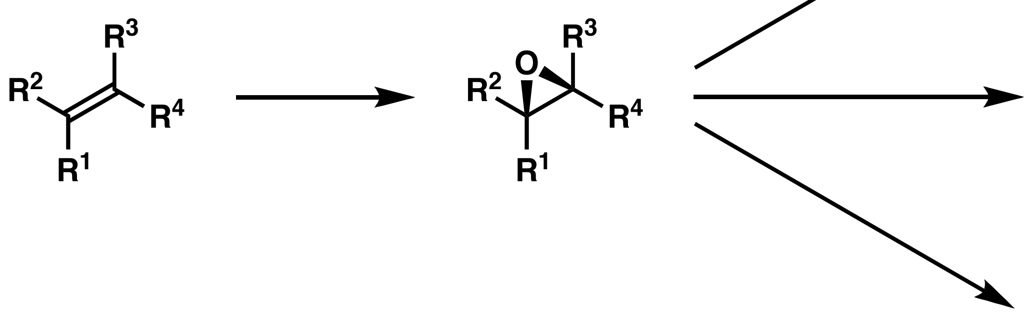
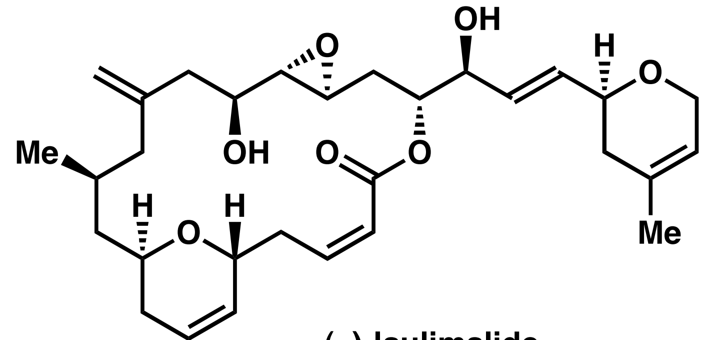
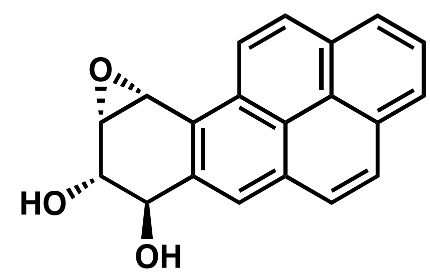
Practical Catalytic Asymmetric Epoxidations

David White
Stoltz Group Literature Presentation
December 13, 2006
8 p.m.
147 Noyes

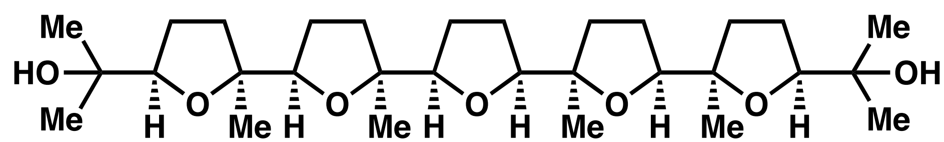




(–)-laulimalide



active metabolite of
benzo[a]pyrene



proposed structure of glabrescol

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
- C. Shi

IV. Nucleophilic Epoxidations
- A. Juliá
- B. Shibasaki

V. Miscellaneous Methods

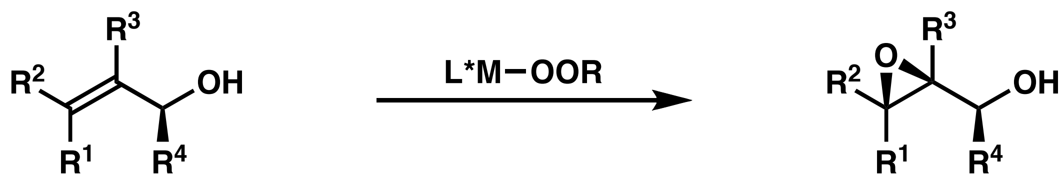
General Section Outline

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

Extensive Current General Review

Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X.; Su, K.-X. *Chem. Rev.* **2005,** *105,* 1603–1662.

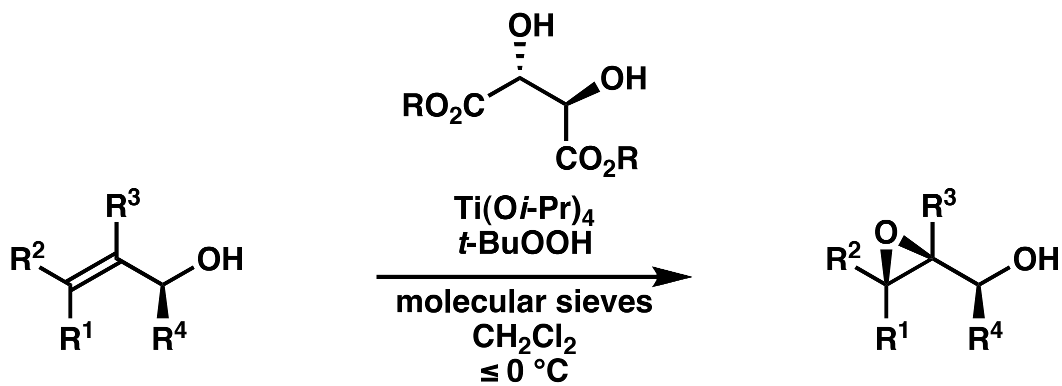
Directed Epoxidations



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

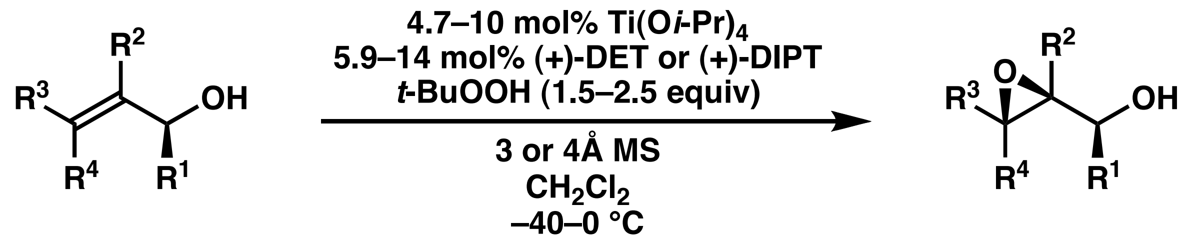
Johnson, R. A.; Sharpless. K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed. Wiley-CVH: New York, 2000; 231–280.

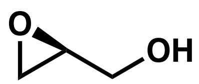
Katsuki, T. Epoxidation of Allylic Alcohols. In *Comprehensive Asymmetric Catalysis,* 1st ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: New York, 1999; Vol. 2, 621–648.

Johnson, R. A.; Sharpless. K. B. Addition Reactions with Formation of Carbon–Oxygen Bonds: Asymmetric Methods of Epoxidation. In *Comprehensive Organic Synthesis,* 1st ed.; Trost, B. M., Fleming, I. Eds.; Pergamon Press: New York,1991; Vol. 7, 389–436.

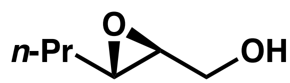
Jacobsen, E. N. Transition Metal-catalyzed Oxidations: Asymmetric Epoxidation. In *Comprehensive Organometallic Chemistry II,* 1st ed.; Abel, E. W.; Stone, F. G. A.; Wilkinson, G. Eds.; Pergamon Press: New York,1995; Vol. 12, 1097–1135

SAE: Substrate Scope

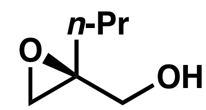




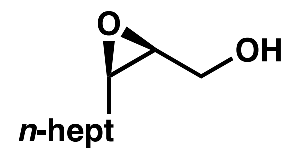
90% ee
65% yield
(cumene hydroperoxide)



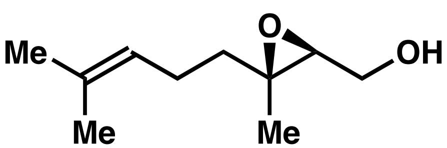
94% ee
85% yield



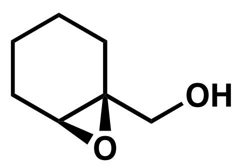
95% ee
88% yield



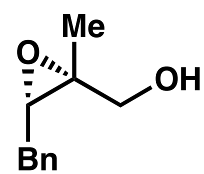
86% ee
74% yield



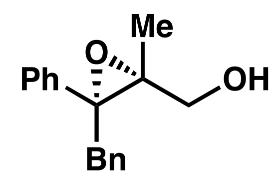
91% ee
95% yield



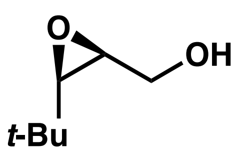
93% ee
77% yield



91% ee
90% yield
Conditions not provided.



91% ee
90% yield
120 mol% $Ti(Oi\text{-}Pr)_4$
150 mol% (–)-DET



25% ee
77% yield
120 mol% $Ti(Oi\text{-}Pr)_4$
150 mol% (+)-DET

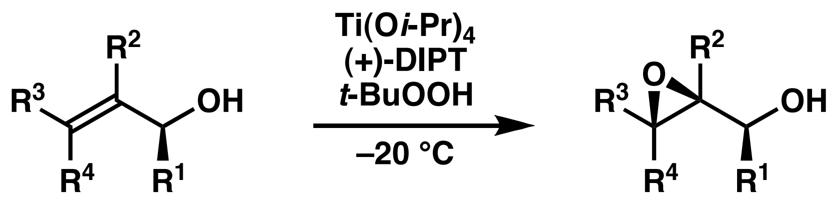
Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Marin, S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard S. S. *Pure & Appl. Chem.* **1983,** *55,* 589–604.

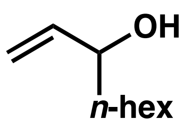
Schweitzer, M. J.; Sharpless, K. B. *Tetrahedron Lett.* **1985** *26,* 2543–2546.

Gao, Y. Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987,** *109,* 5765–5780.

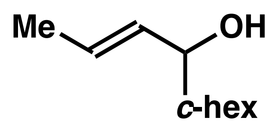
Erickson, T. J. *J. Org. Chem.* **1986,** *51,* 934–935.

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





83



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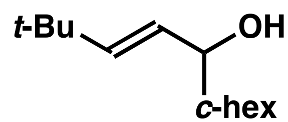

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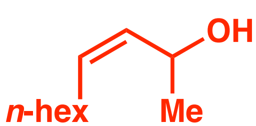
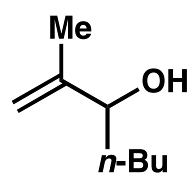


16



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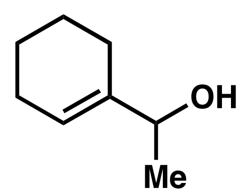
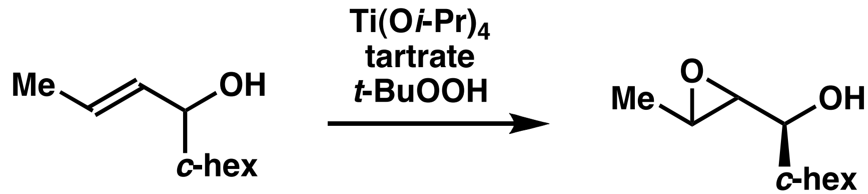
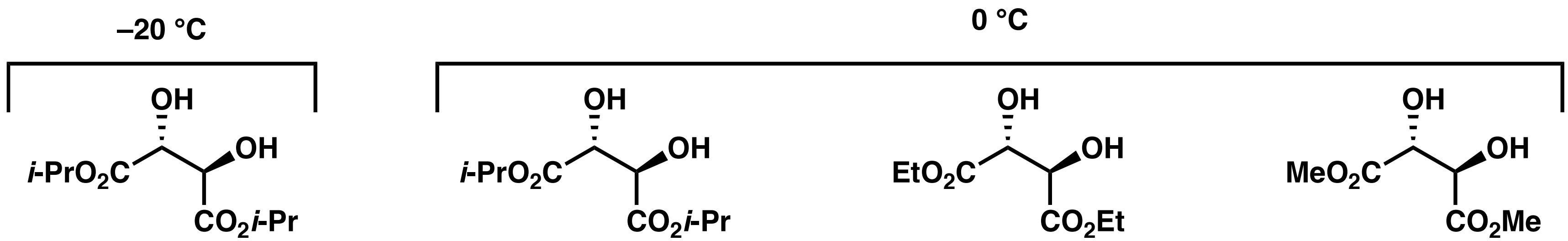


83

Johnson, R. A.; Sharpless. K. B.; Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000; 231–280 and references therein.

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



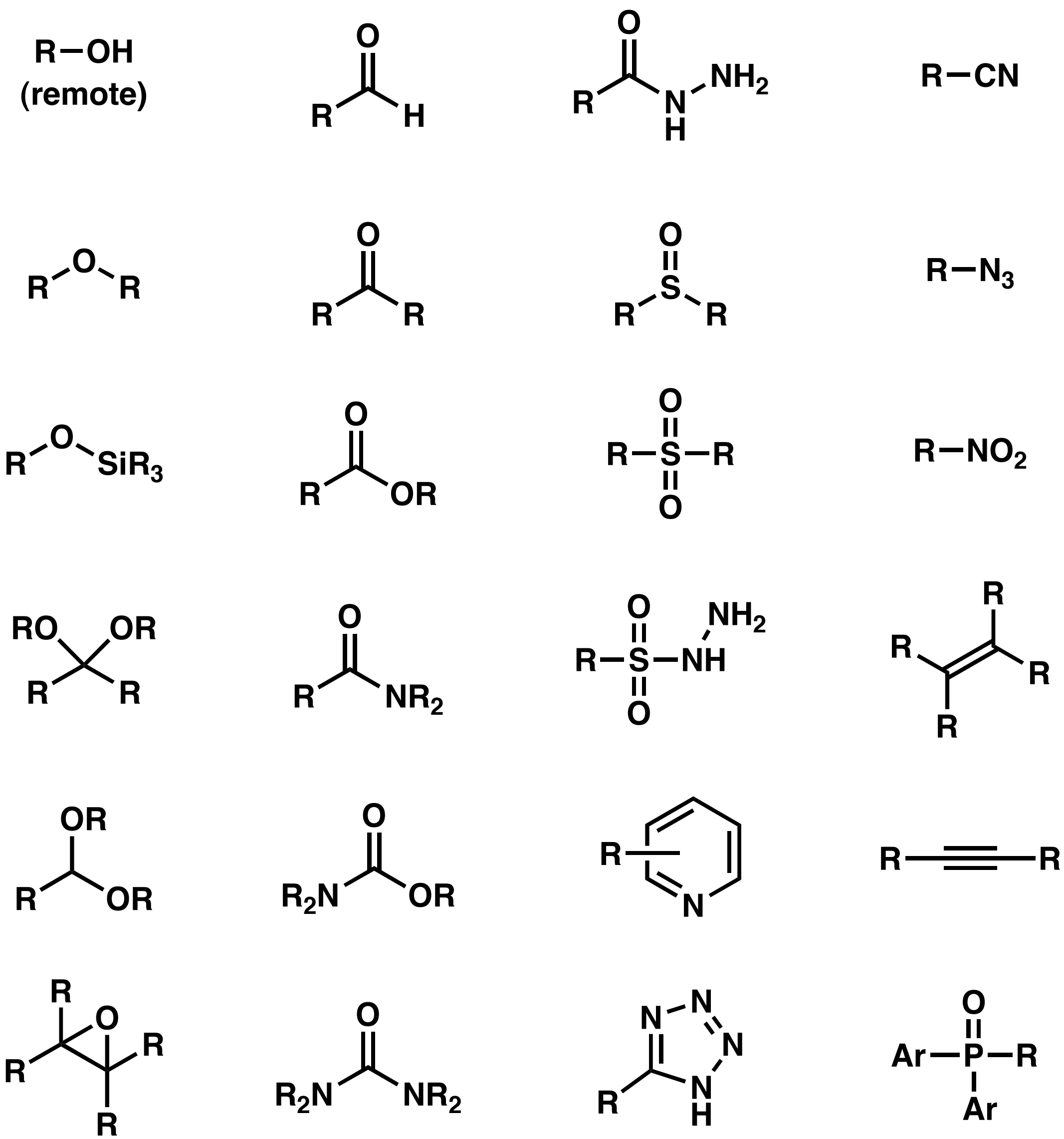


104	74	28	15
DIPT	DIPT	DET	DMT

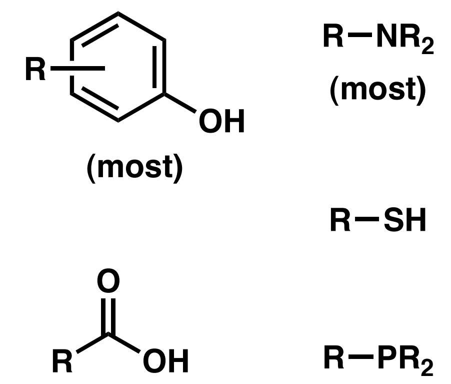
Johnson, R. A.; Sharpless. K. B.; Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000; 231–280 and references therein.

SAE: Substrate Scope

Compatible Functional Groups



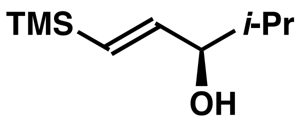
Incompatible Functional Groups



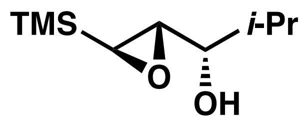
Johnson, R. A.; Sharpless. K. B.; Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000; 231–280.

Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001,** *343,* 5–26, supporting information and references therein.

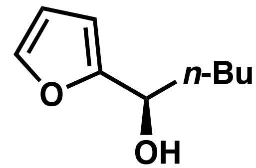
SAE: Kinetic Resolution – Unorthodox Substrates



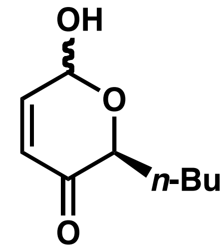
40–48% yield
>99% ee



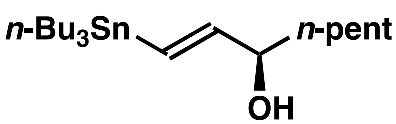
40–48% yield
99% ee



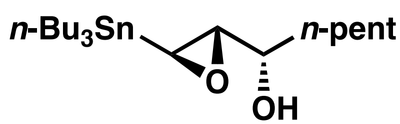
43% yield
94% ee



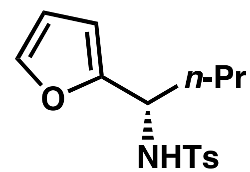
46% yield
ee not determined



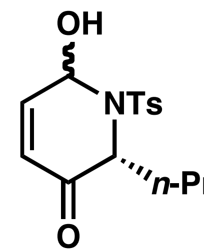
38–42% yield
99% ee



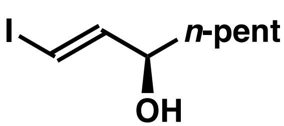
47% yield*
(inferred from text)
80% ee



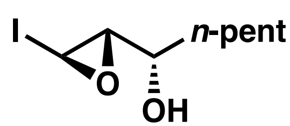
46% yield
95% ee



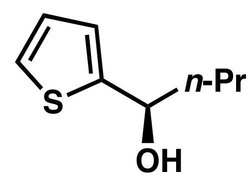
47% yield
ee not determined



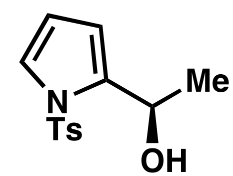
45% yield
99% ee



yield not given
99% ee



39% yield
>95% ee



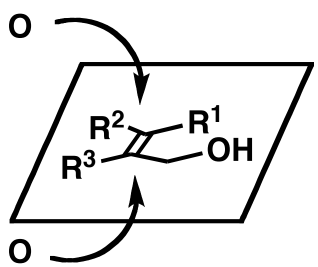
43% yield
>95% ee

Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001,** *343,* 5–26, supporting information and references therein.

SAE: Selectivity Mnemonics

Asymmetric Epoxidation

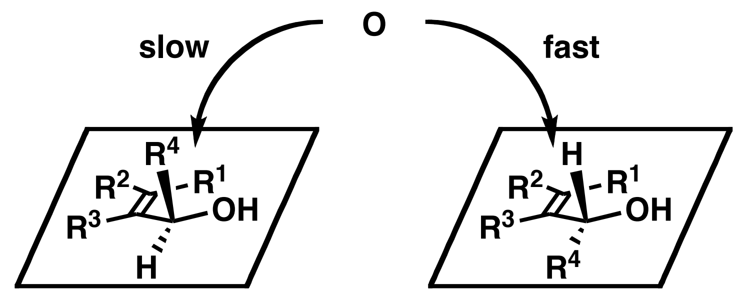
D-(–)-diethyl tartrate (unnatural)



L-(+)-diethyl tartrate (natural)

Kinetic Resolution

D-(–)-diethyl tartrate (unnatural)

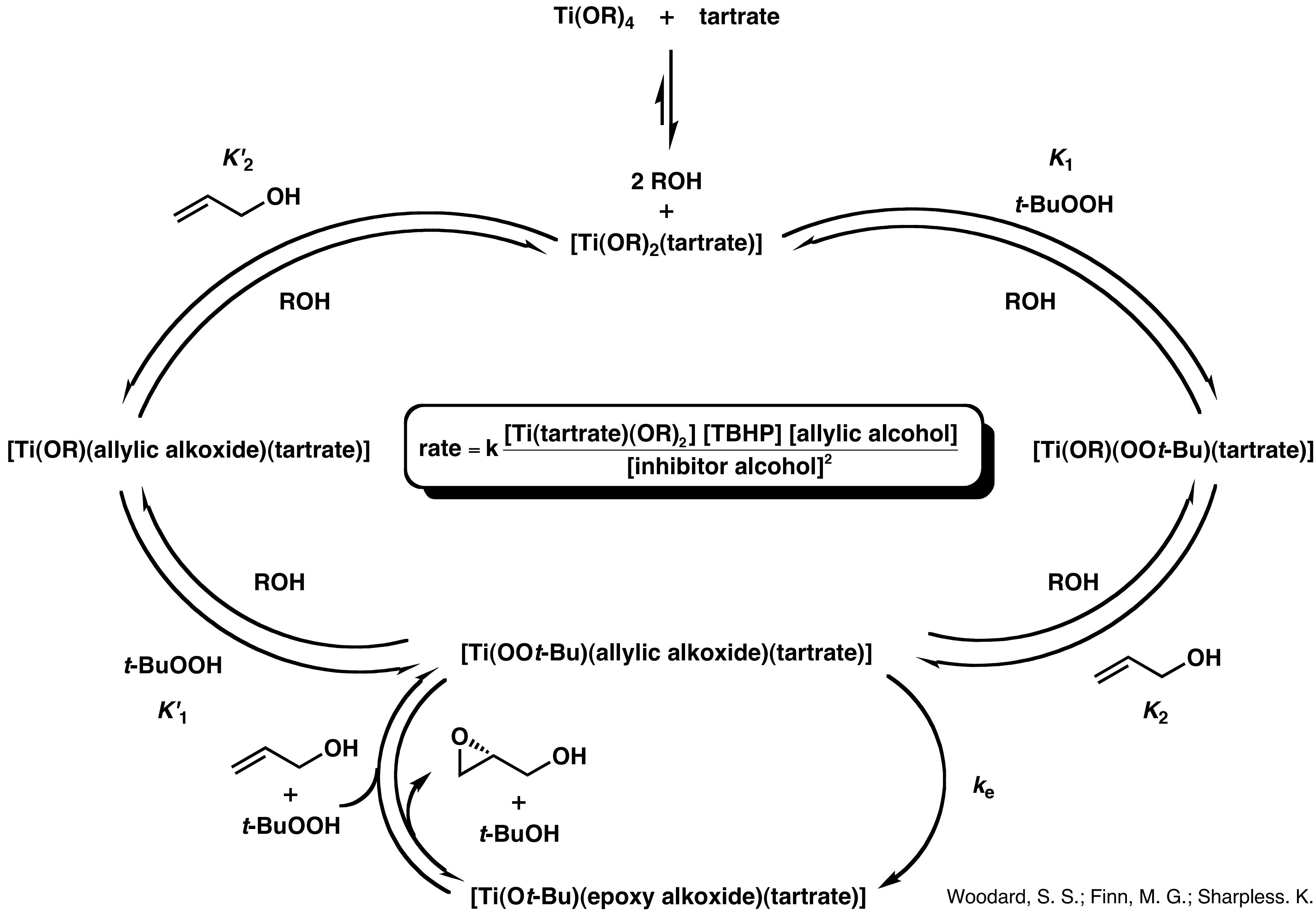


Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980,** *102,* 5974–5976.

Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981,** *103,* 6237–6240.

Johnson, R. A.; Sharpless. K. B.; Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000; 231–280 and references therein.

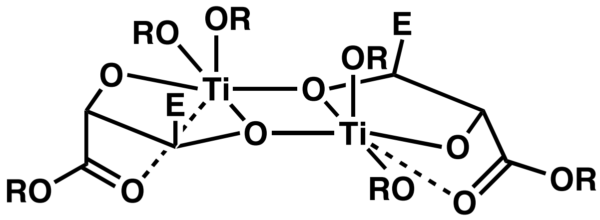
SAE: Proposed Catalytic Cycle



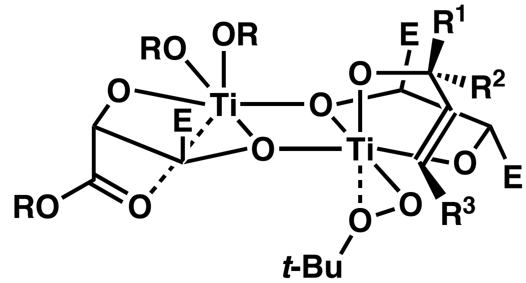
$$\text{rate} = k\,\frac{[\text{Ti(tartrate)(OR)}_2]\,[\text{TBHP}]\,[\text{allylic alcohol}]}{[\text{inhibitor alcohol}]^2}$$

Woodard, S. S.; Finn, M. G.; Sharpless. K. B.
J. Am. Chem. Soc. **1991,** *113,* 106–113.

SAE: Proposed Transition State



Proposed Catalyst Structure
E = CO_2R

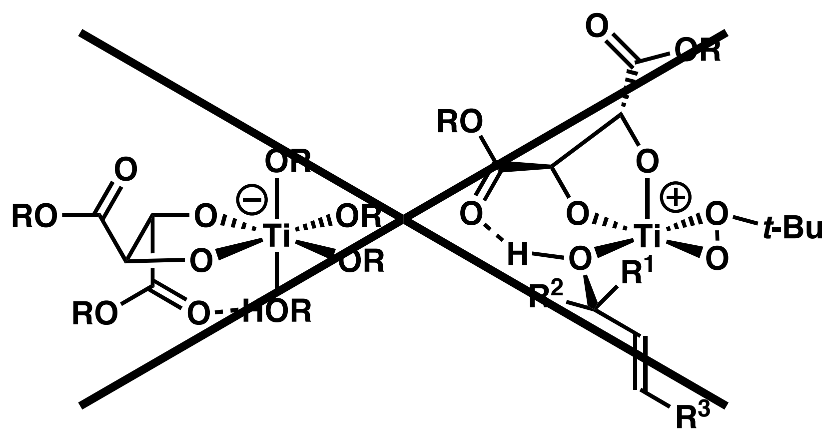


Proposed Transition State
E = CO_2R

Finn, M. G.; Sharpless. K. B. *J. Am. Chem. Soc.* **1991,** *113,* 113–126.

Johnson, R. A.; Sharpless. K. B.; Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000; 231–280.

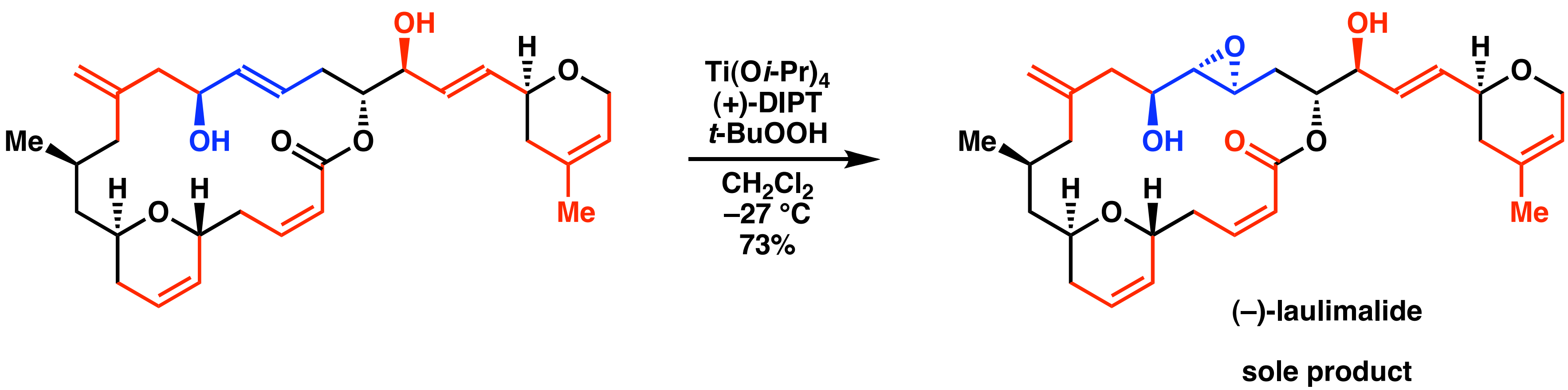
$$\textbf{rate} = \frac{[\text{Ti(tartrate)(OR)}_2]\ [\text{TBHP}]\ [\text{allylic alcohol}]}{[\text{ligand alcohol}]^2}$$



Corey Proposed Transition State

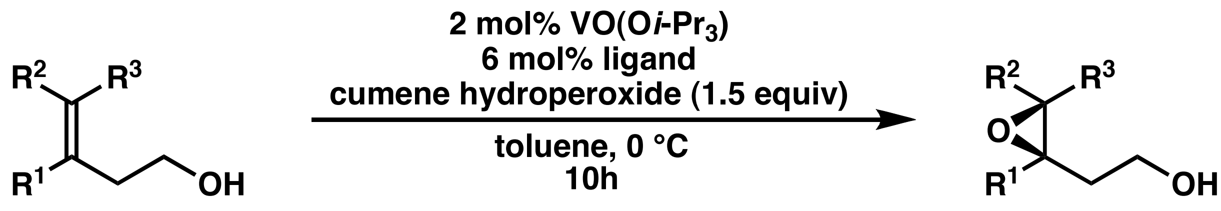
Corey, E. J. *J. Org. Chem.* **1990**, *55*, 1693–1694.

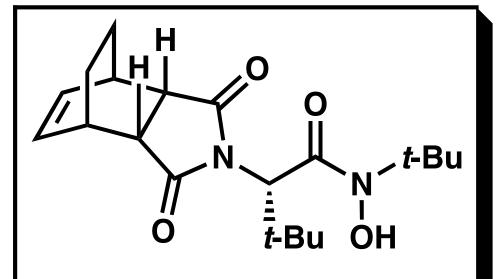
SAE: Synthetic Example



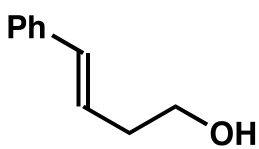
Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett* **2001,** *3,* 3149–3152.

Directed Epoxidation of Homoallylic Alcohols

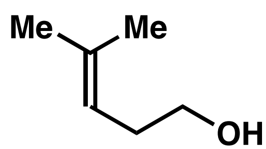




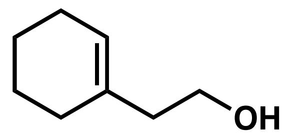
ligand



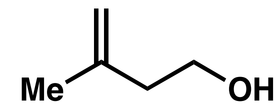
24% yield
46% ee



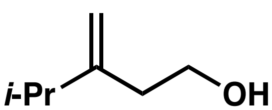
67% yield
36% ee



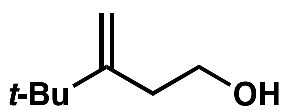
61% yield
74% ee



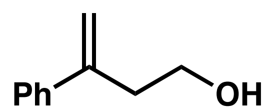
58% yield
84% ee



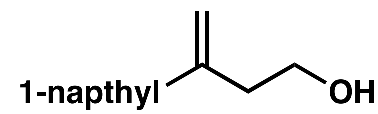
77% yield
90% ee



89% yield
90% ee



70% yield
89% ee

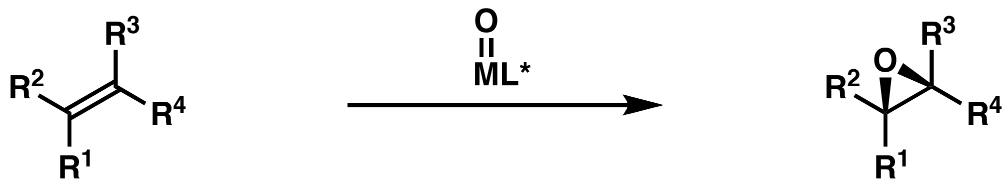


42% yield
91% ee

Makita, N.; Hoshino, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 941–9434.

Also see: Blanc, A.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 2096–2099.

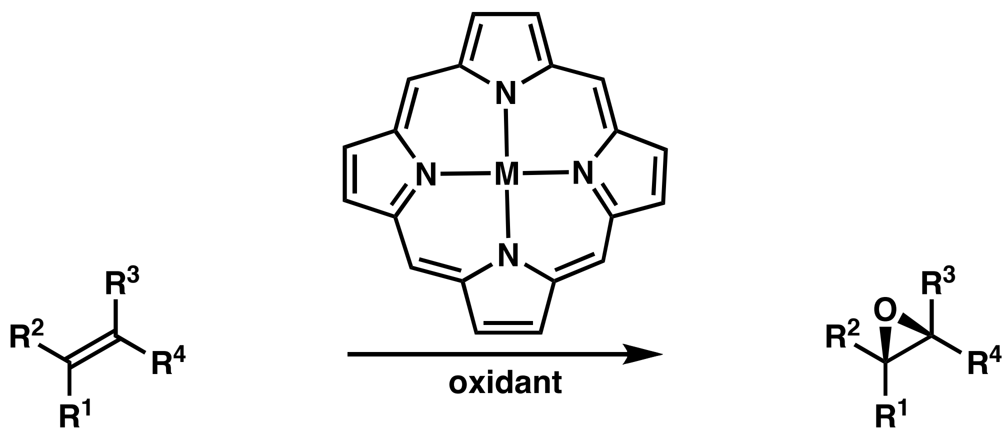
Porphyrin/Salen-Based Epoxidations



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 asymmeric 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

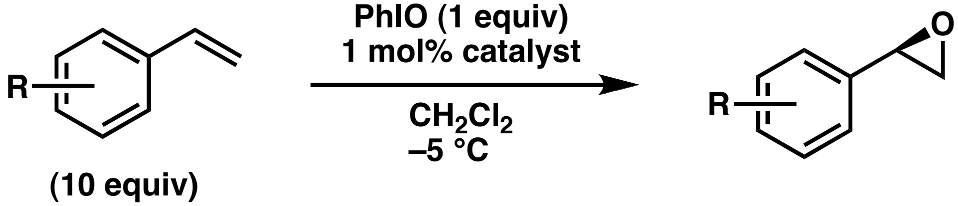
Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu-Ethéve, M. *Chem. Soc. Rev.* **2005,** *34,* 573–583.

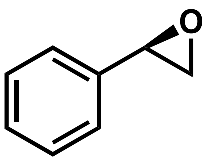
Katsuki, T. Asymmetric Epoxidation of Unfunctionalized Olefins and Related Reactions. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed. Wiley-CVH: New York, 2000; 287–325.

Jacobsen, E. N.; Wu, M. H. Epoxidation of Alkenes other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis,* 1st ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: New York, 1999; Vol. 2, 649–677.

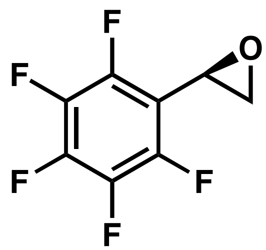
Jacobsen, E. N. Transition Metal-catalyzed Oxidations: Asymmetric Epoxidation. In *Comprehensive Organometallic Chemistry II,* 1st ed.; Abel, E. W.; Stone, F. G. A.; Wilkinson, G. Eds.; Pergamon Press: New York, 1995; Vol. 12, 1097–1135

Porphyrin-Based Epoxidations: An Example

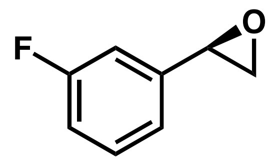




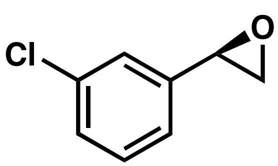
96% yield
97% ee



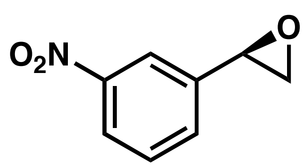
80% yield
96% ee



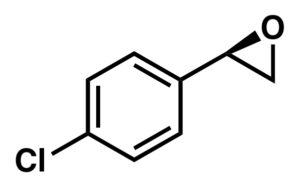
87% yield
93% ee



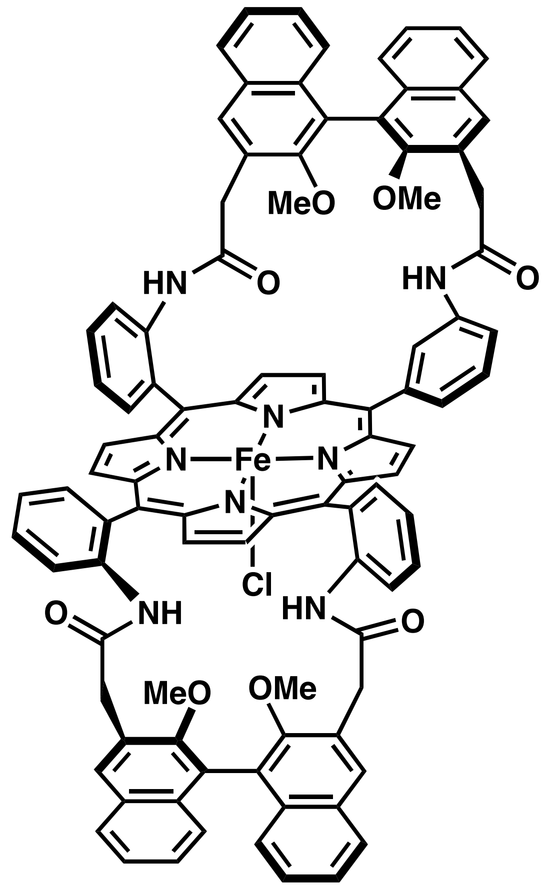
90% yield
88% ee



84% yield
90% ee



75% yield
84% ee

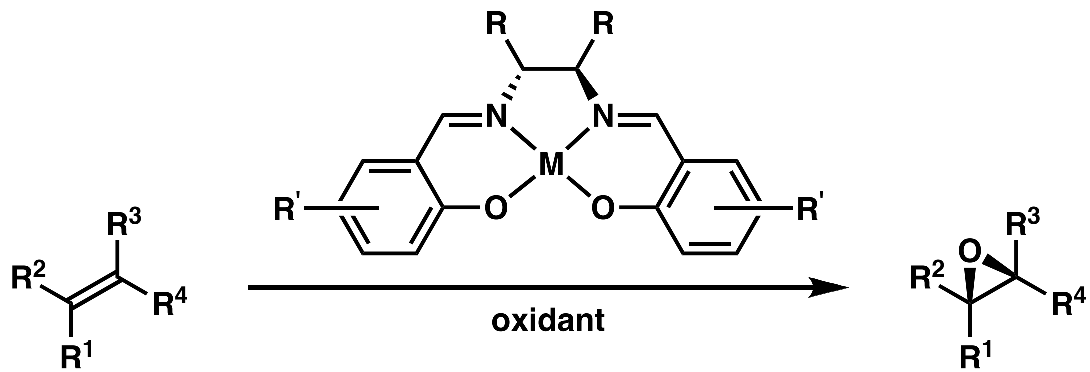


catalyst

Yields based on consumed PhIO

Rose, E.; Ren, Q.-Z.; Andrioletti, B. *Chem. Eur. J.* **2004**, *10*, 224–230.

Salen-Based Epoxidations



Reviews

McGarrige, E. M.; Gilheany, D. G. *Chem. Rev.* **2005,** *105,* 1563–1602.

Katsuki, T. *Adv. Synth. Catal.* **2002,** *344,* 131–147.

Katsuki, T. Asymmetric Epoxidation of Unfunctionalized Olefins and Related Reactions. In *Catalytic Asymmetric Synthesis,* 2nd ed.; Ojima, I. Ed. Wiley-CVH: New York, 2000; 287–325.

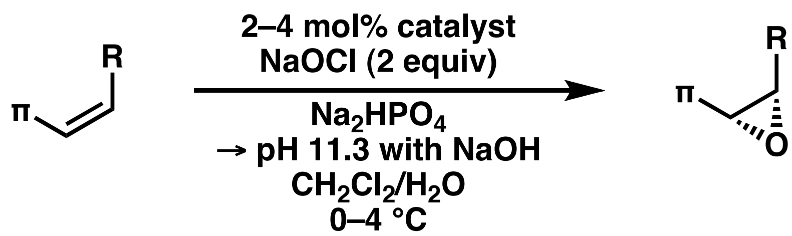
Jacobsen, E. N.; Wu, M. H. Epoxidation of Alkenes other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis,* 1st ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: New York, 1999; Vol. 2, 649–677.

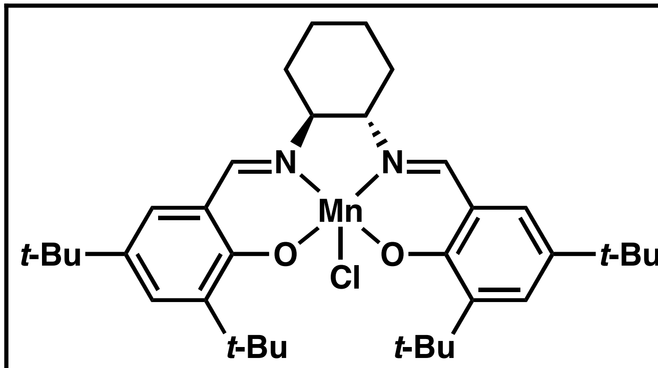
Katsuki, T. *J. Mol. Catal. A: Chem.* **1996,** *113,* 87–107.

Jacobsen, E. N. Transition Metal-catalyzed Oxidations: Asymmetric Epoxidation. In *Comprehensive Organometallic Chemistry II,* 1st ed.; Abel, E. W.; Stone, F. G. A.; Wilkinson, G. Eds.; Pergamon Press: New York,1995; Vol. 12, 1097–1135.

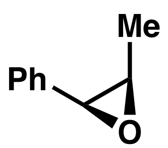
Katsuki, T. *Coord. Chem. Rev.* **1995,** *140,* 189–214.

Jacobsen-Katsuki Epoxidation

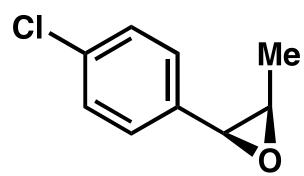




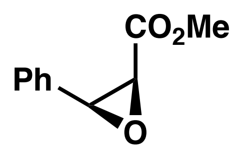
catalyst



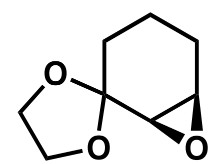
84% yield
92% ee



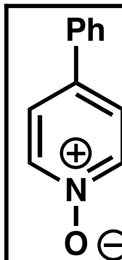
67% yield
92% ee



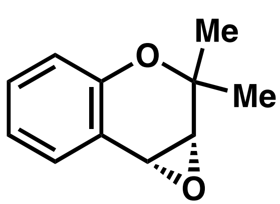
65% yield by GC
89% ee
(with 40 mol% additive)



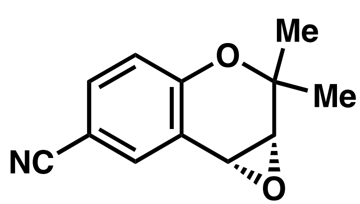
63% yield
94% ee



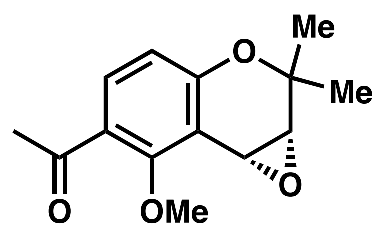
additive



87% yield
98% ee
(*ent*-catalyst)



96% yield
97% ee
(*ent*-catalyst)

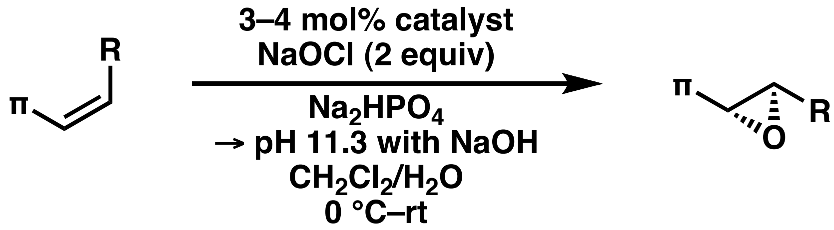


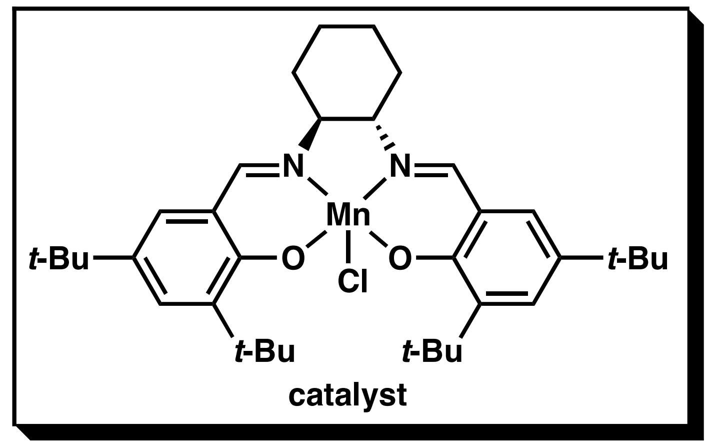
75% yield
98% ee
(*ent*-catalyst)

Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.

