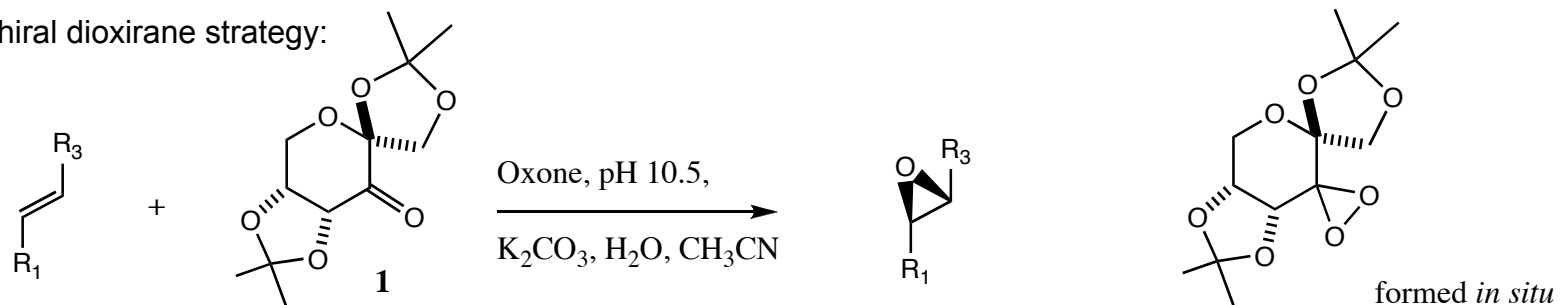
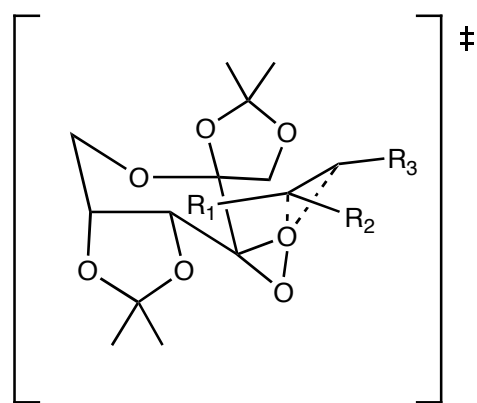


## Shi Asymmetric Epoxidation

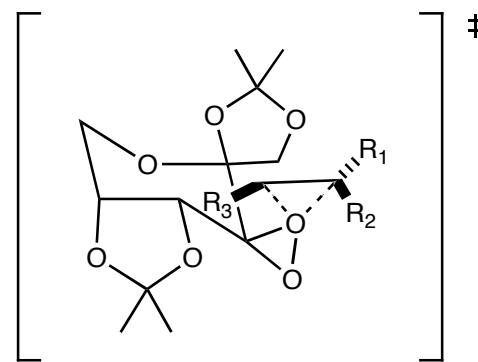
Chiral dioxirane strategy:



- catalyst (10-20 mol%) is prepared from D-fructose, and its enantiomer from L-sorbose
- oxone, the stoichiometric oxidant, is a 2:1:1 mixture of  $KHSO_5$ ,  $KHSO_4$ , and  $K_2SO_4$
- $H_2O_2 / CH_3CN$  may also be used as stoichiometric oxidant.
- a pH of 10.5 is an optimum balance between oxone decomposition and Baeyer-Villiger rearrangement of dioxirane intermediate



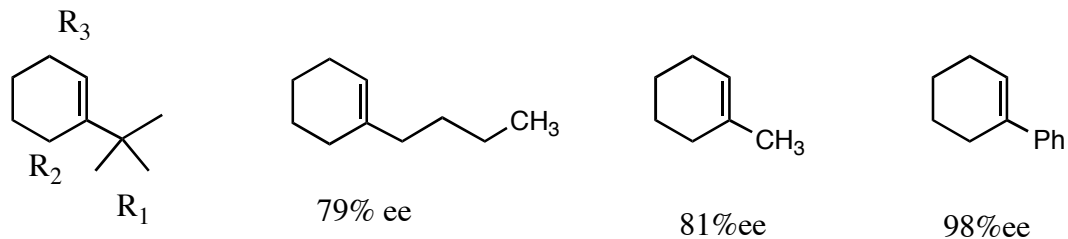
electronically favored  
 $n \rightarrow \pi^*$



