Supplementary Material Available: General and X-ray experimental sections, X-ray data for **10** and the mercurated derivatives of **9**, **11**, and **14**, figures listing the atomic numbering scheme and tables for each compound (**9**-1...**9**-7, **10**-1...**10**-7, etc), ((1) X-ray structure determination summary, (2) atomic positional parameters, (3) bond distances, (4) bond angles, (5) anisotropic temperature factors, (6) hydrogen positional parameters), molecular geometry data after molecular mechanics energy minimization for compounds **9**-**15**, figures listing the numbering scheme for these molecular modeling studies and tables (**9**-1MM and **9**-2MM, **10**-1MM and **10**-2MM, etc) [(-1MM) orthogonal positional parameters and (-2MM) bond lengths, bond angles, and torsion angles] (90 pages). Ordering information is given on any current masthead page.

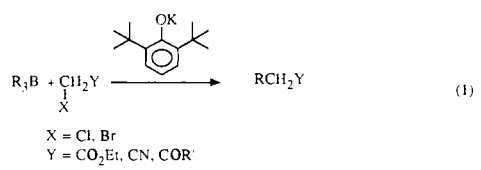
Chiral Synthesis via Organoboranes. 20. Conversion of Boronic Esters of Essentially 100% Optical Purity to *B*-Alkyl-9-borabicyclo[3.3.1]nonanes of Very High Optical Purity. Synthesis of Optically Active Homologated Esters, Nitriles, and Ketones

Herbert C. Brown,* Navalkishore N. Joshi,[1a] Chongsuh Pyun,[1b] and Bakthan Singaram

Contribution from the H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907. *Received May 23, 1988. Revised Manuscript Received September 8, 1988*

Abstract: 2-Alkyl-1,3,2-dioxaborinanes, $R^*BO_2(CH_2)_3$, of essentially 100% optical purity, prepared by the asymmetric hydroboration of readily available prochiral olefins with subsequent removal of the chiral auxiliary, can be transformed into lithium monoalkylborohydrides, R^*BH_3Li, of essentially 100% ee by reaction with lithium aluminum hydride. These borohydrides afford the corresponding monoalkylboranes, R^*BH_2, upon treatment with trimethylsilylchloride. Hydroboration of 1,5-cyclooctadiene with R^*BH_2 affords a mixture of *B*-alkyl-9-borabicyclo[4.2.1]nonane and *B*-alkyl-9-borabicyclo[3.3.1]nonane (*B*-R*-9-BBN). Thermal isomerization, 65 °C, 6 h, leads to isomerically pure *B*-R*-9-BBN without any significant loss of optical purity. The mixture of optically active *B*-alkyl-9-borabicyclo[4.2.1]nonane and *B*-R*-9-BBN react readily with ethyl bromoacetate, chloroacetonitrile, and α-bromo ketones in the presence of alkali metal *tert*-butoxide to give, respectively, homologated esters, nitriles, and ketones of very high optical purity. Since both (+)- and (-)-alkylboronic esters are available in essentially 100% optical purity, it is now possible to synthesize (+)- and (-)-esters, nitriles, and ketones in very high optical purities.

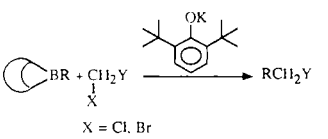
The ether-catalyzed addition of diborane to unsaturated organic molecules—the hydroboration reaction—made organoboranes readily available.[2] The boron atom in these organoboranes can be readily substituted with a variety of functional groups to give organic compounds under mild conditions such that organoboranes are now among the most versatile intermediates available to the organic chemist.[3] Our studies of these substitution reactions revealed that the organoboranes transfer the alkyl group to essentially most of the other elements of synthetic interest, including carbon, with complete retention of stereochemistry. For example, α-halogenated esters, nitriles, and ketones are readily alkylated with trialkylboranes in the presence of potassium 2,6-di-*tert*-butylphenoxide to give the corresponding homologated esters, nitriles, and ketones (eq 1).[4]



(1)

In attempting to apply this reaction to the synthesis of optically active derivatives, R^*CO_2R, R^*CH_2CN, and R^*CH_2COR', we were faced with several problems. First, this reaction involves utilization of only one of the three alkyl groups of the trialkylborane, R_3B. 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.

Use of mixed organoboranes, such as RR'_2B in which group R shows significantly greater migratory aptitude is effective in circumventing this difficulty. It may be stated that selection of the most suitably mixed organoboranes is the key to the successful application of organoboranes to organic synthesis. Indeed, if *B*-alkyl-9-borabicyclo[3.3.1]nonane (*B*-R-9-BBN) derivatives are used in this α-alkylation reaction, a more economical utilization of the organic group introduced is achieved (eq 2).[4]



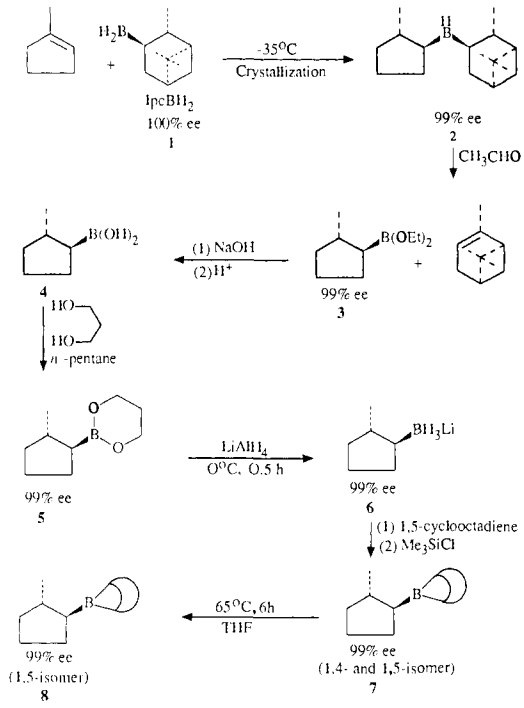
(2)

