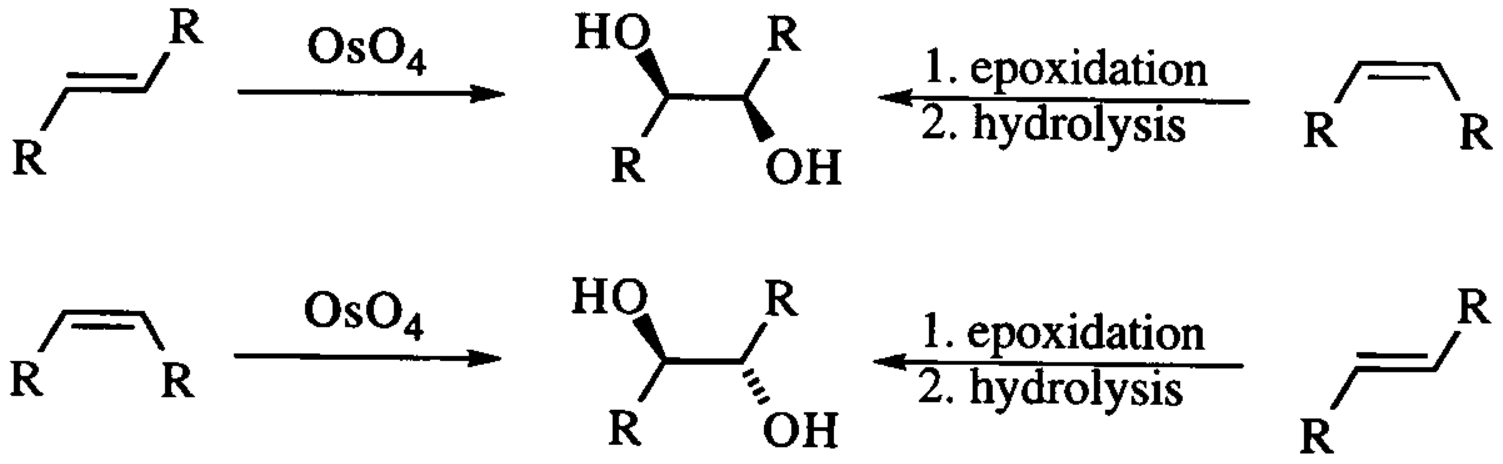
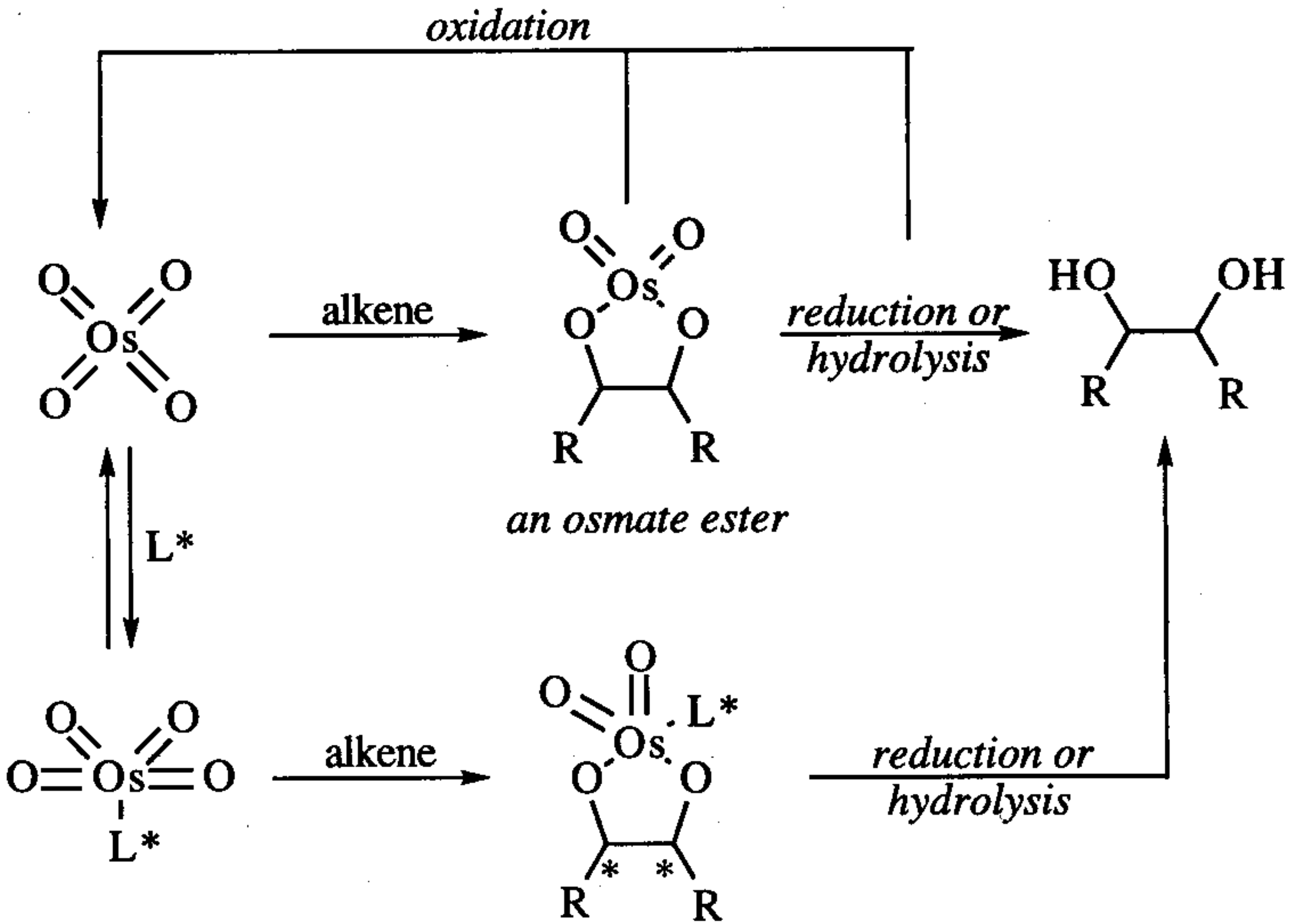
Diidrossilazioni con OsO_4
Reazione stereospecifica

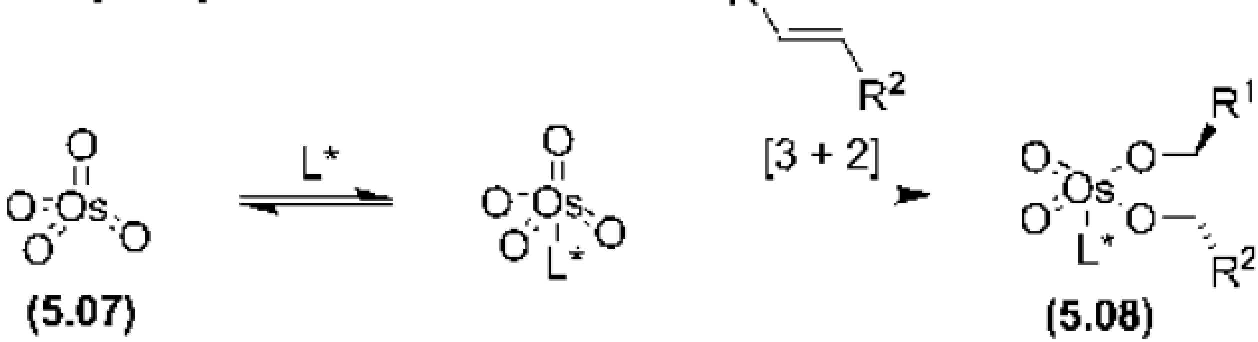


Diidrossilazioni con OsO_4 - Meccanismo

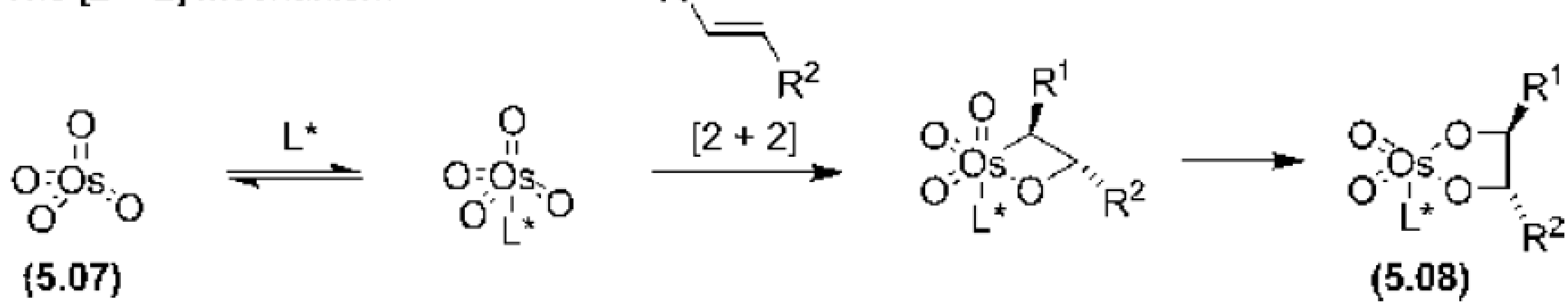


Diidrossilazioni con OsO_4 - Meccanismo

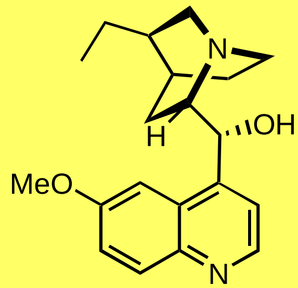
The [3 + 2] mechanism

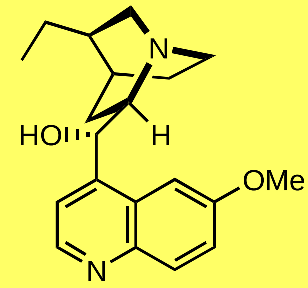


The [2 + 2] mechanism



ALCALOIDI DELLA CINCONA

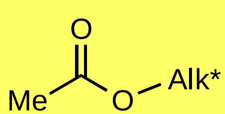




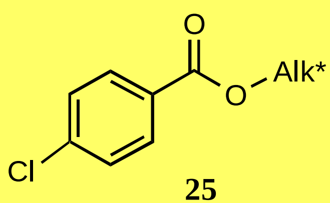
Diidrochinina (DHQ) **Diidrochinidina (DHQD)**

