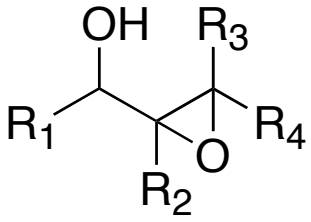
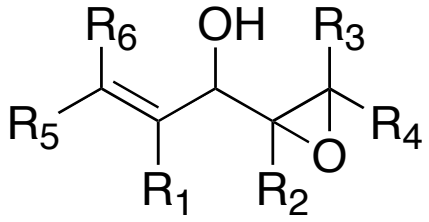
Highly Enantio- and Diastereoselective One-Pot Synthesis of Acyclic Epoxy Alcohols and Allylic Epoxy Alcohols

Ann Rowley Kelly, Alice E. Lurain, and Patrick J. Walsh*

University of Pennsylvania, Philadelphia, PA

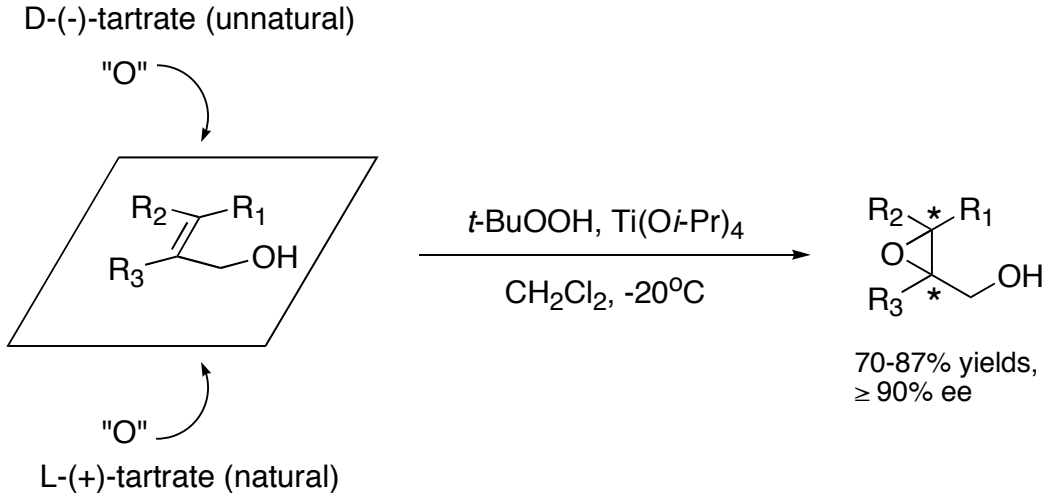
J. Am. Chem. Soc., ASAP (ja051291k)