Higher ee's observed with smaller  $R_1$  and larger  $R_3$  substituents

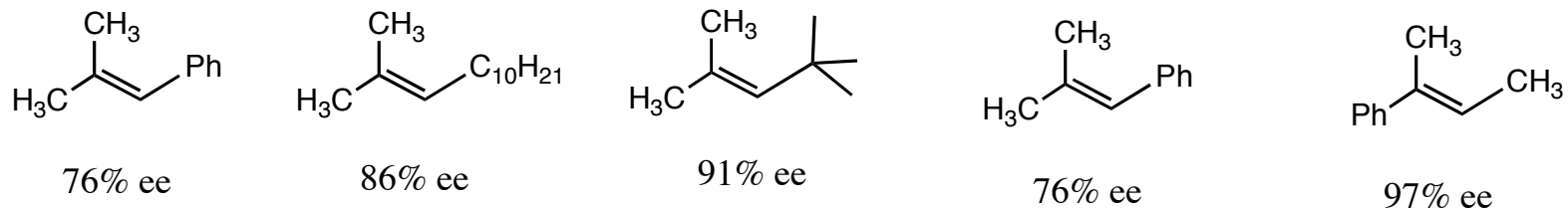
# Shi Asymmetric Epoxidation

Effect: smaller R1 beneficial



26% ee

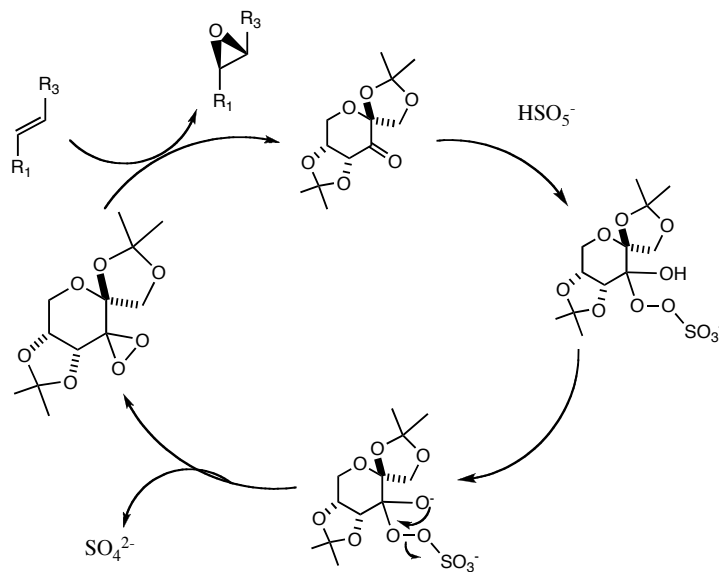
Effect: larger R3 beneficial



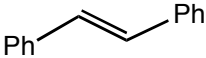

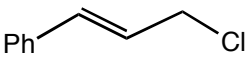

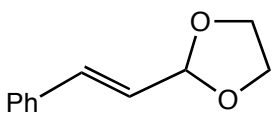
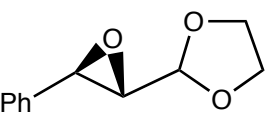
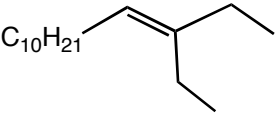
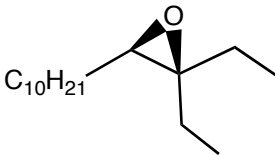
Compare:

Note that the substituent size preferences reflect interactions in the spiro TS.

Proposed Catalytic Cycle:

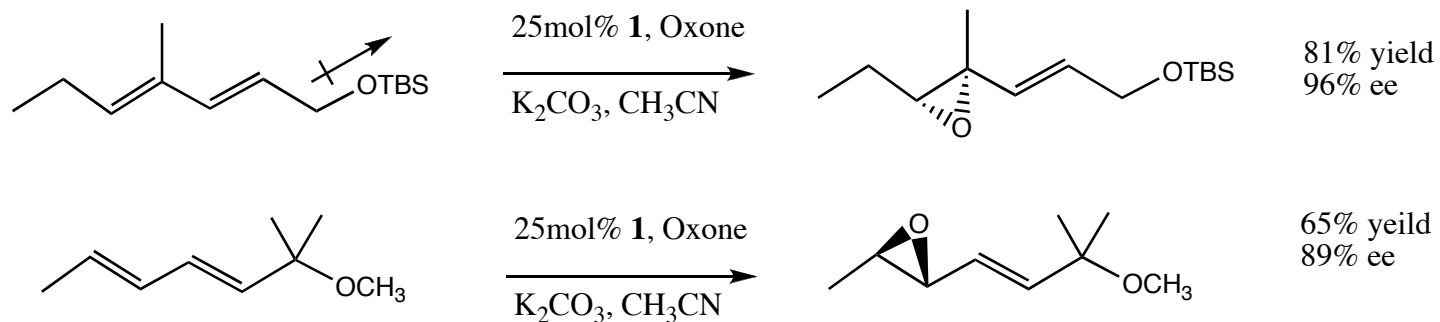


# Shi Asymmetric Epoxidation

Substrate	Product	Yield	ee
		73%	95%
		61%	93%
		91%	93%
		94%	89%

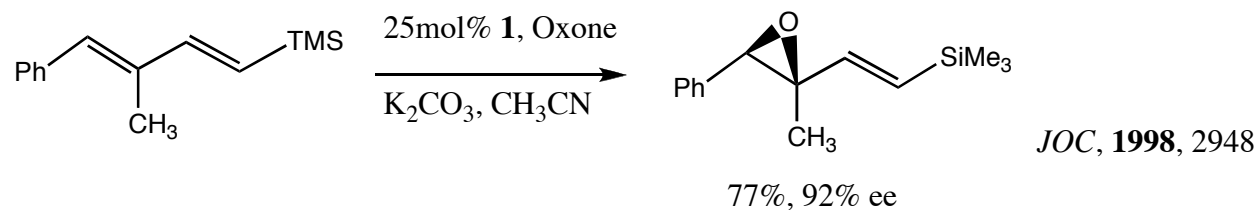
*JACS*, **1996**, 9806  
*JACS*, **1997**, 11224

Monoepoxidation of dienes occurs at the more e<sup>-</sup> rich or less sterically hindered olefin

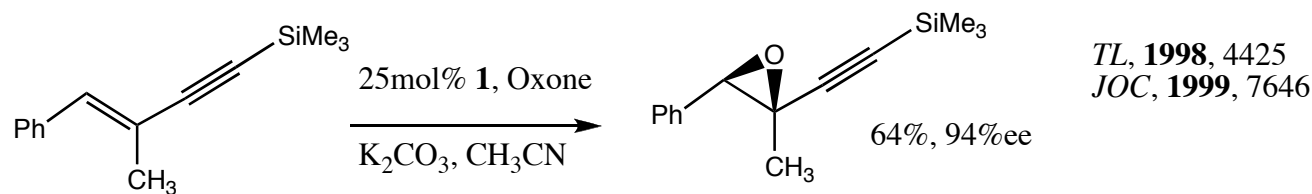


## Shi Asymmetric Epoxidation

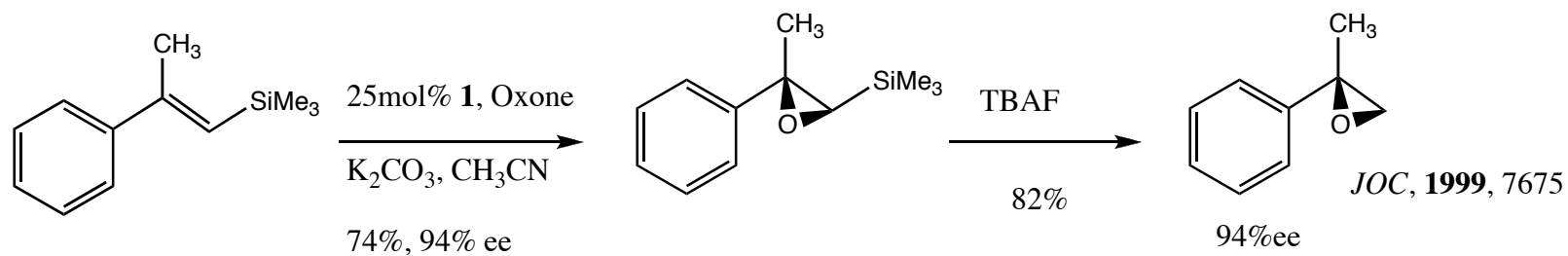
Trisubstituted olefins are selectively epoxidized because they are more e-rich



Epoxidation of enynes occurs selectively at the C-C double bond:

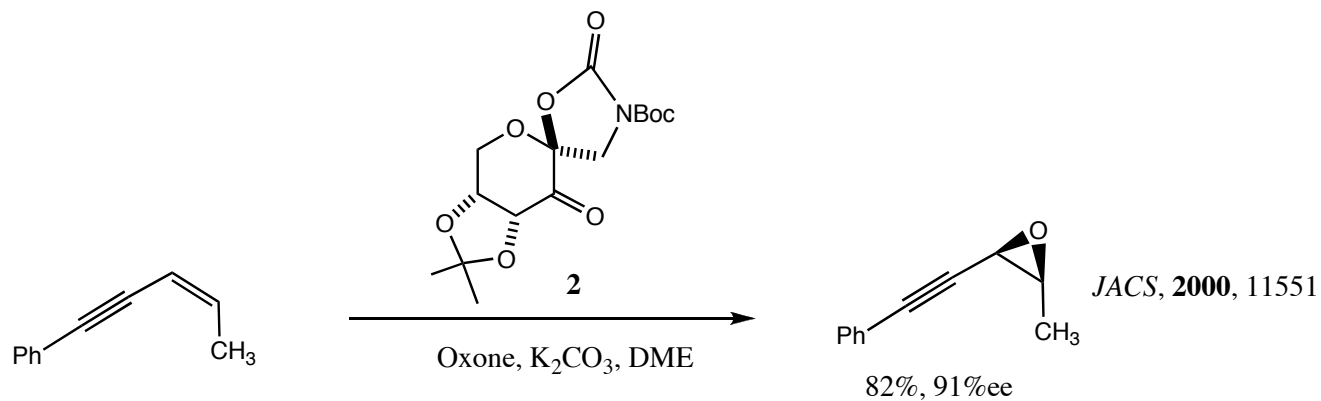


1,1-disubstituted epoxides can be prepared from trisubstituted vinyl silanes by epoxidation and desilylation:

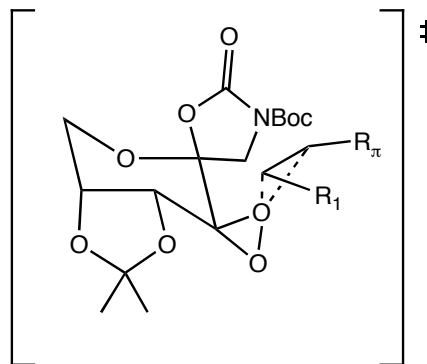


# Shi Asymmetric Epoxidation

A modified catalyst is used for epoxidation of cis-disubstituted olefins and styrenes

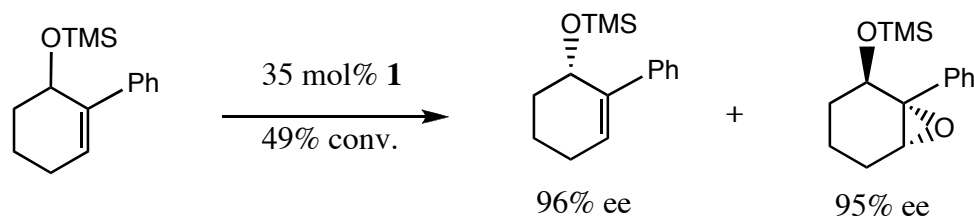


$\pi$ -substituent prefers to be proximal to the spiro oxazolidinone:

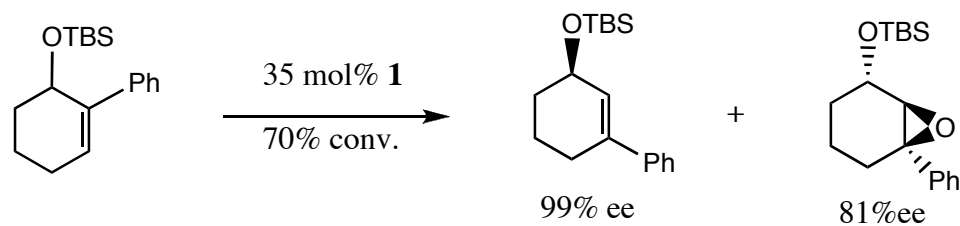


## Shi Asymmetric Epoxidation

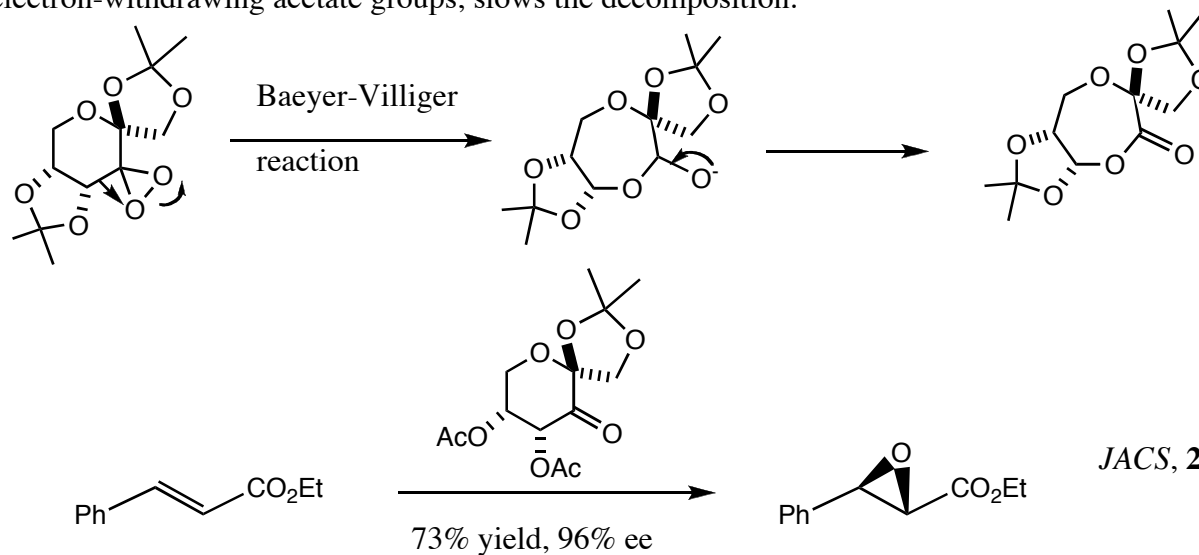
Kinetic Resolution of racemic 1,3- and 1,6-disubstituted cyclohexenes provides optically enriched allylic Silyl ethers