Consequently, it appeared that the *B*-R*-9-BBN derivatives might provide a satisfactory solution. However, we did not have available an established method for the synthesis of these derivatives. Accordingly, we had to devise some convenient procedure for the synthesis of *B*-R*-9-BBN and then attempt a quantitative

(1) (a) Postdoctoral research associate on Grant GM 10937-24 of the National Institutes of Health. (b) Visiting Professor on a grant from the Ministry of Education of the Republic of Korea.
(2) Brown, H. C.; Subba Rao, B. C. *J. Org. Chem.* **1957**, *22*, 1136.
(3) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975.
(4) Brown, H. C.; Nambu, H.; Rogic', M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6852, 6854, 6855.

0002-7863/89/1511-1754$01.50/0

Scheme I



transfer of the R* groups from boron to carbon without a loss of optical activity. Routinely, *B*-R-9-BBN derivatives are prepared from the corresponding olefins by hydroboration with 9-borabicyclo[3.3.1]nonane[5] or from the corresponding organometallic reagents.[6] Consequently, it is difficult to utilize the conventional method for preparing optically active *B*-R*-9-BBN derivatives where R* is an optically active group, either [*R*]- or [*S*]-isomer, in which the boron atom is attached directly to the chiral center. Yet, *B*-R*-9-BBN derivatives could be valuable intermediates in our chiral synthesis. A recent development offered promise of providing not only any *B*-R*-9-BBN derivatives but also of making these intermediates in essentially 100% optical purity.[7]

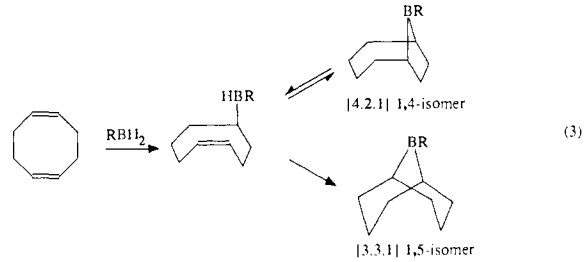
Results and Discussion

Optically active organoborane intermediates needed for the synthesis of optically active *B*-R*-9-BBN derivatives were prepared by the asymmetric hydroboration of prochiral olefins with diisopinocampheylborane, Ipc_2BH (99% ee),[8] and monoisopinocampheylborane, $IpcBH_2$ (**1**, 100% ee),[9,10] prepared from (+)-α-pinene. Thus, asymmetric hydroboration of prochiral olefins with **1** in the molar ratio of 1:1, followed by crystallization, provides the chiral isopinocampheylalkylboranes, IpcR*BH (e.g., **2**),[10] in essentially 100% optical purity. Treatment of these dialkylboranes with acetaldehyde under mild conditions results in the selective, facile elimination of the chiral auxiliary, providing the corresponding boronic ester (e.g., **3**) 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 (e.g., **4** and **5**) (Scheme I). The optical purities of all of these boronic esters were determined by ^{19}F NMR or ^{31}P NMR or capillary GC analyses of the appropriate derivatives of the alcohols obtained following alkaline hydrogen peroxide oxidation.[11]

Chiral alkylboronic esters are exceptionally promising intermediates for carbon–carbon bond-forming reactions. Recently, we utilized these boronic esters for the synthesis of α-chiral aldehydes, β-chiral alcohols, α-chiral acids,[11] and α-chiral amines.[12] Yet the versatility of these boronic esters would be greatly extended if the boron–oxygen bonds in these intermediates could be converted into boron–hydrogen bonds. It was a real breakthrough when we discovered that lithium aluminum hydride ($LiAlH_4$) readily converts these relatively inert boronic esters into the very reactive lithium monoalkylborohydrides, R^*BH_3Li, of very high optical purity (e.g., **5** and **6**).[13a] Diethyl alkylboronate esters (e.g., **3**) can be converted also into R^*BH_3Li, but we routinely used esters (**5**) because of the ease of isolation of the product. These R^*BH_3Li intermediates are very stable and can be stored under nitrogen, even at 25 °C, without any hydride loss, redistribution, isomerization, or racemization of the alkyl groups. The optically active monoalkylboranes (R^*BH_2)[10] is generated as and when needed by a convenient, simple reaction with trimethylsilyl chloride.[13b] Once the R^*BH_2 reagents are generated, they can hydroborate various olefins and dienes to give the corresponding mixed organoborane intermediates. Recently we made use of this methodology to make various optically active thexylmonoalkylboranes for the synthesis of optically active *cis*- and *trans*-olefins, alkynes, and ketones.[14]

The most direct way of preparing *B*-R*-9-BBN derivatives is the hydroboration of 1,5-cyclooctadiene with optically active monoalkylboranes. Surprisingly, very little effort has been devoted to the synthesis of *B*-R-9-BBN derivatives by this route, principally the result of the absence previously of satisfactory synthetic routes to monoalkylboranes. Additionally, during the course of our work on cyclic hydroboration, we observed that the hydroboration of 1,5-cyclooctadiene with thexylborane ($ThxBH_2$)[10] afforded a mixture of *B*-thexyl-9-borabicyclo[4.2.1]nonane (1,4-isomer, 80%) and *B*-thexyl-9-borabicyclo[3.3.1]nonane (1,5-isomer, 20%).[15] In the past, only the *B*-alkyl-9-borabicyclo[3.3.1]nonanes were used in the carbon–carbon bond-forming reactions.[3]

