

Reviews:

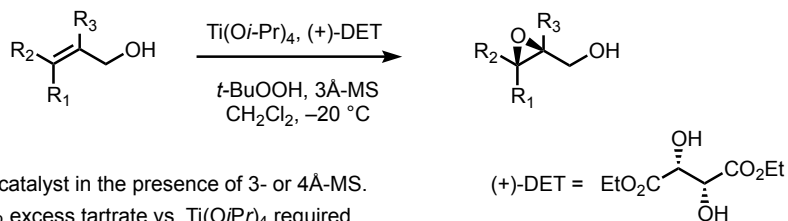
Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–300.

Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, pp. 103–158.

Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 7, pp. 389–436.

Pfenninger, A. *Synthesis* **1986**, 89–116.

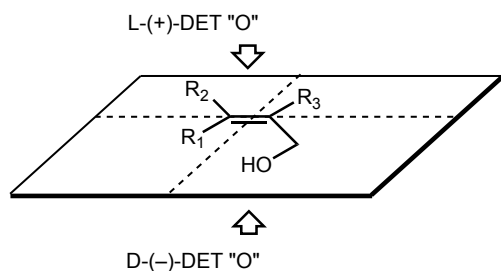
Asymmetric Epoxidation of Allylic Alcohols:



- 5–10 mol% catalyst in the presence of 3- or 4Å-MS.
- 10–20 mol% excess tartrate vs. Ti(OiPr)_4 required.
- (+)- and (–)-DET are readily available and inexpensive.
- (+)- and (–)-DIPT, diisopropyl tartrate, are also available and sometimes lead to higher selectivity.

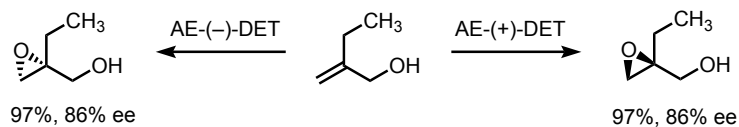
Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

Mnemonic for selectivity:

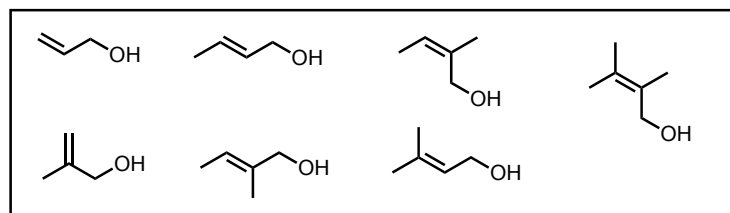


Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

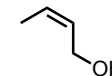
Application of Mnemonic:



Substitution patterns:



- Z-disubstituted olefins are least reactive and selective.



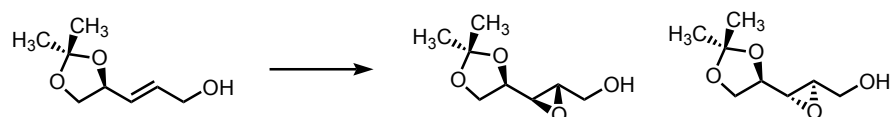
Examples of Sharpless Epoxidation:

product	Ti(%)	tartrate(%)	°C	h	yield (%)	ee (%)
	5	(+)-DIPT (6.0)	0	2	65	90
	5	(+)-DIPT (7.0)	–20	3	89	>98
	4.7	(+)-DET (5.9)	–12	11	88	95
	10	(+)-DET (14)	–10	29	74	86
	5	(+)-DIPT (7.5)	–35	2	79	>98
	100	(+)-DET (142)	–20	14	80	80
	5	(+)-DET (7.4)	–20	0.75	95	91
	120	(–)-DET (150)	–20	5	90	94

From: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780 and Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, pp. 103–158.

M. Movassaghi

Chiral Substrate:



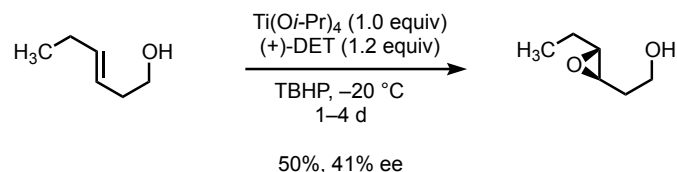
Reagent	Ratio (syn : anti)	
<i>m</i> -CPBA	1 : 1.4	
VO(acac) ₂ -TBHP	1 : 1.8	
Ti(O <i>i</i> Pr) ₄ -TBHP	1 : 2.3	
Ti(O <i>i</i> Pr) ₄ -(-)-DIPT-TBHP	1 : 90	MATCHED
Ti(O <i>i</i> Pr) ₄ -(+)-DIPT-TBHP	22 : 1	MISMATCHED

- Products are diastereomeric.
- Sense of induction is dominated by the catalyst.
- The C4 center reinforces and erodes this in "MATCHED" and "MISMATCHED" cases, respectively, as shown.

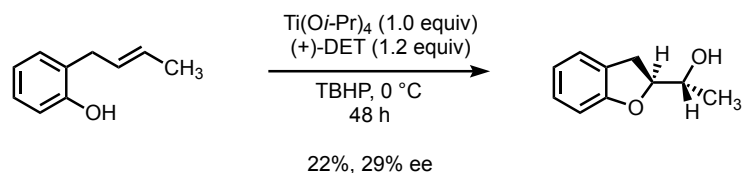
Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245–264.

Homoallylic, bishomoallylic and trishomoallylic:

- Rates of epoxidation are usually slower.
- Enantiofacial selectivity of the catalyst is reversed for all three.
- Enantiofacial selectivity is generally lower.



Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707–3711.

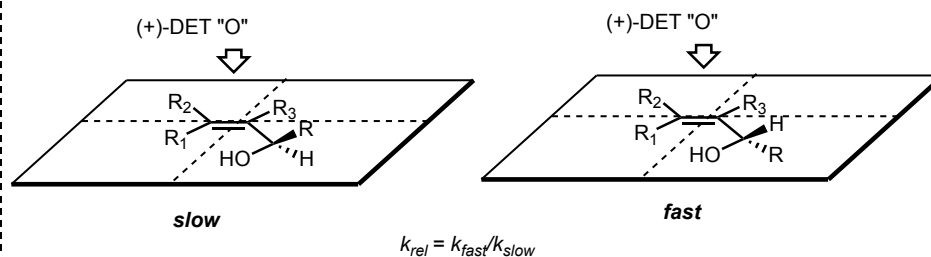


Hosokawa, T.; Kono, T.; Shinohara, T.; Murahashi, S.-I. *J. Organometal. Chem.* **1989**, *370*, C13–C16.

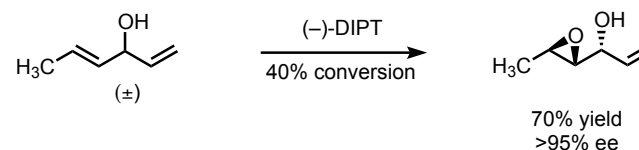
For other examples see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, pp. 103-158. and Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–300.

Kinetic Resolution:

- Products are diastereomeric.
- Using the Sharpless mnemonic, contact between the C1 substituent (R) and the catalyst predicts the slow-reacting isomer.



- With the exception of Z-disubstituted allylic alcohols, $k_{rel} > 25$.
- When $k_{rel} = 25$, the ee of unreacted alcohol is essentially 100% at 60% conversion.
- Allylic tertiary alcohols are not successfully epoxidized under Sharpless conditions.
- Factors may combine for high selectivity:

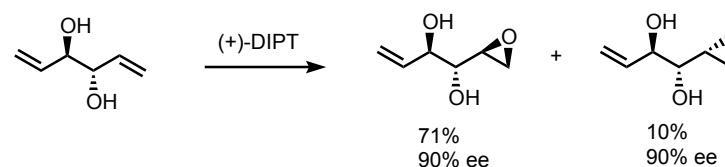


- Disubstituted olefin is more reactive than monosubstituted olefin ($k_{rel} \sim 100$).
- k_{fast}/k_{slow} for chiral *E*-propenylcarbinols is ~ 100 .