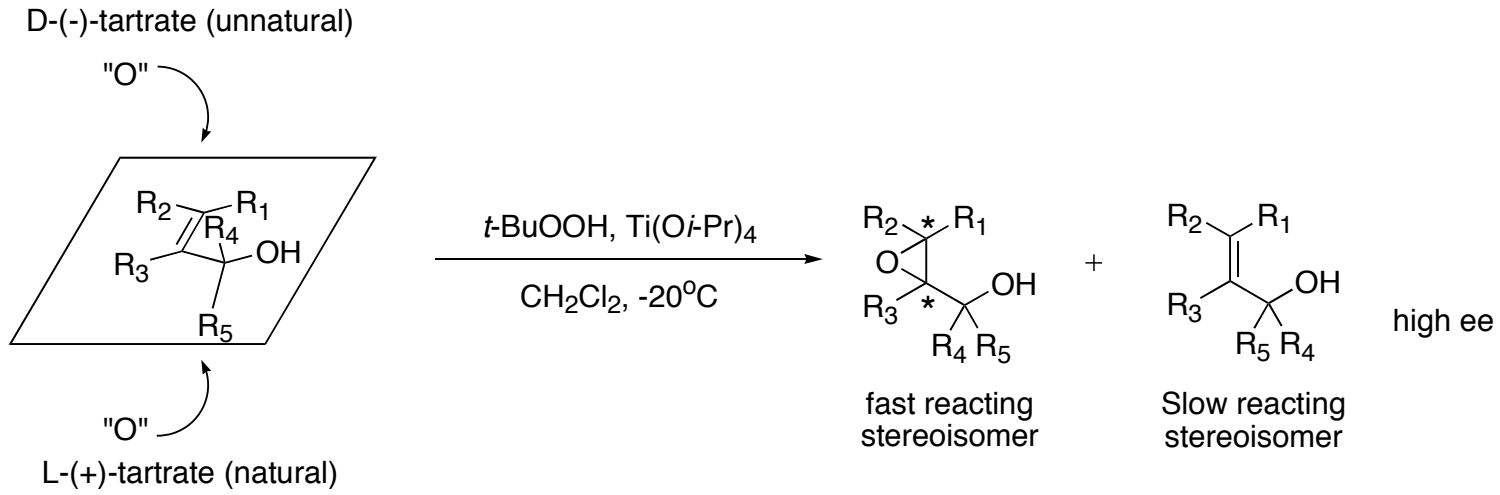


Adam Hoye, Oct. 15, 2005

Sharpless Asymmetric Epoxidation

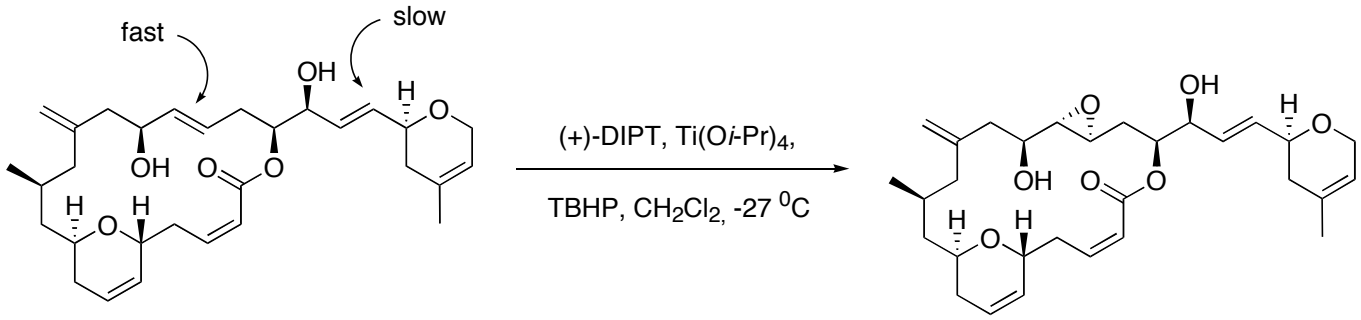


Kinetic Resolution:



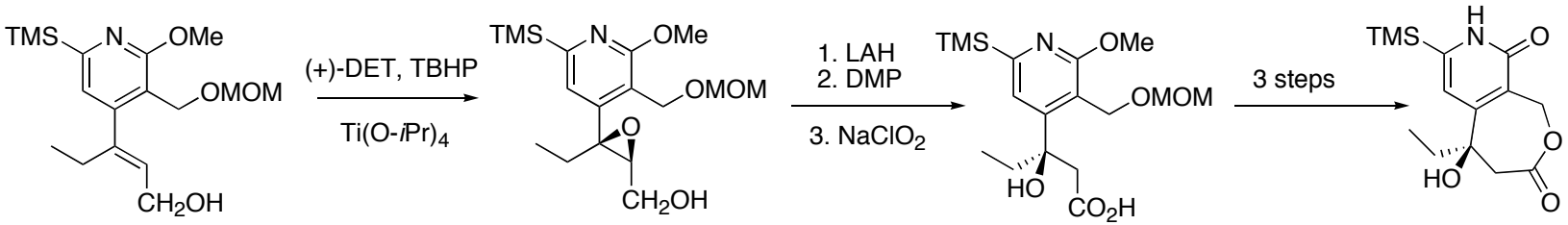
Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S.; Walker, F. J.; Woodard, S.S. *Pure Appl. Chem.* **1983**, *55*, 589

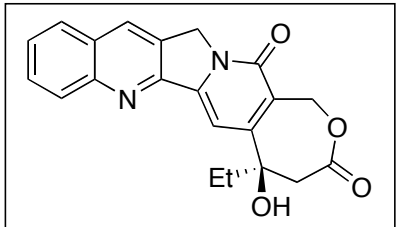
Epoxy Alcohols in Natural Product Synthesis



Laulimalide

Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149
Wender, P. A;, Hedge, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956
Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.*, **2002**, *124*, 13654

