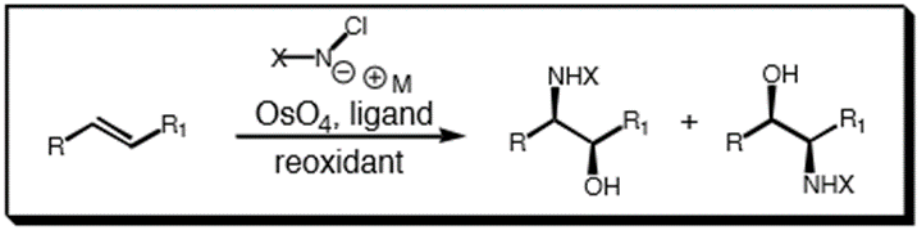
AMINOIDROSSILAZIONE ASIMMETRICA di Sharpless (SAA) DEGLI ALCHENI

La SAA è una variante della SAD (Diidrossilazione Asimmetrica di Sharpless) in cui anzichè installare 2 gruppi OH sui due carboni adiacenti di un alchene (C=C), andremo ad installare 1 gruppo OH ed 1 gruppo NH_2 al fine di ottenere degli amino alcoli vicinali otticamente attivi (cioè con centri chirali con controlllo stereogenico).

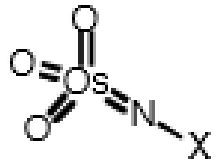


- Questa reazione è una sfida per la regio- chemo- ed stereo-selettività

- Non richiede gruppi funzionali per «dirigere» la reazione (vedi ad es. il gruppo OH degli alcoli allilici usati nella SAE e il suo ruolo nel «dirigere» la posizione dell'lachene rispetto al catalizzatore al titanio)

- Si può considerare l'analogo «aza» della SAD, in quanto usa sempre alcaloidi della cinchona come leganti per indurre la chiralità

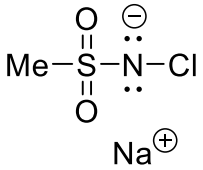
- Si basa sulla generazione in situ di un catalizzatore trioxo (imido) osmio (VIII) in cui rispetto alla SAD, abbiamo di fatto un NX al posto di un O (X è il sostituente sull'N che richiedeun sostituente in più rispetto all'O)



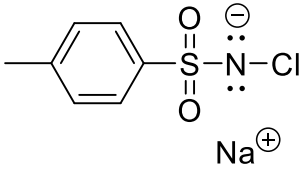
- A seconda della natura di X possiamo avere sulfonammidi, carbammati o amidi

Fonti di AZOTO per la SAA

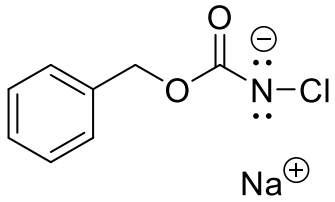
Cloramina M



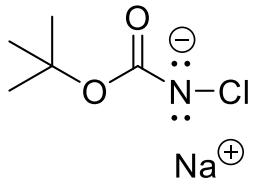
Cloramina T



N-cloro benzil Carbammato



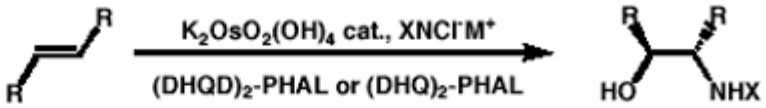
N-cloro ter-butil carbammato



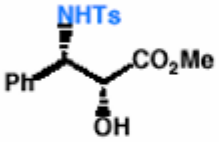
Le fonti di azoto per la SAA possono essere diverse.
Le Cloramine M e T sono ***sulfonammidi*** (confrontate con la struttura del ***mesile*** e del ***tosile*** che abbiamo visto in precedenza). Le sulfonammidi possono dare alte rese ed enantioselettività, ma può essere difficile rimuoverle (per riottenere l'ammina libera nel prodotto).

I ***carbammati*** con minor ingombro sterico danno anche alte rese e selettività. Inoltre si possono rimuvere più facilemente per riottenere l'ammina libera nel prodotto.

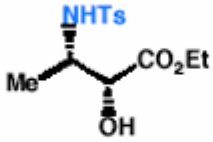
Sharpless Asymmetric Aminohydroxylation : Sulfonamide as Nitrogen Source



Chloramine T
TsNClNa (3.5 equiv.)

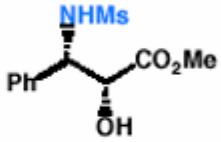


$(DHQ)_2$-PHAL
66% y. 81% ee

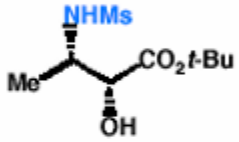


$(DHQ)_2$-PHAL
52% y. 74% ee

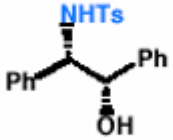
Chloramine M
MsNClNa (3 equiv.)



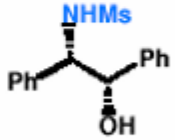
$(DHQ)_2$-PHAL
65% y. 95% ee



$(DHQ)_2$-PHAL
63% y. 80% ee



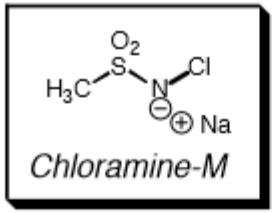
$(DHQ)_2$-PHAL
52% y. 62% ee



$(DHQ)_2$-PHAL
71% y. 75% ee

- Higher yields and enantioselectivities with sterically less demanding nitrogen nucleophiles
- Products are solid, ee can be increased by recrystallisation
- Drawback: Removing the sulfonyl group.