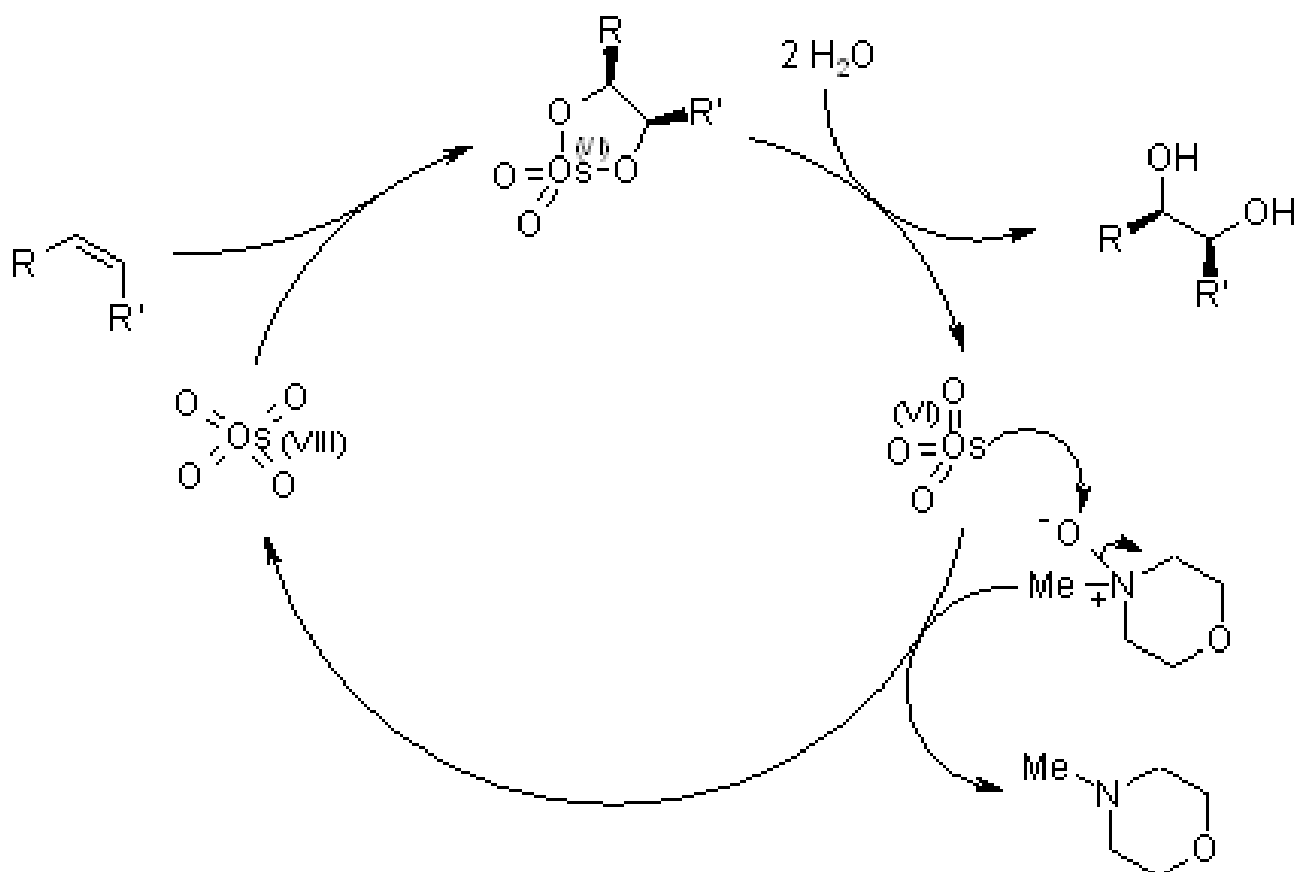
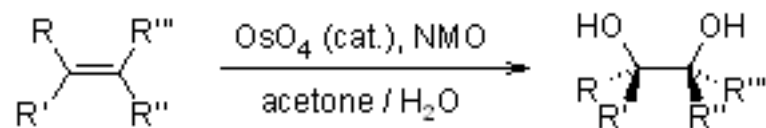
*JACS*, **1999**, 7718



The original Shi catalyst decomposes faster than it reacts with electron-deficient unsaturated esters. A second-generation catalyst, incorporating electron-withdrawing acetate groups, slows the decomposition:

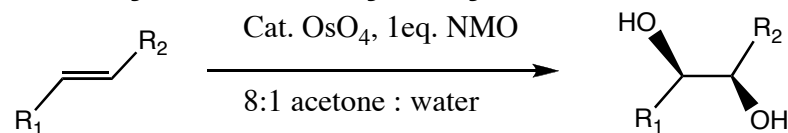


# Upjohn Dihydroxylation

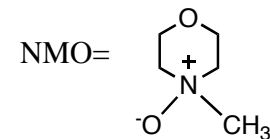


## Sharpless Asymmetric Dihydroxylation Reaction

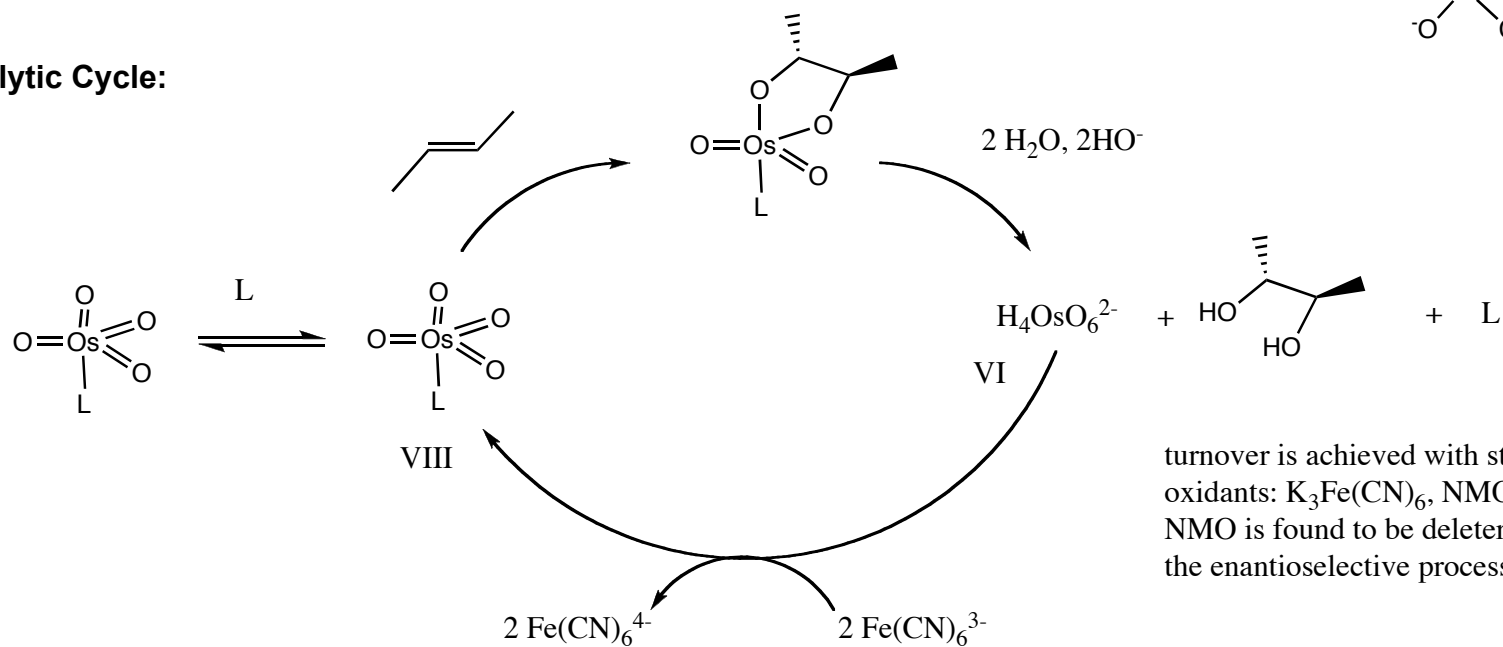
Original UpJohn Procedure:



*TL*, **1976**, 1973

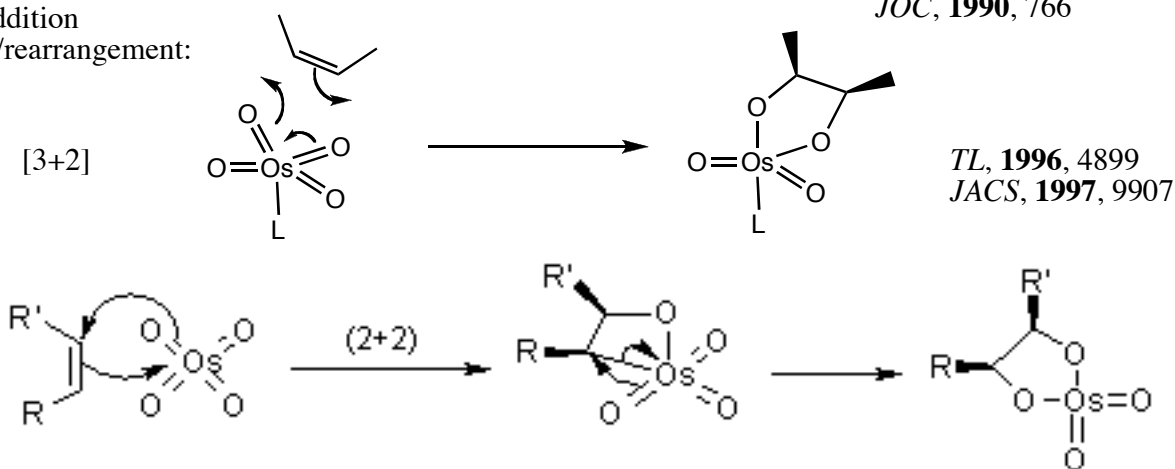


Catalytic Cycle:



*JOC*, **1990**, 766

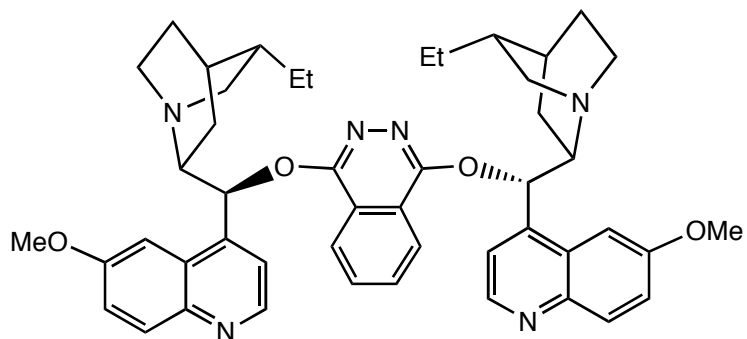
Addition is likely a 3+2 cycloaddition rather than a 2+2 cycloaddition/rearrangement:



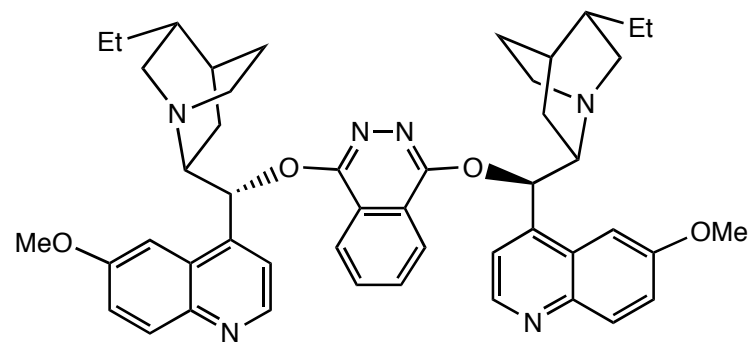


## Sharpless Asymmetric Dihydroxylation Reaction

Ligands: C<sub>2</sub>-symmetric, pseudo-enantiomeric



(DHQD)<sub>2</sub>-PHAL  
ligand for AD-mix-β



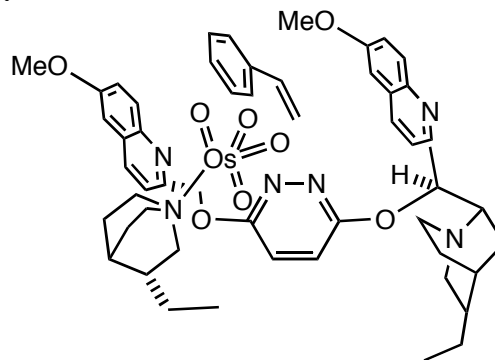
(DHQ)<sub>2</sub>-PHAL  
Ligand for AD-mix-α  
slightly less enantioselective

**AD-mix reagents are commercially available:**

1.4 g Ad-mix-β will oxidize 1mmol olefin  
0.98 g K<sub>3</sub>Fe(CN)<sub>6</sub> (3 mmol)  
0.41g K<sub>2</sub>CO<sub>3</sub> (3 mmol)  
0.0078 g (DHQD)<sub>2</sub>-PHAL (0.01 mmol)  
0.00074 g K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>(0.002 mmol)

*JOC*, **1992**, 2768

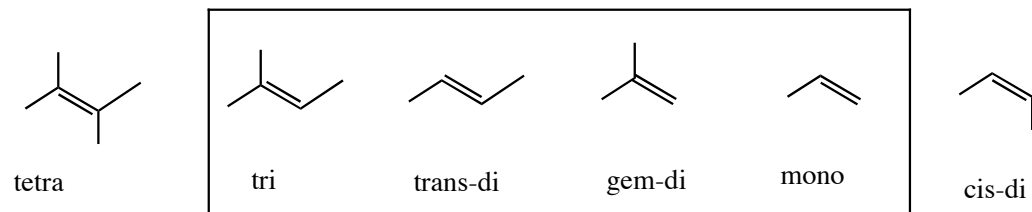
**Corey Proposes a U- shape binding pocket:**



