Catalytic Asymmetric Epoxidation via Chiral Oxaziridines Dioxiranes and Sulfonium Ylides

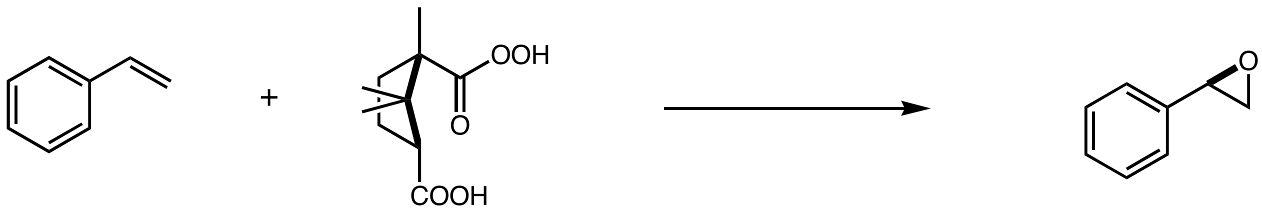
Teresa Beeson

MacMillan Group Meeting

July 6, 2004

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

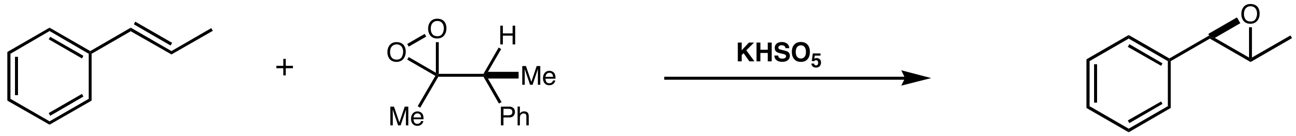
1967 Henbest reports first asymmetric epoxidation:



(+)-Peroxycamphoric acid

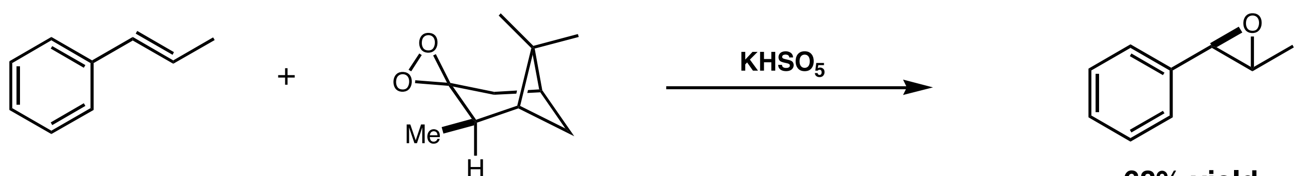
4.4% ee

1984 Curci provides the first catalytic dioxirane-promoted epoxidation:



50 mol%

92% yield
12% ee



20 mol%

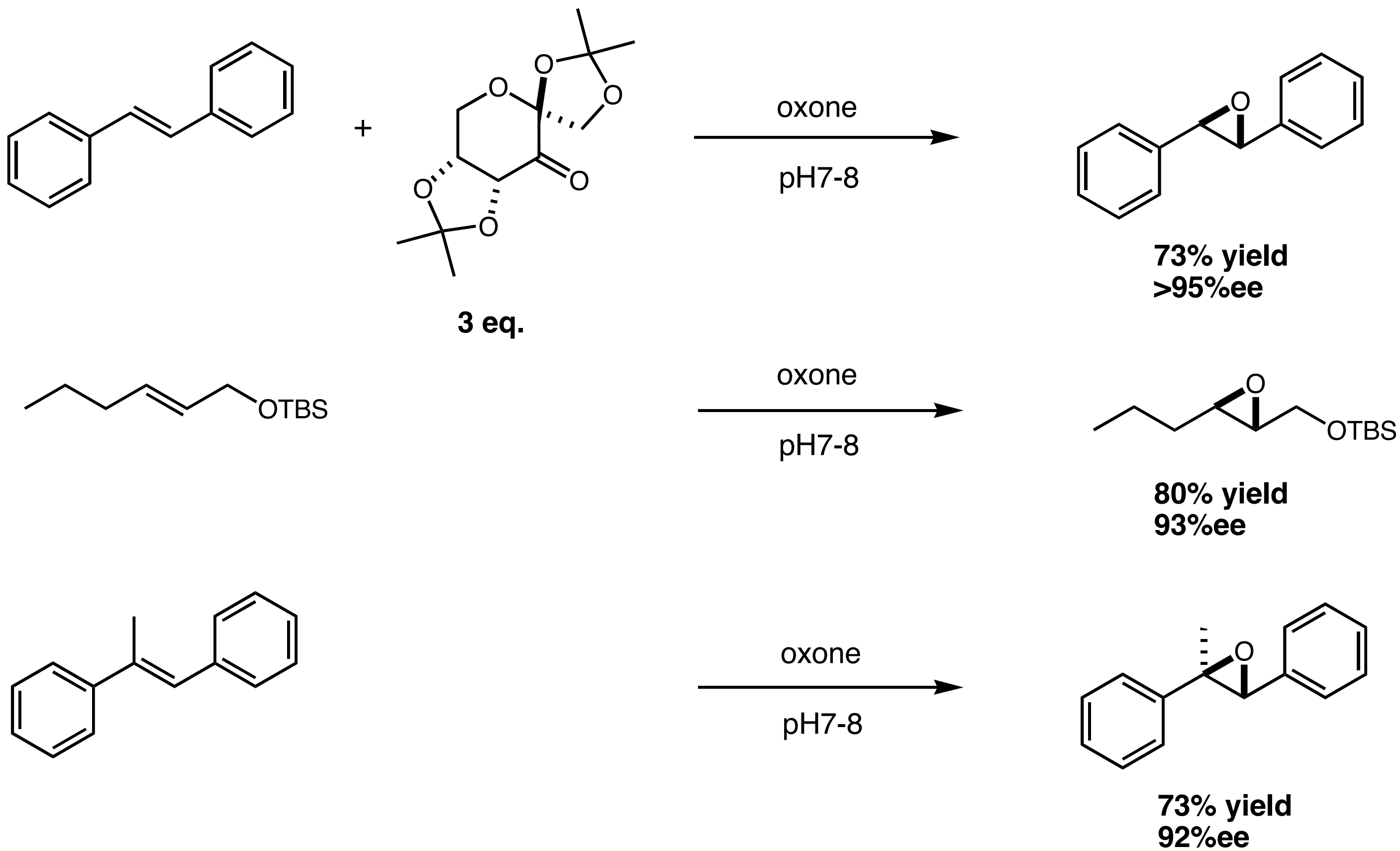
68% yield
11.2% ee

Ewins, R. C.; Henbest, H.B.; McKarvey, M.A. *J. Chem. Soc., Chem. Commun.* **1967**, 1085.

Curci et. al., *J. Chem. Soc., Chem. Commun.*, **1984**,155.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

1996 Shi provides the first general enantioseletive dioxirane epoxidation of *trans*-olefins:



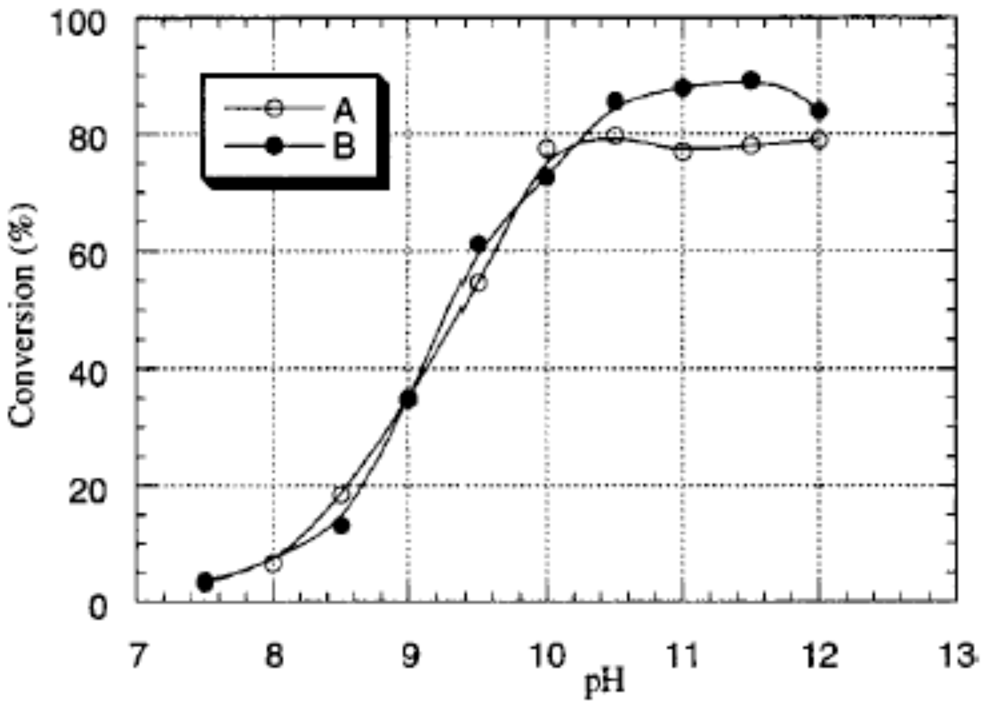
Ketone decomposed under reaction conditions

Reactions were stopped before complete conversion to limit ee reduction

Yang et. al., *J. Amer. Chem. Soc.*, **1996**, 491.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

pH study allows catalytic asymmetric epoxidation:

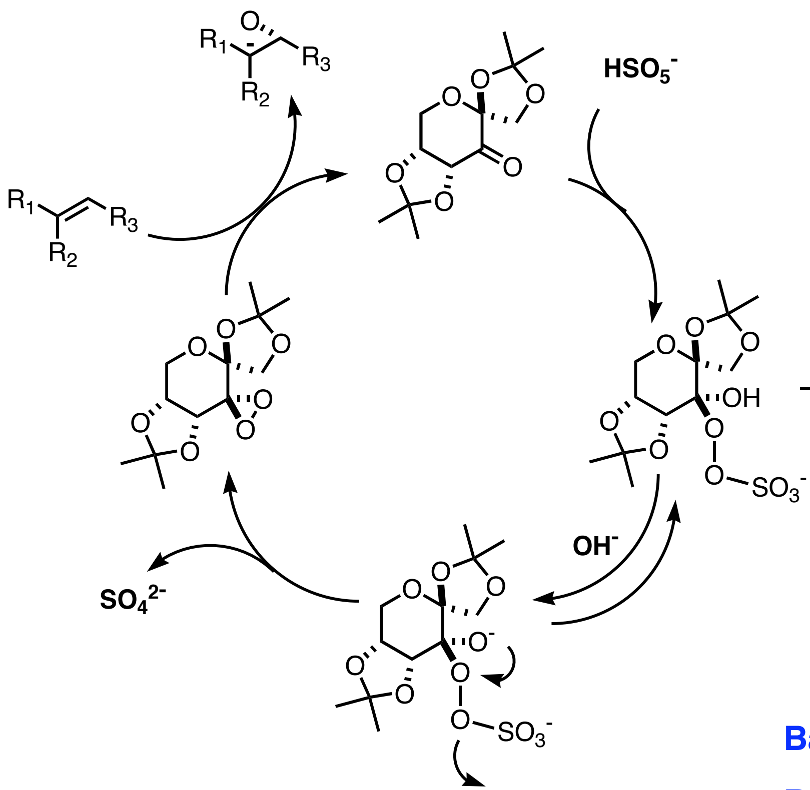


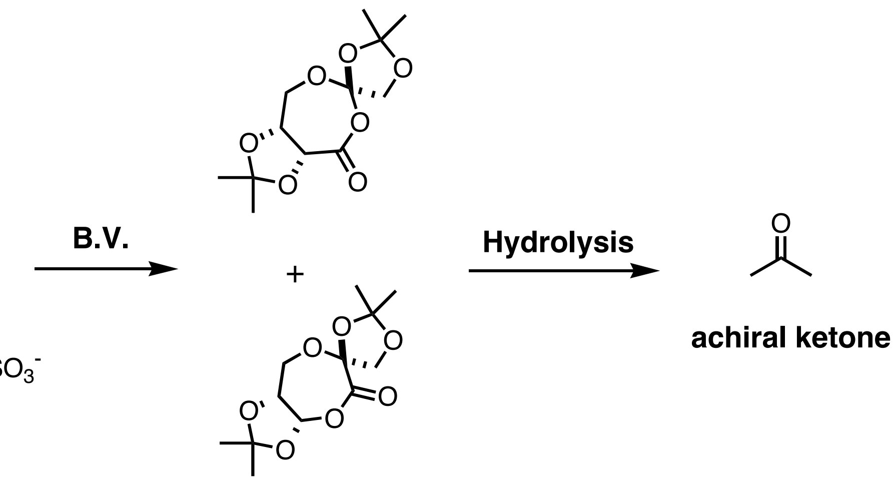
Plot of the conversion of *trans*-methylstyrene against pH using ketone (0.2 eq.) as catalyst in two solvent systems, H_2O-CH_3CN (1:1.5 v/v) (A) and H_2O-CH_3CN-DMM (2:1:2 v/v) (B)

Wang, Z.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.*, **1997**, 2328.
Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Amer. Chem. Soc.*, **1997**, 11224.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Shi Epoxidation catalytic cycle:





Baeyer-Villiger suppressed at higher pH

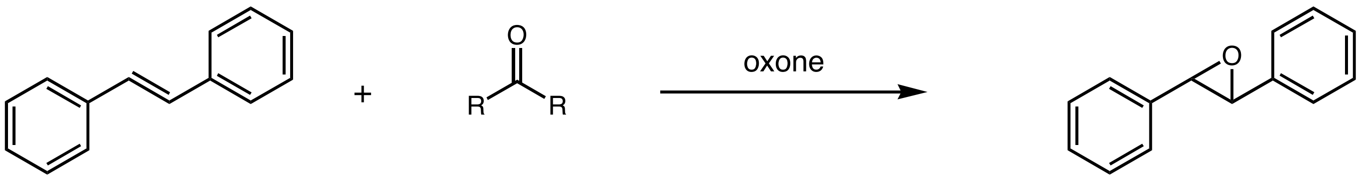
Reactions become catalytic in ketone at 30 mol%

Wang, Z.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.*, **1997**, 2328.

Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Amer. Chem. Soc.*, **1997**, 11224.

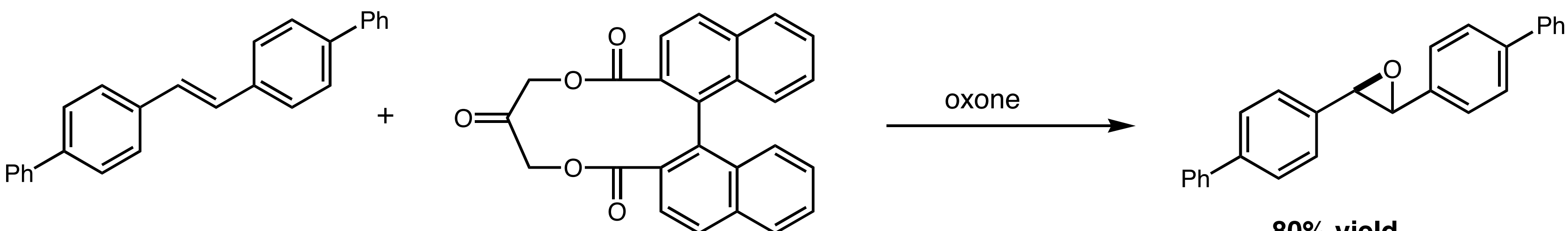
Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

1996 Yang shows electronic effect on ketone catalysts:



R	Reaction Time (min)
Me	300
CF_3	<4
CH_2Cl	18
CH_2OAc	30

Discovery leads to design of C2-symmetric catalyst:



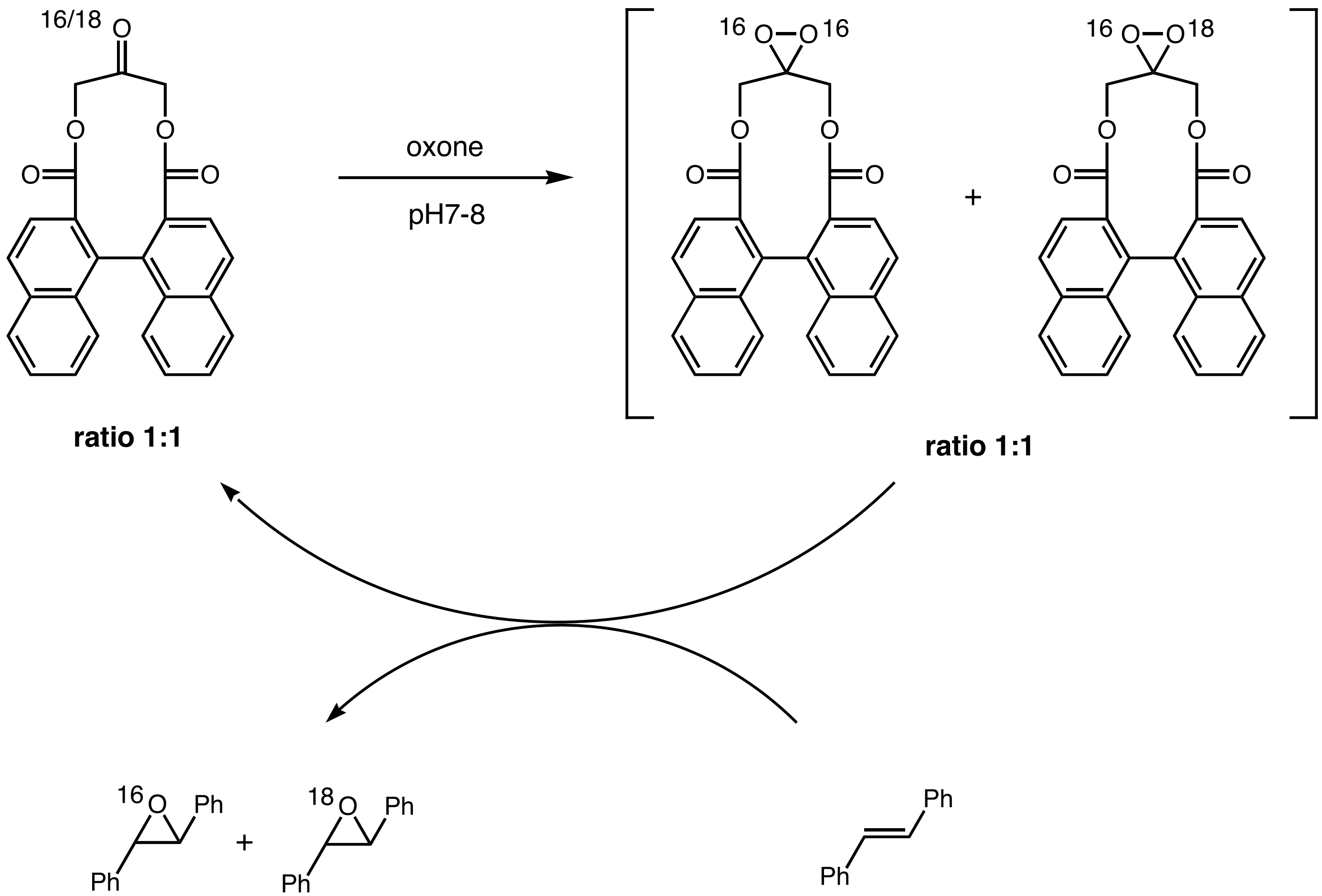
10 mol%

80% yield
87% ee

Yang et. al., *J. Amer. Chem. Soc.*, **1996**, 491.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