Apparently, the hydroboration of 1,5-cyclooctadiene with monoalkylboranes proceeds in two stages. The first step is the hydroboration of one of the double bonds. The second stage is the cyclic hydroboration which produces the regioisomers with the formation of a five-membered boracyclane kinetically favored over that of a six-membered ring (eq 3).[15]



(3)

In the present study, we hydroborated 1,5-cyclooctadiene with R^*BH_2 prepared in situ. The LiR^*BH_3 intermediates are readily converted into optically active *B*-alkyl-9-borabicyclononanes by a simple reaction with trimethylsilyl chloride in the presence of an equivalent of 1,5-cyclooctadiene (e.g., **6** and **7**). Alkaline hydrogen peroxide oxidation of the trialkylborane (e.g., **7**) provides a 70:30 mixture of *cis*-1,4- and 1,5-cyclooctanediols along with *trans*-2-methylcyclopentanol of 99% ee. We then checked the possibility of isomerizing the 1,4-isomer into the 1,5-isomer. On simple thermodynamic consideration, it is easy to see that the 1,5-isomer, with two fused six-membered rings, should be more stable than the 1,4-isomer, with the seven-membered ring fused

(5) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *91*, 5281.
(6) (a) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974**, *73*, 1. (b) Whiteley, C. G.; Zwane, G. *J. Org. Chem.* **1985**, *50*, 1969.
(7) Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797.
(8) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.
(9) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.
(10) 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.
(11) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980.
(12) Brown, H. C.; Kim, K.-W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761.
(13) (a) Brown, H. C.; Singaram, B.; Cole, T. E. *J. Am. Chem. Soc.* **1985**, *107*, 460. (b) Cole, T. E.; Bakshi, R. K.; Srebnik, M.; Singaram, B.; Brown, H. C. *Organometallics* **1986**, *5*, 2303.
(14) Brown, H. C.; Bakshi, R. K.; Singaram, B. *J. Am. Chem. Soc.* **1988**, *110*, 1529.
(15) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1972**, *94*, 3567.

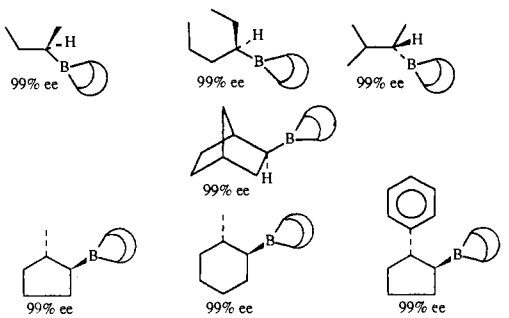
Table I. Alkylation of α-Halo Derivatives with Optically Active *B*-Alkyl-9-borabicyclononanes[a]

trialkylborane, *B*-R*-9-BBN[b] R* =	α-halo derivative	product	yield, % (isolated)[f]	bp, °C (Torr)	α^{23}_D, deg[g]
[*R*]-2-butyl	A[d]	[3*R*]-ethyl 3-methylpentanoate	60	60–62 (20)	−6.46 ± 0.01
[*S*]-3-methyl-2-butyl	A[d]	[3*R*]-ethyl 3,4-dimethylpentanoate	55	80–82 (20)	+5.74 ± 0.01
[1*S*,2*S*]-*trans*-2-methylcyclopentyl	A[d]	[1*S*,2*S*]-ethyl *trans*-2-methylcyclopentylacetate	50	96–98 (20)	+45.89 ± 0.01
[*R*]-3-hexyl	B[d]	[3*R*]-3-ethylhexanenitrile	66	82–84 (20)	−4.63 ± 0.01
[1*S*,2*S*]-*trans*-2-methylcyclopentyl	B[d]	[1*R*,2*S*]-*trans*-2-methylcyclopentylacetonitrile	48	96–98 (20)	+52.51 ± 0.02
[1*S*,2*S*,4*S*]-*exo*-2-norbornyl	B[d]	[1*S*,2*R*,4*R*]-*exo*-2-norbornylacetonitrile	53	112–114 (10)	+14.75 ± 0.01
[*R*]-3-hexyl	C[e]	[4*R*]-4-ethyl-2-heptanone	52	84–86 (30)	+0.69 ± 0.01
[*R*]-2-butyl	D[e]	[5*R*]-2,2,5-trimethyl-3-heptanone	60	80–82 (27)	−15.26 ± 0.01
[*R*]-2-butyl	E[e]	[3*R*]-3-methylvalerophenone	45	130–133 (20)	−17.65 ± 0.01

[a] Organoborane intermediates of 99% ee were prepared starting from (+)-α-pinene. [b] A mixture of 1,4- and 1,5-isomers. [c] A, ethyl bromoacetate; B, chloroacetonitrile; C, bromoacetone; D, bromopinacolone; E, phenacyl bromide. [d] *t*-BuONa was used as the base. [e] *t*-BuOK was used as the base. [f] Calculated starting from boronic ester (e.g., **5**). [g] Observed rotation (neat *l* 1.0).

to a five-membered ring (eq 3). Indeed, the isomerization of the 1,4-isomer takes place under quite mild conditions, 6 h at 65 °C (e.g., **7** and **8**). Oxidation of the trialkylborane (e.g., **8**) affords pure 1,5-cyclooctanediol along with *trans*-2-methylcyclopentanol of 99% ee. Obviously, the thermal isomerization (e.g., **7** and **8**) has proceeded without any significant racemization or epimerization.

