Epoxidation, Dihydroxylation, and the Utility of Epoxides and Diols

Outline:

Epoxidation
   Condensation approaches
      Darzens condensation
      Sulfur ylides
   With organic peroxides
      Peroxy acids
      Peroxy iminic acids
      Dioxiranes
      DMDO
      Enantioselective versions
   Metal-catalyzed Approaches
      V(O)(acac)$_2$
      Sharpless AE
      Metal Oxo’s
      MTO
      Fe, Pt and Mn-based
      (Salen)Mn Jacobsen AE

Dihydroxylation
   General considerations
   Sharpless AD
   Conditions and scope
   Mechanism
   Applications

Epoxide Ring Opening
   Opening under acid or basic conditions
   Organocopper additions
   Reactions of epoxy alcohols
Darzens Condensation

Condensations: general scheme

\[ RX + M \rightarrow \text{Carbene equiv} \rightarrow RO + M \rightarrow RO + LG \rightarrow R-\text{leaving group} \rightarrow R-\text{product} \]

Darzens condensation

\[ \text{Base} \rightarrow \text{CO}_2\text{R} \rightarrow R-\text{carbene equiv} \rightarrow R-\text{leaving group} \rightarrow R-\text{product} \]

\[ \text{PhCO}_2\text{Et} \rightarrow \text{KO}^+\text{Bu} \rightarrow \text{PhCH} \rightarrow \text{CO}_2\text{Et} \rightarrow \text{PhCO}_2\text{Et} \]

\[ \text{BrCH} \rightarrow \text{LDA} \rightarrow \text{ArCH} \rightarrow \text{CO}_2\text{Me} \rightarrow \text{ArCH} \rightarrow \text{dr} = 3:4 \]

\[ \text{SiMe}_3 \rightarrow \text{sBuLi} \rightarrow \text{Li} \rightarrow \text{R} \rightarrow \text{RO-SiMe}_3 \]

Si stabilizes α anions (and β cations)

High yields
Magnus, JACS, 1977, 4536
Corey-Chaykovsky Epoxidation JACS, 1965, 1353

Two flavors of sulfur ylides are common:

\[
\begin{array}{c}
(Me)_2S\text{-CH}_3 \xrightarrow{\text{dimethyl anion (DMSO/NaH)}} (Me)_2S\text{-CH}_2
\\
\text{Dimethyl Sulfonium ylide}
\\
\text{more reactive}
\\
\text{less stable}
\\
\text{generated/used low T}
\\
\text{adds irreversibly (kinetic product)}
\\
\end{array}
\]

\[
\begin{array}{c}
\text{H}_2\text{C-S(Me)_2}
\\
\text{Dimethylsulfoxonium ylide}
\\
\text{less reactive}
\\
\text{adds reversibly (thermodynamic product)}
\\
\end{array}
\]

\[
\begin{array}{c}
\text{t-Bu} \xrightarrow{\text{t-Bu}} \text{t-Bu}
\\
\text{(Me)_2S\text{-CH}_2}
\\
\text{17:83}
\\
\end{array}
\]

\[
\begin{array}{c}
\text{t-Bu} \xrightarrow{\text{t-Bu}} \text{t-Bu}
\\
\text{H}_2\text{C-S(Me)_2}
\\
\text{100:0}
\\
\end{array}
\]

\[
\begin{array}{c}
\text{t-Bu} \xrightarrow{\text{t-Bu}} \text{t-Bu}
\\
\text{(Me)_2S\text{-CH}_2}
\\
\text{17:83}
\\
\end{array}
\]

\[
\begin{array}{c}
\text{t-Bu} \xrightarrow{\text{t-Bu}} \text{t-Bu}
\\
\text{H}_2\text{C-S(Me)_2}
\\
\text{100:0}
\\
\end{array}
\]
Catalytic generation of and catalytic enantioselective epoxidation with sulfur ylides

\[ \text{ArCHO} \rightarrow 5\% \text{ ee's } \sim 90 \\
\text{dr's } \sim 50:1 \\
\text{pretty limited scope} \]

Aggarwal, Chem Rev 2007, 5841
Ready Epoxidation with Peroxides: general considerations