Exercise: Apply the Sharpless mnemonic to predict the stereochemistry of this product.

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

- Allylic 1,2-diols do not follow the Sharpless mnemonic:



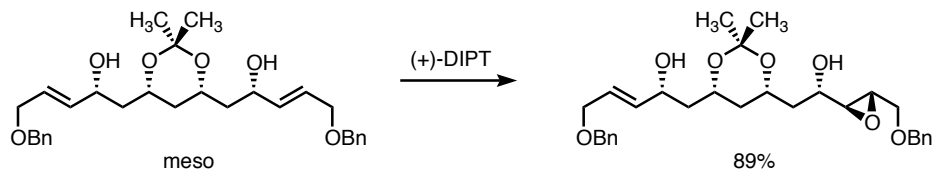
Exercise: What isomer would you have predicted using the Sharpless mnemonic?

Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1991**, *113*, 2786–2787. M. Movassaghi

C2-Symmetric Substrates:

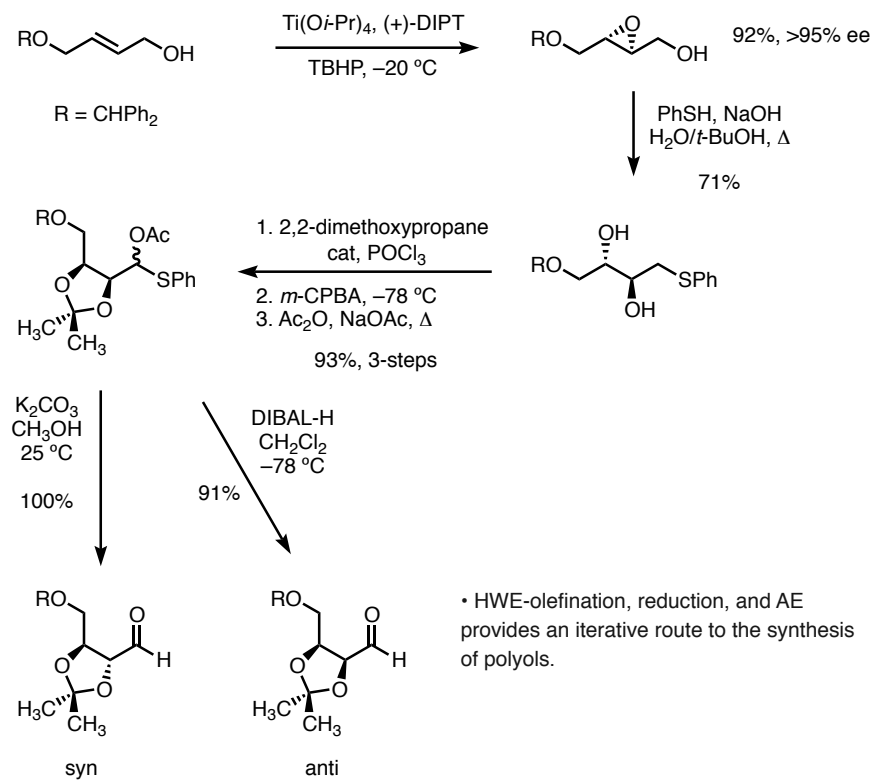
• Any minor diastereomer that is produced is rapidly removed by bis-epoxidation.

Exercise: Why?



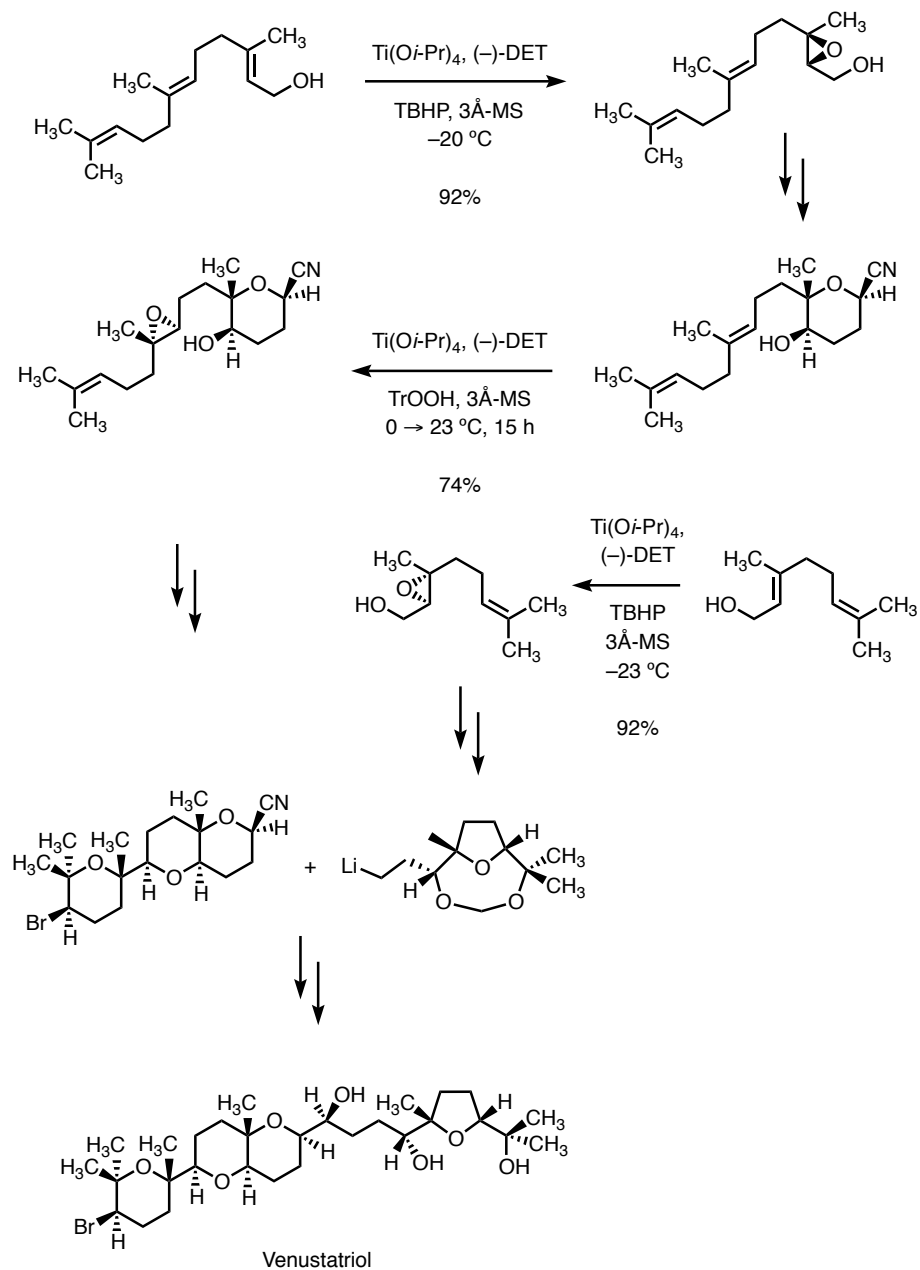
Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529.

Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718–4720.

