), whereas acyclic aryl substituted olefins react with loss of geometric purity, suggesting a stepwise radical mechanism

\[ \text{alkyl substituents: concerted} \]
\[ \text{aryl substituents: radical} \]

- model explains why trans/trisubstituted olefins are poorly reactive (steric hindrance in side-on approach)
- electron rich olefins are most selective, because their transition state is further along the reaction coordinate

Process-scale application of manganese salen catalysed asymmetric epoxidation

No additive, $x = 1$: 90% ee, 12 h, quant.
Isoquinoline-N-oxide, $x = 0.2$: 95% ee, 2 h, quant.

SB potassium channel activator

Dioxirane-Mediated Asymmetric Epoxidation

- Preparation: 2 steps from D-fructose (enantiomer available in 5 steps from L-sorbose)
- Excellent enantioselectivities for epoxidation of trisubstituted and trans-disubstituted alkenes
- Poor ee for cis- and terminal alkenes

- Ketone decomposes by Baeyer-Villiger reaction - cannot be recycled. High pH conditions required.

Asymmetric Epoxide Ring Opening

• Asymmetric ring opening of racemic terminal epoxides

\[
\begin{align*}
\text{R} & \quad \xrightarrow{\text{kinetic resolution}} \\
\end{align*}
\]

• Desymmetrization of meso-epoxides

\[
\begin{align*}
\text{HO} & \quad \text{Nu} \\
\end{align*}
\]
Catalytic asymmetric ring-opening of meso-epoxides

- Asymmetrically substituted cis-epoxides are achiral compounds with a meso-plane of symmetry: opening at either carbon produces enantiomeric products. A range of catalysts have been applied to this problem:

**azide as nucleophile**

![Reaction with azide as nucleophile](image)

**halide as nucleophile**

![Reaction with halide as nucleophile](image)

**thiol as nucleophile**

![Reaction with thiol as nucleophile](image)

**benzoate as nucleophile**

![Reaction with benzoate as nucleophile](image)

**phenolate as nucleophile**

![Reaction with phenolate as nucleophile](image)

**cyanide as nucleophile**

![Reaction with cyanide as nucleophile](image)

*see next slide for catalyst structures and references*
Appendix 1: catalysts for asymmetric ring-opening of meso-epoxides

Catalyst 1:
- a: M = CrCl
- b: M = Co(OAc)

Catalyst 2:
- Zr(OtBu)$_4$/

Catalyst 3:

Catalyst 4:

Catalyst 5:

References from slide
**Kinetic resolution of racemic epoxides by catalytic asymmetric ring-opening**

- Meso-epoxides are necessarily a small subset of all possible epoxides. Broader applicability needs a wider range of substrates - but these will all be chiral. Since terminal epoxides are very cheap, a resolution process is viable:

  \[
  \text{(-)} \quad \text{Cl} \quad \text{O} \quad \text{Cl} \\
  0.25 \text{ mol\% cat-1b} \\
  0.7 \text{ eq. H}_2\text{O, DCM, r.t} \\
  \Rightarrow \\
  >99\% \text{ ee} \\
  \text{92}-95\% \text{ ee}
  \]


  Polymer-supported catalyst: *J. Am. Chem. Soc.*, 1999, 121, 4147

- Reactions can be run neat; now 1000 kg process (Chirex)

- Other nucleophiles can also be used:

  \[
  \text{BocHN} \quad \text{OH} \\
  \text{(-)} \quad \text{C}_4\text{H}_9 \quad \text{O} \\
  2.2 \text{ eq.} \\
  \text{4\% cat-1b} \\
  \text{TBME, r.t.} \\
  \Rightarrow \\
  86\%, 99\% \text{ ee}
  \]


  Also with azide: *J. Am. Chem. Soc.*, 1996, 118, 7420

**Mechanism**

- Catalyst activates both nucleophile and electrophile

![Mechanism diagram]

Alkene Dihydroxylation

Catalytic systems:

• K₃Fe(CN)₆, K₂CO₃, ′BuOH / H₂O: Minato, Yamamoto, Tsuji, J. Org. Chem. 1990, 55, 766.

