76.29, 65.67, 55.69, 53.18, 52.16, 52.06, 50.80, 50.53, 45.68, 44.00, 42.70, 42.04, 38.23, 32.68, 31.00, 30.65, 25.05, 21.01, 7.61; HRMS (FAB) calcd for $C_{42}H_{53}N_4O_8$ (M^+ + 1) 741.3863, found m/e 741.3863.

(+)-(18'*S*)-4'-Desethyl-4'-deshydroxy-7'-norvinblastine (5). To a solution of (+)-**16** (43 mg, 0.058 mmol) in dioxane (4 mL) and glacial acetic acid (1 mL) was added 37% aqueous formaldehyde (2 mL), and the mixture was stirred at 35 °C for 24 h. The solution was evaporated in vacuo, and the residue was suspended in chloroform and washed with cold aqueous 5% K_2CO_3 solution. The chloroform layer was dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed, eluting with EtOAc/MeOH, 10% NH_4OH, to give **5** (35 mg, 81%): mp 195-197 °C (MeOH/Et_2O); $[\alpha]^{28}_D$ = +56.7° (c = 1.5 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) (MeOH) 209 (-118.9), 221 (+72.3), 255 (+27.7), 298 (+7.9), 309 (+7.8); IR ($CHCl_3$) 3456, 2995, 2940, 1740, 1616, 1505, 1460, 1434, 1373, and 1236 cm^{-1}. λ_{max} (ϵ) 213 (67100), 265 (20920), 310 (6870) nm; ^1H NMR ($CDCl_3$) δ 9.86 (1 H, s), 8.42 (1 H, s), 7.75 (1 H, br d, J = 2.1 Hz), 7.14 (3 H, m), 6.34 (1 H, s), 6.08 (1 H, s), 5.84 (1 H, dd, J's = 4.0 and 10.2 Hz), 5.40 (1 H, s), 5.27 (1 H, d, J = 10.1 Hz), 4.66 (1 H, d, J = 13.0 Hz), 4.42 (1 H, br s), 3.81 (3 H, s), 3.78 (3 H, s), 3.71 (3 H, s), 2.70 (3 H, s), 2.55 (1 H, s), 2.10 (3 H, s), 0,70 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9 171.6, 170.9, 157.9, 152.5, 134.6, 129.9, 128.9, 124.6, 123.0, 122.5, 122.4, 121.0, 119.5, 118.4, 111.5, 110.4, 93.8, 83.2, 79.7, 75.1, 65.2, 55.7, 55.5, 53.2, 52.5, 52.1, 51.0, 50.4, 50.2, 48.5, 45.9, 44.4, 42.6, 38.8, 30.9, 30.6, 29.6, 21.1, 14.1, 8.1; HRMS (FAB) calcd for $C_{43}H_{53}N_4O_8$ (M^+ + 1) 753.3863, found m/e 753.3878.

(+)-(18'*R*)-4'-Desethyl-4'-deshydroxy-7'-norvinblastine (19): mp 237 °C dec; $[\alpha]^{23}_D$ = -86.7° (c = 1.5 in $CHCl_3$); CD (MeOH) λ_{max} ($\Delta\epsilon$) 208 (+54.7), 221.5 (-59.2), 271 (+12.9), 294 (-3.0); IR ($CHCl_3$) 3423, 3003, 2931, 1742, 1615, 1498, 1459, 1432, 1372, 1231, and 1039 cm^{-1}; λ_{max} (ϵ) (MeOH) 214 (47600), 267 (14030) nm; ^1H NMR ($CDCl_3$) δ 9.72 (1 H, s), 9.12 (1 H, s), 7.70 (1 H, d, J = 7.15 Hz), 7.22 (1 H, d, J = 7.04 Hz), 7.11 (2 H, m), 6.3 (1 H, s), 6.11 (1 H, s), 5.86 (1 H, dd, J's = 10.17 and 3.67 Hz), 5.34 (1 H, s), 5.25 (1 H, d, J = 10.18 Hz), 4.48 (1 H, d, J = 12.57 Hz), 4.27 (1 H, d, J = 12.57 Hz), 3.91 (3 H, s), 3.77 (6 H, br s), 3.70 (1 H, s), 3.44-3.18 (3 H, m), 2.88-2.53 (5 H, m), 2.70 (3 H, s), 2.45-2.03 (5 H, m), 2.07 (3 H, s), 1.89 (2 H, m), 1.63 (2 H, m), 1.09 (1 H, m), 0.56 (3 H, t, J = 7.28 Hz); ^{13}C NMR ($CDCl_3$) δ 174.77, 171.53, 170.78, 156.51, 152.30, 134.77, 130.16, 128.33, 125.75, 124.51, 123.97, 122.01, 120.76, 119.31, 118.39, 110.43, 94.21, 82.95, 79.68, 76.30, 65.45, 56.02, 54.16, 53.11, 52.18, 52.15, 51.52, 50.55, 50.43, 48.18, 45.35, 43.58, 42.62, 39.40, 38.30, 30.55, 21.04, 13.60, 7.58; HRMS (FAB) calcd for $C_{43}H_{53}N_4O_8$ (M^+ + 1), 753.3863, found m/e 753.3878.

Acknowledgment. The National Institutes of Health are thanked for their support of this research (GM 29801). Dr. Homer Pearce (Eli Lilly) is thanked for gifts of vindoline and biological evaluation of vinblastine analogues.

Registry No. **5**, 131080-18-7; (-)-**6**, 25137-01-3; (-)-**6**·L-tartrate, 83602-37-3; (±)-**6**, 71962-74-8; **6a**, 131080-20-1; (*S,S*)-**6a**, 131080-19-8; **7**, 37675-20-0; **8**, 131080-21-2; **9**, 131080-22-3; **10**, 131080-23-4; **12**, 75400-66-7; (2*R*)-**13**, 131080-24-5; (2*S*)-**13**, 131080-25-6; (2*R*)-**14**, 131080-26-7; (2*S*)-**14**, 131080-27-8; **15**, 131176-68-6; **16**, 131080-28-9; **17**, 131080-29-0; **18**, 131175-57-0; **19**, 131175-56-9; MeO_2CCO_2Me, 553-90-2; *N*-(phenylsulfonyl)-indole, 40899-71-6; vindoline, 2182-14-1.

