DIIDROSSILAZIONE ASIMMETRICA (AD) DEGLI ALCHENI

Olefin oxidation

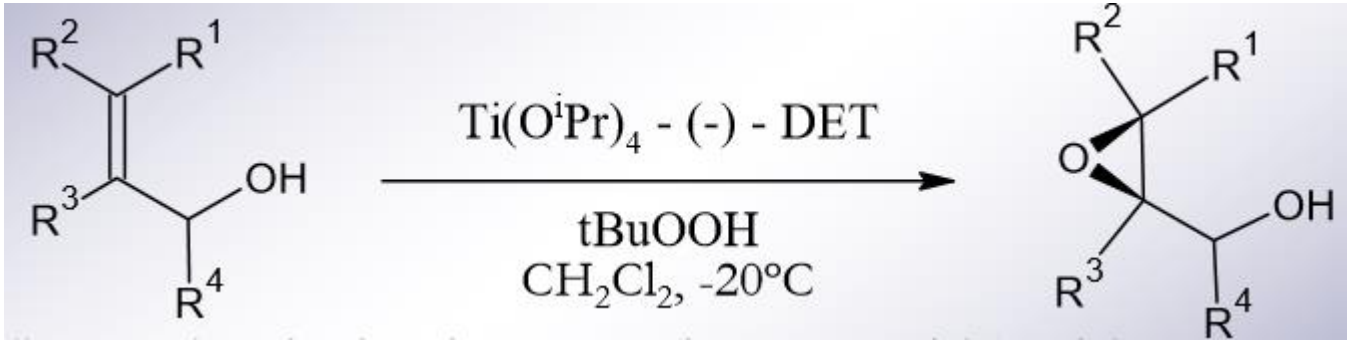
K. Barry Sharpless (The Scripps Research Institute, La Jolla, California) - 2001 Nobel Prize "for his work on chirally catalyzed oxidation reactions".

1980 Asymmetric epoxidation (AE)
1987 Asymmetric dihydroxylation (AD)

The process for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis because of these appealing characteristics of olefins:
- they are among the *cheapest* functionalized organic starting materials,
- most simple olefins are *prochiral*, providing a prominent portal to the chiral world.
(K. B. Sharpless, Nobel Lecture, 2001)

K. Barry Sharpless and his co-workers have discovered and developed widely used catalytic oxidation processes, including the first general methods for stereoselective oxidation– the Sharpless reactions for asymmetric epoxidation, dihydroxylation, and aminohydroxylation of olefins. His mentors at Dartmouth College (BA in 1963), Stanford College (PhD in 1968 and postdoctoral research), and Harvard University (further postdoctoral research) were Prof. T. A. Spencer, Prof. E. E. van Tamelen, Prof. J. P. Collman, and Prof. K. Bloch, respectively. Before 1990, when he became W. M. Keck Professor of Chemistry at the Scripps Research Institute, Prof. Sharpless was a member of Faculty at the MIT (1970 - 77, 1980 - 90) and Stanford (1977 - 80). Prof. Sharpless' s honors include the Chemical Sciences Award of the National Academy of Sciences, the Roger Adams and Arthur C. Cope Awards from the American Chemical Society, the Tetrahedron Award, the King Faisal Prize, the Prelog Medal, the Wolf Prize, the Nobel Prize.

Epossidazione Asimmetrica (AE) di Sharpless



1. Converte **alcol allilici** primari e secondari in 2,3-epossialcoli

2. La reazione è altamente enantioselettiva

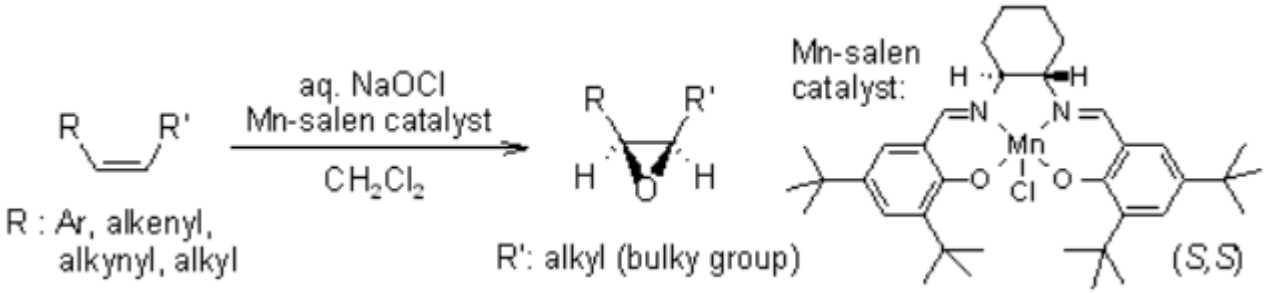
3. L'enantiomero prodotto dipende dalla stereochimica del catalizzatore usato, cioè (+) oppure (–) tartrato

4. Catalizzatore: titanio tetra-isopropossido con dietiltartrato

5. tBuOOH ossidante

6. DCM (CH_2Cl_2) e -80 °C

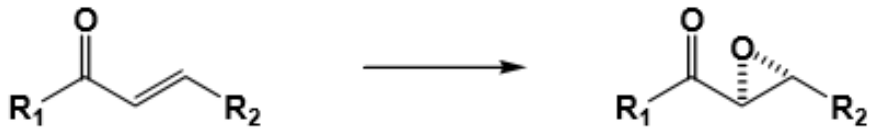
Epossidazione Asimmetrica (AE) di Jacobsen-Katsuki



1. Complementare alla AE di Sharpless
2. Riportata indipendentemente da Jacobsen e Katsuki negli anni 90
3. Catalizzatori simili, più semplici quelli di Jacobsen
4. Catalizzatore: complesso chirale di Mn(III)-salen
5. Ossidante: NaOCl
6. Condizioni: 0°C, DCM

Asymmetric Epoxidation of Electron-Deficient Alkenes

Review: M.J. Porter and J. Skidmore, *Chem. Commun.*, **2000**, 1215.



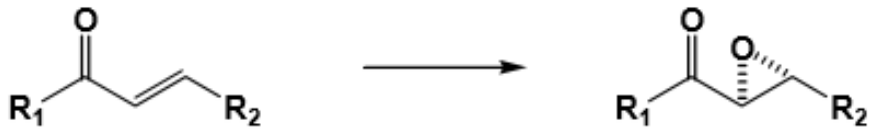
Abstract

Asymmetric epoxidation reactions have the distinction of being among the first enantioselective transformations to be widely sued in organic synthesis. The Sharpless asymmetric epoxidation is arguably one of the most important methods for the synthesis of enantiomerically enriched intermediates uses en route to a wide range of synthetic targets. To date most examples have employed electrophilic oxidizing agents and are thus applicable to electron-neutral or electron-rich double bonds. On the other hand alkenes substituted with electron-withdrawing groups often react inefficiently with electrophilic oxidizing agents; such alkanes are more readily epoxidized using nucleophilic oxidants. The Weitz-Scheffer epoxidation of alpha,beta-unsaturated ketones to the corresponding epoxy ketones using basic hydrogen peroxide is the classical nucleophilic epoxidation reaction.

This chapter considers the more general case of the conversion of an electron deficient alkene into the corresponding epoxide in an enantioselective fashion. Only methods based on chiral reagents or catalysts are covered. This review covers the literature to the end of 2005.

Asymmetric Epoxidation of Electron-Deficient Alkenes

Review: M.J. Porter and J. Skidmore, *Chem. Commun.*, **2000**, 1215.



- Polyleucine, H_2O_2, base: *e.g. Tetrahedron Lett.*, **2001**, *42*, 3741.
  Reviews: *Tetrahedron: Asymmetry* **1997**, *8*, 3163; **1998**, *9*, 1457.

- Catalytic Mg peroxides (^{t}BuOOH, cat. Bu_2Mg, cat. diethyl tartrate): R_1, R_2=Ph
  Jackson, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 410.

- Chiral phase-transfer catalysts (R_2 can be alkyl): Lygo, *Tetrahedron,* **1999,** 55**,** 6289**;** *Tetrahedron Lett.* **2001**, *42*, 1343.

