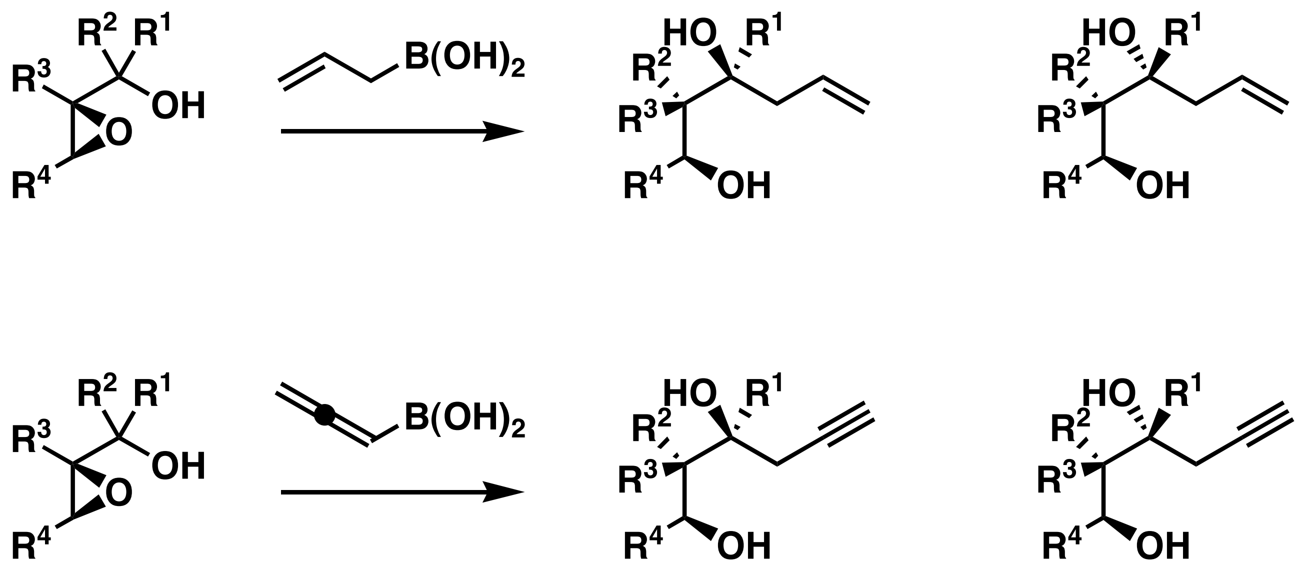
A Tandem Semipinacol Rearrangement/Alkylation of [illegible]-Epoxy Alcohols: An Efficient and Stereoselective Approach to Multifunctional 1,3-Diols



Hu, X.-D.; Fan, C.-A.; Zhang, F.-M.; Tu, Y. Q. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1702

Presentation Outline

▷ **Semipinacol rearrangement of [illegible]-epoxy silyl ethers**

▷ **Semipinacol rearrangement of [illegible]-epoxy alcohols**

- **Lewis acids used**
- **Migrating groups**
- **Substrates scope**

▷ **Halonium ion induced semipinacol rearrangement**

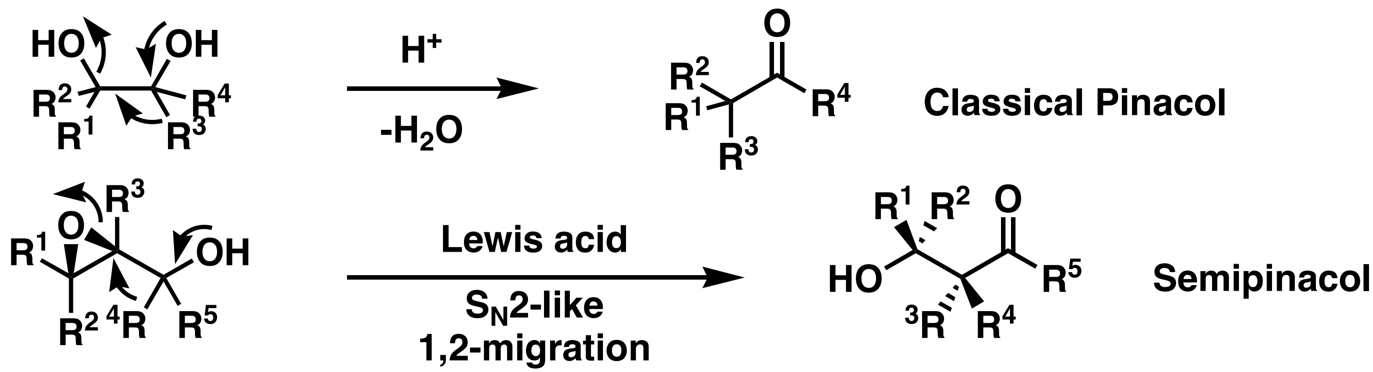
▷ **Reductive rearrangement of [illegible]-epoxy alcohols (tandem semipinacol/MVP reduction)**

▷ **Tandem semipinacol rearrangement/Tishchenko reduction of [illegible]-epoxy alcohols**

▷ **Tandem semipinacol rearrangement/alkylation of [illegible]-epoxy alcohols**

- **Allylation with allyl boronic acid**
- **Reaction with allenyl boronic acid**
- **Proposed transition states**

Semipinacol Rearrangement of [redacted]-Epoxy Alcohols



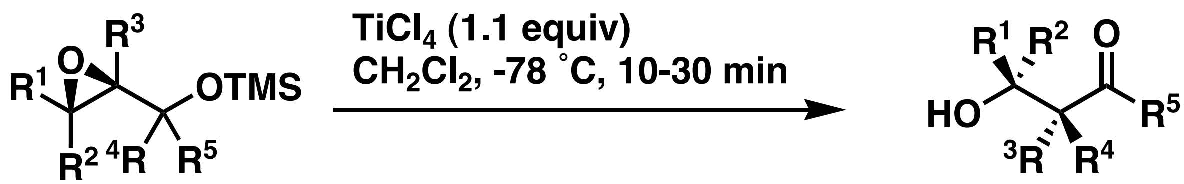
- ▷ **Aldol-type products are obtained, some of which are difficult or impossible to obtain according to the classical aldol reaction**

