Practical Catalytic Asymmetric Epoxidations

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Outline

I. Directed Epoxidations
   A. Sharpless
   B. Yamamoto Homoallylic Alcohol Example
II. Metal Oxo-Catalyzed Epoxidations
   A. Porphyrin Example
   B. Jacobsen-Katsuki
III. Dioxirane-Catalyzed Epoxidations
   A. Yang
   B. Denmark
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IV. Nucleophilic Epoxidations
   A. Juliá
   B. Shibasaki
V. Miscellaneous Methods

General Section Outline

I. History
II. Scope
III. Mechanism
IV. Synthetic Example

Extensive Current General Review

Directed Epoxidations

Timeline

1965-1967  Development of the Halcon Oxirane process for the production of propene oxide
1967      Discovery of directing effects in metal-mediated epoxidations of allylic alcohols
1980      Discovery by Sharpless of the asymmetric Ti tartrate epoxidation of allylic alcohols
1981      First reports of practical synthetic applications of the Ti tartrate technology
1981      Development by Sharpless of the Ti-catalyzed kinetic resolution of secondary allylic alcohols
1986-1987 Discovery by Sharpless that addition of molecular sieves renders Ti tartrate epoxidations truly catalytic
Sharpless Asymmetric Epoxidation (SAE)

Reviews


**SAE: Substrate Scope**

\[
\text{R}_3\text{R}_2\text{R}_1\text{R}_4 \rightarrow \text{R}_3\text{O}\text{R}_2\text{R}_1\text{R}_4
\]

- 4.7–10 mol% Ti(Oi-Pr)_4
- 5.9–14 mol% (+)-DET or (+)-DIPT
- t-BuOOH (1.5–2.5 equiv)
- 3 or 4Å MS
- CH_2Cl_2
- -40–0 °C

\[
\begin{align*}
\text{O}_2\text{OH} \\
\text{90% ee} \\
\text{65% yield} \\
(\text{cumene hydroperoxide})
\end{align*}
\]

\[
\begin{align*}
\text{n-Pr} \text{O}_2\text{OH} \\
\text{94% ee} \\
\text{85% yield}
\end{align*}
\]

\[
\begin{align*}
\text{O}_2\text{OH} \\
\text{n-Pr} \\
\text{95% ee} \\
\text{88% yield}
\end{align*}
\]

\[
\begin{align*}
\text{n-hept} \text{O}_2\text{OH} \\
\text{86% ee} \\
\text{74% yield}
\end{align*}
\]

\[
\begin{align*}
\text{Me} \text{CH} \text{Me} \text{CH} \text{O}_2\text{OH} \\
\text{91% ee} \\
\text{95% yield}
\end{align*}
\]

\[
\begin{align*}
\text{O}_2\text{OH} \\
\text{93% ee} \\
\text{77% yield}
\end{align*}
\]

\[
\begin{align*}
\text{Me} \text{O} \text{Me} \text{Bn} \text{OH} \\
\text{91% ee} \\
\text{90% yield} \\
\text{Conditions not provided.}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} \text{O} \text{Me} \text{Bn} \text{OH} \\
\text{91% ee} \\
\text{90% yield} \\
\text{120 mol% Ti(Oi-Pr)_4} \\
\text{150 mol% (+)-DET}
\end{align*}
\]


SAE: Kinetic Resolution – Relative Rates ($k_{rel}$ values)

## SAE: Substrate Scope

### Compatible Functional Groups

<table>
<thead>
<tr>
<th>R-OH (remote)</th>
<th>R-COOH</th>
<th>R-NH$_2$</th>
<th>R-CN</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-O-R</td>
<td>R-COOH</td>
<td>R-SO$_2$R</td>
<td>R-N$_3$</td>
</tr>
<tr>
<td>R-O-SiR$_3$</td>
<td>R-COOH</td>
<td>R-SO$_2$NH</td>
<td>R-NO$_2$</td>
</tr>
<tr>
<td>R-OR</td>
<td>R-CO$_2$R</td>
<td>R-SO$_2$R</td>
<td>R-PR$_2$</td>
</tr>
<tr>
<td>R-OR</td>
<td>R$_2$CONR$_2$</td>
<td>R$_2$CONR$_2$</td>
<td>R-PR$_2$</td>
</tr>
</tbody>
</table>