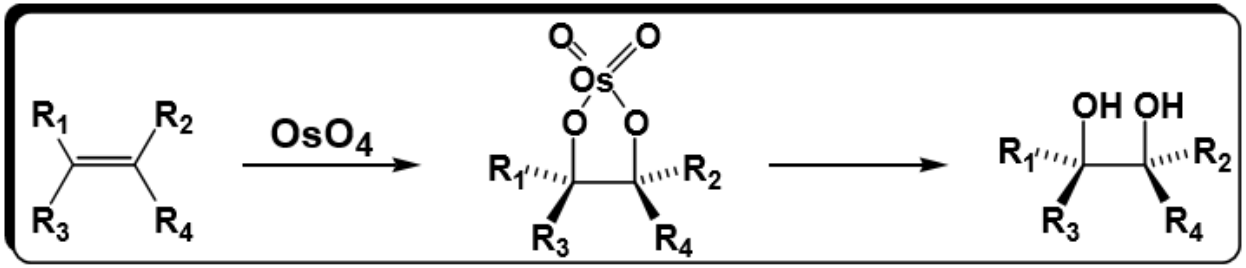
- Lanthanide catalysis (BINOL, $La(O^iPr)_3$ or $Yb(O^iPr)_3$, 4Å MS, ^{t}BuOOH):
  R_1=Ph, ^{i}Pr or Me; R_2=Ph, ^{i}Pr, $Ph(CH_2)_2$ or Me.
  La-BINOL-Ph_3AsO -mechanistic studies: *J. Am. Chem. Soc.*, **2001**, *123*, 2725.

- Chiral hydroperoxides, KOH, CH_3CN: Adam, *J. Am. Chem. Soc.*, **2000**, *122*, 5654.

- Stoichiometric zinc alkylperoxides (O_2, Et_2Zn, R*OH): R_1=Ph or ^{t}Bu, R_2=alkyl or aryl
  Enders, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1725; *Liebigs Ann. Chem.* **1997**, 1101

- Chiral dioxiranes: e.g. *Tetrahedron: Asymmetry*, **2001**, *12*, 1113.

Alkene Dihydroxylation



Catalytic systems:

- NMO / acetone / H_2O (Upjohn procedure): *Tetrahedron Lett*. **1976**, *23*, 1973.

- Cat. $Me_3NO{\bullet}2H_2O$, CH_2Cl_2: Poli, *Tetrahedron Lett*. **1989**, *30*, 7385.

- $K_3Fe(CN)_6$, K_2CO_3, ^tBuOH / H_2O: Minato, Yamamoto, Tsuji, *J. Org. Chem*. **1990**, *55*, 766.

- NMO, $PhB(OH)_2$, CH_2Cl_2: Narasaka, *Chem. Lett*. **1988**, 1721.
  - Diol trapped as boronate ester - useful if diol is unstable or highly water soluble

- Selenoxides as co-oxidants: Krief, *Synlett*, **2001**, 501.

- H_2O_2, cat. flavin, cat. N-methylmorpholine: Backvall, *J. Am. Chem. Soc.* **1999**, *121*, 10424; *J. Am. Chem. Soc.* **2001**, *123*, 1365.
- H_2O_2, cat. $V(O)(acac)_2$, NMM, acetone/water: Backvall, *Tetrahedron Lett*., **2001**, *42*, 2569.

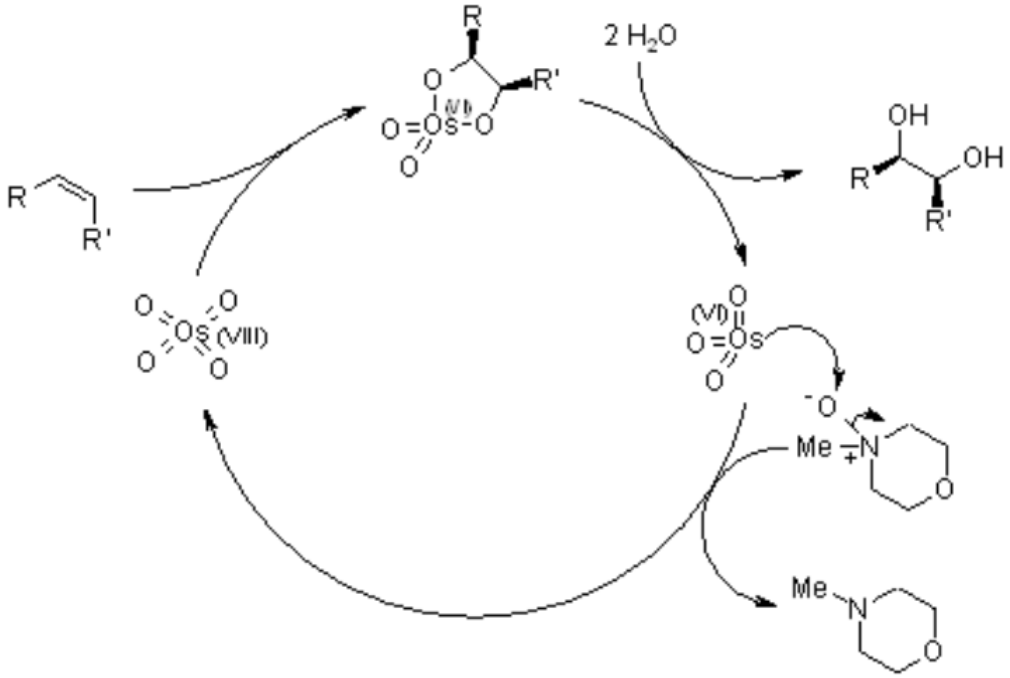
- O_2, $K_2[OsO_2(OH)_4]$, ^tBuOH / H_2O:
  Beller, *Angew. Chem. Int. Ed*. **1999**, *38*, 3026; *J. Am. Chem. Soc*. **2000**, *122*, 10289.
  Wirth, *Angew. Chem. Int. Ed*. **2000**, *39*, 334.

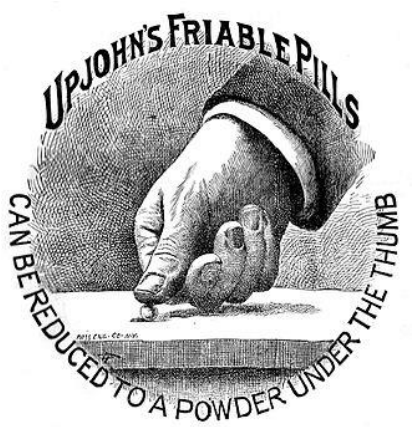
Fe-catalysed asymmetric dihydroxylation: Que, *J. Am. Chem. Soc*. **2001**, *123*, 6722.

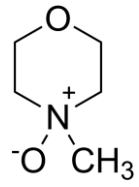
Upjohn: Meccanismo

NB: il TOSSICO e volatile OsO_4 può essere formato *in situ* da $K_2OsO_2(OH)_4$ e NMO*

NMO è anche co-ossidante: permette uso cat. di OsO_4 perché rigenera Os (VIII) da Os (VI) tramite ossidazione