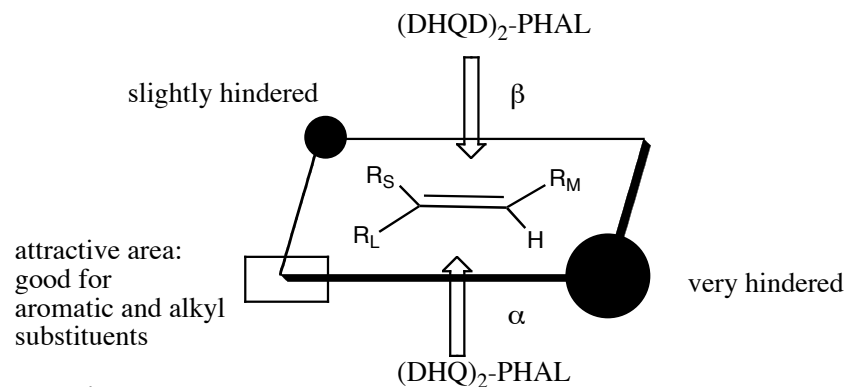
*TL*, **1995**, 3481

# Sharpless Asymmetric Dihydroxylation Reaction: Ligand Accelerated Catalysis

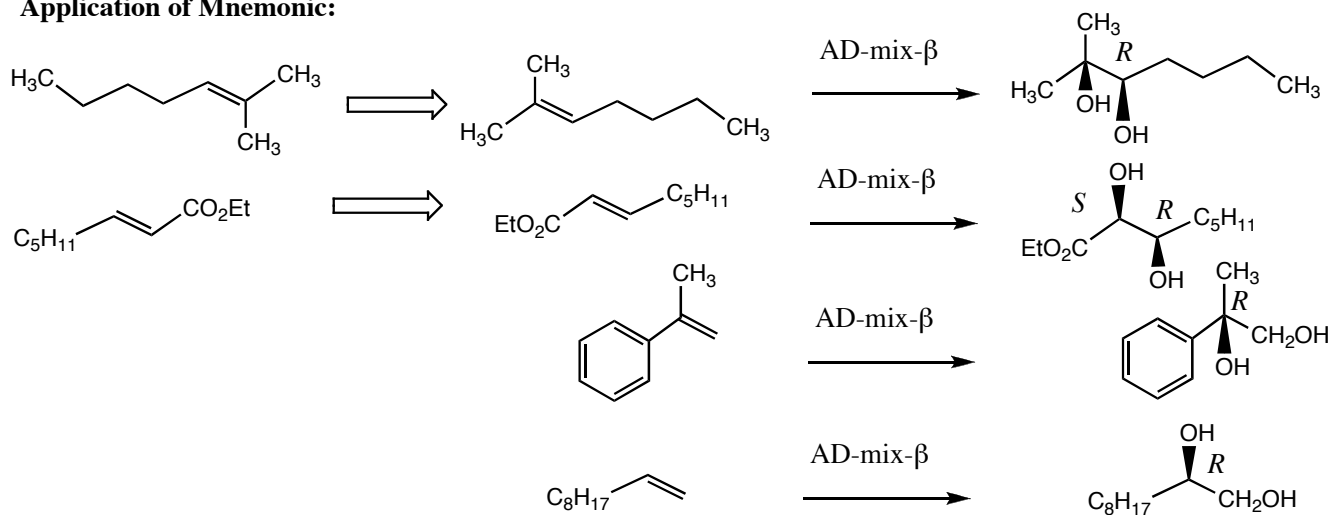
4 of 6 olefin classes are successfully dihydroxylated:



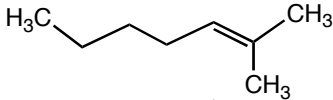
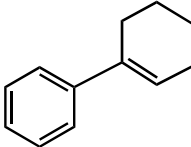
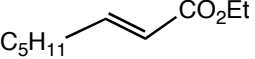
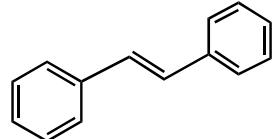
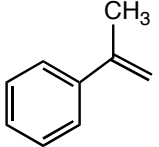
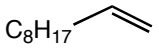
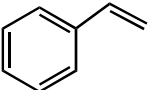
**Mnemonic:**



**Application of Mnemonic:**

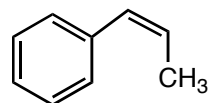


## Generality of Sharpless Asymmetric Dihydroxylation

	AD-mix- $\beta$ (DHQD) <sub>2</sub> -PHAL <u>% ee, config</u>	AD-mix- $\alpha$ (DHQ) <sub>2</sub> -PHAL <u>% ee, config</u>
	98, <i>R</i>	95, <i>S</i>
	99, <i>R, R</i>	97, <i>S, S</i>
	99, <i>2S, 3R</i>	96, <i>2R, 3S</i>
	>99.5, <i>R,R</i>	>99.5, <i>S,S</i>
	94, <i>R</i>	93, <i>S</i>
	84, <i>R</i>	80, <i>S</i>
	97, <i>R</i>	97, <i>S</i>

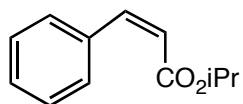
## Generality of Sharpless Asymmetric Dihydroxylation

Cis-Disubstituted Olefins are poor substrates; with a modified catalyst, DHQD-IND, good ee's can be obtained:

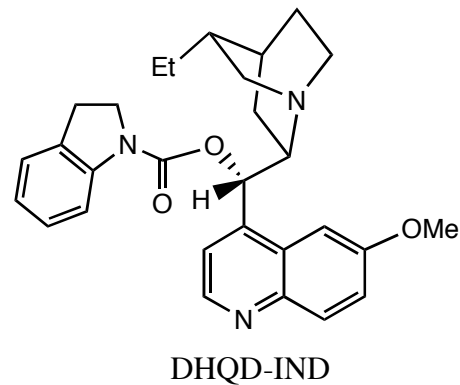


ee at 0°C

72 (1R, 2S)

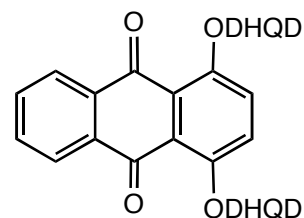


80 (2S, 3R)

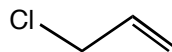


JACS, 1992, 7568

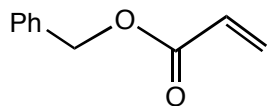
(DHQD)<sub>2</sub>AQN is often a superior ligand:



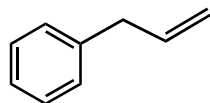
(DHQD)<sub>2</sub>AQN



90% ee vs. 63% ee with (DHQD)<sub>2</sub>PHAL



88% ee vs. 77% ee with (DHQD)<sub>2</sub>PHAL

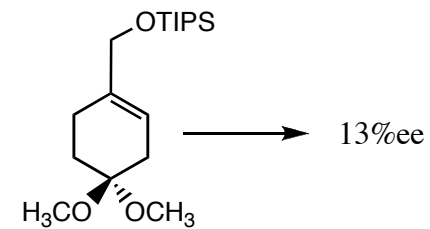
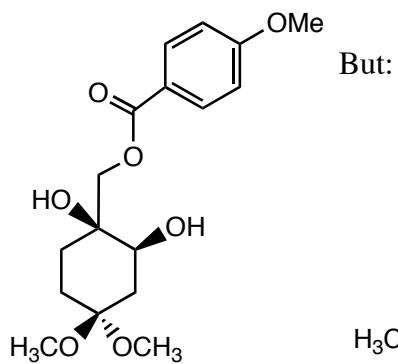
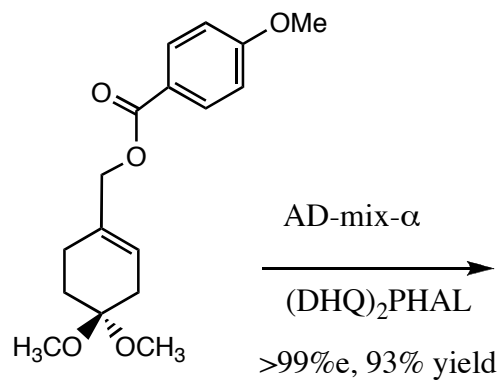


78% ee vs. 44% ee with (DHQD)<sub>2</sub>PHAL

ACIEE, 1996, 448.

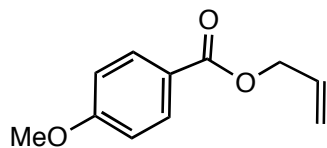
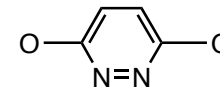
## Generality of Sharpless Asymmetric Dihydroxylation

Good substrates Allylic 4-methoxybenzoates

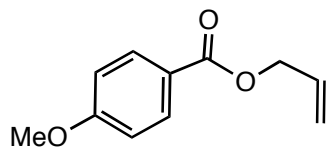


AD. (DHQD)<sub>2</sub>PYDZ

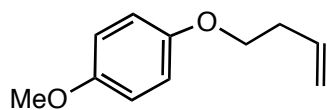
PYDZ =



>99% yield, 98%ee



98% yield, 97% ee

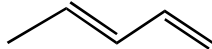
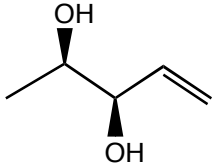
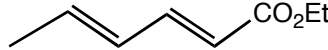
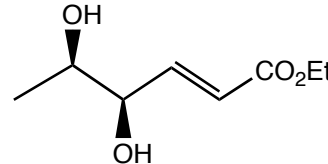
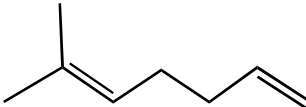
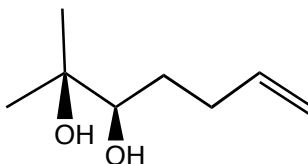
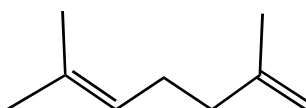
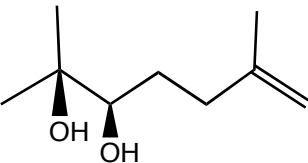


96%, 91% ee

JACS, **1995**, 10805

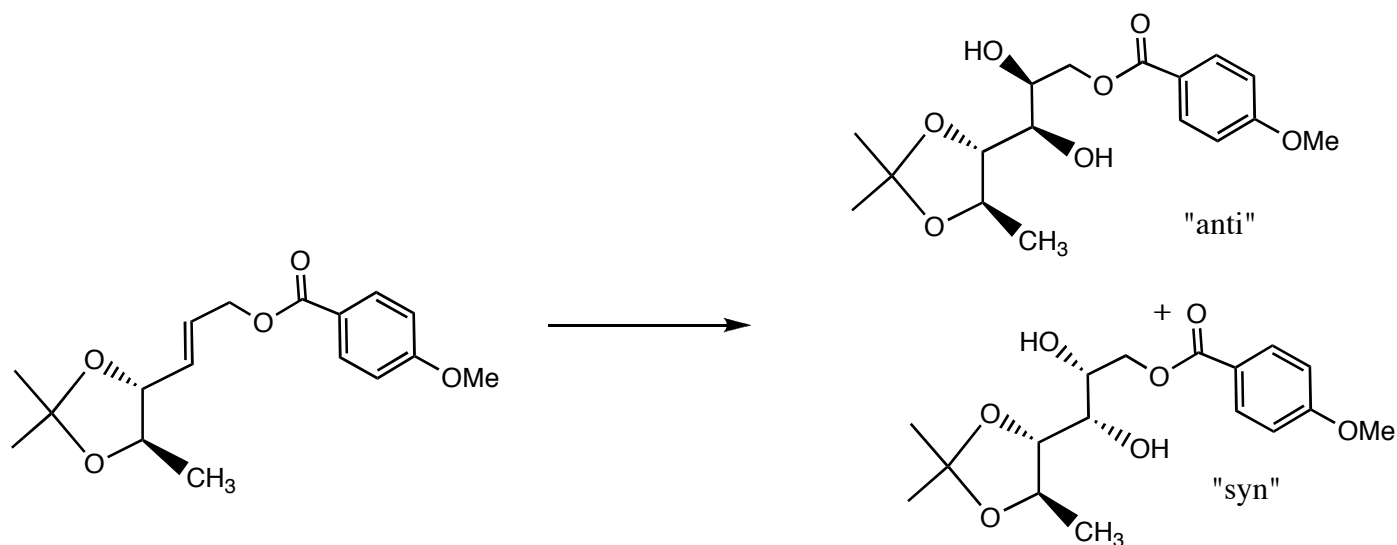
## Generality of Sharpless Asymmetric Dihydroxylation

Regioselectivity of AD with dienes: in general, AD is selective for more electron-rich double bonds

<u>Substrate</u>	<u>Product</u>	<u>% yield, % ee</u>
		78, 93
		78, 92
		73, 98
		70, 98

