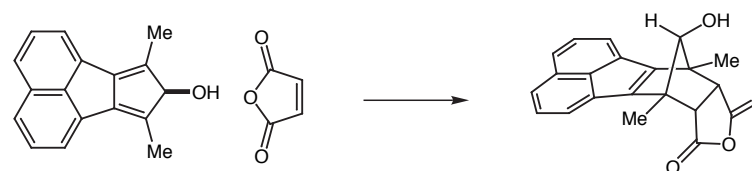


Diastereoselective Attack of Electrophiles on Chiral Olefins

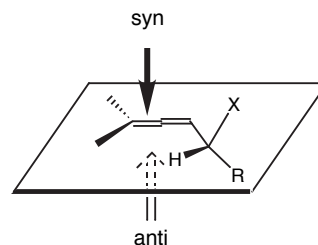
1. Diels Alder reactions
2. Halogenation and related electrophilic additions
3. Reactions of allylsilanes
4. Hydroborations
5. Osmylations

Mick Dart
Evans Group Seminar
Tues. Jan. 18, 1994

Diastereoselective Diels–Alder Reactions: Chiral Dienes



■ Other dienophiles also give adducts derived from *endo* addition *syn* to the hydroxyl
D. Jones, *J. C. S. Chem. Comm.* **1980**, 739.



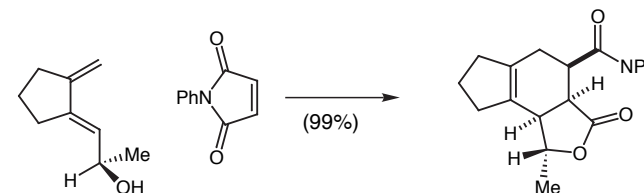
Hehre's Proposal:

Based solely on electrostatic considerations

X	Dienophile
Electron Rich	Syn
Electron Poor	Anti

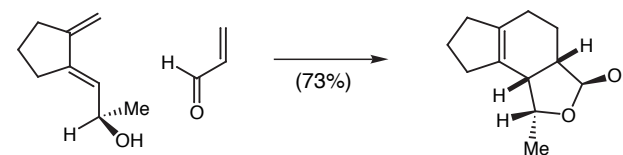
Electron Rich Substituents have lone pairs (OR, NR₂, SR, SO₂R)
Electron Poor Substituents: SiR₃ (electropositive)

Kahn & Hehre, *J. Am. Chem. Soc.* **1987**, 109, 663-666.



■ Stereocontrol: A(1,3) strain

Diastereoselection 91 : 9

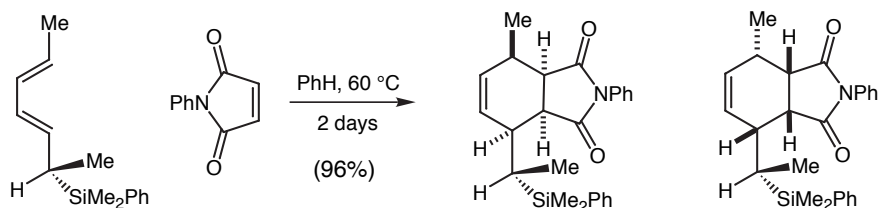


Diastereoselection >95 : 5

■ Opposite diastereofacial selectivity is observed with acrolein.

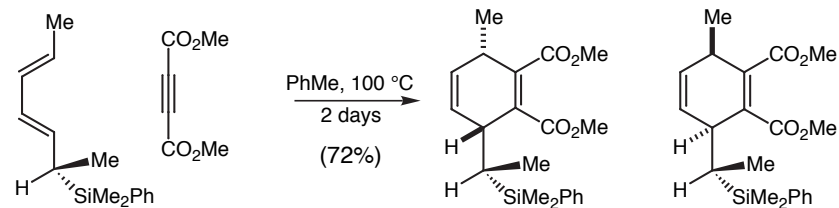
Trost, *J. Org. Chem.* **1989**, 54, 2271-2274.

Diastereoselective Diels–Alder Reactions: Chiral Dienes



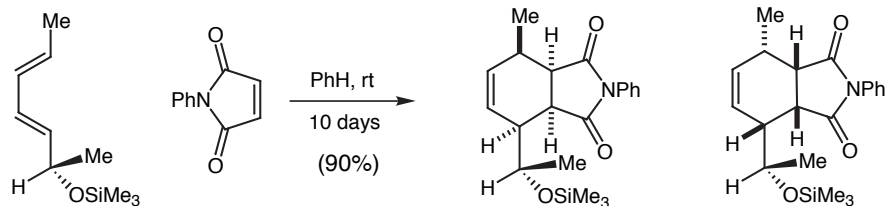
Fleming, *JCS Perkin Trans I*, **1989**, 2023-2030.

Diastereoselection 82 : 18



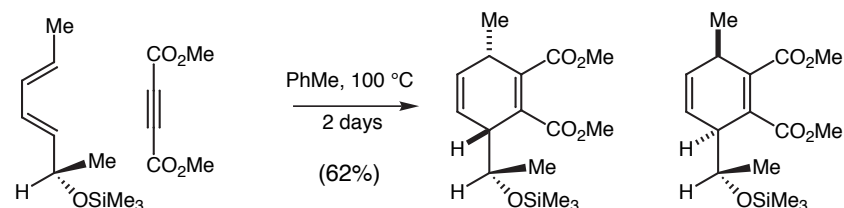
Fleming, *JCS Perkin Trans I*, **1989**, 2023-2030.

Diastereoselection >99 : 1



R. Franck, *J. Am. Chem. Soc.* **1988**, 110, 3257

Diastereoselection 12 : 88

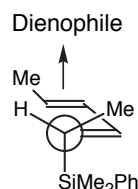
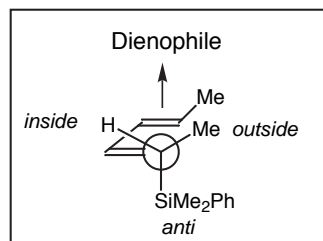


R. Franck, *J. Am. Chem. Soc.* **1988**, 110, 3257

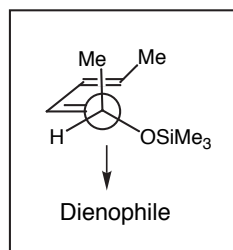
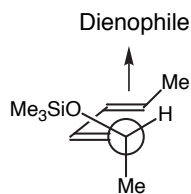
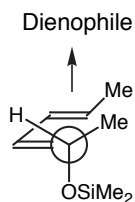
Diastereoselection 27 : 73

■ Rationalization for diastereofacial selectivity:

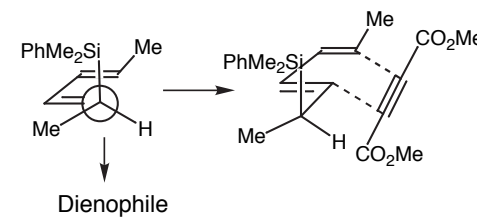
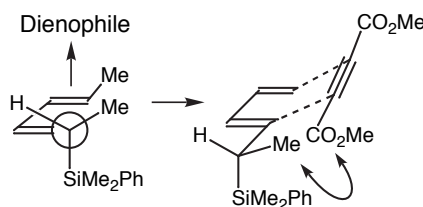
Allylsilane



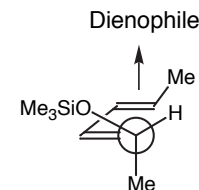
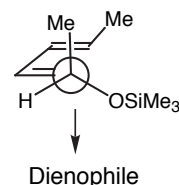
Allylic Ether



See Houk & Co-workers *Science*, **1986**, 221, 1108-1117.