We then discovered that the *B*-alkyl-9-borabicyclo[4.2.1]nonane derivatives also alkylate α-halogenated derivatives readily to afford the corresponding homologated products. Consequently, utilizing the general procedure, we prepared the following representative *B*-alkyl-9-borabicyclononanes (mixture of 1,4- and 1,5-isomer) in very high optical purities. Conversion of the boronic acid (e.g.,

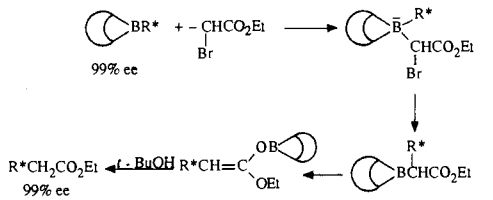


5) to the *B*-alkyl-9-borabicyclononanes (e.g., **7**) proceeds in essentially quantitative yields. The optical purity of all of these *B*-alkyl-9-borabicyclononanes was determined by measuring the rotations of the alcohols obtained following alkaline hydrogen peroxide oxidation and comparing the value with the maximum reported rotations. The enantiomeric excess of most of these alcohols was also determined by ^{19}F NMR of their MTPA esters[16] and/or by ^{31}P NMR with the use of the Anderson and Shapiro reagent[17] and/or by capillary GC analysis of their MTPA esters or their menthyl carbonates.[18]

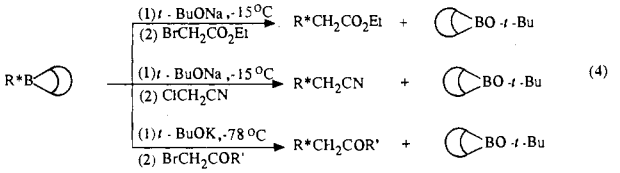
With the availability of *B*-alkyl-9-borabicyclononanes of very high optical purity, we examined the alkylation of representative α-halogenated esters, nitriles, and ketones. We slightly modified the previously known alkylation reactions of achiral *B*-R-9-BBN derivatives[4] to make them useful for the syntheses of optically active homologated esters, nitriles, and ketones via the optically active *B*-alkyl-9-borabicyclononane derivatives. For example, use of potassium 2,6-di-*tert*-butylphenoxide and oxidative workup made the isolation of product from the reaction mixture rather difficult. Fortunately, use of alkali metal *tert*-butoxide in tetrahydrofuran (THF) and a nonoxidative workup facilitated the isolation of the product. Moreover, both lithium and sodium *tert*-butoxides are readily prepared from the corresponding metal hydrides, and potassium *tert*-butoxide is commercially available. All three alkali metal *tert*-butoxides in THF worked equally well for the α-alkylation of ethyl bromoacetate. Sodium *tert*-butoxide in THF was best suited for the α-alkylation of chloroacetonitrile,

(16) Dale, A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(17) Anderson, R. C.; Shapiro, M. *J. Org. Chem.* **1984**, *49*, 1304.
(18) Racemic derivatives give two signals, which are well resolved.

Scheme II



and potassium *tert*-butoxide in THF worked very well for the α-bromo ketones (eq 4).



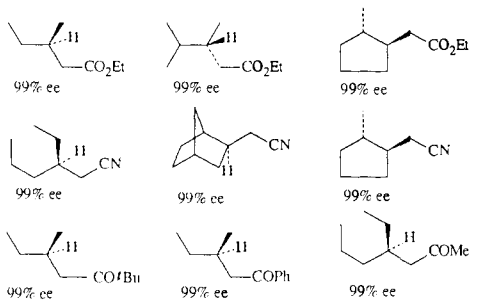
(4)

The present reaction is quite simple. An equimolar quantity of alkali metal *tert*-butoxide is added to the optically active *B*-alkyl-9-borabicyclononanes, followed by the addition of an equimolar quantity of the α-halogenated derivatives. The reaction is very rapid. As far as we could ascertain, in the case of α-bromo esters and α-bromo ketones, the reaction was over immediately following completion of the addition. However, the reaction of α-chloroacetonitrile with *B*-alkyl-9-borabicyclononane is relatively slower and takes about 8 h at 25 °C for completion. The byproduct, *B*-*tert*-butoxy-9-BBN, is readily removed from the reaction mixture by a simple wash with aqueous sodium hydroxide, and distillation affords the pure products. The yields observed were in the range of 50–70%, indicating some competition between migration of the *B*-alkyl group and the *B*-cyclooctyl group. There was no difficulty in utilizing [*R*]-*B*-2-butyl-9-borabicyclononane or [1*S*,2*S*]-*B*-(*trans*-2-methylcyclopentyl)-9-borabicyclononane. However, more hindered *B*-alkyl-9-borabicyclononanes, such as [1*S*,2*S*]-*B*-(*trans*-2-methylcyclohexyl)-9-borabicyclononane, gave lower yields. Evidently the reaction is sensitive to the steric environment of the boron atom.