^{18}O labelling provides evidence for dioxirane intermediate:

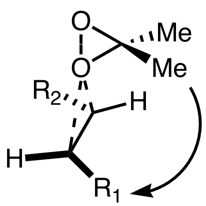


3:1 theoretical ratio
23% experimentally obtained

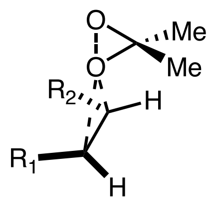
Yang et. al., *J. Amer. Chem. Soc.*, **1998**, 5949.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

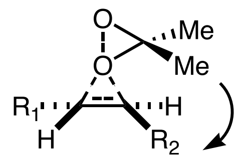
Possible Dioxirane Geometries:



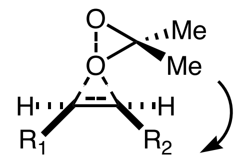
Spiro-*trans*



Spiro-*cis*



Planar-*trans*

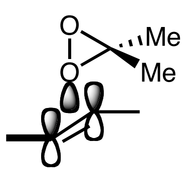


Planar-*cis*

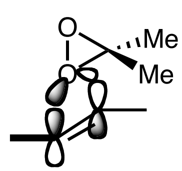
Spiro calculated by Houk to be lower in energy

Cis-olefins epoxidize 7-9 times faster; only the spiro geometery explains this observation

Molecular Orbital Considerations:



olefin π-orbitals attack oxygen σ*-orbital



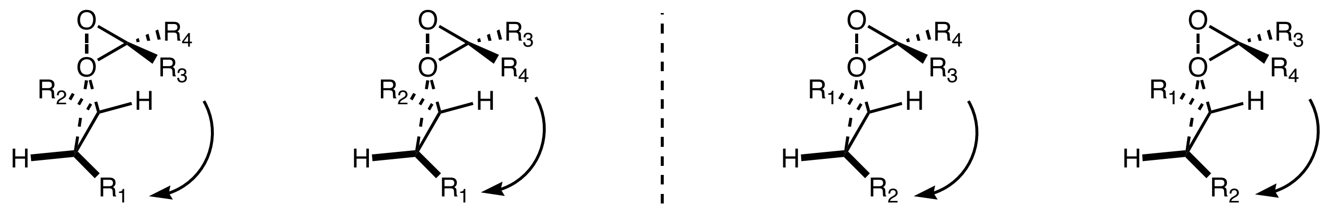
oxygen lone-pair attacks olefin π*-orbital

No overlap in planar geometery

Comprehensive Asymmetric Catalysis, Vol II.
Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds; Springer: Berlin 1999

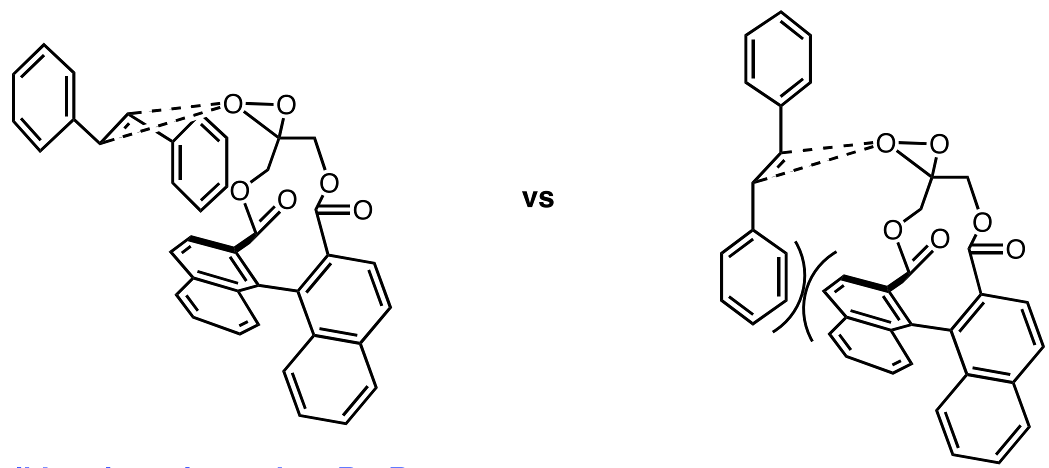
Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Stereochemical Considerations:



Spiro-*trans* Spiro-*trans* Spiro-*trans* Spiro-*trans*

Design of asymmetric catalyst must be able to differentiate between possible dioxirane orientations



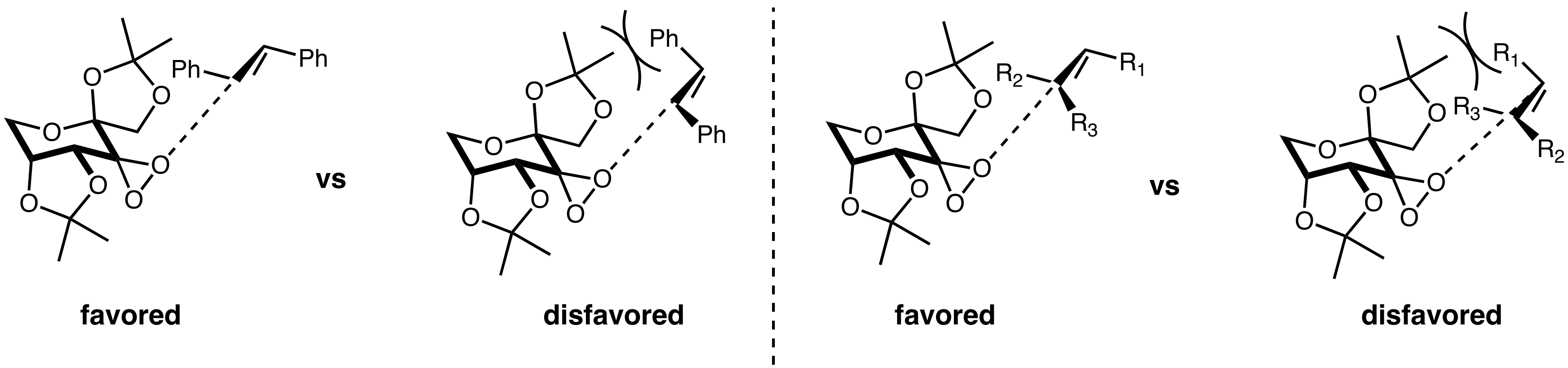
Two possible orientations when R_1=R_2

Distant stereocenter less affective with small or long-chain aliphatic R groups

Yang et. al., *J. Amer. Chem. Soc.*, **1998**, 5943.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Shi's non-C_2-symmetric catalyst proved more effective for other functionalities:

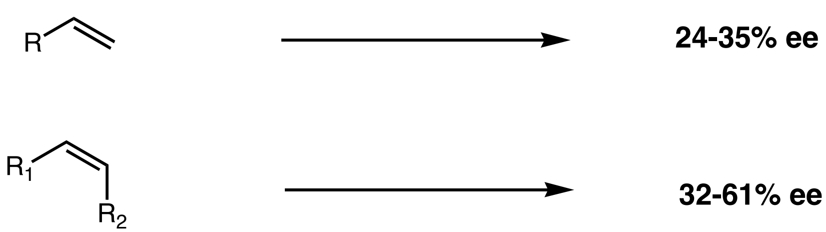


Attack underneath prevented by acetal; olefin approach directed by anomeric acetal

Quaternary center α to carbonyl minimizes epimerization of stereogenic centers

Stereogenicity in close proximity to reacting centers enhances stereocontrol

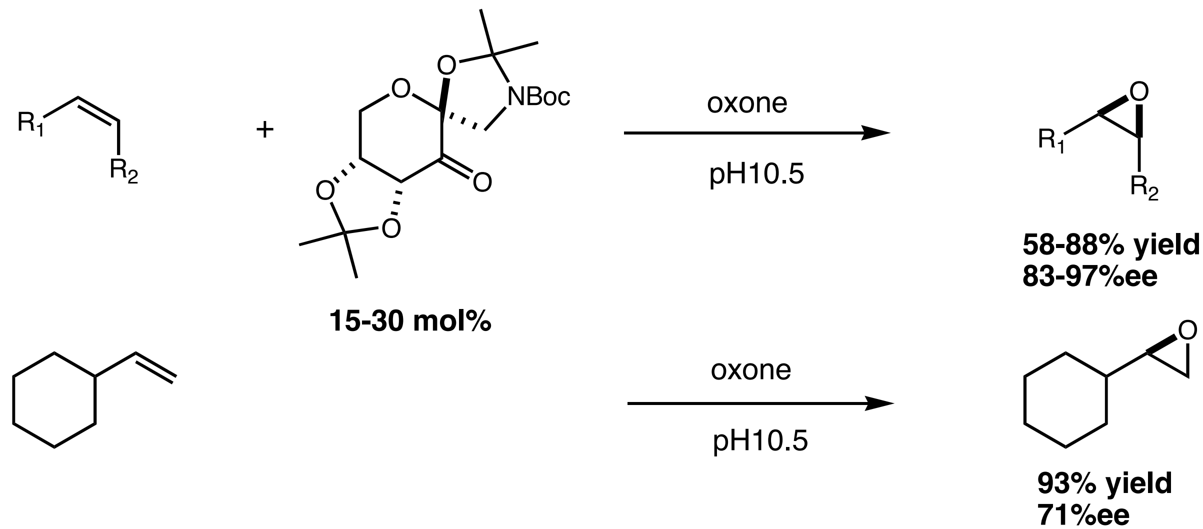
Effective for *trans* or tri-substituted olefins, but not *cis* or terminal olefins