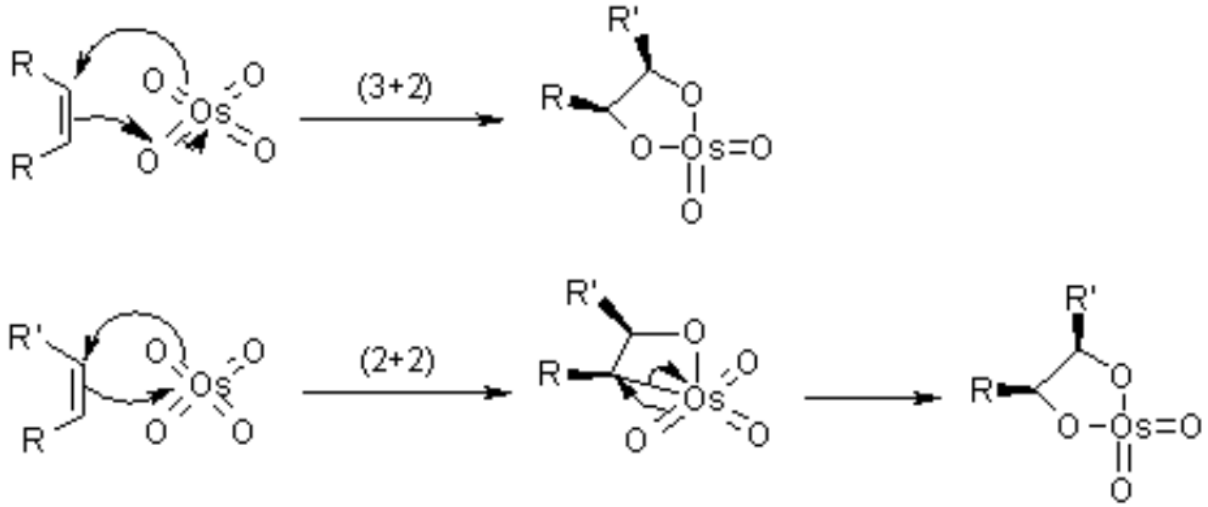


* N-ossido di N-metil morfolina

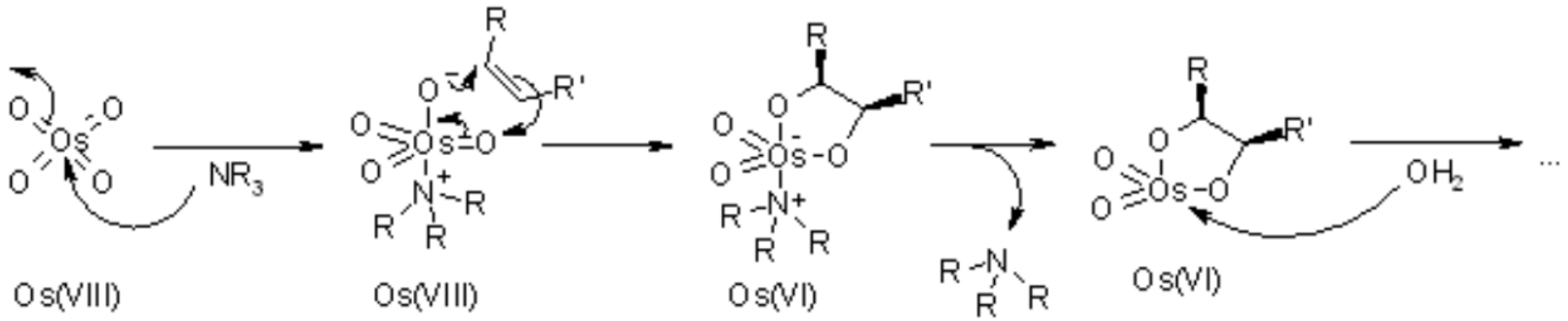
… e se l'alchene è chirale?

Upjohn: Meccanismo

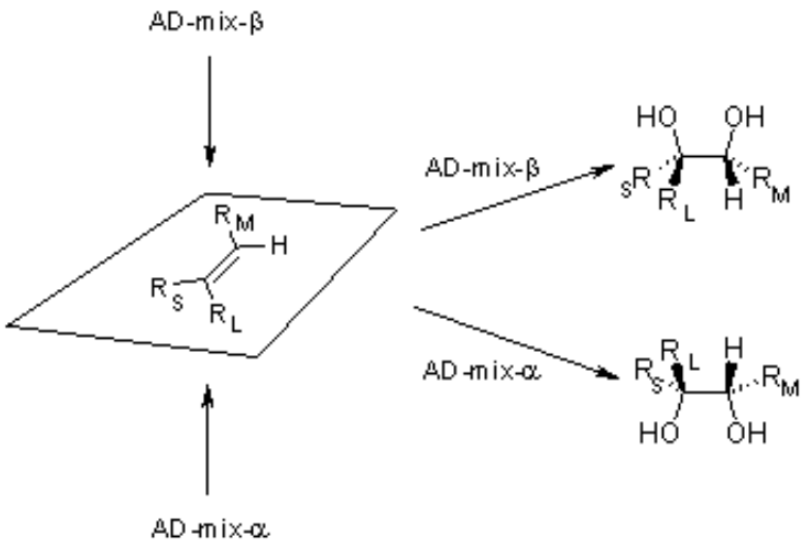
Il passaggio chiave è la **cicloaddizione** di *OsO4* all'olefina. Meccanismo accettato: **[3+2] (1,3-dipolar cycloaddition)**, favorito anche da calcoli quantistici, a lungo tempo dibattuto con meccanismo alternativo a 2 steps: **[2+2] + espansione del metallaciclo**



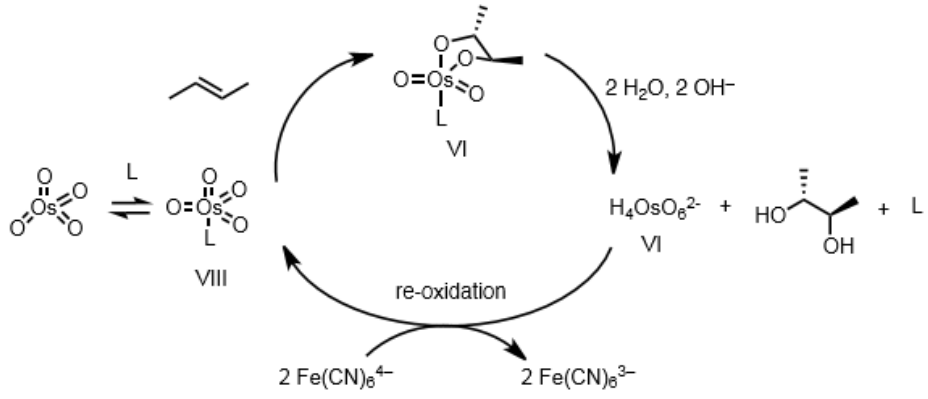
Catalizzatori come DMAP o pyr (amine terziarie) accelerano la reazione:



Sharpless AD (SAD)



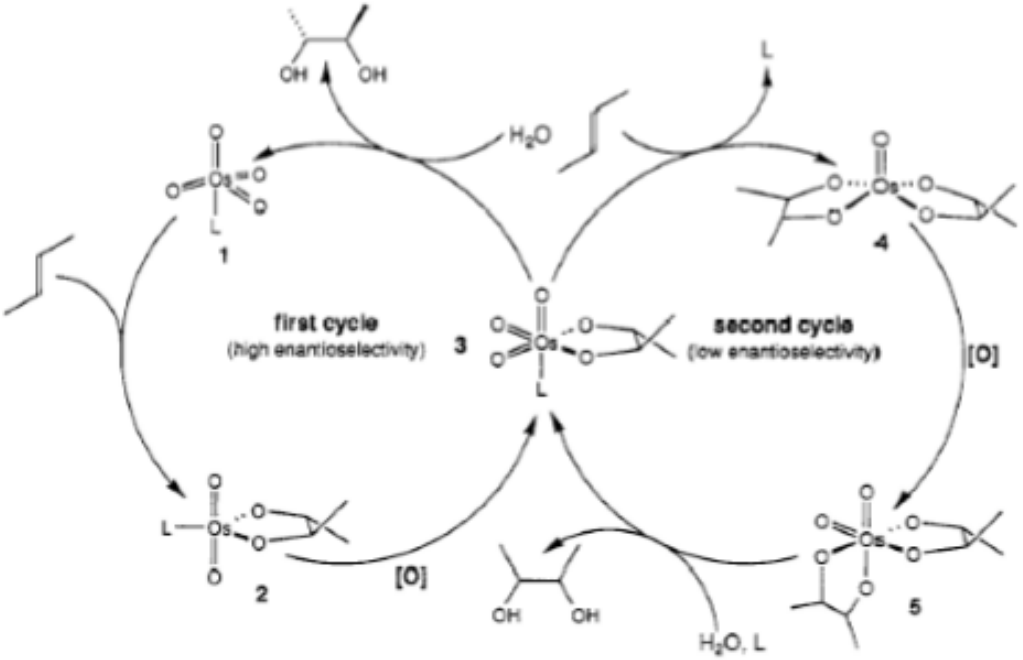
Ciclo catalitico*



1. OsO_4 come ossidante (**CAT!**) + co-ox. (**stechiom.**: NMO oppure $K_3Fe(CN)_6$)
2. Soluzione TAMPONE
3. **Stabile Cat. Mix PRONTO e disponibile per entrambe enantiopreferenze**
4. Enantioselettività ottenuta tramite uso di AMMINE CHIRALI
5. Aria e acqua non sono un problema.