Most common peroxides:
AcOOH, mCPBA, MMPP, Oxone (KHSO₅), DMDO

Exercise 39

[Chemical structures and reaction mechanisms are depicted, illustrating the epoxidation process with peroxy acids and the stereochemistry of the reaction.]

electrophilic reagents:
rate INCREASES with EDG on olefin
EWG on peracid

EWG on olefin requires basic conditions. Epoxidation via stepwise mechanism:

\[
\text{EWG + R-O-O}^- \rightarrow \text{RO-O-} \rightarrow \text{RO-O=O} \rightarrow \text{O-} \rightarrow \text{EWG}
\]

\[
R = \text{H or tBu}
\]

[Examples of epoxidation reactions with different substrates are shown, including stereochemical outcomes and yields.]

R or electron-poor olefins: generally bad substrates
Ready Epoxidation with Peroxides

Payne Oxidation: mechanistically similar to peracids, but under basic conditions.

\[
\text{H}_2\text{O}_2 \quad \text{CH}_3\text{CN} \quad \text{KHCO}_3
\]

'peroxy imidic acid'
epoxidation driven by cleavage of OO bond and by formation of amide

Dimethyl Dioxirane: Very strong oxidant; very easy to use

prep:

\[
\text{K}O \quad \text{S} \quad \text{O} \quad \text{O} \quad \text{O}
\]

Can be prepared in situ or as ~0.1M soln in acetone
Like peracids, reacts via spiro transition state
Most useful for prep of sensitive epoxides b/c byproduct is acetone

For even more horsepower:

\[
\text{CF}_3
\]

1000x as reactive as DMDO
Prepared in situ (JOC, 1988, 3890; 1995, 3887)
Several groups have developed chiral ketones as catalysts for asymmetric epoxidation. The most successful has been the Shi epoxidation. The catalyst is easily prepared from fructose and displays broad generality. Shi, Accts, 2004, 488

Principle drawbacks:
- requires slow addition of two reagent solutions
- Enantiomeric catalyst more difficult to access

But: one of the most effective catalysts for AE.
Several epoxidations en route to periplanone: Still, JACS, 1979, 2493 and Classics, chap 13.

Conversion of silyl enol ether to an α-hydroxy ketone via epoxidation is known as the Rubottom oxidation: Rubottom, TL, 1974, 4319. Note selectivity for 1 of 3 olefins.

S-trans configuration favored for dienes.
Ready Metal-Catalyzed Epoxidation: VO(acac); brief review

\[
\text{OH} + \text{tBuOOH} \xrightarrow{\text{V(O)(acac)}_2} \xrightarrow{\text{tBuOH}} \text{OH}
\]

Ox to \( \text{V}^\dagger \) under rxn conditions
induced proximity
activation of peroxide

Key point: V and Mo show increased reactivity and high selectivity

<table>
<thead>
<tr>
<th>Substrate</th>
<th>( k_{\text{rel}}^{a,b} ) (diastereoselectivity(^c))</th>
</tr>
</thead>
<tbody>
<tr>
<td>peracid</td>
<td>1.00</td>
</tr>
<tr>
<td>Mo(CO)(_6)</td>
<td>1.00</td>
</tr>
<tr>
<td>VO(acac)(_2)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Sharpless, JACS, 1973, 6136
Review: Evans, Chem Rev. 1993, 1307

Key points: VO(acac)\(_2\) reliable, chemoselective and stereoselective

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Selectivity</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>9 : 1 ((\alpha))</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 : 1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(&gt;200 : 1) ((\beta))</td>
<td></td>
</tr>
</tbody>
</table>
Ready

Metal-Catalyzed Epoxidation: VO(acac); origin of selectivity

ca. 40° (vs mCPBA ~ 120°)

Preferred conformation

For table: R1 = Me → threo; R2 = Me → erythro
Can use conformational analysis to understand and predict
A$_{1,3}$ strain between R$_2$ and R$_{\text{cis}}$ favors threo
A$_{1,2}$ strain between R$_{\text{gem}}$ and R$_1$ favors erythro
Interaction b/w L and R$_1$ favors erythro
σ$_{C-R2}$ → π* favors erythro
Metal-Catalyzed Epoxidation: Ti(OiPr)4