• Recent catalytic systems:

• O₂, K₂[OsO₂(OH)₄], ′BuOH / H₂O:
Evolution of Asymmetric Dihydroxylation

Pyridine, tertiary amines accelerates dihydroxylation by OsO$_4$.......  

• Chiral pyridines (Sharpless 1979): poor affinity for OsO$_4$

• Chiral diamines: bind too tightly to OsO$_4$, forming stable chelates - so cannot be used catalytically (but can give excellent enantioselectivities)

\[ \text{Corey} \]
\[ \text{Snyder} \]
\[ \text{Hirama} \]
\[ \text{Tomioka} \]

Quinidine / quinuclidine derivatives.....

\[ \text{Sharpless:} \]
\[ \text{DHQ} \]
\[ \text{DHQD} \]
\[ \text{CLB} = \text{Sharpless:} \]

Good ee obtained using NMO co-oxidant (Upjohn) system. But.....ee often lower for catalytic reaction than stoichiometric. Mechanistic studies showed this to be due to a two-cycle catalytic mechanism.....
Catalytic Cycles for Cis-Dihydroxylation

To avoid second cycle:
With NMO acetone/water system, add alkene slowly (inconvenient)
Better: use biphasic (tBuOH/H₂O), ferricyanide co-oxidant system: co-oxidant is in different phase to osmate ester, thus preventing second cycle
**Sharpless Catalytic Asymmetric Dihydroxylation**


**AD-Mix:**
K₂OsO₂(OH)₄ (non-volatile Os source): 0.2 mol%
(DHQD)₂PHAL or (DHQ)₂PHAL: 1 mol%
K₃Fe(CN)₆: 3 eq
K₂CO₃: 3 eq

Add 1:1 tBuOH: water, alkene, 0°C;
Often supplement K₂OsO₂(OH)₄ to make 1%
MeSONH₂ (1 eq) to accelerate hydrolysis of intermediate osmate ester
(unless alkene is terminal)

Importance of pH control: improved rates for internal olefins at pH 12 (no MeSO₂NH₂);
Structural effects in asymmetric dihydroxylation reactions
(all reactions shown carried out with (DHQD)$_2$-PHAL; figure in parentheses is ee)

**terminal olefins***

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{Ph} & \quad \text{OH} \\
\text{C}_6\text{H}_{17} & \quad \text{OH}
\end{align*}
\]

(84) (97) (84)

**trans-disubstituted olefins**

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} & \quad \text{OH} \\
\text{Ph} & \quad \text{CO}_2\text{Me} \\
\text{C}_4\text{H}_9 & \quad \text{Cl} \\
\end{align*}
\]

(99.8) (97) (94)

**1,1-disubstituted olefins**

\[
\begin{align*}
\text{TBDPSO} & \quad \text{OH} \\
\end{align*}
\]

(91)

**trisubstituted olefins**

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

(98) (84) (84) (97) (69)*

**cis-disubstituted olefins**

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

(72)

**tetrasubstituted olefins**

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

(75)

Epoxides via catalytic asymmetric dihydroxylation

Yield 83-98% over 2 steps (no chromatography)

K B Sharpless et al, Tetrahedron, 1992, 48, 10515
Cyclic sulfates as epoxide equivalents

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

\[
\begin{align*}
i) \text{SOCl}_2, \text{Et}_3\text{N} \\
ii) \text{RuCl}_3, \text{NaIO}_4
\end{align*}
\]

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

\[
\begin{align*}
i) \text{Nu}^- (\text{eg} \text{N}_3^- \text{or } \text{PhCO}_2^-) \\
ii) \text{H}_2\text{O}, \text{cat. } \text{H}_2\text{SO}_4
\end{align*}
\]

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


\[
\begin{align*}
\text{MeO} & \quad \text{OBn} \\
\text{O} & \quad \text{NMe} \\
\text{OH} & \quad \text{O}
\end{align*}
\]

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

65% from diol


reticuline