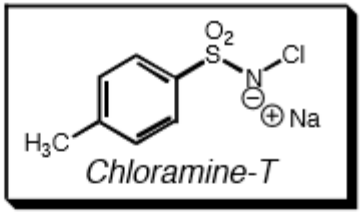
Ts = *p*-toluensulfonyl
Ms = methanesulfonyl



Chloramine-M

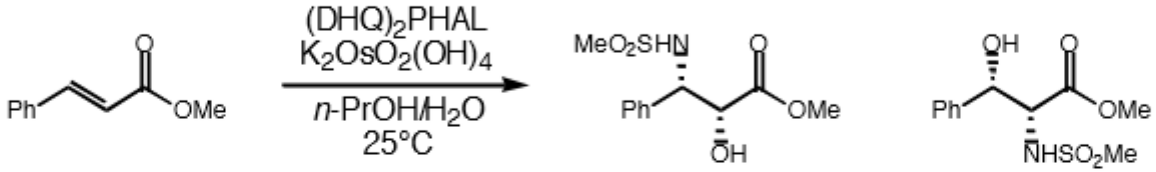
Sulfonamide AA

The Smaller, the Better



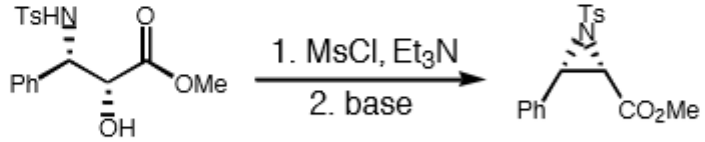
Chloramine-T

- 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 ..

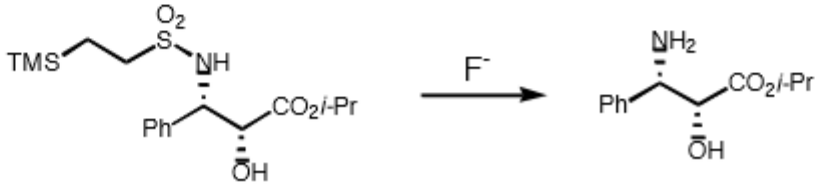


Chloramine-T (3.5h)	76 (60% e.e.)	:	24
Chloramine-M (40 min)	90 (89% e.e.)	:	10

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

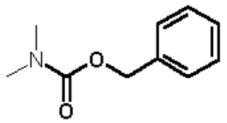


- Sulfonamide cleavage is difficult - Birch conditions, Red-Al, 33% HBr/HOAc
- 2-Trimethylsilylethanesulfonamide is comparable to Chloramine-M



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

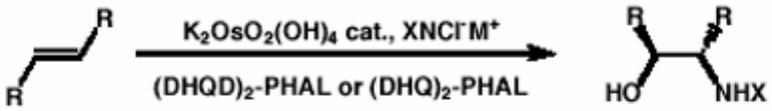
Benzyl carbamates



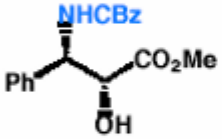
Cbz-NR_2 / Z-NR_2

T. W. Green, P. G. M. Wuts,
Protective Groups in Organic Synthesis,
Wiley-Interscience, New York, **1999**, 531-537, 736-739.

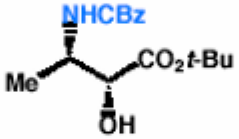
Sharpless Asymmetric Aminohydroxylation : N-Chlorocarbamate as Nitrogen Source



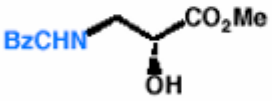
CbzNClNa
(3 equiv.)



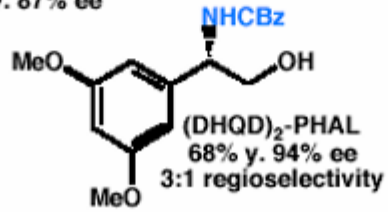
$(DHQ)_2$-PHAL
65% y. 94% ee



$(DHQ)_2$-PHAL
52% y. 74% ee

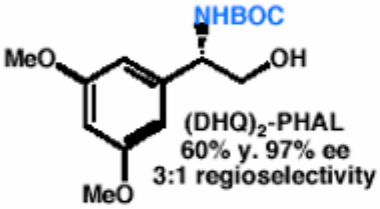


$(DHQ)_2$-PHAL
89% y. 84% ee
$(DHQD)_2$-PHAL
89% y. 87% ee

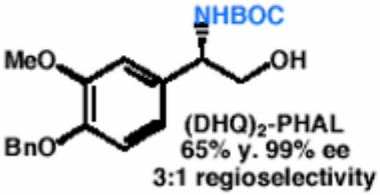


$(DHQD)_2$-PHAL
68% y. 94% ee
3:1 regioselectivity

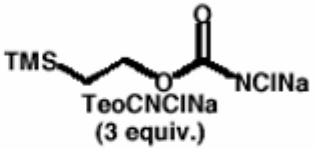
BOCNClNa
(3 equiv.)