It is probable that these reactions involve the steps shown for the formation of the homologated esters in Scheme II: (a) formation of the carbanion from α-bromoacetate; (b) coordination of the carbanion with the optically active *B*-alkyl-9-borabicyclononane; (c) rapid rearrangement of the intermediate to the enolborinate; (d) protonolysis of the enolborinate by *tert*-butyl alcohol.

Utilizing the general procedure, the following representative homologated esters, nitriles, and ketones were prepared in very high optical purities (Table I).

The homologated esters, nitriles, and ketones, reported here, have not been described previously in optically pure form. Consequently, the optical purities of these compounds could not be determined by chiroptical comparison. Attempted analyses of the homologated esters by capillary GC with optically pure α-methylbenzylamine as the derivatizing agent failed. Fortunately, the recently developed complexation gas chromatographic technique was of great help in establishing the optical purities of these



compounds. By using Ni-(R)-Cam as the stationary phase,[19] racemates of ethyl 3-methylpentanoate, ethyl 3,4-dimethylpentanoate, 4-ethyl-2-heptanone, and 3-methylvalerophenone could be cleanly resolved without derivatization. Enantiomeric excess for the corresponding synthesized chiral products was found to be ≥99%.

Previously we have shown that the α-alkylation of ethyl bromoacetate is a highly stereospecific reaction in which the original boron–carbon bond is replaced by a carbon–carbon bond with retention of the original stereochemistry.[20] Thus, *B*-(*trans*-2-methylcyclopentyl)-9-BBN was converted into ethyl *trans*-2-methylcyclopentylacetate. This ester was reduced to the corresponding alcohol and then converted to the pure *trans*-1-methyl-2-ethylcyclopentane through the intermediate formation of the tosylate (Scheme III). Since we start with *B*-alkyl-9-borabicyclononanes of essentially 100% ee and since the α-alkylation reaction proceeds with retention of configuration at the migrating carbon atom, as observed in other related 1,2-migration reaction of organoboranes, it is safe to conclude that the homologated esters, nitriles, and ketones reported here are essentially optically pure.

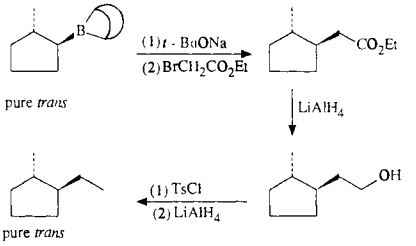
Additionally, we have converted [3*R*]-ethyl-3-methylpentanoate, obtained from optically active *B*-2-butyl-9-borabicyclononane, to the known compound [3*R*]-3-methyl-1-pentanol.[21] Previously, we prepared [3*R*]-3-methyl-1-pentanol by a double homologation of [2*R*]-2-butylboronic ester, followed by oxidation.[22] Chiroptical comparison showed that the [3*R*]-3-methyl-1-pentanol, obtained from the ester, is essentially 99% ee, suggesting that the reaction of [2*R*]-*B*-2-butyl-9-borabicyclononane with ethyl bromoacetate proceeds with retention of configuration (Scheme IV).

Conclusion

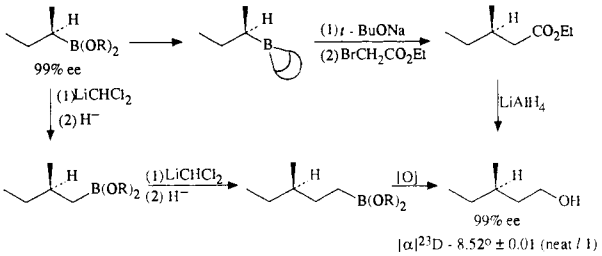
The present study provides a convenient, simple procedure for the synthesis of various optically active *B*-alkyl-9-borabicyclononanes. These are valuable reagents, especially promising for chiral synthesis proceeding through boron intermediates. Both (+)- and (−)-α-pinene are readily available. Consequently, both enantiomers are readily synthesized. The *B*-alkyl-9-borabicyclo[4.2.1]nonanes, formed initially in the hydroboration of 1,5-cyclooctadiene with optically active monoalkylboranes, are isomerized easily to the *B*-alkyl-9-borabicyclo[3.3.1]nonanes. These optically active *B*-alkyl-9-borabicyclononanes alkylate various α-halogenated derivatives in the presence of alkali metal *tert*-butoxide stereospecifically. Consequently, it is now possible by a remarkably simple procedure to achieve the synthesis of optically active functional derivatives involving carbon-atom homologation from olefins via asymmetric hydroboration.

Attempts to use *B*-alkyl-9-borabicyclononanes in which the alkyl groups are hindered, such as *B*-(*trans*-2-methylcyclohexyl)-9-borabicyclononane gave poor results. In spite of this difficulty, it is evident that this chiral alkylation procedure has many promising possibilities. Thus, it has proven possible to alkylate with optically active *sec*-butyl, 3-methyl-2-butyl, 3-hexyl, 2-*exo*-norbornyl, and *trans*-2-methylcyclopentyl groups, groups that are difficult to introduce by the usual reaction of alkyl halides with carbanions. Consequently, this method is not merely an alternative to the procedures presently available for the chiral alkylation of esters, nitriles, and ketones, but it promises to make possible the introduction of groups which cannot be handled by the other processes currently available.