See lecture notes from Synthesis and Catalysis

See handout from Andrew Myers
Fig. 2. Synthesis of \( \tau \)-hexoses. For a, c, e, and g, 1 = Pummerer reaction, 2 = Dibal, 3 = deprotection. a: 1 (90 percent), 2 (81 percent), 3 (90 percent). c: 1 (90 percent), 2 (95 percent), 3 (90 percent). e: 1 (87 percent), 2 (81 percent), 3 (84 percent). g: 1 (71 percent), 2 (77 percent), 3 (61 percent). For b, d, f, and h: 1 = Pummerer reaction, 2 = potassium carbonate and methanol, 3 = deprotection. b: 1 (90 percent), 2 (48 percent), 3 [see (f)]. d: 1 (90 percent), 2 (60 percent), 3 (20 percent). f: 1 (87 percent), 2 (66 percent), 3 (85 percent). h: 1 (71 percent), 2 (41 percent), 3 (27 percent).
Much research has gone into mimicking cytochrome P450, nature's oxidant. The objectives are generally three-fold: 1) Identify highly reactive catalysts. 2) Use H2O2 as the terminal oxidant and 3) induce asymmetry.
Rev on epox with H$_2$O$_2$: Chem Rev 2003, 2457.

MTO: methyl trioxorhenium
Hermann, ACIEE, 1991, 1638

Beneficial effect of added pyridine
Sharpless, JACS, 1997, 6187
Faster reaction
Prevents cat decom
Buffers reaction
Sharpless favors py as ligand; no asymmetric version

0.5% MTO, 12% py (amount is critical)
1.5 equiv 30% aq H$_2$O$_2$
CH$_2$Cl$_2$ or CH$_3$NO$_2$
stereospecific
mild conditions

92%
96:4 dr
82% (48h)
Ready

**Metal-Catalyzed Epoxidation: Epox with H2O2**

TMTACN: Trimethyl-triazacyclononane (TACN)

Discovered by group from Unilever (oxidative stain removal)
De Vos, TO, 1998, 3221

\[
\text{CH}_2=CH_2 \xrightarrow{\text{TMTACN (0.15%), MnSO}_4 (0.1%), \text{Oxalic acid (0.3%)}} \text{CH}_2=CH_2 \xrightarrow{\text{H}_2\text{O}_2 (1.3 \text{ equiv})} \text{O}_\text{CH}_2\text{CH}_2\text{O}
\]

Expensive ligand (difficult to make)
Mostly GC yields
Minimal Functionality demonstrated

Fe-based system
White, Doyle, Jacobsen, JACS, 2001, 7194

\[
\text{CH}_2=CH_2 \xrightarrow{\text{Fe[SbF}_6]_2, \text{AcOH, H}_2\text{O}_2, \text{CH}_3\text{CN}} \text{O}_\text{CH}_2\text{CH}_2\text{O}
\]

Assembles into di-iron core (2 AcO bridges)
Mimic of MMO
Good yields for terminal olefins
Little functionality allowed

Pt-based system
Strukul, JACS, 2007, 7680
Asymmetric version: JACS, 2006, 14006

\[
\text{CH}_2=CH_2 \xrightarrow{\text{Ph}_2\text{OH}_2, \text{OTf, (2 mol%)}} \text{O}_\text{CH}_2\text{CH}_2\text{O}
\]

Propose addition to Pt-coordinated olefin, but details have evolved
Good yields for terminal, unhindered olefins
Very sensitive to sterics and electronics
**Background:** Collman (review: Science, 1993, 261, 1404) showed metal porphyrin complexes could catalyse epoxidation.
Kochi (JACS, 1986, 2309) showed that (salen)Mn and (Salen)Cr complexes could catalyze epoxidation.
Burrows (JACS, 1988, 4087) showed that (salen)Ni complexes could catalyze epoxidation.
Katsuki (TL, 1990, 7345) showed moderate enantioselectivity with (salen)Mn complexes.

