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Chiral Synthesis *via* Organoboranes. 33. The controlled Reaction of B-Alkyldiisopinocampheylboranes with Aldehydes Providing a Convenient Procedure For the Enantiomeric Enrichment of the Boronic Ester Products Through Kinetic Resolution

by

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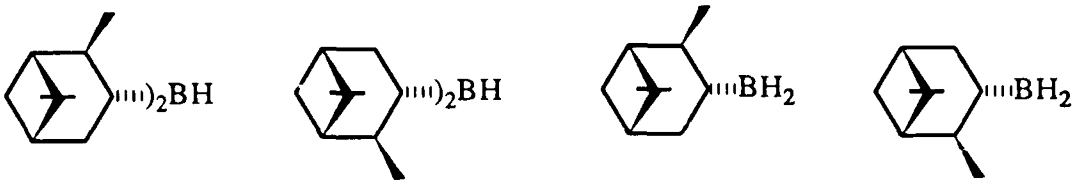
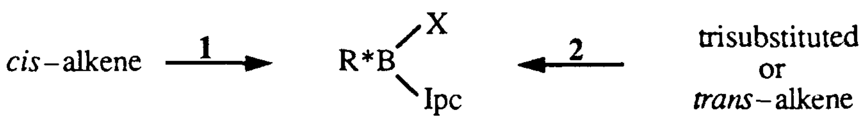
Controlled treatment of *B*-alkyldiisopinocampheylborane (**3a**), Ipc_2BR^*, obtained by asymmetric hydroboration of appropriate olefin, with aldehydes produces chiral boronate esters (**5**) having enantiomeric purities markedly higher than those of the substrate. A systematic study of the reaction revealed that the intermediate borinic esters (**4**) are being kinetically resolved. Since asymmetric hydroboration of alkenes with diisopinocampheylborane (**1**) provides predominantly the diastereomer that reacts faster with aldehydes, the reaction furnishes *in situ* enantiomeric enrichment of the products. Thus, *B*-alkyldiisopinocampheylboranes (**3a**) possessing 81-96% ee are readily converted into boronic esters (**5**) including 2-butyl, 3-hexyl and *exo*-norbornyl derivatives of ≥99% ee. Successful efforts were also made to extend the scope of asymmetric hydroboration -kinetic resolution to representative cyclic dienes making available pure enantiomers of *exo*-5-norbornenyl- and 3-cyclohexenylboronic esters.

Hydroboration is one of the fundamentally novel reactions in organic chemistry. In recent times a variety of procedures have become available for the enantioselective version of this reaction. They include chiral organoboranes derived from terpenes,[2] Masamune's reagent[3] and a modestly successful catalytic procedure involving chiral transition metal complexes.[4] All of these routes transform prochiral alkenes to the corresponding chiral alcohols. However, the reagents derived from (+)- and (–)-α-pinene have given a new dimension to the scope of asymmetric hydroboration, making accessible chiral organoboranes which are readily transformed into an array of pure enantiomers.[5]



*d*1 *l*1 *d*2 *l*2

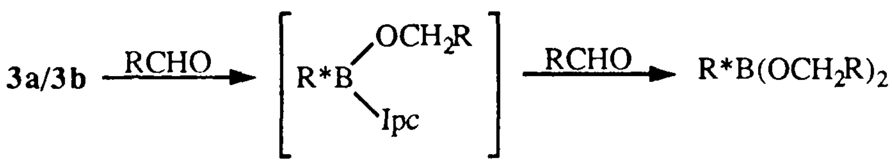
The discovery of the first enantioselective hydroborating reagent,[6a] diisopinocampheylborane (Ipc_2BH, **1**) marked the beginning of a practical non-enzymatic asymmetric synthesis. The reagent provided 51 87% enantiomeric excess (ee) in the hydroboration of *cis*-disubstituted alkenes. Later on, the availability of enantiomerically pure **1**[6b] and modified reaction conditions significantly improved the results.[6c] The reaction of **1** with more hindered olefins, however, is sluggish and proceeds with partial displacement of α-pinene from the reagent. These difficulties prompted us to explore monoisopinocampheylborane ($IpcBH_2$, **2**). The moderate steric requirement of **2** permitted smooth hydroboration of *trans*-disubstituted as well as trisubstituted alkenes in 53-100% ee.[7a-c]



(1)

3a, X = Ipc **3b**, X = H

We subsequently discovered[8] that treatment of the intermediates **3a** and **3b** with an aldehyde regenerated the chiral auxiliary, α-pinene (eq 2). The resulting boronic esters (**5**) could be easily converted into the corresponding chiral monoalkylboranes which proved to be the starting point for a variety of transformations.[9a-c]



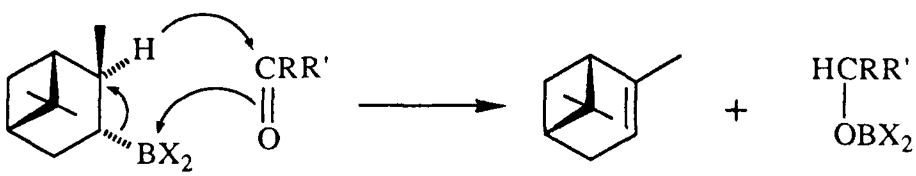
(2)

4 **5**

With the growing synthetic utility of chiral organoboranes,we learned to upgrade the enantiomeric purity of the key intermediates, **5**, to ≥99% ee. In the case of the products arising from **2**, direct crystallization of **3b** itself proved to be the method of choice.[7c] The enantiomeric enrichment of the product from **1** however, was achieved tediously at the later stages.[10] An additional problem encountered with **3a** was the sluggish reaction with aldehydes. The present study was undertaken to overcome these difficulties and also to understand the reaction between **3a** and aldehydes. The investigation provided us with some unexpected observations regarding the reaction mechanism. The most gratifying aspect was the finding that the intermediate diastereomeric borinic esters (**4**) were kinetically resolved, thereby leading to a simple *in situ* procedure for enantiomeric enrichment of the products, *viz.* boronic esters (**5**). A part of the present study was also devoted to extending the scope of asymmetric hydroboration for hitherto unreported cyclic dienes.

Results and Discussion

Isopinocampheylboranes react with aldehydes and ketones liberating the 3-pinyl group as α-pinene, presumably *via* a cyclic mechanism (eq 3). In the case of *B*-alkyldiisopinocampheyl-boranes (**3a**), the reaction with simple aldehyde proceeds stepwise, giving successively borinic (**4**) and boronic (**5**) esters. The first step of the reaction is relatively fast, whereas, the second one is comparatively slow (eq 4).



