Boranes in Synthesis. 6. A New Synthesis of β-Amino Alcohols from Epoxides. Use of Lithium Amides and Aminoborane Catalysts To Synthesize β-Amino Alcohols from Terminal and Internal Epoxides in High Yield†

Clifford E. Harris, Gary B. Fisher, David Beardsley, Lawrence Lee, Christian T. Goralski,‡ Lawrence W. Nicholson,‡ and Bakthan Singaram*

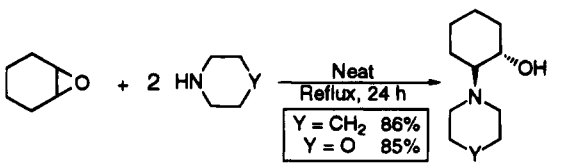
Department of Chemistry and Biochemistry, University of California, Santa Cruz, Santa Cruz, California 95064, and The Dow Chemical Company, Pharmaceuticals Process Research and Analytical Sciences, Core R&D, Midland, Michigan 48674

Received August 1, 1994®

A study of the conversion of terminal and internal epoxides to the corresponding β-amino alcohols using simple primary and secondary lithium amides has been carried out. Thus, styrene oxide and 1,2-epoxydodecane react directly with primary and secondary lithium amides in THF at 25 °C to give a single regioisomer of the corresponding β-amino alcohols in 80–100% isolated yields. Since internal epoxides are known to yield predominantly allylic alcohols when reacted with lithium amides, we employed a series of aminoborane Lewis-acid catalysts, generated *in situ*, to suppress formation of the allylic alcohols. Thus, the reaction of cyclohexene oxide with a variety of primary and secondary lithium amides at 34 °C in diethyl ether in the presence of a catalytic amount of *B*-bromo-9-BBN afforded the corresponding β-amino alcohols in 70–95% isolated yield.

Introduction

The conversion of epoxides to amino alcohols has been known since 1952.[1] Refluxing a neat mixture of the epoxide and the appropriate primary or secondary amine results in fair to excellent yields of the desired amino alcohols (eq 1).



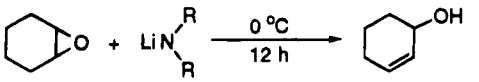
(1)

However, this methodology is limited by highly variable yields, long reaction times, and often drastic reaction conditions.[1] Further, the need to use a large excess of amine in order to achieve a reasonable mass yield of amino alcohol[1] makes this route less desirable if the amine is poorly nucleophilic, highly hindered, or valuable.

During the course of our study of the asymmetric synthesis of β-amino alcohols from the corresponding enamines,[2] we required racemic samples of the chiral β-amino alcohols we had synthesized to use as standards for chiral HPLC determination of enantiomeric excesses.[2d] In searching the literature for various racemic syntheses of β-amino alcohols, we came across a number of references that employed mixtures of lithium amides with various metal reagents to synthesize amino alcohols from epoxides under relatively mild conditions.[3] We were struck by an apparent oversight in all of these references: although comprehensive studies of the reactions of internal epoxides with simple lithium amides were performed over 30 years ago,[4] none of these references reported the reaction of simple primary and secondary lithium amides with terminal epoxides. The reaction of Lewis-acid catalysts with terminal epoxides in the presence of primary and secondary lithium amides has been reported in the literature.[5,6] However, the ratio of amino alcohol regioisomers approached 1:1 in these reactions.[5,6] We therefore began a systematic study of the uncatalyzed and Lewis-acid catalyzed addition of primary and secondary lithium amides to terminal and internal epoxides. The results of this study are reported herein.

Results and Discussion

When we reacted cyclohexene oxide with a variety of lithium amides at 0 °C, we obtained the expected allylic alcohol reported widely in the literature (eq 2).[4] However, when we reacted two terminal epoxides, styrene oxide and 1,2-dodecene oxide, with several lithium



(2)

† Dedicated to the memory of Professor V. Thiagarajan.

‡ The Dow Chemical Co.

® Abstract published in *Advance ACS Abstracts,* November 15, 1994.

(1) Mousseron, M.; Jullien, J.; Jolchine, Y. *Bull. Soc. Chim. Fr.* **1952**, *19*, 757. (b) Freifelder, M.; Stone, G. R. *J. Org. Chem.* **1961**, *26*, 1477. (c) Deyrup, J. A.; Moyer, C. L. *J. Org. Chem.* **1969**, *34*, 175.

(2) (a) Goralski, C. T.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1987**, *52*, 4014. (b) Singaram, B.; Goralski, C. T.; Fisher, G. B. *J. Org. Chem.* **1991**, *56*, 5691. (c) Fisher, G. B.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 7693. (d) Nicholson, L. W; Goralski, C. T.; Fisher, G. B.; Singaram, B. *Abstracts of Papers, Fourth International Symposium on Chiral Discrimination,* Montreal, Quebec, Canada, 1993, Abstract 161.

(3) (a) Aluminum amides: Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195. (b) Al_2O_3: Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208. Posner, G. H.; Hulce, M.; Rose. R. K. *Synth. Commun.* **1981**, *11*, 737. (c) Aminolead: Yamada, J.; Yumoto, M.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *32*, 4255. (d) Halomagnesium reagents: Carre, M. C.; Houmounou, J. P.; Caubere, P. *Tetrahedron Lett.* **1985**, *26*, 3107. (e) Antimony triflates: Fujiwara, M.; Imada, M.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1989**, *30*, 739.

