The Career of K. Barry Sharpless

Nikki Goodwin
MacMillan Group Meeting
August 28, 2002

Sharpless Asymmetric Epoxidation
i. Mechanism
ii. Scope

Sharpless Asymmetric Dihydroxylation
i. Catalytic Cycle
ii. Mechanism
iii. Scope

Sharpless Asymmetric Aminohydroxylation
i. Mechanism
ii. Scope

Usage of AE/AD/AA in Natural Product Synthesis

"Searching for New Reactivity (Nobel Lecture)" *Angew. Chem. Int. Ed. Eng.* **2002**, *41*, 2024

Reviews:

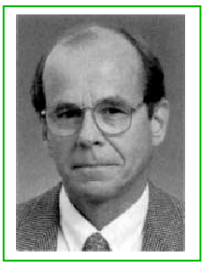
AE: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; Wiley-VCH: Weinheim, 2000; Chapter 6A

AD: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; Wiley-VCH: Weinheim, 2000; Chapter 6D

AA: Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; Wiley-VCH: Weinheim, 2000; Chapter 6E

The Career of K. Barry Sharpless

Biographical Sketch



■ Education
- BA, Dartmouth College (T. A. Spencer), 1963
- PhD, Stanford University (E. E. van Tamelen), 1968
- postdoctoral, Stanford University (J. P. Collman), 1968
- postdoctoral, Harvard University (K. Bloch), 1968

■ Faculty Positions
- Massachusetts Institute of Technology, 1970-1977, 1980-1990
- Stanford University, 1977-1980
- The Scripps Research Institute, W. M. Keck Professor, 1990-present
- Skaggs Institute for Chemical Biology of TSRI, 1996-present

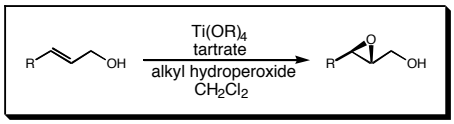
■ International Awards
- the Nobel Prize (with Noyori and Knowles), 2001
- Wolf Prize in Chemistry (with Kagan and Noyori), 2001
- King Faisal Prize for Science, 1995
- Tetrahedron Prize (with Noyori), 1993
- Prelog Medal, 1988
- Janssen Prize, 1986

■ 400 Publications

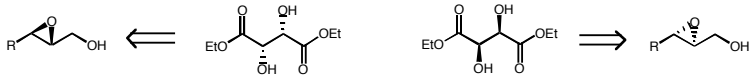
■ U.S./ACS Awards
- Chemical Sciences Award, National Academy of Sciences, 2000
- Top 75 Contributors to the Chemical Enterprise, 1998
- Arthur C. Cope Award, 1992
- Roger Adams Award in Organic Chemistry, 1997
- Arthur C. Cope Scholar, 1986
- Award for Creative Work in Organic Synthesis, 1983

Sharpless Asymmetric Epoxidation

A Powerful and Highly Enantioselective Reaction for Allylic Alcohols



- Readily available starting materials



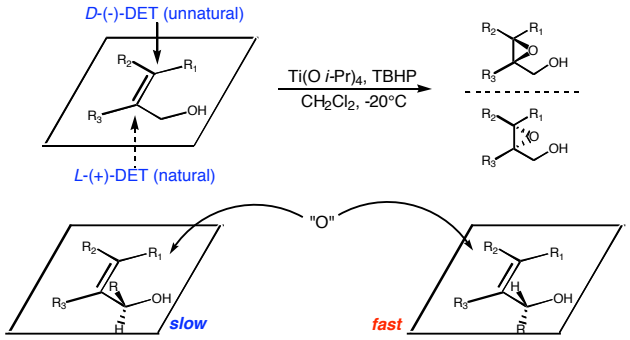
(-)-diethyl tartrate **(DET)** (+)-diethyl tartrate

- Allylic alcohol *must* be present
- Low catalyst loadings (>1%) due to the ligand acceleration effect (LAE) of tartrate
  - usually 5% Ti/6% tartrate to 10% Ti/12% tartrate
- Addition of molecular sieves enhances reactivity
- In situ derivatization is possible when catalytic Ti is used
- Selectivities are easily rationalized by inspection of the catalyst structure
- Generally, good chemical yields (>60%) and excellent enantiofacial selectivity (80-99%)

Asymmetric Epoxidation - Substrate Scope

Mneumonic for Predicting Enantiofacial Selectivity

- Nearly all substitution patterns are epoxidized in good yield with high enantiofacial selectivity

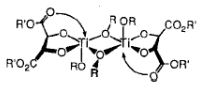


- Ti-catalyzed AE is compatible with a majority of functional groups

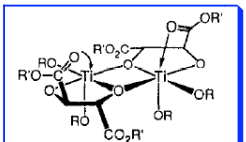
Compatible Functional Groups.				Imcompatible Groups
acetals, ketals	azides	ketones	silyl ethers	amines (most)
acetylenes	carboxylic esters	nitriles	sulfones	carboxylic acids
alcohols (remote)	epoxides	nitro	sulfoxides	mercaptans
aldehydes	ethers	olefins	tetrazoles	phenols (most)
amides	hydrazines	pyridines	ureas	phosphines

AE Catalyst Structure

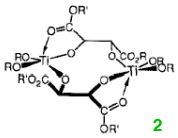
Spectroscopic Studies



1



Catalyst Structure



2

■ Structure of the active catalyst is a dimer

- Average Molecularity of $[Ti(tartrate)(OR)_2]_x$ in solution is 2
- ^{1}H and ^{13}C is consistent with the catalyst structure
- ^{17}O NMR shows two different tartrate alkoxides - of terminal and bridged alkoxides - rules out **2**
- ^{17}O NMR shows one type of monodentate alkoxide .
- FTIR shows only terminal isopropoxides, ruling out bridging alkoxides . → rules out **1**
- Crystal structure of related tartramide catalysts show the catalyst structure ..

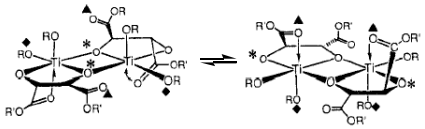
Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113.

Active 2:2 Ti:Tartrate Catalyst Complex

Fluxional Properties

■ Ability of Ti(IV) to exchange bound alkoxide in solution is essential

■ Binding tartrate oxygen provides rigid framework so bound ester can dissociate/associate without large structural changes



■ Unimolecular fluxional process

- when OR is large, association mechanism for exchange . blocked

■ VT NMR shows non-equivalent nature of carbinol methines in dimer complex

■ Lability of bound tartrate carbonyl allows free coordination sites for ligand exchange

- $[Ti(tartrate)(O\textit{i}\text{-}Pr)_2]_2$ and *i*-PrOH - ^{1}H NMR signals coalesce at RT
- $Ti(O\textit{i}\text{-}Pr)_4$ and *i*-PrOH - well-resolved signals at RT

VT NMR of Carbinol Methines of Tartrate Ester

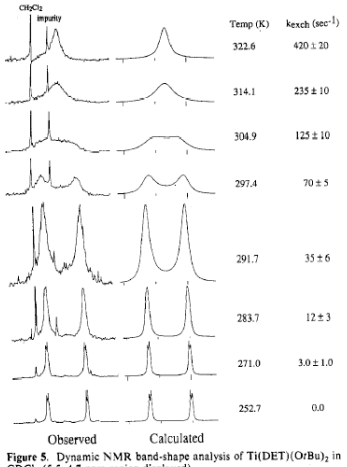
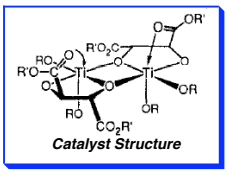


Figure 5. Dynamic NMR band-shape analysis of Ti(DET)(OrBu)$_2$ in $CDCl_3$ (5.5–4.7 ppm region displayed).

Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113

AE Active Titanium Catalyst

Support of a 2 : 2 Titanium : Tartrate Complex in Solution

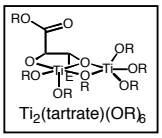


Catalyst Structure

■ A single 2 : 2 Ti:tartrate structure [Ti(tartrate)(OR) $_2$]$_2$ was found in NMR studies to comprise >80% of . solution mixture

■ Other structures are 2:1 Ti:tartrate complex Ti$_2$(tartrate)(OR)$_6$ (3.6 times slower than 2:2 complex) and Ti(OR)$_4$ (2.6 times slower than 2:2 complex)

■ Because the 2:1 complex is slower than the 2:2 complex, no disproportionation of the catalyst complex . is believed to occur



Ti$_2$(tartrate)(OR)$_6$

Pseudo-First-Order Rate Constants for Epoxidation of (E)-2-hexen-1-ol

entry	catalyst	rate$_{obs}$[a]	rate$_{rel}$	rate order in *i*PrOH
1	[Ti(DIPT)(O*i*Pr)$_2$]$_2$	11.5	1.00	−2.0 ± 0.1
2	Ti$_2$(DIPT)(O*i*Pr)$_6$	3.18	0.28	−1.4 ± 0.2
3	Ti(O*i*Pr)$_4$	4.37	0.38	−1.0 ± 0.2
4	[Ti(D*N*BnT)(O*i*Pr)$_2$]$_2$	0.34	0.03	
5	Ti$_2$(D*N*BnT)(O*i*Pr)$_6$	1.32	0.12	

[a] [Ti]$_{active}$ = 0.0130, [*i*PrOH] = 0.300, and [TBHP] = 0.0150. D*N*BnT, (*R*,*R*)-*N*,*N*′-dibenzyltartramide

Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113
Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Anfew. Chem. Int. Ed. Eng.* **1995**, *34*, 1059

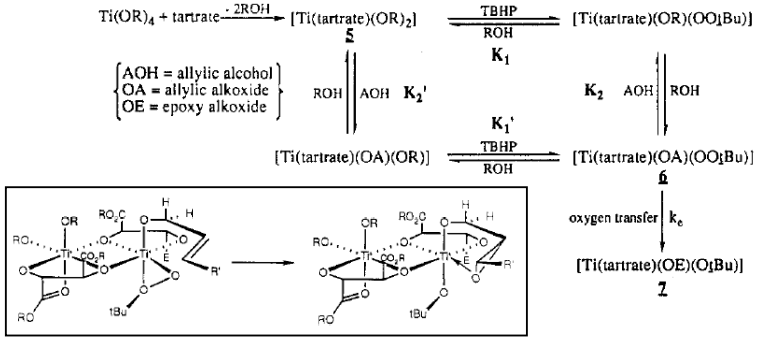
Mechanism for the Asymmetric Epoxidation

$$\text{rate} = k\,\frac{[\text{allylic alcohol}][\text{Ti-tartrate}][\text{ROOH}]}{[\text{ROH}]^2}$$

$k = k_e K_1 K_2$

k_e = rate of epoxidation
K_1, K_2 = equilibrium constants

■ first-order in allylic alcohol holds for several substrates over a 10-fold concentration range
■ active Ti-tartrate complex not thought to change molecularity during the reaction



Woodward, S.S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106
Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826

AE Mechanism

Tartrate and Alkoxide Binding to Titanium

- Tartrate species displaces two alkoxides - Ti complex is always a thermodynamic structure
- Alkyl peroxide is bidentate at oxygen centers
  - K_{eq}<1 for Ti(DIPT)(O *i*-Pr)$_2$ and Ti(DIPT)(O *t*-Bu)$_2$
  - Coordinated alkyl peroxide is more sterically demanding than ROH = bidentate ..