Supplementary Material Available: NMR spectra for compounds **8**, **13**, **14**, **15**, **16**, **17**, **18**, **19**, and **5** (16 pages). Ordering information is given on any current masthead page.

Chiral Synthesis via Organoboranes. 28. Reaction of α-Chiral Organyldichloroboranes with Organyl Azides Providing a Synthesis of Secondary Amines with Exceptionally High Enantiomeric Purities

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2-Alkyl-1,3,2-dioxaborinanes $R^*BO_2(CH_2)_3$ of essentially 100% enantiomeric purity were prepared by the asymmetric hydroboration of readily available prochiral olefins with mono- or diisopinocampheylboranes, followed by removal of the chiral auxiliary (α-pinene). The intermediate $R^*BO_2(CH_2)_3$ reacts readily with lithium aluminum hydride at 0 °C to give the corresponding lithium monoalkylborohydrides stereospecifically in very good yields and in very high enantiomeric purities. The lithium monoalkylborohydrides, on treatment with hydrogen chloride in dimethyl sulfide, give the corresponding monoalkyldichloroboranes in very high enantiomeric purity. The intermediate monoalkyldichloroboranes react readily with organic azides in 1,2-dichloroethane with evolution of gaseous nitrogen and transfer of the organic group from boron to nitrogen with complete retention of configuration to provide the corresponding secondary amines, either (+)- or (-), in very high yields and exceptionally high enantiomeric purities. The procedure was applied to the synthesis of representative optically active amines of high enantiomeric purities (ee or de ≥99%), including (2*S*,2'*S*)-di-2-butylamine, *N*-[(2*S*)-2-methyl-1-butyl]-(1*S*,2*R*)-*trans*-2-phenylcyclopentylamine, *N*-[(3*S*)-3,7-dimethyloct-6-enyl](1*S*,2*S*)-*trans*-2-methylcyclohexylamine, and the *meso*-di-2-butylamine.

The ready availability of pure enantiomers is vital to modern organic synthesis and much effort has been expended in developing new asymmetric methodologies to meet this requirement.[2] Amines are interesting organic compounds due to their physiological activity and their potential as organic intermediates.[3] For example, C_2-symmetric amines have been used both as enantioselective deprotonating agents[4] and as chiral auxiliaries in a number of asymmetric processes.[5] Generally, optically active secondary amines are prepared either by resolution of racemic amines or by synthesis from optically active pre-

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(2) *Asymmetric Synthesis*, Vol. 1-4; Morrison, J. D., Ed.; Academic Press: New York, 1983.

(3) Morris, D. R.; Morton, L. J., Eds. *Polyamines in Biology and Medicine*; Marcel Dekker, Inc.: New York, 1981.

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(5) (a) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403-3406. (b) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1984**, *25*, 857-860.

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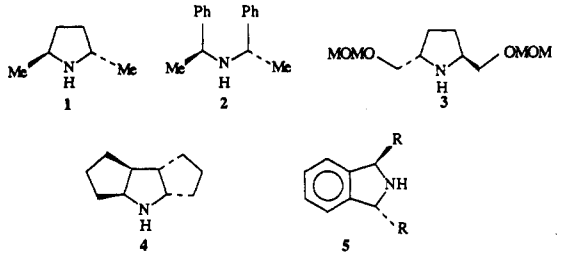
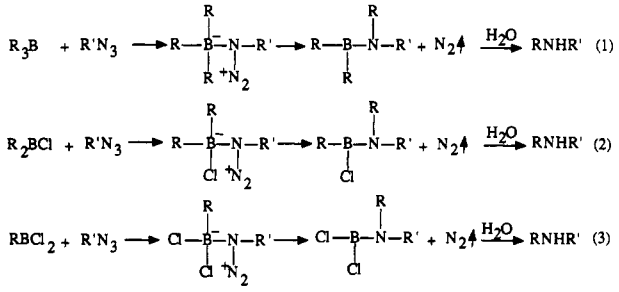
cursors.[4,6] Recently, asymmetric syntheses of secondary amines such as 1,[4,7] 2,[7a,8] 3,[5] 4,[9] and 5[10] have appeared in the literature.



Organoboranes are among the most versatile intermediates available to the organic chemist. Previous studies have shown that organoboranes commonly transfer the alkyl group to essentially most of the other elements of synthetic interest, including carbon, with complete maintenance of stereochemical integrity.[11] Several reactions are known involving the transfer of an alkyl group from organoboranes to nitrogen, providing the secondary amine derivatives.[12] For example, the reactions of organoboranes and their halogen derivatives with organic azides have been described in the literature. Thus trialkylboranes (R_3B),[12b] dialkylchloroboranes (R_2BCl),[12c] and monoalkyldichloroboranes ($RBCl_2$)[12d] react with variable ease with organic azides to give intermediates, which are readily hydrolyzed to form secondary amines (eqs 1–3).

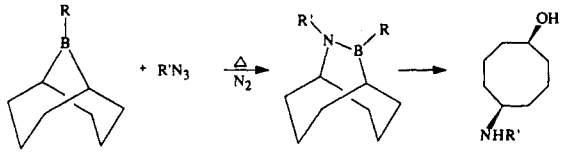


The asymmetric synthesis of secondary amines via borane reagents has not yet been achieved in high enantioselectivity, principally because of the lack of satisfactory synthetic routes to chiral R^*_3B, R^*_2BCl, and R^*BCl_2 derivatives.