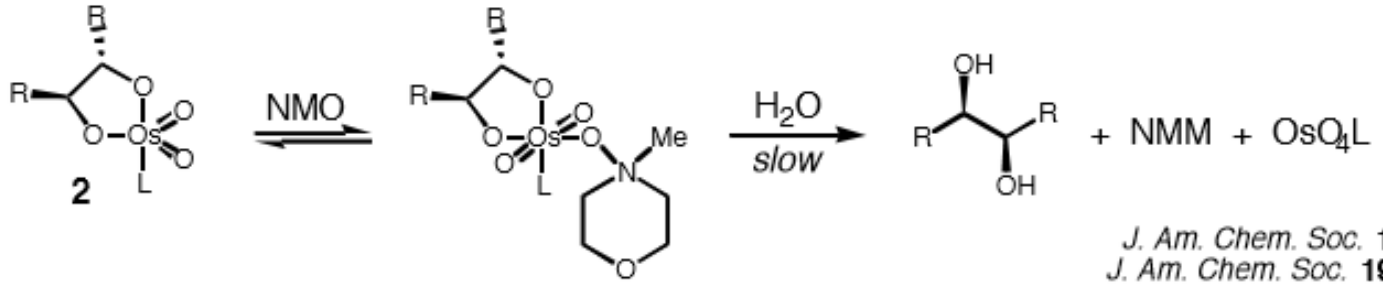
AD Catalytic Cycles

Two Pathways for Dihydroxylation



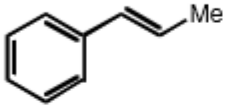
crystals obtained of **1, 2, 4**

- 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**



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

■ 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

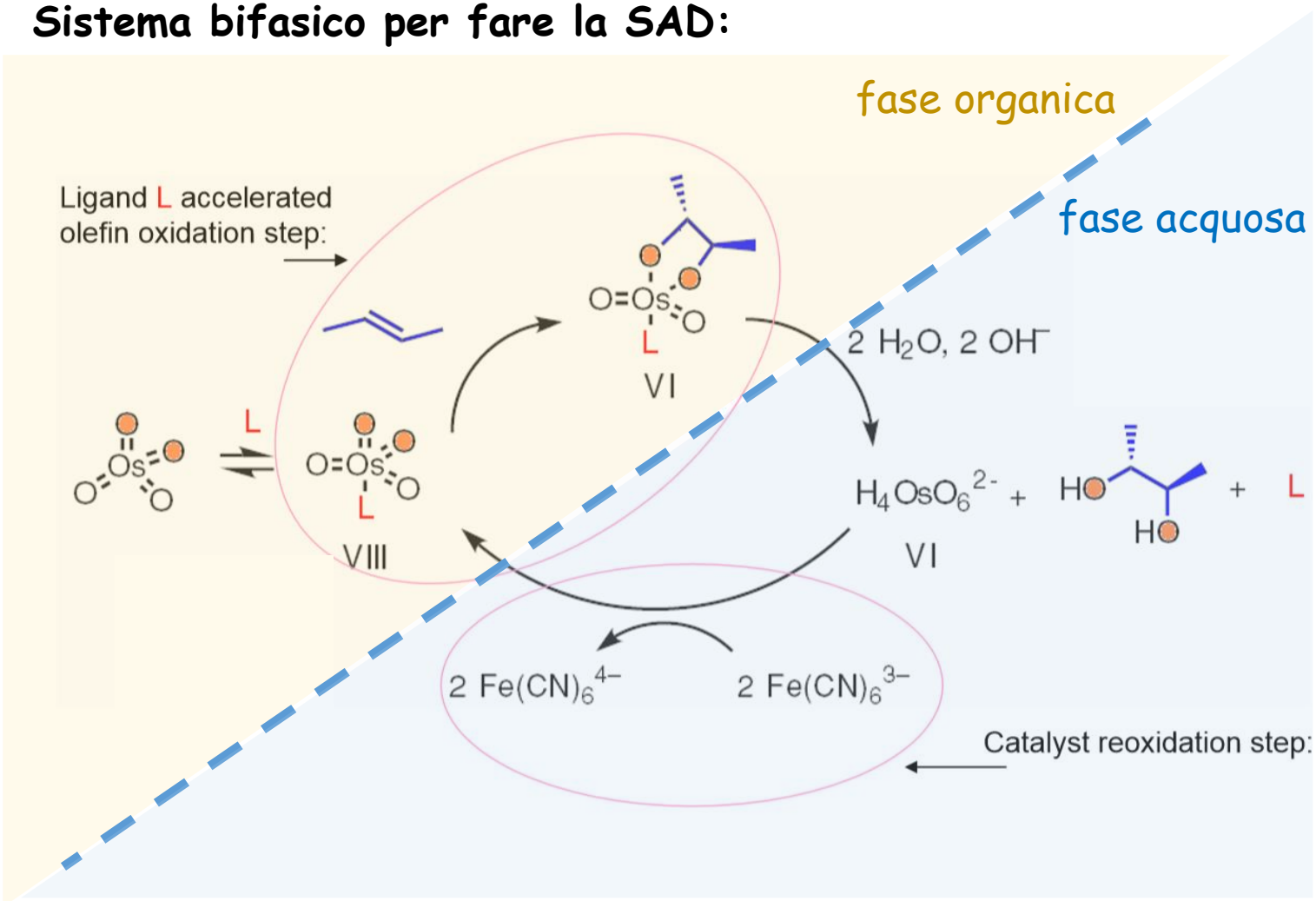
		catalytic[a]		
	stoichiometric[a]	original	acetate[b]	slow addition
	87% e.e.	65	73	86 (5h)
	69% e.e.	20	64	70 (10h)

[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

Sistema bifasico per fare la SAD:



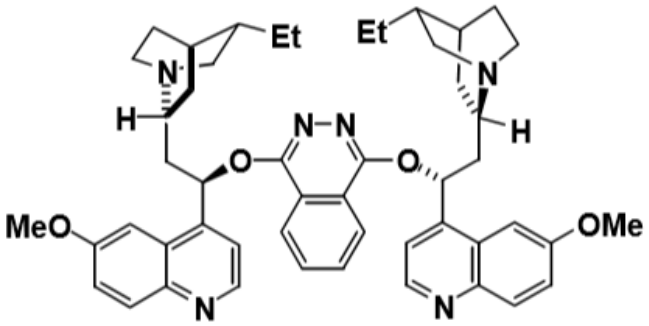
Criegee, *Liebigs Ann. Chem.* **1942**, *550*, 99

- $MeSO_2NH_2$ accelera l'idrolisi del composto ciclico
- La reazione ha caratteristici cambiamenti di colore in solventi non-polari

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

Review: Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

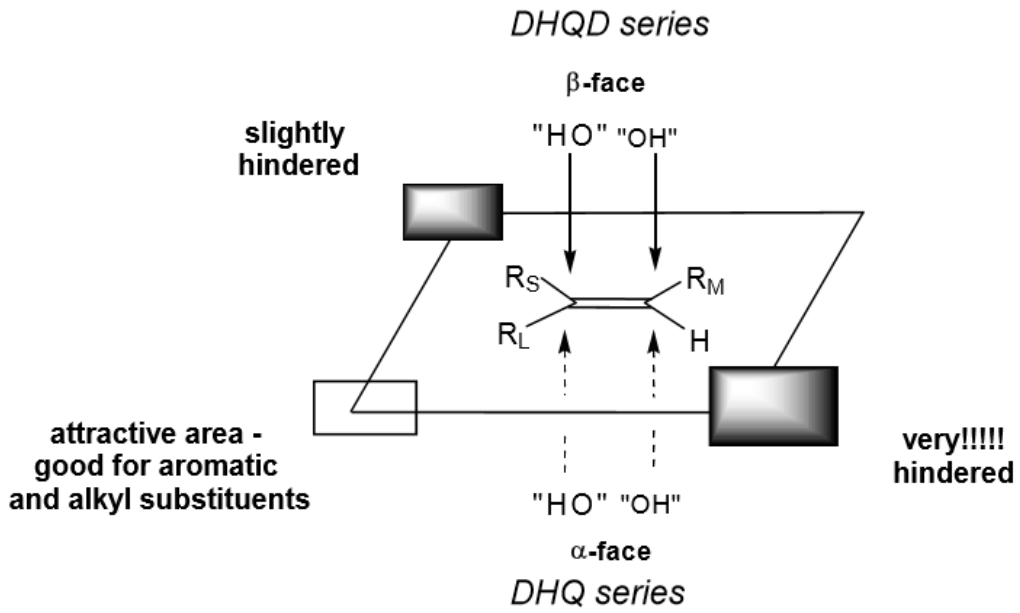
AD-Mix:
$K_2OsO_2(OH)_4$, ligand,
$K_3Fe(CN)_6$, K_2CO_3