Applications in Synthesis:**L-Hexoses:**

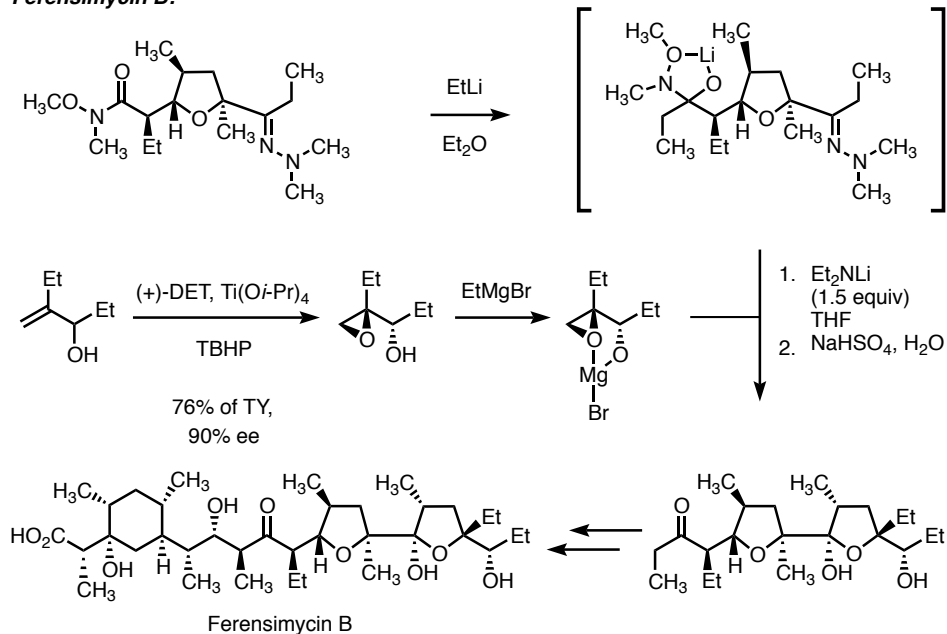
• HWE-olefination, reduction, and AE provides an iterative route to the synthesis of polyols.

Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245–264.

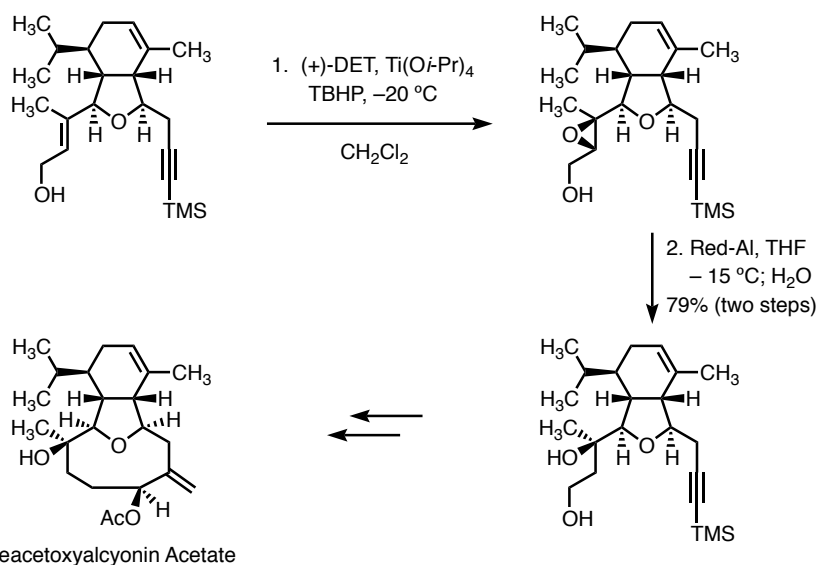
Venustatriol:

Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171–3174.

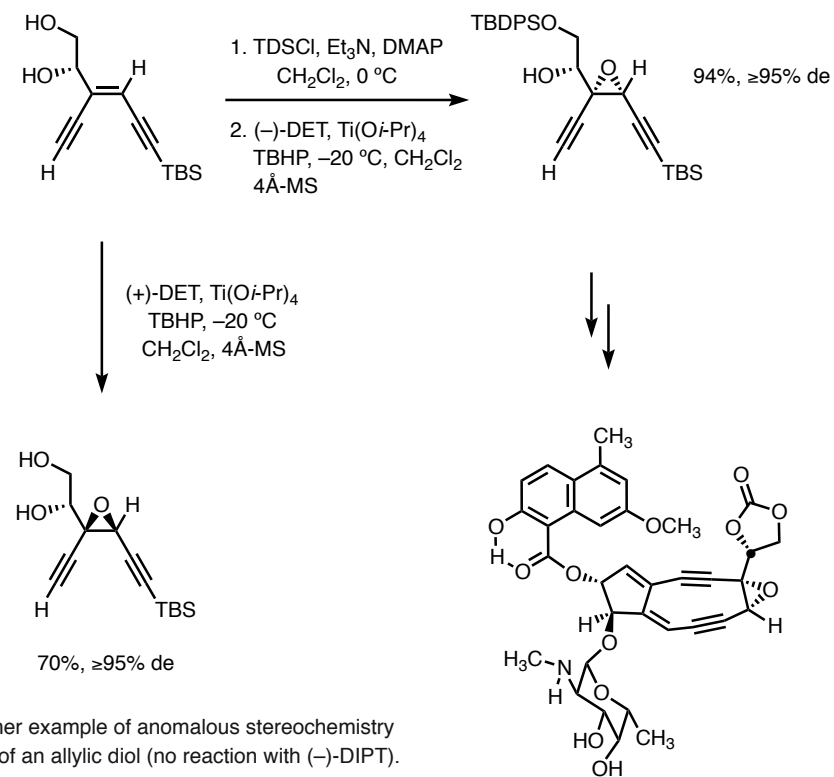
M. Movassaghi

Ferensimycin B:

Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613–7630.

(-)-7-Deacetoxyalcyonin Acetate:

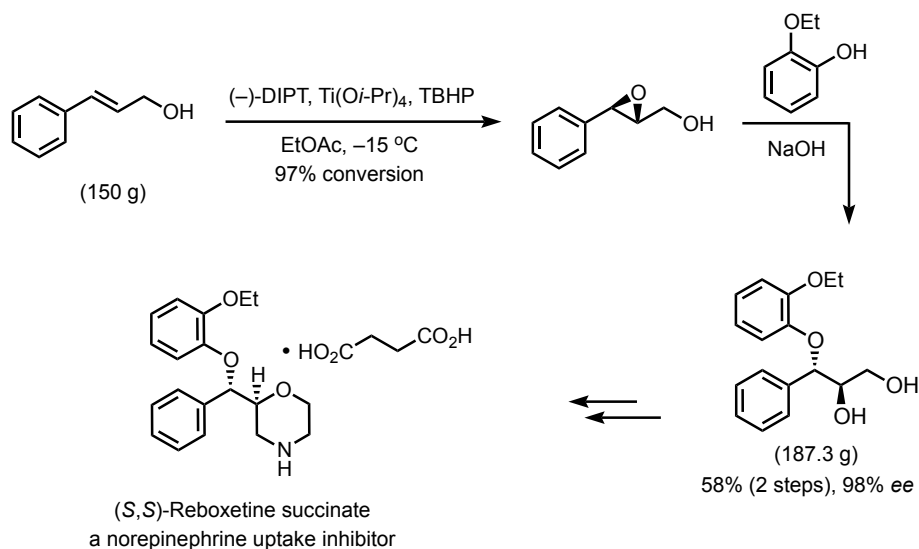
MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392.

(+)-Neocarzinostatin Chromophore:**(+)-Neocarzinostatin Chromophore**

Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J.-N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006–10007.

Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Yusheng, W.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 5319–5320.