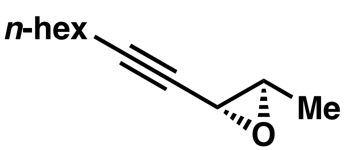
Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055–5058.

Jacobsen-Katsuki Epoxidation

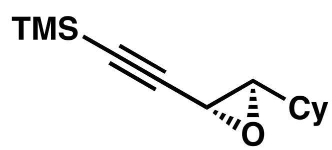




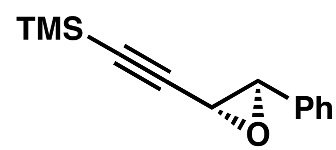
catalyst



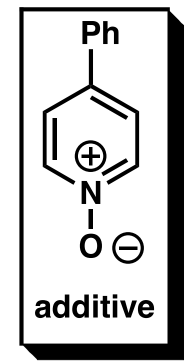
65% yield
1.6:1 trans:cis
90/43 trans/cis % ee



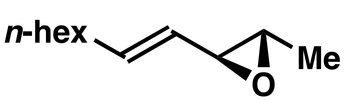
65% yield
5.2:1 trans:cis
98/64 trans/cis % ee
(20 mol% additive)



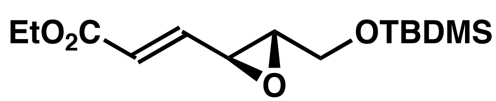
34% yield
1:1 trans:cis
35/35 trans/cis % ee



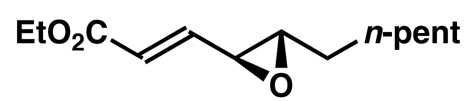
additive



50% yield
1.1:1 trans:cis
92% ee trans
(20 mol% additive;
ent-catalyst)



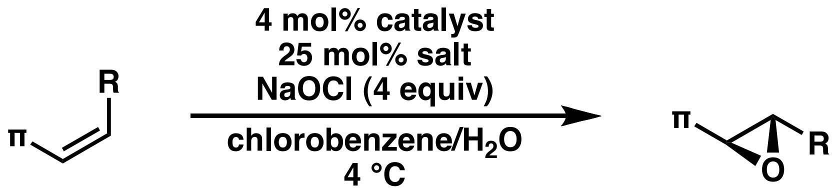
58% yield
7.3:1 trans:cis
83% ee trans
(20 mol% additive;
ent-catalyst)

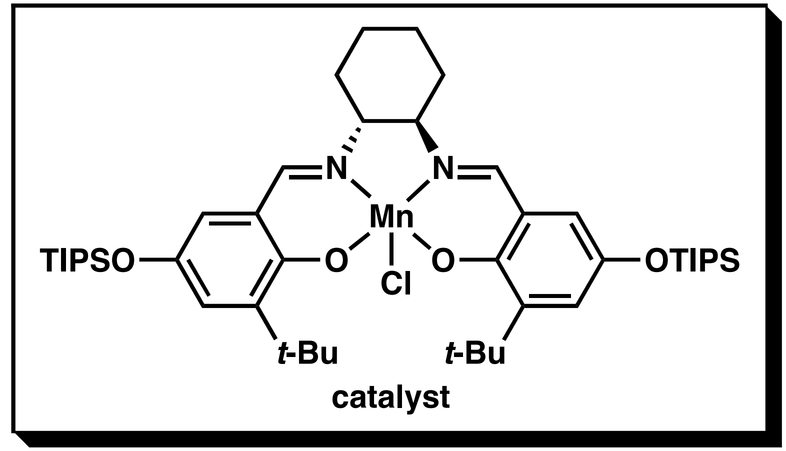


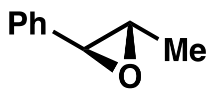
81% yield
9:1 trans:cis
87% ee
(20 mol% additive;
ent-catalyst)

Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533–6536. Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939–6941.

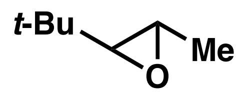
Jacobsen-Katsuki Epoxidation



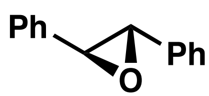




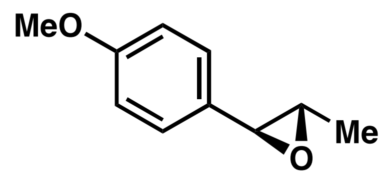
yield not determined
95:5 trans:cis
81% ee trans



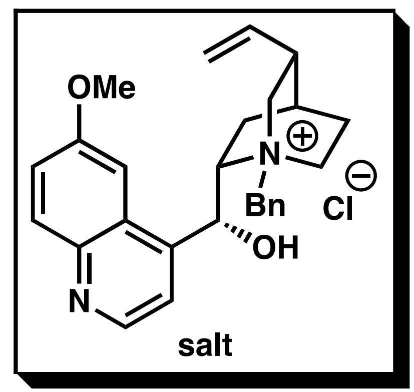
yield not determined
69:31 trans:cis
84% ee trans
configuration not determined



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

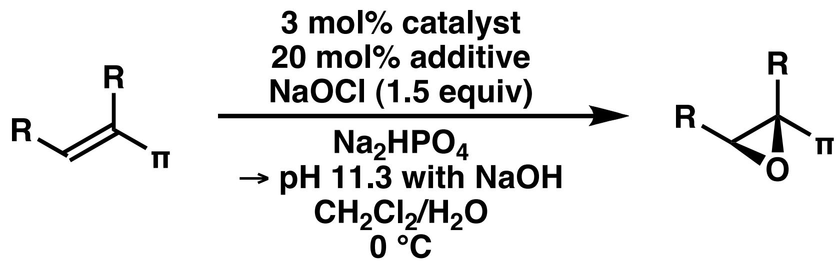


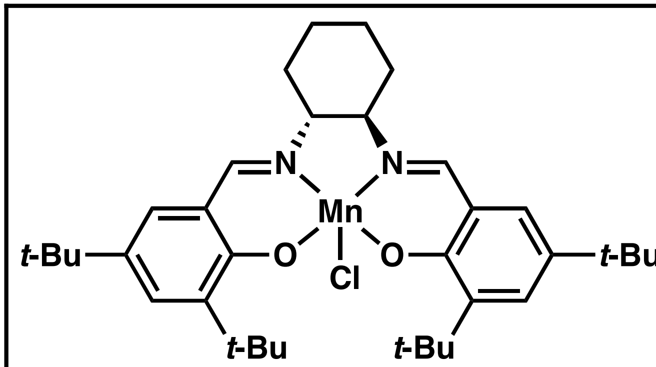
yield not determined
89:11 trans:cis
86% ee trans



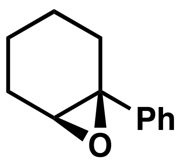
Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937–6938.

Jacobsen-Katsuki Epoxidation

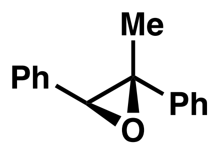




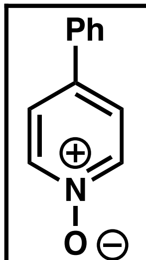
catalyst



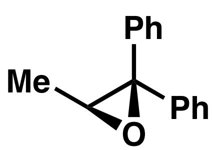
69% yield
93% ee



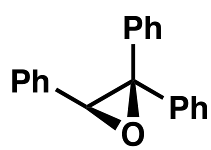
87% yield
88% ee



additive



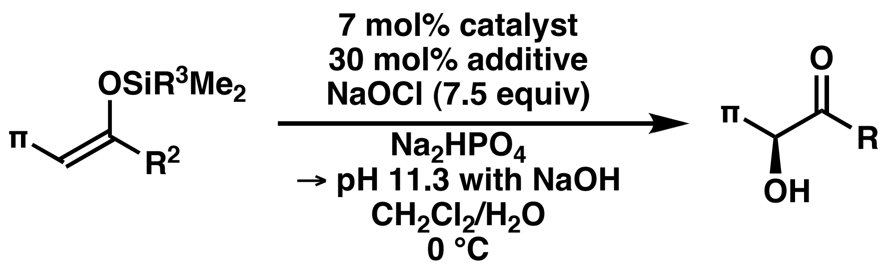
91% yield
95% ee

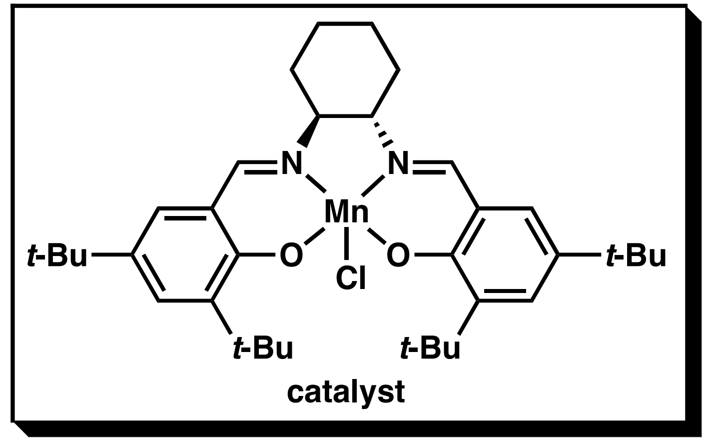


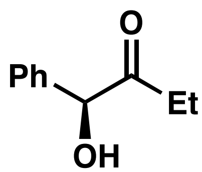
97% yield
92% ee

Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380.

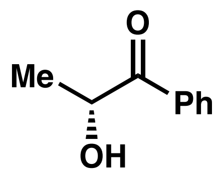
Jacobsen-Katsuki Epoxidation



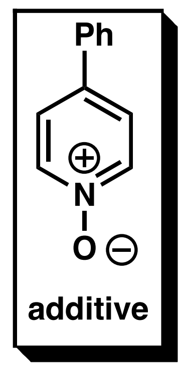


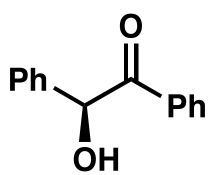


R = Me
82% conv.
87% ee

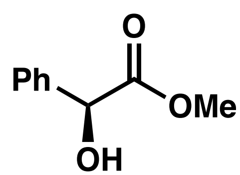


R = *t*-Bu
95% conv.
81% ee





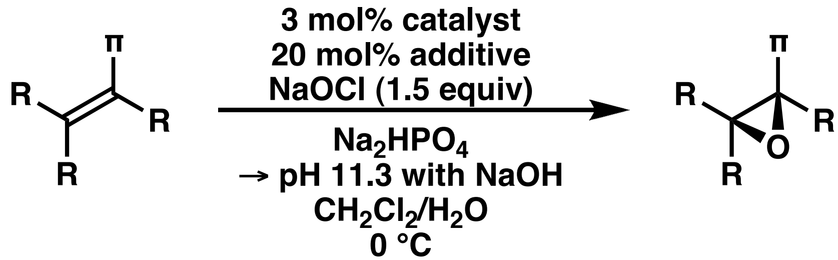
R = Me
88% conv.
12% ee

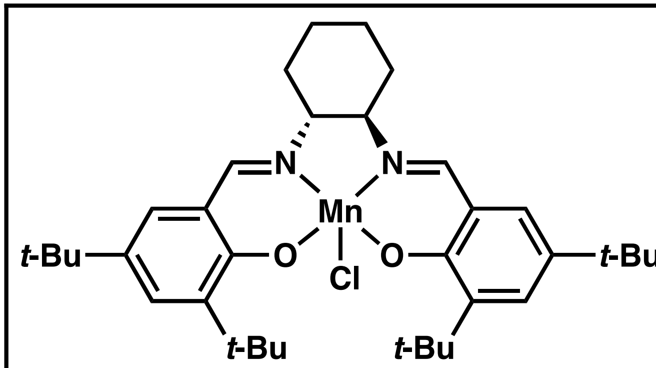


R = *t*-Bu
70% conv.
57% ee

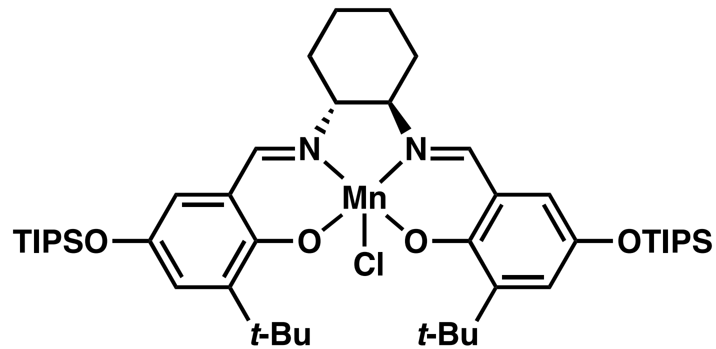
Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Möller, C. R.
J. Am. Chem. Soc. **1998**, *120*, 708–714.

Jacobsen-Katsuki Epoxidation

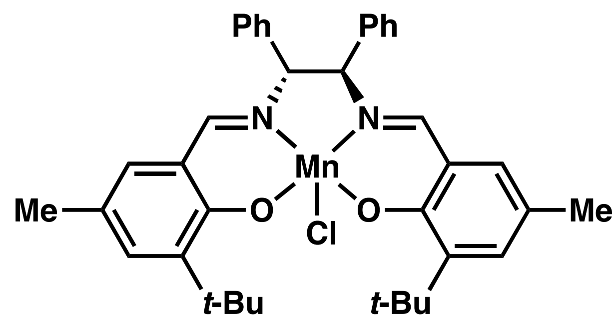




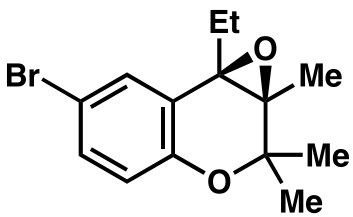
catalyst A



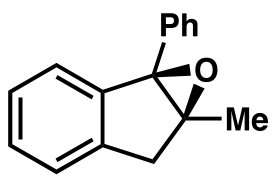
catalyst B



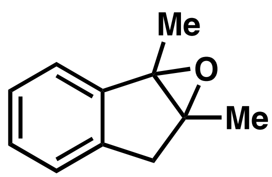
catalyst C



catalyst A: 87% ee
catalyst C: 97% ee (81% yield)



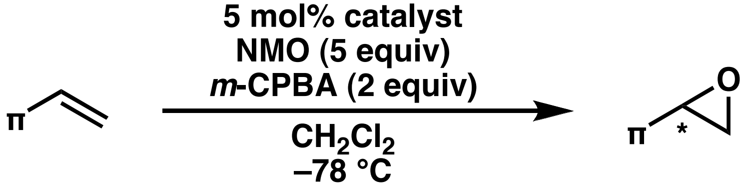
catalyst B: 90% ee (90% yield)
catalyst C: 78% ee

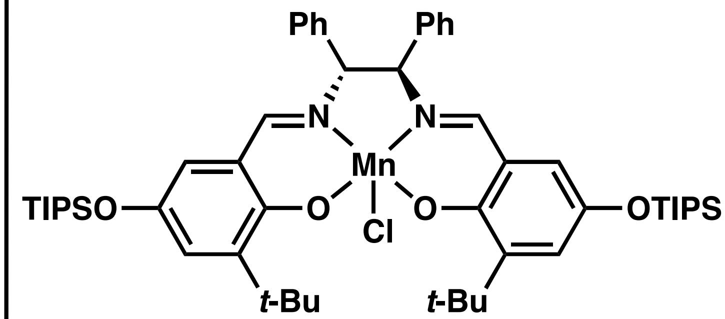


catalyst A: 15% ee
catalyst C: 25% ee
configuration not determined

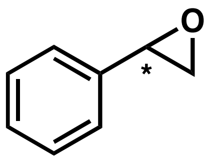
Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123–5126.

Jacobsen-Katsuki Epoxidation

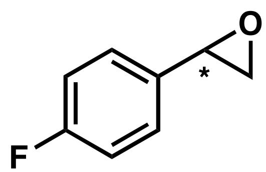




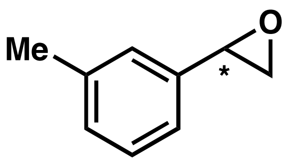
catalyst A



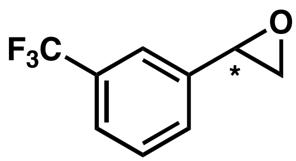
catalyst A
89% yield
86% ee



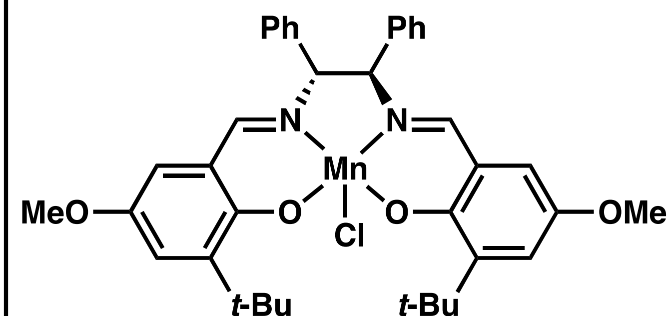
catalyst A
83% yield
85% ee



catalyst B
83% yield
80% ee



catalyst A
85% yield
82% ee



catalyst B

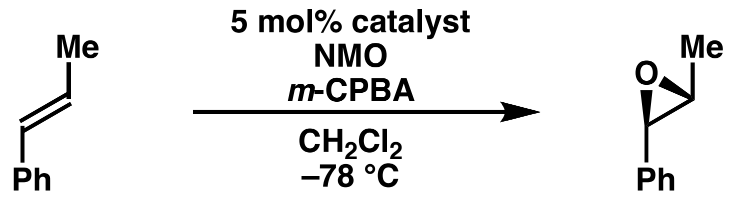
56–69% ee with NaOCl

Configurations not indicated

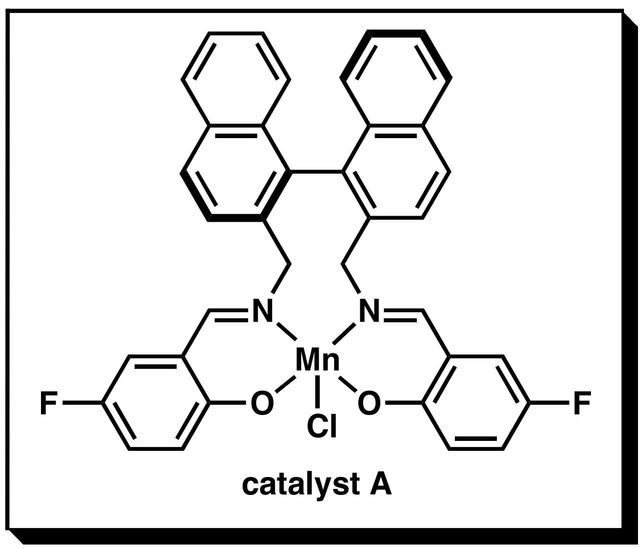
Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457–5460.

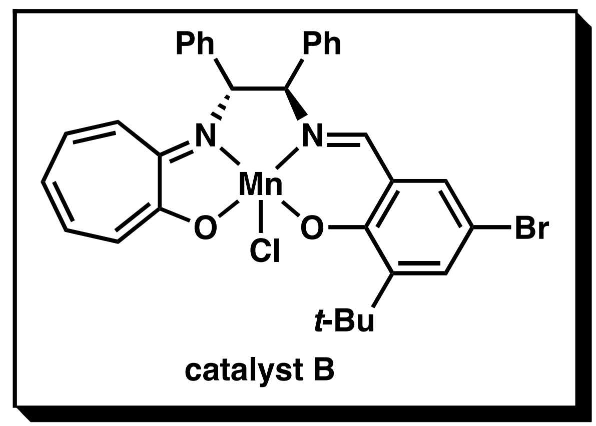
Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333–9334.

Jacobsen-Katsuki Epoxidation



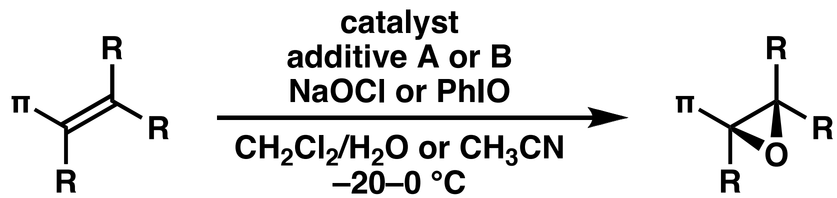
catalyst A: 86% ee
catalyst B: 83% ee

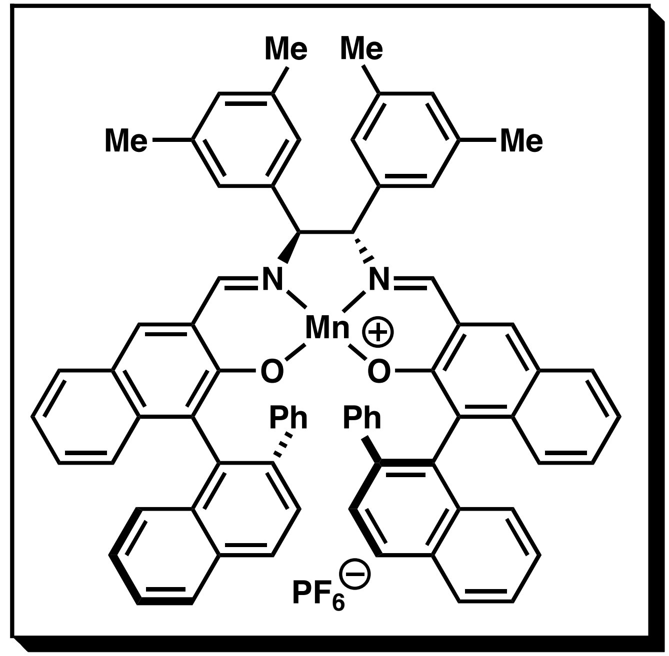


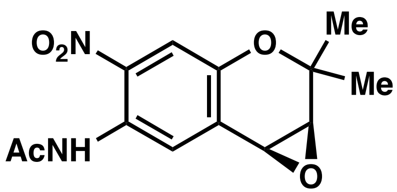


Jacobsen, E. N.; Wu, M. H. Epoxidation of Alkenes other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis,* 1st ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: New York, 1999; Vol. 2, 649–677.

