Boranes in Synthesis. 5. The Hydroboration of Enamines with Mono- and Dialkylboranes. Asymmetric Synthesis of β-Amino Alcohols of Moderate Enantiomeric Purity from Aldehyde Enamines

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The hydroboration of both acyclic and cyclic aldehyde and ketone enamines with such representative mono- and dialkylboranes as thexylborane and dicyclohexylborane, followed by an oxidative workup, yields the corresponding β-amino alcohols in good to excellent isolated yields. The hydroboration of ketone and aldehyde enamines with the asymmetric hydroboration reagents monoisopinocampheylborane (^{d}IpcBH$_2$) and diisopinocampheylborane (^{d}Ipc$_2$BH) was also investigated. ^{d}Ipc$_2$BH is highly effective for the asymmetric hydroboration of acyclic aldehyde enamines, such as 1-(4-morpholino)-3-phenyl-1-propene and 1-(1-pyrrolidino)-1-octene. Oxidation of the intermediate trialkylborane furnishes the corresponding β-amino alcohols in 50–86% ee. The stereogenic center of the carbinol carbon is consistently enriched in the *R*-enantiomer when ^{d}Ipc$_2$BH prepared from (+)-α-pinene is used as the hydroboration reagent. The enantiomeric excesses of the β-amino alcohols synthesized in this study were determined by HPLC using a chiral stationary phase. The absolute configurations of some of the β-amino alcohols synthesized in this study were determined by chiral HPLC comparison with authentic β-amino alcohols prepared from chiral epoxides of known absolute configuration.

Introduction

Enantiomerically pure β-amino alcohols play important roles both in the treatment of a wide variety of human disorders[1] and as chiral auxiliaries in organic synthesis.[2] In medicinal chemistry,[1] β-amino alcohols, such as the β-adrenergic blockers bevantolol,[3a] denopamine,[3d] and propranolol,[3b,c] have been shown to be effective therapeutic agents in the treatment of heart disease (Figure 1).

The importance of enantiomeric purity in pharmaceuticals has been amply demonstrated by the debilitating and sometimes tragic side effects caused by the presence of the nontherapeutic enantiomer of an otherwise beneficial drug.[1,3b,4] Thalidomide is the most notorious example of this problem.[4]

In organic syntheses, enantiomerically pure β-amino alcohols have been shown to be highly effective chiral auxiliaries in asymmetric carbon–carbon bond-forming reactions.[5]

Currently, there are only a few methods available for the synthesis of racemic β-amino alcohols,[6a] and enantiomerically pure β-amino alcohols are generally obtained either from amino acids or by resolution procedures.[3a,7]

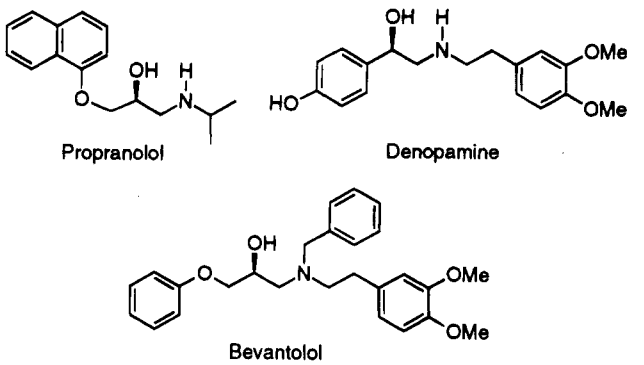

Figure 1. Enantiomerically pure β-amino alcohols that are effective therapeutic agents in the treatment of heart disease.

The reduction of enantiomerically pure amino acids is a simple, high-yield method for obtaining enantiomerically pure amino alcohols. However, this methodology is practical only for the naturally occurring amino acids

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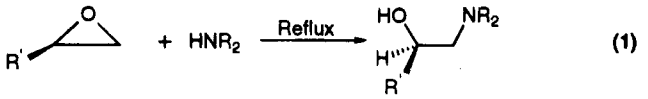
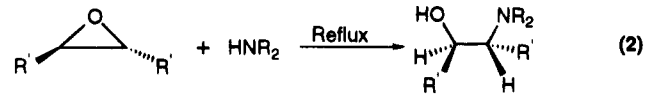
due to the high costs and general lack of availability of the unnatural amino acids.[8]

A second method of obtaining enantiomerically pure amino alcohols is the Sharpless kinetic resolution of a racemic mixture of amino alcohols.[3a] Reaction of a racemic mixture of amino alcohols with diisopropyl tartrate, titanium tetraisopropoxide, and *tert*-butyl hydroperoxide results in the enantioselective oxidation of only the faster reacting enantiomer and leaves behind the slow reacting enantiomer in nearly 100% enantiomeric excess.

Direct synthesis of optically active amino alcohols in high yields is possible by the amination of chiral epoxides.[9] Although this methodology gives enantiomerically pure β-amino alcohols in nearly quantitative yields, it is limited to monosubstituted and *trans* symmetrical disubstituted epoxides; otherwise, a mixture of products results (eqs 1 and 2).



(1)



(2)

There are three general asymmetric syntheses of β-amino alcohols available which involve the transformation of α-amino ketones into the corresponding β-amino alcohols using asymmetric reducing agents: asymmetric hydrogenation using a ruthenium–BINAP catalyst and 100 atm pressure,[7c] reduction with K-glucoride,[7d] and reduction with (diisopinocampheyl)chloroborane (DIPCl).[7e]

As part of our comprehensive investigation of the hydroboration and subsequent elaboration of enamines, we sought to develop a methodology for the synthesis of both racemic and enantiomerically enriched β-amino alcohols. Enamines were chosen as the substrates for conversion to β-amino alcohols by analogy with previous work on the hydroboration of enol ethers.[10] Extensive studies done on the hydroboration of enol ethers indicated that the enol ether double bond was much more reactive toward hydroboration than the unfunctionalized double bond of a simple alkene. This suggested that the enamine double bond should be even more reactive to hydroboration reagents, including bulky chiral reagents,[10d] due to the lower electronegativity of nitrogen relative to oxygen.[11] Enamines were also expected to yield the corresponding amino alcohol after a simple oxidative workup of the enamine hydroboration adduct (Figure 2).

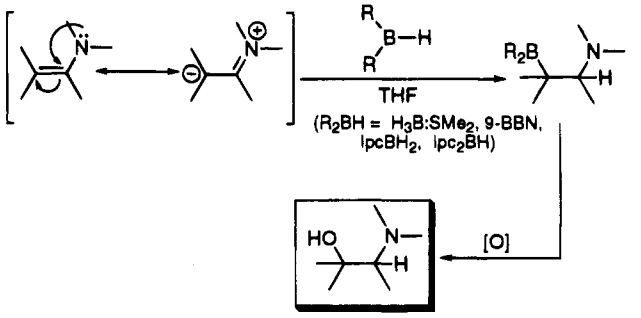
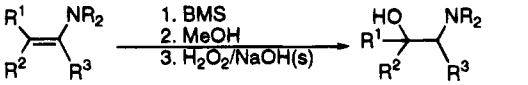


Figure 2. Proposed synthesis of β-amino alcohols from the corresponding aldehyde and ketone enamines.