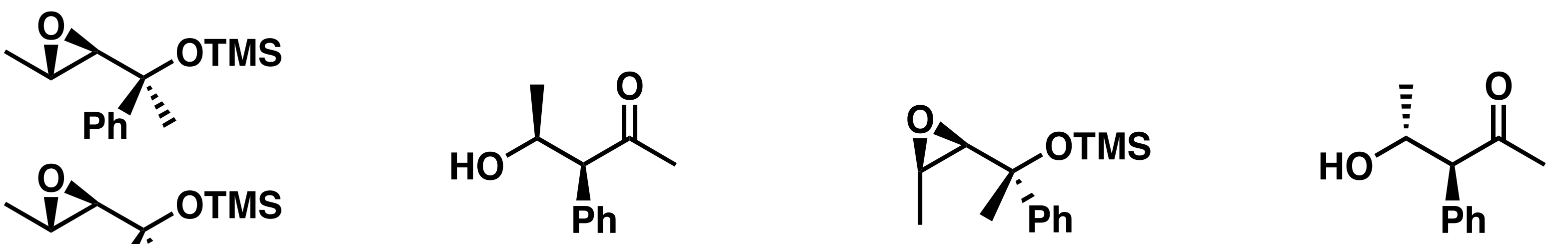
- ▷ **Highly stereoselective, the migrating group attacking *anti* to the epoxide**

- ▷ **The stereochemistry of the hydroxy-bearing carbon center is not important, since both diastereoisomers afford the same product**

- ▷ **Although originally developed for [redacted]-epoxy silyl ethers, work has mostly been focused on the free [redacted]-epoxy alcohols**

Semipinacol Rearrangement of ■-Epoxy Alcohols
First Report





95% and 79%

81%

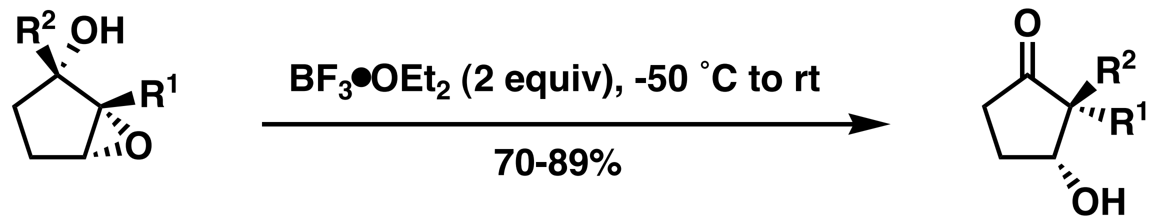
79%

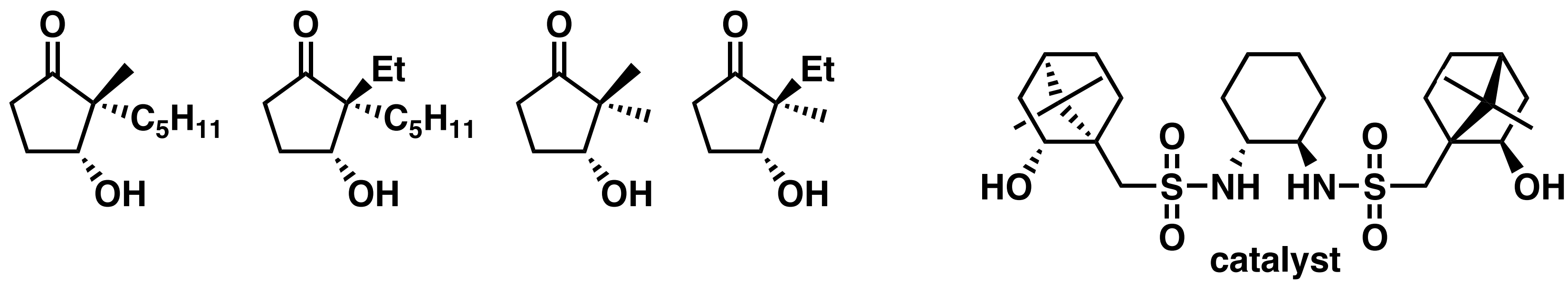
89%

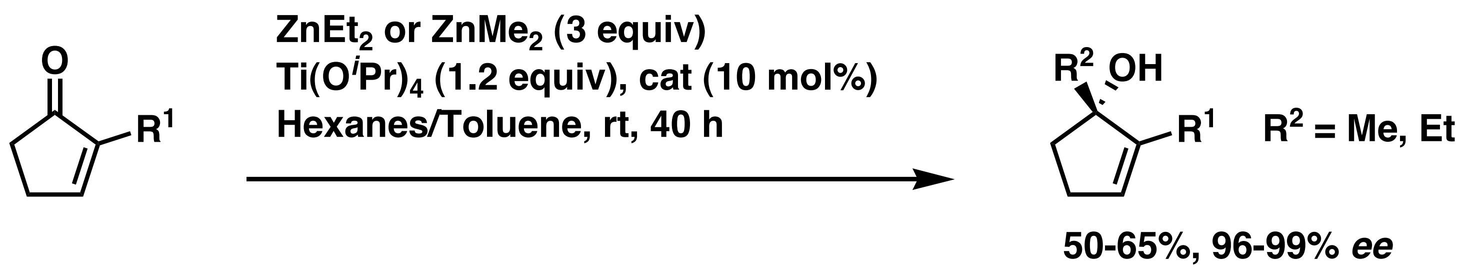
▷ $BF_3 \bullet OEt_2$ can be used for the free alcohols

Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G.-I.
J. Am. Chem. Soc. **1986**, *108*, 3827
Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G.-I. *Tetrahedron Lett.* **1987**, *28*, 5891

BF_3•OEt_2 Promoted Semipinacol Rearrangement of α-Epoxy Alcohols



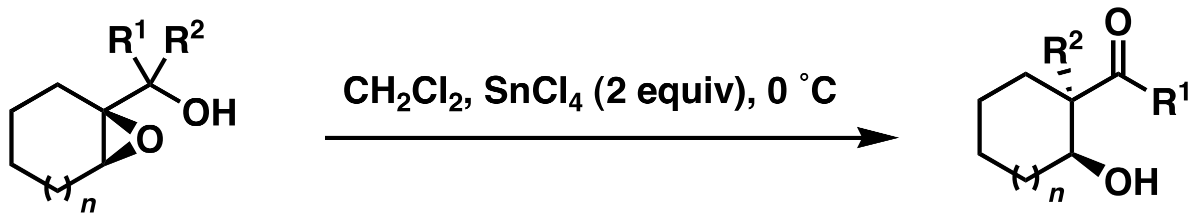




▷ **Diastereoselective epoxydation performed with *m*-CPBA or O_2**

Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9545

Semipinacol Rearrangement of [redacted]-Epoxy Alcohols: Use of $SnCl_4$ and Reaction Scope