### Incompatible Functional Groups

<table>
<thead>
<tr>
<th>R-NR$_2$ (most)</th>
<th>R-SH</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-COOH</td>
<td>R-PR$_2$</td>
</tr>
</tbody>
</table>

---


SAE: Kinetic Resolution – Unorthodox Substrates

SAE: Selectivity Mnemonics

Asymmetric Epoxidation

D-(−)-diethyl tartrate (unnatural)

L-(+)-diethyl tartrate (natural)

Kinetic Resolution

D-(−)-diethyl tartrate (unnatural)

slow

fast


SAE: Proposed Catalytic Cycle

Ti(OR)$_4$ + tartrate

$\xrightarrow{K_2'}$

$\xrightarrow{K_1}$

[2 ROH + [Ti(OR)$_2$(tartrate)]]

$\xrightarrow{2 ROH}$

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**SAE: Proposed Transition State**

\[
\text{rate} = \frac{\left[\text{Ti(tartrate)(OR)}_2\right] \left[\text{TBHP}\right] \left[\text{allylic alcohol}\right]}{\left[\text{ligand alcohol}\right]^2}
\]


SAE: Synthetic Example

Directed Epoxidation of Homoallylic Alcohols


Porphyрин/Salen-Based Epoxidations

Timeline

1975  Report by Collman of the chemically robust class of “picket fence” porphyrins
1979  Discovery by Groves that iron porphyrin complexes mimic the epoxidation activity of cytochrome P-450
1983  First report of porphyrin-catalyzed asymmetric epoxidation. Proposal by Groves of the side-on approach transition state model
1983–1986 Detailed mechanistic studies by Kochi on epoxidation reactions catalyzed by achiral salen complexes
1990–1993 Discovery and development by Jacobsen and Katsuki of enantioselective epoxidation of unfunctionalized alkenes by [Mn(salen)]
Porphyrin-Based Epoxidations

Reviews


Porphyrin-Based Epoxidations: An Example

Yields based on consumed PhIO

Salen-Based Epoxidations

Reviews


Jacobsen-Katsuki Epoxidation

2–4 mol% catalyst
NaOCl (2 equiv)
\[ \text{Na}_2\text{HPO}_4 \rightarrow \text{pH 11.3 with NaOH} \]
\[ \text{CH}_2\text{Cl}_2/\text{H}_2\text{O} \]
\[ 0–4{^\circ}\text{C} \]

84% yield
92% ee

67% yield
92% ee

65% yield by GC
89% ee
(with 40 mol% additive)

63% yield
94% ee

87% yield
98% ee
(\textit{ent}-catalyst)

96% yield
97% ee
(\textit{ent}-catalyst)

75% yield
98% ee
(\textit{ent}-catalyst)


Jacobsen-Katsuki Epoxidation

\[
\text{3–4 mol\% catalyst} \quad \text{NaOCl (2 equiv)} \quad \text{Na}_2\text{HPO}_4 \\
\rightarrow \quad \text{pH 11.3 with NaOH} \quad \text{CH}_2\text{Cl}_2/\text{H}_2\text{O} \quad 0{\,}^\circ\text{C–rt}
\]

\[
\begin{align*}
\text{n-hex} & \quad \text{TMS} & \quad \text{TMS} \\
\text{65\% yield} & \quad \text{65\% yield} & \quad \text{34\% yield} \\
1.6:1 \text{trans:cis} & \quad 5.2:1 \text{trans:cis} & \quad 1:1 \text{trans:cis} \\
90/43 \text{trans/cis \% ee} & \quad 98/64 \text{trans/cis \% ee} & \quad 35/35 \text{trans/cis \% ee}
\end{align*}
\]

\[
\begin{align*}
\text{n-hex} & \quad \text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{50\% yield} & \quad \text{58\% yield} & \quad \text{81\% yield} \\
1.1:1 \text{trans:cis} & \quad 7.3:1 \text{trans:cis} & \quad 9:1 \text{trans:cis} \\
92\% \text{ee trans} & \quad 83\% \text{ee trans} & \quad 87\% \text{ee}
\end{align*}
\]

Jacobsen-Katsuki Epoxidation

\[
\begin{align*}
\text{Ph} & \rightarrow \text{Me} \\
\text{Ph} & \rightarrow \text{Ph}
\end{align*}
\]