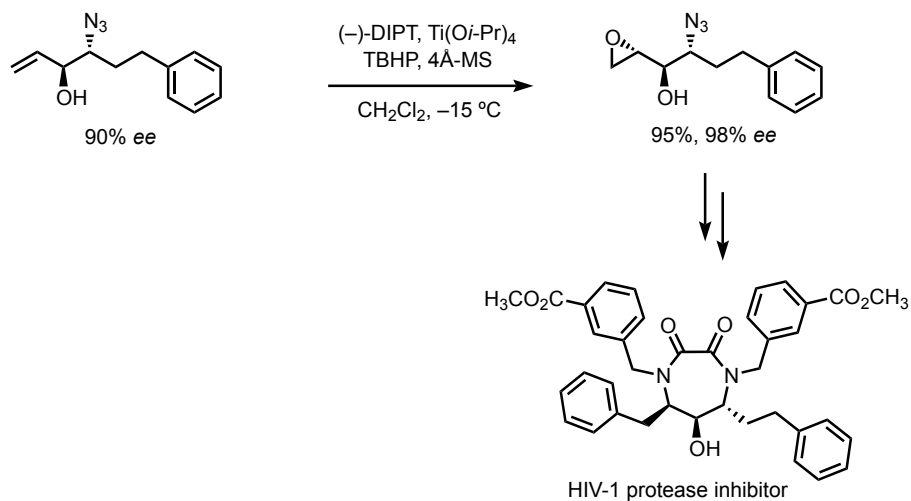
Examples of the Sharpless Asymmetric Epoxidation Reaction in Industry:



In this example, excess TBHP was quenched with triethylphosphite instead of Fe^{II} sulfate.

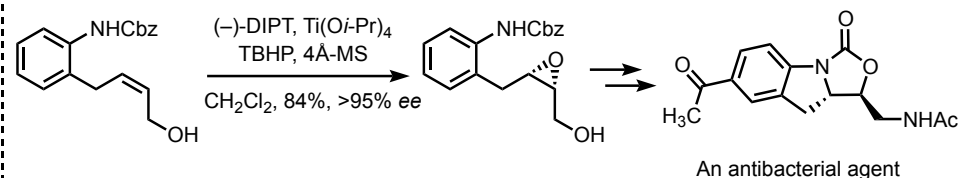
Henegar, K. E.; Cebula, M. *Org. Proc. Res. Dev.* **2007**, *11*, 354–358.

In the following example, the minor enantiomer was unreactive, leading to enantiomeric enrichment:

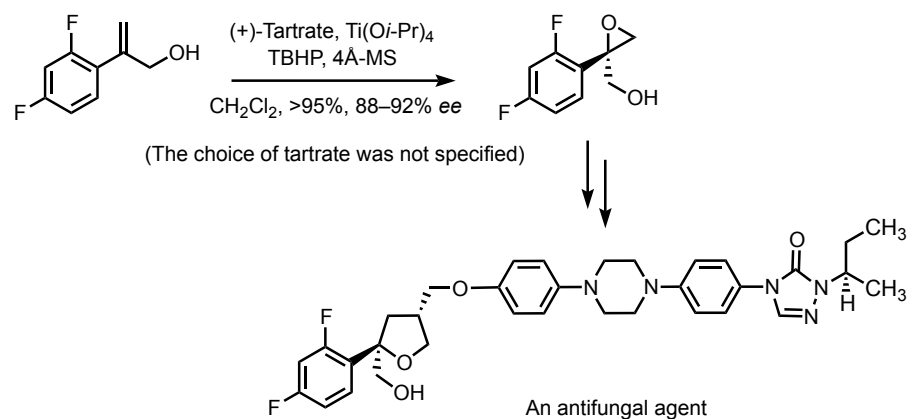


Jadhav, P. K.; Man, H. W. *Tetrahedron Lett.* **1996**, *37*, 1153–1156.

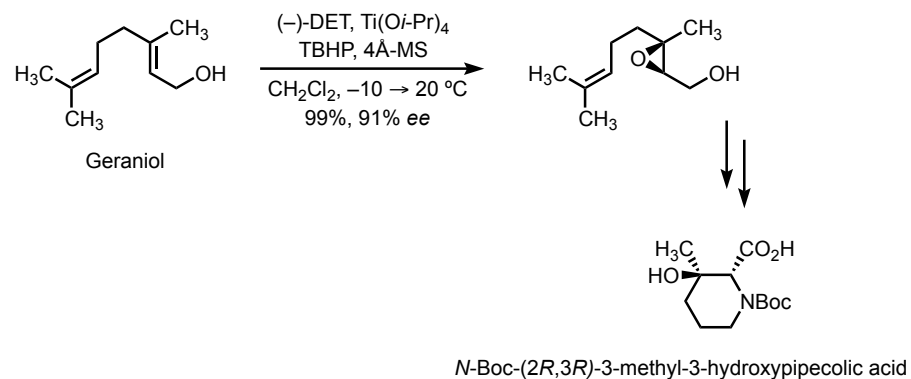
In this example, a stoichiometric amount of titanium and DIPT was necessary for high conversion.



Gleave, D. M.; Brickner, S. J. *J. Org. Chem.* **1996**, *61*, 6470–6474.



Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Hare, R. S.; Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2023–2028.



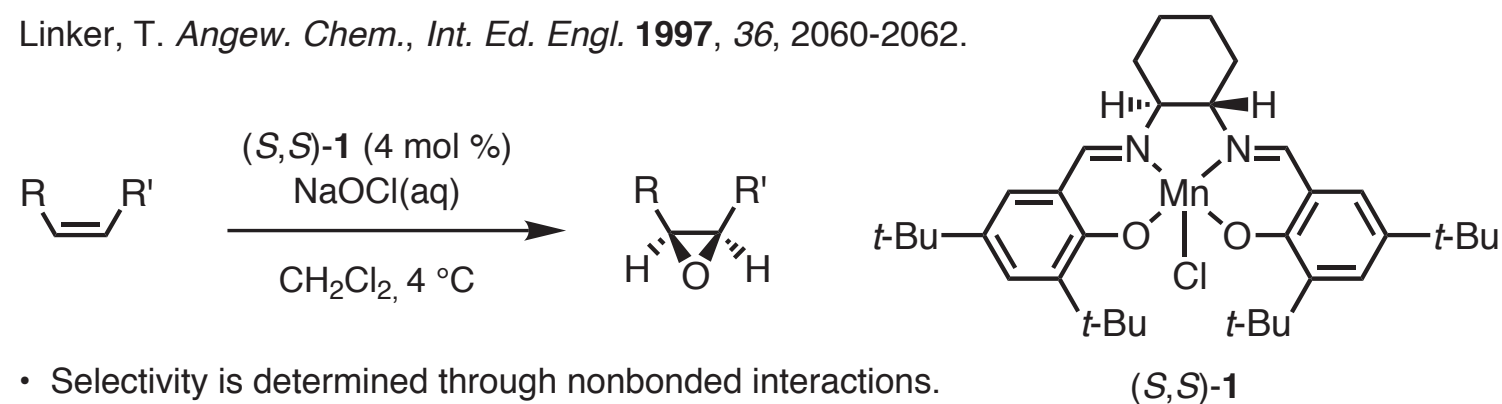
Noe, M. C.; Hawkins, J. M.; Snow, S. L.; Wolf-Gouveia, L. *J. Org. Chem.* **2008**, *73*, 3295–3298.

Jesse Teske, Andy Flick, Daniel Schmitt

Reviews:

Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**; pp. 159-202.

Linker, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2060-2062.