For R^1 = Me and n = 1

Migrating group (R^2)

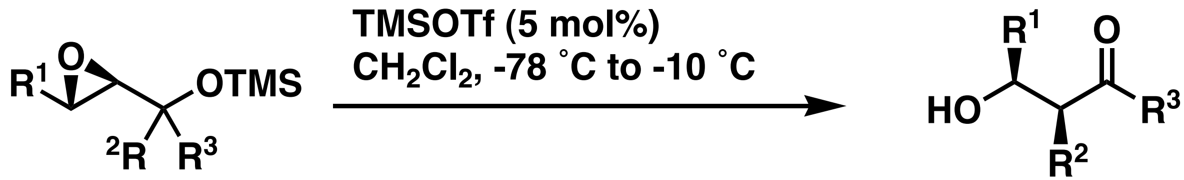
Me, 56%
Vinyl, 95%
Ph, 99%
***t*-Bu, 75%**
2-Furyl, 75%
***c*-C_3H_5, 88%**
[redacted]C[redacted]CPh, 58%
[redacted]CH_2CH_2Ph, 78%

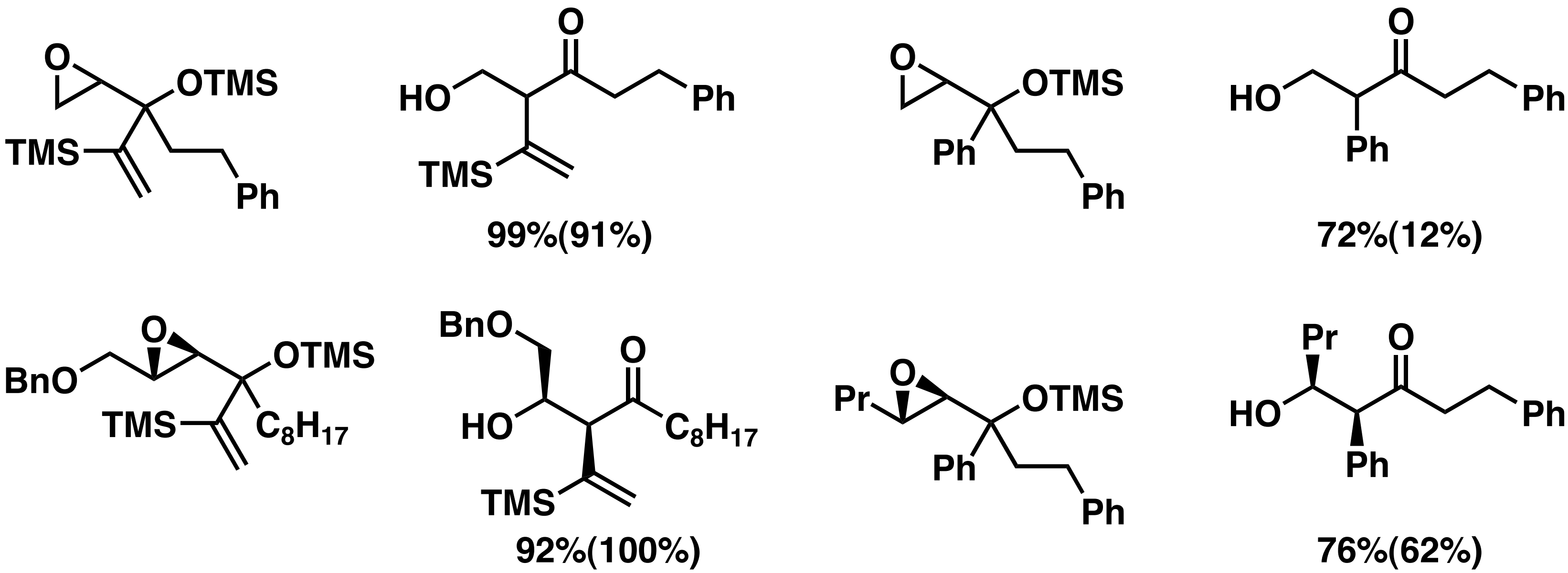
Relative order of migrating ability

Ph, vinyl >> alkynyl, cyclopropyl, *t*-Bu, alkyl > Me > H

Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944

TMSOTf Catalyzed Semipinacol Rearrangement of [illegible]-Epoxy Silyl Ethers



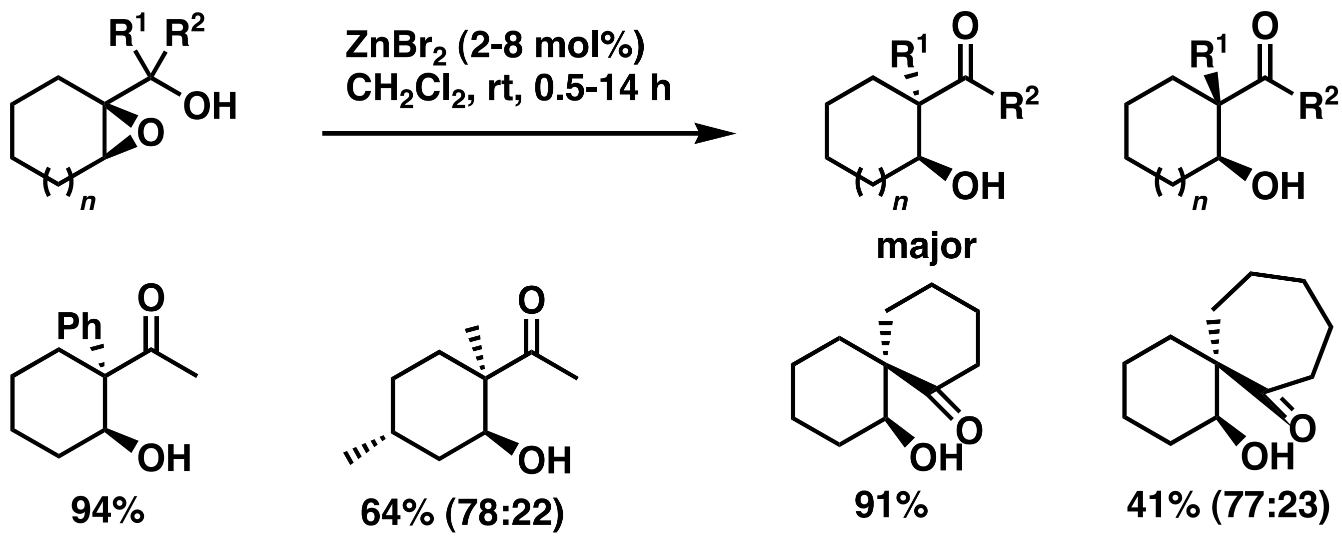


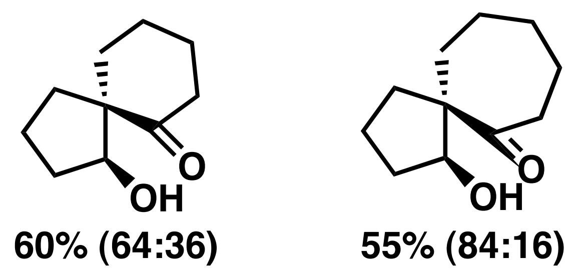
▷ **TMSI works also (yields in parenthesis), but is less effective for terminal epoxydes because of competitive ring-opening**

▷ **TMSBr can be used (1 example, 93%), but not TMSCl (17%)**

Suzuki, K.; Miyazawa, M.; Tsuchihashi, G.-I. *Tetrahedron Lett.* **1987**, *28*, 3515