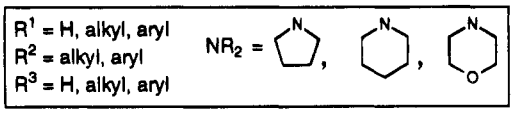
The results of our study of the hydroboration and elaboration of ketone and aldehyde enamines using both achiral and asymmetric hydroboration reagents are reported herein.[12]

Results and Discussion

The initial studies of the hydroboration and oxidation of enamines were conducted with borane methyl sulfide (BMS), an achiral hydroboration reagent. β-Monosubstituted and α,β- and β,β-disubstituted enamines were utilized as substrates. Formation of the hydroboration adduct was followed by a methanol quench of residual borane and oxidation of the resulting borinate ester with alkaline hydrogen peroxide to yield the corresponding β-amino alcohols in moderate to excellent yields (eq 3).[6]



(3)



However, the organoboranes derived from acyclic β-monosubstituted and α,β-disubstituted enamines tended to undergo β-elimination, thus complicating this amino alcohol synthesis.[6b,c] Further, the trialkylboranes prepared from enamines using 9-borabicyclo[3.3.1]nonane (9-BBN) as the hydroboration reagent underwent a facile, methanol-promoted elimination to the corresponding alkene.[6b,c] In order to understand and suppress this elimination reaction, we conducted a comprehensive study of the hydroboration of enamines with mono- and dialkylboranes.

Hydroboration of Enamines with Thexylborane. When a series of 1-aminocycloalkenes were subjected to hydroboration with thexylborane followed by methanolysis and alkaline hydrogen peroxide oxidation, the corresponding β-amino cycloalkanols were obtained in 75–80% isolated yields (eq 4, Table 1).

Although the dialkylborane adduct of 1-(4-morpholino)-cyclopentene displayed a complex ^{11}B-NMR spectrum, the corresponding methylborinic ester, obtained by metha-

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(8) Two extreme examples of this problem are illustrated by a comparison of the D- and L-enantiomers of cysteine and isoleucine. The 1990 cost of L-cysteine, the naturally occurring amino acid, was $26/100 g; the cost of D-cysteine was over $3000/100 g. For isoleucine, the costs were $58 and $21 640 per 100 g, respectively. Streitweiser, A.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*, 4th ed.; MacMillan: New York, 1992; p 956.

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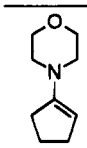
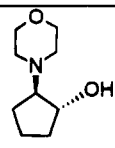
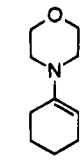
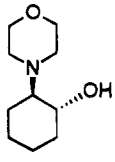
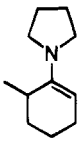
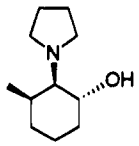
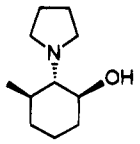
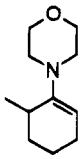
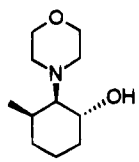
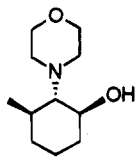
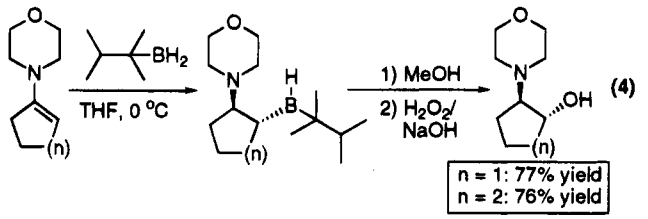
Table 1. Synthesis of β-Amino Alcohols from the Corresponding Enamines Using Thexylborane as the Hydroboration Reagent

enamine[a]	amino alcohol[b,c]	yield, %[d]	bp (Torr)[e]
		77	110-114 (0.6)
		76	90-92 (0.3)
	 **1a** 12%	 **1b** 88%[f,g]	56	72-73 (0.2)
	 **2a** 34%	 **2b** 66%[f,h]	38	90-95 (0.2)

[a] Syntheses carried out as follows: (1) $ThxBH_2$, THF, 0 °C; (2) MeOH, 0 °C; (3) NaOH(s)/H_2O_2. [b] See ref 6b. [c] All β-amino alcohols fully characterized by 300 MHz ^1H- and ^{13}C-NMR. [d] Isolated yield. [e] Boiling points are uncorrected. [f] Product ratios determined by 300 MHz ^1H- and ^{13}C-NMR and GC/MS. [g] Hydroboration using BMS gave a 66:34 ratio of **1a**:**1b**. [h] Hydroboration using BMS gave a 74:17:9 ratio of **2a**:**2b**:**2c**; see Figure 2.



(4)

nolysis of the dialkylborane adduct, displayed a sharp singlet at δ +54 in its ^{11}B-NMR spectrum. Oxidation of the methylborinic ester gave a 77% isolated yield of *trans*-2-(4-morpholino)cyclopentanol and a 60% yield of 2,3-dimethyl-2-butanol (thexyl alcohol). Similarly, when 1-(4-morpholino)cyclohexene was subjected to the hydroboration–oxidation sequence described above, *trans*-2-(4-morpholino)cyclohexanol was obtained in 76% isolated yield.

Hydroboration–oxidation of enamines derived from 2-methylcylohexanone with thexylborane gave particularly interesting results. The first hydroboration–oxidation of these enamines was carried out by Borowitz in 1967 using sterically unhindered borane–tetrahydrofuran (BH_3:THF).[13a] Borowitz reported that the hydroboration–oxidation of the pyrrolidine enamine of 2-methylcylohexanone with diborane in THF afforded a 64% yield of a 63:37 mixture of the diastereomeric amino alcohols **1a** and **1b**.[13a] We have repeated this reaction

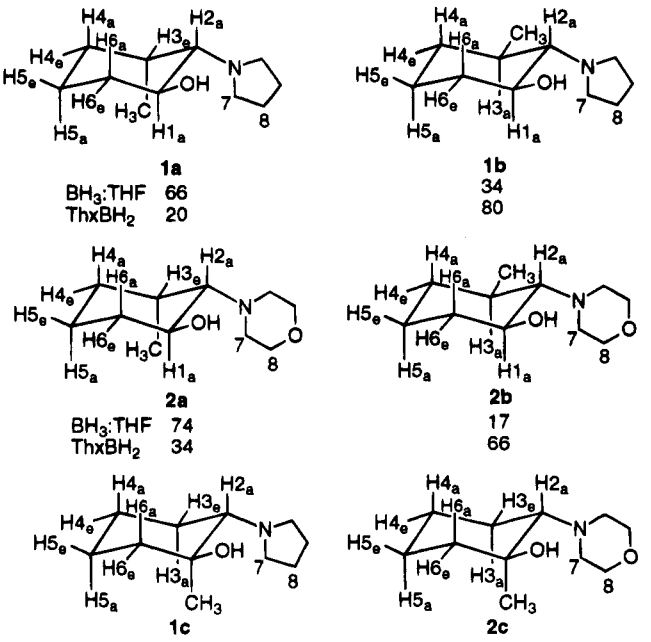


Figure 3. Amino alcohols obtained from the hydroboration/oxidation of enamines derived from 2-methylcyclohexanone.

with borane methyl sulfide (BMS) and obtained a 55% isolated yield of the diastereomeric amino alcohols **1a** and **1b** in a ratio of 66:34. No significant amount of **1c** was observed (Figure 3, Table 1).

The structures of **1a,b** and **2a–c** were confirmed by 2-D, high field NMR studies (Table 2). The reaction was repeated with the morpholine enamine of 2-methylcyclohexanone to give a 37% isolated yield of the three isomeric amino alcohols **2a–c** in a ratio of 74:17:9. The amino alcohols were separated and determined to be isomers by GC/MS.