(4) (a) Cope, A. C.; Heeren, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 3125. (b) Rickborn, B.; Thummel, R. P. *J. Org. Chem.* **1969**, *34*, 3583. (c) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064. (d) Kissel, C. L.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060.

(5) Solladie-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.* **1992**, *57*, 5831.

(6) (a) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661. (b) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939.

0022-3263/94/1959-7746$04.50/0

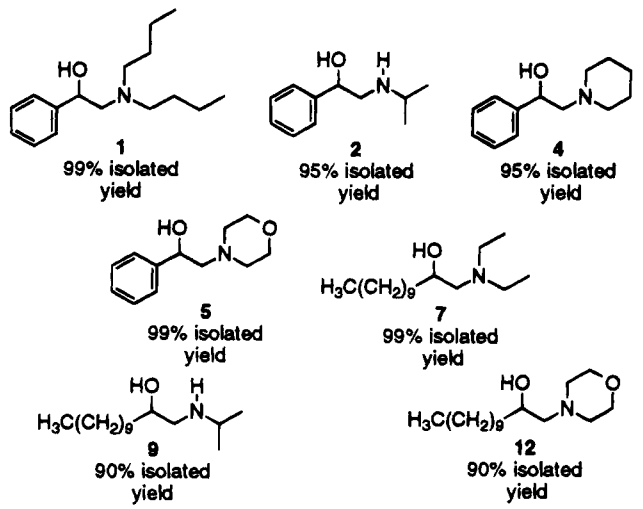
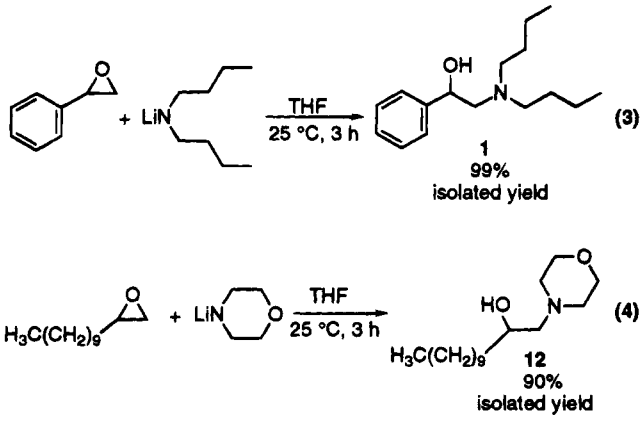


Figure 1. Representative amino alcohols synthesized from styrene oxide or 1,2-epoxydodecane and the corresponding lithium amide. All reactions were run in THF at 25 °C.

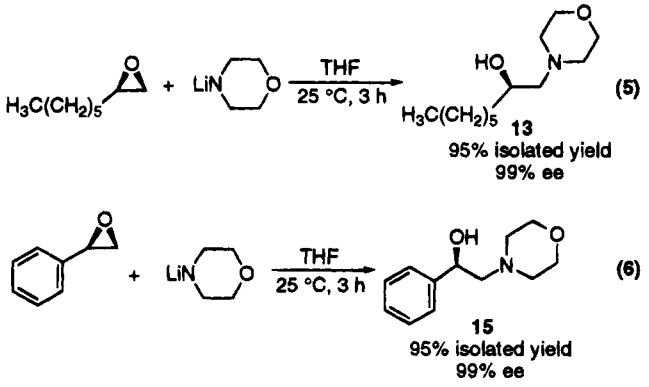
amides at 25 °C, the corresponding amino alcohols (**1**–**12**) were cleanly synthesized in excellent isolated yields (eqs 3 and 4, Figure 1). Yields of the amino alcohols



synthesized from styrene oxide using this methodology were particularly high, generally approaching quantitative (Figure 1, Tables 1 and 2).[5]

Spectroscopic results indicated that the only regioisomer formed was the S_N2 product resulting from reaction of the lithium amide at the terminal position of the oxirane ring. This is noteworthy because the Lewis-acid catalyzed reaction of styrene oxide with lithium amides derived from primary or secondary amines results in the formation of both regioisomers of the corresponding amino alcohol in distributions ranging from 60:40 to 85:15 in favor of the terminal amino alcohol.[5,7] However, in no case was a single regioisomer formed exclusively when primary or secondary amines were reacted with styrene oxide and a catalyst.[5,7] These results differ significantly from those that we obtained by directly reacting simple primary and secondary lithium amides with styrene oxide to give only a single regioisomer.

We also applied our methodology to the synthesis of optically active amino alcohols. For example, when *(2R)*-octene oxide or *(2R)*-styrene oxide was reacted with 1 equiv of lithium morpholide, the corresponding amino alcohols, **13** and **15**, respectively, were obtained in >95% isolated yield and in 99% enantiomeric excess (eqs 5 and 6, Table 3).



