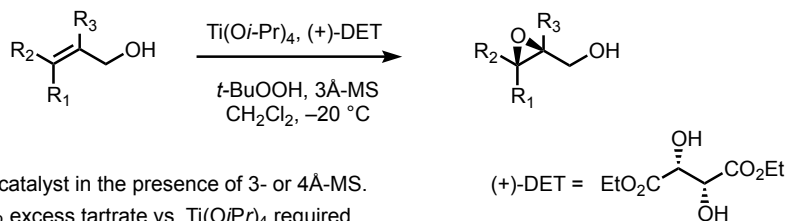**Reivews:**

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(O*iPr*)$_4$ required.
- (+)- and (–)-DET are readily available and inexpensive.
- (+)- and (–)-DIPT, diisopropyl tartrate, are also available and sometimes lead to higher selectivity.
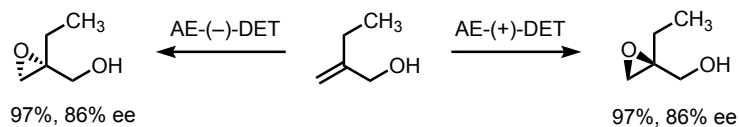
Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
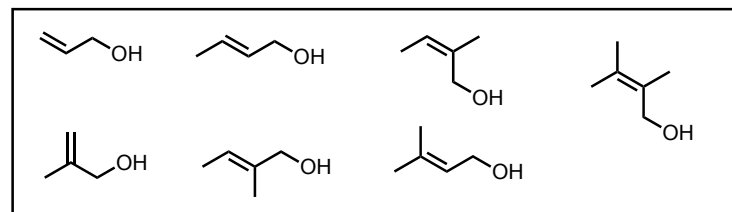
**Mnemonic for selectivity:**
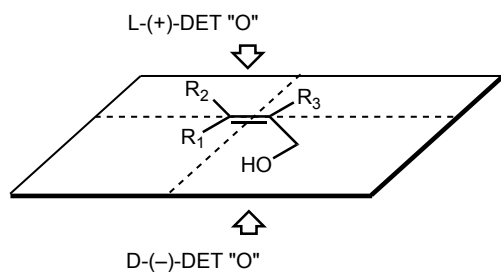


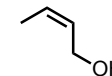Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

**Application of Mnemonic:**



97%, 86% ee                          97%, 86% ee

**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 (7.0) | –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:**
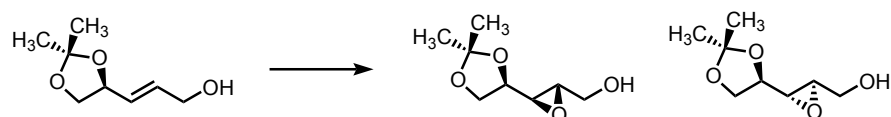


| Reagent | Ratio (syn : anti) | |
|---|---|---|
| *m*-CPBA | 1 : 1.4 | |
| VO(acac)$_2$-TBHP | 1 : 1.8 | |
| Ti(O*i*Pr)$_4$-TBHP | 1 : 2.3 | |
| Ti(O*i*Pr)$_4$-(-)-DIPT-TBHP | 1 : 90 | MATCHED |
| Ti(O*i*Pr)$_4$-(+)-DIPT-TBHP | 22 : 1 | MISMATCHED |

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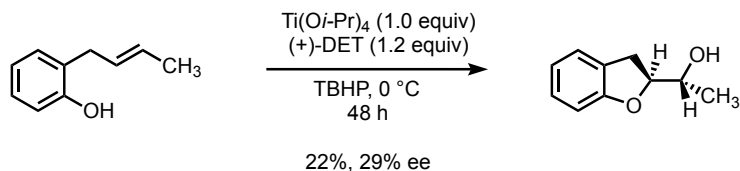
Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46,* 245–264.