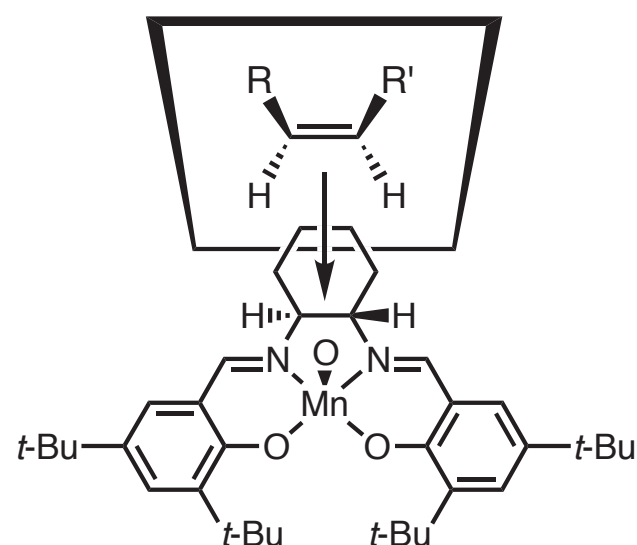
- Selectivity is determined through nonbonded interactions.
- In general, R is aryl, alkenyl or alkynyl and R' is a bulky group.
- *cis*-Disubstituted conjugated olefins are epoxidized with high levels of enantioselectivity.
- *trans*-Disubstituted olefins react more slowly and with diminished selectivity.

olefin	epoxide	yield, %	ee, %	equiv (S,S)-1
		96	97	0.03
		63	94	0.15
		79	84	0.006 ^a

^aReaction carried out in the presence of 4-phenylpyridine *N*-oxide.

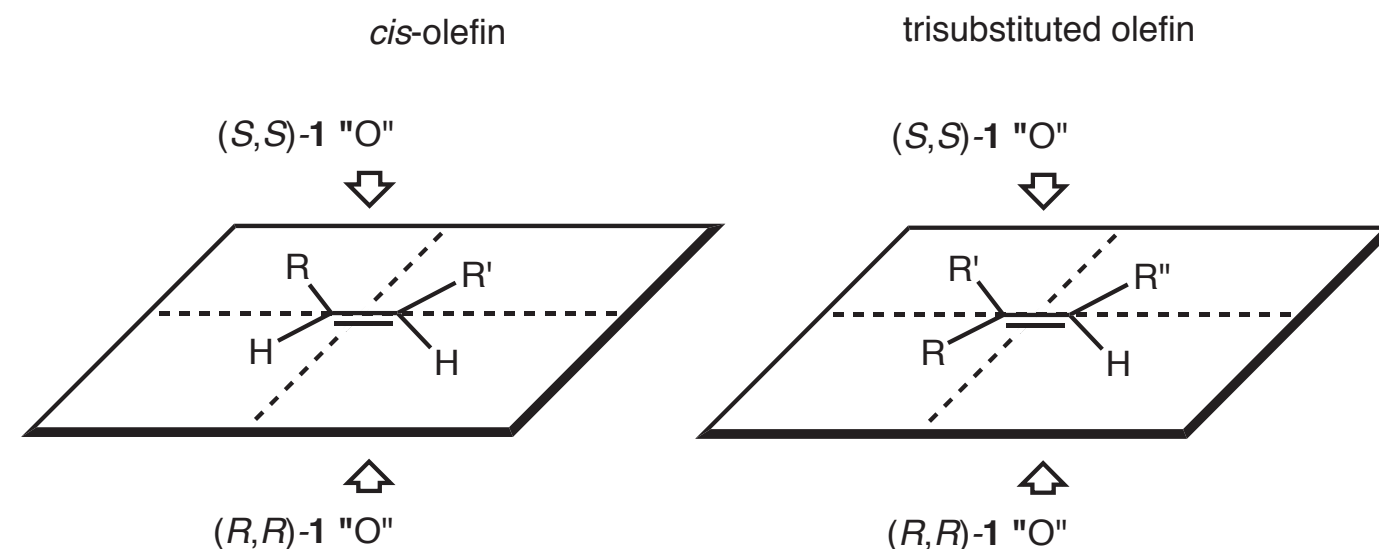
From: Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063-7064.

- The observed selectivities are explained by a side-on approach of olefin:



- Terminal olefins are poor substrates.
- Addition of substoichiometric amounts of 4-phenylpyridine *N*-oxide improves both catalyst selectivity and turnover numbers.

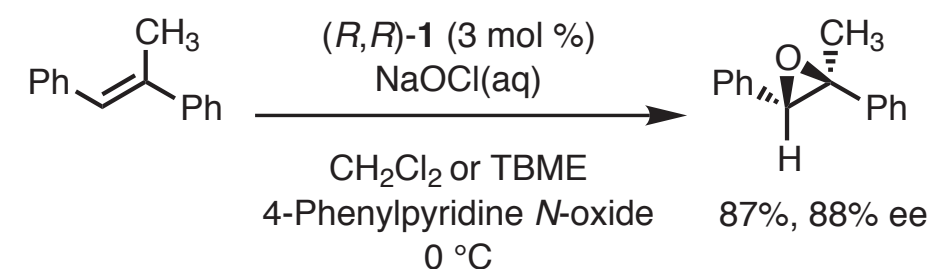
Mnemonics for the observed selectivities:



- *cis*-Olefins: Place Aryl, alkenyl or alkynyl substituent in upper-left quadrant (R) and the corresponding trans hydrogen atom in the lower-right quadrant.
- *trans*-Olefins are poor substrates.
- Trisubstituted olefins: Place the hydrogen atom in the lower-right quadrant.

Trisubstituted olefins:

- Trisubstituted alkenes are excellent substrates for the Jacobsen asymmetric epoxidation.



olefin	epoxide ^a	yield, %	ee, %
		69	93
		91	95
		97	92

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

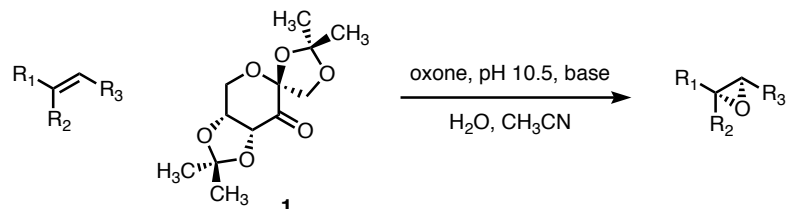
Reviews:

Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958–3987.

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

Frohn, M.; Shi, Y. *Synthesis* **2000**, *14*, 1979–2000.

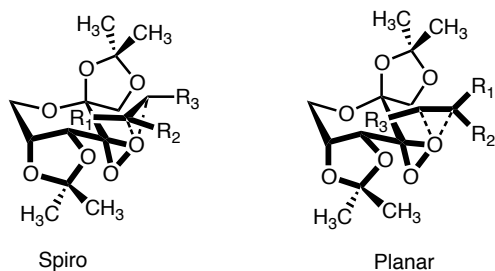
General Transformation:



- Useful for epoxidation of *trans*-disubstituted olefins (ketone **1**), trisubstituted olefins (ketone **1**), conjugated *cis*-disubstituted olefins (ketone **2**, see p. 3), and styrenes (ketone **2**, see p. 3).

Catalyst Conditions:

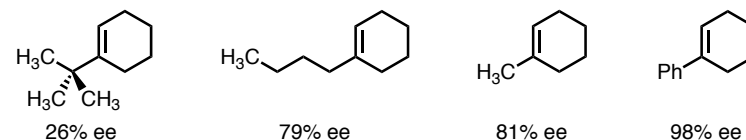
- Ketone **1** can be readily prepared from *D*-fructose (\$15/kg) by ketalization (acetone, HClO_4 , 0 °C, 53%) and oxidation (PCC, 23 °C, 93%). *L*-Fructose can be prepared in 3 steps from readily available *L*-sorbitol.
- Ketone **1** can be used catalytically (20–30 mol %).
- Oxone (a commercial mixture of 2:1:1 KHSO_5 : KHSO_4 : K_2SO_4) is used as the stoichiometric oxidant but $\text{H}_2\text{O}_2/\text{CH}_3\text{CN}$ can also be used (peroxyimidic acid is the proposed oxidant).
- Generally, the optimum pH for dioxirane epoxidation is 7–8. At higher pH, Oxone tends to decompose. However, at pH 7–8 the Shi catalyst decomposes due to competing Baeyer-Villiger reaction. By increasing the pH to 10.5 (by addition of K_2CO_3), the amount of ketone used can be reduced to a catalytic amount (30 mol %) and the amount of Oxone can be reduced to a stoichiometric amount (1.5 equiv), suggesting that at this pH the ketone is sufficiently reactive to compete with Oxone decomposition.
- Dimethoxymethane (DMM) and CH_3CN (2:1 v/v) solvent mixtures generally provide higher ee's.
- Reaction temperatures range from –10 to 20 °C.
- It is proposed that the Shi epoxidation proceeds through a dioxirane intermediate and a spiro transition state and that a so-called planar transition state is a main competing pathway. The spiro transition state is believed to be electronically favored as a result of a stabilizing interaction between an oxygen lone pair of the dioxirane with the π^* orbital of the olefin.