(3)

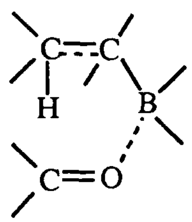
$$\underset{\mathbf{3a}}{R^*BIpc_2} \xrightarrow[6\text{-}8\ h]{CH_3CHO} \underset{\mathbf{4}}{R^*B(OEt)Ipc} \xrightarrow[2\text{-}8\ days]{CH_3CHO} \underset{\mathbf{5}}{R^*B(OEt)_2} \qquad (4)$$

R* = 2-butyl, 3-hexyl, *exo*-norbornyl, etc.

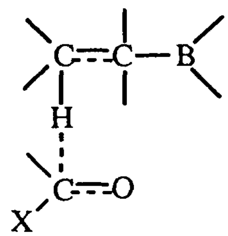
In order to investigate the structural effects of representative aldehydes in the reaction, **3a** (R* = 2-butyl) was selected as the substrate. A standard solution of the organoborane in THF was obtained by hydroboration[6c] of *cis*-2-butene with $^{d}Ipc_2BH$ (derived from (+)-α-pinene) in THF at

−25 °C. Portions of the stock solution were treated with 2 equiv of selected aldehydes at ambient temperature and progress of the reactions was monitored by ^{11}B NMR. It was found that the reaction was slowest with CH_3CHO. There was a small, but significant, difference in the reactivity of $(CH_3)_2CHCHO$ and PhCHO. Very unexpectedly, the reaction with CCl_3CHO was much faster than that with other aldehydes examined!

The mechanism of such reduction process is believed to proceed through a cyclic transition state.[11] The transition state must involve both, coordination of the boron atom to the oxygen of the carbonyl group and abstraction of β-hydride by the carbonyl carbon. Factors which favor stronger coordination in **I** or stronger bonding of β-hydride in **II** will stabilize the transition state and enhance the rate of the transformation. A somewhat different interpretation was earlier forwarded by Midland *et al.*[12]



I



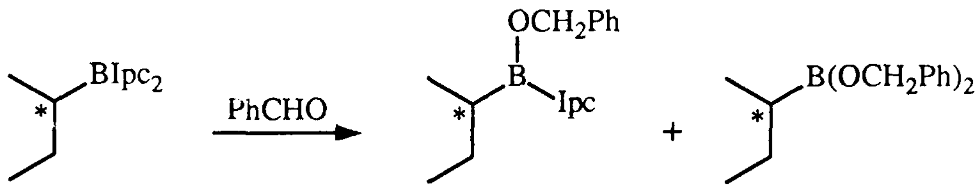
X = electron withdrawing group

II

It occured to us that the addition of an external Lewis acid (such as BF_3) which coordinates with the carbonyl group, should cause an electronic shift away from the carbonyl carbon and enhance the contribution of **II** to the transition state. Indeed, the reaction of PhCHO with **3a** was significantly accelerated by a catalytic amount (5 mol%) of $BF_3{\cdot}Et_2O$. The rate study of 2-butyldiisopinocampheylborane (2-$BuBIpc_2$) with representative aldehydes is summarized in Figure 1.

Kinetic Resolution. The routine procedure[8] for preparing chiral boronate esters (**5**) from the hydroboration products (**3**) involves a simple treatment with an excess of aldehyde. During the above mentioned rate study however, we inadvertently worked up one of the reaction mixtures involving the treatment of 2-$BuBIpc_2$ with PhCHO after ~90% completion. At that stage of the reaction, ^{11}B NMR indicated a ~1:4 mixture of the unreacted intermediate (benzylborinate, δ

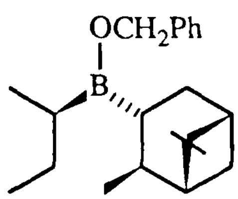
= 53 ppm) and the product (dibenzylboronate, δ = 31 ppm). The reaction mixture was therefore extracted with 3 N NaOH to isolate boronic acid from the reaction mixture. Oxidation of the isolated boronic acid with alkaline H_2O_2 provided optically active 2-butanol. The enantiomeric excess (% ee) of the product was determined by capillary GC analysis of its MTPA ester. To our surprise, the % ee of 2-butanol was significantly higher than that of the starting material, 2-$BuBIpc_2$! To confirm the results, the borinic acid remaining in the organic phase following the extraction of the boronic acid with 3 N NaOH, was isolated and oxidized. Indeed, the % ee of 2-butanol from the borinic acid was very much lower (eq 5).



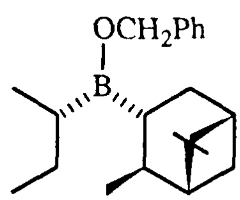
(5)

(**3a**, R* = 2-Bu) 93% ee — (~20%) 71% ee — (~80%) ≥99% ee

It appeared that we had encountered kinetic resolution during the displacement reaction. This unexpected finding appeared to be promising procedure for an *in situ* enantiomeric enrichment of boronic esters. The reaction was therefore examined for a few other diisopinocampheylborane derivatives (**3a**) and appeared to be generally applicable (Table I).