Scheme III



Scheme IV



Experimental Section

All operations were carried out under a nitrogen atmosphere with oven-dried glassware.[3] The spectra were obtained in an inert atmosphere. The ^{11}B NMR spectra were recorded on a Varian FT-80A spectrometer, and the chemical shifts are in δ relative to EE·BF_3 with chemical shifts downfield from EE·BF_3 assigned as positive. The ^1H NMR spectra were scanned on a Varian XL-200 spectrometer, and the ^{13}C NMR spectra were obtained on a Varian FT-80A instrument. The chemical shifts are in δ relative to Me_4Si for ^1H and ^{13}C NMR spectra. ^{19}F NMR spectral analyses of the MTPA esters were performed on a Varian XL-200 spectrometer. ^{19}F NMR spectral analyses were performed on a Varian FT-80A or a Varian XL-200 spectrometer. Gas chromatographic analyses were carried out with a Hewlett-Packard 5750 chromatograph with a TC detector. Optical rotations were measured on a Rudolph Polarimeter Autopol III. Capillary gas chromatographic analyses were carried out with a Hewlett-Packard 5890 chromatograph fitted with 50 m methylsilicone/15 m Supelcowax/25 m Ni-(R)-Cam columns.

Materials. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and was used directly. Lithium aluminum hydride (1.0 M) in EE and (−)-menthyl chloroformate were purchased from Aldrich Chemical Company. The boronic esters used in this study were prepared by procedures described previously[11] starting from (+)-α-pinene. [*R*]-MTPA was purchased from Aldrich Chemical Company and was converted to the acid chloride[16] and distilled.

Isopinocampheyl-[1*S*,2*S*]-*trans*-2-methylcyclopentylborane (2). A 100-mL flask fitted with a rubber septum and a magnetic stirring bar was charged with 34.6 mL of (−)-IpcBH_2[7] (100% ee) in EE (0.723 M, 25 mmol) and cooled to −35 °C. 1-Methylcyclopentene (3.2 mL, 30 mmol) was added to it. The reactants were mixed together well and left at −35 °C without stirring for 12 h. The supernatant solution was decanted with the use of a double-ended needle. The crystalline isopinocampheyl-[1*S*,2*S*]-*trans*-(2-methylcyclopentyl)borane (**2**) was washed with cold (−35 °C) EE (2 × 5 mL) and dried at 25 °C under reduced pressure (12 Torr), 3 g (16.3 mmol, 65% yield). The dialkylborane was methanolyzed and oxidized. The [1*S*,2*S*]-*trans*-2-methylcyclopentanol obtained was purified by preparative GC: $[\alpha]^{23}_D$ +46.8° ± 0.01 (neat), ≥99% ee.

Preparation of 2-Alkyl-1,3,2-dioxaborinanes of Very High Optical Purity. The following procedure for the preparation of (+)-2-[1*S*,2*S*]-*trans*-2-methylcyclopentyl-1,3,2-dioxaborinane (**5**) is typical. Acetaldehyde (4 mL, 75 mmol) was added to a suspension of the dialkylborane (**2**, 25 mmol) in 20 mL of EE at 0 °C. After the vigorous initial reaction, 2 mL of acetaldehyde was added, and the reaction mix-

(19) Ni-(R)-Cam = nickel(II) bis[(1*R*)-3-(heptafluorobutyryl)camphorate]. See: (a) Schurig, V.; Burkle, W. *J. Am. Chem. Soc.* **1982**, *104*, 7573. (b) Schurig, V.; Weber, R. *J. Chromatogr.* **1984**, *289*, 321.

(20) Brown, H. C.; Rogic', M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1969**, *91*, 2150.

(21) (a) Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316. (b) Mori, K.; Watanabe, H. *Tetrahedron* **1984**, *40*, 299. (c) Rossi, R.; Carpita, A.; Chini, M. *Ibid.* **1985**, *41*, 627.

(22) Brown, H. C.; Naik, R. G.; Bakshi, R. K.; Pyun, C.; Singaram, B. *J. Org. Chem.* **1985**, *50*, 5586.

ture was stirred at 25 °C for 6 h. Water (5 mL) was added and stirred for 0.5 h. Excess acetaldehyde was evaporated (25 °C, 12 Torr, 1 h), and pentane (30 mL) was added. The boronic acid was extracted with 3 M NaOH (3 × 20 mL) in a separating funnel. The combined aqueous phase was cooled to 0 °C, acidified with 3 M HCl, extracted with EE (3 × 30 mL), and dried over anhydrous $MgSO_4$. Ethyl ether was evaporated, and boronic acid was esterified with 1,3-propanediol following the published procedure.[23] The ester was purified by distillation (3.4 g, 80% yield) [bp 108–110 °C (15 Torr); $[\alpha]^{23}_D$ +37.8° ± 0.02 (*c* 9, THF); ^{11}B NMR +31 (singlet); ^{1}H NMR ($CDCl_3$) 0.4–0.8 (m, 1 H), 1.0 (d, *J* = 7 Hz, 3 H), 1.3–2.1 (m, 8 H), 3.98 (t, *J* = 6 Hz, 4 H)]. Oxidation of the ester with alkaline hydrogen peroxide gave [1*S*,2*S*]-(+)-*trans*-2-methylcyclopentanol, which exhibited $[\alpha]^{23}_D$ +46.8° ± 0.01 (neat), suggesting ≥99% ee for the ester. The above alcohol was derivatized by using (−)-menthyl chloroformate, and capillary GC analysis on 50 m methyl silicone column showed a single peak.[18]

