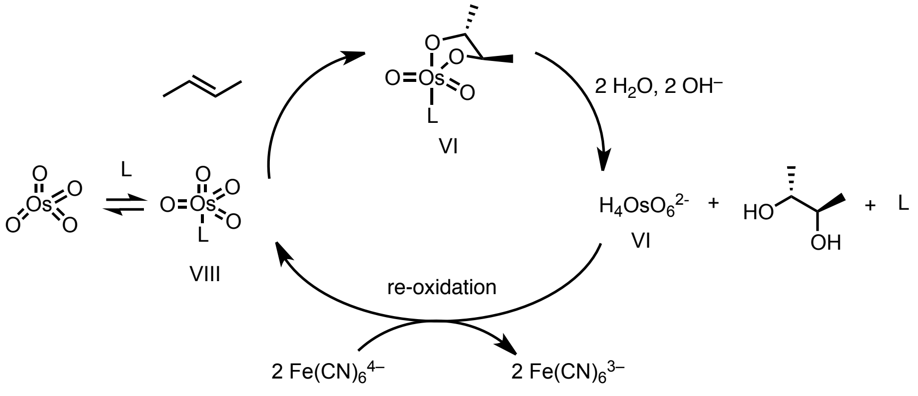
Reviews:

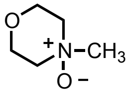
Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
Noe, M. C.; Letavic, M. A.; Snow, S. L.; McCombie, S. W. *Org. React.* **2005***, 66*, 109–626.

Ligands such as pyridine accelerate the osmylation of olefins (Criegee, R.; Marchand, B.; Wannowius, H. *Liebigs Ann. Chem.* **1942**, *550*, 99-133.)

Catalytic Cycle:



Turnover is achieved by reoxidation with stoichiometric oxidants:

NMO =


UpJohn Process: VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.

$K_3Fe(CN)_6$ Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766–768.

In the original Sharpless procedure using NMO, reoxidation was believed to compete with hydrolysis, leading to a ligand-less "second cycle" olefin dihydroxylation that was non-enantioselective:

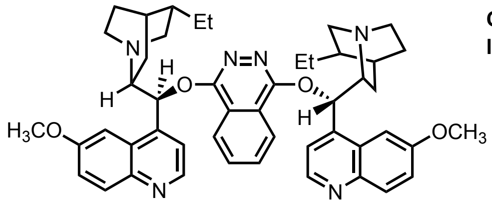
Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965-3968.

Balance of evidence favors 3+2 cycloaddition (vs. 2+2/rearrangement) mechanism between osmium and olefin.

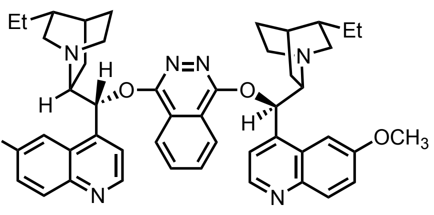
See, e.g., Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1996**, *37*, 4899-4902.

DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*,9907–9908.

C_2-symmetric, pseudo-enantiomeric ligands:



$(DHQD)_2$-PHAL
ligand for AD-mix-β



$(DHQ)_2$-PHAL
ligand for AD-mix-α
(slightly less
enantioselective)

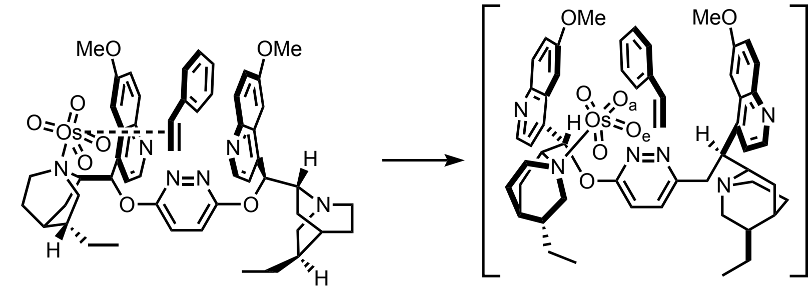
AD-mix reagents are commercially available:

1.4 g AD-mix-β will oxidize 1 mmol olefin, contains:
0.98 g $K_3Fe(CN)_6$ (3 mmol)
0.41 g K_2CO_3 (3 mmol)
0.0078 g $(DHQD)_2$-PHAL (0.01 mmol)
0.00074 g $K_2OsO_2(OH)_4$ (0.002 mmol)

Conditions: *t*-BuOH, H_2O (1:1), 0 °C, 6-24 h
Typical work-up: Na_2SO_3 then extraction

Sharpless, K. B., et al. *J. Org. Chem.* **1992**, *57*, 2768–2771.