In order to compare the β-amino alcohols we synthesized with enantiomerically pure authentic samples, we refluxed enantiomerically pure epoxides (*(2R)*-styrene oxide or *(2R)*-octene oxide) with excess morpholine under

Table 1. Conversion of Styrene Oxide to the Corresponding β-Amino Alcohols Using Lithium Amides as Nucleophiles

amine	amino alcohol[a,b]	yield,[c] %	mp/bp, °C (Torr)[d]	ref
N,N-dibutylamine	2-(*N,N*-dibutylamino)-1-phenylethanol (**1**)	99	113–115 (0.3)	10
N-isopropylamine	2-(*N*-isopropylamino)-1-phenylethanol (**2**)	95	77–80 (0.3)	5
pyrrolidine	2-(1-pyrrolidino)-1-phenylethanol (**3**)	89	45–47	11
piperidine	2-(1-piperidino)-1-phenylethanol (**4**)	99	54–56	11
morpholine	2-(4-morpholino)-1-phenylethanol (**5**)	99	69–71	12
hexamethyleneimine	2-(1-hexamethyleneimino)-1-phenylethanol (**6**)	99	106–108 (0.3)	13

[a] Amino alcohols were synthesized as follows: (1) HNR_2 + *n*-BuLi, THF, 0 °C, 1 h; (2) C_8H_8O, neat, 25 °C, 3 h; (3) H_2O. [b] All amino alcohols fully characterized by 250 MHz ^{1}H- and ^{13}C-NMR. [c] Isolated, nonoptimized yields. [d] Boiling points are uncorrected. Melting points are for crude products.

Table 2. Conversion of 1,2-Epoxydodecane to the Corresponding β-Amino Alcohols Using Lithium Amides as Nucleophiles

amine	amino alcohol[a–c]	yield,[d] %	mp/bp, °C (Torr)[e]
N,N-diethylamine	1-(*N,N*-diethylamino)-2-dodecanol (**7**)	99	120–123 (0.3)
N,N-dibutylamine	1-(*N,N*-dibutylamino)-2-dodecanol (**8**)	99	169–170 (0.3)
N-isopropylamine	1-(*N*-isopropylamino)-2-dodecanol (**9**)	90	129–131 (0.6)
N,N-diisopropylamine	1-(*N,N*-diisopropylamino)-2-dodecanol (**10**)	60	115–117 (0.8)
pyrrolidine	1-(1-pyrrolidino)-2-dodecanol (**11**)	60	*f*
morpholine	1-(4-morpholino)-2-dodecanol (**12**)	90	*f*

[a] See ref 14. [b] Amino alcohols were synthesized as follows: (1) HNR_2 + *n*-BuLi, THF, 0 °C, 1 h; (2) 1,2-epoxydodecane, neat, 25 °C, 3 h. (3) H_2O. [c] All amino alcohols fully characterized by 250 MHz ^{1}H- and ^{13}C-NMR. [d] Isolated, nonoptimized yields. [e] Boiling points are uncorrected. [f] Crude product required no further purification.

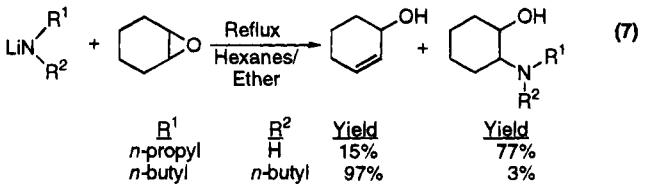
Table 3. Asymmetric Synthesis of β-Amino Alcohols from Enantiomerically Pure Epoxides Using Lithium Amides as Nucleophiles

amine	epoxide	amino alcohol[a,b]	yield,[c] %	ee,[d]	ref
morpholine	(2*R*)-octene oxide	(2*R*)-1-(4-morpholino)-2-octanol (**13**)	99	99[e]	2c
piperidine	(2*R*)-styrene oxide	(1*R*)-2-(1-piperidino)-1-phenylethanol (**14**)	99	99[f]	15
morpholine	(2*R*)-styrene oxide	(1*R*)-2-(4-morpholino)-1-phenylethanol (**15**)	99	99[g]	12
hexamethyleneimine	(2*R*)-styrene oxide	(1*R*)-2-(1-hexamethyleneimino)-1-phenylethanol (**16**)	99	99	13

[a] Amino alcohols were synthesized as follows: (1) HNR_2 + *n*-BuLi, THF, 0 °C, 1 h; (2) styrene oxide, neat, 25 °C, 3 h; (3) H_2O. [b] All amino alcohols fully characterized by 250 MHz ^{1}H- and ^{13}C-NMR. [c] Isolated, nonoptimized yields. [d] Enantiomeric excesses for the underivatized amino alcohols were determined by chiral HPLC using a Daicel CHIRALPAK chiral stationary phase. [e] $[\alpha]^D_{23} = -16.2°$ (*c* 6.0, MeOH). [f] $[\alpha]^D_{23} = -80.3°$ (*c* 2.0, $CHCl_3$). [g] $[\alpha]^D_{23} = -43.6°$ (*c* 1.2, EtOH).

neat conditions to obtain the corresponding enantiomerically pure amino alcohols in 65% and 90% yields, respectively. However, this method required refluxing at high temperatures for up to 24 h to achieve satisfactory yields.[1] Thus, the method we report herein represents a significant improvement over existing procedures for the regiospecific conversion of terminal epoxides to the corresponding β-amino alcohols.

