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Selective Reductions. 56. Exploration of the *B*-Haloisopinocampheylboranes for Asymmetric Reduction of Ketones

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ABSTRACT

A series of diisopinocampheylhaloboranes and monoisopinocampheyldihaloboranes were synthesized by the reaction of the corresponding boranes with the respective HX or X_2 (X = halogen) or by the hydroboration of α-pinene with the corresponding haloboranes. Stabilities of these haloboranes in various solvents were studied. Most of these haloboranes proved capable of reducing prochiral ketones to the alcohols with significant optical induction. When tested against a representative aromatic and aliphatic prochiral ketone, acetophenone and 3-methyl-2-butanone, respectively, α-phenethyl alcohol in 65–98% ee and 3-methyl-2-butanol in 28–59% ee were obtained. Some of them exhibited anomalous behavior.

INTRODUCTION

In our efforts to synthesize optically pure compounds via organoboranes [1], we undertook development of an effective chiral reducing agent for the reduction of all classes of prochiral ketones. Many interesting boron-based reagents have been developed in the past, some of them achieving remarkable success [2]. For example, Midland's *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Aldrich–Alpine-Borane®) reduces deuterated aldehydes [3], α-acetylenic ketones [4], α-keto esters [5], and α-halo ketones [6] with excellent chiral induction. Masamune's (*R*, *R*)-2,5-dimethylborolane successfully reduces prochiral ketones to the alcohols with high optical induction [7]. Unfortunately, its synthesis is not easy and it is not yet available commercially. The Itsuno reagent [8], derived from (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol and borane, whose structure has been examined by Corey and co-workers [9], is notable, not only for the high levels of enantioselectivity realized in the reduction of various classes of ketones, but more so for the catalytic nature of the reagent [9,10], one of the few known catalytic processes involving a boron reagent. Since then, Corey and others have synthesized various amino alcohols as chiral auxiliaries for CBS catalysts [11]. Several reagents involving modified borohydrides have also been explored with varying results. For example, Soai modified $LiBH_4$ with *N*,*N*-dibenzoyl cystine to prepare a reagent for the reduction of β-keto esters [12]. NB-Enantride [13] and Eapine-Hydride [14] are excellent borohydride reagents for the chiral reduction of straight chain aliphatic ketones, and K-Glucoride reduces α-keto esters and hindered aralkyl ketones with essentially quantitative chiral induction [15].

The trialkylborane reagent, Alpine-Borane, though excellent for the asymmetric reduction of α-acetylenic ketones and α-keto esters, proved inefficient for aralkyl ketones and dialkyl ketones. Presumably, a dehydroboration of the reagent to

Dedicated to Prof. Shigeru Oae on the occasion of his seventy-fifth birthday, in appreciation of his outstanding contributions to heteroatom chemistry.

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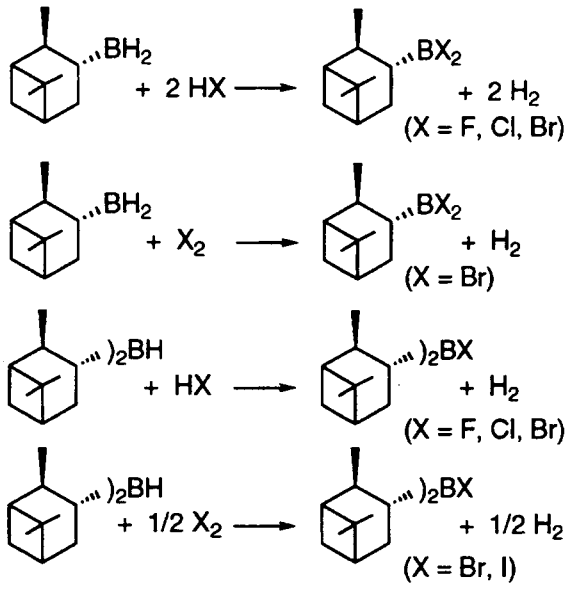


SCHEME 1

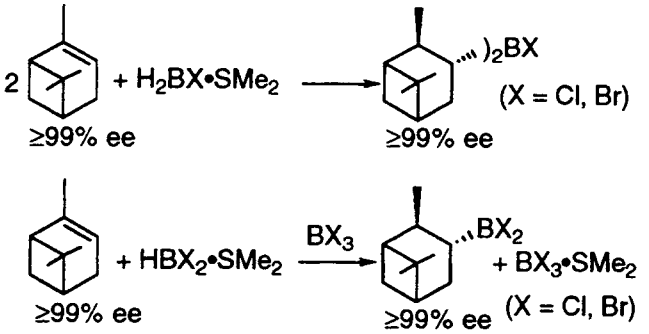
α-pinene and 9-BBN results in an achiral reduction by the 9-BBN and a decreased chiral induction [16]. The reactions are very slow even under neat conditions at room temperature (rt). It occurred to us that a manipulation of the steric and electronic environment of the boron in the pinanylborane derivative might improve the rate as well as the optical induction achieved. We envisaged that the introduction of a halogen might increase the Lewis acidity of the borane, possibly enhancing the reaction rate and increasing the optical induction of product alcohols. Consequently, a series of *B*-halodiisopinocampheylboranes and *B,B*-dihaloisopinocampheylboranes (Ipc_2BX and $IpcBX_2$, where X = F, Cl, Br, or I) were prepared and tested with a representative aromatic and aliphatic ketone, acetophenone and 3-methyl-2-butanone, respectively [17]. The preparation of the individual haloboranes, their properties, and the results of the chiral reduction of these representative ketones by the haloboranes are discussed in this article. The most favorable reagent, *B*-chlorodiisopinocampheylborane (Aldrich—DIP-Chloride) has been studied in detail and discussed in several recent publications [18].

RESULTS AND DISCUSSION

Preparation of the Reagents

The preparation of mono and diisopinocampheylborane ($IpcBH_2$ [19] and Ipc_2BH [20]) of high optical purity has been well studied. Treatment of these compounds either with the appropriate halogen or the corresponding hydrogen halide gave the respective haloboranes (Scheme 1).

In general, the more active halogens, fluorine



SCHEME 2

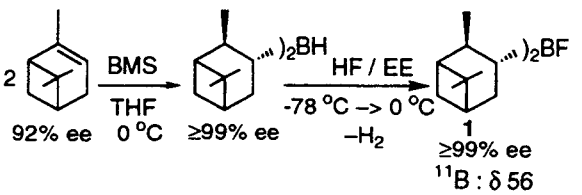
and chlorine, are best used as the hydrogen halides, HF and HCl. The least reactive halogen, iodine, is best used as such. Bromine can be used in either form.

Hydroboration of α-pinene with haloboranes provides certain isopinocampheylhaloboranes (Scheme 2). The drawback with this procedure is that, unlike the previous procedure, there is no optical upgradation of the reagent during the preparation, so that optically pure α-pinene should be used for the preparation of enantiomerically pure reagents.

The preparation of individual haloboranes are discussed subsequently.

B-Fluorodiisopinocampheylborane (Ipc_2BF, DIP-Fluoride, **1**)

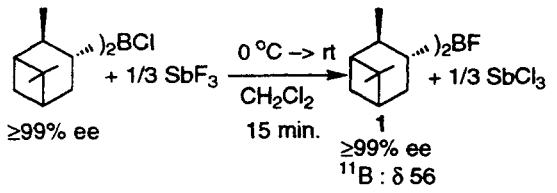
This reagent was prepared from commercially available (+)-α-pinene (92% ee) in high chemical and optical purities by hydroboration with borane-methyl sulfide complex followed by treatment with dry hydrogen fluoride (HF) (Equation 1). HF from a lecture bottle was condensed in a Teflon tube at −78°C and added, neat, to Ipc_2BH suspended in ethyl ether (EE) in a Teflon vessel at −78°C. When the temperature of the reaction mixture was raised to 0°C, Ipc_2BH dissolved with evolution of a gas, presumably hydrogen, and **1** formed in solution. The ^{11}B NMR spectrum showed a doublet at δ 56, which, on methanolysis, showed a singlet at δ 53. Removal of EE provided **1** as a thick slurry, which was used as such for further reactions. Attempts to crystallize **1** were not successful.



(1)

Alternately, **1** could be prepared from *B*-chlorodiisopinocampheylborane (**2**) via a halogen exchange reaction using SbF_3 [21]. Ipc_2BCl in CH_2Cl_2

was added, dropwise, to SbF_3 contained in a round-bottom flask at 0°C. There was an instantaneous reaction, as was shown by the ^{11}B NMR spectrum. The solvent was removed and **1** was separated

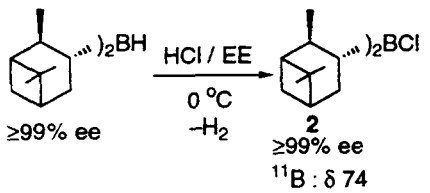


(2)

from solid $SbCl_3$. The reagent prepared using this procedure has identical ^{11}B NMR spectral characteristics to the one prepared using HF. A halogen exchange reaction of *B*-bromodiisopinocampheylborane (Ipc_2BBr, **3**) and KF in acetonitrile has been reported in the literature [22].