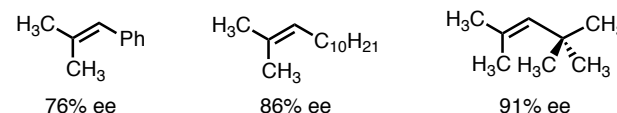
Higher ee's are observed with smaller R_1 and larger R_3 substituents.

Examples:

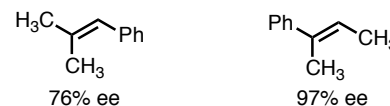
- Effect of smaller R_1 (also known as "T-branch"; phenyl groups can be considered smaller than methyl).



- Effect of larger R_3 (also: "L-branch").

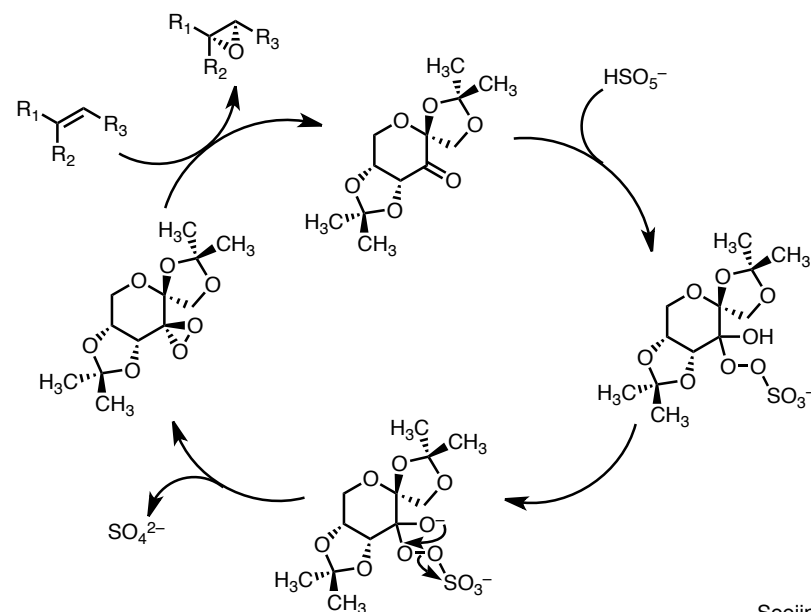


- Comparing the size of R_1 and R_3 .



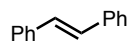

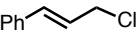

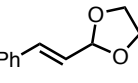
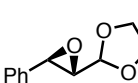
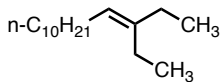
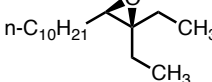
Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

Proposed Catalytic Cycle:



Soojin Kwon

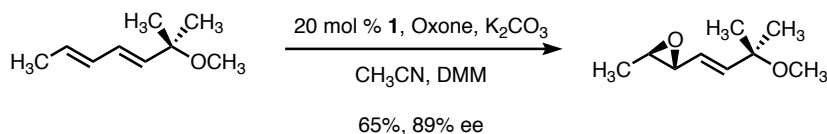
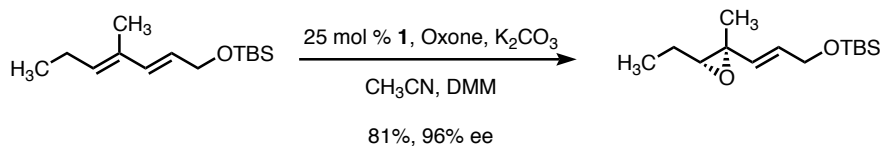
Examples of Shi Epoxidations:

Substrate	Product	Yield	ee (%)
		73%	95%
		61%	93%
		41%	93%
		94%	89%

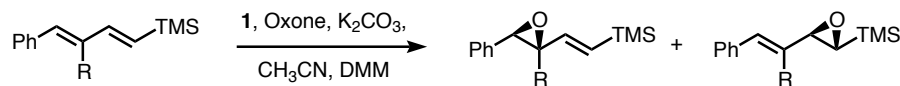
Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807

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

- Monoepoxidation of conjugated dienes favors the more electron-rich or less sterically hindered olefin. The amount of catalyst used must be properly controlled (0.2–0.3 equiv) to prevent bis-epoxidation. Vinyl silanes and allylic silyl ethers are deactivated towards epoxidation (attributed to sterics and inductive deactivation, respectively).



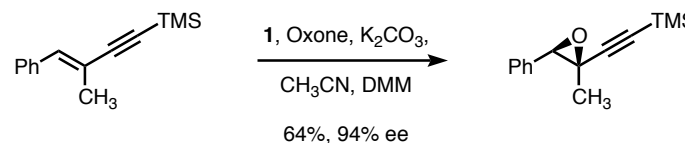
- Regioselectivity increases when either olefin of a 1,3-diene is trisubstituted. It is proposed that the trisubstituted olefin prevents full conjugation of the diene due to A_{1,2} strain, causing each olefin to present an individual steric or electronic environment, as if each were isolated.



	Yield	ee	Ratio
R = H	31%	95%	1:1
R = CH ₃	77%	92%	14:1

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

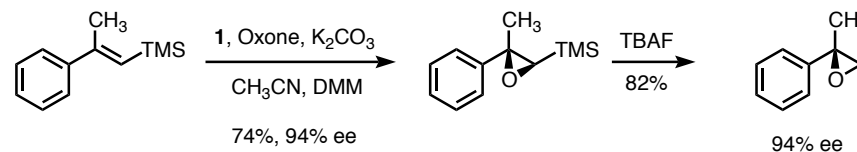
- Epoxidation of enynes occurs selectively at the C–C double bond.



Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425–4428.

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

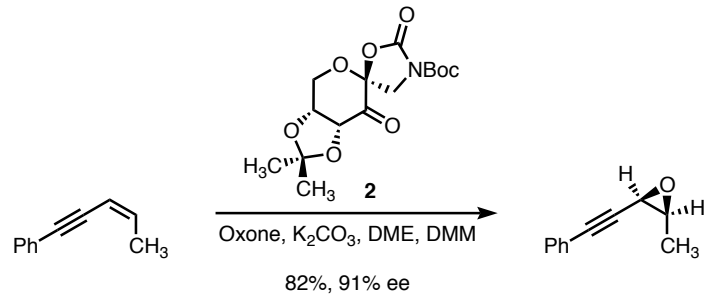
- 1,1-Disubstituted epoxides can be synthesized enantioselectively by Shi epoxidation of trisubstituted vinyl silanes followed by TBAF-mediated desilylation.



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

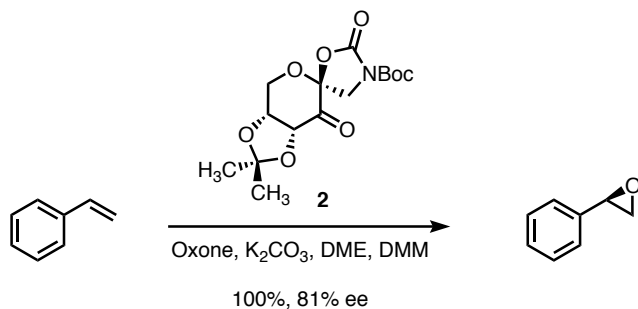
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- A modified catalyst is useful for epoxidation of *cis*-disubstituted olefins and styrenes.