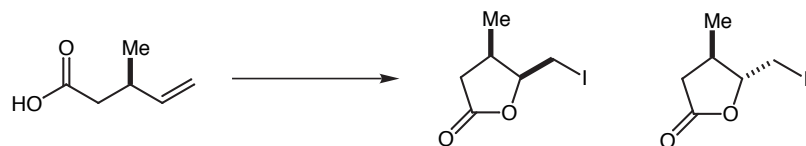


Favored diene conformers in reactions with acetylenic dienophiles



Also see A. Kozikowski, *J. Am. Chem. Soc.* **1987**, 109, 5167-5175.

Iodolactonization



Conditions (cis : trans)

Kinetic	NIS, CHCl ₃ , 25 °C	75 : 25
Thermodynamic	3 equiv I ₂ , MeCN, 0 °C	9 : 91

Bartlett, *J. Am. Chem. Soc.* **1978**, *100*, 3950-3952.

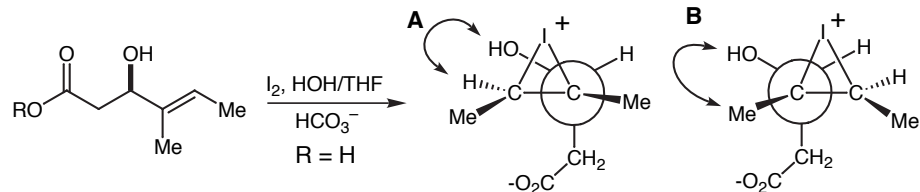
Iodolactonization of allylic alcohols

Substrate	Major Product	Selectivity	Yield (%)
		93 : 7	66
		95 : 5	49
		R = H: 87 : 13 R = Me: 90 : 10	41 94
		R = H: 77 : 23 R = Me: 42 : 58	74 81
		95 : 5	85

- Kinetic conditions: 3 equiv I₂, aq Na₂CO₃, Et₂O, 0 °C
- Bartlett's "thermodynamic conditions" produced complex mixtures
- Protection of the hydroxyl group (TBS or Ac) does not affect selectivity

Chamberlin, *J. Am. Chem. Soc.* **1983**, *105*, 5819-5825.

03-Iodolactonization 3/19/02 2:00 PM

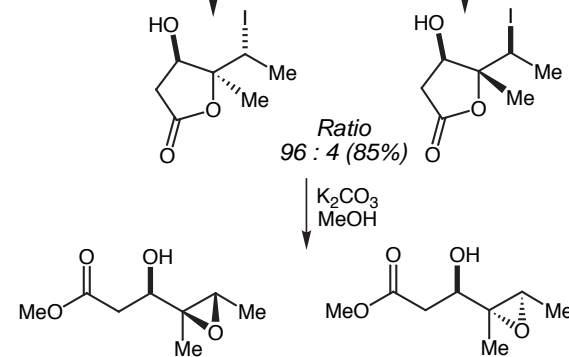


Gauche **B** is more destabilizing than gauche **A**

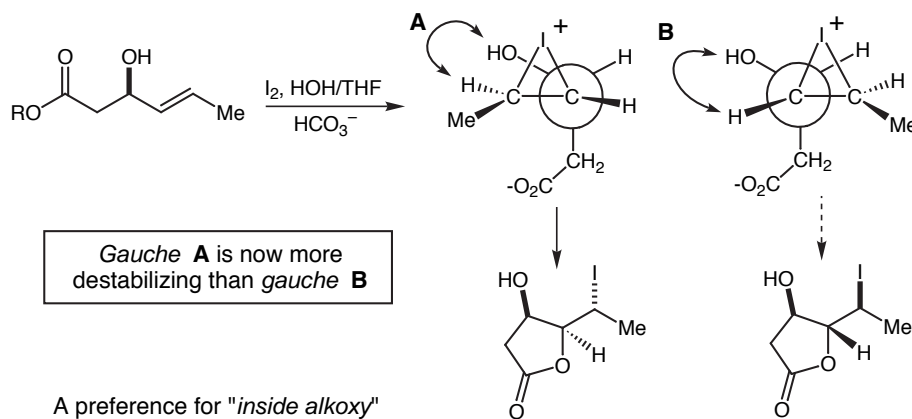
R = Me

t-BuOOH
VO(acac)₂

A(1,2) strain



Lactonization Ratio = 96 : 4
Epoxidation Ratio = 3 : 97



Gauche **A** is now more destabilizing than gauche **B**

A preference for "inside alkoxy" is observed in these cyclizations

Ratio >95 : 5 (49%)
low yield due to δ-lactone formation

Chamberlin, *J. Am. Chem. Soc.* **1983**, *105*, 5819-5825.

How can the above results be rationalized?

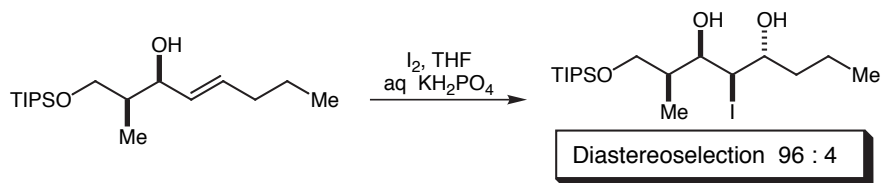
Iodo diol formation from allylic alcohols

Substrate	Major Product	Selectivity	Yield (%)
		98 : 2	78
		95 : 5	90
		94 : 6	85
		80 : 20	

- Prevost conditions: 2 equiv I₂, 2 equiv AgOAc, THF, -78 → 0 °C
- Other conditions: I₂, THF/phosphate buffer; I₂, THF, aq Na₂CO₃ provide 1,3-diols in very high selectivity
- High selectivities are also observed with allylic ethers (OMe, OBn, OTBS)

