Chiral Synthesis via Organoboranes. 6. Hydroboration. 74. Asymmetric Hydroboration of Representative Heterocyclic Olefins with Diisopinocampheylborane. Synthesis of Heterocyclic Boronates and Heterocyclic Alcohols of Very High Enantiomeric Purity

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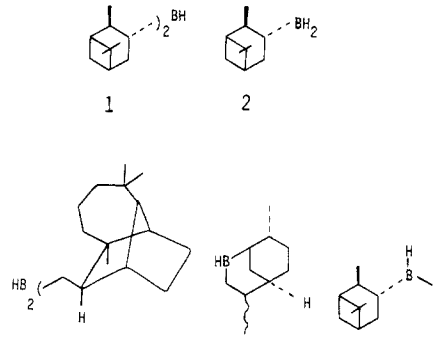
Abstract: The hydroboration of representative heterocycles bearing an endocyclic double bond with diisopinocampheylborane (Ipc_2BH) was investigated systematically to establish the asymmetric induction achieved in the reaction. The hydroboration of 2,3- and 2,5-dihydrofurans, 1,4-epoxy-1,4-dihydronaphthalene, and 2,3-dihydrothiophene with Ipc_2BH in THF at −25 °C proceeded very cleanly to afford the corresponding trialkylboranes. These trialkylboranes readily eliminate α-pinene on treatment with acetaldehyde to give the corresponding boronates, $R^*B(OR)_2$. Oxidation afforded in high yields the corresponding heterocyclic alcohols of 100% ee. *N*-(Carbobenzyloxy)-3-pyrroline could not be hydroborated with Ipc_2BH below 0 °C. The oxidation of the intermediate trialkylborane gave *N*-(carbobenzyloxy)-3-pyrrolidinol in 89% ee. Similarly, six-membered heterocyclic olefins, namely, 3,4-dihydropyran and 3,4-dihydrothiapyran, were hydroborated with Ipc_2BH at 0 °C in THF. The resulting trialkylboranes on treatment with acetaldehyde followed by oxidation yielded 3-hydroxytetrahydropyran and 3-hydroxytetrahydrothiapyran of 83% and 66% ee, respectively. *N*-(Carbobenzyloxy)-1,2,3,6-tetrahydropyridine, hydroborated with Ipc_2BH at 0 °C, followed by oxidation, afforded the corresponding 3- and 4-piperidinols in an 85:15 ratio. The asymmetric induction achieved during hydroboration was 70%. The five-membered heterocyclic boronates of very high optical purity, highly versatile synthetic intermediates, were isolated both as the diethyl and the diethanolamine esters.

Hydroboration is perhaps one of the most efficient reactions in synthetic organic chemistry.[2-5] The discovery of asymmetric hydroboration in 1961 marked the beginning of effective asymmetric synthesis.[6] Recently there has been intense interest in developing efficient methods for asymmetric synthesis.[7] Nevertheless, asymmetric hydroboration[8] remains a valuable procedure for the preparation of chiral products. Since 1961 various chiral hydroborating agents, using naturally abundant, low-cost terpenes, of various steric requirements, have been developed to hydroborate different classes of prochiral olefins.

Diisopinocampheylborane (Ipc_2BH, **1**)[9] hydroborates *cis*-alkenes, resulting in asymmetric hydroboration in the range of 60%–98% ee.[10] Similarly, monoisopinocampheylborane ($IpcBH_2$, **2**) hydroborates *trans*-alkenes and trisubstituted alkenes with optical induction ranging from 53% to 100% ee.[11] Recently *cis*-olefins and trisubstituted olefins were hydroborated with dilongifolylborane (Lgf_2BH, **3**) and limonylborane (LimBH, **4**), realizing moderate to good asymmetric induction.[12,13]

However, in all these cases, with two exceptions, essentially quantitative asymmetric induction was not realized. Only the hydroboration of *cis*-2-butene with Ipc_2BH, followed by oxidation, yields 2-butanol in > 98% ee,[10] and the hydroboration of 1-



phenyl-1-cyclopentene with $IpcBH_2$, followed by methanolysis and oxidation, yields *trans*-2-phenylcyclopentanol in 100% ee.[11] In these two examples, the intermediate organoboranes were converted to alkylboronic esters,[14] which are highly useful intermediates for carbon–carbon bond formation.[15,16] More recently, isopinocampheylalkylboranes (IpcBHR, **5**) of lower optical purities, obtained by the hydroboration of trisubstituted olefins with $IpcBH_2$, were recrystallized to obtain high optical purity materials of 100% ee.[17]

Recently we examined the hydroboration of representative heterocyclic olefins **6**–**9** bearing an endocyclic double bond with appropriate hydroborating agents.[18] These studies revealed clean hydroboration of these heterocyclic olefins with disiamylborane (Sia_2BH), constituting a model for possible asymmetric hydroboration with Ipc_2BH. Moreover, in the literature, there are almost no reports on the asymmetric hydroboration of heterocyclic olefins.[19] Therefore, we undertook a systematic study of the

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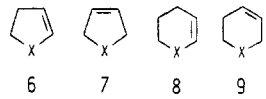


6 7 8 9

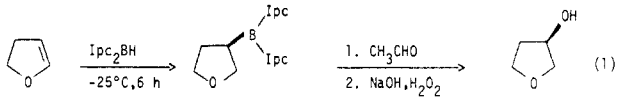
X = O, S or N

hydroboration of representative heterocyclic olefins with Ipc_2BH in the hope of developing a simple and efficient method for the synthesis of chiral heterocyclic compounds.