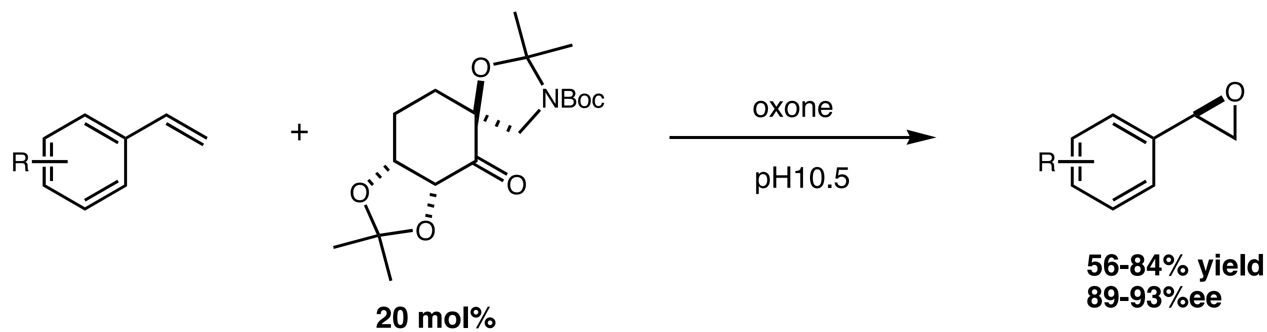
Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J. Shi, Y. *J. Amer. Chem. Soc.*, **1997**, 11224.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

2002 Shi reports catalyst for enantioselective epoxidation of terminal and *cis*-olefins:



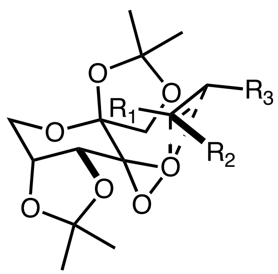
2004 Shi reports catalyst for enantioselective epoxidation of styrenes:



Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002,** 2435.
Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci.* **2004,** xxx.

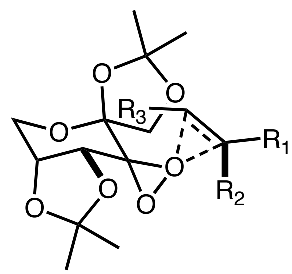
Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Electronic Considerations:



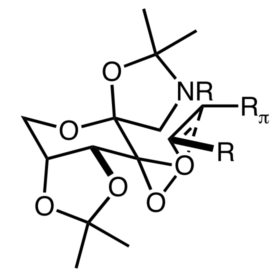
Spiro A
Favored Sterically

(R,R)
76-98% ee



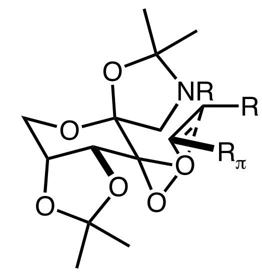
Planar B

(S,S)



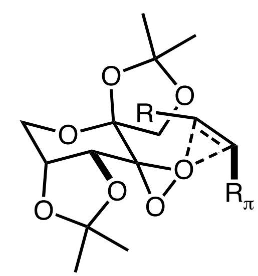
Spiro C
Favored Electronically

(R,S)
87-97% ee



Spiro D

(S,R)



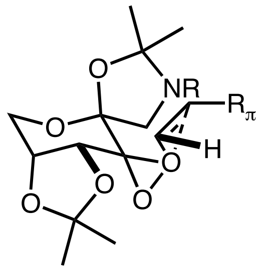
Planar E
Disfavored Sterically

(R,S)

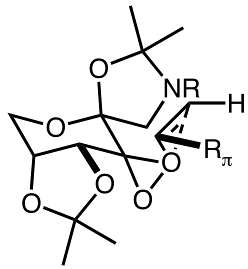
Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci.* **2004,** xxx.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Electronic Considerations:



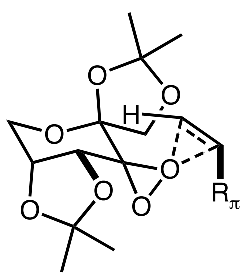
Spiro F
Favored Electronically



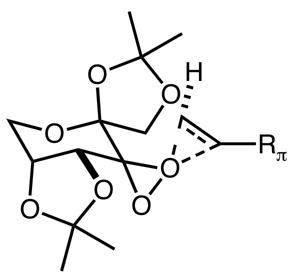
Spiro G

(R)
30-85% ee

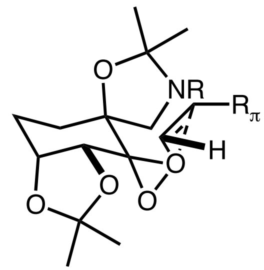
(S)



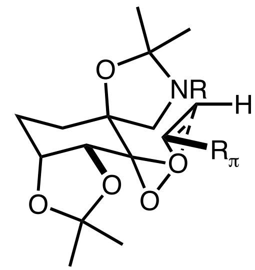
Planar H
(R)



Planar I
(S)



Spiro J
Favored Electronically



Spiro K

(R)
89-93% ee

(S)

Nonbonding orbital of dioxirane oxygen raised

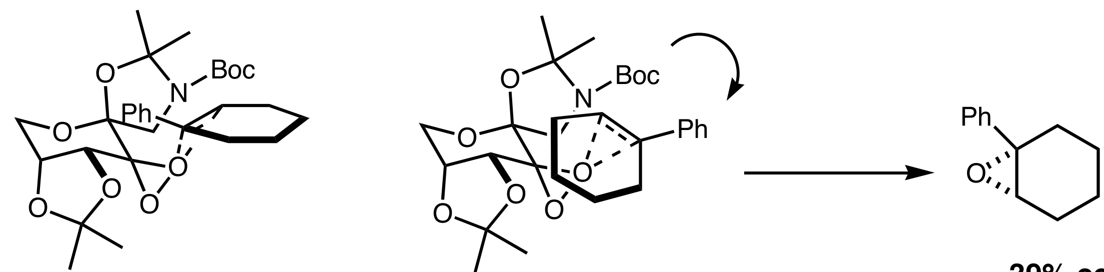
Secondary overlap increased

Spiro even more favored over planar

Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci.* **2004,** xxx.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

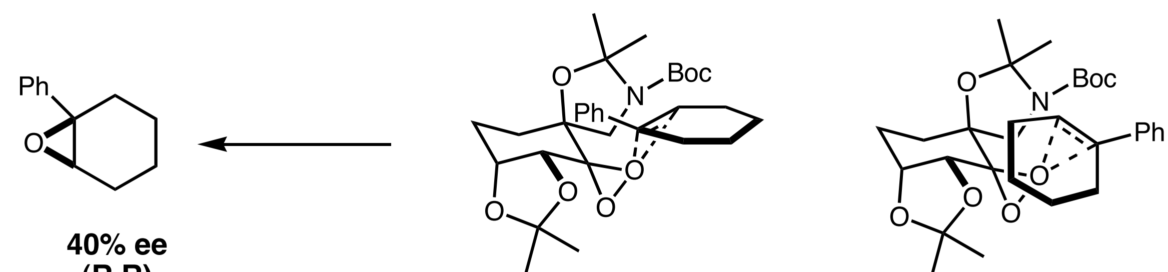
Electronic Considerations:



Spiro L

Planar M
Favored Electronically

39% ee
(S,S)



40% ee
(R,R)

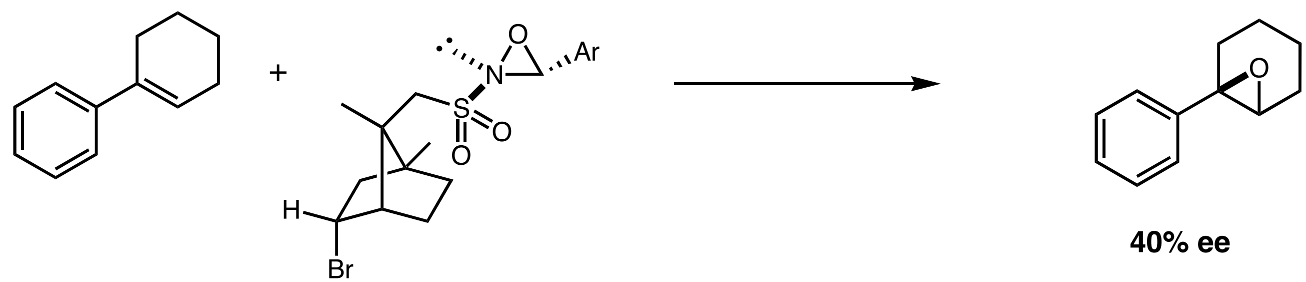
Spiro N
Favored Electronically

Planar O

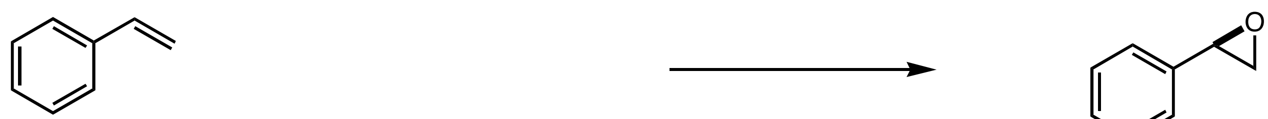
Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci.* **2004,** xxx.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

