5056 *J. Org. Chem.* **1992**, *57*, 5056–5057

Chiral α,β-Epoxy Group as a Stereocontrolling Element in the Reduction of *N*-Metalloimines. A Short Synthesis of *anti*-Epoxy Amines

Hirokazu Urabe, Yoshiaki Aoyama, and Fumie Sato*

Department of Biomolecular Engineering, Tokyo Institute of Technology, Ookayama, Meguro, Tokyo 152, Japan

Received June 16, 1992

Summary: Reduction of the α,β-epoxy *N*-metalloimines generated from the TBS ether of (2*S*,3*S*)-3-cyano-2,3-epoxy-1-propanol (**1**), Grignard reagents, and Me_3SiCl with $NaBH_4$ afforded the TBS ethers of (2*S*,3*S*,4*S*)-4-amino-2,3-epoxy-1-alkanols **4** with diastereoselectivities of up to 95:5.

Diastereoselective addition of nucleophiles to unsaturated bonds with proximal substituents is one of the most fundamental strategies for the construction of complex molecules.[1] Although α- and/or β-oxygen substituents are the most typical[2] examples among a variety of functional groups playing such a role, the α,β-epoxy group has attracted little attention, perhaps because doubts remain concerning its efficiency at chiral induction,[3,4] and the additional complication that epoxide itself is susceptible to nucleophilic addition, which could lead to problems of chemoselectivity. Ever since the Sharpless asymmetric epoxidation made epoxides readily accessible in optically active forms,[5] the utility of this functionality as a stereocontrolling element, rather than solely as the precursor for a ring opening reaction has become increasingly highlighted.[6] Along these lines, we disclose herein the first example[7] of an (optically active) α,β-epoxy group-controlled diastereoselective addition of hydride species to *N*-metalloimines.[8,9]

Scheme I

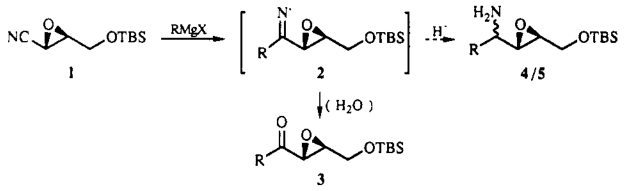
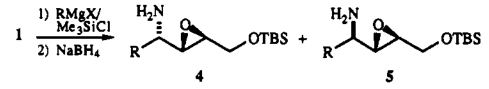
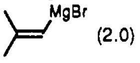
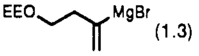


Table I. Preparation of *anti*-Epoxy Amine Derivatives 4[a]



entry	RMgX (equiv)	Me_3SiCl (equiv)	4/5	ratio 4:5[b]	yield (%)[c]
1	BuMgCl (2.4)	4.0	**a**	89:11	67
2	 MgBr (2.0)	3.2	**b**	87:13	82
3	 EEO MgBr (1.3)	2.3	**c**	94:6	75[d]
4	PhMgBr (2.0)	3.0	**d**	95:5	89
5	*p*-$MeOC_6H_4MgBr$ (1.3)	2.3	**e**	95:5	92[d]
6	*o*-$(MOMOCH_2)C_6H_4MgBr$ (2.0)	3.0	**f**	94:6	89

[a] See ref 15 for a general procedure. $NaBH_4$ (2 equiv) was used. [b] Ratio determined by ^1H NMR analysis of a crude product. [c] Combined, isolated yields of **4** and **5**. [d] The starting material **1** with 98% ee afforded the product of 97–98% ee (^1H NMR, MTPA method).

The optically active α,β-epoxy nitrile **1** (98% ee, TBS = $^tBuMe_2Si$) readily available by a catalytic version of the Sharpless epoxidation[10] reacted with Grignard reagents at the nitrile carbon to give the corresponding α,β-epoxy ketones **3** after aqueous workup (Scheme I),[11] demonstrating the intermediary formation of the α,β-epoxy *N*-metalloimine **2**. An in situ reaction of **2** with the second nucleophile, represented by a hydride species, to afford epoxy amine **4**/**5** (hopefully in a diastereoselective manner) is of particular interest in view of the utility of epoxides for the stated purpose.[12] However, as nucleophilic additions to *N*-metalloimines obviously require much more forcing conditions than those to ketones, the ability of the epoxide moiety of **2** to survive the reaction conditions is critical.

The hydride reduction of the *N*-metalloimine generated from **1** and PhMgBr was studied. When the reaction was attempted with a few typical hydrides such as $Zn(BH_4)_2$, Bu_4NBH_4, or $NaBH_4$ in the absence of any additive, the product yields (as well as the diastereoselectivities) were disappointingly low. However, *the addition of* Me_3SiCl

---

(1) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2A, p 125.

(2) Review: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1983**, *13*, 1. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3B, p 111. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. Schinzer, D., Ed. *Selectivities in Lewis Acid Promoted Reactions*; Kluwer Academic Publishers: Dordrecht, 1989.

(3) (a) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *Chem. Lett.* **1990**, 791. (b) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4729. (c) Sugiyama, T.; Yamashita, K. *Agric. Biol. Chem.* **1980**, *44*, 1983. (d) Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549.