B-Chlorodiisopinocampheylborane (Ipc$_2$BCl, DIP-Chloride, **2**)

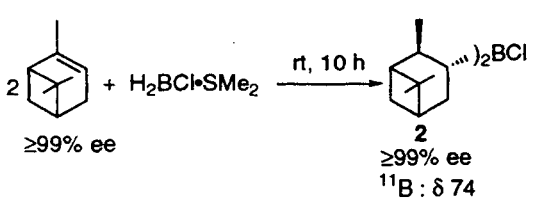
Several years ago, we reported the preparation and properties of *B*-chlorodiisopinocampheylborane (DIP-Chloride, **2**) as a chiral reducing agent [18]. This reagent was prepared from Ipc_2BH and hydrogen chloride (HCl) in EE using a procedure similar to that used for the preparation of **1** (Equation 3). Removal of EE and cooling to 0°C provided solid **2**, recrystallized from pentane, mp 54–56°C. Alternately, **2** was prepared by suspending



(3)

Ipc_2BH in EE at 0°C and bubbling gaseous HCl through the suspension until all of the Ipc_2BH dissolved. Removal of solvent provided **2** of ≥98% chemical purity, as was shown by its oxidation to isopinocampheol and analysis by gas chromatography. Simpson and co-workers prepared **2** by the addition of HCl in tetrahydrofuran (THF) to a mixture of α-pinene and borane-methyl sulfide without isolating Ipc_2BH [23].

A superior method of preparation of **2** is via the hydroboration of α-pinene with monochloroborane etherate [24,25] or monochloroborane-methyl sulfide complex [22,26] (Equation 4).



(4)

Similar to our reported reaction of isopinocampheylborinates with aldehydes to obtain optical upgradation for the borinates [27], a Merck group recently discussed an "asymmetric amplification" in chiral reduction, obtaining the product alcohol of higher ee starting with **2** prepared from α-pinene of lower optical purity (70% ee) and chloroborane-methyl sulfide complex, en route to the synthesis of an LTD_4 antagonist, L-699,392 [28]. This procedure avoids the use of optically pure reagent, though a 0.8 equiv excess of the reagent was used for obtaining optimal ee for the product alcohol. We had reported the hydroboration of α-pinene with chloroborane for the preparation of **2** as an intermediate during our synthesis of *B*-allyldiisopinocampheylborane [25]. However, we preferred the new procedure to prepare **2** for reduction purposes, because it involved an in situ upgradation of α-pinene of lower ee to ≥99% ee. Since we have developed an improved workup method for the recovery of the ≥99% ee α-pinene in quantitative yield [29], the chloroborane procedure can be used in subsequent preparations of the reagent and reductions to give product of maximum ee and yield. The Merck procedure involves a modified workup that destroys the excess reagent, and the recovery of α-pinene was not discussed. The recovery of partially upgraded α-pinene from the reaction mixture, though theoretically possible, might be practically difficult. As a result, even if the starting α-pinene of 70% ee were recovered completely, every subsequent use of the reagent would consume 0.8 equiv excess of chloroborane-methyl sulfide.

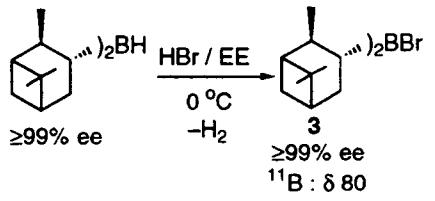
Commercially available monochloroborane-methyl sulfide contains ~5–7% of dichloroborane-methyl sulfide and borane-methyl sulfide. However, upon hydroboration of 2 equiv of α-pinene, in CH_2Cl_2, at rt, we observed a single peak at δ 74 in the ^{11}B NMR spectrum corresponding to Ipc_2BCl [30,31]. The solvent and dimethyl sulfide were removed under vacuum to obtain **2** as a thick syrup that was used as such for reductions.

Recently, Soundararajan and Matteson have described the synthesis of **2** as part of their study of the generation of chloroborane with trichloroborane and trialkylsilane [32]. This procedure can be applied to the synthesis of other diisopinocampheylhaloboranes and isopinocampheyldihaloboranes as well [33].

B-Bromodiisopinocampheylborane (Ipc$_2$BBr, DIP-Bromide, **3**)

This haloborane was prepared using a procedure similar to that used for preparing **1** and **2**. HBr from a lecture bottle was dissolved in ice-cold EE and standardized. Addition of a stoichiometric amount of HBr to Ipc_2BH in EE at 0°C and stirring for 2 hours provided **3** in solution, ^{11}B NMR: δ 80. Re-

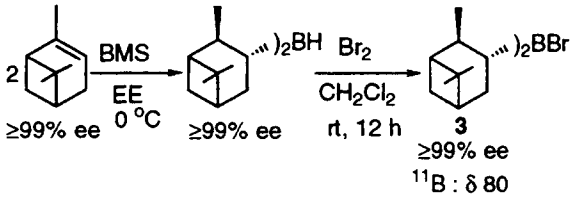
moval of EE provided solid **3**, mp 58–60°C (Equation 5).



(5)

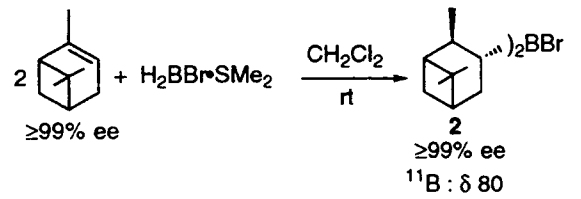
Alternately, **3** was prepared from Ipc_2BH by treatment with Br_2 in CH_2Cl_2 at rt [34] (Equation 6). Ipc_2BH was prepared in EE for this reaction since preparation of Ipc_2BH in THF leaves residual solvent occluded in the crystals, cleaved by **3**, rendering the reagent impure (vide infra).

Since there is no upgradation of α-pinene during the preparation of Ipc_2BH in EE [20], the former procedure is superior in obtaining **3** of ≥99% optical purity. Otherwise, α-pinene of ≥99% ee can be used to overcome this deficiency.



(6)

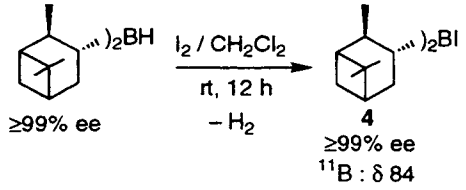
Similar to the preparation of **2**, DIP-Bromide was also prepared by the hydroboration of α-pinene with $H_2BBr \cdot SMe_2$ (Equation 7) [22]. This procedure also requires optically pure α-pinene to prepare the reagent of ≥99% ee.



(7)

B-Iododiisopinocampheylborane (Ipc₂BI, DIP-Iodide, **4**)

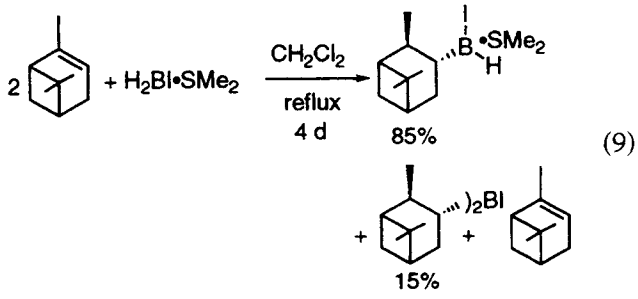
Since anhydrous hydrogen iodide is not easily accessible, this reagent was prepared from Ipc_2BH and I_2 in CH_2Cl_2 using the same experimental setup as that for the preparation of **3** (Equation 8). The reaction mixture was stirred at rt until the color of I_2 disappeared (12 hours). In this case also, Ipc_2BH was prepared in EE since Ipc_2BI reacts violently and instantaneously with THF (vide infra). Ipc_2BI is very hygroscopic and highly unstable in air.



(8)

Attempts to prepare Ipc_2BI by the hydroboration of α-pinene with $IBH_2 \cdot SMe_2$ [35] failed to give the desired product. Hydroboration of α-pinene with 1/2 equiv of $IBH_2 \cdot SMe_2$ in CH_2Cl_2 was slow at rt. Within 5 hours, the ^{11}B NMR spectrum of the reaction mixture showed ~1:1 peaks corresponding to $IpcBHI \cdot SMe_2$ (doublet at δ – 0.3) and unreacted $IBH_2 \cdot SMe_2$ (triplet at δ – 20.0). Even after 4 days, the spectrum revealed no formation of **4**, but the ratio of $IpcBHI \cdot SMe_2$ and unreacted $IBH_2 \cdot SMe_2$ had changed to 95:5. Probably, the hydroboration of α-pinene with $IpcBHI \cdot SMe_2$ is extremely slow. We have reported that $IBH_2 \cdot SMe_2$ is much slower to hydroborate olefins as compared to the corresponding chloroborane and bromoborane complex, and the reaction with iodoborane is normally done under reflux in CH_2Cl_2 [26b]. $IBH_2 \cdot SMe_2$ was readily consumed upon refluxing with 2.1 equiv of α-pinene, and the ^{11}B NMR after 8 hours showed a composition of 85% $IpcBHI \cdot SMe_2$ and 15% Ipc_2BI. Even after 4 days of refluxing, there was no change in the ^{11}B NMR spectrum.