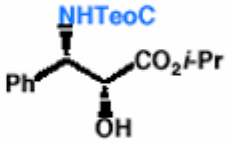
$(DHQ)_2$-PHAL
60% y. 97% ee
3:1 regioselectivity



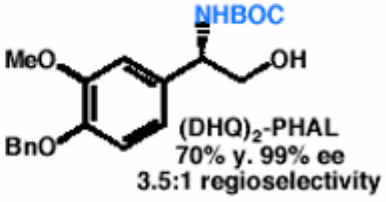
$(DHQ)_2$-PHAL
65% y. 99% ee
3:1 regioselectivity



TeoCNClNa
(3 equiv.)



$(DHQ)_2$-PHAL
70% y. 99% ee



$(DHQ)_2$-PHAL
70% y. 99% ee
3.5:1 regioselectivity

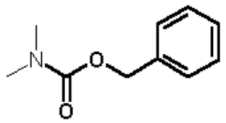
Cbz = benzyloxycarbonyl
Boc = *tert*-butoxycarbonyl
TeoC = 2-trimethylsilylethoxycarbonyl

} si rimuovono piu' facilmente

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 ..

Benzyl carbamates



Cbz-NR_2 / Z-NR_2

T. W. Green, P. G. M. Wuts,
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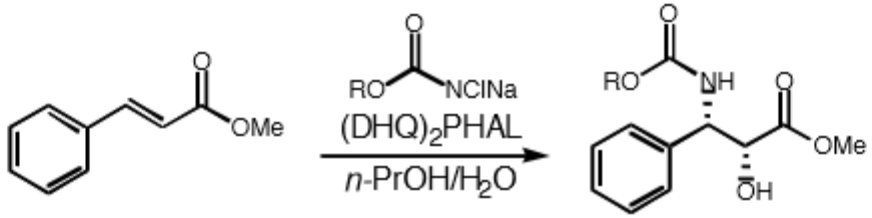
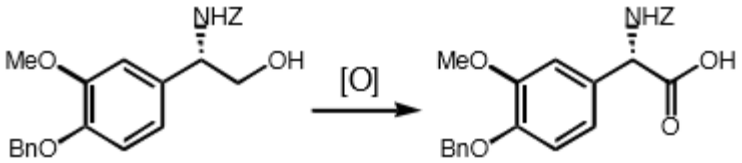
Wiley-Interscience, New York, **1999**, 531-537, 736-739.

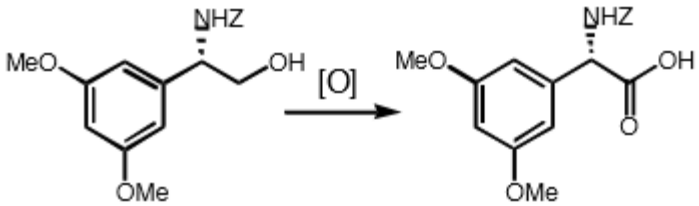


R	% e.e.	% yield
Et	99	78
Bn	94	65
t-Bu	78	71

- 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

Development of an Asymmetric Aminohydroxylation

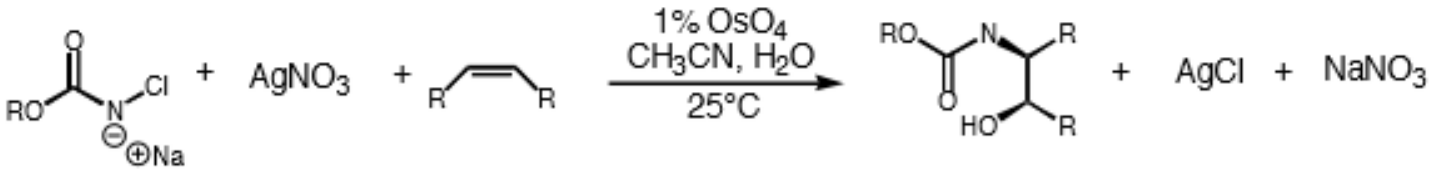
Addition of Sulfonamides and Carbamates as Alternate Nitrogen Sources

■ 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



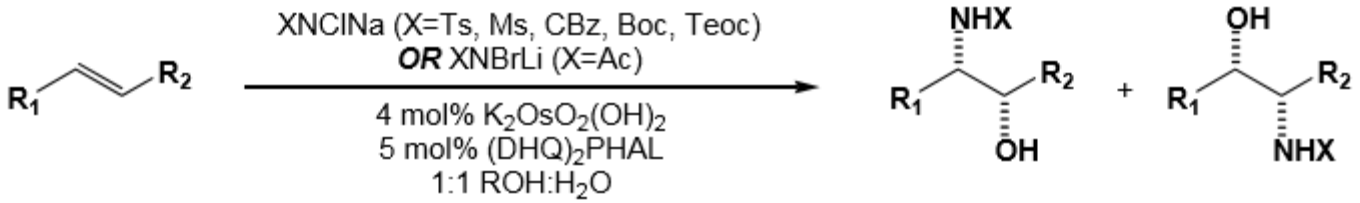
- Better regioselectivity than sulfonamides, more efficient for electron deficient olefins ..
- Addition of $Et_4NOAc \cdot 4H_2O$ accelerates the reaction
- Use of $Hg(NO_3)_2$ for trisubstituted and less reactive mono- and disubstituted olefins

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

Chloramin T

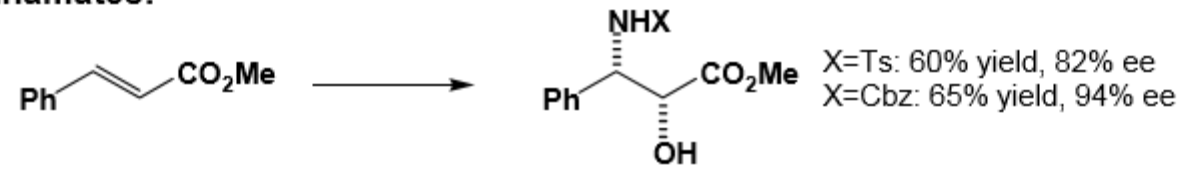
Aminohydroxylation

Review: O'Brien, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 326.



