

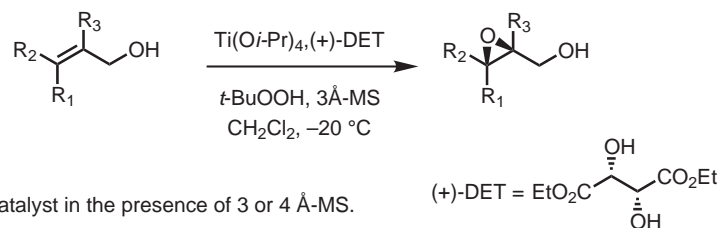
Reviews:

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.

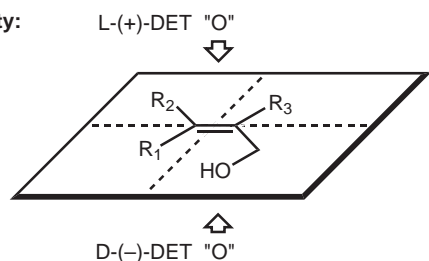
Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 7, pp. 389-436.

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

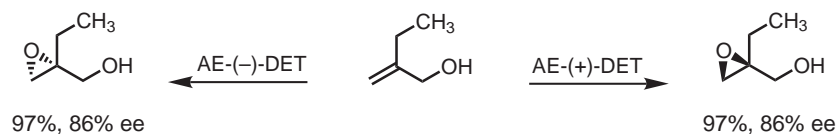
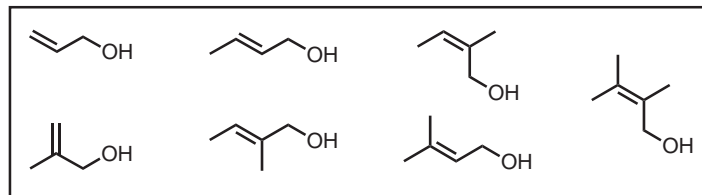
Asymmetric Epoxidation of Allylic Alcohols:

- 5-10 mol% catalyst in the presence of 3 or 4 Å-MS.
- 10-20 mol% excess tartarate vs. $\text{Ti}(\text{O}i\text{Pr})_4$ required.
- (+)- and (-)-DET are readily available and inexpensive.
- (+)- and (-)-DIPT, diisopropyl tartarate, are also available and sometimes lead to higher selectivity.

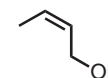
Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

Mnemonic for selectivity:

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

Application of Mnemonic:**Substitution patterns:**

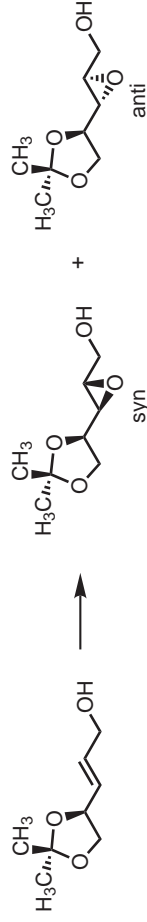
- Z-disubstituted olefins are least reactive and selective.

**Examples of Sharpless Epoxidation:**

product	Ti(%)	tartarate (%)	°C	h	yield (%)	ee (%)
	5	(+)-DIPT (6.0)	0	2	65	90
	5	(+)-DIPT (7.5)	-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.

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
Ti(O <i>i</i> Pr) ₄ -(+)-DIPT-TBHP	22 : 1

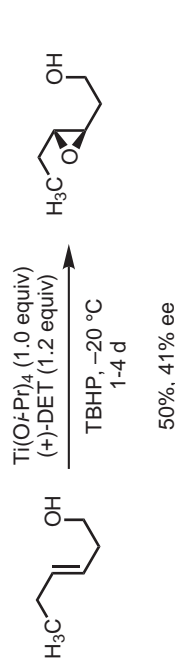
MATCHED
MISMATCHED

- 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.

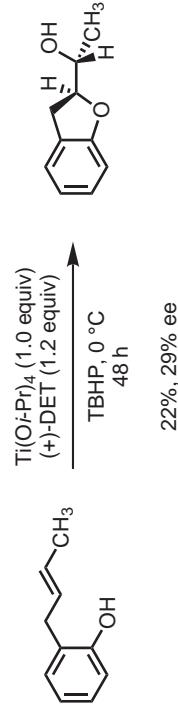
Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245-264.

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.

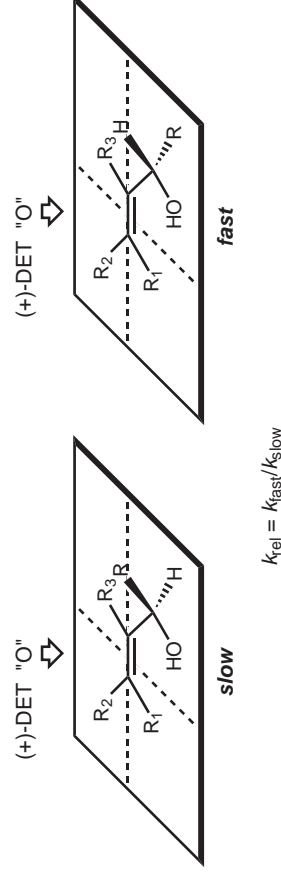


Hosokawa, T.; Kono, T.; Shinohara, T.; Murahashi, S.-I. *J. Organometal. Chem.* **1989**, *370*, C13-C16.

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 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.

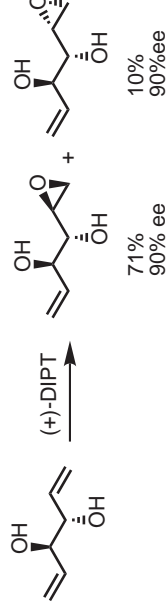


- Disubstituted olefin is more reactive than monosubstituted olefin ($k_{rel} \sim 100$).
- k_{fast}/k_{slow} for chiral *E*-propenylcarbinols is ~ 100 .