Boranes derived from α-pinene exhibit great potential for converting commercially available prochiral olefins into optically active derivatives. A recent development offers promise of providing both chiral organoborane intermediates and all organic compounds containing a chiral center in essentially 100% enantiomeric purity in both (+) and (−) isomers.[13] Recently this development has been utilized for the synthesis of α-chiral aldehydes, β-chiral alcohols, α-chiral acids,[14] α-chiral primary amines,[15] and α-chiral terminal acetylenes.[16] We describe here a stereospecific conversion of enantiomerically pure boronic esters into the corresponding secondary amines of essentially 100% enantiomeric purity.

Results and Discussion

The reaction of trialkylboranes with organic azides[12b] is sensitive to stereoelectronic factors so that, at best, only one of the three alkyl groups can be utilized. Use of symmetrical trialkylboranes in this reaction limits the maximum yield of products to 33.3%. Second, even if we were to accept utilization of only one-third of the optically active groups in the reagent, R^*_3B, we did not have available an established procedure for its synthesis. In the reaction of dialkylchloroboranes R_2BCl,[12c] with organic azides, only one of the two alkyl groups is utilized. Therefore, the application of symmetrical dialkylchloroboranes in this reaction limits the maximum yield of products to 50%. The organoborane reagents derived from 9-borabicyclo[3.3.1]nonane (9-BBN) have been extensively employed in other reactions to achieve improved utilization of the alkyl groups on boron.[17] However, in the reaction with organic azides, the B–cyclooctyl bond migrates to the exclusion of the *B*-alkyl group (eq 4).[12e] On the other hand, application of monoalkyldichloroboranes in this reaction achieves a more economical utilization of the organic group introduced.[12d]



A recent development in our laboratories makes is possible now to synthesize either enantiomer of R^*BCl_2 in essentially 100% ee.

In order to establish the best suitable reaction conditions for the conversion of R^*BCl_2 in optically active secondary amines, we first explored the utilization of achiral $RBCl_2$. Cyclohexyldichloroborane[18] and cyclohexyl azide[19] were selected as representative reagents and their reaction examined in various solvents, such as pentane, diethyl ether (EE), dichloromethane, carbon tetrachloride, cyclohexane, 1,2-dichloroethane, and *n*-heptane, to establish the more favorable solvents for this reaction. This reaction had previously been carried out in benzene as solvent.[12d] Even in complexing solvents, such as EE, the reaction proceeds smoothly with evolution of gaseous nitrogen and gives a 78% yield of the corresponding amine. In nonpolar solvents, such as pentane, the reaction is slower and the yields are less satisfactory. Among the solvents studied, 1,2-dichloroethane, a solvent that has previously not been used, emerged as the most favorable solvent for this reaction. It provided both the fastest rates and highest yields.

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(15) Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761.
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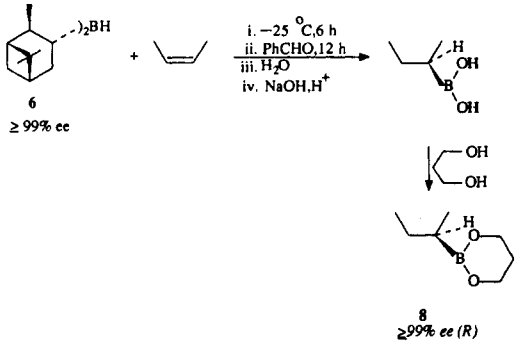
(18) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1976**, *98*, 1798.
(19) Prepared from cyclohexyl bromide and sodium azide in DMSO. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151–7157.

Scheme I



6
≥ 99% ee

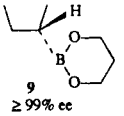
8
≥99% ee (R)

We then studied the interaction of cyclohexyl azide with various cyclohexylborane derivatives, R_3B, R_2BX, RBX_2 (where X = Cl, Br, F). These studies revealed that the fluoro derivatives[20] do not react readily, whereas the chloro and bromo derivatives[21] give comparable favorable results, affording the corresponding amines. Consequently, it appears that for this particular reaction, both the monoalkyldichloroboranes or the monoalkyldibromoboranes are satisfactory. Therefore we selected the more readily synthesized chloro derivatives for further studies, as well as 1,2-dichloroethane for the solvent.

Having established the best reaction conditions for the reaction of $RBCl_2$ with an organic azide, we turned our attention to the synthesis of optically active secondary amines.

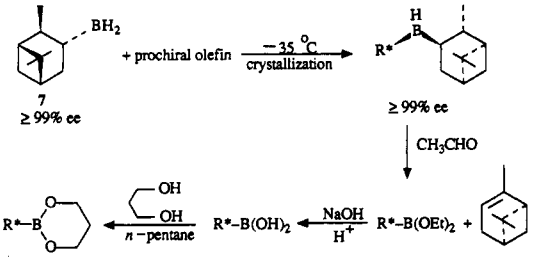
Optically active organoborane intermediates needed for the synthesis of optically active R^*BCl_2 derivatives were prepared by the asymmetric hydroboration of prochiral olefins with either diisopinocampheylborane (**6**), Ipc_2BH, (≥99% ee),[22] or monoisopinocampheylborane (**7**), $IpcBH_2$, (≥99% ee),[23,24] both readily prepared from (+)-α-pinene. Thus, asymmetric hydroboration of *cis*-2-butene with either (+)- or (−)-Ipc_2BH gives trialkylborane,[25] which, upon treatment with 1.8 equiv of benzaldehyde, results in the selective, facile elimination of the chiral auxiliary, providing the corresponding boronate ester. This was extracted from the reaction mixture with 3 N sodium hydroxide. Acidification with 3 N hydrochloric acid provided 2-butylboronic acid in high enantiomeric purity. The optically active 2-alkyl-1,3,2-dioxaborinanes were then prepared by esterification of the corresponding boronic acids with 1,3-propanediol (e.g., **8** and **9**)[26] (Scheme I).

Following the same procedure,[25] using (+)-Ipc_2BH derived from (−)-α-pinene provided (*S*)-2-butylboronic ester (**9**).