Since the predominance of **1a** in the hydroboration of the pyrrolidine enamine of 2-methylcyclohexanone with BH_3:THF had been explained on the basis of approach of the hydroboration agent from the least hindered side of the enamine (the face opposite the axial methyl group),[13a] we expected that hydroboration with the bulkier thexylborane ($ThxBH_2$) would lead to nearly exclusive formation of the *trans, cis* diastereomer.[13a] Much to our surprise, however, hydroboration of the pyrrolidine enamine of 2-methylcyclohexanone with $ThxBH_2$ in THF followed by methanolysis and oxidation with H_2O_2/NaOH gave a 40% isolated yield of **1a** and **1b** in a ratio of 12:88 (Table 1). Similarly, **2a** and **2b** were obtained in a ratio of 34:66 when the morpholine enamine of 2-methylcyclohexanone was subjected to the same conditions. Thus, in both examples, hydroboration with $ThxBH_2$ resulted in diastereoselectivity opposite that observed with BMS. As the hydroboration proceeds, the sp^2 hybridization of the enamine β-carbon changes to the sp^3 hybridization of the product dialkylborane. In doing so, the intermediate stages of the hydroboration take on the steric requirements of the products (Figure 4).

This results in the predominance of the more stable conformer, **3**, the dialkylborane with the ThxBH, pyrro-

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Table 2. NMR Spectral Data ($CDCl_3$) for Methyl-Substituted 2-(Dialkylamino)cyclohexanols (ppm)

	1a *trans*-3-methyl-*trans*-2-(1-pyrrolidino)-cyclohexanol		**1b** *cis*-3-methyl-*trans*-2-(1-pyrrolidino)-cyclohexanol		**2a** *trans*-3-methyl-*trans*-2-(4-morpholino)-cyclohexanol		**2b** *cis*-3-methyl-*trans*-2-(4-morpholino)-cyclohexanol		**2c** 1-methyl-*trans*-2-(4-morpholino)-cyclohexanol	
position	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	3.76	66.7	3.21	69.8	3.71	63.0	3.22	68.1		71.4
2	2.46[a]	67.7	2.15[b]	69.3	2.31[c]	71.3	1.79[d]	75.2	2.17	72.0
3	2.34	30.3	1.67	33.6	2.28	29.5	1.57	33.0	1.79 (e), 1.22 (a)	25.5
4	1.46	33.0	1.63 (e), 1.08 (a)	35.1	1.21	33.7	1.60 (e), ND (a)[e]	34.6	1.58	22.4
5	1.49	18.6	1.64 (e), 1.28 (a)	23.1	1.40	17.9	1.58 (e), ND (a)[e]	22.6	1.79 (e), 1.17 (a)	22.2
6	2.05 (e), 1.24 (a)	34.8	2.06 (e), 1.20 (a)	32.4	2.04 (e), 1.17 (a)	34.3	1.98 (e), 1.18 (a)	32.3	1.63 (e), 1.33 (a)	39.2
7	2.78	49.2	2.82	47.5	~2.80, ~2.60 (e, a)	49.3	~2.85, ~2.61 (e, a)	49.2	~2.65, ~2.45 (e, a)	49.3
8	1.75	23.1	1.74	23.7	3.62	67.0	3.62	67.0	3.62	66.6
CH_3	0.98	14.9	0.93	19.7	1.02	15.9	0.99	19.8	1.11	21.3

[a] Doublet of doublets with coupling constants $^3J_{HH}$ = 10.2 and 4.3 Hz. [b] Triplet with coupling constant $^3J_{HH}$ = 9.8 Hz. [c] Doublet of doublets with coupling constants $^3J_{HH}$ = 10.2 and 4.3 Hz. [d] Triplet with coupling constant $^3J_{HH}$ = 9.8 Hz. [e] Not determined.

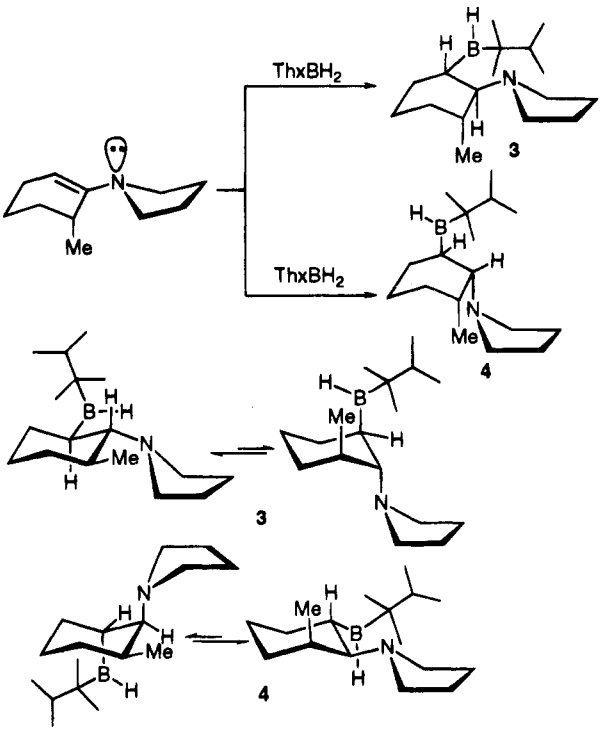
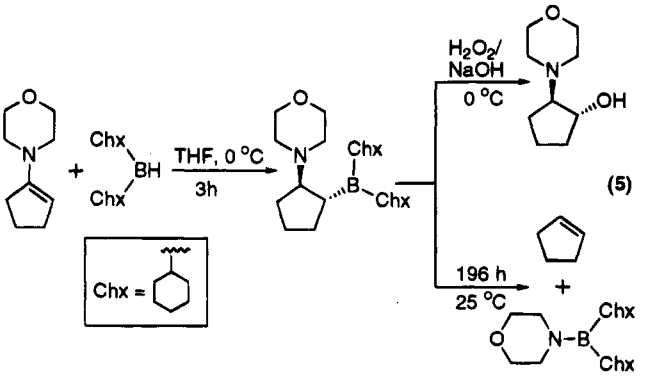


Figure 4. Product ratio resulting from predominant formation of the most stable conformer of the dialkylborane intermediate in the hydroboration of 2-methylcyclohexanone enamines.

lidino, and methyl groups all equatorial. Thus, in the hydroboration of 2-methylcyclohexanone enamines with $ThxBH_2$, the developing sp^3 hybridization appears to be the controlling factor in the stereochemistry of the β-amino alcohols produced.

The amino alcohols were easily separated from the boric acid and thexyl alcohol byproducts by treatment of the crude product mixture with methanolic hydrochloric acid followed by reduced pressure removal of the residual methanol and methyl borate. The resulting amino alcohol hydrochloride salt was washed with Et_2O to remove any remaining thexyl alcohol and the neutral amino alcohol regenerated by basification with NaOH (6M).

Hydroboration with Dicyclohexylborane. The hydroboration of 1-aminocycloalkene enamines with dicyclohexylborane in THF for 2 h at 0 °C afforded a quantitative yield of the corresponding trialkylborane. Thus, when 1-(4-morpholino)cyclopentene underwent hydroboration with dicyclohexylborane, the ^{11}B-NMR of the hydroboration adduct displayed a single peak, a broad singlet at δ +86, indicative of trialkylborane formation. When allowed to stand for 196 h, this trialkylborane underwent slow elimination on stirring in THF at 25 °C to give cyclopentene and *B*-1-(4-morpholino)dicyclohexylborane. However, immediate oxidative workup of the trialkylborane with alkaline hydrogen peroxide gave the corresponding β-amino alcohols in 58–76% isolated yields (eq 5, Table 3).



Hydroboration of Enamines with Disiamylborane. The hydroboration of 1-(4-morpholino)cyclopentene with disiamylborane in THF at 25 °C also took 2 h for completion of the reaction. The corresponding trialkylborane displayed a broad singlet at δ +84 in the ^{11}B-NMR spectrum. This trialkylborane, unlike those obtained with 9-BBN[6] or dicyclohexylborane, was stable toward β-elimination at 25 °C. Oxidative workup gave the desired β-amino alcohols in modest yields (Table 3).

These results suggested that the elimination reaction is sensitive to the nature and the steric requirements of the β-amino organoboranes. Mono- and dialkylboranes containing a β-amino group do not undergo the observed elimination reaction. In the case of trialkylboranes containing a β-amino group, the β-elimination reaction becomes less prominent as the steric requirement around the boron atom increases.