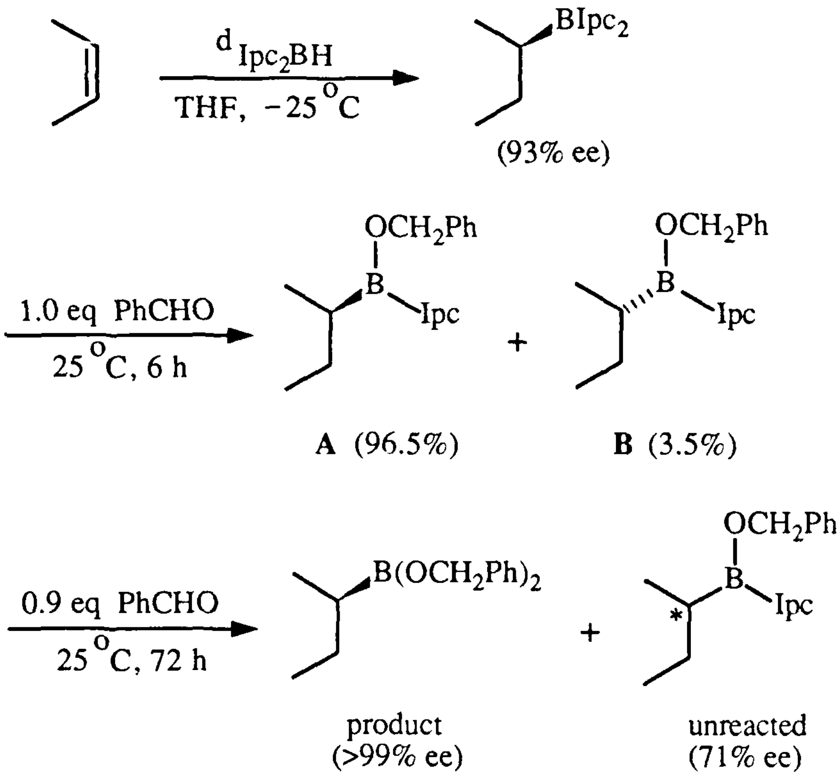
(R,R)-isomer, **A**



(S,R)-isomer, **B**

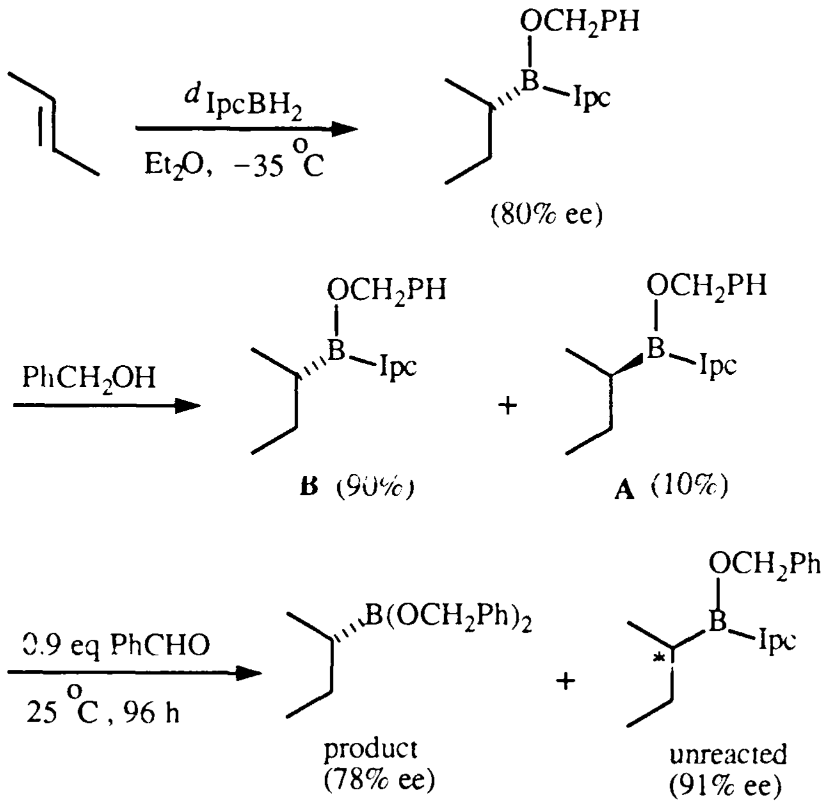
It appeared that the two diastereomers (**A** and **B**) of the intermediate borinic ester react with an aldehyde at different rates. To examine this hypothesis, we proceeded to prepare the two diastereomers by independent methods and to study separately their reaction with PhCHO.

The *(R,R)*-diastereomer (**A**) of 93% ee was obtained by asymmetric hydroboration[6c] of *cis*-2-butene with $^{d}Ipc_2BH$, followed by treatment with one equiv of PhCHO. This is a relatively fast reaction. Subsequent reaction of **A** with an additional 0.9 equiv of PhCHO, and analysis of the reaction mixture was carried out as described above. The enantiomeric excess of the boronic ester produced was ≥99% and that of the unreacted borinic ester was only 70%. The results implied that the major diastereomer **A** in the experiment was the faster reacting component, thereby enhancing the enantiomeric purity of the product, *i.e.*, boronic ester (Scheme I).



Scheme 1. *(R,R)*- Diastereomer Reacts Faster, Leading to the Enantiomeric Upgradation of Boronic Ester

To confirm the above results further, the reaction of the *(S,R)*-diastereomer (**B**) with PhCHO was examined. This diastereomer could be easily prepared[7b,c] from *trans*-2-butene. Hydroboration of *trans*-2-butene with $^{d}IpcBH_2$ (from (+)-α-pinene) gave a dialkylborane, 2-Bu(BH)Ipc which upon treatment with $PhCH_2OH$ provided **B** of 80% ee. The reaction of **B** with PhCHO was significantly slower than that of **A**. Separation of the product (boronic ester) from the unreacted borinic ester, oxidation of each component and determination of % ee of the resulting 2-butanol was carried out as usual. As expected, the product boronic ester had been downgraded (to 78% ee) and the unreacted borinic ester upgraded (to 91% ee). Here the major isomer, *(S,R)*-reacts slower than the minor isomer, *(R,R)*-, thereby upgrading the unreacted borinic ester. However, the extent of upgradation is only moderate due to the fact that the *(R,R)*-diastereomer, though being faster reacting, is present as a minor impurity in the mixture. This confirms our earlier conclusion that *(R,R)*- is the faster reacting diastereomer (Scheme 2).



Scheme 2. *(S,R)*- Diastereomer Reacts Slower, Leading to the Enantiomeric Downgradation of Boronic Ester

Optimization of the Reaction Parameters. Having established the above kinetic resolution as a valuable tool for upgrading the enantiomeric purity of boronic esters from hydroboration of appropriate alkenes with Ipc_2BH, we sought to optimize the procedure. A study was undertaken for evaluating the solvent effect, the structure of the aldehyde, and the stoichiometry of the reactants.

To begin with, it was observed that enantioselection can be slightly improved (3-4%) by performing the hydroboration with Ipc_2BH in Et_2O rather than in THF. This finding is in accord with an earlier observation[6a] that better results are realized by performing hydroboration in diglyme rather than in THF. The use of Et_2O as the solvent proved additionally advantageous in our study since the subsequent step (*i.e.*, treatment with aldehyde) could be carried out in the same solvent. In fact, the reaction of **3a** with PhCHO was faster in Et_2O than in THF. The optimization of the kinetic resolution was studied in detail using **3a** (R* = *exo*-norbornyl) because norbornene provides a product with lower % ee than is achieved with the other *cis* -alkenes. A 0.5 M solution of *exo*-$NrbBIpc_2$ was treated with 2 equiv of representative aldehydes and the reaction was monitored until ~90% complete. The product (boronic ester) was extracted with 3 N NaOH, oxidized with H_2O_2 and the % ee of the resulting *exo*-norborneol determined. All the aldehydes tested, with the exception of CCl_3CHO, provided significant kinetic resolution. Best results were realized with PhCHO, which converted *exo*-$NrbBIpc_2$ of 81% ee to *exo*-$NrbB(OCH_2Ph)_2$ of 93% ee (entry 4, Table II).