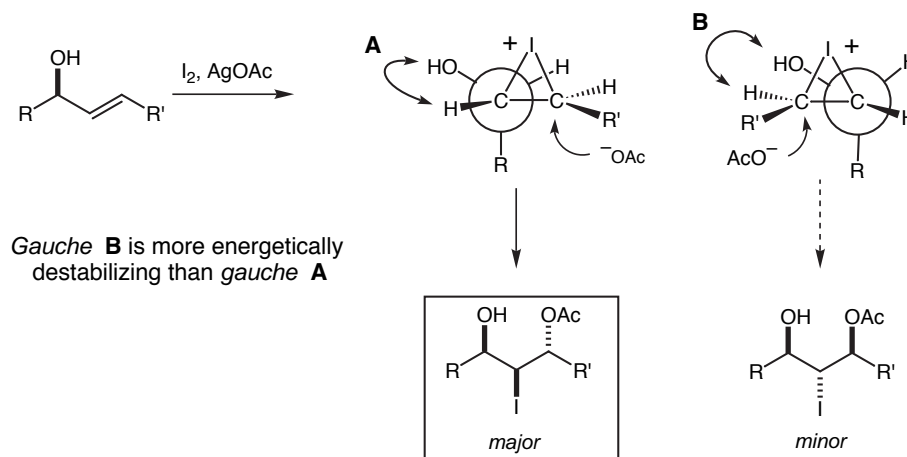
Chamberlin, *Tetrahedron* **1984**, *40*, 2297-2302.

Cytovaricin Synthesis

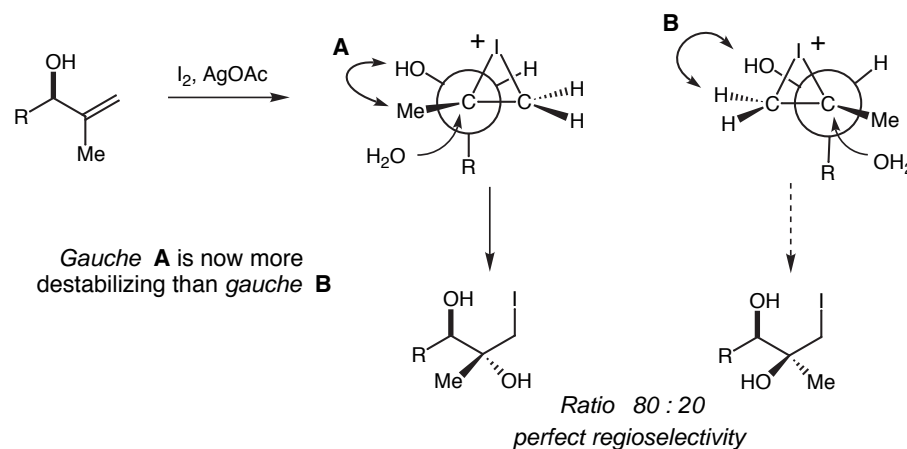


Evans, Kaldor, Jones, *J. Am. Chem. Soc.* **1990**, *112*, 7001.

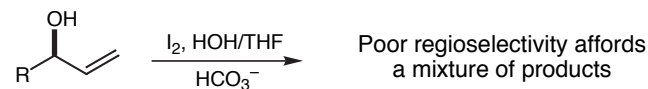
Model for Stereinduction?



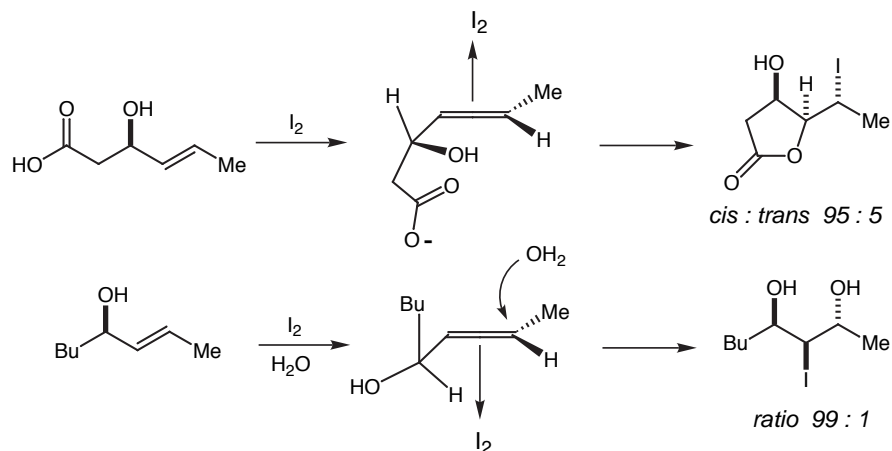
- Analysis: D. A. Evans, Chem. 115, Lecture 23, Dec. 16, 1993



- Place the medium size group (-OH) outside and the small group (-H) inside



- A complete turnover in olefin diastereofacial selectivity is observed when adding *internal* and *external* nucleophiles



General Observation:

For electrophiles that react via onium intermediates (I_2 , Br_2 , $Hg(OAc)_2$, $PhSeCl$), the major diastereomer from electrophile-induced cyclization is opposite to that observed in the analogous intermolecular electrophilic addition.

For a review of electrophilic induced olefin cyclization reactions see: G. Cardillo & M. Orena, *Tetrahedron* **1990**, *46*, 3321.

Chamberlin & Hehre's Rationalization

- "Facial preferences in electrophilic addition reactions are *not* invariant with respect to the location of the transition state along the reaction coordinate."
- Change in diastereoselectivity is a consequence of a change in the **rate-limiting step**

- Addition reactions: Formation of an **onium ion intermediate** (subsequently trapped by a Nu from the medium)
- Cyclization reactions: Intramolecular attack on a **π -complex** (not an onium ion)

- Analysis of the stereoselectivity of electrophilic addition to chiral olefins:

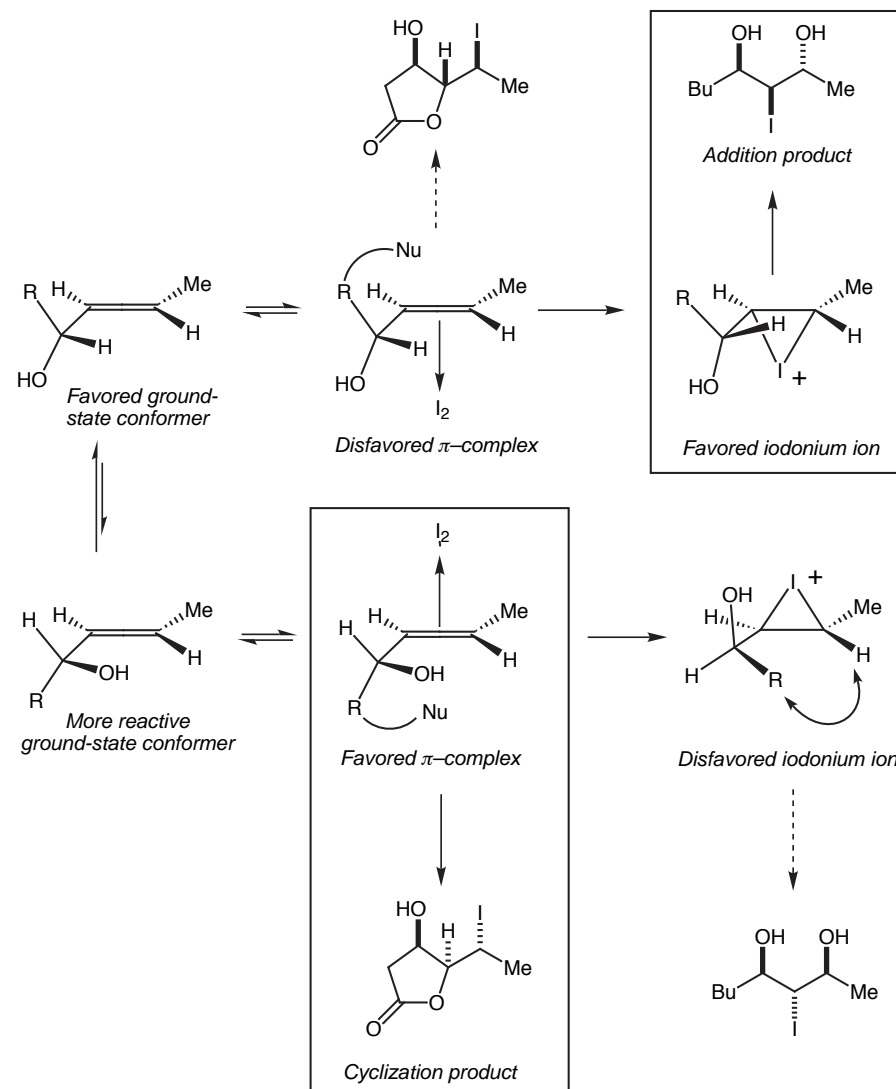
1. Relative abundances of conformational minima
2. *Relative reactivities of the available forms*
3. Stereoselectivities of the individual conformers

Chamberlin & Hehre, *J. Am. Chem. Soc.* **1987**, *109*, 672-677.

For a review of the halogenation reaction see: Andy Ratz, **Evans Group Seminar**, *Synthetic and Mechanistic Review of Electrophilic Halogenation*, May 7, 1992.

05-Iodolact/Hehre 3/19/02 2:00 PM

Hehre's Analysis



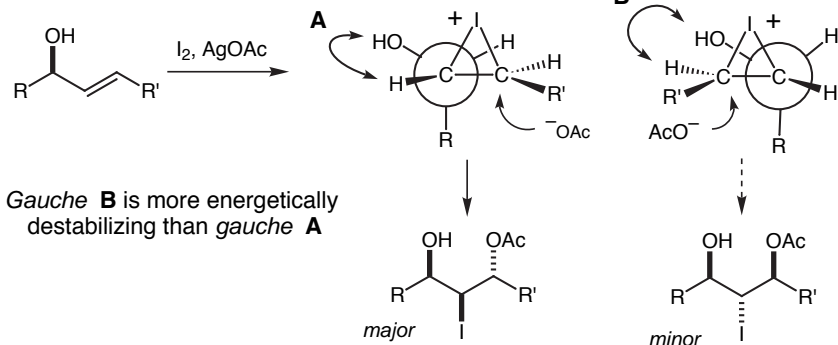
Houk: Argument for the "inside alkoxy effect" in π -complex formation

- π -complex cyclizes if R contains a Nu and its formation is rate determining
- Onium ion formation is rate determining in the addition reactions
- "The presence or absence of an internal nucleophile acts to determine the stereochemical outcome of the reaction by modifying the nature (timing) of transition state."

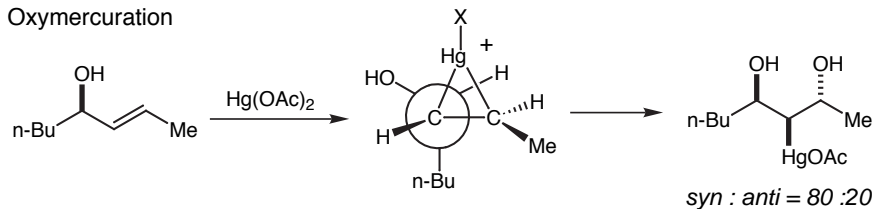
Diastereoselective Functionalization of (*E*) Allylic Alcohols

D. A. Evans, Chem. 115, Lecture 23, Dec. 16, 1993

Halogenation

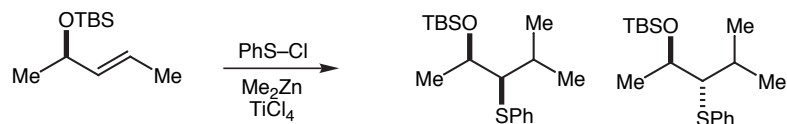
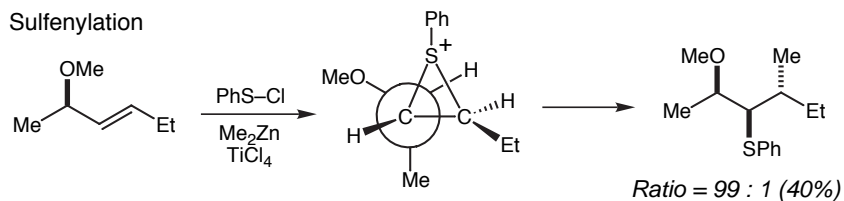


Oxymercuration



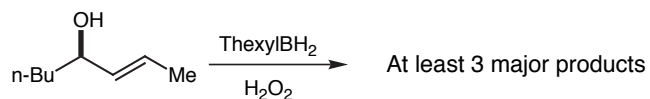
Chamberlin, *Tetrahedron* **1984**, *40*, 2297-2302.

Sulfonylation



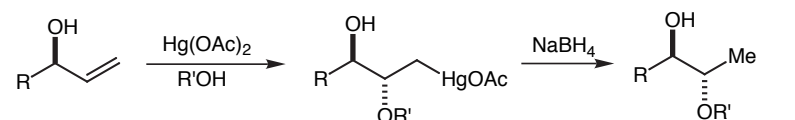
Reetz, *Angew. Chem. Int. Ed.* **1987**, *26*, 1028-1029.

