J|A|C|S
COMMUNICATIONS

Published on Web 10/05/2004

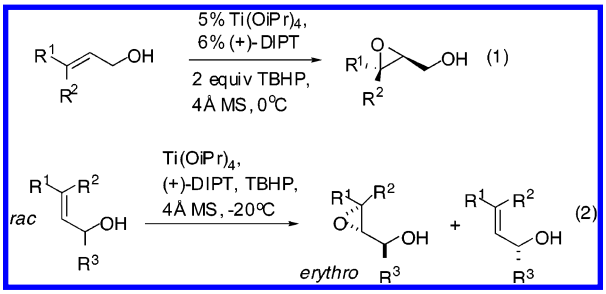
Highly Enantio- and Diastereoselective One-Pot Synthesis of Acyclic Epoxy Alcohols with Three Contiguous Stereocenters

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

P. Roy and Diana T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

Received June 2, 2004; E-mail: pwalsh@sas.upenn.edu

Two of the most significant developments in the history of asymmetric catalysis were the introduction of the Sharpless asymmetric epoxidation of prochiral allylic alcohols[1−3] and the application of this reaction to the kinetic resolution of racemic allylic alcohols (eqs 1 and 2).[4] The products of these processes, enantio-enriched epoxy alcohols, are among the most valuable and versatile intermediates in organic synthesis,[5] because they readily undergo regioselective ring-opening reactions.[6] As a result, the Sharpless asymmetric epoxidation has found extensive utility in the synthesis of natural products.[3]

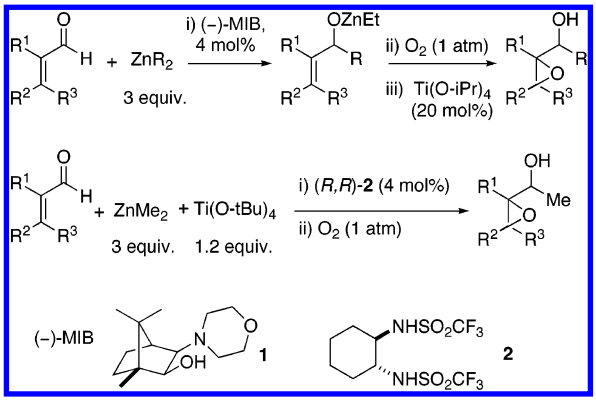


Despite the enduring success of the Sharpless kinetic resolution, there remain significant limitations. If the desired product is the epoxy alcohol, the kinetic resolution must be quenched at low conversion to ensure product of high ee.[6] Alternatively, the resolved allylic alcohol is often isolated and epoxidized in a separate step. Of course, an inherent problem with kinetic resolutions is that the maximum yield is 50%.

In this communication, we disclose a method to address these limitations. We have developed a highly enantio- and diastereoselective method to synthesize acyclic epoxy alcohols with three contiguous stereocenters in good to excellent yields. This protocol entails an enantioselective C−C bond-forming reaction to generate allylic alkoxides that are subsequently epoxidized diastereoselectively via a directed epoxidation using dioxygen.[7] In this process, three new bonds are formed, allowing efficient assembly of complex chiral building blocks.

Our first route is based on the highly enantioselective alkyl addition to α,β-unsaturated aldehydes promoted by a catalyst generated from Nugent's (−)-MIB[8] (**1**, Scheme 1). The ee's of the allylic alcohols formed on quenching the reaction with aqueous NH_4Cl are recorded in Table 1. In the tandem addition/epoxidation procedure, the newly formed allylic alkoxide is exposed to 1 atm of dioxygen at 0 °C (30 min). It is then cooled to −20 °C, and titanium tetraisopropoxide (20 mol %) is added. Epoxidation is complete in 18 h at this temperature. We believe the oxidant is formed upon insertion of dioxygen into a Zn−C bond to generate the peroxy species R−Zn−OOR. Subsequent transmetalation to the titanium allylic alkoxide intermediate is followed by directed epoxidation. After workup, the dr's were determined by ^{1}H NMR