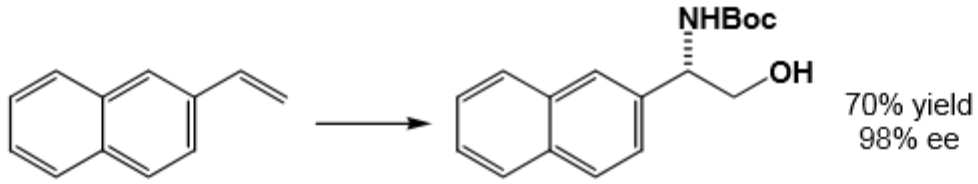
- DHQD-ligand series generally provide opposite enantiomer.
- Effect of substrate structure on regioselectivity: Janda, *Chem. Eur. J.* **1999**, *5*, 1565.

Cinnamates:



- Aryl esters (and AQN-ligands) give opposite regioselectivity! Panek, *Org. Lett.* **1999**, *1*, 1949.
- Can be run at higher concentration in presence of acetamide to suppress diol formation: Wuts, *Org. Lett.* **2000**, *2*, 2667.

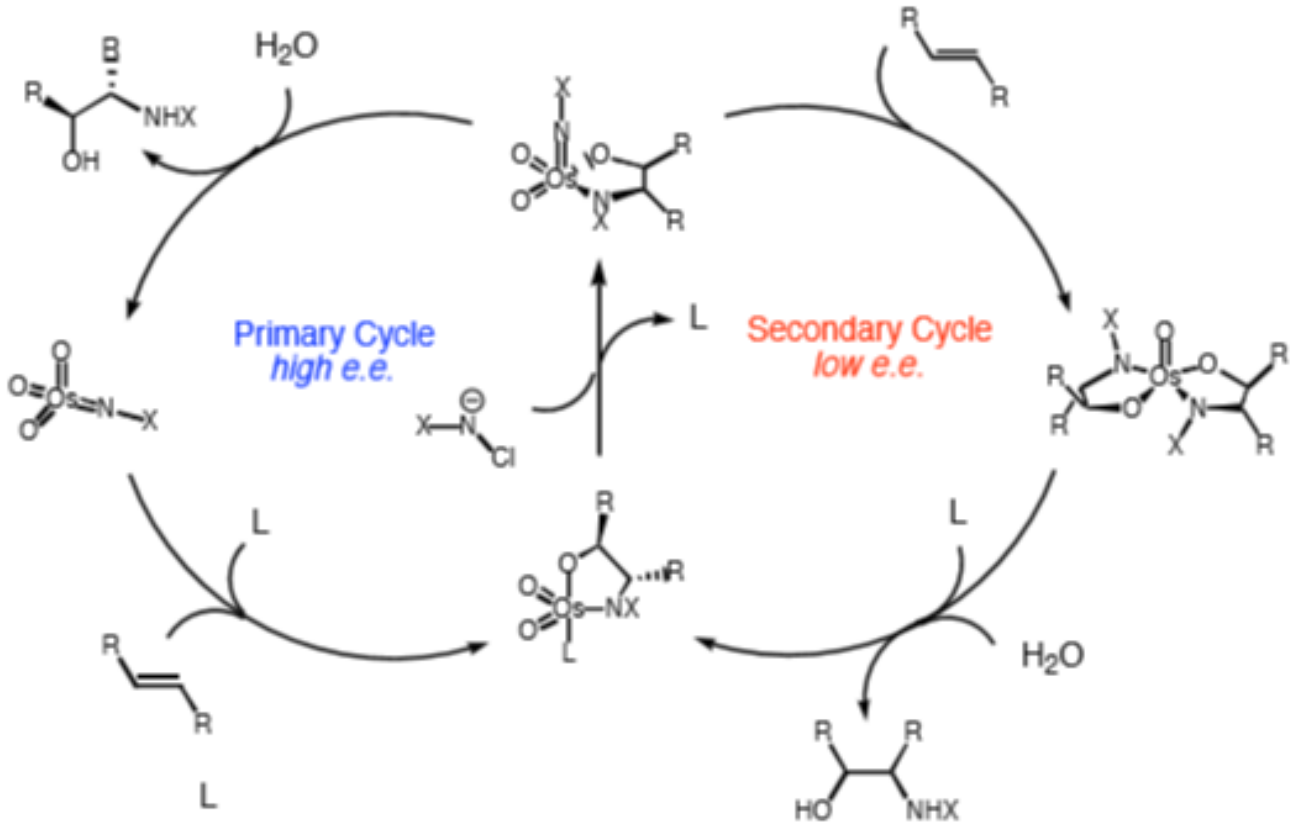
Styrenes, Aryl alkenes (X=Ts, CBz, Boc, Teoc):



- Altering ligand spacer, solvent can reverse regioselectivity without decreasing ee!

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 .