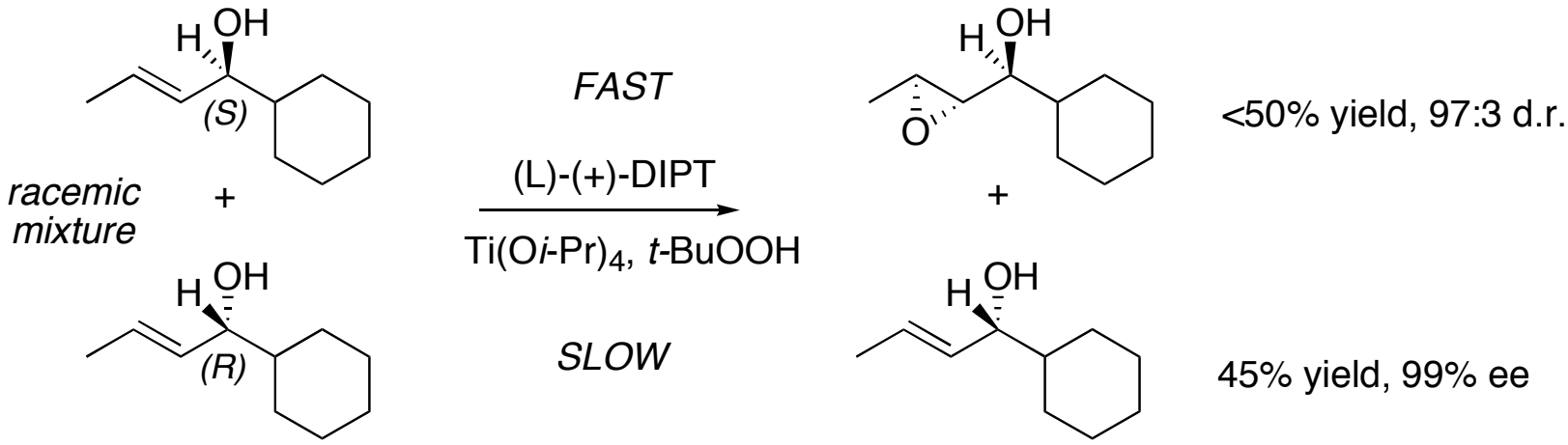




Homocamptothecin

Gabarda, A. E.; Du, W.; Isarno, T.; Tangirala, R. S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 6329

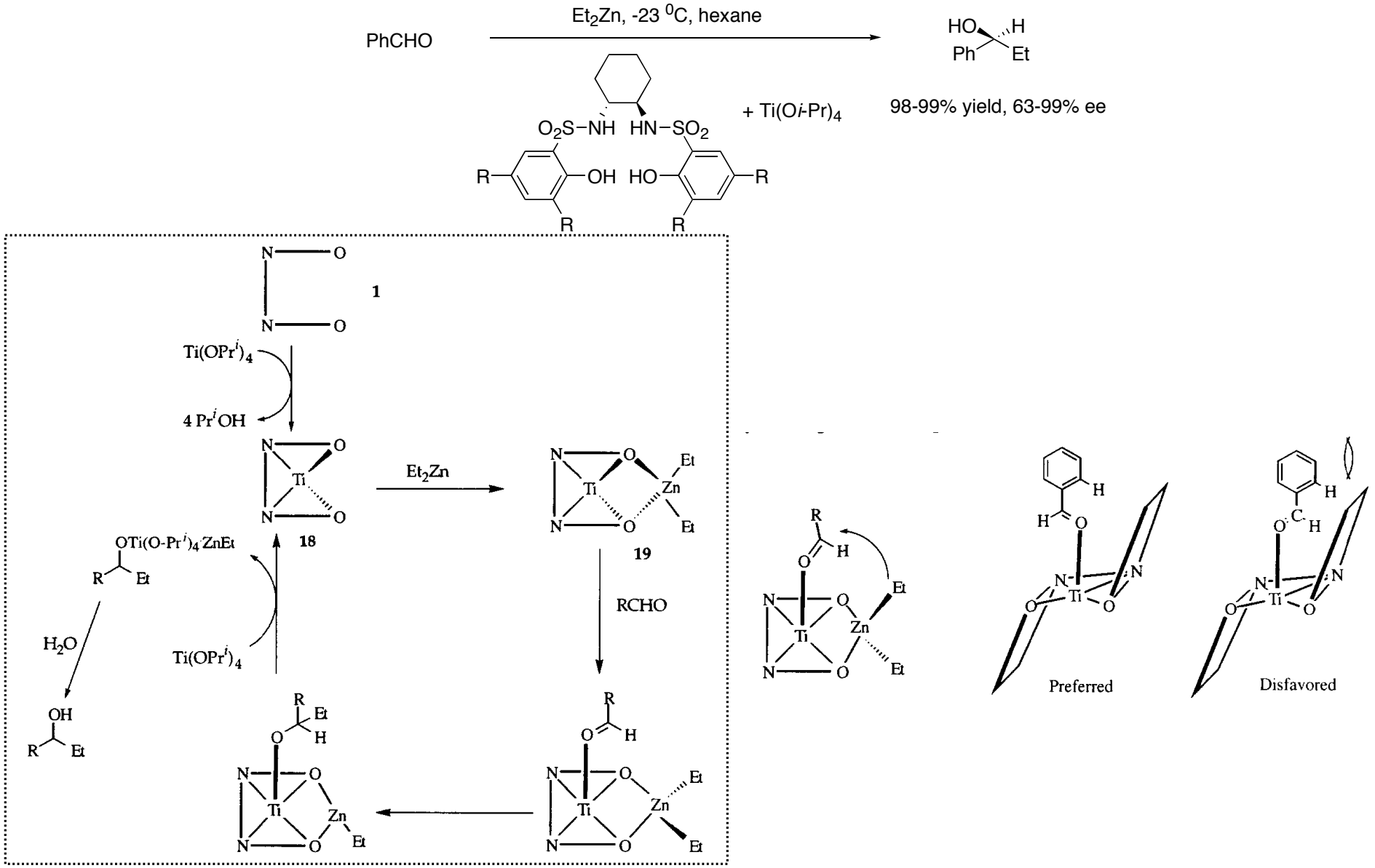
Potential Limitations of Sharpless Methodology