**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.



Ti(O*i*-Pr)$_4$ (1.0 equiv)
(+)-DET (1.2 equiv)

TBHP, –20 °C
1–4 d

50%, 41% ee
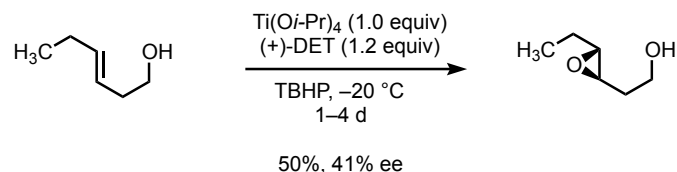
Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984,** *49*, 3707–3711.



Ti(O*i*-Pr)$_4$ (1.0 equiv)
(+)-DET (1.2 equiv)

TBHP, 0 °C
48 h

22%, 29% ee

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.



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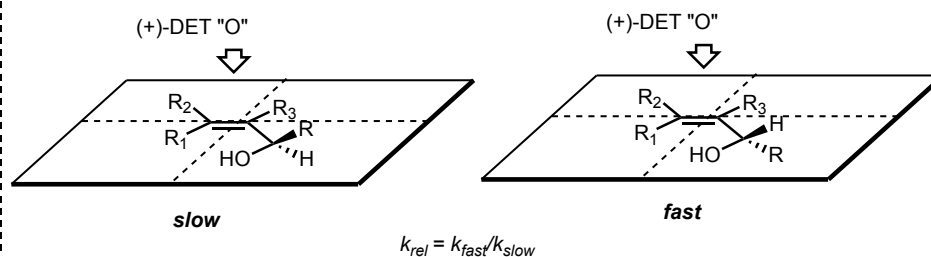
• With the exception of Z-disubstituted allylic alcohols, $k_{rel} > 25$.
• When $k_{rel} = 25$, the ee of unreacted alcohol is essentially 100% at 60% conversion.
• Allylic tertiary alcohols are not successfully epoxidized under Sharpless conditions.
• Factors may combine for high selectivity:



(–)-DIPT

40% conversion

70% yield
>95% ee
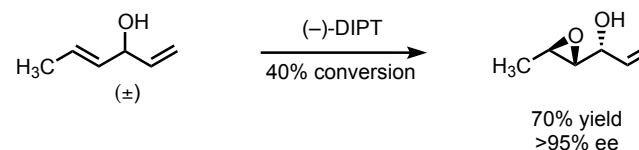
• Disubstituted olefin is more reactive than monosubstituted olefin ($k_{rel}$ ~ 100).
• $k_{fast}/k_{slow}$ for chiral *E*-propenylcarbinols is ~100.

*Excercice*: 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.

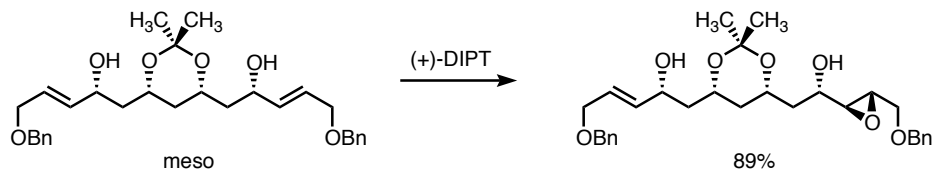• Allylic 1,2-diols do not follow the Sharpless mnemonic:



(+)-DIPT

71%
90% ee

10%
90% ee
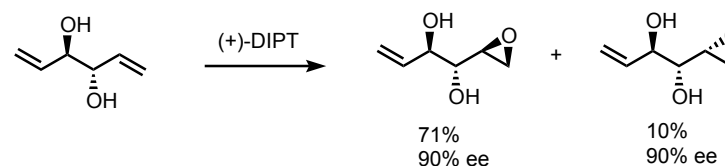
*Excercice*: What isomer would you have predicted using the Sharpless mnemonic?

Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1991**, *113*, 2786–2787.   M. Movassaghi
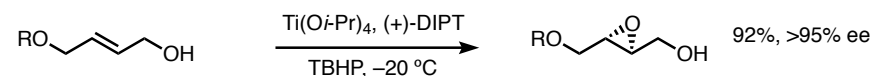
**C2-Symmetric Substrates:**

• Any minor diastereomer that is produced is rapidly removed by bis-epoxidation.
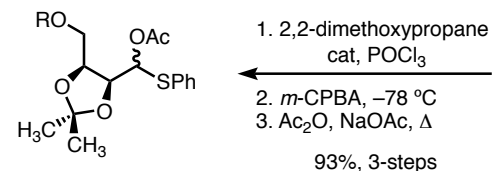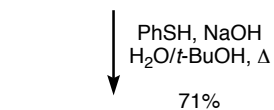
***Exercise:*** Why?