$ZnBr_2$ Catalyzed Semipinacol Rearrangement of ■-Epoxy Alcohols

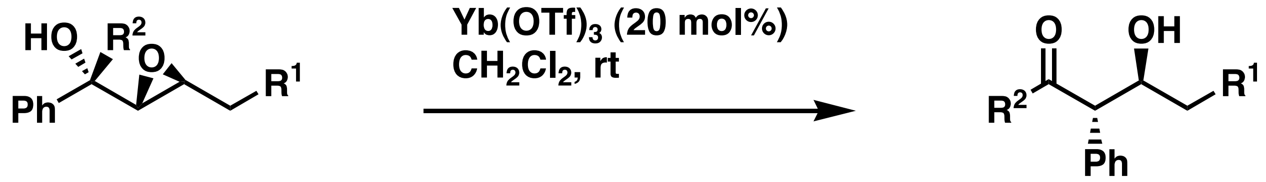


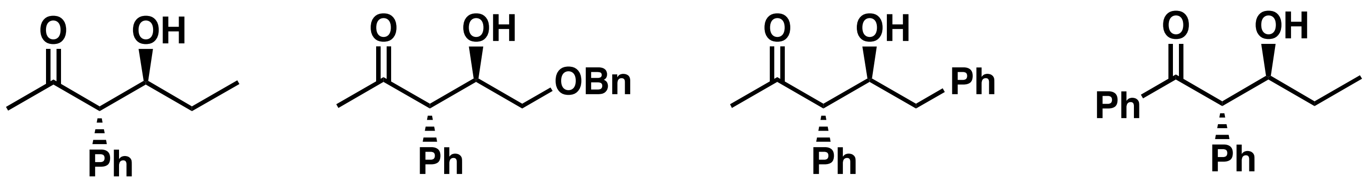


- ▷ $ZnCl_2$ works, but $AlCl_3$ too reactive
- ▷ Formation of *syn*-isomer probably arises from migration onto the carbocation

Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3791

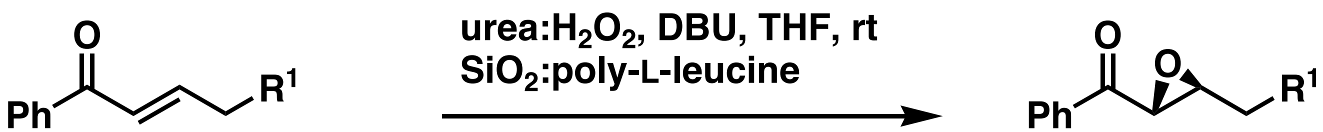
Lanthanide Catalyzed Semipinacol Rearrangement of [illegible]-Epoxy Alcohols





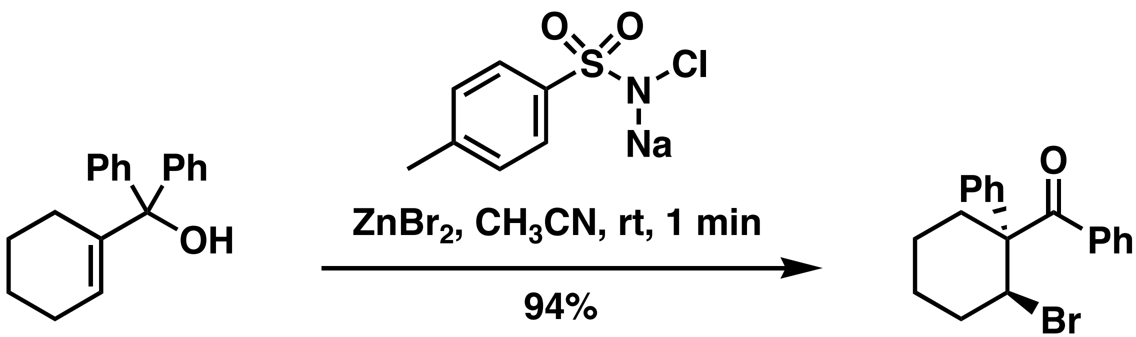
99% | 82% | 100% | 97%

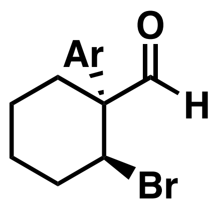
▷ $Sc(OTf)_3$ and $La(OTf)_3$ are also effective, but longer reaction times are needed



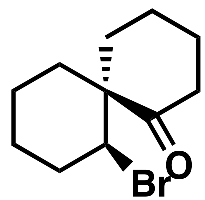
Bickley, J. F.; Hauer, B.; Pena, P. C. A.; Roberts, S. M.; Skidmore, J.
J. Chem. Soc., Perkin Trans 1. **2001**, 1253