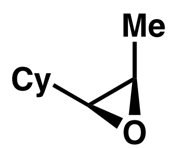
Jacobsen-Katsuki Epoxidation



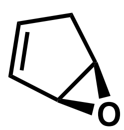




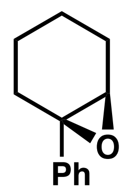
80% yield
>99% ee



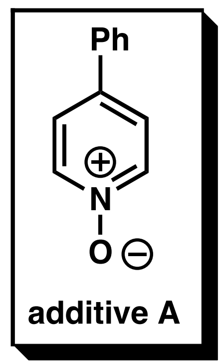
23% yield
82% ee

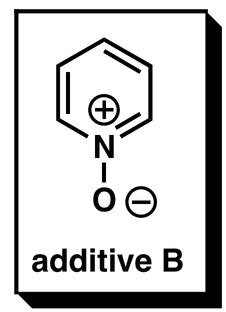


82% yield by ^{1}H NMR
93% ee



26% yield
83% ee



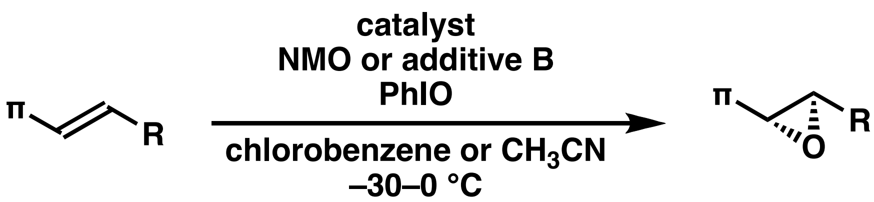


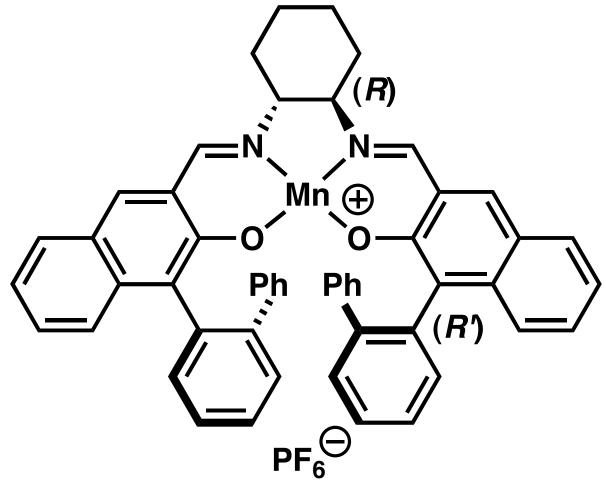
Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827–11838.

Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197–198.

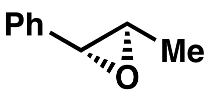
Mikame, D.; Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 827–828.

Jacobsen-Katsuki Epoxidation

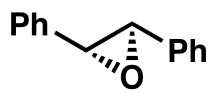




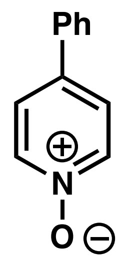
catalyst A



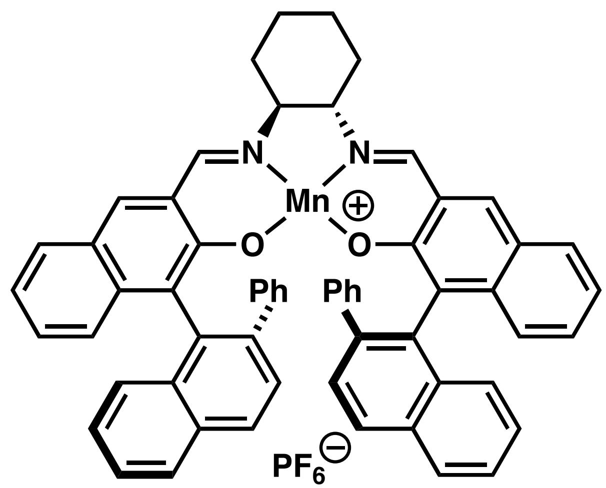
catalyst A
77% yield
91% ee



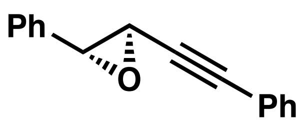
catalyst B
9% yield
87% ee



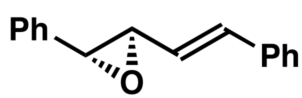
additive B



catalyst B



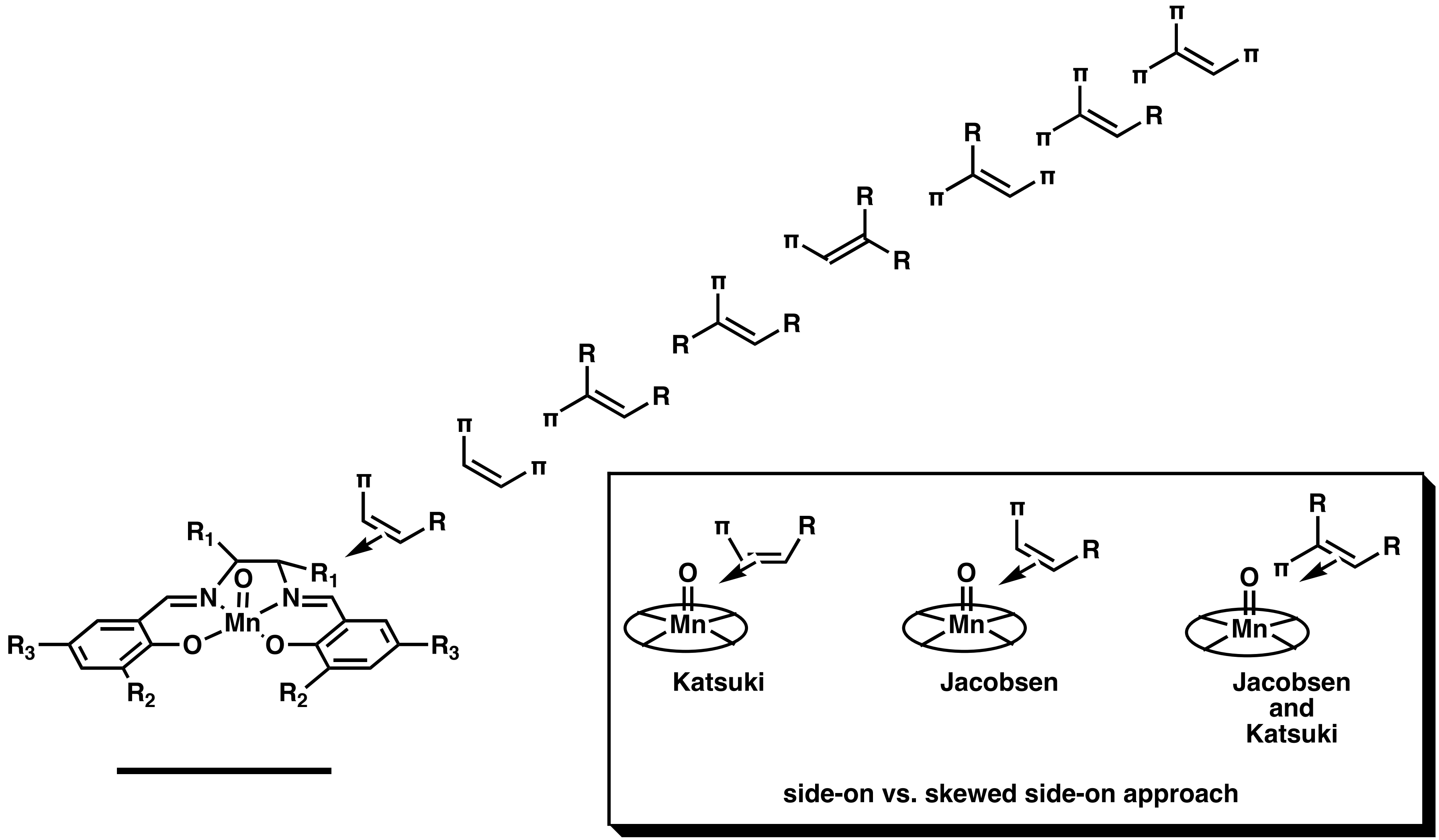
catalyst A (*S,R′*)
20% yield
88% ee



catalyst B
76% yield
88% ee

Nishikori, H.; Ohta, C.; Katsuki, T. *Synlett* **2000**, 1557–1560.

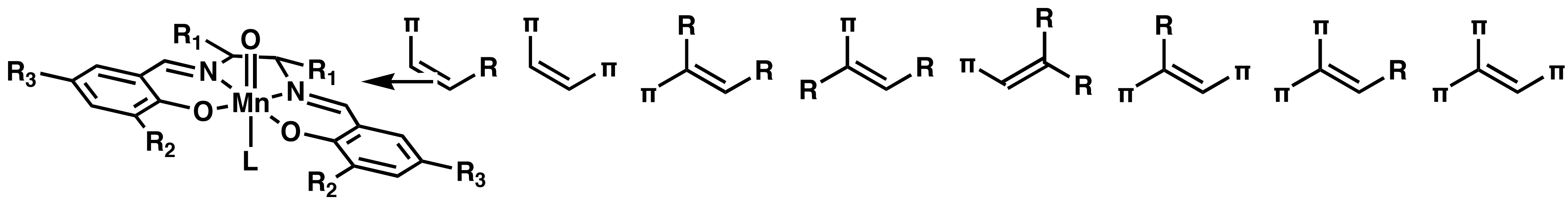
Jacobsen-Katsuki Epoxidation: Stereoselectivity Model

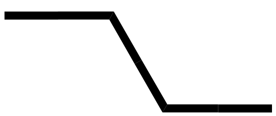


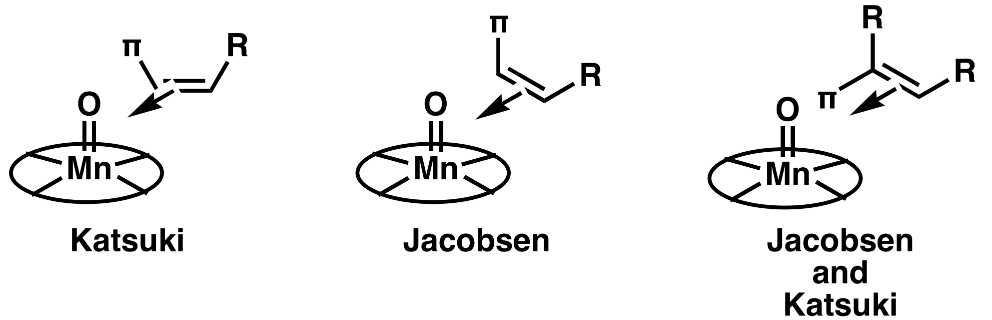
Based on: Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197–198.

Modified based on data from: Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380.

Jacobsen-Katsuki Epoxidation: Stereoselectivity Model





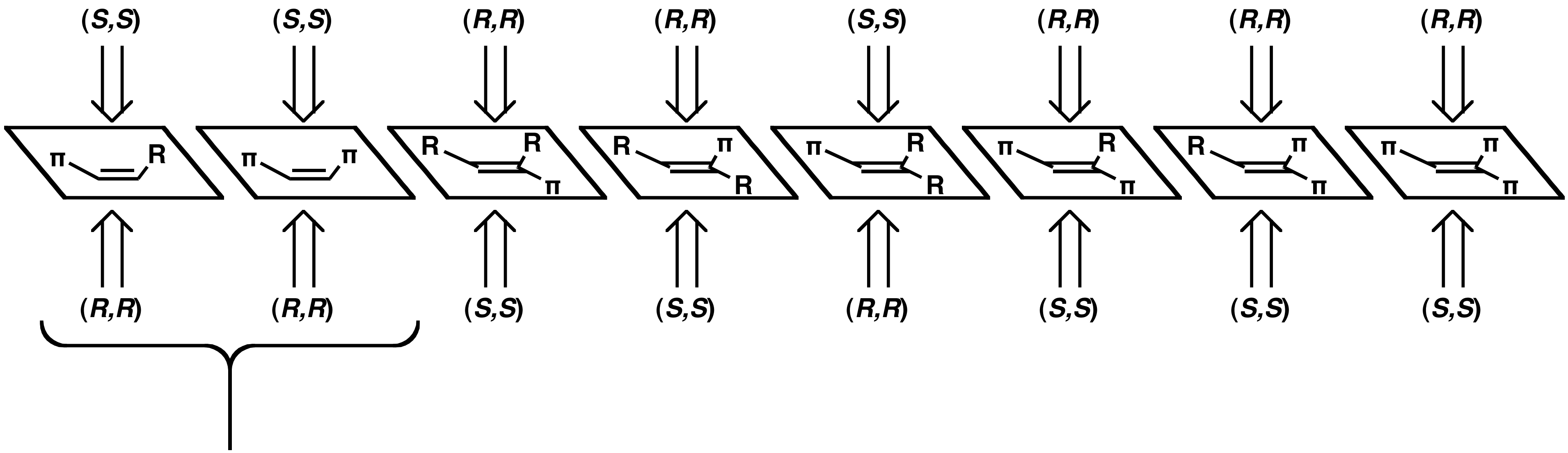


side-on vs. skewed side-on approach

Based on: Katsuki, T. *Adv. Synth. Catal.* **2002,** *344,* 131–147.

Modified based on data from: Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380, and Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197–198.

Jacobsen-Katsuki Epoxidation: Mnemonic

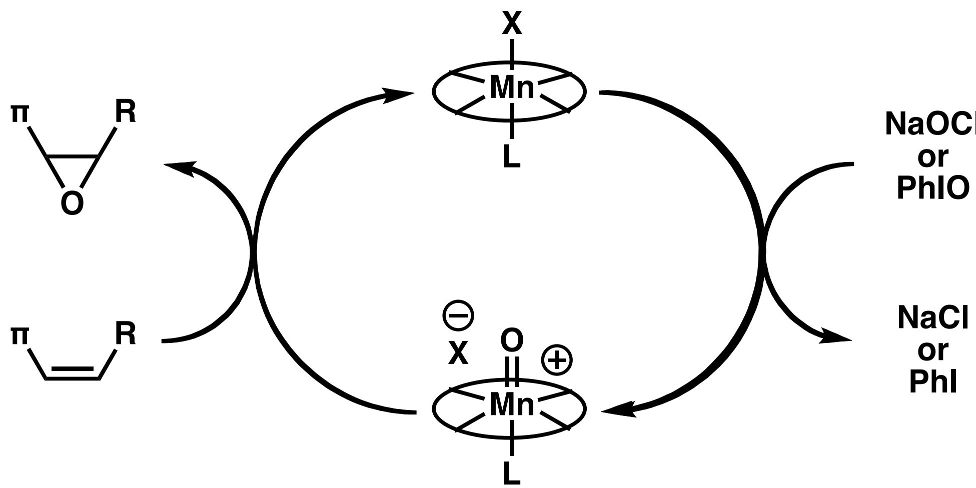


Rotate left π-substituent forward to Predict trans-epoxide stereochemistry.

Adapted from: Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380.

Modified based on data from: Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197–198.

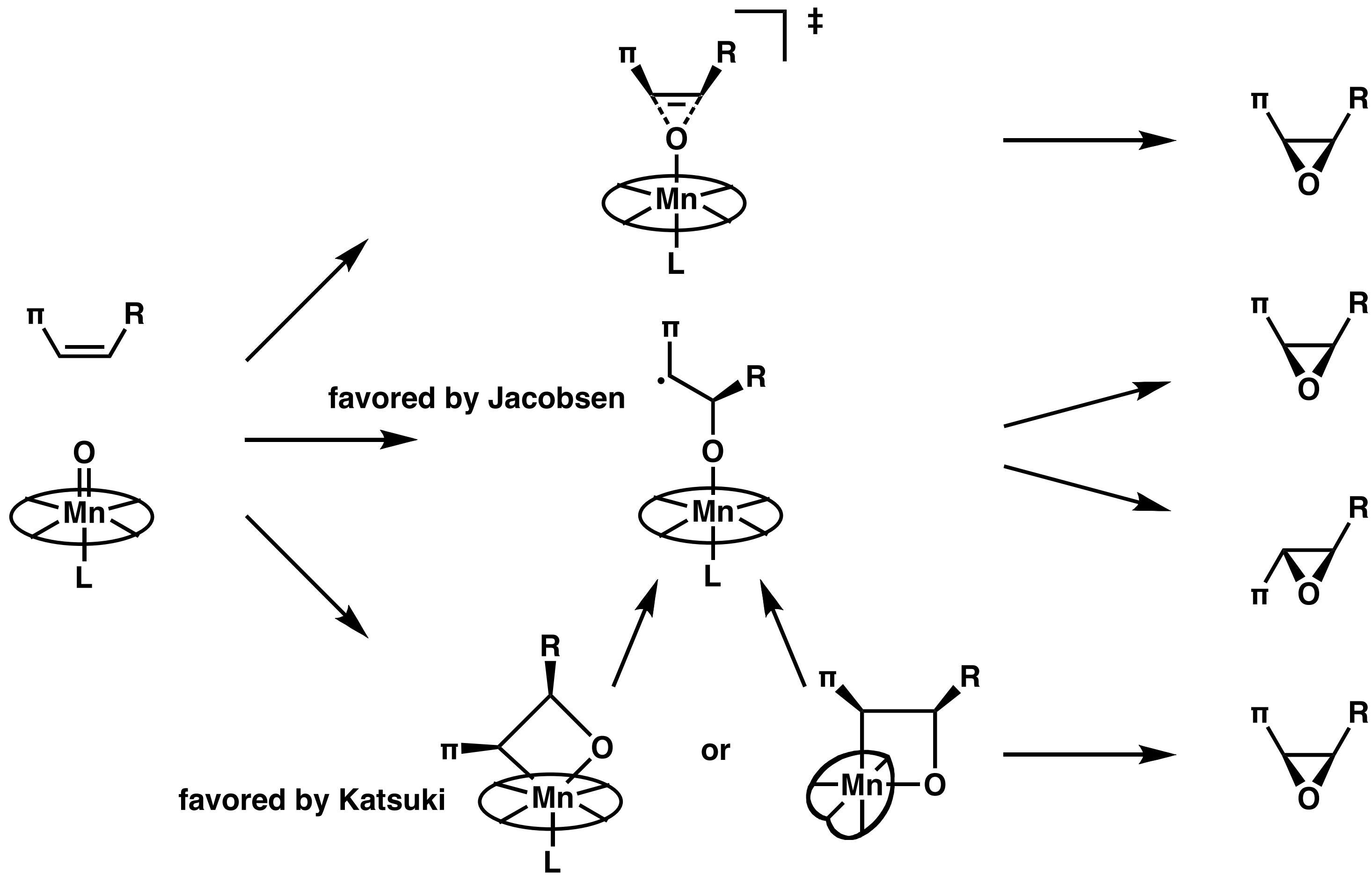
Jacobsen-Katsuki Epoxidation: Simplified Catalytic Cycle



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

McGarrige, E. M.; Gilheany, D. G. *Chem. Rev.* **2005,** *105,* 1563–1602.

Jacobsen-Katsuki Epoxidation: Mechanistic Possibilities

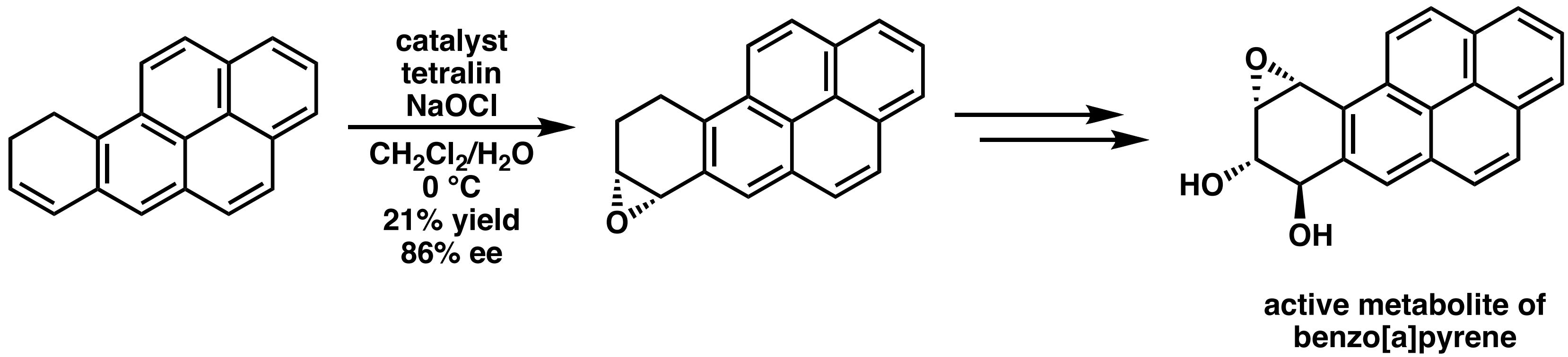


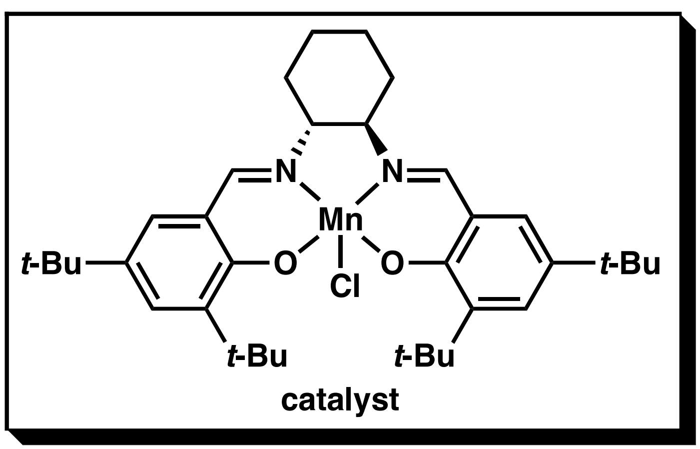
Taken from E. N. Jacobsen lecture notes, Chemistry 153, Harvard University, Spring 2001.

