Aminohydroxylation of Olefins: Development and Applications

by

Manish Rawat

Michigan State University

Jan 17th, 2001

Outline

1. Aminohydroxylation of olefins
   a. t-Butyl amine as N source
   b. Chloramine-T as N source
   c. N-Argentocarbamates as N source

2. Asymmetric aminohydroxylation (AA) of olefins
   a. Chloramine-T/M as N source
   b. N-Sodiocarbamates as N source
   c. N-Chloro-N-sodio trimethylsilylethoxycarbamates as N source
   d. N-Bromo-N-lithio carbamides as N source

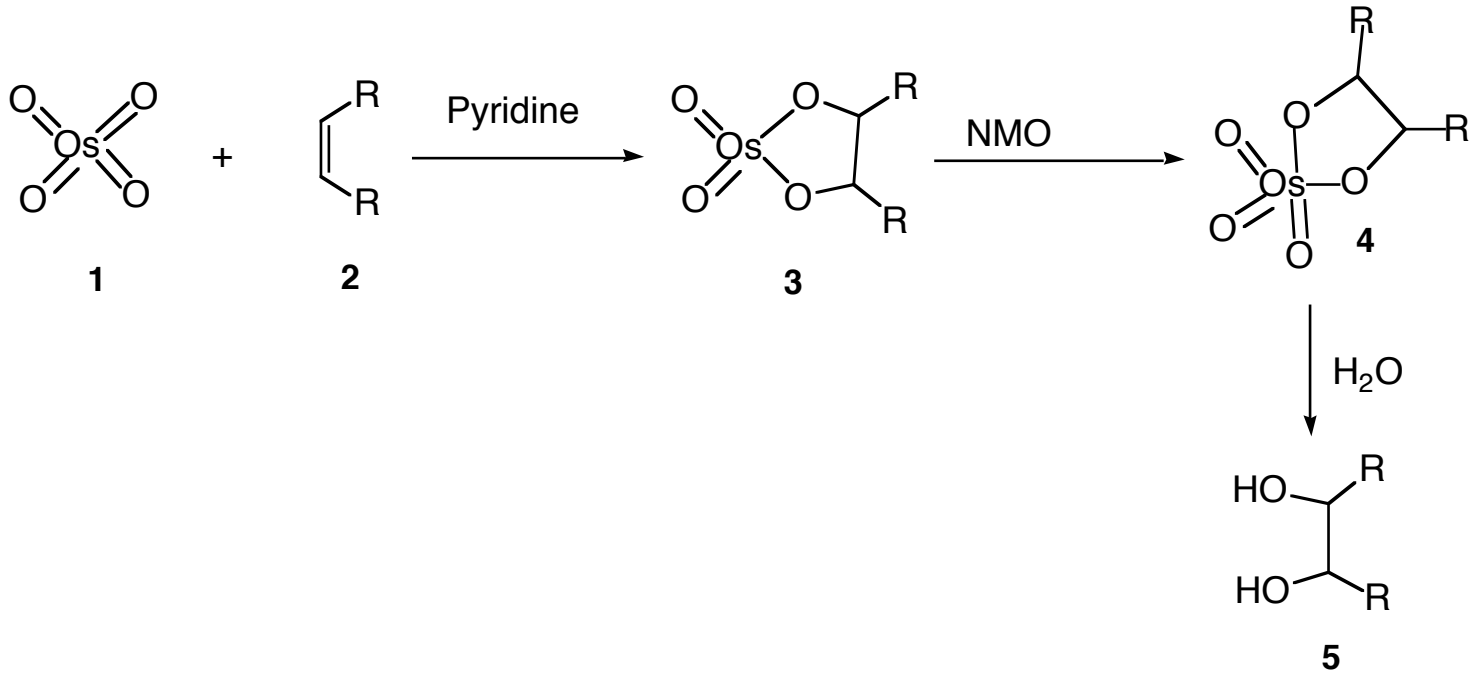
3. Regioselectivity in AA reaction

4. AA on some useful substrates

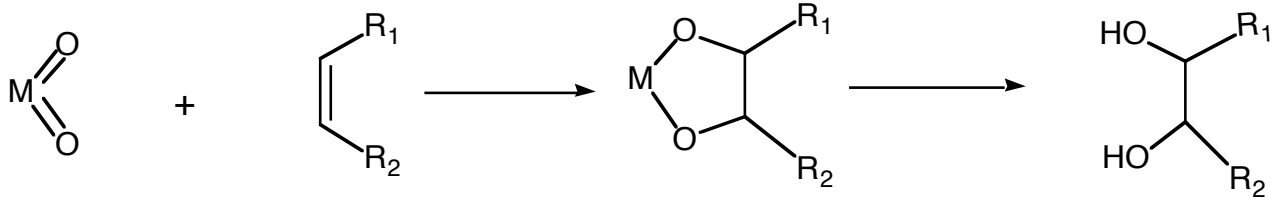
5. Synthetic applications

6. Conclusion

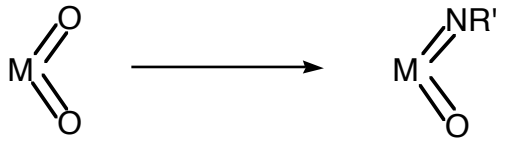
Dihydroxylation of Olefins



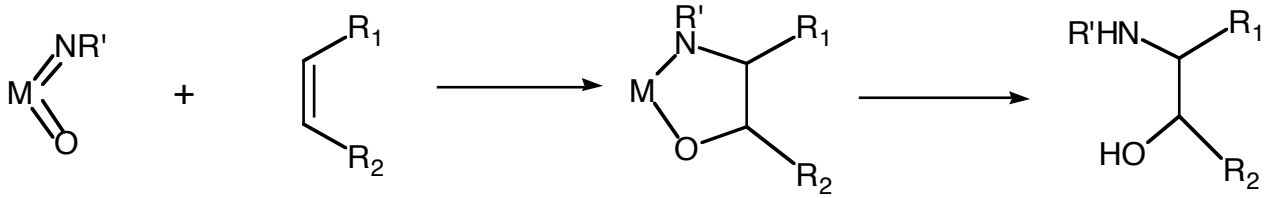
Dihydroxylation of olefins



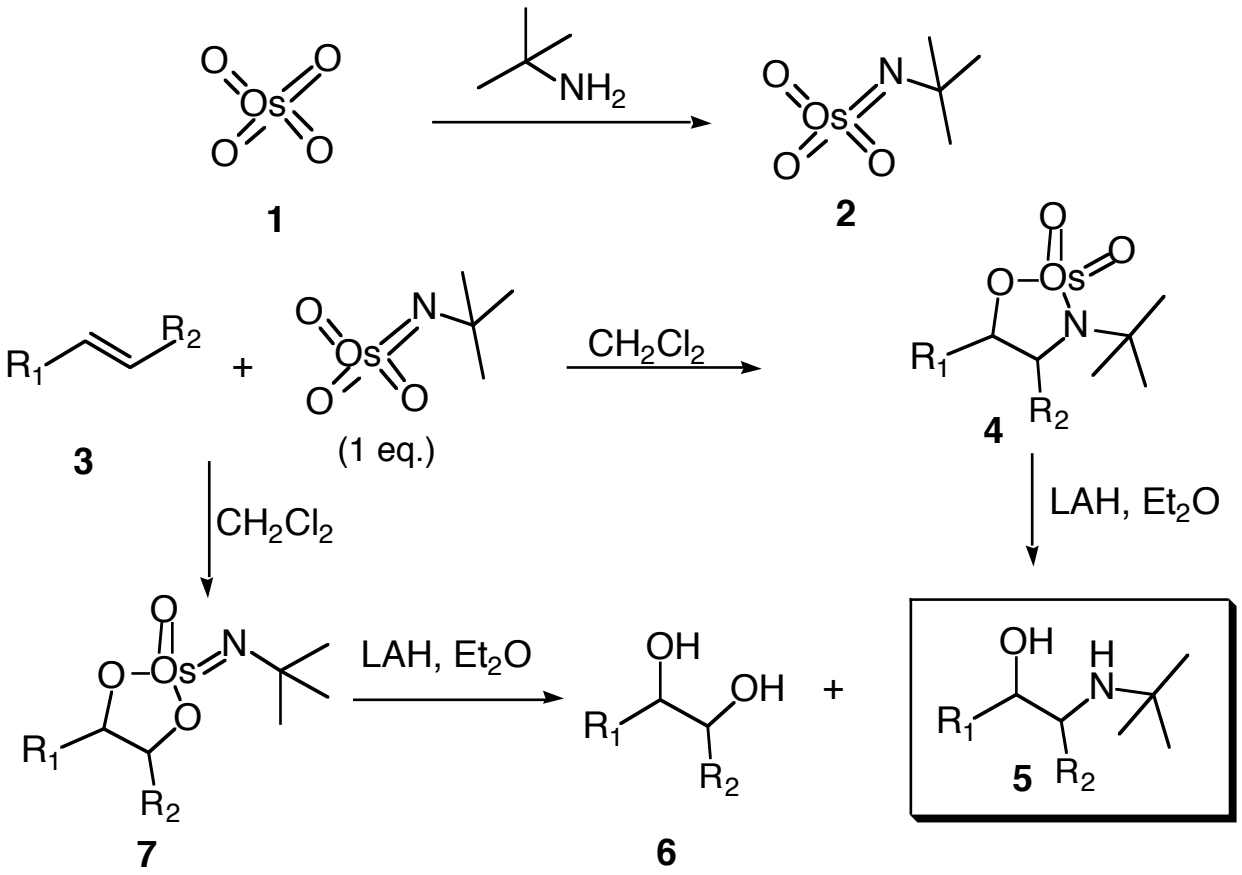
N analogue of transition metal oxo compound



Aminohydroxylation of olefins

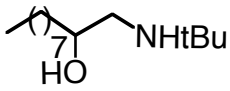
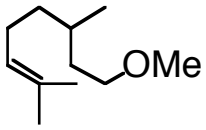
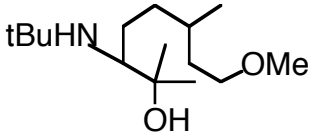
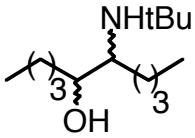
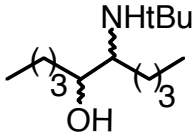


1975 t-Butylamine as N Source for Aminohydroxylation



Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305-2307.

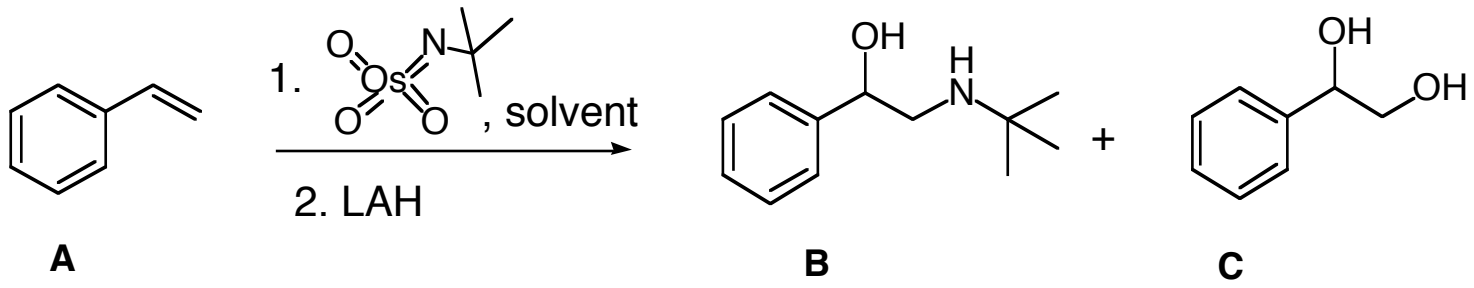
t-Butylamine as Nitrogen Source for Aminohydroxylation

Olefin	Amino alcohol	Solvent	% yield Amino alcohol	% yield Diol
1- Decene		CH_2Cl_2	62	6
		Pyridine	78	1
		CH_2Cl_2	0	78
		Pyridine	38	45
E-5- Decene		CH_2Cl_2	> 20	50 (threo)
		Pyridine	> 95	< 3
Z-5- Decene		CH_2Cl_2	0	53
		Pyridine	25	42

- C - N bond is formed at the least substituted carbon
- Diol formation is more prominent in the sterically hindered system
- Pyridine increases aminoalcohol:diol ratio and rate of the reaction
- trans-Olefins give better results than cis olefins

Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305-2307.