Halonium Ion Induced Semipinacol Rearrangement: Synthesis of I-Haloketones

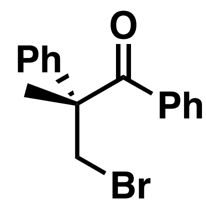




85-87%



75%

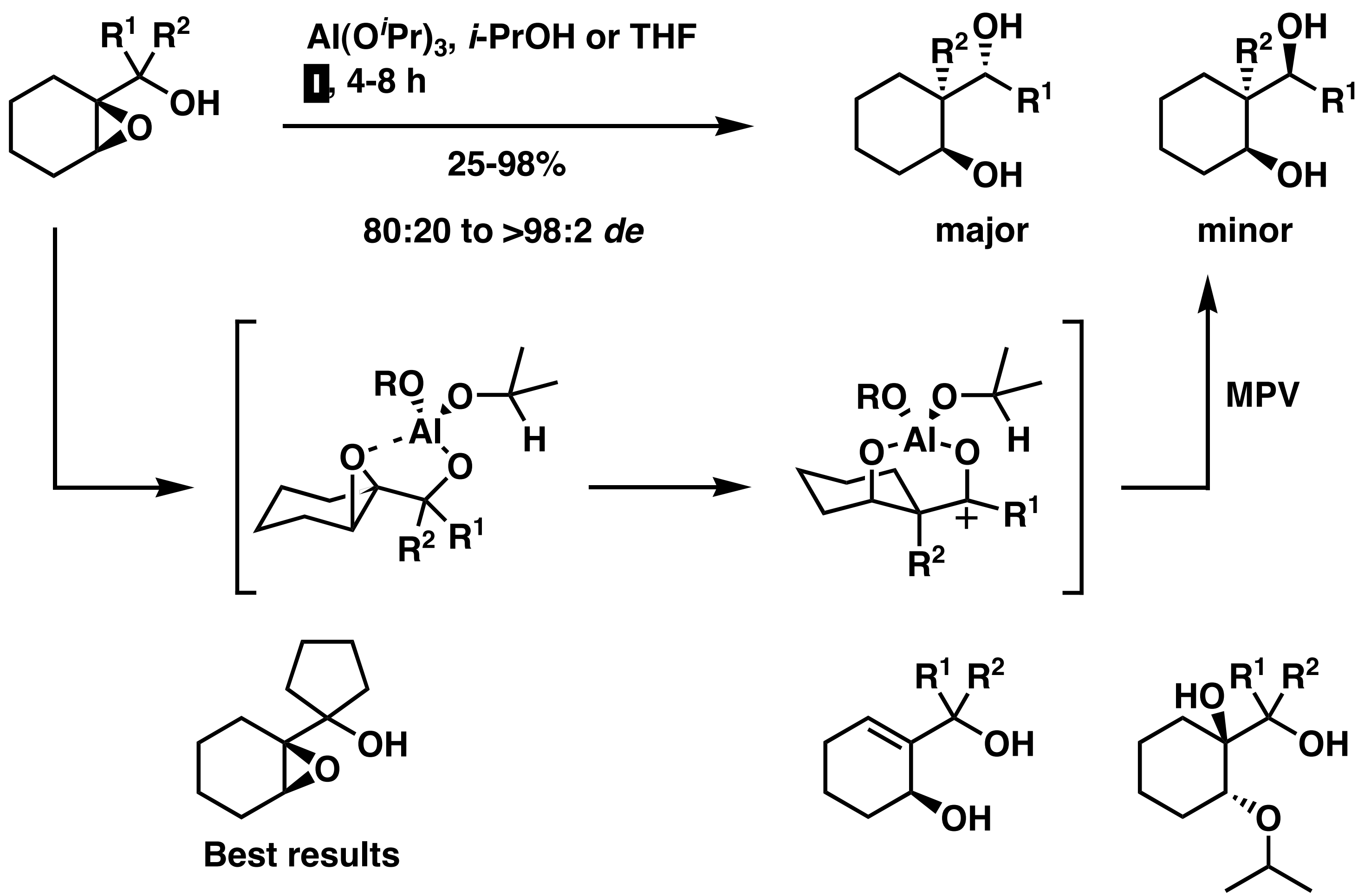


92%

- ▷ **Other solvents: Et_2O, CH_2Cl_2, Acetone**
- ▷ **Work equally well with the cyclopentene alcohols**
- ▷ **$ZnCl_2$ and ZnI_2 can also be used to prepare the chloro and iodo derivatives**

Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Chen, W. M. *Synlett* **2003**, 1497