1983 Davis demonstrates enantioselective epoxidation using chiral oxaziridines:

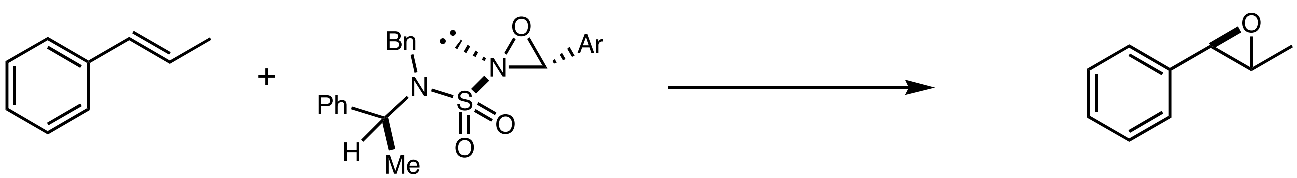


40% ee



16% ee

1986 Davis further increases epoxidation enantioselectivity:

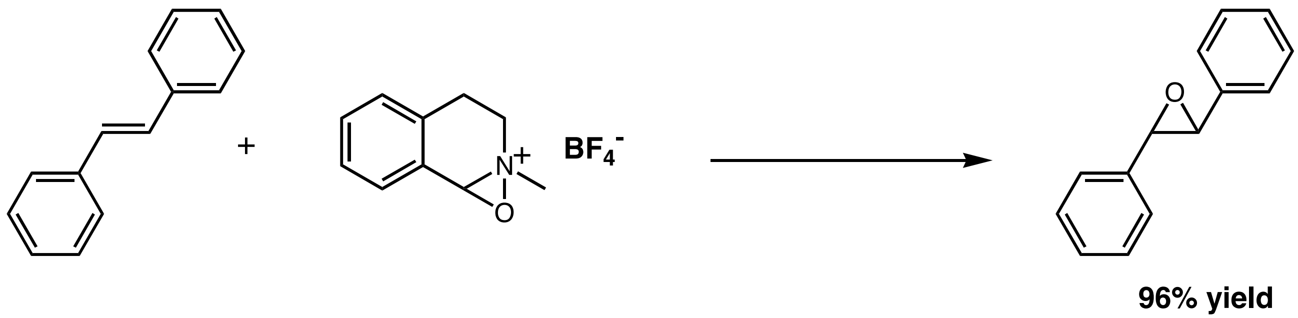


65% ee

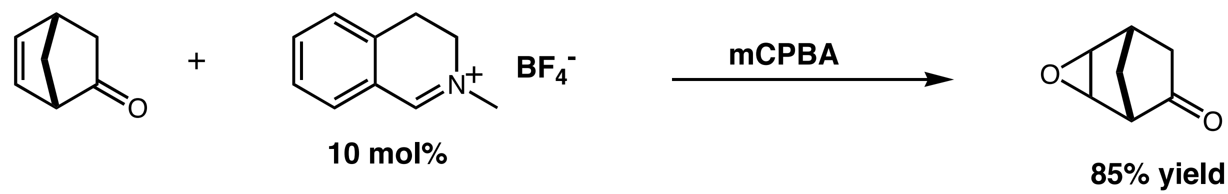
Davis et. al., *J. Amer, Chem. Soc.*, **1983**, 3123.
Davis et. al., *Tet. Lett.*, **1986**, 5079.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

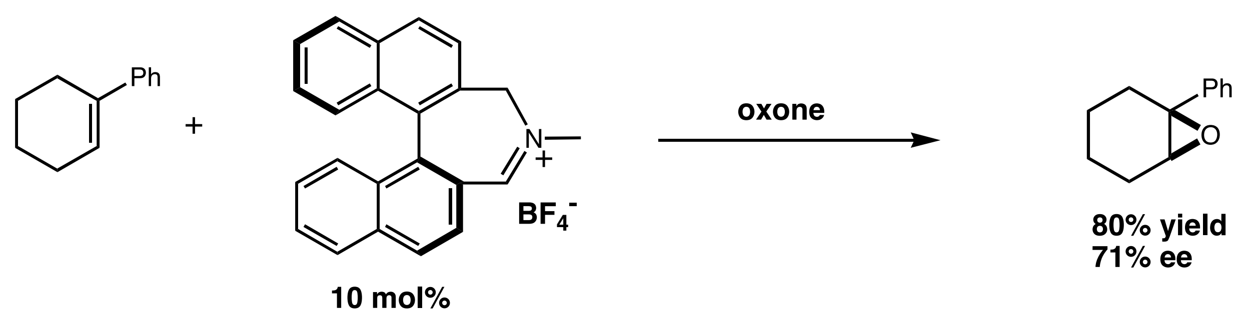
1988 Lusinchi finds oxaziridinium salts to be efficient oxygen transfer agents:



1993 Lusinchi reports first catalytic epoxidation with oxaziridium salts:



1996 Aggarwal reports a catalytic asymmetric epoxidation with oxaziridinium salts:



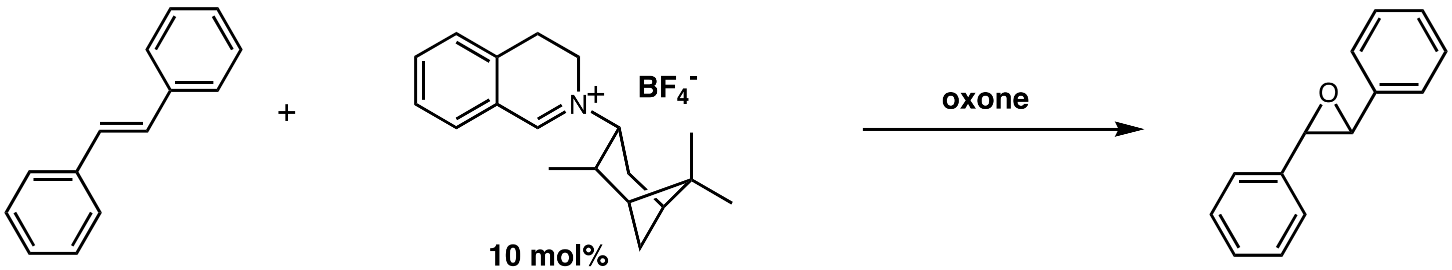
Hanquet, G.; Lusinchi, X.; Milliet, P. *Tet. Lett.* **1988**, 3941.

Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1993**, 423.

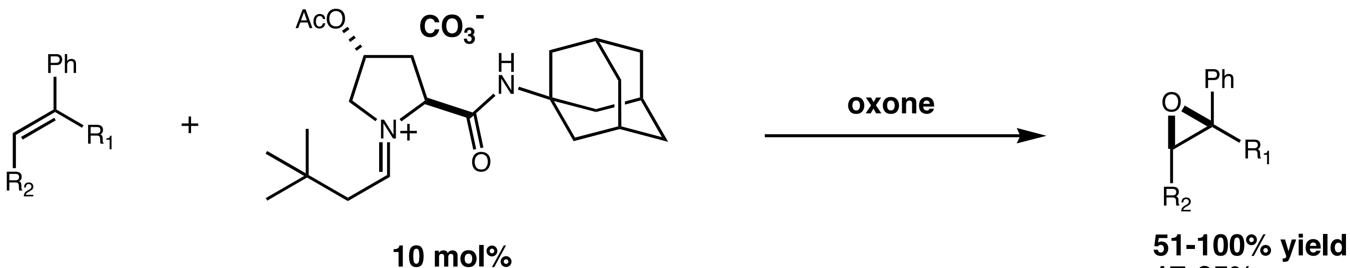
Aggarwal, et. al. *Chem. Commun.* **1996**, 191.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

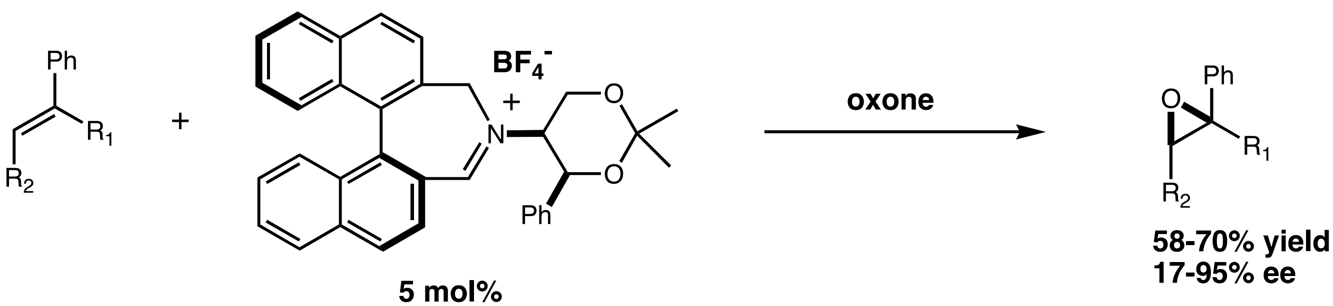
Recent reports show minor improvements in enantioselectivity:



78% yield
73% ee



51-100% yield
17-65% ee

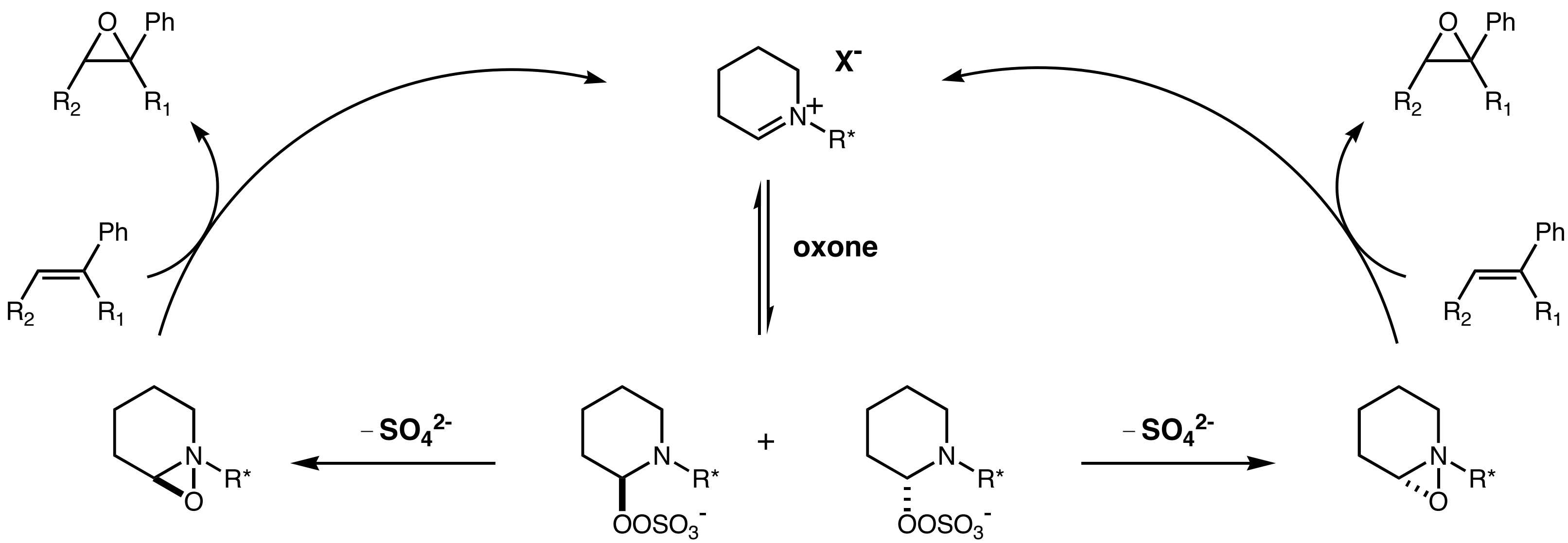


58-70% yield
17-95% ee

Page, et. al. *J. Org. Chem.* **1998**, 2774.
Wong, M. et. al. *Org. Lett.* **2001**, 2587.
Page, P. C. B. et. al. *Org. Lett.* **2004**, 1543.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Stereochemical Considerations:



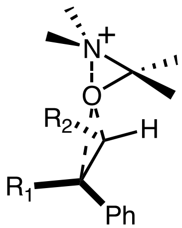
Two diastereomeric oxaziridines may be formed

Each oxaziridine may lead to the same product enantiomer, but will have different selectivities

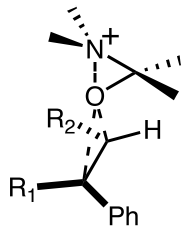
Page, et. al. *J. Org. Chem.* **2001**, 6926.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

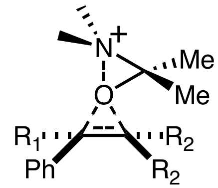
Stereochemical Considerations:



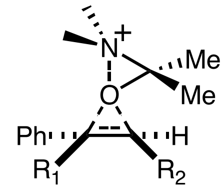
Spiro A



Spiro B

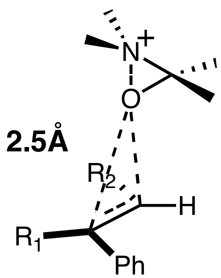


Planar A

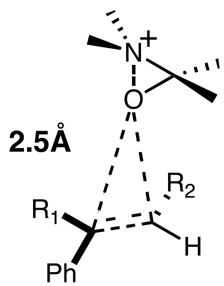


Planar B

Spiro calculated by Houk to be lower in energy by 4.1 kcal/mol



Spiro



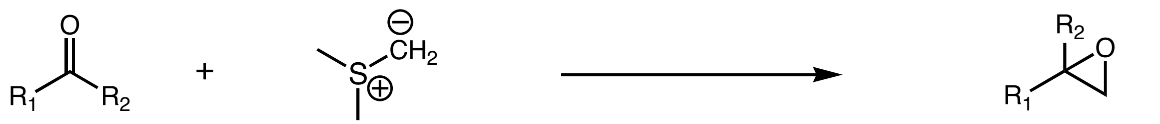
Twisted-Spiro

Early transition state predicted, allowing flexibility unlike dioxiranes

Washington, I.; Houk, K. N. *J. Amer. Chem. Soc.* **2000,** 2948.

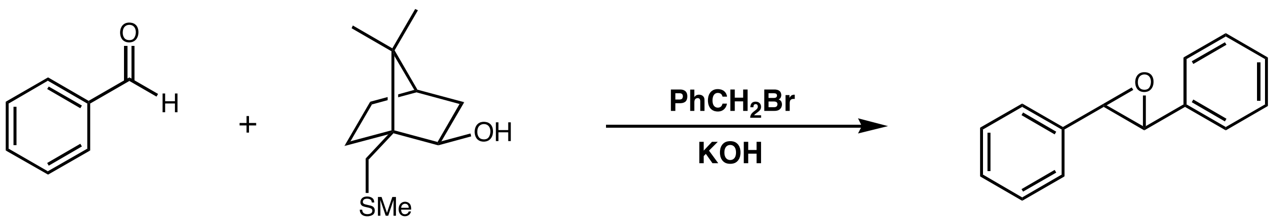
Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

1965 Corey demonstrates epoxidation of aldehydes and ketones with sulfur ylides:



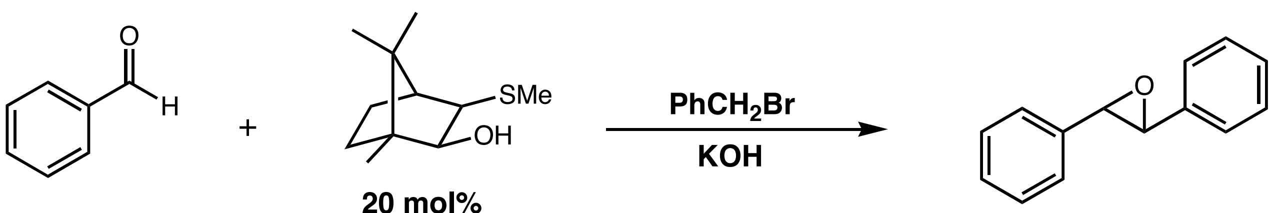
75-97% Yield

1989 Furukawa achieves enantioselectivity and some turnover via sulfide alkylation/deprotonation:



230% Yield (based on sulfide)
31% ee

1996 Dai improves enantioselectivity and turnover for this system:

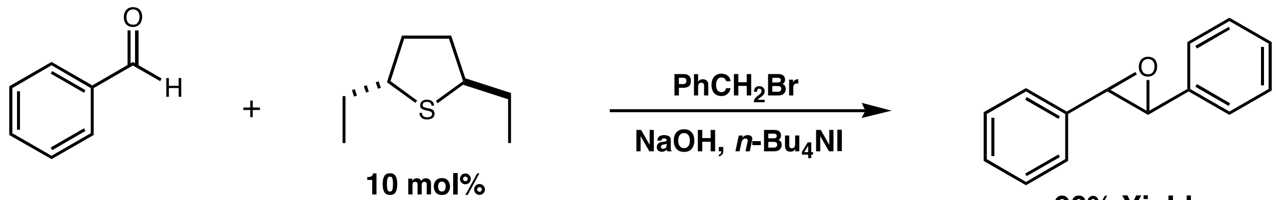


97% Yield
42% ee

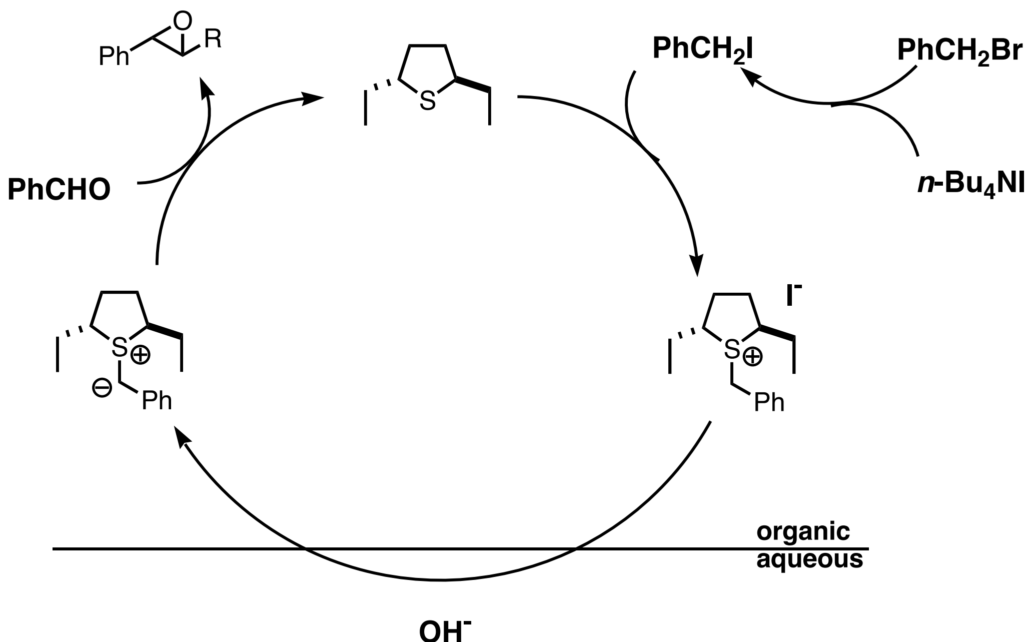
Corey, E. et. al. *J. Amer. Chem. Soc.* **1965**, 1356.
Furukawa, N. et. al. *J. Org. Chem.* **1989**, 4222.
Dai, L. et. al. *J. Org. Chem.* **1996**, 489.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

2001 Metzner's C_2 symmetric catalyst achieves best results to date:



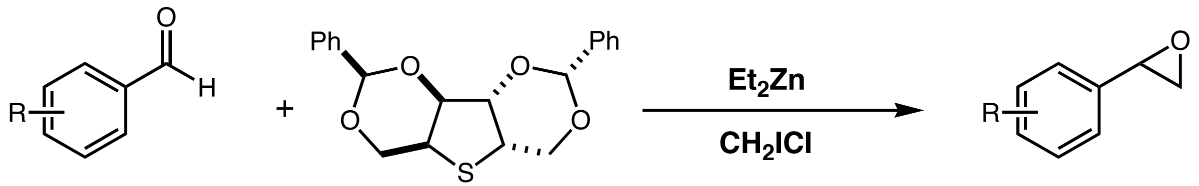
Reactions limited to aromatic aldehydes and benzyl bromides



Zanardi, J.; Leriverend, C.; Aubert, K.; Metzner, P. *J. Org. Chem.* **2001**, 5620.