Our next task was to establish the optimal stoichiometry of R*$BIpc_2$ and PhCHO and also to examine the effect of $BF_3{\cdot}Et_2O$ as a catalyst in the reaction. As expected, a decreased amount of PhCHO provided improved enantiomeric enrichment of the boronic ester (Table III). In fact it was possible to obtain ≥99% ee for *exo*-$NrbB(OCH_2Ph)_2$, *albeit* with a modest 50% conversion. Keeping in view the sluggish reaction rates of other R*$BIpc_2$ with aldehydes, the effect of $BF_3{\cdot}Et_2O$ as the catalyst was also examined. The use of 1 mol % of the catalyst significantly enhanced the reaction rate as well as the chemical conversion. Interestingly though, the addition of $BF_3{\cdot}Et_2O$ at the beginning of the reaction proved detrimental for the kinetic resolution (entry 5, Table III). The desired result was achieved however, if the catalyst was added at the second stage of the reaction, that is, after the formation of the borinic ester (entry 6, Table III). An explanation for the difference could be derived from our earlier observation during the reactions involving

CCl_3CHO. Whereas the reaction of R^*BIpc_2 with simple aldehyde proceeds in two stages (that is, sequential elimination of each of the two isopinocampheyl groups), the same reaction with CCl_3CHO or in the presence of $BF_3{\cdot}Et_2O$ provides random distribution of products (eqn 6).

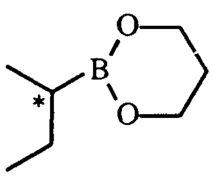
$$\underset{\mathbf{3a}}{R^*BIpc_2} \xrightarrow[\text{or}\ \ CH_3CHO\ +\ 1\ \text{mol}\ \%\ BF_3]{CCl_3CHO\ \ (1\ \text{equiv})} R^*BIpc_2 + R^*B(OCH_2R)\,Ipc + R^*B(OCH_2R)_2 \qquad (6)$$

In another words, the much faster reactions involving CCl_3CHO or CH_3CHO + 1 mol% BF_3 are much less selective than the slower reactions with simple aldehydes.

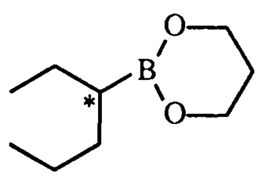
Asymmetric Hydroboration of Cyclic Dienes. Whereas the hydroboration of acyclic dienes is simple and predictable, the hydroboration of cyclic diene is intricately governed by the structure of the diene and the reagent. Hydroboration of 2,5-norbornadiene with a hindered (*e.g.* Sia_2BH)[13a] as well as an unhindered reagent (*e.g.* 9-BBN)[13b] provides a statistical mixture of monohydroborated, dihydroborated and unreacted diene. On the other hand, 1,3- and 1,4-cyclohexadienes can be hydroborated with either reagent to obtain predominantly monohydroboration product. Surprisingly, the hydroboration of 1,5-cyclooctadiene yields predominant dihydroboration with Sia_2BH as well as 9-BBN. Thus, these three dienes exhibit three different behavior patterns in hydroboration.

Before we began the present study, only the chiral boronate esters from simple alkenes were accessible. Except for 1,3-cyclohexadiene,[14] the asymmetric hydroboration of cyclic dienes has been neglected, partly due to the difficulties encountered during such attempts. Asymmetric monohydroboration of nonconjugated cyclic dienes could provide very valuable bifunctional molecules that could be further manipulated *via* a variety of optically active intermediates. The first part of our study, therefore, dealt with the hydroboration of these three representative cyclic dienes *viz.* 2,5-norbornadiene, 1,4-cyclohexadiene and 1,5-cyclooctadiene. Each one of these dienes, upon treatment with 1 equiv $^{d}Ipc_2BH$ in Et_2O at –25 °C, gave varying amounts of white amorphous solid insoluble in the most commonly used solvents. Careful characterization revealed the products to be symmetrically substituted dihydroboration products. Analysis of the reaction mixtures following oxidation revealed that norbornadiene gave a statistical mixture of mono- and dihydroborated products, cyclohexadiene was monohydroborated predominantly, and cyclooctadiene was dihydroborated almost exclusively. Changing the solvent (Et_2O, THF or *n*- Bu_2O) did not alter the product distribution significantly. The only option left for improving the yield of the desired monohydroborated product was to employ an excess of the diene. To obtain a high degree of monohydroboration for norbornadiene, at least a 400% excess of the diene was desirable. A 200% excess was sufficient to realize almost quantitative monohydroboration of the cyclohexadiene. The resulting cycloalkenylboronic esters were of 81% and 89% ee respectively. As described for other boronic esters, the enantiomeric enrichment of the cycloalkenylboronic esters was also achieved *via* kinetic resolution. The use of large excess of dienes was not a serious disadvantage since the excess is easily recovered from the reaction mixture. In the case of cyclooctadiene, a 400% excess of the diene provided 35% yield of the monohydroborated product with 43% ee. Although the yield could doubtless be improved by using even larger excesses of the diene, we did not explore this because of the low optical induction realized (Table IV).

The boronic esters were conveniently isolated as the corresponding acids which were easily reesterified with 1,3-propanediol to obtain very stable cyclic esters *viz.* 1,3,2-dioxaborinanes (**5a-5c**). Needless to emphasize, the use of ^{l}Ipc$_2$BH (derived from (–)-α -pinene) would provide the opposite enantiomers of all of the products obtained in the present study (Table V).



5a



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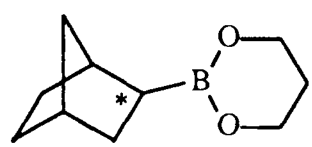

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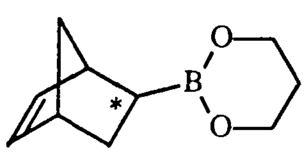

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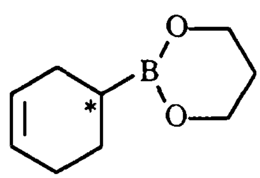

5e

Conclusions

A careful study of the reaction between *B*-alkyldiisopinocampheylboranes (**3a**) and representative aldehydes revealed several interesting aspects of the reaction. Contrary to the expectation, the aldehydes with an electron deficient carbonyl group reacted faster than the simple aldehydes. Accordingly, external activation of the aldehydes with a Lewis acid was proposed and then proved by employing $BF_3{\cdot}Et_2O$ as the catalyst for the reaction. The most fruitful aspect of the study was the observation that the intermediate borinic esters (**4**) were kinetically resolved during the reaction with aldehydes. The finding was developed into a simple and efficient *in situ* procedure for converting the initial hydroboration products (**3a**) of 81-96% ee to the corresponding boronic esters (**5a-e**) of $\geq$99% ee.

Experimental Section

All moisture and air-sensitive reactions were carried out under nitrogen atmosphere using oven-dried glassware. The ^{11}B NMR, ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-300 MHz spectrometer. The chemical shifts are in δ relative to $BF_3{\cdot}Et_2O$ and Me_4Si respectively. Capillary gas chromatographic analyses were carried out using a Hewlett-Packard 5890 chromatograph fitted with a 30m x 0.25mm SPB-5 column. Optical rotations were measured on a Rudolph Autopol III polarimeter.