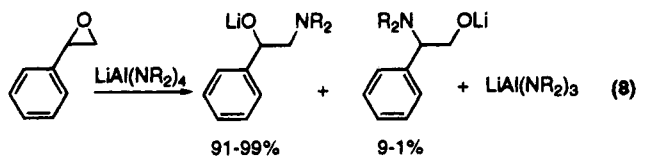
We then turned our attention to the conversion of internal epoxides to the corresponding amino alcohols, using cyclohexene oxide as our model substrate. It is known that in reactions of cyclohexene oxide with simple lithium amides, primary lithium amides give mixtures of amino alcohols and allylic alcohols with the amino alcohol produced in less than 50% yield. In the case of secondary lithium amides, the amino alcohol yields rarely exceed 20% (eq 7).[4d]



(7)

R^1	R^2	Yield	Yield
n-propyl	H	15%	77%
n-butyl	*n*-butyl	97%	3%

Recently, the use of lithium aluminum tetramides to deliver the amine moiety to styrene oxide was reported to result in a highly, but not exclusively, regiospecific conversion of styrene oxide to the corresponding amino alcohols (eq 8).[5] It seemed likely that lithium aluminum



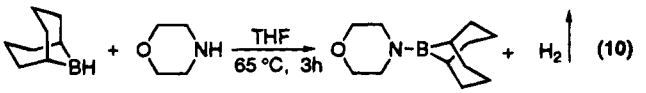
(8)

tetramide was in equilibrium with the corresponding lithium amide and tris-aminoalane shown in eq 9. We

$$LiAl(NR_2)_4 \rightleftharpoons LiNR_2 + Al(NR_2)_3 \quad (9)$$

speculated that the trisaminoalane, a relatively mild Lewis acid, complexes with the epoxide oxygen and activates the ring for an S_N2-type opening by the lithium amide.[8] This suggested to us that boron could be substituted for aluminum in this reaction, thereby making unnecessary the use of 4 equiv of amine per equivalent of epoxide as well as the need to work with alanes. Further, the use of an aminoborane auxiliary might also allow the opening of hindered epoxides to yield the amino alcohol instead of the undesired allylic alcohol from symmetrical internal epoxides.

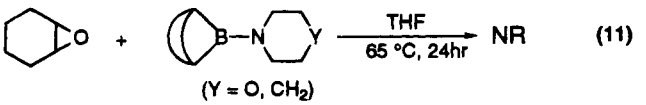
Ideally, we wanted an easily synthesized aminoborane auxiliary that would facilitate an S_N2-type ring opening. Since the synthesis of 9-BBN aminoboranes was known to be a facile, high yield reaction,[9] we decided to employ these compounds as auxiliaries (eq 10).



(10)

Quantitative Yield

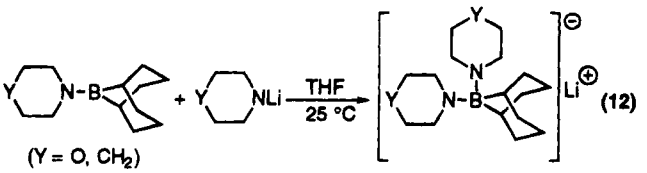
Initially, we examined the possibility that the 9-BBN aminoborane might complex with the epoxide oxygen and that the amine moiety could be delivered intramolecularly to form the amino alcohol. However, when morpholino- and piperidino-9-BBN were reacted with cyclohexene oxide, there was no discernible reaction even after 24 h of refluxing (eq 11).



(11)

(Y = O, CH_2)

In an attempt to increase the nucleophilic character of the amine, we reacted the lithium amide directly with the 9-BBN aminoborane to form the *ate* complex (eq 12).



(12)

(Y = O, CH_2)

We then attempted the reaction of the *ate*-complex with cyclohexene oxide. We reasoned that the epoxide oxygen might displace one of the amine moieties to form the desired *ate*-complex with the concomitant intramolecular transfer of the amine group to an oxirane carbon. However, this reaction proved to be too slow to be of any practical values probably due to THF stabilization of the

(7) For an excellent review of the regioselectivity of epoxide openings, see: Gorzynski-Smith, J. *Synthesis* **1984**, 629.

(8) (a) Winstein, S.; Henderson, R. *Heterocyclic Compounds;* John Wiley and Sons: New York, 1950; Vol. I, p 1–60. (b) Parker, R. E.; Isaac, N. S. *Chem. Rev.* **1959**, *59*, 737. (c) House, H. O. *Modern Synthetic Reactions, 2nd Ed.* Benjamin/Cummings: Menlo Park, 1972, p. 297–302.

(9) (a) Singaram, B. *Heteroatom Chem.* **1992**, *3*, 245. (b) A 1 M solution of *B*-morpholino-9-BBN in THF stored at 0 °C under nitrogen for over 2 months showed only minimal decomposition.

(10) Shapiro, S. L.; Soloway, H.; Shapiro, H. J.; Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 3993.

(11) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608.

(12) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymm.* **1992**, *3*, 341.

(13) Beardsley, D. A.; Fisher, G. B.; Goralski, C. T.; Nicholson, L. W. *Tetrahedron Lett.* **1994**, *35*, 1511.

(14) Shibata, K.; Shimada, S.; Matsuda, S. *Kogyo Kagaku Zasshi* **1965**, *68*, 957 (*Chem. Abstr.* **1965**, *63*, 9761b).

(15) Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* **1994**, *50*, 4455.