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.

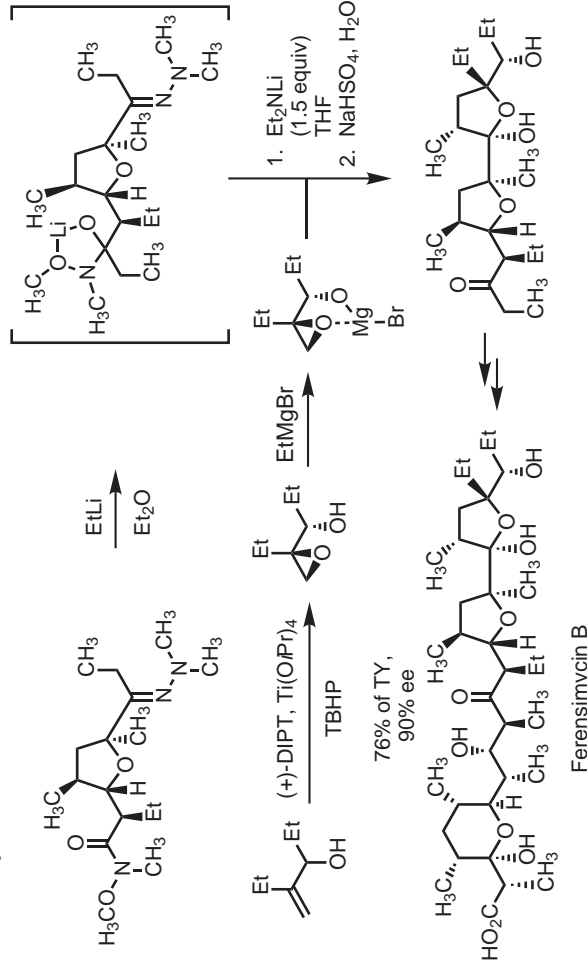
- Allylic 1,2-diols do not follow the Sharpless mnemonic:



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

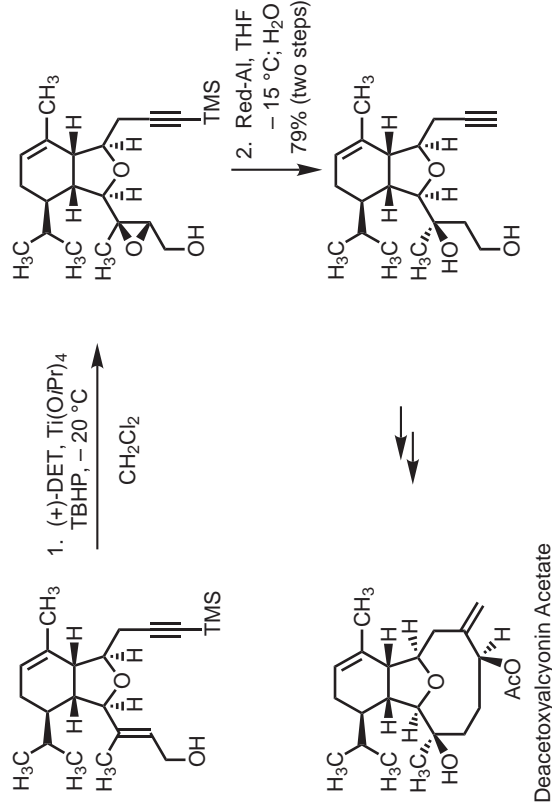
Takano, S.; Iwabuchi, Y.; Ogasawara J. *Am. Chem. Soc.* **1991**, *113*, 2786-2787.

Ferensimycin B:



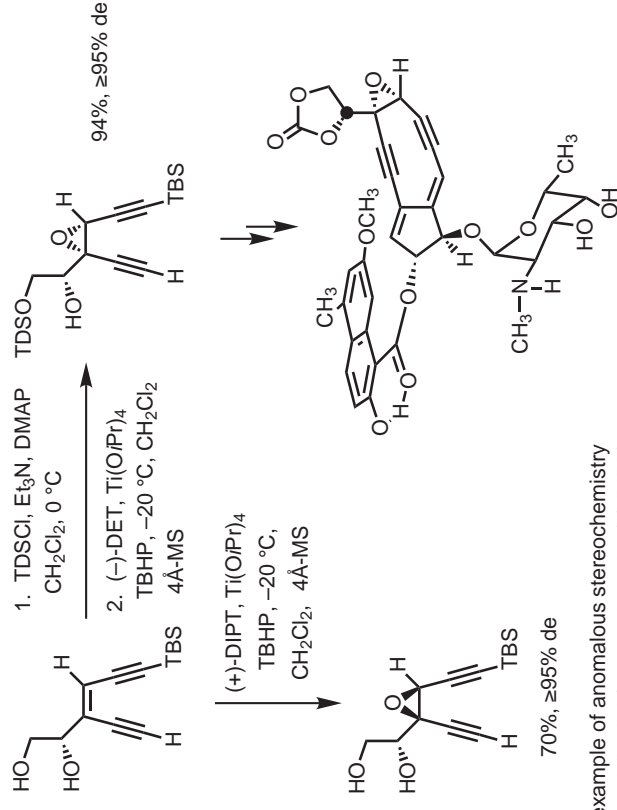
Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613-7630.

(-)-7-Deacetoxyalcyonin Acetate:



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

(+)-Neocarzinostatin Chromophore:



• A further example of anomalous stereochemistry in AE of an allylic diol (no reaction with (-)-DIPT).

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.