pseudo enantiomeri

LEGANTI CHIRALI - PRIMA GENERAZIONE



24



25

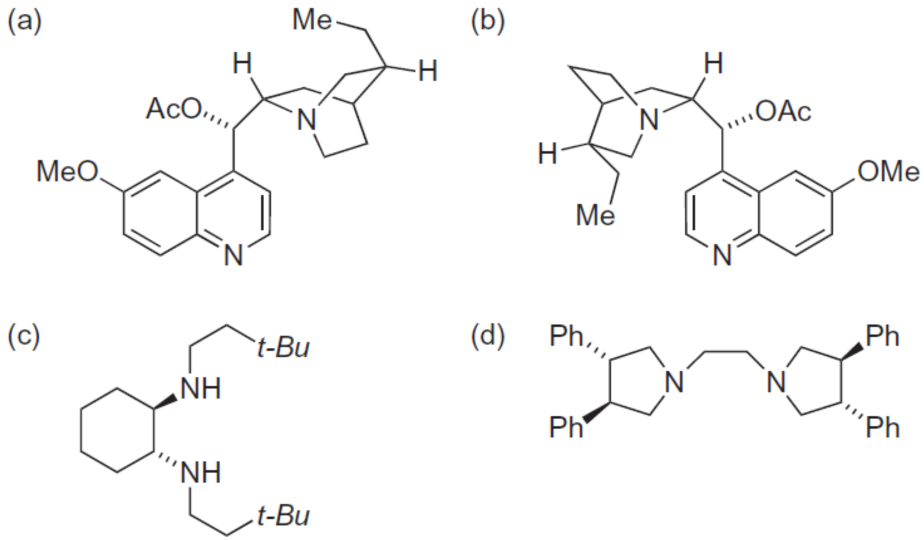
24a Alk*=DHQ
24b Alk*=DHQD

25a Alk*=DHQ
25b Alk*=DHQD

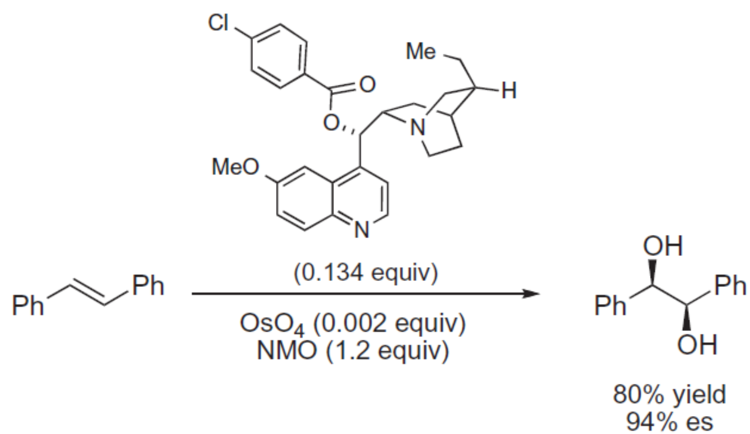
AD stechiometrica
(*J. Am. Chem. Soc.* **1980**, *102*, 4263)

AD catalitica
(*J. Am. Chem. Soc.* **1989**, *111*, 737 e 1123)

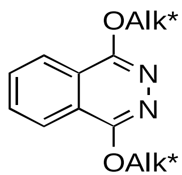
Diidrossilazioni Stereoselettiva con OsO_4 – Leganti chirali per reazione stechiometrica e catalitica



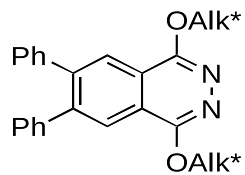
Processo Catalitico:
ossidante primario:
N-metil-morfolina-N-ossido



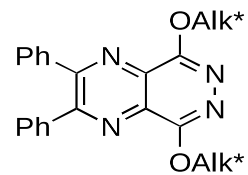
LEGANTI CHIRALI - SECONDA GENERAZIONE



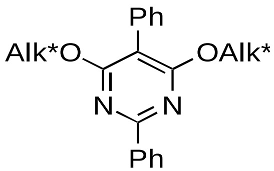
26 (PHAL)



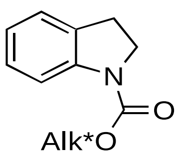
27 (DP-PHAL)



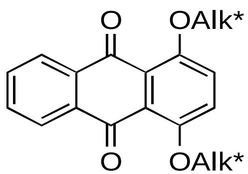
28 (DPP)



29 (PYR)

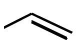
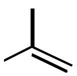
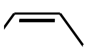
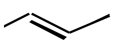
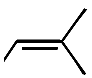
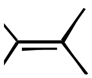


30 (IND)

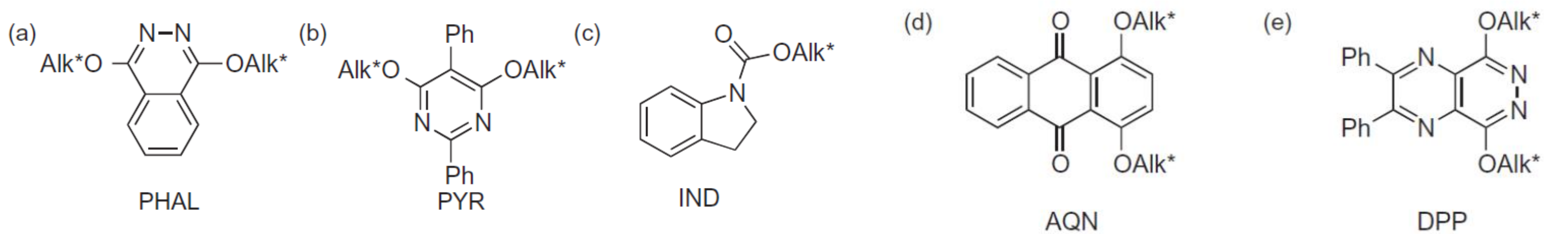


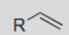
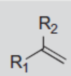
31 (AQN)

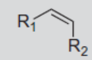
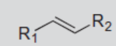
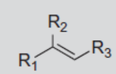
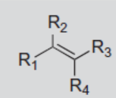
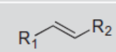
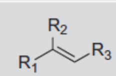
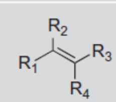
26-31a Alk*=DHQ
26-31b Alk*=DHQD

Olefina						
Legante Migliore	AQN PYR PHAL	AQN DQ-PHAL PHAL	IND	AQN PHAL	PHAL	PHAL PYR
ee, %	80-97	70-99	20-80	90-99.8	90-99	20-97

