Sharpless Asymmetric Epoxidation

[Diagram showing the reaction of two molecules connected by "Magic" to form an epoxide product]
Karl Barry Sharpless

- Born in Philadelphia in 1941
- Ph.D from Stanford University in 1968
- Postdoc at Harvard and at Stanford
- Research on chiral synthesis and catalysts at the Scripps Institute
- Received Nobel Prize in 2001 for his work on stereoselective oxidation reactions
Sharpless Asymmetric Epoxidation (SAE)

- Converts primary and secondary allylic alcohols into 2,3 epoxyalcohols

- The reaction is enantioselective (only one enantiomer produced)

- Enantiomer formed depends on stereochemistry of catalyst
The Reaction

- The catalyst is titanium tetra(isopropoxide) with diethyltartrate.
- The use of + or – tartrate will yield different enantiomers.
- Tertbutylperoxide is used as the oxidizing agent.
- Dichloromethane solvent and -20°C temperature.
The Catalyst

- Ti(O^iPr)_4 catalyst
- Diethyl Tartrate (DET)
  - Chirally controls reaction
- Via rapid ligand exchange of O^iPr and diethyl tartrate
The Mechanism
Transition State
Titanium complex made through ligand exchange

Catalytic Cycle

Product
Improvements

• Many potential areas of improvement to the original reaction
• Possible problems:
  – Stoichiometric amount of catalyst required
  – Water soluble substrates (Polymer Support) cannot be isolated after reaction
  – Requirement for low temperatures (high cost for SAE)
  – Some substrates react very slowly
  – Heterogeneous reaction?
Molecular Sieves

• Original reaction requires stoichiometric amount of Ti(iOPr)_4 catalyst
• Very reactive allyl alcohols need 50% catalysts – still significant
• Major reasons for failure of SAE reactions:
  – Water destroys catalyst
  – Water ring-opens epoxide
• 3Å molecular sieves absorb water improving yield
• Requirement of Ti catalyst reduced to <10% and the tartrate ester to <13%
• Allyl alcohol concentration can be kept high since side reactions are minimized (no ring opening)
Molecular Sieves

- **Advantages:**
  - Economy – less catalyst required
  - Somewhat milder conditions
  - Ease of isolation
  - Increased yields
  - Possible in-situ derivatization

- **Problem:** the substrate may not be soluble in the solvent (low propoxide ion concentration)
Polymer Support

- Metal catalyst is mounted on a polymer which makes it (usually) heterogeneous

- Advantages:
  - Lab scale: facilitate workup and isolation
  - Industry: continuous process
  - Minimizes catalyst loss during workup

- Possible Polymers:
  - silica gel (H$_2$O$_2$ catalysts)
  - alkaloid polymers
  - Polystyrene (heterogeneous Jacobson epoxidation)

- Polymer support vital with water-soluble substrates
Polymer Support

• Early work with polystyrene had low %ee
• A Scottish group used linear chiral poly(tartrate esters)
• Combining benefits of polymer support with the active functionality built in

\[ \text{Reaction gives good yields and } \%\text{ee} \]
• Branched poly(tartrate esters) were found to be even more selective and had higher yields
Higher Temperatures SAE

- **Problem:** High cost due low temperatures
- **Solution:** Titanocene-tartrate (TT) catalyst
- Very good catalytic activity and decent enantioselectivity at higher temperatures
- TT has bulky cyclopentadienyl rings which create steric hindrance, inducing chirality (compare with BINOL)
- In classic SAE, the tartrate-titanium complex forms through ligand exchange
Higher Temperatures SAE

- But the titanocene-tartrate cannot form through ligand exchange (Ti-halide stable)
- Titanocene tartrate is generated before the reaction:
In Situ Modification

- Ideal use for SAE is to make low molecular weight chiral products – synthetic utility
- Low molecular weight substrates react slowly – product is lost during workup
- The epoxide formed may also be ring-opened during workup
- With molecular sieves, the catalyst concentration is reduced, so solubility of product also decreases
- Better solution is in-situ derivatization
In Situ Modification

- Epoxy-alcohol product is converted to an ester derivative:
  - \( p \)-toluene sulfonyl and 2-naphthalene sulfonyl
  - \( t \)-butyl diphenyl silyl and \( t \)-butyl dimethyl silyl
- The derivatives are
  - Easily un-doable (good leaving group)
  - Functionally equivalent to parent for reactions
- Further chemistry can be done on the epoxy-“alcohol” without loss of yield
- Derivative may be isolable in high yield and then converted back to alcohol
Other Modifications

- Numerous minor modifications to the classic SAE
- Ageing the catalyst: the catalyst is synthesized fresh and “aged” for 30 minutes
- Alternative solvents: isooctane, toluene
- The ester: diethyl tartrate vs. diisopropyl tartrate
- Mesoporous silica support for heterogeneous catalysis (MCM-41)
Competing Methods