**Ligand synthesis:**

\[
\begin{align*}
\text{SALicylaldehyde derivative} &+ \text{Ethylene diamine (EN) derivative} \\
\text{Salen ligand}
\end{align*}
\]

**Catalytic epoxidation:**

\[
\begin{align*}
\text{C}_{\text{sp}2} + \text{NaOCl (pH 10-13)} &\rightarrow \text{C}_{\text{sp}2} \\
87-98\% \text{ ee} &\quad 92-98\% \text{ ee} \quad \text{ up to 97\% ee} \\
80's &\quad >90\% \text{ ee} \quad >80\% \text{ ee} \\
\text{JACS, 1991, 7063} &\quad \text{JOC, 1994, 4378} \quad \text{JOC, 1993, 6939} \\
\text{TL, 1995, 5457} &\quad \text{TL, 1991, 6533} \quad \text{JACS, 1994, 9333} \\
\text{Review: Chem Rev. 2005, 1563}
\end{align*}
\]

**Warning:** C_{sp3} and Ar as poor substrates (slow, poor ee).
Metal-Catalyzed Epoxidation: Jacobsen Epoxidation: application

\[
\text{Indinavir - HIV protease inhibitor (Merck)}
\]

\[
\text{Senanayake, Reider, Jacobsen, Org. Syn, 1999, 76.}
\]
in general, three different mechanisms possible for metal oxo epoxidation:

\[
\begin{align*}
\text{[2+2]} & \quad \text{concerted} \\
\text{electron transfer} & \\
\end{align*}
\]

Experimental data:
secondary KIE's

Recall enynes and dienes

Radical traps

Norby, Akermark, ACIEE, 1997, 1723
Note: these authors interpret the data in terms of a [2+2] mechanism
Ready Epoxide Ring-Opening: Overview

Three common classes of epoxide ring-opening reactions

**Nucleophilic addition**

\[
\text{Nu}^- + \text{Nu} \rightarrow \text{Nu} \cdot \text{OH}
\]

generally stereospecific

**Isomerization**

\[
\text{Lewis acid} \rightarrow \text{OH}
\]

generally stereospecific

**Elimination**

\[
\text{Base} \rightarrow \text{OH}
\]

Stereoretentive

**General considerations:**

Addition to more stable partial cation
Common for solvolysis
Common with strong Lewis or protic acids
Total SN1 = loss of stereochemistry

Addition to less hindered C
Often good reaction for H-, RO-, RS-, CN-, N3-, R2N
Common with weak Lewis acids (esp R2N, CN-
Stereospecific

Generally, bond-breaking more advanced than bond-making with epoxides.
Regioselectivity: cation-stabilizing groups can alter selectivity

\[
\begin{align*}
\text{Ar} & \quad \text{Ph} \quad \text{OH} \\
X = \text{NO}_2 & \quad >99 \\
X = \text{OMe} & \quad 99:1
\end{align*}
\]

TL 2004, 9265

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{BF}_3 \cdot \text{Et}_2 \text{O} & \quad 80:20 \\
\text{LiClO}_4 & \quad 6:94
\end{align*}
\]

TL, 1991, 6617

\[
\begin{align*}
\text{HO} & \quad \text{exo (Baldwin)} \\
\text{HO} & \quad \text{endo (anti-Baldwin)}
\end{align*}
\]

Nicolaou, JACS, 1989, 5330
**Furst-Plattner Rule**: experimentally observed that cyclohexene oxides react such that the nucleophile approaches along an axial trajectory.

\[
\text{Furst, Helv Chem Acta, 1949, 275}\]
\[
\text{Barton, " 1954, 4284}\]

Notes: Faster-forming product may be less stable product
Same analysis applies to conjugate additions, additions to halonium ions, additions to cyclic imines.
Also known as 'trans-diaxial rule' for obvious reasons.
Addition of carbon-centered nucleophiles usually involves organocopper chemistry

\[
\text{Epoxide} + \text{R}_2\text{Cu(CN)Li}_2 \rightarrow \text{Product(s)}
\]

low temp, THF or Et\(_2\)O

Review: Lipshutz, Tet, 1984, 5005.
Generally high yielding, stereospecific
Addition to less substituted C
Often waste 1 equiv R