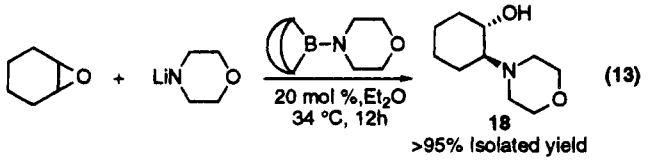
Table 4. Conversion of Cyclohexene Oxide to the Corresponding β-Amino Alcohols Using a *B*-Amino-9-BBN Catalyst and Lithium Amides as Nucleophiles

amine	amino alcohol[a-c]	*B*-amino-9-BBN (cat) yield, %[d]	previously reported yield, %[e]	mp/bp, °C (Torr)[f]
N-ethylaniline	1-(*N*-ethylanilino)-2-cyclohexanol (**17**)	95	N/A	92–93 (0.1)
morpholine	1-(4-morpholino)-2-cyclohexanol (**18**)	95	N/A	92–93 (0.6)
piperidine	1-(1-piperidino)-2-cyclohexanol (**19**)	71	11	57–59 (0.3)
N,N-dibutylamine	1-(*N,N*-dibutylamino)-2-cyclohexanol (**20**)	75	3	95–97 (0.4)
N-isopropylamine	1-(*N*-isopropylamino)-2-cyclohexanol (**21**)	95	10	60–61 (0.3)
N-isobutylamine	1-(*N*-isobutylamino)-2-cyclohexanol (**22**)	80	19	95–96 (1.0)

[a] See ref 4d. [b] Amino alcohols were synthesized as follows: (1) $LiNR_2$ (1.2 equiv) + *B*-Br-9-BBN, Et_2O; (2) $C_6H_{10}O$, Et_2O, 34 °C, 12–24 h. [c] All amino alcohols fully characterized by 250 MHz ^1H- and ^{13}C-NMR. [d] Isolated, distilled, nonoptimized yields. [e] GC yield. [f] Boiling points are uncorrected. Melting points are for crude products.

ate complex which prevented it from dissociating into free lithium amide and aminoborane.

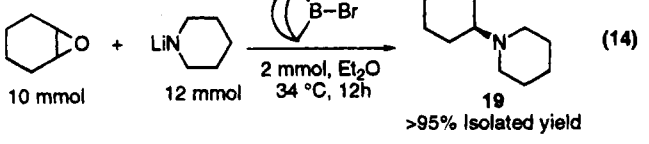
Finally, we reacted the epoxide with a stoichiometric amount of the *ate*-complex in refluxing diethyl ether. After aqueous workup, we were able to obtain the desired amino alcohols in good to excellent yields with only a minor amount of the corresponding allylic alcohol as a side product. We subsequently found that, in diethyl ether, even a catalytic amount (20 mol %) of *B*-morpholino-9-BBN facilitates amino alcohol formation in the reaction of lithium amides with cyclohexene oxide (eq 13, Table 4). However, use of less than 20 mol% of catalyst



(13)

led to significantly lower yields and longer reaction times.

We modified this procedure further by generating the *B*-amino-9-BBN *in situ* by the addition of a catalytic amount of *B*-bromo-9-BBN to a suspension of lithium amide in diethyl ether. Addition of cyclohexene oxide to this mixture followed by refluxing afforded the desired β-amino alcohol (eq 14). This procedure is applicable to



(14)

the synthesis of primary, secondary, and aromatic amino alcohols (Table 4).

The two methods for the conversion of epoxides to amino alcohols described in this paper represent the mildest methods available for the synthesis of these compounds. Further, the combination of these methodologies allows the conversion of any terminal or symmetrical internal epoxide into the corresponding amino alcohol in high yield and purity.

We are currently investigating the use of chiral aminoborane catalysts for the asymmetric opening of epoxides.

Experimental Section

All operations were carried out under a nitrogen atmosphere. All glassware, syringes, and needles were oven-dried at 120 °C and cooled to room temperature with nitrogen gas before use. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone ketyl. Anhydrous diethyl ether (Et_2O) was used directly. The *n*-butyl lithium (*n*-BuLi, 2.5 M in hexanes), 9-borabicyclo[3.3.1]nonane (9-BBN), and all of the amines and epoxides were commercial samples, stored under nitrogen, and used without further purification. *B*-Amino-9-BBN derivatives were prepared according to the literature procedure.[9]

Conversion of Terminal Epoxides to the Corresponding β-Amino Alcohols. Synthesis of 2-(*N,N*-Dibutylamino)-1-phenylethanol (1). The following procedure is representative. *n*-BuLi (2.5 M, 25 mmol, 10 mL) was added dropwise to a THF solution (50 mL) of *N,N*-dibutylamine (3.2 g, 25 mmol) at 0 °C and stirred for 15 min at 0 °C and then at 25 °C for an additional 45 min. Styrene oxide (3.0 g, 25 mmol) was added dropwise and the reaction mixture was stirred for an additional 3 h. Water (10 mL) was added and the reaction mixture allowed to stir for an additional 1 h. The organic layer was separated, the aqueous layer was extracted with Et_2O (4 × 10 mL), and the organic fractions were combined and dried over $MgSO_4$. Filtration and vacuum removal of solvent yielded 2-*N,N*-dibutylamino-1-phenylethanol as a transparent amber oil. (bp: 113–115 °C, 0.3 Torr, 6.2g, 99% yield). ^1H-NMR ($CDCl_3$): δ 0.9 (m, 6H), 1.3–1.5 (m, 8H), 2.4 (m, 4H), 2.5 (m, 2H), 4.6 (dd, *J* = 6.8, 3.6 Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 14.0, 20.6, 29.4, 53.8, 63.1, 69.3, 125.8, 127.3, 128.2, 142.6.