Hydroboration



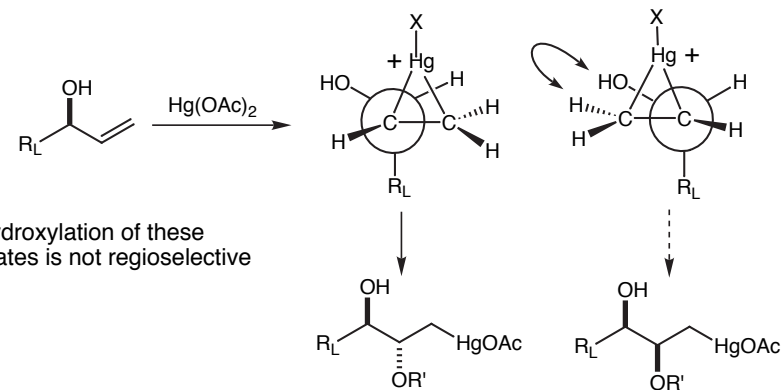
06-Oxymercuration 3/19/02 2:01 PM

Oxymercuration of Acyclic allylic alcohols:

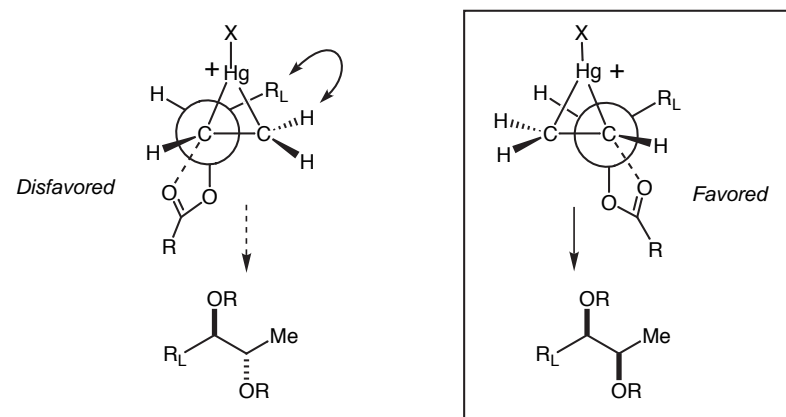
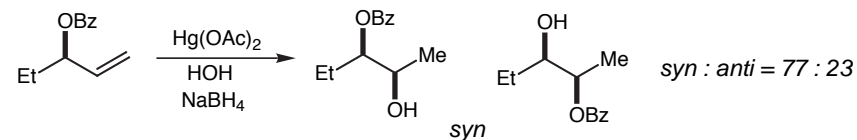


R	R'OH	Ratio	yield
-Et	HOH	76 : 24	65%
-Et	MeOH	93 : 07	72%
-Ph	HOH	88 : 12	66%
-tBu	HOH	98 : 02	70%

Giese, *Tet. Lett.* **1985**, *26*, 1197



O-acetate participation will turn over the stereochemical course of the rxn

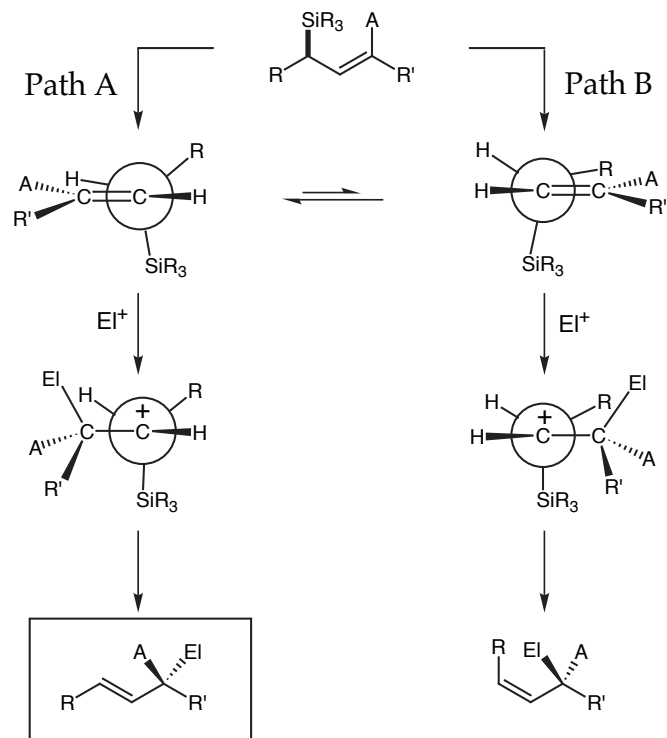


Hehre's model could be invoked to explain turnover in π -facial selectivity

Stereochemical Model For Electrophilic Attack on Allylsilanes

Model assumes:

1. Electrophilic attack *anti* to the silyl moiety
2. The silyl group is the "large" substituent



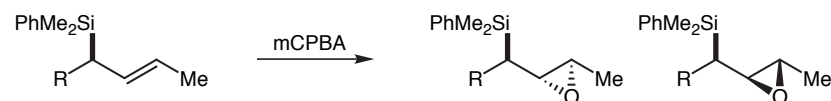
- If $A \geq \text{Me}$, then **Path A** dominates due to A(1,3) strain
- If $A = \text{H}$, then **Path B** can compete

Scott J. Miller *Evans Evening Seminar*, "The Chemistry of Allylsilanes and the β Silicon Effect," Dec 11, 1990, p 45.

Paddon-Row, Rondan, and Houk *JACS* **1982** *104*, 7162.

Electrophilic Attack on Allylsilanes

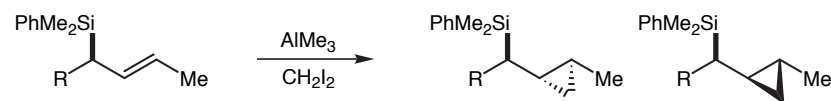
■ Epoxidation



The products on the left correspond to attack by **Path A**

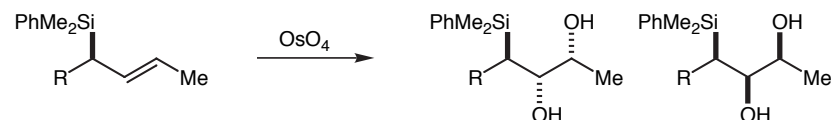
R	Ratio
Me	61 : 39
<i>i</i> Pr	>95 : 05
PH	89 : 11

■ Cyclopropanation



R	Ratio
Me	58 : 42
<i>i</i> Pr	>95 : 05
PH	91 : 09

■ Osmylation



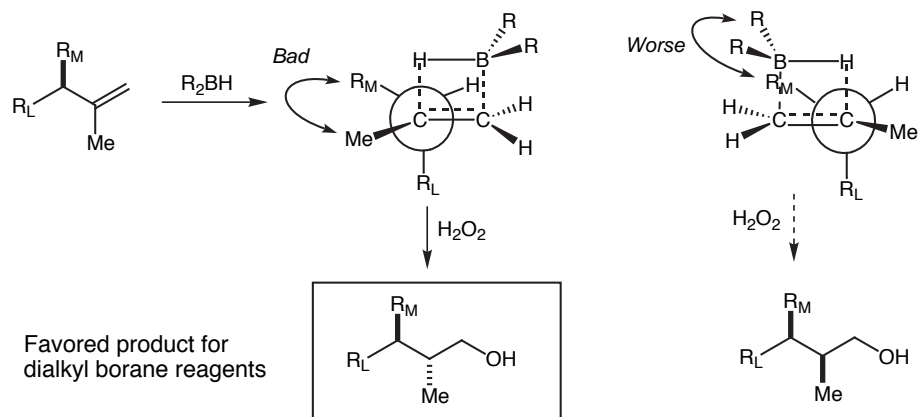
R	Ratio
Me	34 : 66
<i>i</i> Pr	67 : 33
PH	92 : 08