Reductive Rearrangement of ■-Epoxy Alcohols

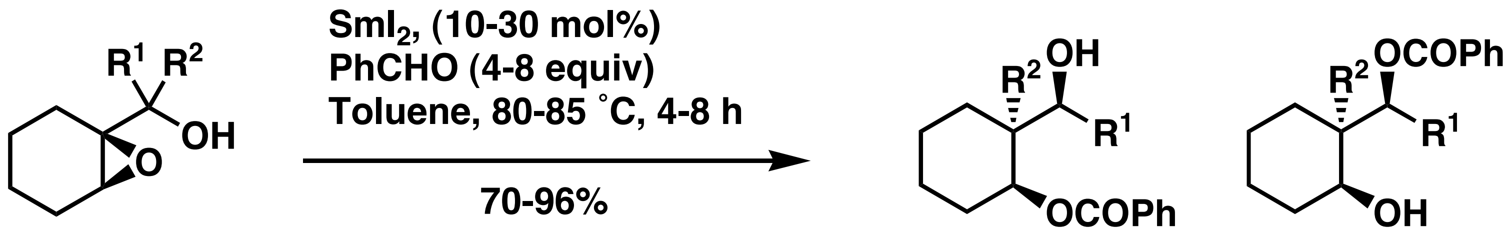


▷ **Works also for cyclopentyl derivatives**

Side-products

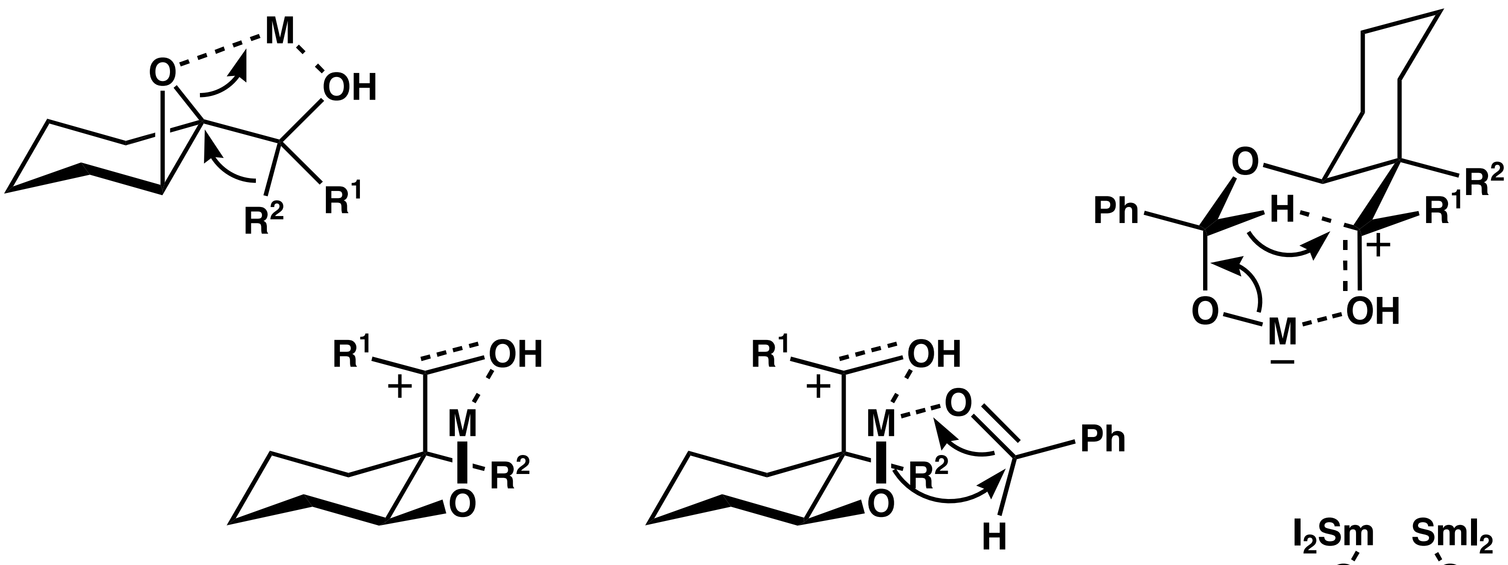
Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem.* **1999**, *64*, 629

SmI_2 Catalyzed Tandem Semipinacol Rearrangement/ Tishchenko Reduction



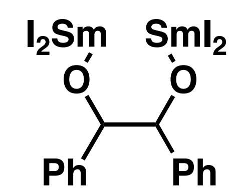
R^2 = Mostly Ph

only isomer



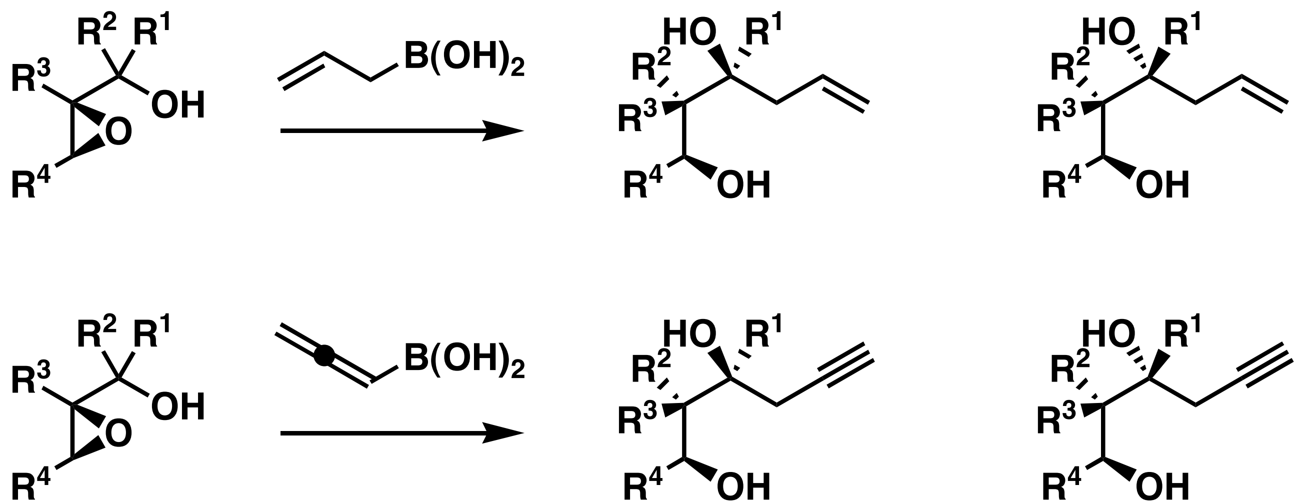
▷ **Opposite relative stereochemistry for the reduction was obtained (compared to reduction with $Al(O^iPr)_3$)**

M =



Fan, C.-A.; Wang, B.-M.; Tu, Y.-Q.; Song, Z.-L. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3877

A Tandem Semipinacol Rearrangement/Alkylation of I-Epoxy Alcohols: An Efficient and Stereoselective Approach to Multifunctional 1,3-Diols

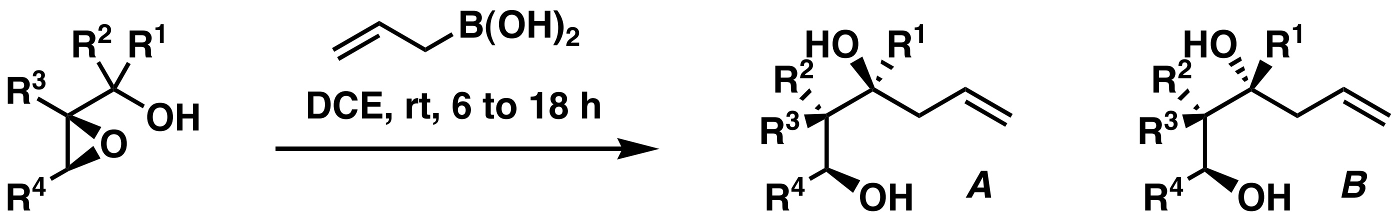


Key feature:

▷ **Boronic acids acts as a Lewis acid in the first step, and as a nucleophile in the second**

Hu, X.-D.; Fan, C.-A.; Zhang, F.-M.; Tu, Y. Q. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1702

