CHIRAL SYNTHESIS *VIA* ORGANOBORANES. 19. THE *SUCCESSFUL ONE-CARBON HOMOLOGATION OF HETEROCYCLIC* BORONATE ESTERS WITH HIGH OPTICAL PURITY#

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Abstract-An exploratory study was undertaken to establish the applicability of the one-carbon homologation to heterocyclic boronic esters. This procedure involves the use of (chloromethyl)lithium, $LiCH_2Cl$, generated *in situ* by the reaction of bromochloromethane and *n*-BuLi in THF at -78 °C in the presence of an enantiomerically pure heterocyclic boronic ester. These heterocyclic boronic esters were prepared *via* asymmetric hydroboration of representative heterocyclic olefins bearing either an *endo*cyclic or *exo*cyclic double bond with either Ipc_2BH or $IpcBH_2$ in THF.

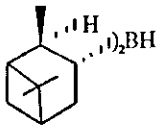
The wide range of biological activity, *e g*. antitumor, microbial growth inhibitor, plant growth inhibitor, antimalarial and antifeedant displayed by a number of compounds possessing the furan, thiophene and pyrrolidine moiety has stimulated considerable efforts to synthesize them[2]. Because of the therapeutic importance of these compounds, we undertook a systematic study on the asymmetric hydroboration of representative heterocyclic olefins bearing either an *endo*cyclic or an *exo*cyclic double bond[3].

Asymmetric hydroboration, since its discovery in 1961[4], has proved to be a highly valuable reaction in synthetic organic chemistry[5]. Since 1961 various chiral hydroborating agents have been developed based on readily available low cost terpenes with different steric requirements and applied to the asymmetric hydroboration of various types of prochiral olefins.

As a part of our ongoing program, a systematic study was undertaken of the asymmetric hydroboration with diisopinocampheylborane(Ipc_2BH, 1) of representative heterocyclic olefins bearing an *endo*cyclic double bond. Optical inductions from 89 to ~ 100% ee[3] were achieved. Asymmetric hydroboration of 1-heteroarylcycloalkenes with monoisopinocampheylborane ($IpcBH_2$, 2) provided optical inductions in the range of 80 to 99% ee.[6]

Previously we established that the heterocyclic derivatives of diisopinocampheylborane, upon treatment

This article is dedicated to Professor D. H. R. Barton in appreciation for his brilliant contributions on the occasion of his 70th birthday.



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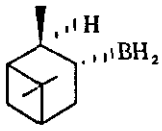

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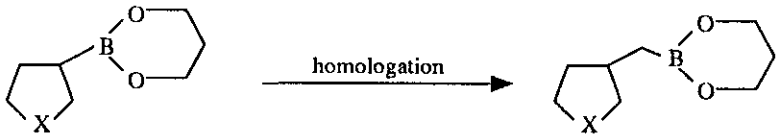
with acetaldehyde, liberates α-pinene quantitatively, providing optically active diethyl heterocyclic boronates[7]. These chiral organoboronic esters containing only one organyl group attached to boron are highly promising intermediates for asymmetric syntheses[8]. However, such heterocyclic boronate esters with a heteroatom in the β-position are known to be unstable with a tendency for elimination or rearrangement during synthetic transformations. To establish whether this side reaction is a serious problem, we examined the one-carbon homologation of these boronate esters. This transformation would shift the position of the boron atom from the β–, **3** , to γ– to the hetero atom, **4**, thereby increasing the stability of these heterocyclic boronate esters. These one-carbon homologated heterocyclic boronate esters, **4**, are valuable synthetic intermediates in organic synthesis[9].



3 X = O, N **4**

In principle, it is possible to prepare such boronate esters *via* asymmetric hydroboration of heterocyclic olefins bearing an *exo*cyclic double bond on a carbon atom β to the heteroatom. Unfortunately, the optical induction achieved in the asymmetric hydroboration of such olefins is known to be considerably lower than that achieved with the parent *endo*cyclic derivatives[10].

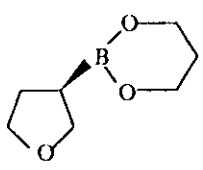
It is a well known fact that homologation transformations proceed with retention of configuration at the chiral center. Hence by starting with an optically pure heterocyclic boronate ester it is possible to get the one-carbon homologated boronic ester with retention of configuration at the chiral center. The ease of preparing such heterocyclic boronate esters with high optical purity *via* asymmetric hydroboration prompted us to study the one-carbon homologation of these heterocyclic boronate esters. This would facilitate the use of these homologated heterocyclic boronate esters for carbon-carbon bond forming reactions. The utility of such reactions has been demonstrated in the synthesis of α-chiral-α'-alkynyl ketones of high optical purity[11].

RESULTS AND DISCUSSION

Many new synthetic methods in organic chemistry involving carbon-carbon bond formation are now based on organoborane chemistry[12]. In the last decade many new reactions and reagents have emerged for the conversion of organoboranes into complex organic molecules with C-C bond formation under very mild conditions[13]. Carbanionic reagents bearing a potential leaving group at the α-position homologates the organyl-B linkage. The reaction proceeds through the formation of an ate-complex, followed by a 1,2-migration of the organyl group from

boron to the carbanionic center with displacement of the leaving group. This offers a convenient practical way to achieve C-C bond forming transformations *via* organoboranes.

Various carbenoid reagents bearing a potential leaving group have been studied for the one-carbon homologation of various classes of organoboranes. (Dichloromethyl)lithium, $LiCHCl_2$, [chloro(trimethylsilyl)methyl]lithium, $LiCHCl(SiMe_3)$, and [methoxy(phenylthio)methyl]lithium, LiCH(OMe)SPh, are now known to homologate all three classes of organoboranes, *viz* R_3B, R_2BOR' and $RB(OR')_2$, cleanly and efficiently[14]. Matteson et al.[15] demonstrated the utility of $LiCH_2Cl$, generated *in situ* by treating iodochloromethane with *n*-BuLi in THF at –78 °C, for the one-carbon homologation of boronic esters. A critical examination of all the available procedures for the one-carbon homologation of boronate esters was undertaken in our laboratory and an elegant and simple procedure achieved[16]. This involves the generation of $LiCH_2Cl$, *in situ* from the treatment of bromochloromethane with *n*-BuLi in THF at –78 °C in the presence of the boronate ester.