Results and Discussion

Diisopinocampheylborane of high enantiomeric purity (99.1% ee), prepared from borane–methyl sulfide and α-pinene (92% ee) by equilibration of the impure reagent with 15% excess of α-pinene,[10] has been used consistently in this study. The following five- and six-membered heterocyclic olefins were selected for study: 2,3-dihydrofuran, 2,5-dihydrofuran, 2,3-dihydrothiophene, 1,4-epoxy-1,4-dihydronaphthalene, *N*-(carbobenzyloxy)-3-pyrroline, 3,4-dihydropyran, 3,4-dihydrothiapyran, and *N*-(carbobenzyloxy)-1,2,3,6-tetrahydropyridine.

Five-Membered Heterocycles. The hydroboration of 2,3-dihydrofuran with (−)-Ipc_2BH (prepared from (+)-α-pinene) proceeded rapidly even at −25 °C and was complete within 6 h. The progress of the reaction is conveniently followed by the disappearance of the solid Ipc_2BH and confirmed by ^{11}B NMR (δ 85.6 relative to BF_3·OEt_2) examination of the formation of trialkylborane. The trialkylborane thus obtained was treated with acetaldehyde to displace α-pinene and yield diethyl 3-tetrahydrofuranylboronate, which upon oxidation with alkaline hydrogen peroxide, afforded 3-hydroxytetrahydrofuran in 92% isolated yield (eq 1). Although direct oxidation of the trialkylborane also yields

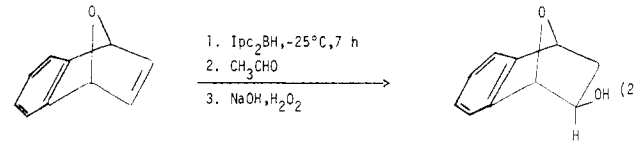


(1)

the alcohol, this type of workup is better for isolating pure product. Moreover, in this way, the chiral auxiliary, α-pinene, can be recycled. This reaction was scaled up to 250 mmol without experiencing any difficulty. The enantiomeric purity of the alcohol was determined to be 100% ee by ^{19}F NMR examination of its Mosher ester,[20] indicating a quantitative asymmetric induction during the hydroboration. The precise reason for the small difference between the apparent optical purity of the reagent, 99.1% ee, and the apparent optical purity of the product by the NMR procedure, 100% ee, was not explored. The absolute configuration is "*R*", as reported in the literature,[21] and is consistent with the expected result. Thus, our procedure constitutes a simple and efficient method for synthesizing 3-hydroxytetrahydrofuran in high yields and in higher enantiomeric purity, as compared to the literature procedure.[21]

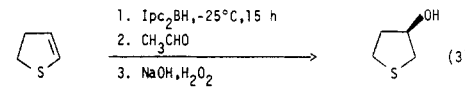
Similarly, hydroboration of 2,5-dihydrofuran with (−)-Ipc_2BH at −25 °C proceeded cleanly to afford the corresponding trialkylborane. The trialkylborane thus obtained on treatment with acetaldehyde, followed by oxidation with alkaline hydrogen peroxide, gave 3-hydroxytetrahydrofuran in good yield. Its optical purity was found to be 100%, and its absolute configuration is, as expected, "*S*". Thus, by changing the position of the double bond in a five-membered heterocycle with the same chiral auxiliary, the opposite enantioselectivity is achieved.

1,4-Epoxy-1,4-dihydronaphthalene, a strained heterocycle, was hydroborated cleanly with (−)-Ipc_2BH, as with Sia_2BH,[22] without any ring opening. Thus, 1,4-epoxy-1,4-dihydronaphthalene on treatment with (−)-Ipc_2BH at −25 °C for 7 h afforded the corresponding trialkylborane. The trialkylborane thus obtained was treated with acetaldehyde, followed by oxidation, and afforded 7-oxa-*exo*-2-benzonorborneol in 80% isolated yield (eq 2). The enantiomeric purity of the alcohol was 100%, as evidenced by ^{19}F NMR examination of its Mosher ester.



(2)

2,3-Dihydrothiophene, the five-membered sulfur heterocycle, was hydroborated with (−)-Ipc_2BH at −25 °C for 15 h to obtain the corresponding trialkylborane. The trialkylborane, upon treatment with acetaldehyde, followed by oxidation with alkaline hydrogen peroxide, afforded 3-hydroxytetrahydrothiophene in excellent yield (eq 1). This alcohol was also 100% ee by ^{19}F NMR of its Mosher ester.



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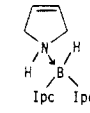
3-Pyrroline on treatment with (−)-Ipc_2BH (1:1 mole ratio) formed an amine–borane complex, **10** (as evidenced by ^{11}B NMR signal at δ 0.2), and no hydroboration was observed. 3-Pyrroline



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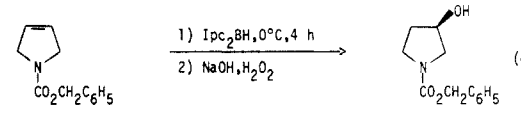
was then treated with 2 equiv (−)-Ipc_2BH and the reaction was stirred at −25 °C for 24 h. Again, no reaction was observed, even under these conditions. Moreover, the reaction failed to proceed even at 0 °C for 48 h. The 3-pyrroline–BF_3 complex, **11**, failed also to hydroborate with (−)-Ipc_2BH at 0 °C for 48 h. The nitrogen atom of 3-pyrroline was then protected by preparing its *N*-carbobenzyloxy derivative to study its hydroboration.

N-(Carbobenzyloxy)-3-pyrroline underwent successful hydroboration with (−)-Ipc_2BH only at 0 °C for 4 h. Oxidation provided *N*-(carbobenzyloxy)-3-pyrrolidinol in 92% isolated yield (eq 4).