- Yield not determined
- 95:5 trans:cis
- 81% ee trans

- 80% yield
- >96:4 trans:cis
- 90% ee trans

\[
\begin{align*}
t-\text{Bu} & \rightarrow \text{Me} \\
\text{MeO} & \rightarrow \text{Me}
\end{align*}
\]

- Yield not determined
- 69:31 trans:cis
- 84% ee trans
- Configuration not determined

- Yield not determined
- 89:11 trans:cis
- 86% ee trans

Jacobsen-Katsuki Epoxidation

\[
\text{R} = \text{R} \xrightarrow{3 \text{ mol\% catalyst}} \text{R} = \text{R}
\]

\[
\begin{align*}
\text{20 mol\% additive} & \quad \text{NaOCl (1.5 equiv)} \\
\text{Na}_2\text{HPO}_4 & \quad \text{pH 11.3 with NaOH} \\
\text{CH}_2\text{Cl}_2/\text{H}_2\text{O} & \quad 0 \degree\text{C}
\end{align*}
\]

69\% yield 93\% ee
87\% yield 88\% ee
91\% yield 95\% ee
97\% yield 92\% ee

Jacobsen-Katsuki Epoxidation

\[
\begin{align*}
\text{OSiR}^3\text{Me}_2 & \quad 7 \text{ mol}\% \text{ catalyst} \\
\text{R}^2 & \quad 30 \text{ mol}\% \text{ additive} \\
\text{NaOCl} (7.5 \text{ equiv}) & \quad \text{Na}_2\text{HPO}_4
\end{align*}
\]

\[
\rightarrow \text{pH} 11.3 \text{ with NaOH} \\
\text{CH}_2\text{Cl}_2/\text{H}_2\text{O} \\
0 ^\circ \text{C}
\]

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

Jacobsen-Katsuki Epoxidation

\[
\begin{align*}
\text{R} & \quad \overset{\pi}{\longrightarrow} & \text{R} \\
\begin{align*}
\text{R} \quad \overset{\pi}{\longrightarrow} & \text{R} \\
\begin{align*}
\text{Br} & \quad \overset{\pi}{\longrightarrow} & \text{Me} \\
\text{Et} & \quad \overset{\pi}{\longrightarrow} & \text{Me} \\
\text{Ph} & \quad \overset{\pi}{\longrightarrow} & \text{Me} \\
\text{Me} & \quad \overset{\pi}{\longrightarrow} & \text{Me}
\end{align*}
\end{align*}
\end{align*}
\]

3 mol% catalyst
20 mol% additive
NaOCl (1.5 equiv)
NaOH
CH\(_2\)Cl\(_2\)/H\(_2\)O
0 °C

\[
\begin{align*}
\text{R} & \quad \overset{\pi}{\longrightarrow} & \text{R} \\
\begin{align*}
\begin{array}{c}
t-\text{Bu} \\
\text{Cl}
\end{array} & \overset{\pi}{\longrightarrow} & \begin{array}{c}
t-\text{Bu} \\
\text{t- Bu}
\end{array} \\
\text{TIPS} & \overset{\pi}{\longrightarrow} & \text{t- Bu}
\end{align*}
\end{align*}
\]

catalyst A: 87% ee
catalyst C: 97% ee (81% yield)
catalyst B: 90% ee (90% yield)
catalyst C: 78% ee
catalyst A: 15% ee
catalyst C: 25% ee
configuration not determined

Jacobsen-Katsuki Epoxidation

\[
\text{Catalyst A:} \quad \text{89% yield, 86% ee} \\
\text{Catalyst A:} \quad \text{83% yield, 85% ee} \\
\text{Catalyst B:} \quad \text{83% yield, 80% ee} \\
\text{Catalyst A:} \quad \text{85% yield, 82% ee} \\
\]

56–69% ee with NaOCl

Configurations not indicated


Jacobsen-Katsuki Epoxidation

Jacobsen-Katsuki Epoxidation


Jacobsen-Katsuki Epoxidation

n-allyl R \( \rightarrow \) n-allyl R

\( \text{catalyst NMO or additive B} \)
\( \text{PhIO} \)

chlorobenzene or CH\(_3\)CN

\(-30-0^\circ\text{C}\)

PhMe

\( \text{catalyst A} \)
77% yield
91% ee

PhPh

\( \text{catalyst B} \)
9% yield
87% ee

PhPh

\( \text{catalyst A (S,R')} \)
20% yield
88% ee

PhPh

\( \text{catalyst B} \)
76% yield
88% ee

Jacobsen-Katsuki Epoxidation: Stereoselectivity Model


Jacobsen-Katsuki Epoxidation: Stereoselectivity Model


Jacobsen-Katsuki Epoxidation: Mnemonic

Rotate left π-substituent forward to Predict trans-epoxide stereochemistry.