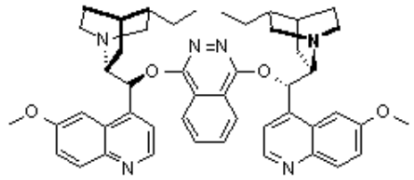
$(DHQD)_2$-PHAL

Simmetria C2 del legante

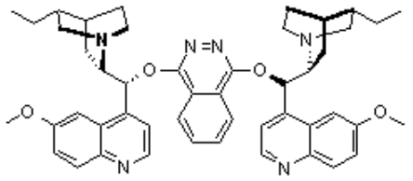
DHQD= dihydroquinidine
DHQ= dihydroquinine
"pseudoenantiomers"

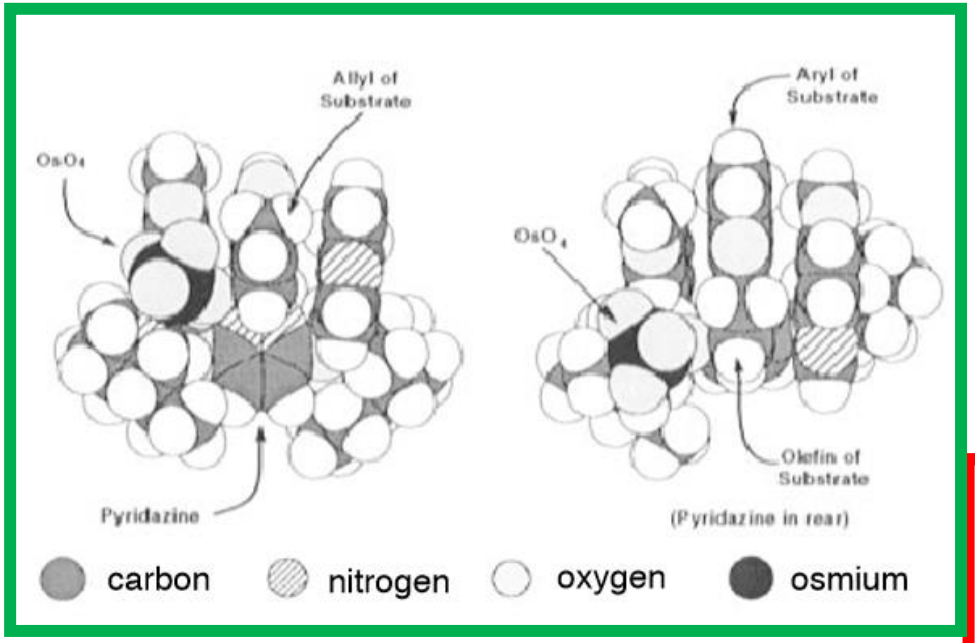


AD-mix-β:
$K_2OsO_2(OH)_4$ (cat), K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2PHAL$ (cat):

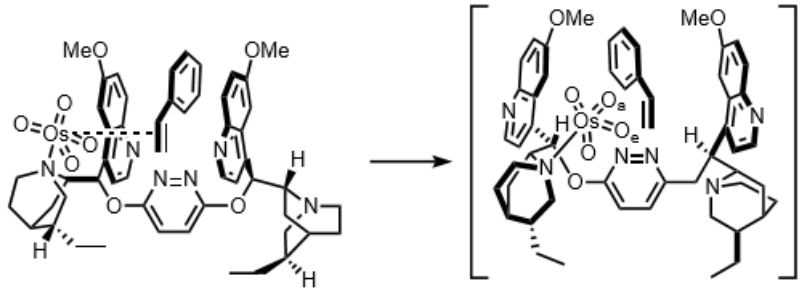


AD-mix-α:
$K_2OsO_2(OH)_4$ (cat), K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$ (cat):

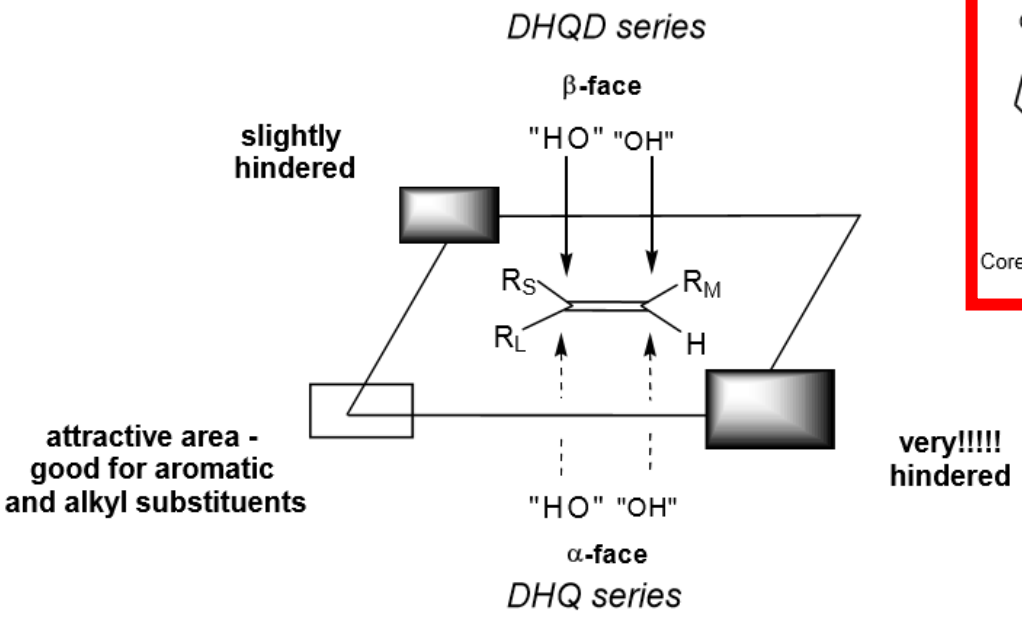




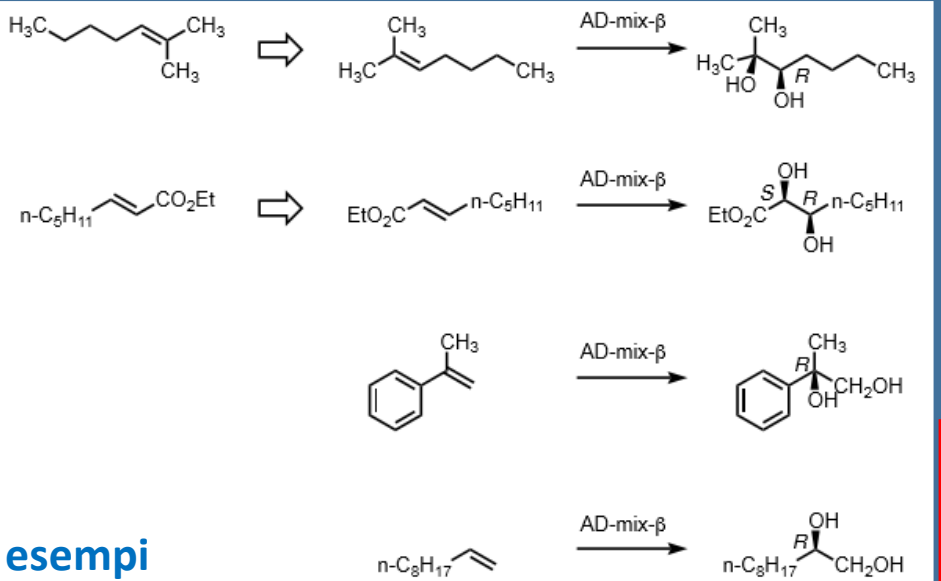
Corey proposes a U-shaped binding pocket:



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



Piridazina (1,2-diazina)



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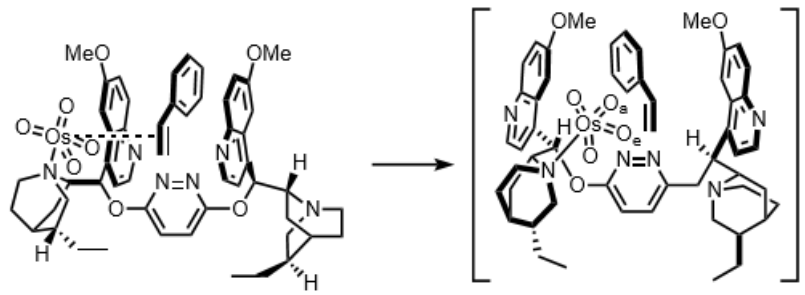
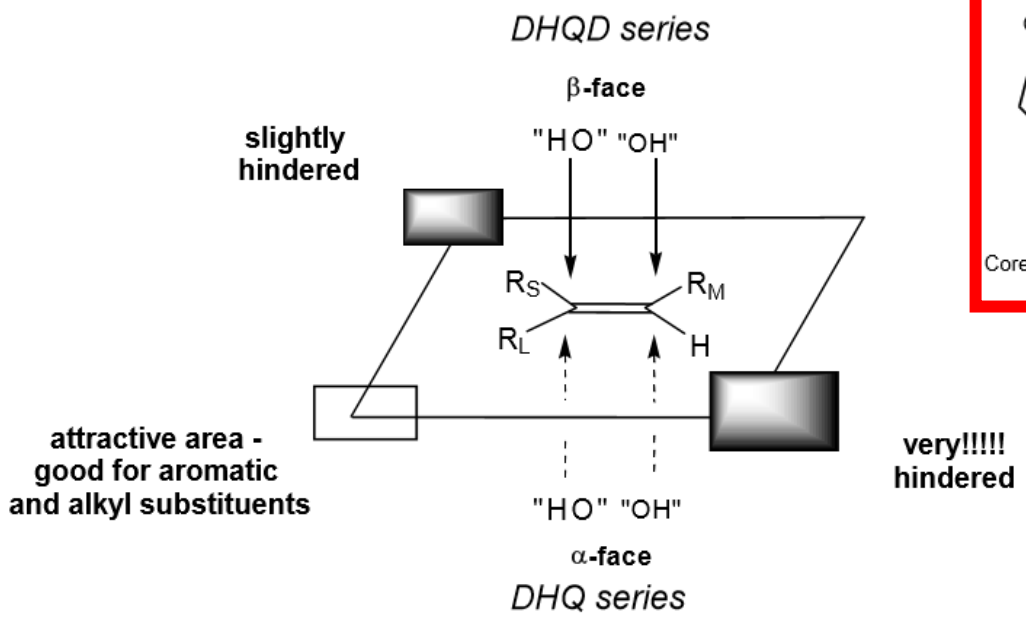
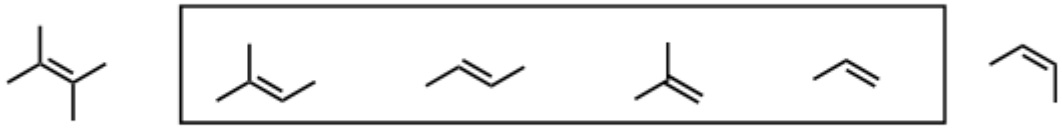


Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481–3484.



APPLICAZIONI

4 of 6 Olefin substitution classes are successfully dihydroxylated:



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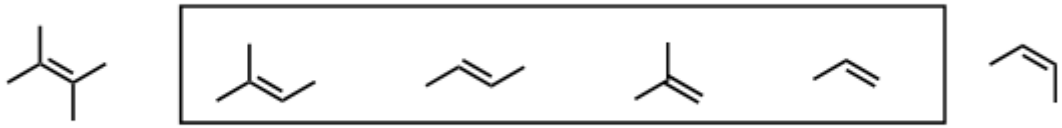
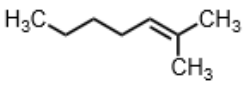
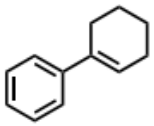
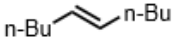
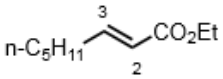
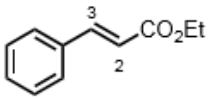
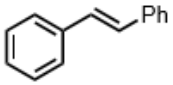
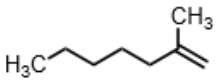


Alcheni TRANS – OK!

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

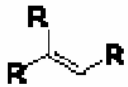
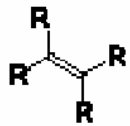
CIS

APPLICAZIONI

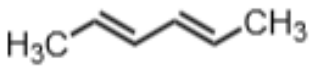
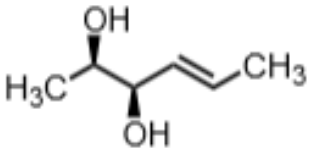
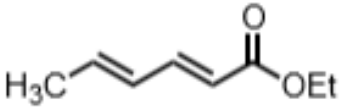
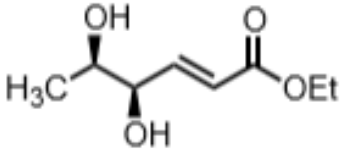
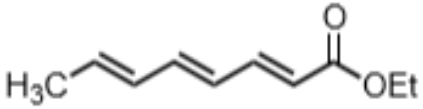
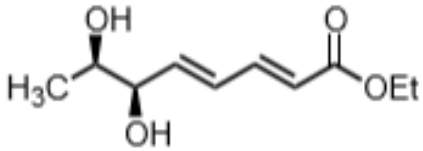
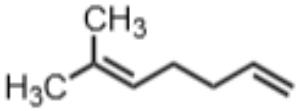
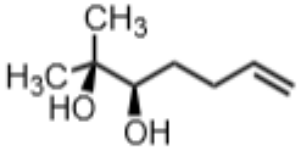
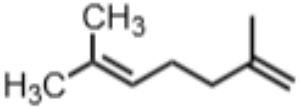
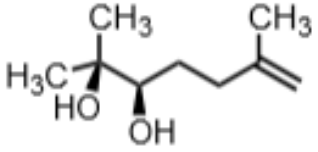
4 of 6 Olefin substitution classes are successfully dihydroxylated:

Alcheni **CIS** e **terminali**…
…tipicamente ee bassi ma grazie a ottimizzazione liganti situazione può migliorare

Table 3. Recommended ligands for the AD of different classes of olefins

Olefin class						
Preferred ligand	R=aromatic DPP, PHAL R=aliphatic AQN R=branched PYR	R=aromatic DPP, PHAL R=aliphatic AQN R=branched PYR	Acyclic IND Cyclic PYR, DPP, AQN	R=aromatic DPP, PHAL R=aliphatic AQN	PHAL, DPP, AQN	PYR, PHAL
ee range	30–97%	70–97%	20–80%	90–99.8%	90–99%	20–97%

Regioselectivity of AD with diene substrates ($(DHQD)_2PHAL$ as ligand):

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

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

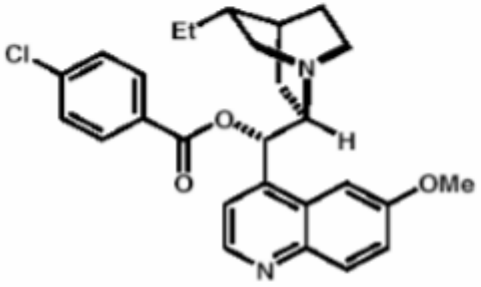
Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571.

Sharpless Dihydroxylation: Chiral Ligands

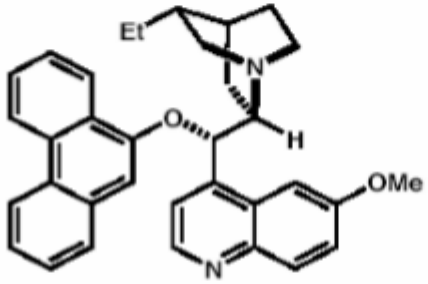
Sharpless' ligands

Reviews: Sharpless, K. B. et al. *Chem. Rev.* **1994**, *94*, 2483-2547.
Sharpless, K. B. In *Catalytic asymmetric synthesis*, Ojima Ed. p. 227.