(4) This partially derives from a consideration on the conformational and electric state of the epoxide oxygen.

(5) Review: Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 247. Jonson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon, Press: Oxford, 1991; Vol. 7, Chapter 3–2. Pfenninger, A. *Synthesis* **1986**, 89.

(6) Recently several papers dealing with highly diastereoselective additions of nucleophiles to α,β-epoxy carbonyl compounds have appeared. Hydride: (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, *22*, 4723. Organometallics: (b) Urabe, H.; Matsuka, T.; Sato, F. *Tetrahedron Lett.*, in press. (c) Escudier, J.-M.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1992**, *33*, 1439. (d) Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1638. (e) Okamoto, S.; Tsujiyama, H.; Yoshino, T.; Sato, F. *Tetrahedron Lett.* **1991**, *32*, 5789. (f) Escudier, J.-M.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1991**, *32*, 5345. (g) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (h) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781. (i) Howe, G. P.; Wang, S.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2629. (j) Iio, H.; Mizobuchi, T.; Tokoroyama, T. *Tetrahedron Lett.* **1987**, *28*, 2379. (k) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 576. (l) See ref 3b. (m) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

(7) Portions of this work were presented orally at the 61st annual meeting of CSJ (the Chemical Society of Japan), Yokohama, March 29–April 1, 1991, and at the 62nd annual meeting of CSJ, Sapporo, September 22–25, 1991. During the course of the study, we were made aware of a reduction of α,β-epoxy imine (ref 8).

(8) $NaBH_3CN$ reduction of an α,β-epoxy imine was mentioned in the total synthesis of the Abbott pseudodipeptidyl insert: Wood, J. L.; Jones, D. R.; Hirschmann, R.; Smith, A. B., III. *Tetrahedron Lett.* **1990**, *31*, 6329.

(9) Cycloaddition of α,β-epoxy imine with ketene: Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065. Frazier, J. W.; Staszak, M. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, *33*, 857.

(10) Yamakawa, I.; Urabe, H.; Kobayashi, Y.; Sato, F. *Tetrahedron, Lett.* **1991**, *32*, 2045.

(11) Aoyama, Y.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1991**, *32*, 6731.

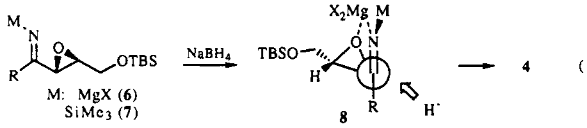
(12) For diastereoselective addition of nucleophiles to α-oxy *N*-metalloimines, see the following. (a) Review: Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, *62*, 605. (b) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045. (c) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; van der Gen, A. *Tetrahedron* **1990**, *46*, 1653. (d) Cainelli, G.; Mezzina, E.; Panunzio, M. *Tetrahedron Lett.* **1990**, *31*, 3481. (e) Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G. *J. Am. Chem. Soc.* **1988**, *110*, 6879. (f) Krepski, L. R.; Jensen, K. M.; Heilmann, S. M.; Rasmussen, J. K. *Synthesis* **1986**, 301.

0022-3263/92/1957-5056$03.00/0

prior to the reduction step remarkably improved the product yields. More surprisingly, in the case of $NaBH_4$ reduction, the presence of Me_3SiCl also catapulted the diastereoselectivity from 2:1 to 19:1 (in an 89% yield) which was far and away the best result obtained![13]

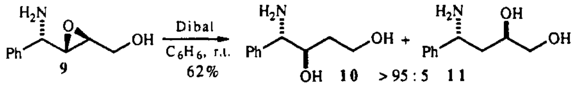
The present reaction was found to be general with respect to Grignard reagents, giving the *anti*-epoxy amines[14] which are summarized in Table I.[15] Alkyl- (entry 1), alkenyl- (entries 2 and 3), and aryl-Grignard reagents (entries 4–6) with a functional group or a sterically demanding substituent participated equally well in this reaction. The use of a slight excess (1.3 equiv) of the Grignard reagent was satisfactory and even an excess of 2–2.4 equiv of reagent (to insure the complete consumption of the starting material) did not show any unfavorable effects on the product yields. The degree of diastereoselectivity obtained seems to reflect the steric hindrance around the imine moiety (hence, that of the group being introduced by the Grignard reagent). The selectivity increased in the following order: alkenyl with no α-substituent < primary alkyl < alkenyl with an α-substituent ≤ aryl-Grignard reagent. The anti structures **4a** and **4d** assigned to the major isomers were derived from a comparison of their ^1H NMR spectra with those of authentic syn diastereoisomers **5a** and **5d**, independently prepared. All other assignments (**4b,c,e,f**) are based on analogy. The enantiomeric purities of **4c** and **4e** have been verified to be 98 and 97% ee, respectively, by the MTPA method (^1H NMR),[16] indicating that the optical purity of the starting material **1** (98% ee) was completely retained in the products.