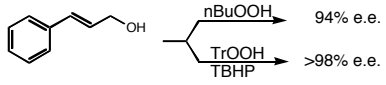
Equilibrium Constants for the Exchange of Hydroperoxide for Alkoxide Ligands

$$Ti(X)_3(OR) + R'OOH \rightleftharpoons Ti(X)_3(OOR') + ROH$$

$$K_{eq} = [Ti(X)_3(OOR')][ROH]/[Ti(X)_3(OR)][R'OOH]$$

entry	$Ti(X)_3(OR)$	R′OOH	K_{eq}
1	$Ti(OiPr)_4$	$(Me)_3COOH$	$K_1 = K_2 = 3.5 \pm 1.0$
2	$Ti(DIPT)(OiPr)_2$	$(Me)_3COOH$	0.7 ± 0.2
3	$Ti(DIPT)(OtBu)_2$	$(Me)_3COOH$	0.34 ± 0.1
4	$Ti(OiPr)_4$	$(Ph)_3COOH$	0.2 ± 0.1
5	$Ti(DIPT)(OiPr)_2$	$(Ph)_3COOH$	~ 0.01

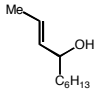
- Ti(O *i*-Pr)$_4$ is a less active epoxidation catalyst although ligands exchange faster = *Ligand Acceleration Effect*
- Asymmetric dependence on steric bulk of the peroxide



AE Mechanism

Tartrate and Alkoxide Ligand Effects on the AE

- 2 : 2 is the optimal Ti:tartrate ratio
  - less than 1 equivalent of tartrate decreases e.e. due to the non-asymmetric epoxidation
  - excess tartrate inhibits reactivity by forming the inert complex $Ti(tartrate)_2$
- Dimethyl, Diethyl, and Di-*iso*-propyl tartrate (DMT, DET, DIPT) all induce asymmetry
  - (*E*)-allylic alcohols - DET gives greater e.e. than DIPT
  - allyl alcohol - DIPT gives higher yield than DET
  - efficiency of kinetic resolution increases with steric bulk of the tartrate alkyl ester, hydroperoxide .. alkyl moiety, and *trans* olefin substituent



	relative rates at -20 C, 15h		
% e.e.	DIPT	DET	DMT
>96	74	28	15

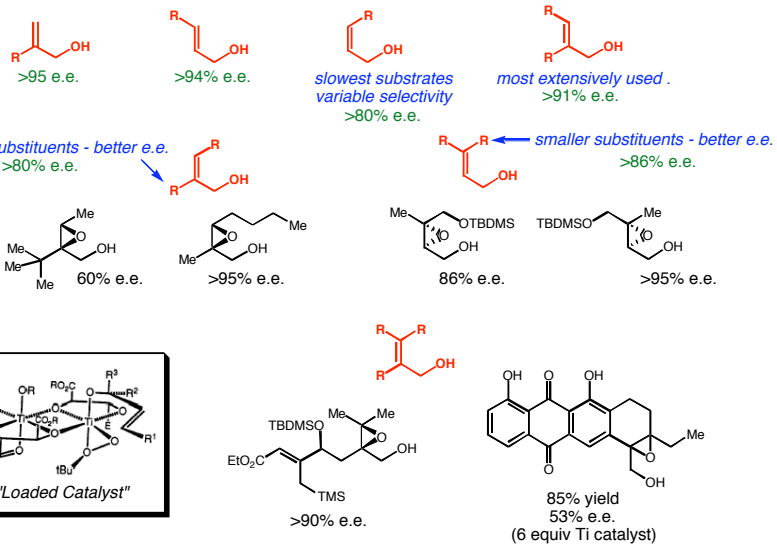
- Free alcohol inhibits catalyst reactivity
  - addition of mol sieves is essential to remove moisture
  - CH_2Cl_2 with MeOH stabilizer results in 10% decrease in reaction rate
- Added alcohols have no effect of the relative rates of kinetic resolutions - free ROH is not associated with the active complex for oxygen transfer

Woodward, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106

Other Efficient Substrates

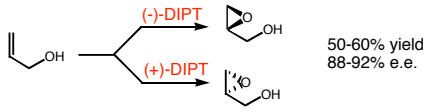
AE is a powerful and expansive transformation

- Most Olefin Classes give good chemical yield and excellent enantiofacial selectivity

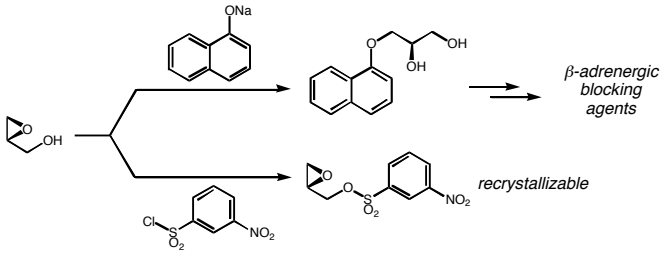


Substrate Scope

Allyl Alcohol



- Products could not be isolated until after the addition of molecular sieves became standard
- In situ derivatization allows for 3 differentiated carbon centers

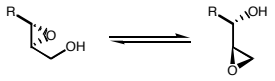


- optically active glycidol is the most versatile epoxy alcohol prepared by AE

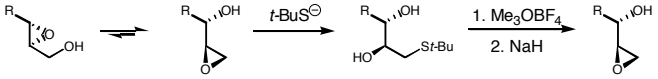
Sharpless, K. B.; et al. *J. Am. Chem. Soc.* **1987**, *109*, 5765
Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710

Exploiting the Payne Rearrangement

Epoxide Rearrangement of 2,3-epoxy-1-alcohols

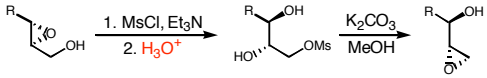


■ Thiolate trapping of product of the Payne equilibrium



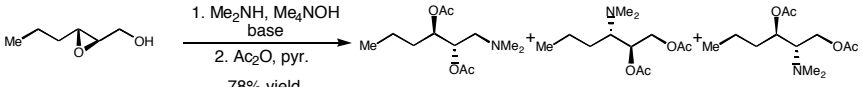
● slow addition of thiolate is necessary to suppress attack at C2 and C3 of undesired epoxide ..

■ Diol sulfonate method



loss of enantioselectivity

■ Amines prefer to react at C1 of epoxide

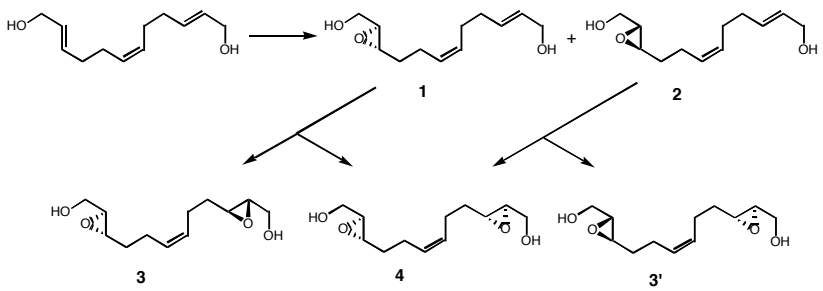


15.5 3.7 1.0

Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687

Epoxidation of Symmetrical Allylic Alcohols

High Selectivity is Still Observed



Distribution of bis-epoxides is determined by (S1 + S2)(S3 + S4)
S1 = selectivity for major epoxide S2 = selectivity for minor epoxide
S3/S4 = major/minor selectivity for second epoxidation

■ Selectivity for first and second expoxidation assumed to be the same value

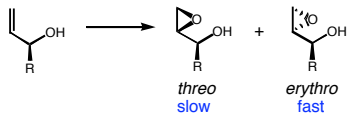
■ 90% e.e.= 19:1 selectivity ⟹ (19+1)(19+1) = 361:38:1 or **3:4:3'**, or a 99.45% e.e.

Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312

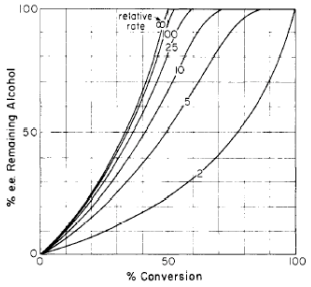
Kinetic Resolutions

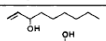
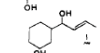
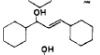
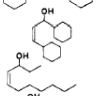
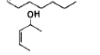
Exceptional Selectivities for the AE

- stereogenic center at C1, one enantiomer is more reactive than another
- Mathematical representation can predict the outcome of the kinetic resolution
  - k_{rel} = 25, need 60% conversion for 100% e.e.
- Ti-tartrate catalytic AE gives *erythro* products



threo slow *erythro* fast



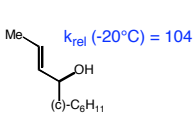
	allylic alcohol	time[b]	unreacted allylic alcohol[c] config[d]	% ee obsd[e]	% ee calcd[f]	rel rate,[a] k_{fast}/k_{slow}	epoxy alcohol product E/T[g]	$Ti(O\text{-}i\text{-}Pr)_4$ TBHP[h] E/T	$VO(acac)_2$ TBHP[i] E/T
(1)		12 days	*R*	>96	100	83	99/1	53/47	75/25
(2)		15 h	*R*	>96	100	104	97/3	38/62	80/20
(3)		15 h	*R*	>96			97/3	37/63	79/21
(4)[j]		15 h	*S*	~10			2/98	2/98	16/84
(5)		2 days	*R*	82[k]	95.2	16	40/60	4/96	22/78
(6)		6 days	*R*	91		~20[l]	81/19	5/95	25/75

(*Z*)-olefin →

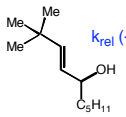
Catalyst System Effects on Kinetic Resolution

Size Does Matter

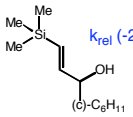
- Steric bulk on tartrate esters increase k_{rel}
  - dicyclohexyl tartrate (DCT) and dicyclododecyl tartrate have been used
- Steric bulk at the (*3E*) position increases k_{rel}



k_{rel} (-20°C) = 104

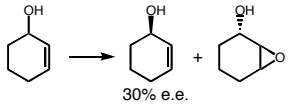


k_{rel} (-20°C) = 300

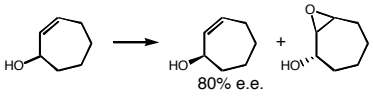


k_{rel} (-20°C) = 700

- Cyclic structures show lower selectivities
  - conformational restraints inhibits planar formation of olefin and carbinol needed for AE ..