Jacobsen-Katsuki Epoxidation: Simplified Catalytic Cycle

Possibility of multiple catalytically active (salen)Mn species present in epoxidation reactions

Jacobsen-Katsuki Epoxidation: Mechanistic Possibilities


Jacobsen-Katsuki Epoxidation: Synthetic Example

Dioxirane-Based Epoxidations

Timeline

1899  Intermediacy of dioxiranes first postulated by Baeyer and Villiger in the oxidation of menthone
1972  Isolation of dioxiranes from the oxidation of dilithioalkoxides reported in a patent by Talbott and Thompson
1974  Montgomery speculates that dioxiranes are the active intermediates in the decomposition of Oxone and the oxidation of halides and dyes
1977  Observation of the parent dioxirane in the gas phase reported separately by Suenram and Martinez
1979  Montgomery’s speculation substantiated by $^{18}$O labeling studies reported by Curci and Edwards
1985  Preparation and isolation of dimethyldioxirane from acetone reported by Murray
1996  Yang reports up to 87% ee in oxidation of olefins with catalytic chiral dioxiranes
1996  Shi reports stochiometric epoxidations in >90% ee with a fructose-derived dioxirane
1997  Shi reports that modification of reaction conditions allow epoxidation with catalytic amounts of his chiral ketone
Dioxirane-Based Epoxidations

Reviews


Yang Epoxidation

$$\text{Ar} \quad \text{10 mol\% catalyst (98\% ee)} \quad \text{Oxone (10 equiv)} \quad \text{Ar}$$

$$\text{NaHCO}_3 \text{ (31 equiv)} \quad 0.4 \text{ mol\% Na}_2\text{EDTA} \quad \text{DME/H}_2\text{O} \quad 0-1 \degree \text{C} \quad \leq 20 \text{h} \quad \geq 89\% \text{ yield}$$

- 84\% ee
- 88\% ee
- 91\% ee
- 91\% ee
- 95\% ee
- 73\% ee*
- 71\% ee*
- 77\% ee with parent complex*

*modified reaction conditions


Dioxirane-Based Epoxidations: Catalytic Cycle

Adapted from: Denmark, S. E.; Wu, Z. *Synlett* 1999, 847–859.
Yang Epoxidation: Stereoselectivity Model

Product stereochemistry supports a spiro TS in dioxirane epoxidations.

Denmark Epoxidation

Ar¼R

30 mol% catalyst
Oxone (4 equiv)
K₂CO₃ (12 equiv)
0.4 mol% Na·EDTA
CH₃CN/H₂O
0 °C

Ar¼R

80% yield
88% ee

46% yield
94% ee

93% yield
89% ee

72% yield
68% ee
(50 mol% catalyst)

78% yield
59% ee

67% yield
12% ee
configuration not determined

55% yield
43% ee

Shi Epoxidation: trans-Disubstituted Olefins

\[
\text{R}^1\text{R}^2 \xrightarrow{\text{30 mol\% catalyst}} \text{Oxone (1.38 equiv)} \xrightarrow{\text{K}_2\text{CO}_3 (5.8 equiv)}, 0.4 \text{ mol\% Na}_2\text{EDTA}, 50 \text{ mol\% Na}_2\text{B}_4\text{O}_7\cdot10\text{H}_2\text{O}} \xrightarrow{-10-0^\circ\text{C}} \text{R}^1\text{O}\text{R}^2
\]

* modified buffer conditions
**absolute configuration assigned by analogy


Shi Epoxidation: trans-Disubstituted Olefins

\[
\begin{align*}
\text{R}^1\text{=C}\text{=}\text{R}^2 & \xrightarrow{20-50 \text{ mol\% catalyst}} \text{Oxone (1.12-2.07 equiv)} \\
& \xrightarrow{\text{K}_2\text{CO}_3 (5.8-8.07 equiv)} \\
& \xrightarrow{\text{K}_2\text{CO}_3/\text{AcOH buffer or Na}_2\text{EDTA/Na}_2\text{B}_4\text{O}_7\cdot10\text{H}_2\text{O buffer}} \\
& \xrightarrow{\text{CH}_3\text{CN/DMM/H}_2\text{O}} \\
& \xrightarrow{-10-0 \degree \text{C}} \\
\end{align*}
\]