Materials. Tetrahydrofuran (THF) was freshly distilled over sodium benzophenone ketyl. Anhydrous ether (Et_2O) was purchased from Mallinckrodt Inc. and was used directly. The alkenes as well as the aldehydes used were commercial products of highest purity available and were used without further purification. (–)-Menthyl chloroformate (MCF)[15] and (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPAA) were purchased from Aldrich Chemical Company. The latter was converted to the corresponding acid chloride as described.[16]

Rate-Study of the Reaction Between R^*BIpc_2 (3a) and Aldehydes. *(R)*-2-Butyldiisopinocampheylborane was chosen as the representative R^*BIpc_2 and a 1.0 M stock solution of the compound in THF was obtained by hydroboration of *cis*-2-butene with $^{d}Ipc_2BH$ as described earlier.[6c] Five 25-mL flasks equipped with rubber septa, N_2-supply and magnetic stirring bars were each charged with portions (10 mL, 10 mmol) of the above solution. To the stirred solution (maintained at 25±1° by external cooling), appropriate aldehyde (20 mmol) was added dropwise The four aldehydes selected for the study were CH_3CHO (flask-1), $(CH_3)_2CHCHO$ (flask-2), CCl_3CHO (flask-3) and PhCHO (flask-4). To the fifth flask $BF_3{\cdot}Et_2O$ (60 µl, 0.5 mmol) was added, followed by PhCHO (2 mL, 20 mmol) added dropwise. After stirring at 25±1° for 1 h, the reaction mixtures were allowed to stand at ambient temperature (and under a positive pressure of N_2). The reactions were periodically monitored by ^{11}B NMR, which revealed the transformation of R^*BIpc_2 (δ ~83) to $R^*B(OCH_2R)Ipc$ (δ ~ 54) and then to $R^*B(OCH_2R)_2$ (δ = 31). The rates of the reactions were in the following order: PhCHO + 5 mol % $BF_3{\cdot}Et_2O$ > CCl_3CHO >> PhCHO ≥ $(CH_3)_2CHCHO$ > CH_3CHO. The results are summarized graphically in Figure 1.

Enantiomeric Purities of the Boronic Esters (5) Obtained by the Treatment of *B*-Alkyldiisopinocampheylboranes (3a) with PhCHO. The reaction with *(R)*- 2-butyldiisopinocampheylborane is representative. A 1.0 M solution of the compound in THF (50 mL, 50 mmol) was treated with PhCHO (10 mL, 100 mmol) and the reaction was monitored as described above.

(a) From the Incomplete Reaction. At ~90% completion (occurring after 3 days), the reaction mixture was found to contain the boronic and borinic esters in ~4:1 ratio. At that stage, 50 mL of the reaction mixture was transferred to another flask and treated with MeOH (2 mL) followed by water (2 mL). Most of the solvent was pumped off under water aspirator. The reaction mixture was diluted with Et_2O (50 mL) and the boronic acid was extracted with 3 N NaOH (3 x 15 mL). A small portion (5 mL) of the extract was treated with 30% H_2O_2 (2 mL) and worked up as usual.[17] The resulting *(R)*-2-butanol was derivatized with MTPACl as described in the literature[16] and analyzed by capillary GC, which revealed ≥99% ee for the product.

(b) From the Completed Reaction. The remaining portion of the above reaction mixture (10 mL, ~8 mmol) containing boronic ester (> 95%) and borinic ester (< 5%) after 4 days was directly oxidized by treatment with 3 N NaOH (3 mL) and 30% H_2O_2 (3 mL). Capillary GC analysis indicated 93% ee for the resulting *(R)*-2-butanol. Since the treatment of R*BIpc$_2$ with an aldehyde as well as the oxidation of organoboranes proceeds with total retention of the configuration, the % ee of 2-butanol from this experiment reflects the initial induction.

The % ee of other optically active alcohols obtained by the oxidation of the corresponding boronic acids are summarized in Table I.

Kinetic Resolution of the Borinic Ester (A) With PhCHO. A 1.0 M solution of 2-BuBIpc$_2$ (20 mL, 20 mmol) in THF was treated with PhCHO (2 mL, 20 mmol) and the reaction was monitored as described above. After stirring at ambient temperature for 6 h, the formation of A (δ = 54) was complete. At that stage, an additional amount of PhCHO (1.8 mL, 18 mmol) was added and the reaction mixture was allowed to stand (for 72h) until ^{11}B NMR indicated no additional change in the ratio (~4:1) of the product, boronic ester (δ = 32) and the unreacted A. The reaction was treated with MeOH (1 mL) followed by water (1 mL), and concentrated under water aspirator. The residue was dissolved in Et_2O (30 mL) and extracted with 3 N NaOH (2 x 10 mL) to recover the boronic acid. The aqueous portion was treated with 30% H_2O_2 (6 mL) and worked up as usual.[17] A small portion (~10 μl) of the resulting *(R)*-2-butanol was converted to MTPA-ester and analyzed by capillary GC, which revealed ≥99% ee for the product.

The organic phase of the above reaction mixture contained the unreacted portion of A. It was concentrated, redissolved in Et_2O (5 mL) and oxidized by the treatment with 3 N NaOH (2 mL) and 30% H_2O_2 (2 mL). The resulting *(R)*-2-butanol had 70% ee.

Kinetic Resolution of the Borinic Ester (B) With PhCHO. Hydroboration of *trans*-2-butene (2.8 mL, 30 mmol) with ^{d}IpcBH$_2$ (3 mL of 0.9 M in Et_2O, 28 mmol) was carried out as described in the literature.[7c] The resulting dialkylborane (80% ee) was isolated (3.8 g, 64% yield), suspended in cold THF (15 mL), and treated with $PhCH_2OH$ (1.6 mL, 18 mmol). An immediate evolution of H_2 was observed and the resulting clear solution was examined by ^{11}B NMR, which showed a single peak at δ = 54, corresponding to the borinic ester. PhCHO (1.6 mL, 16 mmol) was then added and the reaction mixture was allowed to stand at ambient temperature (96h). Monitoring of the reaction, isolation of the product, and determination of the enantiomeric purity was carried out as described above. *(S)*-2-Butanol from the boronic acid and from unreacted **B** was found to be of 78% and 91% ee respectively.

Examination of Representative Aldehydes For the Kinetic Resolution. A 1.0 M solution of *exo*-NrbBIpc$_2$ of 81 % ee was obtained as described[6c] and its reaction with CH_3CHO is representative. A solution of the organoborane (20 mL, 20 mmol) was treated with CH_3CHO (2.2 mL, 40 mmol). The reaction was found to be ~90% complete after 48 h and ^{11}B NMR at that stage revealed the boronic and borinic esters in ~4:1 ratio. Following the details provided in the previous experiments, the reaction was worked up to obtain the boronic acid, which was then oxidized with alkaline H_2O_2. Capillary GC analysis of the MCF derivative of the resulting *(1S,2S)-exo*-norborneol indicated it to be of 86% ee.