- Many competing reactions for generating epoxides:
  - Jacobsen-Katsuki epoxidation
  - Prilezhaev reaction
  - Shi expoxidation
Jacobsen-Katsuki Epoxidation

• Uses cis alkene as a reactant
• Allows broader scope of substrate (R: Ar, alkenyl, alkynyl; R': Me, alkyl)
• Mn-salen catalyst and a stoichiometric oxidant
Jacobsen-Katsuki Epoxidation

- Mechanism’s catalytic cycle shows the formation of an Mn(V)-oxo complex
- Good yields with high enantomeric excess
Prilezhaev Reaction

- Reaction of an alkene with a peracid

\[ R_3^2R_1 \xrightarrow{R_3^3CO_3H} R_3^3O \xrightarrow{H} R_3^2R_1 \]

- meta-chloroperoxybenzoic acid (m-CPBA) is most commonly used as the peracid

- Magnesium mono-perphthalate and peracetic acid

Shi Epoxidation

- Reaction involving a trans alkene
- Oxone is another main component
- Fructose derived catalyst used
- High enantiomeric excess yields
Uses of the Reaction

• The Sharpless Asymmetric Epoxidation converts alkenes into chirally active epoxides
• Innumerable syntheses published that use the SAE
• Chiral epoxides easily converted into:
  – 1,2 Diols
  – Make carbon-carbon bonds (stereospecifically)
  – Aminoalcohols

• Two examples considered:
  – A complex synthesis of Venustatriol by EJ Corey
  – Simpler synthesis of Untenone by Mizutani et al.
Venustatriol

- Marine-derived natural product discovered initially in 1986
- Found in red alga Laurencia venusta
- Derived *in vivo* from squalene, made as a triterpene
- Shown to have antiviral and anti-inflammatory properties
- Structure contains repeated polyether moieties
- Key problems: multiple stereocenters and polyether moieties.
- Corey proposed a “simple and straightforward” disconnection
Venustatriol - Reterosynthetic Analysis

Fragment A

Fragment B
Fragment A

E,E - famesol

SAE

1. CrO_3 Py (Jones Oxid)
2. Ph_3P=CHCO_2Me (Wittig)
3. H_2, Rh-Al_2O_3 (hydrogenation)
4. DIBAL-H, PhCH_3 (reduction)

1. NaCN (SN_2)
Ring closure

1. SAE

1. MsOH (Ring Closure)
2. TBCD / CH_3NO_2 (bromination)
3. DIBAL-H (reduction)
Fragment B

Geraniol

SAE

1. Hydride + BuBr (SN2)
2. HClO₄ (Open diol)
3. PCC/DCM (Ether Ring Close)

1. NaH
2. MOMCl (methyl ether)
3. H₂/(COCl)₂ (oxidize)

1. Ph₃P=CH₂ (Wittig)
2. 9-BBN/H₂O₂ (alcohol)
3. CBr₄ (bromination)
Final Step - Venustatriol

1. $^t\text{BuLi (Li-Grig.)}$
2. $(\text{COCl})_2 \text{[ox]}$
3. $\text{MeMgBr (Grignard)}$
Untenone

• Isolated from a marine sponge in 1993
• Exhibits inhibitory activity against mammalian DNA polymerases
• These enzymes are important for DNA replication, repair and cell divisions (cancer implications)
• Biosynthetic pathway not investigated
• The critical part of the synthesis is the introduction of a quaternary carbon center (done via SAE)
• The total synthesis is 15 steps
Untenone - Reterosynthetic Analysis

Untenone

COO\textsubscript{Me}  
\begin{align*}
\text{O} & \quad \text{OH} & \quad \text{CH}_3 \quad 15 \\
\text{H}_3\text{C} & \quad \text{CHO} \quad 15 \\
\text{H}_3\text{C} & \quad \text{OH} \quad 15
\end{align*}

\text{SAE} \quad \text{Ring Close} \quad \text{steps} 

COO\textsubscript{Me}  
\begin{align*}
\text{HO} & \quad \text{OR} & \quad \text{CH}_3 \quad 15 \\
\text{H}_3\text{C} & \quad \text{CHO} \quad 15 \\
\text{H}_3\text{C} & \quad \text{OH} \quad 15
\end{align*}
Untenone Synthesis

1. Eschenmoser salt
2. NaBH₄ (red'n)

1. SAE
2. Dess Martin [ox]

1. CH₃PPh₃Br (wittig)
2. KCN (SN2 ring open)

DIBAL-H
(reduction)

MgBr
(Grignard)

1. Grubb's
ring closure
2. MnO₂ [ox]

1. LDA/MeOCOCN
2. Deprotection
References


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