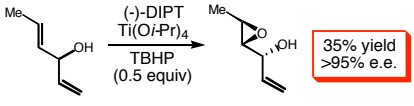


30% e.e.



80% e.e.

- Chemically similar olefins are discriminated with excellent selectivity

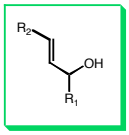


35% yield
>95% e.e.

8 possible faces for epoxide attack!!! .

Other Useful AE Kinetic Resolution Reactions

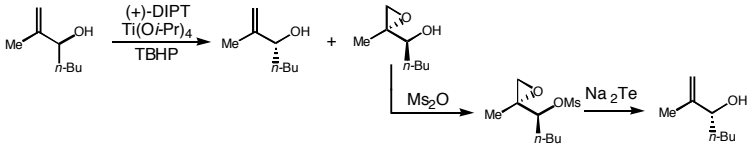
- SiR_3, I, Cl, and SnR_3 are tolerated at the (*3E*) position



Allylic Alcohol		Allylic Alcohol		Epoxy Alcohol	
R_1	R_2	Yield (%)	% e.e.	Yield (%)	% e.e.
C_5H_{11}	$SiMe_3$	42	>99	42	>99
CH_2OBn	$SiMe_3$	43	>99	48	>99
$(CH_2)_3CO_2Me$	$SiMe_3$	43	>99	45	>99
C_5H_{11}	I	49	>99		
Ph	I	43	>98		
C_5H_{11}	Cl	43	>99		
C_5H_{11}	$SnBu_3$	40	>99		84
CH_2OPh	$SnBu_3$	40	>99		

TMS: Kitano, Y.; et al. *J. Chem. Soc., Chem. Commun.* **1986**, 1323
Kitano, Y.; et al. *Tetrahedron.* **1988**, *44*, 4073
I, Cl: Kitano, Y; et al. *Tetrahedron Lett.* **1987**, *28*, 6351
$SnBu_3$: Kitano, Y.; et al. *Chem. Lett.* **1987**, 1523

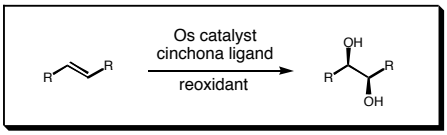
- Converting epoxy alcohol into desired allylic alcohol



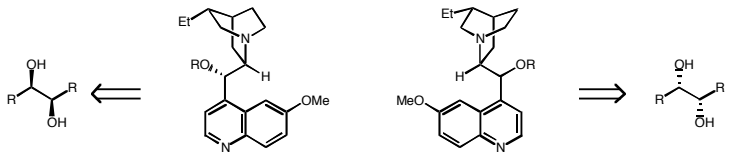
Discordia, R. P.; Dittmer, D. C. *J. Org. Chem.* **1990**, *55*, 1414

Sharpless Asymmetric Dihydroxylation (AD)

A Powerful and Practical Transformation for Enantioselective Synthesis



- No directing functional group is required
- Low levels of osmium catalyst are needed, due to the ligand acceleration effect (LAE)
- Cinchona alkaloid ligands are readily available
- Cinchona alkaloid diastereomers (quinine and quinidine) fulfill enantiomeric function



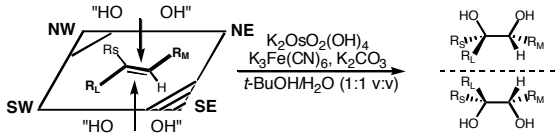
Dihydroquinidine (R=H) **DHQD**

Dihydroquinine (R=H) **DHQ**

- AD reactions are tolerant to air and water, work best at high concentrations = suitable for large scale preparations of enantiomerically pure diols

Mneumonic to Predict Enantioselectivity

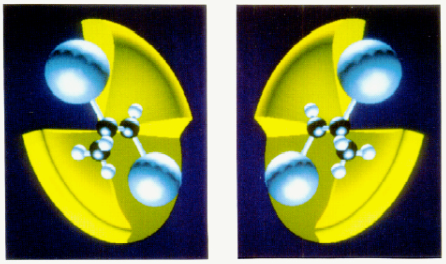
dihydroquinidine DHQD (AD-mix-β)



dihydroquinine DHQ (AD-mix-α)

- SE and NW corners provide modest steric barriers
- SW corner is attractive for flat aromatic or, in their absense, large aliphatic groups

Scheme III. Imaginary Asymmetric Catalyst Surface: A Mnemonic Device for Predicting Enantiofacial Selection[a]



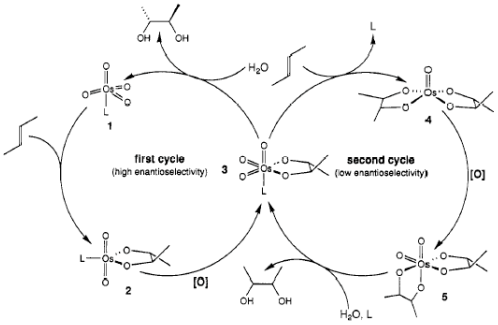
Quinidine-Based Catalyst Quinine-Based Catalyst

[a] The olefin is drawn as in Scheme I (i.e. large ball = R^1, methyl = R^2, medium ball = R^3, hydrogen = R^4).

J. Org. Chem. **1991**, *56*, 4585

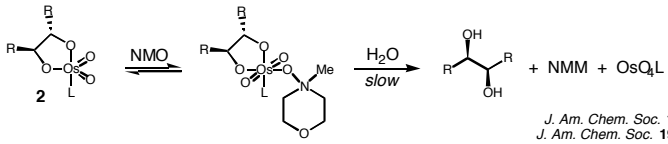
AD Catalytic Cycles

Two Pathways for Dihydroxylation



crystals obtained of **1, 2, 4**

- Extent of participation in secondary cycle depends on the rate of hydrolysis of **3**
- Rate of turnover in the second cycle is slower and tends to tie up the catalyst
- Second cycle is minimized with slow olefin addition and the addition of acetate
- NMO hydrolysis is slow and reversible so a second olefin has increased access to **3**



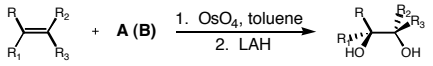
2

J. Am. Chem. Soc. **1989**, *111*, 737
J. Am. Chem. Soc. **1989**, *111*, 1123

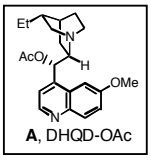
AD - Discovery Process

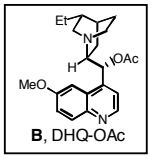
The Search for Enantioselectivity

- 1936 - Creigee showed that pyridine accelerates the rate of the reaction of stoichiometric OsO_4 with olefins
- 1976 - Sharpless and Akashi introduced *tert*-butyl hydroperoxide as cooxidant; Upjohn Process introduced *N*-methylmorpholine *N*-oxide (NMO) as cooxidant
- 1979 - Sharpless and Hentges employed chiral pyridine ligands, low enantioselection observed; cinchona alkaloids gave good asymmetric induction in the stoichiometric dihydroxylation



olefin	ligand	configuration	% yield	% e.e.
styrene	A	*S*	90	65
	B	*R*	62	61
(*Z*)-1-phenylpropene	A	*S,R*	82	27
	B	*R,S*	85	26
(*E*)-1-phenylpropene	A	*S,S*	90	46
	B	*R,R*	66	49
(*E*)-stilbene	A	*S,S*	90	83
	B	*R,R*	85	82
(*Z*)-4,4-dimethyl-2-pentene	A		78	<5
(*E*)-4,4-dimethyl-2-pentene	A		78	37
(*E*)-3-hexene	A	*S*	69	50



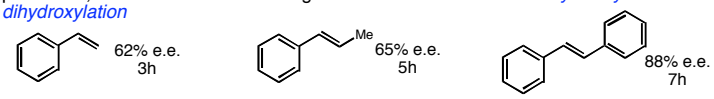


Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986
Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

AD Discovery Process

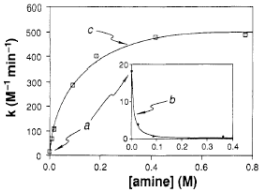
Discovery of a Catalytic, Ligand-Accelerated System

- 1987 - Sharpless and Marko combined the cinchona ligands with Upjohn's NMO reoxidation procedure, Jacobsen uncovers the ligand acceleration effect = *catalytic asymmetric dihydroxylation*



❒ *cis* olefins, terminal olefins, alkyl olefins are still problematic

LAE of AD of styrene at 25 C



(point) a - no added amine, *b* - quinuclidine, *c* - (DHQD)OBz

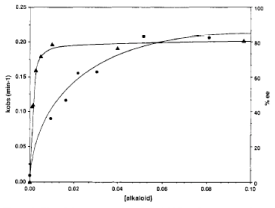


Figure 1. Plot of the concentration of alkaloid ligand **1** vs observed rate constant k_{obsd} (●) and % ee (▲) for the catalytic dihydroxylation of *trans*-stilbene. Conditions: 25 °C, $[OsO_4]_0 = 3.8 \times 10^{-4}$ M, $[NMO]_0 = 0.2$ M, $[stilbene]_0 = 0.1$ M.