The above procedure was repeated using $(CH_3)_2CHCHO$, CCl_3CHO and PhCHO. The results are summarized in Table II.

Boronic Esters (5a-e) of Very High Enantiomeric Purity *via* Asymmetric Hydroboration Followed by Kinetic Resolution.

1. From *cis*-Alkenes. The reported procedure[6c] for asymmetric hydroboration of *cis*-alkenes was modified and is illustrated for the preparation of the 2-butyl derivative (**5a**) as follows. Freshly prepared[18] ^{d}Ipc$_2$BH (28.6 g, 100 mmol) of 99% ee was crushed, placed in a 250-mL flask equipped with the usual assembly and covered with anhydrous Et_2O (50 mL). The reaction flask was immersed in a cryobath maintained at –25 °C and the Et_2O layer covering the ^{d}Ipc$_2$BH was removed using a double-ended needle. This washing ensures removal of any impurity arising from hydrolysis, oxidation or dissociation of Ipc$_2$BH. A precooled solution of *cis*-2-butene (10 mL, 110 mmol) in Et_2O (100 mL) was then introduced into the flask and the reaction mixture was vigorously stirred until a clear solution resulted. At times, certain R*BIpc$_2$ derivatives crystallize out during the reaction, thereby making it difficult to assess the progress of the reaction. In such cases, stirring was continued for 24 h at –25 °C.

After the completion of hydroboration, the reaction mixture was gradually warmed to 0 °C and the resulting clear solution was treated with PhCHO (19.3 mL, 190 mmol). Thereafter, the reaction mixture was allowed to stand at ambient temperature. ^{11}B NMR indicated complete conve. ion of the trialkylborane (**3a**) to the corresponding borinic ester (**4**) within 6 h. At that stage, a catalytic amount (120 µl, 1 mmol) of $BF_3 \cdot Et_2O$ was added and the reaction was allowed to proceed until no additional change in the ratio of boronate and borinate was seen. It was then treated with MeOH (4 mL, to facilitate the cleavage of the benzyl ester), and after 1 h extracted with 3 N NaOH (3 x 30 mL). The NaOH extract was washed once with Et_2O (25 mL) to remove any dissolved $PhCH_2OH$, cooled in an ice bath and acidified with 6 N HCl. The resulting thick white precipitate was extracted with Et_2O (3 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated at water aspirator to obtain *(R)*-2-butylboronic acid (9.3 g), which was esterified with 1,3-propanediol by the known procedure[19] to obtain *(R)*-(–)-(2-butyl)-1,3,2-dioxaborinane, **5a**, 10.5 g (74%, based on $^{d}Ipc_2BH$): bp 81-82 °C (25 Torr) [lit.[21] 70-72 °C (20 Torr)]; $[\alpha]^{23}_D$ –4.2° (*c* 3.6, CCl_4) [lit.[21] –4.8° (*c* 6, THF)].

***(R)*-(+)-(3-Hexyl)-1,3,2-dioxaborinane (5b):** bp 90-91 °C (20 Torr) [lit.[21] 92-94 °C (20 Torr)]; $[\alpha]^{23}_D$ +0.9° (*c* 3.5, CCl_4) [lit.[21] +0.87° (*c* 15, THF)].

***(1S,2S)*-(+)-(*exo*-Norbornyl)-1,3,2-dioxaborinane (5c):** bp 119-120 °C (20 Torr); $[\alpha]^{23}_D$ +18.6° (*c* 4, CCl_4); ^{11}B NMR ($CDCl_3$) δ +30 (s); ^{1}H NMR ($CDCl_3$) δ 0.70-0.87 (m, 1H), 1.05-1.55 (m, 8H), 1.90 (q, J=6Hz, 4H), 2.20 (bd, 2H), 3.96 (t, J=7Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 27.9, 29.8, 32.5, 32.8, 37.0, 38.4, 39.0, 62.0, 96.7. Anal. Calcd. for $C_{10}H_{17}O_2B$: C, 66.70; H, 9.52; B, 6.00. Found: C, 66.33; H, 9.67; B, 5.83.

A small portion of **5c** was oxidized[17] with alkaline H_2O_2 and the resulting *(1S, 2S)*-(–)-*exo*-norborneol was purified by preparative GC. The product revealed $[\alpha]^{23}_D$ –4.9° (*c* 7, $CHCl_3$) [lit.[6c] –4.2° (*c* 7.5, EtOH) for 83% ee], and 97% ee by the capillary GC analysis of its MCF derivative.

2. From Nonconjugated Cyclic Dienes. Following the procedure detailed above, $^{d}Ipc_2BH$ (14.3 g, 50 mmol) was used to hydroborate 2,5-norbornadiene (27 mL, 250 mmol, 400% excess). After stirring for 24 h at –25 °C, the reaction mixture was warmed to 0 °C and treated with PhCHO (9.1 mL, 90 mmol). It was then allowed to stand undisturbed so that the white precipitate of dihydroboration product settles down in the flask and does not react with PhCHO. ^{11}B NMR indicated completion of the reaction in 36 h. The usual procedure was followed to isolate the boronic acid, which was converted into the cyclic ester *viz. (1R,2S)*-(+)-(*exo*-5-norbornen-2-yl)-1,3,2-dioxaborinane, **5d**, 4.3 g (48%, based on ^{d}Ipc$_2$BH): bp 120-122° C (20 Torr); $[\alpha]^{23}_D$ +25.3°(*c* 3.9, CCl_4); ^{11}B NMR ($CDCl_3$) δ +31 (s); ^{1}H NMR ($CDCl_3$) δ 0.55-0.60 (m, 1H), 1.00-1.20 (m, 3H), 1.62-2.02 (m, 3H), 2.80-2.90 (m, 2H), 3.98 (q, J=7Hz, 4H), 3.88-3.92 (m, 1H), 6.04-6.08 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 27.7, 42.4, 44.3, 47.6, 61.9, 96.5, 134.7, 137.9. Anal. Calcd. for $C_{10}H_{15}O_2B$: C, 67.46; H, 8.49; B, 6.07. Found: C, 67.18; H, 8.78; B, 5.89.

Oxidation of **5d** with alkaline H_2O_2 provided *(1R,2S)*-(+)-*exo*-5-norbornen-2-ol which was purified by preparative GC. The product showed $[\alpha]^{23}_D$ +7.5° (*c* 8, $CHCl_3$) [lit.[6c] +6.2° (*c* 8.7, $CHCl_3$) for 79% ee], and 96% ee by the capillary GC analysis of its MCF derivative.