Synthesis of 2-(*N*-Isopropylamino)-1-phenylethanol (2). The representative procedure was followed as described above; bp: 77–80 °C, 0.3 Torr; 1.7 g, 95% yield. ^1H-NMR ($CDCl_3$): δ 1.1 (d, *J* = 6.3 Hz, 6H), 2.4 (br s, 1H), 2.7 (m, 1H), 2.8 (m, 1H), 2.9 (m, 1H), 4.7 (dd, *J* = 3.6, 5.4 Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 22.9, 49.5, 55.5, 72.5, 125.8, 126.5, 128.4, 143.0.

Synthesis of 2-(1-Pyrrolidino)-1-phenylethanol (3). The representative procedure was followed as described above; mp: 45–47 °C, 1.7 g, 89% yield. ^1H-NMR ($CDCl_3$): δ 1.8 (m, 4H), 2.5 (m, 4H), 2.7 (m, 2H), 4.7 (dd, *J* = 3.3, 7.3Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 23.7, 53.9, 64.1, 70.7, 125.9, 127.4, 128.3, 143.0.

Synthesis of 2-(1-Piperidino)-1-phenylethanol (4). The representative procedure was followed as described above; mp: 54–56 °C, 2.1 g, 99% yield. ^1H-NMR ($CDCl_3$): δ 1.5 (m, 2H), 1.6 (m, 4H), 2.4 (m, 4H), 2.7 (m, 2H), 4.7 (dd, *J* = 3.7, 6.5 Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 21.1, 24.3, 26.1, 54.4, 66.9, 68.6, 125.4, 125.8, 127.4, 142.5.

Synthesis of 2-(4-Morpholino)-1-phenylethanol (5). The representative procedure was followed as described above. mp: 69–71 °C, 2.1 g, 99% yield. ^1H-NMR ($CDCl_3$): δ 2.4 (m, 4H), 2.6 (m, 2H), 3.7 (m, 4H), 4.7 (dd, *J* = 4.0, 5.9 Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 53.5, 66.8, 67.1, 67.2, 68.7, 125.9, 127.6, 128.4, 142.0. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.26; N, 6.76. Found: C, 69.50; H, 8.32; N, 6.74.

Synthesis of 2-(1-Hexamethyleneimino)-1-phenylethanol (6). The representative procedure was followed as described above. Crude product required no further purification; 2.2 g, 99% yield. ^1H-NMR ($CDCl_3$): δ 1.6 (m, 8H), 2.4 (m, 2H), 2.7–2.8 (m, 4H), 4.6 (dd, *J* = 3.4, 7.2 Hz, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 27.0, 28.7, 55.6, 66.3, 69.4, 125.9, 127.4, 128.3, 128.5, 142.5.

Synthesis of 1-(*N,N*-Diethylamino)-2-dodecanol (7). The representative procedure was followed as described above; bp: 120–123 °C, 0.3 Torr; 6.4 g, 99% yield. ^1H-NMR

($CDCl_3$): δ 0.8 (m, 3H), 1.0 (t, J = 7.2 Hz, 6H), 1.3 (m, 18H), 2.2 (m, 2H), 2.4–2.5 (m, 4H), 2.5–2.6 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 12.0, 14.1, 22.7, 25.8, 29.3, 29.6, 29.9, 31.9, 35.1, 47.1, 59.6, 66.7.

Synthesis of 1-(*N,N*-Dibutylamino)-2-dodecanol (8). The representative procedure was followed as described above; bp: 169–170 °C, 0.3 Torr; 7.8 g, 99% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (m, 9H), 1.3 (m, 26H), 2.3 (m, 2H), 2.5–2.6 (m, 2H), 2.6–2.7 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.1, 20.6, 22.7, 25.8, 29.5, 29.6, 29.9, 31.9, 35.0, 54.0, 61.0, 66.9.

Synthesis of 1-(*N*-Isopropylamino)-2-dodecanol (9). The representative procedure was followed as described above. Crude product required no further purification; 4.3 g, 89% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (t, J = 6.7 Hz, 3H), 1.0 (d, J = 6.3 Hz, 6H), 1.2–1.5 (br m, 18H), 2.3–2.5 (br m, 1H), 2.7–2.9 (br m, 2H), 3.5 (br s, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.1, 18.3, 22.7, 25.8, 29.3, 29.6, 29.8, 31.9, 35.0, 35.1, 48.7, 53, 56.3, 58.1, 69.7.

Synthesis of 1-(*N,N*-Diisopropylamino)-2-dodecanol (10). The representative procedure was followed as described above; bp: 87–89 °C, 0.2 Torr; 4.2g, 60% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (t, 6.3 Hz, 3H), 0.95 (d, 6.7 Hz, 6H), 0.97 (d, 6.7 Hz, 6H), 1.2–1.6 (br m, 18H), 2.9–3.0 (br m, 2H), 2.7 (m, 2H), 2.9 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.1, 17.4, 19.1, 22.7, 26.0, 29.4, 29.6, 30.0, 31.9, 32.5, 35.4, 47.1, 47.9, 50.6, 52.4, 66.4.

Synthesis of 1-(1-Pyrrolidino)-2-dodecanol (11). The representative procedure was followed as described above. Crude product required no further purification; 1.5 g, 59% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (t, J = 6.3 Hz, 3H), 1.2 (m, 16 H), 1.7 (m, 4H), 2.3 (dd, J = 4.0, 7.5 Hz, 2H), 2.4–2.8 (br m, 6H), 3.6 (m, 1H), 3.9 (Br s, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.0, 22.7, 23.5, 25.6, 29.3, 29.6, 29.8, 31.9, 35.2, 54.0, 62.2, 68.2.