- Larger R groups result in higher selectivity
- The size of R is more important in locking the substrate into the conformation leading to **Path A** than in shielding the El^+

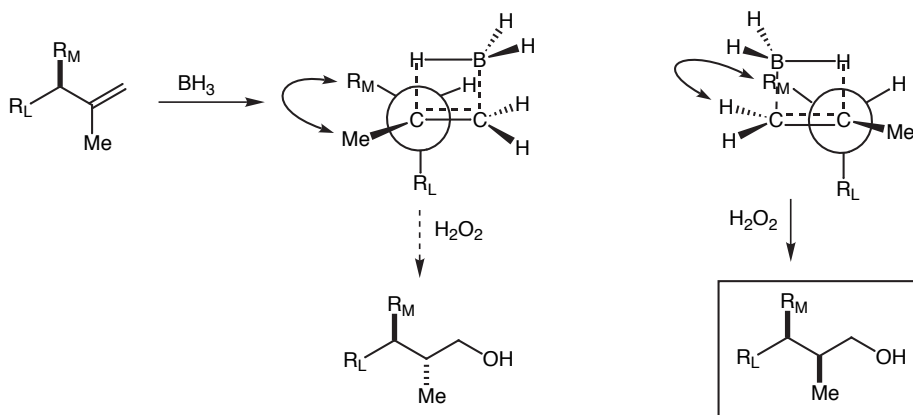
Fleming, *JCS Perkin Trans I*, **1992**, 3303-3308.

A Model for Diastereoselective Hydroborations

Dave Evans, Chem 115, Lecture 22, Dec 14, 1993

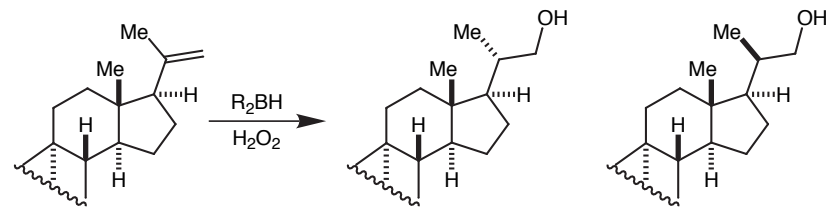


■ A turnover in diastereofacial selectivity is sometimes observed using BH_3



K. N. Houk, M. N. Paddon-Row, & Co-workers,
Tetrahedron **1984**, 40, 2257-2274.

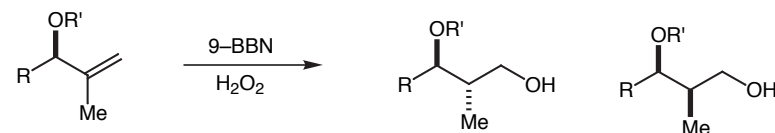
Diastereoselective Hydroboration Examples



R_2BH	Selectivity
$BH_3 \cdot DMS$	50 : 50
Thexyl BH_2	80 : 20
9-BBN	93 : 07
$(Chx)_2BH$	96 : 04

M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, 105, 3725.

■ Hydroboration of allylic alcohols (ethers)



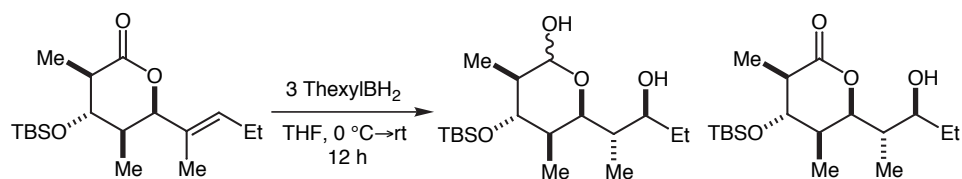
R	OR'	Selectivity
nBu	OH	92 : 08
iPr	OH	96 : 04
nBu	OTMS	91 : 09
nBu	OAc	88 : 12
$BH_3 \cdot THF \rightarrow$		nBu OH 42 : 58

W. C. Still & J. C. Barrish,
J. Am. Chem. Soc. **1983**, 105, 2487.

Assume OH (OR') = R_m and results are consistent with the model

Diastereoselective Hydroborations

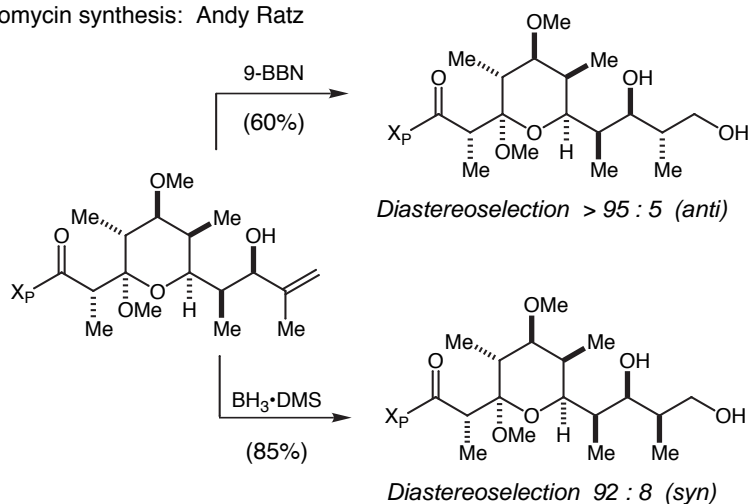
■ Erythronolide synthesis: Annette Kim



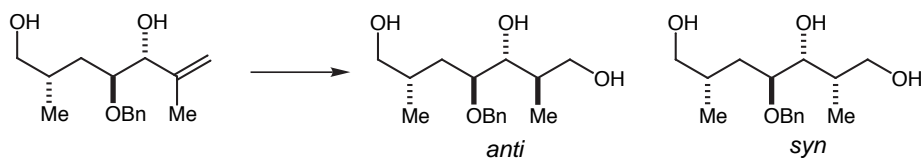
Diastereoselection 93 : 7

A 2:1 mixture of the lactol:lactone was obtained. This mixture was oxidized to the keto-lactone in 73% overall yield from the olefin.