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Cuprate/(equiv)</th>
<th>Conditions (^\circ)</th>
<th>Product(s)</th>
<th>Ratio</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{O} )</td>
<td>(\text{n-Bu}_2\text{Cu(CN)Li}_2) (1.1)</td>
<td>-20(^\circ), 2 h</td>
<td>(\text{OH})</td>
<td>—</td>
<td>95(^c)</td>
</tr>
<tr>
<td>Ph (\text{O} )</td>
<td>38 (1.3)</td>
<td>-40(^\circ), 2 h</td>
<td>(\text{OH} + \text{OH})</td>
<td>85 : 8</td>
<td>93</td>
</tr>
<tr>
<td>Ph (\text{O} )</td>
<td>38 (1.3)</td>
<td>-20(^\circ), 2 h</td>
<td>—</td>
<td>—</td>
<td>96</td>
</tr>
<tr>
<td>(\text{O} )</td>
<td>38 (2.0)</td>
<td>0(^\circ), 6 h</td>
<td>—</td>
<td>—</td>
<td>74(^c,d)</td>
</tr>
<tr>
<td>Ph (\text{O} )</td>
<td>38 (1.3)</td>
<td>0(^\circ), 3 h</td>
<td>(\text{OH} + \text{OH})</td>
<td>1 : 1</td>
<td>61</td>
</tr>
<tr>
<td>(\text{O} )</td>
<td>38 (3.0)</td>
<td>0(^\circ), 6 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(\text{O} )</td>
<td>(\text{Et}_2\text{Cu(CN)Li}_2) (2.0)</td>
<td>0(^\circ), 6 h</td>
<td>—</td>
<td>—</td>
<td>98</td>
</tr>
<tr>
<td>(\text{O} )</td>
<td>(\text{n-Pr}_2\text{Cu(CN)Li}_2) (2.0)</td>
<td>0(^\circ), 8 h</td>
<td>—</td>
<td>—</td>
<td>86(^e)</td>
</tr>
<tr>
<td>Ph(_2\text{Cu(CN)Li}_2)</td>
<td>38 (2.0)</td>
<td>r.t., 10 h</td>
<td>—</td>
<td>—</td>
<td>98</td>
</tr>
<tr>
<td>(\text{O} )</td>
<td>38 (1.1)</td>
<td>-45(^\circ), 1.5 h</td>
<td>(\text{OH} + \text{OH})</td>
<td>3.4 : 1</td>
<td>96</td>
</tr>
<tr>
<td>(\text{O} )</td>
<td>(\text{Et}_2\text{Cu(CN)Li}_2) (1.3)</td>
<td>0(^\circ), 5 h</td>
<td>—</td>
<td>—</td>
<td>94</td>
</tr>
</tbody>
</table>

Problems:
- Tetrasubstituted
- Hindered trisubstituted
- Vinyl epoxides (good Sn\(2'\))
Ready Epoxide Ring-Opening: Additions to epoxy alcohols

**Payne rearrangement**

(Major from SAE) (Major from SAE - KR)

\[
\text{Ph} - \text{O} - \text{O} - \text{Ph} \rightleftharpoons \text{Ph} - \text{O} - \text{Ph} - \text{OH}
\]

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

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

0.5N KOH, Et\(_2\)NH 
slow

0.5N KOH, Et\(_2\)NH 
Fast

Sharpless
Aldrichimica Acta, 16, 1983, 67

**Lewis-Acid promoted addition:**

Sharpless, JOC, 1985, 1557, 1560

\[
\text{OH} + \text{NuH} \quad 1.5 \text{ equiv Ti(OiPr)}_4
\]

\[
\begin{align*}
\text{Nu} & \quad \text{Et}_2\text{NH} \\
\text{Nu} & \quad \text{R}_2\text{NH}, \text{ROH}, \text{RSH}, \text{TMSN}_3, \\
\text{Nu} & \quad \text{KCN}, \text{NH}_4\text{X}, \text{NH}_4\text{OBz}
\end{align*}
\]