9
≥ 99% ee

Scheme II

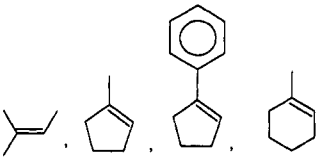


7
≥ 99% ee

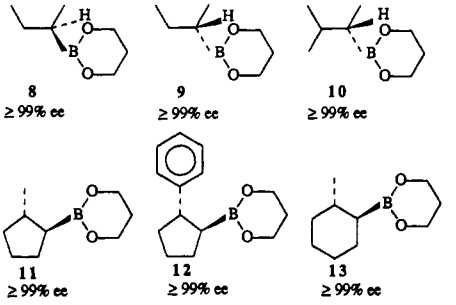
≥ 99% ee

Similarly, the asymmetric hydroboration of prochiral olefins with isopinocampheylborane (**7**), followed by crystallization, provides ≥99% ee optically pure isopinocampheylalkylboranes, IpcR*BH, which, upon treatment with acetaldehyde under mild conditions, eliminates the chiral auxiliary and provides the corresponding boronic ester in very high enantiomeric purity. The optically active 2-alkyl-1,3,2-dioxaborinanes were then prepared by esterification of the corresponding boronic acids with 1,3-propanediol[26] (Scheme II).

The following representative prochiral olefins were hydroborated with isopinocampheylborane[13] (**7**) to get the corresponding chiral alkylboronates of high enantiomeric purity:



Using these general procedures, the following representative chiral alkylboronic esters have been prepared in very high enantiomeric purities:



8
≥ 99% ee

9
≥ 99% ee

10
≥ 99% ee

11
≥ 99% ee

12
≥ 99% ee

13
≥ 99% ee

The enantiomeric excess of all of these organoborane intermediates was determined by capillary GC analyses of the appropriate derivatives of the alcohols obtained following alkaline hydrogen peroxide oxidation.[14]

The synthetic utility of chiral alkylboronic esters in the carbon–carbon bond-forming reactions have been demonstrated in the synthesis of α-chiral aldehydes, β-chiral alcohols, α-chiral acids,[14] α-chiral amines[15] and α-chiral terminal acetylenes.[16] The relatively inert chiral alkylboronic esters, upon treatment with lithium aluminum hydride ($LiAlH_4$), gives quantitatively the more reactive lithium monoalkylborohydrides, R^*BH_3Li, of very high enantiomeric purity.[27] These stable R^*BH_3Li intermediates can be converted into the optically active monoalkylboranes (R^*BH_2) by a simple treatment with trimethylsilyl chloride.[28]

The following representative lithium monoalkylborohydrides were prepared in very high enantiomeric purities

(20) McCusker, P. A.; Makowski, H. S. *J. Am. Chem. Soc.* **1957**, *79*, 5185.
(21) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1980**, *45*, 384.
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(23) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.
(24) These organoboranes actually exist in solution as dimers, that is, as derivatives of diborane molecules. However, it is convenient to refer to them as simple borane derivatives. They are considerably more stable as solutions in diethyl ether than in THF.
(25) (a) Brown, H. C.; Yoon, N. M. *Israel J. Chem.* **1977**, *15*, 12. (b) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Am. Chem. Soc.* **1982**, *104*, 4303.
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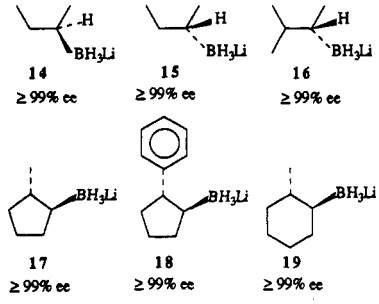
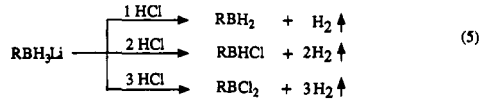
(28) Brown, H. C.; Cole, T. E.; Bakshi, R. K.; Srebnik, M.; Singaram, B. *Organometallics* **1986**, *5*, 2303–2307.

using this standard procedure:



The enantiomeric excess of all of these organoborane intermediates was determined by capillary GC analysis of the appropriate derivatives of the alcohols obtained following alkaline hydrogen peroxide oxidation.[14]

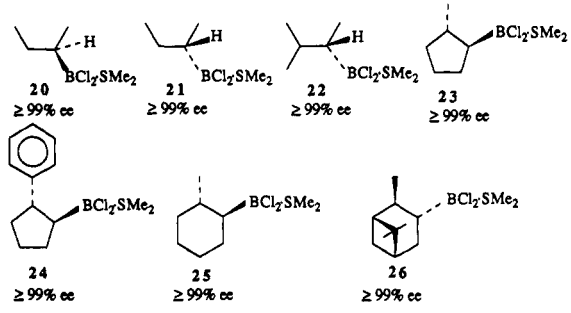
The lithium monoalkylborohydrides, on treatment with 1, 2, and 3 equiv of hydrogen chloride in EE, gives monoalkylborane,[28] monoalkylchloroborane, and monoalkyldichloroboranes, respectively (eq 5).



(5)

The optically active lithium monoalkylborohydrides were converted into the optically active monoalkyldichloroboranes by treatment with 3 equiv of hydrogen chloride in dimethyl sulfide at room temperature for 10 min. We have routinely used hydrogen chloride in dimethyl sulfide for the generation of optically active monoalkyldichloroboranes because they form a stable complex with dimethyl sulfide, which is easy to handle.

Using the general procedure described above, the following optically active monoalkyldichloroborane–dimethyl sulfide complexes were prepared in very high enantiomeric purities:

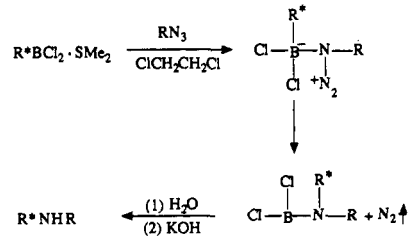


Isopinocampheyldichloroborane–dimethyl sulfide complex (**26**) was prepared from optically pure isopinocampheylborane[13] (**7**) by treatment with 2 equiv of hydrogen chloride in dimethyl sulfide at room temperature for 10 min. The reaction of hydrogen chloride in dimethyl sulfide with lithium monoalkylborohydride or with isopinocampheylborane is exothermic and is controlled by the rate of addition of calculated quantities of the solution of hydrogen chloride in dimethyl sulfide (3.74 M) to the solutions of lithium monoalkylborohydrides or isopinocampheylborane in ethyl ether.

