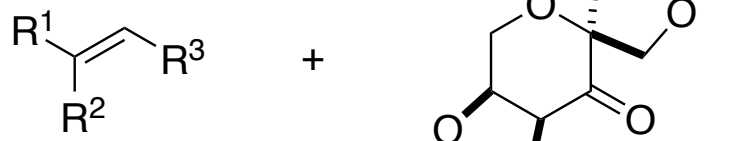
Shi Asymmetric Epoxidation

Shi, 1996
(Colorado State University)

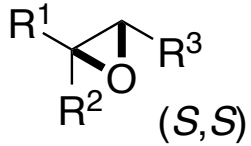


R^{1-3} = H, alkyl, aryl, alkenyl, alkynyl

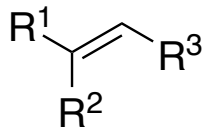
Shi's catalyst
(derived from L-fructose**)**

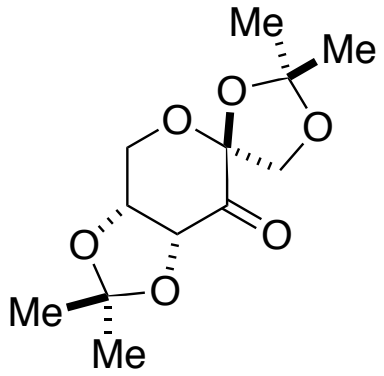
oxone,
inorganic base

H_2O, MeCN
-10 to 23 ºC
pH = ~7-10



(*S*,*S*)

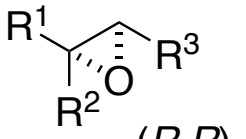




Shi's catalyst
(derived from D-fructose**)**

oxone,
inorganic base

H_2O, MeCN
-10 to 23 ºC
pH = ~7-10



(*R*,*R*)