Synthesis of 1-(4-Morpholino)-2-dodecanol (12). The representative procedure was followed as described above. Crude product required no further purification; 2.5 g, 94% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (t, J = 6.3 Hz, 3H), 1.2 (m, 16H), 2.2–2.4 (br m, 4H), 2.5–2.6 (br m, 2H), 3.3 (s, 1H), 3.6 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ 14.1, 22.7, 25.6, 29.3, 29.6, 29.8, 31.9, 34.9, 53.7, 64.8, 65.9, 67.0.

Conversion of Optically Active Terminal Epoxides to the Corresponding β-Amino Alcohols. Synthesis of (2*R*)-1-(4-Morpholino)-2-octanol (13). The representative procedure was followed as described above. Crude product required no further purification; 2.7g, 99% yield; $[\alpha]^{23}_D$ = −16.2° (*c* 3.33, MeOH). ^{1}H-NMR ($CDCl_3$): δ 0.8 (m, 3H), 1.2–1.4 (m, 14H), 2.2–2.4 (m, 6H), 2.6 (m, 1H), 3.7 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ 14.1, 22.6, 25.6, 29.4, 31.8, 34.8, 53.7, 64.8, 65.9, 67.0.

Synthesis of (1*R*)-2-(1-Piperidino)-1-phenylethanol (14). The representative procedure was followed as described above. Crude product required no further purification; 2.0g, 99% yield; $[\alpha]^{23}_D$ = −80.3° (*c* 2.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 1.5 (m, 2H), 1.6 (m, 4H), 2.3–2.5 (m, 4H), 2.7 (m, 2H), 4.7 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 24.3, 26.2, 54.5, 67.0, 68.7, 125.9, 127.4, 128.3, 142.5.

Synthesis of (1*R*)-2-(4-Morpholino)-1-phenylethanol (15). The representative procedure was followed as described above. Crude product required no further purification; 2.0g, 99% yield; $[\alpha]^{23}_D$ = −43.6° (*c* 1.20, EtOH). ^{1}H-NMR ($CDCl_3$): δ 2.4 (m, 4H), 2.6 (m, 2H), 3.7 (m, 4H), 4.9 (br s, 1H), 4.7 (m, 1H), 7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): δ 53.5, 66.8, 67.0, 68.7, 125.9, 127.5, 128.4, 142.2.

Synthesis of (1*R*)-2-(1-Hexamethyleneimino)-1-phenylethanol (16). The representative procedure was followed as described above. Crude product required no further purification; 2.2g, 99% yield. ^{1}H-NMR ($CDCl_3$): δ 1.5 (m, 8H), 2.4 (dd, J = 10.7, 12.4 Hz, 1H), 2.7–2.8 (br m, 5H), 4.6 (m, 1H), 7.3 (m 5H); ^{13}C-NMR ($CDCl_3$): δ 26.7, 28.7, 55.6, 66.3, 69.4, 125.9, 127.4, 128.3, 142.5.

Conversion of Optically Active Terminal Epoxides to the Corresponding β-Amino Alcohols via Neat Reaction. Synthesis of (*R*)-1-(4-Morpholino)-2-octanol (13). The following procedure is representative. (*R*)-1,2-epoxyoctane (1.28 g, 10 mmol) and morpholine (4 g, 46 mmol) were heated to reflux and held there for 8 h. The residual morpholine was removed by distillation at ambient pressure to yield (*R*)-1-(4-Morpholino)-2-octanol as a colorless liquid; bp 157–158 °C (2 Torr), 1.93g, 90% yield; $[\alpha]^{23}_D$ = −16.2° (*c* 3.33, MeOH). Anal. Calcd for $C_{12}H_{25}NO$; C, 66.90; H, 11.70; N, 6.50. Found: C, 66.78; H, 12.36; N, 6.84.

Synthesis of (*R*)-2-(4-Morpholino)-1-phenylethanol (15). The representative procedure (21 h) was followed as described above; crude product recrystallized from absolute ethanol; mp: 95–97 °C, 5.61 g, 65% yield. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.26; N, 6.76. Found: C, 69.50; H, 8.32; N, 6.74. $[\alpha]^{23}_D$ = −43.6° (*c* 1.20, EtOH).

***In Situ* Generation of *B*-Amino-9-BBN.** The following procedure for the *in situ* generation of *B*-(*N*-ethylanilino)-9-BBN is representative. *n*-BuLi (2.5 M, 9.6 mL, 24 mmol) was added to *N*-ethylaniline (2.9 g, 3.0 mL, 24 mmol) in anhydrous Et_2O (40 mL). The reaction mixture was stirred at 0 °C for 5 min, then at ambient temperature for an additional 20 min. A solution of *B*-bromo-9-BBN (1 M in pentane) was prepared by vacuum removal of CH_2Cl_2 from a stock solution of *B*-bromo-9-BBN (4 mmol, 4 mL, 1 M in CH_2Cl_2) followed by dilution of the *B*-bromo-9-BBN with dry pentane (4 mL). The *B*-bromo-9-BBN in pentane was added dropwise to the reaction mixture and stirred at room temperature for 15 min. This reaction mixture containing 20 mol% of *B*-(*N*-ethylanilino)-9-BBN in 20 mmol of lithium *N*-ethylanilide was used for the reaction with cyclohexene oxide (20 mmol).