McGarrige, E. M.; Gilheany, D. G. *Chem. Rev.* 2005, *105,* 1563–1602.

Jacobsen, E. N.; Wu, M. H. Epoxidation of Alkenes other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis,* 1st ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: New York, 1999; Vol. 2, 649–677.

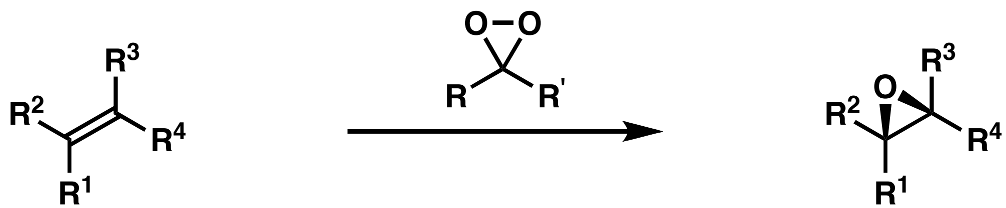
Jacobsen-Katsuki Epoxidation: Synthetic Example





Huang, X.; Harris, T. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1699–1700.

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

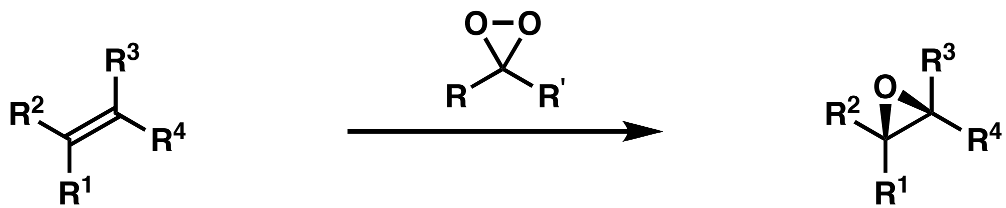
1985 Preparation and isolation of dimethyldioxirane from acetone reported by Murray

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, D. *Acc. Chem. Res.* **2004,** *37,* 497–505.

Shi, Y. *Acc. Chem. Res.* **2004,** *37,* 488–496.

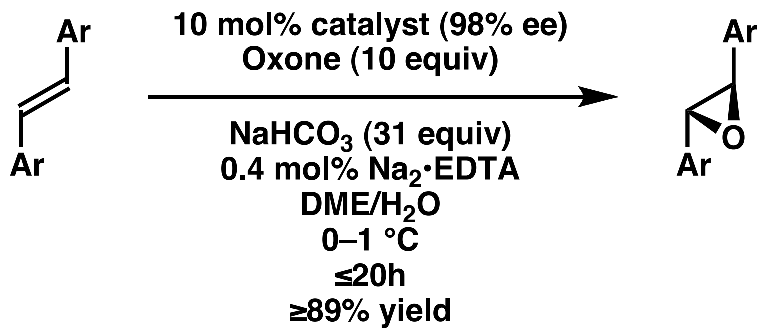
Shi, Y. *J. Synth. Org. Chem. Jpn.* **2002,** *60,* 342–349.

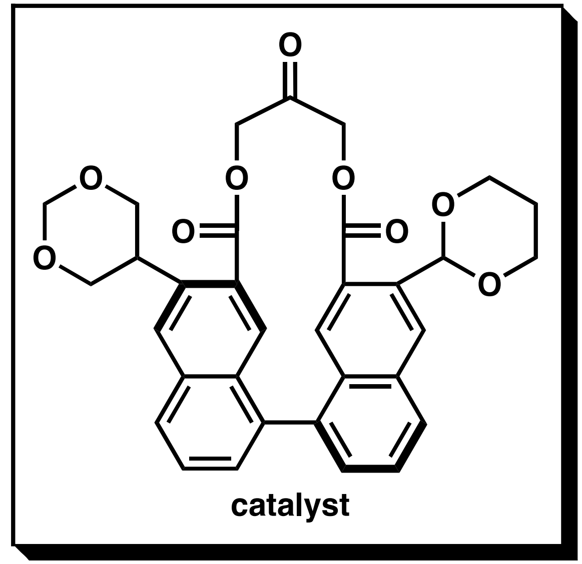
Frohn, M.; Shi, Y. *Synthesis* **2000,** 1979–2000.

Denmark, S. E.; Wu, Z. *Synlett* **1999,** 847–859.

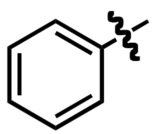
For extensive referencing of other ketone-based catalysts, see: Shing, T. K. M.; Leung, G. Y. C.; Luk T. *J. Org. Chem.* **2005,** *70,* 7279–7289 (not a review).

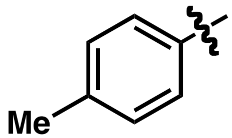
Yang Epoxidation



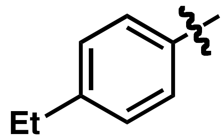


catalyst

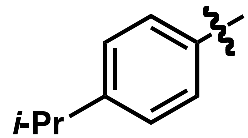

84% ee



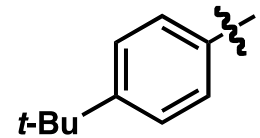
88% ee



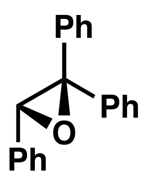
91% ee



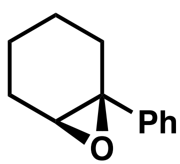
91% ee



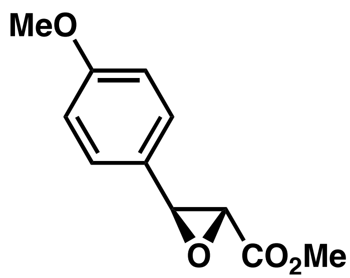
95% ee



73% ee*



71% ee*



77% ee
with parent complex*

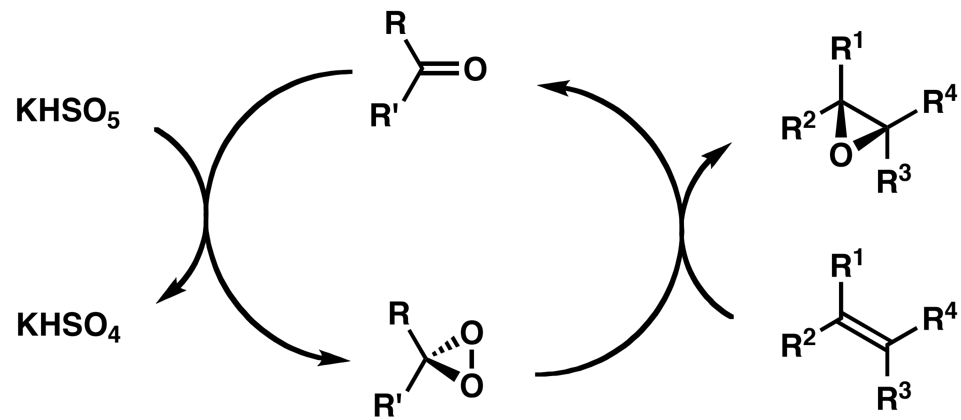
cis-disubstituted, 1,1-disubstituted, and terminal olefins give poor ee.

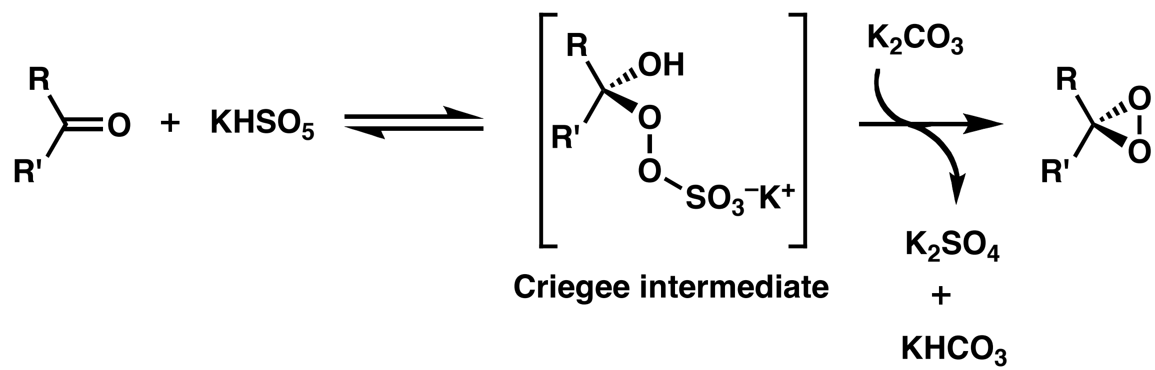
***modified reaction conditions**

Yang, D.; Wong, M.-H.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, H.-K. *J. Am. Chem. Soc.* **1998,** *120,* 5943–5952.

Furutani, T.; Imashiro, R.; Hatsuda, M.; Seki, M. *J. Org. Chem.* **2002,** *67,* 4599–4601.

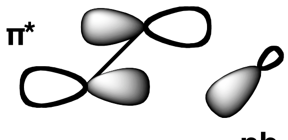
Dioxirane-Based Epoxidations: Catalytic Cycle



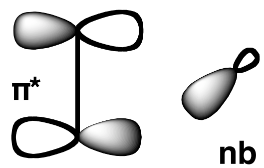


Adapted from: Denmark, S. E.; Wu, Z. *Synlett* **1999,** 847–859.

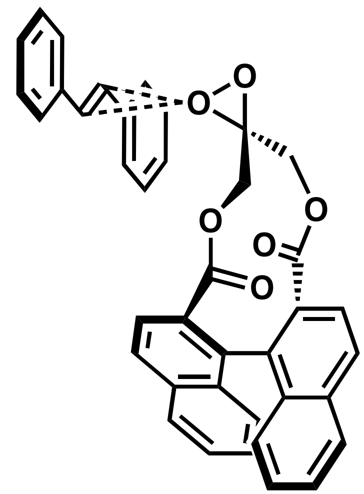
Yang Epoxidation: Stereoselectivity Model



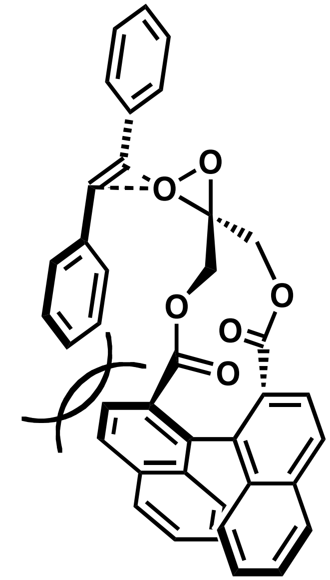
Spiro TS



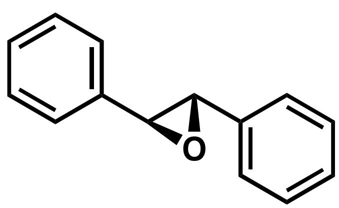
Planar TS



Spiro TS
favored

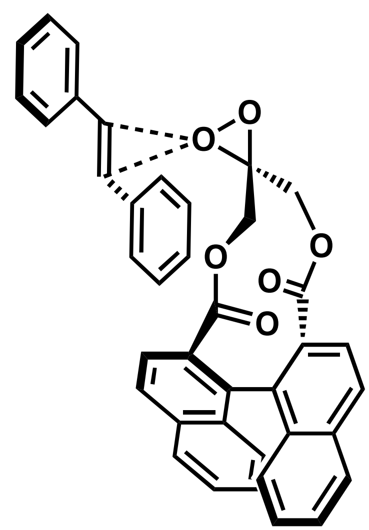


Spiro TS
disfavored

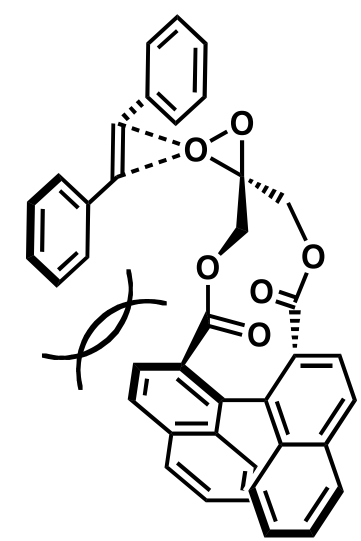


observed

Product stereochemistry supports a spiro TS in dioxirane epoxidations.



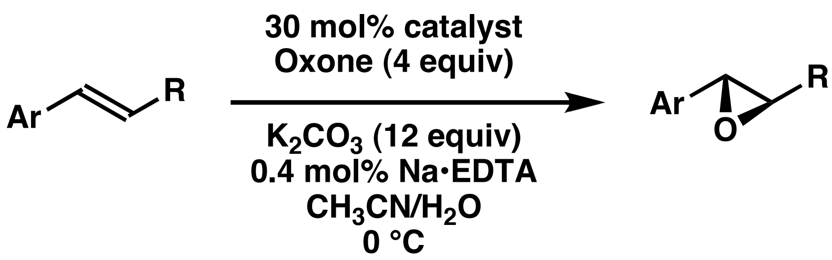
Planar TS
favored

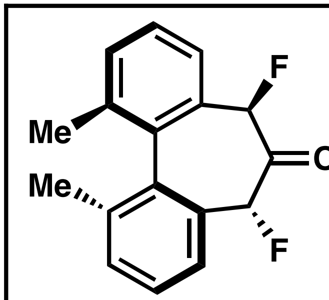


Planar TS
disfavored

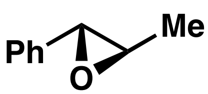
Yang, D.; Wong, M.-H.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, H.-K. *J. Am. Chem. Soc.* **1998,** *120,* 5943–5952.

Denmark Epoxidation

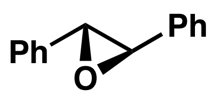




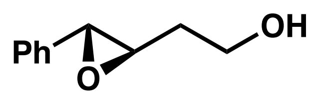
catalyst



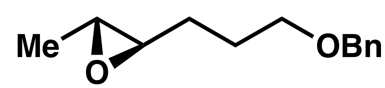
80% yield
88% ee



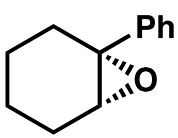
46% yield
94% ee



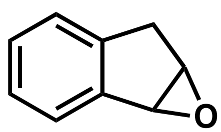
93% yield
89% ee



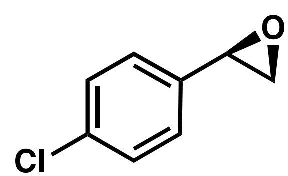
72% yield
68% ee
(50 mol% catalyst)



78% yield
59% ee



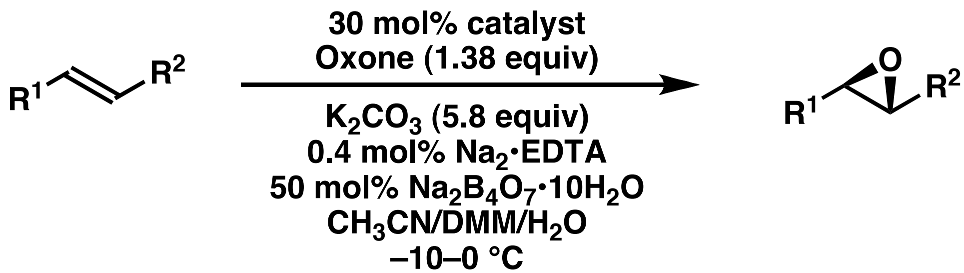
67% yield
12% ee
configuration not determined

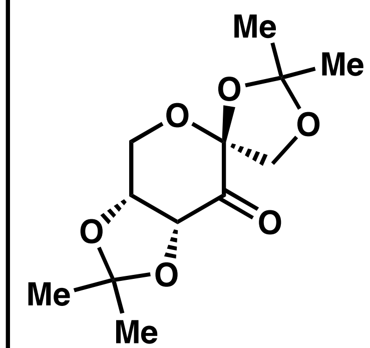


55% yield
43% ee

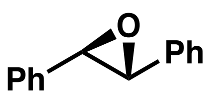
Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002,** *67,* 3479–3486.

Shi Epoxidation: trans-Disubstituted Olefins

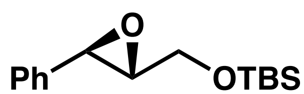




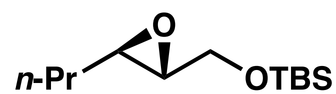
catalyst



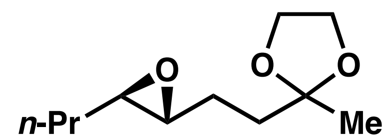
78% yield
98.9% ee



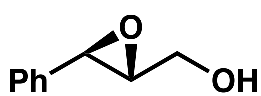
71% yield
95.2% ee



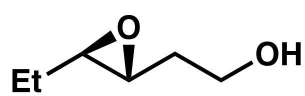
83% yield
94.5% ee



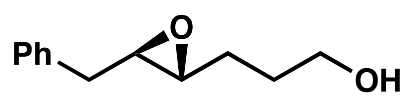
92% yield
92% ee



85% yield*
94% ee



82% yield*
90% ee



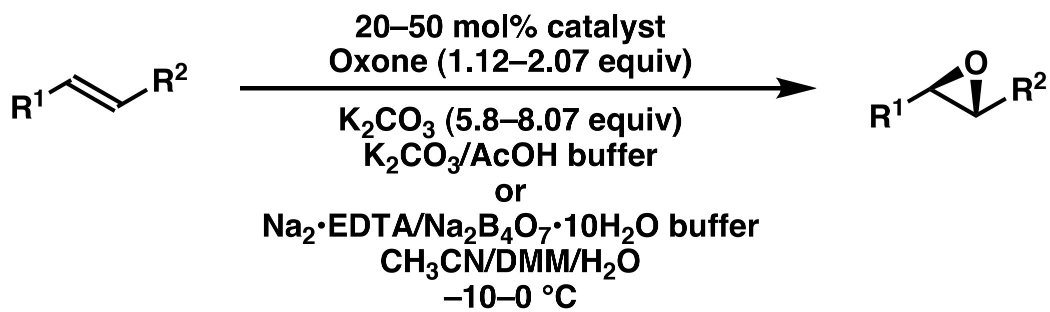
87% yield*
91% ee**

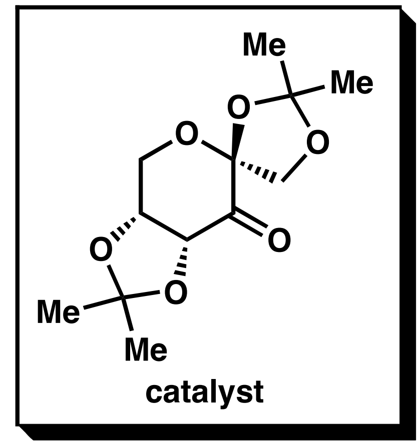
* modified buffer conditions
**absolute configuration assigned by analogy

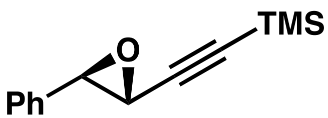
Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997,** *119,* 11224–11235.

Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998,** *63,* 3099–3104.

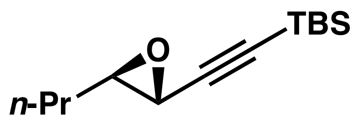
Shi Epoxidation: trans-Disubstituted Olefins



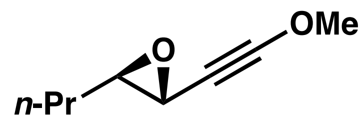




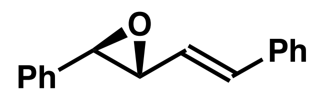
59% yield
96% ee



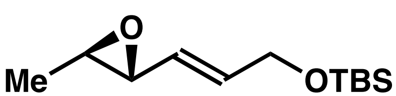
71% yield
89% ee



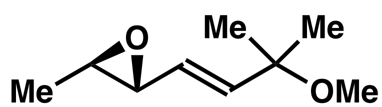
35% yield
89% ee



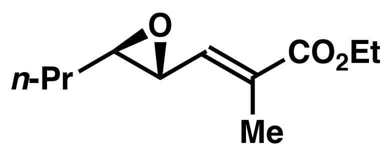
94% conv.
22:1 mono-:bisepoxide
77% yield
94% ee



100% conv.
4.6:1 mono-:bisepoxide
68% yield (13% minor)
96% ee* (91% minor)*



100% conv.
65% yield
89% ee*



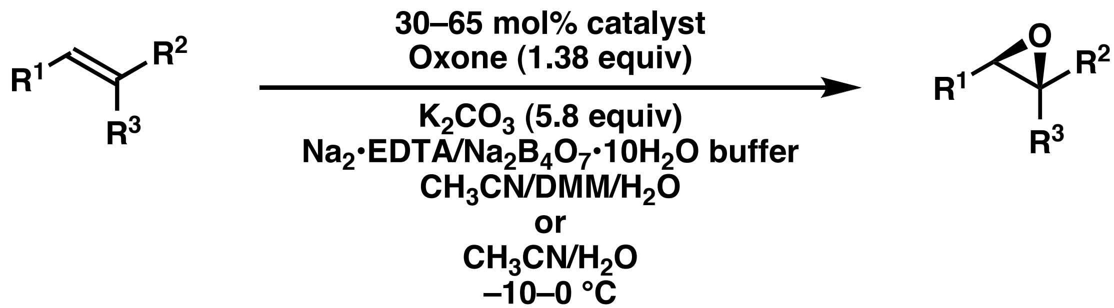
72% conv.
61% yield
94% ee

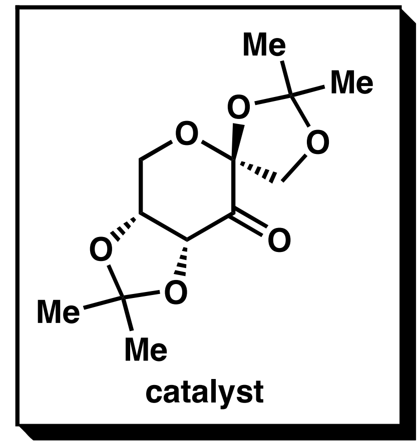
*absolute configuration assigned by analogy

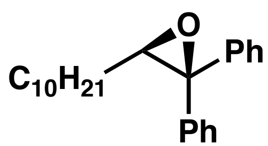
Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999,** *64,* 7646–7650.