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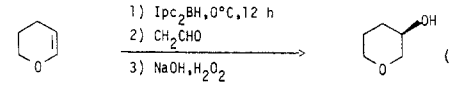
The enantiomeric purity of the alcohol was only 89%. The low asymmetric induction compared to other five-membered ring heterocycles may be due to the higher temperature utilized for the hydroboration stage. However, attempts to perform the hydroboration at the usual temperature, viz., −25 °C, proved unsuccessful.

Recently, *N*-(*tert*-butyloxycarbonyl)-3(*S*)-pyrrolidinol was synthesized in five steps, starting from L-malic acid, in 84% enantiomeric purity.[23] Thus, the hydroboration procedure herein described is a far simpler and more efficient method for synthesizing chiral 3-pyrrolidinols in high yields and high enantiomeric purities as compared to this recent literature procedure.[23]

These results are summarized in Table I. The opposite enantiomers were synthesized by hydroboration of the above olefins with (+)-Ipc_2BH (prepared from (−)-α-pinene) under similar conditions. The results are shown in Table II.

Hydroboration of Six-Membered Heterocycles. The hydroboration of 3,4-dihydropyran with (−)-Ipc_2BH could be achieved only at 0 °C to yield the corresponding trialkylborane. The trialkylborane thus obtained on treatment with acetaldehyde followed by oxidation afforded 3-hydroxytetrahydropyran in 81% isolated yield (eq 5). The ^{19}F NMR examination of its Mosher



(5)

ester showed it to be of 83% ee. The hydroboration could not be

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Table I. Asymmetric Hydroboration of Representative Five-Membered Heterocyclic Olefins with (−)-Diisopinocampheylborane[a]

olefin	product	reaction temp, °C	reaction time, h	isolated yield, %	$[\alpha]^{23}_D$, deg	% ee[b]	abs configuration
2,3-dihydrofuran	3-hydroxytetrahydrofuran	−25	6	92	−17.3 (*c* 2.4, methanol)	100	*R*
2,5-dihydrofuran	3-hydroxytetrahydrofuran	−25	8	68	+17.3 (*c* 2.4, methanol)	100	*S*
1,4-epoxy-1,4-dihydronaphthalene	7-oxa-*exo*-2-benzonorborneol	−25	7	68	+29.7 (*c* 2, methanol)	100	1*R*,2*S*,4*R*
2,3-dihydrothiophene	3-hydroxytetrahydrothiophene	−25	15	80	+14.6 (*c* 1, methanol)	100	*R*
N-(carbobenzyloxy)-3-pyrrolidine	*N*-(carbobenzyloxy)-3-pyrrolidinol	0	4	92	+20.5 (*c* 3.7, methanol)	89	*S*

[a] The reagent was prepared from (+)-α-pinene ($[\alpha]^{23}_D$+47.2° (neat), 91.4% ee) and BMS, and the reactions were carried out on a 25 mmol scale. [b] Determined by ^{19}F NMR of the corresponding Mosher ester on a 200-MHz NMR instrument.

Table II. Asymmetric Hydroboration of Representative Five-Membered Heterocyclic Olefins with (+)-Diisopinocampheylborane[a]

olefin	product	reaction temp, °C	reaction time, h	isolated yield, %	$[\alpha]^{23}_D$, deg	% ee	abs configuration
2,3-dihydrofuran	3-hydroxytetrahydrofuran	−25	6	87	+17.3 (*c* 2.4, methanol)	100	*S*
2,5-dihydrofuran	3-hydroxytetrahydrofuran	−25	8	74	−17.3 (*c* 2.4, methanol)	100	*R*
1,4-epoxy-1,4-dihydronaphthalene	7-oxa-*exo*-2-benzonorborneol	−25	7	72	−29.8 (*c* 2, methanol)	100	1*S*,2*R*,4*S*
2,3-dihydrothiophene	3-hydroxytetrahydrothiophene	−25	15	73	−14.5 (*c* 1, chloroform)	100	*S*
N-(carbobenzyloxy)-3-pyrroline	*N*-(carbobenzyloxy)-3-pyrrolidinol	0	4	85	−20.5 (*c* 3.7, methanol)	89	*R*

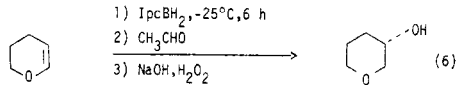
[a] The reagent was prepared from (−)-α-pinene ($[\alpha]^{23}_D$ −47.4° (neat), 92% ee) and BMS, and the reactions were carried out on a 25 mmol scale. [b] Determined by ^{19}F NMR of the corresponding Mosher ester on a 200-MHz NMR instrument.

Table III. Asymmetric Hydroboration–Oxidation of 3,4-Dihydropyran with Chiral Hydroborating Agents

hydroborating agent	reaction temp, °C	reaction time, h	isolated yield, %	$[\alpha]^{23}_D$ deg (neat)	% ee[a]	abs configuration
(−)-Ipc_2BH[b]	0	12	81	+9.8	83	*R*
(+)-Ipc_2BH[c]	0	12	85	−10.1	86	*S*
(−)-$IpcBH_2$[c]	−25	6	71	+4.0	34	*R*
(+)-$IpcBH_2$[b]	−25	6	70	−4.10	35	*S*

[a] The % ee is based on the maximum reported rotation: Durette, P. L.; Paulsen, H. *Chem. Ber.* **1974**, *107*, 937. $[\alpha]^{20}_D$ −11.8 (neat). [b] The reagent was prepared by using (+)-α-pinene of $[\alpha]^{23}_D$ +47.2 (neat) and BMS. [c] The reagent was prepared by using (−)-α-pinene of $[\alpha]^{23}_D$ −47.4 (neat) and BMS.

carried out at −25 °C. However, hydroboration of 3,4-dihydropyran could be performed at −25 °C by using a relatively less-hindered hydroborating agent, namely, $IpcBH_2$. The solid dialkylborane thus obtained on treatment with acetaldehyde followed by oxidation with alkaline hydrogen peroxide afforded 3-hydroxytetrahydropyran in 70% isolated yield (eq 6). The en-



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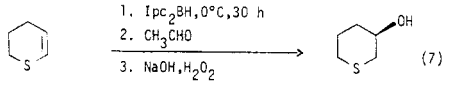
antiomeric purity of the alcohol was determined to be only 35%. The results are summarized in Table III. Thus, it is evident that for asymmetric hydrobortion of 3,4-dihydropyran, Ipc_2BH at 0 °C is better than $IpcBH_2$ at −25 °C, achieving a better asymmetric induction.