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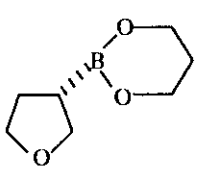

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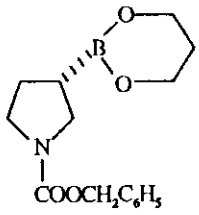

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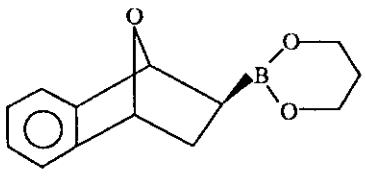

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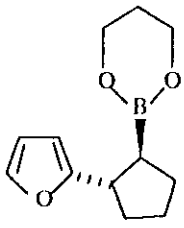

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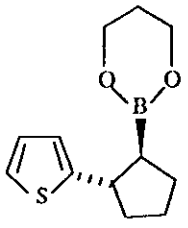

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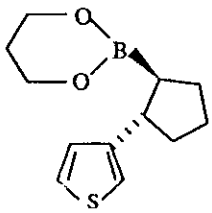

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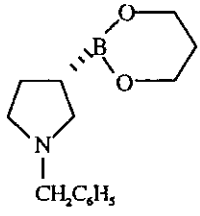

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It appeared desirable to examine the one-carbon homologation of representative heterocyclic boronic esters of high optical purity using $LiCH_2Cl$, generated *in situ* in THF from $BrCH_2Cl$ and *n*-BuLi at-78 °C. The following heterocyclic boronate esters were utilized: (+)-3-tetrahydrofuryl-1,3,2-dioxaborinane **5**, (-)-3-tetrahydrofuryl-1,3,2-dioxaborinane **6**, (-)-*N*-(carbobenzyloxy)-3-pyrrolidinyl-1,3,2-dioxaborinane **7**, 1,4-epoxy-1,4-dihydronapthyl-1,3,2-dioxaborinane **8**, (+)-*trans*-2-(2-furylcyclopentyl)-1,3,2-dioxaborinane **9**, (+)-*trans*-2-(thienylcyclopentyl)-1,3,2-dioxaborinane **10**, (+)-*trans*-2-(3-thienylcyclopentyl)-1,3,2-dioxaborinane **11** and (-)-*N*-benzyl-3-pyrrolidinyl-1,3,2-dioxaborinane **12** (Table 1).

GENERAL PROCEDURES FOR THE PREPARATION OF HETEROCYCLIC BORONATE ESTERS

Asymmetric hydroboration of the heterocyclic olefins bearing an *endo*cyclic double bond (*cis*-disubstituted

alkenes) was performed[3] in THF using Ipc_2BH, **I**, while the asymmetric hydroboration of the heterocyclic olefins bearing an *exo*cyclic double bond (trisubstituted alkenes) was performed[6] using $IpcBH_2$, **2**. The procedure for the preparation of (+)-3-tetrahydrofuryl-1,3,2-dioxaborinane **5**, is representative. This derivative was prepared by the asymmetric hydroboration of 2,3-dihydrofuran[3] in THF at –25 °C. To the stirred suspension of (–)-Ipc_2BH (25 mmol) derived from (+)-α-pinene at –25 °C was added 2,3-dihydrofuran (25 mmol) and the reaction mixture was stirred at –25 °C for 6 h. The solid Ipc_2BH disappeared and the formation of trialkylborane was complete as evident by ^{11}B nmr (δ 86 ppm). The reaction flask was brought to 0 °C and acetaldehyde (100 mmol) was added dropwise, and stirred at 25 °C for 6 h. The excess acetaldehyde was removed *in vacuo* to furnish (+)-diethyl-3-tetrahydrofurylboronate as is evident by ^{11}B nmr (δ 31 ppm). This boronate ester was separated from the liberated α-pinene either by column chromatography or by applying high vacuum (0.1 mm of Hg) at 25 °C for 12 h[3]. The reaction of this purified boronate ester with an equivalent of 1,3-propanediol in pentane[17] furnished (+)-3-tetrahydrofuryl-1,3,2-dioxaborinane **5**, further purified by distillation under reduced pressure.

In the case of *N*-benzyl-3-pyrroline, asymmetric hydroboration was performed by using two equivalents of Ipc_2BH[18]. The first equivalent of Ipc_2BH forms a complex with the nitrogen atom of the *N*-benzyl-3-pyrroline while the second equivalent of Ipc_2BH is utilized for asymmetric hydroboration. The required boronate ester was then prepared from the resulting trialkylborane by treating with acetaldehyde followed by the treatment with 1,3-propanediol[18].