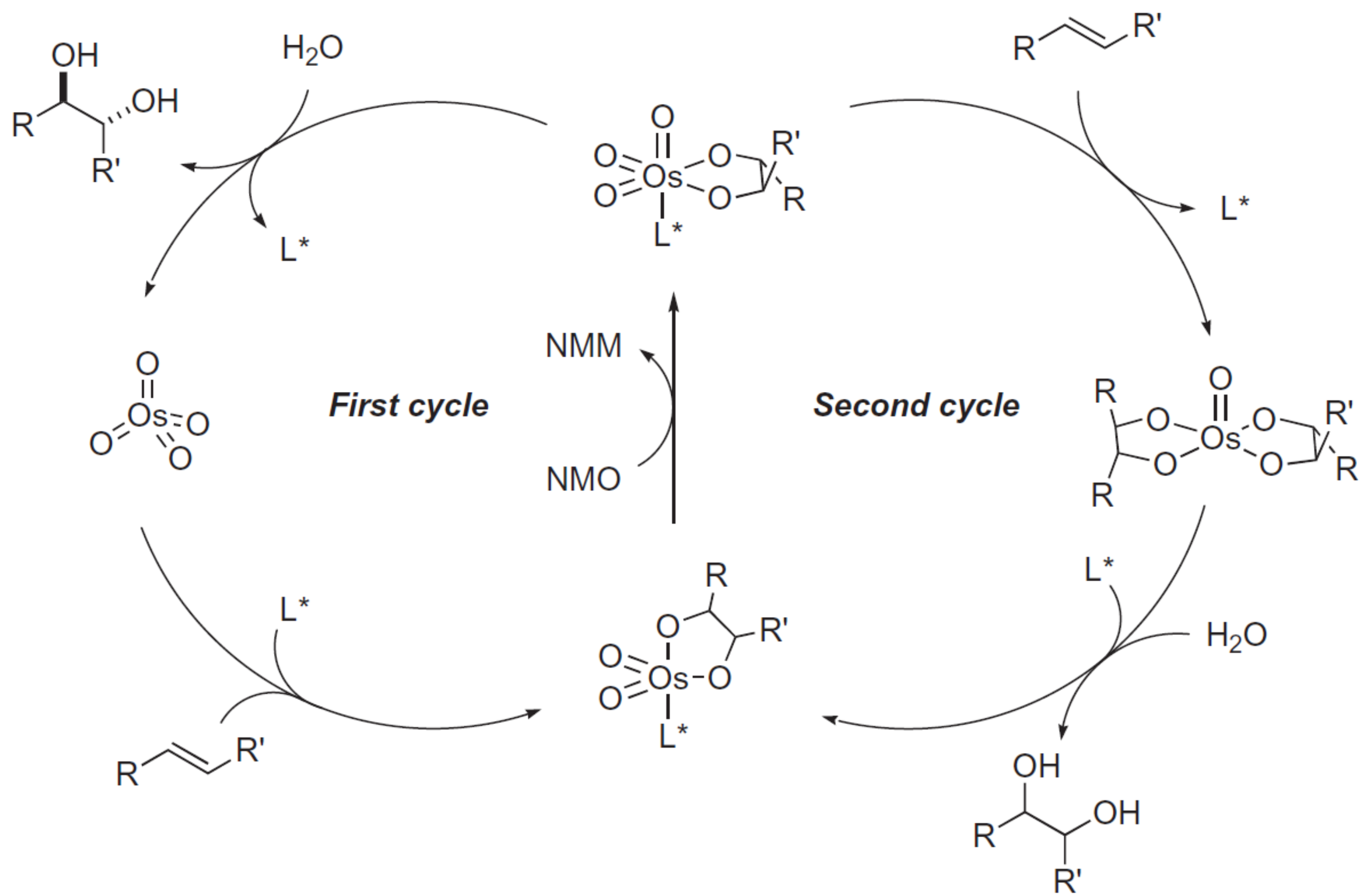
Leganti seconda generazione



	PHAL	PYR	IND	AQN	DPP
					
aromatic	X				X
aliphatic				X	
branched		X			
					
aromatic	X				X
aliphatic				X	
branched		X			

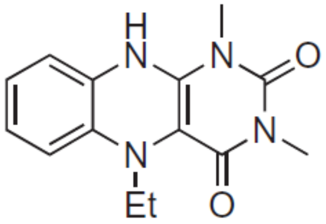
	PHAL	PYR	IND	AQN	DPP
					
acylic			X		
cyclic		X		X	X
					
aromatic	X				X
aliphatic				X	
	X			X	X
	X	X			
					
aromatic	X			X	X
aliphatic				X	
	X			X	X
	X	X			

Ciclo catalitico – Ossidazione con NMO

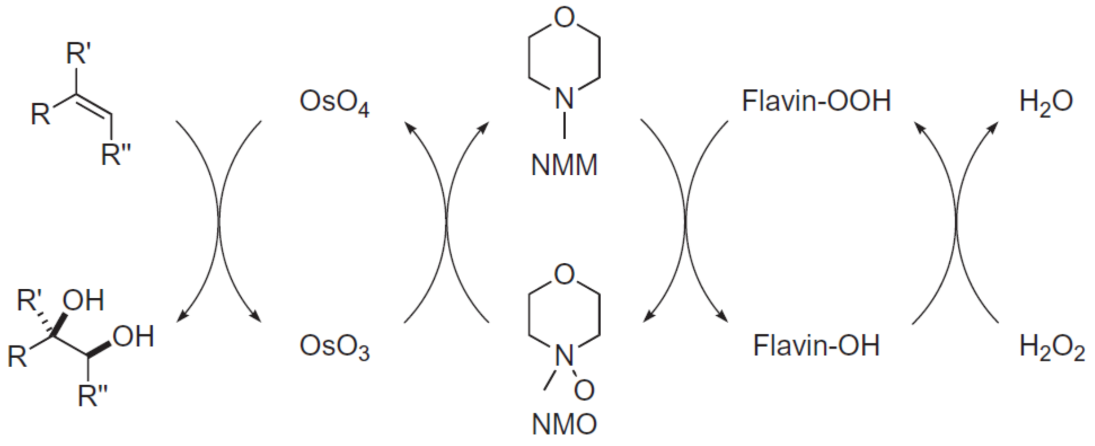


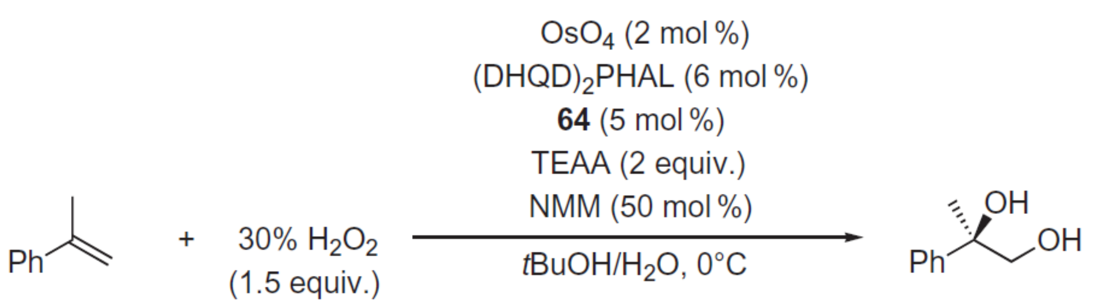
Sharpless, K.B. *et al.* *Tetrahedron Lett.*, **1990**, *31*, 2999 e **1991**, *32*, 3965

Diidrossilazioni con OsO_4 – Ossidazione con acqua ossigenata



Flavin **64**

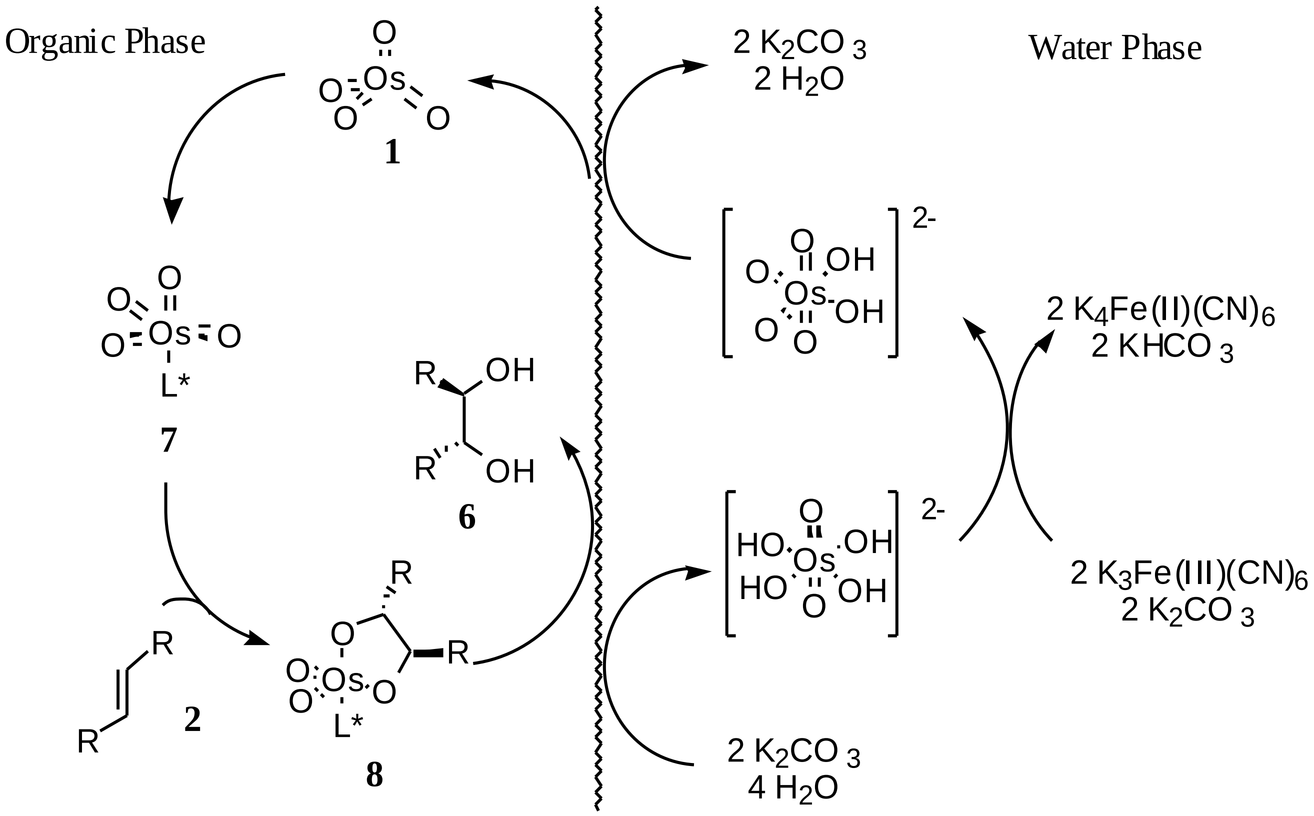




88%, 99% ee

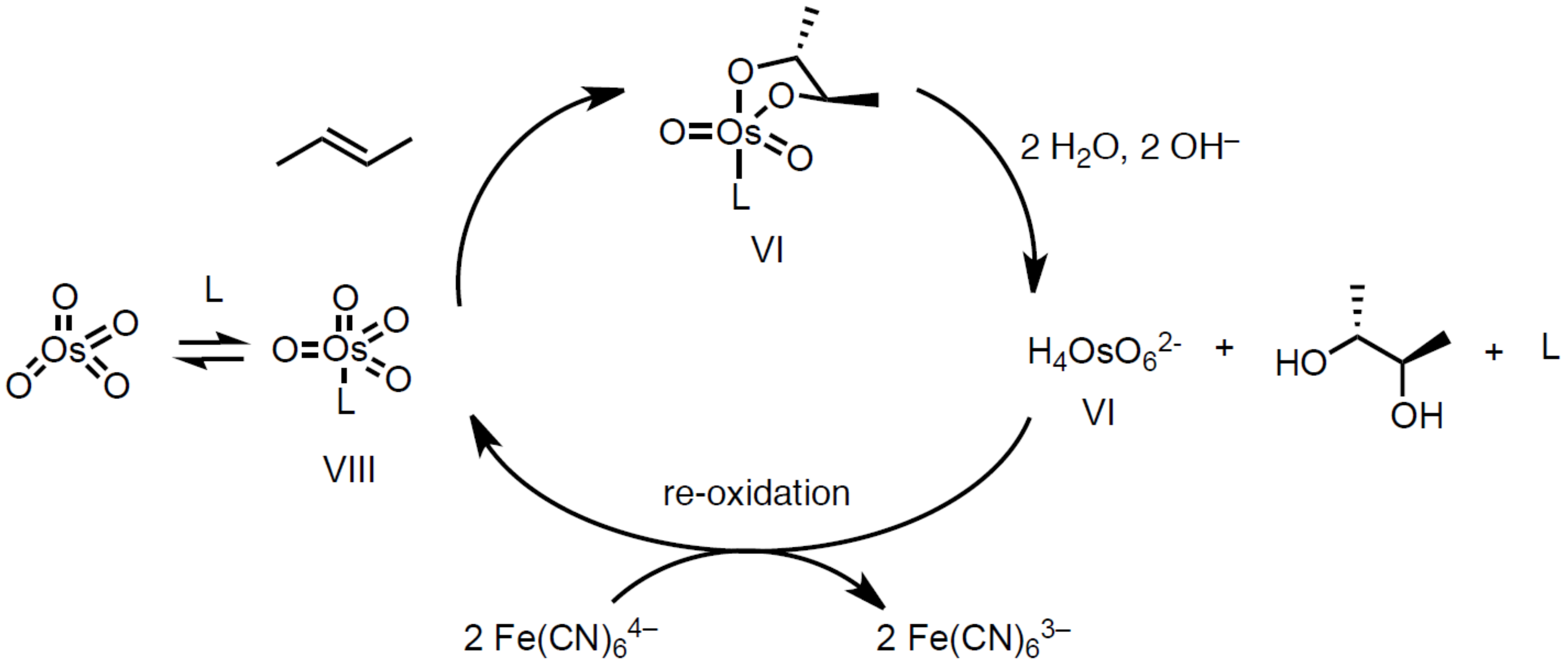
(a) Bergstad, K.; Jonsson, S. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 10424–10425.
(b) Jonsson, S. Y.; Färnegårdh, K.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2001**, *123*, 1365–1371.

Ciclo catalitico - $K_2Fe(CN)_6/K_2CO_3$



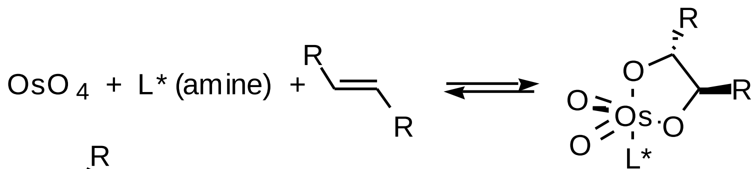
Sharpless, K.B. *et al. Tetrahedron Lett.*, **1990**, *31*, 2999 e **1991**, *32*, 3965

Ciclo catalitico - $K_2Fe(CN)_6/K_2CO_3$

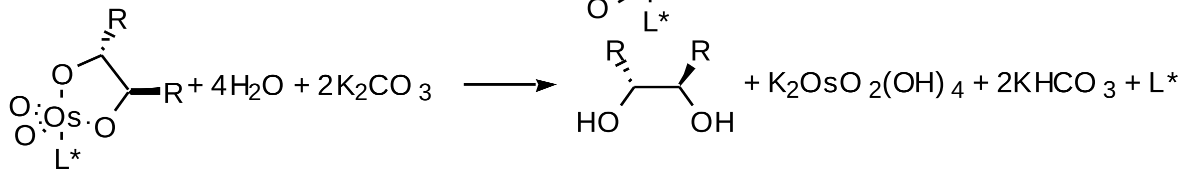


Sharpless, K.B. *et al. Tetrahedron Lett.*, **1990**, *31*, 2999 e **1991**, *32*, 3965