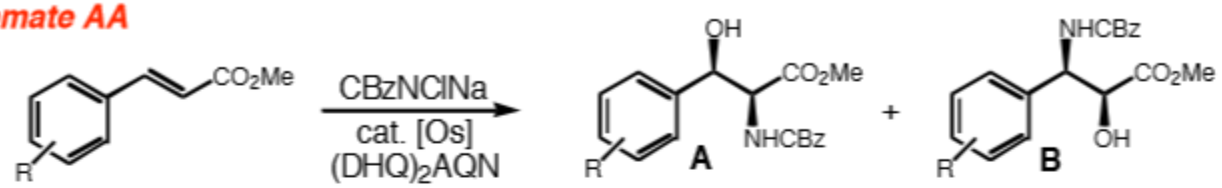
Sharpless, K. B. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 451

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

Reversal of Regioselectivity with AQN alkaloids

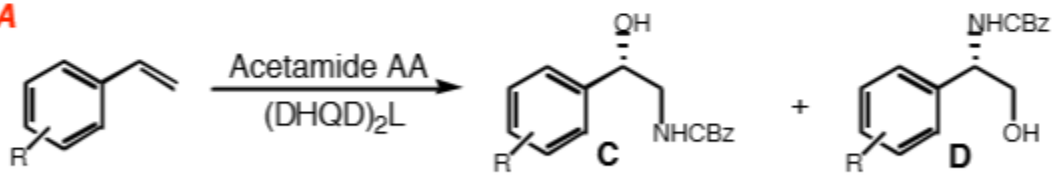
A Phenomenon for Carbamate and Amide AA

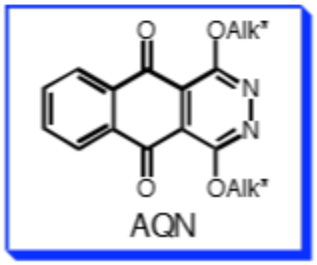
Carbamate AA



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





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

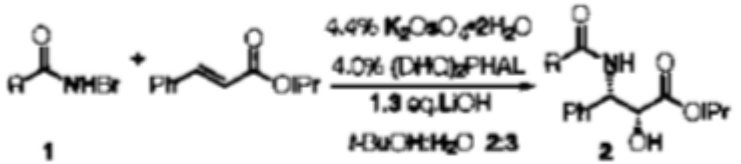
Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507

Amide AA

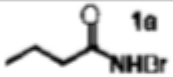
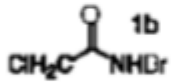
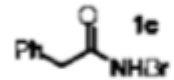
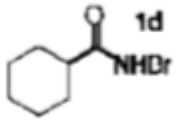
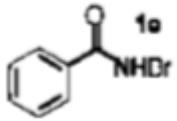
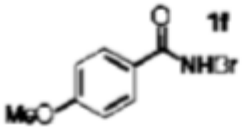
Comparable in Scope to the Carbamate Variant

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

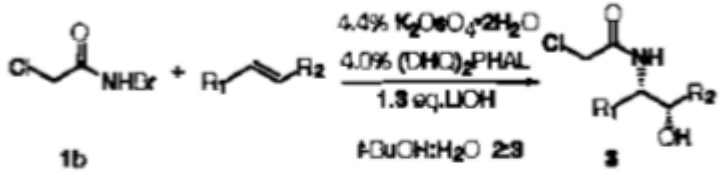
Various Amides as the Nitrogen Source



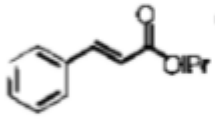
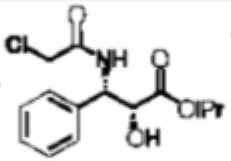
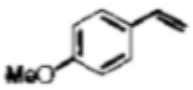
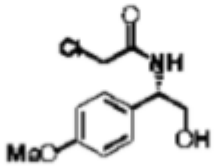
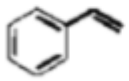
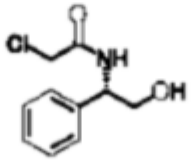
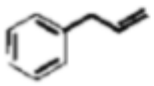
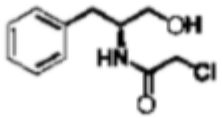
1 2

entry	bromoamide	T(°C)	conversion[a]	yield[b]	ee[c]	regio-selectivity[d]
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%	20 : 1
2f	 1f	0°C	70%	42%[e]	43%	2.5 : 1