Similarly, 3,4-dihydrothiapyran was also hydroborated with (−)-Ipc_2BH at 0 °C. Thus, 3,4-dihydrothiapyran on treatment with (−)-Ipc_2BH at 0 °C for 30 h, followed by treatment with acetaldehyde, yielded the corresponding boronate. Oxidation afforded 3-hydroxytetrahydrothiapyran in good yield (eq 4). The enantiomeric purity of the alcohol was 66% by ^{19}F NMR examination of its Mosher ester.



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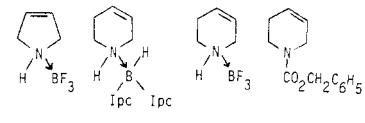
The six-membered nitrogen heterocycle, 1,2,3,6-tetrahydropyridine, behaved in a manner similar to that of the five-membered nitrogen heterocycle, as described previously. No hydroboration was achieved even at 0 °C with (−)-Ipc_2BH, even though an excess of the hydroborating agent was used. Only formation of the amine–Lewis acid complex **12** was observed. Similarly, the 1,2,3,6-tetrahydropyridine–BF_3 complex **13** also did not undergo hydroboration with (−)-Ipc_2BH at 0 °C.



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In this case also, hydroboration was achieved readily following deactivation of the amino moiety as the carbobenzyloxy derivative **14**. Thus, **14**, on treatment with (−)-Ipc_2BH at 0 °C for 24 h afforded the corresponding trialkylborane. Oxidation yielded 68% of *N*-(carbobenzyloxy)-3- and -4-piperidinols in the ratio of 85:15. The mixture of 3- and 4-ols was converted to its corresponding trimethylsilyl derivative, and the optically active *N*-(carbobenzyloxy)-3-(trimethylsilyloxy)piperidine was isolated by preparative gas chromatography. The enantiomeric purity of the regenerated 3-ol was determined to be 70% by examination of the ^{19}F NMR of its Mosher ester.

The absolute configurations of all the product alcohols are known, with two exceptions: 7-oxa-*exo*-benzonorborneol and *N*-(carbobenzyloxy)-3-piperidinol. However, in all the known cases, the same absolute configuration is realized, establishing that Ipc_2BH preferentially attacks from the one enantiotopic face of the heterocycle. Thus, the remarkable consistency of Ipc_2BH in providing alcohols of the same absolute configuration suggests

Table IV. Asymmetric Hydroboration of Representative Six-Membered Heterocyclic Olefins with (−)-Diisopinocampheylborane[a] at 0 °C

olefin	product	reaction time, h	isolated yield, %	$[\alpha]^{23}_D$ deg	% ee[b]	abs configuration
3,4-dihydropyran	3-hydroxytetrahydropyran	12	81	+9.8 (neat)	83	*R*
3,4-dihydrothiapyran	3-hydroxytetrahydrothiapyran	30	68	+30.1 (*c* 1, chloroform)	66	*R*
N-(carbobenzyloxy)-1,2,3,6-tetrahydropyridine	*N*-(carbobenzyloxy)-3-piperidinol + *N*-(carbobenzyloxy)-4-piperidinol	24	68	+8.0 (*c* 2.5, methanol)	70	*R*

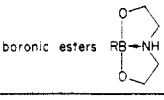
[a] The reagent was prepared from (+)-α-pinene ($[\alpha]^{23}_D$ +47.2° (neat), 91.4% ee) and BMS, and the reactions were carried out on a 25 mmol scale. [b] Determined by ^{19}F NMR of the corresponding Mosher ester on a 200-MHz NMR instrument.

Table V. Diethyl Heterocyclic Boronates of High Optical Purity

boronic esters $RB(OEt)_2$	yield, %	$[\alpha]^{23}_D$ deg	% ee[a]	abs configuration	^{11}B NMR chem shift δ[b]
diethyl 3-tetrahydrofuranylboronate[c]	78	+21.9 (*c* 5.1, chloroform)	100	*R*	30.6
diethyl 3-tetrahydrofuranylboronate[d]	72	−21.9 (*c* 5.1, chloroform)	100	*S*	30.6
diethyl 7-oxa-*exo*-2-benzonorbornylboronate	79	+32.0 (*c* 4.4, ethanol)	100	1*S*,2*S*,4*R*	32.9
diethyl 3-tetrahydrothiophenylboronate	72	−19.6 (*c* 5.9, ethanol)	100	*R*	32.3
diethyl *N*-(carbobenzyloxy)-3-pyrrolidinylboronate	68	−10.0 (*c* 5.3, ethanol)	89	*S*	30.2

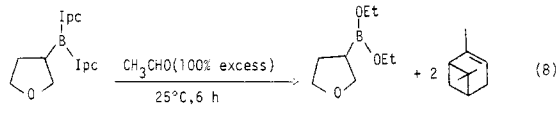
[a] The % ee was determined by oxidizing to the corresponding alcohol and by ^{19}F NMR of its Mosher ester. [b] Relative to $BF_3{\cdot}OEt_2$ (δ 0). [c] Prepared from 2,3-dihydrofuran. [d] Prepared from 2,5-dihydrofuran.