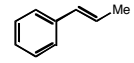
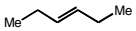
- Cinchona alkaloids exhibit a large ligand acceleration effect, quinuclidine has a deceleration effect
- optimal e.e. values are found with extremely low levels of alkaloid, well below that required to achieve rate saturation
- LAE proposed to be caused by formation of the OsO_4*L complex, which, for styrene, is 23 times more reactive than free OsO_4

Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.;Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968
Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.;Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737

AD Discovery Process

Finding the Optimal Catalytic System

■ Wai found the non-enantioselective second cycle, slow addition of the olefin and the addition of an acetate nucleophile could serve as a partial remedy. *J. Am. Chem. Soc.* **1989**, *111*, 1123

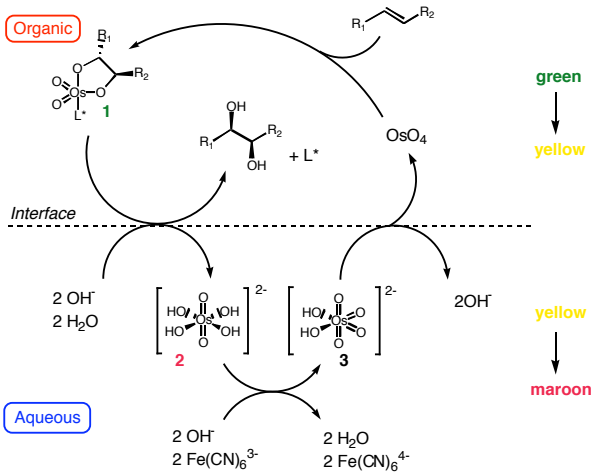
		catalytic[a]		
	stoichiometric[a]	original	acetate[b]	slow addition
	87% e.e.	65	73	86 (5h)
	69% e.e.	20	64	70 (10h)

[a] reactions run at 0 °C with (DHQD)CLB [b] 2 equiv $NH_4OAc \cdot 4H_2O$

■ Kwong applied the biphasic ferricyanide re-oxidant system, eliminating the second catalytic cycle and the need for slow addition of the olefin. *Tetrahedron Lett.* **1990**, *31*, 2999

■ Amberg found the "sulfonamide effect" - the addition of organic sulfonamides facilitates catalyst turnover for substrates whose osmate esters resist hydrolysis *J. Org. Chem.* **1992**, *57*, 2768

Avoiding the Second Catalytic Cycle with $K_3Fe(CN)_6$



■ K_2CO_3 is needed to hydrolyze ester **1**, $K_3Fe(CN)_6$ alone produces no reaction

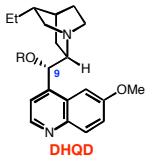
■ Os(VI) species **2** was isolated as an ammonium salt

■ Reaction has characteristic color changes in non-polar solvents

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

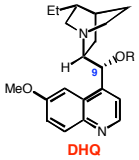
AD Discovery Process

Ligand Modifications in the 1990s



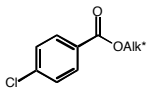
DHQD

derivatization at the C_9 position was found to be the most effective

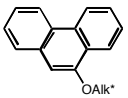


DHQ

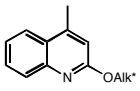
■ First Generation Monomeric Ligands



Chlorobenzoate (CLB)
J. Am. Chem. Soc. **1988**, *110*, 1968



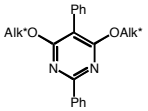
Phenanthryl Ether (PHN)



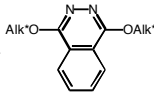
4-Methyl-2-quinolyl Ether (MEQ)
Tetrahedron Lett. **1990**, *31*, 3817.
J. Org. Chem. **1991**, *56*, 4585

■ Second Generation Dimeric Ligands

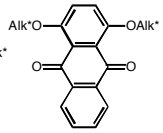
Diphenylpyrimidine (PYR)
J. Org. Chem. **1993**, *58*, 3785

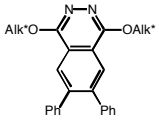


Phthalazine (PHAL)
J. Org. Chem. **1992**, *57*, 2768

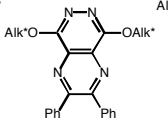


Anthraquinone (AQN)
Angew. Chem. Int. Ed. Eng. **1996**, *35*, 448





Diphenyl phthalazine (DP-PHAL)
J. Org. Chem. **1995**, *60*, 3940



Diphenyl pyrazinopyridazine (DPP)
J. Org. Chem. **1995**, *60*, 3940

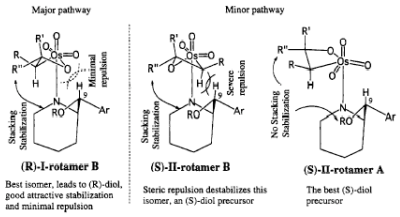
Rationalization for Face Selectivity

Steric and Substitutent Ligand Effects for Sharpless Model

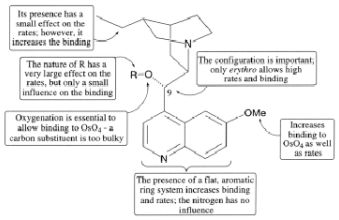
■ Enantioselectivity may arise from two factors:

1. transition state destabilization between an . oxetane substituent and H(9) of the ligand
2. transition state stabilization by favorable stacking interactions between oxetane substituents and aromatic shelf of ligand

■ the AD is thus primarily dependent on non-covalent interactions since both diastereomers allow favorable stacking



■ (S)-II-rotamer B may have increased H - H(9) interactions in the oxetane rearrangement



■ alkaloid core is ideally set up to ensure high rates, binding and solubility

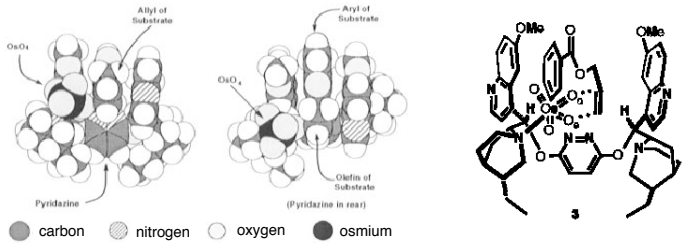
■ rates and enantioselectivities are influenced by the nature of the O9

■ the binding to OsO_4 is independent of the O9 substituent, but the oxygenation is essential for binding

Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8478

Face Selectivity Models

■ The Corey Model

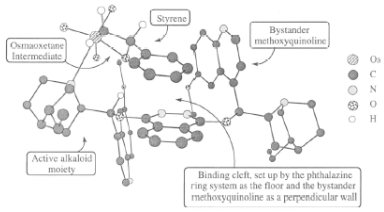


- U-shaped binding pocket, set up by two parallel methoxyquinoline units
- OsO_4 is bound to one quinuclidine unit in a staggered conformation
- aryl-aryl interactions of the substrate position it in the pocket
- olefin π-orbital and low-lying *d*-orbitals on Os(VIII) interact
- directly produces energetically-favored pentacoordinate Os(VI) ester
- relief of N-Os eclipsing interactions when substrate binds to oxygens
- there is no 3-D arrangement for effective binding in U-shaped pocket if substrate comes from .. opposite face

Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038

Face Selectivity Models

■ The Sharpless model



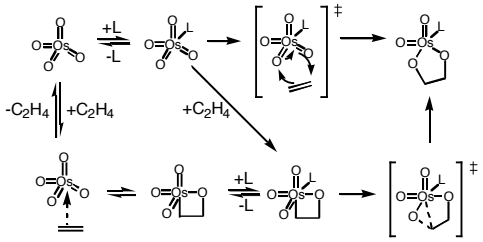
- L-shaped binding cleft formed by aromatic linker and methoxyquinoline - one of the .. most stable conformations of the ligand (*J. Am. Chem. Soc.* **1994**, *116*, 1278)
- aromatic substrates give good stabilization of oxetane-like transition state .
  - ❒ stacking interactions with the PHAL floor, edge-to-face interactions with methoxyquinoline ring
- Sharpless model can rationalize first generation ligands as well
  - ❒ lower selectivities with first generation ligands arise from poorer binding due to lack of the bystander aromatic system and loss of edge-to-face interactions

Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8478

AD Mechanism

[3+2] Creigee-Corey-Noe or [2+2] Sharpless Pathway?

[3+2] Cycloaddition



[2+2] Osmaoxetane Formation

■ The mechanistic studies are inconclusive to date, though recently the [3+2] pathway has become favored.

■ Hammett studies - inconclusive
Sharpless *J. Am. Chem. Soc.* **1997**, *119*, 1840

■ Theory - [3+2]
Maseras *J. Am. Chem. Soc.* **1999**, *121*, 1317
Morokuma *J. Am. Chem. Soc.* **1996**, *118*, 11660
Frenking *ACIEE* **1996**, *35*, 2817
Houk, Norrby *J. Am. Chem. Soc.* **1999**, *121*, 10186

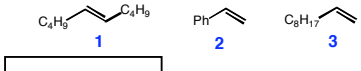
■ Eyring Plots - [2+2]
Sharpless *ACIEE* **1993**, *32*, 1329

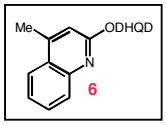
■ Kinetic Isotope Effects - [3+2]
Corey, Noe *Tetrahedron Lett.* **1996**, *37*, 4899
Sharpless, Houk *J. Am. Chem. Soc.* **1997**, *199*, 9907

■ FMO - [3+2]
Sharpless *J. Am. Chem. Soc.* **1997**, *119*, 1840

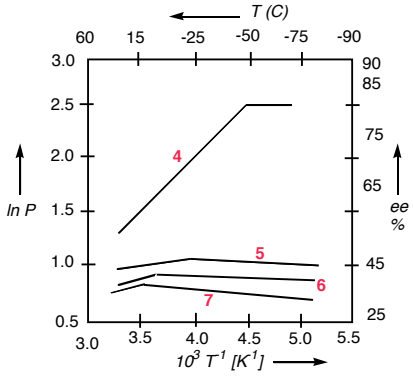
Temperature Effects on the AD

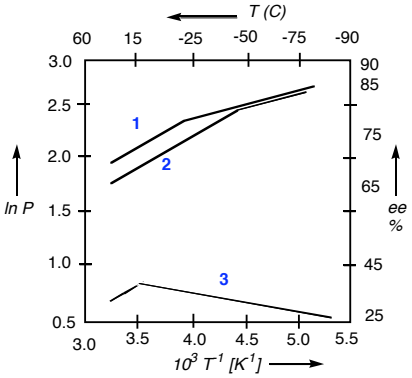
Evidence for a Stepwise Mechanism





4 $(DHQD)_2Pyr$
5 (DHQD)PHN
6 (DHQD)MEQ
7 (DHQD)CLB





■ $P = k_{major\ diol}/k'_{minor\ diol}$

■ 2 linear regions with an inversion point

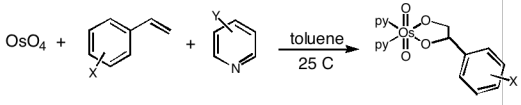
■ Can be explained by a reaction pathway with at least two enantioselective steps whose influences depend on temperature

■ Supports a stepwise [2+2] mechanism and *not* a concerted [3+2] mechanism

Hammett Kinetic Studies

Something More Complex than Expected is Operating

- Non-linearity first observed in the linear free energy plots



  - only minor differences in ceiling rate constants for pyridines of different basicities

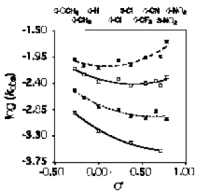


Figure 7. Combined Hammett plots based on the measured pseudo-first-order rate constants for osmylations of substituted styrenes (● = 4-pyrrolidinopyridine, ○ = pyridine, ◆ = 4-cyanopyridine, ◇ = 3,5-dichloropyridine; $[OsO_4]_o = 2.00 \times 10^{-4}$ M, $[styrene]_o = 4.00 \times 10^{-3}$ M, $[pyridine]_o = 1.25 \times 10^{-1}$ M).