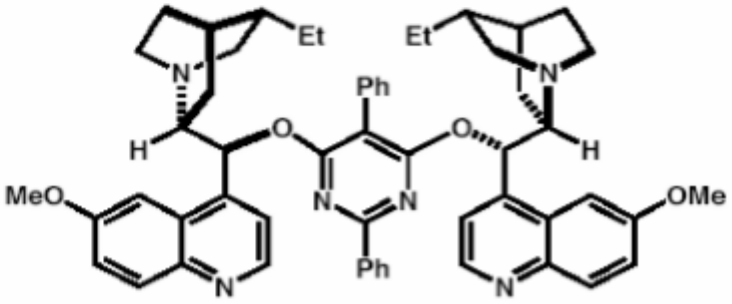
Dihydroquinidine derivatives



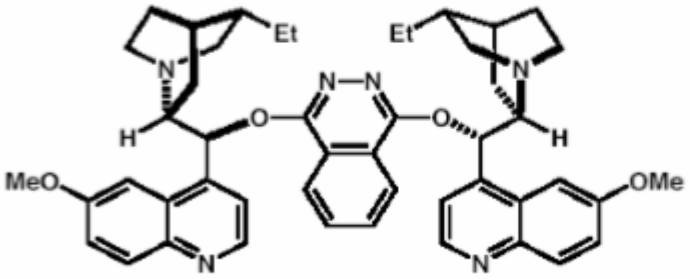
DHQD-CLB



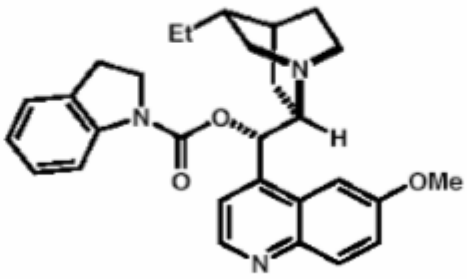
DHQD-PHN



$(DHQD)_2$-PYR



$(DHQD)_2$-PHAL
Ligand used in AD-mix-β



DHQD-IND

AD: il legante

e' l' azoto della quinuclidine che si lega al metallo

ha poco effetto sulla velocita' ma aumenta il binding

la natura di R ha un grosso effetto sulla velocita', ma una piccola influenza sul binding

la presenza dell'ossigeno e' indispensabile per consentire il binding all'Os,

la configurazione e' importante: solo gli eritro consentono alte velocita' e binding

aumenta il binding al OsO_4 e anche la velocita'

la presenza di un sistema planare aromatico aumenta binding e velocita', l'azoto non ha effetto

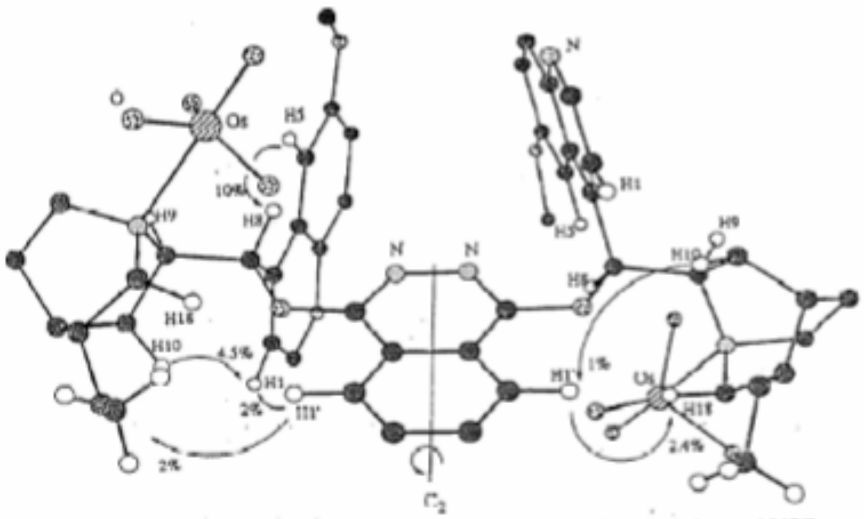
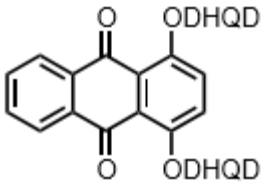


Figure 4. Structure of the bis-OsO_4 complex of $(DHQD)_2PHAL$ based on molecular mechanics calculations and NOE experiments.

Sharpless AD: Recent Developments

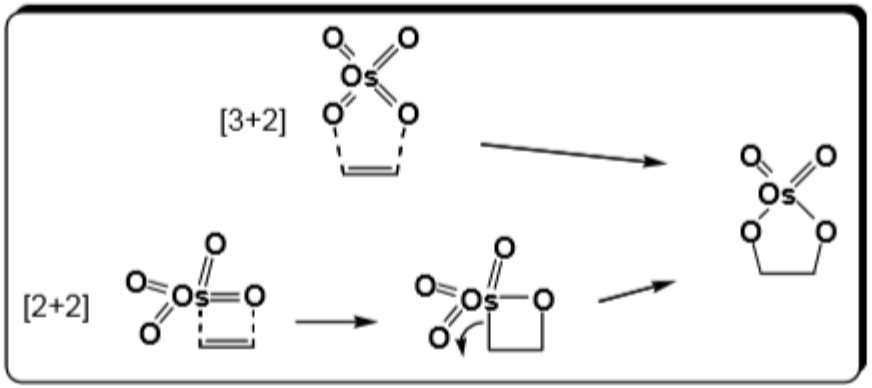
Improved ligands:

- Pyrimidine (PYR) spacer for sterically congested / terminal alkenes: *J.Org. Chem.* **1993**, *58*, 3785.
- Anthraquinone (AQN) spacer gives better results for almost all alkenes having only aliphatic substituents: *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448.



$(DHQD)_2AQN$

Mechanism:



- Comparison of theoretical and experimental kinetic isotope effects supports [3+2]-mechanism Sharpless, Houk *et al. J. Am. Chem. Soc.* **1997**, *119*, 9907.

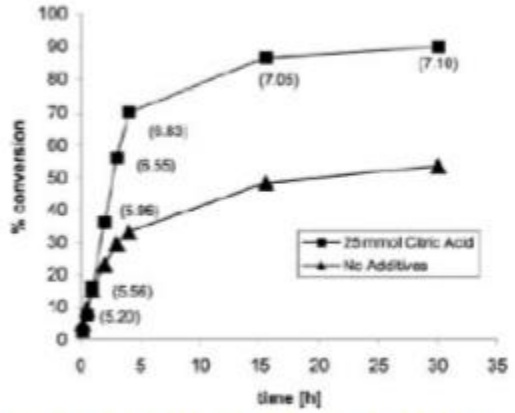
Origins of asymmetric induction:
Sharpless: J. Am. Chem. Soc. **1997**, *119*, 1840.
Corey ("enzyme like" binding pocket)*: J. Am. Chem. Soc.* **1996**, *118*, 319; 11038.

Polymer supported chiral ligands: Review: *Synlett*, **1999**, 1181. Crudden, *Org. Lett.* **2001**, *3*, 2325. Bolm, *Synlett*, **2001**, *93* (AQN-ligands).
Polymer supported Os-catalyst: Kobayashi, *J. Am. Chem. Soc.* **1999**, *121*, 11229. *Org. Lett.* **2001**, *3*, 2649.

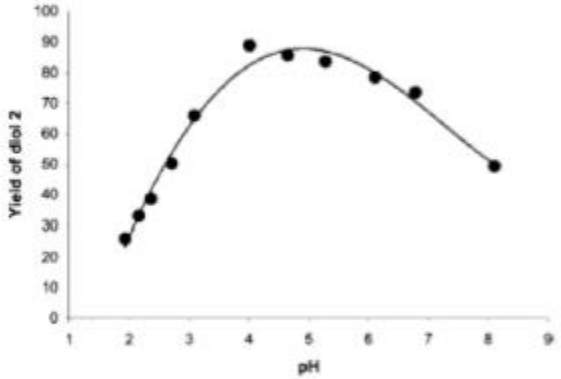
Importance of pH control: improved rates for internal olefins at pH 12 (no $MeSO_2NH_2$); higher ee for terminal olefins at pH 10: Beller, *Tetrahedron Lett.* **2000**, *41*, 8083.