Table VI. Diethanolamine Heterocyclic Boronates of High Optical Purity

boronic esters 	yield, %	mp, °C	% ee	abs configuration	^{11}B NMR chem shifts δ (solvent)
diethanolamine 3-tetrahydrofuranylboronate	82	188	100	*R*	13.5 ($CDCl_3$)
diethanolamine 7-oxa-*exo*-2-benzonorbornylboronate	74	170	100	1*S*,2*R*,4*R*	13.2 ($CDCl_3$)
diethanolamine 3-tetrahydrothiophenylboronate	70	203	100	*R*	14.8 (Me_2SO-d_6)
diethanolamine *N*-(carbobenzyloxy)-3-pyrrolidinylboronate	86	185 (d)	89	*R*	14.6 (Me_2SO-d_6)

the practicality of utilizing the reaction[24,25] to predict the absolute configuration for the two unknown cases. This we have done (Tables I and IV). The absolute configurations of all heterocyclic alcohols synthesized in this study are summarized in Tables I–IV.

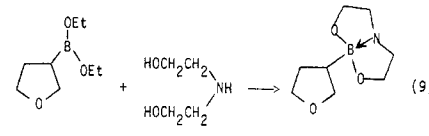
Isolation of Boronic Esters of Very High Enantiomeric Purity. Chiral alkylboronic esters containing only one alkyl group attached to boron are highly promising intermediates for asymmetric synthesis proceeding through boron chemistry.[16,17,26] Previously, we have shown that diisopinocampheylalkylborane, on treatment with acetaldehyde, liberates α-pinene quantitatively, providing optically active diethyl alkylboronate.[27] By adopting a similar procedure, diethyl heterocyclic boronates were prepared. Thus, diisopinocampheyl-3-furanylborane was treated with acetaldehyde at 25 °C for 6 h to yield diethyl 3-furanylboronate (eq 8).



(8)

However, by using the usual workup, the boronate could not be isolated in good yields, as it is highly soluble in water. Moreover, the boronate is unstable to heat and could not be isolated by distillation under reduced pressure. However, the boronate could be freed from α-pinene by pumping off the latter under high vacuum (0.5 mmHg) at 25 °C. Moreover, the pure boronate could also be isolated by column chromatography. The other five-membered heterocyclic boronates were isolated in a similar fashion. The results are summarized in Table V.

Since diethyl heterocyclic boronates possess low thermal stability, they were converted to the more stable, crystalline chelate ester.[28] Thus, diethyl 3-tetrahydrofuranylboronate, after being freed from α-pinene, was treated with diethanolamine to yield a crystalline solid, diethanolamine 3-tetrahydrofuranylboronate (eq 9). From such derivatives, the boronic acids can be easily re-



(9)

generated by treatment with 2 M hydrochloric acid.[28,29] Similarly, other heterocyclic boronates were also converted to their diethanolamine esters. The results are summarized in Table VI.

Conclusion

The present method provides a simple and efficient method for synthesizing heterocyclic alcohols of high enantiomeric purity from the readily available starting materials. Due to the availability of (+)- and (−)-α-pinene, both enantiomers are readily synthesized. The chiral auxiliary a-pinene can be recovered and recycled. The isolation of the five-membered heterocyclic boronic esters of essentially 100% ee offers a new route to synthesize many five-membered heterocyclic compounds in essentially 100% ee. The synthetic implications of such high enantiomerically pure boronic esters have been described.[17]

Experimental Section

The reaction flasks and other glass equipment were stored in an oven at 150 °C overnight and assembled in a stream of dry nitrogen gas. Syringes were assembled and fitted with needles while hot and cooled in a stream of dry nitrogen gas. Special techniques used in handling air-sensitive materials are described in detail elsewhere.[5]

Spectra. ^{11}B NMR spectra were recorded on a Varian FT-80A instrument. The chemical shifts are in δ relative to $BF_3{\cdot}OEt_2$. ^1H NMR (90 MHz), ^{13}C NMR (80 MHz), ^{19}F NMR (200 MHz) were recorded on Perkin-Elmer R-32, Varian FT-80A, and Varian FT-200 instruments, respectively. IR and mass spectra were recorded on Perkin-Elmer 137 and Finengan GC/mass spectrometers, respectively. The spectra of the product alcohols were described elsewhere.[18] Optical rotations were measured on a Rudolph polarimeter Autopol III.

GC Analyses. All GC analyses were carried out with a Hewlett-Packard 5750 chromatograph using (a) 12 ft × 0.125 in. columns packed with 10% Carbowax 20M on Chromosorb W (100–120 mesh) or (b) 12

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ft × 0.125 in. column packed with 10% SE-30 on Chromosorb W (100–120 mesh). For preparative GC, either (c) a 6 ft × 0.5 in. column packed with 20% Carbowax 20M on Chromosorb W (60–80 mesh) or (d) a 6 ft × 0.5 in. column packed with 20% SP-2100 on Chromosorb W (60–80 mesh) was used.