Scheme 1. Tandem Asymmetric Addition/Diastereoselective Epoxidations

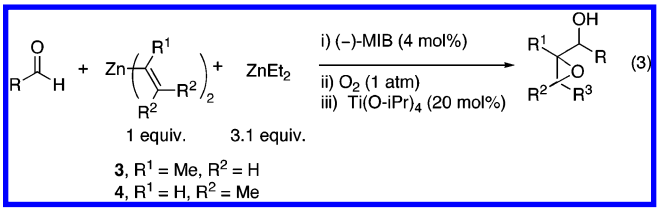


of the crude products and are shown in Table 1, along with the combined yields of both diastereomers after chromatography.

The rate of addition of dimethylzinc to aldehydes with MIB and related amino alcohol-based catalysts is slow at room temperature.[9] We therefore employed bis(sulfonamide) ligand **2**[10,11] in the methyl addition reactions at room temperature (Scheme 1, Table 1)[10] followed by exposure to dioxygen.[11]

The levels of enantioselectivity in the asymmetric addition of a variety of alkyl groups were very high (85−99%, Table 1). Moderate to excellent dr's were found and, in most cases, were better than those we observed on epoxidation of the isolated allylic alcohols with $Ti(O\text{-}iPr)_4$/TBHP, $VO(acac)_2$/TBHP or *m*-CPBA. Allylic alkoxide intermediates possessing $A^{1,2}$-strain in one of the diastereomeric transition states afford mainly the *erythro* products (entries 1−4 and 7−9), while those with $A^{1,3}$-strain primarily furnish the *threo* diastereomers (entries 5, 6, and 10−12).[12] The stereochemistry of the product in entry 5 was confirmed by X-ray crystallography (Supporting Information).

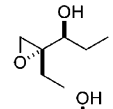
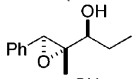
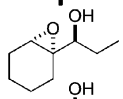
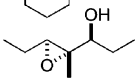
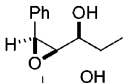
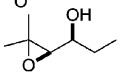
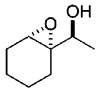
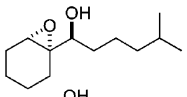
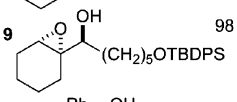
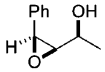
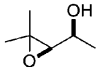
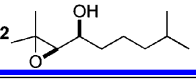
The second route to epoxy alcohols entailed the addition of divinylzinc reagents **3** and **4** to aliphatic and aromatic aldehydes, as illustrated in eq 3. The divinylzinc reagents are easily prepared



and purified by sublimation.[13] To conserve the divinylzinc reagents, 3.1 equiv of diethylzinc was added before the aldehyde. This likely results in formation of ethyl vinyl zinc species, in which the more reactive vinyl group is preferentially transferred. As displayed in Table 2 (entries 1−5), the enantio- and diastereoselectivities with

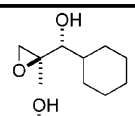
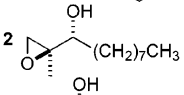
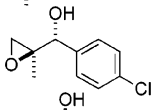
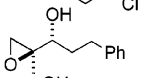
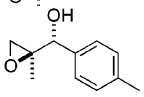
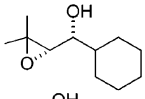
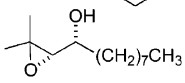
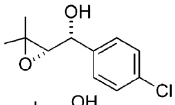
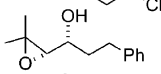
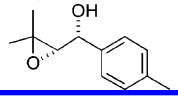
10.1021/ja046750g CCC: $27.50