enantiopure epoxide

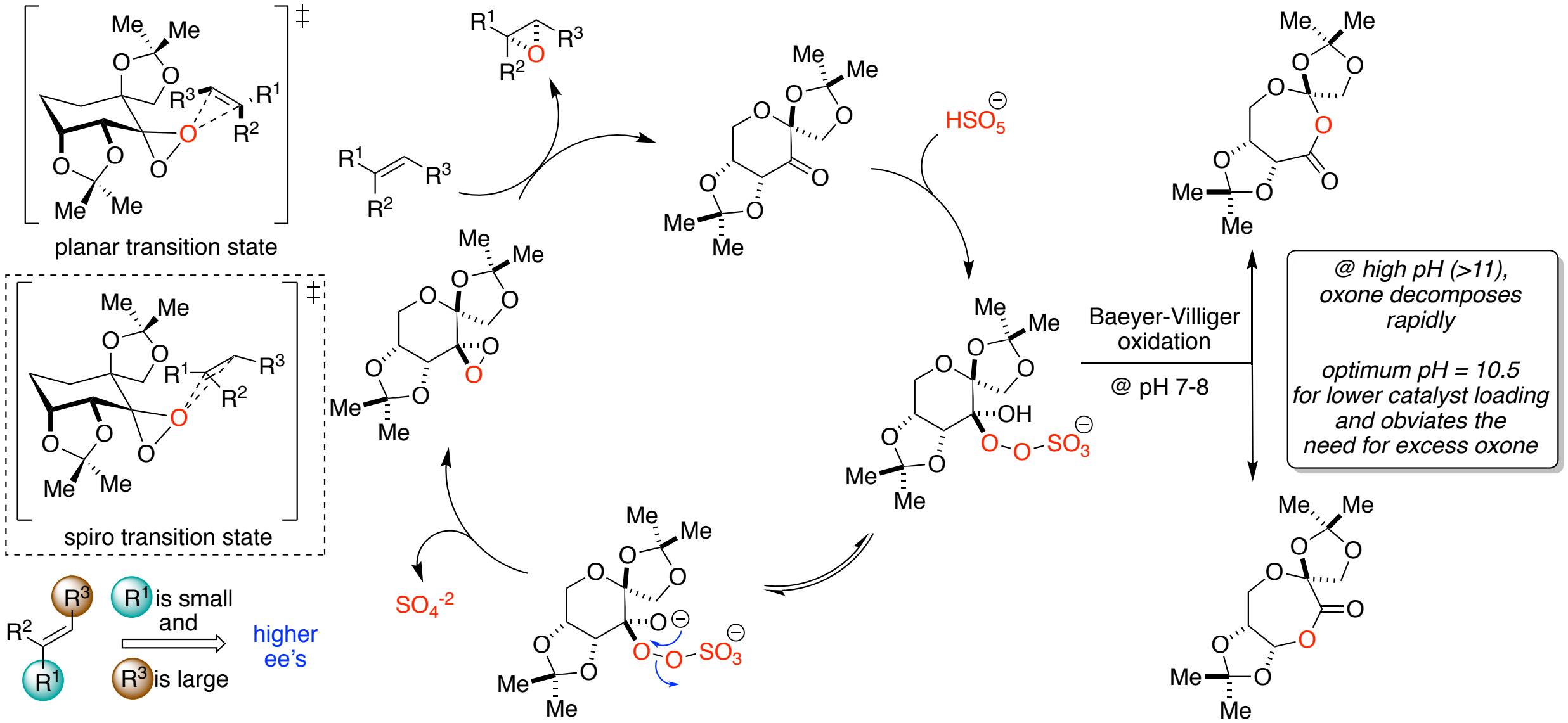
50-90% yield,
> 90% ee

catalyst loading = 20 mol% to excess equiv.

oxone =
$KHSO_5/KHSO_4/K_2SO_4$
(2:1:1)

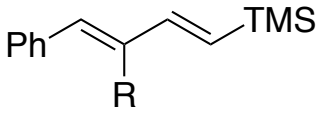
Tu, Y.; Wang, Z.-X.; Shi, Y., *J. Am. Chem. Soc.* **1996**, *118(40)*, 9806.

Mechanism of the Epoxidation



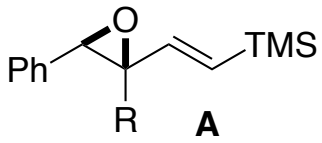
Wang, Z.-X.; *et al.*; Shi, Y., *J. Am. Chem. Soc.* **1997**, *119*, 11224.

Regioselectivity/Chemoselectivity

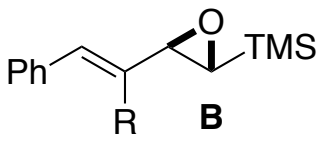


Shi's D-fructose-derived cat. (30 mol%), oxone, K_2CO_3

MeCN/DMM, pH ~ 9, 0 °C, 1.5h

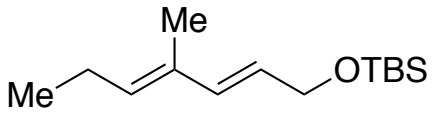


A +



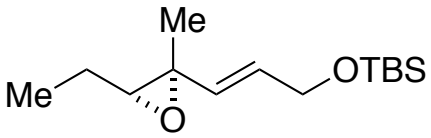
B

	yield (**A**)	ee (**A**)	ratio (**A**:**B**)
R = H	31%	95%	1:1
R = Me	77%	92%	14:1