- Ph\text{O}TMS \quad 59\% \text{ yield} \\
- n-\text{Pr}\text{O}TBS \quad 71\% \text{ yield} \\
- n-\text{Pr}\text{O}OMe \quad 35\% \text{ yield} \\
- Ph\text{O}n-\text{Pr} \quad 94\% \text{ conv.} \\
- 22:1 \text{ mono-:bisepoxide} \\
- 77\% \text{ yield} \\
- 94\% \text{ ee} \\
- Me\text{O}\text{OTBS} \quad 100\% \text{ conv.} \\
- \text{4.6:1 mono-:bisepoxide} \\
- 68\% \text{ yield (13\% minor)} \\
- 96\% \text{ ee* (91\% minor)*} \\
- Me\text{O}Me\text{OTBS} \quad 100\% \text{ conv.} \\
- \text{65\% yield} \\
- 89\% \text{ ee*} \\
- n-\text{Pr}\text{O}n-\text{Pr} \quad 72\% \text{ conv.} \\
- \text{61\% yield} \\
- 94\% \text{ ee} \\
- \text{CO}_2\text{Et} \quad \text{*absolute configuration assigned by analogy} \\


Shi Epoxidation: Trisubstituted Olefins


Shi Epoxidation: Trisubstituted Olefins

Shi Epoxidation: Trisubstituted Olefins

\[
\begin{align*}
\text{R}^1\text{=C} & \quad \text{R}^2 \\
\text{in the presence of} & \quad \text{Me}_2\text{O}
\end{align*}
\]

20–30 mol% catalyst
Oxone (1.12–2.07 equiv)
K\textsubscript{2}CO\textsubscript{3} (5.8–8.07 equiv)
K\textsubscript{2}CO\textsubscript{3}/AcOH buffer
or
Na\textsubscript{2}•EDTA/Na\textsubscript{2}B\textsubscript{4}O\textsubscript{7}•10H\textsubscript{2}O buffer
CH\textsubscript{3}CN/DMM/H\textsubscript{2}O
–10–0 °C

- 60% yield 93% ee*
- 97% yield 77% ee*
- 98% yield 96% ee*
- 100% conv. 12:1 mono-:bisepoxide 54% yield 95% ee*
- 100% conv. 81% yield 96% ee*
- 100% conv. 89% yield 94% ee*

*absolute configuration assigned by analogy

Shi Epoxidation: $\alpha,\beta$-Unsaturated Esters

25–30 mol% catalyst
Oxone (5 equiv)
4 mol% $\text{Bu}_4\text{NHSO}_4$
$\text{NaHCO}_3$ (15.5 equiv)
0.2 mol% $\text{Na}_2\cdot\text{EDTA}$
$\text{CH}_3\text{CN}/\text{H}_2\text{O}$
$0 \, ^\circ \text{C}$

Catalyst is not effective for trans-aliphatic $\alpha,\beta$-unsaturated esters.

Shi Epoxidation: Stereoselectivity Model

Shi Epoxidation: Terminal Olefins

20–30 mol% catalyst
Oxone (3.4 equiv)

20 mol% Bu₄NHSO₄
K₂CO₃ (7.7 equiv)
AcOH/K₂CO₃/EDTA buffer
DME/DMM/H₂O
−10 °C

π

O

π

O

100% conv.
63% yield
90% ee

100% conv.
84% yield
89% ee

100% conv.
91% yield
90% ee

94% conv.
64% yield
90% ee

100% conv.
77% yield
93% ee

81% yield
90% ee

100% conv.
62% yield
89% ee

80–92% ee with a fructose-derived variant


Shi Epoxidation: cis-Disubstituted Olefins

\[ \text{π} \quad \text{R} \quad \text{10–30 mol\% catalyst} \quad \text{Oxone} \quad \text{Bu}_4\text{NHSO}_4 \quad \text{K}_2\text{CO}_3 \quad \text{AcOH/K}_2\text{CO}_3/\text{EDTA buffer} \quad \text{DME/DMM/H}_2\text{O} \quad -10–0 °\text{C} \quad \text{π} \quad \text{R} \]