- If epoxy alcohol is the desired product, kinetic resolution must be quenched at low conversion to ensure high ee (i.e. quenching early to inhibit 'mismatched' enantiomer from reacting)
- Alternatively, the resolved allylic alcohol is often isolated and epoxidized in an additional step
- Inherent to the KR of a racemic substrate, the maximum yield is 50%

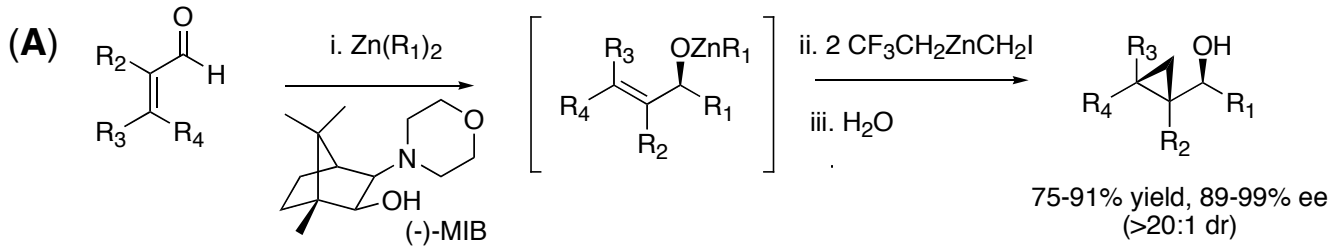
Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237

Previous Work in the Walsh Group

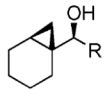
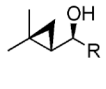
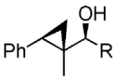
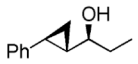
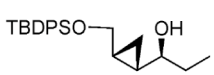
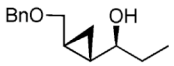


Guo, C.; Qui, J. Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J. *Tetrahedron* **1997**, *53*, 4145

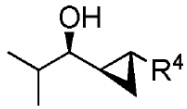
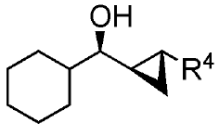
Walsh Cyclopropanation Strategy



Via Method A:

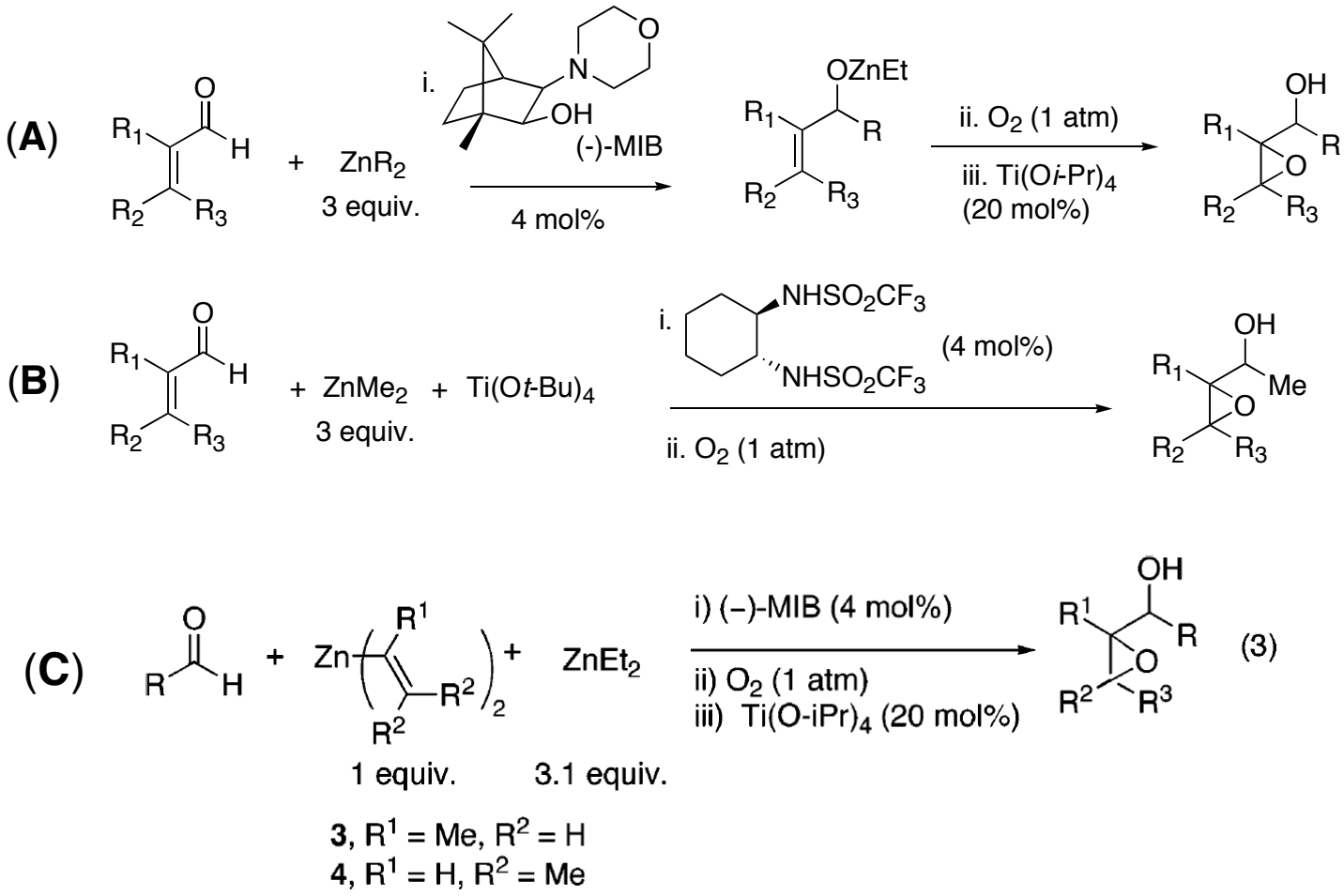
entry	ZnR_2	cyclopropyl alcohol	ee (%)	dr [a]	yield (%)
1	Et[b]		99	>20:1	90
2	$-(CH_2)_4iPr$[c]		97	>20:1	66
3	$-(CH_2)_5OTBDPS$[c]		98	>20:1	75
4	Me[c]		99	>20:1	76
5	Et		95	>20:1	78
6	$-(CH_2)_4iPr$[c]		96	>20:1	64
7	Me[c]		95	>20:1	85
8	Et		96	>20:1	90
9	Et		89	>20:1	87
10	Et		98	>20:1	80
11	Et		91	>20:1	91