Encouraged by these results, we initiated a comprehensive investigation of the synthesis of chiral β-amino alcohols using asymmetric hydroboration reagents. The reagents of choice in the asymmetric synthetic scheme proposed in Figure 5 were mono- and diisopinocampheylborane, the first in an increasingly long list of reagents capable of effecting the nonenzymatic synthesis of chiral molecules in high enantiomeric excesses.[14]

The asymmetric hydroboration reagents shown in Figure 5 were derived from the (+)-enantiomer of α-pinene. Extensive work on the asymmetric hydro-

Table 3. Synthesis of β-Amino Alcohols from the Hydroboration of Enamines Using Dialkylboranes

enamine	amino alcohol[d,e]	yield,[f] %	bp, °C (Torr)[g]
1-(4-morpholino)cyclopentene[a]	*trans*-2-(4-morpholino)cyclopentanol	68	108–110 (0.5)
1-(4-morpholino)cyclopentene[b]	*trans*-2-(4-morpholino)cyclopentanol	63	108–110 (0.5)
1-(1-pyrrolidino)cyclopentene[b]	*trans*-2-(1-pyrrolidino)cyclopentanol	58	96–98 (0.6)
1-(4-morpholino)cyclohexene[a]	*trans*-2-(4-morpholino)cyclohexanol (**5**)	60	100–102 (1.2)
1-(1-piperidino)cyclohexene[a]	*trans*-2-(1-piperidino)cyclohexanol (**6**)	76	94–96 (0.8)
1-(4-morpholino)cyclohexene[b]	*trans*-2-(4-morpholino)cyclohexanol (**5**)	58	94–96 (0.8)
1-(*N*-benzyl-*N*-methylamino)cyclohexene[a]	*trans*-2-(*N*-benzyl-*N*-methylamino)cyclohexanol (**7**)	69	116–118 (0.5)
1-(*N*-benzyl-*N*-methylamino)cyclohexene[b]	*trans*-2-(*N*-benzyl-*N*-methylamino)cyclohexanol (**7**)	72	116–118 (0.5)

[a] Hydroboration carried out with Chx_2BH = dicyclohexylborane. [b] Hydroboration carried out with Sia_2BH = disiamylborane. [c] All hydroborations carried out as follows: (1) 1 M dialkylborane solutions in THF, 0 °C, 3 h; (2) MeOH, 0 °C; (3) NaOH(s)/H_2O_2, 0 °C. [d] Purity determined by capillary GC comparison with an authentic sample synthesized from cyclopentene oxide or cyclohexene oxide and the corresponding amine. [e] All amino alcohols synthesized are known compounds. See ref 6b. [f] Isolated yield. [g] Boiling points are uncorrected.

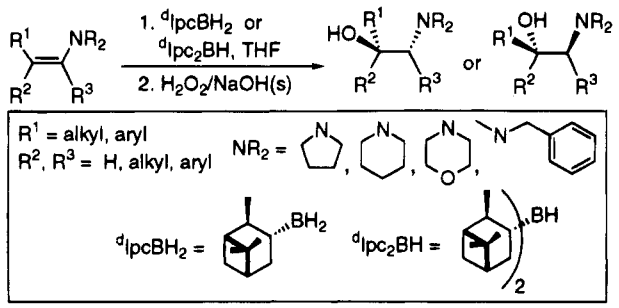
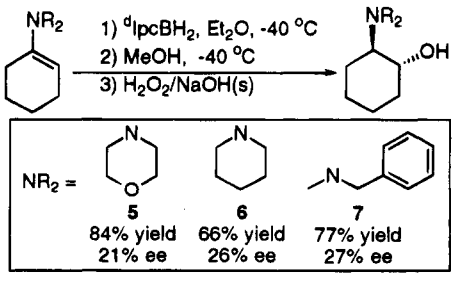


Figure 5. Synthetic strategy for the conversion of enamines to the corresponding enantiomerically enriched β-amino alcohols.

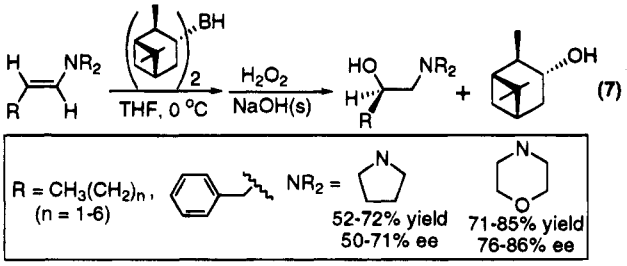
boration/oxidation of prochiral alkenes to the corresponding enantiomerically enriched alcohols demonstrated that the stereochemistry of the final product is completely determined by both the number and stereochemistry of the α-pinene groups appended to the boron in the asymmetric hydroboration reagent.[14] In the case of an aliphatic or aromatic alkene, (monoisopinocampheyl)-borane ($^dIpcBH_2$) derived from the (+)-enantiomer of α-pinene gave predominantly the *S*-alcohol; (diisopinocampheyl)borane ($^dIpcB_2H$) derived from the (+)-enantiomer of α-pinene gave the *R*-alcohol in 90% ee.[14]

The initial asymmetric enamine hydroborations were carried out with $^dIpcBH_2$ on a series of 1-(dialkylamino)-cycloalkenes. After hydroboration at −40 °C, the resulting alkylboranes were methanolyzed followed by oxidation with NaOH(s)/30% H_2O_2 to the corresponding β-amino alcohols (eq 6).



(6)

In all cases, the corresponding chiral β-amino alcohols were obtained in moderate to excellent yields and modest enantiomeric excesses, ranging from 6 to 28% ee (Table 4). The results shown in Table 4 demonstrated that, even at −40 °C, $^dIpcBH_2$ was not sterically hindered enough to significantly enhance the facial selectivity of its reaction with the enamine double bond, thereby resulting in a hydroboration of only modest enantiomeric excess. Additionally, when the hydroboration–oxidation of these enamines was run at 0 °C, the enantiomeric excesses of the resulting amino alcohols decreased significantly. These results suggested that the more sterically demanding diisopinocampheylborane ($^dIpc_2BH$) could be successfully used to give a highly enantioselective hydroboration. Aldehyde enamines were the substrates chosen for the initial asymmetric hydroborations with $^dIpc_2BH$, although this type of enamine is structurally related to *trans*-alkenes (eq 7).



(7)

The experimental results summarized in eq 7 demonstrated that the enhanced reactivity of the enamine double bond is offset by the significantly more sterically demanding $^dIpc_2BH$, resulting in a much slower and more enantioselective hydroboration, even at 0 °C. Since $^dIpc_2BH$ is only sparingly soluble in tetrahydrofuran (THF) at 0 °C, dissolution of the solid $^dIpc_2BH$ indicated the completion of the hydroboration reaction. Oxidation of the intermediate trialkylborane furnished the corresponding β-amino alcohols in isolated yields that ranged from 52% to 85% and enantiomeric excesses from 50% to 86% ee (Figure 6; Tables 5 and 6). The enantiomeric excesses of the underivatized β-amino alcohols were determined using HPLC with a Daicel brand CHIRALPAK AD chiral stationary phase. Authentic samples of the racemic 1-(dialkylamino)-2-alkanols were prepared by the neat reaction of the appropriate secondary amine and 1,2-epoxyalkane[15] or by the hydroboration–oxidation of the appropriate enamines with BMS.[6] Racemic amino alcohols, when analyzed by HPLC using a Daicel brand CHIRALPAK AD chiral stationary phase, gave two peaks of equal intensity. In general, the enantiomeric excess of the pyrrolidine amino alcohols were lower than the

(14) (a) Brown, H. C.; Ayyangar, N. R; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 397. (b) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547 and references cited therein. (c) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287 and references cited therein. (d) Matteson, D. *Acc. Chem. Res.* **1988**, *21*, 284. (e) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.