Allylation of [illegible]-Epoxy Alcohols with Allylboronic Acid



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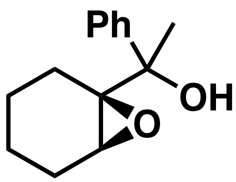
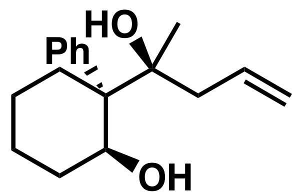
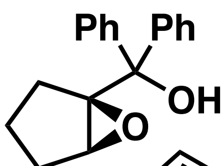
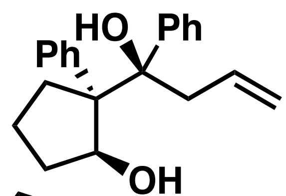
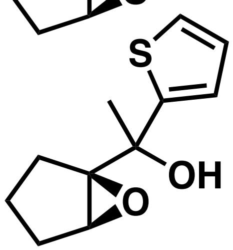
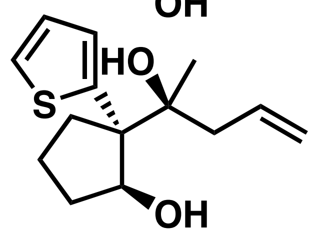
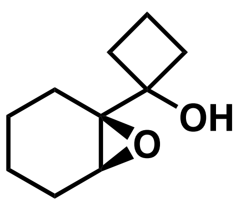
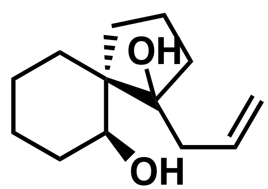
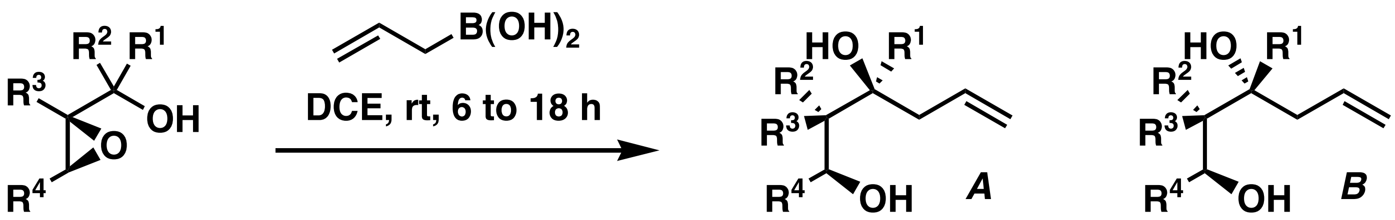
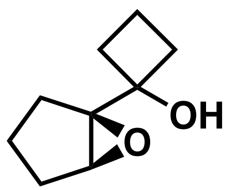
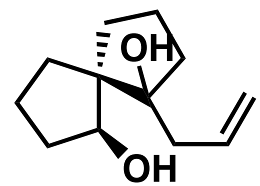
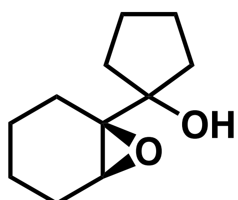
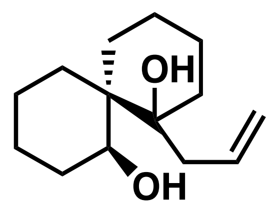
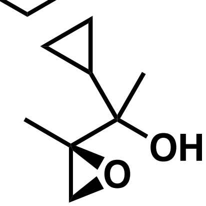
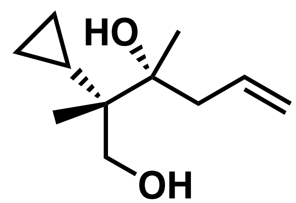
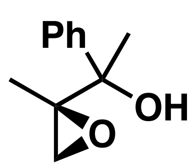
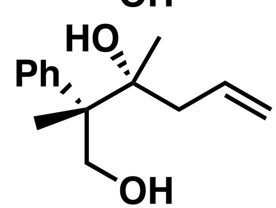
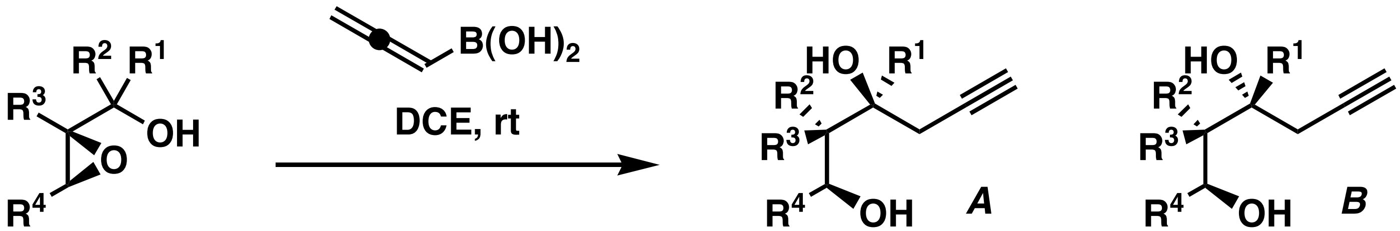
1		70:30		>99:1	75
2				>99:1	81
3		88:12		>99:1	69
4				85:15	80

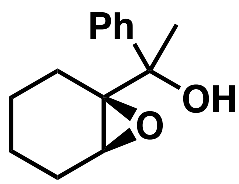
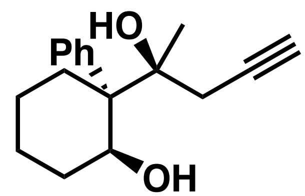
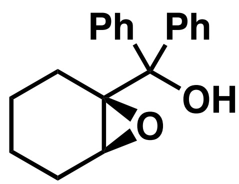
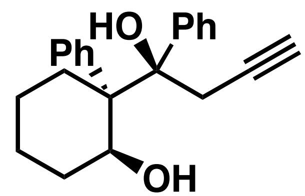
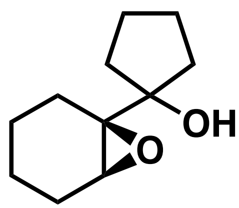
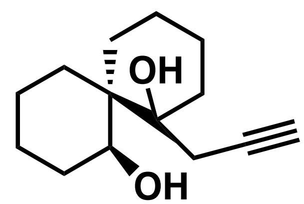
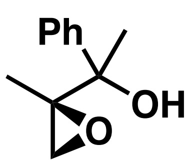
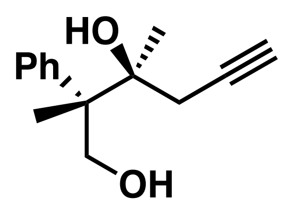
Allylation of α-Epoxy Alcohols with Allylboronic Acid