Solvent Effect on Aminohydroxylation Reaction



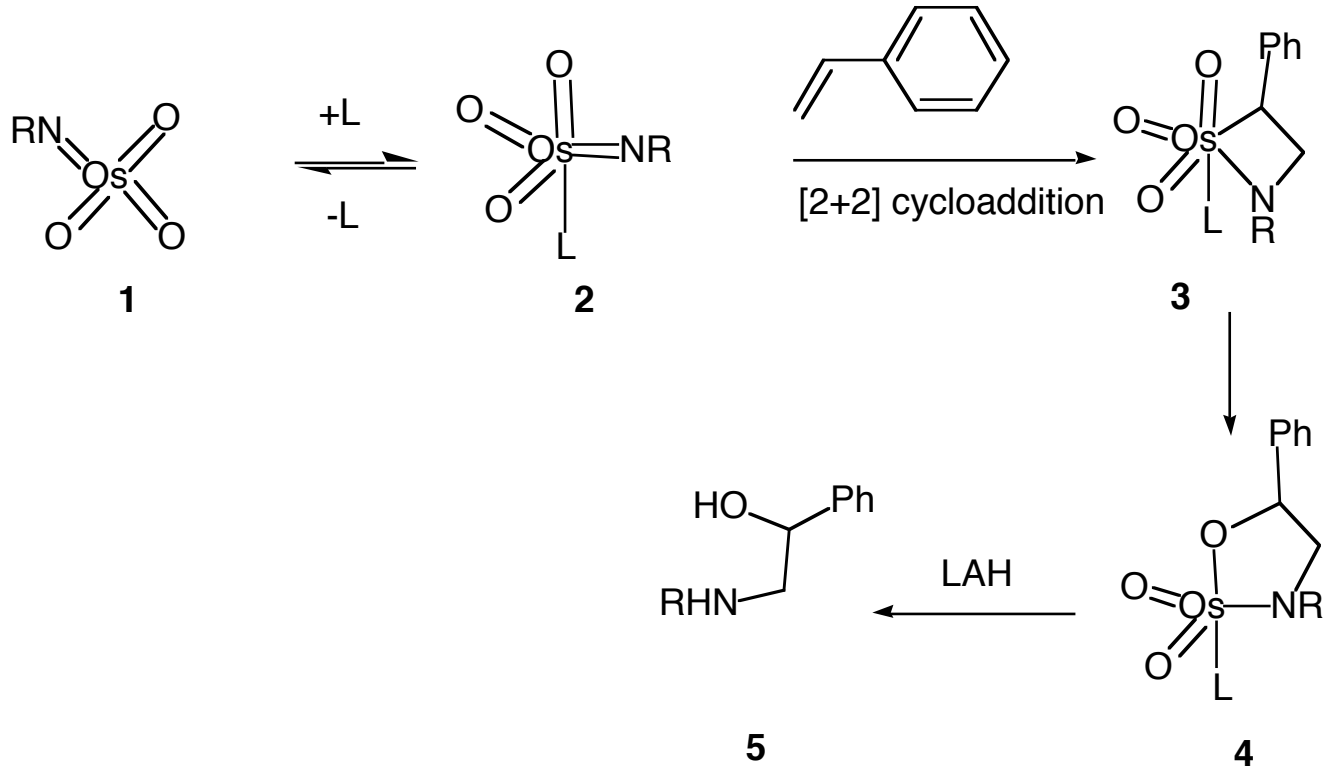
A **B** **C**

Solvent	% yield (**B**)	% yield (**C**)
CH_2Cl_2	37	trace
t-BuOH	52	< 1
THF	64	< 1
Pyridine	92	< 1

- The rate of reaction and yield increase with the increase in coordination ability of the solvent.

Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305-2307.

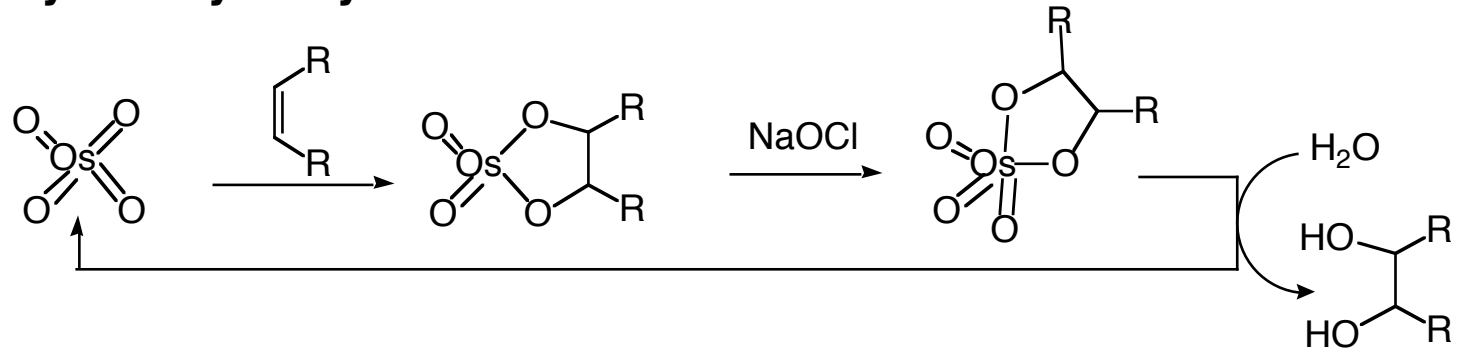
Proposed Mechanism of Aminohydroxylation of Olefins



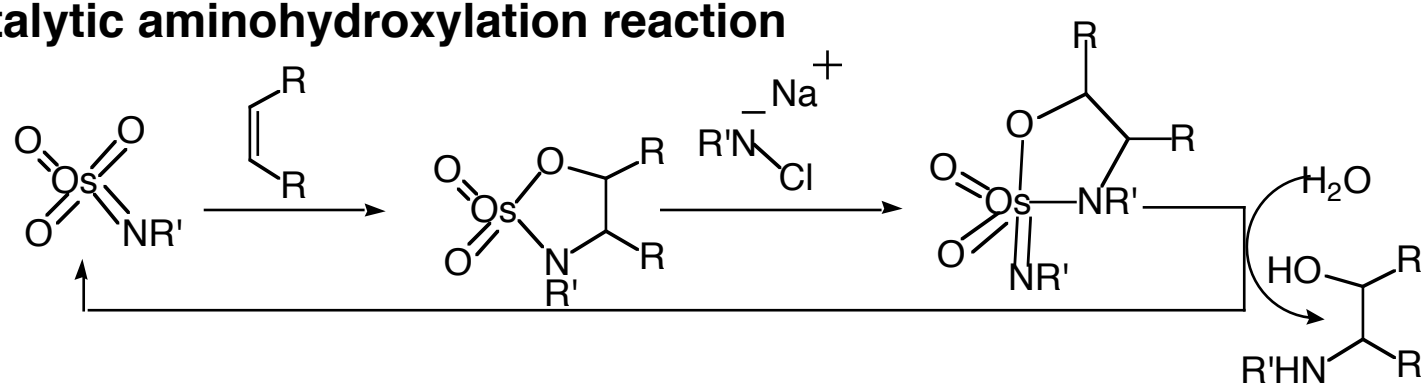
Two major limitations:

- Stoichiometric amount of Osmium reagent
- tert-butyl group is difficult to remove from the product

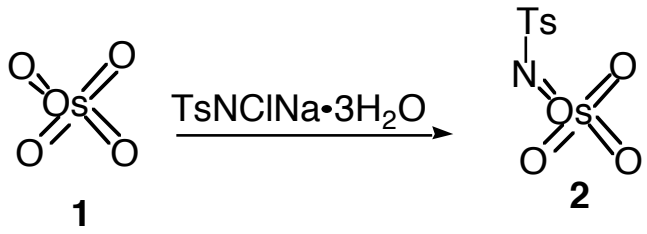
Catalytic dihydroxylation reaction



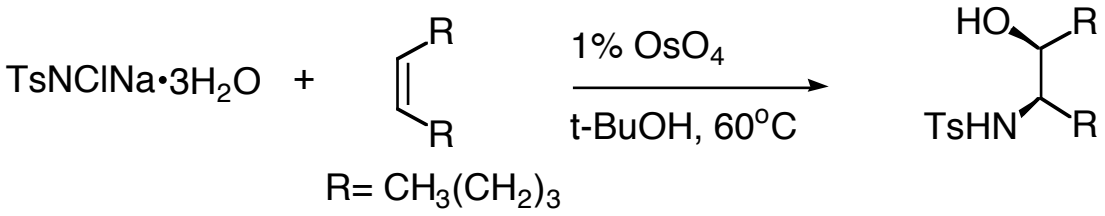
Catalytic aminohydroxylation reaction



1976 Trihydrate of Chloramine-T as N Source



1 **2**



R= $CH_3(CH_2)_3$

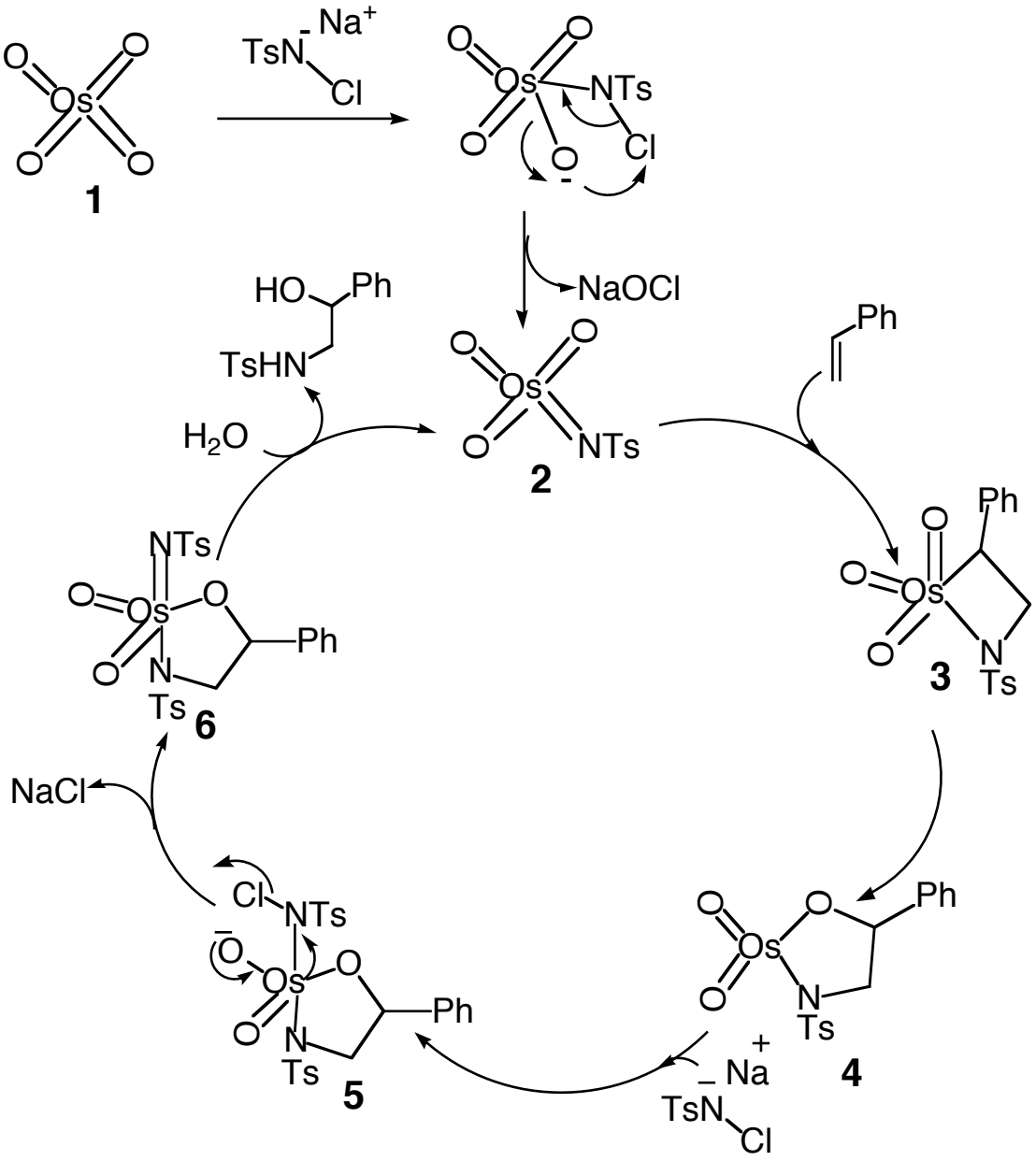
In some cases Cl^- inhibit the rate of reaction:

- $AgNO_3$ addition
- Phase transfer catalysis (1:1 benzene/H_2O + Et_3NBzCl)

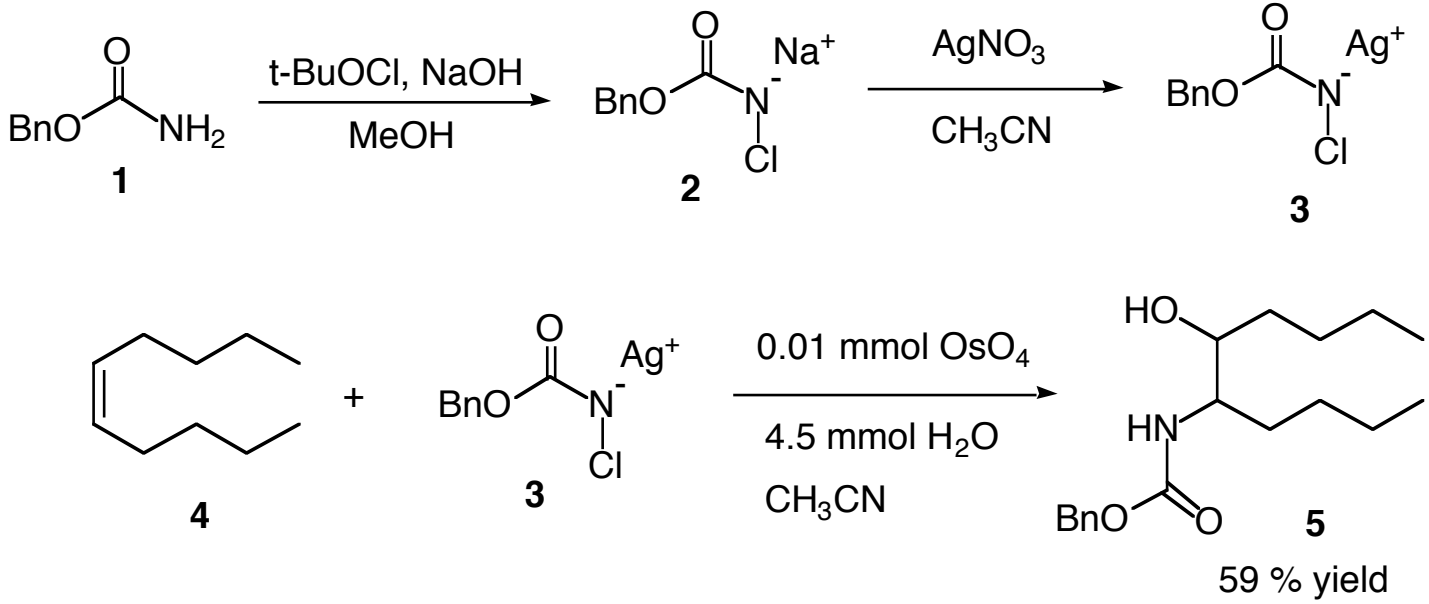
cis Olefins give good yields along with trans olefins.

Sharpless, K. B.; Chong, A. O., Oshima, K. *J. Org. Chem.* **1976**, *41*, 177-179.