This method is fairly general and works well for both hindered and less hindered derivatives. These optically active monoalkyldichloroborane–dimethyl sulfide complexes were used as such for the reaction with azides without further purification.

The optically active monoalkyldichloroborane–dimethyl sulfide complexes were prepared in diethyl ether from which diethyl ether was removed under reduced pressure

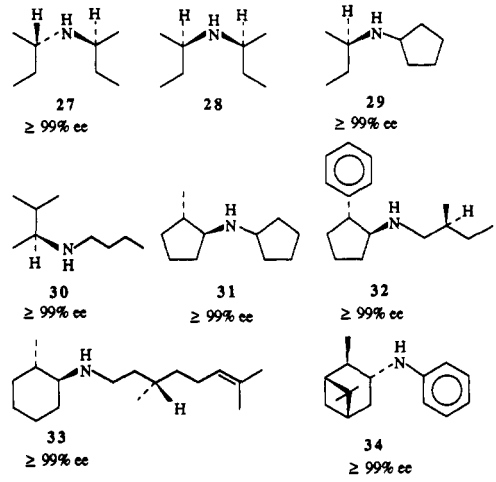
Scheme III



and 1,2-dichloroethane was added to make a 1 M solution of the reagent. The reaction flask was attached to a gas burette and an equimolar quantity of azide added slowly as the evolved nitrogen was measured. The present reaction is quite simple. Addition of an equimolar quantity of azide to a preheated optically active monoalkyldichloroborane–dimethyl sulfide complex results in the smooth evolution of gaseous nitrogen (1 equiv). The reaction is quite rapid. In some cases, the reactions are complete in 2 h at room temperature. The evolution of nitrogen provides a convenient means of monitoring the course of the reaction. Furthermore, the product gives a single ^{11}B NMR absorption at −31 ppm from boron trifluoride etherate, characteristic of (dialkylamino)dichloroboranes.[12d] Simple hydrolysis with water at 0 °C affords the optically active secondary amine, readily recovered by making the aqueous layer strongly alkaline with potassium hydroxide, followed by extraction with diethyl ether. Removal of the solvent gives the amine, further purified by distillation. The yields realized were in the range of 70–80%.

It is probable that this reaction for the formation of the secondary amine involves the steps shown in Scheme III: (a) coordination of the nitrogen with the optically active monoalkyldichloroborane with displacement of dimethyl sulfide; (b) rapid rearrangement of the intermediate to the (dialkylamino)dichloroborane with evolution of the gaseous nitrogen; (c) protonolysis of the (dialkylamino)dichloroborane with the water.

The following representative secondary amines were prepared in very high optical purities (Table I) by utilizing the general procedure:



This procedure makes possible the synthesis of optically active secondary amines having only one or two asymmetric centers (e.g., **29**, **30**, **31**) as well as C_2-symmetric and meso amines (**27**, **28**). *N*-Cyclopentyl-(2*R*)-2-butylamine was synthesized by reacting (2*R*)-2-butyldichloroborane–dimethyl sulfide complex (**20**) with cyclopentyl azide.[19] *N*-*n*-Butyl-(2*S*)-3-methyl-2-butylamine was prepared from the [(2*S*)-3-methyl-2-butyl]dichloroborane–dimethyl sul-

Table I. Optically Active Secondary Amines Synthesized from Optically Pure Monoalkyldichloroboranes: R*BCl_2 + RN_3 → R*NHR

R*BCl_2, R* =	organyl azides RN_3/R*N_3, R/R* =	secondary amines R*NHR/R*NHR*	mp, °C[d]	yield, %[e]	$[\alpha]^{23}_D$[c]	config	% ee
(*S*)-2-butyl[a]	(*S*)-2-butyl	di-2-butylamine (**27**)	176	65	+3.42	2*S*,2′*S*	≥99
(*R*)-2-butyl[b]	(*S*)-2-butyl	di-2-butylamine (**28**)	122	70	−0.002	2*R*,2′*S*	
(*R*)-2-butyl[b]	cyclopentyl	*N*-cyclopentyl-2-butylamine (**29**)	169–170	73	−3.46	*R*	≥99
(*S*)-3-methyl-2-butyl[b]	*n*-butyl	*N*-*n*-butyl-3-methyl-2-butylamine (**30**)	202–203	77	−3.26	*S*	≥99
(1*S*,2*S*)-*trans*-2-methylcyclopentyl[b]	cyclopentyl	*N*-cyclopentyl-*trans*-2-methylcyclopentylamine (**31**)	159–160	72	+39.13	1*S*,2*S*	≥99
(1*S*,2*R*)-*trans*-2-phenylcyclopentyl[b]	(*S*)-2-methyl-1-butyl	*N*(2-methyl-1-butyl)-*trans*-2-phenylcyclopentylamine (**32**)	134	80	+66.2	1*S*,2*R*,2′*S*	≥99
(1*S*,2*S*)-*trans*-2-methylcyclohexyl[b]	(*S*)-3,7-dimethyloct-6-enyl	*N*-(3,7-dimethyloct-6-enyl)-*trans*-2-methylcyclohexylamine (**33**)	136	80	+37.4	1*S*,2*S*,3′*S*	≥99
(1*R*,2*S*,3*R*,5*R*)-isopinocampheyl[b]	phenyl	*N*-3-isopinocampheylaniline (**34**)	216	75	−1.37	1*R*,2*S*,3*R*,5*R*	≥99