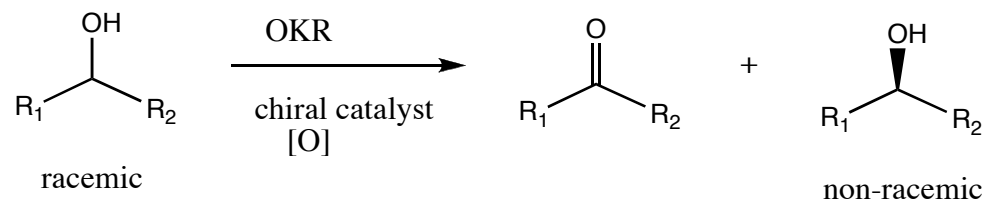
*JACS*, **1992**, 7570

## Use of AD with Chiral Olefins

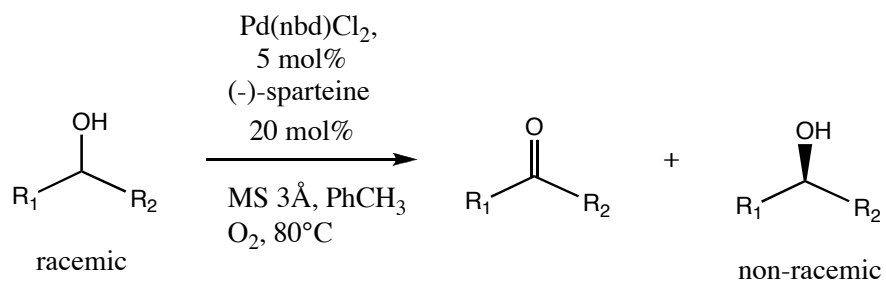


	<u>conditions</u>		<u>anti:syn</u>	
	OsO <sub>4</sub> , NMO	88% yield (mixture)	1.9:1	
matched	(DHQ) <sub>2</sub> PHAL	86% yield (anti)	54:1	<i>TL</i> , <b>1997</b> , 5941
mismatched	(DHQD) <sub>2</sub> PYDZ	86% yield (syn)	1:35	

# Oxidative Kinetic Resolution



It was found that combination of a palladium source, (-) sparteine as a chiral ligand, and O<sub>2</sub> could effect Efficient oxidative kinetic resolution under defined conditions



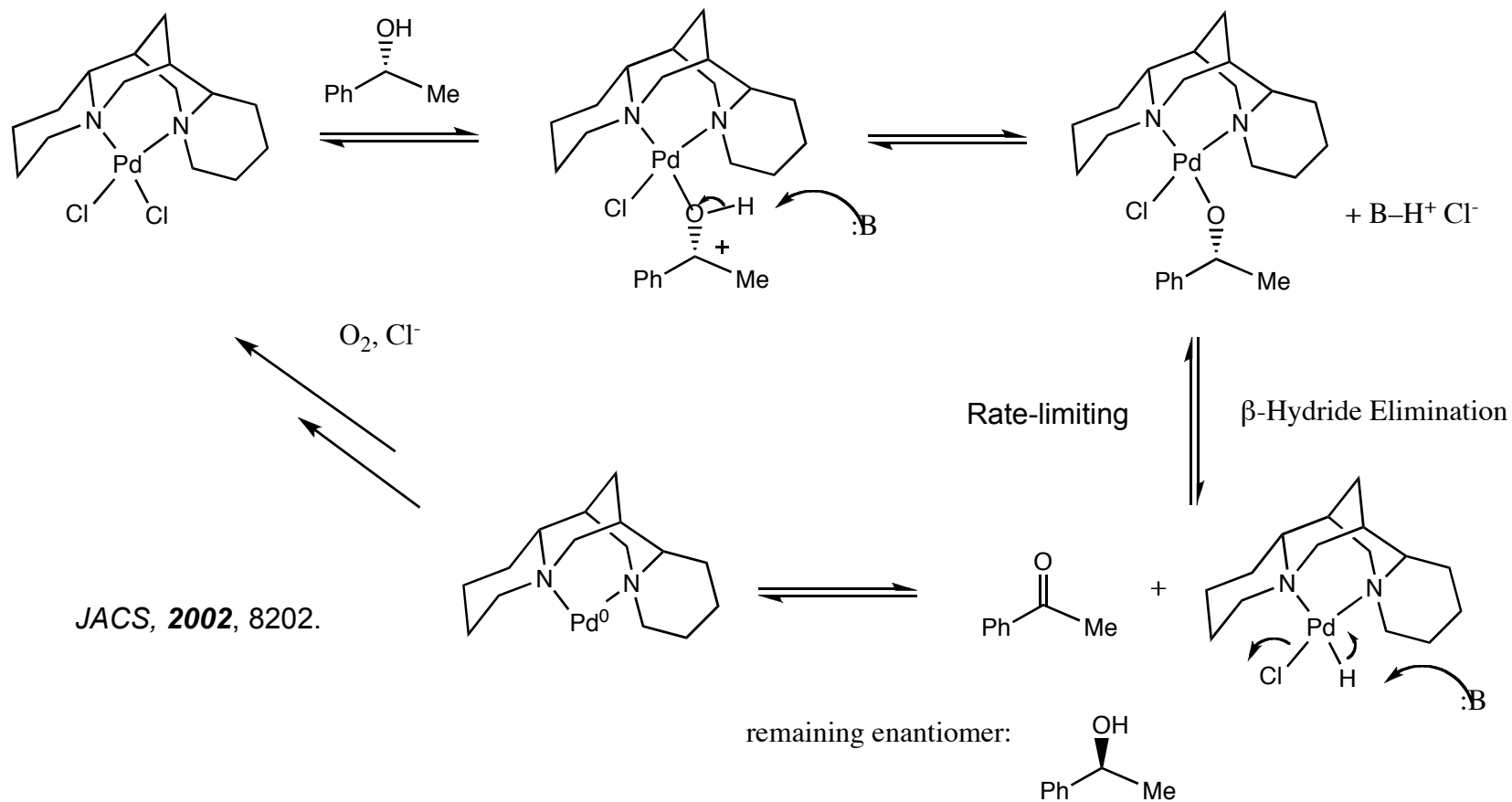
enriched alcohol                      isolated yield                      ee ROH

	40	93.1	
	30	93.4	<b>JACS, 2001, 7725.</b>
	31	99.8	
	29	91.8	



# OKR Mechanism: a Dual Role for (-)-Sparteine

Only one enantiomer binds the chiral catalyst efficiently!



An excess of sparteine is beneficial for the reaction, and it is believed that sparteine not only functions as the chiral ligand, but also as an exogenous base for the deprotonation step, making beta-hydride elimination rate-limiting