Via Method B:

entry	cyclopropyl alcohol	R^4	ee(%)	dr[a]	yield (%)
1		Ph	99	>20:1	75
2		nBu	92	>20:1	71
3		tBu	87	>20:1	78
4		Ph	99	>20:1	78
5		nBu	93	>20:1	84
6		tBu	96	>20:1	74
7		$(CH_2)_4Cl$[b]	94	>20:1	80
8		CH_2CH_2OTr	93	>20:1	73

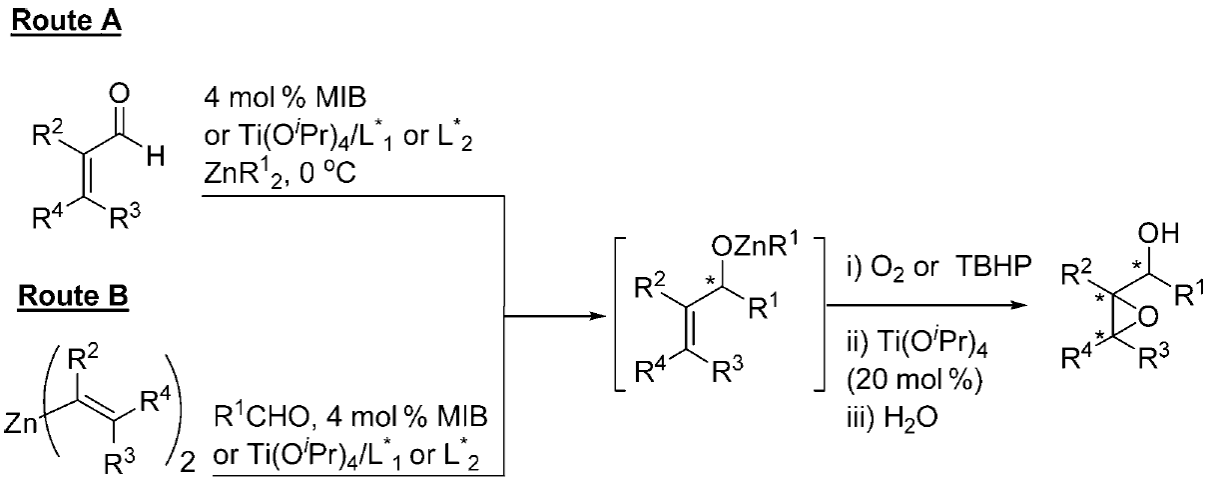
Kim, H. Y.; Lurain, A. E.; García-García, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13138