- **Catalyst A**: 91% conv. 61% yield 95% 97% ee

- **Catalyst B**: 100% conv. 75% yield 92% ee*

- **Catalyst C**: 77% yield 87% ee

- **Catalyst D**: 100% conv. 10:1 mon:bis(epoxide) 80% yield mono(epoxide) 89% ee mono(epoxide)*

- **Catalyst E**: >95% conv. 67% yield 3.3:1 cis-trisubstituted epoxide 91% ee cis-epoxide


Shi Epoxidation: Stereoselectivity Model

Spiro TS favored due to π–π interactions

Planar TS may contribute to lower ee for terminal epoxides

Planar TS π–π interactions may account for reversal in facial selectivity

68% yield 42% ee

88% yield 30% ee
catalyst is still ineffective for 1,1-disubstituted olefins

Shi Epoxidation: Tri- and Tetrasubstituted Olefins

\[
\text{Ar} = \begin{array}{c}
\text{R} \\
\end{array}
\]

20 mol\% catalyst
Oxone

K\(_2\)CO\(_3\)
AcOH/K\(_2\)CO\(_3\)/EDTA buffer
DME/DMM/H\(_2\)O
–10–0 °C

\[
\text{Ar} = \begin{array}{c}
\text{R} \\
\end{array}
\]

*absolute configuration assigned by analogy


Shi Epoxidation: Tri- and Tetrasubstituted Olefins


Shi Epoxidation: Synthetic Example

ketone (3 equiv) oxone
K$_2$CO$_3$
$n$-BuNH$_2$SO$_4$
Na$_2$·EDTA/Na$_2$B$_4$O$_7$·10H$_2$O
CH$_3$CN/DMF/H$_2$O
0 °C

CSA
PhMe
0 °C
31% over two steps

proposed structure of glabrescol

Nucleophilic Epoxidations

Timeline

1980  First highly enantioselective epoxidation reaction reported by Juliá, epoxidizing chalcone in >90% ee
1997  Shibasaki reports that BINOL-derived catalysts provide high enantioselectivity in the epoxidation of \( \alpha,\beta \)-unsaturated ketones

Reviews


Polyamino Acid-Catalyzed Epoxidations: Lead References


Kelly, D. R.; Roberts, S. M. *Biopolymers* 2006, 84, 74–89.
Shibasaki Epoxidation: Enones

\[
\begin{align*}
\text{R}^1\text{C}==\text{C}R^2 & \xrightarrow{5 \text{ mol}\% (R)-\text{BINOL}} \text{R}^1\text{O}==\text{C}R^2 \\
& \xrightarrow{5 \text{ mol}\% \text{ La(Oi-Pr)}_3} \text{R}^1\text{O}==\text{C}R^2 \\
& \xrightarrow{5 \text{ mol}\% \text{ Ph}_3\text{As}=\text{O}} \text{R}^1\text{O}==\text{C}R^2 \\
& \xrightarrow{\text{TBHP} (1.2 \text{ equiv})} \text{R}^1\text{O}==\text{C}R^2 \\
& \xrightarrow{\text{4Å MS (not dried)}} \text{R}^1\text{O}==\text{C}R^2 \\
& \xrightarrow{\text{THF} \text{ rt}} \text{R}^1\text{O}==\text{C}R^2
\end{align*}
\]

Ph\text{O}==\text{CPh} 
99\text{\% yield} 
96\text{\% ee}

\[\text{i-Pr}\text{O}==\text{CPh}\]
95\text{\% yield} 
94\text{\% ee}

\[\text{Ph}\text{O}==\text{Ci-Pr}\]
72\text{\% yield} 
95\text{\% ee}

\[n\text{-pent}\text{O}==\text{CMe}\]
89\text{\% yield} 
95\text{\% ee}

\[n\text{-Pr}\text{O}==\text{CPh}\]
95\text{\% yield} 
96\text{\% ee}

\[n\text{-pent}\text{O}==\text{CMe}\]
61\text{\% yield} 
<10\text{\% trans-epoxide} 
59\text{\% ee} 
(10 \text{ mol}\% \text{catalyst})