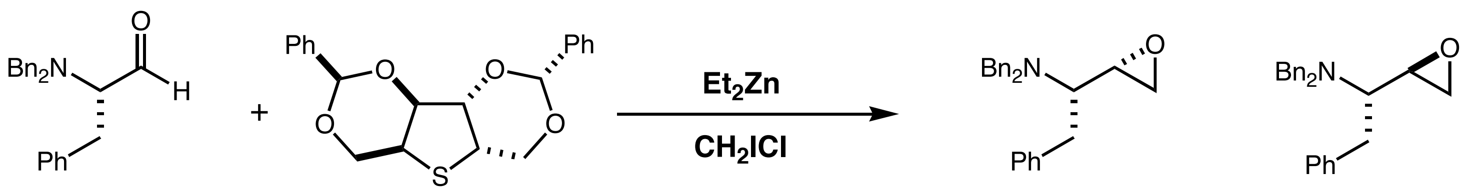
Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

2004 Goodman achieves methylene transfer stoichiometrically:

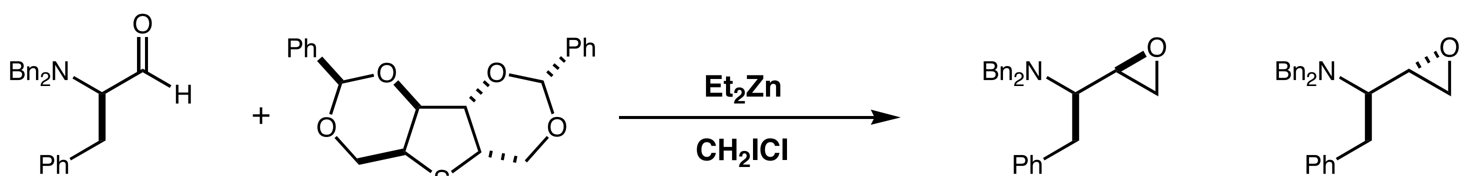


2 eq.

48-96% Yield
34-76% ee



57% conv
***syn:anti* 12:1**

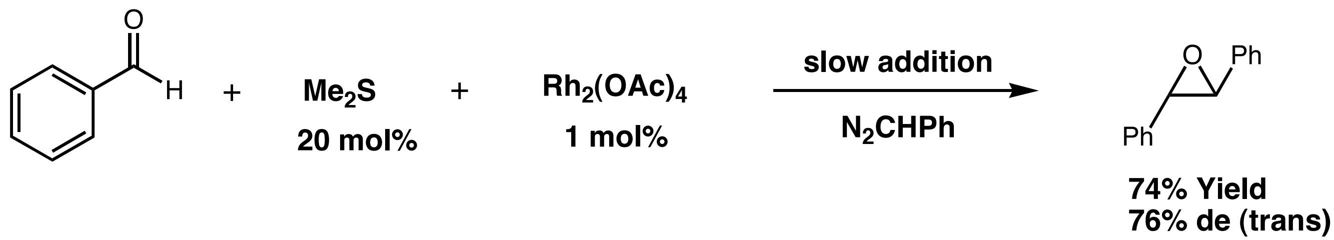


45% conv
***syn:anti* 3:1**

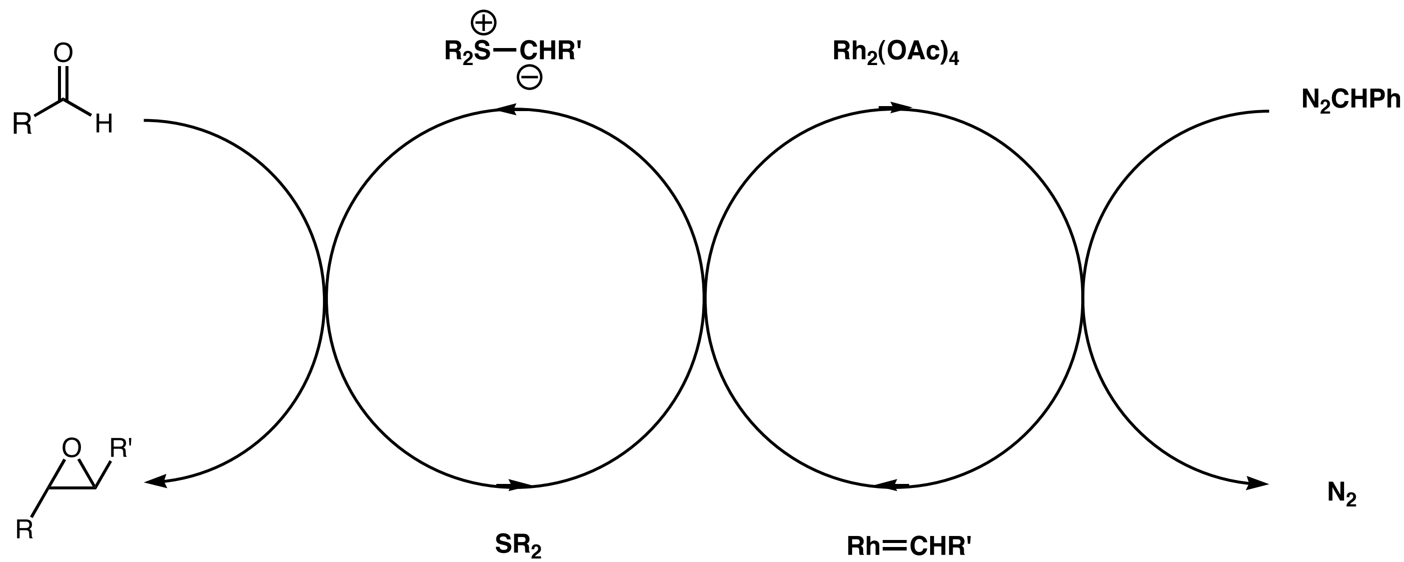
Bellenie, B.; Goodman, J. *Chem Commun.* **2004**, 1076.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

1994 Aggarwal uses diazo compounds to generate sulfur ylide catalyst *in situ*:



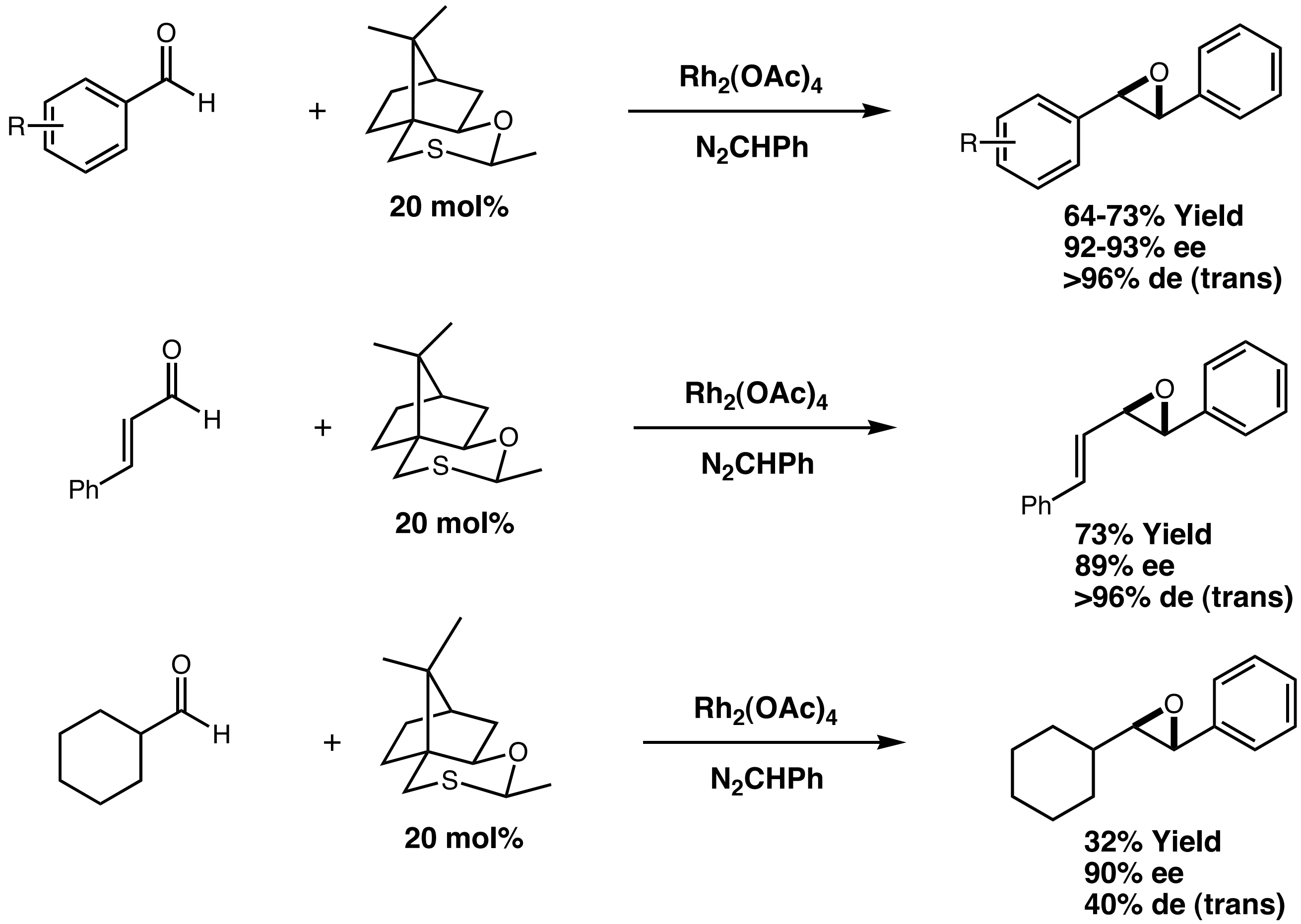
Slow addition of diazo compound to minimize dimerization



Aggarwal, V. et. al. *J. Amer. Chem. Soc.* **1994**, 5973.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