Proposed Mechanism of Catalytic Aminohydroxylation



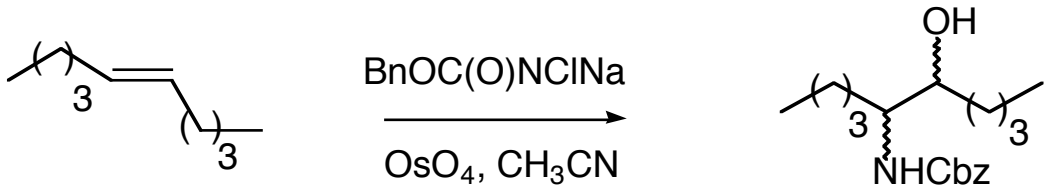
1978 N-Chloro-N-Argento Carbamates as N Source



- Benzyloxycarbonyl group is relatively easily removable protecting group
- cis Olefins give good yields along with trans olefins

Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *100*, 3596-3598.

Effect of Excess Metallic Salt and Et_4NOAc in Aminohydroxylation of Olefins



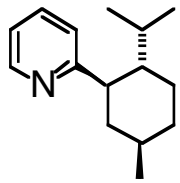
1 **2**

Reagent	Ratio	Rxn time (h)	Reactivity
$BnOC(O)NClNa + AgNO_3$	1.5 : 1.5	80	
$BnOC(O)NClNa + AgNO_3$	1.5 : 3.0	60	
$BnOC(O)NClNa + AgNO_3 + Et_4NOAc$	1.5 : 1.5 : 1	18	INCREASE
$BnOC(O)NClNa + Hg(NO_3)_2$	1.5 : 0.75	24	
$BnOC(O)NClNa + Hg(NO_3)_2$	1.5 : 1.5	12	
$BnOC(O)NClNa + Hg(NO_3)_2 + Et_4NOAc$	1.5 : 0.75 : 1	8	

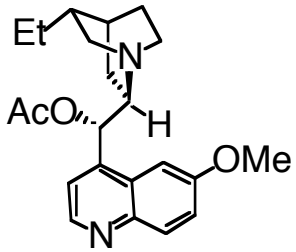
Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *45*, 2710-2713.

Chiral Ligands for Asymmetric Aminohydroxylation (AA)

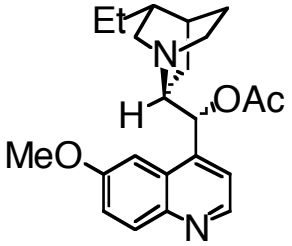
1980 Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263-4265.



(*l*)-2-(2-Menthyl pyridine)

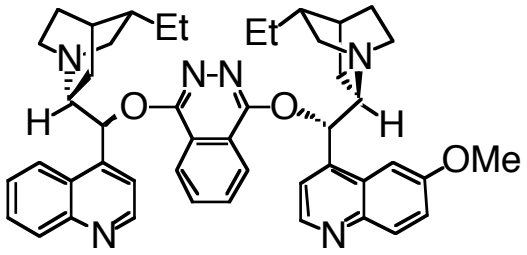


Dihydroquinidine acetate

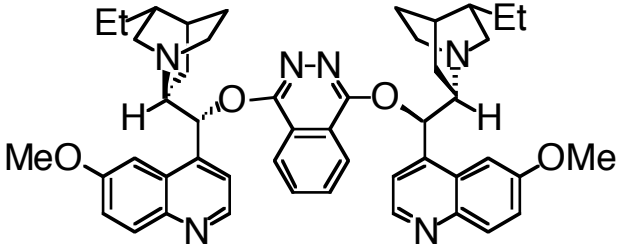


Dihydroquinine acetate

1996 Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451-453.

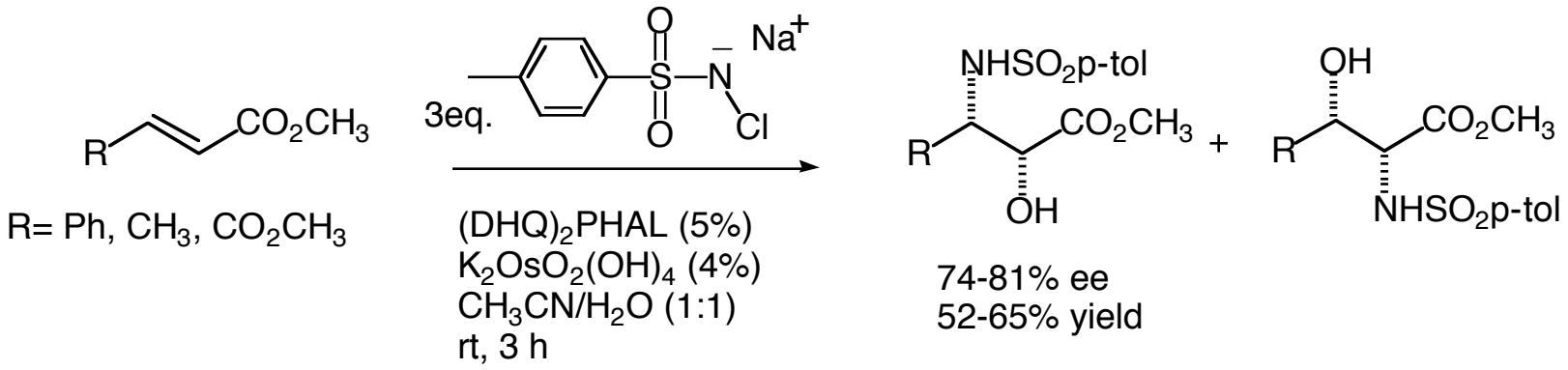


$(DHQD)_2PHAL$



$(DHQ)_2PHAL$

Chloramine-T as N Source for AA



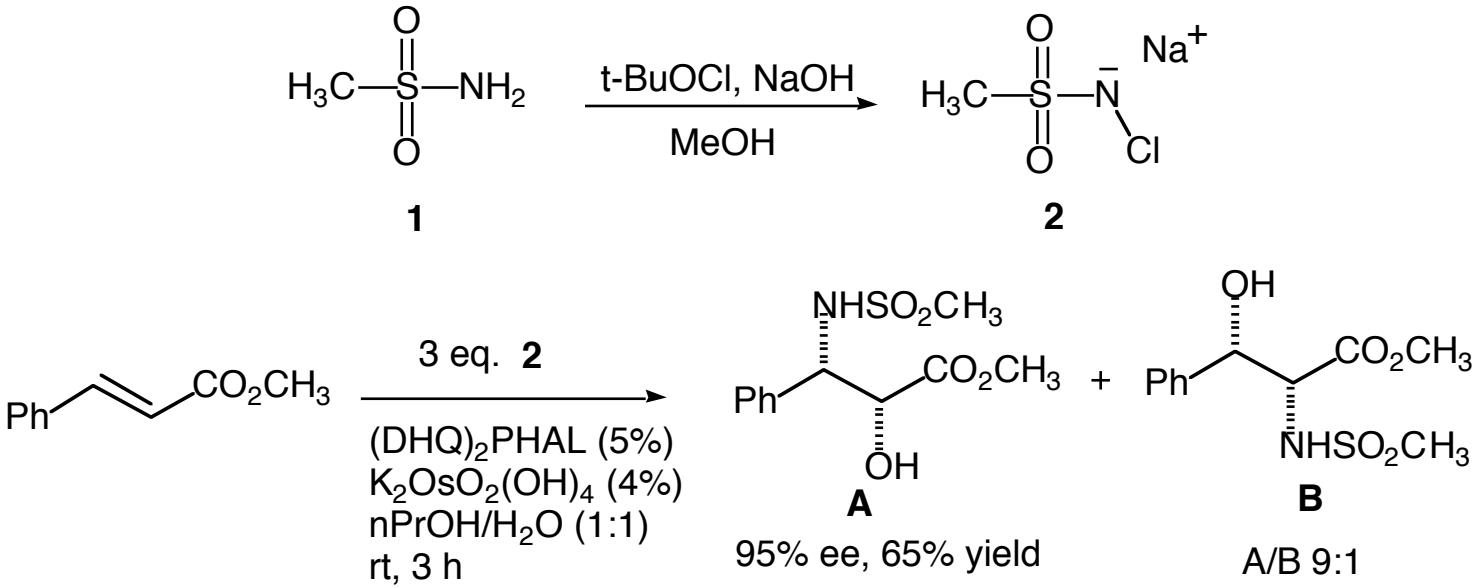
R= Ph, CH_3, CO_2CH_3

$(DHQ)_2PHAL$ (5%)
$K_2OsO_2(OH)_4$ (4%)
CH_3CN/H_2O (1:1)
rt, 3 h

74-81% ee
52-65% yield

Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451-453.

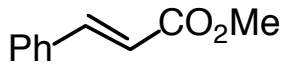
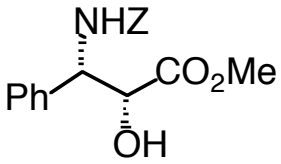
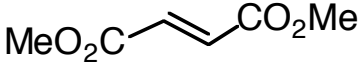
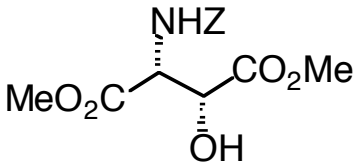
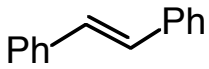
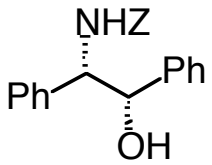
Chloramine-M as N Source for AA



- All the hydroxysulfonamides obtained from Chloramine-M are crystalline solids
- Methanesulfonamide is soluble in water

Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2810-2812.

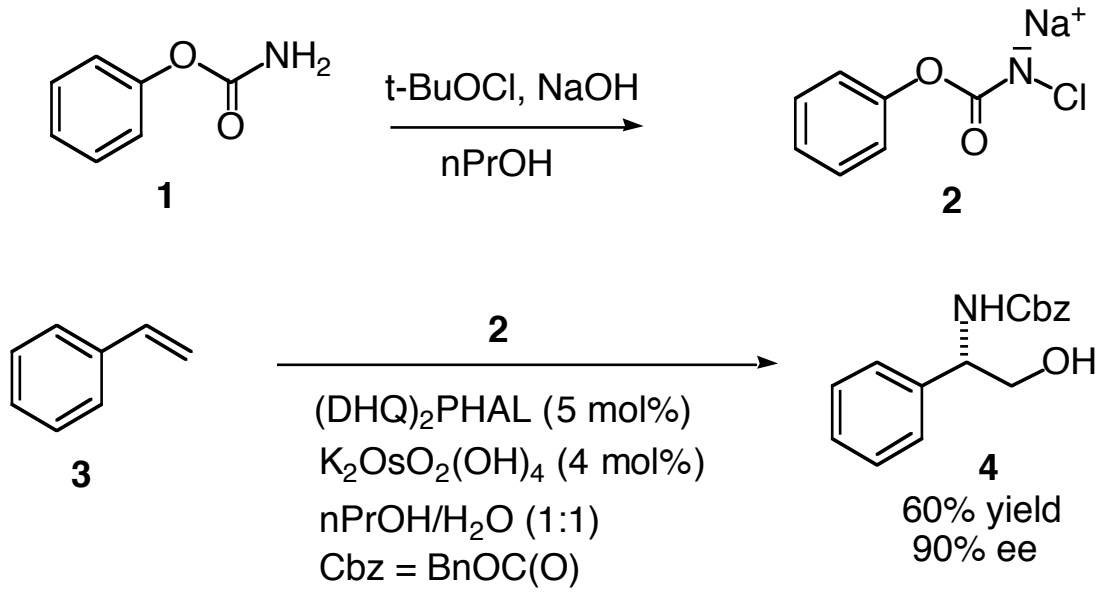
Chloramine-T/M as N Source for AA

Substrate	Product	Z=p-tol-SO_2-		Z=Me-SO_2-	
		%ee	Yield	%ee	Yield
		81	64% [a]	95	65%[b]
		77	65%	95	76%
		62	52%	75	71%

a) Regioselectivity 5:1, b) Regioselectivity 9:1.

Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451-453 and 2810-2812.

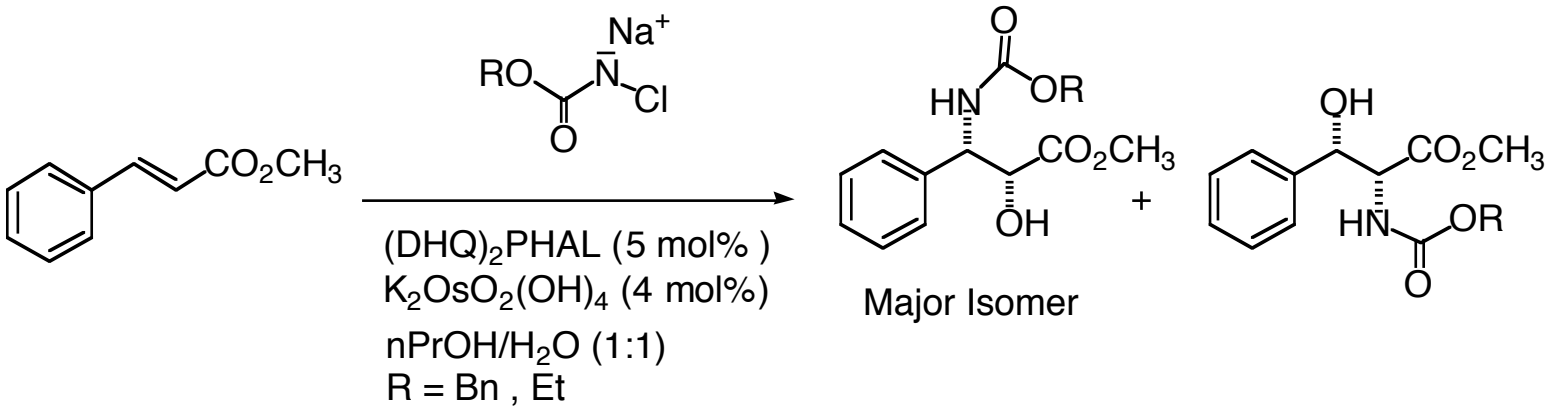
N-Halo Carbamate as N Source for AA



- Benzyloxycarbonyl is a relatively easily removable protecting group.
- Styrene type olefins give good results along with other olefins..

Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2810-2812.

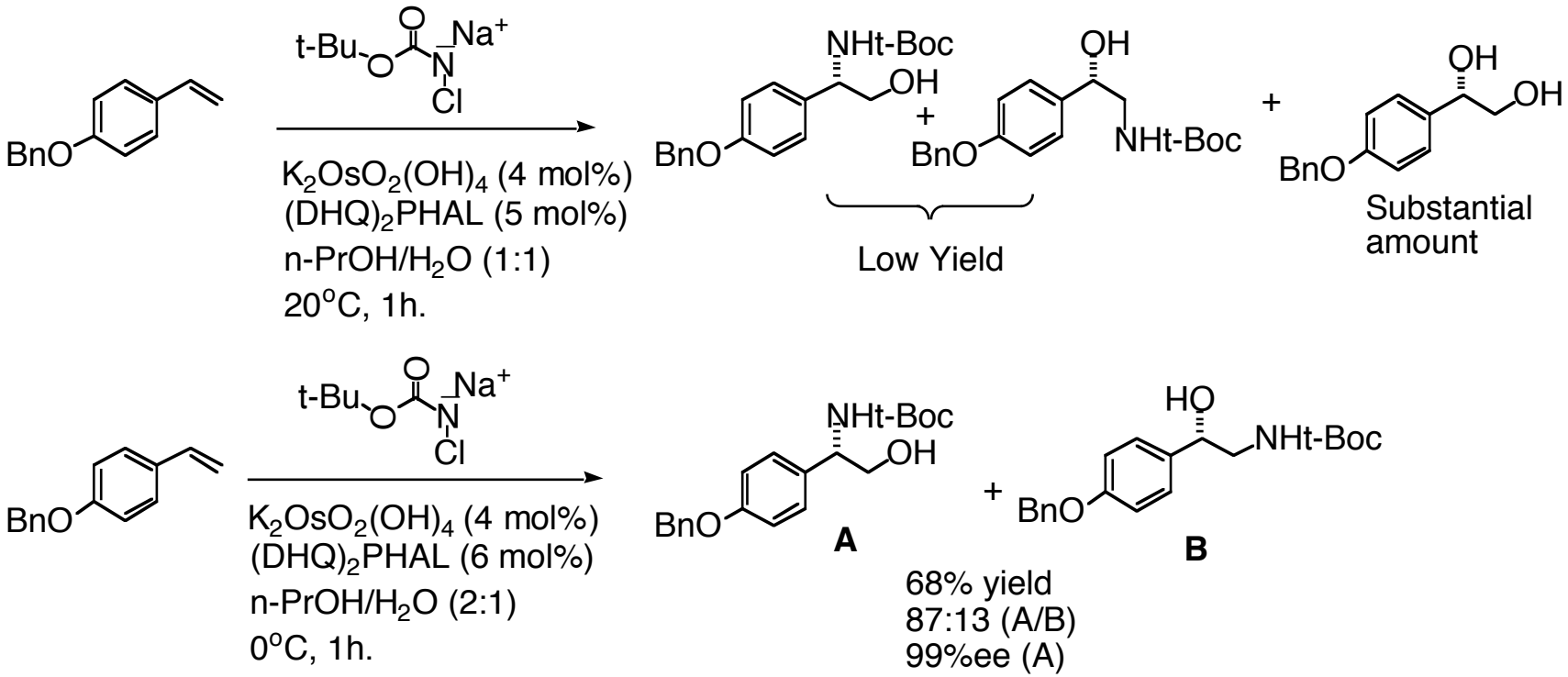
N Halocarbamate as N Source for AA



R	%ee	Yield
Et	99	78%
Bn	94	65%

Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2810-2812.

N-Halo-t-butylcarbamate as N Source for AA

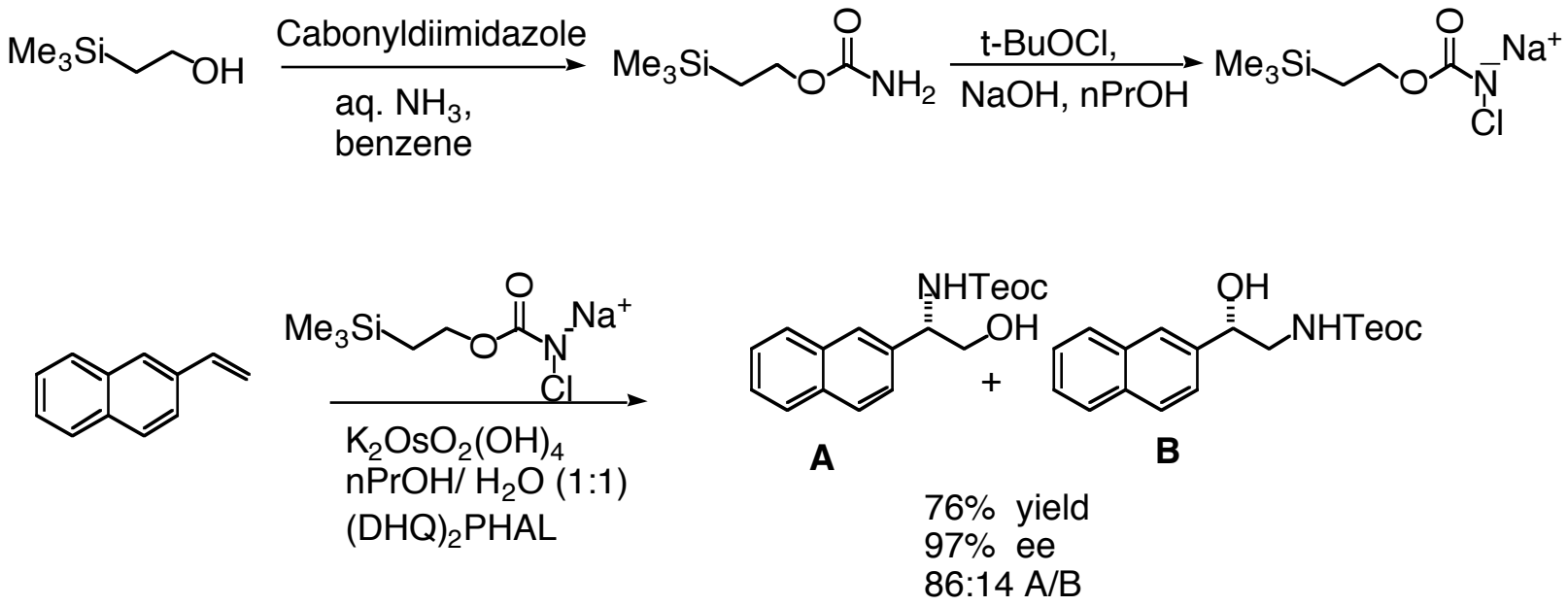


For t-Boc protected vicinal aminoalcohol formation:

- nPrOH/H_2O (2:1) ratio is lower than usual (1:1)
- Lower temperature (0°C)
- Ligand concentration is higher

K. L. Reddy, Sharpless, K. B. *J. Am. Chem. Soc*. **1998**, *120*, 1207-1217.

N-Chloro-N-Sodio-2-Trimethyl Silyl Carbamate (Teoc) as N Source

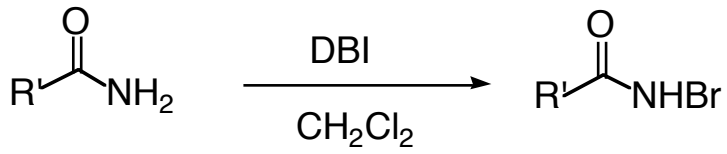


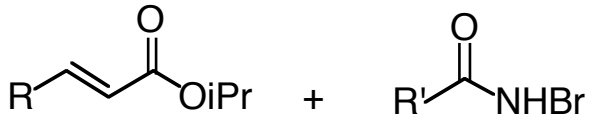
Trimethyl silyl carbamate is

- easily removable protecting group
- good regioselectivity, enantioselectivity
- styrene type olefins gives good yields

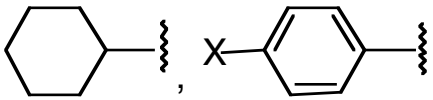
Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Tetrahedron Lett.* ,**1998**, *39*, 3667-3670.

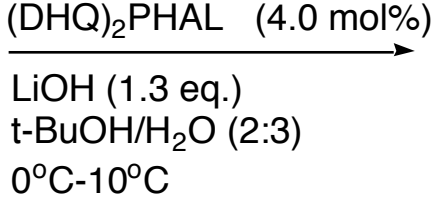
Primary Amides as N Source for AA of Olefin

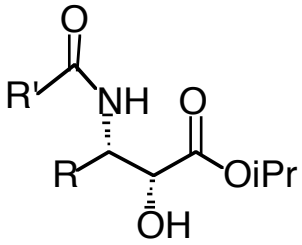




R = Pr, $ClCH_2$, $PhCH_2$,



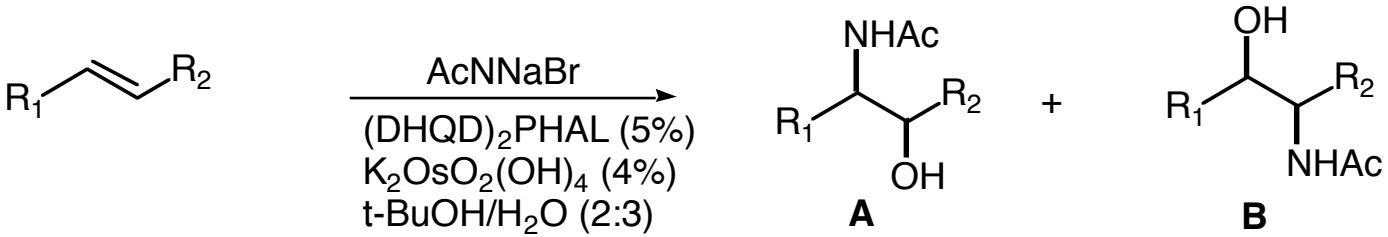


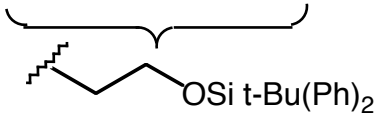
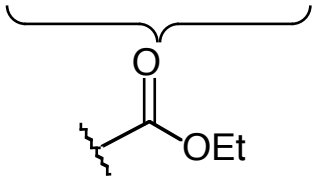
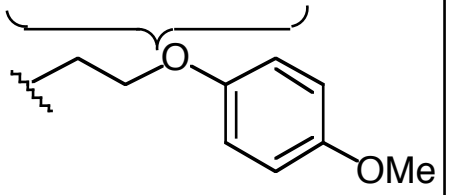


38-94% yield
77-95% ee
2.0:1 - 23:1 regioselectivity

Demko, P. Z.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 2221-2223.

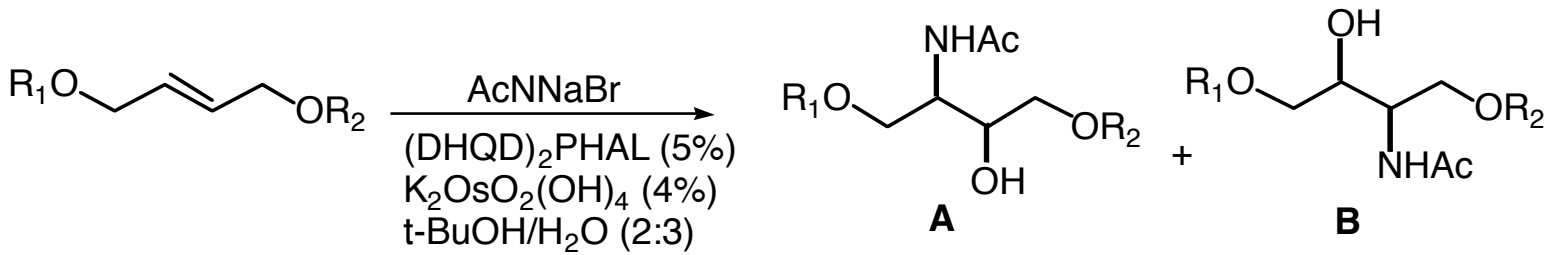
Steric, Electronic and Aromatic Substituent Effect on the Regioselectivity



Entry	1	2	3	4	5	6
R_1 =	H	Et	H	Me	H	Me
R_2 =						
A/B	>20:1	2:1	15.2:1	1.4:1	1.2:1	1:3.2

Han, H.; Cho, C.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565-1569.

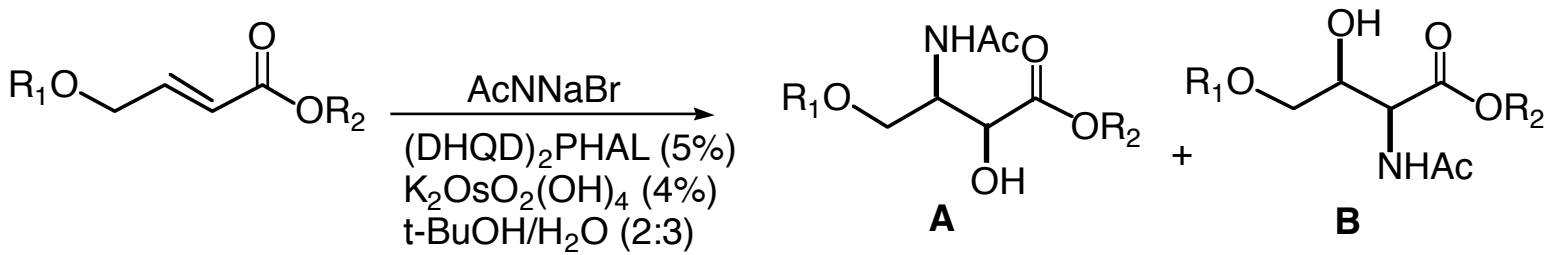
Steric and Aromatic Substituent Effect on the Regioselectivity



Entry	1	2	3	4
R_1 =	TBDPS	t-butyl	TBDPS	TBDPS
R_2 =	p-methoxybenzoyl		2-naphthoyl	(2-naphthyl)methyl
B/A	11.9:1	14.2:1	20:1	3:1

Han, H.; Cho, C.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565-1569.