(15) (a) Mousseron, M.; Jullien, J.; Jolchime, Y. *Bull. Soc. Chim. Fr.* **1952**, 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.

Table 4. Synthesis of Enantiomerically Enriched β-Amino Alcohols from the Corresponding Enamines

enamine[a]	amino alcohol[b,c]	yield,[d] %	ee,[e] %
1-(4-morpholino)cyclopentene	*trans*-2-(4-morpholino)cyclopentanol	86[f]	6
1-(1-piperidino)cyclohexene	*trans*-2-(1-piperidino)cyclohexanol (**6**)	66[f]	26
1-(4-morpholino)cyclohexene	*trans*-2-(4-morpholino)cyclohexanol (**5**)	86[g]	14
1-(4-morpholino)cyclohexene	*trans*-2-(4-morpholino)cyclohexanol (**5**)	84[h]	21
1-(4-morpholino)cyclohexene	*trans*-2-(4-morpholino)cyclohexanol (**5**)	59[g,i]	28
1-(*N*-benzyl-*N*-methylamino)cyclohexene	*trans*-2-(*N*-benzyl-*N*-methylamino)cyclohexanol (**7**)	77[f]	27

[a] All hydroborations carried out as follows: (1) 1 M $IpcBH_2$ solutions in Et_2O, cold; (2) MeOH; (3) NaOH(s)/H_2O_2, 0 °C. [b] Purity determined by capillary GC comparison with an authentic sample synthesized from cyclopentene oxide or cyclohexene oxide and the corresponding amine. [c] See ref 6b. [d] Isolated yield. [e] Determined by capillary GC analysis of the MCF derivative of the amino alcohol. [f] Hydroboration carried out at −40 °C. [g] Hydroboration carried out at 0 °C. [h] Hydroboration carried out at −30 °C. [i] Ipc_2BH used as a complexing agent to retard the rate of hydroboration.

Table 5. Asymmetric Synthesis of β-Amino Alcohols from the Corresponding Pyrrolidino Aldehyde Enamines[a]

enamine	amino alcohol[b,c]	yield,[d] %	bp, °C (Torr)[e]	$[\alpha]_D°$ (c)[f]	ee,[g] %	abs[h,i] confign
(*E*)-1-(1-pyrrolidino)-1-pentene	1-(1-pyrrolidino)-2-pentanol	52	43−45 (0.3)	−1.0 (3.0)	*j*	*R*[i]
(*E*)-1-(1-pyrrolidino)-1-hexene	1-(1-pyrrolidino)-2-hexanol (**9**)	60	63−65 (0.2)	−2.0 (4.8)	50	*R*[i]
(*E*)-1-(1-pyrrolidino)-1-octene	1-(1-pyrrolidino)-2-octanol (**11**)	61	82−84 (0.3)	−3.1 (6.0)	70	*R*[h]
(*E*)-1-(1-pyrrolidino)-1-nonene	1-(1-pyrrolidino)-2-nonanol (**13**)	66	87−89 (0.2)	−1.1 (6.2)	71	*R*[i]
(*E*)-1-(1-pyrrolidino)-3-phenyl-1-propene	1-(1-pyrrolidino)-3-phenyl-2-propanol	72	103−105 (0.4)	−1.1 (5.7)	*j*	*R*[i]

[a] Amino alcohols were synthesized as follows: (1) $^dIpc_2BH$/THF, 0 °C, 1−12 h; (2) H_2O_2/NaOH(s). [b] All amino alcohols fully characterized by 250 MHz ^{1}H- and ^{13}C-NMR. [c] See ref 12. [d] Isolated, nonoptimized yields. [e] Boiling points are uncorrected. [f] All optical rotations taken in anhydrous MeOH. [g] Enantiomeric excesses of the underivatized amino alcohols determined by HPLC using a Daicel CHIRALPAK AD chiral stationary phase. [h] Absolute configuration determined by comparison with an authentic sample synthesized from an enantiomerically pure epoxide of known absolute configuration and the corresponding amine. [i] Absolute configuration assigned based on transition state model. [j] Enantiomers did not separate on chiral HPLC column.

Table 6. Asymmetric Synthesis of β-Amino Alcohols from the Corresponding Morpholino Aldehyde Enamines[a]

enamine	amino alcohol[b,c]	yield,[d] %	bp, °C (Torr)[e]	$[\alpha]_D°$ (c)[f]	ee,[g] %	abs[h,i] confign
(*E*)-1-(4-morpholino)-1-pentene	1-(4-morpholino)-2-pentanol (**8**)	71	57−59 (0.1)	−12.9 (5.5)	83	*R*[i]
(*E*)-1-(4-morpholino)-1-hexene	1-(4-morpholino)-2-hexanol (**10**)	58	74−76 (0.2)	−12.6 (5.0)	86	*R*[i]
(*E*)-1-(4-morpholino)-1-octene	1-(4-morpholino)-2-octanol (**12**)	80	89−91 (0.3)	−13.1 (5.7)	81	*R*[h]
(*E*)-1-(4-morpholino)-1-nonene	1-(4-morpholino)-2-nonanol (**14**)	75	93−95 (0.2)	−15.0 (6.5)	76	*R*[i]
(*E*)-1-(4-morpholino)-3-phenyl-1-propene	1-(4-morpholino)-3-phenyl-2-propanol (**15**)	85	118−120 (0.4)	−11.5 (7.2)	86	*R*[i]

[a] Amino alcohols were synthesized as follows: (1) $^dIpc_2BH$/THF, 0 °C, 1−12 h; (2) H_2O_2/NaOH(s). [b] All amino alcohols fully characterized by 250 MHz ^{1}H- and ^{13}C-NMR. [c] See ref 12. [d] Isolated, nonoptimized yields. [e] Boiling points are uncorrected. [f] All optical rotations taken in anhydrous MeOH. [g] Enantiomeric excesses of the underivatized amino alcohols determined by HPLC using a Daicel CHIRALPAK AD chiral stationary phase. [h] Absolute configuration determined by comparison with an authentic sample synthesized from an enantiomerically pure epoxide of known absolute configuration and the corresponding amine. [i] Absolute configuration assigned based on transition state model.

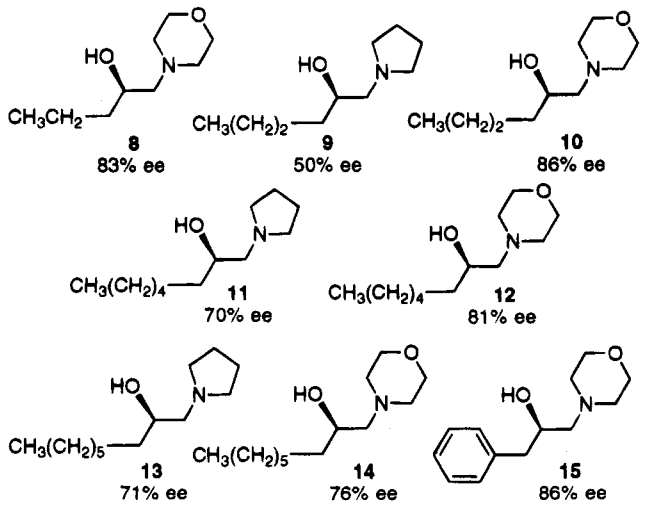
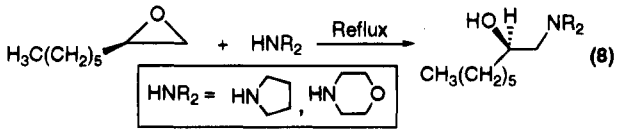


Figure 6. β-Amino alcohols synthesized in high enantiomeric excess from the corresponding enamines, using $^dIpc_2BH$ as the asymmetric hydroboration reagent. Enantiomeric excesses are for β-amino alcohols synthesized at 0 °C.

morpholino analogs. This is probably due to the greater reactivity of the pyrrolidine enamines.