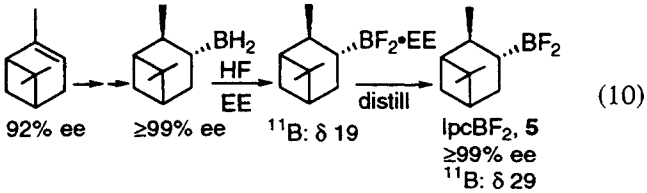
The preceding observation of $IBH_2 \cdot SMe_2$ is different from that of $ClBH_2 \cdot SMe_2$ or $BrBH_2 \cdot SMe_2$. In the case of chloroborane and bromoborane, the reaction cannot be stopped at the monoalkylborane stage unless the olefin is highly hindered, such as 2,3-dimethyl-2-butene [36]. Probably, the steric requirement of $H_2BI \cdot SMe_2$ is larger than that of $ClBH_2 \cdot SMe_2$ and $BrBH_2 \cdot SMe_2$ [37]. This problem, probably, can be circumvented by using H_2BI free of the complex [33].



(9)

B,B-Difluoroisopinocampheylborane (IpcBF₂, **5**)

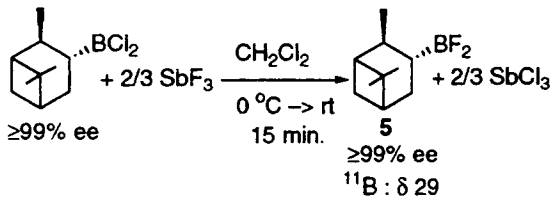
This reagent was prepared by a procedure similar to the one used for the preparation of **1**, using $IpcBH_2$ and HF. HF was condensed in a Teflon tube and added to a measured amount of a standard solution of $IpcBH_2$ in EE in a Teflon flask maintained at −78°C. The mixture was warmed to ice-salt temperature when hydrogen evolution was observed with concurrent formation of **5** as an



(10)

ether complex. The ^{11}B NMR spectrum showed a broad singlet at δ 19. Removal of the solvent and distillation provided **5**, free of the complex, whose ^{11}B NMR spectrum revealed a triplet at δ 29 (Equation 10). On methanolysis, the spectrum contained a singlet at δ 32. $IpcBF_2$ fumes in air and is sensitive to moisture. If not protected properly, the reagent turns brownish.

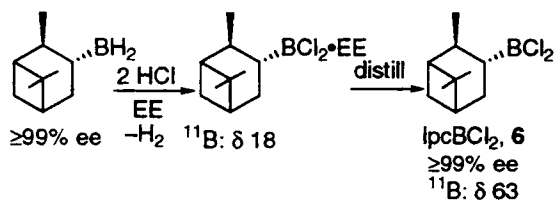
Alternately, **5** was also prepared from *B,B*-dichloroisopinocampheylborane ($IpcBCl_2$, **6**) via a halogen exchange reaction using SbF_3 (Equation 11). A halogen exchange reaction of *B,B*-dibromoisopinocampheylborane ($IpcBBr_2$, **7**) with KF was reported recently in the literature [22].



(11)

B,B-Dichloroisopinocampheylborane (*$IpcBCl_2$*, **6**)

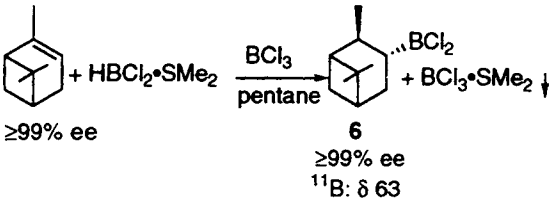
This reagent was prepared from $IpcBH_2$ by the reaction of 2 equiv of HCl in EE at ice-salt temperature (Equation 12). Instantaneous hydrogen evolution was observed with the concurrent formation of $IpcBCl_2 \cdot EE$. The ^{11}B NMR spectrum showed a singlet at δ 18. On methanolysis, the peak in the spectrum shifted to a singlet at δ 32. Attempts to render the reagent free of ether by applying high vacuum were futile. The reaction of ketones with



(12)

$IpcBCl_2 \cdot EE$ was very slow even at rt. The complex can be removed by distillation to obtain pure **6**, bp 52–55°C/0.1 mm Hg. The ^{11}B NMR spectrum (neat and in CH_2Cl_2) showed a singlet at δ 63, which, on methanolysis, was shifted to δ 32. The ^{11}B NMR spectrum of a sample of **6** left at rt for several weeks remained unchanged. $IpcBCl_2$ fumes in air and is sensitive to moisture.

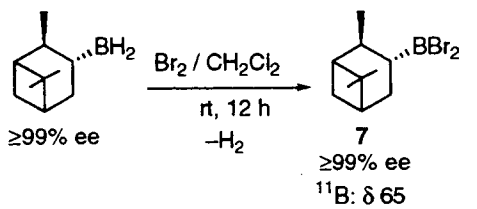
Alternately, **6** was prepared, more easily, by the hydroboration of α-pinene with dichloroborane-methyl sulfide complex in the presence of BCl_3 in pentane [38]. BCl_3 complexes with SMe_2 and the liberated $HBCl_2$ hydroborates α-pinene to provide **6**, distilled, in 90% yield (Equation 13). However, this procedure does not provide optically pure reagent unless the starting α-pinene is optically pure. The procedure using $IpcBH_2$ has an in situ upgradation of α-pinene during the preparation of $IpcBH_2$.



(13)

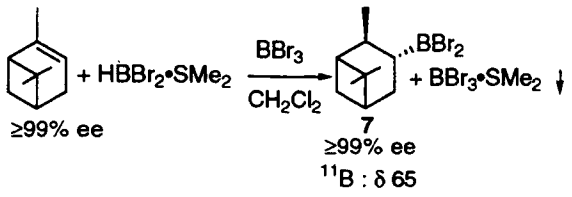
B,B-Dibromoisopinocampheylborane (*$IpcBBr_2$*, **7**)

Reaction of HBr in EE with $IpcBH_2$ provided $IpcBBr_2 \cdot EE$, but the reagent was consumed by cleaving EE within 1 hour (vide infra). Hence, alternate methods were sought and **7** was prepared from $IpcBH_2$ and Br_2. EE was replaced with CH_2Cl_2 from a measured amount of a standard solution of $IpcBH_2$ in EE, and a stoichiometric amount of Br_2 in CH_2Cl_2 was added at 0°C. Surprisingly, the reaction did not proceed at all at 0°C. The mixture was left stirring overnight at rt when hydrogen evolution ceased and a pale yellow solution of $IpcBBr_2$ in CH_2Cl_2 was obtained (Equation 14). The ^{11}B NMR spectrum showed a singlet at δ 65. On methanolysis, the spectrum revealed a singlet at δ 32. The solvent was pumped off and distilled at 82–85°C/0.1 mm Hg to provide pure **7** in 80% yield as a colorless liquid, which is stable at rt, under nitrogen, for several weeks. $IpcBBr_2$ is pyrophoric and is sensitive to moisture.



(14)

As in the case of **6**, $IpcBBr_2$ was also prepared by the hydroboration of α-pinene with $HBBr_2 \cdot SMe_2$ in the presence of BBr_3 in CH_2Cl_2. The reaction of α-pinene and $HBBr_2 \cdot SMe_2$ in CH_2Cl_2, 1 *M*, 0°C was extremely slow. Hence, 10 mol% of BBr_3 was added as a catalyst when the hydroboration was complete in ~10 hours [39]. The ^{11}B NMR spectrum showed a singlet at δ 9.75 corresponding to $IpcBBr_2 \cdot SMe_2$. We expected that removal of CH_2Cl_2 and distillation of the residue would break the SMe_2 complex as was observed for $IpcBCl_2 \cdot EE$. However, we observed that the complex was very strong and did not break on heating and distillation. So, we repeated the hydroboration in the presence of 1 equiv of BBr_3 to remove all of the SMe_2 as a complex and distilled the supernatant liquid to obtain pure **7** in 90% yield (Equation 15). Again, optically pure α-pinene was used for the preparation of optically pure reagent.



(15)

B,B-Diiodoisopinocampheylborane (IpcBI$_2$, 8)

Preparation of IpcBI$_2$ was attempted in a manner similar to the preparation of IpcBBr$_2$, from IpcBH$_2$ and I$_2$. Ether was substituted with CH_2Cl_2 from a standard solution of IpcBH$_2$ in EE, and I$_2$ in CH_2Cl_2 was added at rt. The reaction, as monitored by ^{11}B NMR spectroscopy, was extremely slow, during which time IpcBH$_2$ redistributed to Ipc$_2$BH and BH_3. Ipc$_2$BH thus formed was readily converted to Ipc$_2$BI. Attempts to isolate IpcBI$_2$ by distillation from the reaction mixture resulted in the decomposition of the mixture.