Ti increases rate and selectivity
e.g. w/Et\(_2\)NH: +Ti 20:1 (90%y)
- Ti 3.7:1 (4%y)

\[
\text{OH} + \text{Nu} \quad \text{L}_n\text{Ti}
\]

generally >5:1 regioselectivity

\[
\begin{align*}
\text{Nu} = \text{R}_2\text{NH}, \text{ROH}, \text{RSH}, \text{TMSN}_3, \\
\text{KCN}, \text{NH}_4\text{X}, \text{NH}_4\text{OBz}
\end{align*}
\]

origin of selectivity:
orbital overlap? Least motion? Charge distribution?

\[
\text{R} - \text{O} - \text{OH} \quad \text{[CH}_3\text{OCH}_2\text{CH}_2\text{O}]\text{AlH}_2\text{Na}
\]

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

Sharpless, JOC, 1982, 1378; Kishi, TL, 1982, 2719

\[
\begin{align*}
\text{R} & \quad 1:2 \\
\text{hex} & \quad 1:1 \\
\text{CH}_2\text{OBn} & \quad 5:1 \\
\text{OBn} & \quad 40:1
\end{align*}
\]
Lewis-acid catalyzed rearrangement of epoxides

Rearrangement to more stable carbocation
Often high degree of stereospecificity

Yamamoto, JACS, 1989, 6431
Chen, JACS, 2009, ASAP
Shi, JACS, 1999, 4080
Conversion of epoxides to allylic alcohols

Deprotonation

\[
\text{LiNEt}_2 \quad \text{syn elimination}
\]

milder conditions:

\[
\text{TMS-OTf/Lutidine; DBU}
\]

intermediate observed by NMR
OTf addition to more substituted carbon

- \(79\%\) (only isomer)
- \(66\%\) (from epoxy alcohol)
- \(87\%\)
- \(59\%\)

poor substrates: acyclic di- or mono-substituted epoxides

Noyori, JOC, 1979, 2738.
Conversion of epoxides to allylic alcohols

Addition/oxidation/elimination

Reductive opening of epoxy alcohols

Perkin I, 1979, 1358

TL, 1982, 5413
Ready Dihydroxylation – general considerations

Dihydroxylation: general scheme

\[ \text{RuO}_4, \text{KMnO}_4, \text{OsO}_4 \text{ most common} \]
\[ \text{Stereospecific (cis-dihydroxylation)} \]
\[ \text{Diol cleavage potential side reaction} \]

\[ \text{KMnO}_4 - \text{some uses; mostly replaced by OsO}_4 \]

\[ \text{Ph} - \equiv \text{C}_9\text{H}_7 \xrightarrow{\text{KMnO}_4 \ 58\%} \text{Ph} - \equiv \text{C}_9\text{H}_7 \]

\[ \text{Chem Comm. 2005, 5636} \]

\[ \text{RuO}_4 - \text{generated in situ from RuCl}_3 \text{ (cat.) and NaIO}_4 \]

Stark, OL, 2006, 3433
Ready

**Dihydroxylation – OsO₄**

Best conditions for dihydroxylation of alkenes: Upjohn conditions

1 mol% OsO₄, 1.05 equiv NMO

H₂O/Acetone

NMO:
- Catalytic Os
- Easy workup ([H⁻], H⁺)
- R₃N may accelerate rxn

Upjohn Co
TL, 1976, p1973

![Chemical structures and reactions](image)

(from cis olefin)

>95%

91%

79%

78%

65%
Sharpless asymmetric dihydroxylation

General considerations:
Strategy based on observation that tertiary amines accelerate reaction.
Monodentate ligand required for turnover
Ligands based on cinchona alkaloids
Simple experimental protocol
One of the most general enantioselective reactions

\[ R_3N^*/OsO_4 \text{ (cat)} \rightarrow HO\text{H} \]

\[ \text{Linkers:} \]
- Phthalazine (PHAL) used in AD-Mix; therefore most used
- Anthraquinone (AQN)
- Pyridazine (PYDZ)
- Pyrimidine (PYR)