The hydroboration of 1-heteroarylcycloalkenes was achieved using $IpcBH_2$. Preparation of (+)-*trans*-2-(2-furylcyclopentyl)-1,3,2-dioxaborinane **9**, is representative. To a solution of $IpcBH_2$ (25 mmol) in diethyl ether cooled to –35 °C was added 1-(2-furyl)-cyclopentene (25 mmol) over a period of 5 min. The reaction mixture was allowed to stand at –35 °C for 96 h. A white crystalline precipitate separated out. This was washed with chilled ether and the solid was dried under vacuum (~15 mm of Hg) at 0 °C. This was then suspended in ether (15 ml) and treated with excess acetaldehyde (100 mmol) at 0 °C and then stirred at 25 °C for 6 h. Excess acetaldehyde was removed *in vacuo* and the residue was distilled under reduced pressure to furnish (+)-*trans*-diethyl-2-(2-furylcyclopentyl)boronate[6]. (+)-*trans*-2-(2-Furylcyclopentyl)-1,3,2-dioxaborinane **9** was then prepared by reacting the above obtained diethyl boronate ester with an equivalent of 1,3-propanediol in pentane and purified by fractional distillation under reduced pressure. In most of the cases the optical purity was upgraded by crystallization of the dialkylborane obtained *via* asymmetric hydroboration of 1-heteroarylcycloalkenes. In some exceptions, the dialkylborane could not be induced to crystallize. In such cases, the dialkylborane was treated with excess acetaldehyde to get the desired diethyl boronate ester directly. Hydrolysis of the diethyl boronate ester then furnished the corresponding optically active boronic acid, upgraded by crystallization in ethyl ether-pentane[6]. Treatment of this boronic acid with 1,3-propanediol furnished the corresponding 1,3,2-dioxaborinane in very high optical purity.

The optical purities of these boronate esters were determined by oxidizing them to the corresponding alcohols, analyzed either by direct comparison of their optical rotations, or by analysis of their Mosher esters by ^{19}F nmr[3] or capillary GC.[6] The results are summarized in Table I.

Table I. Preparation of Heterocyclic Boronate Esters; Asymmetric Hydroboration of Representative Heterocyclic Olefins with (–)-Diisopinocampheylborane[a] and/or Monoisopinocampheylborane

olefin	heterocyclic boronate ester $R^*BO_2(CH_2)_3$, R* =	temp °C	time h	yield %	oxidation product	$[\alpha]^{23}_D$ deg	% ee	absol. config.
2,3-dihydrofuran	3-tetrahydrofuryl, **5**	–25	6	92	3-hydroxytetrahydrofuran	–17.3 (*c*2.4, MeOH)	>99[b]	3*R*
2,5-dihydrofuran	3-tetrahydrofuryl, **6**	–25	8	68	3-hydroxytetrahydrofuran	+17.3 (*c*2.4, MeOH)	>99[b]	3*S*
N-(carbobenzyloxy)-3-pyrroline	N-(carbobenzyloxy)-3-pyrrolidinyl, **7**	0	4	92	N-(carbobenzyloxy)-3-pyrrolidinol	+20.5 (*c*3.7, MeOH)	>89[b]	3*S*
1,4-epoxy-1,4-dihydronaphthalene	1,4-epoxy-1,4-dihydronaphthyl, **8**	–25	7	68	7-oxa-*exo*-2-benzonorborneol	+29.7 (*c*2.0, MeOH)	>99[b]	1*R*, 2*S*,4*R*
trans-1-(2-furyl)-cyclopentene	*trans*-2-(2-furyl)-cyclopentyl, **9**	–35	96	70	*trans*-2-(2-furyl)-cyclopentanol	+88.2 (*c*2.3, MeOH)	>99[c]	1*S*,2*S*
trans-1-(2-thienyl)-cyclopentene	*trans*-2-(2-thienyl)-cyclopentyl, **10**	–35	96	64	*trans*-2-(2-thienyl)-cyclopentanol	+70.6 (*c*2.3, MeOH)	>99[c]	1*S*,2*S*
trans-1-(3-thienyl)-cyclopentene	*trans*-2-(3-thienyl)-cyclopentyl, **11**	–35	96	65	*trans*-2-(3-thienyl)-cyclopentanol	+73.0 (*c*2.3, MeOH)	>99[c]	1*S*,2*R*
N-benzyl-3-pyrroline	N-benzyl-3-pyrrolidinyl, **12**	–25	24	89	3-hydroxy-N-benzylpyrrolidinol	–3.14 (*c*1.2, $CHCl_3$)	>99[c]	3*S*

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

GENERAL PROCEDURE FOR THE HOMOLOGATION OF HETEROCYCLIC BORONIC ESTERS

The one-carbon homologation of (+)-3-tetrahydrofuryl-1,3,2-dioxaborinane, **5**, is representative. To a stirred solution of **5** (10 mmol) in THF, cooled to –78 °C was added bromochloromethane (11 mmol) and *n*-BuLi (11 mmol) dropwise over a period of 15 min. The reaction mixture was then allowed to stir at –78°C for about an hour and then slowly warmed to room temperature and stirred at room temperature for 14 h. The progress of the reaction was monitored by ^{11}B nmr, which indicated the completion of migration in the ate-complex (δ 33 ppm). THF was pumped off *in vacuo* and the residue was extracted with anhydrous *n*-pentane (2 x 20 ml). Pumping off pentane *in vacuo* furnished the one-carbon homologated boronate ester, which was further purified by distillation under reduced pressure. Oxidation of this boronate ester with alkaline H_2O_2 furnished an alcohol

which was purified by distillation under reduced pressure and by preparative GC. The optical rotation of the alcohol was recorded and compared with the literature data if available.

It is a well established fact that the one-carbon homologation reaction proceeds with the retention of chirality[19] at the chiral center and hence the starting optical purity is reflected in the homologated boronate esters. By following this general procedure, representative one-carbon homologated boronate esters have been prepared in very high optical purities and the results are summarized in Table II.

However, we encountered problems in the one-carbon homologation of *N*-(benzyl)-3-pyrrolidinyl-1,3,2-dioxaborinane **12**. Treatment of **12** with (chloromethyl)lithium under the identical conditions described above did not furnish the expected one-carbon homologated product. Oxidation of the reaction product with alkaline H_2O_2 furnished a mixture of products. Presumably, the more acidic benzylic group might have interfered in the homologation sequence. This problem could probably be overcome by utilizing *N*-(t-cumyl)-3-pyrrolidinyl-1,3,2-dioxaborinane, but time did not permit a study of this possibility.