■ Lonomycin synthesis: Andy Ratz



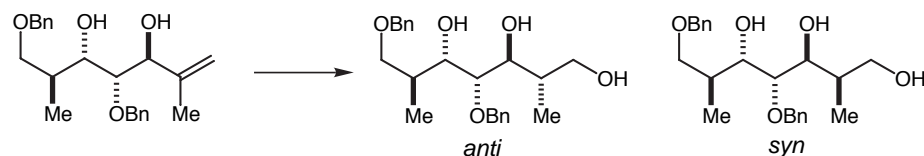
The sense of asymmetric induction is completely turned over in Andy's reaction when using R₂BH ↔ BH₃



Nakata, Tatsuta & Co-workers,
Bull. Chem. Soc. Jpn., **1992**, 65, 2974.

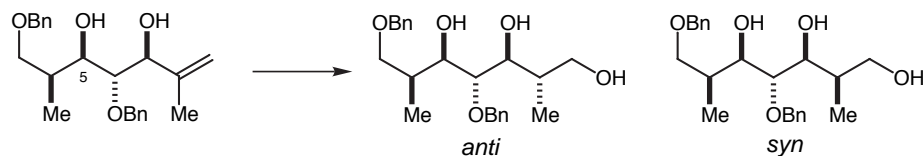
	anti : syn	yield
(Chx) ₂ BH	82 : 18	80%
BH ₃ ·DMS	17 : 83	99%

Diastereoselective Hydroborations



I. Paterson & J. Channon
Tetrahedron Lett., **1992**, 33, 797-800.

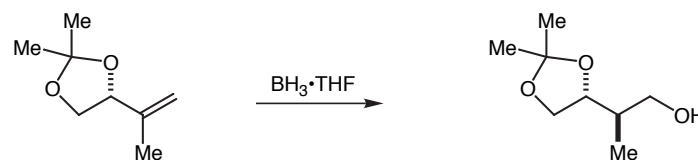
	anti : syn	yield
9-BBN	85 : 15	70%
BH ₃ ·THF	05 : 95	84%



BH₃·THF unexpectedly provided the anti isomer in high selectivity

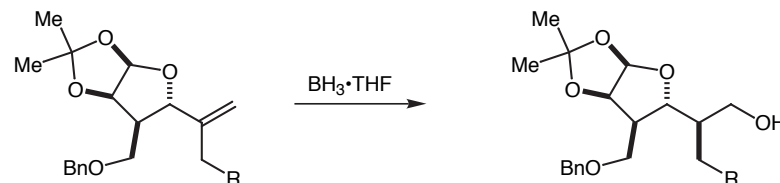
	anti : syn	yield
9-BBN	95 : 05	74%
BH ₃ ·THF	>95 : 05	89%

■ Anti-selective hydroborations with borane



K. Mori
Tetrahedron **1979**, 32, 1979.

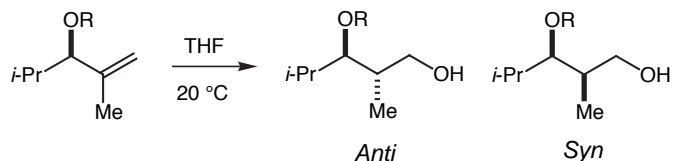
Diastereoselection 92 : 8 (anti)



Oikawa & Co-workers
Tetrahedron Lett., **1983**, 19, 1987.

R = H Diastereoselection 6.8 : 1 (anti)
R = OBn Diastereoselection 6.6 : 1 (anti)

The Catalyzed vs Uncatalyzed Hydroboration Reactions



R	Conditions	Anti : Syn	Yield (%)
Si(<i>t</i> -Bu)Ph ₂	9-BBN	95 : 5	75
	Rh(PPh ₃) ₃ Cl / CB	3 : 97	77
Si(<i>t</i> -Bu)Me ₂	9-BBN	95 : 5	72
	Rh(PPh ₃) ₃ Cl / CB	15 : 85	65
H	9-BBN	96 : 4	67
	Rh(PPh ₃) ₃ Cl / CB	50 : 50	68

Complementary diastereoselectivity for the catalyzed and uncatalyzed reactions is observed for a wide range of substrates.

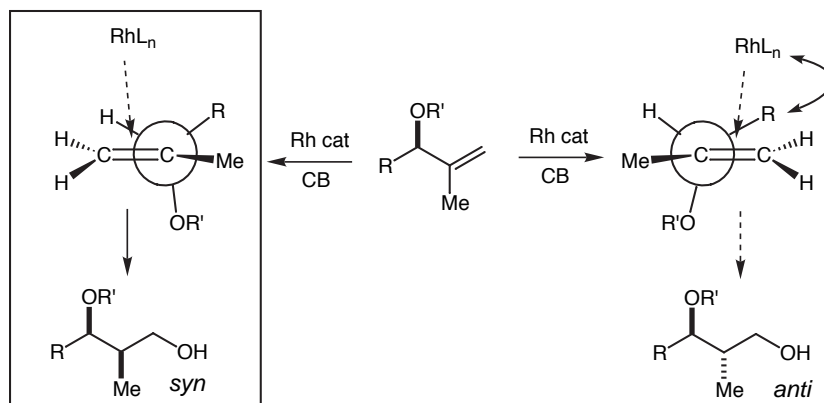
Evans, Fu, & Hoveyda *JACS* **1988**, *110*, 6917 and *JACS* **1992**, *114*, 6671.

The Catalyzed Hydroboration

- Olefin binding to metal is irreversible for 1,1-disubstituted allylic alcohol derivatives
- Olefin \leftrightarrow catalyst complexation is the stereochemistry-determining step

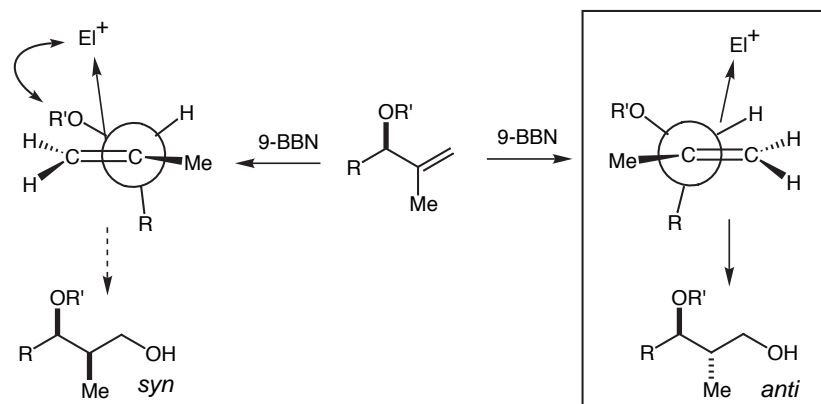
Evans & Fu *JOC* **1990**, *55*, 2280 and Evans, Fu, Anderson *JACS* **1992**, *114*, 6679.