Corey proposes a U-shaped binding pocket:



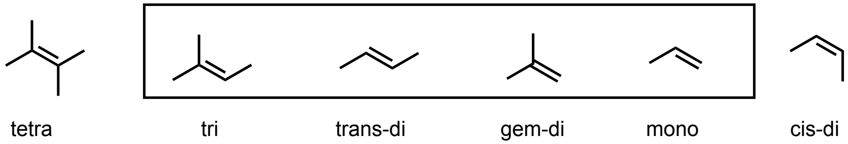
Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481–3484.

For ligand modifications and improvements based on binding model, see:

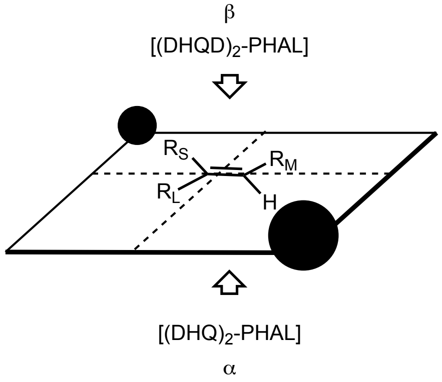
Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427–6430.
Huang, J.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3455–3458.

Sharpless Asymmetric Dihydroxylation Reaction

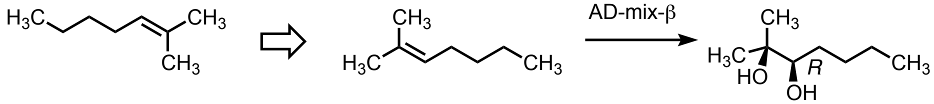
4 of 6 Olefin substitution classes are successfully dihydroxylated:

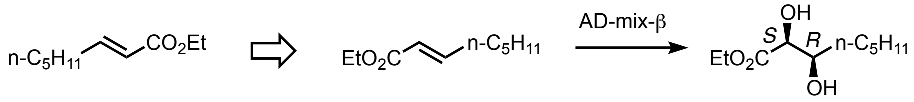


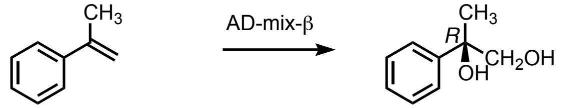
Mnemonic:

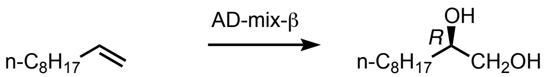


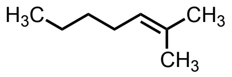
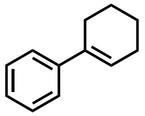
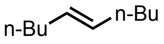
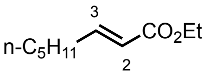
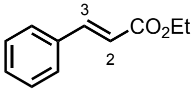
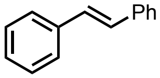
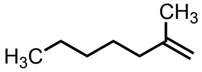
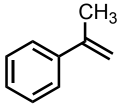
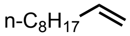
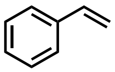
Application of Mnemonic:









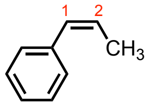
		AD-mix-β [(DHQD)$_2$-PHAL] % ee, config.	AD-mix-α [(DHQ)$_2$-PHAL] % ee, config.
	*	98, *R*	95, *S*
	*	99, *R, R*	97, *S, S*
	*	97, *R, R*	93, *S, S*
	*	99, 2*S, 3R*	96, *2R, 3S*
	*	97, *2S, 3R*	95, *2R, 3S*
	*	>99.5, *R, R*	>99.5, *S, S*
		78, *R*	76, *S*
		94, *R*	93, *S*
		84, *R*	80, *S*
		97, *R*	97, *S*

* addition of $CH_3SO_2NH_2$ (a phase-transfer and general acid catalyst) leads to faster reactions for non-terminal olefins

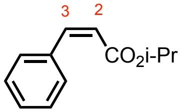
Sharpless, K. B., et al. *J. Org. Chem.* **1992**, *57*, 2768–2771.