(+)-DIPT

meso      89%

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.
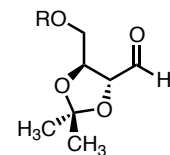
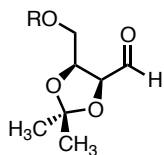**Applications in Synthesis:**

***L-Hexoses:***



R = CHPh₂

Ti(O*i*-Pr)₄, (+)-DIPT, TBHP, −20 ºC → 92%, >95% ee

PhSH, NaOH, H₂O/*t*-BuOH, Δ → 71%

1. 2,2-dimethoxypropane cat, POCl₃
2. *m*-CPBA, −78 ºC
3. Ac₂O, NaOAc, Δ

93%, 3-steps

K₂CO₃ CH₃OH 25 ºC → 100%

DIBAL-H CH₂Cl₂ −78 ºC → 91%

syn      anti

• 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:***



Ti(O*i*-Pr)₄, (−)-DET, TBHP, 3Å-MS, −20 ºC → 92%

Ti(O*i*-Pr)₄, (−)-DET, TrOOH, 3Å-MS, 0 → 23 ºC, 15 h → 74%

Ti(O*i*-Pr)₄, (−)-DET, TBHP 3Å-MS, −23 ºC → 92%

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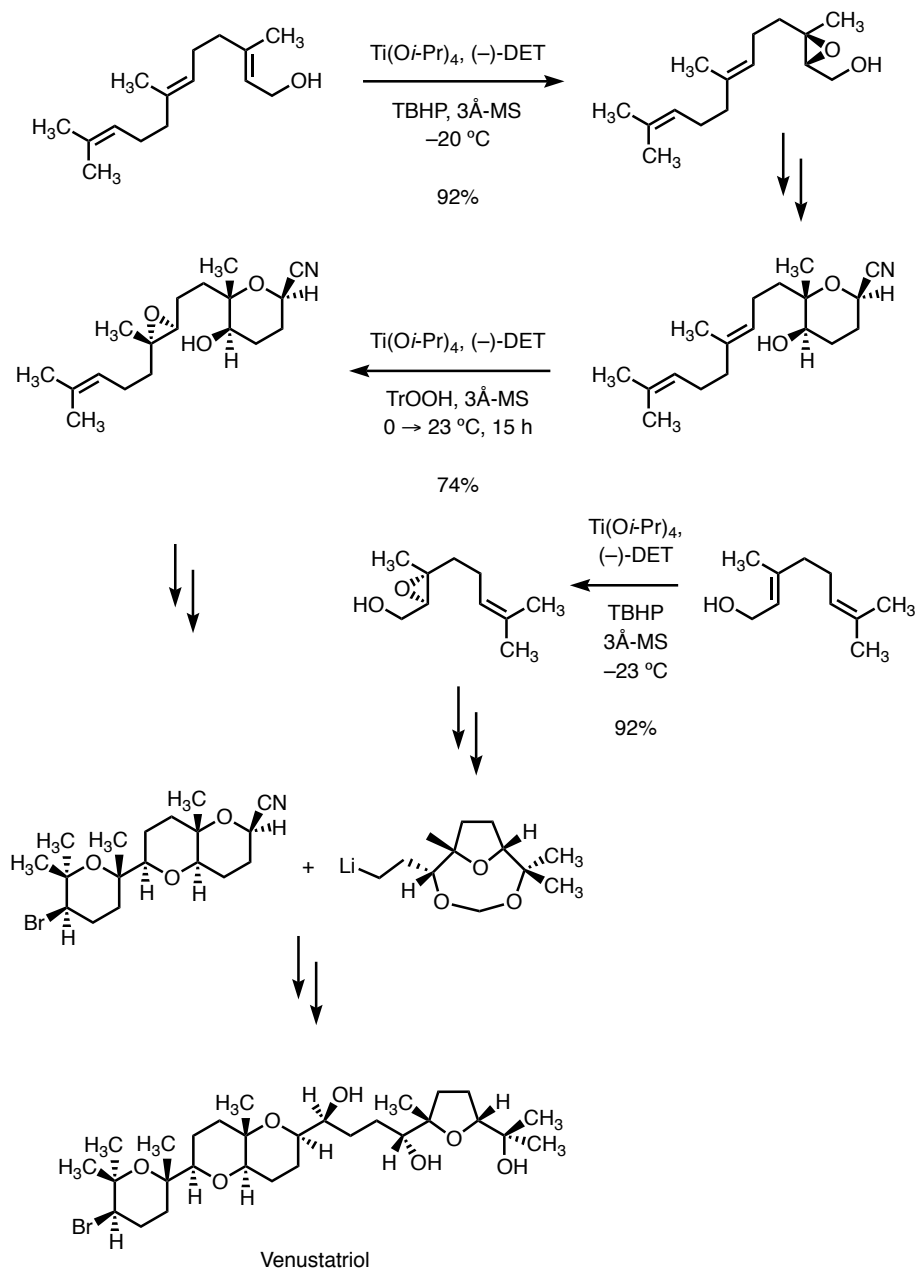
Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171–3174.