Olefin Scope

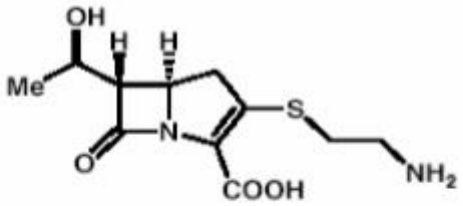


1b 3

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

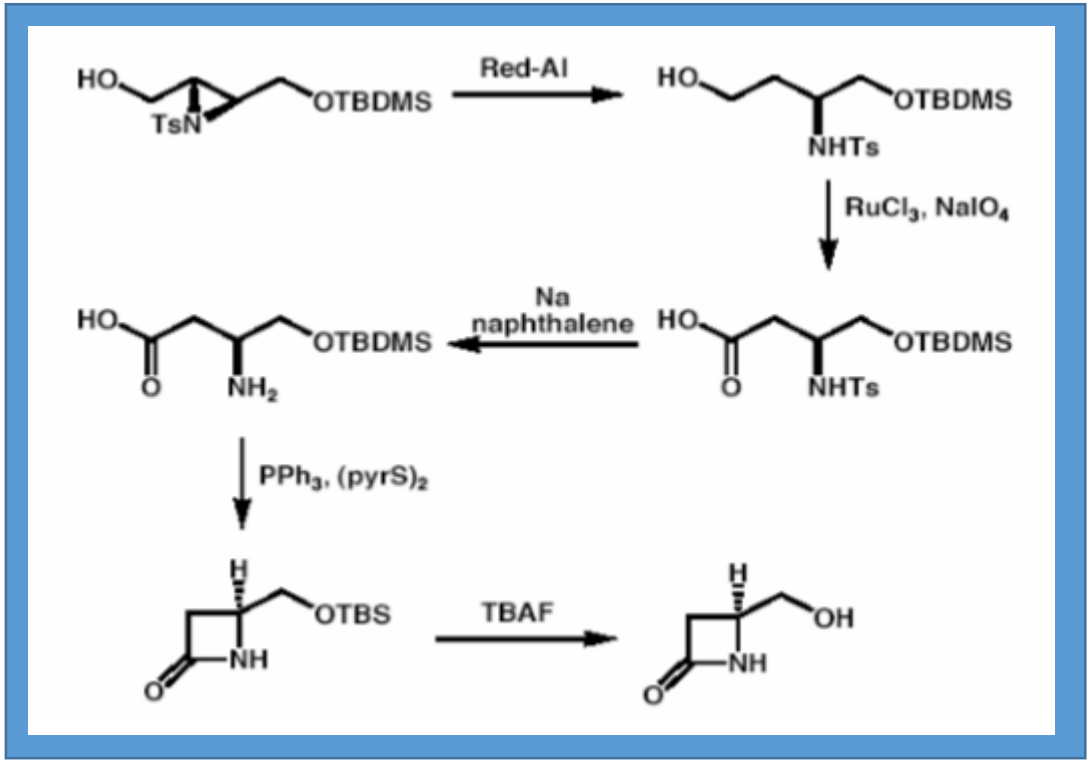
Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221

Aziridines as precursors to β-lactams

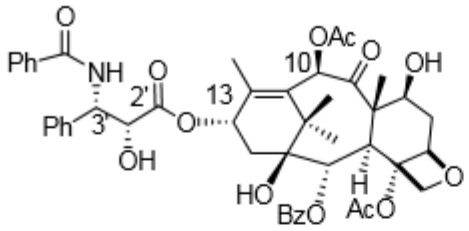


Thienamycin

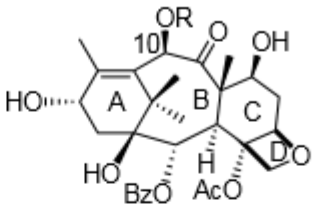
Tet. Lett. **1987**, 1211



TAXOL



$C_{47}H_{51}NO$



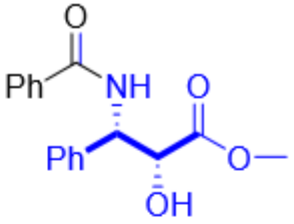
3a: R = H, 10-DAB
3b: R = Ac, BACCATIN III

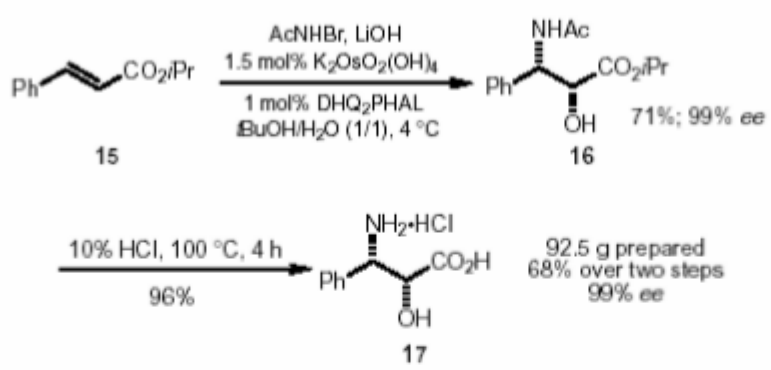
Prodotto da: Bristol-Myers Squibb
Classe: diterpenoide
Sorgente: naturale (estratto da *Taxus brevifloria*) o semisintesi
Area terapeutica: antitumorale
Scoperto: 1971
Tempo per raggiungere il mercato: 21 anni (tumore alle ovaie), 23 anni (tumore al seno)
Formulazione: sterile iniettabile
Marchi registrati: paclitaxel, NSC 125973 BMS, 181339 Taxol, Anzatax, Yewtaxan, Paxene

La ditta italiana Indena (Mi) produce il 10-DAB **3** da cui viene prodotto il tassolo

Sintesi totale
Holton: *J. Am. Chem. Soc.* **1994**, *116*, 1597. *J. Am. Chem. Soc.* **1994**, *116*, 1599
Nicolau: *Nature* **1994**, *367*, 630. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2079
Danishefsky: *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723 e brevetto 30.01.1996

APPLICATIONS: synthesis of the Taxol side chain

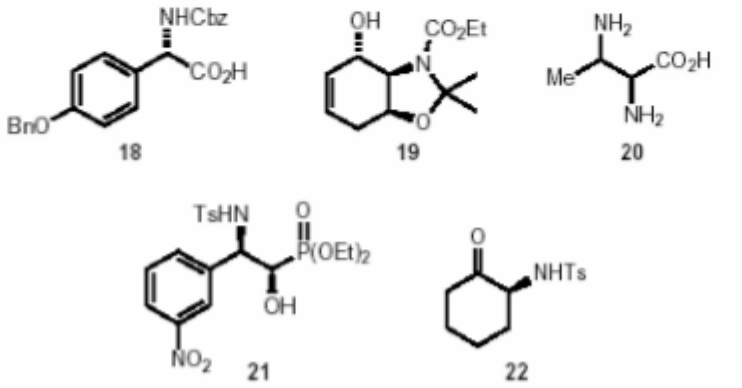




Scheme 5. Large-scale two-step synthesis of precursor to the Taxol side chain.