Stechiometria reazione



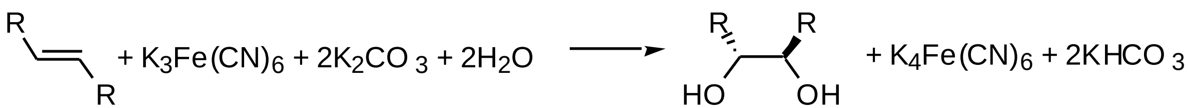
(11)



(12)

$$K_2OsO_2(OH)_4 + K_3Fe(CN)_6 + 2K_2CO_3 \longrightarrow K_2OsO_4(OH)_2 + K_4Fe(CN)_6 + 2KHCO_3 \quad (13)$$

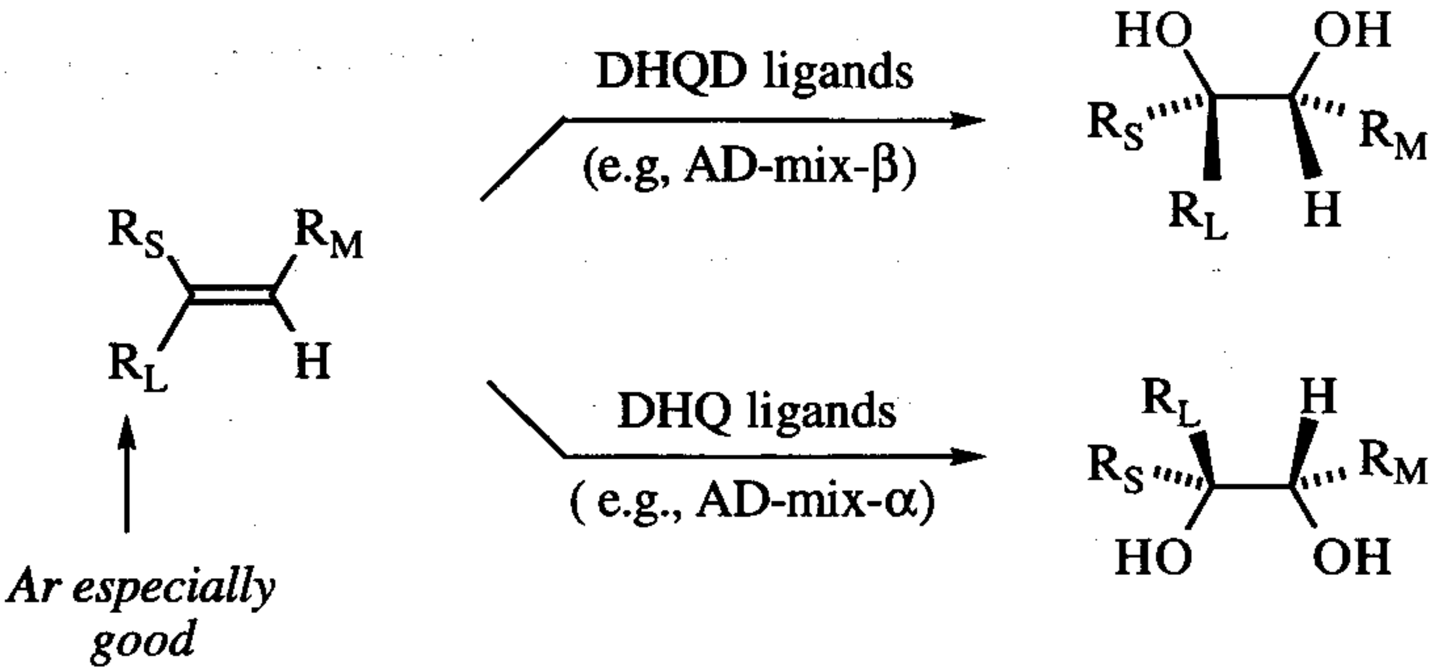
$$K_2OsO_4(OH)_2 + 2KHCO_3 \rightleftharpoons OsO_4 + 2K_2CO_3 + 2H_2O \quad (14)$$



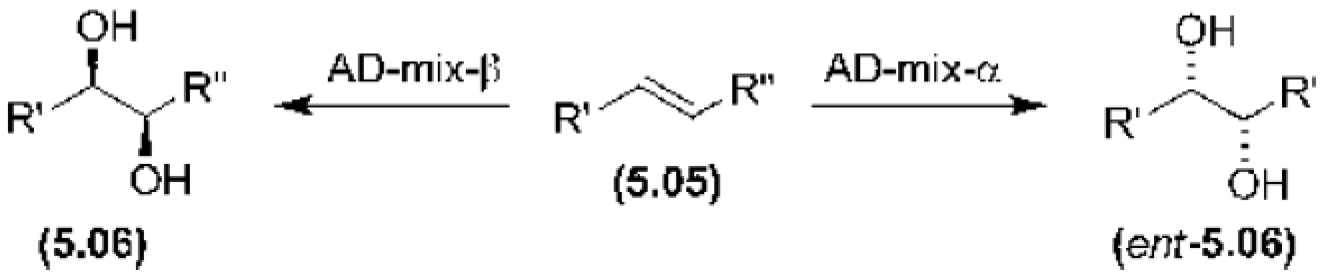
(15)

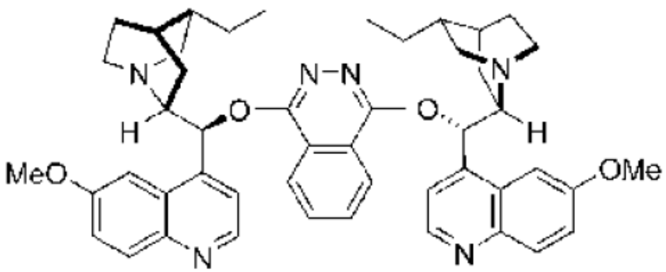
Sharpless, K.B. *et al. Tetrahedron Lett.*, **1990**, *31*, 2999 e **1991**, *32*, 3965

AD-mix: alfa e beta

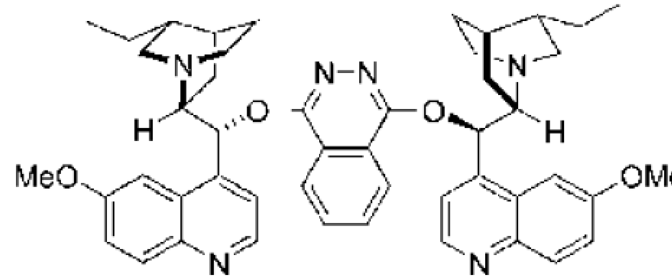


AD-mix-α e AD-mix-β



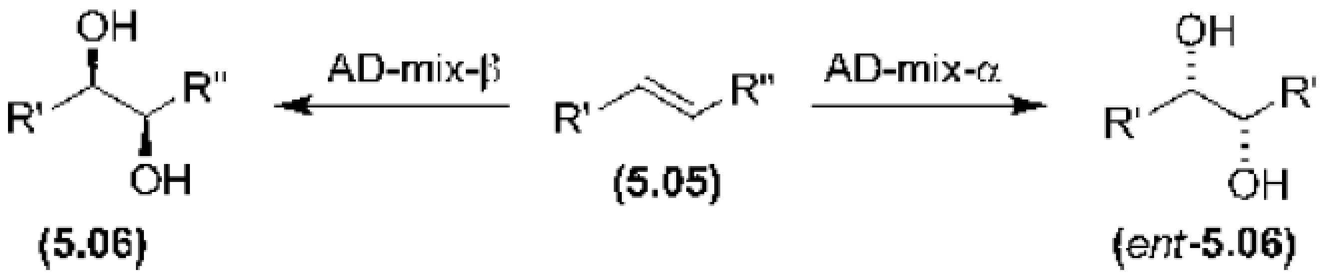


(5.03) (DHQD)$_2$PHAL



(5.04) (DHQ)$_2$PHAL

AD-mix-α e AD-mix-β



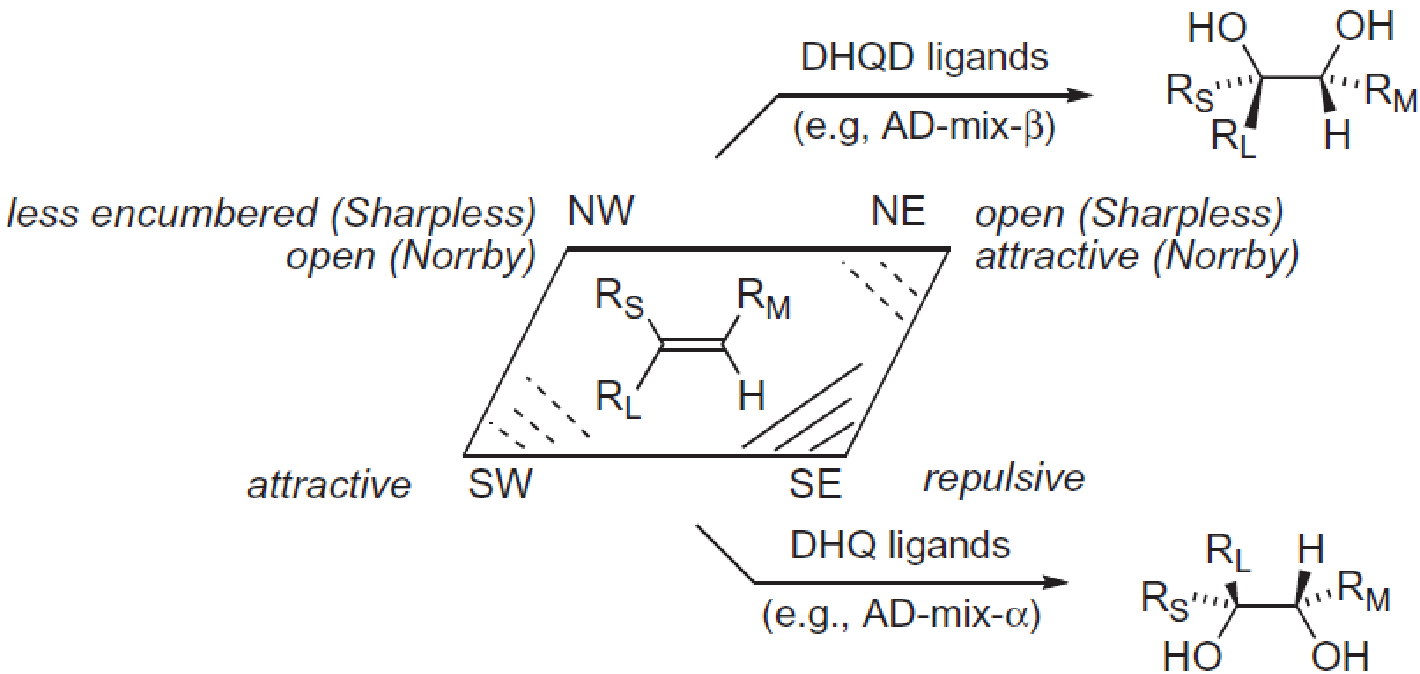
AD-mix reagents are commercially available:

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.