Synthesis of Optically Active *B*-Alkyl-9-borabicyclononanes of Very High Optical Purity. The following procedure for the preparation of [1*S*,2*S*]-*B*-*trans*-2-methylcyclopentyl-9-borabicyclononane (**7**, mixture of 1,4- and 1,5-isomers) is typical. A 100-mL flask fitted with a rubber septum and a magnetic stirring bar was charged with 22 mL of 1.0 M solution of **5** (22 mmol) in EE and cooled to 0 °C. A 1.0 M solution of $LiAlH_4$ in EE (22 mL, 22 mmol) was added with vigorous stirring. After 1 h at 0 °C, 1,5-cyclooctadiene (2.164 g, 20 mmol) was added, followed by the addition of trimethylsilyl chloride (4.78 g, 44 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at 25 °C for 12 h. The reaction mixture was filtered under nitrogen, and the metal salts were washed with EE (3 × 10 mL). The solvent was evaporated (25 °C, 20 Torr) from the combined filtrate, and the weight of the residue indicated the quantitative formation of **7**. The residue was dissolved in THF (16 mL), and the ^{11}B NMR spectrum of the solution showed a single peak at δ +86 due to the clean formation of the trialkylborane **7** (mixture of 1,4- and 1,5-isomer). Alkaline hydrogen peroxide oxidation of the trialkylborane **7** provided a 70:30 mixture of *cis*-1,4- and *cis*-1,5-cyclooctanediols[24] and [1*S*,2*S*]-(+)-*trans*-2-methylcyclopentanol in essentially quantitative yields. The *trans*-2-methylcyclopentanol thus obtained was derivatized by using (−)-menthyl chloroformate and capillary GC analysis showed a single peak, suggesting ≥99% ee for the trialkylborane **7**. The crude trialkylborane **7** (mixture of 1,4- and 1,5-isomers) was used in the α-alkylation reactions without further purifications.

In a separate experiment, a 1.0 M THF solution of the trialkylborane **7** (10 mmol) was refluxed for 6 h and then cooled to 25 °C. Oxidation with alkaline hydrogen peroxide now provided pure *cis*-1,5-cyclooctanediol[24] and [1*S*,2*S*]-(+)-*trans*-2-methylcyclopentanol in essentially quantitative yield. The latter was derivatized by using (−)-menthyl chloroformate, and capillary GC analysis showed a single peak, suggesting that the isomerization of the trialkylborane **7** to *B*-*trans*-2-methylcyclopentyl-9-BBN (**8**) proceeded without any racemization or epimerization.

Alkylation of Ethyl Bromoacetate with *B*-Alkyl-9-borabicyclononanes of Very High Optical Purity. The following procedure for the synthesis of [1*S*,2*S*]-(+)-ethyl *trans*-2-methylcyclopentylacetate is representative. A THF solution containing [1*S*,2*S*]-*B*-*trans*-2-methyl-9-borabicyclononane of 99% ee (20 mL, 20 mmol) was cooled to −15 °C (ice–salt bath), and sodium *tert*-butoxide in THF (20 mL, 20 mmol) was added to it. Ethyl bromoacetate (3.34 g, 20 mmol) was then added slowly with constant stirring. The reaction mixture was stirred at −15 °C for 1 h and then at 25 °C for 1 h. It was then diluted with *n*-pentane (100 mL) and washed successively with 3 M NaOH (3 × 10 mL) and water (2 × 10 mL), and the organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated (25 °C, 12 Torr), and the residue was distilled to give [1*R*,2*S*]-(+)-ethyl *trans*-2-methylcyclopentylacetate[25] 1.7 g (50%): bp 96–98 °C (20 Torr). The ester was further purified by preparative GC: ^{1}H NMR ($CDCl_3$) 0.98 (d, *J* = 7 Hz, 3 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.28–2.04 (m, 8 H), 2.12 (q, *J* = 9, 15 Hz, 1 H), 2.46 (q, *J* = 5, 15 Hz, 1 H), 4.13 (q, *J* = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 14.2, 18.9, 23.3, 32.4, 34.5, 39.4, 40.5, 44.1, 59.9, 173.3; α^{23}_D + 45.89° ± 0.01 (neat, *l* 1.0). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.57; H, 10.8.

Synthesis of Homologated Nitriles of Very High Optical Purity. The following procedure for the preparation of [1*S*,2*R*,4*R*]-(+)-2-*exo*-norbornylacetonitrile is typical. A THF solution containing [1*S*,2*S*,4*S*]-*B*-*exo*-2-norbornyl-9-borabicyclononane of 99% ee (20 mL, 20 mmol) was cooled to −15 °C (ice–salt bath), and sodium *tert*-butoxide in THF (20 mL, 20 mmol) was added to it. Chloroacetonitrile (1.51 g, 20 mmol) was then added slowly with constant stirring. The reaction mixture was stirred at −15 °C for 1 h and then at 25 °C for 12 h. The reaction mixture was then diluted with *n*-pentane (100 mL) and washed successively with 3 N NaOH (3 × 10 mL) and water (2 × 10 mL), and the organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated (25 °C, 12 Torr), and the residue was purified by distillation:[25] 1.43 g (53%); bp 112–114 °C (10 Torr). The nitrile was further purified by preparative GC: IR (neat) 2258 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.1–1.3 (m, 6 H), 1.5–1.6 (m, 2 H), 1.8–1.9 (m, 2 H), 2.1–2.3 (m, 3 H); ^{13}C NMR ($CDCl_3$) 23.7, 28.4, 29.7, 35.1, 37.0, 37.7, 39.0, 41.2, 119.4; α^{23}_D +14.75° ± 0.01 (neat, *l* 1.0). Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.70; H, 10.39; N, 10.34.