1996 Aggarwal achieves good diastereoselectivity and enantioselectivity:

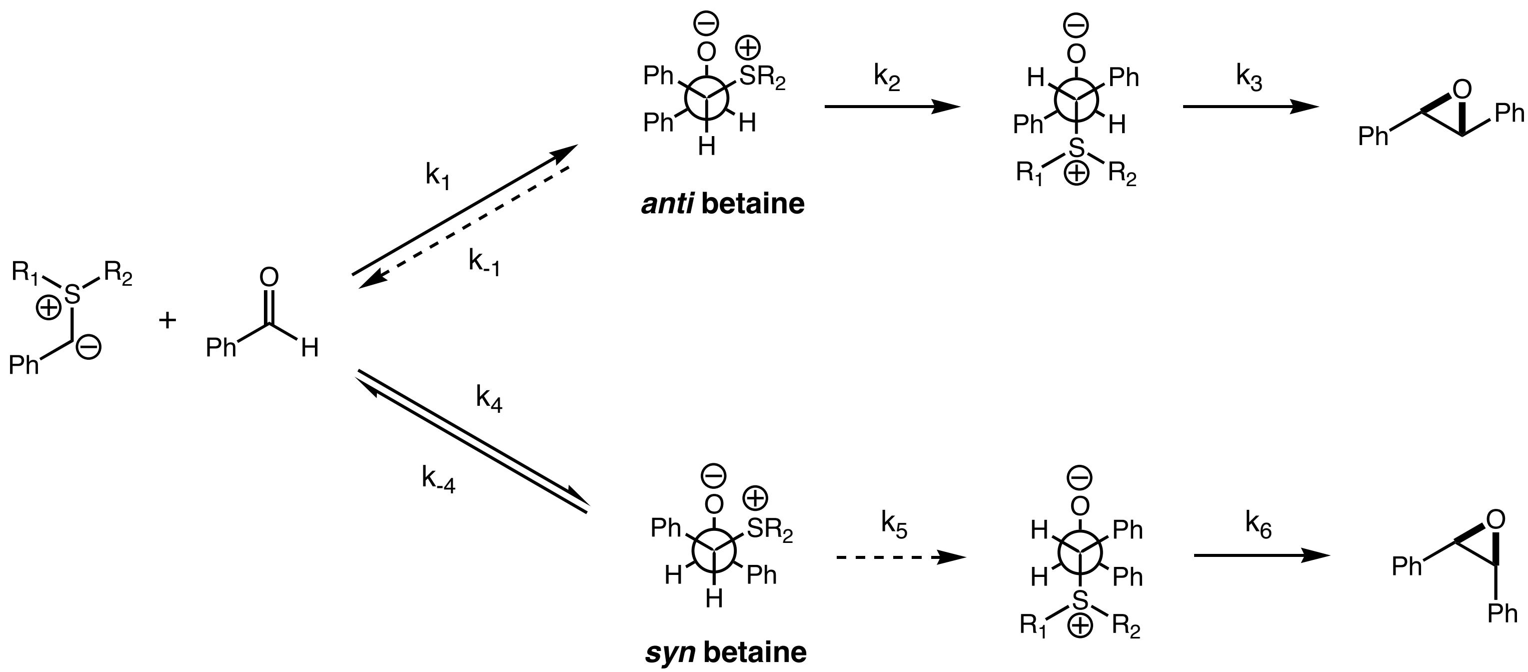


Aggarwal, V. et. al. *J. Amer. Chem. Soc.* **1996**, 7004.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Stereochemical Considerations:

Diastereoselectivity:



***anti* betaine: small barreir of rotation. $k_2 > k_{-1}$**

***syn* betaine: large barrier of rotation. $k_5 < k_{-4}$**

Aliphatics have lower k_5, making *syn* betaine more pronounced

Aggarwal, V. et. al. *Acc. Chem. Res.* **2004**, ASAP.

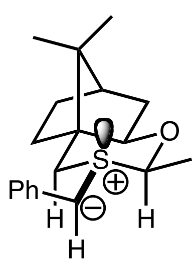
Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Stereochemical Considerations:

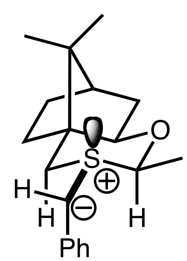
Enantioselectivity:

Sulfur lone pair and filled orbital on ylide carbon calculated to be orthogonal

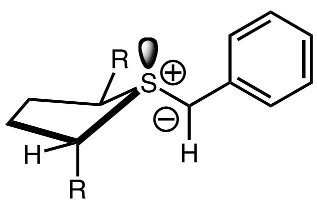
Ylide formation could give mixture of only two diastereomers



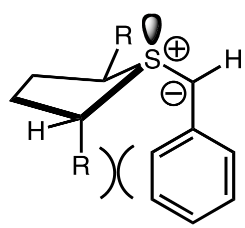
Favored



Disfavored



Favored



Disfavored

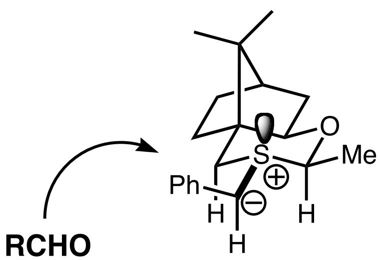
Comprehensive Asymmetric Catalysis, Vol II.
Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds; Springer: Berlin 1999

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

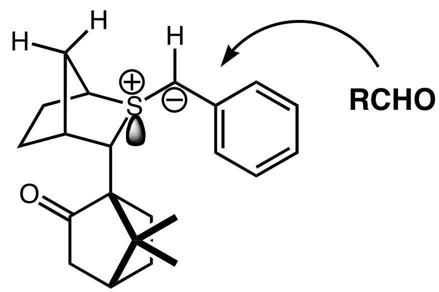
Stereochemical Considerations:

Enantioselectivity:

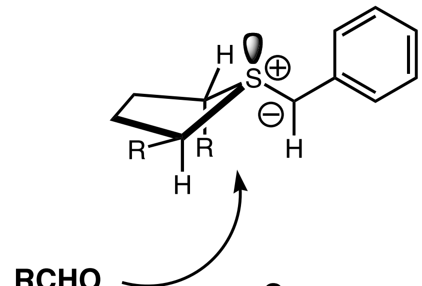
Facial selectivity determined by catalyst



A



B



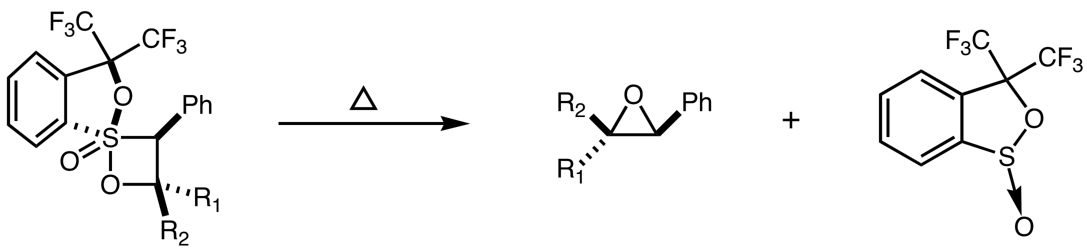
C

Comprehensive Asymmetric Catalysis, Vol II.
Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds; Springer: Berlin 1999

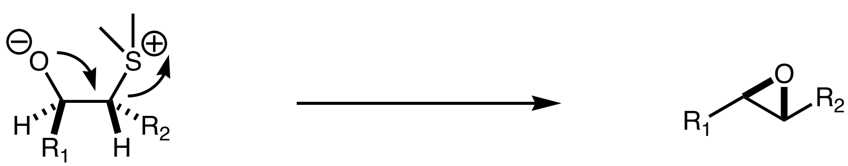
Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

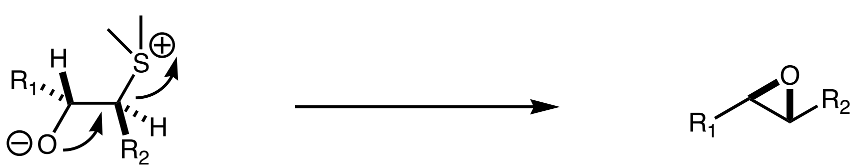
Concerted pathway or *anti*-addition?

Kawashima reports oxirane formation with retention of configuration



Koskinen calculates anti-addition to be lower in energy by atleast 10 kcal/mol

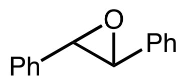
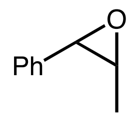
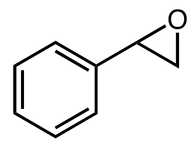
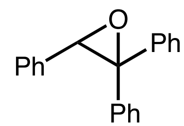
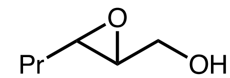
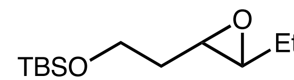




Kawashima, T. et. al. *J. Amer. Chem. Soc.* **1996**, 12455.
Lindvall, M.; Koskinen, A. *J. Org. Chem.* **1999**, 4596.

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Conclusions:

						
Jacobsen[c]	**80% yield 90% ee[a]**	**36% yield 86% ee**	**88% yield 86% ee**	**97% yield 92% ee**		
Shi[d]	**75% yield 97% ee**	**87% yield 91% ee**	**63% yield 90% ee**	**54% yield 97% ee**	**60% yield 78% ee**	**85% yield 93% ee**
Yang[d]	**99% yield 47% ee**			**82% yield 81% ee**		
Page[e]	**78% yield 73% ee**			**43% yield 54% ee**		
Metzner[f]	**97% yield 93% ee[b]**					
Goodman[f]	**61% yield 48% ee**					
Aggarwal[f]	**87% yield 94% ee**					

[a] >92% de
[b] 88% de

[c] metal Salen
[d] dioxirane

[e] oxaziridine
[f] sulfur ylide

Epoxidation With Chiral Oxaziridines, Dioxiranes and Sulfonium Ylides

Conclusions:

Improvements in yield and enantioselectivity are needed for the following substrates:

Aliphatic epoxides

Terminal epoxides

Styrenes

Cis-epoxides

Tetra-substituted epoxides