Table II. One-Carbon Homologation of Heterocyclic Boronate Esters with $LiCH_2Cl$ (generated *in situ* in THF at –78 °C).

boronate ester $R^*BO_2(CH_2)_3$ R^*=	homologated boronate ester R^*-CH_2-$BO_2(CH_2)_3$ R^*=	isolated yield, %	oxidation product	$[\alpha]^{23}_D$ degrees	% ee	absol. config
3-tetrahydrofuryl, **5**	3-tetrahydrofuryl, **13**	86	3-hydroxymethyl-tetrahydrofuran	+24.8 (*c*2.14, MeOH)	> 99	3*S*
3-tetrahydrofuryl, **6**	3-tetrahydrofuryl, **14**	78	3-hydroxymethyl-tetrahydrofuran	–24.8 (*c*2.2, MeOH)	> 99	3*R*
N-(carbobenzyloxy)-3-pyrrolidinyl, **7**	N-(carbobenzyloxy)-3-pyrrolidinyl, **15**	69	N-(carbobenzyloxy)-3-pyrrolidinyl-methanol	+19.04 (*c*2.5, MeOH)	89	3*S*
1,4-epoxy-1,4-dihydronaphthyl, **8**	1,4-epoxy-1,4-dihydronaphthyl, **16**	67	1,4-epoxy-2-hydroxymethyl-1,4-dihydronaphthalene	–2.06 (c2.1, MeOH)	> 99	1*S*, 2*R*,4*R*
trans-2-(2-furyl)-cyclopentyl, **9**	*trans*-2-(2-furyl)-cyclopentyl, **17**	80	*trans*-2-(2-furyl)-cyclopentyl-methanol	+77.02 (*c*2.25, MeOH)	> 99	1*S*, 2*S*
trans-2-(2-thienyl)-cyclopentyl, **10**	*trans*-2-(2-thienyl)-cyclopentyl, **18**	82	*trans*-2-(2-thienyl)-cyclopentyl-methanol	+59.32 (*c*2.2, MeOH)	> 99	1*S*, 2*S*
trans-2-(3-thienyl)-cyclopentyl, **11**	*trans*-2-(3-thienyl) cyclopentyl, **19**	78	*trans*-2-(3-thienyl)-cyclopentyl-methanol	+57.55 (*c*2.1, MeOH)	> 99	1*S*, 2*S*

CONCLUSION

The present study provides a simple procedure for the synthesis of various β-chiral heterocyclic boronate esters with very high optical purities. These are valuable intermediates, especially promising for chiral synthesis

proceeding through boron intermediates. Both (+) and (–)-α-pinenes are readily available. Consequently, both enantiomers can be readily synthesized. Also, the chiral auxiliary, α-pinene, can be readily recovered and recycled. Oxidation of these homologated boronate esters with alkaline H_2O_2 provides heterocyclic alcohols of high enantiomeric purity. An elegant synthesis of α-chiral-α'-alkynyl ketones has been reported from our laboratory starting from α-chiral heterocyclic boronate esters *via* the DCME reaction[11]. By following a similar procedure various β-chiral-α'-alkynyl ketones could be prepared in very high optical purities from β-chiral heterocyclic boronate esters, indicating their synthetic potential for asymmetric synthesis.

EXPERIMENTAL

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. All operations were carried out under a nitrogen atmosphere. Special techniques used in handling air sensitive materials are described in detail elsewhere[21].

Spectra. ^{11}B Nmr spectra were recorded on a Varian FT-80A instrument. The chemical shifts are in δ relative to BF_3: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. Optical rotations were measured on a Rudolph polarimeter Autopol III.

GC analysis. All GC analyses were carried out with a Hewlett-Packard 5890A gas chromatograph using (a) 12 ft x 0.125 in columns packed with 10% carbowax 20 *M* on Chromosorb W (100-120 mesh) or (b) 12 ft x 0.125 in column packed with 10% SE-30 on Chromosorb W (100-120 mesh). For preparative GC either (c) a 6 ft x 0.5 in column packed with 20% carbowax on Chromosorb W (60-80 mesh) or (d) a 6 ft x 0.5 in column packed with 20% SP-2100 on Chromosorb W (60-80 mesh) was used. Capillary GC analyses was performed on a Hewlett-Packard 5890A instrument with (e) 50 m x 0.25 mm column packed with methylsilicone or (f) 15 m x 0.25 mm column packed with Supelcowax with helium as a carrier gas.

Materials. Borane-methyl sulfide (BMS), (+)-α-pinene and β-pinene were purchased from Aldrich Chemical Co. (–)-α-Pinene was prepared by isomerization of (–)-β-pinene[23]. Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under nitrogen atmosphere in an ampoule. 2,3-Dihydrofuran, 2,5-dihydrofuran and 3-pyrroline were kept over anhydrous potassium carbonate overnight and distilled in nitrogen atmosphere. *N*-(Carbobenzyloxy)-3-pyrroline (containing 25% of *N*-(carbobenzyloxy)pyrrolidine) was prepared by reacting 3-pyrroline (contains 25% pyrrollidine, Aldrich) with benzyl chloroformate in the presence of sodium hydroxide[24]. 1,4,-Epoxy-1,4-dihydronaphthalene was purchased from Aldrich. *N*-Benzyl-3-pyrroline was prepared by treating *cis*--1,4-dichloro-2-butene (Aldrich) with an excess of benzylamine in refluxing toluene[25]. 1-Heteroarylcycloalkenes, utilized in this study, were prepared by treating the 2- or 3-lithio-heterocycle with the cycloalkanone followed by the dehydration of the resulting tertiary alcohol with PTS/benzene. (–)-Diisopinocampheylborane[26] [(–)-Ipc_2BH] and (-)-Monoisopinocampheylborane[27][(-)-$IpcBH_2$] of >99% ee were prepared according to the literature procedure. Bromochloromethane (Aldrich) was purified by distillation over P_2O_5 in an atmosphere of nitrogen and stored over 4Å molecular sieves. *n*-Butyllithium (Alfa) in hexane was estimated to be 2.3 *M*.[21]