(+)-α -Pinene and the excess diene were recovered from the organic phase left after the extraction of boronic acid with 3 N NaOH.

***(S)*-2-(–)-(3-cyclohexen-1-yl)-1,3,2-dioxaborinane (5e):** 1,4-cyclohexadiene (14.2 mL, 150 mmol, 200% excess) was hydroborated with ^{d}Ipc$_2$BH (14.3 g, 50 mmol), and worked-up as described above to obtain **5e**, 4.9 g (60%, based on ^{d}Ipc$_2$BH): bp 114-116 °C (20 Torr); $[\alpha]^{23}_D$ –71.5°(*c* 4, CCl_4); ^{11}B NMR ($CDCl_3$) δ +31 (s); ^{1}H NMR ($CDCl_3$) δ 1.02-1.12 (m, 1H), 1.35-1.50 (m, 1H), 1.70-1.80 (m, 1H), 1.90-2.05 (m, 6H), 3.97 (q, J=7Hz, 4H), 5.65 (bq, 2H). ^{13}C NMR ($CDCl_3$) δ 24.2, 25.8, 26.5, 27.7, 61.8, 96.5, 127.4, 128.5. Anal. Calcd. for $C_9H_{15}O_2B$: C, 65.11; H, 9.11; B, 6.51. Found: C, 64.98; H, 9.32; B, 6.32.

Oxidation of **5e** gave *(S)*-(–)-3-cyclohexen-1-ol which exhibited $[\alpha]^{23}_D$ –77.9° (*c* 10, $CHCl_3$) [lit.[22] –5.13° (*c* 0.6, $CHCl_3$) for 19% ee], and ≥99% ee by the capillary GC analysis of its MTPA ester.

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References and Notes

(1) (a) Postdoctoral research associate on a grant from the Office of Naval Research. (b). Department of Chemistry, Sogang University, Seoul, Korea. (c) Postdoctoral research associate on a grant from the National Institutes of Health. (d) Department of Chemistry, The University of California, Santa Cruz.

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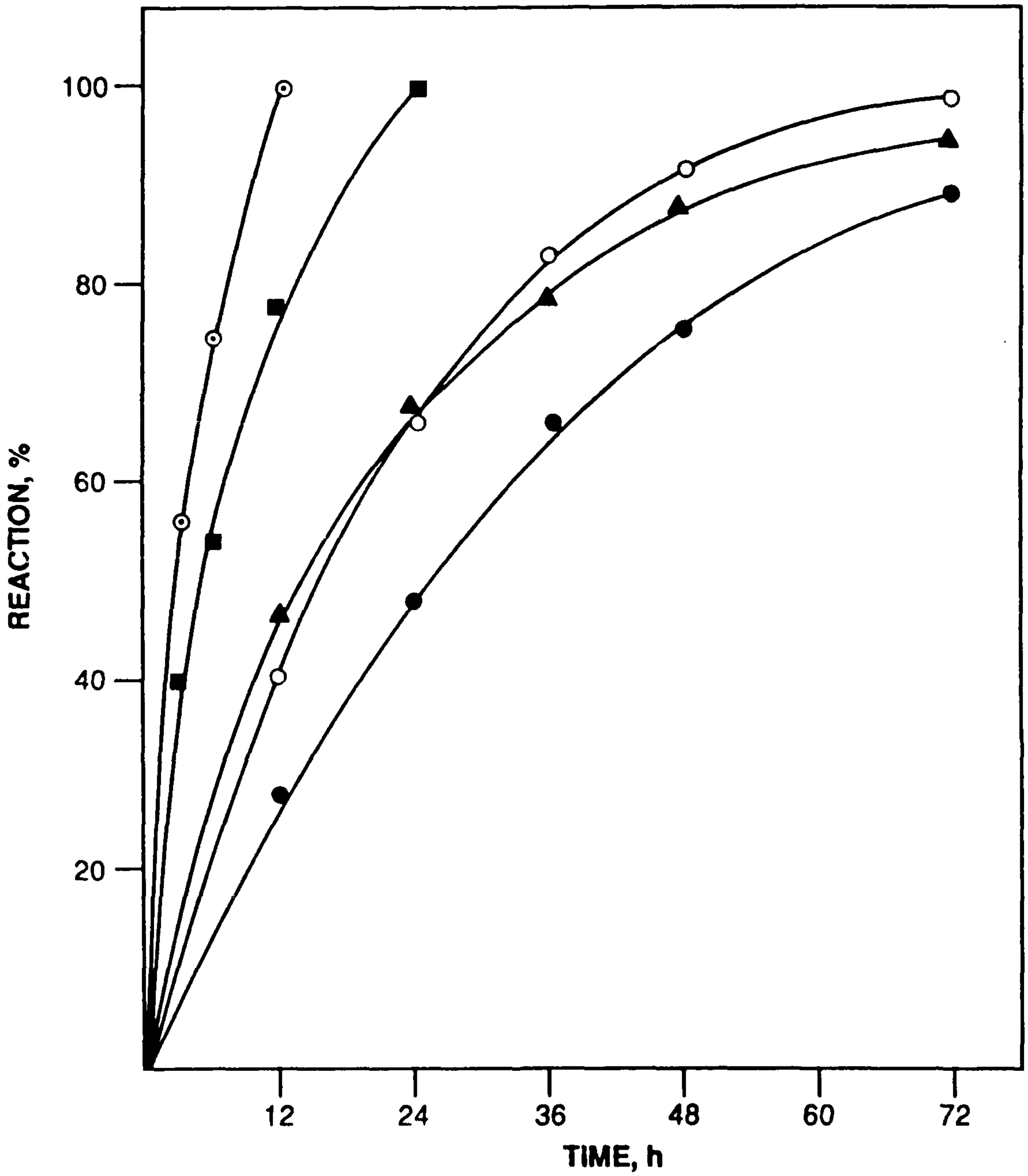


Figure-1. Rate-Study of the Reaction Between (2-Bu) $BIpc_2$ and Representative Aldehydes; 1.0 M THF, 25 ± 1 °C