Since the absolute configurations of the β-amino alcohols prepared in this study have not been reported previously, enantiomerically pure samples of two of the (*R*)-1-(dialkylamino)-2-octanols were prepared from the appropriate amine and (*R*)-1,2-epoxyoctane (eq 8).[9]



Enantiomeric separation of the β-amino alcohols revealed that $^dIpc_2BH$ affords β-amino alcohols enriched in the *R*-enantiomer. On the basis of this result, we are proposing a lowest-energy transition state for the hydroboration of acyclic aldehyde enamines with $^dIpc_2BH$ that is consistent with these experimental observations (Figure 7).[16]

In the case of simple *trans*-alkenes, steric interaction between the "inside" L-group and the alkyl group is large enough to slow the reaction considerably.[16] However, in the case of acyclic aldehyde enamines, the energetically favorable coordination of the β-carbon of the double bond to the boron atom apparently overcomes the steric repulsion between the L-group and the dialkylamino group.

(16) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257.

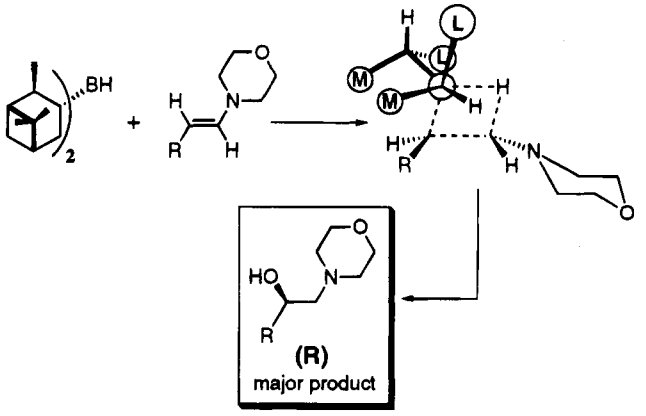


Figure 7. Proposed transition state for the hydroboration of acyclic aldehyde enamines with $^{d}Ipc_2BH$.

Conclusion

The hydroboration of enamines has been shown to be a convenient high-yield method for the synthesis of enantiomerically enriched β-amino alcohols from the corresponding aldehyde enamines. We are currently investigating the extension of this methodology to the more sterically demanding ketone enamines.

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 prior to use. THF was freshly distilled from sodium and benzophenone ketyl. Anhydrous ether (Et_2O) was purchased from Fisher Scientific and used directly. Borane–dimethyl sulfide (BMS, 10.2 M) and all of the amines and aldehydes used in this study were purchased from the Aldrich Chemical Co., stored under nitrogen, and used without further purification. The enamines,[17] the (monoisopinocampheyl)borane,[18] and the (diisopinocampheyl)borane[19] used in this study were synthesized according to literature procedures. (*R*)-(+)-α-pinene was purified by stirring over $LiAlH_4$ for 24 h followed by vacuum distillation (20 Torr) from the $LiAlH_4$. ^{1}H-NMR and ^{13}C-NMR were obtained on a Bruker ACF MultiProbe 250 MHz NMR. Chemical shifts are in δ relative to internal Me_4-Si. IR spectra were obtained on a Perkin-Elmer 1600 Series FT-IR. Enantiomeric excesses were determined by capillary GC analysis of the menthyl chloroformate (MCF) derivatives of the amino alcohols or by chiral column high-pressure liquid chromatography (HPLC) of the underivatized amino alcohols using a Daicel brand CHIRALPAK AD chiral stationary phase.

GC Analysis of Menthyl Chloroformate Derivatives. To a mixture of 60 μL of dry pyridine and 15 μL of the amino alcohol was added 0.5 mL of a 0.55 M solution of menthyl chloroformate (MCF) in toluene. The reaction was stirred at room temperature for 12–16 h, diluted with aqueous potassium carbonate, and extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$ and molecular sieves prior to GC analysis on a 50 m methylsilicone column at 230 °C.

HPLC Analysis of Amino Alcohols Using a Chiral Stationary Phase.[20] Instrumentation. Chromatographic separations were achieved using a liquid chromatograph constructed from the following components: a Milton Roy reciprocating piston pump operating at 1–2 mL/min, a Rheodyne 7125 injector, a 4.6 × 250 mm ID Chiralpak AD column (Daicel Chemical Ind.) from Chiral Technologies, Inc., and a Kratos UV absorbance detector. The mobile phase was 5% methanol/95% pentane with detection at 210 nm. (**NOTE:** Some liquid chromatographic systems are incapable of pumping a pentane-based mobile phase unless modified slightly. Cavitation in the pump heads and bubble formation in the detector flow cell of those systems often can be eliminated by using an 8 psi (low pressure) solvent handling system (part no. 90000481) and back pressure regulator (part no. 02-0175) which may be purchased from Alltech Associates, Inc., Deerfield, IL.

Materials. HPLC-grade pentane and methanol were purchased from Fisher Scientific. Mobile phases were prepared by blending the solvents in a 1-L graduate and mixing with a magnetic stirring bar. The mobile phases were neither vacuum degassed nor sparged with helium before or during their use.

Hydroboration of Cyclohexanone and 2-Methylcyclohexanone Enamines Using Thexylborane ($ThxBH_2$). Synthesis of 1a and 1b from 6-Methyl-1-(pyrrolidino)-cyclohexene. The following procedure is representative. A mixture of THF (6.1 mL) and BMS (10 M, 1 mL, 10 mmol) was cooled to 0 °C and charged dropwise with 2,3-dimethyl-2-butene (0.85 g, 10 mmol) with constant stirring. The reaction mixture was stirred at 0 °C for an additional 3 h. 6-Methyl-1-(1-pyrrolidino)cyclohexene (1.7 g, 10 mmol) was cooled to 0 °C and charged dropwise, with stirring, with the THF/thexylborane solution. The reaction mixture was stirred at 0 °C for an additional 2 h, quenched at 0 °C with methanol (3.0 mL), and stirred for an additional 1 h. The reaction mixture was charged at 0 °C with NaOH(s) (1.2 g, 30 mmol) followed by the dropwise addition of 30% H_2O_2 (3 mL, 24 mmol). After the vigorous reaction had subsided, the reaction mixture was refluxed for 1 h. The reaction mixture was cooled to rt and the organic fraction separated. The aqueous fraction was extracted with Et_2O (4 × 25 mL), the organic fractions were combined and dried over $MgSO_4$, and the Et_2O was removed under vacuum to yield a pale yellow oil. The oil was dissolved in methanol (15 mL), acidified with concentrated HCl (12 M, 1 mL, 12 mmol), and stirred for 15 min. The methanol was removed under vacuum to yield an amber-colored oil and an intractable solid. The residue was washed with Et_2O (2 × 25 mL) to remove byproduct thexyl alcohol, mixed with fresh Et_2O (25 mL), and NaOH (aq, 6 M) added until the reaction mixture was strongly basic to litmus. The organic fraction was separated and the aqueous fraction extracted with Et_2O (5 × 25 mL). The combined organic fractions were dried over $MgSO_4$ and the Et_2O removed under vacuum to yield crude **1a** and **1b** (1.0 g, 56% yield; bp 72–73 °C, 0.15 Torr).[6b]

Hydroboration of Cyclohexanone Enamines Using Dialkylboranes. Synthesis of *trans*-2-(4-Morpholino)-cyclohexanol (5) from 1-(4-Morpholino)cyclohexene Using Dicyclohexylborane (Chx_2BH). The following procedure is representative. A slurry of Chx_2BH (60 mmol) in THF (10 mL) cooled to 0 °C was charged with 1-(4-morpholino)-cyclohexene (1.7 g, 10 mmol). The reaction mixture was stirred at 0 °C for 2 h and then oxidized using NaOH(s) (0.6 g, 14 mmol) and 30% H_2O_2 (4 mL, 32 mmol). After the vigorous reaction had subsided, the reaction mixture was stirred for an additional 1 h at 25 °C and worked up as reported earlier.[6b] The crude amino alcohol was distilled to give pure *trans*-2-(4-morpholino)cyclohexanol: 1.4 g, 76% yield; bp 94–96 °C, 0.8 Torr (lit.[6b,21] bp 95–96 °C, 0.8 Torr); ^{1}H-NMR ($CDCl_3$) δ 1.2 (t, J = 7 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.