General Procedure for the Asymmetric Hydroboration of Heterocyclic Olefins. Preparation of Diethyl Heterocyclic Boronates. Asymmetric hydroboration of 2,5-dihydrofuran is representative . To a stirred suspension of (–) Ipc_2BH (25 mmol) in THF (25 ml) at –25 °C was added 1.9 ml (25 mmol) of 2,5-

dihydrofuran. The reaction mixture was stirred at –25 °C for 8 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 mm of Hg, 1 h). α-Pinene was removed by applying high vacuum (25 °C, 0.1 mm of Hg, 12 h); yield 2.65 g (68%). A part of this boronate ester was dissolved in THF and subjected to oxidation using $NaOH/H_2O_2$. The reaction mixture was stirred at 25 °C for 5 h. The aqueous layer was saturated with potassium carbonate, extracted with 3 x 25 ml of ethyl ether, dried over anhydrous $MgSO_4$, and the ether evaporated. The residue was filtered through silica gel; the ether eluate furnished the alcohol, purified by distillation (bp 80 °C/15 mm of Hg); GC purity 99%. It was further purified by preparative GC using column c to furnish a GC pure material: $[\alpha]^{23}_D$ +17.3° (*c* 2.4, MeOH); >99% ee (lit.[28] $[\alpha]^{23}_D$ +16.23° (*c* 2.427, MeOH), 99% ee).

General Procedures for the Asymmetric Hydroboration of 1-Heteroarylcycloalkenes. Preparation of Diethyl Heterocyclic Boronates.

a) Preparation of tertiary alcohols. Tertiary alcohols were prepared following similar procedures reported in the literature[29]. To an ice-cooled (0 °C) solution of 16.32 g (240 mmol) of furan and ethyl ether (200 ml) was added dropwise *n*-BuLi in hexane, 76.8 ml (176 mmol). The resulting mixture was stirred at 0 °C for 1 h, after which was added an ethereal solution of the corresponding ketone (152 mmol). After being stirred overnight, the reaction mixture was quenched with water (10 ml). The ether layer was decanted, dried over $MgSO_4$, and the solvent removed under reduced pressure.

b) Preparation of 1-heteroarylcycloalkenes. To the crude alcohol taken in 100 ml of anhydrous benzene was added a catalytic amount of *p*-toluenesulfonic acid and the mixture was stirred at 40-50 °C for 30 minutes. The benzene layer was dried over anyhdrous K_2CO_3 and distilled to give the required olefins in 80-90% overall yield and >98% purity by GC.

c) Asymmetric hydroboration of 1-heteroarylcycloalkenes. Preparation of diethyl boronate esters. The procedure used for the asymmetric hydroboration of 1-(2-furyl)cyclopentene is representative. A 250 ml round bottom flask equipped with a sidearm, magnetic stirring bar and a gas lead was flushed with nitrogen. To the flask was added 3.35 g (25 mmol) of 1-(2-furyl)cyclopentene dropwise with stirring. The flask was maintained at –35 °C without stirring for 4 days. A white crystalline solid separated out. The supernatant liquid was removed by a double-ended needle and the crystals were washed with cold ether (3 x 10 ml). The solid was dried under vacuum (~15 mm of Hg) at 0 °C. It was then suspended in 20ml of ether and treated with excess acetaldehyde (3 ml). The reaction mixture was stirred at room temperature for 5 h and ^{11}B nmr (δ 30.97) showed the absence of dialkylborane. The excess acetaldehyde was pumped off and the residue was distilled, bp 65-70 °C/0.02 mm, to furnish [1'*S*, 2'*S*]-(+)-diethyl *trans*-2-(2-furyl)cyclopentylboronate, 3.52 g, 60% isolated yield, $[\alpha]^{22}_D$ +51.58° (*c*2.52, EtOH). A part of this sample was oxidized with $NaOH/H_2O_2$ to give *trans*-2-(2-furyl)cyclopentanol, which was further purified by preparative GC: $[\alpha]^{23}_D$ +88.2° (*c*2.325, MeOH), >99% ee by capillary GC analysis of its Mosher ester.

General Procedures for the Isolation of Heterocyclic Boronic Esters of High Optical Purity.

a) By column chromatography. Diethyl heterocyclic boronates were prepared *via* asymmetric hydroboration of heterocyclic olefins either with Ipc_2BH or $IpcBH_2$ followed by treatment with 100% excess acetaldehyde at 25°C as described above. The crude boronate was freed from the solvent and acetaldehyde and subjected to column chromatography using neutral alumina. Elution with pentane removed α-pinene completely,

whereas elution with ethanol afforded the boronate. Ethanol was removed under vacuum at 25°C to obtain pure diethyl heterocyclic boronate.

b) Diethyl heterocyclic boronates could also be freed from α-pinene by pumping off the latter under high vacuum (0.5 mm of Hg) at 25 °C for 8 h.

The spectral properties of diethyl heterocyclic boronates are as follows:

Diethyl 3-tetrahydrofuranyl boronate: ^{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 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.0-4.2(*m*, 8H), 1.66-2.2(*m*, 2H), 1.23(*t*, 6H), 0.5(*m*, 1H); ms, m/z 173 (M^++1) (100%), 177(22%), 147(10%), 145(6%), 131(8%), 119(13%).

Diethyl *N*-(carbobenzyloxy)-3-pyrrolidinyl boronate: ^{11}B Nmr ($CDCl_3$) δ 30.2; $[\alpha]^{23}_D$ −10°(*c* 5.3, MeOH); ^{1}H nmr ($CDCl_3$) δ 7.3(*s*, 5H), 5.1(*s*, 2H), 3.9(*q*, 4H), 3.6-3.0(*m*, 4H), 2-1.9(*m*, 2H), 1.2(*t*, 6H); ms, m/z 348 (M^++1).