Materials. Borane–methyl sulfide (BMS), purchased from Aldrich Chemical Co., was estimated according to the standard procedure.[5] (+)-α-Pinene, +47.2° (neat) and β-pinene $[\alpha]^{23}_D$ −21.0° (neat), were purchased from Aldrich Chemical Co. and distilled from a small excess of LAH. (−)-α-Pinene, $[\alpha]^{23}_D$ −47.4° (neat), was prepared by isomerization of (−)-β-pinene with KAPA.[30] Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under nitrogen atmosphere in an ampule. 2,3-Dihydrofuran, 2,5-dihydrofuran, 3-pyrroline, 3,4-dihydropyran, and 1,2,3,6-tetrahydropyridine were kept over anhydrous potassium carbonate overnight and distilled in nitrogen atmosphere. 2,3-Dihydrothiophene and 3,4-dihydrothiapyran were prepared according to the literature procedure.[31] *N*-(Carbobenzyloxy)-3-pyrroline (contains 25% of *N*-(carbobenzyloxy)-3-pyrrolidine) and *N*-(carbobenzyloxy)-1,2,3,6-tetrahydropyridine were prepared by the reaction of 3-pyrroline (contains 25% pyrrolidine, Aldrich) and 1,2,3,6-tetrahydropyridine with benzyl chloroformate in the presence of sodium hydroxide.[32]

(−)-Diisopinocampheylborane [(−)-Ipc_2BH] of 99.1% ee was prepared from BMS and (+)-α-pinene according to the literature procedure.[11] Similarly, (+)-Ipc_2BH was prepared from BMS and (−)-α-pinene. The bis adduct of monoisopinocampheylborane with tetramethylethylenediamine (TMED·$IpcBH_2$) and generation of $IpcBH_2$ of 100% ee from it was done as reported in the literature.[33,17]

I. Hydroboration of Five-Membered Heterocycles. (A) Hydroboration of 2,3-Dihydrofuran. To a stirred suspension of (−)-Ipc_2BH (25 mmol) at −25 °C was added 1.9 mL (25 mmol) of 2,3-dihydrofuran. The reaction mixture was stirred at −25 °C for 6 h. The solid Ipc_2BH disappeared, and the formation of trialkylborane was complete. The reaction flask was brought to 0 °C, and 5.6 mL (100 mmol) of acetaldehyde was added dropwise and stirred at 25 °C for 6 h. Excess acetaldehyde was removed under reduced pressure (25 °C, 12 mmHg, 1 h) and to it 20 mL of THF was added. The boronate thus obtained was oxidized with 25 mL of 3 N sodium hydroxide and 3.75 mL of 30% hydrogen peroxide. The reaction mixture was stirred at 25 °C for 5 h. The aqueous layer was saturated with potassium carbonate, extracted with 3 × 25 mL of ether, and dried over $MgSO_4$ and the ether evaporated. The residue was filtered through silica gel. The pentane eluents remove α-pinene, whereas the ether eluents afforded the alcohol, which, on distillation, yielded 1.87 g of the material, bp 80 °C/15 mmHg, 92% isolated yield, GC purity 99%. It was further purified by preparative GC using a column c to furnish a GC-pure material: $[\alpha]^{23}_D$ −17.3° (*c* 2.4, MeOH); 100% ee [lit.[21] $[\alpha]^{22}_D$ +16.23° (*c* 2.427, MeOH), 99% ee].

(B) Hydroboration of 2,5-Dihydrofuran. To a stirred suspension of (−)-Ipc_2BH (25 mmol) in THF at −25 °C was added 1.9 mL (25 mmol) of 2,5-dihydrofuran. The reaction was complete within 8 h (^{11}B NMR) at −25 °C. The reaction mixture was worked up and purified as described above, $[\alpha]^{23}_D$ +17.3° (*c* 2.4, MeOH), 100% ee.

(C) Hydroboration of 1,4-Epoxy-1,4-dihydronaphthalene. To a stirred suspension of (−)-Ipc_2BH (25 mmol) in THF at −25 °C was added 3.6 g (25 mmol) of 1,4-epoxy-1,4-dihydronaphthalene in 5 mL of THF. The reaction mixture was stirred at −25 °C for 7 h. To the trialkylborane thus obtained was added 5.6 mL (100 mmol) of acetaldehyde at 0 °C, and the reaction mixture was stirred at 25 °C overnight. The excess acetaldehyde was removed under reduced pressure as described above, and the reaction mixture was oxidized with 25 mL of 3 N sodium hydroxide and 3.75 mL of 30% hydrogen peroxide and stirred at 25 °C for 5 h. The aqueous layer was saturated with potassium carbonate and extracted with 3 × 25 mL of ether and dried over $MgSO_4$ and the ether was evaporated. The residue was filtered through silica gel. The pentane eluents removed α-pinene, and the ether eluents gave the pure alcohol. Later on, crystallization from pentane afforded 2.9 g of crystalline GC-pure sample: mp 102–104 °C, 68% isolated yield; $[\alpha]^{23}_D$ +29.7° (*c* 2, MeOH), 100% ee.

(D) Hydroboration of 2,3-Dihydrothiophene. To a stirred suspension of (−)-Ipc_2BH (25 mmol) was added 2.2 mL (25 mmol) of 2,3-dihydrothiophene at −25 °C, and the reaction was stirred at −25 °C for 15 h. To the trialkylboranes thus obtained, 5.6 mL (100 mmol) of acetaldehyde was added and stirred at 25 °C for overnight. The reaction mixture was worked up as described for 2,3-dihydrofuran. 3-Hydroxytetrahydrothiophene: bp 42 °C/0.3 mmHg; 2.08 g, 80% isolated yield; $[\alpha]^{23}_D$ +14.6° (*c* 1, $CHCl_3$), 100% ee [lit.[34] $[\alpha]^{25}_D$ −4.31° (*c* 1.1, $CHCl_3$), 33% ee].