Although elucidation of the exact role of Me_3SiCl awaits further investigation, it is reasonable to assume that the species actually reduced would not be the magnesioimine **6**, but most likely the *E*-silylimine **7**[12a] (eq 1, assuming that R is C_nH_{2n+1}), resulting from the addition of Grignard reagent to the CN bond[17] followed by trapping with Me_3SiCl. The latter reacts more smoothly with hydride than the former, thus increasing the product yields and, moreover, the silylimine free from the aggregation which often hinders the reacting species should satisfy the Cram chelate compound **8** (M = Me_3Si)[1,6a] in a straightforward manner to give **4** with higher selectivity. The bulky R group facilitates the formation of the chelate **8** by placing the epoxide chain at a remote site, which is in accord with the observation that an increase in the size of R enhances the selectivity.



(1)

This reaction can be adapted to the preparation of various *anti*-epoxy amines which are otherwise tedious to prepare,[18] by simply changing the Grignard reagents and the substrates,[19] which should not be limited to the particular nitrile **1**. The (2*S*,3*S*,4*S*)-4-amino-2,3-epoxy-1-alkanol derivatives **4** presented herein are versatile intermediates for the synthesis of nitrogen compounds such as alkaloids, amino acids, etc., via regioselective ring opening of their epoxide moieties with an appropriate nucleophile,[20] as precedented by the reactions of diastereomeric (2*S*,3*R*,4*S*)-4-amino-2,3-epoxy-1-alkanols in the synthesis of natural products.[18a,b,d,e] A selective ring opening of the epoxide is illustrated by the reaction of **9** (prepared by desilylation of **4d**) with DIBAL in C_6H_6 at room temperature, affording 1,3-diol **10** (eq 2).[20]



(2)

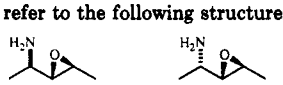
The ability of epoxide to efficiently control the reaction course in a complex system of reagents under the proper choice of reaction conditions, demonstrated herein, illustrates that the prevailing bias against this functionality is not necessarily warranted. In addition, the current work has clearly expanded the utility of this old functionality, which is now available in optically active forms.

Supplementary Material Available: Experimental procedures and characterization data for **1**, **4a–f**, **5a**, and **5d** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

[13] Diastereoselectivities (**4**:**5**) with other hydrides in the presence of Me_3SiCl: $Zn(BH_4)_2$, 5:1; Bu_4NBH_4, 3:1; $LiBH_4$, 2.5:1; $NaAlH_2(OCH_2CH_2OMe)_2$, not determined due to a low yield. $Zn(BH_4)_2$, a standard reagent for the highly diastereoselective reduction of α,β-epoxy *ketones* (ref 6a), was less effective in this case.

[14] Syn and anti refer to the following structures.



[15] The preparation of **4d** is typical: To a mixture of **1** (50 mg, 0.23 mmol) and Me_3SiCl (0.0876 mL, 0.69 mmol) in toluene (2 mL) was added a 1.07 M THF solution of PhMgBr (0.43 mL, 0.46 mmol) at −40 °C. After the mixture had been stirred at −40 °C for 1 h, TLC analysis showed the absence of the starting material **1** and a formation of a new product (phenyl ketone **3**). After cooling to −78 °C, a freshly prepared solution of $NaBH_4$ (17.4 mg, 0.46 mmol) in MeOH (1 mL) was added. After stirring for 30 min at that temperature, the reaction was terminated by the addition of 3 N NaOH (2 mL) and ether (2 mL) at −78 °C. The organic layer was separated and the aqueous layer was extracted with ether. After the combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo*, the residual oil (a 95:5 mixture of **4d** and **5d** by ^1H NMR analysis) was chromatographed on silica gel to afford the title compound (60.4 mg, 89%) again as a 95:5 mixture of **4d** and **5d**.

[16] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

[17] Evidence for the cis addition of Grignard reagent across a CN bond: Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G.; *J. Am. Chem. Soc.* **1986**, *108*, 1311.

[18] For preparation of epoxy amines, see the following. *syn*-Epoxy amine derivatives: (a) Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1992**, *114*, 998. (b) Hori, K.; Ohfune, Y. *J. Org. Chem.* **1988**, *53*, 3886. (c) Ohfune, Y.; Kurosawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587. (d) Kogen, H.; Kadokawa, H.; Kurabayashi, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1240. (e) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311. (f) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P. Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (g) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. (h) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127. (i) Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carrell, H. J. *J. Org. Chem.* **1986**, *51*, 50. *anti*-Epoxy amine derivatives: (j) Reetz, M. T.; Binder, J. *Tetrahedron Lett.* **1989**, *30*, 5425.

[19] Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835. White, D. *J. Chem. Soc., Chem. Commun.* **1975**, 95. Jonczyk, A.; Fedorynski, M.; Makosza, M. *Tetrahedron Lett.* **1972**, 2395. Cantacuzene, J.; Ricard, D. *Bull. Soc. Chim. Fr.* **1967**, 1587.

[20] Ring opening reactions of **4** with a few nucleophiles: Urabe, H.; Aoyama, Y.; Sato, F. *Tetrahedron*, in press.