Diethyl 1,4-epoxydihydronaphthyl boronate: ^{11}B Nmr ($CDCl_3$) δ 32.9; $[\alpha]^{23}_D$ +32° (*c* 4.42, EtOH); ir ($CHCl_3$) 3486, 2972, 2918, 1481, 1415, 1374, 1337, 1221, 1044, 987, 854; ^{1}H nmr ($CDCl_3$) δ 7.16(*m*, 4H), 5.43(*m*, 2H), 3.86(*q*, 4H), 2(*m*, 2H), 1.23(*t*, 6H), 0.9(*m*,1H); ms, m/z 247 (M^++1).

Diethyl *trans*-2-(2-furyl)cyclopentyl boronate: Bp 65-68 °C/0.02 mm of Hg; ^{11}B nmr ($CDCl_3$) δ 30.97; $[\alpha]^{22}_D$ +51.58°(*c* 2.52, EtOH);^{1}H nmr ($CDCl_3$) δ 7.25 , (*m*, 1H), 6.20(*m*, 1H), 5.90(*m*, 1H), 3.85(*q*, 4H), 3.25(*m*, 1H), 2.25-1.60(*m*, 7H), 1.20(*m*, 6H).

Diethyl *trans*-2-(2-thienyl)cyclopentyl boronate: ^{11}B Nmr ($CDCl_3$) δ 30.9; bp 85-90 °C/0.25 mm; $[\alpha]^{23}_D$ +36.10° (*c* 2.54, EtOH); ^{1}H nmr ($CDCl_3$) δ 7.10-6.7(*m*, 3H), 3.90(*m*, 4H), 3.20(*m*, 1H), 2.5-1.5(*m*, 7H), 1.4-0.9(*m*, 6H).

Diethyl *trans*-2-(3-thienyl)cyclopentyl boronate: ^{11}B Nmr ($CDCl_3$) δ 31.42; bp 90-91 °C/0.05 mm; $[\alpha]^{23}_D$ +46.72°(*c* 2.5, EtOH); ^{1}H nmr ($CDCl_3$) δ 7.4-6.8(*m*, 3H), 3.80(*m*, 4H), 3.15(*m*, 1H), 2.40-1.6(*m*, 7H), 1.4-0.9(*m*, 6H).

Diethyl (N-benzyl-3-pyrrolidinyl)boronate: ^{11}B Nmr ($CDCl_3$) δ 32.2; ^{1}H nmr ($CDCl_3$) δ 7.56(*s*, 5H), 4.0(*m*, 2H), 3.80(*q*, 4H), 3.0-1.66(*m*, 7H), 1.4-0.9(*m*, 6H).

General Procedure for the Preparation of Heterocyclic 1,3,2-Dioxaborinane. Heterocyclic-1,3,2-dioxaborinanes were prepared by reacting the diethyl heterocyclic boronate esters with an equivalent of 1,3-propanediol in pentane at room temperature[17].

The spectral properties of heterocyclic 1,3,2-dioxaborinanes are as follows.

[3'*R*]-(+)-3-Tetrahydrofuryl-1,3,2-dioxaborinane 5: Bp 95-100 °C/2 mm of Hg; ^{11}B nmr ($CDCl_3$) δ 31; $[\alpha]^{23}_D$ +25.67°(*c* 2.3, THF); ^{1}H nmr ($CDCl_3$) δ 4.10-3.40(*m*, 8H), 2.1-1.5(*m*, 4H), 1.05(*m*, 1H).

[3'*S*]-(-)-3-Tetrahydrofuryl-1,3,2-dioxaborinane 6: Bp 94-99 °C/2 mm of Hg; ^{11}B nmr ($CDCl_3$) δ 31; $[\alpha]^{23}_D$ −26.8°(*c* 2.4, THF);^{1}H nmr ($CDCl_3$) δ 4.2-3.4(*m*, 8H), 2.2-1.5(*m*, 4H), 1.1(*m*, 1H).

[3'*S*]-(-)-N-(Carbobenzyloxy)-3-pyrrolidinyl-1,3,2-dioxaborinane 7: ^{11}B Nmr ($CDCl_3$) δ 31.96; $[\alpha]^{23}_D$ −5.94° (*c* 8,THF); ^{1}H nmr ($CDCl_3$) δ 7.30(*s*, 5H); 5.10(*s*, 2H), 4.2-3.75(*m*, 4H), 3.60-3.10(*m*, 4H), 2.10-1.60(*m*, 4H), 1.10(*m*, 1H).

[*S*]-(+)-1,4-Epoxy-1,4-dihydronaphthyl-1,3,2-dioxaborinane 8: ^{11}B Nmr ($CDCl_3$) δ 31.88; $[\alpha]^{24}_D$ +31° (*c* 4, THF); ^{1}H nmr ($CDCl_3$) δ 7.16(*m*, 4H), 5.43(*m*, 2H), 4.0(*t*, 4H), 2.26-1.66(*m*, 4H); 0.9(*m*, 1H).

[1'*S*,2'*S*]-(+)-*trans*-2-(2-Furylcyclopentyl)-1,3,2-dioxaborinane 9: Bp 96-100 °C/0.1 mm; $[\alpha]^{23}_D$ +88.22° (*c* 6.35, THF); ^{11}B nmr ($CDCl_3$) δ 30.9; ^{1}H nmr ($CDCl_3$) δ 7.3(*m*, 1H), 6.2(*m*, 1H), 6.0(*m*, 1H), 4.1-3.8(*t*, 4H), 3.10(*m*, 1H), 2.10-1.4(*m*, 9H).