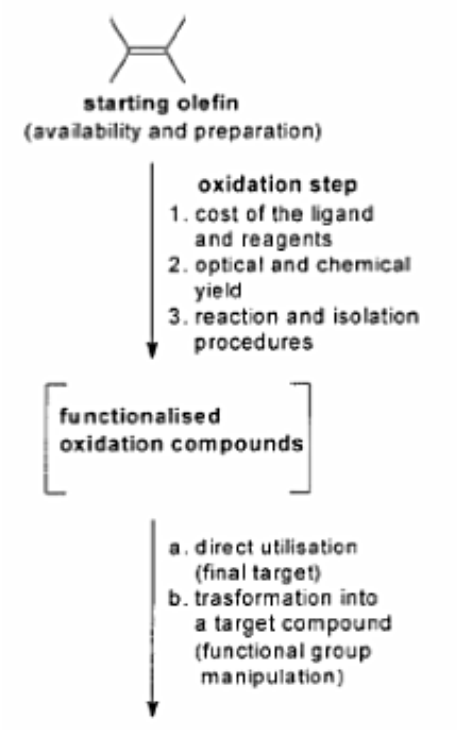
M. Bruncko, G. Schlingloff, K. B. WSharpless *Angew. Chem., Int, Ed. Engl.* **1997**, *36*, 1483-1486.

other examples



Scheme 6. Examples of use of asymmetric aminohydroxylation in synthesis.

Oxidation of olefins: a comparison of different routes



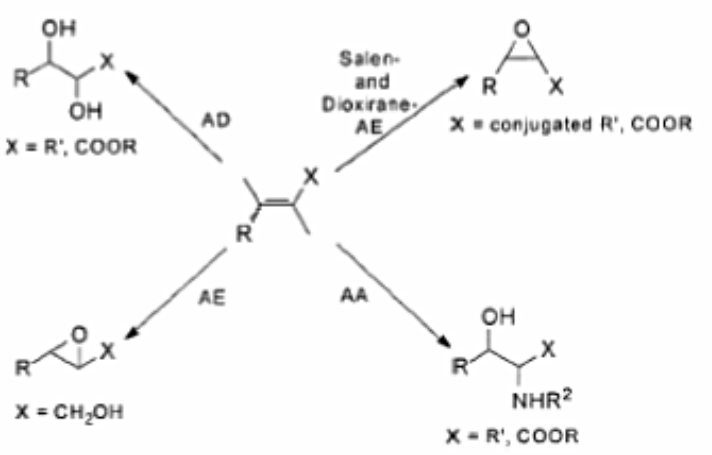


Table 8. Estimate cost for asymmetric oxidation of 1 mmol of olefin

Procedure	Cost (US $)
AE (asymmetric epoxidation)	0.4
AD (asymmetric dihydroxylation)	1.9
AA (asymmetric aminohydroxylation)	5.7
Salen-AE (salen asymmetric epoxidation)	1.6

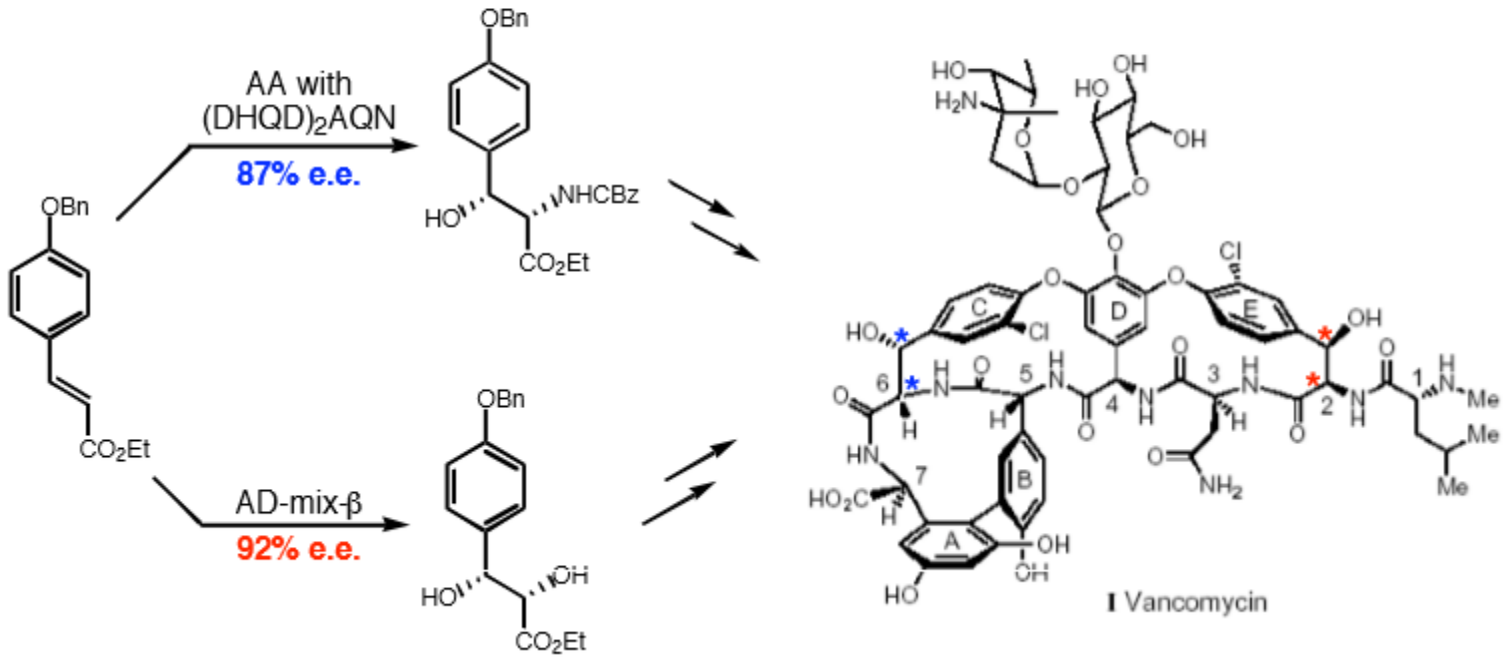
Table 7. Commercially available ligands with average costs