[a] Boronic ester prepared from (−)-α-pinene. [b] These boronic esters prepared by using chiral auxiliary obtained from (+)-α-pinene. [c] Specific rotation of the amine hydrochloride, recorded in solution (*c* 10, MeOH). [d] Melting points of the amine hydrochlorides. [e] Isolated yields reported from the corresponding lithium monoalkylborohydrides.

fide complex (**22**) and *n*-butyl azide.[19] Similarly [(1*S*,2*S*)-*trans*-2-methylcyclopentyl]dichloroborane–dimethyl sulfide complex (**23**) was reacted with cyclopentyl azide to get the *N*-cyclopentyl-(1*S*,2*S*)-*trans*-2-methylcyclopentylamine. Finally, *N*-(1*R*,2*S*,3*R*,5*R*)-3-isopinocampheylaniline (**34**) was synthesized from the (1*R*,2*S*,3*R*,5*R*)-3-isopinocampheyldichloroborane–dimethyl sulfide complex (**26**) and phenyl azide.[29]

The C_2-symmetric amine (2*S*,2′*S*)-di-2-butylamine (**27**) was synthesized by reacting (*S*)-2-butyldichloroborane–dimethyl sulfide complex (**21**) with (*S*)-2-butyl azide in 65% isolated yield and in excellent enantiomeric and distereomeric purity (≥99% ee or de). The (*S*)-2-butyldichloroborane required for the synthesis of (*S*,*S*)-di-2-butylamine was prepared from (+)-Ipc_2BH. The (*S*)-2-butyl azide prepared from the optically active (*R*)-2-butanol, which in turn was prepared by the asymmetric hydroboration of *cis*-2-butene with (−)-Ipc_2BH, followed by oxidation.[25] The (*R*)-2-butanol was converted into the corresponding (*R*)-tosylate, which, upon treatment with sodium azide in dimethy sulfoxide, formed the required azide. The optical purity of the azide was determined by its reduction to the corresponding amine.[30] The same method was applied for the synthesis of *meso* amine **28**. The required (*R*)-2-butyldichloroborane (**20**) was prepared from (−)-Ipc_2BH and treated with (*S*)-2-butyl azide to get the (*R*,*S*)-di-2-butylamine in 70% isolated yield.

This method works equally well for the synthesis of optically active secondary amines having two chiral groups attached to the nitrogen atom (e.g., **32**, **33**). The *N*-[(2*S*)-2-methyl-1-butyl]-(1*S*,2*R*)-*trans*-2-phenylcyclopentylamine (**32**) was prepared by reacting [(1*S*,2*R*)-*trans*-2-phenylcyclopentyl]dichloroborane–dimethyl sulfide complex (**24**) with (2*S*)-2-methyl-1-butyl azide[31] in 80% isolated yield and in ≥99% ee. In the same way *N*-[(3*S*)-3,7-dimethyloct-6-enyl]-(1*S*,2*S*)-*trans*-2-methylcyclohexylamine (**33**) was synthesized from the [(1*S*,2*S*)-*trans*-2-methylcyclohexyl]dichloroborane–dimethyl sulfide complex (**25**) and (3*S*)-3,7-dimethyloct-6-enyl azide[31] in 80% isolated yield and in ≥99% ee.

None of the optically active secondary amines reported here have been described previously in optically pure form. Consequently, the optical purities of these compounds could not be determined by chiroptical comparison. Therefore, the amines had to be derivatized by using enantiomerically pure (*R*)-MTPACl and then resolved on capillary GC. The established procedure for derivatization using pyridine as a base and enantiomerically pure (*R*)-MTPACl as the derivatizing agent worked well for less hindered amines but failed to derivatize the more hindered amines. The enantiomeric purity of these hindered secondary amines could be determined by a modification of the derivatization procedure. The amines were treated with methyllithium in diethyl ether and then either (*R*)-MTPACl or (*S*)-(−)-*N*-(trifluoroacetyl)prolyl chloride was added slowly at room temperature with vigorous stirring, yielding the diastereomeric amides. Each pair of diastereomeric amides was readily resolvable by capillary GC (SPB-5, 30 m/Supelcowax, 15 m). The enantiomeric purities for the synthesized chiral amines were ≥99% ee.

In the present study, the chiral monoalkyldichloroboranes are prepared from optically pure boronic esters. Since chiral boronic esters of either the (+)- or (−)-α-pinenes are readily available in essentially optically pure form, either from asymmetric hydroboration or the Matteson asymmetric synthesis,[32] we can now synthesize a wide variety of both (+) and (−) optically active secondary amines in high enantiomeric purity.

Conclusion

The methodology described in this study provides a convenient, simple, and high-yielding procedure for the synthesis of various secondary amines in essentially 100% enantiomeric purity. Both (+)- and (−)-α-pinenes are readily available. Consequently, both enantiomers of the amines are readily synthesized. This methodology provides the route for the synthesis of C_2-symmetric amines, which can be used as chiral auxiliaries or chiral deprotonating agents in very high enantiomeric purity. By using this method, both optically active C_2-symmetric amines and *meso* amines can be prepared.

This secondary amine synthesis from monoalkyldichloroboranes, described in this paper, provides a new method for introducing an amine functionality into olefins in a regio-, stereo-, and enantioselective manner.

Experimental Section

All operations were carried out under a nitrogen atmosphere with oven-dried glassware.[11] The ^{11}B NMR spectra were recorded

(29) Lindsay, R. O.; Allen, C. F. H.; Shriner, R. L.; Lawler, J. C. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 710.
(30) Maiti, S. N.; Singh, M. P.; Micetich, R. G. *Tetrahedron Lett.* **1986**, *27*, 1423.
(31) Prepared from the corresponding tosylate and sodium azide in DMSO.
(32) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294–300.

on a Varian FT-80A instrument. The ^1H NMR (60 MHz) spectra were recorded on a Varian T-60 spectrometer and the ^{13}C NMR spectra were scanned on a Varian Gemini-200 spectrometer. The chemical shifts are in δ relative to Me_4Si for ^1H and ^{13}C NMR spectra. Optical rotations were measured on a Rudolph Polarimeter Autopol III to ±0.01° but rounded off to 0.1° in Table I. Capillary gas chromatographic analyses were carried out with a Hewlett-Packard 5890 chromatograph fitted with 15-m Supelcowax/30-m SPB-5 columns.