- No amine acceleration gives a LFE linear correlation ($\rho = 0.9$)
- Not a phenomenon just observed with pyridine

Quinuclidine

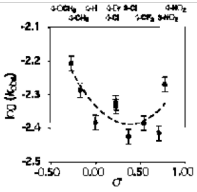


Figure 9. Hammett plot based on the observed pseudo-first-order rate constants for the quinuclidine-accelerated osmylation of substituted styrenes in toluene at 25 °C ($[OsO_4]_o = 2.00 \times 10^{-4}$ M, $[styrene]_o = 4.00 \times 10^{-3}$ M, $[quinuclidine]_o = 1.25 \times 10^{-1}$ M).

DHQD-CLB

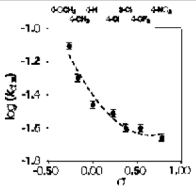
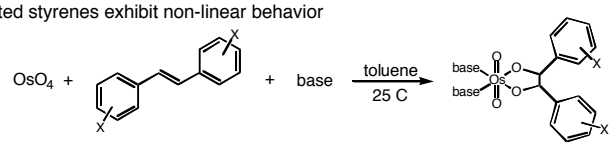


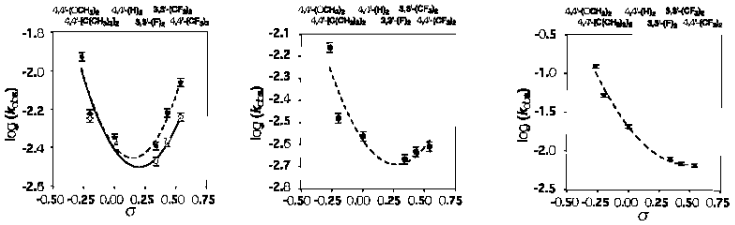
Figure 10. Hammett plot based on the observed rate constants in the DHQD-CLB-accelerated osmylations of substituted styrenes in toluene at 25 °C ($[OsO_4]_o = 2.00 \times 10^{-4}$ M, $[styrene]_o = 4.00 \times 10^{-3}$ M, $[DHQD\text{-}CLB]_o = 5.00 \times 10^{-2}$ M).

Extending the Hammett Studies

Non-linearity applies to all amine-accelerated reactions

- Substituted styrenes exhibit non-linear behavior





DMAP | Quinuclidine | DHQD-CLB

- Deviation of linearity appears to be related to the ability of the amine to coordinate to Os
  - DMAP, quinuclidine - strong curvature, stronger binding
  - 4-cyanopyridine, DHQD-CLB - moderate curvature, weaker binding
- Alkene structure - mono-, di-, or trisubstituted (not shown) - shows no simple correlation

Concluding the Hammett Studies

What does it all mean?

- What is observed
  - all substrates show a non-linear behavior
  - amount of curvature is dependent on basicity of amine, but ceiling rate constants do not drastically . deviate
  - minima position values depend on electronic character of styrenes or binding constant of amine ..
- Keep in mind:
  - LFE plot of non-amine-catalyzed osmylation shows the expected linear behavior ..
  - both [2+2] or [3+2] mechanisms should be close to linear - no charge build-up in the transition state for either pathway
- What can be concluded
  - the rate-determining step is not uniform, even with closely-related reactions
  - two distinct mechanisms for amine-accelerated reactions ..
  - a positive ρ value is consistent with a nucleophilic [3+2] pathway
    a negative ρ value is consistent with an electrophilic [2+2] pathway .
  - taken with temperature studies that show an inversion point in Eyring plots, two different operating mechanisms need to be strongly considered

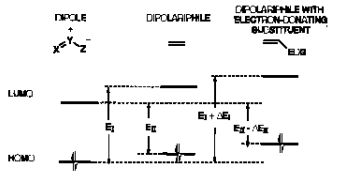
Hammett studies are inconclusive and do not favor one definite mechanism

Frontier Molecular Orbital Considerations

Analogy to 1,3-Dipolar Cycloadditions

- Sustmann proposed an FMO model based on pericyclic cycloadditions to explain non-linear Hammett relationships

Sustmann, R. *Tetrahedron Lett.* **1971**, 2721



- Three types of 1,3-dipolar cycloadditions

Type I - HOMO of dipole, LUMO of dipolarophile; accelerated by EDG on dipole and EWG on dipolarophile ...

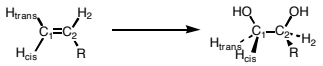
Type II - HOMO/LUMO of dipole and dipolarophile are roughly equal in energy; ideally would result in parabolic Hammett plots

Type III - HOMO of dipolarophile, LUMO of dipole; accelerated by EWG on dipole and EDG on dipolarophile ...

- FMO cannot explain the change in minima on the Hammett plots as a function of ligand
  - Ligand acceleration steric effects must override the electronic effects...

Kinetic Isotope Effects

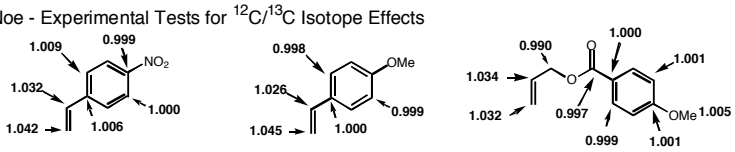
Support of a [3+2] Mechanism



- Houk, Sharpless, and Singleton - calculated and experimental kinetic isotope effects
  - R = *tert*-butyl, regioisomeric control by forcing C_2 to bind away from the Os center.
  - C_1 would be expected to have a large KIE due to the rate-limiting osmaoxetane rearrangement in [2+2] pathway.
  - C_1 and C_2 would be expected to have similar KIE in the concerted [3+2] cycloaddition...

	H_{C2}	H_{cis}	H_{trans}	C_2	C_1
			Calculated[a]		
			(a) "(3 + 2)"		
2	0.907	0.913	0.921	1.025	1.025
3	0.909	0.912	0.921	1.025	1.024
			(b) Formation of an Osmaoxetane		
6	0.892	0.957	0.972	1.050	1.026
7	0.885	0.962	0.980	1.051	1.025
8	0.832	0.927	0.937	1.046	1.021
			(c) Ring-Expansion		
9	0.880	0.964	1.094	0.989	1.039
10	0.933	0.976	1.068	0.984	1.047
			Experiment[b]		
1	0.906(9)	0.919(5)	0.925(7)	1.027(1)	1.028(3)
2	0.908(4)	0.917(8)	0.926(14)	1.026(3)	1.025(3)

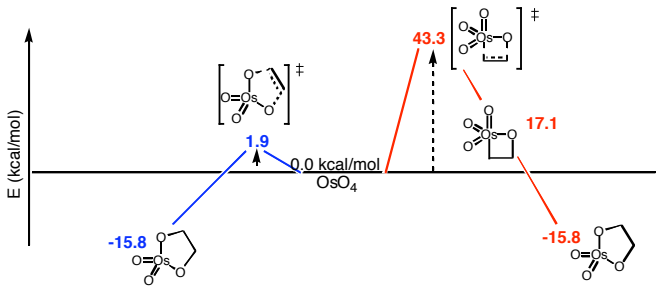
- Corey, Noe - Experimental Tests for $^{12}C/^{13}C$ Isotope Effects



Theory Strongly Refutes a [2+2] Pathway

Osmaoxetane Formation is Energetically Disfavored

- Metalloxetanes are known to form stable adducts, but the barrier to the osmaoxetane formation is believed to be prohibitive to the initial cyclization



- With NH_3 added to computations, activation barrier increases to 50.3 kcal/mol while the [3+2] adduct becomes more exothermic by about 8 kcal/mol.
- Calculations carried out on B3LYP level of density functional theory
- Computations were done with many different levels of theory, but all of them exhibit the same trend. (These values taken from *J. Am. Chem. Soc.* **1996**, *118*, 11660)

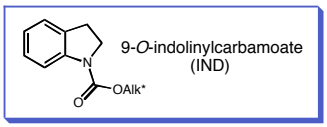
Cinchona Alkaloid Ligands and their Substrate Preferences

Recommended Ligands by Olefin Class

- Second Generation Ligands have the broadest scope
- Phthalazine (PHAL) ligands are most widely used due to their availability and broad scope
  - PHAL ligands gave inferior results for aliphatic olefins, especially if the substituents are small or branched near the double bond

Olefin Class						
Preferred Ligand	R = aromatic DPP, PHAL R = aliphatic AQN R = branched PYR	R_1, R_2 = aromatic DPP, PHAL R_1, R_2 = aliphatic AQN R_1, R_2 = branched PYR	R_1, R_2 = aromatic DPP, PHAL R_1, R_2 = aliphatic AQN	Acyclic IND Cyclic PYR, DPP, AQN	PHAL, DPP, AQN	PYR, PHAL

- "The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substrates"
- PYR ligands - sterically encumbered olefins, terminal alkyl olefins
- DPP, DP-PHAL - aromatic olefins and certain *cis*-1,2-disubstituted olefins, DPP usually better than DP-PHAL
- IND ligands - *cis*-1,2-disubstituted olefins

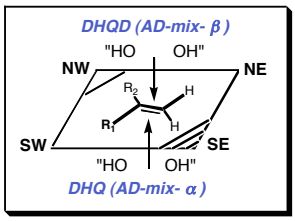


Kolb, H.C.; Sharpless, K.B., *Transition Metals for Organic Synthesis*

α-Alkyl Styrenes

Reveral of Facial Selectivity with PHAL and PYR ligands

"magnet" for aromatic groups (PHAL) *or* alkyl groups (PYR)



R_1	R_2	Best Ligand
aromatic	H	PHAL
aliphatic	H	PYR
aromatic	aliphatic	PHAL
aliphatic	aromatic	PYR

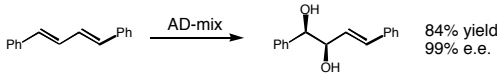
entry	olefin	$(DHQD)_2$-PHAL	$(DHQD)_2$-PYR	entry	olefin	$(DHQD)_2$-PHAL	$(DHQD)_2$-PYR	entry	olefin	$(DHQD)_2$-PHAL	$(DHQD)_2$-PYR
1		94	69	8		8	*-37*	13		58	*-59*
2		78	20	9		95	60	14		55	*-66*
3		60	*-16*	10		82	*-59*	15		57	*-68*
4		56	*-28*	11		92	78	16		*-53*	*-77*
5		48	*-30*	12		70	*-24*				
6		37	*-35*								
7		82	*-8*								

- Enantioselectivity drops with increasing chain length (entries 1-8)
- No reversal in bicyclic cases, unless system is held in an unfavorable conformation (entries 9-11)
- Enantioselectivity decreases with increasing cycloalkyl ring size (entries 12-16)