Hydroboration of 1-(4-Morpholino)cyclohexene with Monoisopinocampheylborane ($IpcBH_2$). Asymmetric Synthesis of *trans*-2-(4-Morpholino)cyclohexanol (5). The following procedure is representative. A 50 mL centrifuge tube equipped with a magnetic stirring bar was charged with 1-(4-morpholino)cyclohexene (1.5 g, 9 mmol) and Et_2O (anhydrous, 1.4 mL). The resulting solution was cooled to −40 °C with a cooling bath. The cooled solution was stirred and charged

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dropwise with $IpcBH_2$[18] (0.9 M, 10 mL, 9 mmol). After the addition was complete, the reaction mixture was stirred at −40 °C for an additional 1 h and then allowed to stand at −40 °C for an additional 20 h. The reaction was treated with methanol (1.0 mL, 25 mmol) and stirred at −40 °C for 1 h. The reaction vessel was transferred to an ice bath, and the reaction mixture was charged with NaOH (s) (1.1 g, 27 mmol) followed by the dropwise addition of H_2O_2 (30%, ~8 M, 2.7 mL, ~22 mmol) *[Caution!! Exothermic reaction!]*. After the addition was complete, the reaction was stirred for an additional 1 h at 25 °C. The supernatant was decanted from the white solid that formed, the solid was washed with Et_2O (2 × 10 mL), and the organic fractions were combined. The solvent was removed under vacuum (6 Torr) to leave a transparent, amber-colored oil. The oil was dissolved in methanol (20 mL), and the solution was acidified with HCl (12 M, 1.0 mL). The acidified reaction mixture was stirred at 25 °C for an additional 15 min. Methanol was removed under vacuum (6 Torr) to leave a mixture of a white solid and an amber-colored oil. The reaction mixture was washed with Et_2O (25 mL) and the supernatant decanted from the solid. The white solid was washed with Et_2O (4 × 25 mL) to remove byproduct isopinocampheol. The solid was mixed with fresh Et_2O (25 mL) and basified with 6 M NaOH until the aqueous layer was strongly basic to litmus. The ethereal fraction was separated, and the aqueous fraction was washed with Et_2O (2 × 25 mL). The organic fractions were combined and dried over $MgSO_4$, and the ether was removed under vacuum (6 Torr) to leave crude *trans*-2-(4-morpholino)cyclohexanol. The crude product was distilled under reduced pressure to give pure *trans*-2-(4-morpholino)cyclohexanol: 1.4 g, 84% yield; bp 43−45 °C, 0.3 Torr;[21] $[\alpha]_D$ +17.5° (*c* 3.0, MeOH). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.02; H, 11.05; N, 7.24. Product purity was verified by GC and FT-IR comparison with an authentic racemic sample synthesized from morpholine and cyclohexene oxide.[6,15] GC analysis of the menthyl chloroformate (MCF) derivative of the distilled *trans*-2-(4-morpholino)cyclohexanol indicated a minimum 21% ee.

Hydroboration of 1-(4-Morpholino)cyclopentene with Monoisopinocampheylborane ($IpcBH_2$). Asymmetric Synthesis of *trans*-2-(4-Morpholino)cyclopentanol. The representative procedure was followed at −40 °C: 1.9 g, 86% yield; bp 94-96 °C (0.2 Torr). Product purity was verified by GC and FT-IR comparison with an authentic racemic sample synthesized from morpholine and cyclopentene oxide.[6,15] GC analysis of the menthyl chloroformate (MCF) derivative of the distilled *trans*-2-(4-morpholino)cyclopentanol indicated a minimum 6% ee.

Hydroboration of 1-(1-Piperidino)cyclohexene with (Monoisopinocampheyl)borane ($IpcBH_2$). Asymmetric Synthesis of *trans*-2-(1-Piperidino)cyclohexanol (6). The representative procedure was followed at −40 °C: 0.9 g, 66% yield; bp 70−72 °C (0.2 Torr);[21] $[\alpha]_D$ +15.7° (*c* 3.0, MeOH). Product purity was verified by GC and FT-IR comparison with an authentic racemic sample synthesized from piperidine and cyclohexene oxide.[6,15] GC analysis of the MCF derivative of the distilled *trans*-2-(1-piperidino)cyclohexanol indicated a minimum 26% ee.

Hydroboration of 1-(*N*-Benzyl-*N*-methylamino)cyclohexene with (Monoisopinocampheyl)borane ($IpcBH_2$). Asymmetric Synthesis of *trans*-2-(*N*-Benzyl-*N*-methylamino)cyclohexanol (7). The representative procedure was followed at −40 °C: 1.4 g, 77% yield; bp 112−114 °C (0.2 Torr); $[\alpha]_D$ +17.7° (*c* 4.0, MeOH). Product purity was verified by GC and FT-IR comparison with an authentic racemic sample synthesized from benzylmethylamine and cyclohexene oxide.[6,15] GC analysis of the menthyl chloroformate (MCF) derivative of the distilled *trans*-2-(*N*-benzyl-*N*-methylamino)-cyclohexanol indicated a minimum 27% ee.

Hydroboration of (*E*)-1-(4-Morpholino)-1-octene with (Diisopinocampheyl)borane (Ipc_2BH). Asymmetric Synthesis of (*R*)-1-(4-Morpholino)-2-octanol (12). The following procedure is representative. To an aliquot of Ipc_2BH[19] (10 mmol) at 0 °C were added (*E*)-1-(4-morpholino)-1-octene (9.9 mmol, 2.13 g, 2.3 mL) and THF (10 mL). The resulting white suspension was stirred at 0 °C until it became transparent. The reaction mixture was added to NaOH (s) (560 mg, 14 mmol) and cooled to 0 °C under nitrogen. Hydrogen peroxide (30%, ~8 M, 4 mL, 32 mmol) was added dropwise by syringe resulting in a vigorous exothermic reaction. The reaction was stirred for 30 min at 0 °C and then 30 min at 25 °C. The organic layer was decanted from the sticky white solid that had formed, the solid was washed with THF (3 × 10 mL), the THF fractions combined, and the THF removed under vacuum (6 Torr, 25 °C). The oil that remained was mixed with methanol (10 mL) and acidified with concentrated HCl (12 M, 1 mL, 12 mmol). The reaction was stirred for 30 min at 25 °C. Trimethyl borate and residual methanol were removed under vacuum (6 Torr, 25 °C), leaving an amber-colored oil. The oil was washed with pentane (2 × 15 mL), 1:1 pentane: diethyl ether (2 × 15 mL), and diethyl ether (1 × 15 mL) (These washes were combined and evaporated, and the yield of isopinocampheol was determined). The amino alcohol hydrochloride was mixed with fresh ether (25 mL) and cooled to 0 °C. Solid sodium hydroxide, followed by 3 M NaOH (aq, 2 mL), was added to the reaction mixture with stirring until the aqueous layer was strongly basic to litmus. The ether was decanted into an Erlenmeyer flask, the white solid was washed with ether (4 × 15 mL), and the combined ether extracts were dried over $MgSO_4$. The ether was removed under reduced pressure (6 Torr, 25 °C), leaving crude (*R*)-1-morpholino-2-octanol as a transparent gold liquid. Chiral HPLC analysis of the distilled (*R*)-1-(4-morpholino)-2-octanol indicated 81% ee: 1.7 g, 80% yield; bp 89−91 °C (0.1 Torr);[9b] $[\alpha]_D$ −13.1° (*c* 6.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.2 (m, 10H), 2.2−2.4 (br m, 4H), 2.6 (m, 2H), 3.6 (m, 5H); ^{13}C-NMR ($CDCl_3$) 14.1, 22.7, 23.4, 23.6, 25.7, 29.3, 29.8, 31.8, 35.2, 54, 62.2, 68.2. Anal. Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70; N, 6.50. Found: C, 66.78; H, 12.36; N, 6.84.