[1'*S*,2'*S*]-(+)-*trans*-2-(2-Thienylcyclopentyl)-1,3,2-dioxaborinane 10: Bp 125-130 °C/0.4 mm; $[\alpha]^{23}_D$ +57.3°(*c* 6.82, THF); ^{1}H nmr ($CDCl_3$) δ 7.10-6.70(*m*, 3H), 4.10-3.8(*t*, 4H), 3.25(*m*, 1H), 2.10-1.50(*m*, 9H).

[1'*S*,2'*S*]-(+)-*trans*-2-(3-Thienylcyclopentyl)-1,3,2-dioxaborinane 11: Bp 139-140 °C/0.4 mm; $[\alpha]^{24}_D$ +88.5° (*c* 6.9, THF); ^{1}H nmr ($CDCl_3$) δ 7.15(*m*, 1H), 6.90(*m*, 2H), 4.05-3.70(*t*, 4H), 3.10(*m*, 1H), 2.20-1.5(*m*, 9H).

[3'*S*]-N-Benzyl-3-pyrrolidinyl-1,3,2-dioxaborinane 12: ^{11}B Nmr ($CDCl_3$) δ 31.96; $[\alpha]^{23}_D$ –16.4° (*c* 2.1, THF); ^{1}H nmr ($CDCl_3$) δ 7.56(*s*, 5H), 4.0(*t*, 4H), 3.6(*s*, 2H), 3.3-1.6(*m*, 8H), 1.0(*m*, 1H).

General Procedure for the Homologation of Heterocyclic 1,3,2-Dioxaborinanes Procedure for the one-carbon homologation of (1'S,2'S)-(+)-*trans*-2-(2-furylcyclopentyl)-1,3,2-dioxaborinane **9** is representative. A solution of **9** (3.3 g, 15 mmol), and bromochloromethane (1.3 g, 21 mmol) in THF (25 ml) was cooled to –78 °C using a dry ice-acetone bath. To this was added chilled *n*-BuLi (9.5 ml, 21 mmol) dropwise from the side of the flask, maintaining a temperature of –78 °C in an atmosphere of nitrogen gas. The reaction mixture was stirred at –78 °C for 1 h, then warmed slowly to room temperature, and stirred at room temperture for 14 h. The solvent THF was pumped off under reduced pressure and the residue extracted with *n*-pentane (2 x 20 ml). The supernatant pentane layer was transferred to another flask by means of a double-ended needle in an atmosphere of nitrogen gas. The combined organic fraction was evaporated under reduced pressure at room temperature to provide crude [*trans*-2-(2-furylcyclopentyl)methyl]-1,3,2-dioxaborinane **17**. This was further purified by distillation: bp 135-138 °C/0.8 mm of Hg; 3.75 g; 80% yield, $[\alpha]^{22}_D$ +59.52° (*c* 2.1, THF).

By following similar procedures, other representative heterocyclic boronate esters were homologated. The spectral properties of one carbon homologated boronate esters are as follows. The structures of these homologated heterocyclic boronate esters were further confirmed by oxidizing them to the corresponding alcohols.

[3'*R*]-(+)-[(3-Tetrahydrofuranyl)methyl]-1,3,2-dioxaborinane 13: Bp 105-108 °C/0.8 mm; yield 86%; ^{11}B nmr ($CDCl_3$) δ 31; $[\alpha]^{23}_D$ +27.6° (*c* 2.2, THF); ^{1}H nmr ($CDCl_3$) δ 4.2-3.20(*m*, 8H), 2.5-1.70(*m*, 4H), 1.6-0.7(*m*, 3H).

[3'*S*]-(-)-[(3-Tetrahydrofuranyl)methyl]-1,3,2-dioxaborinane 14: Bp 104-107 °C/0.8 mm; yield 78%; ^{11}B nmr ($CDCl_3$) δ 30.9; $[\alpha]^{23}_D$ –27.1° (*c* 2.1, THF); ^{1}H nmr ($CDCl_3$) δ 4.3-3.2(*m*, 8H), 2.5-1.7(*m*, 4H), 1.7-0.6(*m*, 3H).

[3'*S*]-(-)-[(N-(Carbobenzyloxy)-3-pyrrolidinyl)methyl]-1,3,2-dioxaborinane 15: yield 69%; ^{11}B nmr ($CDCl_3$) δ 32; $[\alpha]^{23}_D$ –7.7° (*c* 2.52, THF); ^{1}H nmr ($CDCl_3$) δ 7.30(*s*, 5H), 5.10(6*s*, 2H), 4.16-3.33(*m*, 10H) 2.06-0.8(*m*, 5H).

[*S*]-(+)-[(1,4-Epoxydihydronaphthyl)methyl]-1,3,2-dioxaborinane 16: yield 67%; ^{11}B nmr ($CDCl_3$) δ 32; $[\alpha]^{23}_D$ +6.11° (*c* 2.2, THF); ^{1}H nmr ($CDCl_3$) δ 7.66-7.30(*m*, 6H), 5.23(*m*, 2H), 3.66(*t*, 4H), 3.66-1.06(*m*, 5H).

[1'*S*,2'*S*]-(+)-[*trans*-2-(2-Furylcyclopentyl)methyl]-1,3,2-dioxaborinane 17: Bp 135-138 °C/0.8 mm; yield 80%; $[\alpha]^{22}_D$ +59.52° (*c* 2.1, THF); ^{11}B nmr ($CDCl_3$) δ 31; ^{1}H nmr ($CDCl_3$) δ 7.2(*m*, 1H), 6.20(*m*, 1H), 5.95(*m*, 1H), 4.0-3.65(*t*, 4H), 3.40(*m*, 1H), 2.2-1.5(*m*, 11H).

[1'*S*,2'*S*]-(+)-[*trans*-2(2-Thienylcyclopentyl)methyl]-1,3,2-dioxaborinane 18: Bp 138-140 °C/0.8 mm; yield 82%; $[\alpha]^{23}_D$ +25.06° (*c* 2.07, THF); ^{11}B nmr ($CDCl_3$) δ 32; ^{1}H nmr ($CDCl_3$) δ 7.15-6.75(*m*, 3H), 4.10-3.70(*m*, 4H), 3.40(*m*, 1H), 2.30-1.60(*m*, 11H).