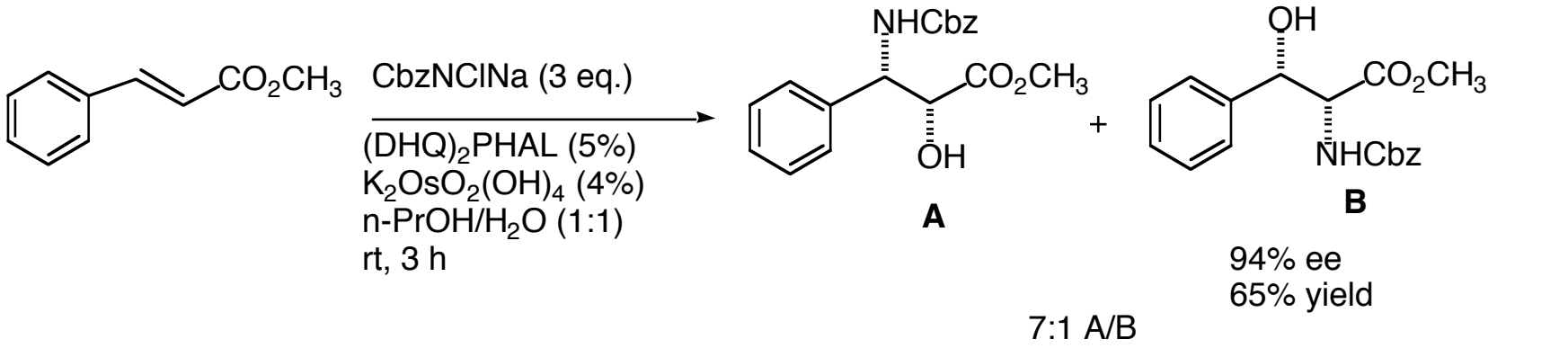
Steric, Electronic and Aromatic Substituent Effect on the Regioselectivity



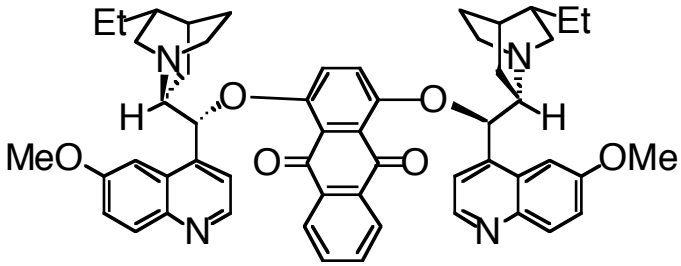
Entry	1	2	3	4	5	6
R_1 =	p-methoxy-benzoyl	benzyl	(2-naphthyl)-methyl	t-butyl	TBDPS	TBDPS
R_2 =	ethyl			p-methoxy-benzyl		(2-naphthyl)-methyl
A/B	20:1.0	2.4:1.0	4.3:1.0	1.0:1.5	1.0:6.0	1.0:17.0

Han, H.; Cho, C.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565-1569.

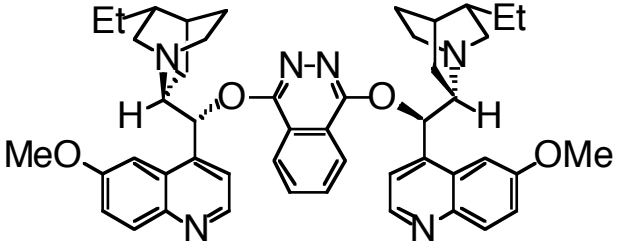
Reversal of Regioselection in the AA of Cinnamates by AQN and PHAL Ligands



Tao, B.; Schlingloff, G; Sharpless, K. B. *Tetrahedron lett.* **1998**, *39*, 2507-2510

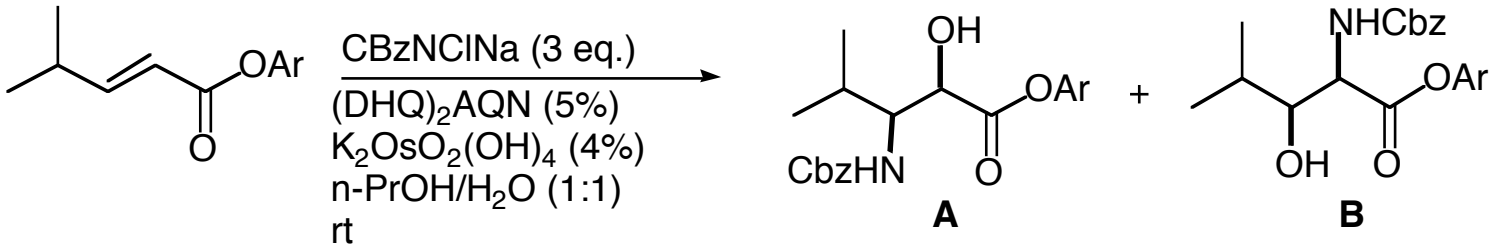


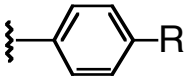
$(DHQ)_2AQN$



$(DHQ)_2PHAL$

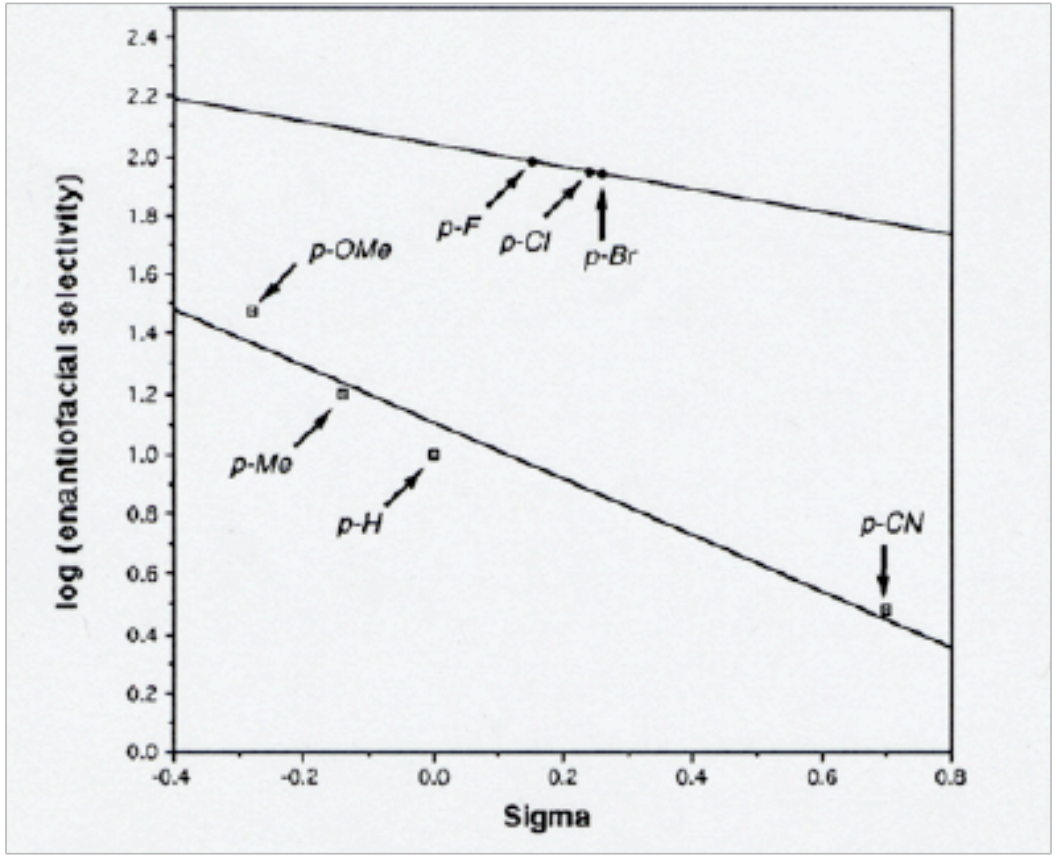
Reversal of Regioselection in the AA of Cinnamates of Aryl Ester Substrate



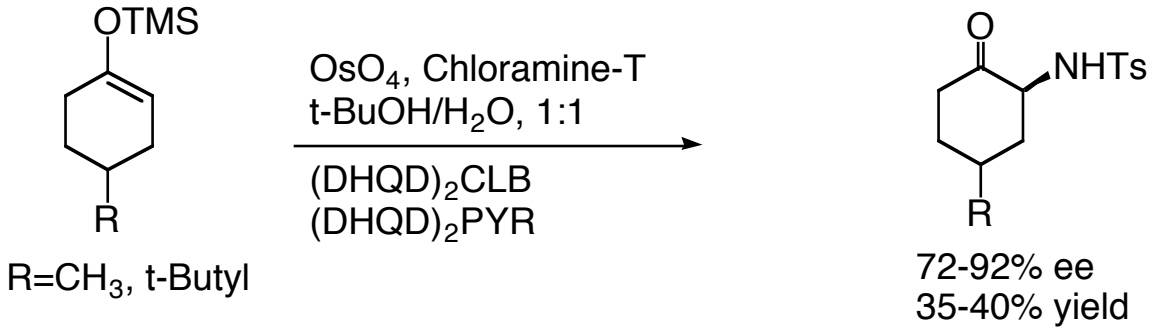
Entry	1	2	3	4	5	6	7	8	9
Ar: 	R = H	Me	OMe	Br	Cl	F	CN	NO_2	I
A/B	1:1	1:4	1:5	1:7	1:5	1:3	1:1.4	NR	NR
Yield %	51	53	55	60	58	59	50	-	-
ee %	10	16	30	87	89	96	3	-	-

Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949-1952.

Hammet-type Analysis for the Aminohydroxylation Process

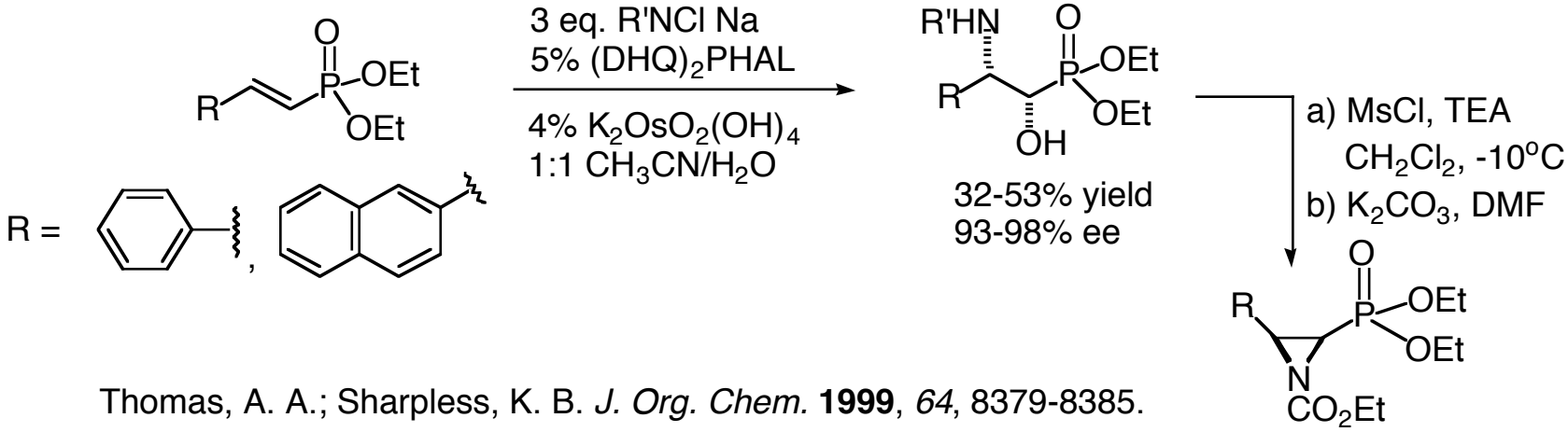


AA of Silyl Enol Ether



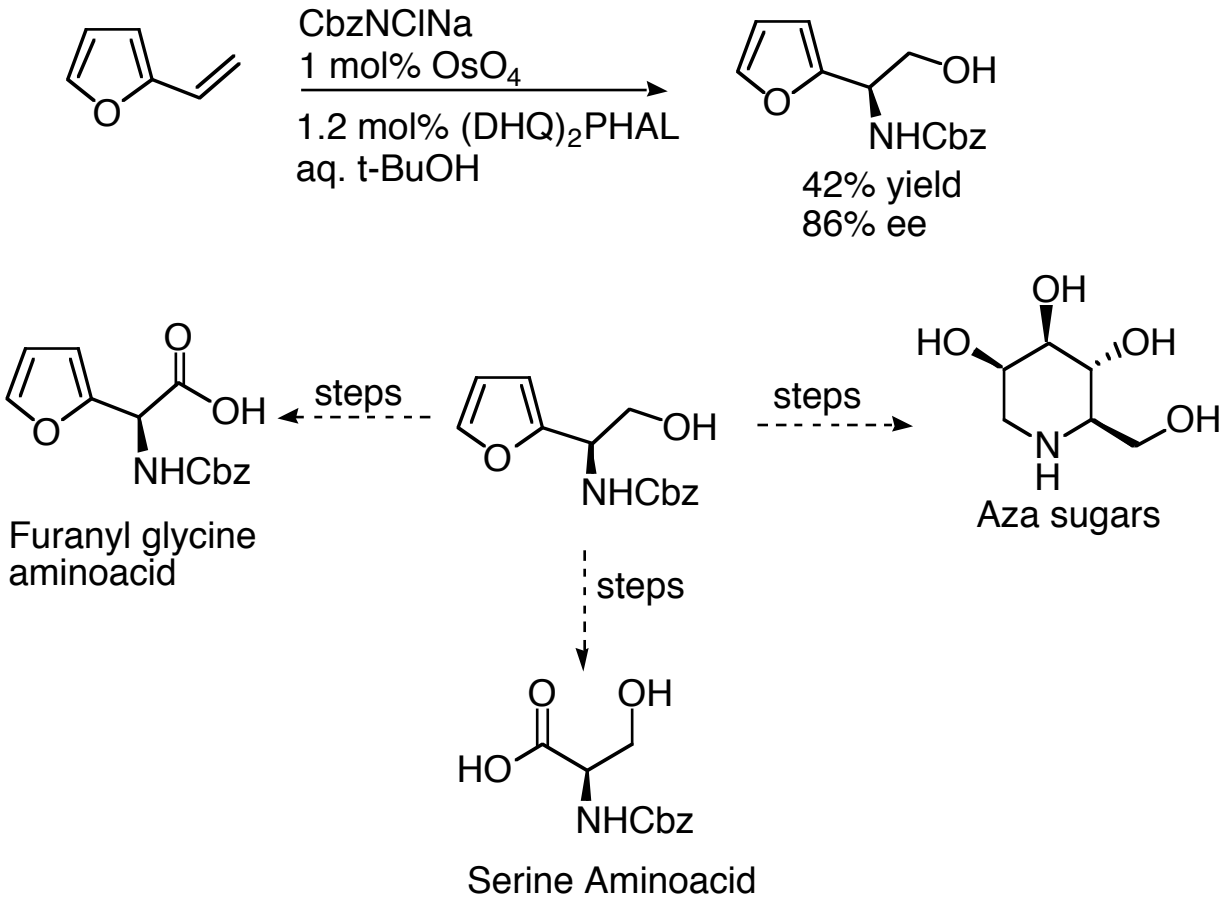
Phukhan, P.; Sudalai, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1001-1005.