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

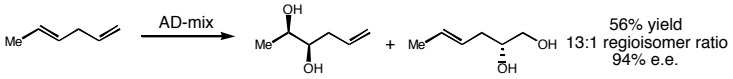
Asymmetric Dihydroxylation of Dienes

A Study in Regioselectivity

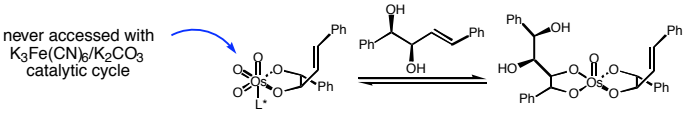


- Unsymmetrical dienes show preference for:
  1. the most electron-rich olefins
  2. *trans* over *cis* olefins
  3. terminal olefins in α,β,δ,γ-unsaturated esters

- Unconjugated dienes follow these rules as well, yields are lower due to overoxidation



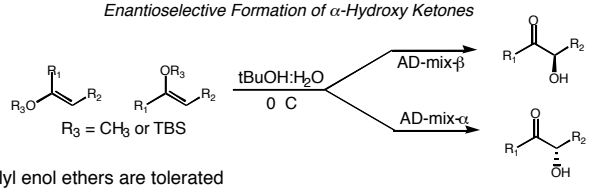
- $K_3Fe(CN)_6/K_2CO_3$ must be used to produce ene-diols, NMO overoxidizes to the tetraol
  - the ene-diol would be preferentially oxidized over the diene in the second catalytic cycle
  - the ene-diol would have a stronger affinity for the trioxo Os(VI) glycolate than the diene



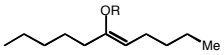
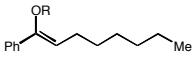
Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.
Zu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495

Asymmetric Dihydroxylation of Enol Ethers

Enantioselective Formation of α-Hydroxy Ketones



- alkyl and silyl enol ethers are tolerated
- good *Z*/*E* ratio is not necessary to obtain useful enantioselectivity

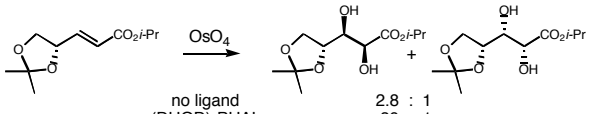
enol ether	R	*E*/*Z* ratio	% e.e. AD-mix-β	% e.e. AD-mix-α
	Me	4/96	95	96
	TBS	25/75	89	86
	Me	33/67	85	85
	TBS	1/>99	97	n.d.
	Me	33/67	94	92
	TBS	1/>99	99	99
	Me	0/100	99	98
		100/0	90	n.d.
	TBS	3/97	97	n.d.

Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J Org. Chem.* **1992**, *57*, 5067

Double Diastereoselection

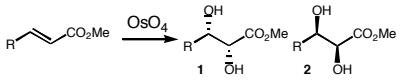
AD of Chiral Olefins

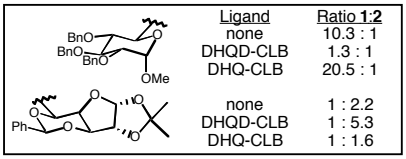
■ Matched/mismatched cases with the diastereoselectivity for chiral olefins



no ligand	2.8 : 1
$(DHQD)_2PHAL$	39 : 1
$(DHQ)_2PHAL$	1 : 1.3

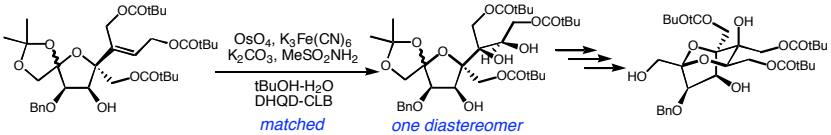
■ Ligands cannot always override inherent diastereoselectivity





Ligand	Ratio **1**:**2**
none	10.3 : 1
DHQD-CLB	1.3 : 1
DHQ-CLB	20.5 : 1
none	1 : 2.2
DHQD-CLB	1 : 5.3
DHQ-CLB	1 : 1.6

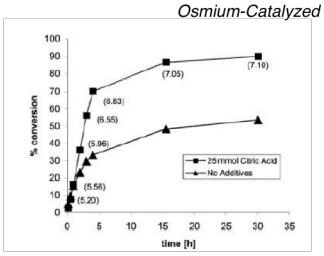
■ Used to set the final two stereocenters in squalestatin 1



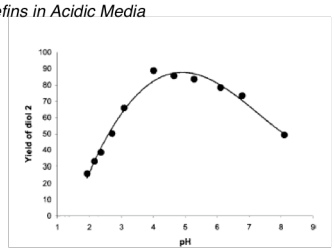
Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483

New Developments in Dihydroxylation

Osmium-Catalyzed Dihydroxylation of Olefins in Acidic Media

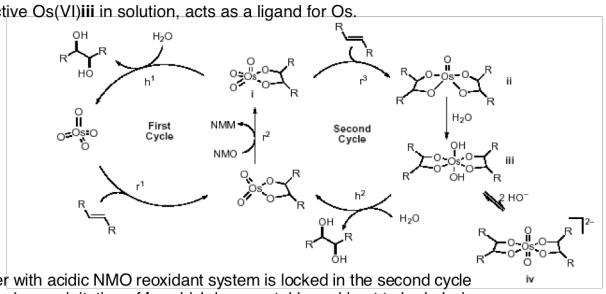


Optimal activity with pH = 4-6



■ Citric acid is the additive of choice

- neutralizes NMM formed, buffers the reaction
- keeps active Os(VI)**iii** in solution, acts as a ligand for Os.



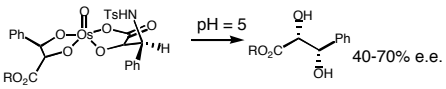
- turnover with acidic NMO reoxidant system is locked in the second cycle
- acid blocks precipitation of **iv**, which is very stable and inert to hydrolysis

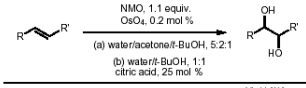
Osmium-Catalyzed Dihydroxylation of Olefins with Citric Acid

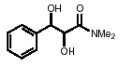
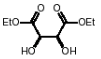
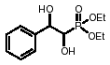
Enhanced Reactivity, Expanded Scope

- Unsaturated esters, amides, phosphonates, nitriles, tertiary amines, tetrazoles can now be dihydroxylated in good yields
- Reactions can now be heated to 100°C without catalyst or oxidant decomposition.
- Trimethylamine oxide (TMO) can be used as the reoxidant = easier purification of diol products
- Adding 10 mol % sodium citrate to AD results in 0% e.e. ⇒ citrate forces system into second catalytic cycle.
- Reactions can now be heated to 100°C without catalyst or oxidant decomposition.
- Chiral acid sources give initial e.e.'s up to 70%

Angew. Chem. Int. Ed. Eng. **2002**, 472



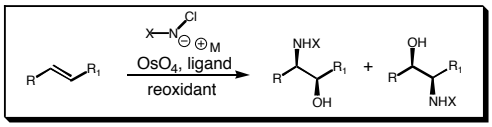


Entry	Product	Yield [%] (a) standard conditions	Yield [%] (b) new conditions
1		50	96
2		<10	76
3		45	67
4		<40	78
5		30	77

Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421

Sharpless Asymmetric Aminohydroxylation (AA)

A Route to Optically Active Vicinal Amino-Alcohols

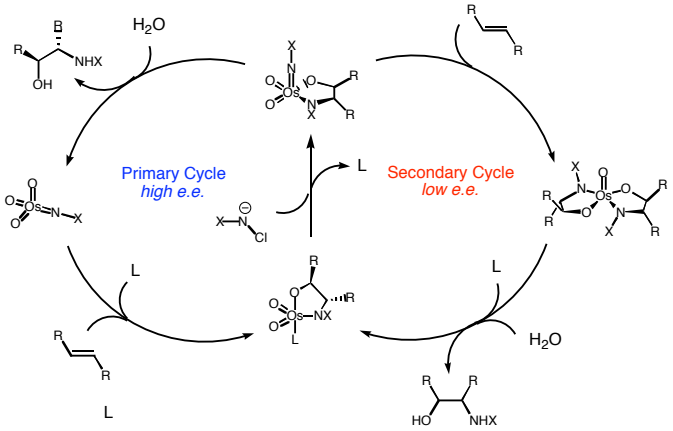


- A challenge in regioselectivity, chemoselectivity, and enantioselectivity
- No directing functional group is required
- Aza-analogue to the AD, uses cinchona alkaloids to induce chirality
- Active osmium catalyst trioxo(imido)osmium (VIII) is generated *in situ*

- Olefin scope is limited ⟹ still a new reaction under investigation
- X = sulfonamide, carbamate, amide

Asymmetric Aminohydroxylation Catalytic Cycle

Similar to the AD Mechanism



- Inhibit secondary cycle by increasing the rate of hydrolysis
  - reactions run in 50% water
  - large, hydrophobic groups on nitrogen decrease the rate of hydrolysis .

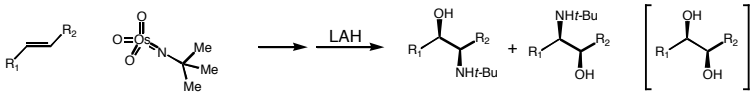
Sharpless, K. B. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 451
Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 2810

Development of an Asymmetric Aminohydroxylation

20 years of an Asymmetric Procedure

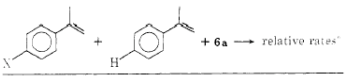
- 1975 - first report of non-catalytic oxyamination to form 1,2 amino-alcohols with OsO_3(N*t*-Bu)
  1976 - addition of Chloramine T makes the oxyamination catalytic
  1996 - Cinchona alkaloid ligands make the first *asymmetric* and *catalytic* hydroxyamination

- Alkylimidoosmium compounds (1975)



- N-C bond is formed at the least hindered carbon .
- reaction rates : mono- > di-, trisubstituted olefins .
- *trans* are faster than *cis* aminohydroxylations
- high functional group compatability
- only *t*-BuNH_2 forms (alkylimido)osmium complexes
- *t*-Bu amine is hard to cleave
- Hammett plots show parabolic behavior .
- pyridine enhances diol formation .
- quinuclidine addition suppresses diol formation

Relative Rates of Oxyamination



X	$\frac{k_X}{k_H}$ (CH_2Cl_2)	$\frac{k_X}{k_H}$ (pyridine)
$N(Me)_2$	4.26	1.63
OMe	1.49	1.04
Me	1.14	1.01
H	1.00	1.00
Cl	0.95	1.23
CN	1.93	1.53

Sharpless, K. B.; Patrick, D. W.; Truesdale, L. R.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305
Patrick, D. W.; Truesdale, L. R.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628
Hentges, S. G.; Sharpless, K. B. *J. Org. Chem.* **1980**, *45*, 2257