The physical properties of reagents **1–7** are summarized in Table 1.

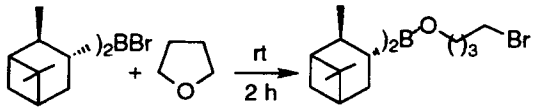
Stabilities of the Reagents in Various Solvents

Before conducting the reaction of these reagents with prochiral ketones, it was felt necessary to ascertain the stability of these reagents in various solvents. Pentane, CH_2Cl_2, EE, and THF were selected as solvents, and the study was made, at rt, by dissolving the reagent in these solvents and plotting their ^{11}B NMR spectrum at different intervals of time in order to detect any change due to redistribution or cleavage of the ether solvent.

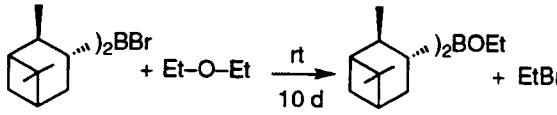
All the reagents are very stable in pentane and CH_2Cl_2.

DIP-Fluoride and DIP-Chloride are stable in all of these four solvents. However, the ^{11}B NMR of **1** in THF revealed a small peak (~5%) at δ 10 after several days and **2** in THF showed a similar peak at δ 16. Since most of the reductions using **1** and **2** in THF were conducted at −25°C, THF can be used safely as a solvent. The slow reactions using **2** were generally done under neat conditions.

DIP-Bromide cleaved THF within 2 hours, and, EE more slowly, with complete destruction of the reagent within 10 days (Equation 16 and 17).

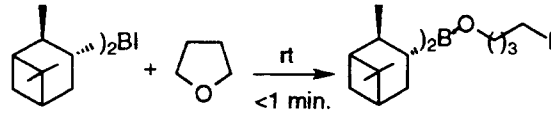


(16)



(17)

DIP-Iodide reacted with THF instantaneously, exothermally, providing the THF cleaved product (Equation 18). EE was cleaved by **4** within 24 hours. The asymmetric ring opening of cyclic ethers with **2–4** was the subject of a study published recently from our laboratory [40].



(18)

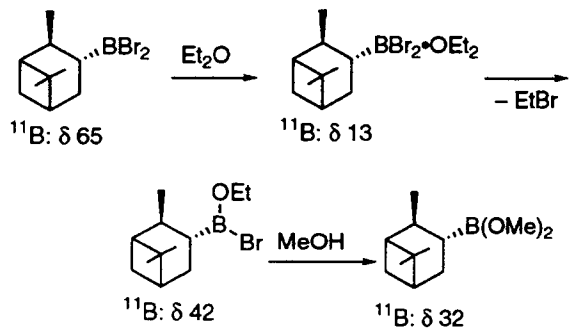
IpcBF$_2$ formed a complex with EE and THF, which was found to be stable. Unlike Ipc$_2$BCl, IpcBCl$_2$ formed a complex with EE, noticed to be stable for several days. Again, contrary to what was observed in the case of Ipc$_2$BCl, IpcBCl$_2$ formed a complex with THF, that was somewhat stable up to 12 hours. Very little cleavage occurred during this period. However, on keeping for ~15 days, The cleavage was almost complete.

While IpcBCl$_2$ did not cleave EE after forming the complex, IpcBBr$_2$ cleaved EE within 1 hour. The ^{11}B NMR spectrum of IpcBBr$_2$ in EE revealed a peak at δ 13, due to a complex, which shifted to δ 42 within 1 hour, attributed to an ether cleaved product, RB(Br)OR′. The product on methanolysis showed a singlet at δ 32 (Equation 19).

TABLE 1 Physical Properties of the *B*-Haloisopinocampheylboranes

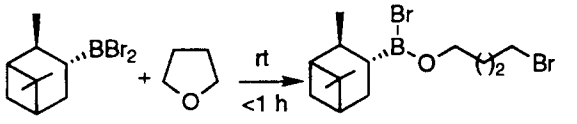
Reagent	*Appearance*	*Mp/Bp (°C)*	*^{11}B NMR δ (CH_2Cl_2)*	*$[\alpha]_D$ (CH_2Cl_2)*[a]
1	colorless syrup	—	56(d)	—
2	white crystals	54–56	74	−67.07
3	white solid	58–60	80	−54.68
4	white solid	60–62	85	—
5	colorless liquid	57–58/9 mm Hg	29(t)	—
6	colorless liquid	52–55/0.1 mm Hg	63	−24.00
7	colorless liquid	82–85/0.7 mm Hg	65	−12.41

[a]For reagents prepared from (+)-α-pinene.



(19)

As in the case of $IpcBCl_2$, $IpcBBr_2$ also cleaved THF (Equation 20). However, the rate of cleavage was much faster, <1 hour for $IpcBBr_2$ as opposed to 15 days for $IpcBCl_2$.



(20)

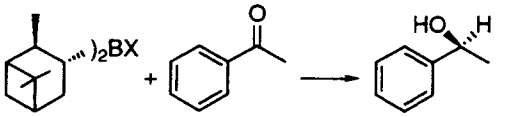
Based on this study, the reductions with **1** and **2** were carried out in THF or EE, the reduction with **3** was carried out in EE or CH_2Cl_2, and the reductions with **4–7** were carried out in CH_2Cl_2.

Asymmetric Reduction of Representative Ketones

Two representative ketones, acetophenone, an aralkyl ketone, and 3-methyl-2-butanone, an aliphatic ketone, were selected to test the reactivities and enantioselectivities in the asymmetric reduction with these new reagents. In general, reactions were carried out in EE or CH_2Cl_2 at −25°C. Reactions were monitored by ^{11}B NMR spectroscopy of a methanolyzed aliquot of the reaction mixture. On completion of the reaction, the alcohol was liberated by removing the boron components using diethanolamine (for reactions of Ipc_2BX) or triethanolamine (for reaction of $IpcBX_2$). The %ee of the alcohol was determined by analysis of the α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA derivative) [41] or (–)-menthylchloroformate (MCF) derivative [42] on a capillary column using a gas chromatograph. The results are summarized in Table 2. The reactions of individual reagents **1–7** are described subsequently.

B-Halodiisopinocampheylboranes

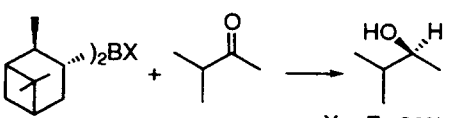
As expected, **1** was the least reactive of all the *B*-halodiisopinocampheylboranes. It reduces acetophenone and 3-methyl-2-butanone, at −25°C, in EE (1 *M*) to the corresponding alcohols in 65% ee and 30% ee, respectively, within 4 days. DIP-Chloride proved to be the best reagent due to the simplicity of preparation, stability of the reagent in all solvents, rate of reduction, and ease of workup. Within 5 hours, at −25°C, it reduces acetophenone in EE to α-phenethanol of 98% ee and 3-methyl-2-butanone to the corresponding alcohol in 32% ee. DIP-Bromide was expected to react faster than DIP-Chloride due to its better Lewis acidity [39,43]. But, surprisingly, the reaction was slower. It reduces acetophenone within 15 hours in EE, 1 *M*, at −25°C, to α-phenethanol of 98% ee. 3-Methyl-2-butanone was reduced to the alcohol with 28% ee. Since the reactions were conducted at −25°C, cleavage of ether by Ipc_2BBr was not observed (the reaction rate is faster than the rate of ether cleavage at this temperature). However, CH_2Cl_2 is the recommended solvent for slow reactions.



X = F, 65% ee
X = Cl, 98% ee
X = Br, 98% ee
X = I, 0% ee

(21)

DIP-Iodide showed some anomalies. It reacted with acetophenone, in CH_2Cl_2, 1 *M*, at −25°C, extremely slowly. The reaction was only 50% complete even after a week. However, on workup, after destroying the excess reagent with acetaldehyde, we obtained a mixture of two compounds, as was shown by the gas chromatographic analysis. The minor product corresponded to α-phenethanol. The IR spectrum showed the corresponding peak due to the presence of an–OH group. On testing the product mixture with ethanolic silver nitrate, we obtained a positive test for iodide. This, we presume, is α-phenethyl iodide (vide infra). The product mixture was derivatized as such using MTPA-Cl and analyzed on a Supelcowax glass capillary column. To our surprise, we found the small amount of alcohol produced in the reaction to be racemic. We do not know, at present, the reasons for this anomaly and are studying this phenomenon more carefully. However, a similar reaction and workup of Ipc_2BI and 3-methyl-2-butanone provided a very low yield (~20%) of the corresponding alcohol. The MCF derivative of this alcohol, on analysis on a methyl silicone column, revealed an ee of 40%. The results of the reduction of acetophenone (Equation 21) and 3 -methyl-2-butanone (Equation 22) are summarized in Table 2.