Synthesis of β-Amino Alcohols from Cyclohexene Oxide Using *B*-Amino-9-BBN Catalysts and Lithium Amides. Synthesis of *trans*-2-(*N*-ethylanilino)-1-cyclohexanol (17). The following procedure is representative. The mixture of lithium *N*-ethylanilide (24 mmol) and *B*-(*N*-ethylanilino)-9-BBN (20 mol %, 4 mmol) was charged by syringe with cyclohexene oxide (1.98 g, 2.0 mL, 20 mmol) and the reaction mixture was refluxed for 12 h. The reaction mixture was cooled to 25 °C, quenched with water (3 mL), and stirred for 5 min. The ether layer was decanted and the aqueous fraction washed with Et_2O (3 × 25 mL). The organic fractions were combined, dried over $MgSO_4$, and the solvent was removed *in vacuo* (12 Torr) to afford crude *trans*-2-(*N*-ethylanilino)-1-cyclohexanol as a transparent yellow oil (The crude material contains a small amount of borinic acid residue which is converted to *B*-methoxy-9-BBN by stirring with MeOH (10 mL) and HCl (2 mL, 12 M, 24 mmoles) for 1 h). The methanol was removed *in vacuo* (12 Torr) and the residue was washed with pentane to remove *B*-methoxy-9-BBN. The amino alcohol hydrochloride was layered with fresh Et_2O (25 mL) and cooled to 0 °C. 3 M NaOH (aq, 1–2 mL) and NaOH(s) were added to the reaction mixture with stirring until the aqueous layer was strongly basic to litmus. The ether layer was decanted and the residue washed with Et_2O (4 × 15 mL), and the combined ether extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent (25 °C, 12 Torr) gave *trans*-2-(*N*-ethylanilino)-1-cyclohexanol as a transparent yellow oil (bp 92–93 °C, 0.1 Torr; 4.5 g, 99% yield). ^{1}H-NMR ($CDCl_3$): δ 1.2 (t, J = 7 Hz, 3H), 1.3 (m, 2H); 1.7 (m, 2H), 2.2 (m, 1H), 3.2 (m, 2H), 3.6 (m, 1H), 6.8 (m, 1H), 6.9 (m, 2H), 7.2 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ 15.0, 24.0, 26.2, 27.5, 33.5, 38.0, 67.5, 71.0, 117.5, 119.0, 129.0, 149.5.

Synthesis of *trans*-2-(4-Morpholino)cyclohexanol (18). The representative procedure was followed as described above; bp: 92–93 °C, 0.6 Torr, 3.3 g, 95% yield. ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, J = 6.9 Hz, 3H), 1.3 (m, 4H), 1.7 (m, 4H), 2.1 (m, 2H), 2.4 (m, 2H), 2.5–2.7 (m, 8H); 3.3 (m, 1H), 3.7 (m, 4H), 4.1 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 21.1, 24.0, 25.4, 33.1, 48.7, 67.5, 68.4, 70.5.

Synthesis of *trans*-2-(1-Piperidino)cyclohexanol (19). The representative procedure was followed as described above; bp: 57–59 °C, 0.3 Torr, 3.8 g, 71% yield. ^{1}H-NMR ($CDCl_3$): δ 1.1–1.2 (m , 14H), 2.3 (m, 4H), 2.6 (m, 1H), 3.3 (m, 1H), 4.1 (br s, 1H); ^{13}C-NMR ($CDCl_3$): δ 22.1, 24.1, 24.8, 25.6, 26.7, 33.2, 49.7, 68.5, 71.0.

Synthesis of *trans*-2-(*N,N*-Dibutylamino)cyclohexanol (20). The representative procedure was followed as described above; bp: 95–97 °C, 0.4 Torr, 3.4 g, 75% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (t, J = 7 Hz, 6H), 1.1–1.3 (br m, 12H), 1.5–1.7 (br m, 2H), 1.9–2.1 (br m, 2H), 2.2 (m, 4H), 2.3–2.6 (m, 1H),

3.2 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.0, 20.5, 22.3, 24.1, 25.7, 31.4, 33.1, 49.5, 66.5, 69.1.

Synthesis of *trans*-2-(*N*-Isopropylamino)cyclohexanol (21). The representative procedure was followed as described above; bp: 60–61 °C, 0.3 Torr, 3.0 g, 95% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (d, J = 6 Hz, 3H), 0.9 (d, J = 6 Hz, 3H), 1.2 (br m, 2H), 1.7 (br m, 2H), 2.1 (m, 2H), 2.2 (m, 2H), 3.0–3.2 (m, 3H), 3.7 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 22.9, 24.4, 24.8, 25.5, 31.4, 33.0, 45.1, 60.7, 74.0.

Synthesis of *trans*-2-(*N*-Isobutylamino)cyclohexanol (22). The representative procedure was followed as described above; bp: 95–96 °C, 1.0 Torr, 2.7 g, 80% yield. ^{1}H-NMR ($CDCl_3$): δ 0.8 (m, 6H), 1.2 (m, 1H), 1.6 (m, 4H), 2.0–2.3 (m, 4H), 2.5 (m, 1H) 3.1 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ 20.7, 24.4, 25.2, 28.9, 30.6, 33.4, 54.7, 63.8, 73.6.

Acknowledgment. The authors gratefully acknowledge a research grant from the Dow Chemical Co. which provided the funds to carry out this research.

Supplementary Material Available: ^{1}H- and ^{13}C-NMR spectra for all β-amino alcohols synthesized (44 pages). This material is contained in 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.