Alkylation of α-Halo Ketones with *B*-Alkyl-9-borabicyclononanes of Very High Optical Purity. The following procedure for the synthesis of [4*R*]-(+)-4-ethyl-2-heptanone is illustrative. A THF solution containing [3*R*]-*B*-3-hexyl-9-borabicyclononane of 99% ee (20 mL, 20 mmol) was cooled to −78 °C (dry ice–acetone bath), and potassium *tert*-butoxide in THF (20 mL, 20 mmol) was added to it. Bromoacetone (2.74 g, 20 mmol) was then added slowly with constant stirring. The reaction mixture was warmed up slowly, and potassium bromide started precipitating from the solution at −40 °C. The reaction was complete when the temperature reached 25 °C (4 h). It was diluted with *n*-pentane (100 mL) and washed successively with 3 N NaOH (3 × 10 mL) and water (2 × 10 mL), and the organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated (25 °C, 100 Torr), and the residue was distilled to give [4*R*]-(+)-4-ethyl-2-heptanone:[25] 1.46 g (52%); bp 84–86 °C (30 Torr). The ketone was further purified by preparative GC: IR (neat) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.85 (t, *J* = 7 Hz, 3 H), 0.89 (t, *J* = 7 Hz, 3 H), 1.2–1.4 (m, 6 H), 1.87 (m, 1 H), 2.13 (s, 3 H), 2.34 (d, *J* = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 10.7, 14.2, 19.8, 26.5, 30.1, 35.2, 36.0, 48.3, 208.6; α^{23}_D +0.69° ± 0.01 (neat, *l* 1.0). Anal. Calcd for $C_9H_{18}O$: C, 75.99; H, 12.75. Found: C, 75.31; H, 12.78.

[3*R*]-(−)-Ethyl 3-Methylpentanoate. ^{1}H NMR ($CDCl_3$) 0.92 (m, 6 H), 1.09–1.45 (m, 2 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.75–1.99 (m, 1 H), 2.01 (q, *J* = 10, 14 Hz, 1 H), 3.32 (q, *J* = 6, 14 Hz, 1 H), 4.12 (q, *J* = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 11.0, 14.1, 19.0, 29.2, 31.8, 41.3, 59.8, 172.9. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.19. Found: C, 66.87; H, 11.49.

[3*R*]-(+)-Ethyl 3,4-Dimethylpentanoate. ^{1}H NMR ($CDCl_3$) 0.86 (m, 9 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.78 (m, 1 H), 1.9 (m, 1 H), 2.08 (q, *J* = 10, 16 Hz, 1 H), 2.36 (q, *J* = 6, 16 Hz, 1 H), 4.13 (q, *J* = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 14.1, 15.7, 18.2, 19.7, 32.0, 35.9, 39.2, 59.9, 173.4. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.40; H, 11.67.

[3*R*]-(−)-3-Ethylhexanenitrile. IR (neat) 2238 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.92 (t, *J* = 7 Hz, 6 H), 1.3–1.6 (m, 7 H), 2.32 (d, *J* = 6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 10.7, 13.9, 19.6, 21.1, 26.1, 35.3, 36.4, 118.6. Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.72; H, 12.06; N, 11.54.

[1*R*,2*S*]-(+)-*trans*-2-Methylcyclopentylacetonitrile. IR (neat) 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.03 (d, *J* = 6 Hz, 3 H), 1.32–1.89 (m, 8 H), 2.29 (q, *J* = 6, 17 Hz, 1 H), 2.46 (q, *J* = 4, 17 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 18.9, 21.4, 23.2, 32.1, 34.6, 40.1, 43.8, 119.1. Anal. Calcd for $C_8H_{15}N$: C, 77.99; H, 10.63; N, 11.37. Found: C, 77.64; H, 10.84; N, 11.10.

[5*R*]-(−)-2,2,5-Trimethyl-3-heptanone. IR (neat) 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.85 (d, *J* = 6 Hz, 3 H), 0.87 (t, *J* = 7 Hz, 3 H), 1.12 (s, 9 H), 1.10–1.50 (m, 2 H), 1.87 (m, 1 H), 2.30 (q, *J* = 7, 16 Hz, 1 H), 2.42 (q, *J* = 6, 16 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 11.3, 19.4, 26.3, 29.5, 30.2, 43.6, 44.1, 197.4. Anal. Calcd for $C_{10}H_{16}O$: C, 76.86; H, 12.90. Found: C, 76.75; H, 12.64.

[3*R*]-(−)-3-Methylvalerophenone. IR (neat) 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.92 (t, *J* = 7 Hz, 3 H), 0.95 (d, *J* = 6 Hz, 3 H), 1.20–1.50 (m, 2 H), 2.10–2.25 (m, 1 H), 2.79 (q, *J* = 8, 17 Hz, 1 H), 2.90 (q, *J* = 6, 17 Hz, 1 H); 7.40–7.95 (m, 5 H); ^{13}C NMR ($CDCl_3$) 11.3, 19.5, 29.7, 31.4, 45.6, 128.0, 128.5, 132.7, 137.7, 200.2. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.87; H, 9.30.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM 10937-24) and the Ministry of Education, Republic of Korea, for their generous support of this work. We thank Dr. G. Rajendran of our group for his assistance in obtaining the 200 MHz ^{1}H NMR spectra of compounds reported in this study.

(23) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.

(24) The cyclooctanediols were silylated and analyzed by using a 50 m methylsilicone capillary column.

(25) The products contained about 5% of cyclooctanone arising from the oxidation of *B*-*tert*-butoxy-9-BBN.