Cis-disubstituted olefins are generally poor substrates. With a modified catalyst, DHQD-IND, fair to good enantioselectivities can be obtained:

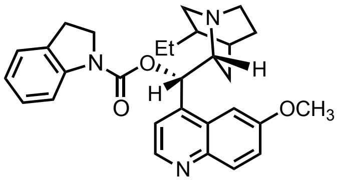
ee at 0 °C



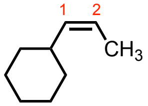
72, (1*R*, 2*S*)



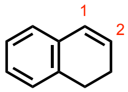
80, (2*R*, 3*S*)



DHQD-IND



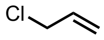
56, (1*R*, 2*S*); 44% ee of the enantiomer obtained with DHQ-IND



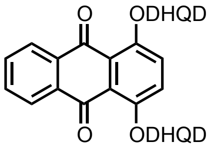
16, (1*R*, 2*S*)

Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568–7570.

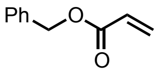
(DHQD)$_2$AQN is often a superior ligand:



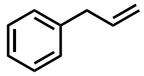
90% ee vs. 63% ee, (DHQD)$_2$PHAL



(DHQD)$_2$AQN



88% ee vs. 77% ee, (DHQD)$_2$PHAL

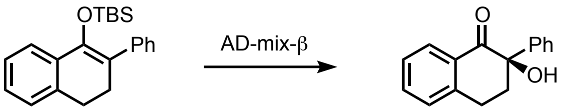


78% ee vs. 44% ee, (DHQD)$_2$PHAL

Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448–451.

A few tetra-substituted olefins work well:

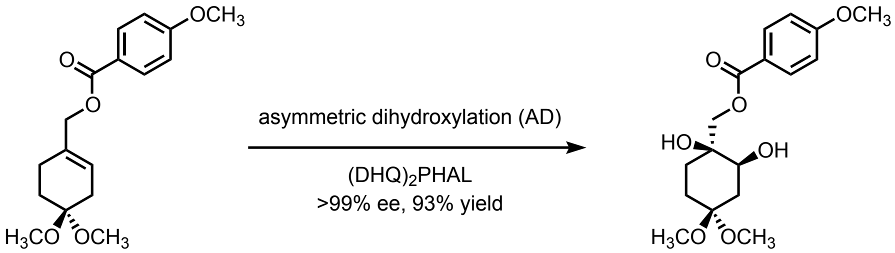
Sharpless, K. B., et al. *J. Am. Chem. Soc.* **1993***, 115*, 8463-8464



93% ee, 94% yield

a best case; ee's and yields are not generally high

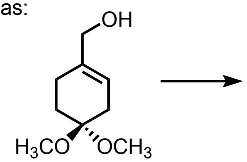
Allylic 4-methoxybenzoates are particularly good substrates:



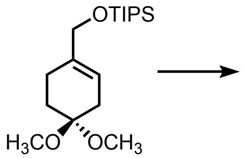
asymmetric dihydroxylation (AD)

(DHQ)$_2$PHAL
>99% ee, 93% yield

whereas:

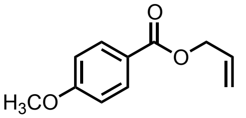


18% ee

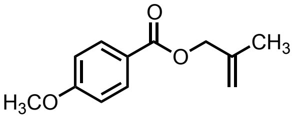


13% ee

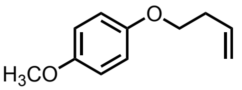
AD, (DHQD)$_2$PYDZ



>99% yield, 98% ee

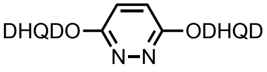


98% yield, 97% ee



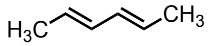
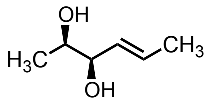
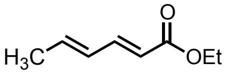
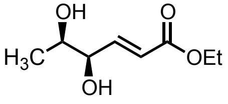
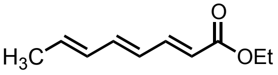
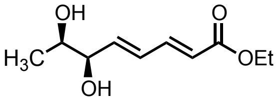
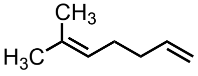
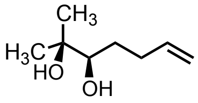
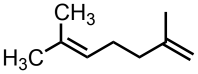
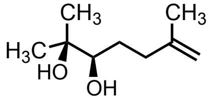
96% yield, 91% ee