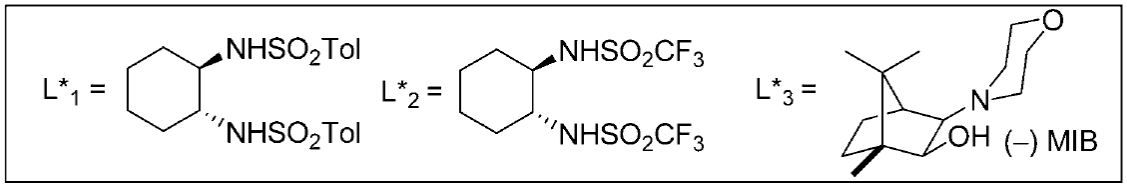
Walsh Epoxidation Strategy

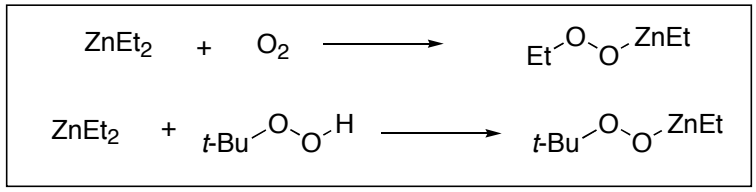


Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608

Current Paper

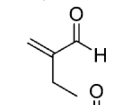
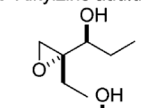
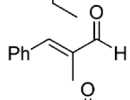
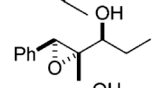
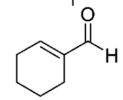
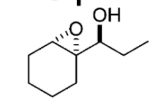
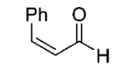
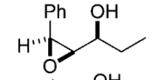
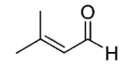
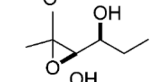
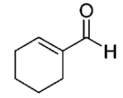
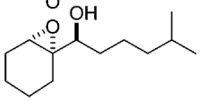
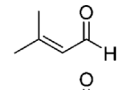
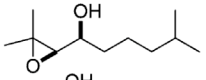
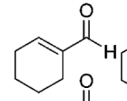
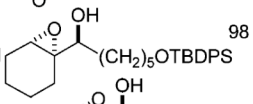
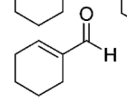
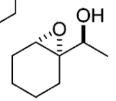
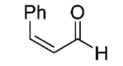
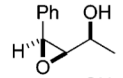
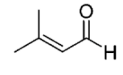
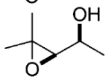
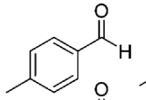
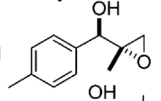
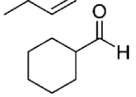
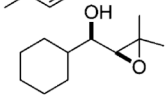




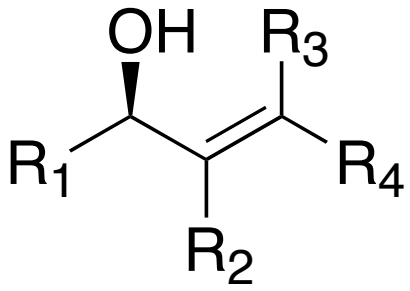


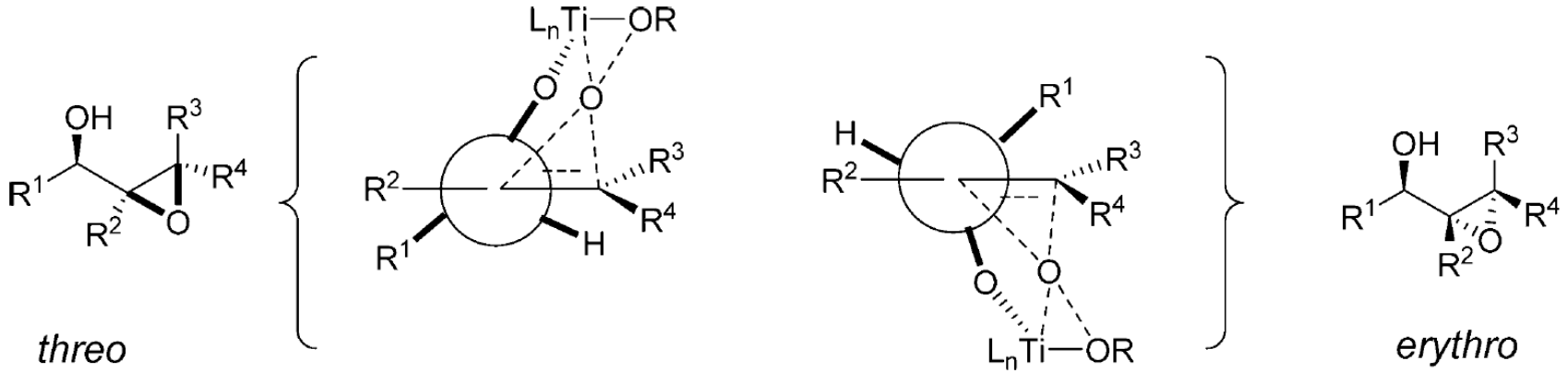
Kelly, A. R.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2005** *ASAP*