DIIDROSSILAZIONI ASIMMETRICHE
MODELLO EMPIRICO (PHAL E PYR)



Vanhessche, P.M.; Sharpless, K.B. *J. Org. Chem.*, **1996**, *61*, 7978

Fristrup, P.; Tanner, D.; Norrby, P.-O. *Chirality* **2003**, *15*, 360−368.

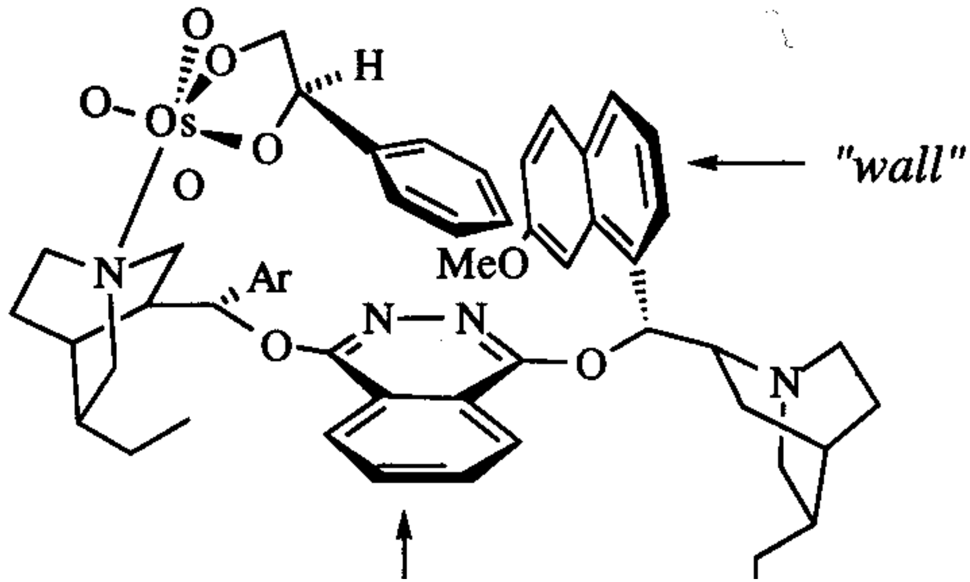
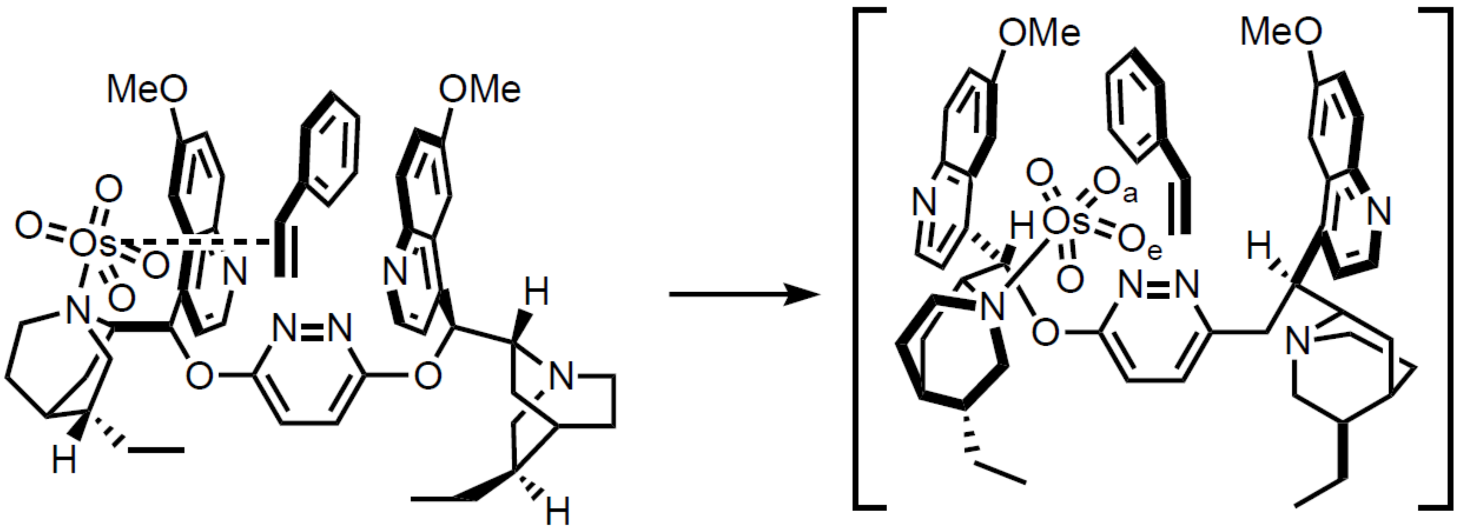


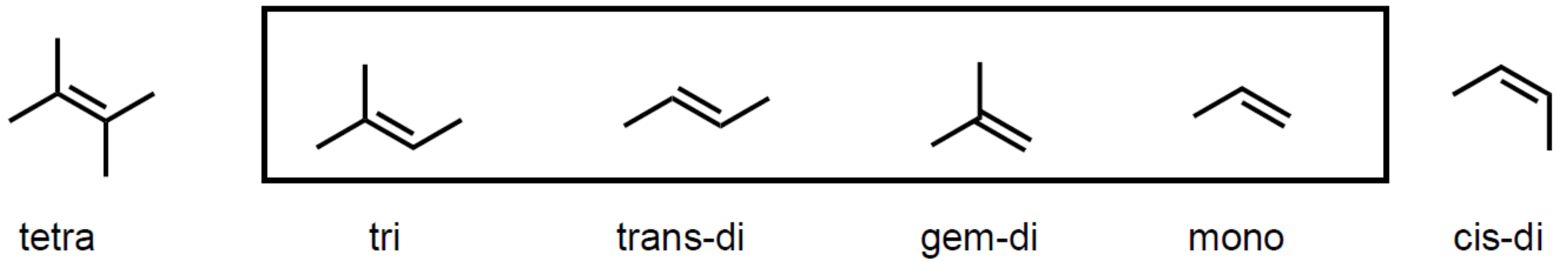
Figure 8.6. One view of a proposed intermediate in the Sharpless AD reaction of the $(DHQD)_2PHAL$-derived osmium species reacting with styrene [80].

Corey proposes a U-shaped binding pocket:

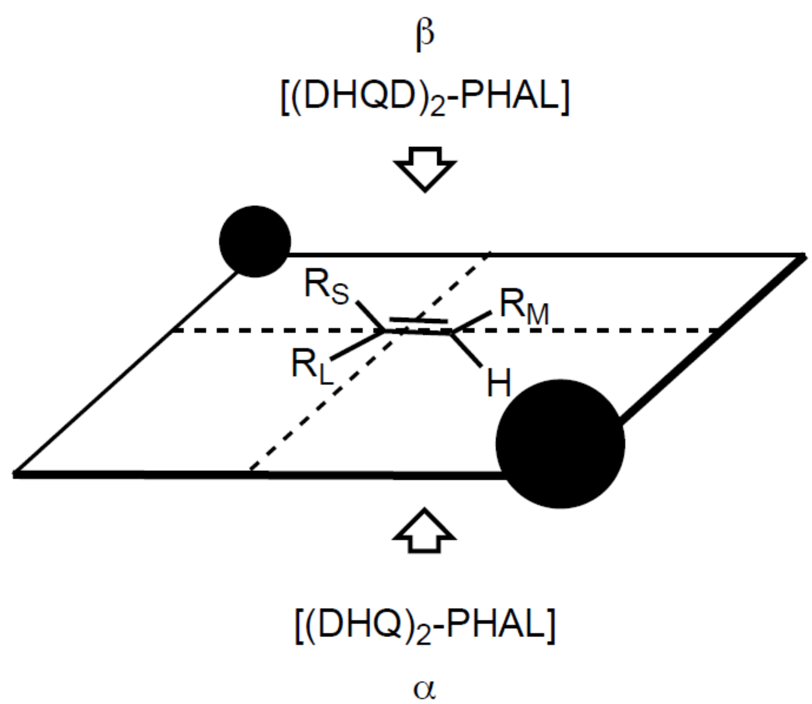


Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481–3484.

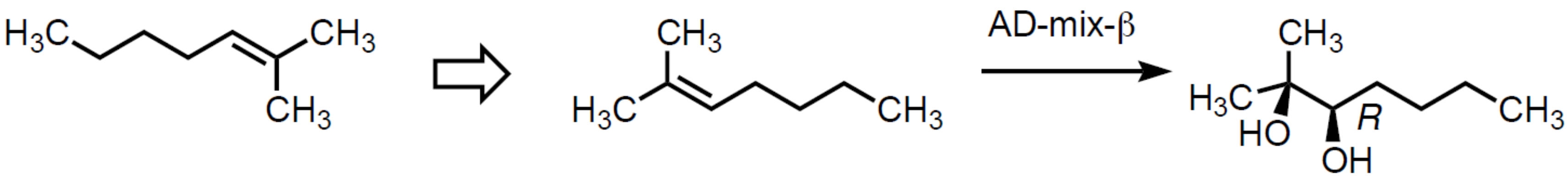
4 of 6 Olefin substitution classes are successfully dihydroxylated:

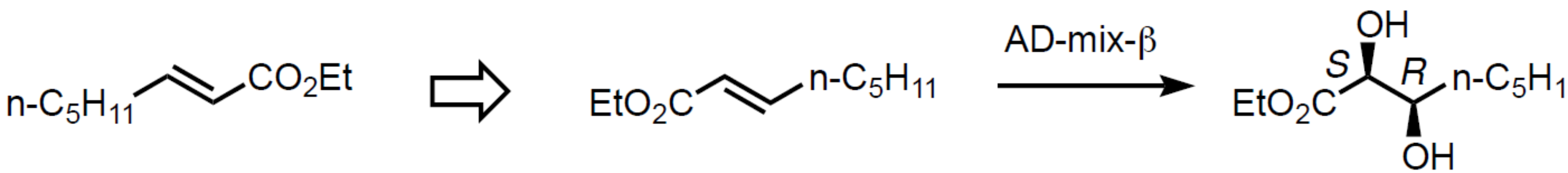


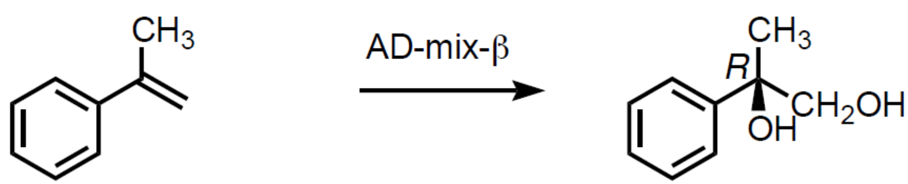
Mnemonic:

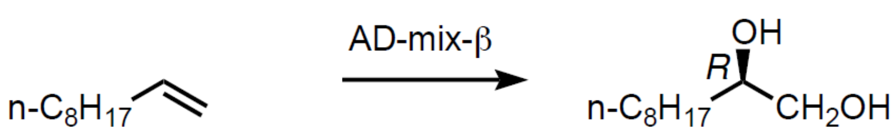


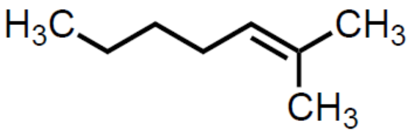
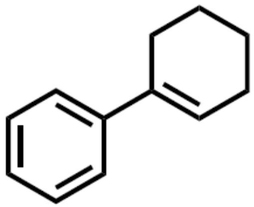
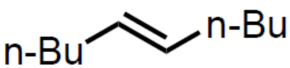
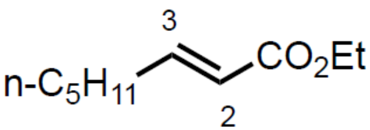
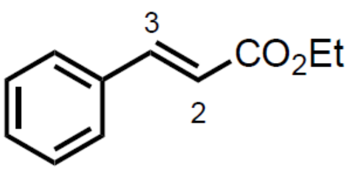
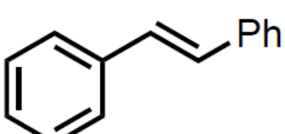
Application of Mnemonic:

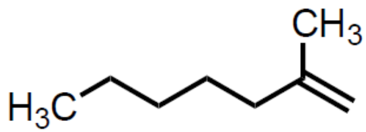
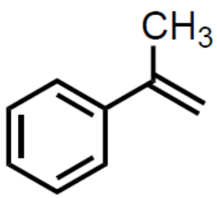
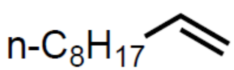
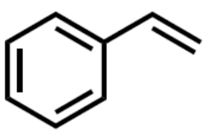






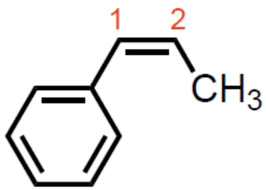


		AD-mix-β [$(DHQD)_2$-PHAL] % ee, config.	AD-mix-α [$(DHQ)_2$-PHAL] % ee, config.
	*	98, *R*	95, *S*
	*	99, *R, R*	97, *S, S*
	*	97, *R, R*	93, *S, S*
	*	99, *2S, 3R*	96, *2R, 3S*
	*	97, *2S, 3R*	95, *2R, 3S*
	*	>99.5, *R, R*	>99.5, *S, S*

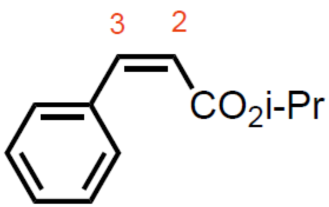
	AD-mix-β [$(DHQD)_2$-PHAL] <u>% ee, config.</u>	AD-mix-α [$(DHQ)_2$-PHAL] <u>% ee, config.</u>
	78, *R*	76, *S*
	94, *R*	93, *S*
	84, *R*	80, *S*
	97, *R*	97, *S*

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

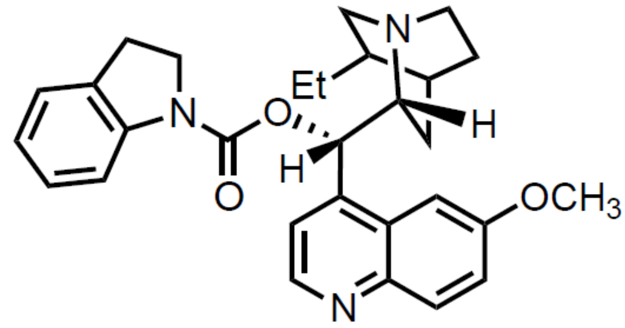
<u>ee at 0 °C</u>



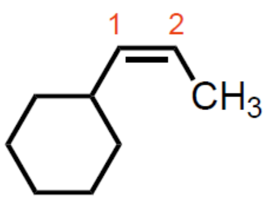
72, (1*R*, 2*S*)



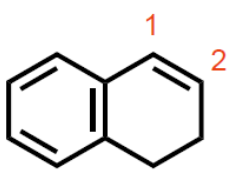
80, (2*R*, 3*S*)



DHQD-IND



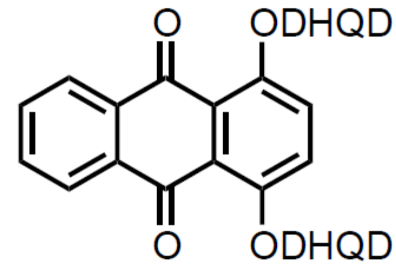
56, (1*R*, 2*S*); 44% ee of the enantiomer obtained with DHQ-IND



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

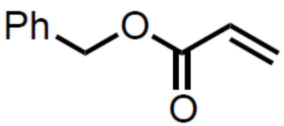
Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568–7570.

$(DHQD)_2AQN$ is often a superior ligand:

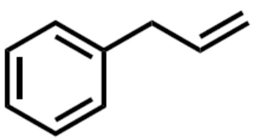


$(DHQD)_2AQN$

90% ee vs. 63% ee, $(DHQD)_2PHAL$

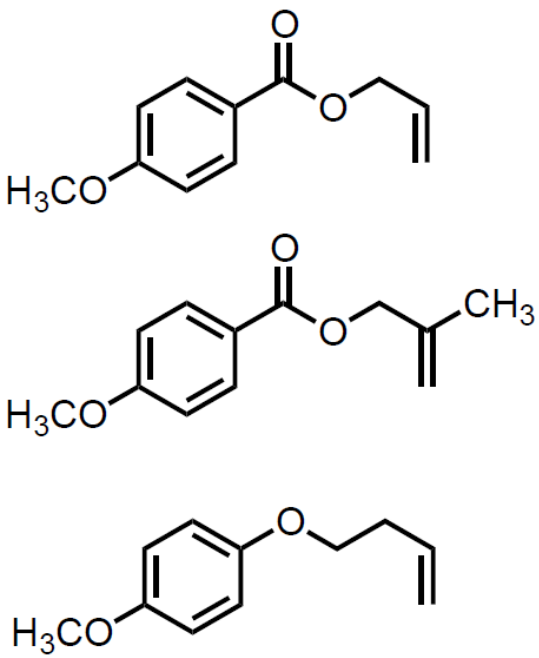


88% ee vs. 77% ee, $(DHQD)_2PHAL$



78% ee vs. 44% ee, $(DHQD)_2PHAL$

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



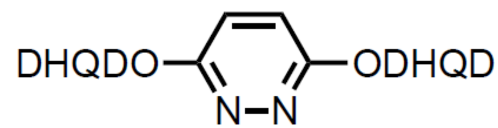
AD, $(DHQD)_2$PYDZ

>99% yield, 98% ee

98% yield, 97% ee

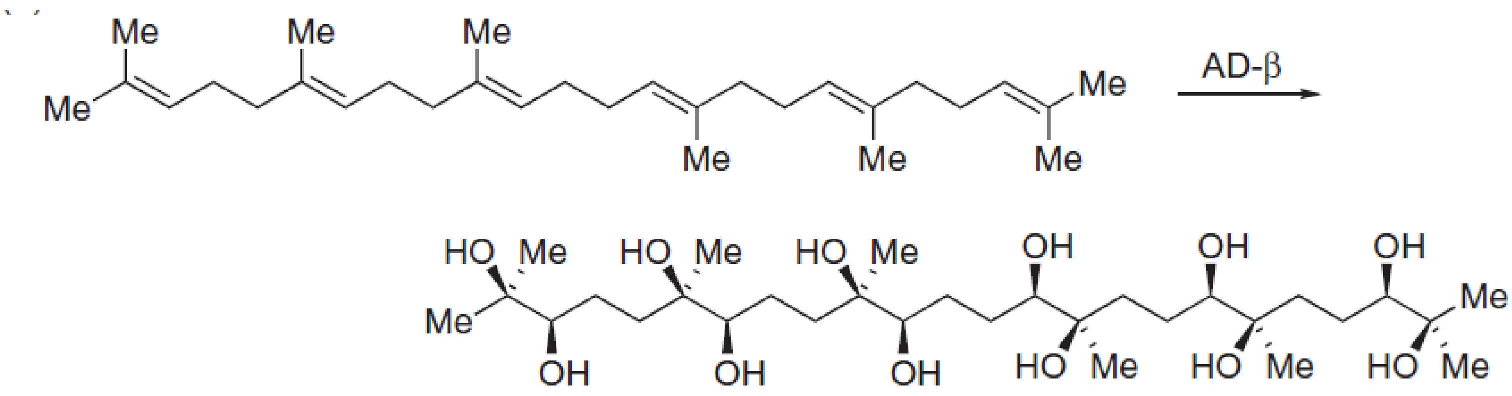
96% yield, 91% ee

$(DHQD)_2$PYDZ =



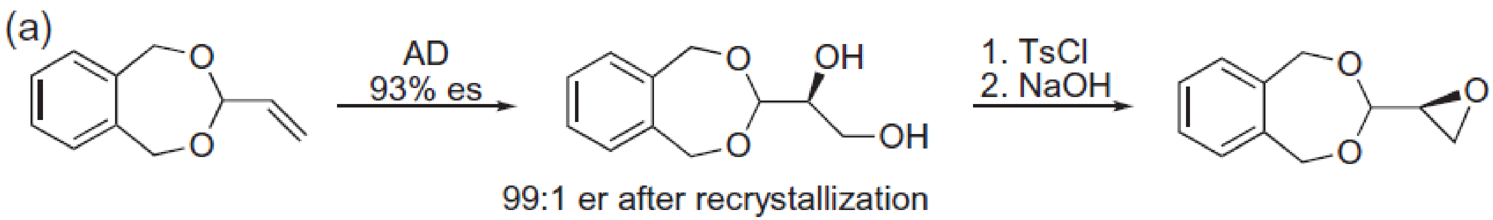
Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805–10816.