AA of Unsaturated Phosphonates



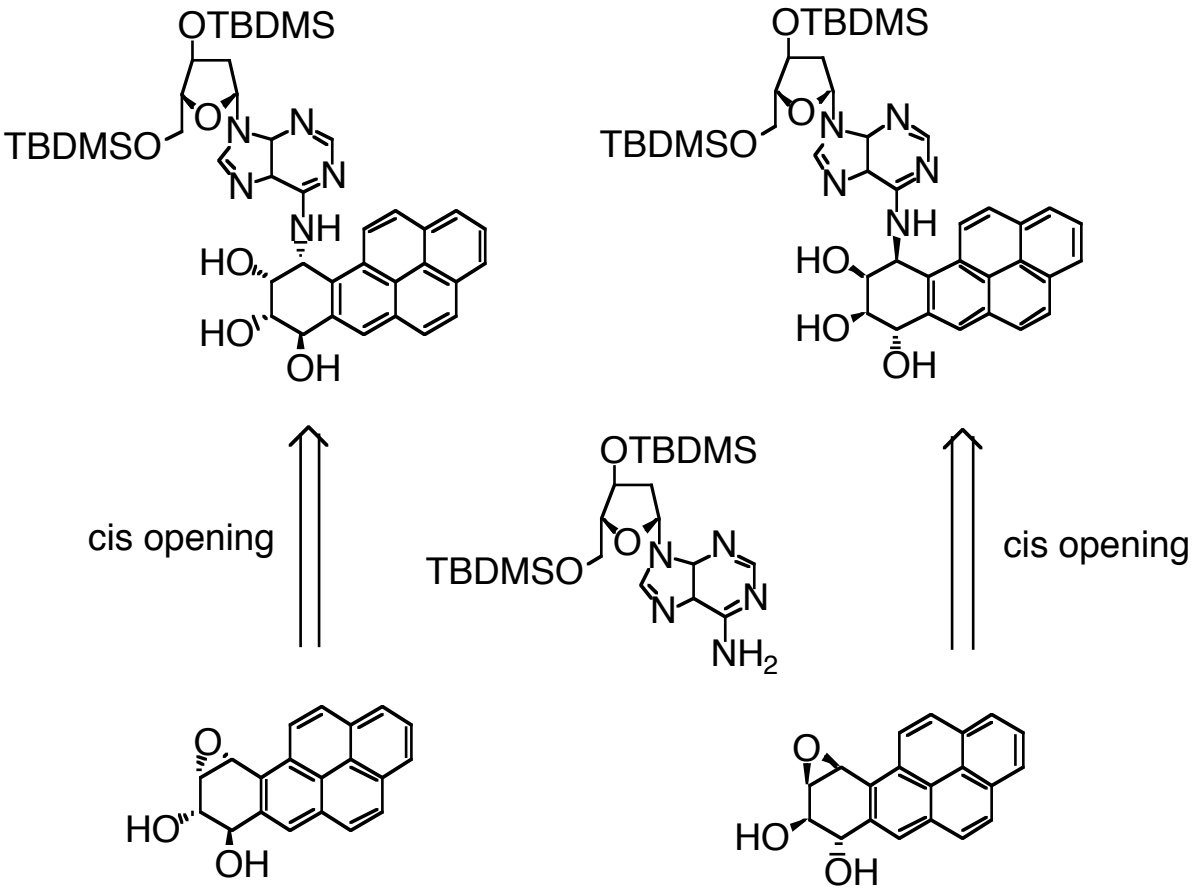
Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379-8385.

AA of Vinyl Furan



O'Doherty, G. A.; Bushey, M. L.; Haukaas, M. H. *J. Org. Chem.* **1999**, *64*, 2984-2985.

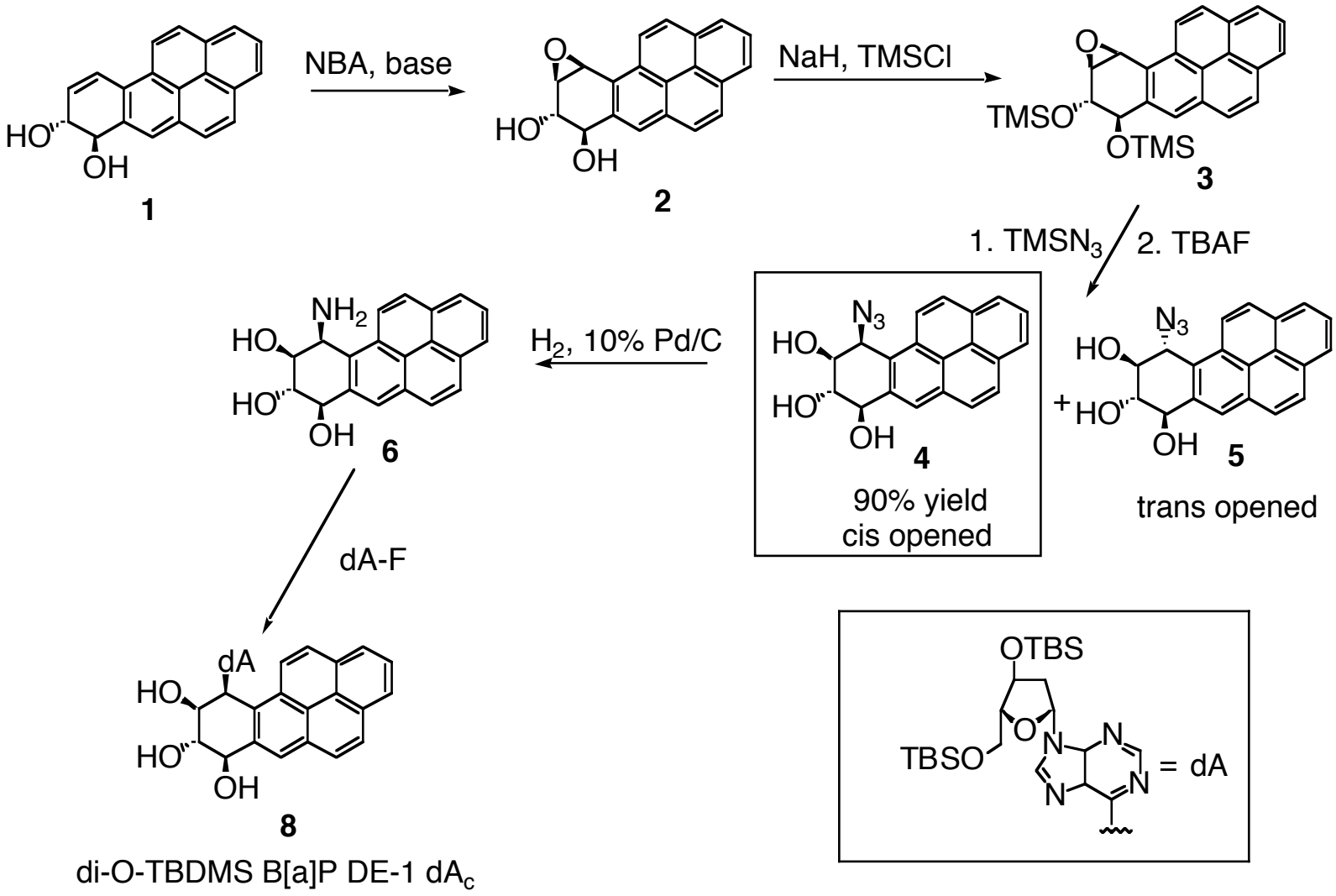
Use of AA in the Synthesis of di-O-TBDMS B[a]P DE-1 dA_c Diastereoisomers



B[a]P DE-1 diastereoisomers

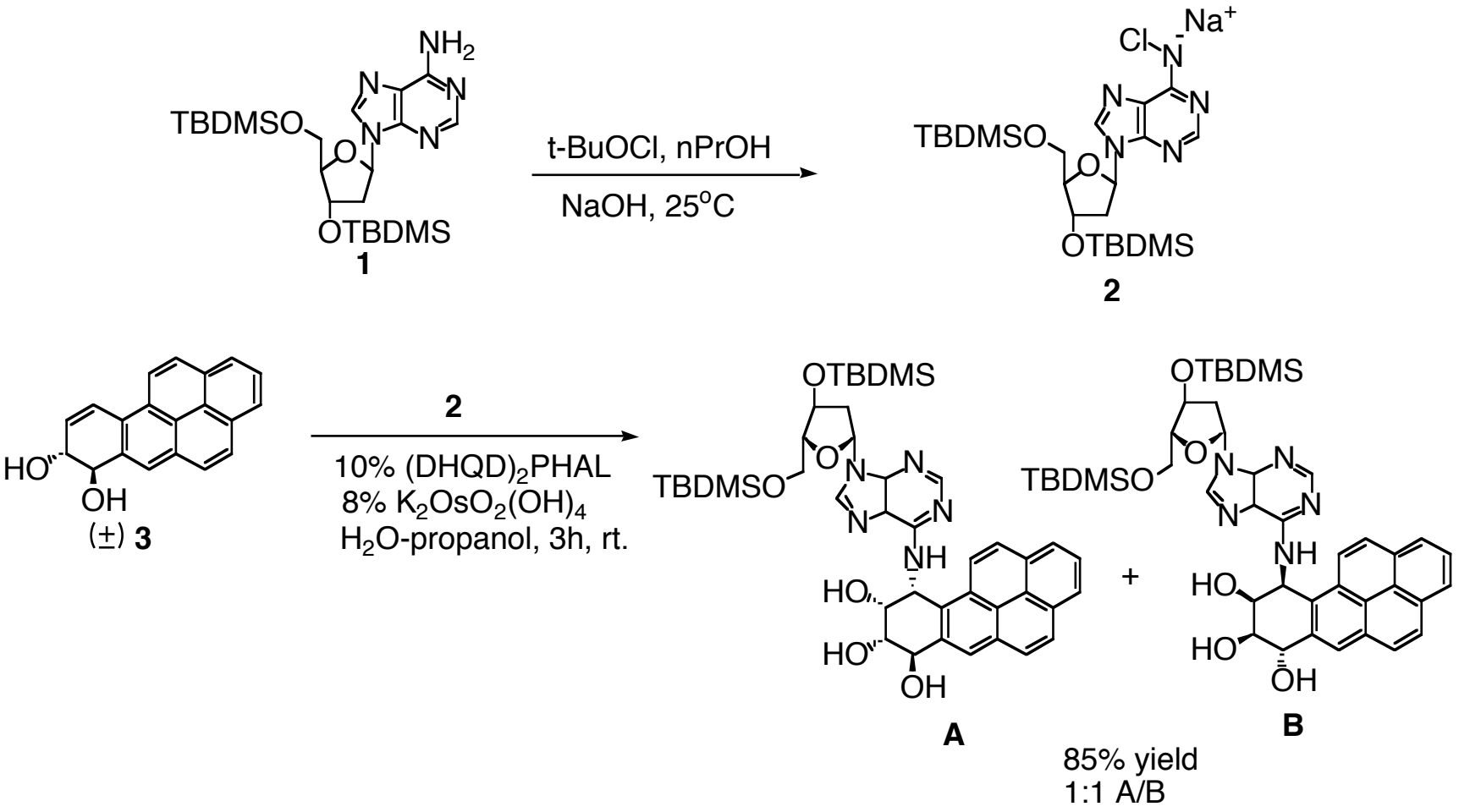
Pilcher, A. S., Yagi, H.; Jerina, D. M. *J. Am. Chem.Soc.* **1998**, *120*, 3520-3521.

Conventional Method



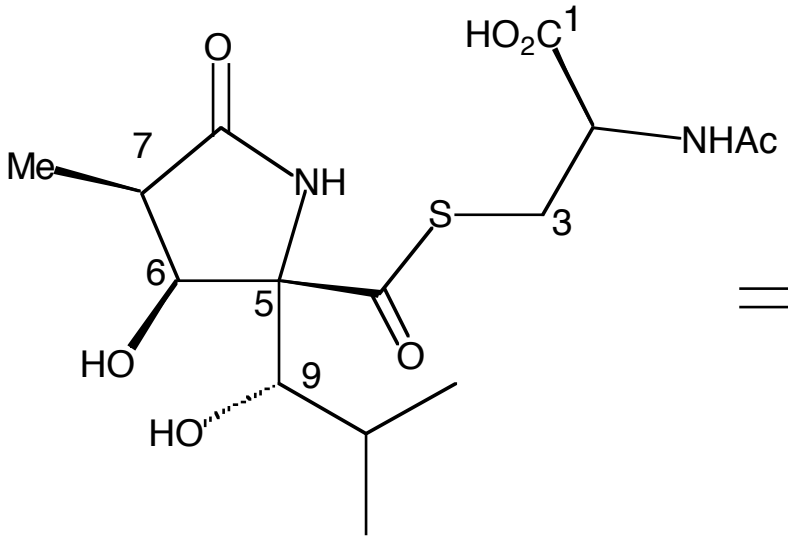
Pilcher, A. S; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 3520-3521.