The enantiomeric excess is generally high for cyclic olefins and for acyclic olefins conjugated with an alkynyl or aromatic group.

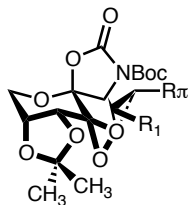
Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551–11552.



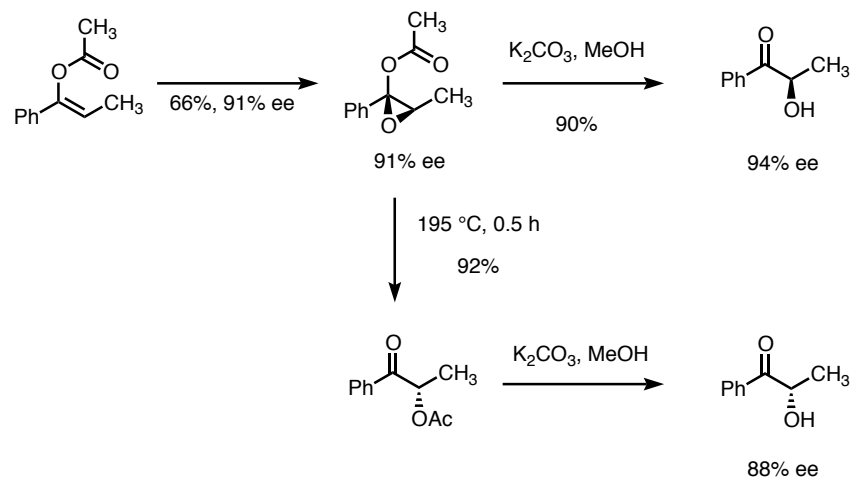
Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929–1931.

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

In both cases, it is proposed that the π -substituent of the substrate prefers to be proximal to the spiro oxazolidinone.

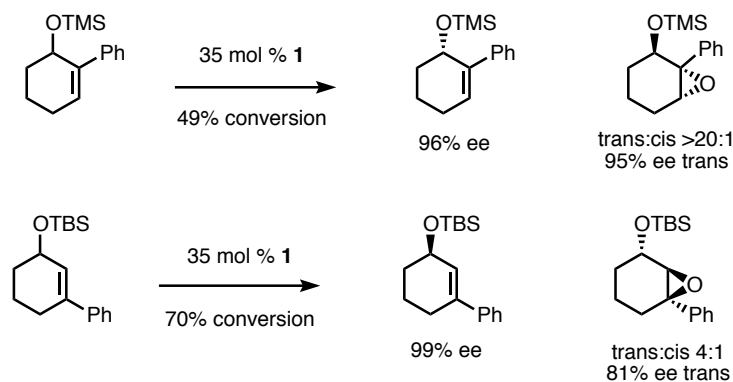


- Enol esters can be used as substrates for the preparation of α -hydroxyketones in either enantiomeric form.



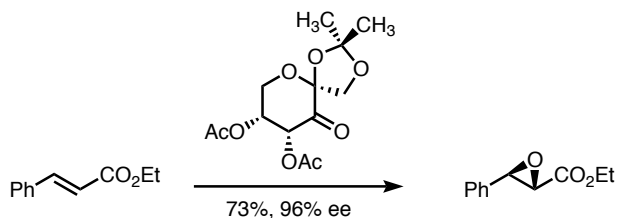
Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819–7822.

- Kinetic resolution of racemic 1,3- and 1,6-disubstituted cyclohexenes can provide optically enriched allylic silyl ethers.



Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718–7719.

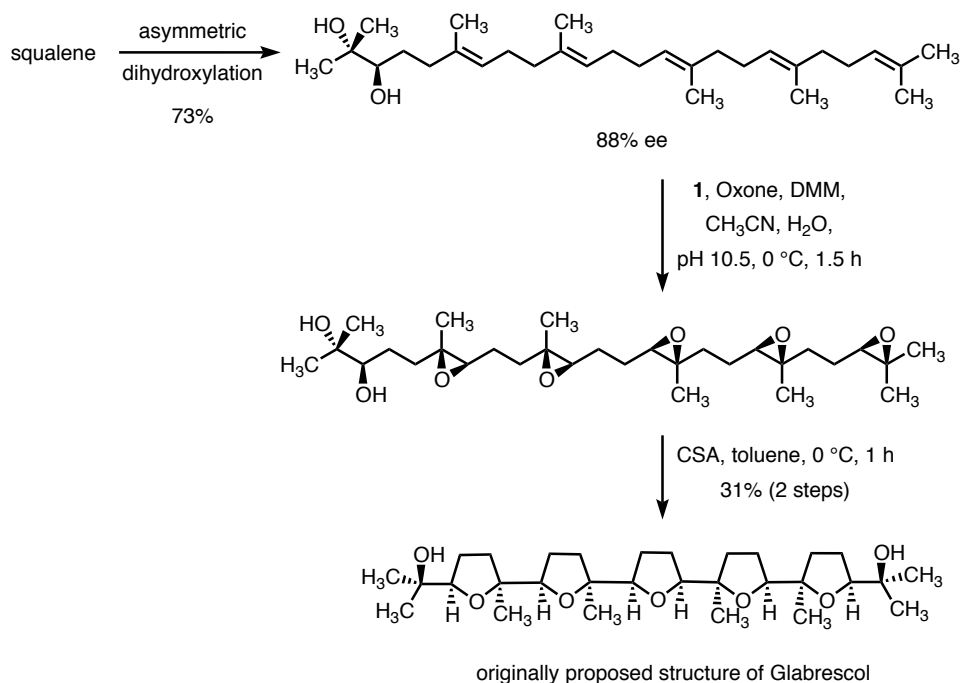
- The original Shi catalyst decomposes (via the Baeyer-Villiger pathway) faster than it reacts with electron-deficient α,β -unsaturated esters. A second-generation catalyst, incorporating electron-withdrawing acetate groups, slows the Baeyer-Villiger decomposition.



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

Applications in Synthesis:

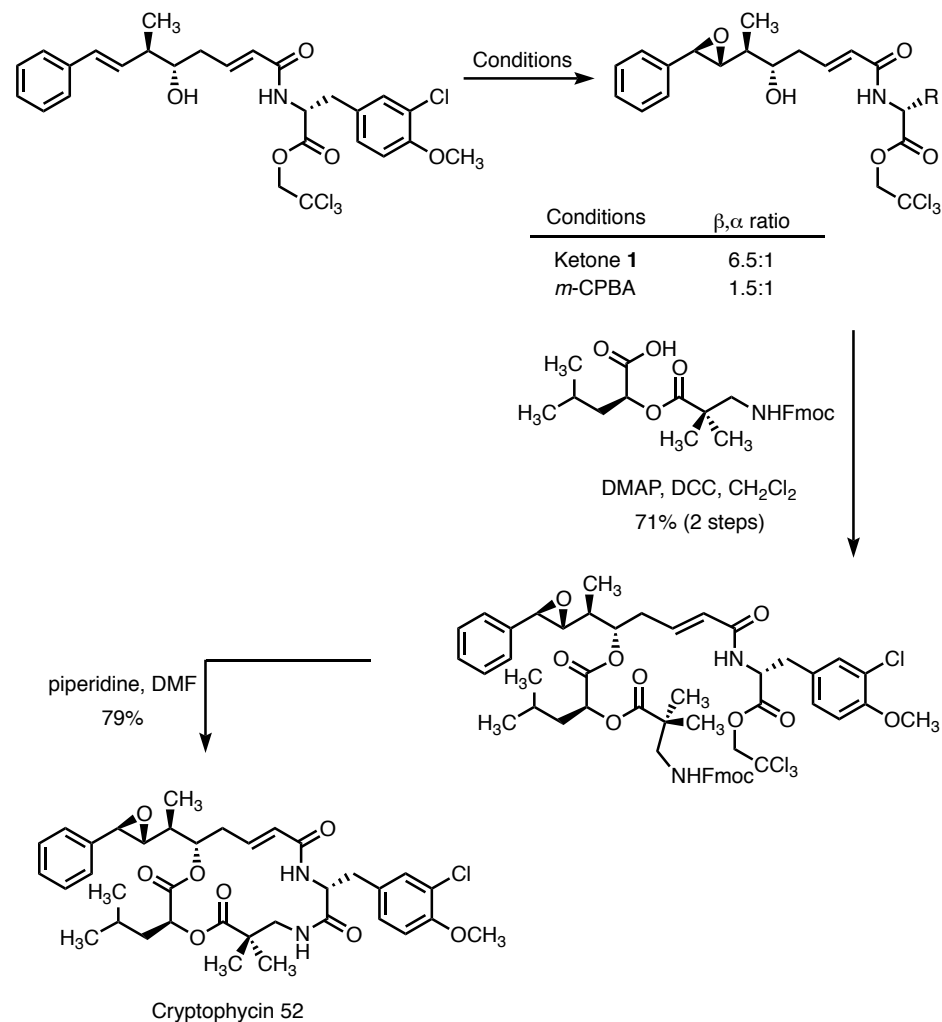
Glabrescol:



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

Cryptophycin 52:

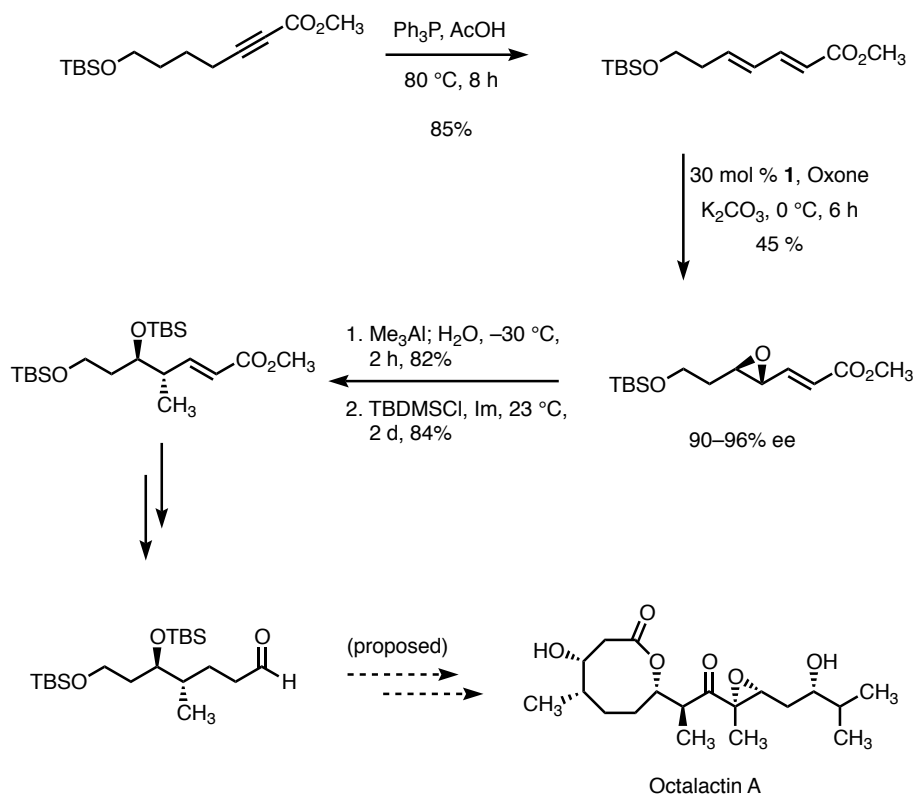
The Shi epoxidation system provided the desired epoxide in a 6:1 diastereomeric ratio, while other epoxidation methods never exceeded a 2:1 ratio.



Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813–1815.

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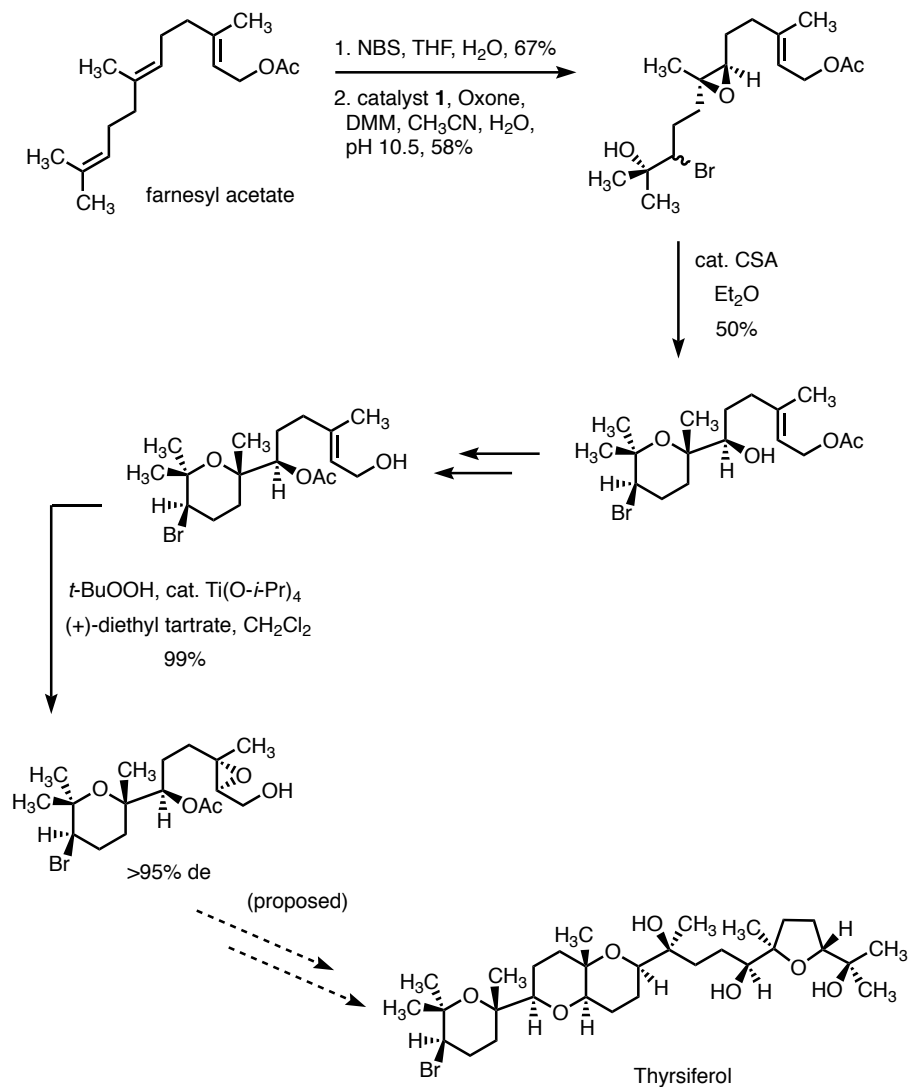
Octalactin A:



Bluet, G.; Campagne, J.-M. *Synlett* **2000**, 1, 221–222.

Thyrsiferol:

Post epoxidation, only one bromohydrin diastereomer cyclized to the bromotetrahydropyran. The unreactive diastereomer was separated from the cyclization product and isolated in 30% yield.



McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, 4, 593–595.

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