Table 1. Synthesis of Epoxy Alcohols from Enals

entry	epoxy alcohol[a]	one-pot method % ee[b] (% y)	one-pot method [dr]	Diastereomeric Ratios (*erythro* : *threo*)[c] Ti(OiPr)$_4$ *t*-BuOOH	VO(acac)$_2$ *t*-BuOOH	*m*CPBA
1		93 (60)	[17 : 1]	8 : 1	20 : 1	1.1 : 1
2		96 (65)	[18 : 1]	8 : 1	20 : 1	1 : 1.1
3		99 (90)	[20 : 1]	6 : 1	18 : 1	1.6 : 1
4		95 (81)	[5.5 : 1]	3.1 : 1	9 : 1	1 : 1.1
5		91 (96)	[1 : 10]	1 : 7	1 : 3	1 : 8
6		95 (96)	[1 : 20]	1 : 6	1 : 2	1 : 20
7		99 (78)	[20 : 1]			
8		97 (62)	[15 :1]			
9		98 (86)	[20 : 1]			
10		85 (89)	[1: 10]			
11		96 (60)	[1 : 18]			
12		96 (81)	[1 : 20]			

[a] Stereochemistry indicated corresponds to that of the major diastereomer. [b] Determined by chiral HPLC or GC analysis. [c] Determined by ^{1}H NMR analysis.

Table 2. Synthesis of Epoxy Alcohols from Divinylzinc Reagents

entry	epoxy alcohol[a]	one-pot method % ee[b] (% y)	one-pot method [dr]	Diastereomeric Ratios (*erythro* : *threo*)[c] VO(acac)$_2$ *t*-BuOOH	*m*CPBA
1		92 (87)	[17 : 1]	18 : 1	1 : 1.1
2		87 (80)	[18 : 1]	18 : 1	1.1 : 1
3		97 (80)	[18 : 1]	17 : 1	1 : 1.1
4		90 (85)	[14 : 1]		
5		96 (82)	[16 : 1]		
6		90 (75)	[19:1]	1 : 4	1 : 17
7		85 (78)	[1:17]	1 : 4	1 : 16
8		96 (84)	[1 : 18]	1 : 3	1 : 17
9		81 (77)	[1 : 20]		
10		95 (81)	[1 : 19]		

[a] Stereochemistry indicated corresponds to that of the major diastereomer. [b] Determined by chiral HPLC or GC analysis. [c] Determined by ^{1}H NMR analysis.

divinylzinc reagent **3** are excellent, and the yields are high. Likewise, reaction of the 2,2′-dimethyl divinylzinc reagent **4** resulted in very high enantio- and diastereoselectivities, except with unbranched aldehydes, where the enantioselectivities were around 80%.

In summary, two expedient routes for the synthesis of acyclic epoxy alcohols containing up to three stereogenic centers have been presented. They involve initial asymmetric C−C bond formation followed by diastereoselective epoxidation. The advantages of these methods are (1) that they circumvent the need to prepare and isolate either racemic or enantioenriched allylic alcohols, (2) the oxidant is generated under the reaction conditions from organozinc reagents and dioxygen, (3) the enantio- and diastereoselectivities are very high for almost all classes of substrates, and (4) the asymmetric C−C bond-forming step can be catalyzed by literally hundreds of catalysts.[14] Like the epoxy alcohols prepared by the Sharpless asymmetric epoxidation, we anticipate that the epoxy alcohols outlined here will find widespread utility in enantioselective synthesis.

Acknowledgment. This work was supported by the NIH (GM58101) and the NSF (CHE-0315913). We are also grateful to Azko Nobel for the gift of alkyl zinc reagents. This work is dedicated to Prof. Lars Hellberg (SDSU and Instituto Tecnológico de Tijuana) on the occasion of his 75th birthday.

Supporting Information Available: A cif file containg crystallographic data for the product in entry 5 of Table 1, text giving procedures and full characterization of new compounds and conditions for determining the enantiomeric excess for the compounds, and figures giving ^{1}H and ^{13}C{^{1}H} NMR spectra for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5776.
(2) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.
(3) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 621−648.
(4) Martín, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240.
(5) Bonini, C.; Righib, G. *Tetrahedron* **2002**, *58*, 4981−5021.
(6) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martín, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589−604.
(7) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544−9545.
(8) Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369−1370.
(9) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036.
(10) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691−5700.
(11) Nowotny, S.; Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 4539−4540.
(12) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703−710.
(13) Shibata, T.; Nakatsui, K.; Soai, K. *Inorg. Chim. Acta* **1999**, *296*, 33−36.
(14) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

JA046750G