(DHQD)$_2$PYDZ =



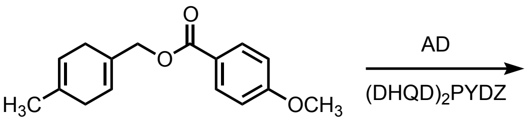
Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805–10816.

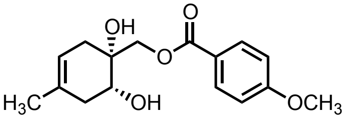
Regioselectivity of AD with diene substrates ((DHQD)$_2$PHAL as ligand)**:**

Substrate	Product	% yield, % ee
		78, 93
		78, 92
		93, 95
		73, 98
		70, 98

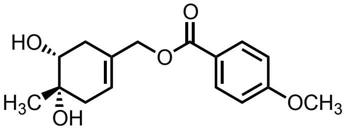
in general, AD is selective for the more electron-rich double bond

Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571.





A 56% yield, >99% ee

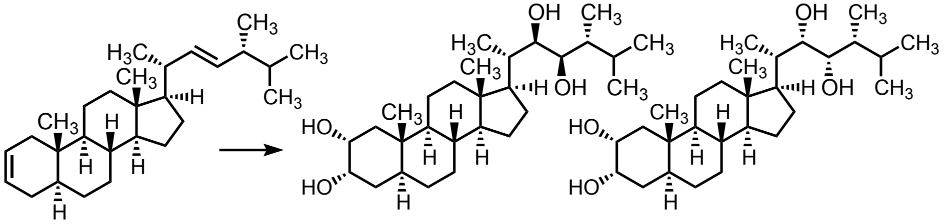


B 10% yield, >96% ee

with ligand (as shown): **A**:**B** = ~6:1
without ligand, only OsO$_4$/NMO: **A**:**B** ≤1:10

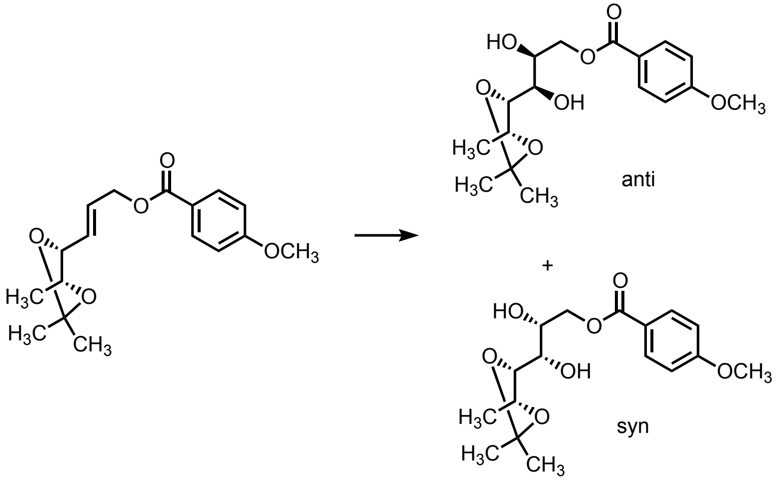
Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805–10816.

Use of AD with chiral olefins:



OsO$_4$ alone	1 : 1.6
(DHQD)$_2$-PHAL	10 : 1

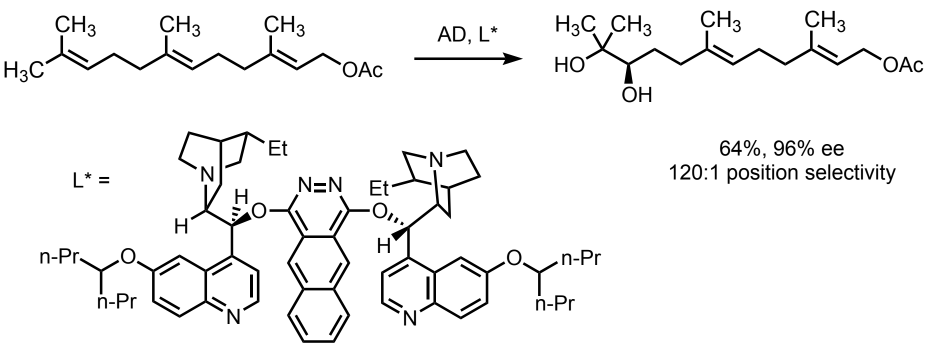
Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547, and refs. therein.