M. Movassaghi

**Ferensimycin B:**



EtLi

Et$_2$O

1. Et$_2$NLi
   (1.5 equiv)
   THF
2. NaHSO$_4$, H$_2$O

(+)-DET, Ti(O*i*-Pr)$_4$

TBHP

76% of TY,
90% ee

EtMgBr
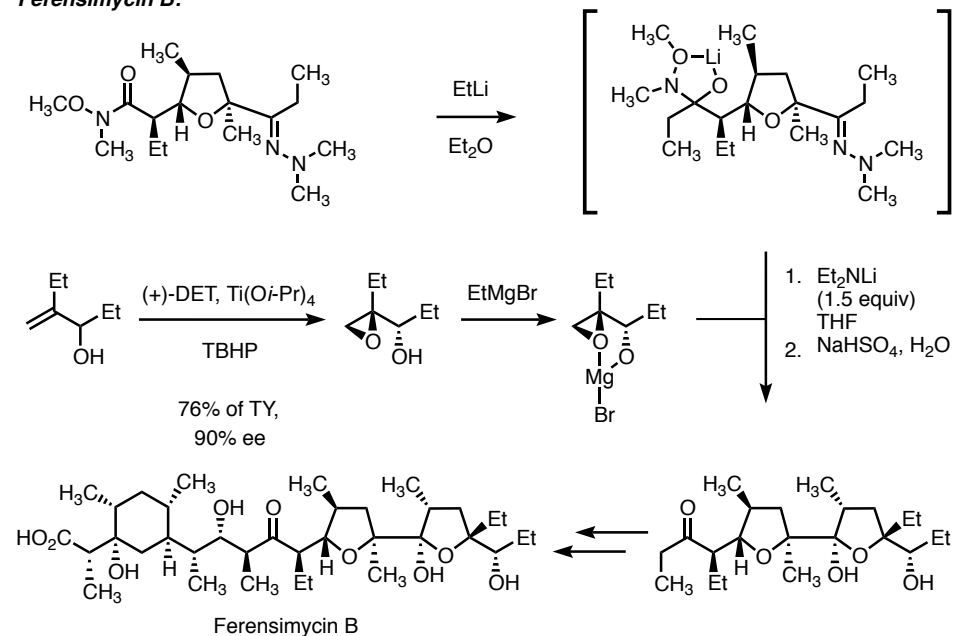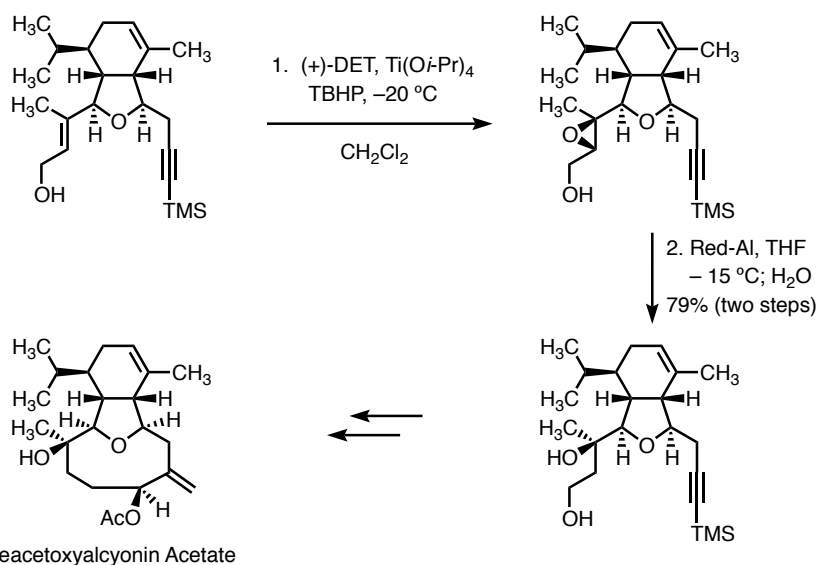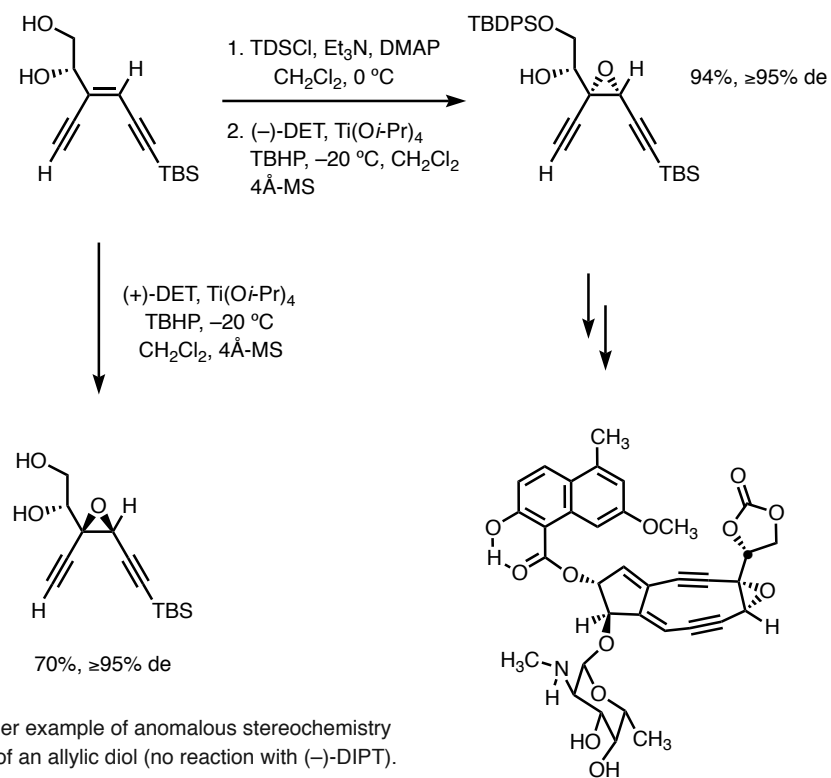
Ferensimycin B