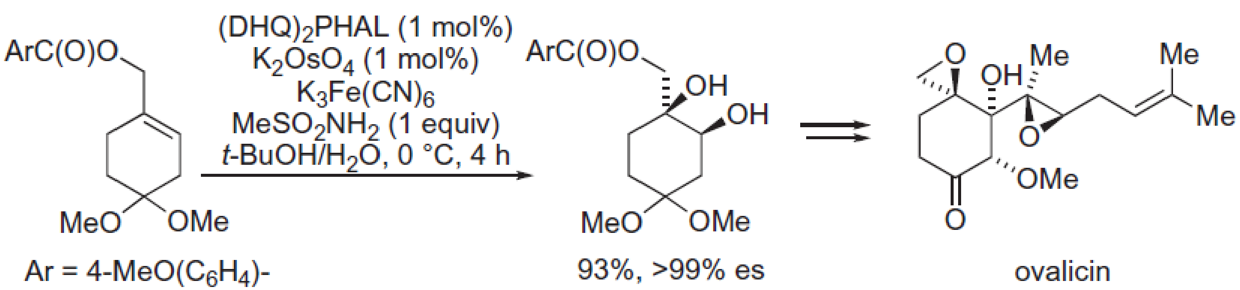
Diidrossilazioni con OsO_4 – Applicazioni



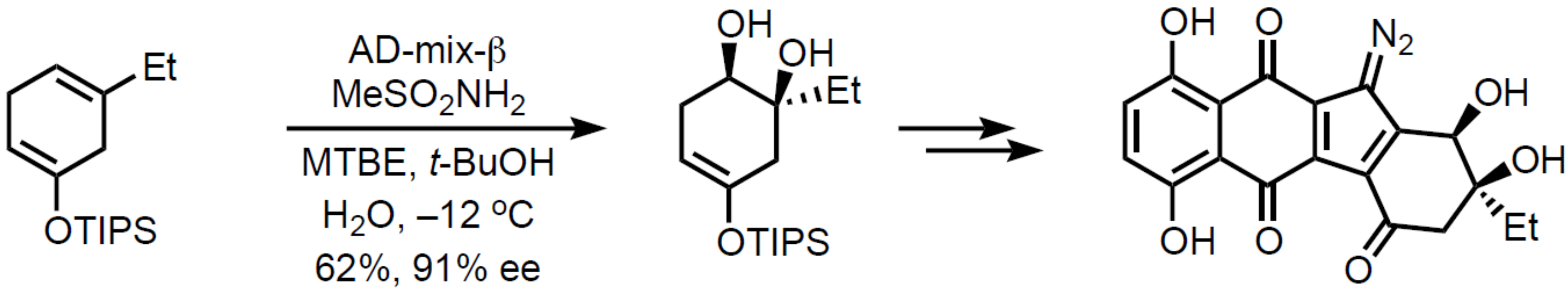
83%
89:11 ratio of this isomer to a mixture containing 35 other isomers

Diidrossilazioni con OsO_4 – Applicazioni





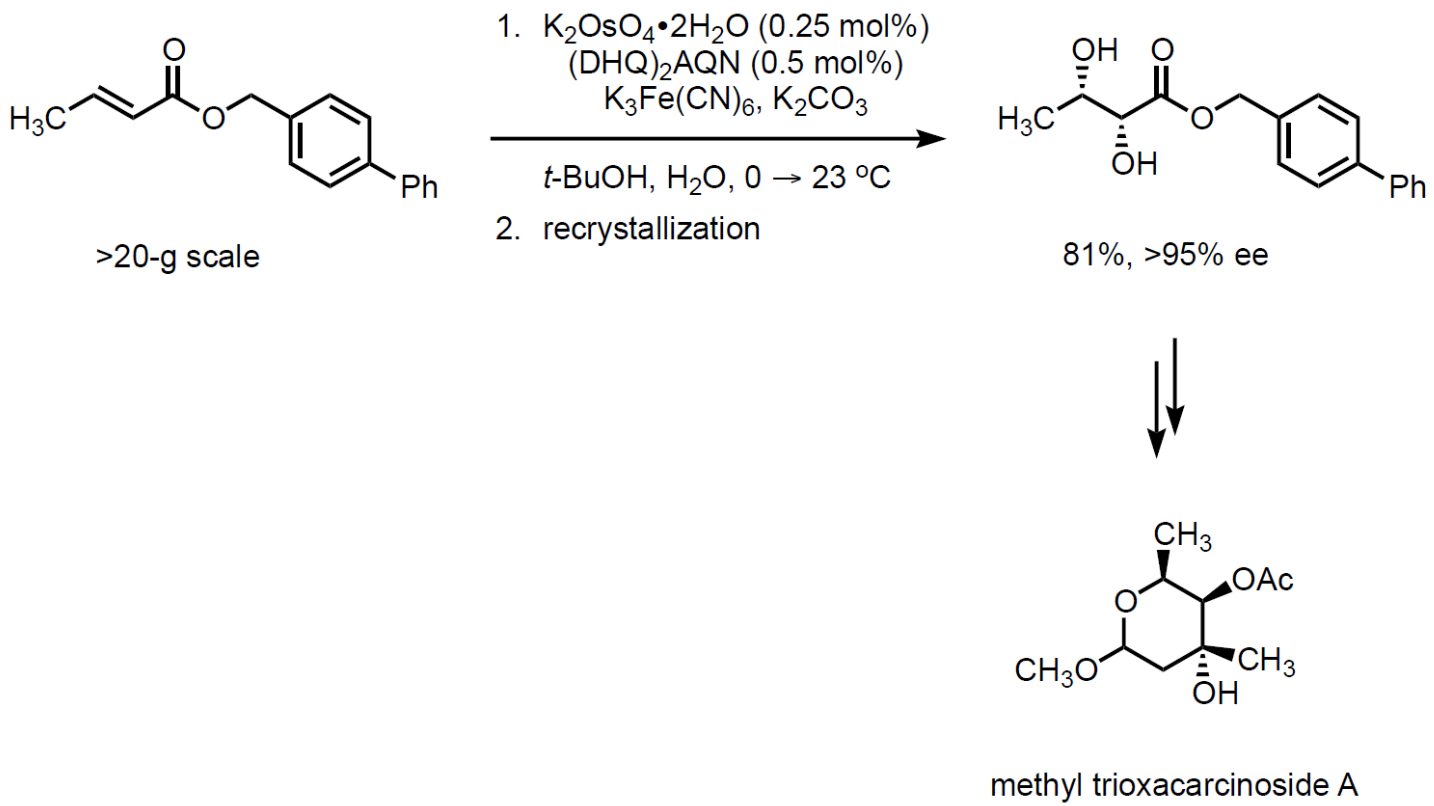
Diidrossilazioni con OsO_4 – Applicazioni



(–)-monomeric lomaiviticin aglycon

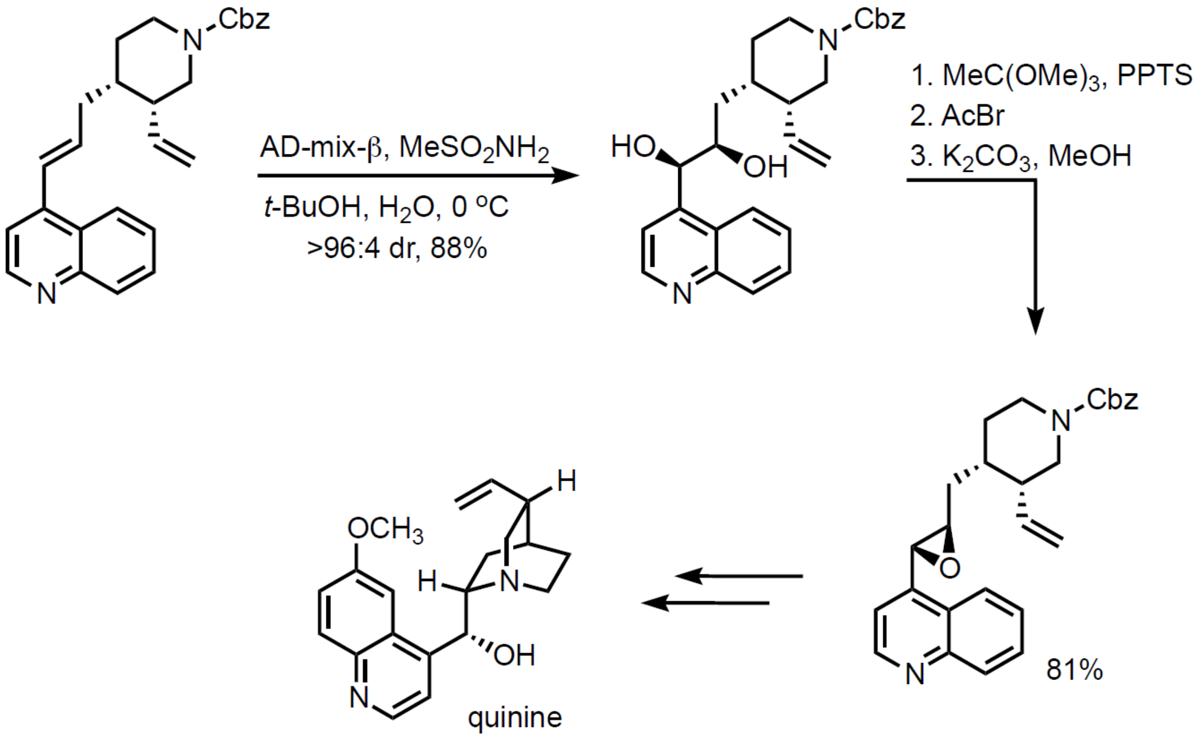
Woo, C. M.; Gholap, S. L.; Lu, L.; Kaneko, M; Li, Z.; Ravikumar, P. C.; Herzon, S. B. *J. Am. Chem. Soc.* **2012**, *134*, 17262–17273.

Diidrossilazioni con OsO_4 – Applicazioni



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.

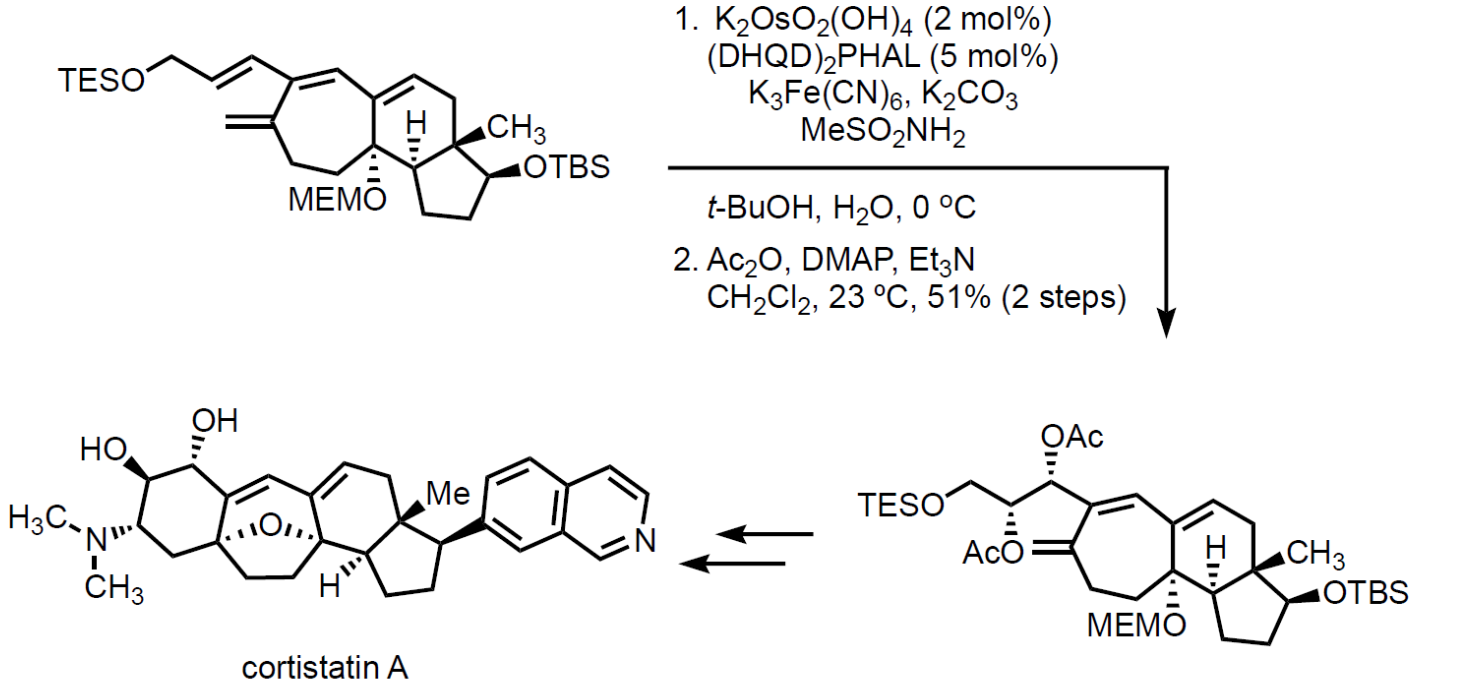
Diidrossilazioni con OsO_4 – Applicazioni



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

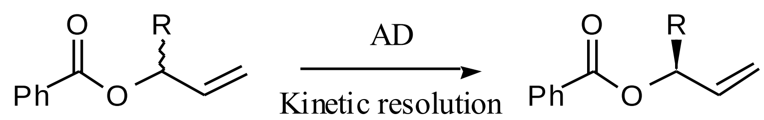
For conversion of diol to epoxide, see Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.