Conditions		anti : syn
OsO$_4$, NMO	88% yield (mixture)	1.9 : 1
(DHQ)$_2$PHAL (matched)	86% yield (anti)	54 : 1
(DHQD)$_2$PYDZ (mismatched)	86% yield (syn)	1 : 35

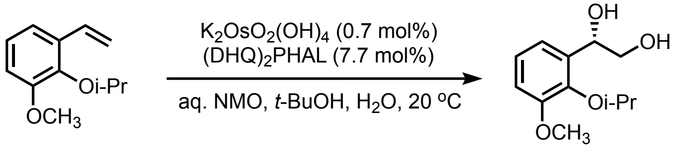
Guzman-Perez, A.; Corey, E. J. *Tetrahedron Lett.* **1997**, *38*, 5941–5944.

Regioselective AD of terminal olefin of oligoprenyl derivatives:



64%, 96% ee
120:1 position selectivity

Examples in Industry

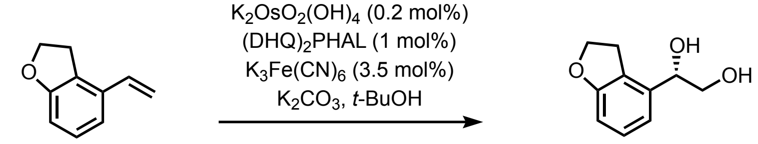


2.5 kg, 13 mol

2.5 kg (94% pure)
90% ee

- Olefin was added over a period of 6.5 h to the reaction mixture to prevent "second cycle" oxidation.

Ahrgren, L.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425–427.