Development of an Asymmetric Aminohydroxylation

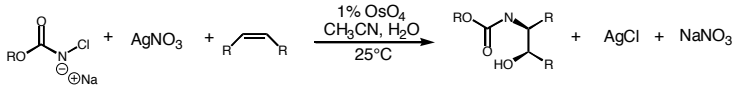
Addition of Sulfonamides and Carbamates as Alternate Nitrogen Sources

■ Chloroamine T (TsHNCl) makes the oxyamination catalytic

- $AgNO_3$ is needed to precipitate Cl, which inhibits catalyst cycle
- Alkyl 1,1-disubstituted olefins and strained cyclic olefins are poor substrates
- Addition of $BnEt_3NCl$ as a phase-transfer catalyst replaces the use of silver

Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177
Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544

■ *N*-Chloro-*N*-argentocarbamates



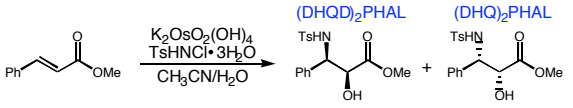
- Better regioselectivity than sulfonamides, more efficient for electron deficient olefins ..
- Addition of $Et_4NOAc \cdot 4H_2O$ accelerates the reaction
- Use of $Hg(NO_3)_2$ for trisubstituted and less reactive mono- and disubstituted olefins

Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1976**, *100*, 3596
Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1980**, *45*, 2710

Development of an Asymmetric Aminohydroxylation

Cinchona Ligands make an Asymmetric System

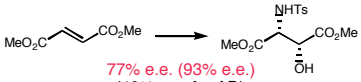
■ Using the same conditions as the stoichiometric Os system, cinchona alkaloids are added to the reaction (33-81% e.e.)



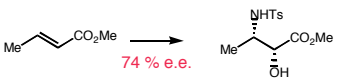
71% e.e.

81% e.e.
89% e.e. ($tBuOH/H_2O$)
>99% e.e. (recryst. MeOH)

■ Electron-deficient olefins give good regioselectivity, good yields

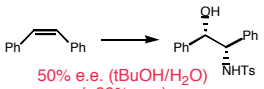


77% e.e. (93% e.e.)
(40% e.e. for AD)

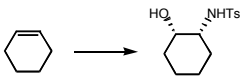


74 % e.e.

■ *Cis* olefins can give useful levels of selectivity



50% e.e. ($tBuOH/H_2O$)
(>99% e.e.)



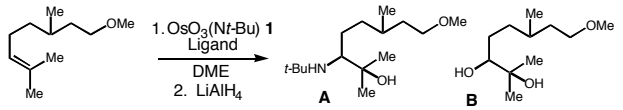
45% e.e.
(>99% e.e.)

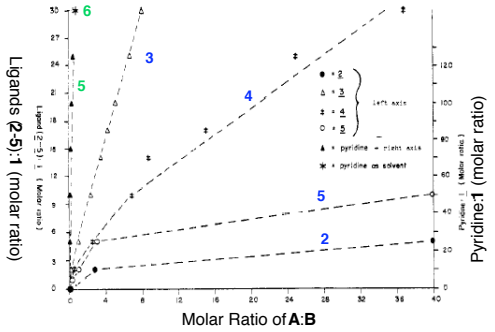
■ *Trans* olefins follow the mneumonic for predicting AD facial selecitvity

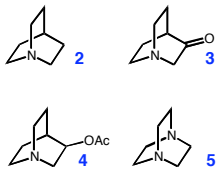
Li. G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 451

Asymmetric Aminohydroxylation

A Challenge in Chemoselectivity







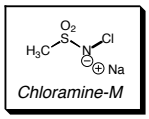
■ All bind more tightly to Os center than pyridine

■ Ratio of **A**:**B** correlates to the nucleophilicity of the ligand

■ Temperatures about 25°C increase diol formation

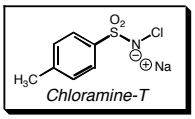
■ Cinchona alkaloids thus provide access to optically active amino-alcohol as major products

Hentges, S. G.; Sharpless, K. B. *J. Org. Chem.* **1980**, *45*, 2257



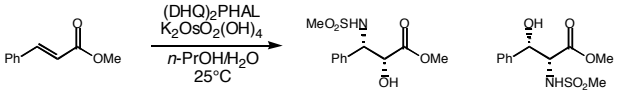
Sulfonamide AA

The Smaller, the Better



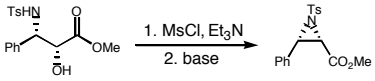
■ Smaller residues on the sulfonamide give better yields, scope, and reactivity

- Chloramine-M is more effective than Chloramine-T .
- Chloramine-M has a ligand accelerating effect, Chloramine-T has a decelerating effect ..



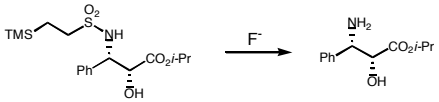
Chloramine-T (3.5h)	76 (60% e.e.)	:	24
Chloramine-M (40 min)	90 (89% e.e.)	:	10

■ Sulfonyl acidifies the N-H bond allow for N-alkylation under basic conditions



■ Sulfonamide cleavage is difficult - Birch conditions, Red-Al, 33% HBr/HOAc

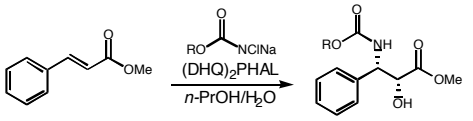
■ 2-Trimethylsilylethanesulfonamide is comparable to Chloramine-M



Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 2810
Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099

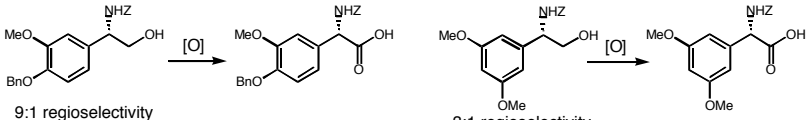
Carbamate AA

- best results in 1:1 *n*-PrOH:H_2O
- smaller carbamates show better enantioselectivity, regioselectivity, and yield
  - suppression of the second catalytic cycle, better fit into the catalyst binding pocket ..



R	% e.e.	% yield
Et	99	78
Bn	94	65
t-Bu	78	71

- Sodiocarbamates are superior to their silver or mercury analogues
- Cinnamates, acrylates, terminal olefins make good substrates
  - TEMPO oxidation (TEMPO/NaOCl) gives optically active arylglycines from AA of styrenes



9:1 regioselectivity
76% yield for AA
98% e.e.

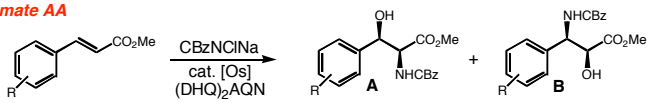
3:1 regioselectivity
71% yield for AA
90% e.e.

Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 2813

Reversal of Regioselectivity with AQN alkaloids

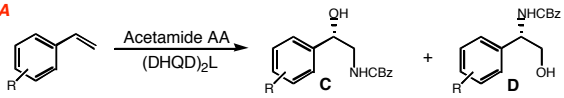
A Phenomenon for Carbamate and Amide AA

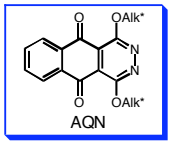
Carbamate AA



R	B:A	% e.e. (% yield)
H	79:21	95 (58)
4-F	82:18	91 (67)
4-Br	80:20	89 (51)
4-Me	78:22	93 (nd)
4-OMe	78:22	94 (67)
2,6-(MeO)$_2$	75:25	91 (50)
4-OBn	66:34	87 (40)

Acetamide AA





AQN

R	L	C : D	% e.e.$_{major}$
H	PHAL	1 : 1.1	91
	AQN	13 : 1	88
OMe	PHAL	1 : 2.5	96
	AQN	9 : 1	86

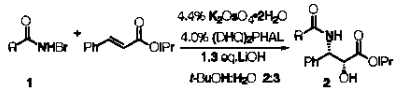
Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507

Amide AA

Comparable in Scope to the Carbamate Variant

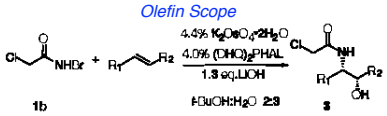
- Terminal olefins (i.e. styrenes) are the best substrates
- Small substrate scope
- AQN ligands reverse the regioselectivity

Various Amides as the Nitrogen Source



entry	bromoamide	T(°C)	conversion[a]	yield[b]	ee[c]	regioselectivity[c]
2a	1a	4°C	96%	94%	95%	21 : 1
2b	1b	10°C	86%	75%	95%	23 : 1
2c	1c	4°C	81%	76%	93%	12 : 1
2d	1d	4°C	84%	71%	80%	20 : 1
2e	1e	4°C	50%	38%	77%	2.0 : 1
2f	1f	0°C	70%	42%[d]	43%	2.5 : 1

Olefin Scope

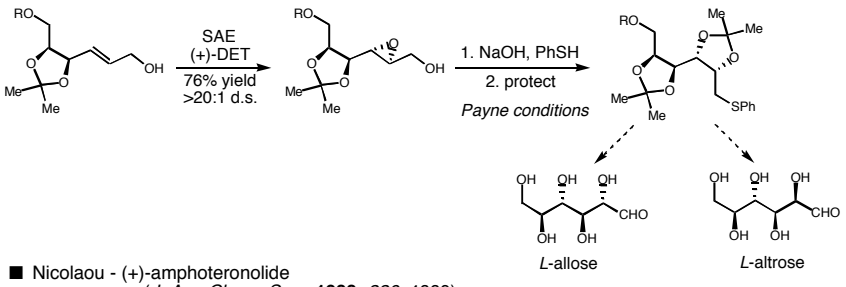


entry	olefin	product	yield[a]	ee[b]	regioselectivity[c]
2b			75%	95%	23 : 1
3a			72%	97%	2.5 : 1
3b			77%	97%	1.3 : 1
3c			40%	50%	2.5 : 1

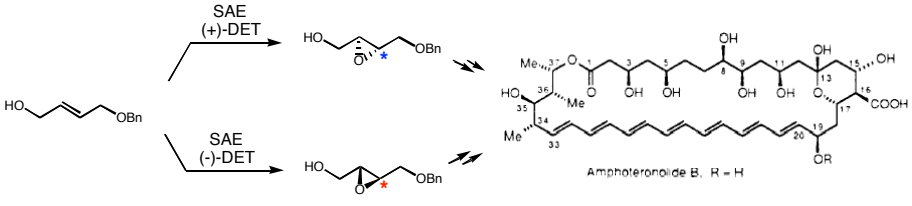
Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221

Asymmetric Epoxidations in Natural Product Synthesis

- Sharpless and Masamune - *L*-hexoses (*Science* **1983**, *220*, 949)