X = F, 30% ee
X = Cl, 32% ee
X = Br, 28% ee
X = I, 40% ee

(22)

TABLE 2 Asymmetric Reduction of Acetophenone and 3-Methyl-2-butanone with the *B*-Haloisopinocampheylboranes

		Reaction Condition					
Ketone	*Reagent*	*Solvent*	*(°C) Temperature*	*Time*	*Yield (%)*	*% ee*[a]	*Configuration*[b]
Acetophenone	**1**	EE	−25	4 days	70	65	*S*
3-Methyl-2-butanone	**1**	EE	−25	4 days	60	30	*S*
Acetophenone	**2**	EE	−25	5 hours	90	98	*S*
3-Methyl-2-butanone	**2**	EE	−25	5 hours	65	32	*S*
Acetophenone	**3**	EE	−25	15 hours	70	98	*S*
3-Methyl-2-butanone	**3**	EE	−25	14 hours	73	28	*S*
Acetophenone	**4**	CH_2Cl_2	−25	7 days	20[c]	0	—
3-Methyl-2-butanone	**4**	CH_2Cl_2	−25	7 days	30	40	*S*
Acetophenone	**5**	CH_2Cl_2	25	14 days	[d]	—	—
3-Methyl-2-butanone	**5**	CH_2Cl_2	25	14 days	30[e]	59	*S*
Acetophenone	**6**	CH_2Cl_2	−25	4 hours	[f]	—	—
3-Methyl-2-butanone	**6**	CH_2Cl_2	−25	3 hours	60	43	*S*
Acetophenone	**7**	CH_2Cl_2	25	7 days	[g]	—	—
3-Methyl-2-butanone	**7**	CH_2Cl_2	25	7 days	[g]	—	—

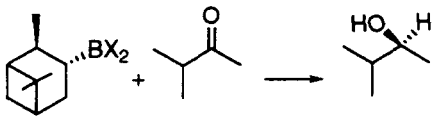
[a] Determined as the MTPA or MCF derivative on a capillary GC.
[b] By comparing the sign of rotation of the product alcohol.
[c] Poor reduction occurred.
[d] No reduction occurred, ketone recovered.
[e] A 1:1 mixture of ketone and alcohol obtained.
[f] α-Phenethyl chloride was formed.
[g] Bromo compound was formed.

B,B-Dihaloisopinocampheylboranes

As expected, reductions of prochiral ketones using boron reagents with an attached halogen were considerably faster than with trialkylboranes, such as Alpine-Borane. A look into the proposed mechanism of reduction [18] suggested that, probably, one isopinocampheyl moiety is sufficient for chiral induction. But, we have recently shown the importance of the second isopinocampheyl moiety by substituting the Ipc moiety with alkyl groups of increasing steric requirements, such as methyl, ethyl, iso-propyl, tert-butyl, and thexyl [44]. We were seeking to understand the effect of substituting the second Ipc group with a halogen atom. We expected much faster rates of reduction with a reasonably good chiral induction. However, the results proved otherwise. Individual dihaloboranes behaved differently.

$IpcBF_2 \cdot EE$ did not react with ketones. The ether-free reagent reacted with 3-methyl-2-butanone but did not react with acetophenone. Since the reactions of **5** with the ketones were violent under neat conditions, the reactants were mixed in CH_2Cl_2, 1*M*, at −25°C. There was an immediate red coloration on addition of the ketones to **5**. As usual, the reaction was followed by methanolyzing an aliquot of the reaction mixture at different time intervals and noting the percent completion by ^{11}B NMR spectroscopy. A methanolyzed aliquot of a reaction of **5** with acetophenone after 1 hour revealed three peaks at δ 32.00, 8.00, and −0.6 in the ^{11}B NMR spectrum. There was no peak due to $B(OMe)_3$ at δ 18.00, which would be expected if reduction had occurred with the elimination of 1 equiv of α-pinene. The ^{11}B NMR spectrum remained the same with time, showing that there was no further reaction. The solvent was removed and the reaction mixture was brought to rt. Yet, we did not observe any reaction even after 7 days. We worked up the reaction mixture using triethanolamine. To our surprise, we recovered the ketone, but there was no trace of the expected α-phenethanol. There was also no fluoride formation as in the reaction of acetophenone with **6** and **7** (vide infra).

The reaction of 3-methyl-2-butanone with **5** was different from that of acetophenone. Upon mixing **5** with the ketone in CH_2Cl_2 at −25°C, a red coloration was observed and the ^{11}B NMR spectrum of a methanolyzed aliquot of the reaction mixture showed four peaks at δ 32.00, 18.00, 10.00, and −0.70. The concentration of the expected δ 18.00 peak increased with time. On working up the reaction mixture after 7 days with triethanolamine as previously done, a 60% yield of a 1:1 mixture of the alcohol and ketone was obtained. This was derivatized as such using (−)-menthylchloroformate. Analysis of the MCF derivative using a capillary GC showed 59% ee for the alcohol in the *S*-isomer (Equation 23).



X = F, 59% ee
X = Cl, 43% ee

(23)

$IpcBCl_2 \cdot EE$ did not react with ketones at −25°C even after several days, as was the case with $IpcBF_2 \cdot EE$. However, ether-free **6** behaved differently from **5**. On addition of acetophenone to a solution of **6** in CH_2Cl_2, 1*M*, at −25°C, the solution turned yellow immediately and became reddish-yellow in 2–3 hours. A methanolyzed aliquot showed a singlet at δ 18.00 corresponding to methyl borate. The reaction was found to be complete within 3 hours. The reaction mixture was brought to rt, the solvent removed with the aid of an aspirator, and the residue subjected to high vacuum to collect the small amount of α-pinene displaced during the reaction. The residue was worked up using triethanolamine, which gave a product that did not show the peak corresponding to an–OH in its IR spectrum or a peak corresponding to α-phenethanol on GC. The product gave a positive silver nitrate test corresponding to the presence of a chloride. The ^1H NMR spectrum showed the compound to be α-phenethyl chloride, which was purified by preparative GC and the specific rotation, $[\alpha]_D^{20}$ −11.56, corresponded to an optical purity of 9% in the (*S*)-isomer.

Again, the reaction of 3-methyl-2-butanone was different. The reaction was complete in 4 hours. The reaction mixture was warmed to rt, and worked up as usual using triethanolamine, whereupon a 60% yield of the alcohol was obtained, which, on analysis using capillary GC as its MCF derivative, showed an ee of 43% in the (*S*)-isomer. We observed that the yield of the alcohol depended on the reaction conditions and workup. At rt, the reaction mixture turned reddish-brown upon adding the ketone to the reagent. Workup provided little or no yield of the alcohol. For the reaction at −25°C, the yield is better if the reaction is worked up as soon as the reaction is complete. Allowing the mixture to stand for some more time decreased the yield of the alcohol, and the product contained an alkyl chloride as well. Another observation was that the continued stirring of the triethanolamine adduct for more than 1 hour dissolved it and complicated the workup.

The reaction of acetophenone with **7**, in CH_2Cl_2, was slow at −25°C as well as at rt. The usual workup after 7 days gave a complex mixture of products, which was shown to contain a bromide (silver nitrate test) rather than an alcohol.

As in the case of acetophenone, the reaction of 3-methyl-2-butanone with **7** in CH_2Cl_2 at −25°C was slow and was carried out at rt. Unlike **5** and **6**, the dibromo reagent **7** gave poor yields of a product for a reaction with 3-methyl-2-butanone. This product did not correspond to 3-methyl-2-butanol by GC or IR spectrum. It gave a positive test for bromide with ethanolic silver nitrate.

All the preceding studies in which the reagents showed an unexpected behavior are being looked into more carefully. Probably, by proper manipulation of the reagent and reaction conditions, we may be able to obtain the *sec*-halides in high ee.

CONCLUSIONS

In conclusion, we have synthesized a series of optically pure mono- and dihaloboranes, from α-pinene, which were tested with a representative aromatic and aliphatic ketone, acetophenone and 3-methyl-2-butanone, respectively, for asymmetric reduction. DIP-Fluoride reduces ketones with decreased ee as compared to the corresponding chloro and bromo derivative. DIP-Chloride proved to be the reagent of choice, especially for aralkyl ketones, due to the simplicity of preparation, stability of the reagent in various solvents, convenient rate of reaction even at −25°C, ease of workup with complete recovery of α-pinene, and very high ee of the product alcohol (98%). DIP-Bromide gives similar results as DIP-Chloride, though the reactions are slower. DIP-Iodide is a poorer reducing agent, providing very low yields of the products from the reduction of both the aromatic and aliphatic ketone, the former (α-phenethanol) in racemic form and the latter (3-methyl-2-butanol) in 40% ee. In contrast, each of the monoisopinocampheyldihaloboranes behaves differently. The difluoro reagent **5** does not reduce acetophenone, whereas it partially reduces the aliphatic ketone in 59% ee. The dichloro derivative **6** reacts with acetophenone to provide the α-phenethyl chloride, whereas 3-methyl-2-butanone produces the alcohol in moderate yield (60%) in 43% ee. The dibromo reagent **7** gives the bromide with both ketones. The anomalous behaviors of reagents **4**–**7** are being studied critically. We have since synthesized monoisopinocampheyldiiodoborane using the silane procedure [33] and are currently studying its properties.