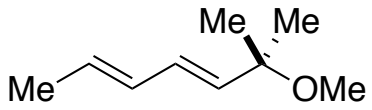


Shi's D-fructose-derived cat. (25 mol%), oxone, K_2CO_3

MeCN/DMM, pH ~ 9, 0 °C, 1.5h

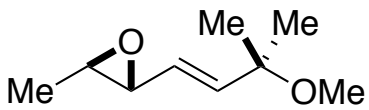


81% yield, 96% ee

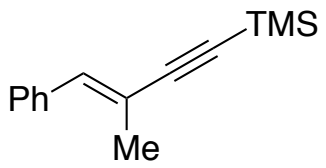


Shi's D-fructose-derived cat. (20 mol%), oxone, K_2CO_3

MeCN/DMM, pH ~ 9, 0 °C, 1.5h

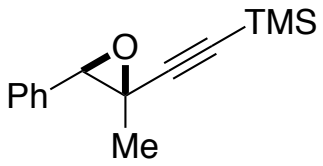


65% yield, 89%ee



Shi's D-fructose-derived cat. (30 mol%), oxone, K_2CO_3

MeCN/DMM, pH ~ 9, 0 °C, 2h



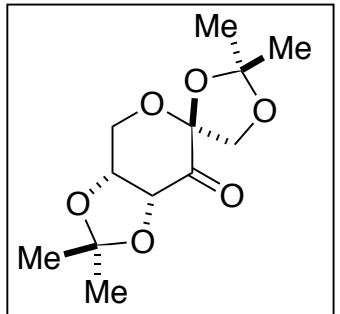
64% yield, 94% ee

Regioselectivity/ Chemoselectivity

tri-substituted alkenes over di-substituted

more electron-rich/less sterically hindered alkenes

alkenes over alkynes in enyne systems



Shi's D-fructose-derived catalyst

Functional Group Sensitivity

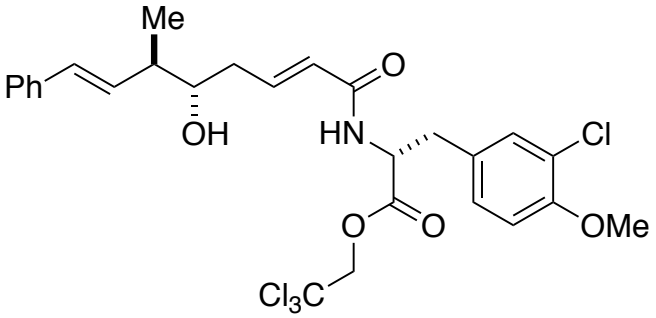
most functional groups tolerated

free amines shut down the reaction

Frohn, M.; *et al.;* Shi, Y., *J. Org. Chem.* **1998**, *63*, 2948.; Wang, Z.-X., *et al.*; Shi, Y., *J. Org. Chem.* **1999**, *64*, 7646.

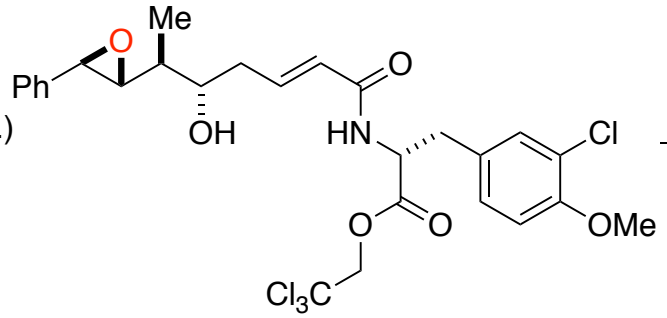
Use with Complex Substrates

Moher, 2002
(Eli Lilly)



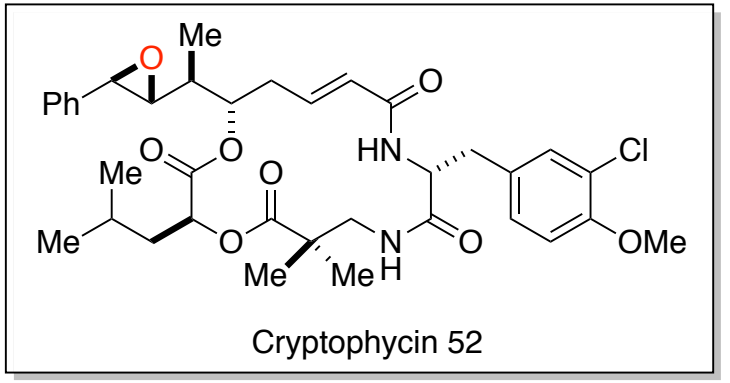
Shi's D-fructose-derived-cat. (2 equiv.)

oxone, K_2CO_3, MeCN, pH ~ 10.5



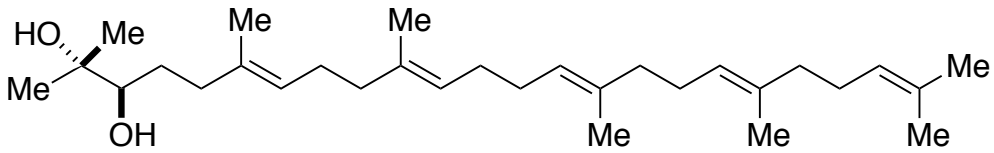
95% yield, 6.5:1 d.r.

2 steps



Cryptophycin 52

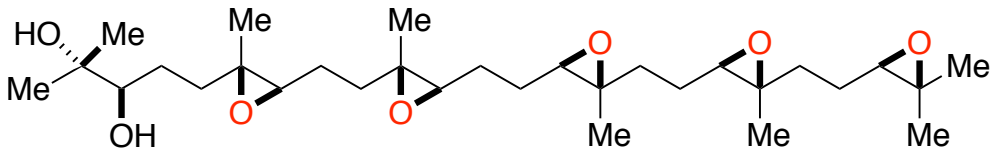
Corey, 2000
(Harvard)



(1 step from squalene)

Shi's D-fructose-derived-cat. (1.5 equiv.)