Frohn, M.; Tu, Dalkiewicz, M.; Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998,** *63,* 2948–2953.

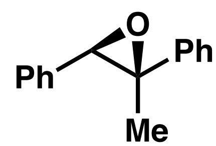
Shi Epoxidation: Trisubstituted Olefins



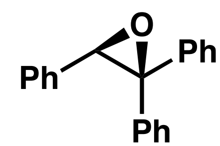




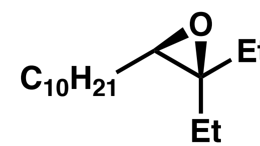
97% yield
92% ee



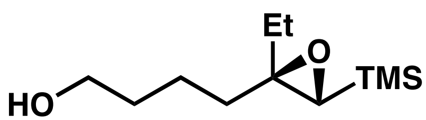
95.5% yield
89% ee



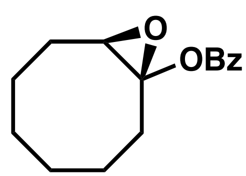
54% yield
96.7% ee



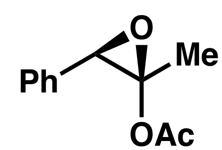
94% yield
88.5% ee*



75% yield
91% ee*



82% yield
95% ee*



66% yield
91% ee

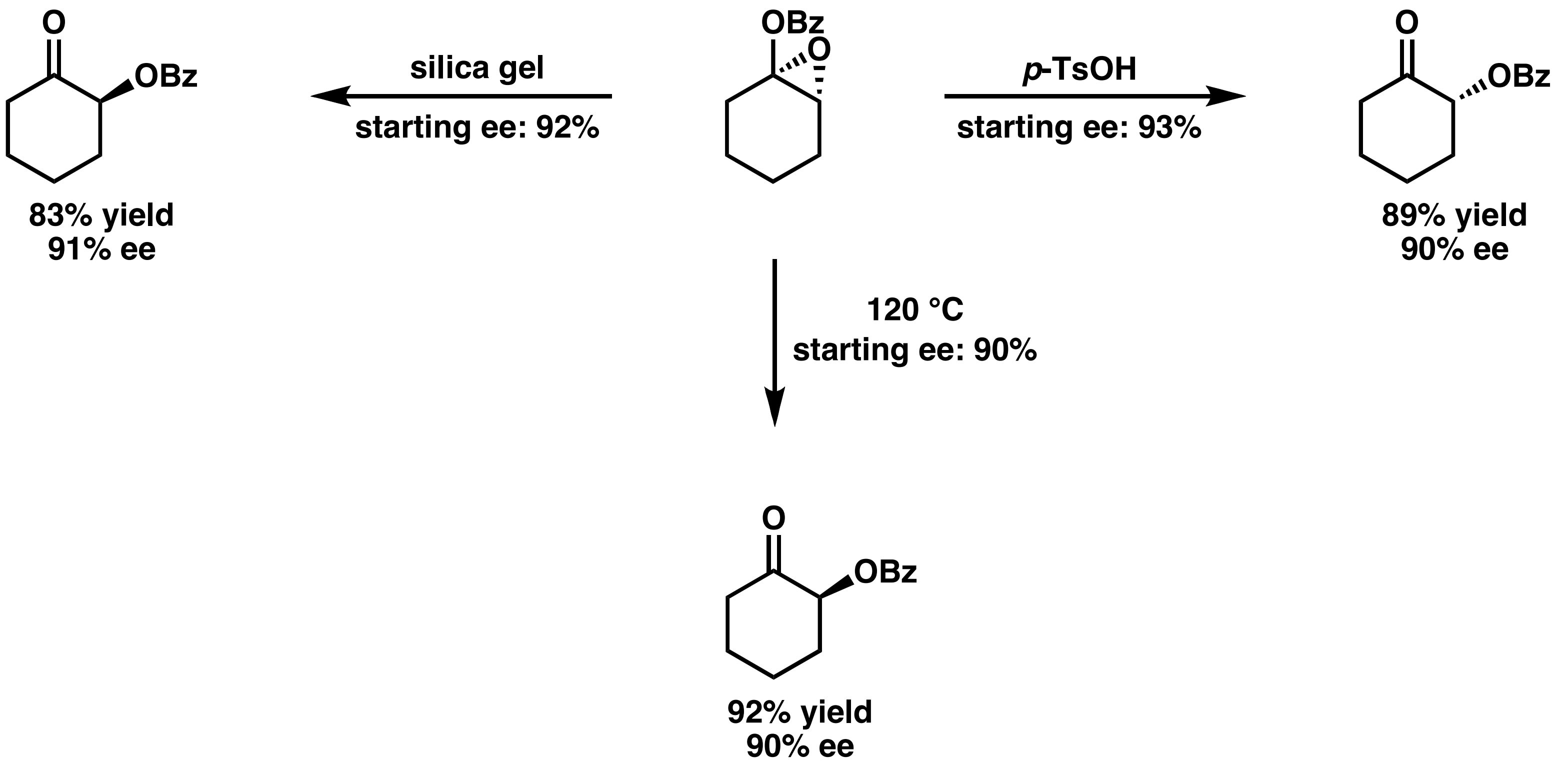
*absolute configuration assigned by analogy

Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997,** *119,* 11224–11235.

Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999,** *64,* 7675–7677.

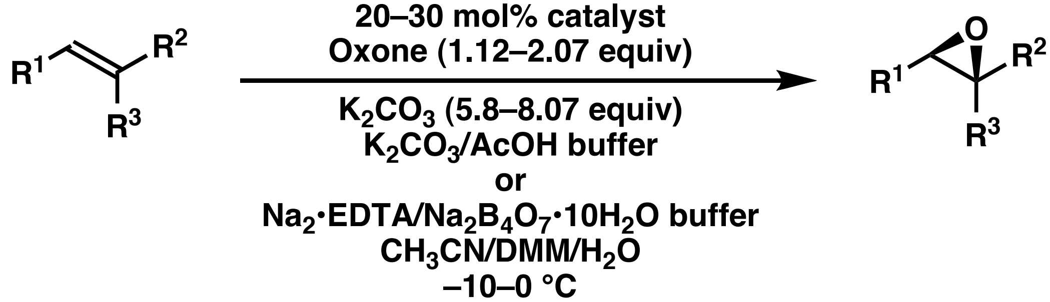
Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001,** *66,* 1818–1826.

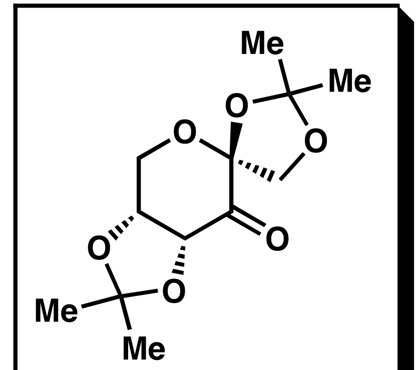
Shi Epoxidation: Trisubstituted Olefins



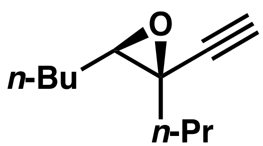
Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001,** *66,* 1818–1826.

Shi Epoxidation: Trisubstituted Olefins

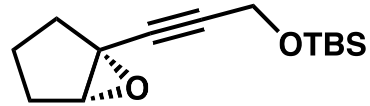




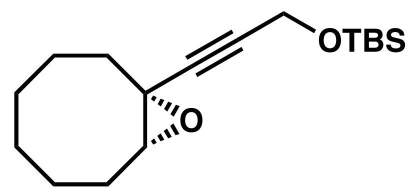
catalyst



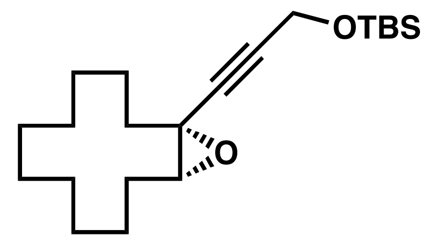
60% yield
93% ee*



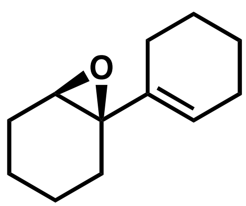
97% yield
77% ee*



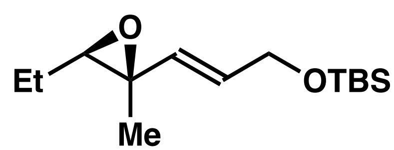
98% yield
96% ee*



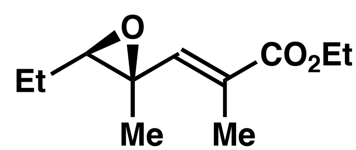
99% yield
86% ee*



100% conv.
12:1 mono-:bisepoxide
54% yield
95% ee*



100% conv.
81% yield
96% ee*



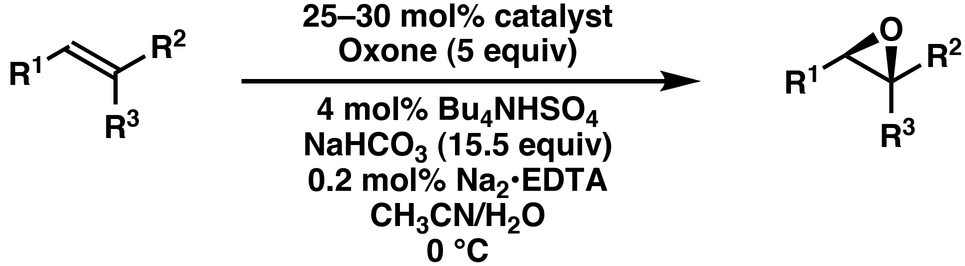
100% conv.
89% yield
94% ee*

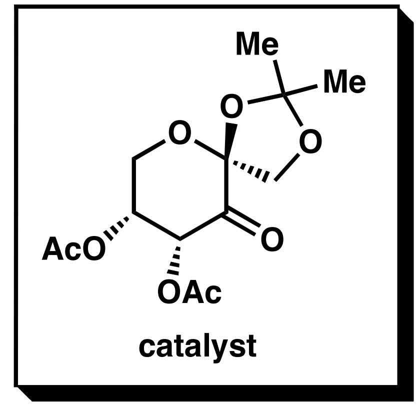
*absolute configuration assigned by analogy

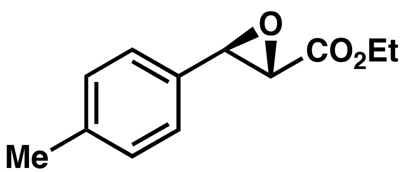
Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999,** *64,* 7646–7650.

Frohn, M.; Tu, Dalkiewicz, M.; Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998,** *63,* 2948–2953.

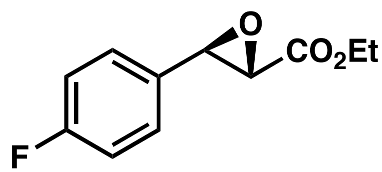
Shi Epoxidation: α,β-Unsaturated Esters



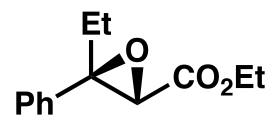




91% yield
97% ee

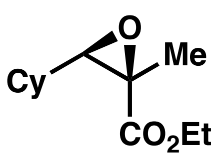


77% yield
96% ee

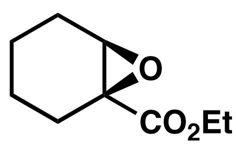


91% yield
93% ee

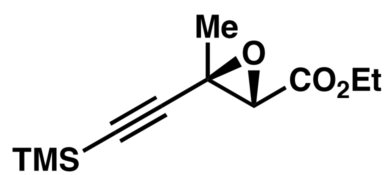
Catalyst is not effective for trans-aliphatic α,β-unsaturated esters.



77% yield
89% ee



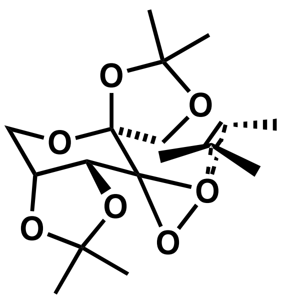
77% yield
93% ee



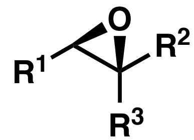
94% yield
94% ee

Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002,** *124,* 8792–8793.

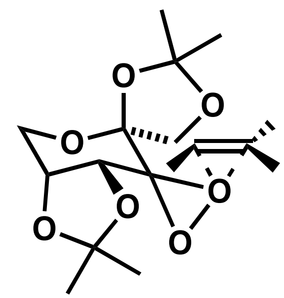
Shi Epoxidation: Stereoselectivity Model



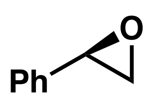
Spiro TS
favored



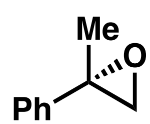
observed



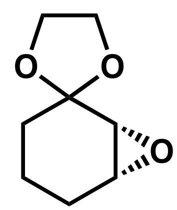
Planar TS
favored



90% yield
24.3% ee



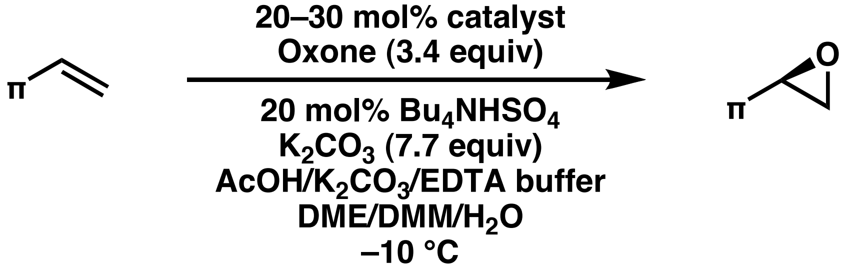
95% yield
19.6% ee

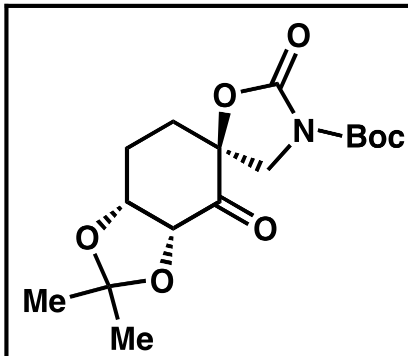


43% yield
61.4% ee

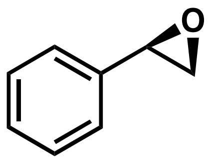
Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997,** *119,* 11224–11235.

Shi Epoxidation: Terminal Olefins

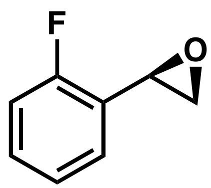




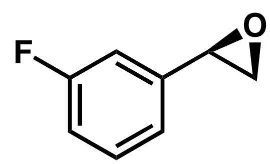
catalyst



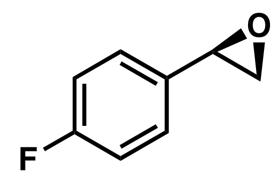
100% conv.
63% yield
90% ee



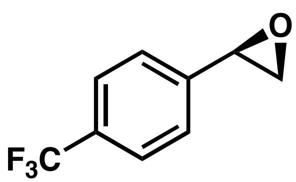
100% conv.
84% yield
89% ee



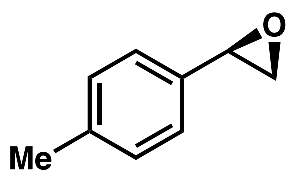
100% conv.
91% yield
90% ee



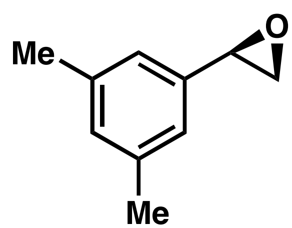
94% conv.
64% yield
90% ee



69% conv.
77% yield
93% ee



81% yield
90% ee



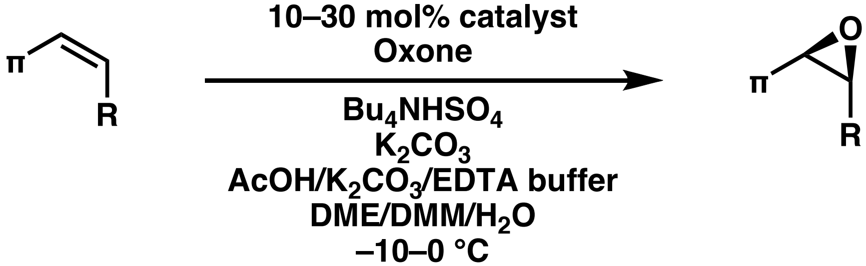
100% conv.
62% yield
89% ee

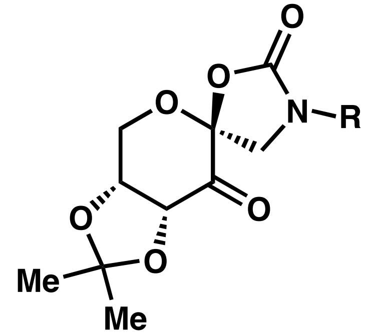
Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101,* 5794–5798.

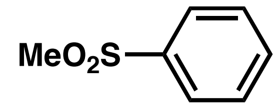
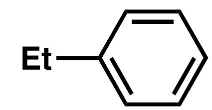
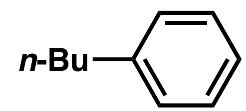
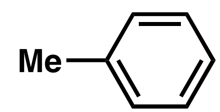
80–92% ee with a fructose-derived variant

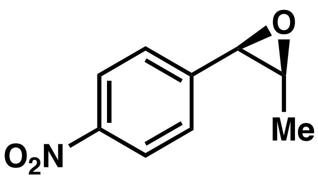
Goeddel, D.; Shu, L.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006,** *71,* 1715–1717.

Shi Epoxidation: cis-Disubstituted Olefins

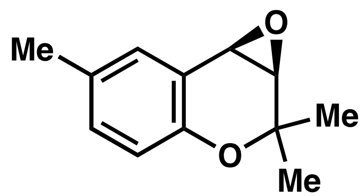




catalyst	R
A	
B	
C	Boc
D	
E	

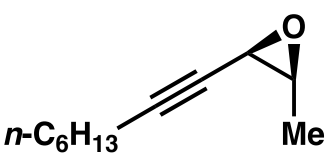


catalyst A
91% conv.
61%≤yield≤95%
97% ee

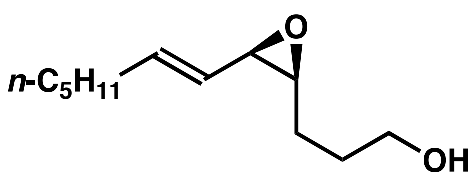


catalyst B
100% conv.
75% yield
92% ee*

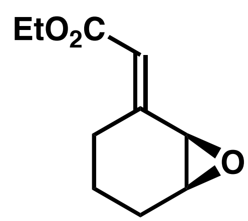
***absolute configuration assigned by analogy**



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

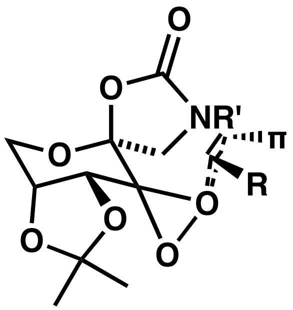
Tian, H.; She, X.; Yu. H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002,** *67,* 2435–2446.

Burke, C. P.; Shi, Y. *Angew. Chem. Int. Ed.* **2006,** *45,* 4475–4478.

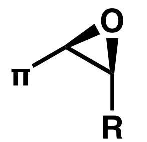
Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004,** *45,* 8115–8117.

Wong, O. A.; Shi, Y. *J. Org. Chem.* **2006,** *71,* 3973–3976.

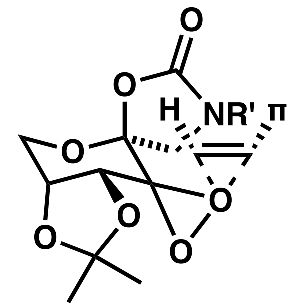
Shi Epoxidation: Stereoselectivity Model



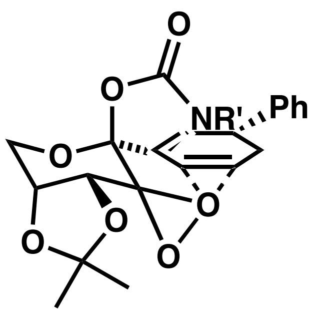
Spiro TS
favored due to
π–π interactions



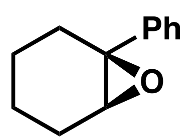
observed



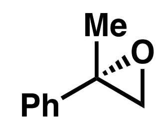
Planar TS
may contibute to lower
ee for terminal epoxides



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



68% yield
42% ee

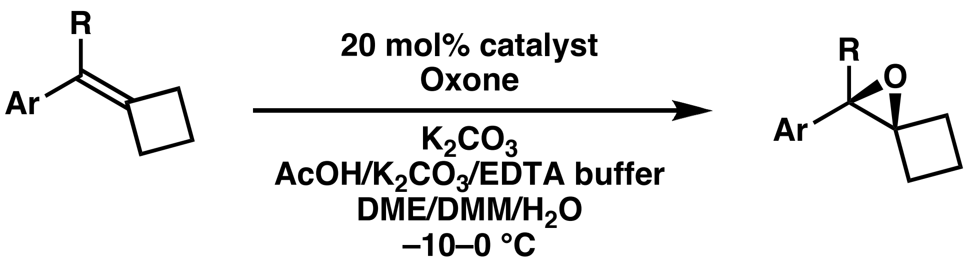


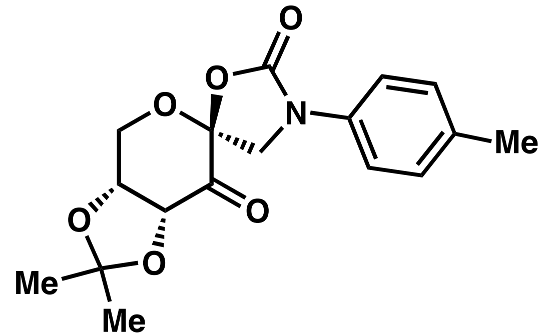
88% yield
30% ee

catalyst is still ineffective for
1,1-disubstituted olefins

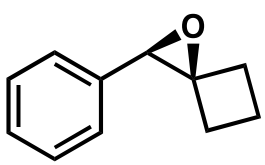
Tian, H.; She, X.; Yu. H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002,** *67,* 2435–2446.