Materials. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and was used directly. 1,2-Dichloroethane was purchased from EM Science, Inc., and was used directly. Lithium aluminum hydride (1.0 M) in EE and (−)-menthyl chloroformate (*l*-MCF) were purchased from Aldrich Chemical Company. The boronic esters used in this study were prepared by procedures described previously,[14] starting from (+)- and (−)-α-pinene. Azides used in this study, such as cyclopentyl azide,[19] *n*-butyl azide,[19] phenyl azide,[29] (*S*)-2-butyl azide,[25] (2*S*)-2-methyl-1-butyl azide,[31] and azido-3(*S*)-3,7-dimethyloct-6-ene [(*S*)-citronellyl acide][31] were prepared according to the literature procedures. (*R*)-MTPAA (α-methoxy-α-(trifloromethyl)-phenylacetic acid) was purchased from Aldrich Chemical Company and was converted to the acid chloride[33] and distilled. (*S*)-(−)-*N*-(Trifluoroacetyl)prolyl chloride (TPC) was prepared according to the literature procedure.[34]

All of the isopinocampheylalkylboranes,[13] 2-alkyl-1,3,2-dioxaborinanes[13] **8–13** and lithium monoalkylborohydrides[27] **14–19**, were prepared in very high enantiomeric purities according to the previously reported general procedures. The enantiomeric purities of all of these organoborane intermediates were determined by capillary GC analysis of the appropriate derivatives of the alcohols obtained following alkaline hydrogen peroxide oxidation.[14]

Preparation of Optically Active Monoalkyldichloroboranes. The following procedure for the preparation of [(1*S*,2*S*)-*trans*-2-methylcyclopentyl]dichloroborane is representative. A 100-mL flask fitted with a rubber septum and a magnetic stirring bar was charged with 20 mL of 0.584 M solution of lithium [(1*S*,2*S*)-*trans*-2-methylcyclopentyl]borohydride (**17**) (12 mmol) in EE. A 3.74 M solution of HCl in SMe_2 (9.6 mL, 36 mmol) was added with vigorous stirring. The stirring was continued for 10 min at 25 °C, and the evolved hydrogen was measured. The white precipitate of LiCl was immediately separated out. The supernatant solution containing the desired dichloroborane was transferred to another flask using a double-ended needle. The precipitate was washed twice with fresh EE (2 × 10 mL) and the washings were combined with the filtrate. The solvent was evaporated at 25 °C under reduced pressure (15 Torr). A ^{11}B NMR singlet was observed at δ +11.57. This signal is attributable to the dichloroborane–dimethyl sulfide complex. The dichloroborane was methanolyzed and oxidized with alkaline hydrogen peroxide. The product alcohol (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol had $[\alpha]^{23}_D$ +46.8 ± 0.01° (neat), suggesting ≥99% ee for the dichloroborane.

Preparation of Isopinocampheyldichloroborane (26). A 50-mL round-bottom flask with a rubber septum and magnetic stirring bar was charged with 13.2 mL of a 0.756 M solution of isopinocampheylborane[13] (**7**) (10 mmol) in EE. Then, a 3.74 M solution of HCl in SMe_2 (5.6 mL, 21 mmol) was added slowly with vigorous stirring at room temperature. The stirring was continued for 10 min and the evolved hydrogen was measured. ^{11}B NMR showed a singlet at δ +12. This signal is attributable to the dichloroborane–dimethyl sulfide complexes. The dichloroborane was then methanolyzed and oxidized with alkaline hydrogen peroxide. The product isopinocampheol had $[\alpha]^{23}_D$ −35.6° (*c* 10 in benzene), suggesting ≥99% ee for the isopinocampheyldichloroborane.

General Procedure for the Preparation of Optically Active Secondary Amines of Very High Enantiomeric Purity. The following procedure for the synthesis of *N*-cyclopentyl-(1*S*,2*S*)-*trans*-2-methylcyclopentylamine is representative. A dry 50-mL flask equipped with a septum inlet, reflux condenser, and magnetic stirrer was flushed with nitrogen. The flask was charged with 12 mL of 1,2-dichloroethane and 12 mmol of [(1*S*,2*S*)-*trans*-2-methylcyclopentyl]dichloroborane–dimethyl sulfide complex. The solution was heated to 60 °C and attached to a gas burette. Then 1.4 g (13 mmol) of cyclopentyl azide was added dropwise (~2.0 h) and the evolved nitrogen was measured. After the addition was complete, the solution was stirred an additional 30 min. Gas evolution had ceased at this point. The solution was cooled to 0 °C and very carefully hydrolyzed by slowly adding 10 mL of water (exothermic!). Then the reaction mixture was made strongly basic with 40% potassium hydroxide. The liberated amine was extracted with ether. The ether solution was dried over anhydrous K_2CO_3 and the ether removed under vacuum. Upon distillation, there was collected 1.2 g (72%) of *N*-cyclopentyl-(1*S*,2*S*)-*trans*-2-methylcyclopentylamine, bp 100 °C/15 Torr. The amine was further purified as its hydrochloride salt, mp 159–160 °C: ^1H NMR ($CDCl_3$) 3.1 (t, 1 H), 2.5 (t, 1 H), 0.9–2.1 (m, 18 H); ^{13}C NMR ($CDCl_3$) 19.3, 22.7, 24.1, 24.2, 33.3, 33.5, 33.6, 34.2, 41.3, 59.0, 65.9; $[\alpha]^{23}_D$ +39.13 ± 0.01° (*c* 10, MeOH). Anal. Calcd for $C_{11}H_{22}NCl$: C, 64.86; H, 10.81; N, 6.88; Cl, 17.44. Found: C, 64.47; H, 10.73; N, 7.11; Cl, 17.60.