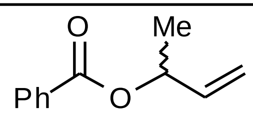
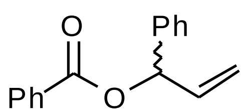
Diidrossilazioni con OsO_4 – Applicazioni



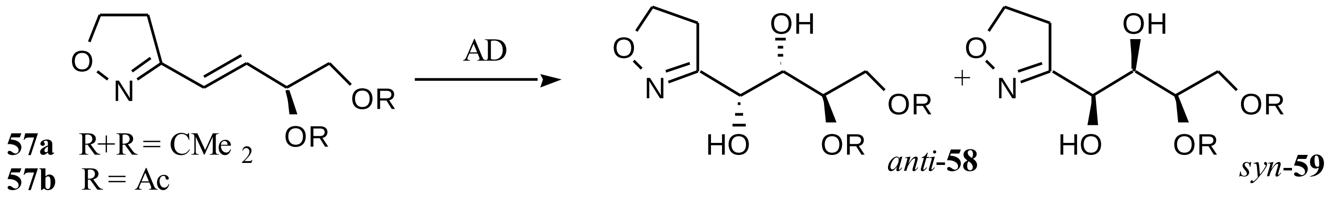
Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.
Adam Kamlet

Diidrossilazioni con OsO_4 – risoluzione cinetica



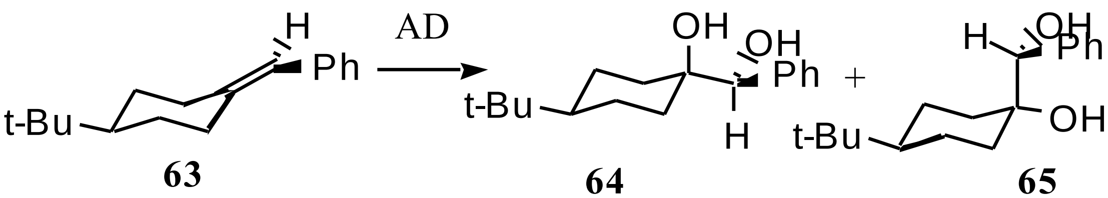
Substrate	Ligand	$k_{rel} = k_{ent}/k$
 **52**	(DHQD)$_2$PYDZ **32b**	3.1
	(DHQD)-PYDZ-(S)-Anthryl **40**	20
 **53**	(DHQD)$_2$PYDZ **32b**	1.9
	(DHQD)-PYDZ-(S)-Anthryl **40**	79

Diidrossilazioni con OsO_4 – doppia stereoselezione

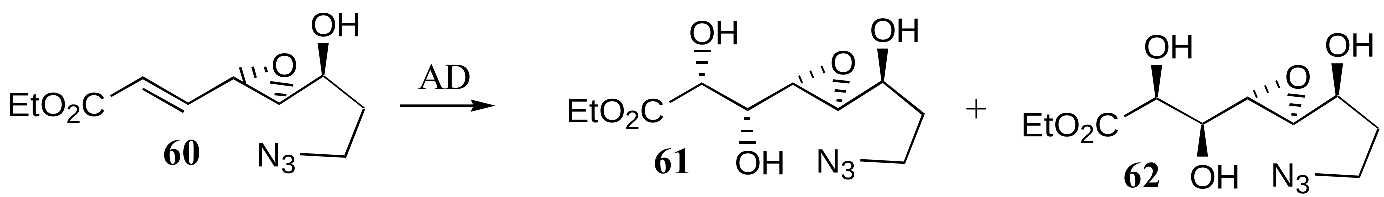


Substrate	Ligand	*anti*-**58** : *syn*-**59**	Yield,%
57a	none	77 : 23	85
57b	none	76 : 25	83
57a	(DHQD)2-PHAL	96 : 4	53
57a	(DHQ)2-PHAL	11 : 89	62
57b	(DHQD)2-PHAL	98 : 2	82
57b	(DHQ)2-PHAL	5 : 95	85

Diidrossilazioni con OsO_4 – doppia stereoselezione

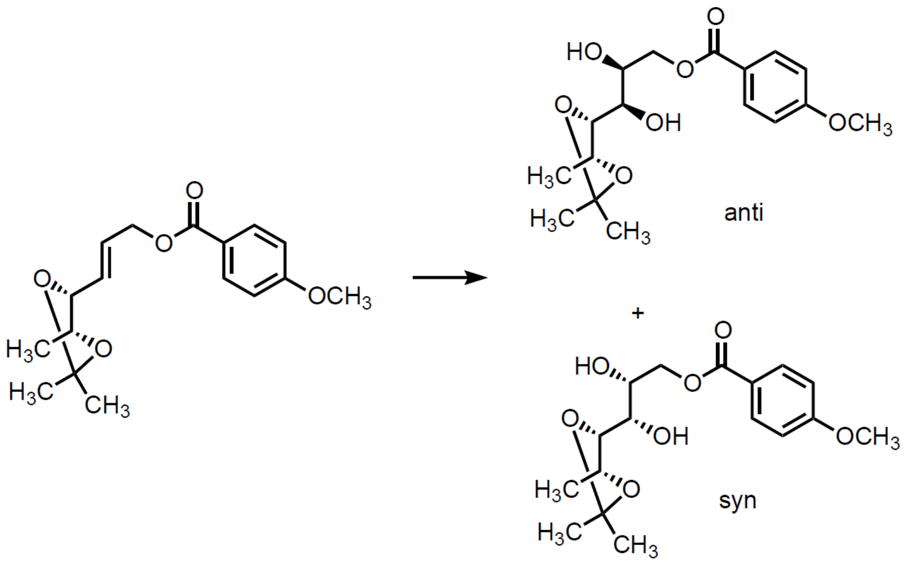


Ligand	**64 : 65**
none	1 : 6
$(DHQ)_2$PHAL **26a**	1 : 36
$(DHQD)_2$PHAL **26b**	35 :1



Ligand	**61:62**	Ligand	**61:62**	Ligand	**61:62**
none	1 : 2	(DHQ)2PHAL **26a**	10:1	(DHQD)2PHAL **26b**	> 1:20

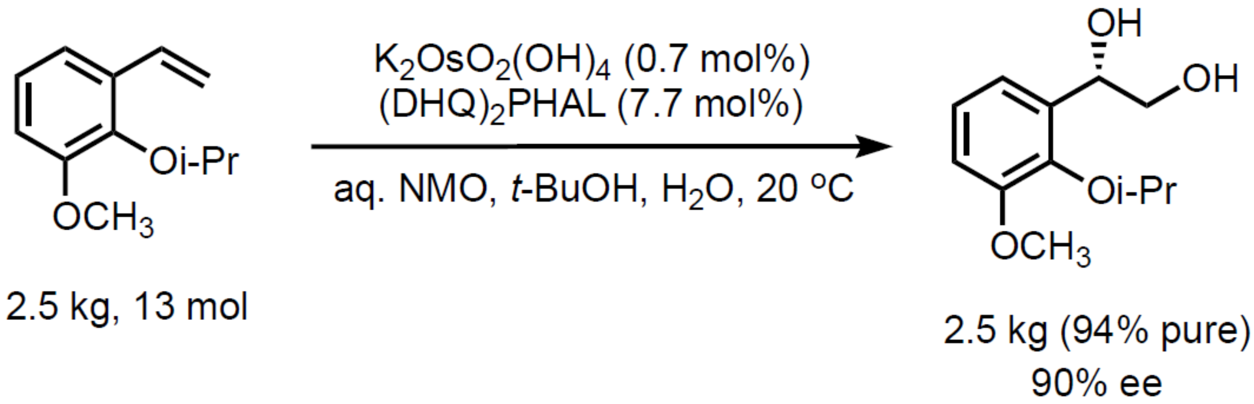
Diidrossilazioni con OsO_4 – doppia stereoselezione



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.

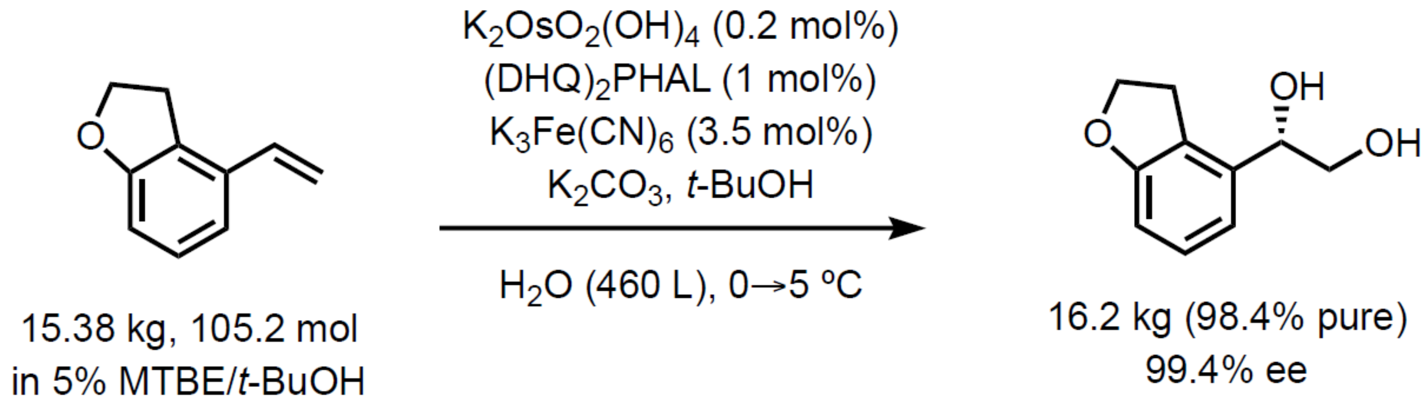
Diidrossilazioni con OsO_4 – applicazioni industriali



- 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.

Diidrossilazioni con OsO_4 – applicazioni industriali



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.