Shi Epoxidation: Tri- and Tetrasubstituted Olefins

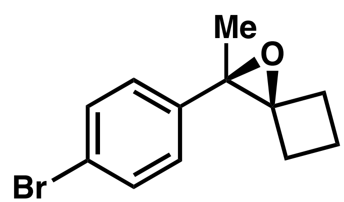




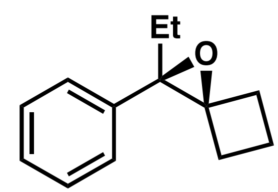
catalyst



93% yield
90% ee*



78% yield
91% ee



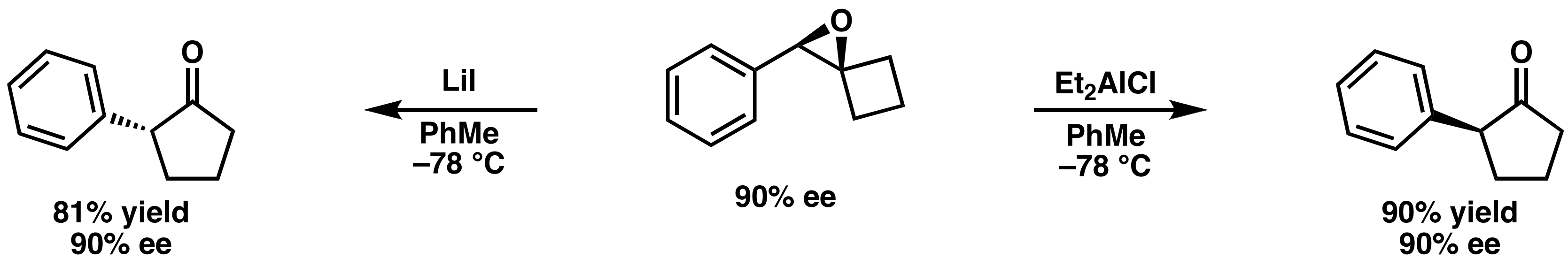
67% yield
77% ee*

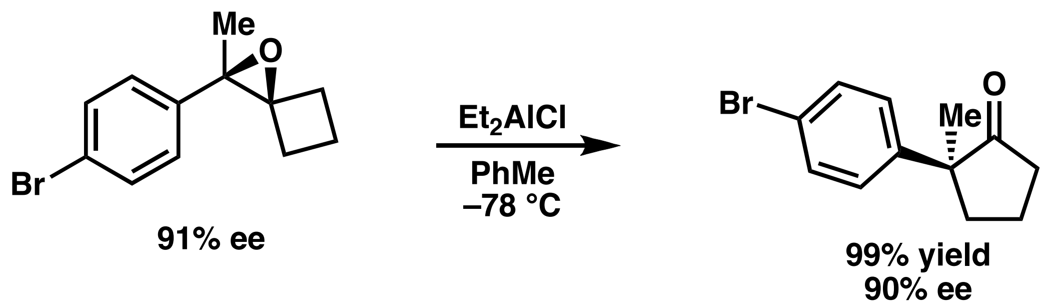
*absolute configuration assigned by analogy

Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem. Int. Ed.* **2006,** *45,* 1429–1472.

Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006,** *47,* 5455–5488.

Shi Epoxidation: Tri- and Tetrasubstituted Olefins

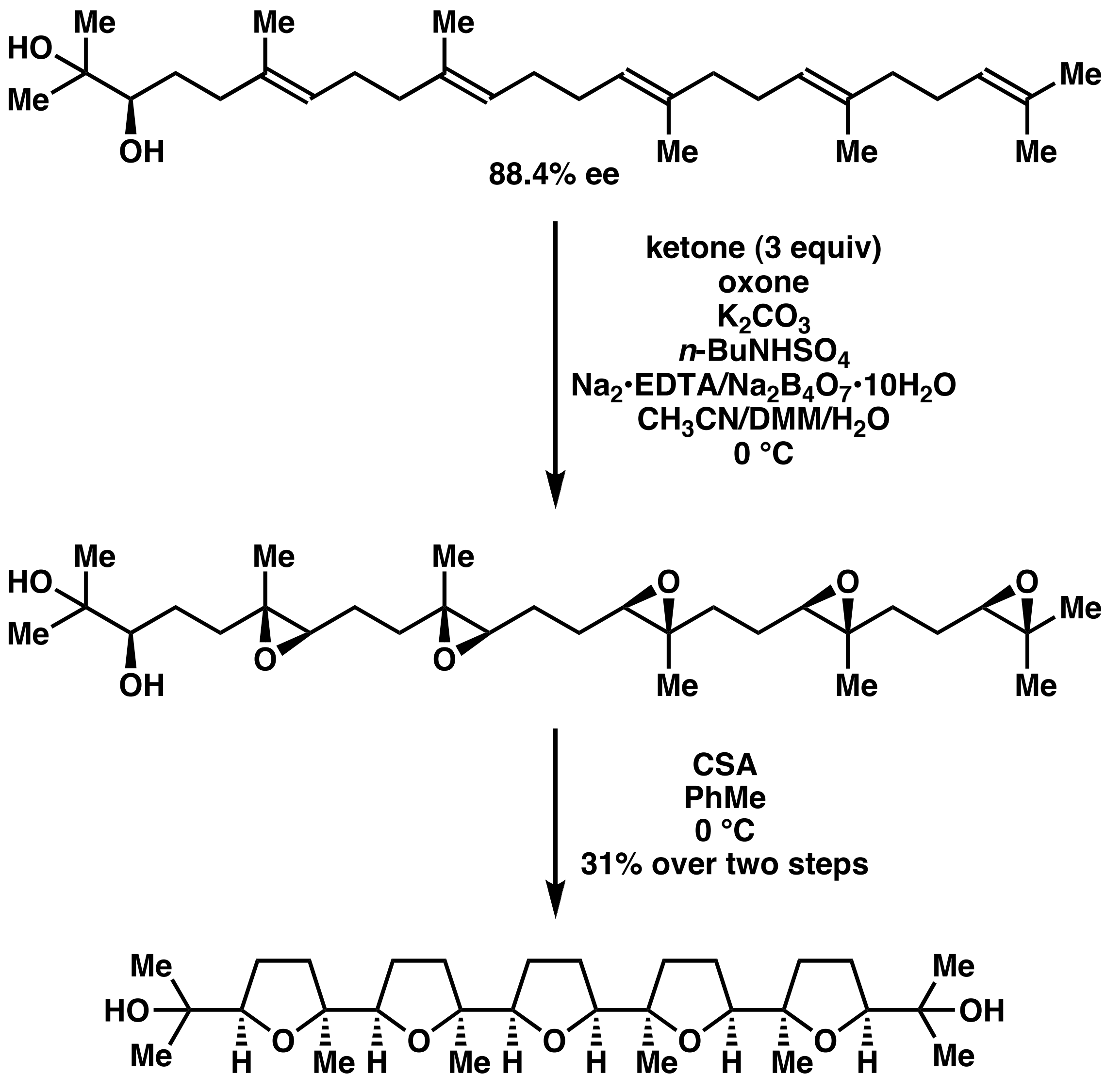




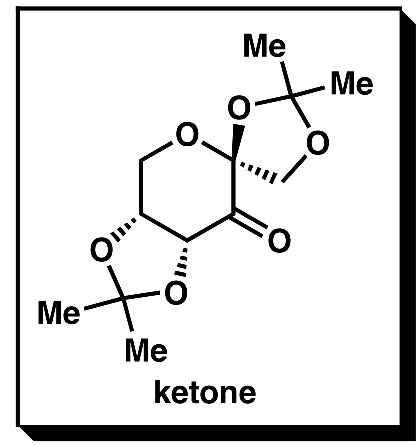
Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem. Int. Ed.* **2006,** *45,* 1429–1472.

Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006,** *47,* 5455–5488.

Shi Epoxidation: Synthetic Example

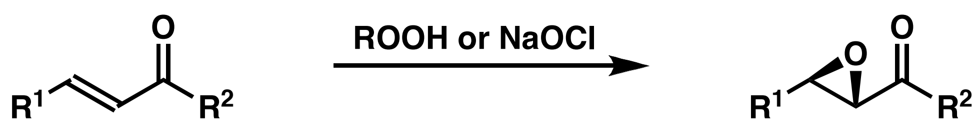


proposed structure of glabrescol



Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000,** *122,* 4831–4832.

Nucleophilic Epoxidations



Timeline

1980 **First highly enantioselective epoxidation reaction reported by Juliá, epoxidizing chalcone in >90% ee**

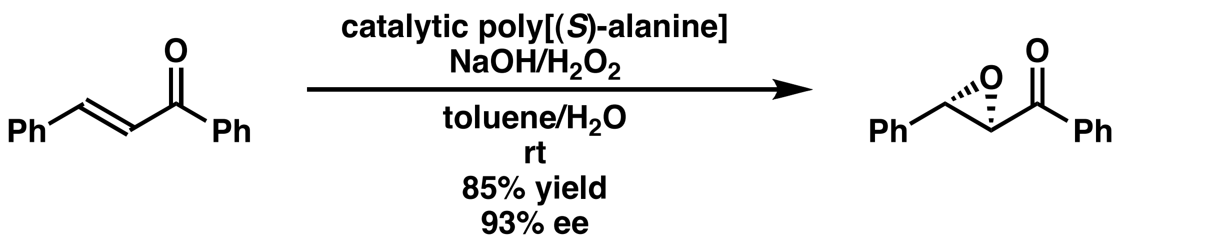
1997 **Shibasaki reports that BINOL-derived catalysts provide high enantioselectivity in the epoxidation of α,β-unsaturated ketones**

Reviews

Shibasaki, M.; Kanai, M.; Matsunaga, S. *Aldrichachim. Acta* **2006,** *39,* 31–39.

Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000,** 1215–1225.

Polyamino Acid-Catalyzed Epoxidations: Lead References

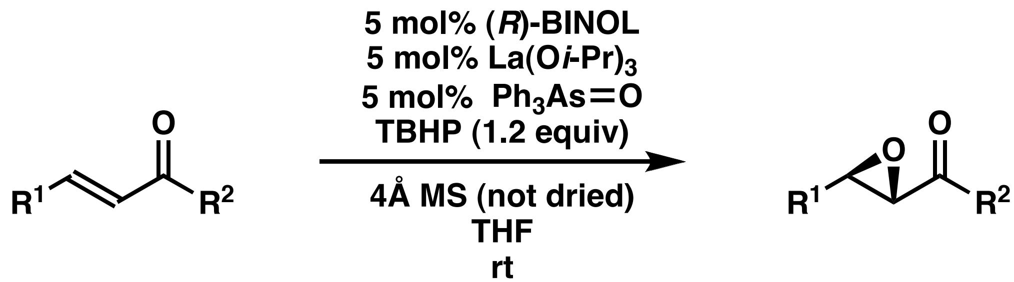


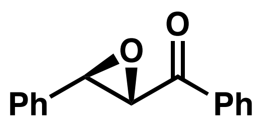
First report: Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem. Int. Ed. Engl.* **1980,** *19,* 929–9310.

For current lead references, see: Lauret, C.; Roberts, S. M. *Aldrichim. Acta* **2002,** *35,* 47–51.

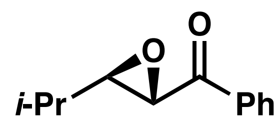
Kelly, D. R.; Roberts, S. M. *Biopolymers* **2006,** *84,* 74–89.

Shibasaki Epoxidation: Enones

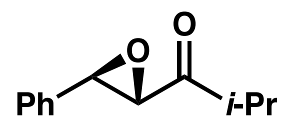




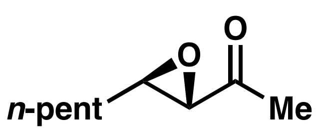
99% yield
96% ee



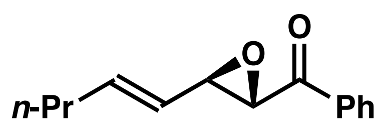
95% yield
94% ee



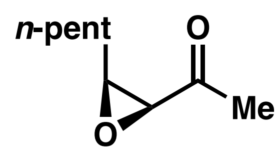
72% yield
95% ee



89% yield
95% ee



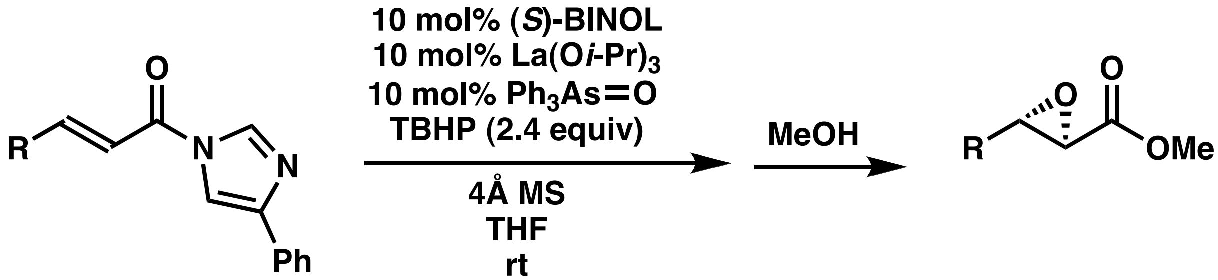
95% yield
96% ee

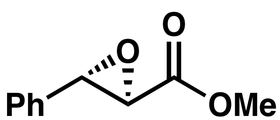


61% yield
<10% trans-epoxide
59% ee
(10 mol% catalyst)

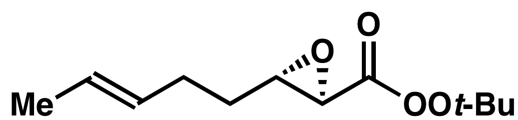
Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001,** *123,* 2725–2732.

Shibasaki Epoxidation: Amides



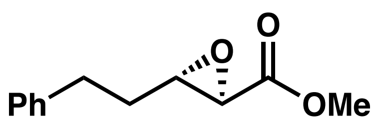


86% yield
92% ee

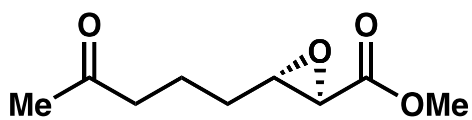


92% yield*
79% ee

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



58% yield
91% ee
(using CMHP)

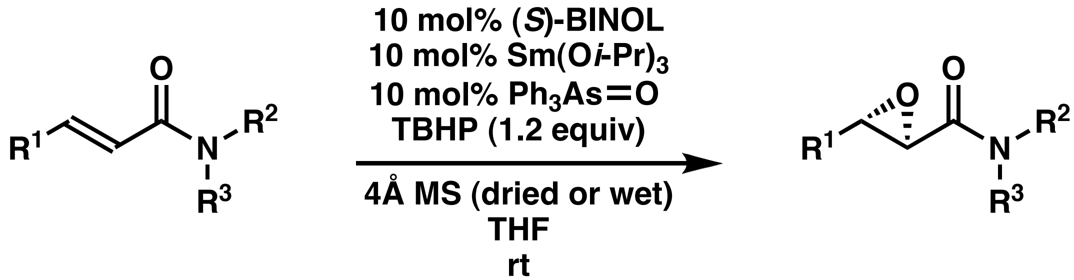


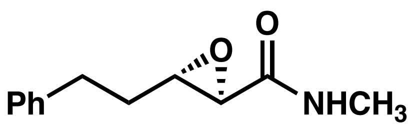
81% yield*
81% ee

Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001,** *123,* 9474–9475.

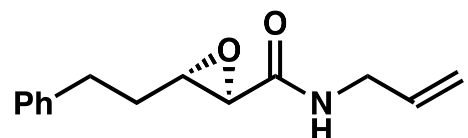
Ohshima, T.; Nemoto, T.; Tosakai, S.-Y.; Kakei, H.; Gnanadesikan, V.; Shibasaki, M. *Tetrahedron Lett.* **2003,** *59,* 10485–10497.

Shibasaki Epoxidation: Amides

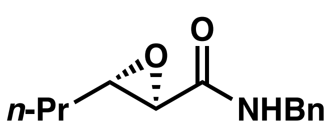




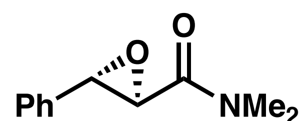
99% yield
>99% ee



95% yield
98% ee



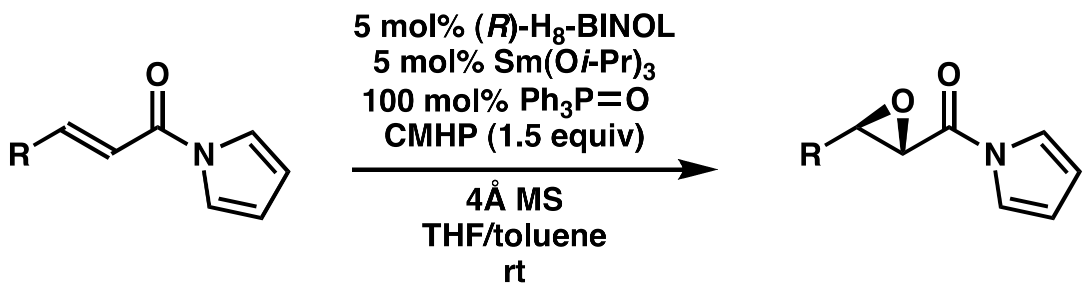
94% yield
94% ee

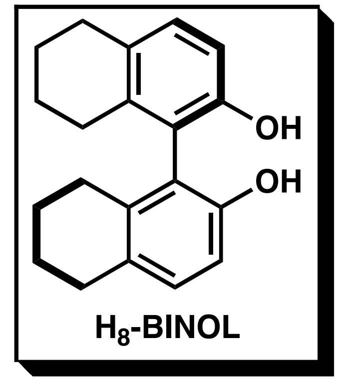


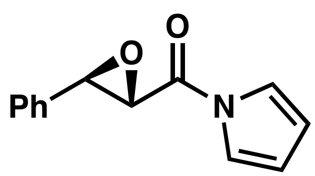
96% yield
>99% ee

Ohshima, T.; Nemoto, T.; Tosakai, S.-Y.; Kakei, H.; Gnanadesikan, V.; Shibasaki, M. *Tetrahedron Lett.* **2003,** *59,* 10485–10497.

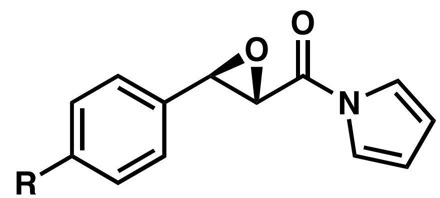
Shibasaki Epoxidation: Amides





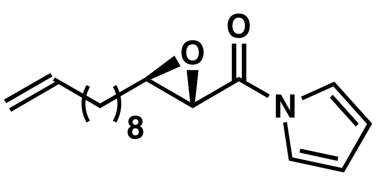


98% yield
>99.5% ee

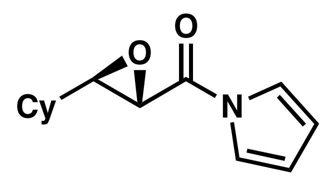


R = OMe
91% yield
99% ee

R = Cl
97% yield
>99.5% ee



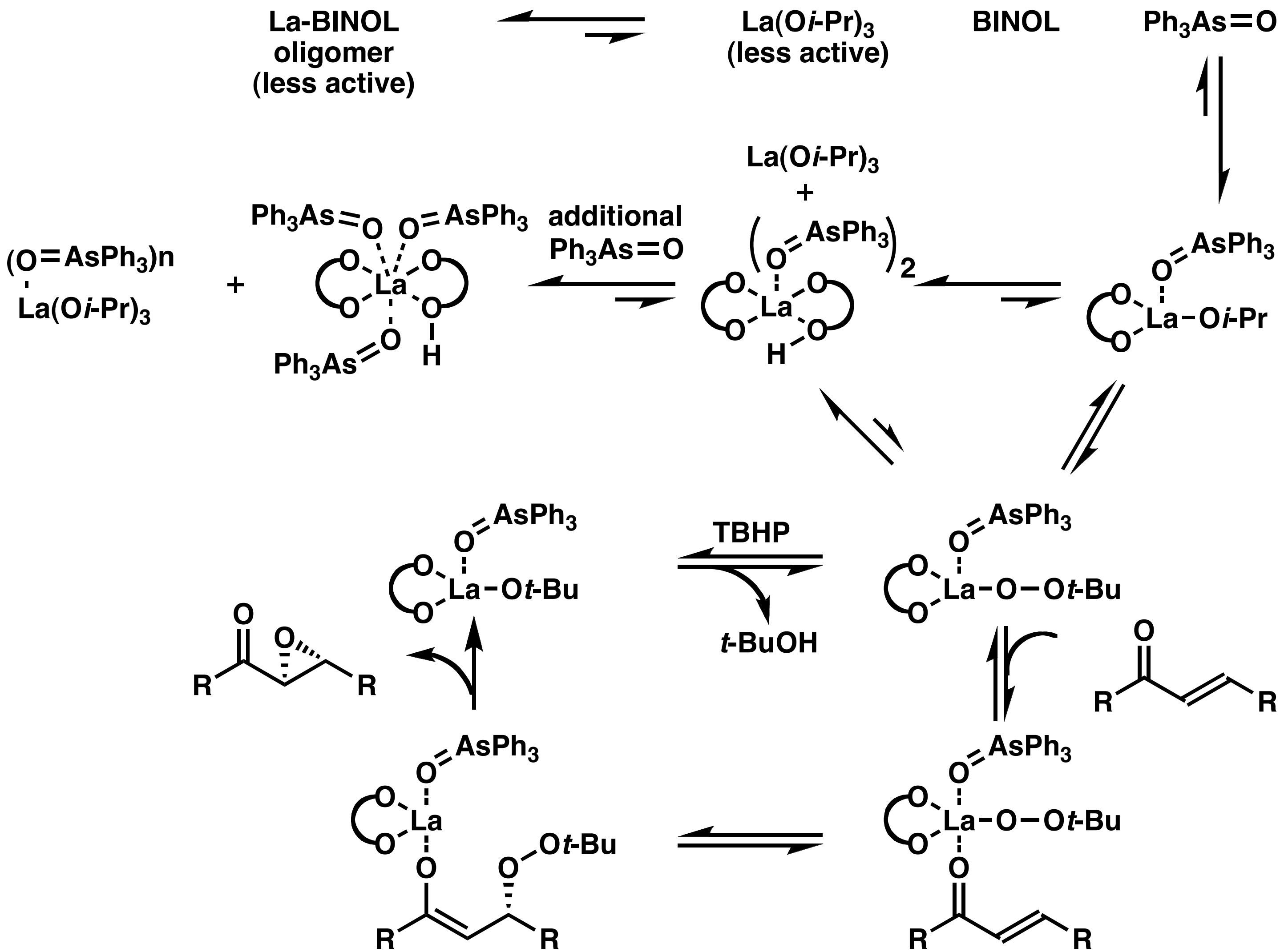
95% yield
99% ee



90% yield
>99.5% ee

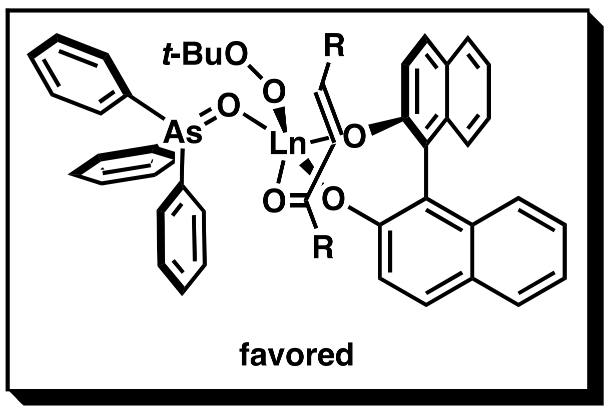
Matsunaga, S.; Qin, H.; Sugita, M.; Okada, S.; Kinoshita, T.; Yamagiwa, N.; Shibasaki, M. *Tetrahedron* **2006,** *62,* 6630–6639.