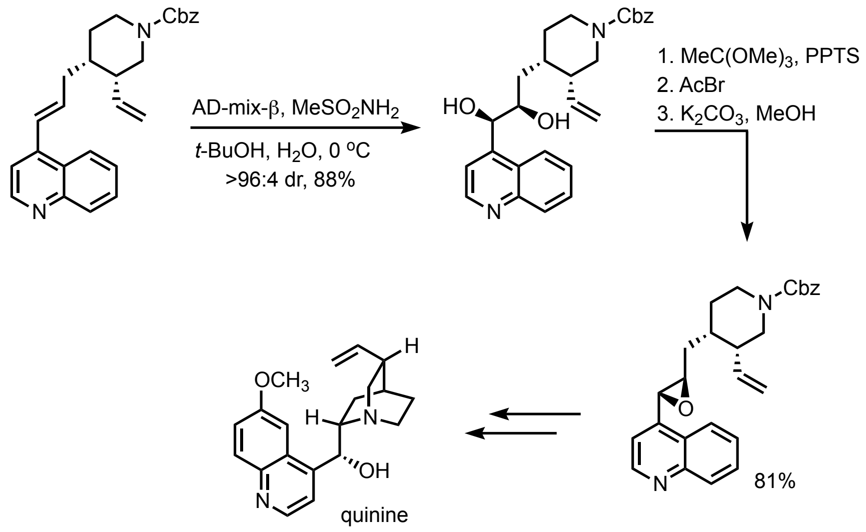


15.38 kg, 105.2 mol
in 5% MTBE/*t*-BuOH

16.2 kg (98.4% pure)
99.4% ee

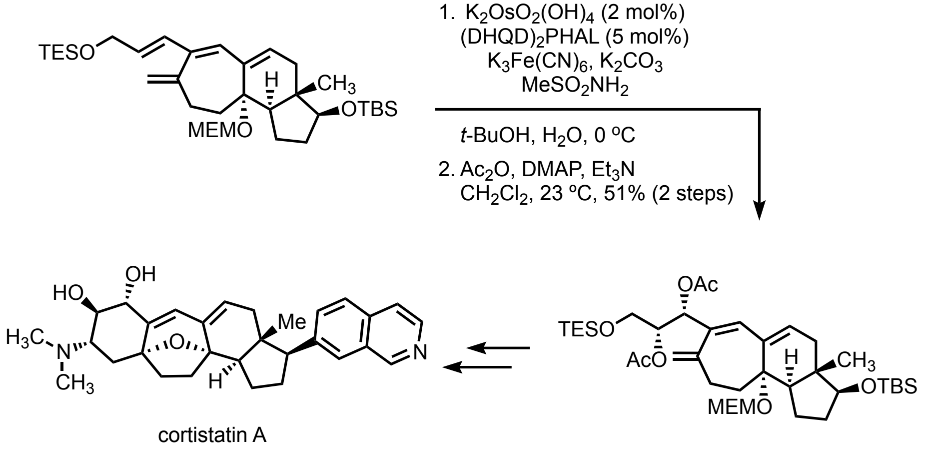
Prasad, J. S; Vu, T.; Totleben, M. J.; Crispino, G. A.; Kacsur, D. J.; Swaminathan, S.; Thornton, J. E.; Fritz, A.; Singh, A. K. *Org. Process Res. Dev.* **2003**, *7*, 821–827.

Examples in Syntheses of Natural Products:



Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706–707.

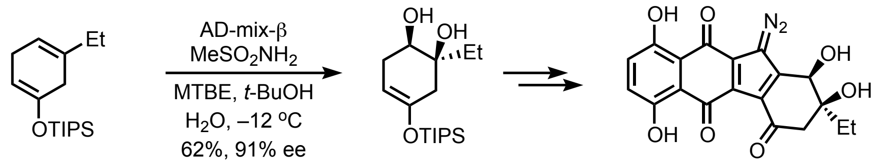
For conversion of diol to epoxide, see Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.



Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.

Adam Kamlet

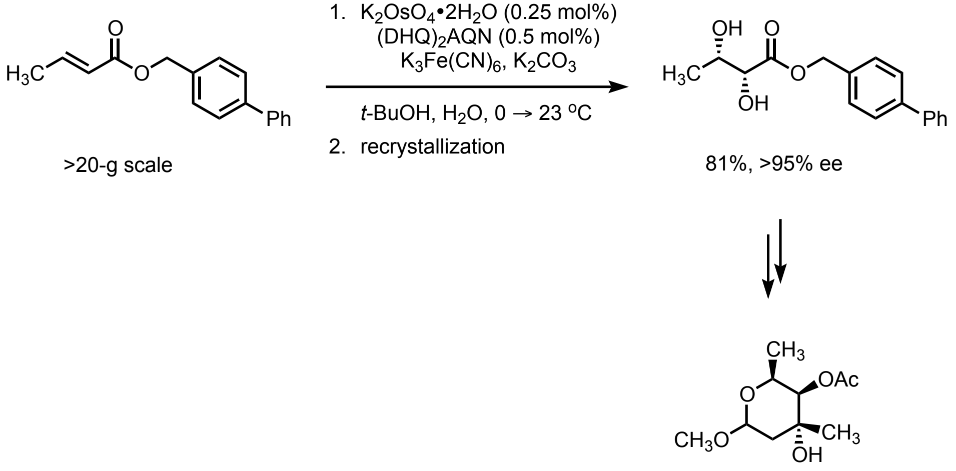
- In the example below, use of the triisopropylsilyl protecting group was crucial to achieve regioselectivity:



(–)-monomeric lomaiviticin aglycon

Woo, C. M.; Gholap, S. L.; Lu, L.; Kaneko, M; Li, Z.; Ravikumar, P. C.; Herzon, S. B. *J. Am. Chem. Soc.* **2012**, *134*, 17262–17273.

- In the example below, a 4-phenylbenzyl ester was incorporated to serve as an expedient for purification and enantioenrichment by re-crystallization:



methyl trioxacarcinoside A

Smaltz, D. J.; Myers, A. G. *J. Org. Chem.* **2011**, *76*, 8554–8559.
Smaltz, D. J.; Svenda, J.; Myers, A. G.; *Org. Lett.* **2012**, *14*, 1812–1815.