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:**



1. (+)-DET, Ti(O*i*-Pr)$_4$
   TBHP, –20 ºC

   CH$_2$Cl$_2$

2. Red-Al, THF
   – 15 ºC; H$_2$O
   79% (two steps)

(–)-7-Deacetoxyalcyonin Acetate

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

**(+)-Neocarzinostatin Chromophore:**



1. TDSCl, Et$_3$N, DMAP
   CH$_2$Cl$_2$, 0 ºC

2. (–)-DET, Ti(O*i*-Pr)$_4$
   TBHP, –20 ºC, CH$_2$Cl$_2$
   4Å-MS

94%, ≥95% de

(+)-DET, Ti(O*i*-Pr)$_4$
TBHP, –20 ºC
CH$_2$Cl$_2$, 4Å-MS

70%, ≥95% de

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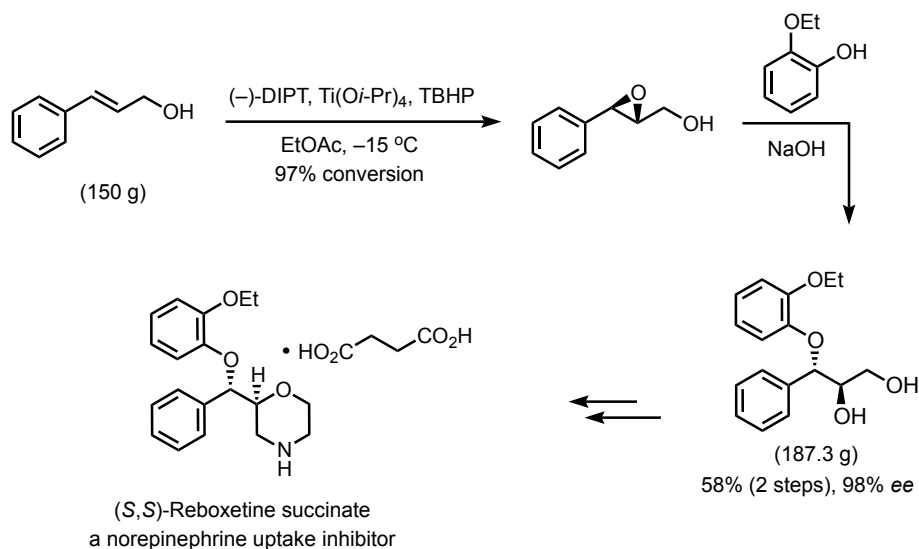  in AE of an allylic diol (no reaction with (–)-DIPT).

(+)-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.

M. Movassaghi

**Examples of the Sharpless Asymmetric Epoxidation Reaction in Industry:**



(150 g)

(–)-DIPT, Ti(O*i*-Pr)$_4$, TBHP
EtOAc, –15 °C
97% conversion

NaOH

(187.3 g)
58% (2 steps), 98% *ee*

(*S*,*S*)-Reboxetine succinate
a norepinephrine uptake inhibitor

• In this example, excess TBHP was quenched with triethylphosphite instead of Fe$^{II}$ sulfate.
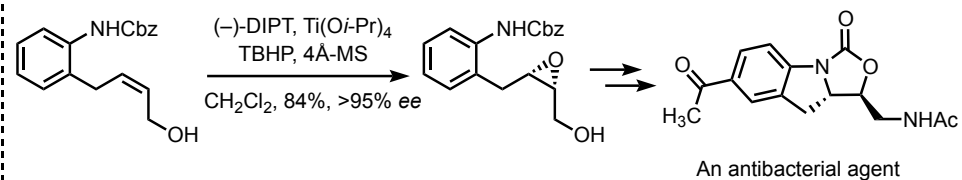
Henegar, K. E.; Cebula, M. *Org. Proc. Res. Dev.* **2007**, *11*, 354–358.

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



90% *ee*

(–)-DIPT, Ti(O*i*-Pr)$_4$
TBHP, 4Å-MS
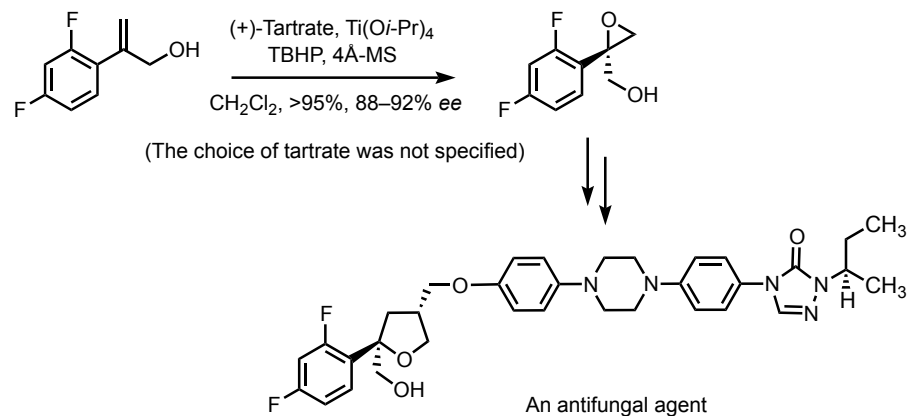CH$_2$Cl$_2$, –15 °C