Shibasaki Epoxidation: Amides

**Scheme:**
10 mol% (S)-BINOL
10 mol% La(Oi-Pr)₃
10 mol% Ph₃As=O
TBHP (2.4 equiv)

\[ \text{R} = \text{MeO} \]

4Å MS
THF
rt

\[ \text{MeOH} \rightarrow \text{R} \quad \text{O} \quad \text{OMe} \]

**Examples:**

\[ \text{Ph} \quad \text{O} \quad \text{O} \quad \text{Me} \]
86% yield
92% ee

\[ \text{Me} \quad \text{O} \quad \text{O} \quad \text{Ot-Bu} \]
92% yield*
79% ee

\[ \text{Ph} \quad \text{O} \quad \text{O} \quad \text{Me} \]
58% yield
91% ee
(using CMHP)

\[ \text{Me} \quad \text{O} \quad \text{O} \quad \text{Me} \]
81% yield*
81% ee

* MeOH not added. could be converted to corresponding ester in similar yield by MeOH addition.


Shibasaki Epoxidation: Amides

10 mol% (S)-BINOL
10 mol% Sm(Oi-Pr)₃
10 mol% Ph₃As=O
TBHP (1.2 equiv)

4Å MS (dried or wet)
THF
rt

Ph
99% yield
>99% ee

Ph
95% yield
98% ee

n-Pr
94% yield
94% ee

Ph
96% yield
>99% ee

Shibasaki Epoxidation: Amides

\[
\text{R} = \text{OMe} \\
\text{R} = \text{Cl} \\
\text{R} = \text{Cy}
\]

Shibasaki Epoxidation: Mechanism

Shibasaki Epoxidation: Stereoselectivity Model

Shibasaki Epoxidation: Esters

\[ \text{R} = \text{OAc} \quad 89\% \text{ yield} \quad 89\% \text{ ee} \]
\[ \text{R} = \text{OMe} \quad 74\% \text{ yield} \quad 99\% \text{ ee} \]
\[ \text{PMBO} \quad 81\% \text{ yield} \quad 96\% \text{ ee} \]

General

Context Dependent

Few Examples
Phase-Transfer Epoxidations: Lead References

\[
\text{R} = \text{Ar, alkyl} \quad \text{up to 99\% ee}
\]


Amine-Catalyzed Epoxidations: Lead References

Oxaziridine-Catalyzed Epoxidations: Lead References


Imminium-Catalyzed Epoxidations: Lead References

R\rightarrow\text{catalyst}\\H_2O_2\text{ or }\text{NsNIPh}\\\text{CH}_2\text{Cl}_2/H_2O\\rt\\\text{or}\\\text{CH}_2\text{Cl}_2/\text{AcOH}\\-30\text{ }^\circ\text{C}\\R\longrightarrow\text{catalyst }A\\R=\text{alkyl or }Ar\text{ or }CO_2R\\63\text{–}90\% \text{ yield}\\\geq 9:1 \text{ dr}\\94\text{–}98\% \text{ ee}\\R\longrightarrow\text{catalyst }B\\R=\text{alkyl or }Ar\\72\text{–}95\% \text{ yield}\\\geq 7:1 \text{ dr}\\85\text{–}97\% \text{ ee}\\Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhung, W.; Jørgensen, K. A. J. Am. Chem. Soc. 2005, 127, 6964–6965.

Sulfur Ylide-Catalyzed Epoxidations: Lead References

\[ \text{Ph} = \text{alkyl, olefin, Ar} \]
\[ \text{R} = \text{alkyl, olefin, Ar} \]
\[ \text{40 °C} \]

R = alkyl, olefin, Ar
21–100% yield
3:1 to ≥98:2 dr
87–94% ee


Hydrolytic Kinetic Resolution of Terminal Epoxides

Schaus, S. E; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N.


For an improved monomer catalyst, see: Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N.


\[
\begin{align*}
R \rightarrow & \quad \text{0.05–2 mol% catalyst} \\
& \quad \text{H}_2\text{O} \ (0.55–0.7 \ \text{equiv}) \\
& \quad \text{various solvents or neat} \\
& \quad \text{rt} \\
\rightarrow & \quad \text{36–48% yield} \\
& \quad >99\% \ \text{ee}
\end{align*}
\]

Highly general for \( R = \text{alkyl, aryl, olefin, alkynyl} \)

Highly functional group tolerant