Entry	Catalyst	Quantity	Cost (US $)[a]
1	$(DHQ)_2AQN$	500 mg	33
2	$(DHQD)_2AQN$	500 mg	33
3	$(DHQ)_2PHAL$	500 mg	31
4	$(DHQD)_2PHAL$	1 g	49
5	$(DHQ)_2PYR$	250 mg	25
6	$(DHQD)_2PYR$	250 mg	25
7	AD-mix-α	10 g	13
8	AD-mix-β	10 g	13
9	D(−)-DET	5 g	14
10	L(+)-DET	25 g	9
11	D(−)-DIPT	10 g	40
12	L(+)-DIPT	25 g	14
13	(*R*,*R*)-Salen	1 g	27
14	(*S*,*S*)-Salen	1 g	26
15	(*R*,*R*)-Co(II)Salen-**ent55**	1 g	35
16	(*S*,*S*)-Co(II)Salen-**55**	1 g	39
17	(*R*,*R*)-Mn(III)Salen-**ent16**	1 g	28
18	(*S*,*S*)-Mn(III)Salen-**16**	1 g	28

[a] From the Aldrich chemical catalogue 2000-2001.

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)

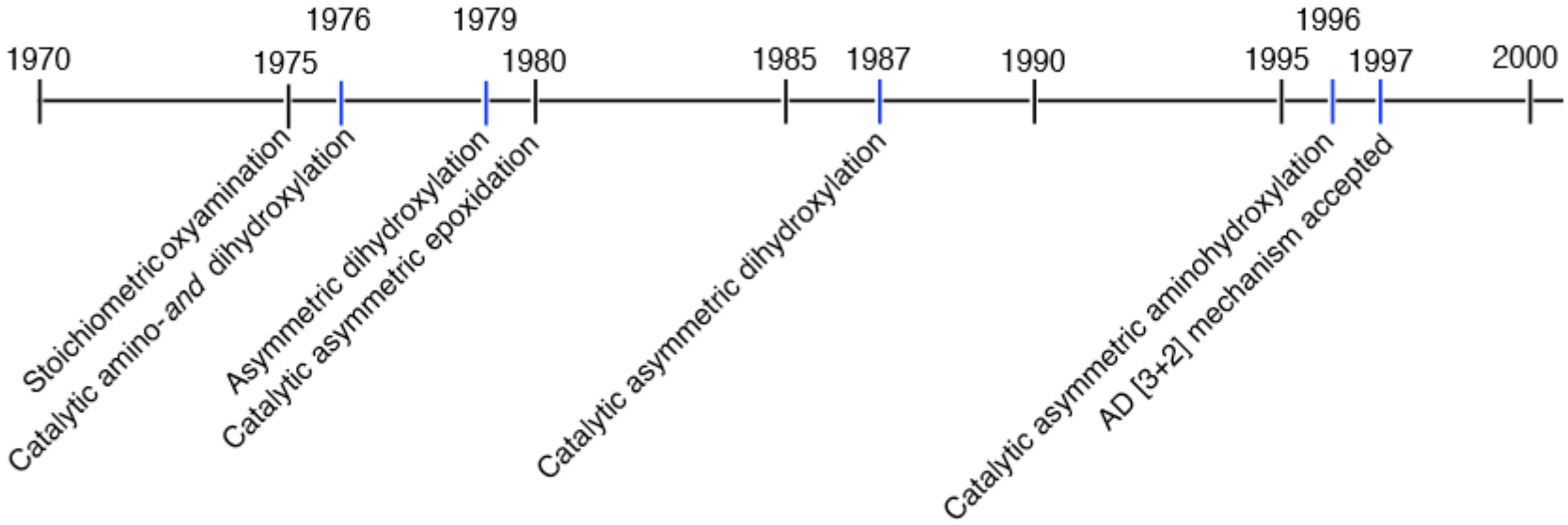


La vancomicina è un peptide ciclico ad azione antibiotica

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