95%, 98% *ee*

HIV-1 protease inhibitor
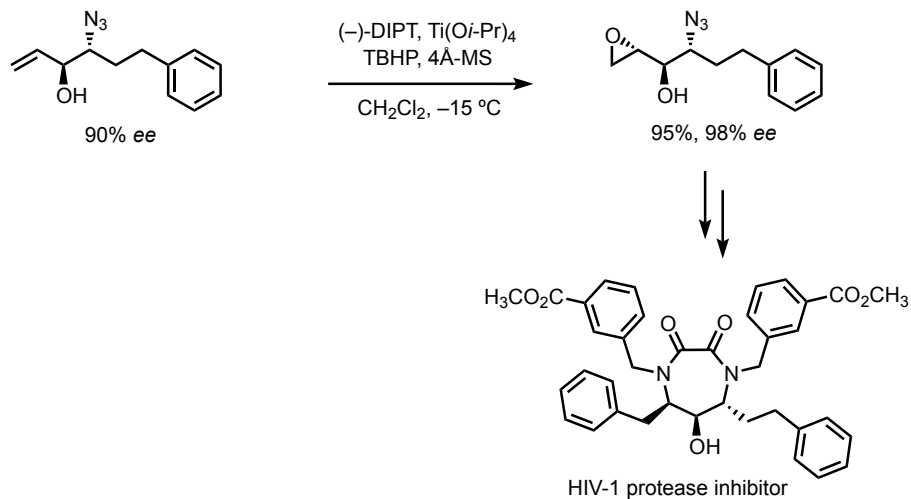
Jadhav, P. K.; Man, H. W. *Tetrahedron Lett.* **1996**, *37*, 1153–1156.

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



(–)-DIPT, Ti(O*i*-Pr)$_4$
TBHP, 4Å-MS
CH$_2$Cl$_2$, 84%, >95% *ee*

An antibacterial agent

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



(+)-Tartrate, Ti(O*i*-Pr)$_4$
TBHP, 4Å-MS
CH$_2$Cl$_2$, >95%, 88–92% *ee*

(The choice of tartrate was not specified)

An antifungal agent

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.



Geraniol

(–)-DET, Ti(O*i*-Pr)$_4$
TBHP, 4Å-MS
CH$_2$Cl$_2$, –10 → 20 °C
99%, 91% *ee*

*N*-Boc-(2*R*,3*R*)-3-methyl-3-hydroxypipecolic acid
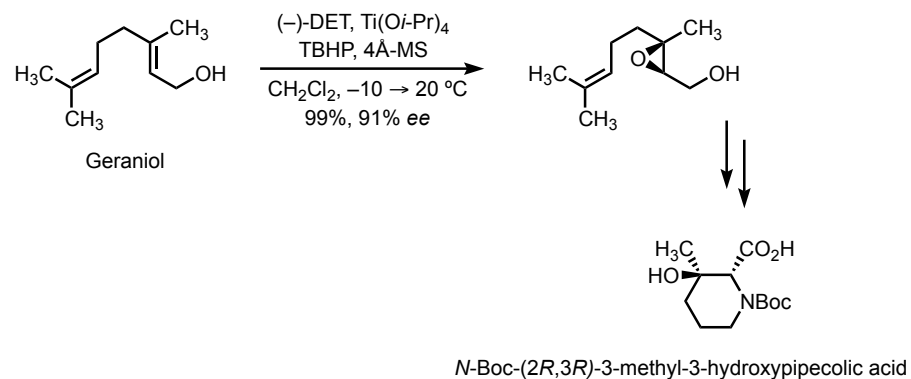
Noe, M. C.; Hawkins, J. M.; Snow, S. L.; Wolf-Gouveia, L. *J. Org. Chem.* **2008**, *73*, 3295–3298.

Jesse Teske, Andy Flick, Daniel Schmitt