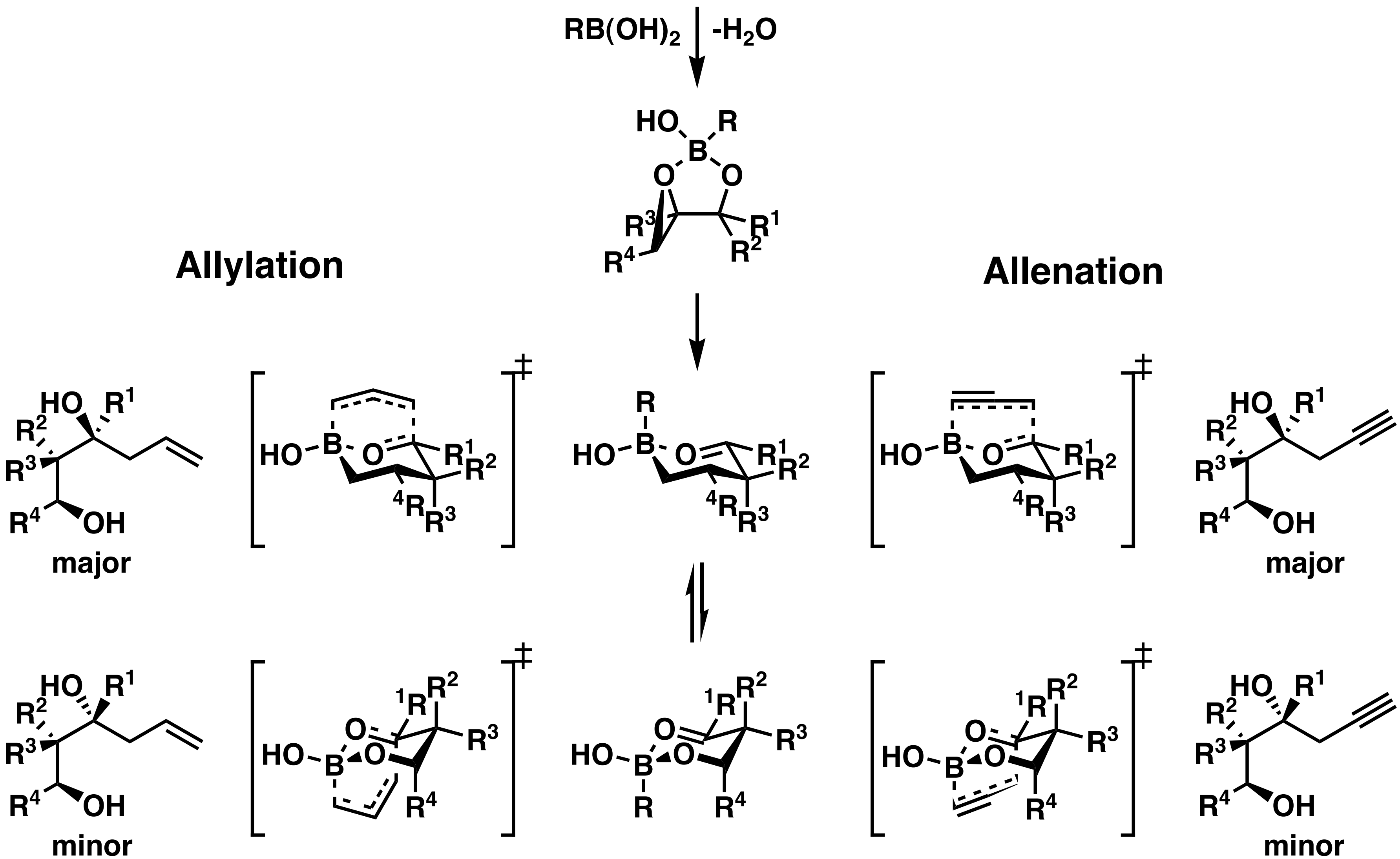
Entry	Substrate	Ratio	Product	A:B	Yield (%)
5				71:29	99
6				99:1	91
7		78:22		31:69	71
8		69:31		1:99	61

Reaction of ■-Epoxy Alcohols with Allenylboronic Acid



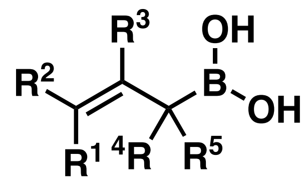
Entry	Substrate	Ratio	Time (h)	Product	A:B	Yield (%)
1		70:30	70		>99:1	55
2			78		>99:1	40
3			65		>99:1	74
4		69:31	96		50:50	48

Proposed Transition States for the Tandem Semipinacol Rearrangement/Alkylation of [illegible]-Epoxy Alcohols

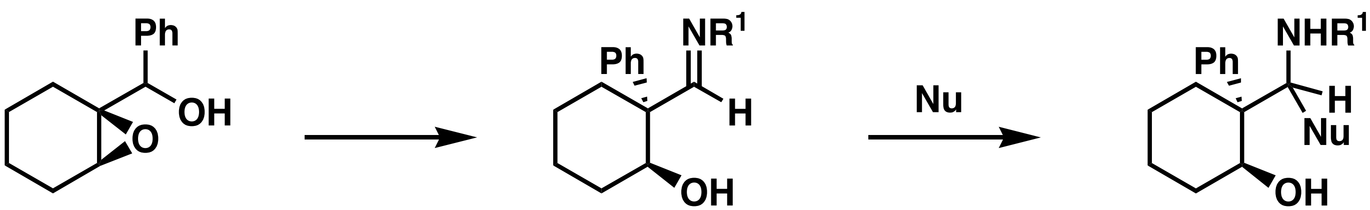


Tandem Semipinacol Rearrangement/Alkylation of ■-Epoxy Alcohols: Other Applications?

▷ **Extend to other allyl boronic acids**



▷ **Preparation of 1,3-amino alcohols**



▷ **Extend to oxetane alcohols**