Epoxidation Results

entry	aldehyde	epoxy alcohol[a]	L*3, Ti(O^{i}Pr)$_4$ and O$_2$ % ee[b] (% y)	[dr]	Diastereomeric Ratios (*erythro* : *threo*)[c] L*1 or L*2, Ti(O^{i}Pr)$_4$ or Ti(O^{t}Bu)$_4$ and O$_2$ % ee[b] (% y)	[dr]	L*2 or L*3, Ti(O^{i}Pr)$_4$ or Ti(O^{t}Bu)$_4$ and TBHP % ee[b] (% y)	[dr]
Scheme 2, Route A: Alkylzinc additions to enals								
1			93 (60)[f]	[17 : 1]	91 (89)[d]	[20 : 1]	93 (65)[f]	[20 : 1]
2			96 (65)[f]	[18 : 1]	92 (90)[d]	[20 : 1]	96 (79)[f]	[20 : 1]
3			99 (90)[f]	[20 : 1]	99 (91)[d]	[20 : 1]	99 (82)[f]	[10 : 1]
4			91 (96)[f]	[1 : 10]	96 (60)[d]	[1 : 10]	91 (60)[f]	[1 : 10]
5			95 (96)[f]	[1 : 20]	95 (93)[d]	[1 : 20]	95 (98)[f]	[1 : 20]
6			97 (62)[f]	[15 : 1]	97 (85)[d]	[20 : 1]	97 (74)[f]	[17 : 1]
7			96 (81)[f]	[1 : 20]	96 (86)[d]	[1 : 20]	96 (83)[f]	[1 : 20]
8			98 (86)[f]	[20 : 1]	94 (80)[d]	[20 : 1]	98 (85)[f]	[20 : 1]
9					99 (78)[e]	[20 : 1]	99 (89)[e]	[19 : 1]
10					85 (89)[e]	[1 : 10]	85 (65)[e]	[1 : 10]
11					96 (60)[e]	[1 : 18]	96 (72)[e]	[1 : 18]
Scheme 2, Route B: Vinylzinc additions to aldehydes								
12			96 (82)[f]	[16 : 1]	94 (89)[d]	[16 : 1]	96 (90)[f]	[20 : 1]
13			90 (75)[f]	[1 : 19]	97 (90)[d]	[1 : 20]	90 (80)[f]	[1 : 20]

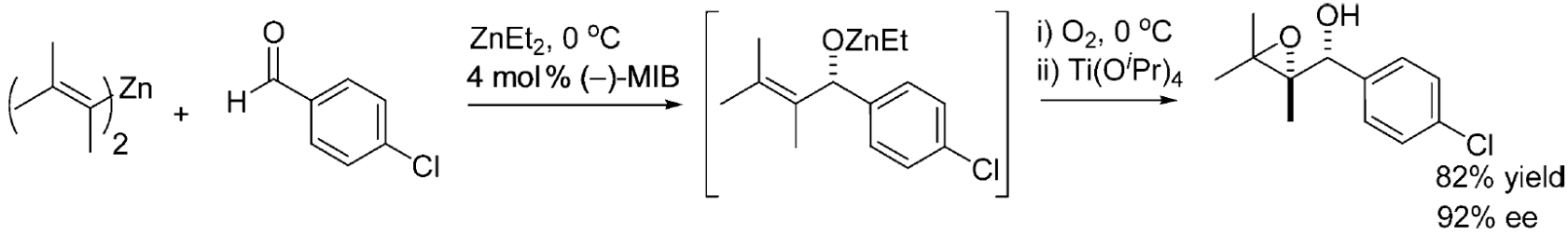
Diastereoselectivity of Epoxidation





Kelly, A. R.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2005** *ASAP*

Determination of Predominant Steric Interaction in Epoxidation



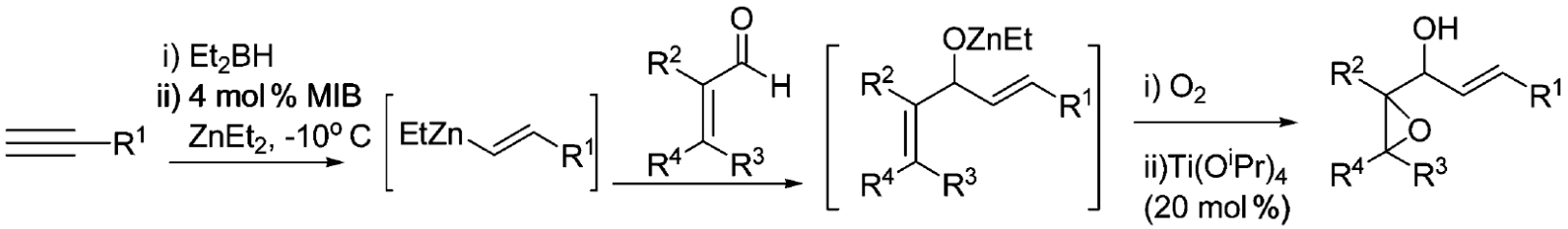
Diastereomeric Ratios (*erythro* : *threo*)[a]