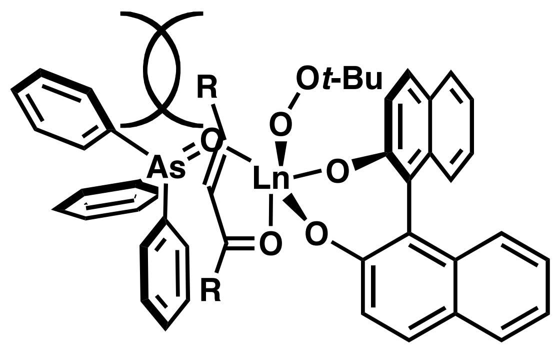
Shibasaki Epoxidation: Mechanism



Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001,** *123,* 2725–2732.

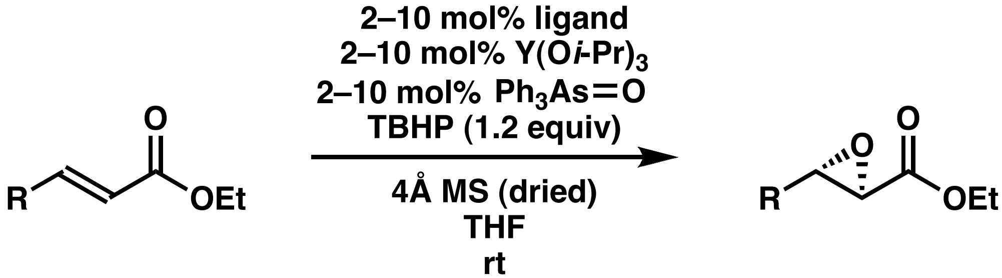
Shibasaki Epoxidation: Stereoselectivity Model

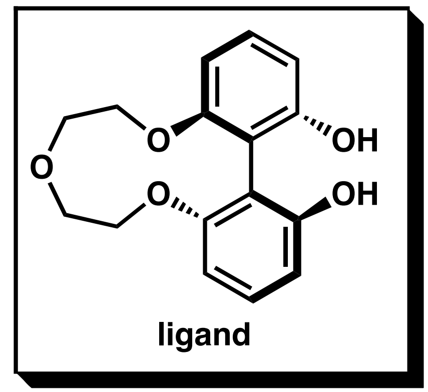


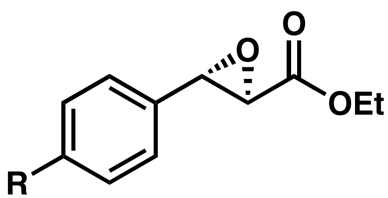


Tosakai, S.-Y.; Horiuchi, Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Chem. Eur. J.* **2004,** *10,* 1527–1544.

Shibasaki Epoxidation: Esters

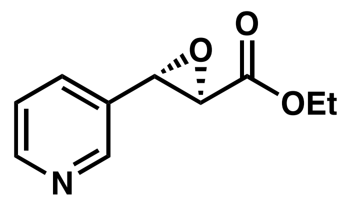




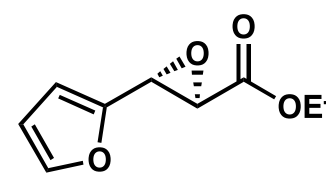


R = OAc
89% yield
89% ee

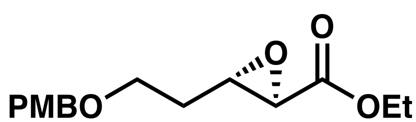
R = OMe
74% yield
99% ee



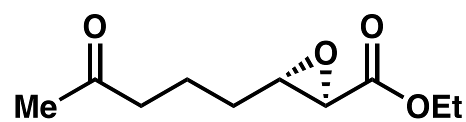
93% yield
98% ee



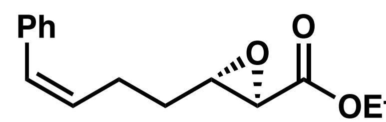
78% yield
92% ee



81% yield
96% ee



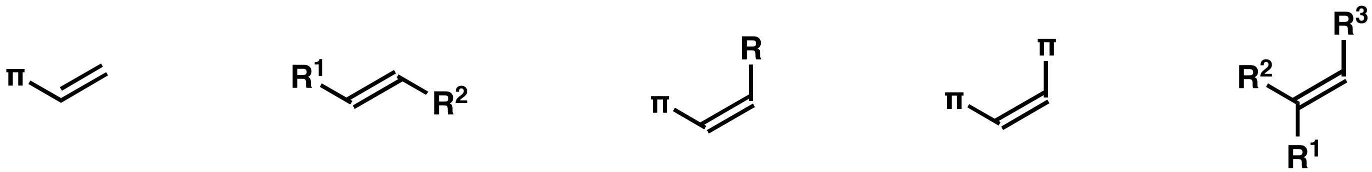
78% yield
92% ee



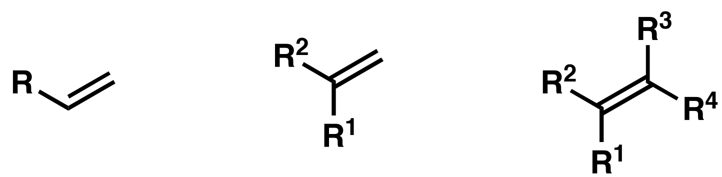
81% yield
93% ee

Kakei, H.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005,** *127,* 8962–8963.

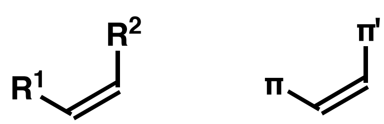
General



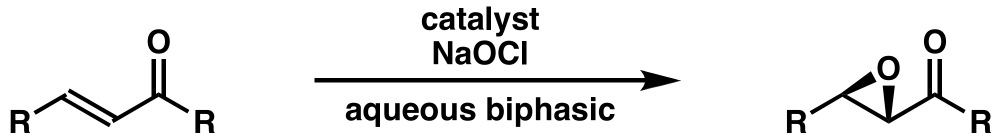
Context Dependent

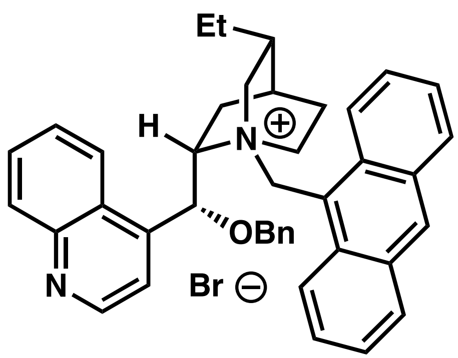


Few Examples

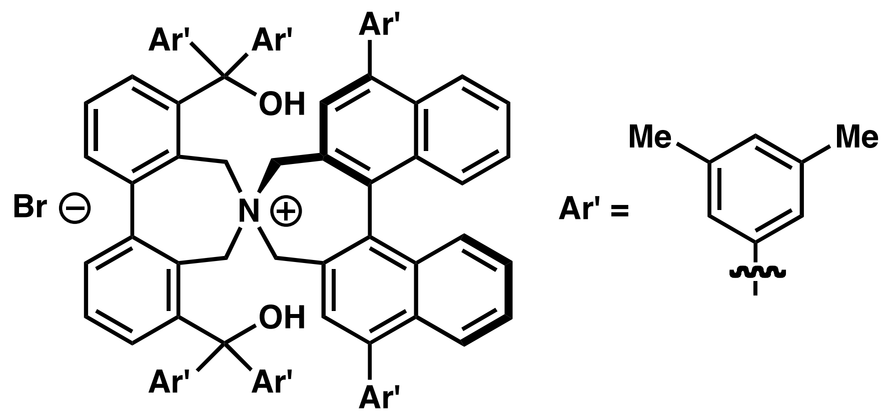


Phase-Transfer Epoxidations: Lead References





R = Ar
up to 98.5% ee



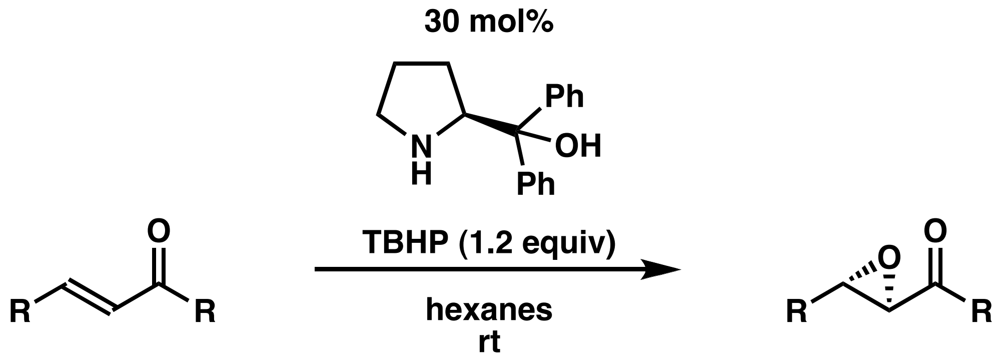
R = Ar, alkyl
up to 99% ee

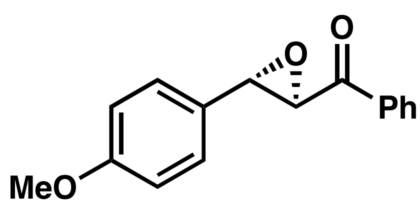
Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **1999,** *1,* 1287–4832.1290.

Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001,**, *42,* 1343–1346.

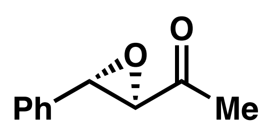
Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K.
J. Am. Chem. Soc. **2004,** *126,* 6844–6845.

Amine-Catalyzed Epoxidations: Lead References

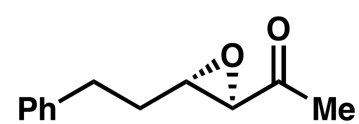




46% yield
80% ee



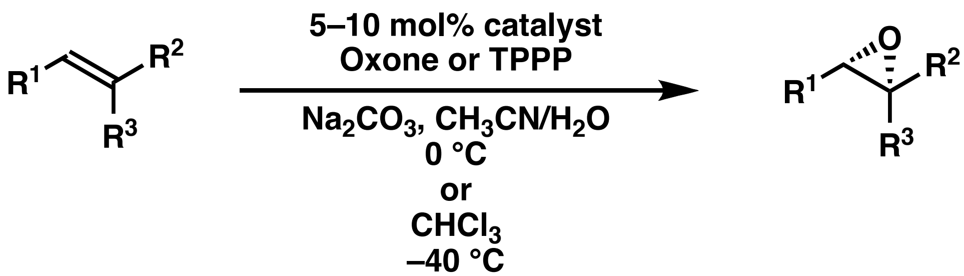
52% yield
79% ee

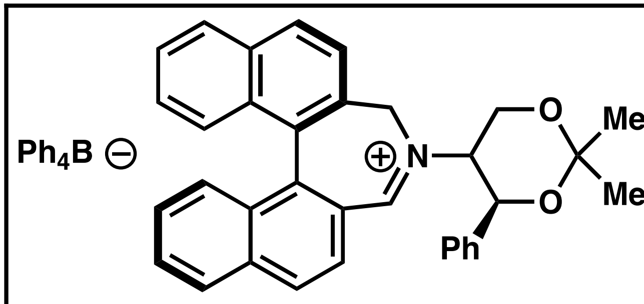


75% yield
66% ee

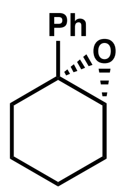
Lattanzi, A. *Org. Lett.* **2005,** *7,* 2579–2582.

Oxaziridine-Catalyzed Epoxidations: Lead References

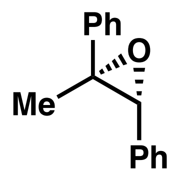




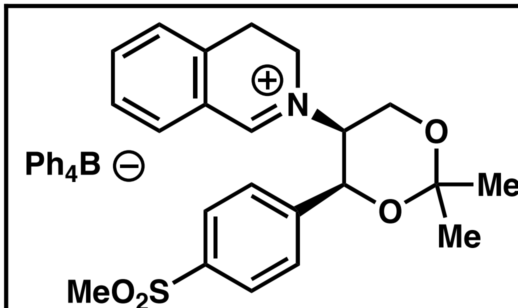
catalyst A



catalyst A
66% yield
95% ee

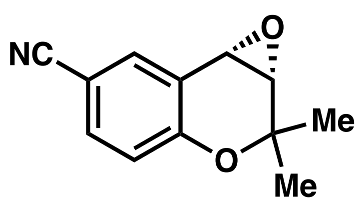


catalyst A
58% yield
49% ee



catalyst B

catalyst A
58% yield
20% ee

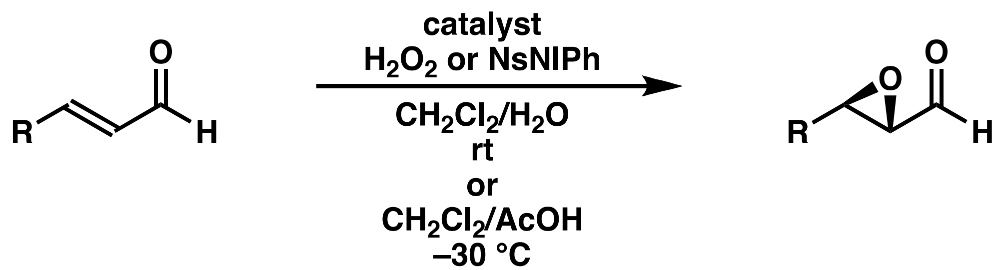


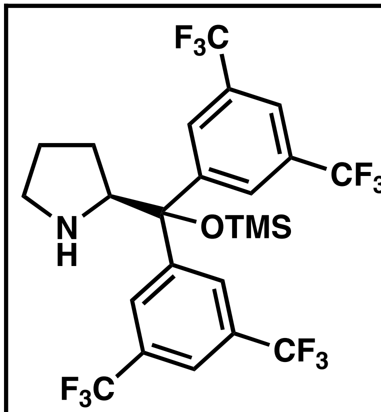
catalyst B
59% yield
97% ee

Page, P. C. B.; Buckley, B. R.; Blacker, A. J.
Org. Lett. **2004,** *6,* 1543–1546.

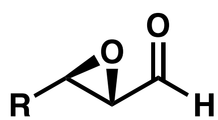
Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J.
Org. Lett. **2005,** *7,* 375–377.

Imminium-Catalyzed Epoxidations: Lead References

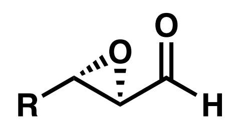




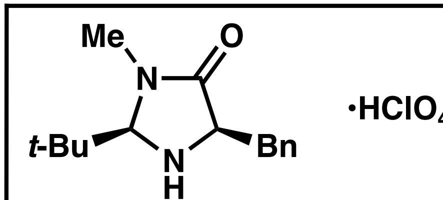
catalyst A



catalyst A
R = alkyl or Ar or CO_2R
63–90% yield
≥9:1 dr
94–98% ee



catalyst B
R = alkyl or Ar
72–95% yield
≥7:1 dr
85–97% ee

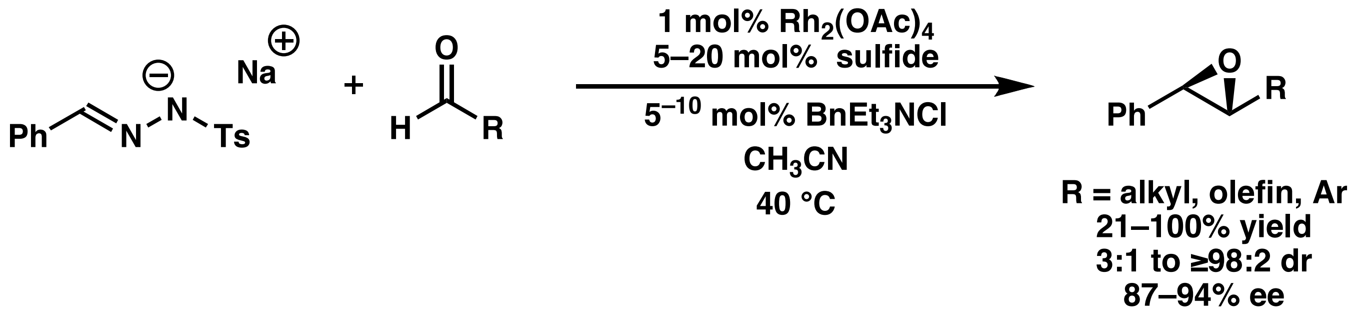


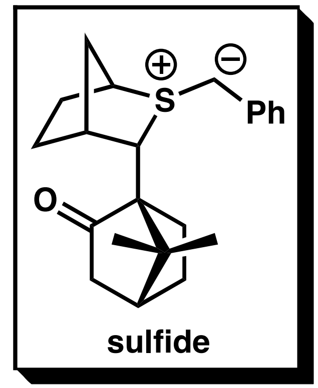
catalyst B

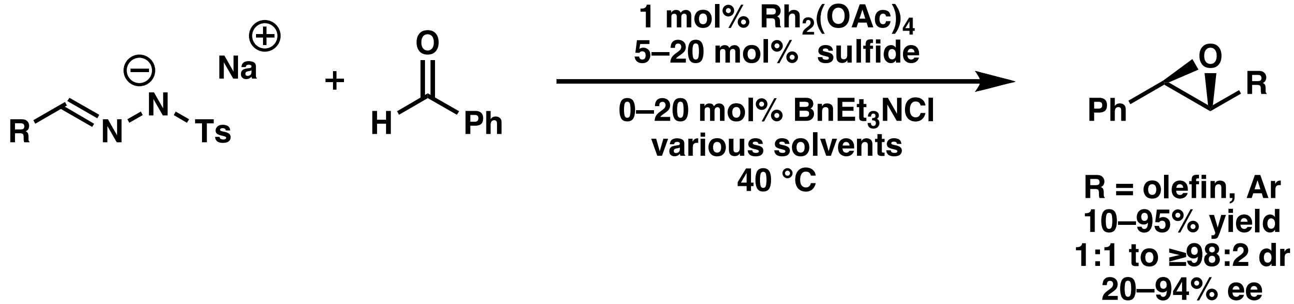
Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhung, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005,** *127,* 6964–6965.

Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006,** *62,* 11413–11424.

Sulfur Ylide-Catalyzed Epoxidations: Lead References







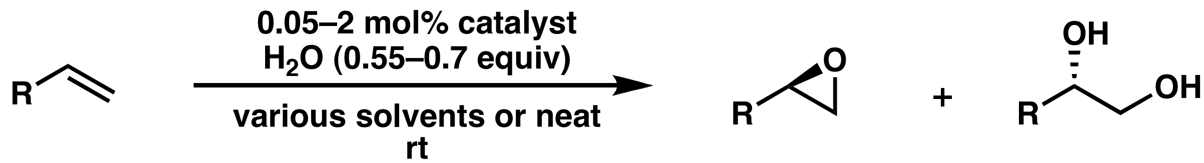
Aggarwal, V. K. et al. *J. Am. Chem. Soc.* **2003,** *125,* 10926–10940.

Aggarwal, V. K. *Acc. Chem. Res.* **2004,** *37,* 611–620.

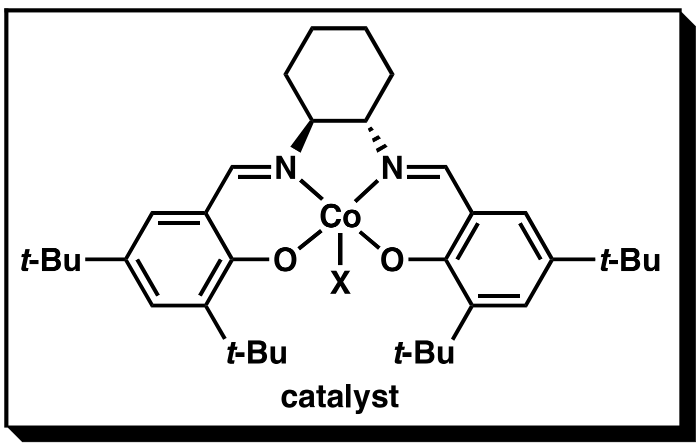
Also see: Winn, C. L.; Bellanie, B.; Goodman, J. M.; *Tetrahedron Lett.* **2002,** *43,*, 5427–5430.

Davoust, M.; Brière, J.-F.; Jaffrès, P.-A.; Metzner, P. *J. Org. Chem.* **2005,** *70,* 4166–4169.

Hydrolytic Kinetic Resolution of Terminal Epoxides



36–48% yield
>99% ee



Highly general for R = alkyl, aryl, olefin, alkynyl

Highly functional group tolerant

Schaus, S. E; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

For an improved monomer catalyst, see: Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362.

For a highly active oligomeric catalyst, see: White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633–3638.