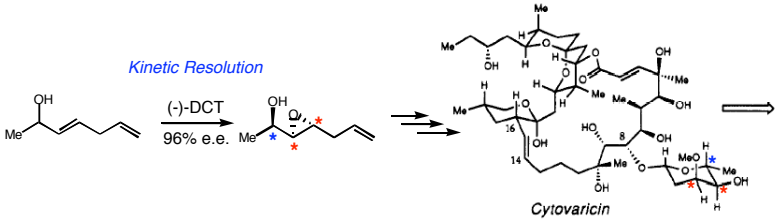


- Nicolaou - (+)-amphoteronolide
(*J. Am. Chem. Soc.* **1988**, *220*, 4660)

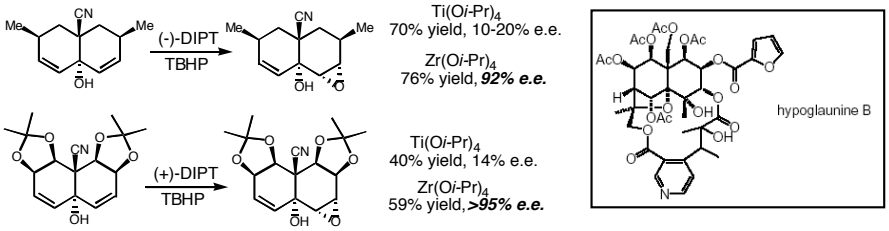


Asymmetric Epoxidations in Natural Product Synthesis

■ Evans - Cytovaricin (*J. Am. Chem. Soc.* **1990**, *112*, 7001)



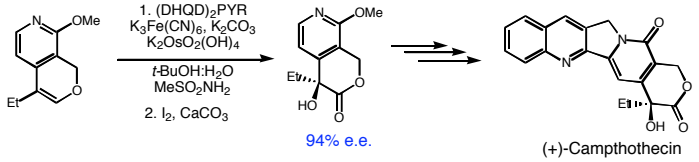
■ Spivey - studies toward Hypoglaunine B (*Angew. Chem. Int. Ed. Eng.* ***2001***, *40*, 768)



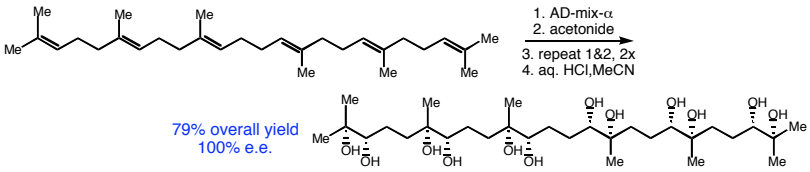
AE of 1,1-disubstituted allylic alcohols! .

AD in Natural Product Synthesis

■ Campthothecin (Fang, F. G.; et al. *J. Org. Chem.* **1994**, *59*, 6142)

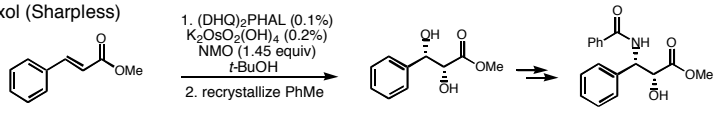


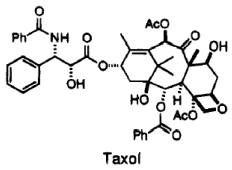
■ Dihydroxylation of Squalene (Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science.* **1993**, *259*, 64)



AD and AE in Natural Product Synthesis

■ Taxol (Sharpless)

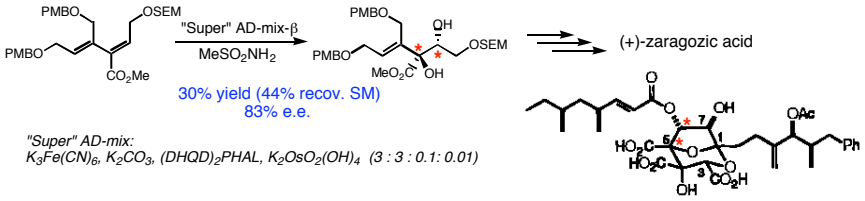




Taxol

AA: *Acta. Chem. Scand.* **1996**, *50*, 649
AD: *J. Org. Chem.* **1994**, *59*, 5104

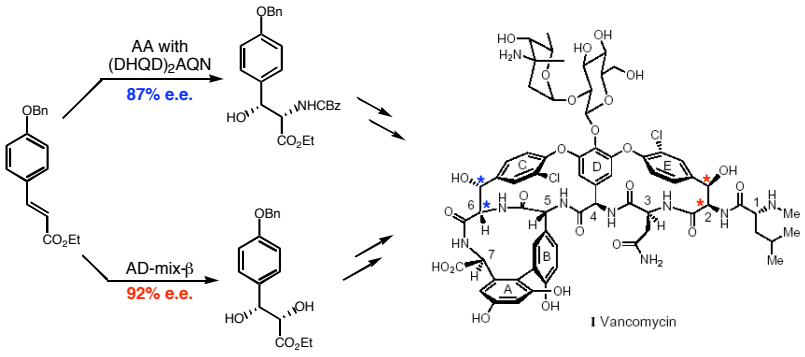
■ Zaragozic Acid (Nicolaou, et al. *Chem. Eur. J.*, **1995**, *1*, 467)



"Super" AD-mix:
$K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$ (3 : 3 : 0.1: 0.01)

AA and AD in Natural Product Synthesis

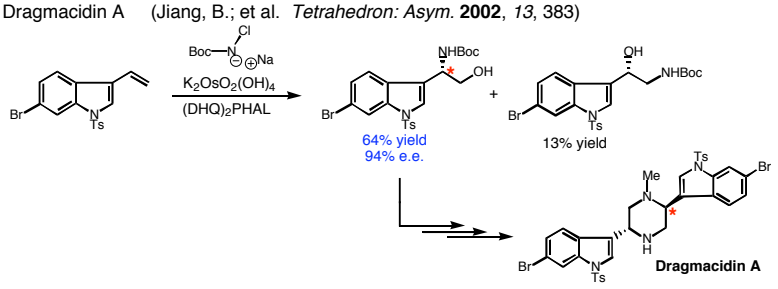
■ Vancomycin (Nicolaou, K. C.; et al. *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 2708
Nicolaou, K. C.; et al. *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 2714
Nicolaou, K. C.; et al. *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 2717)



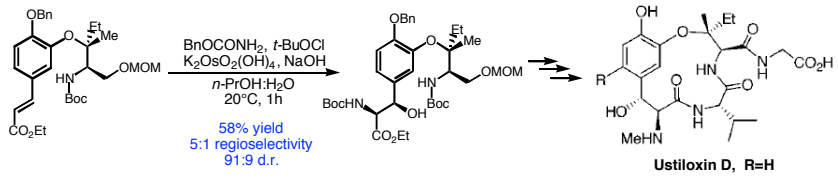
Vancomycin

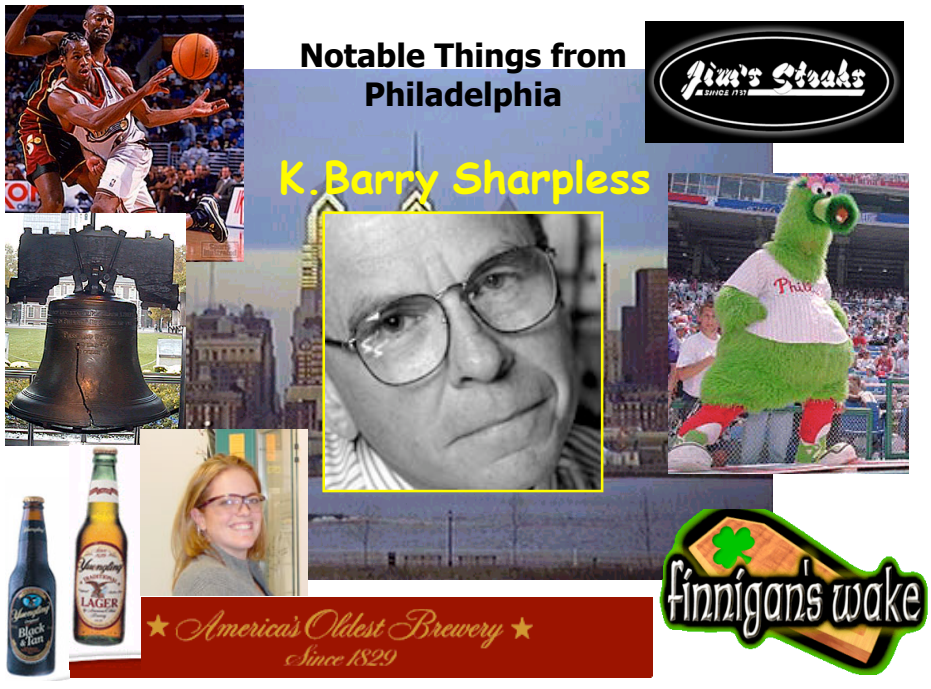
AA in Natural Product Synthesis

■ Dragmacidin A (Jiang, B.; et al. *Tetrahedron: Asym.* **2002**, *13*, 383)



■ Ustiloxin D (Jouillie, M,; et al. *J. Am. Chem. Soc.* **2002**, *124*, 520)

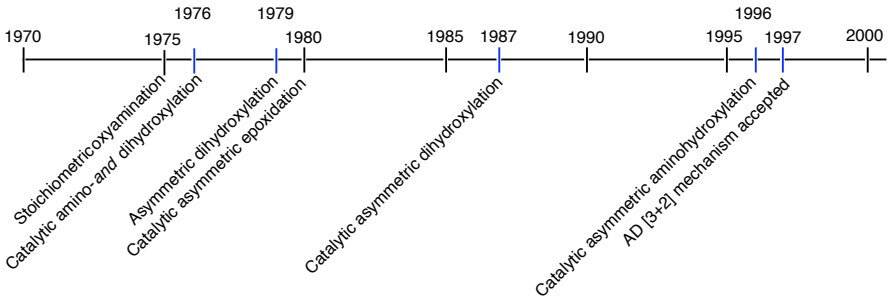




Conclusions

Pioneering Asymmetric Synthesis

2001 - Nobel Prize in Chemistry



- Sharpless Asymmetric Epoxidation on allylic alcohols - high yield, excellent enantioselectivities
- Sharpless Asymmetric Dihydroxylation of olefins to 1,2-diols
  - cinchona alkaloid ligand variations make most olefins good substrates in terms of yields and enantioselectivities
  - most studied area in terms of reaction mechanism understanding
- Sharpless Asymmetric Aminohydroxylation of olefins to 1,2-aminoalcohols
  - good yields and enantioselectivities, limited substrate scope
  - most recent development