EXPERIMENTAL SECTION

General Methods

Techniques for handling air-sensitive compounds have been previously described [45]. All glassware was oven-dried, assembled hot, and cooled to rt in a stream of nitrogen. All reactions involving air-sensitive materials were carried out under a static pressure of nitrogen. The liquids were transferred with syringes or double-ended needles. ^{11}B NMR spectra were plotted on a Varian FT-80 A spec-

trometer (25.517 MHz) relative to $BF_3 \cdot OEt_2$. ^1H NMR spectra were obtained on a Varian T-60 instrument relative to TMS. ^{13}C NMR spectra were recorded on a Varian FT-80 A spectrometer (20.000 MHz) relative to TMS. IR spectra were plotted on a Perkin-Elmer 1420 ratio recording spectrophotometer. Analyses of the product alcohols were performed on a Varian 3400 gas chromatograph with a built-in integrator. GC columns, 1/8 in. × 12 ft, were packed with 10% SP-2100 on Chromosorb W (80–100 mesh) or 5% Carbowax 1540 on Chromosorb W (80–100 mesh). Analysis of the MTPA esters or MCF derivatives was performed on a Hewlett-Packard 5890 A gas chromatograph using a Supelcowax glass capillary column (15 m) or a methylsilicone capillary column (50 m) at appropriate temperatures and integrated using a Hewlett-Packard 3390 A integrator. Optical rotations were recorded on a Rudolph Autopol III polarimeter.

Materials

Anhydrous diethyl ether (Mallinkrodt) was used without further purification. Pentane (Philips) was stored over 4 Å molecular sieves (Davison), and THF (Fisher) was distilled from benzophenone ketyl and stored under nitrogen in an ampule. CH_2Cl_2 was distilled over P_2O_5. α-Pinene, borane-methyl sulfide (BMS), monochloroborane-methyl sulfide complex, monobromoborane-methyl sulfide complex, dichloroborane-methyl sulfide complex, dibromoborane-methyl sulfide complex, trichloroborane, tribromoborane, iodine, carbon disulfide, antimony trifluoride, acetophenone, 3-methyl-2-butanone, and menthyl chloroformate were purchased from Aldrich Chemical Co. MTPA was obtained from Aldrich Chemical Co. and converted to the acid chloride using a literature procedure [41]. Anhydrous etheral hydrogen chloride (~3*M*) was prepared from hydrochloric acid and sulfuric acid using a Brown apparatus [46].

Preparation of the Reagents B-Fluorodiisopinocampheylborane (Ipc₂BF, 1)

(a) From Ipc₂BH and HF

HF was condensed from a lecture bottle (Mathieson) at −78°C. A stainless steel needle was used to deliver the gas into a polyethylene centrifuge tube capped with a rubber septum and vented with a nitrogen bubbler.

To Ipc_2BH (22.3 g, 78.1 mmol), prepared from (+)-α-pinene (230 mmol) and $BH_3 \cdot SMe_2$ (100 mmol) in THF (96 mL) at 0°C by the reported procedure [19], suspended in EE (75mL) in a Teflon bottle, at −78°C was added HF (2 mL, neat) condensed from a lecture bottle. The mixture was stirred for 15 minutes at −78°C and warmed to 0°C when the solid dissolved and H_2 evolution was observed. The reaction was complete when all of the solid disappeared and H_2 evolution ceased. The ^{11}B NMR spectrum of an aliquot showed a broad singlet at δ 56. On methanolysis, the NMR revealed a singlet at δ 53. The solvent was removed to obtain 21.3 g (90%) of **1** as a thick slurry, which was used as such for further reactions with ketones.

(b) From DIP-Chloride and SbF_3

Reagent **2** (9.6 g, 30 mmol) in 50 mL CH_2Cl_2 was added, dropwise, to a 100 mL round-bottom flask containing SbF_3 (1.79 g, 10 mmol) at 0°C when an instantaneous reaction was observed. The ^{11}B NMR spectrum of the mixture showed a doublet at δ 56. The mixture was warmed to rt and stirred for 15 minutes, and the solvent was removed under aspirator vacuum and cooled, when the solid $SbCl_3$ separated. Concentration of the supernatant liquid provided 5.4 g (59%) of **1** as a thick slurry.

B-Chlorodiisopinocampheylborane, (DIP-Chloride, 2). (a) From Ipc₂BH and HCl

Dry HCl (67.3 mL of 3.33*M* solution in EE) was added to Ipc_2BH (64 g, 224 mmol) suspended in EE at 0°C in a 250 mL round-bottom flask and stirred at that temperature until all of the solid dissolved and gas evolution ceased (2 hours). The ^{11}B NMR spectrum showed a singlet at δ 74. Upon removal of the solvent and cooling, **2** solidified (mp 54–56°C, after crystallization from pentane). Yield: 61 g (85%), $[\alpha]_D^{22} = -67.03$ (*c* 13.5, CH_2Cl_2).

(b) From α-pinene and H_2BCl-SMe_2

To a 250 mL round-bottom flask containing α-pinene (33.3 mL, 210 mmol) in 75 mL of CH_2Cl_2 was added $ClBH_2 \cdot SMe_2$ at 0°C, and the mixture was warmed to rt and stirred for 10 hours. The ^{11}B NMR spectrum of the mixture revealed a singlet at δ 74, which was shifted to δ 52 after methanolysis. The solvent was removed under aspirator vacuum to provide 31.4 g (98%) of **2** as a thick slurry.

B-Bromodiisopinocampheylborane (DIP-Bromide, 3). *(a) From Ipc₂BH and HBr*

HBr in ether was prepared by passing the gas from a lecture bottle (Mathieson) through ice-cold ether. The solution was standardized using standard NaOH solution. Under nitrogen, 21.38 mL of 3.11 *N* HBr in EE was added to Ipc_2BH (19.0 g, 66.5 mmol) in EE (50 mL) contained in a 250 mL round-bottom flask, and the mixture was cooled to 0°C and stirred until all of the solid dissolved (~2 hours). The ^{11}B NMR spectrum showed a singlet at δ 80. Following methanolysis, the NMR spectrum revealed a singlet at δ 53. The solvent was pumped

off to obtain a white solid in a yield of 21.47 g (88%): mp 58–60°C.

(*b*) *From Ipc_2BH and Br_2*

Ipc_2BH was prepared in EE [20] [preparation of Ipc_2BH in THF leaves some THF occluded in the crystal, which can be cleaved by Ipc_2BBr, causing the reagent to become impure (see text)]. At 0°C, Br_2 (6.26 g, 2.2 mL) in CH_2Cl_2 (10 mL) was added to 25.06 g (87.78 mmol) of Ipc_2BH suspended in 75 mL of CH_2Cl_2 in a 250 mL two-necked round-bottom flask attached with a cold finger and connecting tube. After having been stirred for 15 minutes, the temperature of the mixture was raised to rt and the mixture was stirred overnight, during which time the solid Ipc_2BH dissolved and the color of Br_2 disappeared. The ^{11}B NMR spectrum showed a singlet at δ 80. Methanolysis gave a product that exhibited a singlet at δ 53. Solvent was removed to obtain a white solid. Yield: 31.35 g (99%), mp 58–60°C. $[\alpha]_D^{22} = -54.68$ (*c* 2.35, CH_2Cl_2).

(*c*) *From α-Pinene and $H_2BBr \cdot SMe_2$*

At 0°C, $BrBH_2 \cdot SMe_2$ was added to a 250 mL round-bottom flask containing α-pinene (33.3 mL, 210 mmol) in 75 mL CH_2Cl_2, and the mixture was warmed to rt and stirred for 12 hours. The ^{11}B NMR spectrum of an aliquot showed a singlet at δ 80, which was shifted to δ 52 upon methanolysis. The solvent was removed under aspirator vacuum to provide 36.2 g (98%) of **3** as a thick slurry.

B-Iododiisopinocampheyliodoborane (DIP-Iodide, **4**)

I_2 (3.35 g, 13.2 mmol) dissolved in a minimum amount of CH_2Cl_2 was added, dropwise, to a cold suspension of 7.54 g (26.4 mmol) of Ipc_2BH, prepared in EE, and kept at 0°C in 75 mL of CH_2Cl_2. After an additional stirring for 15 minutes the flask was warmed to rt and the mixture was stirred overnight, when the solid Ipc_2BH dissolved and the color of I_2 disappeared. The ^{11}B NMR spectrum showed a singlet at δ 85, which, on methanolysis shifted to δ 53. CH_2Cl_2 was pumped off to obtain a pure white solid, mp 60–62°C. Yield: 10.8 g (99%). The solid is extremely hygroscopic, fumes in air, and is pyrophoric.