(E) Hydroboration of *N*-(Carbobenzyloxy)-3-pyrroline. To a stirred suspension of (−)-Ipc_2BH (25 mmol) was added 5.1 g (25 mmol) of *N*-(carbobenzyloxy)-3-pyrroline at 0 °C for 4 h. The trialkylborane thus obtained was oxidized by using 8.4 mL of 3 N sodium hydroxide and 9.4 mL of 30% hydrogen peroxide at 25 °C for overnight. The aqueous layer was saturated with potassium carbonate, extracted with 3 × 25 mL of ether, and dried over $MgSO_4$. The ether was evaporated. The crude product was subjected to column chromatography using silica gel. The 40% ether in pentane eluents removed α-pinene; isopinocampheol and ether eluents afforded 5.1 g of *N*-(carbobenzyloxy)-3-pyrrolidinol: GC purity ~98%, 92% isolated yield. It was further purified by preparative GC using column d to furnish a GC-pure sample: $[\alpha]^{23}_D$ +20.5° (*c* 3.7, MeOH); 90% ee.

II. Hydroboration of Six-Membered Heterocycles. (A) Hydroboration of 3,4-Dihydropyran. (i) With Ipc_2BH. The reaction was done at 0 °C and is as described for 2,3-dihydrofuran. 3-Hydroxytetrahydropyran: bp 90 °C/20 mmHg; 2.1 g, 81% isolated yield; preparative GC was done by using column d to obtain a GC-pure sample; $[\alpha]^{23}_D$ +9.8° (neat), 83% ee [lit.[34] $[\alpha]^{20}_D$ −11.8° (neat)].

(ii) With $IpcBH_2$. To (+)-$IpcBH_2$ (0.85 M, 29.4 mL, 25 mmol) in ethyl ether was added 2.3 mL (25 mmol) of dihydropyran at −25 °C. A solid was formed within 6 h. To it 5.6 mL (100 mmol) of acetaldehyde was slowly added at 0 °C, and the reaction mixture was stirred at 25 °C for 4 h. Then acetaldehyde was pumped off, and the reaction mixture was oxidized and worked up as described above: $[\alpha]^{23}_D$ −4.1° (neat), 35% ee.

(B) Hydroboration of 3,4-Dihydrothiapyran. The hydroboration with (−)-Ipc_2BH at 0 °C was done as described for 2,3-dihydrofuran: bp 50 °C/0.5 mmHg; 2 g, 68% isolated yield; preparative GC was done using column d to obtain a GC-pure sample: $[\alpha]^{23}_D$ +30.1° (*c* 1, chloroform), 66% ee [lit.[35] $[\alpha]^{25}_D$ −3.89°, 8% ee].

(C) Hydroboration of *N*-(Carbobenzyloxy)-1,2,3,6-tetrahydropyridine. The hydroboration with (−)-Ipc_2BH followed by oxidation and workup was done as described for *N*-(carbobenzyloxy)-3-pyrroline. Thus, a mixture (85:15) of *N*-(carbobenzyloxy)-3- and -4-piperidinols was obtained, 3.91 g, 68% isolated yield. These isomeric alcohols on treatment with bis(trimethylsilyl)acetamide at 25 °C for 2 h were converted to the corresponding trimethylsilyl derivatives. From this mixture, *N*-(carbobenzyloxy)-3-(silyloxy)piperidine was isolated by preparative GC using column d: $[\alpha]^{23}_D$ +8.5° (*c* 2.5, MeOH). *N*-(Carbobenzyloxy)-3-piperidinol was liberated by treatment of the silyloxy derivative with acetic acid in water at 25 °C for 4 h: $[\alpha]^{23}_D$ +8° (*c* 2.5, MeOH), 70% ee.

III. General Procedures for Isolation of Boronic Esters of High Optical Purity. (A) By Column Chromatography. Ethyl heterocyclic boronates were prepared by the reaction of diisopinocamphenyl heterocyclic borane with 100% excess of acetaldehyde at 25 °C as described above. Thus, the crude boronate obtained was freed from solvent and acetaldehyde and subjected to column chromatography using neutral alumina. Pentane eluents removed α-pinene completely, whereas ethanol eluents afforded the boronate. Ethanol was removed under vacuum at 25 °C to obtain pure ethyl heterocyclic boronate.

(B) Ethyl heterocyclic boronates could also be freed from α-pinene by pumping off the latter under high vacuum (0.5 mmHg) at 25 °C for 8 h.

The spectral properties of ethyl heterocyclic boronates are as follows.

Ethyl 3-Tetrahydrofuranylboronate. ^{11}B NMR ($CDCl_3$) δ 30.6; $[\alpha]^{23}_D$ +21.9° (*c* 5.1, $CHCl_3$); IR (pentane) 3373, 1328, 1415, 1224, 1017; ^1H NMR ($CDCl_3$) δ 3–4.2 (m, 8 H), 1.66–2.2 (m, 2 H), 1.23 (t, 6 H), 0.5 (m, 1 H); mass spectrum, *m/e* 173 (M + 1) (100%), 177 (22%), 147 (10%), 145 (6%), 131 (8%), 119 (13%).

Ethyl 3-Tetrahydrothiophenylboronate. ^{11}B NMR ($CDCl_3$) δ 32.2; $[\alpha]^{23}_D$ −19.6° (*c* 5.9, EtOH); IR (pentane) 3413, 1331, 1278, 1044; ^1H NMR ($CDCl_3$) δ 3.86 (q, 4 H), 1.63–2.36 (m, 4 H), 1.53 (m, 2 H), 1.16 (t, 6 H), 0.43 (m, 1 H); mass spectrum, *m/e* 189 (M + 1) (67%), 188 (17%), 147 (30%), 137 (100%), 114 (27%), 105 (14%).