AA Approach towards di-O-TBDMS B[a]P DE-1 dA_c Diastereoisomers

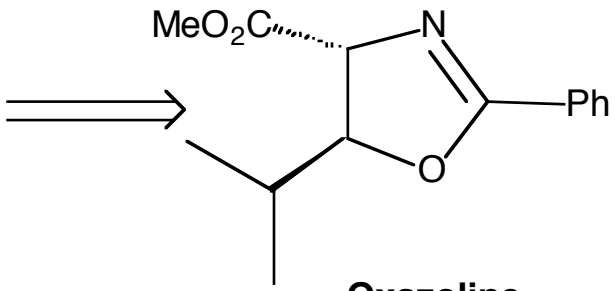


Pilcher, A. S., Yagi, H.; Jerina, D. M. *J. Am. Chem.Soc.* **1998**, *120*, 3520-3521.

Use of AA in Synthesis of (+)-Lactacystin



(+)-Lactacystin

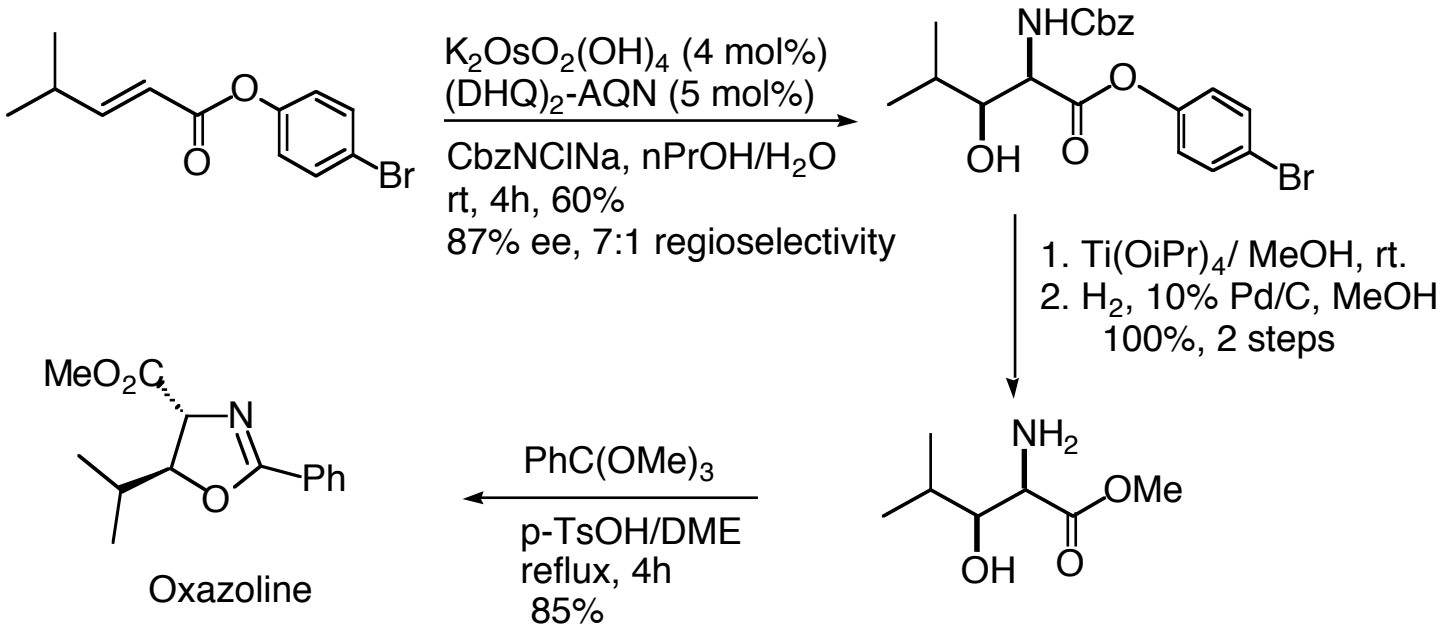


Oxazoline

- Isolated from a streptomyces bacterial strain in 1991
- Potent activities against arthritis, ischemia and asthma.

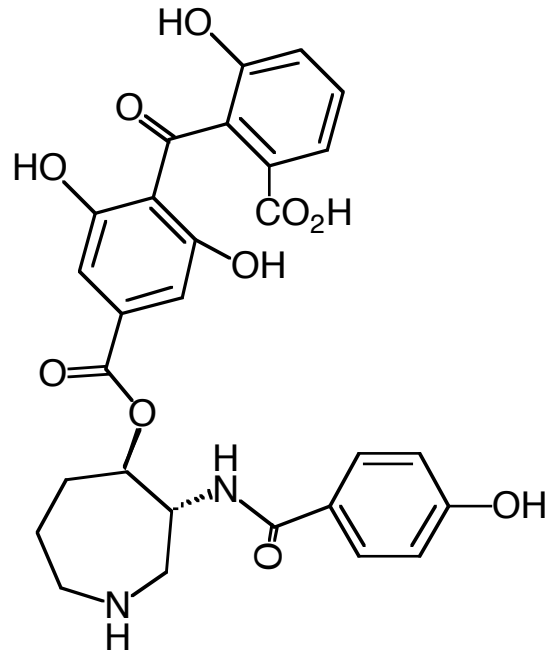
Panek, J. S.; Masse, C. E. *Angew. Chem. Int. Ed.* **1999**, *38*, 1093-1095.

Panek's Approach towards Oxazoline



Panek, J. S.; Masse, C. E. *Angew. Chem. Int. Ed.* **1999**, *38*, 1093-1095.

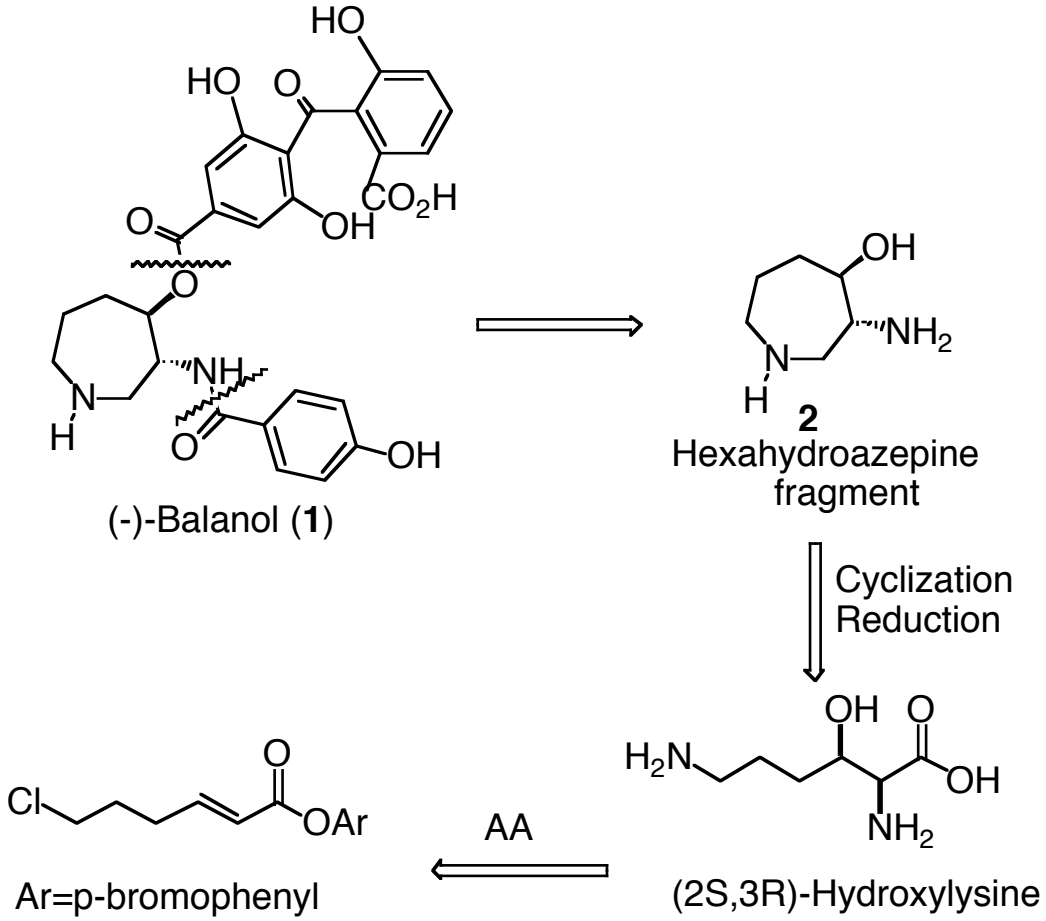
Use of AA in the Synthesis of Azepine Core of (-) Balanol



- Isolated from the fungus *Verticillium balanoides* in 1993.
- Potent inhibitor of human protein kinase C (PKC)

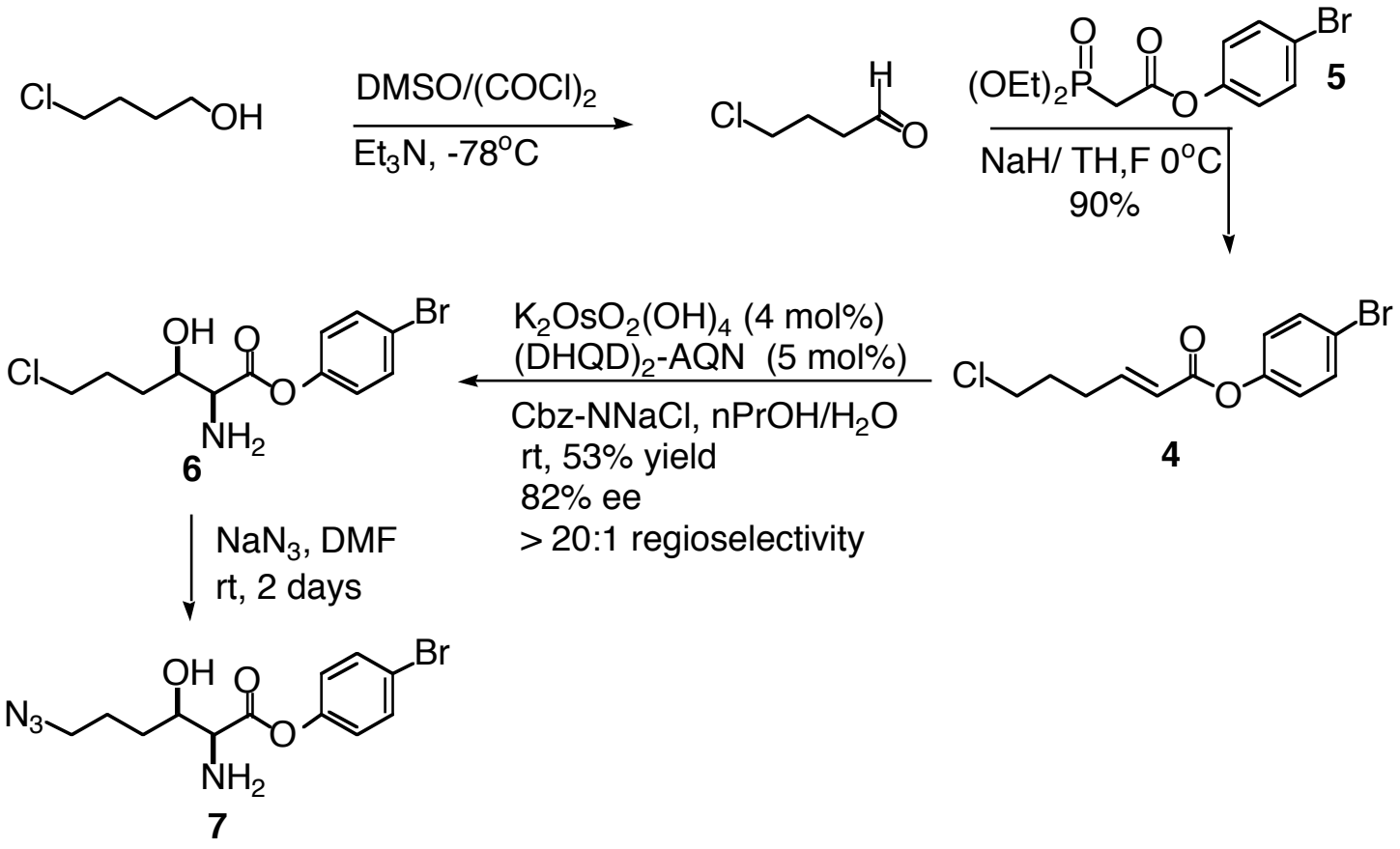
Panek, J. S.; Masse, C. E. *Org. Lett*. **2000**, *2*, 2571-2573.