Reaction of α-pinene with $IBH_2 \cdot SMe_2$. (*a*) *At rt*

100 mmol of $IBH_2 \cdot SMe_2$ prepared from $BH_3 \cdot SMe_2$ and I_2 in CS_2 according to a literature procedure [35] was added, at rt, to a 250 mL round-bottom flask containing α-pinene (210 mmol) in CH_2Cl_2. The ^{11}B NMR spectrum of the mixture after 5 hours revealed two peaks in ~1:1 ratio at δ −20.0 (t, J = 136 Hz) and −0.3 (d, J = 127 Hz) corresponding to $IBH_2 \cdot SMe_2$ and $IpcBHI \cdot SMe_2$, respectively. The reaction was followed by ^{11}B NMR spectroscopy. After 4 days, the 95% of hydroboration to $IpcBHI \cdot SMe_2$ was complete. Even after 2 weeks, traces of the starting iodoborane were left and none of **4** was formed.

(*b*) *At ~40°C (Refluxing CH_2Cl_2)*

Another reaction with the same ingredients as those used previously was set up at reflux. The ^{11}B NMR spectrum after 2 hours showed unreacted iodoborane, which was consumed completely within 8 hours, when the spectrum revealed two peaks at δ 85 (s), corresponding to **4** (15%), and δ −0.3 (d), corresponding to $IpcBHI \cdot SMe_2$ (85%). The reaction was followed by ^{11}B NMR spectroscopy, but the profile of the spectrum did not change much with time. Even after 4 days at reflux, the mixture still contained 15% of **4** and 85% of $IpcBHI \cdot SMe_2$.

Monoisopinocampheyldifluoroborane (IpcBF₂, **5**). (*a*) *From $IpcBH_2$ and HF*

To $IpcBH_2$ (120 mL of 0.68 M solution in EE) [19] contained in a Teflon bottle maintained at −78°C was added HF (2 mL, condensed from a lecture bottle at −78°C) and, while being stirred, was allowed to warm to ice-salt temperature. The mixture was stirred until the evolution of H_2 ceased, when the reaction was complete. The ^{11}B NMR spectrum showed a singlet at δ 19.6, presumably due to an ether complex, which, on methanolysis, shifted to δ 32. EE was pumped off and the residue distilled at 57–58°C/9 mm Hg to obtain a 50% yield of **5**. ^{11}B NMR: δ 29. (Distillation must be done carefully and slowly. Otherwise, the colorless reagent becomes dark brown with simultaneous evolution of white fumes, probably BF_3, inside the flask.)

(*b*) *From $IpcBCl_2$ and SbF_3*

Reagent **6** (9.6 g, 30 mmol) in 30 mL of CH_2Cl_2 was added, dropwise, to a 100 mL round-bottom flask containing 2.58 g (20 mmol) of SbF_3, when an instantaneous exothermic reaction was observed. The color of the solution turned pale yellow and the ^{11}B NMR spectrum of an aliquot revealed a triplet at δ 29 (J = 60 Hz). The mixture was warmed to rt and stirred for an additional 15 minutes, and the solvent was removed under aspirator vacuum, when solid $SbCl_3$ separated. The supernatant liquid was decanted and distilled at 57–58°C/9 mm Hg to yield 3.9 g (70%) of **5** as a clear liquid.

Monoisopinocampheyldichloroborane, $IpcBCl_2$, **6**. (*a*) *From $IpcBH_2$ and HCl*

To $IpcBH_2$ in EE (78 mL of 0.64 M, 50 mmol) contained in a 250, mL round-bottom flask was added

HCl in ether (35.5 mL of 2.82 N, 100 mmol) at ice-salt temperature. There was an immediate vigorous reaction with simultaneous evolution of hydrogen. The ^{11}B NMR spectrum showed a peak at δ 19, presumably due to an ether complex. Methanolysis shifted the peak to δ 32. Ether was pumped off at aspirator vacuum, and the residue was distilled at 52–55°C/0.1mm Hg to give ether-free **6** as a clear liquid. (Frothing occurs while distilling. It is necessary to use a large flask and a distillation head with a long vigreux column.) Yield: 8.9 g, 81.3%; the ^{11}B NMR spectrum, neat and in CH_2Cl_2, showed a peak at δ 63, $[\alpha]_D^{22} = -24$ (*c* 7.62, CH_2Cl_2). $IpcBCl_2$ fumes in air, is pyrophoric, and is stable at rt, under nitrogen.

(*b*) *From α-pinene and* $HBCl_2 \cdot SMe_2$

To a 250 mL round-bottom flask containing α-pinene (15 g, 110 mmol) in 50 mL of pentane was added, at 0°C, $ClBH_2 \cdot SMe_2$, followed by BCl_3 (100 mmol of 1.0 *M* solution in hexane). The mixture was warmed to rt and stirred for 2 hours when $BCl_3 \cdot SMe_2$ separated. The ^{11}B NMR spectrum of an aliquot of the supernatant liquid showed a singlet at δ 63, which shifted to δ 32 upon methanolysis. The solid was filtered off, the filtrate was concentrated under aspirator vacuum, and the residue was distilled to provide 20.0 g (92%) of **6** as a colorless liquid.

Monoisopinocampheyldibromoborane ($IpcBBr_2$, **7**). (*a*) *From* $IpcBH_2$ *and* Br_2

Ether was removed from a solution of $IpcBH_2$ in EE (100 mL of 0.68 *M*, 68 mmol) in a 250 mL two-necked round-bottom flask attached with a connecting tube. Freshly distilled CH_2Cl_2 (60 mL) was added, followed by, in drops, bromine (10.88 g, 3.5 mL, 68 mmol) in CH_2Cl_2 (10 mL) at rt. The mixture was stirred for 12 hours, when the hydrogen evolution ceased and the color of bromine disappeared. The ^{11}B NMR spectrum revealed a singlet at δ 65, which on methanolysis shifted to δ 32. The solvent was removed and **7** was distilled as a colorless liquid at 82–85°C/0.7 mm Hg; yield 16.6 g (80%). $[\alpha]_D^{22} = -12.41$ (*c* 9.71, CH_2Cl_2). $IpcBBr_2$ fumes in air, is pyrophoric, and is stable at rt, under nitrogen.

(*b*) *From α-Pinene and* $HBBr_2 \cdot SMe_2$

To a 250 mL round-bottom flask containing α-pinene (15 g, 110 mmol) in 50 mL of CH_2Cl_2 was added, at 0°C, 100 mmol of $BrBH_2 \cdot SMe_2$, followed by BBr_3 (100 mmol). The mixture was warmed to rt and stirred for 2 hours, when the reaction was complete; $BBr_3 \cdot SMe_2$ had separated and was filtered off. The ^{11}B NMR spectrum of an aliquot showed a singlet at δ 63, which shifted to δ 32 upon methanolysis. The solvent was removed under aspirator vacuum, and the residue was distilled to provide 27.6 g (90%) of **7** as a clear liquid.

Attempted Preparation of Monoisopinocampheyldiiodoborane ($IpcBI_2$, **8**)

Ether was removed from a solution of $IpcBH_2$ in ether (20 mL of 0.68 *M*, 13.6 mmol) in a two-necked 100 mL round-bottom flask attached with a cold-finger condenser and connecting tube. Dry CH_2Cl_2 (10 mL) was added, followed by I_2 (3.45 g, 13.6 mmol) in a minimum amount of CH_2Cl_2 (~75 mL) at rt. The reaction, monitored by ^{11}B NMR spectroscopy, was very slow, and $IpcBH_2$ redistributed to Ipc_2BH and BH_3. The ^{11}B NMR spectrum showed peaks at δ 85 and δ 57, in a ratio of 1:3, corresponding to Ipc_2BI and, probably, $IpcBI_2$. Attempts to distill the $IpcBI_2$ formed (Ipc_2BI being a solid) failed as the reaction mixture decomposed on heating.

Stability Study of the Reagents

50 mg of each of the reagents **1**–**7** were dissolved in 0.5 mL of pentane, CH_2Cl_2, EE, and THF and transferred to an NMR tube. The ^{11}B NMR spectra of these samples were plotted periodically and the changes were noted. The reagents were stable in pentane and CH_2Cl_2 but showed different characteristics in EE and THF. These are discussed in the text.

Reduction of Acetophenone with **1**

An oven-dried, 100 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. To this was added 5.3 mmol of **1** (1.6 g) and EE (2.8 mL), and this solution was cooled to −25°C, followed by the addition of 4.8 mmol (0.58 g, 0.56 mL) of acetophenone. A yellow color developed indicating a complex formation. The ^{11}B NMR spectrum, after methanolysis at the reaction temperature, indicated progressive disappearance of **1**. Two peaks were found in the spectrum, one at δ 32 corresponding to the expected boronate and the other peak at δ 9. The reagent **1** was consumed in 4 days, whereupon the mixture was warmed to 0°C and treated with 2.2 equiv of diethanolamine. The ether layer was separated from the solid obtained, concentrated, passed through a silica gel bed to remove the α-pinene liberated during the reaction and the eluate distilled using a Kugelrohr apparatus (140°C/12 mm Hg) to obtain 0.41 g (70%) of α-phenethanol. The MTPA ester of this product [41], on analysis using a Supelcowax capillary column, showed an enantiomeric composition of 83% *S* and 18% *R*, indicating an ee of 65% in the *S*-isomer.