Ethyl 7-Oxa-*exo*-2-benzonorbornylboronate. ^{11}B NMR ($CDCl_3$) δ 32.9; $[\alpha]^{23}_D$ +32° (*c* 4.42, EtOH); IR (chloroform) 3486, 2972, 2918, 1481, 1415, 1374, 1337, 1221, 1044, 987, 854; ^1H NMR ($CDCl_3$) δ 7.16 (s, 5 H), 5.43 (m, 2 H), 3.86 (q, 4 H), 2 (m, 2 H), 1.23 (t, 6 H), 0.9 (m, 1 H); mass spectrum, *m/e* 247 (M + 1) (0.8%), 239 (2%), 147 (14%), 137 (13%), 130 (12%), 129 (100%), 119 (11%).

Ethyl *N*-(Carbobenzyloxy)-3-pyrrolidinylboronate. ^{11}B NMR ($CDCl_3$) δ 30.2; $[\alpha]^{23}_D$ −10° (*c* 5.3, EtOH); ^1H NMR ($CDCl_3$) δ 7.3 (s, 5

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H), 5.1 (s, 2 H), 3.9 (q, 4 H), 3-3.6 (m, 4 H), 2-1.9 (m, 2 H), 1.2 (t, 6 H); mass spectrum, *m/e* 348 (M + 1) (11%), 347 (15%), 305 (18%), 304 (99%), 303 (27%), 302 (13%), 223 (11%), 222 (100%), 204 (65%), 91 (18%).

IV. General Procedure for Preparation of Diethanolamine Heterocyclic Boronate. Ethyl heterocyclic boronate (5 mmol) prepared as described above (IIIB) was taken in 15 mL of ether. To it 0.52 mL (5.4 mmol) of diethanolamine in 5 mL of 2-propanol was added, and the reaction mixture was stirred at 25 °C for 1 h. A crystalline solid formed, was filtered, and washed with 5 mL of cold ether. The results are shown in Table VI.

Acknowledgment. This article is dedicated on his 60th year to Prof. George Zweifel, University of California, Davis, for his pioneering work on both asymmetric hydroboration and hydroboration of heterocyclic olefins.

Onium Ions. 34.[1] The Methoxydiazonium Ion: Preparation, ^1H, ^{13}C, and ^{15}N NMR and IR Structural Studies, Theoretical Calculations, and Reaction with Aromatics. Attempted Preparation and the Intermediacy of the Hydroxydiazonium Ion

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Abstract: Nitrous oxide is methylated with $CH_3F \rightarrow SbF_5$ in SO_2F_2 or with CH_3O^+SOClF in SO_2ClF to give the stable methoxydiazonium ion $CH_3ON_2^+$ (**1**), which was characterized by NMR (^{15}N, ^{13}C, ^1H) and FT IR spectroscopic studies. It is stable below −30 °C, above which it decomposes, regenerating N_2O. When reacted with aromatics, such as toluene, **1** gives only methylation products and no methoxy derivatives are formed. Spectroscopic and chemical data indicate that the mesomeric form $CH_3O—N{=}N^+$ is a significant contributor to the overall structure of **1**. Consideration of computed charge distribution (4-31 G with full geometry optimization and 4-31 G*) also supports this conclusion. Independent generation of **1** was also studied by solvolysis of methylazoxy triflate and diazotization of methoxylamine with $NO^+BF_4^-$. Preparation of the elusive hydroxydiazonium ion HON_2^+ (**4**) was attempted by protonation of nitrous oxide in superacids, but no long-lived ion could be observed. Diazotization of hydroxylamine with $NO^+BF_4^-$ gives nitrous oxide indicative of the intermediacy of **4**.

There is continued interest in non-benzenoid diazonium ions and their chemistry. The ability of electron-withdrawing substituents in stabilizing diazonium ions is well demonstrated by preparation[3] of fluorodiazonium ion salts $FN_2^+AsF_6^-$ or $FN_2^+SbF_6^-$ as well as fluorinated alkyldiazonium ions[4,5] $(CF_3)_2CHN_2^+$ and $CF_3CH_2N_2^+$ in superacidic media. The methyldiazonium ion $CH_3N_2^+$ was observed by McGarrity and co-workers[6] by protonation of diazomethane below −100 °C.

We have reported in our previous studies the generation of the aminodiazonium ion $H_2NN_2^+$ by protonation of hydrazoic acid in superacids and its use for aromatic amination.[7] Eberson, Nilsson, and Rietz reported the cyanation of aromatics via diazotization of cyanamide with isoamyl nitrite/acetic acid[8a] in a radical-type reaction. More recently, we reported that aromatics can be cyanated and nitrated with NCN_2^+ and $O_2NN_2^+$ generated via diazotization of cyanamide and nitramide, respectively, with $NO^+BF_4^-$,[8b] and we attempted with Christie fluorination of aromatics with $FN_2^+AsF_6^-$.[8b] We also reported our observation of the formation of $^{14}N^{15}N$ from diazotization of NH_3, $HN[(CH_3)_3Si]_2$, and HNCO, respectively, with $^{15}NO^+BF_4^-$, indicating intermediate formation of the parent diazonium ion HN_2^+.[9]

In continuation of our studies on non-benzenoid diazonium ions we now report our investigation of the preparation of the methoxydiazonium ion $CH_3ON_2^+$ (**1**) via methylation of N_2O with stable ion conditions in low nucleophilic solvents and its spectroscopic (by ^1H, ^{13}C, ^{15}N NMR and FT IR) characterization. Independent preparation of **1** by cleavage of methylazoxy triflate and diazotization of methoxylamine hydrochloride was also attempted. Our studies also included attempted preparation of the related hydroxydiazonium ion HON_2^+ (**4**).

Results and Discussion

Methylation of Nitrous Oxide and Spectroscopic Studies. When a slow stream of nitrous oxide was passed through the strong methylating reagent $CH_3F \rightarrow SbF_5$ in SO_2F_2 or CH_3O^+SOClF/SbF_6^- in SO_2ClF[10] at −80 °C a white precipitate of **1** was

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