(2*S*,2′*S*)-Di-2-butylamine: yield 65%; mp of hydrochloride salt, 176 °C; ^1H NMR (D_2O) 0.9 (t, 6 H), 1.22 (d, 6 H), 1.5 (m, 2 H), 1.7 (m, 2 H), 3.27 (m, 2 H); ^{13}C NMR (D_2O) 11.5, 17.3, 28.6, 55.4; $[\alpha]^{23}_D$ +3.42 ± 0.01° (*c* 10, MeOH). Anal. Calcd for $C_8H_{20}NCl$: C, 57.98; H, 12.17; N, 8.45; Cl, 21.45. Found: C, 57.59; H, 12.54; N, 8.68; Cl, 21.47.

(2*R*,2′*S*)-Di-2-butylamine: yield 70%; mp of hydrochloride salt, 122 °C; ^1H NMR (D_2O) 0.9 (t, 6 H), 1.21 (d, 6 H), 1.48 (m, 2 H), 1.71 (m, 2 H), 3.27 (m, 2 H); ^{13}C NMR (D_2O) 11.4, 17.9, 27.9, 55.3. Anal. Calcd for $C_8H_{20}NCl$: C, 57.98; H, 12.17; N, 8.45; Cl, 21.45. Found: C, 57.94; H, 12.23; N, 8.32; Cl, 21.36.

***N*-Cyclopentyl-(2*R*)-2-butylamine**: yield 73%; mp of hydrochloride salt, 169–170 °C; ^1H NMR ($CDCl_3$) 0.8–2.16 (m, 16 H), 2.6 (m, 1 H), 3.2 (m, 1 H); ^{13}C NMR (D_2O) 11.2, 17.5, 26.1, 28.3, 31.7, 32.0, 57.0, 58.7; $[\alpha]^{23}_D$ −3.46 ± 0.01° (*c* 10, MeOH). Anal. Calcd for $C_9H_{20}NCl$: C, 60.85; H, 11.27; N, 7.89; Cl, 20.00. Found: C, 60.75; H, 11.33; N, 8.22; Cl, 19.85.

***N*-*n*-Butyl-(2*S*)-3-methyl-2-butylamine**: yield 77%; mp of hydrochloride salt, 202–203 °C; ^1H NMR (D_2O) 0.5–1.7 (m, 17 H), 2.5 (m, 2 H); ^{13}C NMR (D_2O) 13.1, 15.3, 17.4, 20.9, 21.8, 30.2, 32.0, 47.7, 61.9; $[\alpha]^{23}_D$ −3.26 ± 0.01° (*c* 10, MeOH). Anal. Calcd for $C_9H_{22}NCl$: C, 60.17; H, 12.26; N, 7.80; Cl, 19.78. Found: C, 60.28; H, 12.37; N, 7.57; Cl, 19.86.

***N*-[(2*S*)-2-Methyl-1-butyl](1*S*,2*R*)-*trans*-2-phenylcyclopentylamine**: yield 80%; mp of hydrochloride salt, 134 °C; ^1H NMR ($CDCl_3$) 0.8 (m, 6 H), 0.9–2.4 (m, 12 H), 2.7 (m, 1 H), 3.1 (m, 1 H), 7.26 (m, 5 H); ^{13}C NMR ($CDCl_3$) 11.3, 17.7, 23.0, 27.6, 32.8, 34.0, 34.8, 53.2, 55.0, 66.9, 126.6, 127.9, 128.9, 145.0; $[\alpha]^{23}_D$ +66.2 ± 0.01° (*c* 10, MeOH). Anal. Calcd for $C_{16}H_{26}NCl$: C, 71.78; H, 9.72; N, 5.23; Cl, 13.27. Found: C, 71.70; H, 9.52; N, 5.60; Cl, 13.53.

***N*-[(3*S*)-3,7-Dimethyloct-6-enyl](1*S*,2*S*)-*trans*-2-methylcyclohexylamine**: yield 80%; mp of hydrochloride salt, 136 °C; ^1H NMR ($CDCl_3$) 0.8–1.7 (m, 23 H), 1.7 (d, 6 H), 2.0 (d, 2 H), 2.63 (m, 1 H), 5.1 (m, 1 H); ^{13}C NMR ($CDCl_3$) 17.7, 19.4, 19.8, 25.6, 25.7, 25.8, 26.2, 30.8, 32.5, 34.8, 37.4, 37.9, 38.0, 45.1, 63.5, 125.3, 131.5; $[\alpha]^{23}_D$ +37.4 ± 0.01° (*c* 10, MeOH). Anal. Calcd for $C_{17}H_{34}NCl$: C, 70.96; H, 11.83; N, 4.87; Cl, 12.35. Found: C, 71.31; H, 12.14; N, 4.86; Cl, 12.67.

***N*-(1*R*,2*S*,3*R*,5*R*)-3-Isopinocampheylaniline**: yield 75%; mp of hydrochloride salt, 216 °C; ^1H NMR ($CDCl_3$) 1.1 (s, 3 H), 1.2 (s, 3 H), 1.3 (s, 3 H), 1.5–2.8 (m, 8 H), 3.7 (m, 1 H), 6.7 (m, 3 H), 7.2 (t, 2 H); ^{13}C NMR ($CDCl_3$) 21.5, 23.6, 28.1, 34.7, 37.8, 38.7, 42.0, 47.3, 48.0, 52.6, 114.1, 117.6, 129.7, 148.5; $[\alpha]^{23}_D$ −1.37 ± 0.01° (*c* 10, MeOH). Anal. Calcd for $C_{16}H_{24}NCl$: C, 72.32; H, 9.04; N, 5.27; Cl, 13.37. Found: C, 72.43; H, 8.85; N, 5.37; Cl, 13.38.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM 10937-27) for their generous support of this work.

Supplementary Material Available: ^{13}C and ^1H NMR spectra for **27–34** (16 pages). Ordering information is given on any current masthead page.

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