New Developments in Dihydroxylation

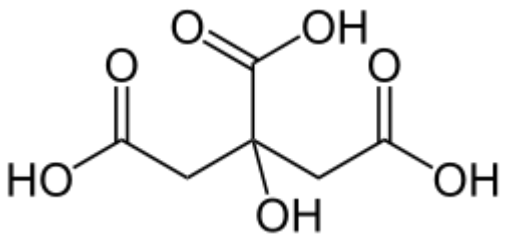
Osmium-Catalyzed Dihydroxylation of Olefins in Acidic Media

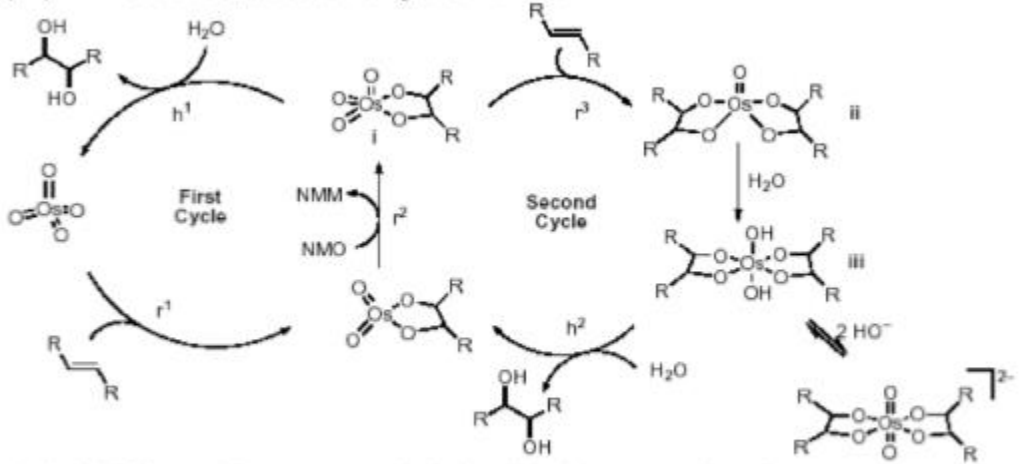


Optimal activity with pH = 4-6



- 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.

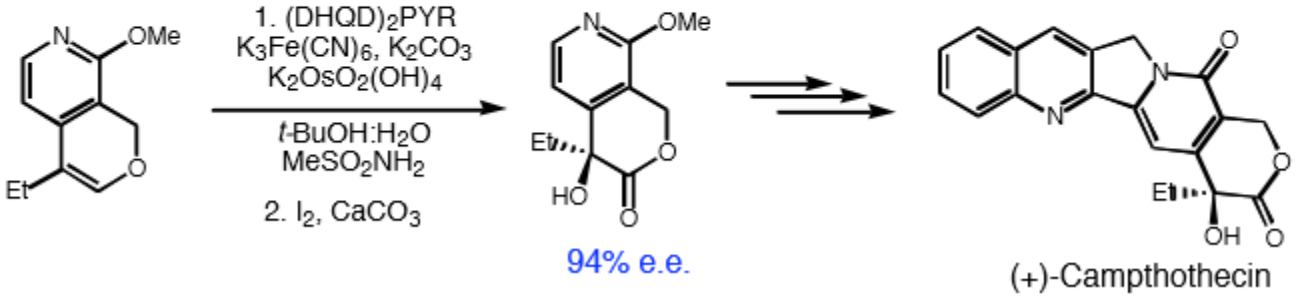




- turnover with acidic NMO reoxidant system is locked in the second cycle
- acid blocks precipitation of **iv**, which is very stable and inert to hydrolysis

AD in Natural Product Synthesis

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



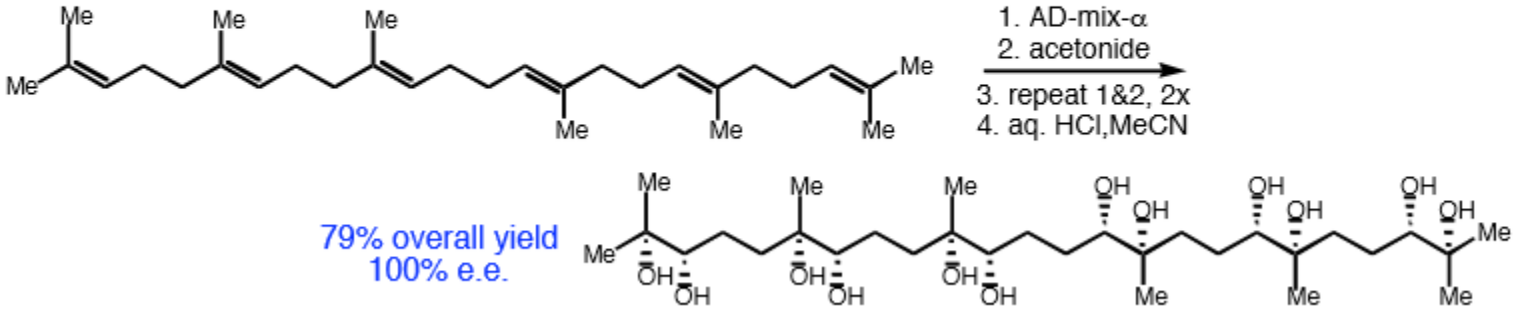
Camptotheca acuminata

La camptotecina è un alcaloide pentaciclico naturale che si può estrarre dalla corteccia dell'albero Captotheca acuminata, con attività antitumorale. Oggi si preferiscono usare a tale scopo suoi derivati più solubili.

AD in Natural Product Synthesis

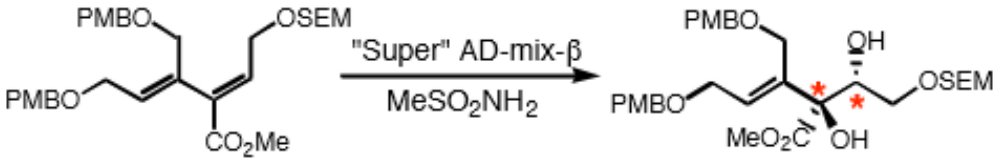
Lo squalene è un'importante sostanza naturale, precursore del colesterolo e di molti steroidi. Si trova naturalmente nell'olio di fegato di squalo (usato come integratore), da cui deriva il nome. La sua bassa densità permette il galleggiamento dei pesci, come gli squali, che sono privi della vescica natatoria. Viene anche utilizzato nella formulazione di alcuni vaccini.

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

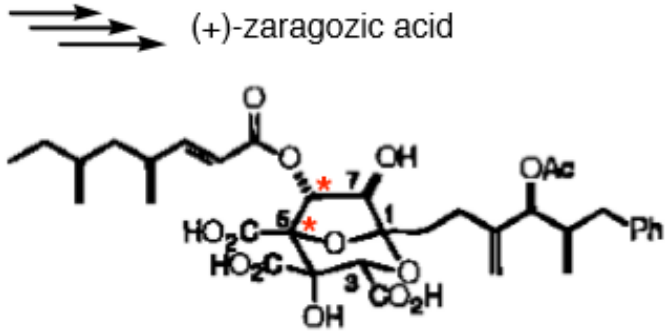


L'acido zaragozico si trova naturalmente in alcuni funghi microscopici (ad es. del genere Sporormiella, in foto, che appartiene alla famiglia delle Sporormiacee), che si trovano nella zona di Zaragoza (Spagna), da cui deriva il nome. L'acido e i suoi derivati sono potenti inibitori della squalene sintasi, quindi inibiscono la sintesi dello squalene e perciò degli steroli, risultando di fatto in un abbassamento di livelli di colesterolo. Purtroppo il loro accumulo e la loro tossicità ne previene l'uso terapeutico.

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



30% yield (44% recov. SM)
83% e.e.



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