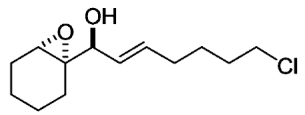
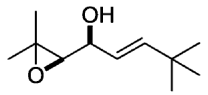
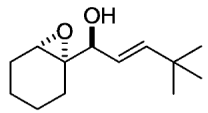
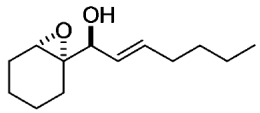
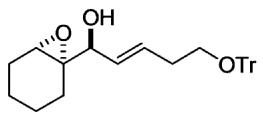
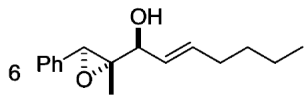
One-Pot Method	$Ti(O^iPr)_4$ TBHP	$VO(acac)_2$ TBHP	*m*CBPA
1 : 3	1 : 5[b]	2 : 1[b]	1 : 10[b]

[a]dr determined by ^1H NMR analysis.
[b]epoxidaton performed on isolated allylic alcohol.

Kelly, A. R.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2005** *ASAP*

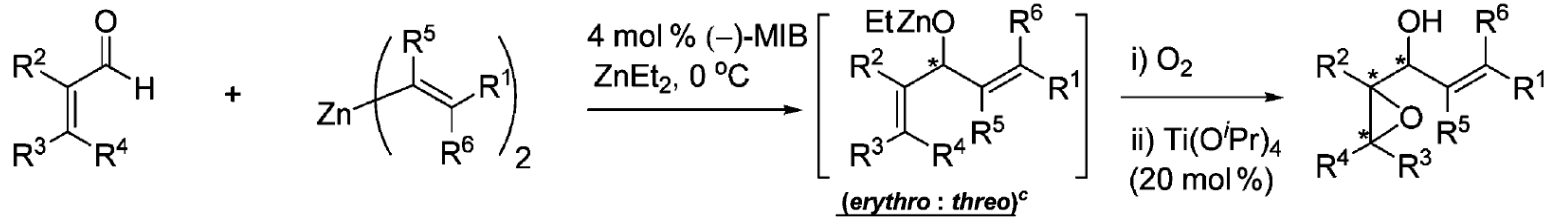
Allylic Epoxy Alcohol Synthesis - in Situ Vinylzinc Reagents



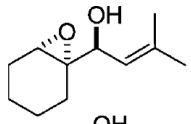
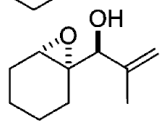
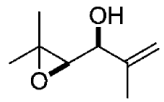
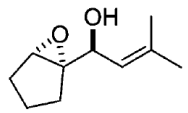
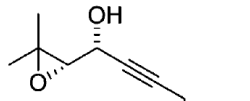
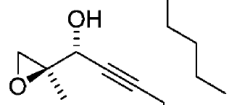
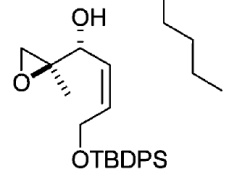
entry	allylic epoxy alcohol	% ee(% y)	(erythro : threo)[c] [dr]
1		99[a](78)	[20 : 1]
2		98[a](76)	[1 : 20]
3		97[a](87)	[20 : 1]
4		99[a](78)	[20 : 1]
5		92[b](60)	[20 : 1]
6		90[b] (80)	[20 : 1]

Kelly, A. R.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2005** *ASAP*
Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 10677

Allylic Epoxy Alcohol Synthesis - Isolated Divinylzinc Reagents



(*erythro* : *threo*)[c]

entry	allylic epoxy alcohol	% ee (% y)	[dr]
1		96[a] (61)	[20 : 1]
2		95[a] (90)	[20 : 1]
3		91[a] (91)	[1 : 20]
4		96[a] (76)	[20 : 1]
5		87[a] (92)	[1 : 5]
6		86[a] (90)	[4 : 1]
7		95[b] (80)	[20 : 1]

Kelly, A. R.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2005** *ASAP*

Conclusion

• Convenient one-pot method for the synthesis of epoxy alcohols and allylic epoxy alcohols, involving an initial asymmetric C-C bond formation followed by diastereoselective epoxidation in high yields and stereoselectivities.

• Circumvents the need to prepare and isolate allylic or bis(allylic) alcohol intermediates, and offers a choice of both stoichiometric oxidant and ligand environment to be used.

Kelly, A. R.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2005** *ASAP*