[1'*S*,2'*S*]-(+)-[*trans*-2-(3-Thienylcyclopentyl)methyl]-1,3,2-dioxaborinane 19: Bp 140-144 °C/0.8 mm; yield 78%; $[\alpha]^{22}_D$ +47.53° (*c* 2.12, THF); ^{11}B nmr ($CDCl_3$) δ 32.6; ^{1}H nmr ($CDCl_3$) δ 7.10(*m*, 1H), 6.90(*m*, 2H), 4.0-3.60(*m*, 5H), 2.20-1.50(*m*, 11H).

Oxidation of Heterocyclic Boronate esters. Oxidation of these homologated boronic esters was performed with alkaline hydrogen peroxide to furnish β–chiral alcohols of high optical purity. These alcohols were purified by distillation under reduced pressure and further purified by preparative GC. The optical purities of these β-chiral alcohols were determined by measuring their optical rotation and comparing them with the optical rotations reported in the literature. The Mosher esters of these alcohols were also analyzed by capillary GC and were found to be enantiomerically pure. Further support for the optical purity is provided by ^{13}C nmr.

The spectral properties of these alcohols are as follows:

[*S*]-(+)-3-Hydroxymethyltetrahydrofuran: Bp 94-95 °C/15 mm; yield 80%; $[\alpha]^{23}_D$ +24.83° (*c* 2.14, MeOH)[30]; ir (neat) 3378, 2937, 2875, 1468, 1450, 1437, 1384, 1054, 985, 903 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 4.10-3.40(*m*, 6H), 2.10-1.10(*m*, 4H); ms, m/z 113 (M^++1); ^{13}C nmr ($CDCl_3$) δ 70.67, 67.86, 64.93, 41.47 and 28.71.

[*R*]-(-)-3-Hydroxymethyltetrahydrofuran.: Bp 94-95 °C/15 mm; yield 78%; $[\alpha]^{23}_D$ –24.8° (*c* 2.2, MeOH); ir, nmr and mass spectral data was identical with the reported S isomer.

[*S*]-(+)-[N-Carbobenzyloxy-3-pyrrolidinyl]methanol: $[\alpha]^{23}_D$ +19.04° (*c* 2.5, MeOH); ir (neat) 3450, 3010, 2940, 1720, 1410, 1390, 1230, 1150, 1020, 905, 800, 730 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.3(*s*, 5H), 5.1(*s*, 2H), 4.14(*m*, 1H), 3.60-3.35(*m*, 6H), 3.0 (bs, 1H), and 1.90(*m*, 2H); ^{13}C nmr ($CDCl_3$) δ 155.26, 136.89, 128.47, 128.14, 127.73, 70.42, 69.75, 66.83, 54.42, 44.17, 33.86, 33.47.

[*R*]-(-)-1,4-Epoxy-2-hydroxymethyl-1,4-dihydronaphthalene: yield 75%; $[\alpha]^{23}_D$ –2.06° (*c* 2.1, MeOH); ir (neat): 3359, 3057, 2922, 2870, 1595, 1457, 1385, 1364, 1278, 1083, 1054, 1044, 1032, 794, 773, 753, 648, 634 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.66-7.3(*m*, 4H), 5.23(*m*, 2H), 3.6(*m*, 3H), 1.5-0.9(*m*, 3H); ms, m/z 177 (M^++1).

[1*S*,2*S*]-(+)-*trans*-2-(2-Furylcyclopentyl)methanol: yield 85%; bp 80-82 °C/0.02 mm; $[\alpha]^{23}_D$ +77.02° (*c* 2.25, MeOH); ir (neat), 3357, 2953, 2872, 1449, 1148, 1058, 1011, 799, 730 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.1(*m*, 1H), 6.10(*m*, 1H), 5.80(*m*, 1H), 3.50(*m*, 2H), 2.65(*m*, 1H), 2.2-1.4(*m*, 8H); ms, m/z 166 (M^++1); ^{13}C nmr ($CDCl_3$) δ 140.82, 110.0, 103.8, 70.3, 65.66, 47.66, 41.42, 32.26, 29.23 and 24.46.

[1*S*,2*S*]-(+)-*trans*-2-(2-Thienylcyclopentyl)methanol: Bp 100-102 °C/0.02 mm; yield 87%; $[\alpha]^{22}_D$ +59.32° (*c* 2.2, MeOH); ir (neat) 3361, 2950, 2870, 1465, 1441, 1322, 1277, 1238, 1058, 1020, and 823 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.15-6.7(*m*, 3H), 3.56(*m*, 2H), 3.0(*m*, 1H), 2.30-1.60(*m*, 8H); ms, m/z 183 (M^++1); ^{13}C nmr ($CDCl_3$) δ 149.8, 126.7, 123.22, 122.7, 65.36, 50.9, 43.6, 36.7, 29.2, 24.41.

[1*S*,2*S*]-(+)-*trans*-2-(3-Thienylcyclopentyl)methanol: Bp 100-104 °C/0.02 mm; yield 82%; $[\alpha]^{23}_D$ +57.55° (*c* 2.1, MeOH); ir (neat) 3367, 2949, 2869, 1465, 1449, 1413, 1387, 1080, 1056, 1020 and 776 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.3 (*m*, 1H), 7.0(*m*, 2H), 3.60(*m*, 2H), 2.90(*m*, 1H), 2.20-1.50(*m*, 8H); ms, m/z 183 (M^++1); ^{13}C nmr ($CDCl_3$) δ 127.0, 125.7, 125.6, 119.4, 66.13, 49.7, 44.1, 35.1, 29.3 and 24.3.

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