Retrosynthetic Analysis of (-) Balanol



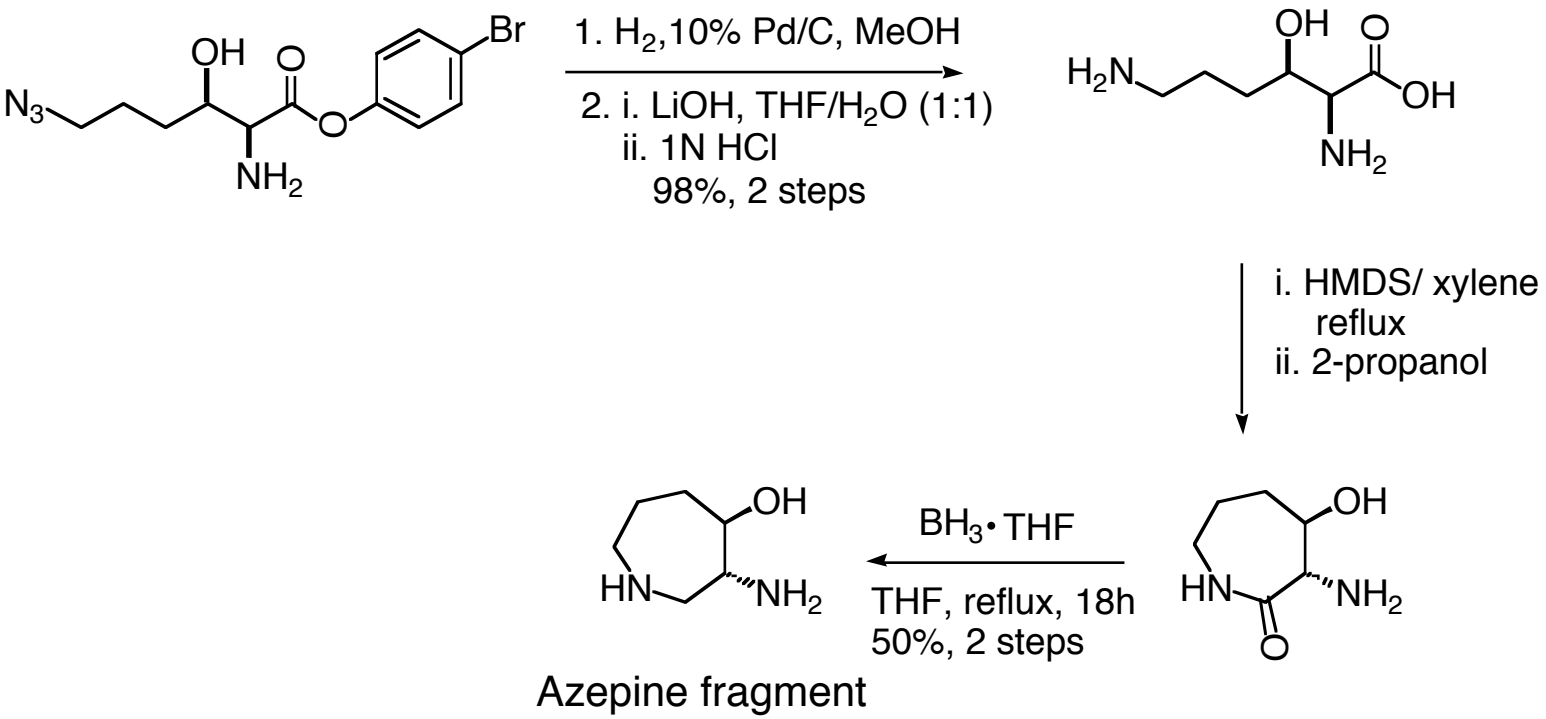
Panek, J. S.; Masse, C. E. *Org. Lett.* **2000**, *2*, 2571-2573.

Synthesis of Azepine Fragment of (-) Balanol



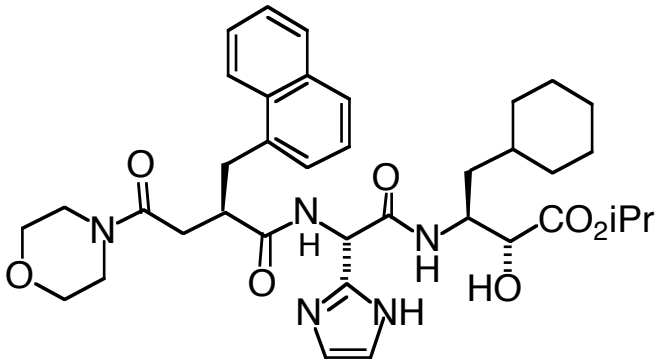
Panek, J. S.; Masse, C. E. *Org. Lett.* **2000**, *2*, 2571-2573.

Synthesis of Azepine Fragment of (-)-Balanol

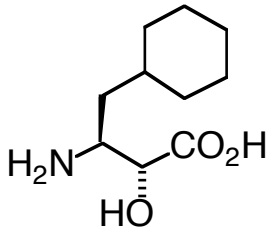


Panek, J. S.; Masse, C. E. *Org. Lett.* **2000**, *2*, 2571-2573.

Use of AA in Synthesis of Cyclohexyl norstatin, a key Component of Tripeptide KRI 1314



KRI - 1314

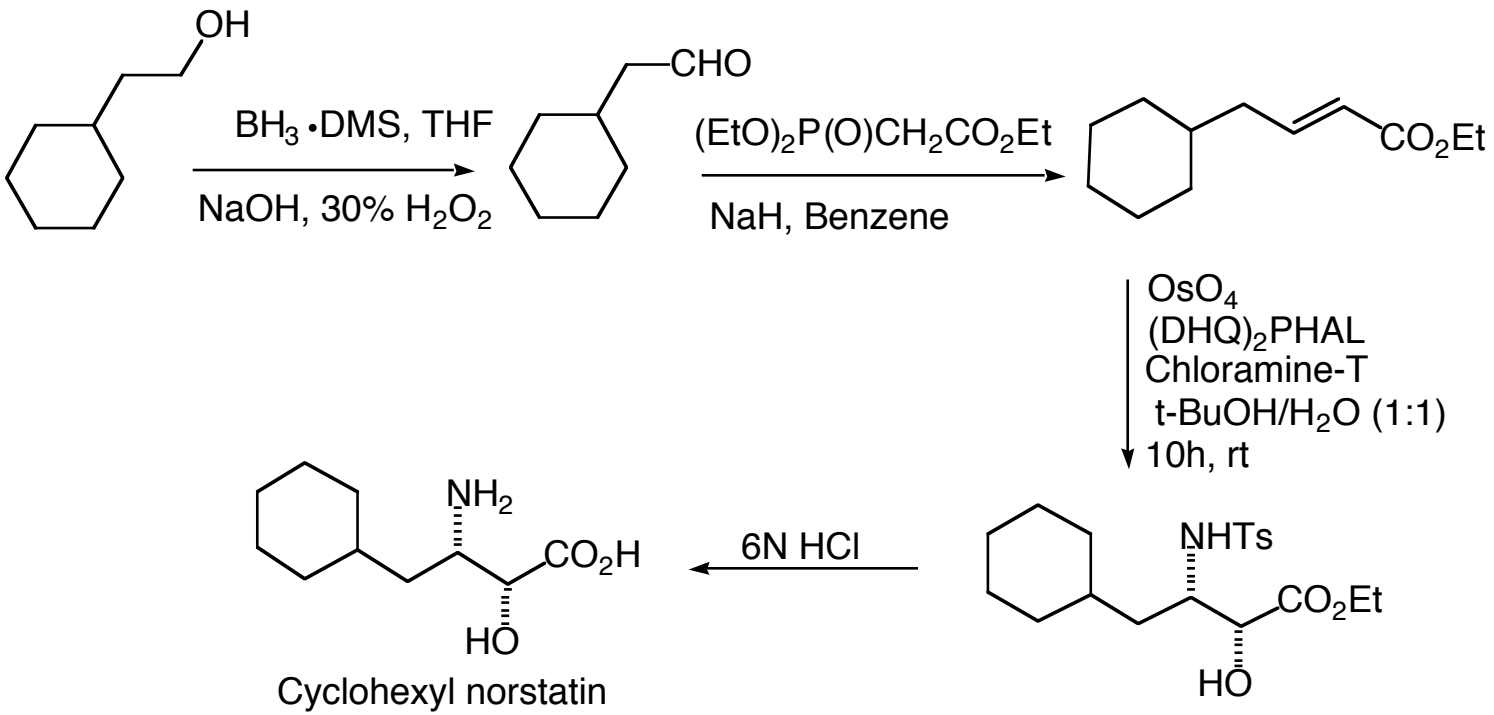


Cyclohexyl norstatin

- Isolated in 1988
- Potent renin inhibitor and hence potential agent of antihypertensive therapy

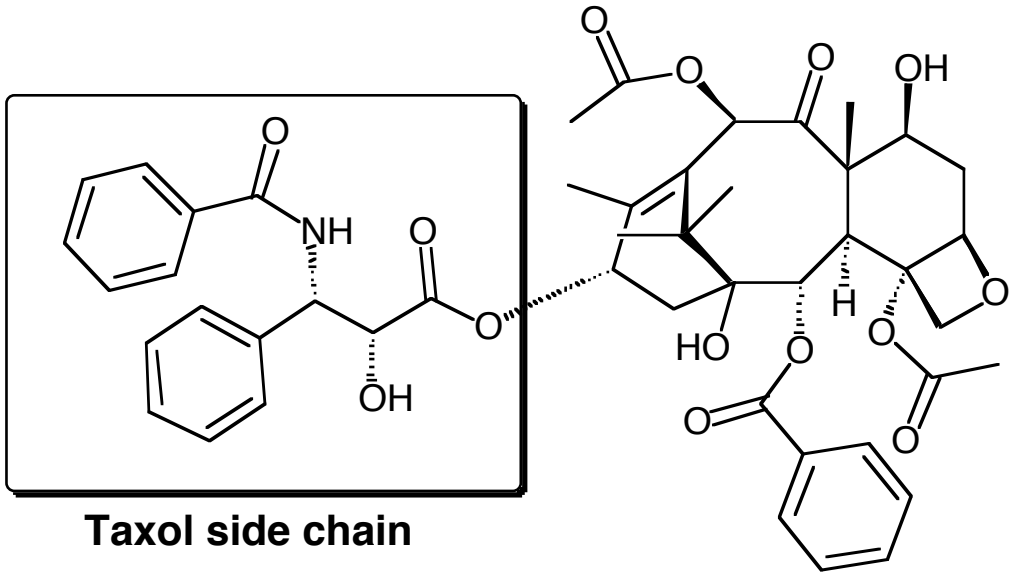
Upadjua, T. T.; Sudalai, A. *Tetrahedron:Asymmetry* **1997**, *21*, 3685-3689.

Synthesis of Cyclohexyl norstatin



Upadjua, T. T.; Sudalai, A. *Tetrahedron:Asymmetry* **1997**, *21*, 3685-3689.

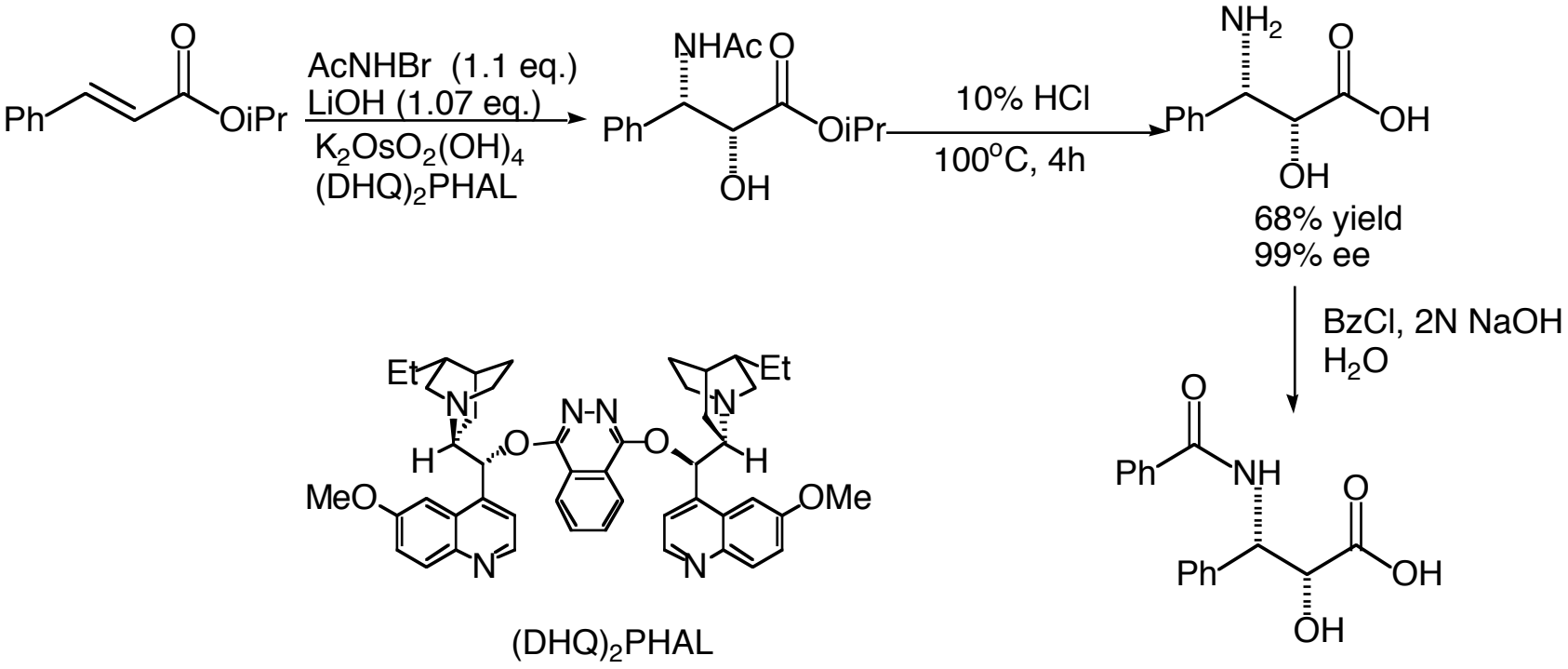
Use of AA in the Synthesis of Taxol Side Chain



Paclitaxel

Bruncko, M.; Schingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1483-1486.

Use of AA in the Synthesis of Taxol Side Chain



Bruncko, M.; Schingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1483-1486.

Conclusions

- Using AA, alkenes can be converted to enantiomerically enriched N-protected amino alcohols.
- a, b-unsaturated esters, styrenes, vinylarenes and cyclohexenes are good substrates for AA.
- N sources with smaller substituent give higher yields and better enantioselectivity.
- Steric, electronic, and aromatic substituent effects can be used to influence the regiochemistry in AA.
- $(DHQ)_2PHAL$ and $(DHQ)_2AQN$ ligands give opposite regioselectivity.