● CH_3CHO ▲ $(CH_3)_2$ CHCHO ■ CCl_3 CHO ○ PhCHO

⊙ PhCHO + 5 mol % $BF_3 \cdot Et_2O$

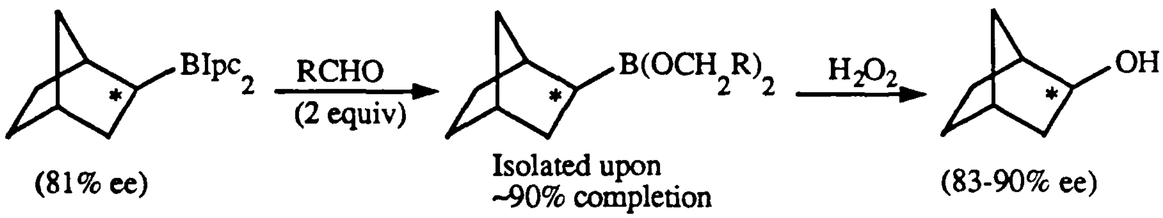
Table I. Enantiomeric Purities of the Boronic Esters (**5**) Obtained by the Treatment of *B*-Alkyldiisopinocampheylboranes (**3a**) with PhCHO

$$\underset{\mathbf{3a}}{R^*BIpc_2} \xrightarrow{PhCHO} \underset{\mathbf{4}}{R^*B(OCH_2Ph)Ipc} \xrightarrow{PhCHO} \underset{\mathbf{5}}{R^*B(OCH_2Ph)_2}$$

entry	R* =	time [a]	ratio [b]		% ee [c]
		da	**4**	**5**	of **5**
1	2-butyl	4 [d]	0	100	93 [d]
2		3	20	80	>99
3	3-hexyl	9 [d]	0	100	91 [d]
4		6	20	80	>99 [d]
5	*exo*-norbornyl	3 [d]	0	100	81 [d]
6		2	20	80	90
7		1.5	30	70	93

[a] All reactions were carried out as 1.0 M in THF, and at ambient temperature. [b] Approximate, established by ^{11}B NMR. [c] Of the corresponding R*OH obtained by the oxidation of **5**.
[d] Represents the initial induction. **4** and **5** were not separated prior to oxidation.

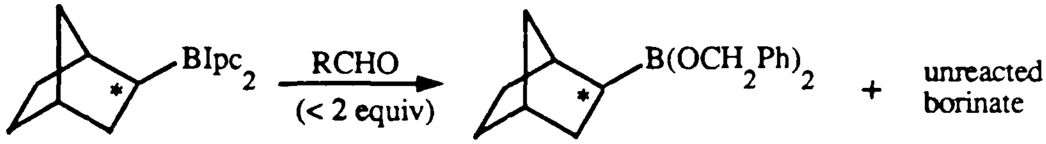
Table II. Examination of Representative Aldehydes for Kinetic Resolution



entry	RCHO	time [a,b] h	% ee [c]
1	CH_3CHO	48	86
2	$(CH_3)_2CHCHO$	36	87
3	CCl_3CHO	12	83
4	PhCHO	36	90

[a] All reactions were carried out as 1.0 M in THF, and at ambient temperature. [b] Based on approximate estimation by ^{11}B NMR. [c] Determined by the capillary GC analysis of the corresponding MCF derivative.

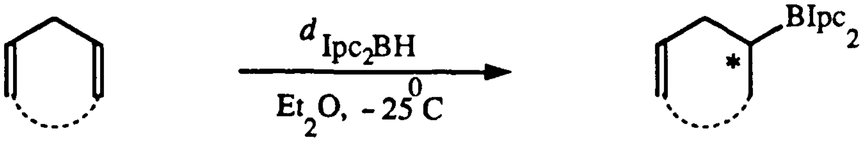
Table III. Enantiomeric Upgradation of Boronic Esters by Kinetic Resolution



entry	PhCHO	time [a]	ratio [b]		% ee [c]
	equiv	h	borinate	boronate	
1	1.9[d]	48[d]	0	100	85(81)[e]
2	1.9	36	20	80	93
3	1.8	36	30	70	97
4	1.7	24	50	50	99
5	1.7[f]	6[g]	20	70	87
6	1.7[h]	12	30	70	97

[a] The reactions were carried out as 0.5 M in Et_2O and at ambient temperature. [b] Approximate, established by ^{11}B NMR. [c] Of *(1S,2S)- exo-* norborneol obtained by the oxidation of the boronic acid extracted from the reaction mixture with 3 N NaOH. [d] The entire reaction mixture was oxidized after 48 h and represents initial induction. [e] The figure in the parenthesis corresponds to the hydroboration. [f] 1 mol % $BF_3{\cdot}Et_2O$ was added at the beginning of the reaction. [g] The final reaction mixture still had ~10% of the unreacted R^*BIpc_2. [h] 1 mol % $BF_3{\cdot}Et_2O$ was added after the removal of the first isopinocampheyl group.

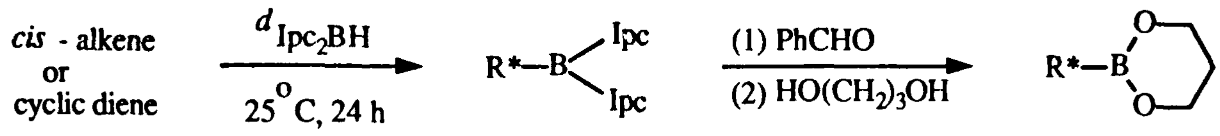
Table IV. Asymmetric Monohydroboration of Cyclic Nonconjugated Dienes



entry	diene	% excess of diene	% yield [a]	% ee [b]
1	2,5-norbornadiene	0	27	
2		100	55	
3		200	74	
4		400	85	83
5	1,4-cyclohexadiene	0	55	
6		100	81	
7		200	97	89
8	1,5-cyclooctadiene	0	<5	
9		200	14	
10		400	35	43

[a] Of monohydroboration, estimated by GC. [b] Of the corresponding 3-alkenols obtained by oxidizing the hydroboration product.

Table V. Preparation of 2-Alkyl-1,3,2-dioxaborinanes of Very High Enantiomeric Purity *via* Asymmetric Hydroboration Followed by Kinetic Resolution



3a **5**

R* =	% ee[a] of 3a	PhCHO equiv	time h	% yield	% ee[a] of 5	config.
2-butyl	96(93)[b]	1.9	24[c]	74	≥99	*R*[d]
3-hexyl	91	1.8	48[c]	67	≥99	*R*[d]
exo-norbornyl	85(81)[b]	1.8	36	54	97(≥99)[e]	1*S*, 2*S*[f]
exo-5-norbornen-2-yl	83	1.8	36	48	96(≥99)[e]	1*R*, 2*S*[f]
3-cyclohexen-1-yl	89	1.7	12	60	≥99	*S*[g]

[a] Based on the corresponding alcohol obtained by oxidation with alkaline H_2O_2. A small descripancy with the values published earlier, may arise from the use of optical rotation to establish % ee in those studies. [b] The figures in parentheses correspond to the hydroboration performed in THF instead of Et_2O as the solvent. [c] The reaction was catalyzed by 1 mol % $BF_3 \cdot Et_2O$.
[d] Ref. 6a. [e] The figures in parentheses correspond to the boronic acid crystallized from H_2O-EtOH (2:1), see ref. 10b. [f] Ref. 20.
[g] By analogy.

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