Reduction of 3-Methyl-2-butanone with **1**

A 4 mmol scale reaction of 3-methyl-2-butanone with **1** following the above procedure was complete in 4 days. Workup provided a 60% yield of 3-methyl-2-butanol. Analysis of the MCF derivative on a methyl silicone capillary column showed an ee of 30% in the *S*-isomer.

Reduction of Acetophenone with **2**

The reduction of acetophenone with **2** followed by a diethanolamine workup has been reported by us earlier [18]. A similar reaction, followed by the improved acetaldehyde workup, is as follows. An oven-dried, 100 mL round-bottom flask equipped with a side arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. (–)-DIP-Chloride (8.8 g, 27.5 mmol) was transferred to the flask in a glove bag and dissolved in EE (25 mL). The solution was cooled to −25°C, and acetophenone (2.9 mL, 25 mmol) was added using a syringe. The reaction was followed by ^{11}B NMR spectroscopy after aliquots were methanolyzed at the reaction temperature at periodic intervals. When the reaction was complete (^{11}B δ: 32, <5 hours), the mixture was warmed to 0°C and acetaldehyde (1.7 mL, 30 mmol) was added. The mixture was then warmed to rt and stirred for 3 hours, when the reaction was complete (^{11}B NMR spectrum of a methanolyzed aliquot: a singlet at δ 18). The solvents were removed under aspirator vacuum, and the residue was distilled to separate α-pinene (7.0 g, 94%) and α-phenethanol (2.75 g, 90%). The alcohol was further purified by preparative GC using a SP-2100 column. The rotation was measured. $[\alpha]_D^{22}$ = −42.6 (neat) which corresponds to 98% ee in the *S*-isomer [47]. The analysis of the MTPA ester of this alcohol showed a composition of 98.5% of the *S*-isomer and 1.5% of the *R*-isomer, i.e., an ee of 97% in the *S*-isomer.

Reduction of 3-Methyl-2-butanone with **2**

The reduction of this ketone has been published elsewhere [18].

Reduction of Acetophenone with **3**

Acetophenone (2.91 mL, 25 mmol) was reduced with **3** (10.44 g, 28.6 mmol) in EE at −25°C as previously done. The reaction was complete in 15 hours (^{11}B NMR spectrum of methanolyzed aliquot δ: 32). The standard workup using diethanolamine provided 2.12 g (69.5%) of α-phenethanol. $[\alpha]_D^{20}$ = −42.5 (neat), which corresponds to an optical purity of 98% (*S*). The MTPA ester also showed an ee of 98% in the *S*-isomer.

Reduction of 3-Methyl-2-butanone with **3**

A reduction of 3-methyl-2-butanone (1.72 g, 2.14 mL, 20 mmol) with **3** (7.64 g, 21 mmol) was carried out in EE at −25°C as previously done. The reaction was complete in 14 hours (^{11}B NMR spectrum of methanolyzed aliquot δ: 32). The standard workup using diethanolamine provided 1.29 g (73.3%) of 3-methyl-2-butanol. This was further purified by preparative GC (5% Carbowax column) and the rotation was noted; $[\alpha]_D^{20}$ = +1.39 (neat), which corresponds to an optical purity of 26% (*S*) based on the literature rotation of +5.34 for 100% ee (*S*) [48]. The MTPA ester showed an ee of 28% in the *S*-isomer.

Reduction of Acetophenone with **4**

Acetophenone (0.63 mL, 5.47 mmol) was added to **4** (2.48 g, 6.02 mmol) in CH_2Cl_2 (4 mL) at −25°C. The ^{11}B NMR spectroscopy showed a very slow reaction. After 7 days, only 50% reaction had occurred. Acetaldehyde (3 mmol) was added to destroy the excess reagent, and the mixture was worked up using 2.2 equiv of diethanolamine. The product was distilled to obtain 0.88 g of a mixture, which showed a positive result for iodide in a test with alcoholic silver nitrate. A GC analysis showed ~10% of α-phenethanol. The MTPA ester of this crude mixture was analyzed on a Supelcowax capillary column, which showed it to be racemic.

Reduction of 3-Methyl-2-butanone with **4**

A 10 mmol reaction of 3-methyl-2-butanone with **4** in CH_2Cl_2 at −25°C was extremely slow. The reaction was 60–70% complete after 1 week (^{11}B NMR spectroscopy). The reaction was quenched with acetaldehyde (5 mmol) and worked up with diethanolamine. The product showed the presence of 20% of the alcohol. Analysis of this mixture as the MCF derivative on a methyl silicone capillary column showed an ee of 39.6% in the *S*-isomer.

Reduction of Acetophenone with **5**

Reagent **5** (1.19 g, 5.9 mmol) was added to a 20 mL round-bottom flask containing 4 mL of CH_2Cl_2 and 0.6 mL (5 mmol) of acetophenone maintained at −25°C. There was an immediate red coloration. The reaction was followed by ^{11}B NMR spectroscopy of a methanolyzed aliquot. After 1 hour, the ^{11}B NMR spectrum showed peaks at δ 32.00, 8.00 (major), and −0.60. After 20 hours, the spectrum still showed the three peaks, but the δ 32.00 peak became the major one. The reaction mixture was warmed to rt, and the solvent was removed. After 7 days, the spectrum remained the same. Dichloromethane was substituted with ether, and the reaction mixture was worked up with triethanolamine (3 equiv),

when it separated into two layers. The upper ether layer was separated, concentrated, and distilled to yield 0.8 g of a material that contained mostly recovered acetophenone.

Reduction of 3-Methyl-2-butanone with **5**

A reaction of 2.42 g (2.2 mL, 13 mmol) of **5** with 1.3 mL (12 mmol) of 3-methyl-2-butanone in 10 mL of CH_2Cl_2 at −25°C was carried out as previously done. The reaction mixture became red immediately. The ^{11}B NMR spectrum of a methanolyzed aliquot after 1 hour showed four peaks at δ 32.00, 18.00, 10.00, and −0.70. The δ 18.00 peak increased with time. However, the reaction was very slow. The mixture was warmed to rt and the solvent was removed. After 7 days, the reaction mixture was worked up as above using triethanolamine. Distillation provided 0.57 g of the product, which was a 1:1 mixture of the recovered ketone and product alcohol. The MCF derivative of this mixture was prepared as usual and analyzed on a methyl silicone capillary column, which showed an ee of 58.7% in the *S*-isomer.

Reduction of Acetophenone with **6**

To **6** (1.05 g, 1 mL, 5 mmol) in CH_2Cl_2 (4 mL) maintained at −25°C was added acetophenone (0.5 mL, 4.5 mmol). An immediate yellow coloration was observed which became reddish-yellow after 1 hour. The progress was monitored by ^{11}B NMR spectroscopy of a methanolyzed aliquot, which showed the complete formation of the expected δ 32.00 peak after 4 hours. CH_2Cl_2 was substituted with EE (50 mL), triethanolamine (3 equiv) was added, and the mixture was stirred for 1 hour. The white precipitate of boron components was filtered off and washed with pentane, and the combined filtrate was concentrated. Distillation provided 0.24 g of a product that did not show the peak corresponding to α-phenethanol in GC. The IR spectrum showed neither the ketone nor the expected product alcohol. Treatment with ethanolic $AgNO_3$ showed a positive test. The ^1H NMR and ^{13}C NMR spectra corresponded to α-phenylchloroethane. This was further purified by preparative GC using a SP-2100 column; $[\alpha]_D^{20} = -5.78$ (neat, l = 0.5 dm) corresponds to 9% ee in the *S*-isomer based on the literature rotation of +129 (neat) for the *R*-(+)-isomer [49].

Reduction of 3-Methyl-2-butanone with **6**

3-Methyl-2-butanone (2.67 mL, 25 mmol) was treated with 5.5 mL (27.5 mmol) of **6** in 16.5 mL CH_2Cl_2 at −25°C as previously done. The reaction was complete in 3 hours. The solvent was removed and α-pinene generated during the reaction was collected using a vacuum pump. EE (50 mL) was added, followed by triethanolamine (80 mmol), and worked up as above to obtain 1.39 g (63%) of 3-methyl-2-butanol. This was purified by preparative GC (5% Carbowax column) and the rotation noted: $[\alpha]_D^{24} = +2.29$ (neat), which corresponds to an ee of 42.9% in the *S*-isomer based on the literature value of $[\alpha]_D = +5.34$ for 100% optical purity. Analysis of the MCF derivative showed a composition of 71.5% of *S*-isomer and 28.5% of *R*-isomer, i.e., and ee of 43% in the *S*-isomer.

Reduction of Acetophenone with **7**

A reaction of 10 mmol of acetophenone with 11 mmol of **7** in CH_2Cl_2 at −25°C was extremely slow. The mixture was warmed to rt and the progress monitored using ^{11}B NMR spectroscopy. The reaction mixture was worked up after 7 days. Distillation provided a complex mixture of products. There was no trace of the expected product, α-phenethanol. The product mixture showed a positive test with ethanolic $AgNO_3$.

Reduction of 3-methyl-2-butanone with **7**

The reduction of 3-methyl-2-butanone with **7** also yielded the same results as that of acetophenone.

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