oxone, DMM/MeCN/H_2O, pH = 10.5, 0 °C, 1.5h

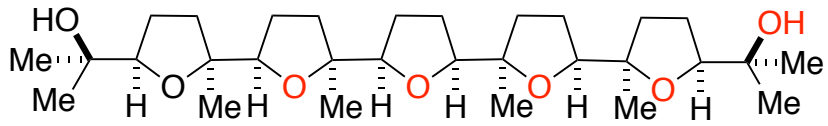


R/*S* selectivity >20:1

CSA, toluene

0 °C, 1h

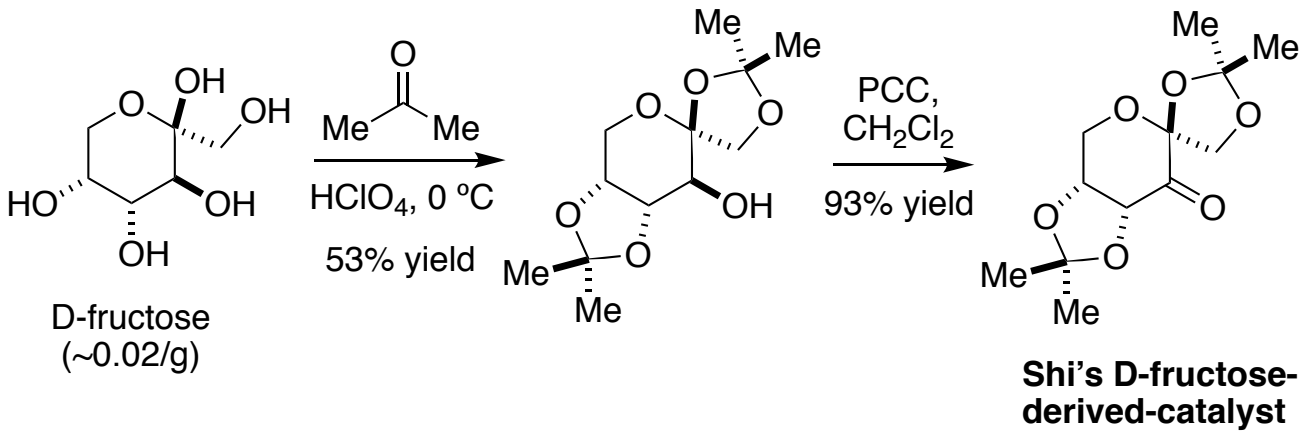
31% (2 steps)

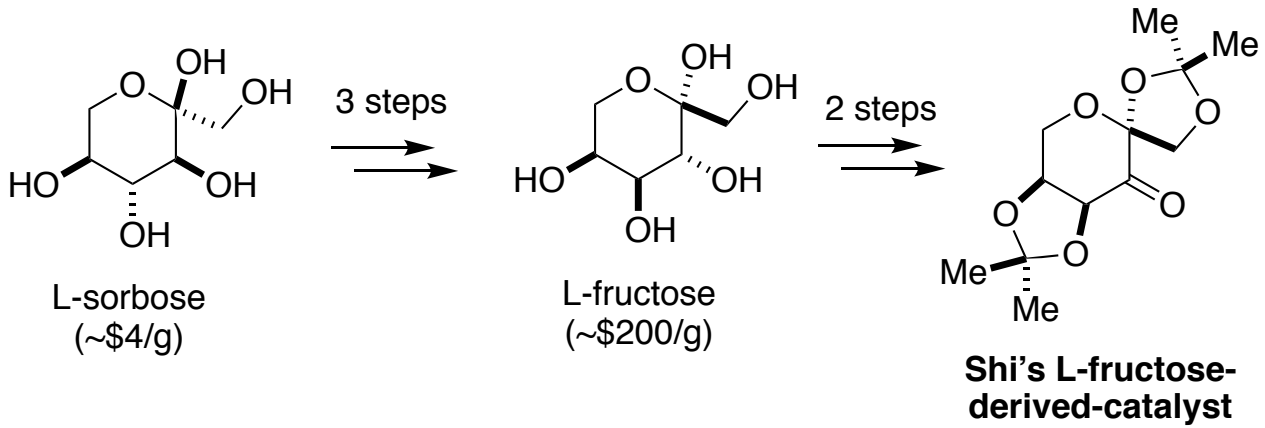


Glabrescol (originally proposed structure)

Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. Org. Lett. 2002, 4, 1813–1815.; Xiong, Z.; Corey, E. J. J. Am. Chem. Soc. 2000, 122, 4831–4832.

Synthesis of Shi's Fructose-Catalyst





Tu, Y.; Wang, Z.-X.; Shi, Y., *J. Am. Chem. Soc.* **1996**, *118(40)*, 9806; Zhao, M.-X.; Shi, Y., *J. Org. Chem.* **2006**, *71*, 5377.