Stereochemical Model



- Complexation involves back-donation from a filled metal d orbital $\rightarrow \pi^*_{C=C}$
- The EWG (alkoxy substituent) is aligned perpendicular to the olefin ($\pi \rightarrow \sigma^*_{C-O}$)
- This stereoelectronic interaction lowers the energy of π^*
- The small group is placed "inside", the most sterically congested site

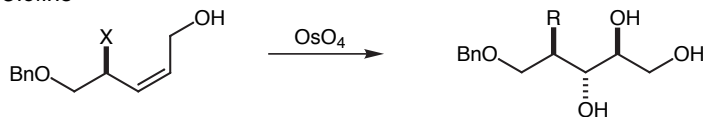
The uncatalyzed variant:



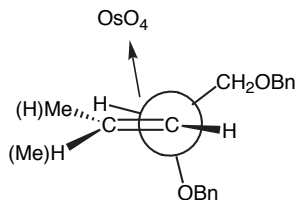
K. Burgess & Co-workers, *J. Org. Chem.* **1991**, *56*, 1020-1027

Diastereoselective Osmylations

(z) Olefins



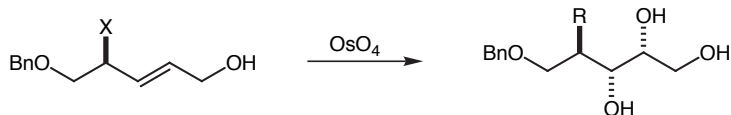
X	selectivity
Me	50 : 50
OBn	86 : 14



■ Kishi's Empirical Model:

Arrange olefin in the stable ground state conformer
 OsO₄ attacks anti to the allylic oxygen substituent
 Works for both (Z) and (E) allylic ethers (alcohols)

(E) Olefins



X	selectivity
Me	60 : 40
OBn	81 : 19

■ Allylic oxygen protecting group:

H, Bn, SiR₃, acetonides → all work well
 Acetates give lower selectivity

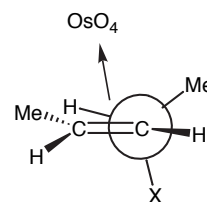
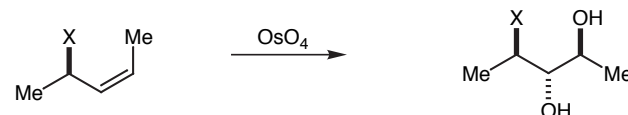
Kishi & Co-workers

Tetrahedron Lett., **1983**, 24, 3943 and *Tetrahedron*, **1984**, 40, 2247.

James Barrow, *Evans Group Seminar*, "Osmium Mediated Dihydroxylation: Mechanism and Application" April 21, 1993.

Diastereoselective Osmylations

(z) Olefins

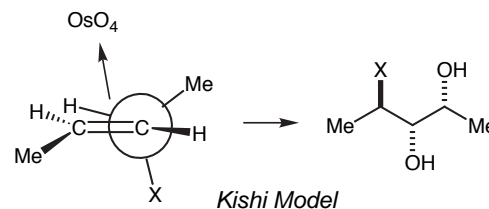
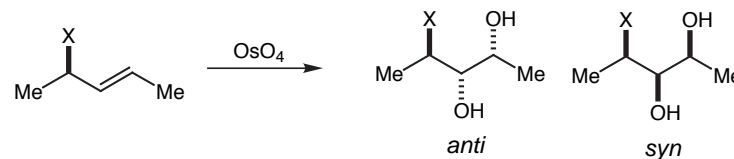


X	selectivity
PhMe ₂ Si	78 : 22
PhSO ₂	80 : 20
PhS	83 : 17
TBSO	62 : 38
AcO	70 : 30

■ Addition occurs *anti* to the allylic heteroatom functionality

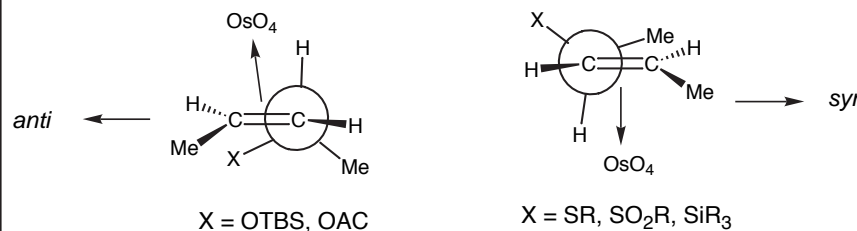
■ Vedejs argues that hyperconjugative effects are not important because both EDG and EWG provide the same sense of induction

(E) Olefins

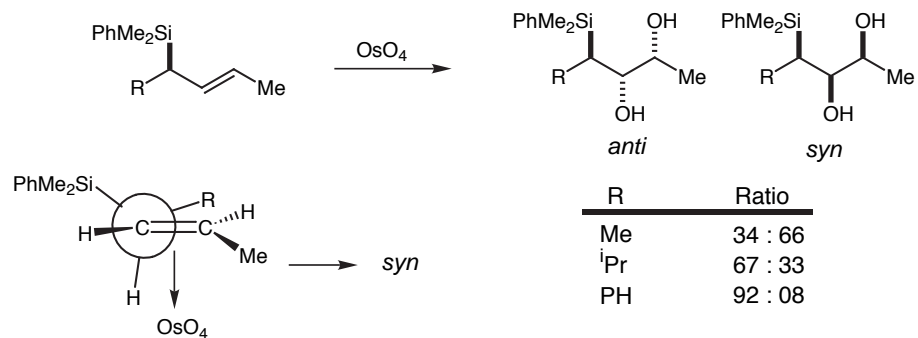


X	selectivity
PhMe ₂ Si	34 : 66
PhSO ₂	22 : 78
PhS	33 : 67
TBSO	61 : 39
AcO	62 : 38

Vedejs Model



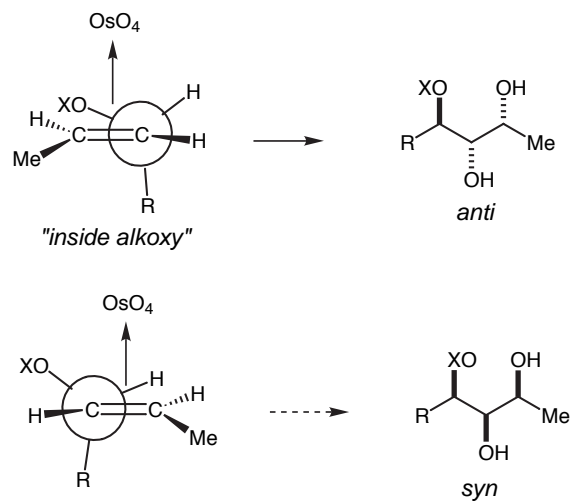
Diastereoselective Osmylations



Vedejs model breaks down
or $i\text{Pr}$, $\text{Ph} > \text{Me}_2\text{PhSi}$

Fleming, *JCS Perkin Trans I*, **1992**, 3303-3308.

Houk Model: Staggered transition states



■ Oxygen avoids "outside" position to avoid repulsive electrostatic interactions with the incoming OsO_4

Houk, *JACS*, **1986**, 108, 2754.