Synthesis of (*R*)-1-(1-Pyrrolidino)-2-pentanol. The representative procedure was followed: 0.8 g, 52% yield; bp 43−45 °C (0.3 Torr); $[\alpha]_D$ −1.0° (*c* 3.0, MeOH);[12] enantiomers did not separate on chiral HPLC column; ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.3 (m, 4H), 1.7 (m, 4H), 2.1 (m, 1H), 2.3−2.6 (br m, 4H), 3.6 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 18.8, 23.5, 37.3, 54, 62.2, 68.0.

Synthesis of (*R*)-1-(4-Morpholino)-2-pentanol (8). The representative procedure was followed: 1.2 g, 71% yield, bp 57−59 °C (0.1 Torr); $[\alpha]_D$ −12.9° (*c* 6.0, MeOH);[12] chiral HPLC analysis of the distilled (*R*)-1-(4-morpholino)-2-pentanol indicated 83% ee; ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.3 (m, 4H), 2.1−2.3 (br m, 4H), 2.5 (m, 2H), 3.6 (m, 5H); ^{13}C-NMR ($CDCl_3$) 14.2, 18.8, 37.0, 53.6, 64.8, 65.7, 67.0.

Synthesis of (*R*)-1-(1-Pyrrolidino)-2-hexanol (9). The representative procedure was followed: 1.0 g, 60% yield; bp 63−65 °C (0.2 Torr); $[\alpha]_D$ −2.0° (*c* 5.0, MeOH);[12] chiral HPLC analysis of the distilled (*R*)-1-(1-pyrrolidino)-2-hexanol indicated 50% ee; ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.2−1.4 (br m, 6H), 1.7 (m, 4H), 2.2 (m, 2H), 2.4−2.6 (br m, 4H), 3.6 (m, 1H); ^{13}C-NMR ($CDCl_3$) 14.0, 22.8, 23.7, 27.8, 34.8, 54.0, 62.2, 68.2.

Synthesis of (*R*)-1-(4-Morpholino)-2-hexanol (10). The representative procedure was followed as described above: 1.1 g, 58% yield; bp 74−76 °C (0.2 Torr); $[\alpha]_D$ −12.6° (*c* 5.0, MeOH);[12] chiral HPLC analysis of the distilled (*R*)-1-(4-morpholino)-2-hexanol indicated 86% ee; ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.2−1.4 (br m, 6H), 2.2−2.4 (br m, 4H), 2.6 (m, 2H), 3.6 (m, 5H); ^{13}C-NMR ($CDCl_3$) 14.1, 22.8, 27.7, 34.5, 53.7, 64.8, 65.9, 67.0.

Synthesis of (*R*)-1-(1-Pyrrolidino)-2-octanol (11). The representative procedure was followed: 1.2 g, 61% yield; bp 82−84 °C (0.3 Torr); $[\alpha]_D$ −3.1° (*c* 6.0, MeOH);[12] chiral HPLC analysis of the distilled (*R*)-1-(1-pyrrolidino)-2-octanol indicated 70% ee; ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.2 (m, 10H), 1.7(m, 4H), 2.1 (m, 2H), 2.3−2.6 (br m, 4H), 3.6 (m, 1H); ^{13}C-NMR ($CDCl_3$) 14.1, 22.6, 23.5, 25.6, 29.5, 31.8, 35.2, 54.0, 62.2, 68.2. Anal. Calcd for $C_{12}H_{25}NO$: C, 72.73; H, 12.64; N, 6.94. Found: C, 72.06; H, 12.92; N, 7.50.

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Synthesis of (*R*)-1-(1-Pyrrolidino)-2-nonanol (13). The representative procedure was followed: 1.4 g, 66% yield; bp 87–89 °C (0.2 Torr);[12] $[\alpha]_D$ −1.1° (*c* 6.0, MeOH); chiral HPLC analysis of the distilled (*R*)-1-(1-pyrrolidino)-2-nonanol indicated 71% ee; ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.2 (m, 12H), 1.7 (m, 4H), 2.4–2.6 (br m, 6H), 3.6 (m, 1H); ^{13}C-NMR ($CDCl_3$) 14.1, 22.7, 23.4, 25.7, 29.3, 29.8, 31.8, 35.2, 54.0, 62.2, 68.2.

Synthesis of (*R*)-1-(4-Morpholino)-2-nonanol (14). The representative procedure was followed: 1.7 g, 75% yield; bp 93–95 °C (0.2 Torr); $[\alpha]_D$ −15.0° (*c* 7.0, MeOH).[12] Chiral HPLC analysis of the distilled (*R*)-1-(4-morpholino)-2-nonanol indicated 76% ee: ^{1}H-NMR ($CDCl_3$) δ 0.8 (m, 3H), 1.2 (m, 12H), 2.2–2.4 (br m, 4H), 2.6 (m, 2H), 3.6 (m, 5H); ^{13}C-NMR ($CDCl_3$) 14.1, 22.6, 25.6, 29.2, 29.7, 31.8, 34.8, 53.7, 64.8, 65.9, 67.0.

Synthesis of (*R*)-1-(1-Pyrrolidino)-3-phenyl-2-propanol. The representative procedure was followed: 1.4 g, 72% yield; bp 103–105 °C (0.4 Torr); $[\alpha]_D$ −1.1° (*c* 6.0, MeOH);[12] enantiomers did not separate on chiral HPLC column; ^{1}H-NMR ($CDCl_3$) δ 1.7 (m, 4H), 2.3 (m, 2H), 2.4 (m, 2H), 2.5–2.7 (br m, 4H), 3.8 (m, 1H), 7.2 (m, 5H); ^{13}C-NMR ($CDCl_3$) 23.6, 41.7, 54.1, 61.7, 69.4, 126.2, 128.3, 129.4, 138.6.

Synthesis of (*R*)-1-(4-Morpholino)-3-phenyl-2-propanol (15). The representative procedure was followed: 1.9 g, 85% yield; bp 118–120 °C (0.4 Torr); $[\alpha]_D$ −11.5° (*c* 7.0, MeOH);[12] chiral HPLC analysis of the distilled (*R*)-1-(4-morpholino)-3-phenyl-2-propanol indicated 86% ee; ^{1}H-NMR ($CDCl_3$) δ 2.3 (m, 4H), 2.5 (m, 2H), 2.5–2.8 (m, 2H), 3.6 (m, 4H), 3.9 (m, 1H), 7.2 (m, 5H); ^{13}C-NMR ($CDCl_3$) 41.4, 53.7, 64.1, 67.0, 67.3, 126.3, 128.4, 129.4, 138.3.

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Supplementary Material Available: ^{1}H- and ^{13}C-NMR spectra of the enantiomerically enriched acyclic β-amino alcohols synthesized (20 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.

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