\[ X = N: \text{DPP} \]
\[ X = \text{CH}: \text{DP-PHAL} \]
Ready Sharpless Asymmetric Dihydroxylation: details

\[ \text{AD-Mix} \alpha (\text{Lig} = \text{DHQ}) \]
\[ \text{AD-Mix} \beta (\text{Lig} = \text{DHQD}) \]

\[ \begin{align*}
K_3\text{Fe(CN)}_6 & : 0.94 \text{ g (3 equiv)} \\
K_2\text{CO}_3 & : 0.41 \text{ g (3 equiv)} \\
\text{Lig-PHAL} & : 7.8 \text{ mg (1 mol\%)} \\
K_2\text{OsO}_2(\text{OH})_4 & : 0.74 \text{ mg (0.2 mol\%)} \\
\end{align*} \]

1 mmol

\[ \text{tBuOH:H}_2\text{O (1:1)} \]

Proposals to rationalize stereochemistry:
Corey, JACS, 1995, 10805; 1996, 319
Sharpless, JACS, 1994, 8470
**Sharpless Asymmetric Dihydroxylation: scope**

<table>
<thead>
<tr>
<th>Class</th>
<th>PYR</th>
<th>PHAL</th>
<th>PD-PHAL</th>
<th>PHAL</th>
<th>PHAL</th>
<th>PYR</th>
<th>PYDZ</th>
</tr>
</thead>
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<td>DP-PHAL</td>
<td>DPP</td>
<td>DPP</td>
<td>DPP</td>
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<td>&gt;90</td>
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<th>Olefin</th>
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<th>3a (3b) (DPP)</th>
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<td>68; S</td>
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<td>64; 1S, 2R</td>
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<td>73; 1S, 2R</td>
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Chem Rev. 1994, 2483 and JACS, 1995, 10805

Shapless, JOC, 1995, 3940
A non-linear Eyring plot is taken as evidence for a stepwise mechanism. Sharpless interpreted these data to support a mechanism involving [2+2] cycloaddition (to yield an osmaoxetane) followed by ring expansion.

\[ \text{OsO}_4 \text{ (1 equiv)} \rightarrow \text{OH} \]
Corey observed enzyme-like kinetics which he interpreted in terms of reversible binding followed by rate-limited [3+2] cycloaddition (aka Criegee mechanism).

JACS, 1996, 319
Houk, Singleton and Sharpless performed natural abundance KIE studies of the dihydroxylation of tBu ethylene. The data are more consistent with a concerted [3+2] addition. JACS, 1997, 9907

<table>
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<th>( H_{C2} )</th>
<th>( H_{cis} )</th>
<th>( H_{trans} )</th>
<th>( C_2 )</th>
<th>( C_1 )</th>
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<td>(a) “[3+2]”</td>
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<td>(b) Formation of an Osmaoxetane</td>
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<td>1</td>
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<td>0.919(5)</td>
<td>0.925(7)</td>
<td>1.027(1)</td>
<td>1.028(3)</td>
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<td>2</td>
<td>0.908(4)</td>
<td>0.917(8)</td>
<td>0.926(14)</td>
<td>1.026(3)</td>
<td>1.025(3)</td>
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</table>
‘no other known organic reaction comes close to achieving such enormous scope coupled with such great selectivity.’ – Sharpless in Chem Rev.

OL, 2008, 5007 (95% ee)

OL, 2009, 293. Often AD-Mix is best way to do dihydroxylation regardless of stereochemistry

AcO

(-)-pestalotiopsin A (1)
Diol-to-epoxide is common application of AD. ‘d’ in scheme is 1. TsCl. 2. K₂CO₃ Furstner, ACIEE, 2006, 5510, From the conclusion: macrolide is now covered. Nevertheless, we are well aware that this venture is no more but an auspicious start for the conquest of this challenging natural product because of the as of yet unanswered stereochemical issues delineated in the introduction. Undaunted, however, we are now actively pursuing possible end games with the hope of reaching this monumental target soon.

Synthesis of amphidinolide A: Trost, JACS, 13589.

In scheme 2: d: 11:1 24/25, 90%ee.